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# INVASIVE INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM AND PANCREATIC DUCTAL ADENOCARCINOMA

## A COMPARISON IN CLINICOPATHOLOGY AND LONG-TERM OUTCOME

Marcus Holmberg

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# INVASIVE INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM AND PANCREATIC DUCTAL ADENOCARCINOMA – A COMPARISON IN CLINICOPATHOLOGY AND LONG-TERM OUTCOME

## THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

**Marcus Holmberg**

The thesis will be defended in public at B64, Karolinska Universitetssjukhuset, Huddinge, Friday September 30th, at 09:00

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*To Bruno, Otto, and Pilar*

# POPULAR SCIENCE SUMMARY OF THE THESIS

Pancreatic ductal adenocarcinoma (PDAC) is one of deadliest cancers there is, only one in five survive five years after surgery and chemotherapy. The main reason is early and aggressive relapse and heterogeneity among tumours that evade current rather narrow chemotherapy. A deeper understanding of the differences and the variants of PDAC will facilitate prognosticating relapses and hopefully personalize adequate treatment. One such variant is invasive Intraductal Papillary Mucinous Neoplasm (inv-IPMN).

This thesis aims to take the first steps in improving the understanding of the similarities and differences that exist between inv-IPMN and conventional PDAC in order to improve long-term outcome for these tumour groups.

The thesis is based on four studies. *Study I* and *study IV* that compared the survival outcomes after pancreas operation between inv-IPMN and conventional PDAC from a regional and national perspective respectively. *Study II* assessed on a regional level the prognostic impact of one type of lymph node station (PALN) that is believed to be a negatively associated with survival. *Study III* explored the impact of initial recurrence pattern on survival for inv-IPMN and conventional PDAC on a regional level.

*Study I* included 513 patients, 122 inv-IPMN and 391 PDAC. Inv-IPMN had more favourable survival compared to PDAC.

*Study II* included 403 patients, 89 inv-IPMN and 314 PDAC. PALN were metastatic equally often between tumour groups. PALN was not as negative as previously believed.

*Study III* included 396 patients, 92 inv-IPMN and 304 PDAC. Both recurrence rate and death rate within three-years were lower for inv-IPMN compared to PDAC. Adjuvant chemotherapy had similar effect in the two groups.

*Study IV* included 1909 patients, 293 inv-IPMN and 1616 PDAC. Inv-IPMN had more favourable survival compared to PDAC, in later years and in earlier, less advanced tumours. For other tumours survival was similar.

This thesis can therefore conclude that inv-IPMN seemed to have favourable survival outcome compared to PDAC in earlier less advanced tumours, and similar in more advanced. PALN status does not influence survival as much as previously believed. Inv-IPMN exhibited less aggressive recurrences.

# ABSTRACT

**Background:** The resections for both pre-malignant and invasive intraductal papillary mucinous neoplasm (inv-IPMN) have increased the last decades. Long term outcome, and the impact of adjuvant chemotherapy, non-regional lymph node status and recurrence pattern on overall survival (OS) is known for conventional pancreatic ductal adenocarcinoma (PDAC), but not so for inv-IPMN.

**Aims:** I) Investigate differences and similarities in clinicopathology and overall survival between patients resected for inv-IPMN and PDAC. II) Elucidate whether the raised numbers of pancreatic resections for inv-IPMN in combination with the improvement in OS recent years have influenced outcome. III) Assess the prognostic significance of para-aortal lymph node (PALN) involvement in patients resected for inv-IPMN and PDAC in the pancreatic head**.** IV) Explore the impact of adjuvant chemotherapy and spatio-temporal recurrence pattern on overall survival for inv-IPMN compared with PDAC.

**Methods:** All studies were retrospective observational studies of consecutive patients ≥ 18 years of age resected for inv-IPMN and PDAC. *Study I-III* were single-centre studies of in total 515 patients resected at Karolinska University Hospital between 2009-2018, *Study IV* was a national multi-centre study of patients resected in Sweden between 2010–2019. Clinicopathological variables were analysed in multivariable Cox regression models. Outcome was assessed by calculating two- or three-year OS rate and estimating OS using the Kaplan-Meier model. Survival functions were compared with log-rank test.

In *study I* were clinicopathological variables also analysed in multivariable logistic regression models. *Study II* only comprised patients with PDAC or inv-IPMN in the pancreatic head who underwent partial or total pancreatoduodenectomy including PALN resection. In *study III*, that only included patients residing in the Stockholm area, different initial recurrence sites and time frames as well as predictors for death including the impact of adjuvant chemotherapy were assessed with multivariable logistic and Cox regressions. In *study IV*, clinicopathological variables were retrieved from the Swedish national pancreatic and periampullary cancer registry. The effect on death was assessed in two multivariable Cox regression models, one for patients resected 2010-2015, one for patients resected 2016-2019.

**Results:** In *study I*, 513 patients were included, 122 inv-IPMN and 391 PDAC. The proportion resected inv-IPMN and two-year OS increased during the study period. In Kaplan-Meier survival analysis, inv-IPMN had more favourable median OS compared to PDAC. In multivariable Cox Regression analysis, tumour type was not a predictor for death.

In *study II*, 403 patients were included, 89 inv-IPMN and 314 PDAC. PALN were metastatic in 16% and there was no difference between the groups. N0- and N2-stage were present in 16% and 53% respectively for patients with inv-IPMN compared to 6% and 65% respectively for patients with PDAC (p=0.007). Median OS was 12.7 and 22.7 months in the presence or absence of PALN metastases respectively (p<0.001), and similar in N2-stage regardless the presence of PALN status. PALN status was not an independent prognostic factor.

In *study III*, 396 patients were included, 92 inv-IPMN and 304 PDAC. Both recurrence rate and death rate within three-years were lower for inv-IPMN compared to PDAC. The most common recurrence patterns were multi-site (25%), single-site liver (21%) and single-site locoregional (10%) recurrence. The most important predictors for death were multi-site, single-site peritoneal and single-site liver recurrence. These predictors were less common in inv-IPMN compared to PDAC. Adjuvant chemotherapy had similar effect in the two groups.

In *study IV*, 1909 patients were included, 293 inv-IPMN and 1616 PDAC. Tumour type was an independent predictor for death in the 2016-2019 cohort, but not in the 2010-2015 cohort. In Kaplan-Meier survival analysis, inv-IPMN was associated with longer median OS in stage N0-1 and in stage M0 compared to PDAC. However, in stage T2-4 and stage N2 median OS was similar, whereas median OS in stage M1 was even shorter for inv-IPMN compared to PDAC.

**Conclusions:**
Inv-IPMN seemed to have favourable survival outcome compared to PDAC in lower stages, and similar to worse in higher.
Outcome was dependent on the combination of a pronounced increase in resected inv-IPMN and a concurrent hazard reduction for death within 2 years during the study period.
PALN status is not an independent risk factor for death and does not influence survival in N2-staged disease. The M1-stage for PALN positivity may therefore need reconsideration.
Resected inv-IPMN exhibited a less aggressive recurrence pattern than PDAC that translated into a more favourable overall survival.

# LIST OF SCIENTIFIC PAPERS

I. **Outcome after resection for invasive intraductal papillary mucinous neoplasia is similar to conventional pancreatic ductal adenocarcinoma.**
Holmberg, M.; Ghorbani, P.; Gilg, S.; Del Chiaro, M.; Arnelo, U.; Löhr, J-M., Sparrelid, E. Pancreatology. 2021;21(7):1371-7

II. **Prognostic impact of para-aortic lymph node status in resected pancreatic ductal adenocarcinoma and invasive intraductal papillary mucinous neoplasm – Time to consider a reclassification?**
Linder S.; Holmberg, M.; Engstrand, J.; Ghorbani, P.; Sparrelid, E. Surg Oncol 2022; 41:101735

III. **Impact of initial recurrence pattern on overall survival for intraductal papillary mucinous neoplasia – a comparison with conventional pancreatic ductal adenocarcinoma.**
Holmberg, M.; Kordes, M.; Liljefors M.; Ghorbani, P.; Löhr, J-M.; Sparrelid, E. Pancreatology 2022;22(5):598-607

IV. **Outcome after resection for invasive intraductal papillary mucinous neoplasia compared to conventional pancreatic ductal adenocarcinoma – a nationwide study from Sweden.**
Holmberg, M.; Radkiewicz, C.; Strömberg C.; Öman M.; Ghorbani, P.; Löhr, J-M.; Sparrelid, E. Submitted manuscript

# CONTENTS

# LIST OF ABBREVIATIONS

| | |
|---|---|
| ACG | American College of Gastroenterology |
| AGA | American Gastroenterology Association |
| AJCC | American Joint Committee on Cancer |
| ASA | American Society of Anesthesiologists |
| BRCA | Breast cancer susceptibility gene (i.e., BRCA1 and BRCA2) |
| CA19-9 | Carbohydrate antigen 19-9 |
| CA125 | Carbohydrate antigen 125 |
| Cap | Capecitabine |
| CEA | Carcinoembryonic antigen |
| CI | Confidence interval |
| CK | Cytokeratin (i.e. CK7, CK19, CK18 and CK20) |
| CKN | Cyclin dependent kinase inhibitor (i.e. CKN1A and CKN2A) |
| CRP | C-reactive protein |
| CT | Computerized tomography |
| DFS | Disease-free survival |
| E | Units (for example, kE/l) |
| EPN | Etikprövningsmyndigheten – the Swedish authority for ethical approval |
| FOLFIRINOX | Multicombination of folinic acid (FOL), fluorouracil (F), irinotecan (IRIN) and oxaliplatin (OX) |
| Gem | Gemcitabine |
| Gem-comb | Gemcitabine in combination with other chemotherapy |
| GNAS | Guanine nucleotide binding protein gene |
| HR | Hazard ratio |
| IAP | International Association of Pancreatology |
| Inv-IPMN | Invasive intraductal papillary mucinous neoplasm |
| IPMN | Intraductal papillary mucinous neoplasm |
| IQR | Interquartile range |
| KRAS | Kirsten rat sarcoma virus gene |
| L | Lymphovascular invasion (i.e. L0 and L1) |
| LN | Lymph node |
| LNR | Lymph node ratio |
| M | Metastases stage |
| MCN | Mucinous cystic neoplasm |
| MRI | Magnetic Resonance Imaging |
| MUC | Mucin proteins (i.e. MUC1, MUC4 and MUC5AC) |

| | |
|---|---|
| N | Lymph node stage (i.e. N0, N1 and N2) |
| NEC | Neuroendocrine carcinoma |
| NET | Neuroendocrine tumours |
| OR | Odds ratio |
| OS | Overall survival |
| Pac | Paclitaxel |
| PALN | Para-aortal lymph nodes |
| PanIN | Pancreatic intraepithelial neoplasia |
| PARP | Poly ADP-ribose polymerase |
| PCN | Pancreatic cystic neoplasms |
| PDAC | Pancreatic ductal adenocarcinoma, conventional |
| Pn | Perineural invasion (i.e. Pn0 and Pn1) |
| PRIME | Pathway inhibitors, Repair, Immunotherapy, Metabolism, Extracellular matrix |
| PP | Pancreatic pseudocyst |
| R | Surgical margin (i.e. R0 and R1) |
| SCN | Serous cystic neoplasm |
| SMAD4 | Mothers against decapentaplegic homolog 4 |
| SPPN | Solid pseudopapillary neoplasia |
| T | Tumour stage (i.e. T1, T2, T3 and T4) |
| TNM | Tumour, Nodes, Metastasis; TNM-classification of malignant tumours |
| TP53 | Tumour protein 53 |
| V | Microvascular invasion (i.e. V0 and V1) |
| WHO | World Health Organisation |

# 1 INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is one of deadliest cancers, only one in five survive five years after surgery and chemotherapy (1). The main reason is early and aggressive relapse and extensive tumour heterogeneity that evades current medical treatment (2, 3). A deeper understanding of the inherent differences in tumour biology of PDAC will facilitate prognosticating relapses and personalizing adequate treatment (4).

This thesis aims to take the first steps in improving the understanding of the similarities and differences that exist between inv-IPMN and conventional PDAC in order to ameliorate long-term outcome for these tumour groups.

The thesis is based on four studies. *Study I* and *study IV* compared the survival outcomes after resection between inv-IPMN and conventional PDAC from a regional and national perspective respectively. *Study II* assessed the prognostic impact of PALN involvement in inv-IPMN and conventional PDAC on a regional level. *Study III* explored the impact of initial recurrence pattern on overall survival for inv-IPMN and conventional PDAC on a regional level.

# 2 LITERATURE REVIEW

## 2.1 THE PANCREAS

The pancreas is a gland in the retroperitoneal part of the upper abdomen that has exocrine and endocrine functions, both vital for health and life. The exocrine component is crucial for proper alimentation as the produced pancreatic juice contains proteo-, lipo- and carbolytic digestive enzymes. The endocrine component regulates appetite and blood glucose homeostasis by secernating insulin and glucagon, thus decreasing and increasing glucose levels respectively.

The pancreas is anatomically subdivided into the head, uncinate process, neck, body and tail. Dispersed throughout the entire gland runs a duct system consisting of several small branch ducts and a main pancreatic duct that passes through the whole gland from tail to head. Downstream in the head, it merges with the common bile duct and terminates at the major papilla in the duodenal wall, facilitating secretion of the produced pancreatic juice to the duodenum. Also dispersed throughout the entire gland are isolated islets of cells of Langerhans, responsible for the endocrine function, secernating the hormones directly to the blood stream.

Several benign, pre-malignant and malignant lesions may manifest themselves in the pancreas. The most common and important solid and cystic neoplasms are presented below.

### 2.1.1 Solid neoplasms in the pancreas

Solid neoplasms encountered in the pancreas are usually malignant, although some benign conditions such as chronic pancreatitis, autoimmune pancreatitis, accessory spleen may mimic a cancerous lesion.

PDAC is by far the most common neoplasm in the pancreas and comprises 90% of all and 85% of all malignant encountered lesions in the pancreas (1). It is presented more in detail below.

Neuroendocrine neoplasms is a group of malignant tumours that encompasses neuroendocrine tumours (NET), neuroendocrine carcinoma (NEC) and other hormonally active neoplasms such as gastrinoma, glucagonoma, insulinoma, somatostatinoma and vipoma (5). It is much rarer and only constitute 5% of the malignant pancreatic lesions (1).

Other occasional encounters in the pancreas are mesenchymal neoplasms and metastases (renal, malignant melanoma).

### 2.1.2 Pancreatic cystic neoplasms

Pancreatic cystic neoplasms (PCN) comprise a wide spectrum of epithelial or non-epithelial, serous or mucinous cystic lesions with different biological behaviours and risks of malignant progression (6).

Intraductal papillary mucinous neoplasm (IPMN) is an epithelial neoplastic lesion that arises from the cells lining the pancreatic ducts. It produces excessive amounts of glycosylated proteins (mucin) causing the pancreatic duct(s) to dilate (7). It is the most common PCN and has invasive potential .

Mucinous cystic neoplasm (MCN) is also an epithelial lesion but have no communication with the pancreatic duct(s). It is usually located in the body or tail of the pancreas and almost always occurs in middle aged women. 25% of MCN are found incidentally and around 10-40% transform to invasive carcinoma (6). They are surveilled and treated in a very similar way as IPMN.

Serous cystic neoplasm (SCN) is a benign epithelial lesion that contrary to IPMN and MCN contain a serous secretion. Like MCN's there is no connection with the pancreatic main duct and women are overrepresented, usually in their 60:ies. Invasive disease is only anecdotal, but the disease may become multifocal.

Cystic pancreatic neuroendocrine tumour is more rare and usually non-functional compared to its solid counterpart. 10% become invasive (6).

Solid pseudopapillary neoplasia (SPPN) is a rare epithelial tumour of low malignant potential that accounts for 1-2% of the exocrine malignancies and usually affects younger women. It is characterized by cystic and solid areas with cells arranged in a pseudopapillary way.

Contrary to abovementioned true cysts, pancreatic pseudocysts (PP) lack inner lining cells and occur as a late complication of acute pancreatitis, manifested by amylase-rich aspirate if punction is undertaken. Symptomatic PP may need to be drained (trans-abdominally and/or trans-gastric) but surgery is rarely indicated. However, sometimes PP has been interpreted as an IPMN or MCN and revealed first on post-operative pathology report.

## 2.2 PANCREATIC DUCTAL ADENOCARCINOMA

PDAC is an intractable malignancy with a five-year OS of 5-10% (8), mainly due to late onset of symptoms and advanced stage at diagnosis combined with resistance to treatment (9) and high rate of relapse after successful surgical resection (10). Even after curatively intended resection and adjuvant chemotherapy five-year OS is as low as 15-20% (11). As such, it is one of the deadliest cancer forms and it is projected to become the second most common cause for cancer related death in 2030 (12).

### 2.2.2 Epidemiology, aetiology and risk factors

#### *2.2.2.1 Epidemiology*

Worldwide, nearly half a million new cases of PDAC are diagnosed annually (13) and in Sweden the number is around 1,200. It is responsible for 5% of all cancer deaths and 22% of all gastrointestinal cancer deaths. It is a malignancy of the elderly and 80% of the cases occur after the age of 60. The median age is 71 years (13).

Europe and North America have the highest age-standardized rate (ASR) incidence with just above 7,5 per 100 000 and it is slightly more common in men than in women 5,5 versus 4,0 per 100 000 (1). It is seldom diagnosed before 55 years of age and the highest incidence is reported in people over 70 years. Regardless of gender and to a certain extent age, the observed incidence and mortality rates of pancreatic cancer tend to increase (1).

The aetiology of pancreatic cancer has been extensively studied and several risk factors have been identified (1), modifiable and non-modifiable.

#### *2.2.2.2 Modifiable risk factors*

*Smoking* represents the most important environmental factor for PDAC and the risk in smokers is nearly twice as high compared to non-smokers. The risk is proportional to the duration of smoking and the daily numbers of cigarettes smoked. High *alcohol* consumption (liquor, but not beer and wine) is undoubtedly also associated with pancreatic cancer, but the effect seem to be heavily modified by smoking (1).

*Obesity* (body mass index $\geq$ 30 kg/m$^2$), *physical inactivity* and *new onset diabetes* are associated with increased risk for PDAC (13). Also, *dietary factors* impact the development of pancreatic cancer. Certain foods, such as red and/or processed meat, are associated at higher risk, while others such as nuts, vegetables, and fruits, seem to have protective actions. *Exposure* to the carcinogenics Cadmium, Arsenic and Nickel increase the risk for pancreatic cancer.

#### *2.2.2.3 Non-modifiable risk factors.*

As described above *age* and *gender* are risk factors, direct or indirectly. *Familial history* with two or three first grade relatives with PDAC gives a 6 and 30 times (14) higher risk respectively for developing PDAC and it is estimated that 5-10% of all PDAC has an *inherited* component (8). Some hereditary syndromes have been identified (hereditary non-polyposis colorectal cancer, familial breast cancer, familial atypical multiple mole melanoma, hereditary pancreatitis, ataxia-telangiectasia, Peutz-Jeghers syndrome, Lynch syndrome). *Chronic pancreatitis*, hereditary or not, increases the lifetime risk for developing PDAC.

### 2.2.3 Morphology and grading

At diagnosis, PDAC is usually between 2–4 cm and located in the pancreatic head (60-70%) (14) where it can obstruct the common bile duct and cause painless jaundice (5). Involvement of the pancreatic body or tail occurs in 20-25% of the cases (14) and since associated symptoms are less common in this region, the tumour is often larger and has already infiltrated surrounding structures (5). Regional lymph node metastases are commonly present.

Histologically, PDAC consists of atypical pancreatic-duct-resembling tubular glands with strikingly heterogeneous growth patterns. PDAC can also include non-tubular (clear-cell, cribriform or gyriform) components. PDAC´s irregular tumour glands are often embedded in a prominent desmoplastic stroma, consisting of extracellular matrix proteins as well as stromal and inflammatory cells that contributes to the aggressive biological behaviour.

Based on criteria defined by WHO, PDAC is histopathologically graded according to the tumour's cytoarchitecture, nuclei polymorphism and mitotic frequency (15) and has important prognostic implications. Conventional histology usually suffices for proper diagnosis, but occasionally immunohistochemistry is necessary. PDAC normally expresses cytokeratin (CK7, CK19, CK18 and CK20), mucin proteins (MUC1, MUC4 and MUC5AC) and tumour markers (CEA, CA19-9 and CA125).

#### *2.2.3.1 Morphological variants*

Several morphological variants of PDAC exist. Most share similar molecular background, biological behaviour and prognosis, but some are characterized by a different molecular pathogenesis and outcome. The "classic" tubular, adenosquamous, undifferentiated (anaplastic), undifferentiated (osteoclastic giant cells), micropapillary, signet-ring cell and

large-duct type share similar molecular pathogenesis, whereas colloid, medullary and hepatoid variants have a distinct molecular pathogenesis (15).

In the *adenosquamous* variant, a squamous component makes up at least 30% of the tumour mass, while the glandular component can be minimal. Although the molecular carcinogenesis is similar, their prognosis is even worse than for classical PDAC. Similarly, the *anaplastic* variant, characterized by presence of large, strikingly polymorphous tumour cells, also have a poorer prognosis than classical PDAC. The anaplastic variant is not to be confused with the *osteoclastic giant cell* variant which is characterized by histiocytic giant cells and bear a markedly better prognosis with a 5-year survival rate of 60% (15).

The *colloid* variant is characterized by the presence of extracellular mucin aggregates and associated with the intestinal-type IPMN. It has a reported 5-year survival rate of 50%. The *medullary* variant has a distinct syncytial growth pattern and like colorectal counterparts may be associated with microsatellite instability.

#### *2.2.3.2 Precursors*

The precursor lesion pancreatic intraepithelial neoplasia (PanIN) is responsible for most PDAC. PanIN are small, radiologically non-detectable mucinous-papillary intraepithelial neoplasms with a ductal phenotype. Both IPMN and MCN are visible on imaging but is only responsible for around 10-15% of all PDAC.

Pancreatic carcinogenesis follows a “adenoma-metaplasia-dysplasia-carcinoma”-sequence and the progression from precursor to cancer involves a stepwise acquisition of genetic alterations (8).

All three precursors can be induced by point mutation of the KRAS oncogene alone, but progression to high grade dysplasia or invasive carcinoma in general also requires mutations of CKN2A and CKN2A, TP53 and SMAD4 (8). GNAS mutations are typical for IPMN and are found in up to two thirds of IPMN cases, especially in the intestinal subtype (see below).

#### *2.2.3.3 Molecular profile*

While the mentioned cancer-related genes KRAS, CKN1A, CKN2A, TP53, SMAD4 and GNAS have been well known for PDAC carcinogenesis for many years, the development of sophisticated sequencing techniques the last decade has enabled a much more elaborated molecular characterization of PDAC and identification of gene signatures. Different subgroups have been hypothesized depending on the character of the tumoral cells (16) (17), their genomic stability (18) and the activity of the tumoural stroma (19). that seem to be relevant for survival and susceptibility to chemotherapy. However, the molecular subtypes do not correlate well with the histomorphological variants and attempts to over bridge this gap have just begun (20)

### 2.2.4 Presentation and symptoms, diagnostics and staging

#### *2.2.4.1 Presentation and symptoms*

PDAC frequently causes few, if any, symptoms before it develops to advanced surgically non-resectable stage, and those who do develop symptoms often have non-specific complaints (8). This is especially true for the tumours localized in the body and tail.

The most frequent symptoms at the time of diagnosis include abdominal pain (40–60%), jaundice (30%), dyspepsia (20%), new-onset diabetes (13–20%), nausea or vomiting (16%),

back pain (12%) and weight loss (10%) (8). Other presenting symptoms include pancreatitis and steatorrhea.

#### *2.2.4.2 Diagnostics*

For accurate and timely diagnosis of PDAC, the recommended initial imaging technique is multidetector computer tomography (CT) with pancreatic protocol including arterial and venous phases (14). Pancreatic tumours typically appear hypodense relative to surrounding pancreatic parenchyma, and the regional vasculature may properly be visualized to assess staging and resectability.

Magnetic Resonance Imaging (MRI) can provide a detailed assessment of the biliary tract and has a higher sensitivity for the detection of liver lesions (8) and can serve a valuable complementary modality.

The association of the serum biomarker CA19-9 with PDAC is well documented and validated. For the diagnosis of PDAC in symptomatic patients, sensitivity is around 80% and specificity close to 90% (8) Preoperative CA19-9 levels can predict survival after resection, and monitoring CA19-9 levels in systemic treatment in the neoadjuvant or metastatic setting may reflect response of treatment.

#### *2.2.4.3 Staging*

Patients with PDAC can be staged according to the American Joint Committee on Cancer Staging Manual, eighth edition (21), using the well-established TNM-classification were the size of the tumour and its relation to adjacent vessels are assessed (T-stage); the number of cancer positive lymph nodes harvested (N-stage); and possible metastases (M-stage). This can be used both radiologically and pathologically.

Most clinicians also use a four-tier staging system based on tumour resectability: resectable, borderline resectable, locally advanced, and metastatic (13). Assessment of the primary tumour and involvement of the adjacent vessels (celiac axis, hepatic artery, superior mesenteric artery and vein, and portal vein) in combination with biological risk and patient condition is critical in determining resectability (13).

### 2.2.5 Treatment

As more than half of the patients have disseminated disease at presentation, no cure can be offered, only palliative chemotherapy or best supportive care (22). About a fifth of the patients do have a localized situation that is potentially curable with surgical resection. About another fifth have a locally advanced situation – involving adjacent visceral vessels – that is non-resectable or borderline resectable. In these cases, up-front surgery is technically demanding, and more importantly, oncologically strongly questionable. These tumours can be treated with neo-adjuvant chemotherapy hoping to cause tumour regression (23).

Chemotherapy may lengthen overall survival for both resected patients and patients with disseminated disease (24). Five-year survival rate after surgical resection alone is around 10% but additional adjuvant chemotherapy increases this figure to 16-21% (25). For patients with disseminated disease at diagnosis and at recurrence after surgery, palliative chemotherapy may slacken the aggressive growth (26). Likewise, for patients with locally advanced disease, neoadjuvant chemotherapy may halt further growth and reduce the crucial vessel involvement (23).

A more detailed presentation of treatment options is found in 2.4 Treatment with curative intention.

### 2.2.6 Outcomes

PDAC is a malevolent cancer with limited options for effective therapy (13). Best outcome for resected patients depends heavily on low tumour stage at diagnosis, access to swift and safe surgery, effective systemic treatment, and evasion of early recurrence (27).

Recurrence frequently occurs and the most common initial sites are locoregional, peritoneum, liver and lung (2). Four fifths of the relapses are diagnosed within two years after resection (28) and once relapsed, it is characterized be aggressive growth and multifocal patterns (3). Most patients undergoing curative intent surgery become victims of recurrence and eventually succumb (29). Five-year survival rate is only 15 to 25% (30).

Factors predictive for recurrence and survival in patients resected for PDAC include larger tumour size (T-stage), high tumour grade (low tumour differentiation), a high lymph node ratio (arbitrarily N-stage), presence of microvascular (V) and perineural (Pn) invasion, as well as positive surgical margins (R) (9). Tumour variants and different molecular profiles affect the abovementioned prognostic factors.

## 2.3 INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM

IPMN is a pancreatic cystic neoplasm characterized by duct dilatation and mucin over-production. In 1982 it was first scientifically reported, in 2000 recognized as an own entity by WHO and in 2004 it was endowed with its first criteria for definition, evaluation and management that have dictated the structure for following contemporary guidelines (31) . It is one of is five known precursors (32) for PDAC and accounts for a little more than 10% of all PDAC (33).

### 2.3.1 Epidemiology

The numbers of encountered incidental IPMN have increased sharply last decades (7, 34), mainly due to more imaging performed (35, 36), increased awareness for this entity among medical practitioners (34) and possibly due to a rise in true incidence. The numbers will likely continue to increase.

#### *2.3.1.1 Incidence and prevalence*

Available data on incidence and prevalence is scarce and primarily based on extrapolation from single tertiary health care centre reports. Based on one such study from United States the age and sex-adjusted cumulative incidence were estimated to be 2 per 100000 person-years between 1984 and 2005 (31).

The point-prevalence for 2005 from the same study was 26 cases per 100000 persons, and 99 cases per 100000 in those older than 60 years. The majority of patients were asymptomatic when diagnosed and the median age at the time of diagnosis was 73 years (31).

#### *2.3.1.2 Risk factors*

There seem to be a clear causative link between IPMN and diabetes mellitus, especially if insulin-dependent and perhaps even for chronic pancreatitis (6). Diabetes mellitus increases the risk for the transformation to high grade dysplasia and even to invasive carcinoma (37), particularly the colloid subtype (38). No clinical reports have yet identified any geographic, viral or familial connection to IPMN (31).

### 2.3.2 Morphology

IPMN can morphologically be divided into main-duct, branch-duct or mixed type IPMN (39, 40). Based on histological features and routine immunohistochemistry distinct IPMN subtypes can be discerned – *gastro-foveolar*, *pancreato-biliary, intestinal* and *oncocytic* (7) – that all have different characteristics and outcomes. Intestinal-type IPMN is associated with main duct-type IPMN to a greater extent than pancreatobiliary- or gastric-type IPMN, and gastric-type is more often associated with branch-duct type IPMN.

### 2.3.3 Invasive transformation

The clinical relevance for IPMN is related to the potential invasive transformation to the malicious PDAC with pessimistic long-term outcome. The transformation follows a "adenoma-metaplasia-dysplasia-carcinoma"-sequence (8) and when carcinoma is manifested the suggested nomenclature is invasive-IPMN (inv-IPMN) (15). The term "malignant-IPMN" may still be encountered in the literature and is usually referred to lesions with either IPMN with high-grade dysplasia or inv-IPMN (41).

The risk of malignancy is lower in branch-duct IPMN (11-30%) and higher in case of main duct or mixed type IPMN (36-100%) (6). Recent findings suggest that the intestinal and pancreatobiliary subtypes progress to an invasive form (15, 42). The intestinal subtype develops into the indolent colloid cancer with more favourable outcome and the predominant pancreatobiliary subtype evolves to tubular cancer with properties similar to conventional PDAC (43, 44). The adenosquamous subtype is occasionally encountered as an ominous variant of PDAC and rarely mentioned in the IPMN-context but has nevertheless also been reported for inv-IPMN (45). The oncocytic variant with a reported median overall survival more than ten years (46) is no longer considered an inv-IPMN according to the 2019 WHO classification of tumours of the digestive system (15). Few studies comparing inv-IPMN with PDAC have been undertaken after the new classification.

### 2.3.4 Management

Suitable management for IPMN depends on the presumed level of neoplasia on imaging: from surveillance with imaging for pre-malignant lesions with no worrisome features to pre-emptive or curatively intended surgery for premalignant lesions with worrisome features, high risk stigmata and invasive lesions respectively (7, 47). If partial pancreatectomy is undertaken, continued surveillance is usually motivated as IPMN with worrisome features still can develop in the pancreatic remnant.

For invasive lesions, adjuvant chemotherapy is usually also offered and follows the same regime as for conventional PDAC, even though the current evidence suggest selective administration based on individual tumour characteristics such as node-positive disease, higher TNM-stage, positive resection margins, poor differentiation and tubular subtype (48).

#### *2.3.4.1 Guidelines*

Balancing the decision of *surveillance* for potentially malignant lesions with *major surgery* associated with important morbidity, and even mortality, for lesions with potential low-grade dysplasia solely on imaging is challenging. Pancreatic associations around the globe have worked out guidelines to aid this decision making, but there are still some disagreements. The most important associations are: American College of Gastroenterology (ACG), American Gastroenterology Association (AGA), American College of Radiology, The European Study Group on Cystic Tumours of the Pancreas and International Association of Pancreatology (IAP)/Fukuoka guidelines.

#### *2.3.4.2 Surgery*

According to the European Study Group on Cystic Tumours of the Pancreas from 2016, absolute indications for surgery are: positive cytology for high grade dysplasia or malignancy; solid mass or a contrast enhancing mural nodule ≥ 5mm; main duct dilatation ≥ 10mm and/or jaundice (47).

Relative indications for surgery are: branch duct cyst size ≥ 40mm or growth rate ≥5mm/year; contrast enhancing mural nodule < 5mm; increased levels of serum CA19-9 ≥ 37 U/ml; main duct between 5 and 10mm; new onset diabetes and/or acute pancreatitis (caused by IPMN) (47).

#### *2.3.4.3 Surveillance*

If the lesion is not associated with abovementioned worrisome features, surveillance is recommended with MRI and CA19-9 every six months the first year, then once per year if lesion stable.

### 2.3.5 Outcomes

Whether inv-IPMN and PDAC have similar outcome is under debate (49-53). Even though some data suggest that inv-IPMN and PDAC have similar outcome, some data demonstrate a more favourable outcome for inv-IPMN, such as findings from two recent meta-analyses but only in early stages (51, 52). If this is secondary to heterogeneities in study design, a inclination for inv-IPMN to manifest itself early (54), or if it represents a distinct tumour biology (46) is not clear. It is also unclear if last decade's change in resection pattern for IPMN/inv-IPMN has affected outcome. Concurrently, peri-operative and mid-term outcome after pancreatic resections have improved last decade (55), due to introduction of new adjuvant chemotherapy regime (25) and standardized peri-operative management (56). It is not studied if this improved survival has altered the outcome for inv-IPMN compared with PDAC.

## 2.4 TREATMENT OPTIONS WITH CURATIVE INTENTION

The only current curative treatment option for pancreatic cancer is surgery (ref). Partial resection usually suffices but for oncological and/or technical reasons a total pancreatectomy is occasionally necessary. Chemotherapy is in general considered adjuvant therapy to surgery and is usually given post-operatively but when tumour is border-line resectable and/or has characteristics suggesting high risk for early metastases, part of the treatment is given pre-operatively and part post-operatively. Non-metastasized, non-resectable tumours are given chemotherapy in palliative fashion, but occasionally tumour become resectable and is surgically resected.

### 2.4.2 Surgical resection

Surgical resection is the only potential cure for pancreatic cancer (13). The type of pancreatic resection depends mainly on tumour localization.

#### *2.4.2.1 Partial pancreatectomies*

Partial pancreatoduodenectomy (Whipple procedure) is used when tumour is located in the pancreatic head (including uncinate process) and involves removing pancreatic head, distal part of stomach and duodenum, gallbladder and distal part of the bile three *(13)*. The anatomy

is reconstructed by anastomosing pancreatic, gastric and bile tree remnants to jejunum by three separate stomas.

Distal (left) pancreatectomy is used when tumour is located in the pancreatic body/tail and involves removing the body and tail of pancreas (left of the superior mesenteric vein). For oncological reasons a splenectomy is normally done.

#### *2.4.2.2 Total pancreatoduodenectomy*

Total pancreatectomy is performed when tumour is extensive or badly located in the pancreatic neck jeopardizing an oncologically sound pancreatic division.

Since morbidity after pancreatic resections is high (around 40%), success of pancreatic surgery is closely linked to proper management of the complications. Failure to rescue may explain why surgical mortality is as high as over 10% in low volume centras and as low as some percent in high volume centras (57).

#### *2.4.2.3 Lymph node resection*

Lymphadenectomy is important for adequate nodal staging. Standard regional lymphadenectomy for pancreatoduodenectomy and for distal pancreatectomy should strive to resect regional lymph node stations (5, 6, 8a, 12b, 12c, 13a-b, 14a-b and 17a-b) and (10, 11 and 18) respectively (58).

For non-regional lymph node stations, there is however no specific consensus whether pancreatic resection should include non-regional lymph node stations, such as para-aortic lymph node station 16b1 (i.e. M1-stage) (21).

### 2.4.3 Chemotherapy

#### *2.4.3.1 Adjuvant therapy*

During the first years of the study period current adjuvant chemotherapy involved six months of Gemcitabine monotherapy for fit patients, generally commencing within 3 months after surgery. After having participated in the randomized controlled study ESPAC-IV study (25), run by the European Study Group for Pancreatic Cancer, that compared Gemcitabine (Gem) monotherapy with Gemcitabine and Capecitabine (Cap) in combination, combination therapy gained popularity and became standard treatment, sometimes with paclitaxel (Pac). Treatment is, if tolerated and regardless of mono- or combination therapy, given for six months, once weekly for three weeks, and a recovery week every four weeks (25, 59). Occasionally, for young and/or fit patients the more effective, but also more toxic, multicombination of folinic acid (FOL), fluorouracil (F), irinotecan (IRIN) and oxaliplatin (OX) – FOLFIRINOX – may be considered (60). Although chemotherapy for PDAC has evolved the last decade, the improvements in overall survival have only been modest due to toxicity and chemoresistance (61) and most patients will relapse following surgery (24). Novel therapies are urgently needed.

#### *2.4.3.2 Neo-adjuvant therapy*

For borderline resectable or locally advanced tumours (with reasonable possibility to reach a resectable situation by downsizing the tumour) neo-adjuvant adjuvant chemotherapy is the current recommended treatment option . Generally it is administered for three mounts before and three months after surgery. Principally, multicombination of the therapeutic agents is administered, FOLFIRINOX.

#### *2.4.3.3 Personalized medicine*

The emerging knowledge of the genomic landscape in PDAC provide a scaffold for comprehensive stratification into tumour subgroups and identification of potential druggable targets (24). Based on their general mechanism of action, novel treatment approaches can be categorizing using the acronym ”PRIME” (Pathway inhibitors, Repair, Immunotherapy, Metabolism, Extracellular matrix) (24). Although theoretically promising, the abovementioned hypothesized molecular subgroups are far from validated and do not correlate well with the histomorphological variants, and the druggable targets seem to be extremely difficult to just target (24). PARP for BRCA1 and 2. Personalized medicine for PDAC is therefore still in the cradle.

#### *2.4.3.4 Radio chemotherapy*

Radiotherapy in combination with chemotherapy or not, before and/or after surgery is a treatment option that is occasionally encountered abroad, but it is not current practice in Sweden.

## 2.5 CONCLUSION

This literature review illustrates that PDAC is a malevolent disease with a dismal prognosis, partly because of wide heterogeneities in precursors, morphologies and molecular profiles, partly because the current systemic treatment is rather limited and ineffective, and that these disparities need to be addressed and targeted if systemic treatment is to be effective. The literature review further illustrates that inv-IPMN is one such targetable subgroup and that there is an important knowledge gap between inv-IPMN and conventional PDAC.

The thesis intends to improve the understanding of the similarities and differences that exist between inv-IPMN and conventional PDAC in order to ameliorate long-term outcome for this tumour group.

# 3 RESEARCH AIMS

**I**
Explore similarities and differences in clinicopathology and overall survival between patients resected for inv-IPMN and PDAC

Examine whether the improvement in survival in combination with the increased numbers of pancreatic resections for inv-IPMN the last years have affected outcome.

**II**
Elucidate the pattern and prognostic significance of PALN involvement in patients with PDAC or inv-IPMN in the head of the pancreas, that underwent partial or total pancreatoduodenectomy.

**III**
Investigate the impact of tempo-spatial recurrence pattern on overall survival for inv-IPMN compared to PDAC.

Explore the impact of adjuvant chemotherapy on overall survival for inv-IPMN compared to PDAC.

**IV**
Determine similarities and differences in clinicopathology and overall survival between patients resected for inv-IPMN and PDAC on a national level.

Examine whether the improvement in survival in combination with the increased numbers of pancreatic resections for inv-IPMN the last years have affected outcome.

# 4 MATERIALS AND METHODS

## 4.1 DATA SOURCES AND ETHICAL CONSIDERATIONS

Studies I-III relied on data collected from a local prospectively kept quality register. Additional data was collected from patient journals, whereas study IV relied on data retrieved from Swedish Pancreatic Registry.

As such, the studies in this doctoral project comprise the collection and handling of clinico-pathological data of patients resected for pancreatic ductal adenocarcinoma. After having been granted ethical permits (EPN 2019-00645, 2021-01875), additional data was collected from patient journals and retrieved data has been entirely pseudonymized. Patients are/were not expected to have any medical benefit from their participation in this research nor suffer from any integrity related issues.

## 4.2 STUDY DESIGN AND STUDY POPULATIONS

This thesis is based on four retrospective observational studies of consecutive adults resected for inv-IPMN and PDAC during a ten-year period. Two principal populations were studied: one regional cohort comprising resections at Karolinska University Hospital between 2009 and 2018 included 515 patients, 123 inv-IPMN and 394 PDAC (study I-III); one national cohort comprising resections in Sweden between 2010 and 2019 included 1909 patients, 293 inv-IPMN and 1616 PDAC (study IV).

### 4.2.1 Study I

Retrospective observational single centre study of consecutive adults resected for inv-IPMN and PDAC between 2009 -2018 at Karolinska University Hospital. Patients pre-treated with neo-adjuvant chemotherapy were excluded. The study included 513 patients, 123 inv-IPMN and 392 PDAC.

### 4.2.2 Study II

Retrospective observational single centre study of consecutive adults resected for inv-IPMN and PDAC in the *pancreatic head* and underwent either partial or total pancreatoduodenectomy between 2009 -2018 at Karolinska University Hospital. Patients pre-treated with chemotherapy were excluded. The study included 403 patients, 89 inv-IPMN and 314 PDAC.

### 4.2.3 Study III

Retrospective observational Single centre study of consecutive adults resected for inv-IPMN and PDAC between 2009-2018 at Karolinska University Hospital (n=587) that were residing in the Stockholm region (to get full access to information regarding adjuvant chemotherapy and recurrence). Patients not residing in the Stockholm region (n=145) or pre-treated with neo-adjuvant chemotherapy (n=43) were excluded. Likewise, postoperative deaths that occurred within 30 days (n=3) were excluded. The study included 396 patients, 92 inv-IPMN and 304 PDAC

### 4.2.4 Study IV

Retrospective observational national multicentre study of consecutive adults resected for inv-IPMN and PDAC between 2010-2019 at six pancreatic centras in Sweden. The study included 1909 patients, 293 inv-IPMN and 1616 PDAC. A subgroup analysis of patients resected 2016-2019 yielded 905 patients, 175 inv-IPMN and 730 PDAC.

## 4.3 STATISTICAL ANALYSES

### 4.3.1 Study I

Descriptive statistics differences between tumour types
Multivariable logistic regression for death within 24 months as well as for recurrence within 18 months (recurrence since recurrence )
Multivariable Cox regression for death using a backwards stepwise selection approach
Survival analyses were performed with the Kaplan-Meier method and survival curves were compared with the log-rank test.

### 4.3.2 Study II

Descriptive statistics differences between tumour types.
Multivariable logistic regression for death within 24 months as well as for recurrence debut the first or second year after resection, recurrence sites (locoregional, peritoneum, liver or lung) and whether the recurrence debuted unifocally or part of a multifocal recurrence.
Multivariable Cox regression for death using a backwards stepwise selection approach.
Survival analyses were performed with the Kaplan-Meier method and survival curves were compared with the log-rank test.

### 4.3.3 Study III

Descriptive statistics differences between tumour types.
Multivariable logistic regression for PALN positivity.
Multivariable Cox regression for death using a backwards stepwise selection approach
Survival analyses were performed with the Kaplan-Meier method and survival curves were compared with the log-rank test.

### 4.3.4 Study IV

Descriptive statistics differences between tumour types.
Multivariable logistic regression for death within 2 years and for 5-years in the subgroup analysis.
Multivariable Cox regression for death using a backwards stepwise selection approach.
Survival analyses were performed with the Kaplan-Meier method and survival curves were compared with the log-rank test.

# 5 RESULTS

Altogether, the regional cohort from Karolinska University Hospital (study I-III) included 515 patients, 123 (24%) inv-IPMN and 392 (76%) PDAC, and the Swedish national cohort (study IV) included 1,909 patients, 293 (15%) inv-IPMN and 1616 (85%) PDAC.

Study I included 513 patients, 122 (24%) with inv-IPMN and 391 (76%) with PDAC; study II included 403 patients, 89 (22%) inv-IPMN and 314 (78%) PDAC; and study III included 396 patients, 92 (23%) with inv-IPMN and 304 (77%) with PDAC.

The reverse Kaplan-Meier estimated median follow-up was between 54.8-65.5 months (46.1-58.1 months for inv-IPMN and 71.7 - 79.2 months for PDAC) in the regional cohort and 66.8 months (55.1 months for inv-IPMN and 68.9 months for PDAC) in the national cohort.

## 5.1 BASELINE CHARACTERISTICS

Baseline characteristics are detailed in **Table 1**. The median age was around 70 years and half of the patients were of male sex and with normal BMI. A fifth were present smokers. A third was considered to suffer critical comorbidity (ASA 3-4). Critical comorbidity was more common among patients with inv-IPMN in the regional cohort, but this was not the case in the national cohort.

Cardiac comorbidity was present in a third of the patients. A quarter suffered from diabetes mellitus, and this comorbidity was more common among patients with inv-IPMN. Respiratory comorbidity was present in less than 10%.

Tumour was in the regional cohort radiologically assessed to be localised in the pancreatic head region (including distal bile duct and duodenum) in four fifths of the patients and there was no difference between tumour groups.

Almost two thirds had undergone biliary decompression, and this was significantly more common among patients with PDAC. 60% of the patients had CA19-9 levels <200. This was more common among inv-IPMN in the national cohort.

In study I, patients with inv-IPMN were less often symptomatic (86% vs. 94%; p=0.010) and had incidental or surveilled lesions (20% vs. 7%; p<0.001) more frequently compared to PDAC. They were also assessed premalignant at pre-operative multidisciplinary therapy conference more frequently (10% vs. 3%; p<0.001).

Incidental/surveilled lesions were more frequently staged T1 (16% vs. 7%; p=0.038) and staged N0 (32% vs. 8%; p<0.001) and they had more frequently CA19-9 levels < 200 kE/L (72% vs. 56%; p=0.042) compared to non-incidental or surveilled tumours.

**Table 1. Descriptive statistics of pre-and peri-operative characteristics**

| | Regional cohort (studies I-III) | | | | National cohort (study IV) | | | |
|---|---|---|---|---|---|---|---|---|
| | **Overall** | **inv-IPMN** | **PDAC** | | **Overall** | **inv-IPMN** | **PDAC** | |
| **Variable** | N = 515[1] | n=123[1] | n=392[1] | **p-value[2]** | N = 1909[1] | n=293[1] | n=1624[1] | **p-value[2]** |
| **Sex** | | | | 0.058 | | | | 0.070 |
| Female | 238 (46) | 66 (54) | 172 (44) | | 943 (49) | 159 (54) | 784 (49) | |
| Male | 277 (54) | 57 (46) | 220 (56) | | 966 (51) | 134 (46) | 832 (51) | |
| **Age** | | | | 0.133 | | | | 0.657 |
| < 70 years | 269 (52) | 56 (46) | 213 (54) | | 978 (51) | 144 (49) | 834 (52) | |
| 70 to 79 | 201 (39) | 52 (42) | 149 (38) | | 811 (42) | 128 (44) | 683 (42) | |
| ≥80 years | 45 (8.7) | 15 (12) | 30 (7.7) | | 120 (6.3) | 21 (7.2) | 99 (6.1) | |
| **BMI** | | | | 0.608 | | | | 0.787 |
| <25 kg/m$^2$ | 295 (57) | 68 (55) | 227 (58) | | 1,014 (55) | 154 (54) | 860 (55) | |
| ≥25 kg/m$^2$ | 220 (43) | 55 (45) | 165 (42) | | 831 (45) | 130 (46) | 701 (45) | |
| **ASA score** | | | | 0.002 | | | | 0.689 |
| 1 - 2 | 316 (61) | 61 (50) | 255 (65) | | 1,357 (71) | 205 (70) | 1,152 (72) | |
| 3 - 4 | 199 (39) | 62 (50) | 137 (35) | | 543 (29) | 86 (30) | 457 (28) | |
| **Smoking** | | | | 0.157 | | | | 0.233 |
| Non-smoker | 404 (79) | 102 (84) | 302 (78) | | 1,540 (83) | 245 (85) | 1,295 (82) | |
| Smoker | 107 (21) | 20 (16) | 87 (22) | | 324 (17) | 43 (15) | 281 (18) | |
| **Respiratory comorbidity** | | | | 0.098 | | | | 0.889 |
| No | 410 (91) | 98 (88) | 312 (93) | | 1,783 (94) | 273 (94) | 1,510 (94) | |
| Yes | 39 (8.7) | 14 (12) | 25 (7.4) | | 108 (5.7) | 16 (5.5) | 92 (5.7) | |
| **Diabetes mellitus** | | | | 0.032 | | | | 0.008 |
| No | 389 (76) | 84 (68) | 305 (78) | | 1,410 (74) | 197 (68) | 1,213 (75) | |
| Yes | 126 (24) | 39 (32) | 87 (22) | | 490 (26) | 93 (32) | 397 (25) | |
| **Cardiac comorbidity** | | | | 0.295 | | | | 0.265 |
| No | 329 (73) | 76 (69) | 253 (74) | | 1,315 (70) | 209 (72) | 1,106 (69) | |
| Yes | 122 (27) | 34 (31) | 88 (26) | | 576 (30) | 80 (28) | 496 (31) | |
| **Neoadjuvant chemotherapy** | | | | | | | | 0.058 |
| No | 515 (100) | 123 (100) | 392 (100) | | 1,788 (94) | 281 (96) | 1,507 (93) | |
| Yes | 0 (0) | (0) | (0) | | 119 (6.2) | 11 (3.8) | 108 (6.7) | |
| **Weight loss** | | | | 0.031 | | | | <0.001 |
| No | 179 (36) | 54 (45) | 125 (34) | | 1,038 (55) | 120 (42) | 918 (57) | |
| Yes | 312 (64) | 67 (55) | 245 (66) | | 844 (45) | 165 (58) | 679 (43) | |
| **Biliary decompression** | | | | <0.001 | | | | <0.001 |
| No | 212 (41) | 71 (58) | 141 (36) | | 727 (38) | 198 (69) | 529 (33) | |
| Yes | 300 (59) | 52 (42) | 248 (64) | | 1,170 (62) | 91 (31) | 1,079 (67) | |
| **CA19-9 levels** | | | | 0.769 | | | | 0.004 |
| <200 kE/L | 286 (58) | 70 (59) | 216 (57) | | 820 (60) | 140 (69) | 680 (58) | |
| ≥200 kE/L | 210 (42) | 49 (41) | 161 (43) | | 557 (40) | 64 (31) | 493 (42) | |
| **Procedure** | | | | <0.001 | | | | <0.001 |
| *Pancreatoduodenectomy* | 355 (69) | 66 (54) | 289 (74) | | 1,417 (74) | 148 (51) | 1,269 (79) | |
| *Distal pancreatectomy* | 85 (17) | 23 (19) | 62 (16) | | 285 (15) | 91 (31) | 194 (12) | |
| *Total pancreatectomy* | 72 (14) | 32 (26) | 40 (10) | | 198 (10) | 50 (17) | 148 (9.2) | |
| *Other* | 3 (0.6) | 2 (1.6) | 1 (0.3) | | 6 (0.3) | 3 (1.0) | 3 (0.2) | |
| **Artery resection** | | | | 0.230 | | | | 0.317 |
| *Nej* | 497 (97) | 116 (95) | 381 (97) | | 925 (97) | 151 (96) | 774 (97) | |
| *Ja* | 16 (3.1) | 6 (4.9) | 10 (2.6) | | 30 (3.1) | 7 (4.4) | 23 (2.9) | |
| **Venous resection** | | | | 0.501 | | | | <0.001 |
| *Nej* | 332 (65) | 82 (68) | 250 (64) | | 1,344 (71) | 232 (79) | 1,112 (69) | |
| *Ja* | 177 (35) | 39 (32) | 138 (36) | | 562 (29) | 60 (21) | 502 (31) | |
| **Clavien-Dindo** | | | | 0.156 | | | | 0.258 |
| *0-2* | 411 (80) | 94 (76) | 317 (81) | | 1,573 (83) | 230 (80) | 1,343 (84) | |
| *3a-b* | 68 (13) | 15 (12) | 53 (14) | | 242 (13) | 47 (16) | 195 (12) | |
| *4a-b* | 29 (5.6) | 11 (8.9) | 18 (4.6) | | 42 (2.2) | 6 (2.1) | 36 (2.3) | |
| *5* | 7 (1.4) | 3 (2.4) | 4 (1.0) | | 28 (1.5) | 5 (1.7) | 23 (1.4) | |

[1] n (%)

[2] Pearson's Chi-squared test, Fisher's exact test

## 5.2 PERI-OPERATIVE CHARACTERISTICS

About half of the resections were performed in the latter time period: 2015-2018 for the regional and 2016-2019 for the national cohort. and the proportion of resected inv-IPMN relative to PDAC increased from 6.5 and 13.3 per cent in the early periods to 39.3 and 19.2

per cent in the latter time periods for the regional and national cohorts respectively ($p<0.001$).

Meanwhile, two-year OS rate increased, from 38% to 57% and from 38% to 58% (both $p<0.001$) for the entire cohort and for PDAC respectively, ruling out that the diminished hazard for death was due to the shift in proportions resected tumours.

Partial pancreatoduodenectomy was the most common operative procedure in both cohorts, followed by distal pancreatectomy and total pancreatoduodenectomy. Around three fourths among patients with PDAC had undergone partial pancreatoduodenectomy, but among patients with inv-IPMN in in the regional cohort, only a third of the patients had undergone this procedure.

In the national cohort, extended resections were more common among inv-IPMN compared to PDAC (n=51, 17% versus n=162, 10%; $p<0.001$). Venous resection was undertaken in around a third of the patients, but while there was no difference between tumour groups in the regional cohort, it was less common among inv-IPMN compared to PDAC in the national cohort. Artery resection was performed in 3 percent of the procedures.

Complication grades were similar between tumour groups. Most patients did not develop major complications and 90-day mortality was low. However, in study II that only studied tumours in the pancreatic head, almost a third (31.2%) developed major complications and as many as half among inv-IPMN (51.2% versus 26%, $p<0.001$).

## 5.3 HISTOLOGY AND TUMORAL CHARACTERISTICS

### 5.3.1 Tumour specifics

Tumoral characteristics for the regional and national cohorts are detailed in **Table 2**.

#### *5.3.1.1 Tumour localization*

The tumours were in four fifths of the patients localized in the head, and equally common in the body and tail in one fifth of the patients. In the national study, as many as a third of the patients with inv-IPMN was localised in the body or tail.

#### *5.3.1.2 Tumour size and differentiation*

The invasive part of the tumours measured between 30-36 mm and was equal in size between tumour groups. Differentiation was assessed poor-undifferentiated in about half of the cases in the national cohort but almost two thirds in the regional and was in general less poorly differentiated among inv-IPMN.

#### *5.3.1.3 Tumour subtypes*

Tumour subtypes were explored in study I and III. Pancreatobiliary subtype was most common followed by intestinal and adenosquamous (81-83%, 21-26% and 9-11% respectively). Intestinal subtype was more common in inv-IPMN compared with PDAC and the opposite was true for adenosquamous subtype (19-20% versus 3% and 5% versus 10-14%, $p<0.001$).

#### *5.3.1.4 Tumour morphology for inv-IPMN tumours*

Morphologically, the origin for inv-IPMN tumours was isolated branch- and main-duct in only 6% and 4% respectively; Three quarters (78%) were mixed-type and 12% unspecified (study I).

**Table 2. Descriptive statistics of pathological characteristics**

| | Regional cohort (studies I-III) | | | | National cohort (study IV) | | | |
|---|---|---|---|---|---|---|---|---|
| **Characteristic** | **Overall** N = 515[1] | **inv-IPMN** n=123[1] | **PDAC** n=392[1] | **p-value**[2] | **Overall** N = 1909[1] | **inv-IPMN** n=293[1] | **PDAC** n=1624[1] | **p-value**[2] |
| **Tumour localisation** | | | | 0.030 | | | | <0.001 |
| Head | 425 (83) | 96 (78) | 329 (84) | | 1,543 (82) | 166 (61) | 1,377 (85) | |
| Body | 31 (7.7) | 13 (15) | 18 (5.7) | | 143 (7.6) | 37 (14) | 106 (6.6) | |
| Tail | 52 (10) | 11 (8.9) | 41 (11) | | 182 (9.6) | 57 (21) | 125 (7.7) | |
| Extensive | 5 (1.2) | 3 (3.6) | 3 (0.6) | | 22 (1.2) | 14 (5.1) | 8 (0.5) | |
| **Tumour size (invasive)** | 36 (29-45) | 35 (28-45) | 36 (30-45) | 0.443 | 30 (25-40) | 30 (21-44) | 30 (25-40) | 0.498 |
| **Tumour differentiation** | | | | 0.028 | | | | 0.005 |
| Well | 7 (1.4) | 4 (3.3) | 3 (0.8) | | 147 (8.6) | 31 (14) | 116 (7.8) | |
| Moderate | 183 (36) | 50 (41) | 133 (34) | | 784 (46) | 88 (39) | 696 (47) | |
| Poor-Undifferentiated | 322 (63) | 67 (55) | 255 (65) | | 783 (45) | 105 (47) | 678 (45) | |
| **Tumour-stage** | | | | <0.001 | | | | <0.001 |
| 1 | 25 (4.9) | 14 (11) | 11 (2.8) | | 258 (14) | 50 (17) | 208 (13) | |
| 2 | 307 (60) | 58 (48) | 249 (64) | | 1,112 (58) | 138 (47) | 974 (60) | |
| 3 | 179 (35) | 49 (40) | 130 (33) | | 420 (22) | 94 (32) | 326 (20) | |
| 4 | 3 (0.6) | 1 (0.8) | 2 (0.5) | | 119 (6.2) | 11 (3.8) | 108 (6.7) | |
| **Nodes-stage** | | | | 0.002 | | | | <0.001 |
| 0 | 55 (11) | 23 (19) | 32 (8.2) | | 436 (23) | 114 (40) | 322 (20) | |
| 1 | 164 (32) | 42 (34) | 122 (31) | | 679 (36) | 84 (29) | 595 (37) | |
| 2 | 295 (57) | 58 (47) | 237 (61) | | 766 (41) | 89 (31) | 677 (42) | |
| **Metastases-stage** | | | | 0.899 | | | | 0.120 |
| 0 | 429 (83) | 102 (83) | 327 (83) | | 1,774 (93) | 266 (91) | 1,508 (93) | |
| 1 | 86 (17) | 21 (17) | 65 (17) | | 135 (7.1) | 27 (9.2) | 108 (6.7) | |
| **Lymphovasc. invasion** | | | | 0.504 | | | | <0.001 |
| 0 | 62 (12) | 17 (14) | 45 (12) | | 373 (24) | 73 (33) | 300 (23) | |
| 1 | 450 (88) | 106 (86) | 344 (88) | | 1,163 (76) | 147 (67) | 1,016 (77) | |
| **Perineural invasion** | | | | 0.281 | | | | <0.001 |
| 0 | 35 (6.9) | 11 (9.0) | 24 (6.2) | | 202 (12) | 62 (26) | 140 (9.5) | |
| 1 | 475 (93) | 111 (91) | 364 (94) | | 1,504 (88) | 178 (74) | 1,326 (90) | |
| **Microvasc. invasion** | | | | <0.001 | | | | 0.349 |
| 0 | 120 (23) | 43 (35) | 77 (20) | | 664 (40) | 100 (43) | 564 (40) | |
| 1 | 394 (77) | 80 (65) | 314 (80) | | 976 (60) | 131 (57) | 845 (60) | |
| **Surgical margin** | | | | 0.316 | | | | 0.002 |
| Negative | 109 (21) | 30 (24) | 79 (20) | | 906 (48) | 161 (56) | 745 (47) | |
| Positive | 406 (79) | 93 (76) | 313 (80) | | 974 (52) | 124 (44) | 850 (53) | |

[1] n (%)
[2] Pearson's Chi-squared test, Wilcoxon rank sum test; Fisher's exact test

### 5.3.2 Lymph node specifics and metastases

#### *5.3.2.1 Regional stations*

In the regional study, a mean of 31 regional lymph nodes were resected. Among patients with inv-IPMN and PDAC, a mean of 3 and 5 respectively were deemed positive (p=0.003), corresponding to a lymph node ratio (LNR) of 10% and 16% respectively. A total LNR of >15% was more common in PDAC (52%) than inv-IPMN (34%) (p=0.004).

#### *5.3.2.2 Non-regional stations and PALN-specific findings*

In study II, the resected pancreatoduodenectomies (partial and total) were associated with a concomitant retrieval of a mean of 4 para-aortal lymph nodes (PALN), and 16% of the procedures presented with positive PALN. There was no difference between inv-IPMN and PDAC (p=0.962).

PALN-positive tumours were larger compared to PALN-negative, 40mm versus 35mm (p<0.001). While the number of retrieved regional lymph nodes were equal between tumour groups (n=27), positive nodes were more common in PALN-positive compared to PALN negative tumours, 10 versus 4 (p<0.001). Consequently, N2 status and LNR >15% were more common in PALN-positive compared to PALN negative tumours (98% versus 56%;

p<0.001) and (92% versus 47%; p<0.001) respectively. PALN-status did not affect tumour differentiation and CA19-9 levels.

### 5.3.3 TNM-staging

*5.3.3.1 Tumour stage*

Tumour stage differed between tumour groups in both cohorts. T2-stage was the most common stage in both tumour groups, especially in PDAC. In the regional cohort, T1-stage was more common in inv-IPMN compared to PDAC (p<0.001), and in the national cohort T3-stage was more common in inv-IPMN compared to PDAC (p<0.001).

*5.3.3.2 Nodes stage*

Nodes-stage differed between tumour groups in both cohorts. N2-stage was the most common stage in both cohorts, but this was more pronounced in the regional cohort and for inv-IPMN in the national cohort, N0-stage was actually more common. N0-stage was most common in inv-IPMN compared to PDAC in both cohorts (p≤0.001).

*5.3.3.3 Metastasis stage*

Metastasis stage did not differ between tumour groups in neither cohort. M1-stage was twice as common in the regional cohort compared to the national, but statistics were not run to test significance of this observation.

### 5.3.4 Microscopic invasion and surgical margin

*5.3.4.1 Lymphovascular invasion*

Lymphovascular invasion was most common in both tumour groups in both cohorts. It was less common among inv-IPMN compared to PDAC in the national cohort, but not in the regional.

*5.3.4.2 Perineural invasion*

Perineural invasion was most common in both tumour groups in both cohorts. It was less common among inv-IPMN compared to PDAC in the national cohort, but not in the regional.

*5.3.4.3 Microvascular invasion*

Microvascular invasion was most common in both tumour groups in both cohorts. It was less common among inv-IPMN compared to PDAC in the regional cohort but not in the national.

*5.3.4.4 Surgical margin*

Tumours resected with a positive surgical margin were most common in the regional cohort, and there was no difference between tumour groups. About half of the tumours in the national cohort were resected with a positive margin, and this was more frequent in PDAC.

## 5.4 ADJUVANT CHEMOTHERAPY

Enrolment for adjuvant chemotherapy was not studied in the national group, but in study III enrolment was 58% (n=229), and there was no difference between tumour groups (p=0.870). Of the enrolled patients, two thirds (n=142, 62%) completed treatment, about one third did not complete treatment due to adverse effects (n=36, 16%) or recurrence (n=51, 22%) and there was no difference between the tumour groups (p=0.765).

Two thirds (n=154, 67%) received adjuvant chemotherapy in the form of monotherapy with Gemcitabine and one third in combination, mostly consisting of Gemcitabine in combination with Capecitabine, but occasionally FOLFIRINOX. Monotherapy was less common in inv-IPMN compared to PDAC (n=27, 51% versus n=127, 71%; p=0.009).

## 5.5 RECURRENCE PATTERNS

Recurrence rate and recurrence patterns were investigated in study III. Three-year recurrence rate was 68% (n=63) in inv-IPMN and 82% (n=247) in PDAC (p=0.009). When present, recurrence was single- and multi-site in 63% (n=195) and 37% (n=115) for inv-IPMN and PDAC respectively, but there was no difference between tumour groups (p=0.668).

The four most common recurrence sites were liver (n=155, 50%), locoregional (n=133, 43%), lung (n=81, 26%) and peritoneum (n=64, 21%), and only liver site differed between inv-IPMN and PDAC (n=27, 43% versus n=128, 52%; p=0.04). Spatial recurrence patterns for tumour types as well as intestinal and adenosquamous tumour subtypes are depicted in Euler diagrams in **Figure 1.** Recurrence occurred most often within the first year, followed by second and third year 59% (n=183), 28% (n=88) and 13% (n=39) respectively and there was no difference between tumour groups. The three abovementioned spatio-temporal dimensions are summarized in **Figure 2**.

Patients with relapses within 3 months (n=60, 15%) tended to have tumours greater than 4 cm on pre-operative imaging and presented with CA19-9 levels >200 more often than the rest of the cohort (n=10, 17% vs n=30, 9.2%; p<0.065) and (n=35, 60% vs n=128, 40%; p<0.009) respectively, but did not differ in sex, age, ASA, BMI, tumour localization on pre-operative imaging or operative procedure (p>0.2).

**Figure 1**

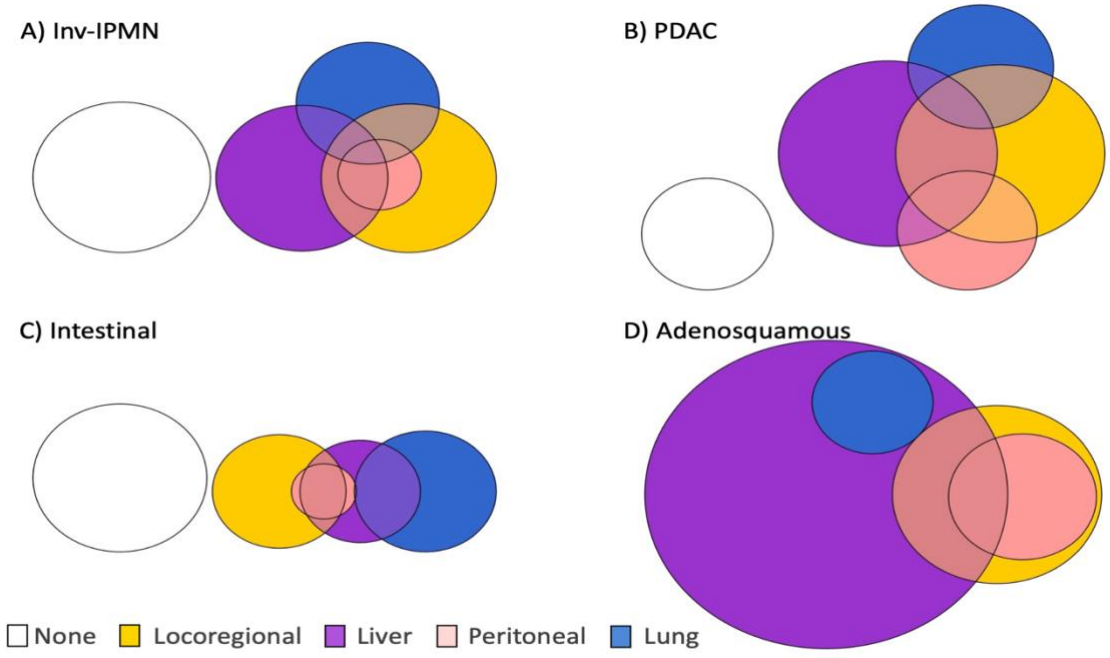


**Figure 1**: Euler diagram illustrating spatial recurrence patterns within three years for tumour types and subtype extremes. A) Inv-IPMN. B) PDAC. C) Intestinal subtype. D) Adenosquamous subtype. From study III (62) DOI: 10.1016/j.pan.2022.04.007. Printed with permission from Elsevier for non-commercial thesis use, published with a Creative Commons Attribution 4.0 license.

**Figure 2**

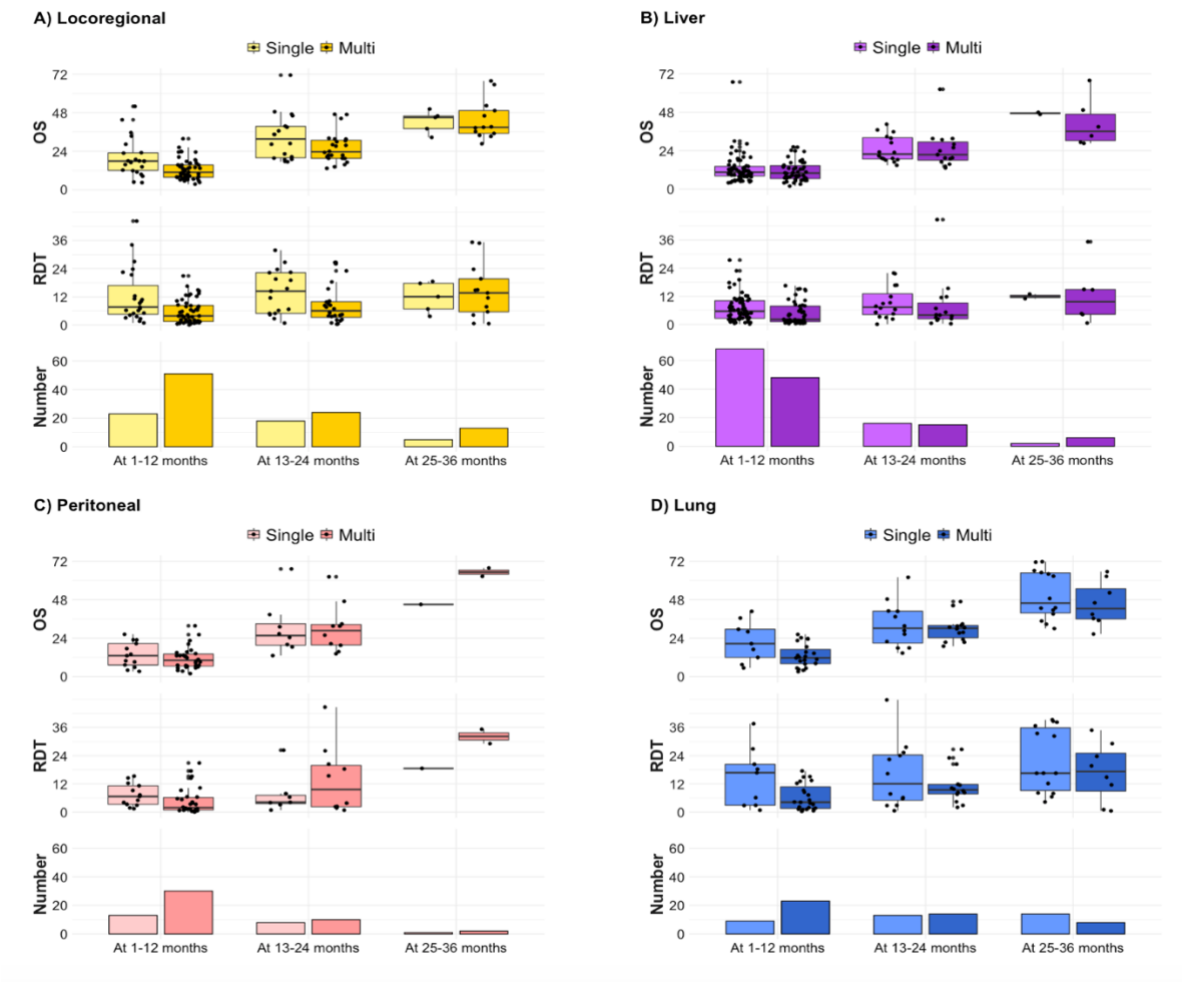


**Figure 2**: Spatio-temporal recurrence patterns for the four main relapse sites depicted by numbers of cases, recurrence free survival in three 12-months periods for single and part of multifocal recurrences, as well as recurrence to death time (RDT) and overall survival (OS). A) Locoregional. B) Liver. C) Peritoneal. D) Lung. From study III (62) DOI: 10.1016/j.pan.2022.04.007. Printed with permission from Elsevier for non-commercial thesis use, published with a Creative Commons Attribution 4.0 license.

## 5.6 OVERALL SURVIVAL AND SURVIVAL ANALYSES

Overall survival was assessed by calculating two-and three-year overall survival rate as well as estimating median overall survival by Kaplan analyses. Cox proportional hazards regression analyses were used to retrieve possible independent predictors for death.

### 5.6.1 Two- and three-year survival rate

Two-year overall survival rate was 53% (n=65) and 59% (n=172) for inv-IPMN, and 41% (n=162) and 49% (n=162) for PDAC in study I (p=0.028) and study IV respectively (p=0.003). In both studies, two-year survival rates increased between earlier and latter resection periods. In study IV, two-year survival rate increased in all patients from 45.4 per cent in 2010-2015 to 56.3 per cent in 2016-2019 (p<0.001) – in patients diagnosed with PDAC from 44.4 per cent to 54.9 per cent (p<0.001), and in patients with inv-IPMN from 53.4 per cent to 63.2 per cent (p=0.163). Three-year overall survival rate in study III was 41% and 27% respectively for inv-IPMN and PDAC (p=0.007).

### 5.6.2 Cox proportional hazards regression analyses

Multivariable Cox regression analyses revealed that age and tumour differentiation were independent predictors for death in all studies, and CA19-9 and N-stage in all studies but study III. T-stage was an independent predictor for death in study I and IV, M-stage in study III and IV, and V-stage in study II and III. Tumour type was an independent predictor for death in study II and IV, and tumour subtype in study I. Adjuvant chemotherapy was an independent predictor for survival in study II and III.
Additional independent predictors for death were resection year in study I, recurrence within three years in study III as well as venous resection and surgical margin in study IV. Independent predictors for death from each study are detailed in **Table 3**.

**Table 3. Multivariable Cox regressions**

| | Study I | | | Study II | | | Study III | | | Study IV[3] | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Characteristic** | **HR[1]** | **95% CI[2]** | **p-value** | **HR[1]** | **95% CI[2]** | **p-value** | **HR[1]** | **95% CI[2]** | **p-value** | **HR[1]** | **95% CI[2]** | **p-value** |
| **Age** | | | | | | | | | | | | |
| <60 years | — | — | | | | | | | | | | |
| 60 to 69 years | 1.01 | 0.67, 1.52 | 0.967 | — | — | | — | — | | — | — | |
| 70 to 79 years | 1.75 | 1.17, 2.61 | **0.006** | | | | | | | | | |
| ≥80 years | 2.78 | 1.57, 4.94 | **<0.001** | 1.51 | 1.20, 1.90 | **<0.001** | 1.38 | 1.09, 1.75 | **0.007** | 1.45 | 1.23, 1.70 | **<0.001** |
| **Neoadj. chemotherapy** | | | | | | | | | | | | |
| No | | | | | | | | | | — | — | |
| Yes | | | | | | | | | | 1.62 | 1.14, 2.29 | **0.007** |
| **CA19-9 levels** | | | | | | | | | | | | |
| <37 kE/L | — | — | | | | | | | | | | |
| 37 to 200 kE/L | 1.19 | 0.80, 1.77 | 0.384 | — | — | | | | | — | — | |
| ≥200 kE/L | 2.13 | 1.47, 3.08 | **<0.001** | 1.63 | 1.29, 2.06 | **<0.001** | | | | 1.45 | 1.19, 1.76 | **<0.001** |
| **Op period** | | | | | | | | | | | | |
| 2017 - 2018 | — | — | | | | | | | | | | |
| 2015 - 2016 | 1.56 | 1.08, 2.25 | **0.017** | | | | | | | | | |
| 2013 - 2014 | 2.97 | 1.98, 4.46 | **<0.001** | | | | | | | | | |
| 2011 - 2012 | 2.08 | 1.31, 3.31 | **0.002** | | | | | | | | | |
| 2009 - 2010 | 5.33 | 3.11, 9.16 | **<0.001** | | | | | | | | | |
| **Venous resection** | | | | | | | | | | | | |
| No | | | | | | | | | | — | — | |
| Yes | | | | | | | | | | 1.23 | 1.03, 1.47 | **0.023** |
| **Tumour type** | | | | | | | | | | | | |
| Inv-IPMN | | | | — | — | | | | | — | — | |
| PDAC | | | | 1.65 | 1.20, 2.26 | **0.002** | | | | 1.31 | 1.05, 1.64 | **0.017** |
| **Tumour subtype** | | | | | | | | | | | | |
| Intestinal | | | | | | | | | | | | |
| Pancreatobiliary | 1.35 | 0.49, 4.17 | 0.478 | | | | | | | | | |
| Adenosquamous | 4.64 | 5.10, 5.42 | **<0.001** | | | | | | | | | |
| **Tumour differentiation** | | | | | | | | | | | | |
| Well-Moderate | — | — | | — | — | | — | — | | — | — | |
| Poor-Undifferentiated | 1.89 | 1.37, 2.61 | **<0.001** | 1.83 | 1.41, 2.36 | **<0.001** | 1.88 | 1.46, 2.41 | **<0.001** | 1.63 | 1.37, 1.94 | **<0.001** |
| **Tumour-stage** | | | | | | | | | | | | |
| 1 | — | — | | | | | | | | — | — | |
| 2 | 1.32 | 0.59, 2.94 | 0.506 | | | | | | | 1.33 | 1.01, 1.77 | **0.044** |
| 3 | 2.21 | 1.32, 3.71 | **<0.001** | | | | | | | | | |
| 4 | | | | | | | | | | | | |
| **Nodes-stage** | | | | | | | | | | | | |
| 0 to 1 | — | — | | — | — | | | | | — | — | |
| 2 | 1.79 | 1.33, 2.42 | **<0.001** | 1.84 | 1.42, 2.38 | **<0.001** | | | | 1.40 | 1.18, 1.67 | **<0.001** |
| **Metastases-stage** | | | | | | | | | | | | |
| 0 | | | | | | | — | — | | — | — | |
| 1 | | | | | | | 1.69 | 1.22, 2.34 | **0.002** | 1.58 | 1.19, 2.08 | **0.001** |
| **Microvascular invasion** | | | | | | | | | | | | |
| 0 | | | | — | — | | — | — | | | | |
| 1 | | | | 1.54 | 1.13, 2.10 | **0.006** | 1.87 | 1.38, 2.54 | **0.004** | | | |
| **Surgical margin** | | | | | | | | | | | | |
| Negative | | | | | | | | | | — | — | |
| Positive | | | | | | | | | | 1.27 | 1.06, 1.51 | **0.009** |
| **Adjuvant chemotherapy** | | | | | | | | | | | | |
| Completed | | | | | | | — | — | | | | |
| Not compl., adverse effects | | | | | | | 1.39 | 0.93, 2.09 | 0.113 | | | |
| Not compl., recurrence | | | | | | | 1.81 | 1.23, 2.66 | **<0.001** | | | |
| Not enrolled | | | | | | | 2.23 | 1.68, 2.97 | **<0.001** | | | |
| **Recurrence** | | | | | | | | | | | | |
| None within three years | | | | | | | — | — | | | | |
| Rec. within first year | | | | | | | 43.2 | 23.8, 78.5 | **<0.001** | | | |
| Rec. second year | | | | | | | 12.6 | 7.04, 22.6 | **<0.001** | | | |
| Rec. third year | | | | | | | 4.51 | 2.32, 8.78 | **<0.001** | | | |

[1] HR - Hazard ratio
[2] CI - CIonfidence interval (95 per cent)
[3] Resection period 2016-2019

### 5.6.3 Kaplan-Meier estimates for overall survival

In all four studies, inv-IPMN was associated in more favourable median OS compared to PDAC, in the spectra 26.3 – 34.5 months and 18.9 – 23.5 months respectively ($p<0.005$). However, in subclass analysis of outcome for different independent predictors for death retrieved from Cox regression analyses, results changed considerably.

#### *5.6.3.1 Subclass analyses*

Later resection years rendered a more favourable median OS compared to earlier in both study I and study IV (**Figure 3**). Tumour *subtype* analysis in study I revealed that intestinal subtype rendered more favourable median OS and adenosquamous subtype less favourable compared to pancreatobiliary subtype.

**Figure 3**

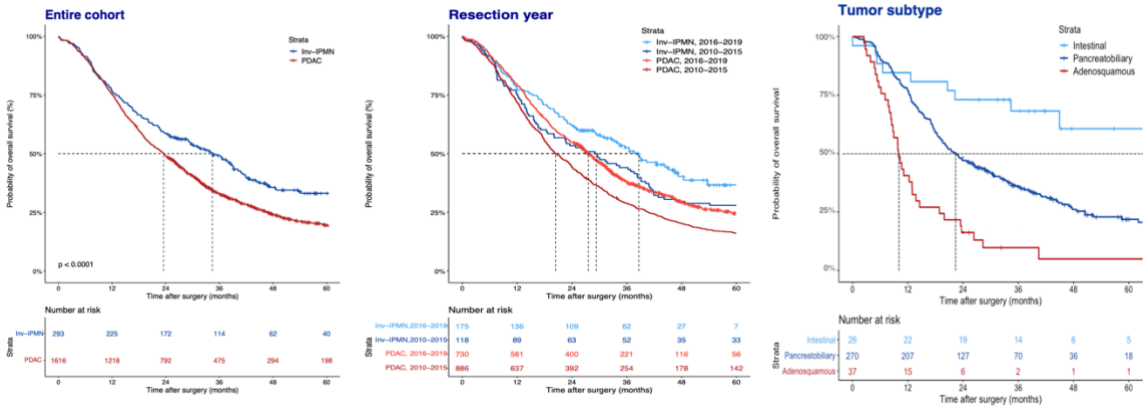


**Figure 3**: Kaplan-Meier survival curves for inv-IPMN and PDAC as well as tumour subtypes, and comparisons in median OS with log-rank test. A) In the entire cohort study IV B) In the 2010-2015 and 2016-2019 cohort in study IV C) Tumour subtypes in study I (63) DOI: 10.1016/j.pan.2021.07.009. Printed with permission from Elsevier for non-commercial thesis use, published with a Creative Commons Attribution 4.0 license.

TNM-stage analysis in study I, study II and study IV revealed that lower N- and M-stage rendered more favourable median OS for inv-IPMN compared to PDAC, but T-stage did not (**Figure 4**).

**Figure 4**

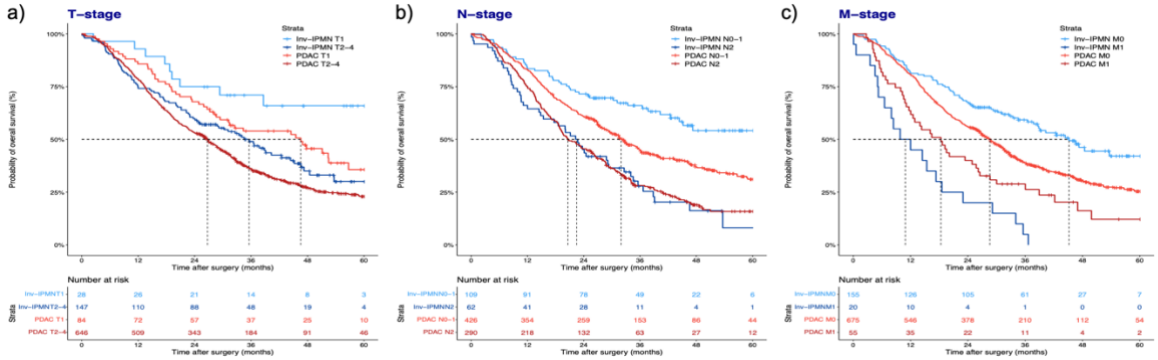


**Figure 4:** Kaplan-Meier survival curves for inv-IPMN and PDAC in different TNM-stages, and comparisons in median OS with log-rank test from study IV. a) T-stages b) N-stages c) M-stages.

Recurrence site analysis in study III revealed that there was no difference in median OS between inv-IPMN and PDAC when recurrence was present, no matter site (p = 0.1) but when recurrence was absent, inv-IPMN showed a more favourable median OS compared with PDAC (p = 0.01). Nevertheless, presence of specific recurrence had widely different effects on median OS (**Figure 5**). Presence of locoregional recurrence affected median OS only slightly compared to if locoregional recurrence was absence (19.7 vs 20.8 months; p = 0.008), but the difference was not significant within each tumour type (p>0.05). Neither did presence of lung metastases affect median OS negatively (28.4 versus 18.9 months; p = 0.3), and this was true both for inv-IPMN (27.1 versus 26.3 months; p = 0.5) and PDAC (28.4 versus 18.0 months; p = 0.08). However, presence of liver metastasis and peritoneal metastasis impacted median OS clearly and presented a difference between tumour groups.

Analyses of adjuvant chemotherapy in study III revealed that enrolment to treatment in general rendered more favourable outcome than no enrolment, that diagnosis of recurrence during treatment affected survival negatively and that combination therapy was associated with more favourable outcome than monotherapy (**Figure 5**).

**Figure 5**

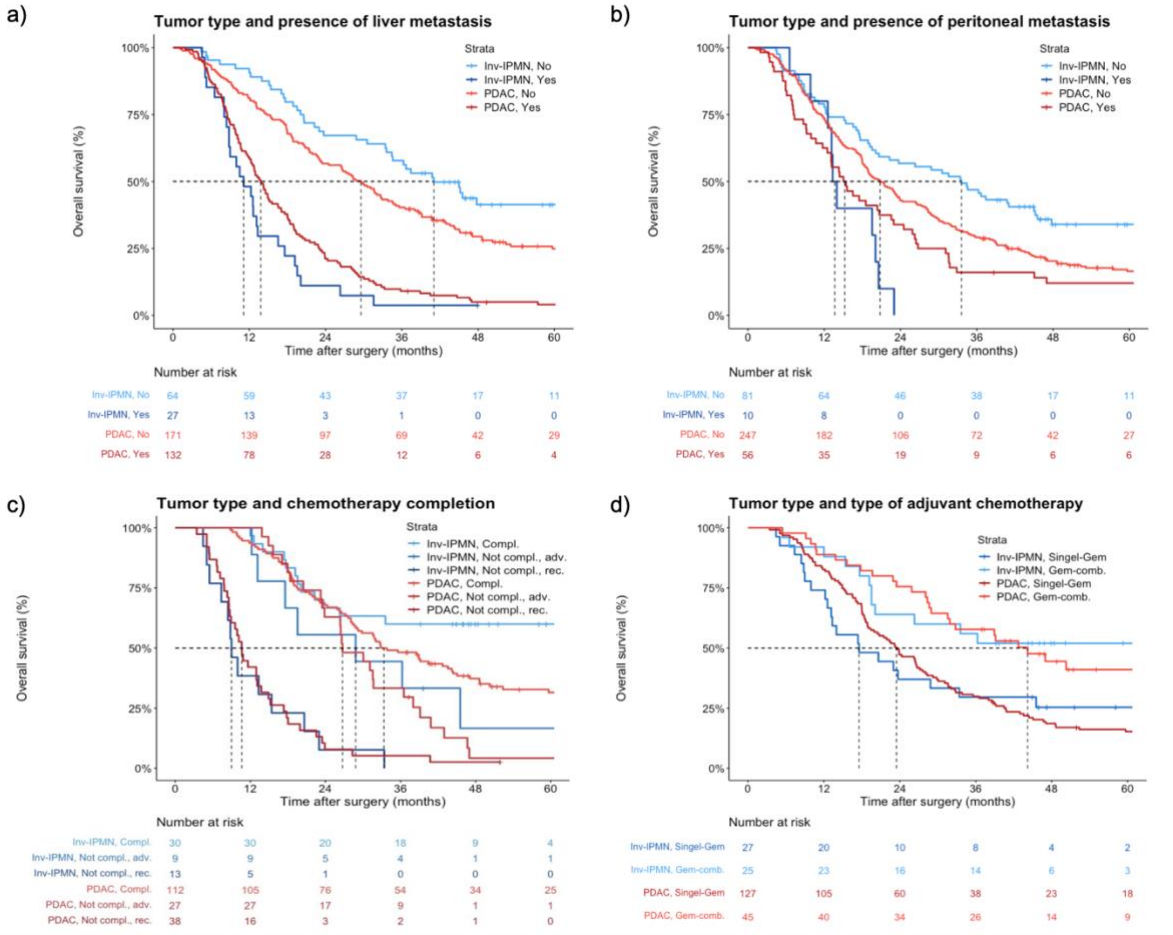


**Figure 5**: Kaplan-Meier survival curves for inv-IPMN and PDAC in different TNM-stages, and comparisons in median OS with log-rank test. a) Presence of liver recurrence clearly affected median OS negatively b) Presence of peritoneal recurrence also impacted survival negatively c) Completion of treatment d) Enrolment to Gemcitabine monotherapy was associated with an inferior median OS compared to Gemcitabine in combination therapy. Patients with inv-IPMN received combination therapy more often compared to PDAC.

# 6 DISCUSSION

The clinical importance of IPMN has undoubtedly increased dramatically over the last decade, but the long-term prognosis of inv-IPMN compared to PDAC has remained unsettled. This doctoral thesis, consisting of four retrospective observational studies of one regional and one national cohort, intended to elucidate similarities and differences between inv-IPMN and PDAC after pancreatic resection. *Study I* and *study IV* compared, from a regional and national perspective respectively, clinicopathological characteristics and overall survival between inv-IPMN and PDAC. *Study II* assessed the prognostic impact of PALN involvement in inv-IPMN and PDAC, and *Study III* explored the impact of initial recurrence patterns and effect of adjuvant chemotherapy for inv-IPMN and PDAC.

The doctoral thesis found that inv-IPMN were associated with a more indolent clinical presentation and pathological characteristics, less aggressive recurrence patterns despite similar exposure of adjuvant chemotherapy, more favourable outcome in early stages (T1, N0-1 and M0) and similar outcome in the more advanced stages T3-4-, N2-, M1. The doctoral thesis found that inv-IPMN were, compared to PDAC, generally resected in later years when survival was more favourable and were thus as a group not exposed to the higher mortality that patients with PDAC resected in earlier resection years were exposed.

## 6.1 BASELINE CHARACTERISTICS

### 6.1.1 Patient characteristics and clinical presentations

There were no significant differences in sex, age, BMI or CA19-9 levels between tumour groups in neither study. However, inv-IPMN were compared to PDAC more often asymptomatic, incidentally found or surveilled, and assessed pre-malignant at pre-operative radiologic assessment (study I). Also, both weight loss and biliary decompression were much less frequent in patients with inv-IPMN compared to PDAC in study IV. Weight loss seems to not impact survival in patients with resectable pancreatic cancer (64). Jaundice on the other hand is associated with increased risk for altered immunity, induction of the inflammatory cascade, tumour growth and metastases (65). Jaundiced patients treated with biliary decompression were indeed associated with worse median OS regardless of tumour group in study IV. Biliary obstruction is naturally highly dependent on tumour localisation (i.e. the pancreatic head) and even though both tumour types were equally often localized in the pancreatic head on pre-operative radiology, inv-IPMN underwent biliary decompression less often compared to PDAC, indicating that tumour microenvironment may differ between the tumour groups.

Certainly, these observations may constitute natural features of malignant cysts of the pancreas compared to their solid counterpart, but it may naturally also represent earlier presentation and/or less aggressive features. Incidentally found and/or surveilled tumours were more often staged T1 and N0-1, and had lower CA19-9 levels, characteristics that also demonstrated to be independent predictors for survival. Being over-represented among tumours diagnosed early surely may have important implications for outcome. The understanding of the importance of early detection in inv-IPMN has grown the last decade (34). It entails less aggressive tumours with lower risk for recurrence (46) and improved survival (33).

Findings from study I and study IV showed that the favourable outcome after inv-IPMN resection is limited to early-stage disease is partly in line with previous meta-analyses and series (51, 52, 66). Thus, possible explanation is that inv-IPMN are more often incidentally detected at early stages before symptoms have emerged or accidentally found after pre-emptive surgery among surveilled patients for suspected non-invasive IPMN with worrisome features.

### 6.1.2 Resection year

During the study periods, resected PDAC remained fairly stable but there was a substantial change in resection pattern for inv-IPMN, witnessed both in the national and the regional cohorts. As two-year OS concurrently improved in both study I and study IV, inv-IPMN being resected later were exposed to a relative survival benefit compared to PDAC. Resection period was actually found to be the strongest predictor for death in study I. This observation has previously not been reported but has likely occurred unnoticed elsewhere and earlier. In future comparisons of long-term survival in inv-IPMN and PDAC it is appropriate to adjust survival analysis for resection period.

## 6.2 HISTOPATHOLOGICAL CHARACTERISTICS

### 6.2.1 Tumour specifics

Although T1-staged inv-IPMN presented the longest median OS in study I, the difference was not statistically significant compared to T1-staged PDAC. N0-staged tumours were in study I associated with a promising two-year OS, regardless of tumour subtype, but only constituted a tenth of the entire cohort and although being twice as common in inv-IPMN compared to PDAC the survival benefit compared to N1-staged tumours vanished after five years according to Kaplan- Meier survival estimates. Nevertheless, for low staged N- and M-tumours in study IV, inv-IPMN demonstrated a clear survival benefit compared to PDAC.

Additionally, while the invasive part in N0-staged tumours were equal in size between groups in study IV (data not presented), node negative inv-IPMN was less often associated with venous resection, positive surgical margin and perineural invasion compared to node negative PDAC, thereby further demonstrating that the local tumoral conditions among lower staged PDAC tumours may be more hostile. Tumour biology and intrinsic neoplastic characteristics are important and differs between tumours (46) and epithelial subtypes seem to impact outcome more than underlying tumour type (63).

In study I, the vast majority had regional lymph node involvement, and more than half of the tumours were staged N2, a strong predictor for death according to studies I, II and IV. Fewer inv-IPMN were compared to PDAC staged N2 in study I, but this did not translate to a difference in two-year OS.

### 6.2.2 Regional and non-regional lymph nodes

As previous studies have reported (67-69), all cases with positive PALN in study II were also associated with positive regional lymph nodes. This finding indicates that the lymphatic spread from the pancreatic head to PALN share same key route, regardless of tumour type, of before entering the systemic system (70, 71).

Even though overall survival was shorter for PALN-positive patients in study II, PALN-status was not an independent predictor for death. This indicates that PALN-positivity may be associated with independent predictors for death, such as tumour differentiation, N-stage and microvascular invasion but is itself only a surrogate marker for death.

In study II, survival was similar in patients with N2 disease, regardless of PALN-status. As in previous studies, prognosis was poor when patients with PALN-positive tumours also presented with highly elevated CA19-9 levels (72) or did not receive adjuvant treatment (68, 73). Pancreatic resection in the presence of PALN metastases – if assessed intra-operatively – may therefore be questioned in patients with high age, low possibility of adjuvant chemotherapy and/or high CA19-9 levels, regardless of tumour type.

The abovementioned observation and previous reports that nodal negative tumours may have different outcome between tumour groups (52) and are not spared from recurrence (49) suggests that tumour biology and intrinsic neoplastic characteristics are important. Irrespective of underlying tumour type, three subtypes were identified and analyzed in study I and study III: intestinal, pancreatobiliary and adenosquamous subtype. The pancreatobiliary subtype was the most common. The adenosquamous subtype showed to be involved in ominous recurrence patterns and the strongest adverse predictor for death. It was luckily the least common subtype, but not as sparse as previously reported (45), neither for inv-IPMN, nor for PDAC. Intestinal subtype presented a favourable outcome as previously reported (74-76) and N2-staged tumours with intestinal subtype presented an outcome that was on par with N0-staged tumours with pancreatobiliary and adenosquamous subtypes. Although not a beneficial predictor for death in Cox regression, the superior outcome was clearly demonstrated in Kaplan-Meier survival analysis. Altogether, the abovementioned observations indicate that tumour subtype matters more than tumour type itself.

### 6.2.3 Metastases stage – presence of para-aortal lymph nodes

Although outcome was comparable between tumour groups in T3-4 and N2 disease, survival in M1-staged tumours was intriguingly worse among inv-IPMN compared to PDAC. A possible explanation is the association between M1-staged inv-IPMN and diabetes mellitus, a known promotor of high grade dysplasia and invasive carcinoma in IPMN (37) – especially for the colloid subtype (38) – and a risk factor of perineural invasion (77), an independent negative prognostic factor in pancreatic cancer (77), even for patients who have undergone pancreatic resection and receive adjuvant chemotherapy (78). Interestingly, all M1-staged inv-IPMN presented with perineural invasion. To the best of our knowledge this association between diabetes, perineural invasion, and higher staged inv-IPMN has not previously been reported and motivates further investigation to better understand the underlying biological mechanisms.

As data of epithelial subtypes was lacking in study IV and such comparisons were not undertaken in the regional studies, further exploration in the matter has not been possible, but the equal distribution of M1 disease in inv-IPMN and PDAC together with the inferior outcome in M1 inv-IPMN contrasts the previous reports of an association between inv-IPMN and the indolent colloid subtype (38) and indicates that other aspects than diabetes also may play a role.

Indeed, M1-staged inv-IPMN was associated with increased frequency of total pancreatectomies compared to both M1-staged PDAC and M0-staged inv-IPMN. At least

some of the total pancreatoduodenectomies were most likely performed as a consequence of considerable tumour extension and intra-operative commitment to carry on with radical resection to obtain negative surgical margin. Patients with PDAC situated in the head of the pancreas, where a positive intraoperative frozen section results in a total pancreatoduodenectomy in about ten per cent of the cases, have worse prognosis than patients with a negative frozen section (79), especially if R0-situation is not achieved (80). Although two-year OS for patients undergoing total pancreatoduodenectomy was similar between tumour groups (not shown data from study IV), it is reasonable to believe that the higher proportion of this procedure, with its inherently poorer survival, in M1-staged inv-IPMN has affected outcome negatively.

## 6.3 ADJUVANT CHEMOTHERAPY AND RECURRENCE PATTERN

Study III elucidated similarities and differences in spatio-temporal patterns for initial recurrences between inv-IPMN compared to PDAC, which clinicopathological factors were associated with the site of initial recurrence, and how adjuvant chemotherapy affected OS for different tumour types and recurrence patterns. Inv-IPMN was found to recur less frequently within three years after surgery and once relapsed the site of first recurrence was less often single site liver, single site peritoneum or multifocal – sites that proved to be involved with ominous outcome. Adjuvant chemotherapy had similar effect on OS between tumour groups. Median OS as well as three-year survival rate were more favourable for inv-IPMN compared with PDAC.

### 6.3.1 Adjuvant chemotherapy

Adjuvant chemotherapy improves outcome after resection for pancreatic cancer, although the effect is modest (25, 60, 81-84). For inv-IPMN the effect is vague (41, 85-88) and only seems to benefit patients with tumours that are higher staged, poorly differentiated and of tubular subtype (48). In study III, adjuvant chemotherapy was indeed associated with improved survival for inv-IPMN compared with PDAC. However, recurrence under chemotherapy occurred equally often between tumour groups and there was no survival difference between tumour groups stratified for therapy regimens. The observed difference may originate from inv-IPMN, having been resected proportionally more often in later years, benefitting more of the combination-therapy-regimen that dominated later years in the study period.

Evaluation studies of tailored treatments to match pancreatic cancer heterogeneity do show encouraging results, but the potential number of patients is unfortunately still small (89). A better understanding of how to match the distinct tumour biology with potent medical treatment will with luck delay the systemic dissemination and hopefully even bring cure to the patient. The first elemental step in this direction is to correlate different patterns of recurrence with distinctive clinicopathological traits (28). To understand *what* type of, and *when*, pancreatic cancers recur, will improve pre-operative patient selection in whom will benefit from neo-adjuvant treatment strategies in up-front resectable tumours with unrevealed systemic disease as well as aid planning adjuvant chemotherapy when more potent regimes will be available.

### 6.3.2 Recurrence pattern

Pancreatic cancer usually recur within two years after resection (28, 60, 82) and determines outcome (90). Early disease evolution is therefore pivotal for survival. The

effect of different adjuvant chemotherapeutical regimes have been evaluated in seven randomized controlled trials (25, 60, 81-84), and recent comprehensive meta-analysis and systematic review are available (2, 91). According to these studies the most common recurrence sites were locoregional (16-50%), liver (24-41%), peritoneal (11-23%), and lung (10-11%), depending on follow up and how multiple-site recurrences were handled.

Liver relapse, the most common single-site recurrence study III, was also important in multi-site recurrence and clearly linked with curtailed OS as previously reported (28), especially if relapsed within the first year. Interestingly, single- and multi-sited liver recurrences presented particularly similar OS, emphasizing the detrimental effect liver metastases entail. Adverse predictors for liver recurrence were adenosquamous subtype and poor tumour differentiation. Outcome for lung metastases, on the other hand, was clearly dependent on whether recurrence was single or multi-sited –single-site recurrence entailed a clearly superior OS but when part of a multi-site recurrence, outcome mimicked other simultaneous recurrences (**Figure 2**).

Predictors for lung metastases were T3-staged tumours, CA19.9 levels below (!) 200 and high-moderate tumour differentiation, highlighting that lung metastases often constitute a less aggressive form of relapse (25, 60, 83, 92-94) that represent an indolent biological subtype with a more gradual spread through distinct dissemination paths and/or homing mechanisms (2, 42, 95). Interestingly, when lesser common sites were present, such as brain and skeleton, lung metastases were overrepresented as concurrent site, suggesting shared disseminating paths.

Peritoneal metastasis was one of three ominous relapse sites, and if relapsed during the first year, poor outcome was particularly evident. Tumour localization in the pancreatic tail was the only adverse predictor, and this was almost three times more common in inv-IPMN compared to PDAC in study IV. Peritoneal metastasis seems to be the result from cell spillage from the primary tumour before or during surgery (2, 96). Interestingly, none of the patients with peritoneal metastasis derived from inv-IPMN survived two years. Even though median OS was not statically different compared to peritoneal metastases from PDAC, it is tempting to speculate that the inv-IPMN lesions results in cell-spillage more easily or to a greater extent, and thereby increase peritoneal tumour load compared to PDAC.

Multi-site recurrences were, together with single-site peritoneal and single-site liver metastases, the strongest predictors for death in study III, especially within first year after resection. Multi-site recurrence naturally involves a capacity for the tumour population to thrive in different environments as well as various paths for dissemination, and frequently a substantial tumour load. Interestingly, inv-IPMN were less commonly associated with these ominous recurrences compared to PDAC, and the intestinal subtype even less common compared to the other subtypes. Adenosquamous subtype, that was less frequently associated with inv-IPMN, was linked with recurrence in *all* cases.

The histological adenosquamous subtype is linked with the molecular squamous subtype that is associated with poor survival (17). In a recent study, squamous tumours correlated with liver recurrence and poor prognosis, and tumours derived from classical molecular subtype were more linked with lung recurrence and longer OS (94). This was evidently also the case study III (**Figure 3**).

As previously reported (90, 97), recurrences within the first year after resection in study III entailed poor outcome, especially if recurrence was multi-site, single site liver or single

site peritoneum and regardless of initial recurrence site (except for single site lung). Interestingly, as time to relapse increased, time from relapse to death also tended to increase, especially when diagnosed more than two years after resection. Tumour phenotype aggressiveness thus not only differs between recurrence sites, but also in time point. This implicates that patients with later relapses may benefit tailored management, even from prognostically aggressive sites (2). A patient with a single-site solitary liver metastasis that appears late, for example, may in selected cases be a better aspirant for directed therapy than a patient with a single-site lung metastasis with early debut, even though lung metastases generally are considered less aggressive.

Inv-IPMN compared to PDAC thus exhibit a more favourable initial recurrence pattern but do not hail the same survival benefit of adjuvant chemotherapy, which may explain why two-year OS between the tumour groups was similar. Based only on tumour type and its inherent recurrence pattern, this opens the way for prognosis stratification targets of treatment, and a more patient-tailored approach for patients with PDAC.

## 6.4 STRENGTHS

The major strength of this study is the large patient material including validated, high-quality, high-coverage data over a longer time period, especially for the national cohort.

Moreover, the population-based approach and the linkage of patient with death register data in the national study yielded an unbiased, long-term follow-up of all included study participants.

The three regional studies investigated various aspects of the similarities and differences between inv-IPMN and PDAC using one large common cohort, and not various.

## 6.5 LIMITATIONS

There are several limitations in this thesis that should be considered when interpreting the findings.

All four studies were retrospective analyses of registry databases with inferior data quality and lack of the standardization that controlled studies are endowed with. Three of the studies were single centre studies from one centre.

Patients pre-treated with neo-adjuvant chemotherapy were excluded in the analyses. The rationale was that pre-treatment may have influenced the pathological assessment of tumour size and differentiation, lymph node assessment (especially non-regional) as well as tumour subtype analyses. A “clean” histopathological assessment was prioritized.

The notably low frequency of inv-IPMN in the first half of the study period may represent a misdiagnosis of tumour type that potentially could have affected the results. This was at least partly handled in study I by creating a time-dependent variable in Cox regression and in study IV subgroup analyses restricted to the latter time period 2016-2019.

Initial recurrence sites that occurred within three years after resection were only regarded in study III. The extent of or the evolution of the relapses were not further assessed. Moreover, later recurrences after three years after resection were not analyzed. However, they

reportedly only account for a minor part of all recurrences and should have a limited impact on outcome.

The discrepancy of proportions resected between the regional and national cohort is disturbing. It may be caused by underreporting of other Swedish centras than Karolinska, it may represent regional differences in incidence and/or resection pattern

# 7 CONCLUSIONS

This thesis suggests that:

Overall survival is in general more favourable for inv-IPMN compared to PDAC (study I, study II, study III, study IV), especially for lower staged tumours (study IV). Overall survival for mid- and advanced-staged tumours seems comparable (study IV).

The shift in clinical practice with increased resected inv-IPMN in combination with subsiding hazard for death during the study period was an important predictor for death (study I and IV).

Post-surgical prognostication should be done with established predictors and tumour subtype rather than tumour type (study I).

PALN-status is equally present in inv-IPMN and PDAC. PALN-positive tumours impair survival, but PALN-status seems to be a surrogate marker for outcome and if found positive intra-operatively should not discourage from further resection, unless patient is of higher age, suffers severe comorbidity and/or presents with highly elevated CA19-9 levels (study II).

Inv-IPMN exhibit a more favourable initial recurrence pattern that translates into a survival benefit compared to PDAC. Later recurrences, regardless of site, entail an acceptable outcome and should be considered for tailored treatments (study III).

# 8 POINTS OF PERSPECTIVE

## 8.1 CLINICAL IMPLICATIONS

This thesis:
Highlights that inv-IPMN should continue to be regarded as a variant of PDAC with poor prognosis, but that outcomes are encouraging in some instances such as for lower staged tumours and intestinal tumour subtype. Consequently, continued effort for early detection by medical practitioners, surgeons and radiologists should persist and surveillance of pre-malignant IPMN should continue and be further optimised. Also, focus on tumour subtypes rather than tumour type entail a more precise prognosticating after resection and possibly even for selecting adjuvant chemotherapy in the future.

Strengthens the lacking evidence to treat inv-IPMN with adjuvant chemotherapeutic regimes designed for conventional PDAC. Studies are required for further confirmation and to optimising selection of chemotherapies.

Shows that positive PALN is inferior to N2-stage as an adverse predictor for outcome. As such the M1-status for positive PALN should be questioned. Also, intra-operative PALN-positivity (if analysed) should in general not disqualify further resection. It can however be questioned in patients of high age, high CA19-9 levels and low possibility of adjuvant chemotherapy.

Demonstrates that patients with recurrences within 3 months, regardless of tumour type, presented with highly elevated CA19-9 levels and tended to have tumours exceeding 4 cm on pre-operative radiology. As such instances motivate neo-adjuvant treatment abroad, this may also be adapted in Sweden.

Lifts up the question whether the correlation to diabetes is even stronger for inv-IPMN compared to PDAC.

## 8.2 FUTURE RESEARCH

Future research should aim to:
Find the sweet-spot for resection of pre-malignant IPMN. Balancing the decision of *surveillance* for potentially malignant lesions with major *surgery* associated with important morbidity and mortality for lesions with potential low-grade dysplasia solely on imaging is challenging.

Bridge the knowledge gap between clinicopathological traits and on the one hand genetic markers to find new ways of medically treat resected patients on the other hand to radiologic traits to improve decision making in surveilled patients.

Focus on optimizing adjuvant chemotherapy for inv-IPMN and explore the necessity for medical treatment for intestinal subtypes. The pessimistic prognosis of adenosquamous subtype also motivates further studies that investigate the benefits versus risks of adjuvant chemotherapy in this subtype.

Explore the relation between inv-IPMN and diabetes, and if surveillance should be designed differently for patients with diabetes mellitus and concomitant pancreatic cystic lesions.

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