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Intraductal papillary mucinous neoplasms of the pancreas

Clinical management, health economy and biomarkers

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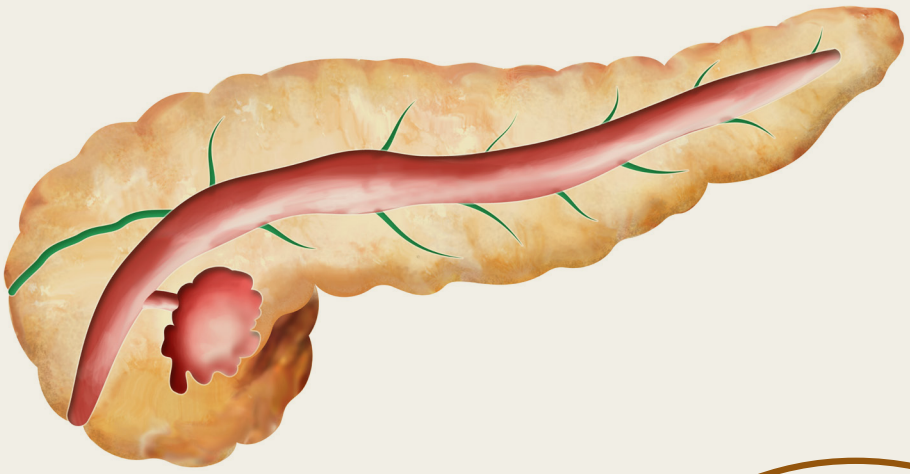

Intraductal papillary mucinous neoplasms of the pancreas

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Clinical management, health economy and biomarkers

Linus Aronsson, MD

LUND
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DOCTORAL DISSERTATION

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Abstract

Intraductal papillary mucinous neoplasm of the pancreas (IPMN) is a premalignant tumor with the potential for invasive transformation to carcinoma (IPMC). The location within the ductal structure has prognostic relevance; lesions in the main pancreatic duct (MD-IPMN) have a higher risk of being invasive compared to those in the branch ducts (BD-IPMN). Most IPMN are found incidentally. The ubiquitous use and improved sensitivity of imaging techniques have resulted in a prevalence increase. Specific clinical and radiological factors are used to assess the likelihood of high risk tumors that warrant surgical resection. The preoperative diagnosis is, however, a clinical conundrum, with risks of misdiagnosis, overtreatment and undertreatment. Rigorous surveillance programs are recommended preoperatively and postoperatively.

The aim of this thesis was to study the surgical management and outcome of IPMN in Sweden, to evaluate the cost-effectiveness of management of low risk IPMN, to investigate the postoperative survival of IPMC and to analyze blood-based biomarkers in the preoperative setting.

Analysis of a nationwide pancreatic resection registry showed an increase in the number of surgical procedures being performed for IPMN in Sweden (2010-2016). Overall, 3-year survival for non-invasive IPMN was 90%, compared to 39% in IPMC. The proportion of IPMC decreased during the study period. The findings support an increasing prevalence of IPMN and use of a more aggressive surgical approach.

A Markov decision model, for an incidentally identified low risk IPMN in an otherwise healthy person aged 65 years, compared four different management strategies. A surveillance strategy was the most cost-effective with a QALY of 9.31 and cost of €26,305, resulting in an incremental cost-effectiveness ratio of €31,682 compared to a “wait and see” approach.

Meta-analysis showed that IPMC has an improved postoperative survival compared to pancreatic ductal adenocarcinoma (PDAC) (OR 0.23, CI 95% 0.09-0.56), especially at lower tumor grades. From an American registry, data from 440 patients with resected IPMC were used to predict long term survival. Artificial neural networks (ANN) and regression analyses performed well with accuracy of about 80%. An ANN implementing variable selection had a precision of 0.83, recall of 0.95 and F1 score of 0.89.

Preoperative serum glycoprotein panels showed high AUC for PDAC, IPMN and healthy control differentiation. Further investigation and validation of glycoprotein panels is thus required. Their use may aid preoperative therapeutic decisions.

Key words: intraductal papillary mucinous neoplasm, invasive IPMN, health economy, prognosis, biomarkers

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Intraductal papillary mucinous neoplasms of the pancreas

Clinical management, health economy and biomarkers

Linus Aronsson, MD

Department of Surgery, Clinical Sciences

Faculty of Medicine

Lund University

2020

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List of papers and manuscripts

This thesis is based on the following papers. They will be referred to in the text by the corresponding Roman numerals.

I. **Aronsson L**, Andersson B, Andersson R, Tingstedt B, Bratlie SO, Ansari D. Intraductal papillary mucinous neoplasms of the pancreas: a nationwide registry-based study. Scand J Surg 2018;107:302-307.

II. **Aronsson L**, Ansari D, Andersson B, Persson U, Fridhammar A, Andersson R. Intraductal papillary mucinous neoplasms of the pancreas – a cost-effectiveness analysis of management strategies for the branch-duct subtype. HPB (Oxford) 2018;20:1206-1214.

III. **Aronsson L**, Bengtsson A, Torén W, Andersson R, Ansari D. Intraductal papillary mucinous carcinoma versus pancreatic ductal adenocarcinoma: a systematic review and meta-analysis. Int J Surg 2019;71:91-99.

IV. **Aronsson L**, Andersson R, Ström A, Ansari D. Artificial neural networks versus lasso regression for the prediction of long-term survival after surgery for invasive IPMN of the pancreas. Manuscript.

V. **Aronsson L**, Andersson R, Bauden M, Andersson B, Bygott T, Ansari D. High-density and targeted glycoproteomic profiling of serum proteins in pancreatic cancer and intraductal papillary mucinous neoplasm. Scand J Gastroenterol 2018;53:1597-1603.

Thesis at a glance

Paper	Objective	Method	Results / Conclusion
I	To investigate the trend and outcome of surgical resection of IPMN in Sweden.	Data (2012 – 2016) from the Swedish National Pancreatic Resection Database was queried. A total of 251 patients with IPMN was included.	There was an increase in resections performed on noninvasive IPMN. The 3-year overall survival was 90 and 39% for noninvasive and invasive IPMN, respectively. There was no difference in survival comparing the different dysplastic grades. Biliary obstruction was the only predictive factor for invasive disease.
II	To study the cost-effectiveness of different management strategies for low-risk IPMN.	Four strategies: total pancreatectomy upfront, partial pancreatectomy upfront, initial surveillance (current guidelines), wait and see, were compared in a Markov-model. The model evaluated a 65-year old, otherwise, healthy person with an incidentally found suspected low-risk IPMN.	The current strategy from the most recent guidelines, utilizing initial surveillance, was the most cost-effective method (ICER of €31,682 per QALY compared to wait and see). The total cost for the surveillance strategy was €26,305. Tailored strategies are needed.
III	To compare the postoperative outcomes of invasive IPMN and PDAC.	A systematic review and meta-analysis was performed, incorporating 14 studies that met inclusion and exclusion criteria.	The pooled five-year overall survival was worse for PDAC (OR 0.23, 95% CI 0.09-0.56). Survival was, however, similar at higher tumor stages. PDAC had, generally, a more aggressive tumor biology at resection.
IV	To develop a predictive model for long-term postoperative survival in invasive IPMN.	ANN and LASSO models were created on 440 patients from the Surveillance, Epidemiology and End Results (SEER) database.	The accuracy of the models in predicting 5-year survival was approximately 80%. The ANN-model with variable selection had particularly good performance in recall and NPV. Prediction models can aid in patient management.
V	To analyze biomarkers to aid in the discrimination between healthy controls and disease states, i.e. IPMN or PDAC.	Preoperatively assessed serum glycoprotein profile to distinguish IPMN, PDAC and healthy controls. The top 10 biomarkers from a discovery analysis on 1000 glycoproteins were selected for further evaluation. Serum CA19-9, as routinely measured, was also included.	A biomarker panel of CA19-9, Eotaxin2, CD163 and BMP3b had an AUC of 0.915 for discrimination of IPMN and healthy controls. Serum glycoprotein profiles can aid in the preoperative assessment of suspected IPMN or PDAC.

Abbreviations

ACG	American College of Gastroenterology
AGA	American Gastroenterology Association
AIGO	Italian Association of Hospital Gastroenterologists and Endoscopists
AISP	Italian Association for the Study of the Pancreas
AJCC	American Joint Committee on Cancer
AMSTAR	Assessing the methodological quality of systematic reviews
ANN	Artificial neural network
AUC	Area under the curve
BD-IPMN	Branch-duct IPMN
CA19-9	Carbohydrate antigen 19-9
CEA	Carcinoembryonic antigen
CI	Confidence interval
CT	Computed tomography
DM	Diabetes mellitus
DGE	Delayed gastric emptying
DP	Distal pancreatectomy
DSS	Disease-specific survival
ERCP	Endoscopic retrograde cholangiopancreatography
EUS	Endoscopic ultrasonography
FNA	Fine-needle aspiration
GNAS	Guanine nucleotide binding protein, alpha stimulating
HC	Healthy controls
HU	Health utility
HGD	High-grade dysplasia
HRS	High-risk stigmata
IAP	International Association of Pancreatology
ICER	Incremental cost effectiveness ratio
IFC	Incidental findings committee
IGD	Intermediate-grade dysplasia
IOPN	Intraductal oncocytic papillary neoplasm
IPMN	Intraductal papillary mucinous neoplasm
IPMC	Intraductal papillary mucinous neoplasm with an invasive carcinoma
ITPN	Intraductal tubulopapillary neoplasm
KRAS	Kirsten rat sarcoma 2 viral oncogene homolog
LASSO	Least absolute shrinkage and selection operator
LGD	Low-grade dysplasia
LY	Life years
M	Markov node
MCAR	Missing completely at random
MCN	Mucinous cystic neoplasms

MD-IPMN	Main-duct IPMN
MeSH	Medical subject headings
MOOSE	Meta-analysis of observational studies in epidemiology
MPD	Main pancreatic duct dilatation
MRI	Magnetic resonance imaging
MRCP	Magnetic resonance cholangiopancreatography
MT-IPMN	Mixed-type IPMN
MUC	Mucin
NGS	Next generation sequencing
NIH	National Institutes of Health
NPV	Negative predictive value
OS	Overall survival
OR	Odds ratio
PanIN	Pancreatic intraepithelial neoplasia
PCN	Pancreatic cystic neoplasm
PET	Positron emission tomography
PC	Pancreatic cancer
PCF	Pancreatic cystic fluid
PD	Pancreatoduodenectomy
PDAC	Pancreatic ductal adenocarcinoma
PJC	Pancreatic juice cytology
PMM	Predictive mean matching
PNEN	Cystic pancreatic neuroendocrine neoplasm
POPF	Pancreatic fistula
PP	Pseudocyst
PPV	Positive predictive value
PRISMA	Preferred reporting items for systematic reviews and meta-analysis
QALY	Quality-adjusted life-years
QoL	Quality of life
RFS	Recurrence-free survival
ROC	Receiver operator curve
SCN	Serous cystic neoplasm
SEER	Surveillance, epidemiology and end results
SPN	Solid-pseudopapillary neoplasm
STROBE	Strengthening the report of observational studies in epidemiology
TNM	Tumor node metastasis
TP	Total pancreatectomy
US	Ultrasonography
WF	Worrisome features
WHO	World Health Organization
WTP	Willingness to pay

Abstract

Background: Intraductal papillary mucinous neoplasm (IPMN) is a cystic tumor originating from the cells lining the pancreatic ducts. The disease spectrum ranges from low-grade dysplasia to invasive carcinoma (IPMC). Preoperative diagnosis is challenging. Lesions considered as high risk for malignancy, based on radiological and clinical parameters, should undergo pancreatic surgery. Post-operatively, management guidelines recommend surveillance to detect recurrence or metachronous cancer. Surveillance is also warranted for low-risk IPMN not yet surgically resected to monitor for potential transformation into a high risk lesion or metachronous cancer development.

Aims: The aims are: (I) to investigate the trends of surgical treatment and postoperative outcomes of IPMN in Sweden, (II) to explore the cost-effectiveness of different management strategies for low risk IPMN, (III) to examine and to compare the postoperative outcome of IPMC to pancreatic ductal adenocarcinoma (PDAC), (IV) to create a model to predict long-term survival of IPMC, and (V) to investigate if glycoprotein biomarkers in serum can aid in the preoperative setting to distinguish between IPMN, PDAC and healthy controls.

Methods: The National Quality Register of Pancreatic and Periampullary Cancer and the Surveillance, Epidemiology and End Results databases were interrogated. Regression analyses and artificial neural networks (ANN) were applied. A Markov decision model was built to analyze cost-effectiveness comparing four different management strategies. A systematic review and meta-analysis was conducted. A total of 14 studies were included. Glycosylation assays were performed on prospectively collected preoperative blood samples in patients with PDAC and IPMN as well as healthy controls.

Results and conclusion: There was an increase in surgical procedures performed for IPMN. Postoperative survival was heavily impacted in IPMC with a 3-year survival of 39% compared to 90% in non-invasive IPMN (paper I). Current management strategies for low risk IPMN is the most cost-effective. Improved strategies are, however, warranted (paper II). Paper III showed that IPMC patients have improved postoperative survival compared to PDAC, possibly due to earlier detection and tumor biology. ANN and LASSO regression have good performance in predicting long-term survival of IPMC (paper IV). Paper V indicates that preoperative analysis of glycoproteins can aid in management by discriminating between disease and healthy controls.

Populärvetenskaplig sammanfattning

Intraduktal papillär mucinös neoplasi (IPMN) är en cystisk (slembildande) förändring i bukspottkörteln som är ett förstadium (låggradig dysplasi till höggradig dysplasi) till cancer men kan i sig själv även övergå till invasiv cancer. IPMN utgår från gångarna i bukspottkörteln och delas in i huvudgångs- (MD), sidogångs- (BD) eller blandad typ (MT). IPMN hittas vanligtvis av en slump, när patienter genomgår radiologiska undersökningar av andra anledningar. Detta då de flesta IPMN inte ger symptom. Eftersom det krävs radiologiska undersökningar för att upptäcka IPMN är prevalensen inte helt känd men uppskattas till över 2% i befolkningen. Man vet att prevalensen och således incidensen ökar med ålder och att IPMN är sällsynt hos yngre individer (<50 år).

De första rapporterna om IPMN kommer under tidigt 1980-tal och WHO (World Health Organization) klassar år 1996 IPMN som en ”egen” entitet, skild från andra cystiska förändringar i bukspottkörteln. Under 2000-talet har forskningen om IPMN varit explosionsartad. Flertalet riktlinjer har utformats för att ge stöd åt läkare i handläggningen av IPMN. Det föreligger dock fortsatta svårigheter att preoperativt (före operation) förutsäga om det rör sig om en höggradig dysplastisk förändring eller cancer (högrisk IPMN) från låggradig dysplastisk förändring (låg-risk IPMN), där de förstnämnda bör opereras bort enligt gällande riktlinjer. Risken för död anses för högrisk IPMN överstiga riskerna med bukspottkörtelkirurgi. Det finns även en osäkerhet kring att skilja IPMN mot andra typer av cystor eller tumörer i bukspottkörteln. Vid histopatologiskt konfirmerad cancer (operationspreparat granskat av patolog) följs patienten upp som vid vanlig bukspottkörtelcancer. Vid en icke-invasiv IPMN (ej cancer) finns det efter operation (om delar av bukspottkörteln finns kvar) en risk för återfall och patienten bör följas upp årligen. Eftersom det i dagsläget är omöjligt att förutsäga vilka av de preoperativt klassade låg-risk IPMN som kommer progrediera och kräva operation är standard att även dessa följs upp med täta kontroller. Studier visar att personer med IPMN har en ökad risk för att få en ”vanlig” bukspottkörtelcancer vilket ytterligare stärker indikationen av uppföljande kontroller.

På grund av den ovannämnda osäkerheten finns indicier från flera håll i världen att antalet operationer för misstänkta IPMN ökar och utgör en ökande andel av det totala antalet bukspottkörteloperationer. I det första delarbetet av avhandlingen kartlade vi förekomst och resultat vid kirurgisk behandling av IPMN i Sverige. Vi använde data från det nationella kvalitetsregistret över cancer i och runt bukspottkörteln. Antalet operationer av histopatologiskt konfirmerad IPMN ökade från 13 till 56 mellan 2010 – 2016 (4.7 – 11% av det totala antalet operationer i registret). Överlevnaden efter kirurgi var likvärdig oberoende graden dysplasi för icke-invasiv IPMN (p=0.417). Vid invasiv IPMN var 3-årsöverlevnaden 39% och för icke-invasiv IPMN var den 90%.

Incidentell upptäckt av låg-risk IPMN har ökat under de senaste åren. Detta förklaras framför allt av en ökad användning av och bättre radiologiska metoder. Denna ökning leder till att fler individer inkluderas i uppföljningsrutinerna. Den optimala handläggningen rent kostnadseffektivt undersöktes i delarbete II där vi jämförde fyra olika strategier i en Markov-modell. Utfallet var inkrementell kostnads-effekt ratio (ICER) per kvalitetsjusterade levnadsår (QALY). Modellen analyserade en 65-årig, annars väsentligen frisk, individ med nyupptäckt misstänkt låg-risk IPMN. Sannolikheter och kostnader baserades på lokala data samt syntes av vetenskapliga skrifter och i vissa fall estimat från experter inom fältet. Handläggning enligt rådande rutin, med initial uppföljning, jämfört med att vänta till symptom uppstod var mest kostnadseffektiv i vår analys (ICER €31,682 per QALY). Denna handläggning resulterade in en QALY på 9.31 under 13.4 levnadsår. Kostnaden för denna strategi var €26,305, vilket då motsvarar snittkostnaden per 65-årig patient med nyupptäckt låg-risk IPMN. Mot bakgrund av ett ökat antal patienter som inkluderas i uppföljningsrutinerna är förbättrade strategier nödvändiga. Dels för att minska själva kostnaden och belastning på sjukvården men framför allt för att gynna den enskilda patienten med optimerad handläggning.

IPMN som utvecklats till invasiv cancer skiljer sig från ”vanlig” bukspottkörtelcancer (PDAC) där 5-årsöverlevnaden efter operation är påtagligt försämrad för de med PDAC jämfört för dem med invasiv IPMN (OR 0.23, CI 95% 0.09 – 0.56), vilket är resultatet från delarbete III som är en litteraturgenomgång och kvantitativ syntes av resultat från 14 studier. Överlevnadsskillnaden försvinner dock vid högre stadier av cancer. Det verkar således finnas en skillnad rent biologiskt. Detta ger ytterligare bevis av att tidig upptäckt och operation av IPMN som övergått till cancer är livsavgörande.

I delarbete IV användes olika modeller för att förutsäga långtidsöverlevnad efter kirurgi av invasiv IPMN. Artificiella neurala nätverk (ANN), som är en avancerad datakrävande statistisk metod, jämfördes med mer traditionella regressionsanalyser inkluderande en specialmetod (LASSO). Målet var att med vanligt förekommande variabler kunna förutsäga 5-årsöverlevnad. Dataunderlaget byggde på uppgifter från en stor amerikansk databas (SEER: Surveillance, Epidemiology and End Results). Metoderna presterade väl även vid statistisk selektion av inkluderade variabler och uppnådde träffsäkerhet kring 80%. Prediktiva modeller kan ge tillförlitligt stöd till vidare handläggning och en uppfattning om framtida prognos vilket kan komma patienter och behandlande läkare till gagn.

På grund av osäkerheten kring diagnos preoperativt (om det är högrisk IPMN, cancer eller annan förändring) finns ett behov av nya eller förbättrade metoder. Blodprovsbaserade markörer är högaktuellt inom alla former av sjukdomar, så även för IPMN. Vi valde att analysera glykoproteiner. Glykosylering (komplettering med sockerkedjor på protein) är en av de mest frekvent förekommande förändringarna

av proteiner och spelar viktig roll i normal cellfunktion men även i tumörutveckling. I delarbete V kunde vi efter analys av glykoproteiner i blodprover tagna från 109 patienter (preoperativt) samt 47 friska kontrollpersoner skapa biomarkörpaneler. Paneler med CA19-9 och tre utvalda glykoprotein kunde med hög träffsäkerhet skilja ut de med IPMN och PDAC från friska kontrollpersoner (AUC 0.92 respektive 0.99).

Biomarkörer, så som glykoproteiner, kommer att spela en viktig roll i framtida kliniska beslut och deras värde kan integreras i ANN-modeller (vilka kan hantera stora mängder av data och variabler på ett bättre sätt än traditionella metoder) för att bättre predicera olika utfall och förbättra riskvärdering och således klinisk handläggning. Integrering av biomarkörer behövs för att kunna hantera det ökande antalet patienter med nyupptäckta misstänkta IPMN eller andra cystor för att inte överbelasta de ändliga resurserna i sjukvården. Viktigast är att patienterna gynnas av en mer individuell och specifik behandlingsplan.

Introduction

The pancreas

The pancreas is a retroperitoneal organ in the upper abdomen (Figure 1). It can be divided anatomically into head, neck, body and tail. The main pancreatic duct, ductus Wirsung, passes through the whole gland from tail to head, merging with the common bile duct immediately prior to the major duodenal papilla. The accessory pancreatic duct, ductus Santorini, runs from the head of the pancreas and into the duodenum through the minor duodenal papilla. Several smaller ducts, dispersed throughout the entire gland, connect to the main pancreatic duct.

The pancreas has both exocrine and endocrine functions. The exocrine component plays an important role in digestion. It manufactures pancreatic juice, which contains digestive enzymes and alkaline, bicarbonate-rich fluid. The digestive enzymes include proteolytic enzymes, lipolytic enzymes and amylase. The proteolytic enzymes are secreted in an inactive form to protect the pancreas from autodigestion and are activated in the duodenum. The endocrine component regulates appetite and blood glucose homeostasis; insulin decreases serum glucose and glucagon increases glycemic levels. The cells responsible for hormone production are located in the islets of Langerhans[1].

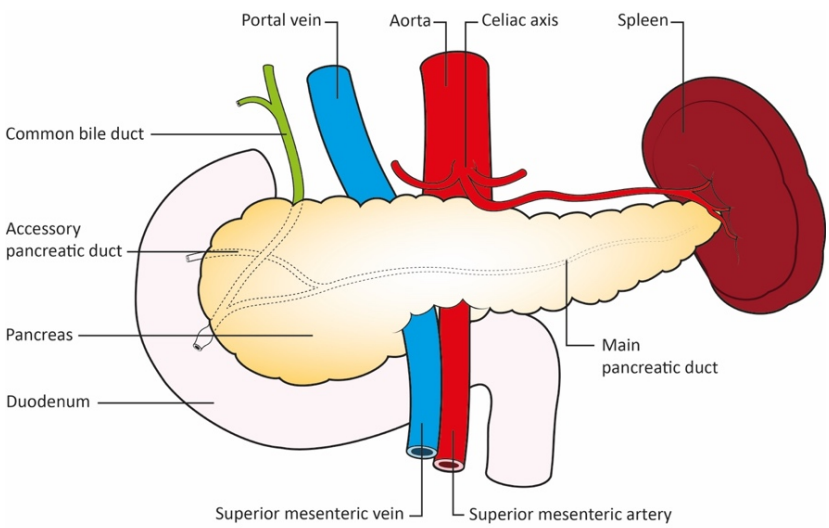


Figure 1. Anatomy of the pancreas. Image courtesy of Dr Daniel Ansari and medical illustrator Jan Funke.

Cystic neoplasms of the pancreas

Pancreatic cystic neoplasms (PCN) comprise a large spectrum of pathologies that can be classified into distinct categories; epithelial neoplasms, non-epithelial neoplasms, epithelial non-neoplasms, non-epithelial non-neoplasms. Additionally, several diseases can be tumor-like in appearance[2-4].

Intraductal papillary mucinous neoplasm (IPMN)

IPMN is a cystic epithelial neoplastic lesion that stems from the cells lining the pancreatic ducts. As the name implies, IPMN often produces excessive amounts of mucin, giving rise to cystic duct dilatation[4].

The term IPMN, referred to in the original publication as 'intraductal papillary-mucinous tumor', was first coined in 1994[5]. It was classified as a separate entity, distinct from mucinous cystic neoplasm (MCN) by the World Health Organization (WHO) in 1996[2], and renamed 'intraductal papillary mucinous neoplasm' in 2000[6]. A study from 1982, describing four cases of what is now known to be IPMN, is often referred to as the first published report on IPMN[7]. However, IPMN obviously existed before 1982, as has been shown when reviewing pathological specimens[8].

IPMN is the focus of this thesis. However, it is appropriate to include a brief review of other relevant cystic and tumor-like lesions of the pancreas. These are frequently considered as differential diagnoses and are mentioned in the major guidelines. A comparison of clinicopathological factors is shown in Table 1.

Mucinous cystic neoplasm (MCN)

MCN differ from IPMN in that the former have no communication with the pancreatic ducts, contain an ovarian stroma component, occur almost entirely in women and arise in the body or tail of the pancreas[4]. The average age of patients presenting with MCN is approximately 50 years[4]. 25% of MCN are incidental findings[9]. The management of MCN is similar to that of IPMN as MCN have a risk of neoplastic transformation to invasive carcinoma. In surgical patient series, invasive carcinoma is present in 5 – 16% of patients[9-13]. MCN are rare tumors; in one large institution they represented less than 2% of all pancreatic resections[11]. According to two major current guidelines: (1) resection should be carried out in all surgically fit patients[14], (2) resection is warranted for MCN measuring ≥40 mm, those lesions displaying high risk characteristics, e.g. mural nodule or fast growth rate, those causing symptoms, and tumors presenting in younger patients[15]. The 5-year survival following resection for non-invasive MCN is 100% whereas the equivalent statistic for MCN with an associated invasive carcinoma ranges from 26 – 75%[4,9,10,12]. The 10-year disease specific survival was, however, reported in one study to be 80% for MCN with an associated invasive carcinoma[11]. Preoperative

distinction between MCN and IPMN, especially IPMN located in the branch-ducts, can be challenging and a combination of clinical characteristics, imaging, cytology, and, chemical and molecular analyses may be needed[16].

Serous cystic neoplasms (SCN)

SCN is another epithelial neoplastic cyst consisting of cells with a glycogen-rich, clear cytoplasm that produces a watery, serous secretion. SCN have three morphological patterns including polycystic, honeycomb and oligocystic types[14]. SCN have no connection with the main or branch pancreatic ducts. The median age of diagnosis is approximately 60 years, with a strong female predilection[17]. SCN should be considered a benign entity; invasive disease is extremely rare[15,17,18]. Radiological examination including endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) with chemical analysis may be used for correct diagnosis[16]. However, preoperative diagnostic uncertainty is common[17,19]. The majority of SCN are discovered incidentally and only about 40% of patients presents with symptoms, which include abdominal pain, pancreaticobiliary symptoms and diabetes mellitus (DM)[17]. Symptomatic SCN may warrant surgical resection[15].

Solid-pseudopapillary neoplasm (SPN)

SPN are rare cysts and should be surgically resected[15]. They are classified into "*malignant epithelial tumors*" in the latest WHO classification[4]. SPN represented less than 1% of all PCN in a large prospective survey[20], and between 1 – 2% of the total number of pancreatic surgeries performed[21,22]. Approximately 15 – 20% resected cases are malignant[22,23]. The mean age at diagnosis is between 30 and 40 years[21,23,24]; >80% of SPN occur in women[21,22,24]. The majority of SPN cases present with abdominal pain or are found incidentally[21,22]. Long-term prognosis following resection is good, approaching 100% disease specific survival[25].

Cystic pancreatic neuroendocrine neoplasms (PNEN)

Cystic PNEN are rare, less likely to be functional and more often benign compared to their solid counterparts. The 5-year and 10-year disease-free survival is excellent, >95% and 64%, respectively[26,27]. About 1 in 4 of pancreatic neuroendocrine neoplasms are cystic rather than solid[28]. Diagnosis is based on histopathological examination. However, EUS-guided cytology is useful preoperatively. Resection is recommended for larger (>20 mm) cystic PNEN, whereas smaller ones without features suggestive of malignancy can be kept under surveillance[15].

Pseudocysts (PP)

Apart from the above true pancreatic cysts, PP are defined by their lack of cyst-lining cells. PP occur as a late complication in pancreatitis, often arising more than 4 weeks after onset. The incidence of PP in acute and chronic pancreatitis is 7% and

10 – 30%, respectively[29]. PP are one type of peripancreatic fluid collection, the differential diagnosis including acute necrotic collections and walled-off necrosis. PP contain no or extremely limited amounts of solid material; aspirates show high amylase and lipase levels[30]. PP often resolve spontaneously, but should be drained if causing clinical issues or they become long-standing in order to reduce the risk of severe complications such as hemorrhage, rupture or infection[31]. The optimal management of PP is debated. However, they can be managed with open surgical, endoscopic or EUS-guided drainage[32]. Cystic neoplasms can cause pancreatitis and so preoperative identification is essential as PP have no malignant potential. PP can be mistaken for IPMN involving a branch duct[16].

Table 1. Clinical features of common pancreatic cysts.

	IPMN	MCN	SCN	SPN	Cystic PNEN	PP
Gender (% female)	50	>95	70	>80	50	50
Age (decade at presentation)	6th, 7th	4th, 5th	6th	3th ,4th	5th, 6th	Variable
Connection with the MPD	Yes	No	No	No	No	Yes
Predominant location	Even distribution	Body / tail	Even distribution	Even distribution	Body/tail	Even distribution
Invasive carcinoma[a]	MD: 44% MT: 45% BD: 17%	5 - 16%	<1%	15-20%	10%	0%
Incidental findings	>50%	25%	60%	15%	40%	NA
Common symptoms	Abdominal pain, acute pancreatitis	Abdominal pain, acute pancreatitis, abdominal mass	Abdominal pain, abdominal mass	Abdominal pain	Abdominal pain	Abdominal pain

BD, branch duct IPMN; IPMN, intraductal papillary mucinous neoplasm; MCN, mucinous cystic neoplasm; MD, main duct IPMN; MPD, main pancreatic duct; MT, mixed type IPMN; NA, not applicable; PNEN, pancreatic neuroendocrine neoplasm; PP, pseudocyst; SCN, serous cystic neoplasm; SPN, solid pseudopapillary neoplasm.
[a]in resected cases.
References:[4,10,11,13,17,20-22,27,28,33]

Intraductal papillary mucinous neoplasm (IPMN)

The most recognized categorization of IPMN is into three major subtypes, depending on involvement of the pancreatic ductal system: main duct-type (MD-) IPMN, branch duct-type (BD-) IPMN and a mixed duct-type (MT-) IPMN (Table 2, Figure 2 and 3). This classification is primarily performed by radiological assessment preoperatively. It has direct clinical implications; involvement of the main pancreatic duct (MPD) is an important factor in the management owing to its increased association with high-grade dysplasia (HDG) and invasiveness[4,16].

Table 2. Radiological classification of ductal types of IPMN from the International Consensus Guidelines 2012[16].

Main duct IPMN (MD-IPMN)	Segmental or diffuse dilation of the MPD of >5 mm without other causes of obstruction.
Branch duct IPMN (BD-IPMN)	Pancreatic cyst of >5 mm in diameter that communicates with the MPD.
Mixed type IPMN (MT-IPMN)	Criteria for both MD- and BD-IPMN.

MPD, main pancreatic duct.

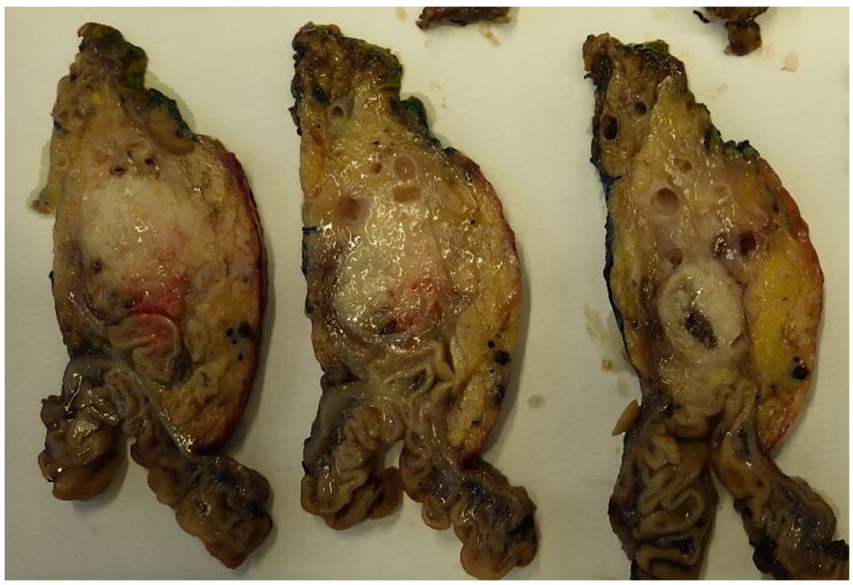


Figure 2. Macroscopic picture of a mixed-type IPMN. Image courtesy of Dr Agata Sasor.

The most important question to answer in the preoperative setting relates to the dysplastic grade, i.e. presence of HGD or invasiveness, a dilemma that has undoubtfully triggered this area of research. There are unfortunately no preoperative predictive factors reaching a negative predictive value (NPV) or positive predictive value (PPV) over 90%[34]. Computed tomography (CT) and magnetic resonance imaging (MRI) have an accuracy of identifying malignancy, i.e. HGD or invasive IPMN, of 80%, and an area under the ROC curve (AUC) of approximately 85% in diagnosis[35]. The inter-modality agreement between CT and MRI is not perfect (k=0.70)[35], which can present a problem in follow-up if different imaging methods are alternated. To increase the accuracy of CT and MRI, positron emission tomography (PET)/CT can be used[36-38]. There is, however, a substantial cost-difference which has not been investigated. Endoscopic retrograde cholangiopancreatography (ERCP) and EUS with cytology have high specificity but low sensitivity[39,40]. Recently, a predictive score based on EUS findings on BD-IPMN achieved high accuracy in identifying invasive cancer[41]. Nomograms for

predicting the risk of cancer has been made with AUC-values and C-index of approximately 0.8[42-46]. Several guidelines have been created with the primary goal of estimating the current and future risks of malignancy and thus surgical indication and surveillance strategy (see section "guidelines").

The ductal type represents one of the most important factors in determining the risk of HGD or invasiveness. From surgical data, the risk of HGD and invasiveness in MD-IPMN ranges from 22 – 33% and 11 – 81%, respectively[14,47-49]. The numbers for BD-IPMN are 15% and 6 – 38%, respectively[14,48,49]. Regarding clinical risk factors, similarities between IPMN and pancreatic ductal adenocarcinoma (PDAC) exist. Diabetes, and especially new-onset diabetes, has been associated with increased risk of HGD and invasiveness in IPMN[50]. The major guidelines focus on identification of high-risk disease and includes relevant risk factors (see below). A meta-analysis investigating mortality during follow-up in patients unfit for surgery with suspected IPMN classified as a "risk-lesion", found a pooled overall mortality and IPMN-related mortality of 31 (20 – 45)% and 11 (6 – 21)%, respectively. The incidence rate for IPMN-related mortality was 5 (0 – 10) per 1000 patient-years in BD-IPMN and 32 (12 – 52) per 1000 patients-years in MD-IPMN[51]. One study on IPMN, subjected to initial surveillance, found a 5- and 10-year survival rate of 100% and 94%, respectively. The rates of progression were 71% and 98% during a 4 and 10-year period, respectively; 58% experienced disease progression. Interestingly, IPMN requiring surgery based on the European guidelines, but which were inoperable for different reasons, had an IPMN-specific 5-year survival of 75%[52].

Patients with a diagnosis of IPMN also seem to have an increased risk of developing a distinct metachronous PDAC[14,53]. Inflammation may be an underlying driver of this occurrence[54].

Follow-up studies on BD-IPMN have found a relatively low, but not negligible risk for developing cancer with meta-analysis data of 0.007 – 0.01 per person years[55,56]. The 5-year incidence rate of pancreatic cancer in BD-IPMN was 1.4 – 4%[57-59]. The 10-year risk of cancer for classified low risk IPMN was estimated to be 8%[60,61] and increased up to 25% for those with higher risk profile[61]. However, a verification bias has been suggested with studies overestimating the risk of cancer progression[62].

The 5-year risk of cancer development in MD-IPMN was estimated to be 46%[59]. MD-IPMN not undergoing surgery developed cancer in 36% of cases within a median time of 29 months (range 8 – 141)[63]. Following partial surgery of an MD-IPMN with negative margin of HGD and cancer, there was a 12% 5-year risk and a 21% 10-year risk of developing metachronous cancer. The results were largely influenced by the degree of dysplasia or cancer; 10-year risk was 3% in low-grade dysplasia (LGD), 40% in HGD and 61% in cancer[64].

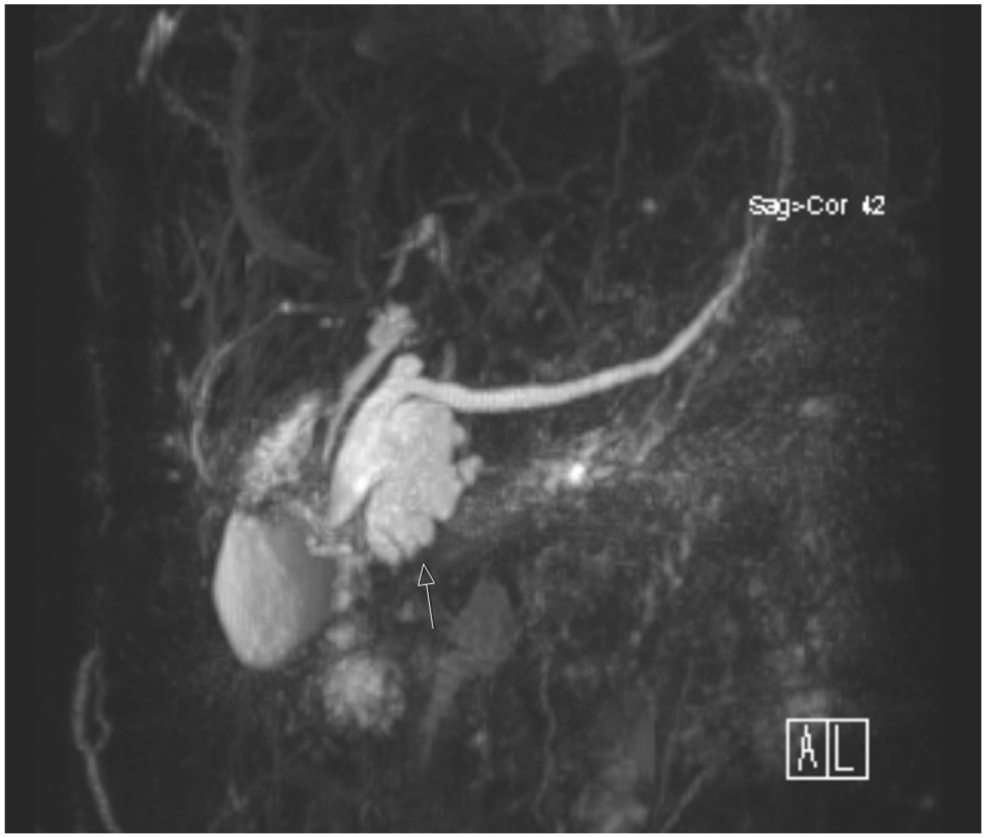


Figure 3. Magnetic resonance cholangiopancreatography of the pancreatic ductal system showing a mixed-type IPMN illustrated by the arrow.

Epidemiology of IPMN

Risk factors

To date, no well-established risk factors for acquiring IPMN have been identified[4]. However, a case-control study found that DM, a history of chronic pancreatitis and a family history of PDAC increased the risk of developing IPMN[65]. IPMN is a common finding in individuals with a strong family history of pancreatic cancer and cystic lesions in individuals with p16-Leiden germline mutations are seemingly more susceptible to progression[66-68]. DM has been associated with increased risk of harboring HGD or invasive carcinoma, especially new-onset DM[69]. New-onset DM is included as a relative surgical indication in the European guidelines from 2018[15].

Studies show contradictive results regarding smoking and an associated increased risk of HGD and invasive carcinoma[70-73]. Smoking may accelerate the rate of malignant progression[73]. Current smoking, as opposed to a previous history of smoking, has been associated with PDAC concomitant with IPMN[72].

Rare genetic disorders e.g. McCune-Albright Syndrome, which is caused by a mutation of the GNAS (guanine nucleotide binding protein, alpha stimulating) gene, have been found to increase the risk of IPMN[74,75].

Incidence and prevalence

Some studies have tried to estimate the incidence and prevalence of IPMN, which is a difficult task owing to the fact that diagnostic gold standard is histopathological examination of a resected specimen.

The age and sex-adjusted cumulative incidence of IPMN between 1984 and 2005 in the United States of America, (USA) was found to be 2.04 per 100 000 persons[76]. With the use of magnetic resonance cholangiopancreatography (MRCP), the incidence of new pancreatic cysts was 2.6% per year during a 5-year follow-up; the mean age of participants was approximately 56 years. Interestingly, no pancreatic cancers where observed but most cysts were small (<10 mm)[77].

Several studies have investigated the prevalence of IPMN or incidental pancreatic cysts (IPC) / pancreatic cystic lesions (PCL) (Table 3 and 4). A meta-analysis of studies up to January 2018 found a prevalence of 8% of incidentally detected PCL[78]. Depending on the radiological method utilized, age of the studied population, and size criterion used, the reported prevalence ranged from 0.7% up to almost 50% in asymptomatic individuals, although some selection bias may undoubtedly be present. In some studies, suspected IPMN, predominantly BD-IPMN, appears to be the most common of the IPC[79-82]. However, some studies performed with MRI in asymptomatic individuals have found a prevalence of clinically relevant cysts, i.e. those with risk factors according to guidelines, ranging from 0 – 1.7%[83-86]. Of those with cysts, the presence of two or more cysts was common[77,82,85]. Prevalence is highly correlated with increasing age. Cysts are rare in individuals below the age of 50[79,87,88], but amongst those over 70 years prevalence as high as 60% has been reported[81]. The above radiological findings are in line with autopsy cases; a majority of those with cysts have several cysts and there is a similarly increasing prevalence with age[89]. Further studies have found a positive correlation of increasing prevalence with DM, obesity and female gender[77,80,81,84,90].

Increase in prevalence and incidence of cystic lesions in the pancreas can to some extent be explained by improved radiological technologies. Use of new MRI software and hardware was strongly correlated to increased prevalence (30 versus 50%)[81].

When examining surgical data and thus histopathological diagnoses, a peculiar picture materializes. Even though invasive IPMN seems uncommon in comparison to PDAC when analyzing large databases[91,92], analysis from surgical specimens shows a high percentage of pancreatic resections being performed on IPMN with an increase during the recent decades[93,94]. From being fairly uncommon before the 2000s, IPMN now represents almost 10% of pancreatic resections[95-98]. Asymptomatic pancreatic lesions accounted for 23% of all pancreatic resections during the period 2002 – 200 in USA, with IPMN being the most common[99], a pattern recognized around the world with 40% of resected PCN in Finland[100] and Korea[101] being IPMN.

Approximately 20% (439 / 2134) of patients referred to a specialized PCN clinic with presumed or histopathological confirmed IPMN, underwent surgery. Approximately 8% and 13% of total IPMNs underwent surgery upfront and following initial surveillance, respectively[102]. Of presumed BD-IPMN, 30% (240 / 762) underwent surgery, 19% upfront and 11% following surveillance. Regardless of time of resection, HGD and invasive carcinoma were found in 13% and 10%, respectively[103]. The proportions of HGD and invasive carcinoma in resected IPMN ranges from 20 – 50%[97,102,103].

In a nationwide Italian survey (PANCY), 80% of patients with cystic pancreatic neoplasms were IPMN (majority was BD-IPMN), 6% of total cases (68% IPMN) and 5% of IPMNs underwent surgery, respectively[20].

Table 3. Prevalence of pancreatic cystic lesions in adult populations without known pancreatic disease. Where available, age of the total population studied and for those with cystic finding is presented.

Pancreatic cystic lesions (PCL)					
Imaging	Prevalence	Age all	Age PCL	Country	Reference
US	1.3	53 mean	NA	Japan	104
EUS	21.5	61 mean	NA	Spain	105
	9.4	59 mean	NA	US	80
CT	8.7	NA	NA	Argentina	83
	2.1	NA	58 median	South Korea	79
	2.1	NA	77 median	San Marino	88
	2.6	58 mean	NA	US	87
	0.7 [b]	64 mean	NA	US	106
	10[a]	68 mean	NA	Italy	107
MRI/MRCP	27.5	NA	NA	Argentina	83
	49.1	56 mean	NA	Germany	77
	41.6	60 median	64 mean	US	81
	9.3	47 mean	61 mean	Brazil	85
	2.4	51 mean	60 mean	Netherlands	108
	44.7	57 mean	NA	Italy	82
	13.5	NA	NA	US	109
	0.7 [b]	64 mean	NA	US	106
	10 [a]	68 mean	NA	Italy	107
	10 [a]	62 median	69 median	Japan	110
	13.7	56 mean	63 mean	Japan	90

CT, computed tomography; EUS, endoscopic ultrasonography; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; NA, not applicable; US, ultrasonography.
[a]Prevalence in the "control group" [b]Only stated CT or MRI, not specified

Table 4. Prevalence of suspected IPMN in adult populations without known pancreatic disease. Where available, age of the total population studied and for those with suspected IPMN is presented.

Intraductal papillary mucinous neoplasm (IPMN)					
Imaging	Prevalence	Age all	Age IPMN	Country	Reference
US	3.4[b]	NA	NA	Italy	84
	0.2	53 mean	NA	Japan	104
EUS	5.4	61 mean	NA	Spain	105
CT	2.1	NA	NA	South Korea	79
	7[a]	68 mean	NA	Italy	107
MRI/MRCP	3.4[b]	NA	NA	Italy	84
	6.6	NA	62 median	France	86
	35	NA	NA	US	81
	31.7	57 mean	NA	Italy	82
	7[a]	68 mean	NA	Italy	107

CT, computed tomography; EUS, endoscopic ultrasonography; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; NA, not applicable; US, ultrasonography.
[a]Prevalence in the "control group" [b]Only stated US or MRI, not specified

Pathophysiology of IPMN

Genetic mutations occurring early in IPMN carcinogenesis, include mutations in GNAS, more common in colloid carcinomas, and KRAS (Kirsten rat sarcoma 2 viral oncogene homolog), more frequently seen in tubular carcinomas[111-113]. GNAS mutations are rarely found in other types of pancreatic lesions[112-114]. The clinical relationship between IPMN and McCune-Albright syndrome strengthens the correlation between GNAS mutation and IPMN[115]. In combination with other drivers, GNAS and KRAS mutations appear to be important in tumorigenesis[116,117]. Other important driver mutations implicated in the malignant transformation of IPMN include hTERT, Shh[118] and TP53, which has also been shown to be a prognostic factor[119]. Different genetic pathways have been described for the progression to cancer[120]. Comprehensive genomic analysis has found frequent heterogeneity in mutations, suggesting a polyclonal origin of IPMN[121].

IPMN cytoarchitecture and cytology

IPMN evolves in an adenoma-carcinoma sequence, i.e. benign / non-invasive to malignant / invasive. The degree of dysplasia ranges from low-grade to high-grade (noninvasive)[4,122]. Current recommendations classify low-grade and intermediate-grade dysplasias (IGD) as low-grade dysplastic IPMN[4]. This two-tiered system was proposed previously and may be more in line with current guidelines[123].

In 2003 it was established that non-invasive IPMN can be further categorized into four different cytological or morphological subtypes; intestinal, gastric, pancreatobiliary and oncocytic tumors[124]. These subtypes have been associated with different risks of invasive transformation, with the pancreatobiliary subtype having the greatest risk[125,126]. There also seems to be an increased risk in recurrence following resection in those with pancreatobiliary and intestinal subtype[127]. In the latest classification by the WHO, intraductal oncocytic papillary neoplasms (IOPN) are deemed a separate disease entity to IPMN, owing to their distinct genomic and morphological features[4]. IOPN appears to have an improved prognosis compared to the other subtypes of IPMN[128]. It was recently suggested that the pancreatobiliary subtype could be categorized into two subtypes, i.e. monotypic, which has an outcome similar to PDAC, and polytypic[129]. Figure 4 illustrates the microscopic features of intestinal, pancreatobiliary and gastric subtypes, together with normal pancreas.

Accurate subtyping may be challenging. Several subtypes may exist within the same lesion, and even immunohistochemical analysis may be discordant[130]. In subtyping without immunohistochemistry, in one study agreement was only reached in 58%

of cases[131]. Immunohistochemistry seems to add limited value[130,131]. A resent consensus study on subtyping found a low kappa-value of 0.6, which is in keeping with the above studies. They also concluded that in the mixed cases, the most dysplastic papillae should be used to assess type in mixed papillae types[132].

Pancreatic intraepithelial neoplasia (PanIN) is the main precursor to PDAC and is a microscopic non-invasive epithelial neoplasm in the pancreatic ducts. PanIN is usually undetectable with imaging, frequently being identified incidentally in resected pancreatic specimens. PanIN differ from IPMN with respect to the macroscopic appearance of the latter, and genetic changes[4]. However, small IPMN of gastric subtype may be impossible to distinguish from PanIN. A size-criterion is usually employed, whereby lesions >1cm are designated as IPMN[122].

When invasive, IPMN are often of tubular or colloid subtype; the recommended nomenclature is 'IPMN with an associated invasive carcinoma'[4,122]. For convenience, IPMN with an associated invasive carcinoma will be referred to as 'invasive IPMN' or 'IPMC' in this thesis. The adjective 'malignant' is not recommended; variable usage of this term has caused confusion[3,122]. 'Malignant' is, however, often used to refer to HDG IPMN and invasive IPMN[14]. 'Malignant' will therefore be used in this thesis when describing invasive carcinoma.

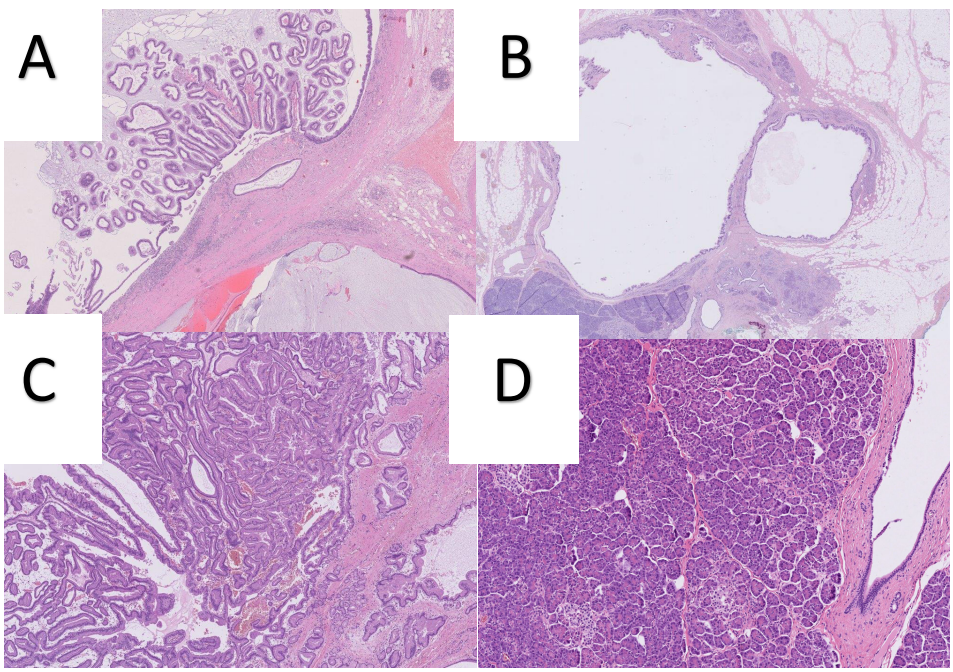


Figure 4. Morphological subtypes of IPMN. A) intestinal. B) gastric. C) pancreatobiliary. D) normal pancreas. Image courtesy of Dr Agata Sasor.

Intraductal tubulopapillary neoplasm (ITPN)

ITPN is a rare epithelial neoplastic tumor originally recognized in 1992[133]. The first report of its malignant form was published in 2004[134]. ITPN was initially considered to be a subtype of IPMN, but since 2010 it has been regarded as a separate entity[3]. ITPN is defined by tubulopapillary growth and absence of mucin. Its genomic characteristics have been investigated and show differences compared to IPMN and PDAC[135]. ITPN is reported to have a more favorable prognosis compared to IPMN, even though most lesions show invasive growth on histopathology following resection[136,137]. The rarity of ITPN and consequent scarcity of data makes it hard to draw solid conclusions. However, 5-year postoperative overall survival (OS) has been estimated to be 80%[138]. Table 5 compares the different subtypes of IPMN, IOPN and ITPN.

Table 5. Morphological subtypes of IPMN, IOPN and ITPN.

	Intestinal	Gastric	Pancreatobiliary	IOPN	ITPN
Frequency	20%	70%	10%	Rare	Rare
Ductal type	MD > BD	BD > MD	MD = BD	BD > MD	NA
Risk progression / invasive carcinoma	++	+	+++	++	+++
Carcinoma histology	Colloid	Tubular > colloid	Tubular	Oncocytic / tubular	Tubular
MUC1	-	-	+	+	+
MUC2	+	-	-	+[a]	-
MUC5AC	+	+	+	+	-
MUC6	-	-/+	-/+	+	+
CDX2	+	-	-	+[a]	-

BD, branch duct IPMN; CDX, homeobox protein; IOPN, intraductal oncocytic papillary neoplasm; IPMN, intraductal papillary mucinous neoplasm; ITPN, intraductal tubulopapillary neoplasm; MD, main-duct IPMN; MUC, mucin; NA, not applicable.
[a]in goblet cells
References:[4,126,128,131,135]

Is IPMN a multifocal disease?

Aside from the obvious multifocal disease of MT-IPMN, it is relatively common with multiple BD-IPMN. In one study, more than 60% of BD-IPMN were multifocal with the majority of subjects having three or more cysts[139]. As discussed above, two or more cysts are often present, based on radiological and autopsy data. MD-IPMN can also be multifocal with different segments of the MPD being affected by skip-lesions[140,141].

A concept, first recognized in oral squamous cell carcinomas[142] and known as field cancerization or field effect, has been proposed for IPMN[143]. In the case of IPMN,

it entails an underlying genomic instability or susceptibility in the whole pancreas, promoting dysplastic changes[14,143,144]. This is supported by the multifocal nature, the relatively high risk of recurrences[53,145] even in margin-negative subjects[146], and the increased risk of developing a PDAC in patients with IPMN[14].

Recent genomic studies have shown that multifocal IPMN including invasive carcinoma and recurrences, i.e. lesions within the same patient, are often separate clones[141,147-149], which potentially further strengthens the concept of a field effect.

The multifocality in IPMN does not seem to increase the risk of local progression[150], although every single cyst should be assessed separately[15]. However, multifocal disease throughout the pancreas may be associated with an increased risk of developing concomitant PDAC[151].

Diagnosis

The diagnosis of cystic lesions in the pancreas, and in particular IPMN, presents a clinical conundrum. The preoperative diagnosis is primarily based on radiological characteristics of ductal type[16]. However, there is inter-observer variability reported in the classification of pancreatic cysts by MRI and EUS[152-154], as well as risks for underestimation and overestimation of cyst size[155]. These findings are further strengthened by the relatively large risk of misdiagnosis in pancreatic neoplasms / cysts of 5 – 30%[103,156-159]. The problem of misdiagnosis has been an issue since IPMN was first recognized[160]. When comparing preoperative radiological findings with the histopathological conclusions, misdiagnosis ranges from 5 – 35% for IPMN[156-158,161,162]. With respect to the ductal types of IPMN, approximately 20 – 30% of BD-IPMN had MPD involvement[161,163,164]; conversely 30% with suspected MPD involvement showed no MPD involvement on histology[161]. The clinical relevance of a suspected radiological BD-IPMN which ultimately proves to have histological finding of MPD-involvement (MT-IPMN) is unclear. Some have found an increased risk of HGD / IPMC[161,164], which is consistent with the increased risk seen in suspected MT-IPMN. The macroscopic versus microscopic extent of MPD may however be important[165].

There is no specific symptom pathognomonic for IPMN; the majority of cases are found incidentally as they are asymptomatic[16,20,102,166]. Retrospective data of surgically resected IPMN report asymptomatic patients from the majority of BD-IPMN and to a lesser degree, MD-IPMN[165]. Symptomatic lesions are more often associated with HGD and invasive disease[14,15]. If symptomatic, common complaints and symptoms include abdominal pain, pancreatitis, weight loss, cachexia, back pain, steatorrhea, jaundice and new-onset diabetes[20,102,139,165,167]. However,

abdominal pain is not obviously caused by the IPMN under surveillance as the frequency seems similar when matched to a control cohort[168].

To date, the only blood-based marker used in the preoperative setting is carbohydrate antigen 19-9 (CA19-9)[14,15]. However, the accuracy for predicting malignant disease is limited[34,158,169]. Sources of error include jaundice regardless of underlying cause, which increases CA19-9, and lack of the Lewis antigen and consequently an inability to synthesize CA19-9, which is present in approximately 5% of the general population[170,171]. Other methods used in the differentiation of cystic lesions and their dysplastic grade / invasiveness include pancreatic juice cytology (PJC)[172,173], pancreatic cyst fluid (PCF) analysis[174,175] and EUS-FNA[14,166,176,177].

Guidelines

The risks of malignant disease, i.e. HGD or invasiveness must be balanced against the risks of surgery. Since the management of IPMN presents a challenge, several guidelines have emerged to support clinical decisions and to provide better information to patients. The most reputed are those from the International Association of Pancreatology (IAP) first published in 2006 (Sendai)[178], then updated in 2012 (Fukuoka)[16] and revised in 2017 (revised, Fukuoka)[14]. Several other guidelines on cystic lesions in general include publications from: the European Study Group on Cystic Tumors of the Pancreas from 2013[179], subsequently updated in 2018[15]; the Italian Association of Hospital Gastroenterologists and Endoscopists (AIGO) and Italian Association for the Study of the Pancreas (AISP) from 2014[176]. Guidelines relating to asymptomatic cystic lesions were presented from the American Gastroenterology Association (AGA) from 2015[177], and from the American College of Gastroenterology (ACG) in 2018[166]. The ACG guidelines are focused on the surveillance of pancreatic cysts in general. The American College of Radiology (ACR) Incidental Findings Committee (IFC) have also presented their management algorithm for pancreatic cysts detected incidentally[180]. A revision of the national recommendations in Sweden for management of pancreatic cancer, including IPMN, was completed in 2017[181]. These are based on the European guidelines from 2013[179], with the main difference of not intensifying surveillance following 5 years, a recommendation not stated in the European guidelines from 2018. Quality assessment and clinical applicability have been evaluated for the guidelines presented before 2015[182,183].

Some general principles are largely consistent between the guidelines and include a rigorous preoperative surveillance of low risk lesions, surgical resection of MD-IPMN and follow-up for all IPMN postoperatively (Tables 6 – 9). According to the

IAP guidelines, the risks of HGD or invasiveness are denoted by worrisome features (WF) and high-risk stigmata (HRS), whilst principles of absolute and relative criteria for surgery are used in the European guidelines. A consensus is that surveillance should be discontinued in patients unfit for surgery. Follow-up is also influenced by the personal choice of the informed patient.

In proposing the optimal management, one has to consider resource limitations, especially since the absolute number of detected pancreatic cysts is increasing. This is unfortunate, but a reality. The costs of a pancreatic MRI and EUS are €406 and €1246, respectively, based on figures from Skåne University Hospital, Lund, Sweden 2017. Health care resources and cost aspects are mentioned in the AGA, ACG, European 18 and AIGO/AISP guidelines[15,166,176,177]. Interest in economic aspects increased during the later 2010 and has been discussed repeatedly in several articles. However, investigation is limited with only two studies analyzing the cost-effectiveness of management strategies, both set in a Sendai era[184,185], and one additional study on integration of cyst fluid molecular analysis[186].

Several studies have evaluated the robustness of the guidelines. The IAP 2012 publication appears to differentiate between low and high risk relatively well[187], the development of HRS having high accuracy and prediction of HGD and IPMC[139,188]. The PPV and sensitivity increased in the IAP 2012 recommendations compared to IAP 2006; however the NPV did diminish slightly and specificity was still low[189]. On the other hand, a systematic review confirmed a similarly low PPV of the IAP 2012 versus the IAP 2006[190]. Even when classified as low risk (IAP 2012), up to one out of four have HGD / IPMC[103,191]. Inclusion of PJC has been proposed to increase the accuracy of the IAP 2012 recommendations[173]. The AGA and IAP 2012 guidelines were comparable with a low sensitivity and a PPV and NPV of approximately 75%[192]. Another study found a high sensitivity for the European 2013 and IAP 2012 guidelines at the expense of more unnecessary resections when compared to AGA strategy[193]. The PPV of any criteria in the European 2018 guidelines ranged from 71% to 87%; fulfillment of three relative criteria reached 100%[48]. The European 2018 and ACG guidelines were comparable in one study[194]. All of the high-risk features in the IAP 2017 were associated with malignancy[35]. However, it is beyond any doubt that improvements are needed to avoid both unnecessary resection and undertreatment.

Table 6. IAP guidelines on IPMN (and MCN) and their surgical recommendations.

Guideline	Surgery recommended	Surgery may be considered
Sendai 2006[178]	Symptomatic lesions. MD/MT (MPD≥10mm). BD: >30mm size, HRS (MN, dilated MPD, positive cytology).	
Fukuoka 2012[16]	Symptomatic lesions. MD/MT (MPD 5-9mm = WF as in BD). BD: HRS (obstructive jaundice, enhancing solid components within cyst, MPD≥10mm).	BD: WF (size ≥30mm, enhancing cyst walls, MPD 5-9mm, non-enhancing MN, abrupt change in MPD caliber with distal atrophy, lymphadenopathy), rapid cyst growth, high-grade atypia in cytology, young patients (<65) with cysts >2cm.
Revision Fukuoka 2017[14]	Symptomatic lesions. MD/MT (MPD 5-9mm = WF as in BD). BD: HRS (obstructive jaundice, MPD≥10mm and enhanced MN ≥5mm).	BD: WF (enhancing MN <5mm, enhancing cyst walls, MPD 5-9, abrupt change in MPD caliber with distal atrophy, lymphadenopathy, elevated S-CA19-9, growth >5mm/2 years). high-grade atypia in cytology, young patients (<65) with cysts >2cm.

BD, branch duct IPMN; DM, diabetes mellitus; FNA, fine needle aspiration; HDG, high-grade dysplasia; HRS, high-risk stigmata; IAP, international association of pancreatology; IPMN, intraductal papillary mucinous neoplasms of the pancreas; MCN, mucinous cystic neoplasm; MD, main duct IPMN; MN, mural nodule; MPD, main pancreatic duct; MT, mixed type IPMN; PC, pancreatic cancer; S-CA 19-9, serum carbohydrate antigen 19-9; TR, tumor related; WF, worrisome features.

Table 7. Guidelines on cystic tumors (not IPMN-specific) and their surgical recommendations.

Guideline	Surgery recommended	Surgery may be considered
European 2013[179]	MD/MT. BD: symptoms, MN, MPD >6mm, size ≥40mm.	BD: rapidly increasing size (>2mm/year), elevated S-CA19-9. Young age (long life expectancy).
European 2018[15]	Positive cytology for malignant/HGD, solid mass, jaundice (TR), enhancing MN ≥5mm, MPD ≥10mm.	Growth-rate ≥5mm/year, increased S-CA19-9, MPD 5-9.9mm, size≥40mm, new-onset DM, acute pancreatitis due to IPMN, enhancing MN<5mm.
Italian (AIGO and AISP) 2014[176]	Enhancing solid component, MPD >10mm. Positive FNA with: (size ≥30mm, thickened enhancing cyst wall, MPD 5-9mm, non enhancing MN, abrupt change in MPD caliber with distal atrophy).	Young age (long life expectancy). Elevated S-CA19-9. Family history of PC, new-onset/worsening DM.
AGA 2015[177a]	Both solid component and a dilated MPD and/or concerning features on EUS and FNA.	EUS and FNA if 2 out of: ≥30mm size, dilated MPD, solid component.
ACG 2018[166 b]		Referral to MDT: MPD >5mm, obstructive jaundice, acute pancreatitis (TR), elevated S-CA19-9, MN, solid component, ≥30mm, increase in size ≥3mm/year, HD-dysplasia on cytology.

ACG, American College Gastroenterology; AGA, American Gastroenterology Association; AIGO, Italian Association of Hospital Gastroenterologist and Endoscopists; AISP, Italian Association for the Study of the Pancreas; BD, branch duct IPMN; DM, diabetes mellitus; FNA, fine needle aspiration; HDG, high-grade dysplasia; HRS, high-risk stigmata; IPMN, intraductal papillary mucinous neoplasms of the pancreas; MD, main duct IPMN; MDT, multidisciplinary team; MN, mural nodule; MPD, main pancreatic duct; MT, mixed type IPMN; PC, pancreatic cancer; S-CA 19-9, serum carbohydrate antigen 19-9; TR, tumor related; WF, worrisome features.
[a]Only asymptomatic patients considered [b]Specified for gastroenterologist (no surgical decisions)

Table 8. Surveillance strategies preoperatively in suspected IPMN without indications of surgery (for surgical indications see Table 7) and no hereditary risk of pancreatic cancer.

Guideline	Cyst	Features	Imaging	Surveillance interval	Comment
IAP 2006[178]	BD-IPMN	< 1 cm	MRI / CT	Annually	
		1 – 2 cm	MRI / CT	Every 6 – 12 months	
		1 – 3 cm	MRI / CT	Every 3 – 6 months	
IAP 2012[16]	No HRS, no WF[a]	< 1 cm	MRI / CT	2 – 3 years	
		1 – 2 cm	MRI / CT	Annually x 2	Lengthen interval if no change
		2 – 3 cm	EUS / MRI	EUS in 3– 6 months, then lengthen interval	
		>3 cm	EUS / MRI	Every 3 – 6 months	Consider surgery
	WF. no HRS[a]	-	EUS	Once, if no MN, MD, positive cytology, see above	
IAP 2017[14]	WF, no HRS[a]	<1 cm	MRI / CT	In 6 months then every 2 years	
		1 – 2 cm	MRI / CT	Every 6 months x 2, annually x 2, if no change every second year	
		2 – 3 cm	EUS / MRI	EUS in 3 – 6 months, then annually	
		>3 cm	EUS / MRI	Every 3 – 6 months	Consider surgery
	WF, no HRS[a]	-	EUS	Once, if not: MN ≥5mm, MD, positive cytology, see above	
European 2013[179]	Without "risk factors"[a]	<3 cm	MRI / EUS	Every 6 months during the first year, then yearly x 4 then every 6 months	If size increase: every 6 months
		3 – 4 cm	MRI / EUS	Every 6 months during the first year, then yearly x 4 then every 6 months	If size increase: every 6 months
European 2018[15]	Without "risk factors"[a]	0 relative indication	MRI / EUS	Every 6 months during the first year, then yearly	
		1 relative indication	MRI / EUS	Every 6 months	
AIGO and AISP 2014[176]	BD-IPMN	< 1 cm	MRI/MRCP	Annually for 2 years, if stable every 24 months	
		1 – 2 cm	MRI/MRCP	Every 6 – 12 months for 2 years, if stable every 18 months	
		>2 cm	MRI/MRCP	Every 3 – 6 months for 2 years, if stable ever 12 months	
AGA 2015[177]	Pancreatic cyst	<3 cm	MRI	After 1 year then every 24 months for a total of 5 years	No solid component, no dilated MPD
	[b]	-	MRI	After 1 year then every 24 months (for 5 years)	

ACG 2018[166]	IPMN	<1 cm	MRI	Every 24 months for 4 years, if stable lengthening interval	
		1 – 2 cm	MRI	Annually for 3 years then if stable see <1 cm above	
		2 – 3 cm	MRI / EUS	Every 6 – 12 months for 3 years, if stable MRI annually for 4 years then lengthen interval	
		>3 cm	MRI / EUS	MRI / EUS every 6 months for 3 years, if stable annually for 4 years then lengthen interval	Consider referral

ACG, American College Gastroenterology; AGA, American Gastroenterology Association; AIGO, Italian Association of Hospital Gastroenterologist and Endoscopists; AISP, Italian Association for the Study of the Pancreas; BD-IPMN, branch-duct intraductal papillary mucinous neoplasm; CT, computed tomography; EUS, endoscopic ultrasonography; HRS, high risk stigmata; IAP, international association of pancreatology; MD, main duct IPMN; MN, mural nodule; MPD, main pancreatic duct dilation; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; WF, worrisome features.
[a]see Table 6 and 7. [b] EUS-FNA without concerning features

Table 9. Surveillance strategies postoperatively for confirmed IPMN in patients without hereditary risk of pancreatic cancer.

Guideline	Cyst	Histology	Imaging	Surveillance interval	Comment
IAP 2006[178]	IPMN	Noninvasive	MRI / CT	Annually	Interval can be lengthened after several years without recurrence
	IPMN	Invasive	MRI / CT	Every 6 months	
IAP 2012[16]	IPMN, with BD-IPMN in remnant	Noninvasive	-	Same as preoperative surveillance	
	IPMN	Negative margin	MRI / CT	At 2 and 5 years	
		Positive margin	MRCP	Every 6 months	
	BD-IPMN	Negative margin	CT / MRCP	Every 6 months	
	IPMN	Invasive, stage II/III	-	As for PDAC	
IAP 2017[14]	IPMN	Negative margin, intestinal	MRI / CT	Every 6 – 12 months	
		Margin with HGD	MRI / CT	Every 6 months	
		Non-intestinal subtype	MRI / CT	Every 6 months	
		Invasive	-	As for PDAC	
European 2013[179]	IPMN	Noninvasive	MRI / EUS	Annually	Following partial pancreatectomy
		Invasive	-	As for PDAC	
European 2018[15]	IPMN	HGD or MD	MRI / EUS	Every 6 months for 2 years, then annually	
		LGD	MRI / EUS	As for non-resected IPMN	
	IPMN in remnant	No HGD or MD	MRI / EUS	As for non-resected IPMN	
		Invasive	-	As for PDAC	
AGA 2015[177]	Pancreatic cysts	Invasive	MRI	Every 2 years	Following partial pancreatectomy
		HGD	MRI	Every 2 years	Following partial pancreatectomy
		Positive margin	MRI	< 24 months between	Surgeons choice
ACG 2018[166]	IPMN	Invasive	-	As for PDAC	
	IPMN	HGD	MRI / EUS	Every 6 months	Following partial pancreatectomy
	IPMN	LGD/MGD	MRI	Every 24 months	Following partial pancreatectomy
	Remnant cyst		-	As for non-resected IPMN	

ACG, American College Gastroenterology; AGA, American Gastroenterology Association; AIGO, Italian Association of Hospital Gastroenterologist and Endoscopists; AISP, Italian Association for the Study of the Pancreas; BD-IPMN, branch-duct intraductal papillary mucinous neoplasm; CT, computed tomography; EUS, endoscopic ultrasonography; HGD, high-grade dysplasia; IAP, international association of pancreatology; LGD, low-grade dysplasia; MD, main duct IPMN; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; PDAC, pancreatic ductal adenocarcinoma.

Biomarkers

A biomarker is defined by the National Institutes of Health (NIH) Biomarker Working Group as "*a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic response to a therapeutic intervention*"[195]. Dependent on study design and assigned utility, biomarkers can be categorized as diagnostic, prognostic or predictive[196]. Biomarker research in pancreatic disease is generally performed on tissue or biofluid, e.g. pancreatic juice, cyst fluid and blood serum or plasma[197]. In the preoperative setting, biofluids are readily available. In the latest guidelines, only serum CA19-9 is considered to contribute to the management of IPMN[14,15]. To distinguishing mucinous (IPMN and MCN) from non-mucinous pancreatic lesions, cyst fluid analysis for carcinoembryonic antigen (CEA), amylase/lipase, and the DNA markers, GNAS and KRAS can be performed[14,15,20,198,199]. Mutational patterns, cytology and CEA levels can also be analyzed in pancreatic juice to detect malignancy[172,200,201]. Novel techniques, such as next generation sequencing (NGS) of cyst fluid or pancreatic juice offer explorative and targeted approaches towards the identification of genetic biomarkers[202-204].

Use of EUS-FNA and ERCP to collect samples of cystic fluid and pancreatic juice, respectively[205] are invasive methods of acquiring biofluids for analysis, and consequently have an associated complication risk[206,207]. ERCP is not recommended in the clinical management for IPMN, whereas EUS-FNA might be used in unclear cases and in experienced centers[14,15]. EUS-FNA does, however, play an important role in the American guidelines[166,177].

The most accessible biofluid is plasma / serum[208]. CA19-9 and CEA are glycoproteins heavily investigated in IPMN research[169]. Glycosylation of proteins is one of the most common posttranslational changes and is essential for a multitude of biological functions[209,210]. Glycosylation patterns / changes have been linked to a plethora of diseases including cancerous development of different cells[211,212]. Mucins (MUC) are a type of glycoproteins, either membrane-associated or gel-forming, with a primary role in protecting ductal surfaces in the body. Alterations in their expression have been linked to tumorigenesis[213]. MUC1, 2, 4, 5AC, and 6 expression differs between histological IPMN types (Table 2) and may vary with dysplasia[4,214].

Whilst not a classical biomarker per se, the emerging field of radiomics offers a great addition to the armamentarium to support clinical decisions[215]. Advancements in imaging technology, data storage and analysis have made this possible as the technique relies on machine learning[216]. Recent studies on IPMN show promising results in differentiating low from high risk (HDG or IPMC), and LGD from HGD[217-222]. Additional accuracy can be achieved when combined with other

markers such as those analyzed in cyst fluid or biopsies[222]. Studies utilizing radiomics on pancreatic cysts reported an accuracy of approximately 80% in differentiating SCA, MCN and IPMN[223], and an AUC of 0.989 in distinguishing between MCN and macrocystic serous cystadenoma[224].

Treatment

The only treatment for IPMN is a surgical resection of the pancreas, with the aim of total tumor clearance. The type of pancreatectomy, i.e. partial or total, depends on the anatomical location of disease. A pancreatoduodenectomy (PD), e.g. Whipple´s operation or pylorus-preserving PD, is performed for lesions restricted to the head of the pancreas. For masses in the body or tail, a distal pancreatectomy (DP) may be more suitable. The indication for surgery relies on the presence of specific criteria presented by the different guidelines (see section "guidelines"). For partial resections, intraoperative findings may warrant extension of resection[14]. Some techniques, including frozen sectioning[225], PJC[140], pancreatoscopy[226] and irrigation cytology[227] can be performed during surgery to improve the likelihood of total tumor clearance.

Pancreatic resections carry a high risk of morbidity and mortality, which is influenced by the chosen surgical technique. In 2012, the mortality of a PD was reported to be nearly 15% in low volume centers[228]. However, due to improvements in health care and specialty centralization, recent published mortality rates approximate <2 to 3%[96,229-231]. A total pancreatectomy (TP) has an increased mortality and morbidity risk compared to partial pancreatectomies[230,232].

The morbidity following pancreatic surgery is high, with a complication risk of >50% for partial pancreatectomies[229,233]. Common issues include delayed gastric emptying (DGE), pancreatic fistulas (POPF), and wound infections[96]. POPFs following PD of DP occur in about 30% of cases[233]. A TP has no risk of POPFs but there is a total loss of endocrine and exocrine function. Recent improvements in postoperative care, however, ensure that quality of life is almost comparable to that following partial resections[234-236]. DM as a consequence following pancreatic disease or surgical resection is often referred to as type 3c DM, i.e. 'pancreatogenic'[237]. In type 3c DM there is in addition to decrease of insulin secretion an impaired secretion of glucagon. Bihormonal devices, regulating insulin and glucagon, are being evaluated. This technique can theoretically handle type 3c DM better than the state of art insulin therapy[238]. Endocrine-related morbidity following TP needs improvement[239]. The concept of "brittle diabetes" following TP is somewhat feared, but it is essentially comparable to type 1 diabetes[240], and diabetes-related mortality is, in modern medicine, very rare[239].

The risks of pancreatic surgery may be increased when performed on low-grade dysplastic IPMN compared to HGD and invasive IPMN[48]. A more targeted and less invasive method such as enucleation may be carried out in low-risk BD-IPMN[241]. However, enucleation is not risk free and complications of pancreatic fistulas are fairly common[242].

Recurrence of disease is particularly high for IPMN, especially in the case of invasive disease[47,53,64,243]. Where there is tumor recurrence in the remnant pancreas following partial pancreatectomy, a remnant or secondary surgical procedure can be carried out[53]. It may be challenging to determining the presence of recurrence of a MD-IPMN following proximal pancreatectomy as the remnant main pancreatic duct may be dilated owing to causes unrelated to IPMN[244].

For invasive disease on histology, adjuvant therapy is recommended[15]. However, no specific regimens exist and to date, no randomized controlled studies have been performed. The conclusions from existing research is that adjuvant therapy, i.e. chemotherapy and / or radiotherapy, may be beneficial in those with more aggressive tumor characteristics[245]. Microsatellite instability caused by mismatch repair deficiency appears to be more prevalent in IPMN-related tumors compared to PDAC (7% and 1.3%, respectively). This subset of tumors may be susceptible to immune checkpoint inhibitors[246].

Aims of the thesis

Since its "discovery" in the late 1980s, the research area relating to IPMN has exploded and much has been learned. However, several important questions persist and the management of IPMN remains complex. The aim of this thesis was to shed light on different areas regarding the clinical management, health economy and biomarkers relating to IPMN.

The specific aims of the individual studies were as follows:

I. To investigate the surgical aspects relating to IPMN on a Swedish national level.

II. To examine the cost-effectiveness of varying management strategies of low-risk IPMN.

III. To evaluate and compare the postoperative outcome of IPMC and PDAC.

IV. To develop a predictive model for postoperative survival in IPMC using ANN and LASSO.

V. To explore the potential use of preoperative serum glycoprotein analysis to aid in the discrimination between healthy individuals, non-invasive IPMN and PDAC.

Material and methods

Study population

The Swedish National Quality Registry for Pancreatic and Periampullary cancer

The registry started in 2010 and collects data on patients with pancreatic and periampullary cancer as well as on those with premalignant and benign lesions. The objective of the registry is to register all patients with a suspected tumor in the pancreatic or periampullary region[247]. Collected data includes patient characteristics, surgery, if performed, and postoperative information. The coverage of the registry, controlled against the Cancer Registry Statistics by the National Board of Health and Welfare in Sweden, was for 2010 – 2016: 74%, 77%, 89%, 90%, 95%, 94% and 88%, respectively. The certification level at the time of data request was 2 (1-4)[248]. We analyzed data on histopathologically confirmed IPMN, registered between 2010 and 2016.

Local Pancreatic Resection Registry, Lund, Sweden

Data on pancreatic resections performed in the Department of Surgery, Skåne University Hospital, Lund, Sweden, from 1st of January 2000 onwards has been gathered prospectively via computerized search of medical records. Information retrieved included patient demographics, surgical and histopathological parameters and follow-up data checked against the National Death Registry. Detailed data on surgical procedures performed between January 1st, 2012 and August 9th, 2016 was used for the estimation of costs in paper II. Patient and tumor characteristics for patients included in study V was assessed via this registry.

Surveillance, epidemiology, and end results (SEER)

SEER is a prospective database derived from population-based cancer registries in the US. It is maintained by the National Cancer Institute. Patients with a diagnosis of invasive IPMN were identified on the basis of criteria set out in the 'International Classification of Disease for Oncology', 3rd edition (ICD-O-3) for tumors of the exocrine pancreas, i.e. C25.0, C25.1, C25.2, C25.3, C25.7, C25.8, and C25.9, and the ICD-O-3 histology codes 8050, 8260, 8450, 8453, 8471, 8480, 8481 and 8503[249,250]. Data analysis was performed on subjects entered onto the registry between 2004 and 2016.

Systematic review and meta-analysis

Systematic reviews are considered to be high quality clinical evidence. They focus on a specified objective, have a predetermined protocol for data inclusion and exclusion, and incorporate a rigorous literature search to identify all available studies. They can be divided into qualitative or quantitative reviews, the latter including a statistically analysis of the collective data, i.e. a meta-analysis[251].

The search term "pancreatic ductal adenocarcinoma" or "PDAC" and "IPMN" or "intraductal papillary mucinous neoplasm" in medical subject headings (MeSH) were used in the computerized search. Databases included Medline and Embase. The study was reported in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis)[252] and AMSTAR (assessing the methodological quality of systematic reviews)[253] guidelines. The MOOSE (Meta-analysis Of Observational Studies in Epidemiology)[254] checklist was also used. The main inclusion criterion was postoperative comparison of invasive IPMN and PDAC, including information regarding the primary outcomes of OS, disease-specific survival (DSS), recurrence-free survival (RFS), recurrence rate. Secondary outcomes were clinicopathological data. Subgroup analysis on the primary outcomes evaluated matched and unmatched samples, histological types of IPMC versus PDAC and also PDAC with concomitant IPMN. Full text versions were acquired for relevant studies published in English between 2000 and December 2018. Studies were then accepted for the review according to a pre-defined protocol. Data search and extraction were performed independently by Linus Aronsson and Axel Bengtsson. The search was completed in December 2018, and generated 5578 articles, out of which 14 studies were deemed eligible for inclusion in the analysis (Figure 5).

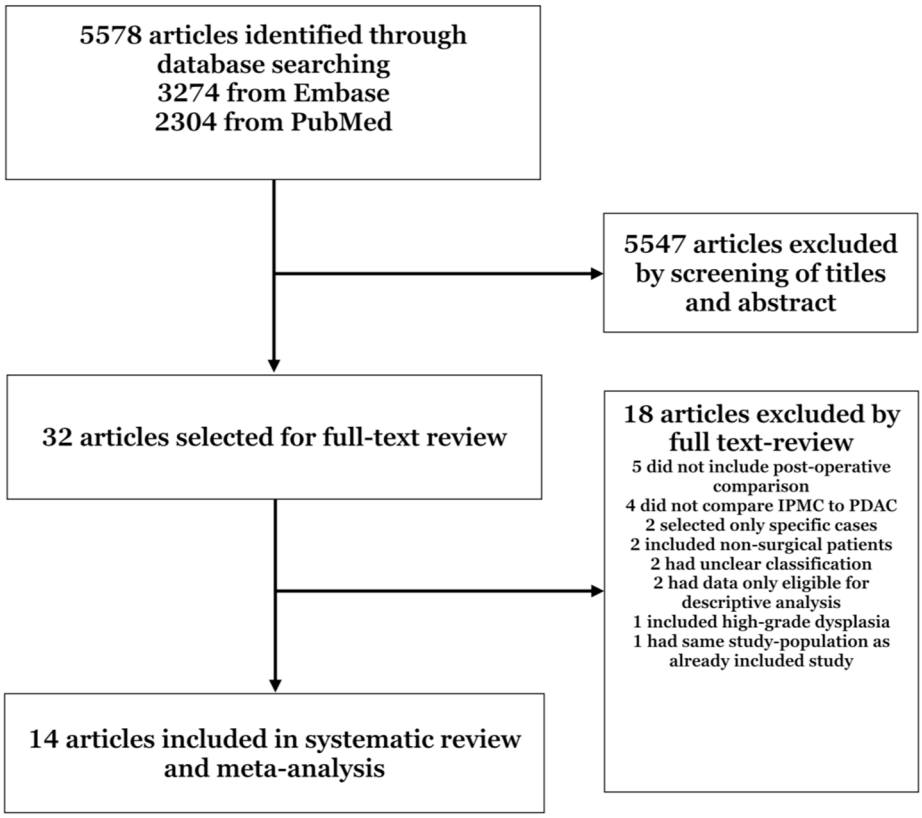


Figure 5. PRISMA flow chart of the study selection.

Biobank

Serum samples were collected from patients undergoing pancreatic surgery for PDAC and IPMN at Skåne University Hospital, Lund, Sweden during the period 2012 to 2017. Samples were handled by a few expert laboratory personnel. Age-matched serological controls were collected from healthy individuals donating blood at the local blood donation center in Lund. All serum samples were stored at -80°C until analysis.

Ethical approval

Ethical approval for studies I (dnr 2015/393), II (dnr 2015/833), IV (dnr 2016/100) and V (dnr 2017/320) was obtained by the Regional Human Ethics Committee in Lund. Written informed consent was obtained from all subjects in study V. Studies I and IV entailed registry data collection on patients; study II included data from the local pancreatic resection database, Lund, Sweden. Follow-up data on mortality was acquired from the National Death Registry (studies I and II). No study altered or impacted on participating patients' care in any way.

Glycosylation array

In the discovery phase, simultaneous screening of 1000 glycosylated proteins in serum was performed with RayBio ® human glycosylation antibody array 1000 (RayBiotech, Inc. Norcross, GA) (Figure 6, Table 10). The 10 most promising glycoproteins from the discovery phase were entered into the verification phase and analyzed with a custom-made glycosylation antibody array from RayBiotech.

Serum samples from 16 cases, i.e. 8 patients with resectable PDAC and 8 healthy controls (HC) were used in the initial discovery phase. Serum samples from 109 cases, i.e. 49 patients with resectable PDAC, 13 patients with resectable non-invasive IPMN and 47 HC, were used in the verification phase.

The serum samples were incubated with the arrays; these consist of antibodies printed onto glass slides with their corresponding glycans deleted. After removing unbound proteins, the array was incubated with a mixture of five biotin-labeled lectins with sugar specificity: αMan, αGlc, αGaINAc, Galß3GalNAc, αFuc, GlcNAc. This process permitted binding to the respective glycan moieties of the antibodies. Streptavidin-conjugated fluorescent dye was then added and, after being dried, the glass slide underwent fluorescence scanning to acquire signal intensity. This was then compared to the array map for identification of the respective glycosylated proteins. Negative and positive controls in the array were used for normalization and optimization of scanning. Numerical data of signal intensity and thus semi-quantified expression levels of glycosylation were calculated with the excel-based RayBio® Analysis Tool Software.

The concentration of CA19-9, in all included samples, was separately measured with the same antibody assay (electro-chemiluminiscence immunoassay) used in clinical practice in Lund, Sweden[255].

Table 10. Included targeted glycosylated proteins in RayBio ® human glycosylation antibody array 1000.

11b-HSD1, 2B4, 4-1BB, 6Ckine, A1BG, A2M, ABL1, ACE, ACE-2, ACK1, ACPP, ACTH, Activin A, Activin B, Activin C, Activin RIA / ALK-2, Activin RIB / ALK-4, Activin RII A/B, Activin RIIA, ADAM-9, ADAMTS-1, ADAMTS-10, ADAMTS-13, ADAMTS-15, ADAMTS-17, ADAMTS-18, ADAMTS-19, ADAMTS-4 , ADAMTS-5, ADAMTS-L2, Adiponectin / Acrp30, Adipsin, Afamin, AFP, AgRP, ALBUMIN, ALCAM, Aldolase A, Aldolase B, Aldolase C, ALK, Alpha 1 AG, Alpha 1 Microglobulin, Alpha Lactalbumin, ALPP, AMICA, AMPKa1, Amylin, Angiogenin, Angiopoietin-1, Angiopoietin-2, Angiopoietin-4, Angiopoietin-like 1, Angiopoietin-like 2, Angiopoietin-like Factor, Angiostatin, ANGPTL3, ANGPTL4, Annexin A7, APC, APCS, Apelin, Apex1, APJ, APN, ApoA1, ApoA2, ApoA4, ApoB, ApoB100, ApoC1, ApoC2, ApoC3, ApoD, ApoE, ApoE3, ApoH, ApoM, APP, APRIL, AR (Amphiregulin), Artemin, ASPH, Attractin, Axl, B3GNT1, B7-1 /CD80, BACE-1, BAF57, BAFF, BAFF R / TNFRSF13C, BAI-1, bax, BCAM, BCMA / TNFRSF17, BD-1, BDNF, Beta 2M, Beta Defensin 4, Beta IG-H3, beta-Catenin, beta-NGF, Biglycan, BIK, BLAME, BLC / BCA-1 / CXCL13, BMP-15, BMP-2, BMP-3, BMP-3b / GDF-10, BMP-4, BMP-5, BMP-6, BMP-7, BMP-8, BMP-9, BMPR-IA / ALK-3, BMPR-IB / ALK-6, BMPR-II, BMX, BNIP2, BNP, BTC, Btk, C2, C3a, C5/C5a, C7, C8B, C9, CA125, CA15-3, CA19-9, CA9, Cadherin-13, Calbindin, Calbindin D, Calcitonin, Calreticulin, Calsyntenin-1, Cardiotrophin-1 / CT-1, CART, Caspase-3, Caspase-8, Cathepsin B, Cathepsin D, Cathepsin L, Cathepsin S, CBP, CCK, CCL14 / HCC-1 / HCC-3, CCL28 / VIC, CCR1, CCR2, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CD 163, CD14, CD200, CD23, CD24, CD27 / TNFRSF7, CD30 / TNFRSF8, CD30 Ligand / TNFSF8, CD36, CD38, CD40 / TNFRSF5, CD40 Ligand / TNFSF5 /CD154, CD44, CD45, CD46, CD47, CD55, CD59, CD61, CD71, CD74, CD79 alpha, CD90, CD97, CEA, CEACAM-1, Cerberus 1, Ceruloplasmin, CFHR2, Chem R23, Chemerin, CHI3L1, Chordin-Like 1, Chordin-Like 2, Chromogranin A, Chymase, cIAP-2, Ck beta 8-1, CK-MB, Claudin-3, Claudin-4, CLC, CLEC3B, Clusterin, CNDP1, CNTF R alpha, CNTF, Coagulation Factor III / Tissue Factor, Coagulation Factor X/Xa, COCO, Complement factor H, Contactin-1, Contactin-2, Corticosteroid-binding globulin, COX-2, C-peptide, CPN2, Creatinine, CRIM 1, Cripto-1, CRP, CRTAM, CRTH-2, Cryptic, CSH1, Csk, CTACK / CCL27, CTGF / CCN2, CTLA-4 /CD152, cTnT / Troponin T, CutA, CV-2 / Crossveinless-2, CXCL14 / BRAK, CXCL16, CXCR1 / IL-8 RA, CXCR2 / IL-8 RB, CXCR3, CXCR4 (fusin), CXCR5 /BLR-1, CXCR6, Cyclin D1, Cystatin A, Cystatin B, Cystatin C, Cytochrome C, Cytokeratin 8, Cytokeratin18, Cytokeratin19, D6, DAN, DANCE, DBI, DCBLD2, DcR3 / TNFRSF6B, D-Dimer, Decorin, DEFA1/3, Defensin, Desmin, Dkk-1, Dkk-3, Dkk-4, DLL1, DLL4, DMP-1, DPPIV, DR3 / TNFRSF25, DR6 / TNFRSF21, Dtk, E-Cadherin, EDA-A2, EDAR, EDG-1, EGF, EGF R / ErbB1, EG-VEGF / PK1, EMAP-II, ENA-78, Endocan, Endoglin / CD105, Endorphin Beta, Endostatin, Endothelin, Endothelin Receptor A, Enolase 2, ENPP2, EN-RAGE, Eotaxin / CCL11, Eotaxin-2 / MPIF-2, Eotaxin-3 / CCL26, EpCAM, EphA1, EphA2, EphA3, EphA4, EphA5, EphA6, EphA7, EphA8, EphB1, EphB2, EphB3, EphB4, EphB6, Epiregulin, ErbB2, ErbB3, ErbB4, ERRa, Erythropoietin R, Erythropoietin, ESAM, E-Selectin, EV15L, EXTL2, FABP1, FABP2, FABP3, FABP4, Factor XIII A, Factor XIII B, FADD, FAK, FAM3B, FAP, Fas / TNFRSF6, Fas Ligand, Fc RIIB/C, Fen 1, FER, Ferritin, Fetuin A, Fetuin B, FGF Basic, FGF R3, FGF R4, FGF R5, FGF-10 / KGF-2, FGF-11, FGF-12, FGF-13 1B, FGF-16, FGF-17, FGF-18, FGF-19, FGF-20, FGF-21, FGF-23, FGF-4, FGF-5, FGF-6, FGF-7 / KGF, FGF-8, FGF-9, FGF-BP, FGFR1, FGFR1 alpha, FGFR2, Fibrinogen, Fibrinopeptide A, Fibronectin, Ficolin-3, FIH, FLRG, Flt-3 Ligand, Follistatin, Follistatin-like 1, FOLR1, FOXN3, FoxO1, FoxP3, Fractalkine, Frizzled-1, Frizzled-3, Frizzled-4, Frizzled-5, Frizzled-6, Frizzled-7, FRK, FSH, Furin, Fyn," GADD45A, Galanin, Galectin-1, Galectin-3, Galectin-3BP, Galectin-7, gamma-Thrombin, Gas1, GASP-1 / WFIKKNRP, GASP-2 / WFIKKN, Gastrin, GATA-3, GATA-4, GCP-2 / CXCL6, GCSF, G-CSF R / CD 114, GDF1, GDF11, GDF-15, GDF3, GDF5, GDF8, GDF9, GDNF, Gelsolin, GFR alpha-1, GFR alpha-2, GFR alpha-3, GFR alpha-4, Ghrelin, GITR / TNFRF18, GITR Ligand / TNFSF18, GLO-1, GLP-1, Glucagon, Glut1, Glut2, Glut3, Glut5, Glypican 3, Glypican 5, GM-CSF, GM-CSF R alpha, GMNN, GPBB, GPI, GPR-39, GPX1, GPX3, Granzyme A, Grb2, GREMLIN, GRO, GRO-a, Growth Hormone (GH), Growth Hormone R (GHR), GRP, GRP75, GRP78, GSR, GST, HADHA, HAI-1, HAI-2, Haptoglobin, HB-EGF, HCC-4 / CCL16, hCG alpha, hCGb, Hck, HCR / CRAM-A/B, HE4, Hemopexin, Hepassocin, Hepcidin, HGF, HGFR, HOXA10, HRG-alpha, HRG-beta 1, HSP10, HSP20, HSP27, HSP32, HSP40, HSP60, HSP70, HSP90, HSPA8, HTRA2, HVEM / TNFRSF14, I-309, IBSP, ICAM-1, ICAM-2, ICAM-3 (CD50), ICAM-5, IFN-alpha / beta R1, IFN-alpha / beta R2, IFN-beta, IFN-gamma, IFN-gamma R1, IGF2BP1, IGFBP-1, IGFBP-2, IGFBP-3, IGFBP-4, IGFBP-5, IGFBP-6,

IGFBP-rp1 / IGFBP-7, IGF-I, IGF-I SR, IGF-II, IGF-II R, IL-1 alpha, IL-1 beta, IL-1 F10 / IL-1HY2, IL-1 F5 / FIL1delta, IL-1 F6 / FIL1 epsilon, IL-1 F7 / FIL1 zeta, IL-1 F8 / FIL1 eta, IL-1 F9 / IL-1 H1, IL-1 R3 / IL-1 R AcP, IL-1 R4 /ST2, IL-1 R6 / IL-1 Rrp2, IL-1 R8, IL-1 R9, IL-1 ra, IL-1 sRI, IL-1 sRII, IL-10, IL-10 R alpha, IL-10 R beta, IL-11, IL-12 p40, IL-12 p70, IL-12 R beta 1, IL-12 R beta 2, IL-13, IL-13 R alpha 1, IL-13 R alpha 2, IL-15, IL-15 R alpha, IL-16, IL-17, IL-17B, IL-17B R, IL-17C, IL-17D, IL-17E, IL-17F, IL-17R, IL-17RC, IL-17RD, IL-18 BPa, IL-18 R alpha /IL-1 R5, IL-18 R beta /AcPL, IL-19, IL-2, IL-2 R alpha, IL-2 R beta /CD122, IL-2 R gamma, IL-20, IL-20 R alpha, IL-20 R beta, IL-21, IL-21 R, IL-22, IL-22 BP, IL-22 R, IL-23, IL-23 R, IL-23p19, IL-24, IL-26, IL-27, IL-28A, IL-29, IL-3, IL-3 R alpha, IL-31, IL-31 RA, IL-33, IL-34, IL36RN, IL-4, IL-4 R, IL-5, IL-5 R alpha, IL-6, IL-6 R, IL-7, IL-7 R alpha, IL-8, IL-9 , INSL3, INSRR, Insulin, Insulin R, Insulysin / IDE, Integrin alpha V, IP-10, I-TAC / CXCL11, Itk, ITM2B, Kallikrein 10, Kallikrein 11, Kallikrein 14, Kallikrein 2, Kallikrein 5, Kallikrein 6, Kallikrein 7, Kallikrein 8, KCC3, KCTD10, KIF3B, Kininostatin / kininogen, KLF4, Kremen-1, Kremen-2, LAG-3, Latent TGF-beta bp1, Layilin, LBP, Lck, LDL R, LECT2, Lefty - A, Legumain, Leptin (OB), Leptin R, LFA-1 alpha, LH, LIF R alpha, LIF, LIGHT / TNFSF14, LIMPII, LIN41, Lipocalin-1, Livin, LOX-1, LPS, LRG1, LRP-1, LRP-6, L-Selectin (CD62L), LTF, LTK, Luciferase, Lumican, Lymphotactin / XCL1, Lymphotoxin beta / TNFSF3, Lymphotoxin beta R / TNFRSF3, Lyn, LYRIC, LYVE-1, LZTS1, MAC-1, Mammaglobin A, Marapsin, MATK, MBL, MBL-2, MCP-1, MCP-2, MCP-3, MCP-4 / CCL13, M-CSF, M-CSF R, MDC, Mer, Mesothelin, MFG-E8, MFRP, MICB, Midkine, MIF, MIG, MINA, MIP 2, MIP-1a, MIP-1b, MIP-1d, MIP-3 alpha, MIP-3 beta, MMP-1, MMP-10, MMP-11 /Stromelysin-3, MMP-12, MMP-13, MMP-14, MMP-15, MMP-16 / MT3-MMP, MMP-19, MMP-2, MMP-20, MMP-24 / MT5-MMP, MMP-25 / MT6-MMP, MMP-3, MMP-7, MMP-8, MMP-9, MSHa, MSP alpha Chain, MSP beta-chain, MTUS1, Musk, Myoglobin, NAIP, Nanog, NAP-2, NCAM-1 / CD56, NELL2, NEP, Nesfatin, Nestin, NET1, Netrin G2, Netrin-4, Neuritin, NeuroD1, Neurokinin-A, Neuropeptide Y, Neuropilin-2, Neurturin, NF1, NGF R, NM23-H1/H2, Notch-1, NOV / CCN3, NPTX1, NPTXR, NR3C3, NRG1 Isoform GGF2, NRG1-alpha / HRG1-alpha, NRG1-beta1 / HRG1-beta1, NRG2, NRG3, NT-3, NT-4, Ntn1, OCT3/4, Omentin, Orexin A, Orexin B, OSM, Osteoactivin / GPNMB, Osteocalcin, Osteocrin, Osteopontin, Osteoprotegerin / TNFRSF11B, OX40, OX40 Ligand / TNFSF4, p21, p27, p53, PAI-1, PAK7, Pancreastatin, Pancreatic Polypeptide, Pappalysin-1, PARC / CCL18, PARK7, P-Cadherin, PCAF, PD-1, PD-ECGF, PDGF R alpha, PDGF R beta, PDGF-AA, PDGF-AB, PDGF-BB, PDGF-C, PDGF-D, PDX-1, PECAM-1 /CD31, PEDF , Pentraxin3 / TSG-14, PEPSINOGEN I, PEPSINOGEN II, Peroxiredoxin 6 (Prdx6), Persephin, PF4 / CXCL4, PGRP-S, PI 16, PI 3Kinase p85 beta, PIM2, PKM2, Plasminogen, PlGF, PLUNC, Podocalyxin, POMC, PON1, PON2, PPARg2, PPP2R5C, Pref-1, Presenilin 1, Presenilin 2, Pro-BDNF, Procalcitonin, Pro-Cathepsin B, Progesterone, pro-Glucagon, Progranulin, Prohibitin, Prolactin, Pro-MMP-13, Pro-MMP-7, Pro-MMP-9, ProSAAS, Prostasin, Protein p65, PSA-Free, PSA-total, P-selectin, PSP, PTH, PTHLP, PTN, PTPRD, PYK2, PYY, RAGE, RANK / TNFRSF11A, RANTES, Ras, RBP4, RECK, RELM alpha, RELM beta, RELT / TNFRSF19L, Resistin, RET, RIP1, ROBO4, ROCK1, ROCK2, ROR1, ROR2, ROS, RYK, S100 A8/A9, S100A10, S100A4, S100A6, S100A8, S-100b, SAA, SART1, SART3, SCF, SCF R /CD117, SCG3, SDF-1 / CXCL12, Selenoprotein P, SEMA3A, Serotonin, Serpin A1, Serpin A12, Serpin A3, Serpin A4, Serpin A5, Serpin A8, Serpin A9, Serpin B5, Serpin D1, Serpin I1, SERTAD2, sFRP-1, sFRP-3, sFRP-4, sgp130, SHBG, SIGIRR, Siglec-5/CD170, Siglec-9, SLPI, SMAC, Smad 1, Smad 4, Smad 5, Smad 7, Smad 8, SNCG, Soggy-1, Somatotropin, Sonic Hedgehog (Shh N-terminal), SOST, SOX17, SOX2, SPARC, SPARCL1, Spinesin, SPINK1, SRMS, SSEA-1, SSEA-4, SSTR2, SSTR5, Survivin, SYK, Syndecan-1, Syndecan-3, TACE, TACI / TNFRSF13B, TAF4, Tarc, TCCR / WSX-1, Tec, TECK / CCL25, TFF1, TFF3, TFPI, TGF-alpha, TGF-beta 1, TGF-beta 2, TGF-beta 3, TGF-beta 5, TGF-beta RI / ALK-5, TGF-beta RII, TGF-beta RIII, Thrombin, Thrombomodulin, Thrombopoietin (TPO), Thrombospondin-1, Thrombospondin-2, Thrombospondin-4, Thymidine Kinase-1, Thymopoietin, Thyroglobulin, Thyroid Peroxidase (TPX), Tie-1, Tie-2, TIM-1, TIMP-1, TIMP-2, TIMP-3, TIMP-4, TL1A / TNFSF15, TLR1, TLR2, TLR3, TLR4, TMEFF1 / Tomoregulin-1, TMEFF2, TNF RI / TNFRSF1A, TNF RII / TNFRSF1B, TNF-alpha, TNF-beta, TNK1, TOPORS, TPA, TPM1, TRA-1-60, TRA-1-81, TRADD, TRAIL R1 / DR4 / TNFRSF10A, TRAIL R2 / DR5 / TNFRSF10B, TRAIL R3 / TNFRSF10C, TRAIL R4 / TNFRSF10D, TRAIL / TNFSF10, TRANCE, Transferrin, Trappin-2, TREM-1, TRKB, Troponin C, Troponin I, TROY / TNFRSF19, TRPC1, TRPC6, TRPM7, Trypsin 1, TSG-6, TSH, TSLP, TSLP, TWEAK / TNFSF12, TWEAK R / TNFRSF12, TXK, Tyk2, TYRO10, Ubiquitin+1, uPA, uPAR, Uromodulin, Vasopressin, Vasorin, VCAM-1 (CD106), VDUP-1, VE-Cadherin, VEGF, VEGF R1, VEGF R2 (KDR), VEGF R3, VEGF-B, VEGF-C, VEGF-D, VEGI / TNFSF15, VGF, VIP Receptor 2, Visfatin, Vitamin D Receptor, Vitamin D-BP, Vitamin K-dependent protein S, Vitronectin, VWF, WIF-1, Wilms Tumor 1, WISP-1 / CCN4, XEDAR, XIAP, ZAG, ZAP70

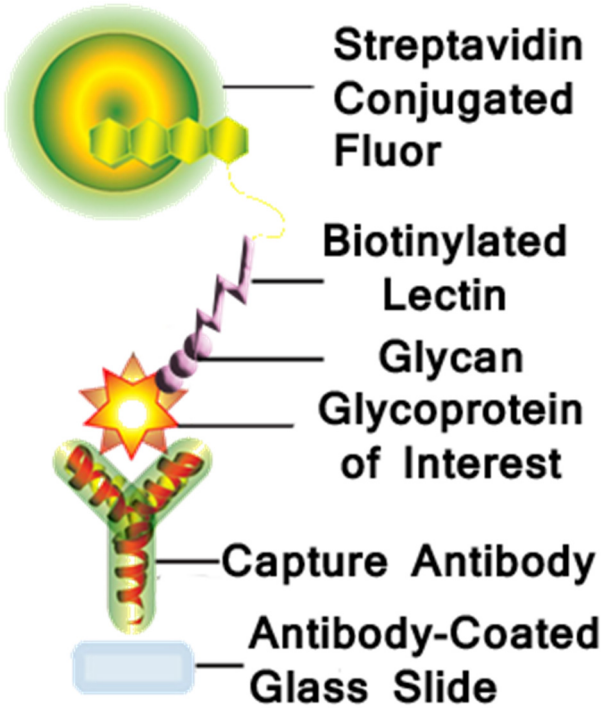


Figure 6. Schematic of glycoarray. With permission from Ray Biotech®.

Statistical analysis

Paper I

Statistical analyses were performed with STATA MP Version 14.1. Baseline data were compared statistically between non-invasive IPMN and invasive IPMN with Mann-Whitney U test for continuous variables, and Chi-square or Fischer´s exact test for categorical variables. Survival analysis was performed with the log-rank test, including Kaplan-Meier graphs. Prior to logistic regression, multiple imputation was performed due to missing values. The percentage of missing values ranged from 0.8% to 28.3%. Invasiveness, age and gender had no missing data. Missing values were assumed to be missing completely at random (MCAR). Predictive mean matching (PMM) with 10 imputations with 10 iterations were performed. All factors were included in the model. Odds ratio (OR) with 95% confidence interval (CI) for different factors for invasiveness was assessed by univariable and multivariable logistic regression. Factors with a p-value of <0.25 in univariable regression were

included in the multivariable regression. Forward and backward stepwise selection was performed. Factors were removed (p>0.1) or added (p<0.1) in the iterative process.

Paper II

Figure 7 and 8 shows a simplified decision tree and Markov model, respectively. In this example, the decision tree compares two strategies, I and II, with different percentages remaining healthy. Each transition is based on probabilities, represented by the numbers below the lines. The "patient" is sent back to the Markov-node (M) following each cycle end and starts the next cycle based on where they finished in the previous cycle, i.e. healthy or sick. It consists of two nodes or states, i.e. healthy or sick. The decision tree in study II had 644 nodes in total. The Markov model has three states and transitions between them (arrows) governed by some, here unknown, probabilities. At each step or transition a predetermined cost or health utility (HU) (positive or negative value), influenced by the discount rate, is added. Using these methods, cost-effectiveness can be evaluated and compared between different strategies.

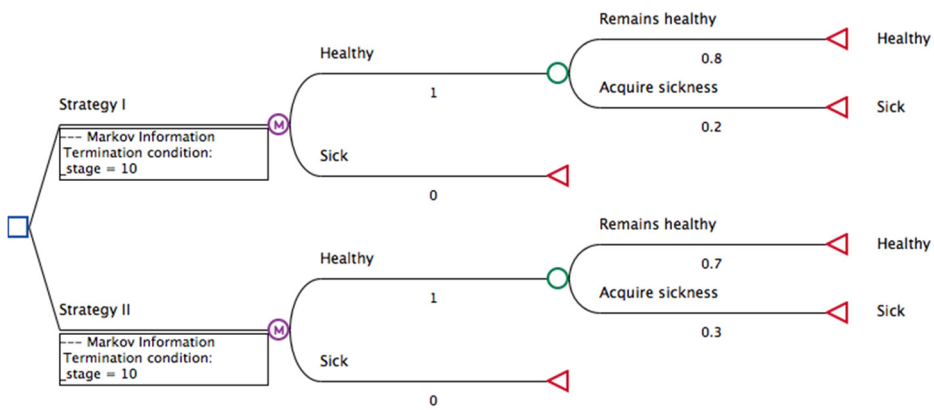


Figure 7. Simplified schematic picture of a decision tree (from TreeAge Pro 2017).

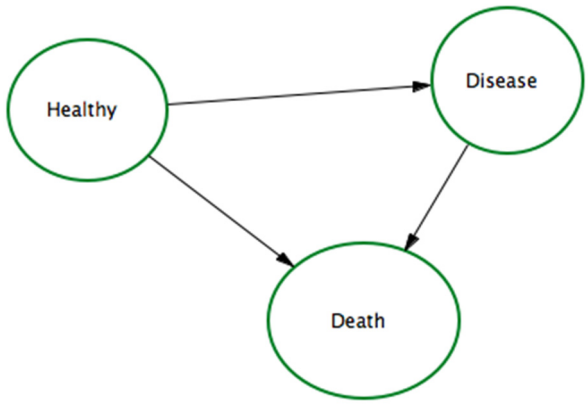


Figure 8. Simplified Markov model (from TreeAge Pro 2017).

Four (I – IV) competing strategies for management of low-risk BD-IPMN were designed; I = upfront TP, II = upfront partial pancreatectomy, III = initial surveillance, IV = watchful waiting. A decision analysis software (TreeAge Pro 2017: TreeAge Software Inc., Williamstown, MA, USA) was used for the development of the Markov model. The index case was a 65-year old patient with a suspected low-risk BD-IPMN, i.e. no WF and HRS or absolute and relative criteria. Transitions between health states occurred at the end of each model cycle, which were considered to represent 1 year. Simulation ran over 35 cycles, representing 35 years, and included age-dependent mortality rates based on Swedish data (mean between men and female). The transitions were governed by probabilities acquired from the literature or, where no available data existed, assumed by expects in the field. Quality of life (QoL) assessment were based on studies investigating different health states by the generic preference-based EuroQol (EQ-5D). Health gains between the different strategies were measured as Quality Adjusted Life Years (QALY). The costs were based on a price list from Region Skåne, Sweden, from 2017, and estimated by data from the local pancreatic resection database (2012 – 2016), national reports and studies from a Swedish setting. All costs were adjusted to year 2017 using the consumer price index and converted to Euro (€) at the mean exchange rate for 2017 (1€:SEK9.63). An annual discount rate of 3% was used[256].

The cost-effectiveness between the four strategies were assessed by calculating the incremental cost-effectiveness ratio (ICER). The willingness to pay (WTP) per QALY gain was set to €100,000[257].

Sensitivity analyses were performed with tornado analysis for all variables, combined for highly influencing factors in the tornado analysis and / or clinically relevant factors, as well as for different WTP values and discount rates.

Paper III

With the use of Review Manager (RevMan, version 5.3: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) analysis was performed on pooled data on odds ratio (OR) with a 95% CI. Results were considered statistically significant if the 95% CI did not include 1. Pooled analysis on hazard ratio (HR) could not be calculated, owing to lack of information and different statistical models performed between studies. A random-effects method was used for all analyses owing to assumed heterogeneity among studies, i.e. difference in follow-up strategies such as use of adjuvant therapy, different proportions in tumor stages, different health care systems and demography. A fixed effects model is seldom used in meta-analyses because it assumes that all studies are evaluating one true underlying effect, i.e. only taking within-study variance into consideration. This yields a more precise result (narrow CI) and the weights are basically influenced proportionally by the study size. In addition to within-study variance, a random-effects model also incorporates between-study variation[258,259]. The Mantel-Haenszel method was used for the random-effects model. Heterogeneity was assessed using Higgins´I^2 and chi^2 test. Primary and secondary outcomes where presented numerically and graphically with forest plots. Data unsuitable for pooled analysis due to variations in definitions or containing statistical models unfit for direct / pooled comparison was descriptively presented.

Paper IV

The aim was to predict long-term survival following surgery in invasive IPMN. DSS was used as endpoint. Owing to the structure of the database, DSS was calculated from date of diagnosis to date of death or until last follow-up. Individuals who died causes unrelated to IPMN were censored. Prediction of long-term survival following surgery was evaluated using artificial neural network (ANN) and the least absolute shrinkage and selection operator (LASSO). The binary endpoint made regression analysis a suitable comparison method. Model performance was assessed using the outcomes “accuracy”, “precision”, “recall” and “F1 score”, which can be calculated from a confusion matrix (Figure 9). F1 score is the weighted average of recall and precision: 2 * ((precision * recall) / (precision + recall)).

		Model prediction: Positive	Model prediction: Negative	
True value	Positive	**True positive (TP)**	**False negative (FN)** (type II-error)	Recall $\frac{TP}{(TP + FN)}$
True value	Negative	**False positive (FP)** (type I error)	**True negative (TN)**	Specificity $\frac{TN}{(TN + FP)}$
		Precision $\frac{TP}{(TP + FP)}$	Negative predictive value $\frac{TN}{(TN + FN)}$	Accuracy $\frac{TP + TN}{(TP + TN + FP + FN)}$

Figure 9. Confusion matrix.

ANN are computing systems inspired by the biology of the human brain. They consist of nodes (neurons) ordered in distinct layers, i.e. input, hidden and output, connected by "synaptic weights". Flow of information goes from the input layer via an activation function through the hidden layer or layers and output layer, which often consists of one node. The activation function is triggered if a certain threshold is reached by the sum of inputs to the node[260]. A model consisting of more than one hidden layer is often referred to as deep learning algorithm[261]. The multiple layers of nodes and activation function are responsible for the ANN's ability to perform non-linear function estimations. It is therefore capable of detecting complex relationships between dependent and predictor variables[262]. The weights can increase or decrease via a gradient descent affecting the outcome prediction of the model, a process thought of as "learning", which is governed by a learning rate or adjustment of gradient. The model is "trained" on a training set and cross validated on a test-set. Variable selection is important in order to reduce complexity, making training more efficient and reducing redundancy in network design.

Overtraining, i.e. overfitting function approximation, occurs when a model becomes too specific for the training data and incorporates random noise or coincidences from the presented data. Generalizability is reduced leading to low performance on, for the model, novel data. If the model is too simplistic, i.e. underfitted, it does not capture the structure of the data[260].

Regularization methods forces the model to be more generalized by addition of penalties within the model structure; this often means reducing the size of network weights. This can be applied in the input as well as the hidden layers. The most common form is L2, often called weight decay. On the other hand, L1 reduces the weights by a constant factor. The bias term is usually unregularized, as the gradient does not flow through the biases, and it may result in underfitting[263]. Ensemble methods, i.e. training multiple models and average results is another method to circumventing overfitting.

ANN represents a decision-making aid for clinicians[260,264] and has been shown to have benefits over existing statistical methods in the field of cancer research[265].

LASSO is a type of regression analysis that facilitates variable selection and regularization[266]. This is done by altering the fitting process to select a subset of variables. LASSO works by forcing the sum of the absolute value of the regression coefficients to be less than or equal to a predetermined value, some becoming zero and thus excluded, i.e. variable selection usage.

Limitations of neural networks include the "black box" nature, meaning lack of interpretability of variable contribution on the final results. Logistic regression, such as LASSO, produce coefficients interpretable as weights, explaining influence on the outcome. Neural networks have a large computation burden compared to the traditional statistical methods[262].

In study IV, a multi-layer perceptron artificial neural network was developed. It was structured in three layers: input, hidden and output. Two models were created, one with variable selection and one incorporating all variables (Figure 10). Corresponding regression analyses were created, i.e. a logistic regression and a LASSO. Cases were randomly assigned to the modelling (training and test) and validation sets in a 7/3 ratio. The ensemble method was performed for the ANN algorithms with the modelling set split into training and testing eleven times. A majority vote ensemble prediction was used for final prediction.

Five-year DSS was used as endpoint. A total of 440 patients with complete data from the SEER-database fulfilled criteria of follow-up or event / death from disease ≥60 months. Variables examined were: age at diagnosis, size of tumor lesion (cm), gender (male or female), type of surgery, radiotherapy (yes or no), adjuvant chemotherapy (yes or no / unknown if administered) and staging according to the American Joint Committee on Cancer (AJCC) classification separated according to T, N and M stage, location of lesion (head versus other), histological grade (well differentiated, moderately differentiated and poorly differentiated / anaplastic), and year of diagnosis. All analyses on modelling were performed in R v. 3.6.3.

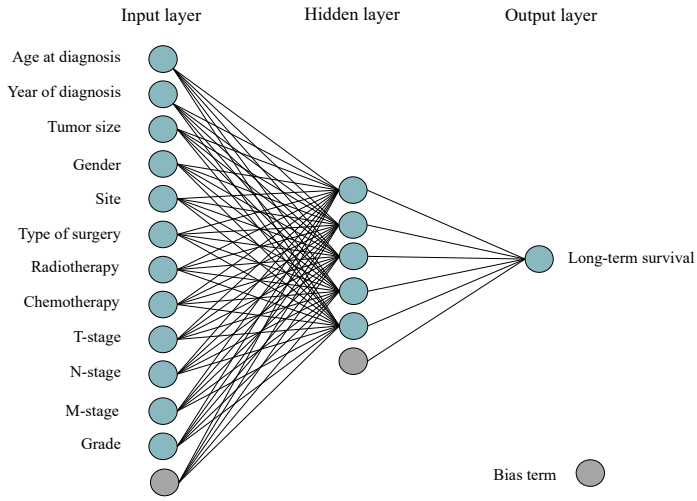


Figure 10. Schematic structure of the applied multilayer perceptron neural network with three layers.

Paper V

Statistical analysis was performed with the statistical analysis software R. Models created with logistic regression performed for all combinations of biomarkers, with a maximum of 4 variables to reduce risk of overfitting where deemed valid, i.e. if the p-value for the model receiver operator characteristic (ROC) curve and each included biomarker variable were <0.05. Further analysis was performed for the most promising models with dot-, box- and ROC curve plots. Comparison was performed between PDAC versus HC, PDAC stage 1 versus HC, PDAC and IPMN versus HC, IPMN versus HC, PDAC versus IPMN and HC, PDAC versus IPMN. AUC and sensitivity at 80% and 90% specificity were calculated.

Main results

Paper I

A total of 3038 pancreatic resections were identified from the registry, of which 251 patients had histopathological diagnosis of IPMN during the study period, 2010 – 2016. The trend in numbers of resections performed on IPMN demonstrated an increase in both absolute numbers and prevalence over time (Figure 11).

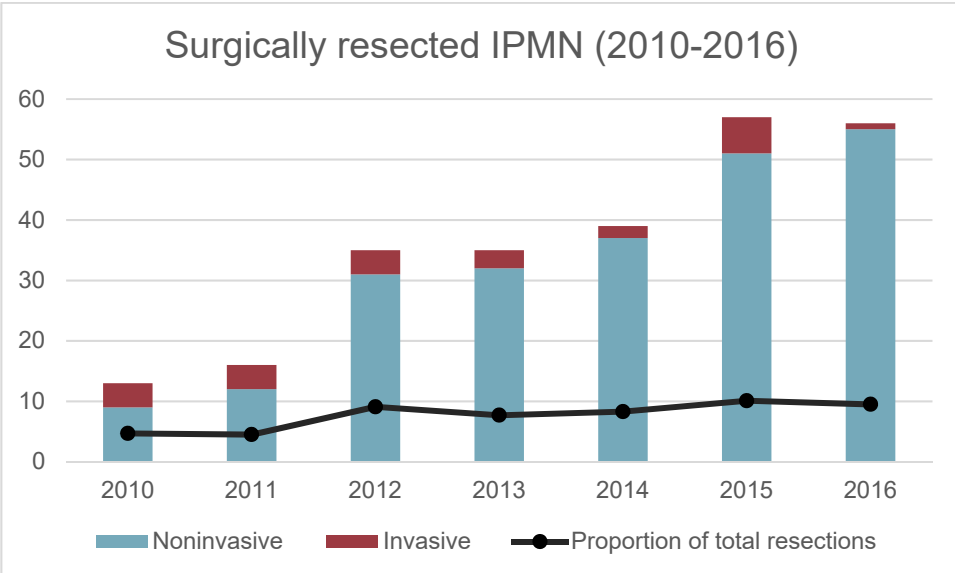


Figure 11. Annual number of surgically resected IPMN. Data from the Swedish National Registry for Pancreatic and Periampullary Cancer (2010-2016). Includes proportions of resections in relation to the total reported number of cases each year.

The study population was split into two groups according to the presence of invasiveness (n=24) and non-invasiveness (n=227). The non-invasive category was further divided into dysplastic grades, i.e. LGD (n=65), IGD (n=88) and HGD (n=60). In 14 patients, no information was available regarding dysplastic grade.

Analyzed clinicopathological factors included: age, gender, body mass index, ASA-score, DM, smoking, biliary obstruction as defined by serum bilirubin >50 µmol/l

or preoperative requirement of biliary drainage, serum CA19-9 ≥37 U/mL, tumor size, type of surgery and postoperative complications classified utilizing the Clavien-Dindo score. The only statistically significant difference found between invasive and non-invasive IPMN was the presence of biliary obstruction (p=0.044).

Following multiple imputation, univariable and multivariable logistic regression for prediction of invasiveness were performed. Biliary obstruction was the only parameter demonstrating significance in both regression types (OR: 3.1 (95% CI 1.1 – 8.6), p=0.03).

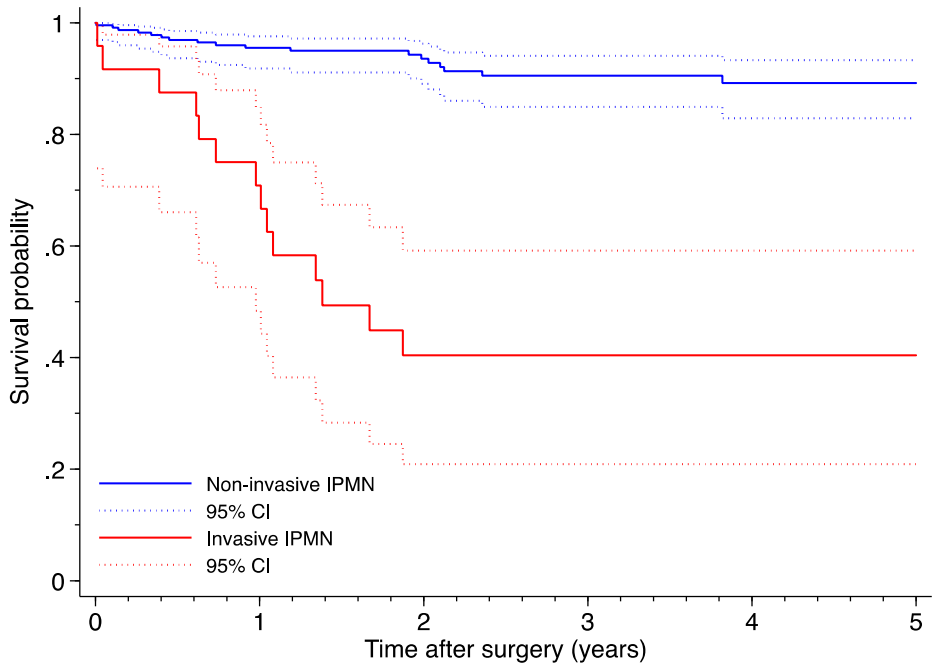


Figure 12. Kaplan-Meier survival curves on non-invasive and invasive IPMN. The solid lines show the observed cumulative survival and the dotted lines show the 95% confidence interval, estimated with Kaplan-Meier survival function.

Survival, assessed by the log-rank test, was significantly decreased in invasive versus non-invasive IPMN (p<0.001) (Figure 12), as well as in invasive IPMN without lymph-node spread versus non-invasive IPMN (p<0.001). There was no difference in 1-year and 3-year survival rates between the varying dysplastic grades of non-invasive IPMN. However, the survival was severely impacted in those with invasive IPMN (Table 11).

Table 11. Survival rates (1- and 3-year survival) in IPMN.

	LGD	IGD	HGD	Invasive
1-year survival	95%	94%	96%	71%
3-year survival	89%	88%	93%	39%

HGD, high-grade dysplasia; IGD, intermediate grade dysplasia; IPMN, intraductal papillary mucinous neoplasm; LGD, low-grade dysplasia.

Paper II

The model simulation of the index case showed that strategy III, one of initial surveillance, was the most cost-effective management strategy, with an ICER of €31,682, compared to strategy IV (Figure 13, Table 12).

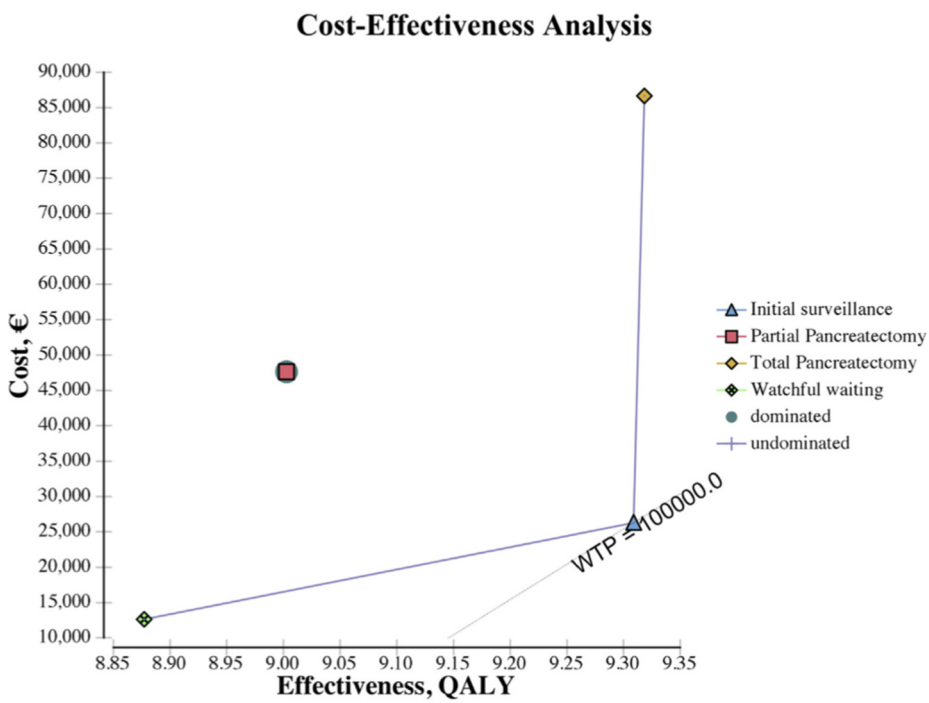


Figure 13. Plot of cost (€) versus effectiveness (QALY) for the four competing strategies.

Table 12. Cost-effectiveness of management strategies for low-risk branch-duct intraductal papillary mucinous neoplasms, index case analysis.

Strategy	Cost, 2017 Euros	Incremental cost, 2017 Euros[a]	Effectiveness QALY	Incremental QALY[b]	ICER (QALY)	Life years (LY)	Incremental LY[c]	ICER (LY)
Watchful waiting	12,624	-	8.88	-	-	12.47	-	-
Initial surveillance	26,305	13,680	9.31	0.43	31,682	13.36	0.89	15,412
Partial pancreatectomy	47,635	35,011	9.00	0.12	278,696	13.48	1.01	34,890
Total pancreatectomy	86,653	74,029	9.32	0.44	167,731	14.12	1.65	44,833

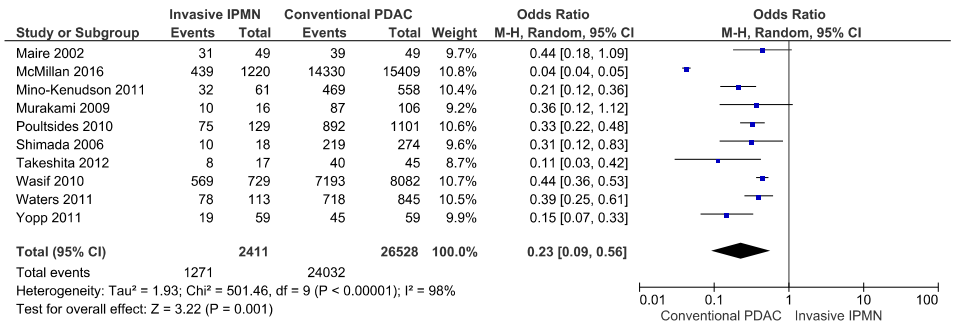
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-years.
[a] Compared with "watchful waiting" [b] Cost per additional QALY compared with "watchful waiting" [c] Cost per additional LY compared with "watchful waiting"

Tornado sensitivity analysis demonstrated that strategy I is the most cost-effective when the annual risk of metachronous PDAC is ≥1.9%. However, when the annual risk of a low-risk BD-IPMN transforming to a high-risk lesion is below 0.7%, or when the annual risk for a high-risk BD-IPMN turning malignant is below 2.9%, strategy IV becomes the most cost-effective.

In specified one-way sensitivity analysis, altering one parameter to a predetermined value, strategy III was the most cost-effective one in all tested scenarios except when the time frame (number of cycles) was set to 10 years. Strategy III was still the most cost-effective when increasing or decreasing the cut-off age for eligibility for surgery from <80 to <85 years, or from <80 to <75 years, with an ICER of €34,038 and €28,064, respectively. When changing follow-up method from MRI to EUS (€406 versus €1246), the estimated cost for strategy III increased from €26,305 to €33,936; the ICER was correspondingly raised from €31,682 to €49,353. Different starting ages, with no correction for loss of productivity, were tested using the following values: 40 years of age, 50 years of age and 70 years of age, each with corresponding health utility start values, i.e. 1.0, 0.96 and 0.76, respectively. In these circumstances, strategy III out-competed the three other strategies.

Paper III

Meta-analysis for the primary outcomes of OS, DSS, RFS, recurrence rate could only be performed for 5-year OS. Significantly improved 5-year OS in IPMC compared to PDAC was seen (OR 0.23, 95% CI 0.09 – 0.56) (Figure 14).



Study or Subgroup	Invasive IPMN Events	Invasive IPMN Total	Conventional PDAC Events	Conventional PDAC Total	Weight	Odds Ratio M-H, Random, 95% CI
Maire 2002	31	49	39	49	9.7%	0.44 [0.18, 1.09]
McMillan 2016	439	1220	14330	15409	10.8%	0.04 [0.04, 0.05]
Mino-Kenudson 2011	32	61	469	558	10.4%	0.21 [0.12, 0.36]
Murakami 2009	10	16	87	106	9.2%	0.36 [0.12, 1.12]
Poultsides 2010	75	129	892	1101	10.6%	0.33 [0.22, 0.48]
Shimada 2006	10	18	219	274	9.6%	0.31 [0.12, 0.83]
Takeshita 2012	8	17	40	45	8.7%	0.11 [0.03, 0.42]
Wasif 2010	569	729	7193	8082	10.7%	0.44 [0.36, 0.53]
Waters 2011	78	113	718	845	10.5%	0.39 [0.25, 0.61]
Yopp 2011	19	59	45	59	9.9%	0.15 [0.07, 0.33]
Total (95% CI)		**2411**		**26528**	**100.0%**	**0.23 [0.09, 0.56]**
Total events	1271		24032			

Heterogeneity: Tau² = 1.93; Chi² = 501.46, df = 9 (P < 0.00001); I² = 98%
Test for overall effect: Z = 3.22 (P = 0.001)

Figure 14. Five-year overall survival comparing IPMC and PDAC (event = death).

In five studies, time-to-event data, analyzed using multivariable cox-regression regarding survival, showed HR ranging from 0.38 to 0.76 (95% CI 0.23 – 0.97)[250,267-270]. Only one study reported comparison on recurrence, i.e. 42% in IPMC and 37% in PDAC[271].

Median survival time ranged from 21 to 58 months in IPMC, compared with 12 to 23 months in PDAC. In several studies no significant survival difference was seen when higher TNM-stage and lymph node-positive disease were compared.

Three studies[269,272,273] provided comparative data for colloid and tubular types of IPMC versus PDAC, with OR 0.12 (95% CI 0.05 – 0.25) and OR 0.38 (95% CI 0.26 – 0.54), respectively. Data on PDAC with concomitant IPMN were deemed unsuitable for comparison due to variations in definition and outcome measures.

Differences in secondary outcomes were identified: TP was more often performed in IPMC (OR 1.55, 95% CI 1.36 – 1.77), positive resection margin appeared less common in IPMC (OR 0.53, 95% CI 0.36 – 0.78), IPMC was more likely to be TNM-stage 1 (OR 4.40, 95% CI 2.71 – 7.15), have a lower tumor grade (OR 0.51, 95% CI 0.44 – 0.59) and a lesser frequency of lymph node positive disease (OR 0.43, 95% CI 0.32 – 0.57) (Table 13). Perineural, vascular and lymphatic invasion were more common in PDAC.

Table 13. Univariable meta-analysis of 5-year overall survival and clinicopathological variables in patients with PDAC and IPMC.

Parameters	No. of studies	IPMC (event[a])	PDAC (event[a])	Heterogeneity		Overall effect	
				I^2	P	OR (95% CI)[b]	P
Survival data							
5y-OS	10	2411 (1271)	26528 (24032)	98%	<0.001	0.23 (0.09-0.56)	0.001
5y-OS (matched)	2	108 (50)	108 (84)	68%	0.08	0.25 (0.09-0.73)	0.01
5y-OS[c]	3	860 (657)	9201 (8130)	0%	0.74	0.43 (0.36-0.51)	<0.001
5y-OS[d]	4	1426 (556)	17174 (15778)	98%	<0.001	0.17 (0.05-0.67)	0.01
PDAC vs colloid IPMC 5y-OS	3	74 (24)	1718 (1406)	44%	0.17	0.12 (0.05-0.25)	<0.001
PDAC vs tubular IPMC 5y-OS	3	162 (98)	1718 (1406)	0%	0.69	0.38 (0.26-0.54)	<0.001
Clinicopathological data							
Gender (male)	11	2520 (1339)	34613 (18418)	0%	0.54	1.06 (0.97-1.15)	0.18
Total vs partial pancreatectomy	5	2267 (290)	25839 (2285)	93%	<0.001	1.55 (1.36-1.77)	<0.001
Resection margin (positive)	5	1473 (289)	17236 (4495)	64%	0.03	0.53 (0.36-0.78)	0.001
AJCC TNM1 vs higher	7	2450 (695)	34014 (3729)	93%	<0.001	4.40 (2.71-7.15)	<0.001
Tumor grade poor vs other	2	1078 (255)	15611 (5878)	0%	0.64	0.51 (0.44-0.59)	<0.001
Lymph node spread	10	2503 (1088)	33841 (21301)	85%	<0.001	0.43 (0.32-0.57)	<0.001
Perineural invasion	3	212 (124)	1872 (1479)	83%	0.003	0.25 (0.10-0.63)	0.004
Vascular invasion	2	193 (54)	1698 (769)	0%	0.76	0.46 (0.33-0.64)	<0.001
Lymphatic invasion	2	80 (16)	744 (281)	76%	0.04	0.25 (0.03-2.08)	0.20
Adjuvant therapy							
Adjuvant therapy	6	2169 (1000)	24185 (10315)	95%	<0.001	0.67 (0.34-1.30)	0.23

AJCC, American Joint Committee on Cancer; I^2, Higgins test; IPMC, intraductal papillary mucinous neoplasm with an associated invasive carcinoma; OS, overall survival; PDAC, pancreatic ductal adenocarcinoma; TNM, tumor-node-metastasis.
[a] number of patients with the specific outcome studied [b] result of pooled analysis [c] not matched and excluding postoperative death [d] not matched and including or no report on postoperative death

Paper IV

Prior to analysis, 132 of 440 included patients were randomly assigned for validation. Ninety-nine patients (75%) had died from the disease. The ANN using variable selection, i.e. ANN model 1, had one hidden node and a weight decay of 0.01. The variables included were: age at diagnosis, T-stage 1, 3 and 4, N-stage and well differentiated grade. The corresponding regression using LASSO selected these parameters: gender, tumor size, radiotherapy, chemotherapy, N-stage, M-stage, T-stage 3 and 4 and poorly differentiated / anaplastic grade. The lambda value was 0.023. The ANN model including all variables, i.e. ANN model 2, had 8 hidden nodes and a weight decay of 0.3.

The performance of the four models was similar with respect to accuracy, precision and F1-score, i.e. approximately 82%, 0.84 and 0.88, respectively. However, ANN model 1 had a higher recall and NPV, 0.95 and 0.74, respectively, at the expense of a lower specificity of 42%. The higher specificity of the logistic regression analysis resulted in the best positive likelihood ratio (Table 14).

Table 14. Performance of the four different models used in the prediction of 5-year disease-specific survival.

	ANN model 1	ANN model 2	LASSO-model	Logistic regression
Accuracy	81.82%	81.06%	79.55%	81.06%
Precision	0.832	0.849	0.846	0.856
Recall	0.949	0.909	0.889	0.899
F1 score	0.887	0.878	0.867	0.877
NPV	0.737	0.654	0.607	0.643
Specificity	42.42%	51.52%	51.52%	54.55%
Positive LR	1.648	1.875	1.834	1.978
Negative LR	0.120	0.177	0.215	0.185
Hidden nodes	1	8	NA	NA
Weight decay	0.01	0.3	NA	NA
Lambda	NA	NA	0.023	NA

ANN, artificial neural network; LASSO, least absolute shrinkage and selection operator; NA, not applicable; NPV, negative predictive value. ANN model 1: variable selection process was carried out. ANN model 2: all twelve variables were included in the network.

Paper V

The discovery phase yielded the following ten glycoproteins: Eotaxin-2/MPIF-2, IL-17E, CD163, DKK-1, BMP-3b/GDF-10, B7-1/CD80, IL12Rβ2, PDGF-AA, DR6/TNFRSF21 and IL-R4/ST2.

CA19-9, IL-17E, B7-1 and DR6 provided the best model for discriminating PDAC from HC with an AUC of 0.974 (Table 15). The same model performed an AUC of 0.988 for the discrimination of stage 1 PDAC from HC (Figure 15, Table 15).

Table 15. Best models for pancreatic cancer versus healthy controls.

	Pancreatic cancer vs healthy controls					**Pancreatic cancer stage 1 vs healthy controls**		
Panel	AUC	Sens80 (%)	Sens90 (%)	R^2	Maxp	AUC	Sens80 (%)	Sens90 (%)
CA19-9 + IL17E + B7-1 + DR6	0.974	95.9	95.9	0.812	0.02662	0.988	100	100
CA19-9 + B7-1	0.953	91.8	91.8	0.728	0.0576	0.988	100	100
CA19-9	0.903	87.8	85.7	0.662	0.00256	0.972	100	88.9
CA19-9 + Eotaxin-2 + DR6	0.946	93.9	89.8	0.746	0.04775	0.939	88.9	88.9
IL17E + B7-1 + DR6	0.830	69.4	59.2	0.379	0.00338	0.870	77.8	55.6
Eotaxin-2 + DR6	0.704	57.1	49	0.185	0.01029	0.679	55.6	55.6

Maxp, highest individual p-value; sens80, sensitivity at 80% specificity; sens90, sensitivity at 90% specificity; AUC, area under the ROC curve.

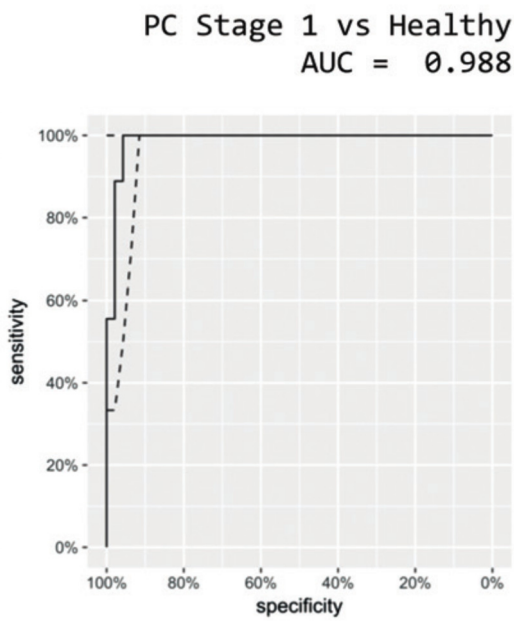


Figure 15. Glycosylation profile: CA19-9, IL-17E, B7-1 and DR6.

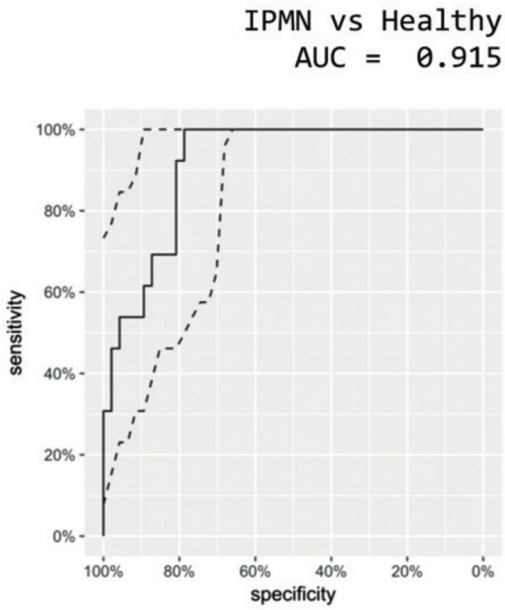


Figure 16. Glycosylation profile: CA19-9, Eotaxin-2, CD163 and BMP-3b.

CA19-9, Eotaxin-2, CD163 and BMP-3b yielded highest AUC when comparing IPMN and HC, AUC = 0.915 (Figure 16, Table 16). The same panel had a good performance for discrimination between PDAC and IPMN from HC (AUC 0.947). B7-1 alone had a higher AUC compared to CA19-9, 0.771 and 0.747 respectively. The specificity of B7-1 at 80% sensitivity was 77% compared to 38% for CA19-9. However, at 90% sensitivity the specificity was 8% for B7-1 compared to 31% for CA19-9.

For discrimination between PDAC and IPMN no model reached an AUC above 0.85; the best model had a specificity of 80% at 80% sensitivity.

Table 16. Best models for IPMN versus healthy controls.

	Pancreatic cancer and IPMN vs healthy controls					**IPMN vs healthy controls**		
Panel	AUC	Sens80 (%)	Sens90 (%)	R^2	Maxp	AUC	Sens80 (%)	Sens90 (%)
CA19-9 + Eotaxin2 + CD163 + BMP3b	0.947	95.2	83.9	0.717	0.02213	0.915	92.3	53.9
CA19-9 + B7-1	0.921	87.1	79	0.630	0.02701	0.812	69.2	38.5
B7-1	0.732	58.1	30.6	0.172	0.00694	0.771	76.9	7.7
CA19-9	0.870	77.4	74.2	0.543	0.00423	0.747	38.5	30.8

Maxp, highest individual p-value; sens80, sensitivity at 80% specificity; sens90, sensitivity at 90% specificity; AUC, area under the ROC curve.

Discussion

Aspects of surgery

The proportion of pancreatic resections performed for IPMN has been increasing in recent decades. Several different centers around the world report that the number of resections for histopathologically confirmed IPMN is approaching 10% of the total number of procedures carried out[93-98]. This seems to be true even in Sweden, as was observed in study I. During the time-period studied, 2010 – 2016, the percentage of IPMC diminished markedly. To some extent this may be explained by increased awareness and the availability of updated, widely distributed and more surgically active guidelines. The increased surgical volume on IPMN and simultaneous decreased in percentage of HDG / IPMC following the introduction of IAP 2012 and European 2013 guidelines have been observed elsewhere[274,275]. However, the degree of impact generated by the guidelines may be questioned; one study found guidelines to be poorly followed in clinical reality[276].

The decision to resect is based on the underlying nature of the lesion and the risks of surgery. The risk stratification of pancreatic lesions based on the recommendations from the current guidelines, is fairly accurate with high sensitivity; it captures most HGD and IPMC. However, specificity is still lacking as explored in the section on guidelines above. The surgeons´ concern of missing potentially resectable invasive disease or possibly curing HGD IPMN may also play an important factor. Resection at earlier stages of invasive disease is desired; the percentage of invasive component may have a survival impact[277]. In study I, 27% (n=65) and 37% (n=88) had LGD or IGD, respectively. Regardless of ductal type and other preoperative factors, surgery might be considered to be over-treatment and unnecessary. Improvements in patient selection is necessary, even though the 30-day surgical mortality was low at 1.6%, in line with larger centralized centers in the world[96,103,228].

In study I, the survival following resection was great for those with non-invasive IPMN, with a 3-year OS of 90%, irrespective of dysplastic grade. In IPMC, however, the 3-year OS was 39%. Of the IPMC in the studied cohort, approximately 4 / 10 had lymph node spread; this is in keeping with the findings in study III (43%, 1088 / 2503). Evidence points towards PDAC being a more aggressive disease, which to some degree might be a result of its elusiveness of detection; this may be

a consequence of the microscopic nature of its precursor, PanIN. However, PDAC seems to have an intrinsic aggressiveness and risk of rapid progression[278,279], evident, even clinically[280]. In study III, 62% (21301 / 33841) of PDAC had lymph node spread at resection; only about 10% had TNM-stage I compared to almost 30% of IPMC. PDAC also had significantly higher proportion of poor (lower differentiation) tumor grade, perineural and vascular invasion. The 5-year OS was undeniably better in IPMC compared to PDAC as a group. However, on qualitative analysis, the survival differences seemed to be less significant when comparing more aggressive tumors. PDAC had a worse 5-year OS even when stratifying on IPMC subtype, i.e. colloid and tubular, with the colloid subtype having the best prognosis. However, the analyses did each only include three studies. It is evident from other studies that the colloid carcinoma subtype has improved survival compared to the tubular subtype[126]. Some features on preoperative CT-imaging may be used in differentiating colloid versus tubular IPMC[281]. However, to date, this does not change the management as upfront resection is recommended when cancer is suspected.

The 5-year disease specific mortality of IPMC in study IV was 76% (336 / 440). Additionally, 17 patients (4%) succumbed to mortality from other causes during that period. The 5-year overall mortality in study III was 53% (1271 / 2411). However, the patients included in study IV had more aggressive pathological factors, such as lymph node spread in 54% compared to 43%, poorly differentiated / anaplastic tumor in 28% compared to 24%, and even metastatic spread (M-stage) in 8%. The studies included in study III were based on survival data following surgery, whereas in study IV survival was calculated from date of diagnosis, a difference in data recording. This should not, however, make a huge difference to the whole cohort, as surgery should be performed within a reasonably short time period following suspected cancer diagnosis. Unfortunately, carcinoma subtype could not be assessed in either study. The intention of investigate the impact of PDAC with and without a concomitant IPMN could not be achieved due to heterogeneity in definitions and general uncertainty. The relationship between IPMN and PDAC is an interesting topic and may even have implications in outcome[148]. The presence of a concomitant IPMN in cases with PDAC is, however, seldom presented and may be a result of current protocols or some demographic differences. From the pancreatic resection database from Lund, used in study II and V, 20% of PDAC had a concomitant, non-invasive IPMN.

Survival prediction models may assist clinicians in treatment selection, thus maximizing survival benefit. In addition, proper and uniform prediction models can be used to facilitate more accurate enrolment in clinical trials. Study IV showed good performance with ANN and LASSO on survival prediction in IPMC. The twelve variables included are generally used and easily assessable, which is an important factor in constructing clinically useful models as well as facilitating

validation on other patient cohorts. The models did perform similarly, with ANN model 1, inclusive of all variables, being the optimal model with respect to recall and NPV. It was interesting to see that the ANN model 1 and LASSO, both of which had a reduced number of variables through selection processes, did not suffer in performance. Minimizing need for redundant data is important when creating models for clinical application. The resection margin status could not be assessed from the SEER database, an important consideration for future prediction models[145].

Methodological considerations

The relatively short time-period studied (2010-2016) in study I, together with the lack of information regarding surgical decision, makes it hard to draw precise conclusions. Biases in data collection must be acknowledged; this is a retrospective analysis of a large database with several different contributors from all over Sweden. However, systematic negligence in reporting surgeries performed with a histopathological outcome of IPMN seems unlikely. Equivalent limitations exist for study IV. However, when studying relatively rare diseases, these large databases play an important contribution in initial investigation.

Survival data was limited to OS in study I and DSS would have better stratified underlying cause. In study IV, mortality was over-represented by cancer specific etiologies; only a minority died of other causes (76% versus 4%). In non-invasive IPMN in study I, excluding 1% due to presumed surgical complications (30-day mortality), a 9% mortality was observed during a 3-year period. This was most likely due to causes unrelated to pancreatic disease as recurrence of non-invasive IPMN or development of metachronous invasive cancer following partial pancreatectomy is low within this time frame[146,282]. There was no difference in survival between dysplastic grades in our cohort. However, others have found dysplastic grade (HGD) to impact recurrence[64]. HGD IPMN are in the AGA, ACG and European 2018 guidelines managed with closer postoperative surveillance compared to other non-invasive IPMN[15,166,177].

Several of the pooled analyses in study III had a moderate to high heterogeneity. This was most likely owing to different demographics, health care systems and hospital volume. All included studies ensured a histopathological confirmed diagnosis of IPMC or PDAC and so the correct underlying cause of heterogeneity would probably not impact the results of the primary outcome, i.e. survival. Further investigation on heterogeneity is feasible and should be carried out when comparing therapeutic interventions and randomized controlled trials.

Aspects of health economy

Advancements in imaging technology and its widespread usage have resulted in an increased incidental detection of pancreatic cysts, closing the gap towards the prevalence seen in autopsy series. Together with an aging and healthier population, this results in an increase in the number of cystic lesions being included in surveillance programs, which has been observed during the recent decade[283]. Presumed IPMN seems to represent the majority of these cystic lesions[79] and in accordance with the above discussion, pancreatic resections of IPMN increase. This increased incidence has, however, not translated into decreased disease-related mortality in IPMN or pancreatic cancer[284,285].

The health-economic aspect considers both the patients well-being and societies resources. The literature is, to date, scarce with regard to studies evaluating QoL and cost-effectiveness on IPMN management, despite high demand for information.

In study II, a health-economic model was used to evaluate management options in a presumed low-risk IPMN, which according to the above chapter on prevalence is the most likely diagnosis to increase. Initial surveillance, i.e. strategy III, was the most cost-effective, ICER €31,682 per QALY, in comparison to a "wait and see" strategy or the two upfront surgical options of partial pancreatectomy or TP. The total cost of strategy III was €26,305. When the risk of misdiagnosis was eliminated, (the base model did include a 10% misdiagnosis of a completely benign PCL and 5% of a cancerous lesion), the cost increased to €28,128. However, so did the QALY (9.57) with a decreasing ICER (€30,146 per QALY) compared to the "wait and see" strategy. This indicates a high cost even with a correct preoperative diagnosis.

A cost-effective model on BD-IPMN in the Sendai era found an ICER of $20,096 (costs converted to 2008 US $) for surveillance compared to a no-surveillance strategy[184]. Direct comparison between this study and study II is not possible. However, a surveillance strategy seems to be the best option. Another group found that initial EUS-FNA for risk stratification on asymptomatic pancreatic cystic neoplasms was the most cost-effective strategy[185]. In a study from 2005, the actual cost of radiographic and endoscopic procedures in some 60 patients with cystic pancreatic tumors was estimated to be $8080 per patient[286]. These numbers are concerning considering the increasing numbers of patients with PCL and presumed BD-IPMN. However, it is unreasonable to completely abandon surveillance strategies as a majority of patients undergoing surveillance will, owing to progression of the index cyst, be recommended to undergo surgery[20,52,102,103]. Improvements in specificity is, however, necessary as only 10 – 50% have HGD or IPMC on histopathological evaluation following surgery[97,102,103]. The actual rate of "unnecessary" resections and consequently unnecessary risks are hard to elicit but may, based on the above figures, represent a considerable proportion. A resource-

related aspect, that is infrequently discussed, is the availability of surgery, i.e. surgeon, surgical personnel, operating room, surgical ward for pre- and postoperative care, and possibility of crowding out other operations. It may be difficult to study, but has unquestionably a clinical implication as pancreatic surgeons, surgical wards et cetera are limited resources.

The incremental life years between initial surveillance and watchful waiting was 0.9 years (13.4 versus 12.5) in our model. Another study modelling follow-up as opposed to no follow-up in BD-IPMN, concluded a life-expectancy benefit of 6.4 and 5.3 months in men and women, respectively aged 60 and without comorbidities. The life expectancy benefit did drastically decrease with increasing age and comorbidities[287]. Patients with severe comorbidities may not benefit from surveillance, owing to their increased risk of death from causes unrelated to the IPMN[288].

QoL has only been investigated in a few studies. In one series QoL was not affected during surveillance of BD-IPMN[289]. When comparing 16 patients undergoing prophylactic surgery with 16 receiving surveillance, no difference in QoL or anxiety was observed[290]. A recent study of matched patients, i.e. 74 patients with a presumed IPMN undergoing surveillance versus 74 that had undergone surgery, did however find that those undergoing surveillance experience more anxiety, stress and reduced QoL[291]. This comparison might be questioned, although it is unsurprising to find that patient awareness of a precancerous pancreatic lesion causes anxiety. Modelling on management strategies to optimize QALY has been performed for BD-IPMN with WF, with early resection out-competing surveillance in patients with long life expectancy, i.e. >18 years, low surgical mortality and good preoperative HU (>0.78)[292]. A "do nothing" approach yielded the best quality-adjusted survival in smaller (<3 cm) presumed BD-IPMN in patients <75 years old, whereas initial surgery out-competed the other strategies in cysts ≥2 cm[293]. Study II indicated that upfront surgery and, in our model, specifically TP, might be considered in younger patients where the risk of metachronous PDAC is increased. The annual risk to be considered in the model was a risk greater than 1.9%. At present an accurate percentage is impossible to acquire. According to the current guidelines a TP might be considered in high risk patients with multifocal high risk lesions or MPD dilatation of the entire pancreas[14,15].

The rigorous surveillance strategies of the guidelines appear to result in improved outcome and cost-effectiveness within acceptable limits, usually a WTP between €50 – 100,000 per QALY. Following the introduction of the 2013 European guidelines, an increase in the use of MRI and endoscopy has been seen in Norway[274]. Considering health care resources available, improved strategies are needed to decrease the cost per patient. Optimal usage of imaging technologies is also warranted to not waste resources. To achieve this, some studies have investigated

the possibility of shorter MRI protocols[294,295], ultrasonography-based surveillance[296] and increased interval length between follow-up for selected patients[297]. Large prospective clinical trials evaluating surveillance of pancreatic cysts with the aim of structuring improved, tailored surveillance strategies and thus greater cost-effectiveness, are ongoing[298]. The guidelines should derive the best recommendations possible, theoretically yielding the best patient outcomes. However, tailored strategies may be used in less resourceful countries and regions or where different welfare systems are applied, making adherence difficult. This aspect is only discussed in the AIGO/AISP guidelines[176].

Methodological considerations

Modelling reality is cumbersome and there is a fine balance between simplicity and accuracy. Too much detail may interfere with the interpretation and hamper generalization whilst too crude a model may impair precision.

In sensitivity analysis changes of included parameters in study II yielded different results as described. However, the results must be interpreted with caution as the uncertainty of the model is increased by altering factors and relevant information for correct interpretation may be lacking. For example, when changing the starting age to 40 years instead of 65 as in the index case, changes in health utility were made appropriately, however, loss of productivity must the added for a reliable result.

In our model, an otherwise healthy 65-year old patient was considered. A different approach has to be adopted in those with substantial co-morbidities and thus increased risks of undergoing pancreatic surgery. The aforementioned study concluded a very low life-expectancy benefit in surveillance of BD-IPMN in older patients with severe comorbidities[287]. The surveillance is however, recommended to be discontinued if the patient becomes unfit for surgery. In our model, no specific modelling on acquiring co-morbidities or frailty risks was performed. We instead used a cut-off of 80 years to simulate an average limit.

The 5-year cancer mortality in strategy III, initial surveillance, was 6.9% in the index case compared to 3.3% when no misdiagnosis was incorporated into the model. The corresponding values for strategy IV, watchful waiting, were 8.8% and 5.4%, respectively. These numbers are in line with several real case studies[57-59]. However, there is a somewhat substantial interstudy variability. A holistic view must be held incorporating the risks of the pancreatic lesion, risks of surgery and existing co-morbidities.

The perceived risk of DM following pancreatectomy varies in the literature. One study actually found no difference in incidence and prevalence of DM in resected IPMN compared to those undergoing surveillance[299]. However, our model did not consider existing diabetes and the tornado sensitivity analysis included a zero risk

of DM following partial pancreatectomy, which was not highlighted as having substantial impact on cost-effectiveness.

The surveillance schedule was similar to the Swedish recommendations, which are themselves based on the European guidelines. Intensified surveillance following 5 years was deliberately not modelled as the exact impact of this is uncertain; there is a lack of quality evidence for this strategy even though the rationale may be appropriate. Additionally, this recommendation is not included in the updated 2018 version of the European guidelines[15].

Aspects of biomarkers

PDAC is one of the most lethal cancers, and it is projected to become the second leading cause of cancer-related death[300]. IPMN is often referred to as a precursor to pancreatic cancer and thus presents an opportunity of finding and treating it before malignant transformation occurs, or at least at early stages[301]. Study III demonstrates that an improved survival is seen in invasive IPMN if diagnosed early or if of colloid subtype. However, there is also the issue of an increased risk of metachronous PDAC in patients with IPMN. Tailored management can, in the future, be applied if patients with particularly high risk can be distinguish from those with low risk.

The current guidelines are fairly accurate but lack specificity; changes with altering cut-offs are suggested[302,303], which may improve them further. More accurate stratification of MD-IPMN may even be warranted. Some patients may be better suited to receive surveillance, thus avoiding unnecessary upfront pancreatic surgery. However, high hopes are placed on the potential assistance of biomarkers in clinical decision making regarding IPMN, to provide much-needed improved specificity and to offer confidence in surveillance strategies.

In this thesis there was a focus on serum glycoproteins. However, biomarker research on IPMN includes assessment of DNA-alterations, proteomics, immune-response related factors / cells, miRNA, incRNA and metabolomics. Samples are derived from various sources, including saliva, cyst fluid, pancreatic juice, blood, and tissue[304]. The glycome and glycoproteome present important possibilities in oncology research; changes in glycosylation have been linked to all phases of tumorigenesis[211,212]. Studies investigating glycoproteins and glycosylation have been performed on cyst fluid to improve preoperative diagnosis of pancreatic cysts[305,306]. Research relating to use of serum glycoproteins in IPMN has been highly constrained to CA19-9 and CEA[169].

Currently, the primarily used serum biomarker is CA19-9. In study I, the only predictable covariate for invasive disease was biliary obstruction, which when

present indicates the need for resection[14,15]. CA19-9 was not a strong predictor in this study. However, one third (5 / 15) of those with invasive disease and complete data available for review, had serum CA19-9 ≥37 U/mL; logistic regression following imputation showed OR 2.4 (95% CI 0.9 – 6.6).

In study V, serum CA19-9 had an AUC of 0.90 when comparing PDAC with HC, and an AUC of 0.87 when differentiating between PDAC and IPMN versus HC. The aim of study V was differentiation between PDAC, IPMN and HC. Ten out of 1000 glycoprotein in an initial discovery phase were selected to comprise biomarker panels with and without serum CA19-9. Serum CA19-9 was measured as routinely performed in the clinic, whilst the method investigating the other glycoproteins assessed the degree of glycosylation. Several promising panels were created. The best panel discrimination between IPMN and HC consisted of CA19-9, Eotaxin-2, CD 163 and BMP3b; this had an AUC of 0.91 with 92% sensitivity at 80% specificity. The same panel scored an AUC of 0.95 and offered 95% specificity at 80% sensitivity when comparing PDAC and IPMN with HC. The glycoprotein B7-1 (CD80), which has been investigated in PDAC[307,308] but not IPMN, had an improved performance compared to CA19-9 in discriminating IPMN with HC, giving rise to AUC of 0.77 and 0.75, respectively. At 90% sensitivity, the specificity was extremely low for both, especially B7-1 (8 and 31%, respectively). The combination of the two had some additional effect on the AUC.

According to the findings in study V, glycosylation levels merit further investigation. They have the potential to assist in preoperative clinical management, especially to distinguish between patients with cancerous lesions and healthy individuals.

In addition to supporting preoperative clinical decision making, biomarkers may also become a useful diagnostic adjunct during postoperative follow-up, and offer the ability to highlight those patients with increased risk of recurrence or metachronous cancer. Prospective biomarker research is ongoing[203] and some interesting results have been found evaluating the assistance of biomarkers in risk stratification[309].

Methodological considerations

The method measured the relative, i.e. semi-quantitative, glycosylation levels of serum proteins, rather than altered glycans or protein titer. This may be the reason why serum CA19-9, which is included in the glycosylation protein profile (RayBio ® human glycosylation antibody array 1000), was not singled out as one of the top 10 biomarkers from the discovery phase. Quantitative analysis can, however, be performed with antibody arrays, e.g. the assay used in clinical practice for serum CA19-9 measurement. Orthogonal methods, not dependent on antibodies, such as mass spectrometry have the power to investigate both qualitatively and

quantitatively the exact post-translational alteration in the glycosylation and can therefore quantify glycoprotein levels[197].

The results from study V are encouraging with biomarker panels reaching high AUC values even with restriction to four biomarkers, i.e. CA19-9 and three other glycoproteins. However, further trials and validation are needed in order to achieve clinically useful cut-offs or nomograms to predict underlying diagnosis. Only IPMN patients were included; no other pancreatic cystic lesions were assessed which limits conclusions. Since additional pathologies may be present, e.g. diabetes[310], use of biomarkers in larger cohorts with emphasis on underlying conditions and co-morbidities also needs to be addressed.

Conclusion

The major conclusions from the included studies are detailed below.

I. Pancreatic resections for IPMN represent approximately 10% of the total number of pancreatic resections. The majority of IPMN-related resections are performed on non-invasive disease. The 3-year survival following surgery for a non-invasive IPMN is excellent; no difference was found between the dysplastic grades. For invasive disease (IPMC) survival is severely impacted, especially in lymph node positive disease. Biliary obstruction is associated with invasive disease.

II. In accordance with published guidelines, for a patient with suspected low-risk BD-IPMN, initial surveillance seems to be the most cost-effective strategy in comparison to upfront surgery or watchful waiting. Compared to watchful waiting, surveillance had an ICER of €31,682 per QALY.

III. As a group, IPMC have an improved 5-year OS compared to PDAC following surgery. The tubular subtype of IPMC is more aggressive compared to the colloid subtype, each type compared with PDAC. Surgery at earlier disease stages seems to be part of this difference as the survival between IPMC and PDAC is similar at higher TNM-stages.

IV. Models with ANN and LASSO achieve high accuracy in predicting long-term survival following resection for invasive IPMN, even with a limited set of variables.

V. Panels of serum glycoproteins can be used as an adjunct for the discrimination of PDAC, IPMN and HC.

Future perspectives

The research on IPMN has undergone a remarkable shift in priority during the last decade, thus increasing knowledge and understanding of this disease entity. The field is considered by some to be chaotic as several different guidelines and approaches exist. Numerous topics are still the subjects of ongoing debates and even controversies. Advances in readily available cross-sectional imaging techniques and consequent improved diagnostic sensitivity, have given rise to increased incidental discoveries of pancreatic cysts, with presumed IPMN being common. This has resulted in a shift towards increasing proportions of resections being performed on IPMN, with the majority being non-invasive. This trend is possibly influenced by the present guidelines, which lacks specificity, a development supported by study I. It is not well defined as to what degree this has influenced the mortality associated with invasive disease. The rational for resection is possibly influenced by the knowledge that excellent postoperative mortality is associated with a non-invasive IPMN, even in HGD, compared to invasive disease. If cancerous changes have already occurred, resection at early stages still offers an improved survival as seen in study I and III.

The low mortality of surgical resection seen in study I (<2%) is due to modernization and possibly specialty centralization. The morbidity, however, is still relatively high. Both mortality and morbidity need to be balanced against the risks associated with the pancreatic lesion in question. Although not directly investigated in this thesis, further studies on MD-IPMN to evaluate risk stratification are warranted to avoid unnecessary resection. Initial surveillance seems to be the optimal cost-effective option in those with presumed low-risk IPMN, as demonstrated in study II. However, modifications of surveillance strategies are needed to further decrease costs. Further work focusing on the quality of life is required, as the number of patients included in surveillance strategies will presumably increase.

Non-invasive and invasive IPMN are a heterogenous group with outcomes influenced by the underlying genetic and morphological subgroups. Invasive IPMN have a generally improved postoperative survival compared to PDAC (study III). This may stem from a combination of tumor biology and earlier detection. Following resection, ANN and LASSO provide solid methods for the prediction of survival (study IV). Prediction models can provide additional information with

respect to management options and prognosis estimation, benefiting both clinicians and patients.

It is debatable whether biomarkers will be the panacea for IPMN management in the near future considering challenges in biomarker development and the rigorous validation that is necessary before clinical implementation. However, one day the addition of biomarkers will surely be a valuable adjunct to support clinical decision and to improve and tailor management strategies. Study V showed the feasibility of glycosylation panels with high discriminatory values to distinguish between different health and disease states. The addition of biomarkers to sophisticated models like ANN and LASSO can enhance predictive and prognostic models.

The aim of this thesis was to increase the knowledge on IPMN with a broad focus on clinical management, health economy and biomarkers. The five included studies have presented valuable research contributions to the larger context of improved care of patients with IPMN.

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