2024

PANCREATODUODENECTOMY FOR MALIGNANCY: FACTORS INFLUENCING SURGICAL AND ONCOLOGICAL OUTCOMES

Russell, Thomas Brendon

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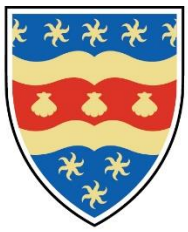


UNIVERSITY OF PLYMOUTH

PANCREATODUODENECTOMY FOR MALIGNANCY: FACTORS INFLUENCING SURGICAL AND ONCOLOGICAL OUTCOMES

by

Thomas Brendon Russell

A thesis submitted to the University of Plymouth in partial fulfilment for the degree of

DOCTOR OF MEDICINE

Peninsula Medical School

January 2024

Acknowledgements

Firstly, I would like to thank my Director of Studies, Somaiah Aroori, for providing me with the opportunity to undertake this piece of work. Secondly, I would like to thank my colleague, Pete Labib, for getting the ball rolling with the Recurrence After Whipple's (RAW) study. Thirdly, I would like to thank my supervisors, Jemimah Denson, David Sheridan and Adam Streeter, for their advice and input. Fourth, I must thank all those who contributed to the RAW study, and all those who commented on the RAW study papers. Fifth, I would like to thank my father-in-law, John Ovens, for the wonderful illustrations. Finally, I would like to thank my wife, Holly, for her patience and support, and my daughter, Eloise, for being a very cute distraction.

Author's declaration

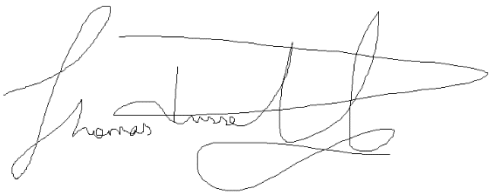
At no time during the registration for the degree of Doctor of Medicine has the author been registered for any other University award without prior agreement of the Doctoral College Quality Sub-Committee

This thesis has not been proofread by a third party.

Work submitted for this research degree at the University of Plymouth has not formed part of any other degree either at the University of Plymouth or at another establishment.

This study was financed with the aid of a studentship from University Hospitals Plymouth NHS Trust and carried out in collaboration with University Hospitals Plymouth NHS Trust.

Word count of main body of thesis: 43,091

Signed: 

Date: January 5th, 2024

Research outputs

List of publications related to thesis

1. Russell TB, Aroori S. The pancreas from a surgical perspective: an illustrated overview. *Art Surg* 2022. DOI: 10.21037/aos-21-2. Open access.
2. Russell TB, Aroori S. Pancreatic ductal adenocarcinoma from a surgical perspective. *Int J Cancer Res Ther* 2021;6(2): 67-74. Open access.
3. Russell TB, Aroori S. Procedure-specific morbidity of pancreatoduodenectomy: a systematic review of incidence and risk factors. *ANZ J Surg* 2022. DOI: 10.1111/ans.17473. Reproduced with written permission from John Wiley & Sons, Inc.
4. Russell TB, Labib PL, Aroori S. Selected preoperative factors which affect pancreatoduodenectomy outcomes: a systematic review. *Ann Pancreat Cancer* 2021. DOI: 10.21037/apc-21-15. Open access.
5. Russell TB, Labib PL, Aroori S. Selected intraoperative factors which affect pancreatoduodenectomy outcomes: a narrative review. *Ann Pancreat Cancer* 2022. DOI: 10.21037/apc-21-16. Open access.
6. Russell TB, Labib PL, Aroori S. Five-year follow-up after pancreatoduodenectomy performed for malignancy: a single-centre study. *Ann Hepatobiliary Pancreat Surg* 2023. DOI: 10.14701/ahbps.22-039. Open access.
7. Russell TB, Labib PL, Bowles M, Aroori S. Serious complications of pancreatoduodenectomy correlate with lower rates of adjuvant chemotherapy: would high-risk patients benefit from neoadjuvant chemotherapy? *Eur J Surg Oncol* 2022. DOI: 10.1016/j.ejso.2022.08.032. Reproduced with written permission from Elsevier.
8. Russell TB, Labib PL, Murphy P, et al. Do some patients receive parenteral nutrition unnecessarily after pancreatoduodenectomy? Results from an international multicentre study. *Ann Hepatobiliary Pancreat Surg* 2023. DOI: 10.14701/ahbps.23-071. Open access.
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pancreatic cancer: an international multicentre retrospective cohort study. *Eur J Surg Oncol* 2023. DOI: 10.1016/j.ejso.2023.04.018. Reproduced with written permission from Elsevier.

11. Russell TB, Labib PL, Denson J, et al. Predictors of actual five-year recurrence and survival after pancreatoduodenectomy for ampullary adenocarcinoma: an international multicentre cohort study. *HPB (Oxford)* 2023. DOI: 10.1016/j.hpb.2023.03.010. Reproduced with written permission from John Wiley & Sons, Inc.

List of oral presentations related to thesis

1. Russell TB, Labib PL, RAW Study Collaborators, Aroori S. Pancreatoduodenectomy for malignancy: which patients are high-risk? **SRS Research & Academic Prize Session:** *ASiT 2023* (Liverpool, UK) and **BJS Prize Session:** *ASGBI 2023* (Harrogate, UK). DOI: 10.1093/bjs/znad258.022.
2. Russell TB, Labib PL, RAW Study Collaborators, Aroori S. Predictors of five-year recurrence and five-year survival after pancreatoduodenectomy for ampullary adenocarcinoma: an international multicentre study. **BASO Prize Session:** *ASiT 2023* (Liverpool, UK) and **Oral Prize Session:** *National Research Collaborative Meeting 2023* (Cardiff, UK). DOI: 10.1093/bjs/znad241.002 and 10.1093/bjs/znad258.068, respectively.
3. Russell TB, Labib PL, RAW Study Collaborators, Aroori S. The impact of serious postoperative complications on adjuvant treatment following pancreatoduodenectomy for pancreatic cancer: an international multicentre retrospective cohort study. **Oral Prize Session:** *National Research Collaborative Meeting 2023* (Cardiff, UK).
4. Russell TB, Labib PL, RAW Study Collaborators, Aroori S. Do some patients receive parenteral nutrition unnecessarily after pancreatoduodenectomy? Results from an international multicentre study. **Oral Prize Session:** *National Research Collaborative Meeting 2023* (Cardiff, UK).
5. Russell TB, Labib PL, RAW Study Collaborators, Aroori S. Pancreatoduodenectomy for malignancy: results from the Recurrence After Whipple's (RAW) study. **Prize Session:** *RCS England South West Research Prize Session 2023* (Bristol, UK).

6. Russell TB, Labib PL, RAW Study Collaborators, Aroori S. Histological TNM stage and five-year survival after pancreatoduodenectomy for pancreatic ductal adenocarcinoma. *ASGBI 2023* (Harrogate, UK). DOI: 10.1093/bjs/znad241.028.
7. Blege H, Muhammad Q, Russell TB, RAW Study Collaborators, Marangoni G. Is routine nasogastric tube placement following pancreatoduodenectomy really necessary? *ASGBI 2023* (Harrogate, UK). DOI: 10.1093/bjs/znad241.029.
8. Pande R, Alfarah J, Roberts KJ, Russell TB, et al. Positive resected lymph nodes and long-term survival after pancreatoduodenectomy for pancreatic cancer: results from the Recurrence After Whipple's (RAW) study. E-AHPBA Congress 2023 (Lyon, France). DOI: 10.1016/j.hpb.2023.07.074.

List of poster presentations related to thesis (selected posters only)

1. Russell TB, Labib PL, RAW Study Collaborators, Aroori S. Serious complications of pancreatoduodenectomy correlate with lower rates of adjuvant chemotherapy: would high-risk patients benefit from neoadjuvant therapy? *AUGIS 2022* (Aberdeen, UK). DOI: 10.1093/bjs/znac404.123.
2. Russell TB, Labib PL, RAW Study Collaborators, Aroori S. Pancreatoduodenectomy for confirmed malignancy: a complication profile from the Recurrence After Whipple's (RAW) study. *AUGIS 2022* (Aberdeen, UK). DOI: 10.1093/bjs/znac404.109.
3. Russell TB, Labib PL, Aroori S. Five-year follow-up after pancreatoduodenectomy performed for malignancy: a fourteen-year experience. *AUGIS Annual Scientific Meeting 2022* (Aberdeen, UK). DOI: 10.1093/bjs/znac404.157.
4. Russell TB, Labib PL, RAW Study Collaborators, Aroori S. Resection margin status and five-year survival following pancreatoduodenectomy for pancreatic ductal adenocarcinoma. *AUGIS 2022* (Aberdeen, UK). DOI: 10.1093/bjs/znac404.159.
5. Russell TB, Labib PL, RAW Study Collaborators, Aroori S. Resection margin status, five-year recurrence and five-year survival in ampullary carcinoma and cholangiocarcinoma patients who undergo pancreatoduodenectomy. *AUGIS 2022* (Aberdeen, UK). DOI: 10.1093/bjs/znac404.160.
6. Russell TB, Labib PL, RAW Study Collaborators, Aroori S. C-reactive protein/albumin ratio may be helpful for assessing suitability for resection in patients with pancreatic head malignancy. *AUGIS 2022* (Aberdeen, UK). DOI: 10.1093/bjs/znac404.121.

7. Russell TB, Labib PL, RAW Study Collaborators, Aroori S. Patterns of recurrence after pancreatoduodenectomy for pancreatic cancer and the effect of palliative chemotherapy on survival. *AUGIS 2022* (Aberdeen, UK). DOI: 10.1093/bjs/znac404.161.
8. Russell TB, Labib PL, P Murphy, RAW Study Collaborators, Aroori S. Pancreatoduodenectomy for malignancy: which patients are high-risk? *PSGBI 2022* (Leeds, UK). Available at: psgbi.org/2022-annual-general-meeting/asm-2022-posters/.
9. Russell TB, Labib PL, RAW Study Collaborators, Aroori S. Histological stage and five-year recurrence/survival in patients who undergo pancreatoduodenectomy for ampullary adenocarcinoma. *ASGBI 2023* (Harrogate, UK). DOI: DOI: 10.1093/bjs/znad241.169.
10. Russell TB, Labib PL, RAW Study Collaborators, Aroori S. Histological stage and five-year outcomes in patients who undergo pancreatoduodenectomy for distal cholangiocarcinoma: an international multicentre study. *ASGBI 2023* (Harrogate, UK). DOI: 10.1093/bjs/znad241.176.
11. Russell TB, Labib PL, RAW Study Collaborators, Aroori S. Whipple's for ampullary adenocarcinoma: can we predict who will develop local only recurrence and tailor treatment to individuals? *ASGBI 2023* (Harrogate, UK). DOI: 10.1093/bjs/znad241.249.
12. Labib PL, Russell TB, RAW Study Collaborators, Aroori S. Patterns of recurrence following pancreatoduodenectomy for pancreatic cancer: results from the Recurrence After Whipple's (RAW) international retrospective cohort study. Scandinavian Baltic Pancreas Symposium 2023 (Stockholm, Sweden). DOI: 10.1016/j.hpb.2023.07.199.
13. Labib PL, Russell TB, RAW Study Collaborators, Aroori S. Predictors of local-only recurrence following pancreatoduodenectomy for pancreatic cancer: results from the Recurrence After Whipple's (RAW) international cohort study. E-AHPBA Congress 2023 (Lyon, France). DOI: 10.1016/j.hpb.2023.07.457.
14. Labib PL, Russell TB, RAW Study Collaborators, Aroori S. Risk of pancreatic cancer recurrence after surface/margin involvement on pancreatoduodenectomy specimens: implications for surgical radicality. Scandinavian Baltic Pancreas Symposium 2023 (Stockholm, Sweden). DOI: 10.1016/j.hpb.2023.07.609.

Honours and awards related to thesis

ASiT 2023 BASO Prize

ASGBI 2023 BJS Prize

E-AHPBA 2021 Travel Award

ASiT 2023 SRS Research & Academic Prize (shortlisted)

RCS England South West Research Prize 2023 (shortlisted)

National Research Collaborative 2023 Oral Presentation Prize (shortlisted)

AUGIS 2022 RCSEd Plenary Prize (shortlisted)

Abstract

Pancreatoduodenectomy for malignancy: factors influencing surgical and oncological outcomes

Thomas B. Russell

Introduction:

Fit patients with a resectable pancreatic head adenocarcinoma (PDAC), ampullary adenocarcinoma (AA) or distal cholangiocarcinoma (CC) may be offered pancreatoduodenectomy (PD) with curative-intent. However, perioperative morbidity and cancer recurrence rates are high. This thesis aimed to explore the factors influencing PD outcomes. A focus was placed on nutrition, postoperative complications, and recurrence in AA patients. It is hoped the findings will guide patient selection/consenting and have implications for patient management.

Methods:

A retrospective cohort study of patients who underwent PD for histologically-confirmed malignancy was carried out (2012-2015). Twenty-nine centres from eight countries were involved. Data on the following were collected: preoperative comorbidities and investigations, neoadjuvant treatment, operative details, postoperative complications, histology, adjuvant treatment, cancer recurrence, palliative treatment, and overall survival (OS).

Results:

In total, 1484 patients were included; 885 (59.6%), 394 (26.5%) and 205 (13.8%) had PDAC, AA and CC, respectively. Overall morbidity, major morbidity (Clavien-Dindo grade

≥III) and 90-day mortality rates were 53.4%, 16.9% and 3.8%, respectively. A high body mass index (BMI), an American Society of Anesthesiologists (ASA) grade >II and a classic Whipple approach all correlated with morbidity. Additionally, ASA grade >II patients were at increased risk of major morbidity and a raised BMI correlated with a greater risk of pancreatic leak. Almost half of the cohort received nutritional support (NS). Of these, 55.6% received parenteral nutrition (PN). In total, 19.6% of the patients who had an uneventful postoperative recovery received PN. Among the PDAC cohort, commencing adjuvant chemotherapy (AC) correlated with improved OS, and those who experienced major morbidity commenced AC less frequently. Among the AA cohort, 176 patients (44.7%) developed recurrence and the median time-to-recurrence was 14 months. Local only, local and distant, and distant only recurrence affected 34, 41 and 94 patients, respectively (site unknown: 7). A higher number of resected nodes, histological T stage >II, lymphatic invasion, perineural invasion (PNI), peripancreatic fat invasion (PPFI) and ≥1 positive resection margin all correlated with AA recurrence. Further, ≥1 positive margin, PPFI and PNI were associated with reduced time-to-recurrence.

Conclusions:

A considerable number of the patients that had an uneventful recovery received PN. Patients with a high BMI or ASA grade had worse perioperative outcomes. Those who experienced major morbidity commenced AC less frequently. Numerous histopathological predictors of AA recurrence and reduced time-to-recurrence were identified.

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Abbreviations

5YR = five-year recurrence

5YS = five-year survival

A/W = associated with

AA = ampullary adenocarcinoma

AC = adjuvant chemotherapy

ADM = acinar-to-ductal metaplasia

AF = atrial fibrillation

AJCC = American Joint Committee on Cancer

ALP = alkaline phosphatase

APC = adenomatous polyposis coli gene

AR = arterial resection

ARad. = adjuvant radiotherapy

ASA = American Society of Anesthesiologists

BL = bile leak

BMI = body mass index

BRCA1 = breast cancer 1 gene

BRCA2 = breast cancer 2 gene

CA = coeliac axis

CA 19-9 = cancer antigen 19-9

CABG = coronary artery bypass graft

CC = cholangiocarcinoma

CCF = congestive cardiac failure

CD = Clavien-Dindo

CDK4 = cyclin-dependent kinase 4 gene

CDKN2A = cyclin-dependent kinase inhibitor 2a gene

CDX2 = caudal related homeodomain transcription factor 2 gene

CEA = carcinoembryonic antigen

CHA = common hepatic artery

CK20 = cytokeratin 20 protein

CK7 = cytokeratin 7 gene

CL = chyle leak

COPD = chronic obstructive pulmonary disease

COX-2 = cyclooxygenase-2

CPET = cardiopulmonary exercise test

CRP = C-reactive protein

CR-POPF = clinically-relevant postoperative pancreatic fistula

CSS = cancer specific survival

CT = computed tomography

DFA = drain fluid amylase

DFS = disease-free survival

DGE = delayed gastric emptying

DM = diabetes mellitus

DP = distal pancreatectomy

EBL = estimated intraoperative blood loss

EGFR = epidermal growth factor receptor gene

ELF3 = ETS-related transcription factor 3 gene

EN = enteral nutrition

ERAS = Enhanced Recovery After Surgery

ERCP = endoscopic retrograde cholangiopancreatography

ESPAC = European Study Group of Pancreatic Cancer

ESPEN = European Society for Clinical Nutrition and Metabolism

EUS = endoscopic ultrasound

FAMMM = familial atypical multiple mole and melanoma syndrome

FBC = full blood count

FNA = fine needle aspiration

FOLFIRINOX = folinic acid, fluorouracil, irinotecan and oxaliplatin chemotherapy

G-J = gastro-jejunostomy

HA = hepatic artery

Hist. = Histological

H-J = hepato-jejunostomy

HPB = hepatopancreatobiliary

HR = hazard ratio

ICD-9-CM = International Classification of Diseases (9th revision)

ICU = intensive care unit

IL-6 = interleukin-6

Int. = intestinal subtype

IPDA = inferior pancreatoduodenal artery

IPMN = intraductal papillary mucinous neoplasm

IQR = interquartile range

ISGLS = International Study Group for Liver Surgery

ISGPS = International Study Group of Pancreatic Surgery

IVC = inferior vena cava

JT = jejunostomy tube

KRAS = Kirsten rat sarcoma virus gene

LFTs = liver function tests

LPD = laparoscopic pancreatoduodenectomy

MA = meta-analysis

MCL1 = myeloid leukaemia cell differentiation protein

MCN = mucinous cystic neoplasm

MD = median difference

MDT = multidisciplinary team

MI = myocardial infarction

MRI = magnetic resonance imaging

MSH2 = DNA mismatch repair Msh 2 gene

MUC1 = mucin 1 gene

MUC2 = mucin 2 gene

MUC5AC = mucin 5AC gene

NAC = neoadjuvant chemotherapy

NACRT = neoadjuvant chemoradiotherapy

NAT = neoadjuvant treatment/therapy

NG = nasogastric

NICE = National Institute for Health and Care Excellence

NJ = nasojejunal

NLR = neutrophil/lymphocyte ratio

NS = nutritional support

OR = odds ratio

OS = overall survival

PALB2 = partner and localiser of BRCA2 gene

PB = pancreatobiliary

PBS = preoperative biliary stenting

PD = pancreatoduodenectomy

PDAC = pancreatic ductal adenocarcinoma

PE = pulmonary embolism

PEI = pancreatic exocrine insufficiency

PET = positron emission tomography

P-G = pancreato-gastrostomy

P-J = pancreato-jejunostomy

PMS2 = postmeiotic segregation increased 2 gene

PN = parenteral nutrition

POD = postoperative day

POPF = postoperative pancreatic fistula

PP = pancreatic polypeptide cell

PPH = post-pancreatectomy haemorrhage

PPI = proton pump inhibitor

PTC = percutaneous transhepatic cholangiography

PV = portal vein

PVD = peripheral vascular disease

QoL = quality of life

R0 = complete resection (no positive resection margins)

R1 = microscopically incomplete resection (at least one positive margin)

R2 = macroscopically incomplete resection (tumour left *in situ*)

Rad. = radiological

RCS = Royal College of Surgeons of England

RCT = randomised controlled trial

RPD = robotic pancreatoduodenectomy

RR = relative risk

SD = standard deviation

SEER = Surveillance, Epidemiology, and End Results Program

SMA = superior mesenteric artery

SMAD4 = Mothers against decapentaplegic homolog 4 gene

SMV = superior mesenteric vein

SPDA = superior pancreatoduodenal artery

SR = systematic review

SSI = surgical site infection

STK11 = serine-threonine kinase 11 gene

TG13 = Tokyo Guidelines 2013

TNM = Tumour Node Metastasis

TP = total pancreatectomy

TP53 = tumour protein p53 gene

TSG = tumour suppressor gene

TTA = time to administration

TTD = time to death

TTR = time to recurrence

U&Es = urea and electrolytes

UICC = Union for International Cancer Control

USS = ultrasound scan

UTI = urinary tract infection

VIP = vasoactive intestinal peptide

VR = venous resection

Chapter 1: Introduction

Researcher's background

I qualified as a doctor in 2014 and have worked at several hospitals across the south of England since graduating. I am currently a surgical trainee and I aspire to become an upper gastrointestinal surgeon. I took two years out of my formal training to complete this piece of work. Prior to this, my experience in clinical research was very limited.

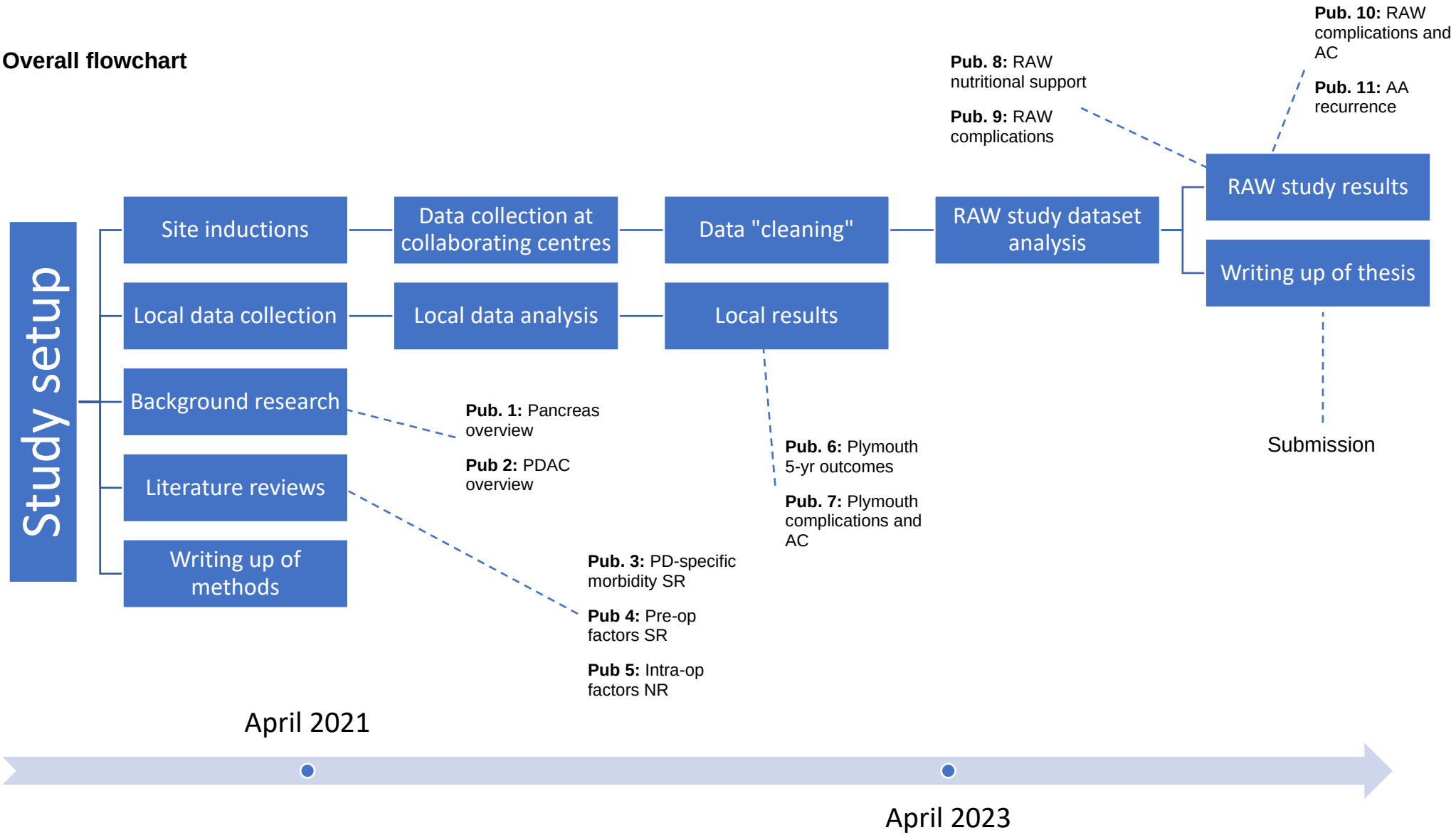
Structure of thesis

This thesis is centred around the findings of the Recurrence After Whipple's (RAW) study. This was a retrospective multicentre observational study which primarily aimed to study cancer recurrence patterns in pancreatoduodenectomy (PD) patients. Chapter 2 aimed to set the scene and provide an overview of the pancreas, the cancers which can affect the head of pancreas region, and the surgical treatment of these. The latter part of this chapter aimed to explore the short- and long-term outcomes of the PD (when performed for a malignant indication). Chapter 3 aimed to consolidate the recent evidence on the variables which were investigated as part of the RAW study. Chapter 4 aimed to describe the rationale for the RAW study and outline the methods in detail. Chapters 5 to 8 describe the results obtained and explore the clinical relevance of these. Chapter 9 is a summary of the thesis.

Coronavirus

Unfortunately, the coronavirus pandemic had an impact on the RAW study. Understandably, many research and development departments were not prepared to authorise new (unrelated) research projects and many clinicians were redeployed to other (non-surgical) departments. This was not something that could have been foreseen.

Overall flowchart



Background to research

Patients with a pancreatic head or periampullary malignancy have a poor prognosis. This is because this group of cancers are aggressive and they typically present late. An early diagnosis is uncommon as a screening programme is not feasible and there are no useful biomarkers. Therefore, preoperative imaging alone often guides decision making and a histological diagnosis is usually only obtained after PD. Most newly diagnosed patients are not surgical candidates and treatment is palliative. A minority may be offered PD with curative intent. However, this is a huge undertaking and morbidity/mortality rates are high. In addition, most patients develop recurrent disease, particularly those with PDAC or CC. Hence, both the surgical and oncological outcomes of PD are poor. However, PD remains the only treatment which can offer the possibility of long-term survival. Hence, it remains an attractive option and a commonly performed procedure.

Since PD outcomes are known to be suboptimal, surgeons are keen to try and improve patient care wherever possible, even if this only results in marginal gains. This can only be achieved by studying PD outcomes comprehensively. This may allow for the more accurate prediction of unfavourable outcomes. This information is useful for patient selection, the consenting process and healthcare systems planning, and could have implications for the management of individual patients. For example, a patient who is deemed to be high-risk for a serious postoperative complication may wish to consider their options. They may elect not to undergo PD or might be tempted to receive neoadjuvant chemotherapy (NAC) prior to PD. Additionally, if, after a course of NAC, repeat staging demonstrates a poor response to treatment, it may be that that particular patient was not a good surgical candidate in the first place. A patient who is deemed unlikely to achieve a positive long-term outcome may also feel the same way. The identification of patients who are more likely to develop disease recurrence could have implications for patient selection, preoperative treatment, the PD itself, adjuvant treatment, and postoperative surveillance/follow-up.

Rationale

- A detailed understanding of the pre- and perioperative factors which affect the outcomes of PD performed for histologically-confirmed malignancy could inform:
    - Patient selection
    - Consenting
    - The identification of the group of patients that might benefit from a tailored treatment approach e.g., targeted preoperative optimisation or NAC
- A detailed understanding of the factors associated with recurrent AA after PD could inform:
    - The prediction of individual patient outcomes
    - The identification of the group of patients that might benefit from a tailored treatment approach e.g., a more radical resection, adjuvant chemotherapy (AC) or earlier/more intensive postoperative surveillance

Objectives

- To describe the variations in the type of nutritional support provided after PD performed for malignancy
- To study PD perioperative outcomes in detail and investigate the impact of postoperative complications (if any) on AC rates and OS
- To study patterns of recurrence following PD performed for AA

Explanation

To better understand how to tailor treatment to individual patients, the factors associated with favourable/adverse PD outcomes must be better understood. Although prior studies have investigated the surgical outcomes of PD, few have done this with strict inclusion criteria and strict diagnostic criteria. For example, many previous studies have included studied age and sex, but few have considered medical history, preoperative treatment,

intraoperative details, the postoperative course and histopathological details. Further, very few have included five-year follow-up for all the included patients. This is essential if one wishes to study recurrence patterns and OS. Having a greater understanding of which patients are likely to achieve a favourable long-term outcome is imperative, as it is the possibility of a cure which motivates patients to opt for a resection in the first place. In addition, when one studies the long-term outcomes of PD, it is also essential that one considers the perioperative period, as this could have implications for OS. Finally, although some recently published studies have studied long-term survival after PD for malignancy, very few have investigated recurrence patterns in detail. The relative prognostic significance of the first recurrence and the most common anatomical sites is also not well described.

Many known factors influence the likelihood of recurrence, such as the use of AC or NAC, the proximity of tumour cells to the surgical margin, and histopathological details, such as the tumour size or evidence of lymphovascular invasion. Also, the width of the uninvolved resection margin required to fulfil the criteria for tumour involvement varies depending on which guidelines are consulted. British guidelines state that one mm of uninvolved tissue must be present. In contrast, American guidelines state that only the margin itself must be uninvolved, and do not stipulate a margin thickness. Correlating recurrence patterns with resection margin status may help to clarify which method is most appropriate. In addition, the potential association of other pathological staging elements with recurrence patterns has not been previously performed. Finding nodal involvement at the time of surgery may influence the likelihood of developing locoregional, rather than distant, metastases. Several other factors also influence the likelihood of recurrence that have not been fully explored. For example, detailed information on whether the specific site of local recurrence is related to the tumour site or a positive resection margin. These need to be considered as confounding variables that could influence OS.

The “perioperative and oncological outcomes of PD performed for malignancy” is a vast topic. Therefore, this thesis specifically focused on perioperative nutrition, postoperative complications, and oncological outcomes in patients with AA. I aimed to describe the variations in the types of nutritional support provided after PD and explore the implications of this. I also aimed to study PD perioperative outcomes in-depth and investigate the impact of postoperative complications (if any) on AC rates and OS. Finally, I aimed to study recurrence patterns in patients with AA.

Chapter 2: Background

2.1. The pancreas: a surgical perspective

This section aimed to provide an overview of the aspects of the pancreas which are relevant to the surgeon. It is a condensed version of the article listed below.

Russell TB, Aroori S. The pancreas from a surgical perspective: an illustrated overview. *Art Surg* 2022. DOI: 10.21037/aos-21-2. Open access.

Introduction

The human pancreas is a solitary, retroperitoneal organ. It has a flat leaf shape and lies obliquely across the upper abdomen at the level of the transpyloric plane. Its principal roles include the secretion of digestive enzymes and the regulation of serum glucose levels. The deep location of the pancreas and its proximity to other structures make pancreatic surgery challenging and high-risk[1]. This section aimed to provide an overview of the aspects of the pancreas which are relevant to the surgeon.

Anatomy

The pancreas comprises of a head, uncinate process, neck, and tail, and lies in the pararenal space. Its superior relations include the origin of the coeliac trunk, the common hepatic artery (CHA) and the splenic artery[1]. Anteriorly, the stomach, lesser sac (omental bursa) and transverse mesocolon can be found. Posteriorly are the aorta, inferior vena cava (IVC), portal vein (PV), and body of the second lumbar vertebra[1]. The head, the widest part; is disc-shaped and is wrapped by the inner curve created by the first three parts of the duodenum, to which it is connected via connective tissue. The head lies lateral to (to the right of) the superior mesenteric artery (SMA) and the superior mesenteric vein (SMV). The inferior extension of the head is the uncinate process. This

is a hook-shaped continuation of the inferomedial part of the head. It sits within the curve of the fourth part of the duodenum. The SMV and, occasionally, the SMA descend on its anterior surface. The neck of the pancreas, which connects the head to the body/tail, overlies the superior mesenteric vessels, which form a grove in its posterior surface[1]. The body lies to the left of the superior mesenteric vessels. Its anterior surface is covered by peritoneum which forms part of the posterior surface of the lesser sac. The body is anterior to the aorta and protrudes superiorly towards the spleen. The splenic artery follows the course of the body and creates a grove in its posterior and superior surfaces[1]. The tail is extra-peritoneal and lies in close proximity to the splenic hilum.

The head and uncinate process receive their blood supply from the superior (SPDA) and inferior pancreatoduodenal (IPDA) arteries, which each contribute to the anterior and posterior pancreatoduodenal arcades (**Figure 2.1**)[1]. The SPDA is a branch of the gastroduodenal artery. This derives from the CHA, a branch of the coeliac trunk. The IPDA arises from the SMA. Thus, the head and uncinate process receive blood from both embryological fore- and midgut sources[1]. The body and tail receive blood from numerous branches of the splenic artery[2]. The neck is a watershed area between these two vascular systems and venous drainage is via the portal system. The head and neck are mostly drained via the superior mesenteric branches of the PV. Short, fragile branches of the splenic vein drain the body and tail of the pancreas. The splenic vein passes posteriorly to the body where it joins the SMV to form the PV behind the pancreatic neck[1].

The pancreas is drained by a lymphatic network that largely follows that of the arterial supply. The vessels draining the head empty into the pyloric nodes, and the vessels draining the body and tail drain into the pancreatosplenic nodes. These ultimately drain into the superior mesenteric and coeliac nodes. The pancreas receives rich autonomic innervation as separate signalling pathways regulate the exocrine and endocrine functions. The parasympathetic component is received via fibres from the tenth cranial nerves, the vagus nerves[3]. Sympathetic innervation is from the lesser splanchnic nerves, which originate from the fifth to the twelfth thoracic vertebral levels[3].

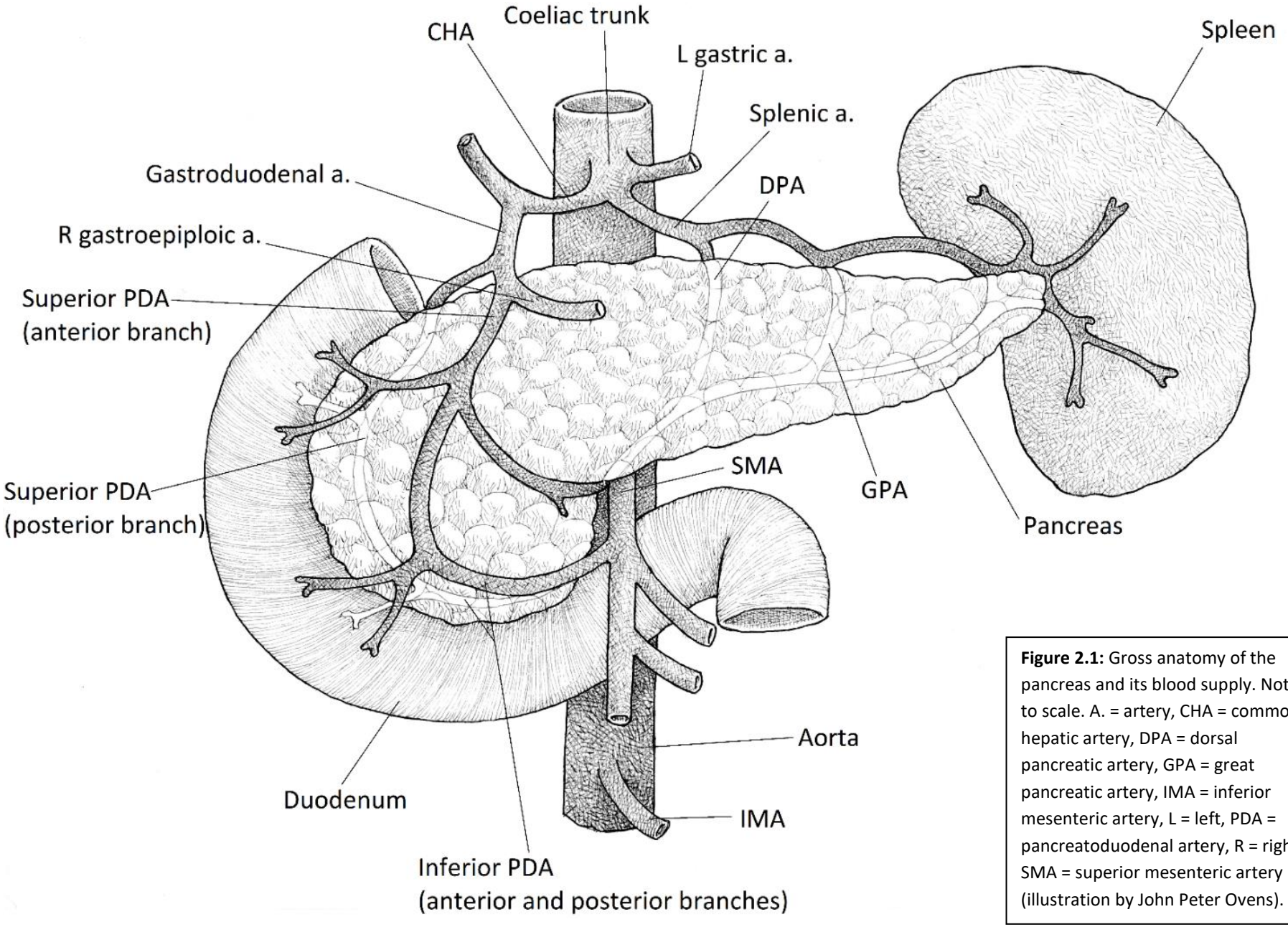


Figure 2.1: Gross anatomy of the pancreas and its blood supply. Not to scale. A. = artery, CHA = common hepatic artery, DPA = dorsal pancreatic artery, GPA = great pancreatic artery, IMA = inferior mesenteric artery, L = left, PDA = pancreatoduodenal artery, R = right, SMA = superior mesenteric artery (illustration by John Peter Ovens).

Within the pancreas is a system of ducts (**Figure 2.2**). Typically, the main pancreatic duct (of Wirsung) travels the entire ventral length of the pancreas from the tail to the bile duct, where the ampulla of Vater is formed. This opens into the second part of the duodenum at the major duodenal papilla[4]. The passing of secretions is controlled by the sphincter of Oddi, a smooth muscle sphincter which also prevents the reflux of enteral content into the ampulla.

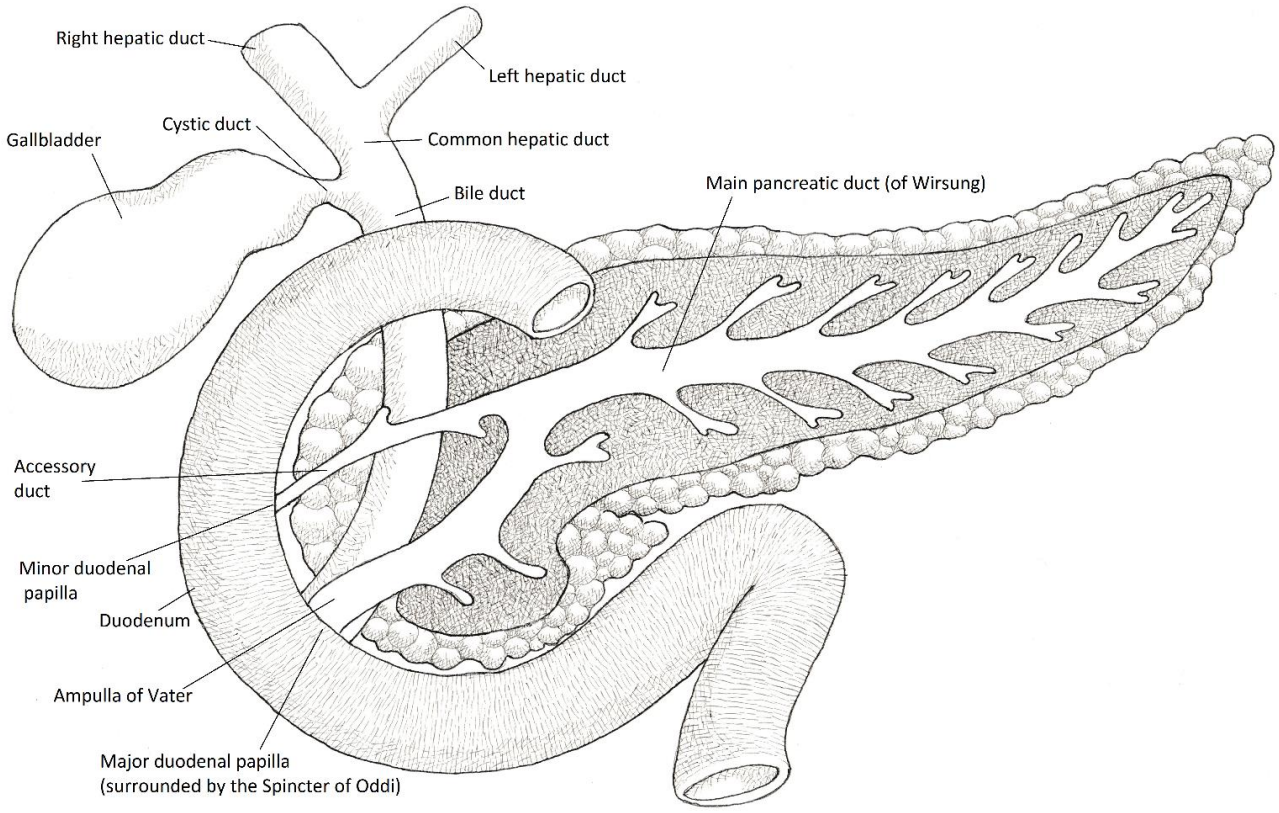


Figure 2.2: The pancreatic ductal system. Not to scale (illustration by John Peter Ovens).

Development

To understand how the pancreas develops it is reasonable first to consider how the duodenum develops (**Figure 2.3**). Information regarding the development of the human pancreas (**Figure 2.4**) is limited and most of our understanding regarding the critical steps is extrapolated from chick and mouse models[4]. Congenital abnormalities are illustrated in **Figure 2.5**.

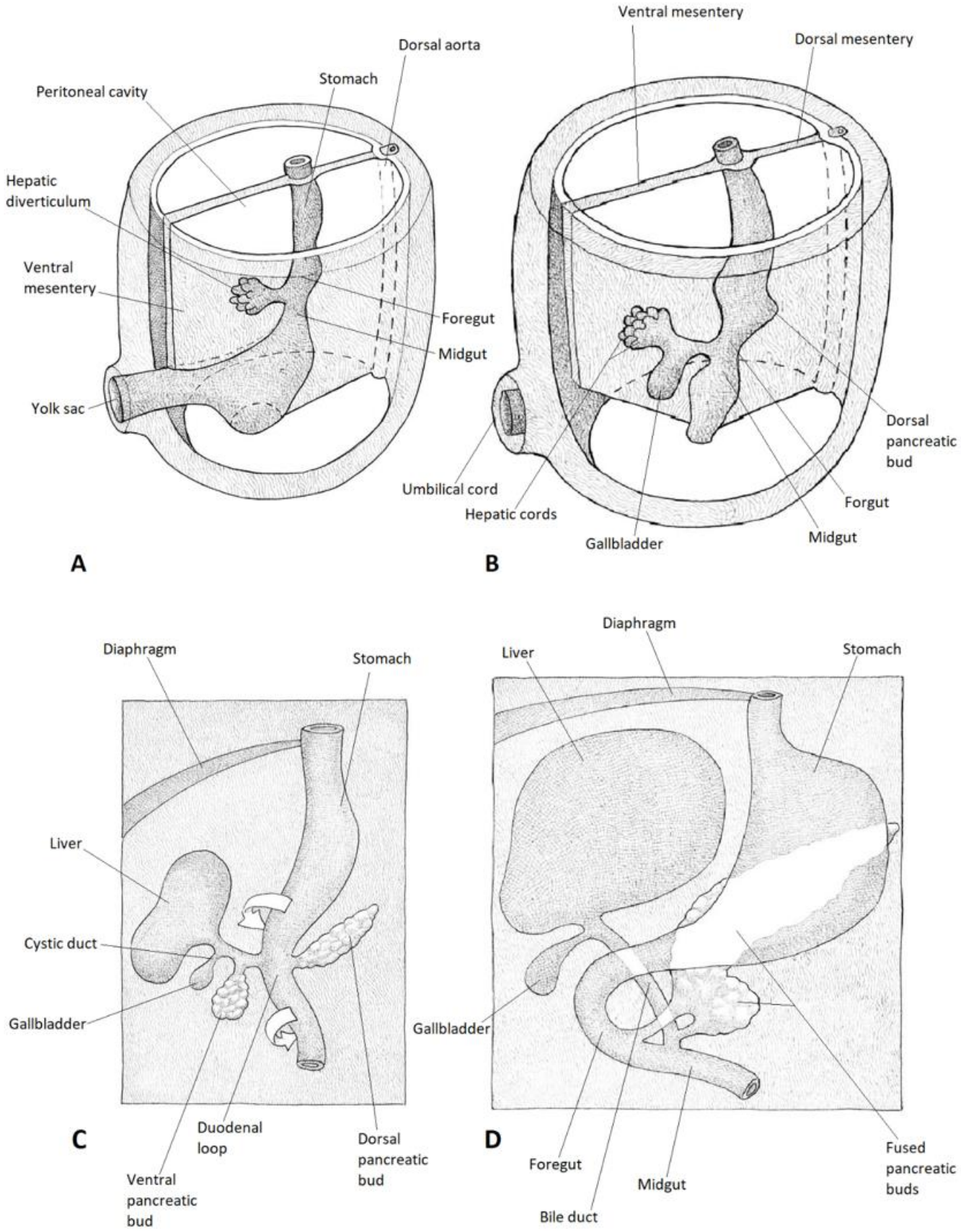


Figure 2.3: Development of the human duodenum. (A) Fourth gestational week, (B) early in the fifth week, (C) late in the fifth week, (D) sixth gestational week (illustrations by John Peter Ovens).

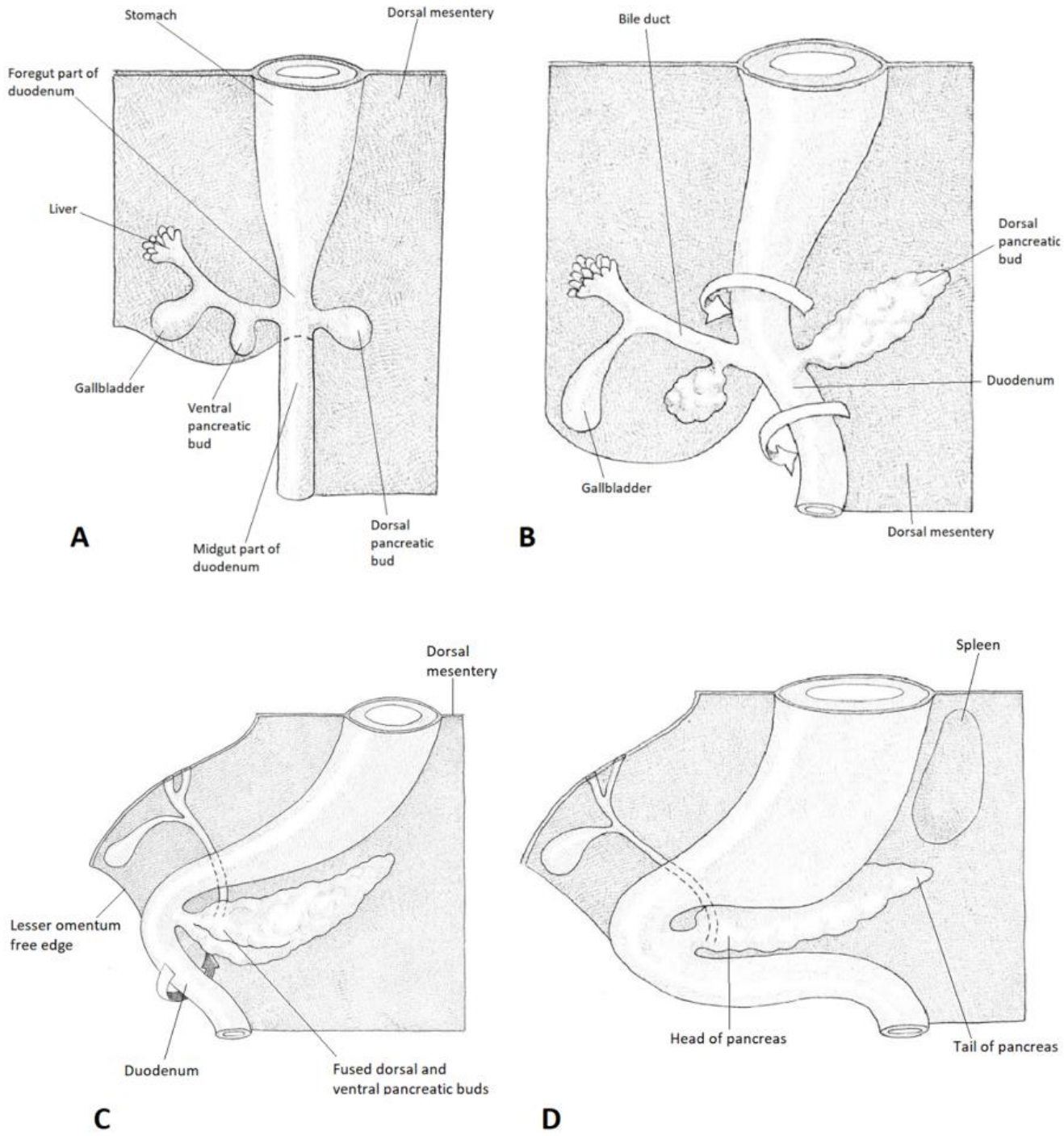


Figure 2.4: Development of the human pancreas. The dorsal and ventral buds form between the layers of mesentery. These groups of endodermal cells arise from the caudal foregut. (A) Fifth gestational week, (B) sixth week, (C) seventh week, (D) eighth week (illustrations by John Peter Ovens).

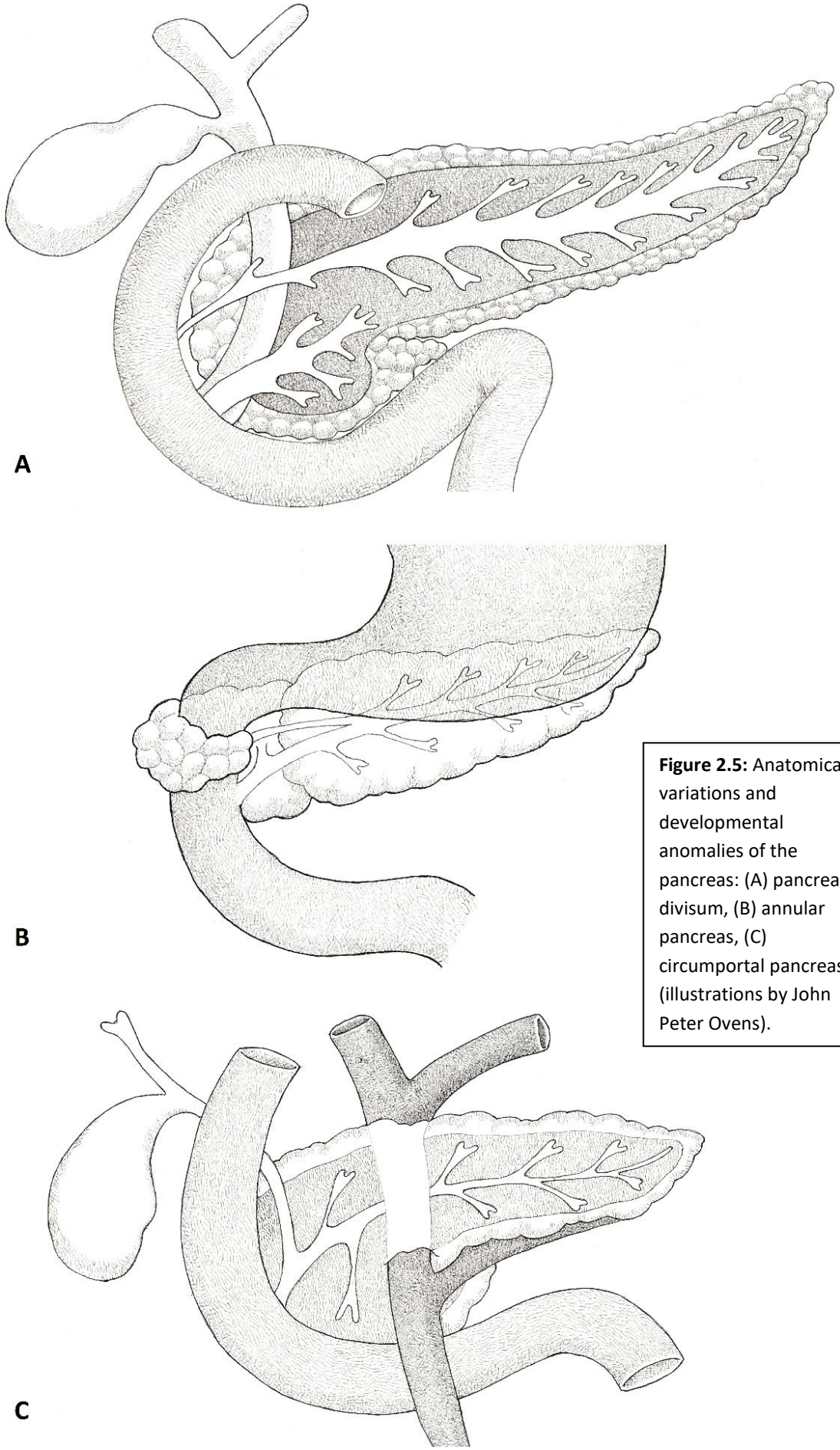


Figure 2.5: Anatomical variations and developmental anomalies of the pancreas: (A) pancreas divisum, (B) annular pancreas, (C) circumportal pancreas (illustrations by John Peter Ovens).

Exocrine function

An exocrine gland secretes a substance into a ductal system or onto an epithelial surface, whereas an endocrine gland secretes a substance directly into the bloodstream. Over 85% of the total pancreatic tissue is exocrine in nature; this is composed of units called acini, which are made up of acinar cells (**Figure 2.6**)[5]. Under the tight regulation of the neuroendocrine system, these cells synthesise and secrete enzymes which aid in the digestion of carbohydrates, proteins and fats[6]. These enzymes include trypsinogen, chymotrypsinogen, elastase, carboxypeptase, pancreatic lipase, nucleases, and amylase. Each acinar bundle is in direct communication with the pancreatic ductal system[5]. Centroacinar cells are the most peripheral exocrine cells; they partially cover the apical surface of the acini. These connect to a system of intercalated ducts which form intra- and interlobular ducts[5]. These ducts ultimately collect into the main pancreatic duct.

The secretions of the acinar cells combine with an alkaline, isotonic, bicarbonate-rich solution produced by the pancreatic ductal epithelial cells to form pancreatic juice[7]. This process is principally regulated by acetylcholine, released from vagal nerve endings, and cholecystokinin, an intestinal hormone. Secretin and vasoactive intestinal peptide (VIP) are also involved in this process. Cholecystokinin and secretin are released by the duodenal epithelial cells in response to the luminal presence of acidic chyme[8]. The bicarbonate-rich nature of the pancreatic juice ensures optimal enzyme function within the digestive tract. The rate of secretion, which itself is hormone-regulated, is markedly increased during mealtimes. Twenty-four hour total output is between two and three litres; this includes approximately 20 g of digestive enzymes[5].

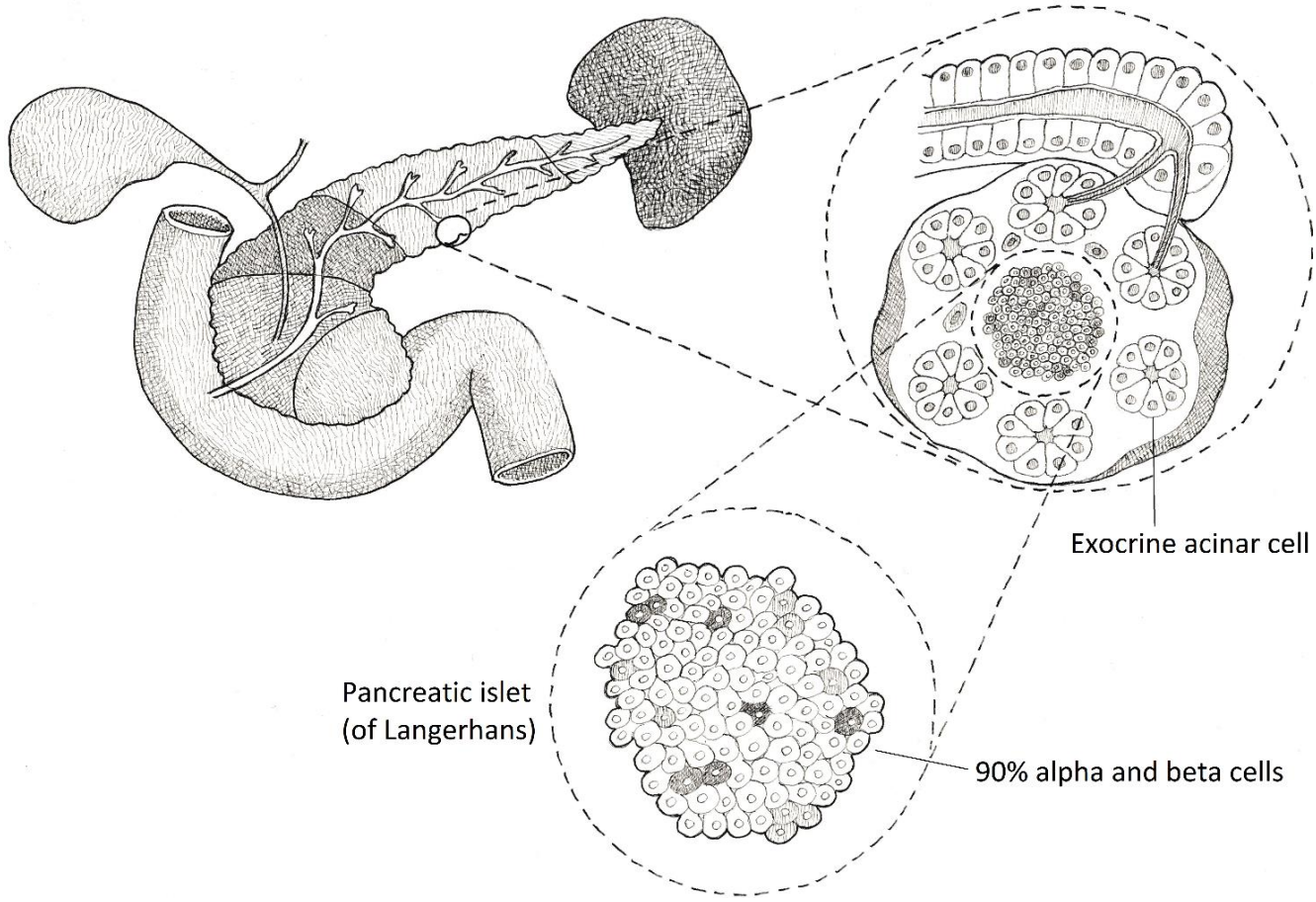


Figure 2.6: The acini and the islets of Langerhans (illustration by John Peter Ovens).

Endocrine function

The endocrine function is provided by groups of cells known as the pancreatic islets, or islets of Langerhans (**Figure 2.6**). These take their name from the German pathologist, Paul Langerhans, and are scattered throughout the parenchyma[9, 10]. A typical human pancreas has 3.2-14.8 million islets[10, 11]. Whilst each can contain up to a few thousand endocrine cells, the islets themselves make up only 2% of the total pancreatic tissue mass[11]. Each islet contains a central core of beta cells surrounded by a ring of alpha cells. Beta cells secrete the peptide hormone insulin, which stimulates glucose uptake by the cells. Alpha cells secrete glucagon, another peptide hormone, which counteracts insulin and increases serum glucose concentrations[12]. In healthy individuals, the production of insulin and glucagon is mediated by negative feedback mechanisms[12].

Alpha and beta cells make up around 90% of the islet cells[9]. The remaining 10% include delta cells, pancreatic polypeptide (PP) cells, epsilon cells, and others. Delta cells release somatostatin in response to acetylcholine, glutamate, urocortin-3, ghrelin, and high glucose concentrations[13]. Also known as growth hormone inhibiting hormone, somatostatin is a cyclic peptide which is known for its strong regulatory effects on various gastrointestinal and central nervous system functions[13]. It is a negative regulator of both insulin and glucagon[14]. PP cells, also known as F or gamma cells, comprise 1-2% of the islet cells[9]. They secrete pancreatic polypeptide, an inhibitor of glucagon when serum glucose concentrations are low[15], and are thought to have a role in satiety[16]. Ghrelin, produced by epsilon cells, inhibits insulin secretion and induces hunger.

2.2. Pancreatic head, ampullary and distal bile duct malignancies

2.2.1. Pancreatic ductal adenocarcinoma

This section aimed to cover the aspects of PDAC which are relevant to the surgeon. It is a condensed version of the article listed below.

Russell TB, Aroori S. Pancreatic ductal adenocarcinoma from a surgical perspective. *Int J Cancer Res Ther* 2021;6(2): 67-74.

Introduction

Most cases of PDAC affect the head of the pancreas. Around 80% of patients present with locally advanced or metastatic disease. Unfortunately, surgery is not possible in this group. About 20% of patients present with resectable disease and those with an appropriate performance status may be offered PD. Whilst this is a high-risk operation, it remains the only treatment option which offers the possibility of long-term survival. This section aimed to cover the aspects of PDAC which are relevant to the surgeon.

Epidemiology

Pancreatic cancer is the eleventh most common cancer worldwide and its incidence is set to increase[17]. Globally, 340,000 cases were diagnosed in 2012[18] and 460,000 cases were diagnosed in 2018, an increase of 36%[19]. During this time, the global population increased from 7.1 to 7.6 billion, an increase of 7%[19]. This trend was mainly due to population aging, which is set to continue[20]. Other contributory factors include increasing

rates of type II DM and obesity[17]. PDAC is more common in Western countries (**Figure 2.7**)[18] and its incidence is highest in those over seventy years[17].

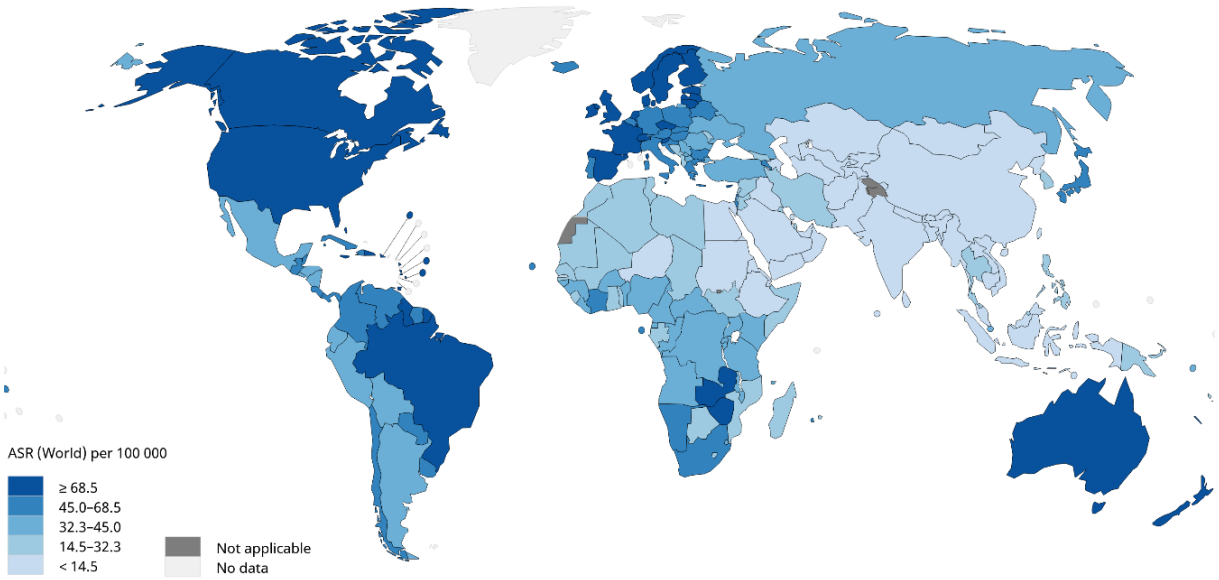


Figure 2.7: Estimated age-standardised incidence rates for pancreatic cancer worldwide in 2018 (reproduced, with written permission, from: gco.iarc.fr[21]).

Risk factors

There are both non-modifiable and modifiable risk factors for PDAC. The non-modifiable risk factors include increasing age, male sex, black ethnicity, non-O blood group, a family history, and type one DM[22]. Modifiable risk factors include smoking, high alcohol consumption, chronic pancreatitis, and obesity[22]. The International Agency for Research on Cancer concluded that smoking is causally associated with PDAC[23]. Indeed, lifetime risk is nearly twice as high in smokers. The risk increases with the number of cigarettes smoked per day and the duration of smoking[24]. There is limited evidence to suggest that a diet high in red or processed meat may be associated with PDAC[25]. Studies have also suggested an association with *Helicobacter pylori*[26] and hepatitis C infection[27].

Whilst most patients develop PDAC sporadically (see below), 5-10% of cases are hereditary and can be linked to a familial syndrome or a single mutation. Almost all cases

of Peutz-Jeghers syndrome are the result of a germline mutation in the serine-threonine kinase 11 (STK11) gene[28]. This syndrome results in the development of hamartomatous polyps within the digestive tract. Peutz-Jeghers patients have a highly increased risk of PDAC and other pancreatobiliary malignancies[28]. Mutations within the cyclin-dependent kinase inhibitor 2a (CDKN2A) or cyclin-dependent kinase 4 (CDK4) genes can result in familial atypical multiple mole and melanoma syndrome (FAMMM). People with this syndrome have large numbers of abnormal nevi. They are at increased risk of melanoma and PDAC[29]. Lynch syndrome (type II) can result from a mutation in one of several DNA mismatch repair genes: MLH1, MSH2, MSH6, or postmeiotic segregation increased 2 (PMS2)[30]. Lynch syndrome is an autosomal dominant condition which has long been associated with colorectal cancers, but patients with this condition also have a higher risk of PDAC[30]. A further syndrome which is strongly linked to PDAC is Li-Fraumeni syndrome, which is caused by a mutation in the tumour protein p53 (TP53) gene. Patients with this syndrome are also at greater risk of breast cancer, brain tumours and leukaemias[31]. Mutations in breast cancer genes 1 (BRCA1) and 2 (BRCA2), and the partner and localiser of BRCA2 (PALB2) gene also have a strong association with PDAC[31].

Pathogenesis

Most cases of PDAC are sporadic[32]. It is generally accepted that PDAC develops following a series of stepwise mutations and three precursor lesions have been identified[22]. Acinar-to-ductal metaplasia (ADM) is the process whereby acinar cells transition to epithelial cells when exposed to certain stimuli, such as cellular injury or chronic inflammation[33]. ADM results in acinar cells acquiring characteristics more typically associated with progenitor cells. As such, they are more prone to pro-oncogenic “hits” (the process whereby mutations in proto-oncogenes are activated) which results in the development of PDAC precursor tumours. The most common PDAC precursor tumours are pancreatic intraepithelial neoplasms (PanINs)[34]. The lifetime risk of a single

PanIN developing into a detectable PDAC is 1.3-1.5%[35]. Other malignant precursors include intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms (MCNs).

Following the initial hit, further hits to tumour suppressor genes (TSGs) ultimately result in the development of malignancy[36]. Several genes have been identified which exhibit the most frequent alterations/mutations in PDAC. These include the proto-oncogene Kirsten rat sarcoma virus (KRAS), as well as the TSGs TP53, CDKN2A, and Mothers against decapentaplegic homolog 4 (SMAD4)[37]. Whilst KRAS has been found to exhibit a mutation in over 90% of PDAC tumours, mutations in numerous other genes have been identified in certain subsets of PDAC tumour[38]. The extensive heterogeneity of PDAC is one of the reasons traditional cancer therapies have such limited efficacy[39]. A key feature of PDAC is its early progression to metastatic disease[40]. The proponents of this behaviour are not well understood since the genetic composition of most metastases is comparable to that of the primary tumour[41].

Presentation

The signs and symptoms typically associated with PDAC are not clinically apparent in the early stages of disease, so early diagnosis is challenging. Jaundice and weight loss are the most common presenting complaints. Jaundice is more common in patients with right sided lesions since they are more likely to cause biliary obstruction[42]. Unexplained weight loss can be the result of anorexia or malabsorption due to pancreatic exocrine insufficiency (PEI), or a combination of the two[42]. PEI can also result in steatorrhoea[42].

Whilst not typically a symptom associated with PDAC, around two thirds of patients experience abdominal pain[42, 43]. This is often in the epigastrium, and it is not uncommon for pain to radiate through to the back, as is common in pancreatitis. This may indicate involvement of the coeliac plexus. Some patients will present with back pain alone[42]. Less common forms of presentation include new onset diabetes mellitus (DM) and

venous thromboembolism[44]. The former is thought to be a paraneoplastic phenomenon in a subset of patients that precedes PDAC diagnosis[45]. Occasionally, peripancreatic oedema or a large tumour can result in gastric outlet obstruction[42].

Diagnosis

Almost half of all PDAC patients present acutely and just 13% are diagnosed via the two-week wait pathway. Most patients who present acutely will undergo routine blood tests (full blood count (FBC), urea and electrolytes (U&Es), liver function tests (LFTs), C-reactive protein (CRP), clotting screen, and serum amylase/lipase). Patients with biliary obstruction are likely to have abnormal LFTs. Otherwise, blood tests are unremarkable unless the disease is advanced. A transabdominal ultrasound scan (USS) may be requested at this point. This modality is readily available, inexpensive, non-invasive, and does not use ionising radiation. However, it is operator-dependent and reliability may be reduced by over-lying bowel gas, or if the patient is overweight[46]. Whilst ultrasound is useful for quickly identifying biliary obstruction, the retroperitoneal position of the pancreas means it is difficult to visualise with any level of detail. If malignancy is suspected, USS does not allow for accurate staging.

If PDAC is suspected, a timely pancreatic protocol computed tomography (CT) scan should be requested[47]. This includes arterial, late arterial, and venous phases[48]. Triphasic CT is advised as the difference in contrast enhancement between tumour and parenchyma is highest during the late arterial phase[48]. In addition to its diagnostic benefits, CT is the preferred modality for staging[48]. Future software developments may allow for the three-dimensional reconstruction of CT data so that even greater detail is provided on the anatomical relationship between the tumour and adjacent structures[49].

Staging and resectability status

If a patient with PDAC has not undergone a pancreatic protocol CT scan, a scan should be carried out which covers the chest, abdomen, and pelvis[47]. The National Institute for Health and Care Excellence (NICE) guidelines recommend that positron emission tomography (PET)-CT is offered to patients with locally advanced disease who are considering treatment. If further information is required, magnetic resonance imaging (MRI) is the modality of choice for suspected liver metastases and endoscopic ultrasound (EUS) may provide further information regarding tumour and node staging[47]. If resectional surgery is being considered but small-volume peritoneal or liver metastases are suspected, diagnostic laparoscopy is indicated[50]. The TNM staging system (officially known as the Tumour Node Metastasis classification system of malignant tumours) from the Union for International Cancer Control (UICC) is the most commonly used staging system for PDAC (**Figure 2.9**)[51]. The American Joint Committee on Cancer (AJCC) publishes its own cancer staging manual which is based upon this system. This standardised method is used to assess the extent of disease and guide treatment. It is important for determining whether a patient's disease is resectable or not (**Figure 2.3**)[52]. The resectability of a tumour is dependent on its location in the pancreas, the involvement of local vessels and/or lymph nodes, and the presence of metastases[53]. It is important to note that exocrine and endocrine tumours of the pancreas are now staged using different systems.

Primary tumour stage (T)	Tx	Cannot be assessed
	T0	No evidence of primary tumour
	Tis	Carcinoma *in situ*
	T1	≤2cm*
	T2	>2cm but ≤4cm*
	T3	>4cm*
*Greatest dimension	T4	Involvement of SMA or coeliac axis
Regional lymph nodes (N)	Nx	Cannot be assessed
	N0	No evidence of nodal involvement
	N1	1-3 regional lymph node metastases
	N2	>3 regional lymph node metastases
Metastases (M)	Mx	Cannot be assessed
	M0	No evidence of metastases
	M1	Distal metastases present

Figure 2.8: The 2017 (8th edition) UICC staging system for PDAC (data extracted from Shin et al., 2020[54]).

Biliary drainage

There are many potential pathophysiological consequences of obstructive jaundice. Firstly, cholestasis favours microbial proliferation within bile, which is usually sterile[55]. Secondly, raised pressure within the biliary tree has a knock-on effect in the liver where hepatocyte cellular function is affected[55]. Third, an absence of bile salts within the intestinal lumen can result in dysfunction of the intestinal mucosal barrier[55]. Fourth, due to liver dysfunction, there is increased absorption of endotoxin which can cause a systemic inflammatory response[55]. Fifth, reduced PV flow results in hepatocellular dysfunction[55]. Additionally, immune function, coagulation and wound healing may all be affected[55]. As such, in an attempt to reduce morbidity rates, surgical candidates traditionally underwent biliary drainage prior to PD. Indeed, Whipple first described a two-stage procedure for this very purpose[56]. NICE guidelines now recommend against this unless there is a clear indication, or the patient is enrolled in a trial[47]. This remains controversial. A recent Cochrane review found no strong evidence for or against

preoperative biliary drainage (PBD)[57]. In contrast, a recent multicentre randomised trial concluded that morbidity rates were higher in those who underwent PBD[58].

Vessel	Resectable	Borderline resectable	Unresectable
PV/SMV	No contact or contact <180° without vein contour irregularity	Contact >180° with deformity of vein or thrombosis but allowing safe and complete resection Contact with IVC	Unreconstructable obstruction Contact with most proximal draining jejunal branch
CHA	No arterial tumour contact	Contact without extension to CA or HA bifurcation	Contact with extension to CA or CHA bifurcation
CA	No arterial tumour contact	No contact (head) Contact <180° (body and tail)	Contact >180° Any contact with aorta
SMA	No arterial tumour contact	Contact <180°	Contact >180° Contact with 1st jejunal SMA branch Contact with aorta

Figure 2.9: The criteria which define resectability status PDAC (data extracted, with permission, from: jnccn.org[59]).

Preoperative treatment

In patients who have a clear indication for PBD, the preferred approach is via ERCP[58]. This includes patients with severe pruritis, acute cholangitis, or renal dysfunction secondary to jaundice[60]. This may also include patients with borderline resectable disease who are due to receive neoadjuvant therapy (NAT) prior to restaging. ERCP involves upper gastrointestinal endoscopy and intubation of the duodenum. The endoscopist locates and canulates the ampulla. Contrast can then be injected, and fluoroscopy is used to image the pancreatobiliary tree. A stent can then be deployed to the area of obstruction to allow the passage of bile and pancreatic juice. Metal stents are generally preferred to plastic stents since they are associated with lower complication rates[61]. Aside from the management of obstructive jaundice, ERCP (+/- sphincterotomy) can also be used to manage choledocholithiasis, inflammatory strictures, and surgical complications. ERCP is an effective and safe tool, but its potential complications must be considered. These include cholangitis, pancreatitis, duodenitis, haemorrhage (usually

only following sphincterotomy), and perforation of the bile duct, pancreatic duct, or duodenum[62]. In some circumstances, a serious complication of ERCP can prevent a patient from undergoing PD. In selected patients, if ERCP fails, percutaneous transhepatic cholangiography (PTC) may be utilised. In this technique, a needle is passed via the skin, abdominal wall, and liver under image guidance. The biliary tree is catheterised, and contrast is injected to allow fluoroscopic delineation of the anatomy. As with ERCP, an expanding stent can be deployed to relieve biliary obstruction. PTC is invasive and can be complicated by sepsis, haemorrhage, and pneumothorax (if the thoracic cavity is inadvertently breached)[61].

In the UK, NAT is not offered to patients with resectable disease; these patients proceed straight to PD. Patients with borderline resectable disease (**Figure 2.9**) may be offered neoadjuvant chemotherapy (NAC). If there is an appropriate response to treatment at the time of restaging, surgical resection may be offered to fit patients. See **Chapter 2.3** for the surgical management of PDAC.

Histological examination and pathological staging

A minimum of twelve lymph nodes must be sent with the specimen for staging to be considered accurate. PDAC is rarely diagnosed early and hence it is usual for a tumour to be 2-4cm (maximum diameter) at the time of examination, and the invasion of adjacent structures is common. PDAC tumours are typically a firm, poorly defined mass of an off-white colour. PDAC comprises abnormal tubular glands which mimic small pancreatic ducts, but a high level of heterogeneity is seen[63]. The circumferential resection margin consists of the anterior, posterior, and medial pancreatic surfaces. A resection margin is considered clear is there are no malignant cells within one millimetre of the cut surface (British guidelines)[63].

Adjuvant treatment

Adjuvant chemotherapy (AC) has become the gold standard following resectional surgery[64]. UK guidelines recommend that patients are given sufficient time to recover after PD before AC is administered[47]. This is commenced once they are deemed fit enough to tolerate six cycles. First-line therapy is gemcitabine plus capecitabine, and gemcitabine alone can be considered in those not fit enough to tolerate combination therapy[47]. The ESPAC-4 trial demonstrated that combination therapy can significantly improve median overall survival (compared to monotherapy)[64]. Patients who received adjuvant gemcitabine and capecitabine lived for a median of 1.7 months longer than those who received gemcitabine alone, and the former were found to have significantly higher five-year survival rates (28% vs 20%, p=0.049)[65]. Unfortunately, prognosis remains poor even in those who do receive AC as disease recurrence is common. Some patients who commence AC are unable to complete their planned course due to drug toxicity or early recurrence.

Treatment and prognosis

In the absence of metastases, patients with resectable disease affecting the pancreatic head/uncinate process are offered PD with curative intent, providing they have an appropriate performance status. Patients with an unresectable tumour and/or metastatic disease, and those not fit for major surgery, are offered palliative therapy only. When all newly diagnosed PDAC patients are considered, around a quarter survive for one year and only around 7% survive five years (irrespective of staging and the treatment received)[17]. See **Chapter 2.3** for the outcomes of PD when performed for PDAC.

2.2.2. Ampullary adenocarcinoma

Introduction

Most ampullary carcinomas are ampullary adenocarcinomas (AA). These are rare tumours of the ampullary complex. They can arise at any point from the confluence of the distal bile duct and the main pancreatic duct to the ampulla terminal. This is the anatomical region where the embryological fore- and midguts meet. In the Western world, the overall incidence of AA is less than 0.5 cases per 100,000, but incidence is increasing due to the growing use of endoscopy for unrelated causes, the screening of patients with familial adenomatous polyposis, and population aging[66]. Relative to other periampullary cancers, patients with an AA have a favourable prognosis. However, distinguishing an AA from other malignancies is challenging and outcomes remain poor compared to most other cancers which affect the digestive system. PD is the only curative-intent treatment. Although less aggressive surgical options have been explored[67], these are not commonly performed. Up to half of all newly diagnosed patients are potential surgical candidates. This section aimed to focus on the aspects of AA which are relevant to the surgeon.

Aetiology, epidemiology and histopathology

Around half of AAs are of intestinal epithelial subtype (originating from the intestinal epithelium overlying the ampulla) and around a quarter are pancreatobiliary (PB) subtype (arising from the epithelium of the distal bile duct and distal pancreatic duct). The remainder are “mixed” and display features of each subtype. Although most AAs occur sporadically, some individuals have a genetic predisposition. Those with a hereditary polyposis syndrome or hereditary nonpolyposis colorectal cancer are around 200 times more likely to develop AA than the background population[68]. Adenomatous polyposis coli (APC), TP53 and KRAS mutations have all been linked to intestinal type tumours, and

KRAS, TP53 and SMAD4 mutations have been linked to PB tumours[69]. AA most commonly presents in the seventh decade of life and, in the absence of a predisposing syndrome, is very rare in young individuals[70].

Intestinal subtype AAs more commonly resemble adenocarcinomas of gastrointestinal origin as opposed to those of PB origin. These tend to express cyclooxygenase-2 (COX-2), whereas those of PB origin do not[71]. Also commonly expressed are cytokeratin 20 (CK20), mucin 2 (MUC2) and caudal related homeodomain transcription factor 2 (CDX2), all of which are classical intestinal markers[72]. Intestinal subtype tumours are thought to be histologically similar to colorectal cancers which have central necrosis and cribriform or tubular glands[73]. PB subtype tumours are thought to arise from ampullary adenomas. These are premalignant precursor lesions associated with KRAS mutations[74]. PB subtype tumours are histologically more similar to cholangiocarcinomas (CC) or PDACs, and frequently express mucin 1 (MUC1), cytokeratin 7 (CK7) and mucin 5AC (MUC5AC)[75].

Presentation, investigation and management

Diagnosing AAs early is a challenge since patients may be asymptomatic in the early stages of disease. However, since even a small AA is likely to impede the flow of bile, patients often present earlier than in PDAC with jaundice. Other possible signs/symptoms include diarrhoea, weight loss, abdominal/back pain, gastrointestinal haemorrhage and lethargy[76]. As with PDAC, a patient's serum LFTs may demonstrate an obstructive picture but other blood tests are likely to be normal. An abdominal USS may demonstrate the classic double duct sign (around half of cases[77]) and MRI may delineate the presence of an ampullary mass or a bulging papilla. Whilst MRI is more sensitive than other imaging modalities for depicting AAs, specificity is low. Important differential diagnoses include ampullary adenomas, papillitis, and post-inflammatory stenosis, as well as PDAC and CC. If an AA is suspected, staging should be performed

using CT (chest, abdomen and pelvis). Unless clinically indicated, ERCP (+/- stenting) should not be performed. If ERCP (and/or EUS) is performed, fine needle aspiration (FNA) cytology may provide further information, but this still may not be definitive.

Treatment for patients with unresectable disease focusses on extending life and/or improving remaining quality of life. Fit patients with resectable disease may be offered PD via a straight-to-surgery approach. Although around half of AA patients who undergo PD will develop recurrent disease, NAT is not given as standard due to a lack of high quality evidence from randomised controlled trials (RCTs)[78].

After PD, patients who make a good recovery may be offered adjuvant therapy. Those who undergo a complete resection do not typically receive AC as there is no evidence to support this. However, recent authors have argued that this group may benefit from gemcitabine-based AC[79]. Patients with a large tumour, at least one positive resection margin and/or node positive disease are usually given gemcitabine-based AC, providing they are fit enough. However, most of the studies which have examined the role of AC were either retrospective or had a limited sample size with a potential for selection bias or confounding variables[80]. As such, the use of AC is variable since its true benefit is difficult to quantify.

The role of radiation therapy is even less clear. Radiotherapy may be considered in those who are deemed high-risk for recurrence e.g., patients who undergo an incomplete resection. However, definitive evidence on the overall clinical benefit of this is lacking[81]. If radiotherapy is given, the most commonly used dose is 50.4 Gy given in four to six weeks, either between chemotherapy cycles or after AC is completed. Post-treatment surveillance varies from country to country, and there are no specific guidelines. Patients who are high-risk for recurrence are often followed-up every three to six months for up to five years. The use of CT surveillance is also highly variable[82].

Treatment and prognosis

Since distinguishing between periampullary tumours preoperatively can be challenging (a preoperative histological diagnosis is not usually obtained), patients with a suspected AA are managed in the same way as those with a suspected pancreatic head adenocarcinoma. However, patients with an AA can expect to survive considerably longer. When all newly diagnosed patients are considered, one-year survival is in the region of 70% and five-year survival is around 40%[83]. See **Chapter 2.3** for the outcomes of PD.

2.2.3. Distal cholangiocarcinoma

Introduction

Cholangiocarcinomas are an aggressive and heterogenous group of cancers which account for around 2% of cancer-related deaths globally[84]. They can arise from anywhere along the biliary tract. Incidence is in the region of 0.3-6 per 100,000 per year[85]. CCs are generally divided into perihilar, distal and intrahepatic. Around 60% are perihilar and just 10% are intrahepatic[86]. This section aimed to focus on the 30% of CCs which affect the distal bile duct since, in selected patients with early disease, these can be managed surgically.

Aetiology, epidemiology and histopathology

CCs are slightly more common in Eastern countries/regions and, among Western populations, incidence is highest among individuals of Asian origin/ethnicity[87]. Many of the risk factors associated with CC tend to have an association with chronic inflammation of the biliary epithelium and biliary stasis, both of which can contribute to carcinogenesis[86]. High alcohol consumption, smoking, obesity and certain viral infections have been linked to CC development[88]. However, like AAs, most cases are sporadic.

Mutations in genes associated with detoxification, deoxyribonucleic acid repair, multidrug resistance, immune response and folate metabolism have all been linked to CC, e.g., KRAS, TP53 and ETS-related transcription factor 3 (ELF3)[86].

Distal CCs are usually flat or poorly defined nodular sclerosing tumours. The majority are conventional mucin-producing adenocarcinomas or papillary tumours[89]. They derive from columnar mucous cholangiocytes or peribiliary glands[84]. CCs tend to develop in cells affected by chronic inflammation since this can facilitate cholangiocyte transformation in a stepwise manner, e.g., through sustained interleukin-6 (IL-6)-signal transducer and activator of transcription (STAT) signalling, which can contribute to mitogenesis[84]. Similarly, although bile acids are not directly genotoxic, they may also promote cholangiocyte transformation via the activation of epidermal growth factor receptor (EGFR), the induction of COX-2, myeloid leukaemia cell differentiation protein (MCL1) and IL-6, and the downregulation of farnesoid X receptor[90].

Presentation, investigation and management

Distal CCs are often asymptomatic in the early stages of disease. Hence, they often present late. This limits treatment options considerably and results in a dismal prognosis. Around 70% of patients are diagnosed with advanced disease and are palliated. The remainder may present with jaundice or symptoms/signs typical of PDAC or AA. They tend to be investigated in the same way with blood tests and an abdominal USS, followed by MRI (+/- ERCP/EUS). All patients with a suspected periampullary malignancy should then undergo a CT of the chest, abdomen and pelvis for staging purposes. Around 25% of newly diagnosed patients are candidates for PD. Prior to surgery, PBD should only be performed in patients in whom there is a clear indication. Like in PDAC and AA, NAT is not recommended in those with resectable disease. Postoperatively, Patients that make an appropriate recovery may be offered gemcitabine-based AC[84]. The role of chemoradiotherapy remains unclear. This may provide an additional survival benefit in

those with positive resection margins or other risk factors for disease recurrence, but this requires further investigation.

Treatment and prognosis

Patients with a suspected distal CC are managed in the same way as patients with a suspected periampullary PDAC or AA (diagnosis is challenging using imaging alone and a histological diagnosis is often not obtained preoperatively). Unfortunately, over a third of CC patients present with advanced disease and their prognosis is very poor. In a study of 1338 patients with a newly diagnosed distal CC by Strijker et al., one-, three- and five-year OS rates were 46%, 18% and 11%, respectively (all patients considered)[91]. Patients who present with unresectable disease have a median OS of just twelve months and those with resectable disease have a median OS of around 50 months[84]. See **Chapter 2.3** for the outcomes of PD performed for distal CC.

2.3. The pancreatoduodenectomy

2.3.1. The procedure

Introduction

Pancreatoduodenectomy is the only curative-intent treatment option for patients with a pancreatic head carcinoma, AA or distal CC. This section aimed to focus on the procedure itself, the associated risks, and patient outcomes.

History

The origin of the PD procedure remains controversial. Alessandro Codivilla carried out a version of the operation in Italy in 1898[92]. Codivilla's patient died on the eighteenth postoperative day; this led to the thinking that the duodenum was essential for human survival. It was Abel Desjardins, in 1907, and Louis Sauvé, in 1908, both Frenchman, who first suggested that life after duodenal resection was possible. However, they only attempted this in cadavers[92]. In 1900, the British surgeon, Sir Arthur Mayo-Robson, had attempted to excise a cylindrical segment of duodenum, but his patient died on the operating table[93]. The German surgeon, William Koerte, attempted the same procedure four years later but his patient also died[93]. In 1912, also in Germany, Walther Kausch performed an incomplete duodenectomy with partial pancreatectomy[93]. He left part of the duodenum *in situ* and fashioned a pancreatoduodenostomy, believing the patient could not survive if the entire duodenum was excised. In 1918, the American surgeon Lester Dragstedt demonstrated that duodenectomy was compatible with survival in dogs[94]. However, it was almost twenty years later, in 1935, when the Iran-born American, Allen Whipple, described a total duodenectomy as part of a two-stage operation[56]. Whilst the technique has been modified greatly, the PD is often referred to as the Kausch-Whipple procedure. Some historians argue that this is perhaps unfair since numerous individuals were instrumental in the development of the modern operation. Although Whipple popularised the operation in the 1930s, it wasn't until the 1980s that it was commonly performed.

Surgical approach

The classic approach involves *en bloc* removal of the antrum of the stomach, the entire duodenum, the head and uncinate process of the pancreas, the entire bile duct up to the confluence of the left and right hepatic ducts, and the gallbladder (**Figure 2.10**)[95]. In the pylorus-preserving PD, a cuff of duodenum and the antrum are left *in situ* to preserve the pyloric sphincter[95]. Regardless of the technique used, PD is a major operation; around

half of all PD patients experience morbidity and 2-4% experience perioperative mortality[96]. Non-specific surgical complications include chest infection, haemorrhage, myocardial infarction (MI), arrythmias, stroke, venous thromboembolism, ileus, wound infection/dehiscence, and incisional hernias[97]. Procedure-specific complications include POPF, PPH, biliary tree injury, bile leak (BL), G-J leak, intra-abdominal sepsis, acute pancreatitis, DGE, and chyle leak (CL)[96, 98]. Longer-term complications include anastomotic stricture, malnutrition, pancreatic endocrine and/or exocrine insufficiency, and low mood/reduced quality of life[96].

Patients will usually have a nasogastric (NG) tube and urinary catheter placed once they are anaesthetised. The initial incision depends on the surgeon's preference. Modifications of a right subcostal (extended Kocher), bilateral subcostal (rooftop), or upper midline laparotomy are the most commonly utilised. After examining for extra-pancreatic disease, the surgeon will mobilise the hepatic flexure of the colon and "Kocherise" the duodenum to lift the head of the pancreas and the duodenum from the inferior vena cava and abdominal aorta. Dissection behind the neck of the pancreas can then be carried out to develop a plane between the SMV/PV junction and the neck of the pancreas. The lesser sac is then opened to inspect the entire pancreas and separate the posterior wall of the stomach from the body and tail of the pancreas.

The next step in the PD procedure is cholecystectomy; the gallbladder is isolated and detached from the liver, and the common hepatic duct is divided before the lymph nodes adjacent to the porta are excised[99]. The gastroduodenal artery is then divided, and the surgeon proceeds to divide the distal stomach or the first part of the duodenum. The pancreas is divided in front of the PV and the specimen is extracted and sent for histological examination[99]. The reconstructive phase of the operation can then take place; the surgeon proceeds to form a P-J (or P-G), a H-J, and a G-J (**Figure 2.11**). A surgical drain is typically placed adjacent to the P-J/P-G and H-J prior to closure.

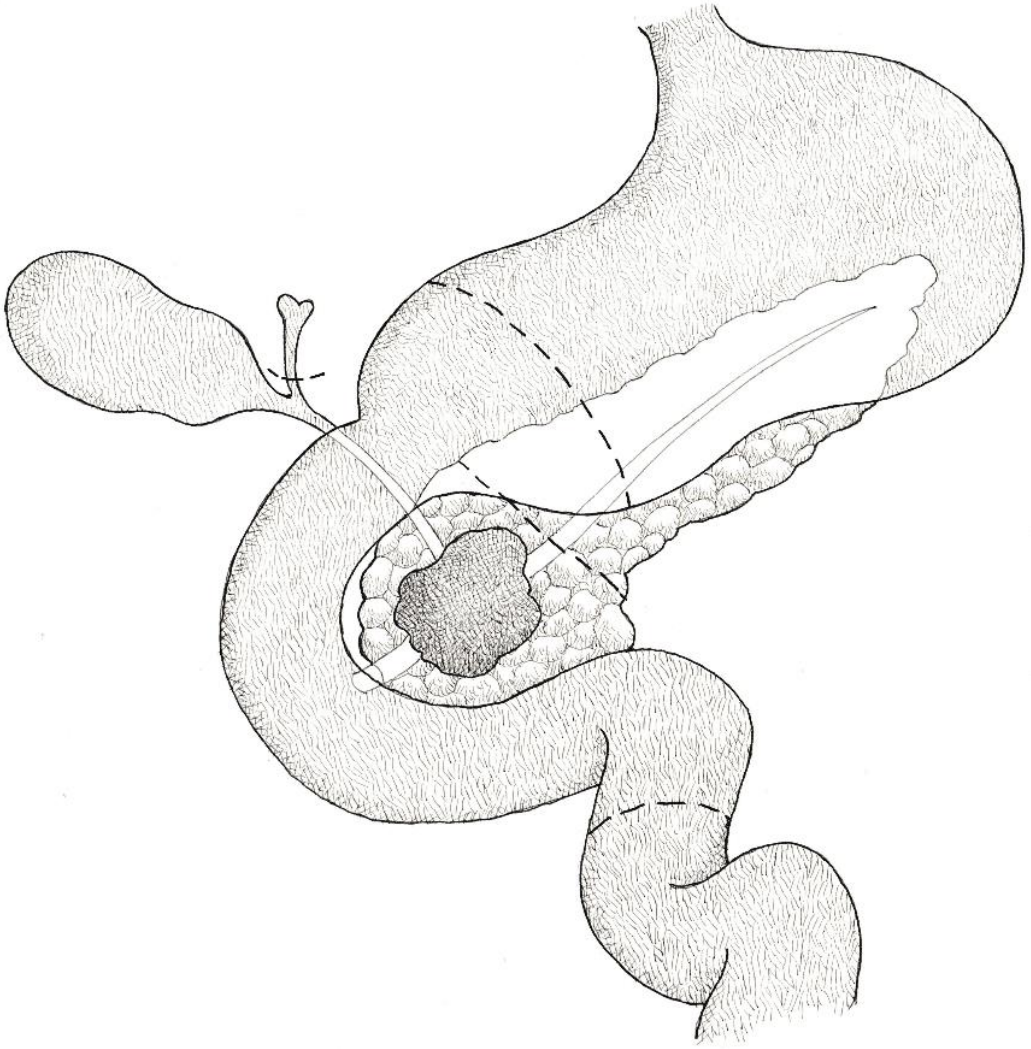


Figure 2.10: An illustration of what is resected during the PD (illustration by John Peter Ovens). The procedure involves the resection of the distal stomach, duodenum, pancreatic head and gallbladder. Some surgeons prefer to perform a pylorus-preserving procedure, where the pyloric ring is left *in situ*.

Postoperative care

Providing there are no intraoperative complications, postoperative management is guided by the Enhanced Recovery After Surgery (ERAS) protocol[100]. The NG tube, urinary catheter, and surgical drain/s are removed as soon as is reasonable[100]. Early oral diet and mobilisation are encouraged[100]. In recent years, PD has been performed laparoscopically and with robotic assistance in some specialist centres. Open PD remains the standard of care[101].

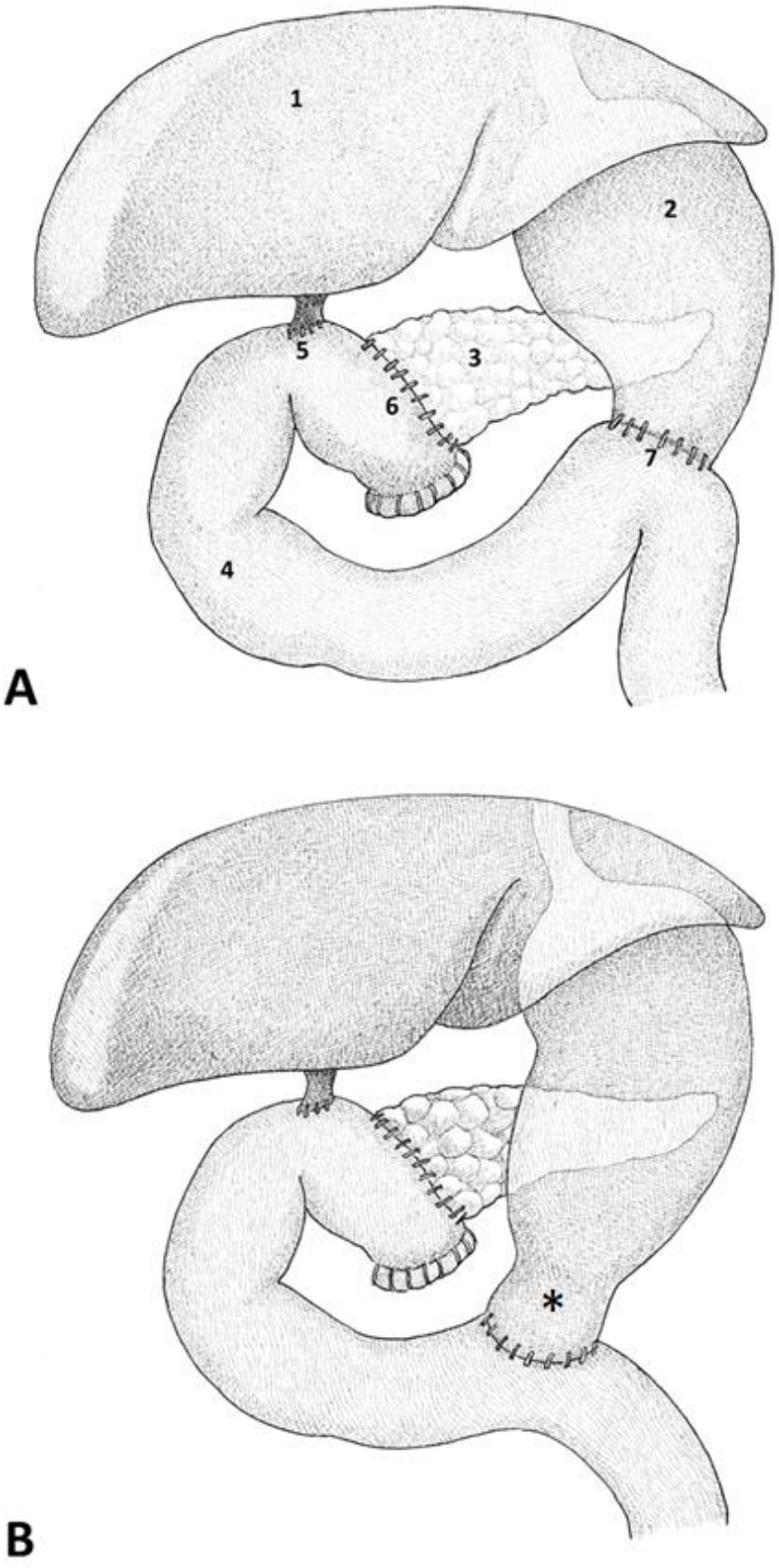


Figure 2.11: Patient anatomy following the PD. The classic (A) and pylorus-preserving (B) approaches (both are acceptable). 1 = liver, 2 = stomach, 3 = remnant of pancreas, 4 = loop of jejunum, 5 = H-J, 6 = P-J, 7 = G-J, * = pylorus/proximal duodenum (Illustrations by John Peter Ovens).

2.3.2. Procedure-specific morbidity: a systematic review

In this section, a systematic review (SR) is presented that provides a detailed overview of the existing evidence relating to the incidence of selected procedure-specific PD complications, and risk factors for these complications.

Russell TB, Aroori S. Procedure-specific morbidity of pancreatoduodenectomy: a systematic review of incidence and risk factors. *ANZ J Surg* 2022. DOI: 10.1111/ans.17473. Reproduced with written permission from John Wiley & Sons, Inc.

What is known:

- Around half of all PD patients experience a perioperative complication
- An in-depth understanding of the recent evidence on these will inform patient selection, guide the consenting process and allow surgeons to evaluate their own performance when auditing

What is new:

- The following incidence rates were obtained: POPF (excluding biochemical leak): 10-26%, BL: 3.0-7.9%, gastro-jejunal leak: 0.4-1.2%, PPH: 7.3-14%, cholangitis: 0.1-21% and CL: 2.6-19%
- Numerous risk factors, both modifiable and nonmodifiable, were identified for each studied complication
- Most of the recent evidence on the studied complications comes from single institution studies of retrospective design

Introduction

Despite recent improvements to patient selection, the surgical approach, and perioperative care, almost half of all patients who undergo PD experience significant morbidity. Due to the complex nature of the resection and the subsequent anastomoses required, multiple procedure-specific complications may occur. An in-depth understanding of the recent literature on these will guide the consenting process and enable surgeons to evaluate their own performance when auditing. This section aimed

to review the recent literature on the incidence of, and risk factors for, the procedure-specific complications of PD.

Method

The complications included were selected prior to carrying out the literature search. These were: POPF, BL, G-J leak, PPH, cholangitis, and CL. Seven separate online searches of the PubMed database were conducted on July 1st, 2021. For each, the search terms used were [“complication in question” AND [“pancreatoduodenectomy” OR “Whipple”]]. Articles from July 2011 through to July 2021 were included if they met the following criteria: 1) English language, 2) human study, 3) clinical study, SR, or MA reporting on the incidence of, and/or risk factors for, complications of open PD, 5) minimum of 100 PDs. Only statistically significant results were considered ($p<0.05$). Where available, exact figures have been listed. Otherwise, odds ratio (OR), relative risk (RR), hazard ratio (HR) or mean/median difference (MD) is provided.

Results

The initial search returned 297 records (**Figure 2.12**). After screening, 226 articles were excluded as they did not meet the inclusion criteria. Following an in-depth review of the remaining 71 articles, a further 34 were excluded. Thirty-seven articles were included in the final analysis. Two of these were MAs and the remaining 35 were single/multicentre clinical studies. No amendments were made to the initial methods.

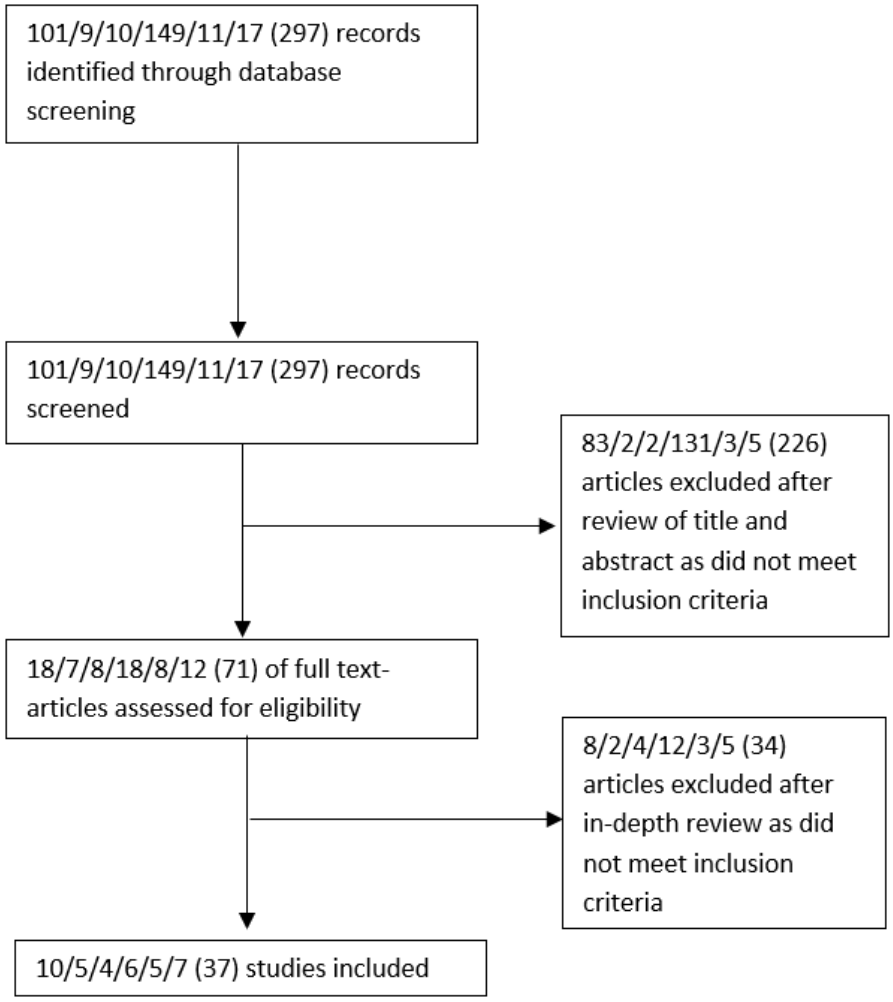


Figure 2.12: Flow of information diagram. Numbers represent total number of articles POPF/BL/G-J leak/PPH/cholangitis/CL (total number of studies). Two SRs/MA were included (POPF: two, all other complications: zero). The remaining 35 studies were single/multicentre clinical studies. Effect estimates and precision figures are quoted in the main text.

Pancreatic fistula

A POPF is an abnormal communication between the pancreatic ductal system and another epithelial surface. POPF was defined by the ISGPS in 2016 (**Figure 2.13**)[102]. For a diagnosis, postoperative day (POD) three drain fluid amylase (DFA) must be at least three times the upper limit of the serum reference range. In addition, the patient's clinical course must be altered. What was previously termed a grade A POPF, i.e., a fistula which does not result in a change to patient management, is now a "biochemical leak". Ten studies were included: two MAs, one prospective single centre, three

retrospective multicentre and four retrospective single centre. We defined clinically-relevant POPF (CR-POPF) as any POPF which alters patient management; this includes grade B POPF and grade C POPF.

In a MA, Eshmuminov et al. (47 studies, n=10,395) found the incidence of CR-POPF was 15%[103]. Many of the included studies did not provide information on the treatment provided and there was a high degree of heterogeneity between the studies, which led to inconclusive aggregated results. Whilst a soft pancreas was a risk factor (RR: 4.4, p<0.001), methods for defining and measuring this varied and most of the included studies were retrospective. In another MA, Kamarajah et al. (122 studies, n=52,774) found the incidence was 19%. This was associated with: preoperative pancreatitis (OR: 0.5, 95% CI: 0.4-0.8), NAC (OR: 0.3, 95% CI: 0.1-0.4), prophylactic somatostatin (OR: 3.2, 95% CI: 1.8-5.7), concomitant vascular resection (OR: 0.5, 95% CI: 0.3-0.9) and high POD one DFA (MD: 203 IU, 95% CI: 135-270 IU)[104]. The association with somatostatin is likely as this is often used in patients with a soft pancreas texture, a known risk factor. Assessing for covariance between the studied factors and/or meta-regression was not possible as not all the included studies reported on the same variables. As in the Eshmuminov et al. MA, most were retrospective and there was a high degree of heterogeneity.

In a prospective, single centre study, Dhayat et al. (n=222) found that 21% of patients developed CR-POPF. Body mass index (BMI) ≥25 kg/m^2 (25% vs 11%, p=0.03) was a risk factor[105] and CR-POPF patients had a prolonged length of stay (23% vs 3% >21 days, p<0.001) and reduced DFS (HR: 0.5, p=0.006)[105]. Although a prospective study, the risk factor analysis included data from DP patients (26% of cases), who are higher risk, and the primary objective was to study survival.

POPF grade	Required for diagnosis (one or more)
Biochemical leak (previously grade A)	POD 3 DFA ≥3x upper limit of reference range
Grade B	Persistent drain output >3 weeks
	Change to patient management
	Angiographic procedure for POPF-related bleeding
	POPF-related infection without organ failure
Grade C	Reoperation for POPF
	POPF-related infection with organ failure
	POPF-related organ failure
	POPF-related death

Figure 2.13: Classification of POPF as per the ISGPS. Adapted, with written permission, from Bassi et al.[102].

In a retrospective study using Swedish national data, Williamsson et al. (n=2503) found the incidence of CR-POPF was 10%; this correlated with major morbidity (75% vs 21%, p<0.001) and a longer length of stay (23 vs 11 days, p<0.001)[106]. Obesity (OR: 1.1, p<0.001) was a risk factor, whereas DM (OR: 0.6, p=0.01) and PBD (OR: 0.3, p<0.001) were protective[106]. CR-POPF was significantly more likely in patients who underwent P-J, versus P-G (OR: 2.4, p<0.001)[106]. Whilst data from several high-volume units was included, this study was retrospective and did not consider important confounding variables, such as main pancreatic duct size. In addition, although a P-J was protective, a separate analysis for duct-to-mucosa versus invaginating techniques was not performed. In another retrospective, multicentre study using American national data, Mirrielees et al. (n=10,922) found the incidence of CR-POPF was 10%[107]. However, this only considered complications occurring within 30 days and risk factors were not studied. In a further retrospective, multicentre analysis, Ellis et al. (n=15,033) found the incidence was 17%[108]. This correlated with male sex (OR: 1.5), a BMI ≥30 kg/m^2 (OR: 2.0), and a small pancreatic duct (OR: 1.8, all p<0.01)[108]. The following were protective: DM (OR: 0.6), NAC (OR: 0.6), biliary obstruction (OR: 0.9) and PDAC histology (OR: 0.5, all p<0.01)[108]. The authors acknowledged that several of these may be associated with PDAC and that these may not be directly related to CR-POPF.

The remaining included studies were all single institution and retrospective. Chen et al. (n=301) found 10% of patients developed CR-POPF[109]. This correlated with intra-abdominal collection (58% vs 1%, p<0.001), PPH (32% vs 2%, p<0.001), and reoperation (26% vs 3%, p=0.002)[109]. Risk factors included a soft pancreas texture (15% vs 6%, p=0.003), a pancreatic duct diameter ≤4 mm (13% vs 6%, p<0.05), an interrupted suture anastomosis (14% vs 8%, p=0.01), obesity (OR: 1.1, p=0.001), and a biliary neoplasm on histology (OR: 3.0, p=0.03), whereas PDAC was protective (OR: 0.3, p=0.04)[109]. In a smaller series, Ke et al. (n=170) found 26% of patients developed CR-POPF[110]. Soft pancreas texture (39% vs 10%, p<0.001) and a fasting blood glucose <108 mg/dL (33% vs 13%, p=0.005) were risk factors. Fu et al. (n=532) found incidence was 10%[111]. Intraoperative blood loss >500 ml (57% vs 37%, p=0.002) and a pancreatic duct diameter ≤3 mm (75% vs 50%, p<0.001) were risk factors, but this analysis also included biochemical leaks[111]. Finally, Luu et al. (n=722) found 15% of patients developed CR-POPF[112]. Those with grade C POPF were more likely to have a pre-existing cardiac disease (78% vs 52%, p=0.009) and less likely to have pancreatic exocrine insufficiency (PEI, 9% vs 34%, p=0.01)[112]. Further, grade C POPF correlated with a soft pancreas texture (74% vs 28%, p<0.001) and a small main pancreatic duct diameter (3.3 vs 5.5 mm, p=0.001). Pooled data for CR-POPF was not analysed.

Bile leak

The ISGLS defines BL as drain or intra-abdominal fluid with an elevated bilirubin level on or after POD three[113]. The bilirubin level must be at least three times the serum range (taken on the same day)[113]. BLs can be classified into grades A, B and C (**Figure 2.14**)[113]. Compared with POPF, BL is less common and less well studied. Five studies were included, all of which were single centre and retrospective. None used the ISGLS definition.

Bile leak grade	Criteria for classification
Grade A	Little or no change to patient management
Grade B	Change to patient management but manageable without a return to theatre OR Grade A BL lasting >1 week
Grade C	Return to theatre required

Figure 2.14: Classification of BL as per the ISGLS[113].

Andrianello et al. (n=1618) diagnosed a BL if drain fluid was bile stained on or after POD three[114]. Incidence was 4%; 32% were grade C and 38% of the total had a concomitant POPF[114]. The only independent predictor of bile leak was small common bile duct diameter (HR: 0.6, p<0.01)[114]. In another series, Jester et al. (n=924) diagnosed BL clinically in 6% of patients and 57% had a concomitant POPF[115]. When the POPF patients were excluded, the remainder with BL had higher overall morbidity (54% vs 24%, p<0.05) and perioperative mortality (17% vs 4%, p<0.05) rates, and a longer median length of stay (17 vs 7 days, p=0.001), than those without a BL[115]. Similarly, El Nakeeb et al. (n=555) found that on POD four, 8% of patients had a clinical BL and 23% of these had a concomitant POPF[116]. Male sex (11% vs 6%, p=0.002), BMI ≥25 kg/m^2 (13% vs 6%, p=0.01), PBD (61% vs 44%, p=0.03), pancreatic duct diameter ≤3 mm (50% vs 31%, p<0.01) and time needed for the H-J formation (40 vs 30 min, p=0.0001) were all independent associations[116]. In a similar study, Malgras et al. (n=352) found 3% of patients developed a clinical BL[117]. None of these had a concomitant POPF at the time of diagnosis, although two subsequently developed a POPF[117]. Four patients (44%) required re-laparotomy and no independent risk factors were identified[117]. Finally, Qiu et al. (n=292) diagnosed fourteen (5%) cases which were all confirmed radiologically[118]. Dilation of the common hepatic duct was protective (43% vs 71%, p=0.03)[118]. Those with a BL were more likely to develop POPF (36% vs 11%, p=0.02), intra-abdominal collection (36% vs 11%, p=0.02), SSI (21% vs 4%, p=0.02) and DGE (35% vs 10%, p=0.02), or require reoperation (29% vs 6%, p=0.01)[118].

Gastro-jejunal anastomotic leak

Failure of the gastroenteric anastomosis is far less common than failure of the pancreatic or biliary anastomoses. Nonetheless, a leak can result in major morbidity and most patients require re-laparotomy. A diagnosis is usually confirmed by contrast extravasation in a radiological study or at the time of reoperation. Gastro-jejunal leak following PD is not well studied. Just four studies were included, all were single centre and retrospective, and the diagnostic criteria for leakage was different in each.

Eshuis et al. (n=1036) identified twelve patients (1%) with a leak (intraoperative finding) and five of these (42%) had a concomitant POPF[119]. Leak patients had higher rates of POPF (42% vs 15%, p=0.01), and a longer length of stay (41 vs 14 days, p=0.001)[119]. Labori et al. (n=1494) intraoperatively diagnosed a leak in eight patients (0.5%) and four of these (50%) had a concomitant POPF[120]. Risk factors were not studied. Winter et al. (n=3029) identified a G-J leak in thirteen patients (0.4%). A blood urea nitrogen-to-creatinine ratio >20 (OR: 6.0, p=0.01) and intraoperative blood loss >1 L (OR: 6.0, p=0.03) were both associated with a leak[121]. Finally, Mazza et al. (n=73) matched thirteen leak patients (radiologically confirmed) to 60 controls and found leakage was associated with a low preoperative serum haemoglobin (p<0.001) and preoperative radiotherapy (p=0.04)[122]. Leak patients had a higher mortality rate (23% vs 2%, p=0.02), as well as longer operation times (360 vs 318 min, p=0.04) and higher estimated intraoperative blood loss (600 vs 400 ml, p<0.05)[122]. One patient was managed with a conservative approach but the remainder required re-laparotomy[122].

Post-pancreatectomy haemorrhage

Post-pancreatectomy haemorrhage is an uncommon but serious complication of PD. The ISGPS last defined PPH in 2007[123]. Early PPH is diagnosed within twenty-four hours of surgery and late PPH occurs after twenty-four hours[123]. The location can be

intraluminal or extraluminal, and severity can be mild (mild clinical impairment with no therapeutic consequence) or severe (significant clinical impairment with invasive treatment required) (**Figure 2.15**)[123]. Following infective complications secondary to an anastomotic failure, PPH is the second most common cause of perioperative mortality[124] and indication for reintervention[125] among PD patients. Six studies (one multicentre, five single centre) were included, all of which were retrospective. All used the ISGPS classification.

In a multicentre series, Kasumova et al. (n=2548) identified 217 patients (9%) with PPH; 139 of these (64%) required reintervention[126]. Overall mortality (25% vs 4%, p<0.0001), length of stay (22 vs 13 days, p<0.0001), and cost of admission (43% vs 8% >$30,000, p<0.0001) were all higher in PPH patients[126]. Compared to those diagnosed in the first postoperative week, mortality was significantly higher in those who were diagnosed in the second week (54% vs 22%, p=0.007). Male sex (11% vs 7%, p=0.003), concomitant vascular resection (15% vs 9%, p=0.02), very low hospital volume (13 vs 11%, p=0.02), Elixhauser score >3 (13% vs 5%, p<0.0001) and intra-abdominal collection (19% vs 8%, p<0.0001) were all independent predictors of PPH[126]. The authors accepted that some mild haemorrhages were not included as they were not able to quantify the number of units transfused in each patient, and the coding system used was only able to identify bleeds that required reintervention.

Garcés et al. (n=2429) identified 165 cases of PPH (7%); 44 were grade C (27%)[127]. Compared to patients without PPH, grade B and grade C patients had a longer length of stay (10 vs 16 vs 33 days, p<0.01), increased mortality (0.4% vs 1% vs 16%, p<0.01), and increased re-laparotomy rates (0% vs 60% vs 87%, p<0.01). Grade B/C PPH was also associated with POPF (7% vs 25% vs 64%, p<0.01), intra-abdominal collection (17% vs 47% vs 66%), BL (2% vs 7% vs 25%, p<0.01), postoperative pancreatitis (3% vs 12% vs 30%, p=0.01), G-J leak (1% vs 7% vs 21%, p=0.04), and DGE (5% vs 9% vs 19%, p<0.01)[127]. Similarly, Gao et al. (n=423) found the incidence was 10%; independent risk factors included a concomitant vascular resection (OR 6.8, p=0.005), a history of

previous abdominal surgery (OR: 5.0, p=0.001) and a low preoperative serum albumin (OR: 4.9, p=0.001)[128]. These were also independent risk factors for late PPH, as were POPF (OR: 5.0, p=0.005), BL (OR: 6.1, p=0.009), and intra-abdominal collection (OR: 4.6, p=0.04)[128]. The authors acknowledged that their small sample size may have prevented the observation of some associations and suggested a larger, multicentre study is required. Finally, Ansari et al. (n=500) found 68 (14%) patients developed PPH; nineteen were grade C (4%)[129]. Both CR-POPF (OR: 9.5, p<0001), and BL (OR: 4.8, p=0.02) were associated with PPH[129]. This study had a long accrual period and the authors accepted that some aspects of patient care will likely have changed during the study period.

PPH grade	Timing and severity	Characteristics
Grade A	Early (<24 hr) and mild	No clinical impairment Observation only No therapeutic consequence
Grade B	Early and severe OR Late (>24 hr) and mild	Rarely life-threatening May require endoscopy/embolisation/surgery
Grade C	Late and severe	Life-threatening Requires intervention

Figure 2.15: Classification of PPH as per the ISGPS. Adapted, with written permission, from Wente et al.[123].

Cholangitis

Few recent studies have reported on the incidence of cholangitis following PD. One multicentre study and four single centre studies were included. In the multicentre study, Persaud et al. (n=10,145) found just five patients (0.1%) developed this complication. Cases were identified using the ICD-9-CM code “5761”; a formal definition was not provided. Patients who developed cholangitis had a prolonged length of stay (OR: 1.4,

p<0.001) and increased treatment costs[130]. Risk factors were not studied. The authors acknowledged that their findings will have been affected by coding inaccuracies. They suggested that, in the future, minimally invasive surgeries and robotics could play a role in reducing the incidence of biliary complications. They argued that, whilst robotic procedures are typically longer, they may reduce overall morbidity[130].

In the study by Malgras et al. (n=353), 20 patients (6%) developed postoperative cholangitis, which was defined as clinical signs of infection, raised serum inflammatory markers and abnormal LFTs improving over time with antibiotic therapy; in fifteen of these (75%) the diagnosis was made after POD fifteen[117]. This was the most common early biliary complication[117]. Benign disease on histology was the only independent predictor of cholangitis (OR: 2.2, p=0.002)[117]. The authors accepted that diagnosing cholangitis postoperatively is not straightforward, particularly in patients who originally present with obstructive jaundice, and that cases were likely missed. They argued that appropriate use of perioperative antibiotics might help to reduce the number of cases[117]. In a similar study using the 2013 Tokyo Guidelines (TG13) diagnostic criteria[131], Ueda et al. (n=155) found that 21 patients developed refractory cholangitis (19%), which resulted in three or more hospital admissions; seventeen of these (80%) had at least one episode diagnosed in the first year following surgery. Benign disease (OR: 18.5, p=0.001) and a long operation time (OR: 18.7, p=0.002) were independent risk factors, and elevated C-reactive protein (CRP, OR: 6.6, p=0.01), elevated alkaline phosphatase (ALP, OR: 6.0, p=0.02) and pneumobilia (OR: 28.8, p=0.009) were associated with cholangitis[132]. The authors argued that if a patient is to develop cholangitis, their first presentation will likely occur within a year of resection and advise anastomotic dilatation (if there is evidence of biliary stricture) in order to prevent repeat presentations[132].

In a further study, Brown et al. (n=628) retrospectively analysed the outcomes of patients who survived the perioperative period. Eight per cent experienced either cholangitis or a biliary stricture occurring at least 90 days after surgery[133]. A further breakdown was not provided, and risk factors were not studied. Also concerning only

late cholangitis, Ito et al. (n=133) used the TG13 criteria and found 28 patients (21%) developed this complication. Signs and symptoms occurring in the first 28 days were ignored. Th median duration to diagnosis was 275 days and the only significant association was an ALP ≥410 IU (OR: 3.8, p=0.003), which was associated with pneumobilia (p=0.04)[134]. The authors concluded that an ALP ≥410 IU/L was useful for predicting the development of late cholangitis and advised follow-up in the late postoperative course for patients with this finding[134]. Although the underlying mechanism behind this complication is unknown, they argued PBD may be beneficial, accepting this may result in additional morbidity[134].

Chyle leak

The true incidence of CL after PD is difficult to appreciate due to differing definitions among authors and the presence of subclinical cases. The ISGPS defines CL as the output of milky-coloured fluid from a drain, drain site or wound on, or after, POD three[135]. The fluid must have a triglyceride content of ≥110 mg/dL, be culture-negative, and amylase-free[135]. Most recent studies reporting on CL have not used these strict diagnostic criteria. Grade A leaks require no specific intervention other than dietary restrictions, grade B leaks result in significant changes to management and/or a prolonged hospital stay, and grade C leaks require more invasive treatment, intensive care unit (ICU) admission, and/or contribute to patient death (**Figure 2.16**)[135]. Seven retrospective studies were included. One of these was multicentre and the remaining six were single institution.

In the multicentre series (which included all pancreatic resections), Strobel et al. (n=3324) found the incidence of CL was 10%[136]. CR-POPF (HR: 1.8, p=0.003), intra-abdominal collection (HR: 1.8, p=0.001), DP (vs PD, HR: 1.7, p=0.001), DM (HR: 1.3, p<0.05), duration of surgery ≥180 minutes (HR: 1.4, p=0.02), and PDAC histology (HR: 2.0, p<0.001) were independent risk factors[136]. CL resulted in an increased length of stay

(12 vs 9 days, p<0.001) but did not affect overall mortality[136]. In a large, single centre series by Pan et al. (n=1127), CL (ISGPS definition) affected 3% of open PD cases and risk factors included: intraoperative manipulation of the para-aortic (OR: 4.5, p<0.001) or SMA root (OR: 2.3, p=0.006) areas, concomitant vascular resection (OR: 2.0, p=0.04), malignant disease on histology (OR: 4.4, p=0.03), lymph node metastases (OR: 2.0, p=0.03), retroperitoneal invasion (OR: 2.5, p=0.002), and chronic pancreatitis (OR: 2.3, p=0.02)[137].

CL grade	Therapeutic consequence	Discharge with drain or readmission	Prolonged LoS
Grade A	None or dietary restrictions	No	No
Grade B	Nasoenteric nutrition with dietary restriction +/- TPN, IR drainage, maintenance of drain/s, or octreotide	Possibly	Yes
Grade C	Other invasive treatment, ICU admission, +/- death	Possibly	Yes

Figure 2.16: Classification of CL as per the ISGPS. IR = interventional radiology, LoS = length of stay, TPN = total parenteral nutrition. Adapted, with written permission, from Besselink et al.[135].

In a smaller series by Russell et al. (n=560), a clinical diagnosis of CL was made in 3% of cases[98]. CL patients had a higher BMI (31 vs 27 kg/m^2, p=0.02) and longer operation times (6.2 vs 5.6 hours, p=0.03)[98]. They were also more likely to undergo PV resection, but this was not significant (24% vs 16%, p=0.06)[98]. Abu Hilal et al. (n=194) found a clinical diagnosis was made in 19% of cases. Radical (vs standard) lymphadenectomy (OR: 4.9, p=0.002) was a risk factor, but this analysis included data from distal and TPs[138]. Kuboki et al. (n=366) found the incidence of CL was 3% (ISGPS definition)[139]. This correlated with intraoperative manipulation of the para-aortic area (76% vs 22%, p<0.001), concomitant vascular resection (53% vs 28%, p=0.03), positive histological lymph nodes (76% vs 40%, p=0.004), retroperitoneal invasion (76% vs 41%,

p=0.005), and early enteral feeding (59% vs 18%, p<0.001)[139]. This risk factor analysis also included total/DPs[139].

Shyr et al. (n=165) found the incidence of CL was 11% (ISGPS definition) [140]. This correlated with a higher number of harvested nodes (MD: 4, p=0.001), higher number of positive nodes (MD: 2, p=0.001) and PDAC histology (19% vs 9%, p=0.02). Paiella et al. (n=945) observed CL (ISGPS definition) in 43 patients (5%) although this included DP cases; ten (23%) were grade A, 31 (72%) were grade B and two (4%) were grade C[141]. An economic analysis revealed that increasing CL grade correlated with increasing treatment cost (grade A: €2,806, grade B; €7,150, grade C: €15,684)[141]. This study was intended to validate the ISGP classification, so risk factors were not studied. Finally, Singh et al. (n=137) found 4% of patents developed CL (ISGPS definition). Risk factors were not studied.

Discussion

Unfortunately, most patients with a pancreatic head or periampullary cancer are not appropriate candidates for a curative-intent resection. A minority can undergo PD providing they have early disease and an appropriate performance status. With the exception of BL and G-J leak, most of the complications covered are well studied (**Table 2.1**). Whilst incidence rates and risk factors have been stated, few of the included studies used the most recent diagnostic criteria which are recognised internationally. The vast majority of the included studies were single institution and retrospective.

The diagnostic criteria for POPF have recently been updated and now only those which alter management (grade B and C) are considered clinically-relevant. What was previously termed a grade A fistula is now a “biochemical leak”. The incidence of CR-POPF ranged from 10-26%. Most recent authors agree that a soft pancreas and a small main pancreatic duct are significant risk factors. This is likely because a fibrotic pancreas is more forgiving and secretes less pancreatic juice. Further, it is less technically

challenging to suture an adequate anastomosis when the duct can be easily visualised. This becomes more challenging in obese patients who have a higher fat content within and around the pancreatic parenchyma. Surgical access is also more challenging in this group.

Following resection of the pancreatic head, either a P-J or P-G must be fashioned to restore continuity between the pancreatic ductal system and the bowel. Both are accepted techniques and they each have their advantages and drawbacks. Regarding CR-POPF, several of the included articles suggested a P-J is more high-risk. However, this can be performed using either a duct-to-mucosa or an invaginating technique. Most of the studies did not perform a separate analysis to reflect this. Ideally, a prospective trial should compare P-J to P-G and consider the different P-J approaches.

Complication	Incidence	Impact/correlates with	Risk factors/associations	Protective factors
CR-POPF	10.0 - 25.9%	↑ LoS ↓ DFS Major morbidity Relaparotomy Intra-abdo collection PPH	↑BMI Biliary neoplasm histology Cardiac disease High POD 1 DFA Interrupted suture anastomosis Low fasting blood glucose Male gender P-J (vs P-G) Prophylactic somatostatin Small pancreatic duct Soft pancreas texture	Biliary obstruction Diabetes PDAC histology PEI Pre-op biliary drainage Pre-op NAC Pre-op pancreatitis Vascular resection
BL	3.0 - 7.9%	↑ LoS ↑ Relaparotomy ↑ SSI DGE Intra-abdo collection Major morbidity Peri-op mortality POPF	↑BMI Low serum albumin Male gender Pre-op biliary drainage Small bile duct diameter Small pancreatic duct Time needed for H-J	Dilated common hepatic duct
G-J leak	0.4 - 1.2%	↑ LoS ↑ Mortality ↑ POPF	↑ Intra-op blood loss ↑ Operation time Pre-op radiotherapy High BUN:creatinine ratio Low pre-op Hb	
PPH	7.3 – 13.6%	↑ Cost of admission ↑ LoS ↑ Mortality ↑ Relaparotomy	Bile leak DGE Elixhauser score >3 Gastro-jejunostomy leak History of abdominal surgery Intra-abdo collection Low pre-op albumin Male gender CR-POPF Post-op pancreatitis Vascular resection Very low volume centre	
Cholangitis	0.1 - 21.1%	↑ LoS ↑ Treatment cost	↑ ALP ↑ CRP Benign histology Long operation time	

			Pneumobilia	
CL	2.6 – 19.0%	↑ LoS ↑ Treatment cost	↑ Operation time ↑BMI Concomitant vascular resection CR-POPF Diabetes Extensive lymphadenectomy Intra-abdo collection Lymph node metastases Pancreatitis Para-aortic/SMA root area manipulation PDAC histology Retroperitoneal invasion	

Table 2.1: The incidence of, and risk factors for (vs patients without the factor), selected procedure-specific complications of PD: significant ($p<0.05$) findings from the included studies. References and p-values can be found in the main text. LoS = length of stay.

BL affects less than 8% of cases and is less well-studied. Most of the included studies did not use the ISGLS definition. Most recent authors suggest a small bile duct and PBD are risk factors as they make fashioning the H-J more challenging. A dilated common hepatic duct is protective for the opposite reason. Obesity is an additional risk factor as excess intra-abdominal adipose tissue creates technical challenges. G-J leaks are rare, affecting less than 1.2% of cases. Although this can increase length of stay and the mortality risk, few studies have identified risk factors except for preoperative radiotherapy and preoperative patient factors. PPH affects less than 15% of PDs but it is associated with an additional mortality risk. Concomitant vascular resection is a significant risk factor. Patients who experience other intra-abdominal complications, those with poor preoperative fitness and those operated on at very low volume centres are also high-risk. Late PPH is usually more serious and can be life-threatening.

Depending on the diagnostic criteria, up to 21% of patients may develop cholangitis after PD. Whilst risk factors have been identified, it is difficult to predict who will develop

this complication or know how identifying risk factors will alter management. Patients with benign histology and those in whom the time needed for the H-J is prolonged are high-risk. A raised CRP and/or ALP, as well as pneumobilia, may be early signs. The pathophysiology of early cholangitis following PD is unknown. Several suggestions have been proposed, including minimal stricture of the H-J, DGE/ileus, obstruction by enteric debris or bile contamination[117]. The appropriate use of perioperative antimicrobial therapy may reduce the incidence of cholangitis[117]. In patients who develop refractory cholangitis, their first presentation is likely to be in the first year following PD, and this may be associated with an underlying biliary stricture. Some authors have argued that aggressive dilatation should be considered in these patients to reduce the number of admissions[132]. Hiyoshi et al. (n=161) suggested hepaticoplasty, where the left side of the bile duct is cut to widen its diameter prior to forming the H-J, may help to reduce the incidence. In this retrospective, single institution study the only independent predictor of cholangitis (TG13 definition) was the ratio of the postoperative bile duct diameter to that before surgery ($p=0.001$)[142]. Whilst hepaticoplasty was found to be safe, a prospective trial is required to validate these findings. A RCT utilising scintigraphy to evaluate biliary flow is planned[142].

CL affects up to 16% of PDs. This is because retroperitoneal dissection adjacent to the cisterna chyli is necessary. Unsurprisingly, CL is associated with more advanced disease and a more aggressive resection, as lymphatic channels are more likely to be inadvertently disrupted. Obesity is also a risk factor, likely because excessive adipose tissue makes it more difficult for the surgeon to identify lymphatics. Surgeons should avoid unnecessary dissection and address any leakages noticed intraoperatively with meticulous care.

The limitations of this SR have been outlined in **Chapter 9**.

Conclusion

Pancreatoduodenectomy remains a high-risk operation. It is important that surgeons have a sound understanding of the recent evidence on the complications which can occur postoperatively. This will guide the consenting process and allow surgeons to evaluate their own performance when auditing. Robust case-control studies are required so that predictive models can be created which estimate the likelihood of complications in individual patients.

Post hoc comment

This SR did not include data from the Cochrane Library. Additional Cochrane Library searches were carried out to identify any additional relevant articles. The same search methods were used as described above. No review articles were identified which described the incidence of the studied complications. Concerning risk factors for POPF, a review by Dong et al. (eight studies, n=1018) concluded it was unclear if main pancreatic duct stents were beneficial due to the low quality of the evidence available[143]. The authors suggested a RCT is warranted. Hai et al. (eleven RCTs, n=1696) concluded it was unclear if P-J technique affected the incidence of POPF[144]. Lai et al. (fourteen RCTs, n=1989) concluded that fibrin sealants had little or no impact on the rate of POPF[145]. They suggested that all the included RCTs were at high risk of bias. No further articles were identified which commented on risk factors for the other studied complications.

2.3.3. Outcomes of pancreatoduodenectomy: a narrative review

In this section, a narrative review is presented that provides an overview of the existing evidence relating to the short- and long-term outcomes of PD.

What is known:

- PD is a major operation with poor short- and long-term outcomes

What is new:

- The overall morbidity rate has fallen in recent years, but this remains significant
- Long-term survival rates remain poor, even in those who have an uncomplicated recovery
- Most studies suggest it takes up to six months before a patient's QoL returns to preoperative baseline

Introduction

Pancreatic ductal adenocarcinoma has the lowest survival of all common cancers; overall five-year survival is less than 10%[17]. Patients with a distal CC have a slightly better prognosis but the difference is not drastic. Whilst those with an AA are likely to live longer, the prognosis is still worse than for most other gastrointestinal cancers. Approximately 20% of UK PDAC cases are diagnosed at stage I or II, and surgical resection is recommended in fit patients. The median survival following PD for PDAC is around 24 months[146]. Those with stage III disease are not usually offered a resection since this has not been shown to improve OS.

Surgical resection is a major undertaking and morbidity/mortality rates may be under-estimated due to publication bias. Therefore, it is important that clinicians and patients are aware of the morbidity and mortality rates associated with PD, as well as the impact the operation can have on a patient's quality of life (QoL). Informed decisions can then be made regarding treatment. This section aimed to consolidate the recent literature on these topics.

Resection vs no resection

No large studies have compared the outcomes of patients with resectable PDAC who have undergone PD to those who have not. A retrospective study by Lee et al. analysed

the outcomes of PDAC patients at a single Korean centre between 2007-2014. Of the 1646 included patients, 475 (29%) had resectable PDAC, 129 (8%) had borderline resectable disease, 384 (23%) had locally-advanced disease, and 658 (40%) had metastatic PDAC[147]. Among those with resectable disease, 91% underwent PD with curative intent, 4% received chemotherapy only, and 5% received only palliative care. The median survival was 22 months in the surgery group, eight months in the chemotherapy group ($p<0.001$), and eleven months in the palliative care group ($p<0.001$)[147]. In the borderline group, 35% underwent surgery without NAT, 22% underwent up-front surgery followed by AC, 33% received chemotherapy alone, and 10% received only palliative care. In those who underwent PD, patients who received NAT had a significant survival advantage (24 months vs 16 months, $p<0.05$)[147]. PD with NAT was associated with a longer median survival when compared with chemotherapy alone (16 vs 12 months), but this difference was not significant ($p=0.1$)[147]. In those with locally advanced disease, there was no significant difference in median survival between those who underwent PD (with or without adjuvant therapy, 10 months), those who underwent NAT prior to PD (19 months), and those who received only chemotherapy (13 months, $p=0.1$)[147]. The authors did not specify why patients with resectable disease did not undergo PD; these patients are likely to have represented a group that were not fit enough to undergo resection. This study highlighted the survival benefit of PD in those with resectable disease. The picture was less evident in those with borderline disease, and PD did not improve survival in those with locally advanced disease.

Chakraborty et al. carried out a survival analysis of patients diagnosed with stage I-II PDAC between 1973-2009 using the Surveillance, Epidemiology, and End Results (SEER) Program database (n=1759). This study was not limited to tumours affecting the head of the pancreas and considered all forms of pancreatic resection. Of those included, 93% underwent curative-intent surgery[148]. Resection was associated with longer OS (18 vs 7 months, $p<0.0001$). Other factors associated with improved OS were age <50 years,

a maximum tumour diameter <20 mm, an absence of positive histological lymph nodes, radiation therapy, and a well-differentiated tumour[148].

Elderly patients are more likely to have a poor performance status and may not be appropriate surgical candidates, even if they have early disease. Older patients also have lower OS rates when all causes of death are considered. Park et al. investigated whether PD provided a survival benefit to patients aged over 75 years. Only those with resectable disease were included and patients were excluded if they had another malignancy, or a history of another malignancy. Thirty-eight patients underwent PD and eleven did not; three could not undergo surgery due to their performance status, and eight elected to decline all forms of treatment[149]. Of those who underwent PD, 41% were alive at two years after their diagnosis, whereas all those who did not undergo PD had died[149]. The authors concluded that an aggressive surgical approach may provide a significant survival benefit in selected older patients[149].

Major outcomes

Perioperative mortality

Perioperative mortality following PD has traditionally been quoted at 5%, however, this has decreased slightly in recent years[150]. High-volume centres have been shown to have lower mortality rates compared to low-volume centres, but the optimum volume has not been defined. A series published by Narayanan et al. studied 551 PDs at a single American centre from 2007-2016 (all pathologies, including PD for other cancers and benign indications). Thirty-day, 90-day, and one-year mortality rates were 1%, 4%, and 17%, respectively[124]. The most common causes of death were multiorgan failure secondary to sepsis or aspiration, PPH, MI, and pulmonary embolism (PE)[124].

Whilst some single centre studies have reported very low mortality rates, studies using national data usually report higher rates. A less recent (2001-2016) but larger (n=14,935) multicentre UK study found that in-hospital, 30- and 90-day mortality rates

were 5%, 4%, and 7%, respectively[151]. The authors concluded that 90-day mortality was highest in very low-volume centres, but no additional benefit was obtained once a centre performed more than 36 procedures per year. A further highlight was that 90-day mortality fell dramatically from 10% in 2001-2004, to 4% in 2013-2016[151].

In a multicentre American study, Merath et al. studied the outcomes of 9639 PDs from 2004-2014 (all pathologies included). Inpatient mortality was 3%, regardless of the histological diagnosis[152]. Unlike in the British study, smaller hospitals did not have higher mortality rates. No significant difference was observed between "rural" and "urban nonteaching" hospitals. Inpatient mortality was significantly lower at "urban teaching" hospitals, but the difference was marginal[152]. Patients who died as an inpatient were more likely to be male, have chronic obstructive pulmonary disease (COPD), liver disease, chronic kidney disease, peripheral vascular disease (PVD), or congestive cardiac failure (CCF)[152].

Study	Operation	Number of patients	30-day mortality	90-day mortality
Narayanan et al. (2018)	PD	551	1.1%	3.6%
Liu et al. (2018)	PD	14,935	3.7%	6.5%
Mittel et al. (2020)	CABG	72,398	2.2%	3.7%

Table 2.2: Thirty- and 90-day mortality after PD and CABG. References in the main text.

To put these figures into perspective, PD can be compared to another commonly performed elective operation which is considered high-risk e.g., a coronary artery bypass graft (CABG) (**Table 2.2**). A 2020 study by Mittel et al. followed up 72,398 patients who underwent a CABG (2008-2014). Thirty-day mortality was 2% and 90-day mortality was 4%[153]. Whilst the two operations should be compared with caution, this would suggest PD can be grouped with other non-emergency operations that are considered high-risk.

Study	Number of patients	Five-year survival
Luu et al. (2020)	167	20.4%
Acedo et al. (2019)	114	26.6%
Hsu et al. (2018)	223	10.1%
Huang et al. (2018)	125,183	11-20%

Table 2.3: Five-year survival after PD for PDAC. References in the main text.

Long-term survival

Although PD is performed for early PDAC with curative intent, most patients develop recurrent disease. Unfortunately, this is also the case for most patients with CC or AA. DFS refers to the time between treatment and the point at which recurrent disease is identified on surveillance imaging. However, definitions vary, and it is more challenging to measure than other endpoints. Hence, few recent studies have attempted to calculate DFS after PD performed for malignancy. A multicentre retrospective study by Lubrano et al. followed up 942 PDs from multiple European centres from 2004-2009 (PDAC only). Patients were excluded if they died in the perioperative period. Among the remaining patients, the median DFS was 19 months[154]. A serious postoperative complication was associated with reduced DFS[154]. The authors suggested that serious postoperative complications may have resulted in AC being delayed or omitted. DFS is also heavily influenced by the completeness of the resection. A retrospective study by Roessel et al. studied 531 PDs (2000-2014) from centres across the USA and the Netherlands (PDAC only). Patients who received NAT and those who had an incomplete resection were excluded. DFS was thirteen, fifteen, and 24 months for surgical margin clearances of 0, <1, and ≥1 mm, respectively.

Overall survival refers to the time between the date of diagnosis and the date of death. A recent single centre American study by Pugalenthi et al. followed up 596 patients who underwent PD for PDAC (2001-2009). The median OS was 24 months[155]. The results from this study are compared to those from other similar studies in **Table 2.3**. In a German single centre study by Luu et al. (2007-2014), the median five-year

survival was 20%[146]. In a prospective observational study, Acedo et al. followed up 114 PDAC patients who underwent PD with total mesopancreatic excision at a single Spanish centre (2008-2014) and five-year survival was 27%[156]. In a less recent Taiwanese study by Hsu et al. (1995-2010), three- and five-year survival rates were 21% and 10%, respectively[157]. In a multicentre European study, the OS of PDAC patients who received a resection was compared to the OS of all patients diagnosed with PDAC[158]. Using the most recent cohort (2009-2011), five-year survival after PD ranged from 11% (Slovenia) to 20% (Norway). The Netherlands and Belgium both reported a five-year survival rate of 18%.

Aspect of QoL/symptom	Time to recovery to baseline after PD
Physical functioning	3-6 months
Fatigue, nausea, dyspnoea, insomnia, loss of appetite, change of bowel habit	6 months
Emotional functioning	3-12 months
Social functioning, pain	Highly variable and difficult to assess

Table 2.4: QoL after PD. Summary of the key findings from the van Dijk et al.[159] study.

Patients with a histological diagnosis of AA can expect to survive considerably longer than those with PDAC. In a study of 887patients who underwent PD for AA, Moekotte et al. observed one-, three-, five- and ten-year OS rates of 89%, 63%, 52% and 37%, respectively[160]. The long-term outcomes of patients with distal CC are not quite as positive. In a study of 201 patients who underwent PD for CC, Courtin-Tanguy et al. observed one-, three- and five-year OS rates of 85%, 53% and 39%, respectively[161].

Quality of life

Since PD is associated with high morbidity rates and poor long-term survival, it is important that a patient's QoL after the procedure is considered. A recent SR by van Dijk

et al. evaluated all prior studies which assessed QoL using validated questionnaires in patients who had undergone PD for PDAC. The authors concluded that PD negatively affected QoL in the short term but that a recovery to baseline was made between three and six months postoperatively (**Table 2.4**)[159]. Most of the included studies reported that physical functioning initially declined but then recovered to baseline at three to six months, and that emotional functioning initially declined before recovering to baseline at three to twelve months[159]. Results regarding social functioning were highly variable. Except for one, all studies which reported on fatigue suggested an increase before recovery to baseline by six months[159]. All studies which reported on nausea showed an initial increase before a return to baseline by six months[159]. Most studies reported on pain, although the results were highly variable. Six studies reported on dyspnoea and five on insomnia, all of these suggested a return to baseline by six months[159]. The results for loss of appetite, diarrhoea and constipation were highly variable. None of the included studies suggested these symptoms were worse than baseline at six months[159].

Discussion

Most patients diagnosed with a pancreatic head or periampullary malignancy are not appropriate surgical candidates. Resection is only recommended in fit patients who present with early disease. Whilst PD is high-risk, it has been shown to improve OS in those with resectable disease. It is less clear if PD improves survival in those with borderline resectable disease. Perioperative mortality rates have fallen considerably in recent years. This is likely the result of improved patient selection, surgical advances, and improved perioperative care. The centralisation of services may also have contributed. Perioperative mortality was traditionally quoted at 5% but a figure between 2-3% is probably more up to date. If patients who die in the perioperative period are excluded, the median OS is around two years in those with PDAC and between 15-20% achieve five-year survival. Around half of PD patients with AA and around a third of those with CC can expect to survive five years.

PD has a profound impact on a patient's QoL. Physical, emotional, and social functioning are all likely to be affected in the early postoperative phase. Most studies suggest a return to baseline between three and six months postoperatively. Many patients also suffer with pain, dyspnoea and insomnia following PD. Whilst results from prior studies are highly variable, most suggest symptoms return to baseline by six months. It is important to remember that only patients who survived the perioperative period will have taken part in these studies, and that three to six months is a considerable amount of time for PDAC patients who have a median OS of just 24 months.

Conclusion

Perioperative mortality following PD has fallen slightly in recent years. However, the risk remains significant. Whilst very few PDAC patients achieve five-year survival, the prognosis in those with AA and CC is considerably better. PD has a profound negative impact on a patient's QoL. In the absence of postoperative complications, it may still take six months for a patient to recover to their preoperative baseline level of fitness. It is important that clinicians and patients with resectable disease have a comprehensive understanding of these issues before PD is considered.

Chapter 3: Factors influencing pancreatoduodenectomy outcomes

This chapter aimed to consolidate the recent evidence on the variables which were investigated as part of the Recurrence After Whipple's (RAW) study.

3.1. Selected preoperative factors: a systematic review

In this section, a SR is presented that provides a detailed overview of the existing evidence relating to pre-selected preoperative factors and their impact on PD outcomes.

Russell TB, Labib PL, Aroori S. Selected preoperative factors which affect pancreatoduodenectomy outcomes: a systematic review. *Ann Pancreat Cancer* 2021. DOI: 10.21037/apc-21-15. Open access.

What is known:

- A greater understanding of the preoperative factors which affect PD outcomes will improve patient selection, guide risk/benefit discussions with patients and allow for preoperative patient optimisation

What is new:

- Advanced age and pre-existing cardiac/respiratory disease increase perioperative morbidity/mortality risk but the impact of DM is less clear
- An unhealthy BMI is associated with worse short-term outcomes and evidence is emerging which suggests sarcopenia and myosteatosis may affect short- and long-term outcomes
- The impact of preoperative biliary stenting remains controversial
- Numerous laboratory/imaging findings can predict survival
- The influence of many of the factors discussed are limited to single-centre retrospective analyses

Introduction

Pancreatoduodenectomy is a complex and technically challenging operation. Despite recent improvements, PD morbidity rates remains high, and most patients develop recurrent cancer. This section aimed to consolidate the recent literature on preselected preoperative factors which affect perioperative and survival outcomes following PD performed for suspected malignancy. An appreciation for these will guide patient selection, preoperative optimisation, and risk/benefit discussions with potential surgical candidates. Data on these factors will also allow for the development of predictive models which can estimate individual patient outcomes.

Method

The preoperative factors included were all selected before carrying out the literature search. These were: age, gender, BMI, sarcopenia, myosteatosis, DM, cardiac disease, respiratory disease, radiological tumour characteristics, NAT, PBS, bilirubin, CRP, albumin, CRP/albumin ratio (CAR) and neutrophil/lymphocyte ratio (NLR). A systematic search of the literature was carried out on June 1st, 2021. The PubMed database were searched using the terms ["preoperative factor in question", "pancreatoduodenectomy", AND "outcome"] from May 2011 through May 2021. The following articles were included: 1) human studies, 2) English language, 3) MAs, SRs or clinical studies reporting on perioperative outcomes and survival following open PD performed for suspected malignancy, 4) excluding the radiology and NAT sections, minimum of 100 PDs (if final histological diagnosis specified, at least 100 PDs performed for PDAC), 5) in terms of risk factors/associations, only statistically significant results were included ($p<0.05$), 6) to reduce the impact of bias, studies were only included if the "preoperative factor in question" was investigated as a primary outcome measure. For the radiological features section, a non-systematic search was undertaken (not using the stated criteria) to identify articles reporting on specific radiological features which affect PD outcomes. Concerning

NAT, only articles reporting on comparisons between NAT and standard treatment (upfront surgery) were included, and those comparing different NAT regimens were excluded. For the PBS section, only studies comparing stenting to upfront surgery were included, and studies comparing stenting methods or timing of PBS were excluded.

Results

The initial search returned 1913 records (**Figure 3.1**). After an initial screen, 1711 were excluded as they did not meet the inclusion criteria. Following an in-depth review of the remaining articles, a further 106 were excluded. Therefore, 96 articles were included in the final analysis. Eleven of these were SRs/MAs and the remainder were single/multicentre studies. No amendments were made to the original methods.

Age

The median age at PDAC diagnosis is 70 years (67% of newly diagnosed patients are ≥65 years) and the average age of patients presenting with resectable disease is set to rise[162]. Whilst decisions to operate must never be based solely on numerical age, a pragmatic and patient-centred approach should be employed. Multiple recent studies have concluded that it is safe and reasonable to perform PD in selected older patients[163-166]. Shamali et al. (n=524) showed that patients aged ≥75 years had similar rates of overall morbidity and major morbidity compared to younger patients[163]. Further, age was not an independent predictor of five-year or OS[163]. However, the older patients were more likely to experience cardiac complications (11% vs 4%, p=0.008) and had higher perioperative mortality rates (6% vs 2%, p=0.04). In contrast, El Nakeeb et al. (n=828) found that patients aged >70 years had the highest overall morbidity, followed by those aged 60-70 years, followed by under 60s (26% vs 37% vs 38%, p=0.006)[164]. However, perioperative mortality rates were similar[164]. Zhang et al. (n=216) reached similar conclusions; patients >70 years had similar morbidity and mortality rates to those ≤70,

but were more likely to experience cardiac (p=0.008) or respiratory (p=0.01) complications, and had a longer length of stay (p=0.01)[165]. Similarly, Wiltberger et al. (n=370) found that age did not affect overall mortality, but that increasing age was associated with major morbidity (p<0.05)[167].

Gruppo et al. (n=106) found that being aged >70 years did not affect overall morbidity, perioperative mortality, or OS[168]. Other authors have reached similar conclusions using thresholds of 75 [169-171] and 80 years[162, 172]. In contrast, Oguro et al. (n=561, 13 months vs 82 months, p=0.01) and Kim et al. (n=165, 17 vs 23 months, p<0.05) found OS was reduced in those aged >80 years[173, 174].

The studies discussed will have been influenced by selection bias as older patients will have been pre-assessed as suitable surgical candidates based on their performance status and pre-existing comorbidities. Hence, the effect of increasing age is likely underestimated. Following a recent SR, Kim et al. (18 studies, n=49,449) concluded that over 80s have a 50% increased risk of perioperative morbidity and a 100% increased risk of perioperative mortality compared to under 80s[175]. Haigh et al. (n=2610), also found that those over 70 had higher rates of morbidity (41% vs 34%, p=0.01) and mortality (5% vs 1%, p=0.01)[176]. Further authors have reached similar conclusions using thresholds of 75[177] and 80 years [178]. As such, careful patient selection is required when deciding to operate on elderly patients, but advanced age alone is not an absolute contraindication to PD.

Sex

No recent studies have specifically compared outcomes in males and females. Williamsson et al. investigated for gender differences in treatment and outcomes following a diagnosis of a pancreatic head malignancy. All patients in the Swedish national database (2012-2017) were included (n=5677). Females were significantly older than males at the time of diagnosis (72 vs 70 years, p<0.001) and a lower proportion

underwent curative-intent surgery (41% vs 44%, p=0.008)[179]. However, once age and tumour location were adjusted for, no differences were observed[179]. Females had shorter operation times (376 vs 402 minutes, p<0.001) and reduced intraoperative blood loss (400 vs 600 ml, p<0.001), which may be because men tend to have a higher proportion of intra-abdominal fat[179]. No difference in overall morbidity, length of stay or perioperative mortality was observed[179]. Five-year survival following resection was significantly higher in females (8% vs 6%, p<0.05)[179]. Hence, the authors concluded that it may be reasonable to offer females PD at a more advanced age[179].

Mazmudar et al. (n=22,086) found, after adjusting for confounding factors, males were more likely to have an operation lasting more than six hours (28% vs 18%), and had higher intraoperative blood transfusion rates (14.4% vs 14.0%), higher SSI rates (20% vs 17%) and longer length of stay (9.4 vs 9.1 days, all p<0.001)[180]. Again, the authors suggested that this may be because abdominal-type obesity is more common in males[180]. Male sex was not associated with increased perioperative mortality rates, and long-term outcomes were not studied[180].

Body mass index

Numerous studies have concluded that patients of an unhealthy weight are at increased risk of postoperative complications. The threshold BMI used has varied considerably. Chen et al. (n=362) concluded that a BMI >24 kg/m^2 was associated with increased morbidity (43% vs 30%, p=0.009) but mortality was unaffected[181]. Aoki et al. found that a BMI >25 kg/m^2 was a risk factor for grade C POPF (OR: 1.8) and major morbidity (OR: 1.8, both p<0.001)[182]. Tang et al. (n=227) reached similar conclusions[183]. El Nakeeb et al. (n=471) found that a BMI >25 kg/m^2 was associated with longer operation times (5.4 vs 5.0 hours, p=0.003), POPF (25% vs 8%, p<0.001), overall morbidity (33% vs 17%, p=0.001) and perioperative mortality (7% vs 1%, p=0.001)[184]. Del Chiaro et al. (n=367) also found that a BMI >25 kg/m^2 was associated with increased intraoperative blood loss

(1392 vs 1121 ml, p=0.01) and an increased risk of POPF (20% vs 10%, p=0.006)[185], and Greenblatt et al. (n=4945) concluded that a BMI >25 kg/m^2 was a predictor of overall morbidity (p<0.05), but not perioperative mortality[186]. A recent MA by You et al. (22 studies, n=8994) compared patients with a high BMI (>25 kg/m^2) to those with a low BMI (<25 kg/m^2)[187]. A high BMI was associated with increased operation times (mean difference (MD): 15 minutes), increased intraoperative blood loss (MD: 271 ml), POPF (OR: 2.0), delayed gastric emptying (DGE, OR: 1.6), SSI (OR: 1.4), and a longer length of stay (MD: 2.9 days, all p<0.05)[187].

Using a threshold BMI of 30 kg/m^2, Wiltberger et al. (n=405) concluded that obese patients were more likely to experience major morbidity (p<0.05)[167]. Similarly, Ekström et al. (n=328) found that obesity was associated with increased major morbidity (OR: 1.7, p=0.001) and grade B/C POPF (OR: 4.2, p=0.001)[188]. Using the same threshold, Chang et al. (n=3484), concluded that obesity was associated with increased rates of SSI (OR: 1.4, p=0.01), unplanned return to theatre (OR: 1.4, p<0.05), failure to extubate after 48 hours (OR: 1.6, p=0.02), septic shock (OR: 2.2, p=0.0002), and perioperative mortality (OR: 1.7, p<0.05)[189]. Zorbas et al. (n=2667), found that morbid obesity (BMI ≥40 kg/m^2) was a risk factor for pulmonary embolism (PE, 2% vs 1%, p<0.05), POPF (30% vs 16%, p<0.0005), SSI (15% vs 9%, p<0.0005), renal failure (3% vs 0.4%, p=0.003), and overall morbidity (65% vs 48%, p<0.001), but not perioperative mortality[190].

The increased risks associated with obesity are well documented but being underweight also has associated risks. Pausch et al. (n=408) found that patients with a BMI <18.5 kg/m^2 had higher perioperative mortality rates (p<0.05)[191]. However, this included just sixteen patients in the underweight category, and larger studies have not validated these findings. It is likely that malnutrition and cachexia, rather than a low BMI, contribute to an adverse outcome.

Whilst many studies have investigated the impact of BMI on short-term outcomes, few have considered the long-term outcomes of PD. Tsai et al. (n=795) concluded that overweight (BMI ≥25 kg/m^2) and obese (BMI ≥30 kg/m^2) patients had improved five-year

survival compared to normal weight patients (22% vs 22% vs 15%, p=0.02)[192]. Two other similar studies did not observe this[193, 194].

Sarcopenia

Sarcopenia is a syndrome which results in the progressive loss of skeletal muscle quality and mass, and a low physical performance[195]. Sarcopenia can be evaluated by assessing psoas muscle mass and density on abdominal CT at the level of the third lumbar vertebra[196]. Numerous recent studies have investigated the impact of CT changes associated with sarcopenia on PD outcomes. Linder et al. (n=139) found an association between preoperative sarcopenia and severe POPF (OR: 4.3, p=0.03)[197]. Several other authors have arrived at the same conclusion[198-201]. Takagi et al. (n=219) showed sarcopenic patients had higher rates of infective complications (67% vs 40%, p<0.001) and perioperative mortality (6% vs 0%, p=0.004)[202].

Concerning the long-term outcomes of PDAC patients, Ryu et al. (n=252) found that preoperative sarcopenia was associated with decreased five-year survival (23% vs 28%, p<0.05)[201]. An association was also demonstrated between sarcopenic obesity and POPF (p=0.02)[201]. Stretch et al. (n=123) also found that sarcopenic PDAC patients had reduced OS (16.0 vs 26.4 months, p=0.005)[203]. Peng et al. (n=116) and Gruber et al. (n=133) reached similar conclusions[204, 205]. The latter also showed that PDAC patients with sarcopenic obesity had even worse OS (14 vs 23 months, p=0.007) and higher major morbidity rates (13.5% vs 1.5%, p<0.001) than sarcopenic patients of a healthy weight[205].

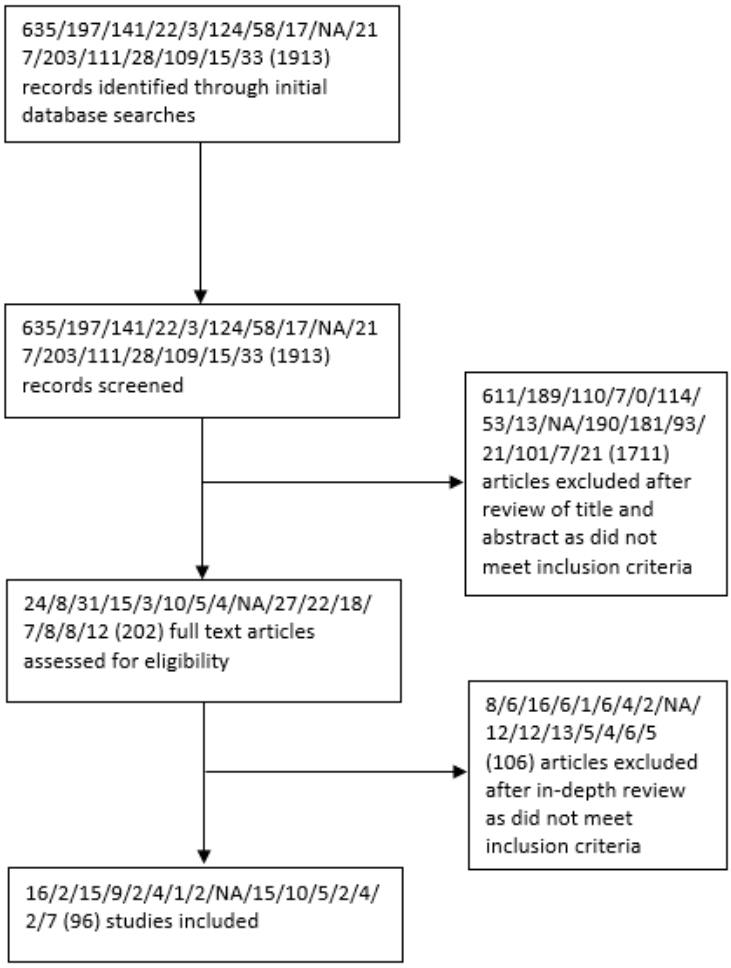


Figure 3.1: Flow of information diagram. Numbers represent total number of articles on age/gender/BMI/sarcopenia/myosteatosis/DM/cardiac disease/respiratory disease/radiological staging/NAT/PBS/bilirubin/CRP/albumin/CAR/NLR (total number of studies). Eleven SRs/MAs were included (age: one, BMI: one, DM: two, NAT: three, PBD: two, CRP: one, NLR: one). The remaining studies were single/multicentre clinical studies. Risk of bias assessment was not performed for each individual study. Effect estimates and precision figures are quoted in the main text.

Myosteatosis

Myosteatosis refers to fat deposition within the muscles; it can be assessed using CT or MRI, where it appears as low skeletal muscle radiation attenuation. Although few studies have investigated the impact of myosteatosis on long-term outcomes of PD, Stretch et al. (n=123) concluded that myosteatosis was associated with reduced OS in PDAC patients, but only when in combination with sarcopenia (p=0.002)[203]. Only a trend was observed in myosteatosis patients without sarcopenia (p=0.06). Similarly, few studies

have investigated the impact of preoperative myosteatosis on perioperative outcomes. However, there is recent evidence to suggest an association with increased morbidity following resection for oesophageal and gastric cancers[206]. West et al. (n=123) prospectively studied patients undergoing hepatobiliary and pancreatic surgery (all resections) and found that myosteatosis on preoperative CT was associated with worse preoperative fitness as measured by cardiopulmonary exercise testing (CPET, $p<0.001$)[207]. The authors concluded that combining myosteatosis and physical fitness variables may help in stratifying risk[207]. One would expect patients with myosteatosis to have worse perioperative outcomes, but this remains unproven. Further, it is unknown if optimising patients with myosteatosis would be of benefit.

Diabetes mellitus

The impact of DM on PD outcomes remains controversial. Lv et al. carried out a MA (17 studies, n=5407 patients, all forms of pancreatic resection included) and found that patients with diabetes had a higher prevalence of male sex ($p=0.01$) and a higher median BMI ($p<0.001$)[208]. No differences were observed in age, smoking status, prevalence of jaundice, operation time, or rate of intraoperative blood transfusion[208]. Histologically, DM patients were more likely to have poorly differentiated ($p=0.03$), larger ($p<0.001$) tumours, and a "hard" pancreas consistency ($p<0.001$)[208]. Cancer stage and margin status were comparable between the two groups[208]. Lv et al., like Nakata et al. in another SR, did not find that DM affected overall morbidity or perioperative mortality[208, 209].

POPF is a significant and well-documented complication of pancreatic resection. It has been associated with DM since diabetics are thought to have a softer pancreas due to a higher fat content. A small calibre pancreatic duct and a soft pancreas consistency are known predisposing factors. Lv et al. and Xia et al. (MA of sixteen studies) found a similar prevalence of a small pancreatic duct and a soft pancreas consistency among diabetics and non-diabetics[208, 210]. No association between DM and POPF was

observed[208, 210]. This may be accounted for by patient selection and the high attention levels often given to high-risk patients. Another complication often linked with DM is DGE. In contrast to a few small case series, no large studies have suggested that diabetics are at increased risk of DGE.

Long-term hyperglycaemia is known to impair immune function. Hence, DM is often presumed to increase the risk of infective complications. King et al. concluded that poorly controlled diabetics are more likely to experience infective complications when undergoing general surgical and vascular operations[211]. Whilst the underlying mechanisms are not well understood, it is thought hyperglycaemia can affect chemotaxis, the activation of macrophages, pathogen opsonisation, and phagocytosis[212]. However, the MA by Lv et al. did not identify DM as a predictor of infective complications[208]. This study did suggest that a recent diagnosis of DM (within two years of resection) was associated with reduced OS following PD for PDAC (RR: 1.4, $p<0.001$)[208].

Cardiac disease

The impact of acute and chronic cardiac disease on pancreatic resection outcomes was investigated by Ronnenkleiv-Kelly et al. in a large retrospective cohort study (n=13,021) using American national data (two thirds of the cohort underwent PD)[213]. Patients were categorised as having a history of cardiac disease if they had a prior diagnosis of CCF, angina, or MI, or if they had any history of percutaneous coronary intervention or cardiac surgery. Eleven percent of patients had pre-existing cardiac disease and a 1% sub-set had “acute cardiac disease” (defined as CCF symptoms within 30 days, angina within one month, or MI within six months of surgery). Those with cardiac disease were older, more comorbid, more likely to be male, and were more likely to experience cardiac complications (all $p<0.001$). Patients with acute cardiac disease had an even higher risk of cardiac complications ($p<0.001$)[213]. A history of cardiac disease and acute cardiac

disease were associated with a 1.6-fold (p<0.0001) and 1.8-fold (p<0.0007) increase in major morbidity, and a 2.3-fold (p<0.0001) and 4.2-fold (p<0.0001) increase in perioperative mortality, respectively[213]. Other studies which did not specifically investigate the impact of pre-existing cardiac disease have come to similar conclusions[186, 214, 215]. It is unknown whether pre-existing cardiac disease affects long-term PD outcomes.

Respiratory disease

Identifying patients with pre-existing respiratory disease and optimising their functional status wherever possible is essential. It is also important that patients are risk-stratified and that, as with cardiac disease, their increased level of risk is discussed with them preoperatively. Preoperative CPET can provide estimates of aerobic and anaerobic thresholds to aid in preoperative planning for the perioperative period. Few large studies have specifically investigated the impact of preoperative respiratory comorbidities on PD outcomes. This is likely because those with significant respiratory disease are unlikely to be considered surgical candidates. Shia et al. (n=8490) found pre-existing COPD independently reduced 90-day survival (aHR: 1.4, p<0.001)[216] and Aoki et al. (n=17,564) found those with pre-existing respiratory comorbidities had higher major morbidity (OR: 1.9, p=0.01) and grade C POPF (OR: 2.1, p=0.0002) rates[182].

Radiological features

To our knowledge, no studies have specifically investigated the impact of radiological stage on PD outcomes. A more advanced stage is likely associated with worse short- and long-term outcomes. Several recent studies have attempted to identify radiological features as prognostic predictors. Lee et al. (n=143) studied PDAC patients who underwent MRI within one month of PD and were subsequently found to have no positive resection margins. Rim-enhancement at dynamic contrast material-enhanced MRI was

associated with reduced three-year DFS (8% vs 24%, p=0.008) and three-year OS (20% vs 41%, p=0.001)[217]. Rim-enhancing lesions were also associated with more aggressive tumours on pathological staging (p=0.002)[217]. Several studies have investigated PDAC CT tumour characteristics. Kim et al. (n=116) found tumours with a heterogeneous texture were associated with reduced DFS (7 vs 11 months, p=0.03)[218] and Zhu et al. (n=79) found that lower relative enhancement change was associated with shorter DFS (11 vs 18 months, p=0.01) and three-year OS (20 vs 29 months, p=0.01)[219]. Cassinotto et al. (n=99) studied the portal venous phase of preoperative scans and concluded that hypoattenuating tumours were associated with reduced one-year DFS (35% vs 68%, p=0.04)[220].

Positron emission tomography (PET)-CT is a further imaging modality which has been studied. Choi et al. (n=64) found patients with a PDAC with a maximum standardised uptake value >3.5 had reduced DFS (9 vs 26 months, p=0.002) and OS (24 vs 45 months, p=0.002)[221]. Yamamoto et al., who performed a similar study but used a cut-off value of six, reached the same conclusion[222]. Lee et al. (n=87) identified both metabolic tumour volume and total lesion glycolysis as independent predictors of DFS (HR: 2.3, p=0.001, and HR: 2.6, p=0.003, respectively) and OS (HR: 3.7, p=0.02, and HR: 4.9, p=0.003, respectively)[223].

Neoadjuvant treatment

Neoadjuvant treatment aims to treat micrometastases, downstage primary tumours, and increase the chance of patients completing a course of systemic therapy. Currently, UK guidelines only advise NAT in PDAC patients if this is part of a clinical trial[47]. The use of NAC for resectable/borderline resectable PDAC remains a source of debate and has been the subject of several recent trials. The two-arm randomised phase II/III Prep02/JSAP05 trial involved 57 Japanese centres. One arm received gemcitabine and S-1 prior to surgery, and the other had upfront surgery. All patients with resectable or

borderline resectable PDAC who could tolerate curative-intent surgery were included (n=362). OS was significantly longer in the NAC arm (37 vs 27 months, p=0.02)[224]. No difference was observed in terms of resection rate, R0 resection rate, and overall morbidity[224]. The international phase II ESPAC-5F trial contained four arms. This aimed to compare resection rates in those who underwent upfront surgery to gemcitabine/capecitabine NAC, FOLFIRINOX (folinic acid, fluorouracil, irinotecan and oxaliplatin-based) NAC, and neoadjuvant chemoradiotherapy (NACRT) (n=90). The resection rate was slightly higher in the upfront surgery group, but this was not significant [225]. Upfront surgery was associated with reduced one-year survival compared to all NAT arms (40% vs 77%, p<0.001). The authors concluded that NAT should be considered in those with borderline resectable PDAC[225].

The phase III PREOPANC trial involved sixteen Dutch centres and aimed to compare outcomes in those who received NACRT to those who received conventional treatment (upfront surgery followed by gemcitabine-based adjuvant chemotherapy) (n=248). All surgical candidates with a resectable or borderline resectable PDAC were included. T1 tumours were excluded, and randomisation took place prior to biliary drainage (if this was performed). Those in the NACRT arm had a slight survival benefit although this was not significant[226]. When those in the NACRT group who failed to progress to surgery were excluded, the R0 resection rate was significantly higher in the NACRT group compared to the upfront surgery group (71% vs 40%, p<0.001). Hence, NACRT likely improved the process of selecting appropriate surgical candidates[226]. When only those who underwent resection and subsequently started adjuvant therapy were included, NACRT provided a further survival benefit (35 vs 20 months, p=0.03)[226].

A recent MA by Rangarajan et al. included 27 studies: three were RCTs and 24 were retrospective cohort studies (n=63,151). Improved survival outcomes (HR: 0.7, p<0.001), reduced morbidity rates (RR: 0.8, p=0.001) and improved R0 resection rates (RR: 0.5, p<0.001) were observed in those who received NAC[227]. Greco et al (n=8472) reached similar conclusions[228]. These studies will have been affected by selection bias since

patients who received NAC but failed to progress to surgery were excluded. Both authors concluded that, whilst there may not be strong evidence for NAC in resectable disease, it does confer a survival benefit for certain patients[227, 228]. In a further MA by Lee et al. (fourteen studies, n=9691), NAC was not found to provide a survival benefit[229]. However, patients who received NAC had improved OS when compared to patients who had upfront surgery and then completed adjuvant treatment (HR: 0.8, p<0.001)[229]. The authors concluded that, whilst NAC may not provide an obvious survival benefit for all patients, it may have a role in selecting the most suitable candidates for resection[229].

Whilst the survival benefits of NAT continue to be investigated, it is important to consider whether NAT affects perioperative outcomes. Kamarajah et al. (n=7975) found that patients receiving NAT had lower rates of unplanned readmission (6% vs 7%, p=0.006) and that NAT had no effect on length of stay or perioperative mortality[230]. Cho et al. (n=4416) found that patients who received NAT had longer operation times (423 vs 368 minutes, p<0.001) and were more likely to undergo a concomitant vascular reconstruction (21% vs 8%, p<0.001)[231]. This is likely because patients who underwent NAT were more likely to have named vessel involvement as their indication for chemotherapy. No difference was observed in morbidity or mortality rates, and those in the NAT group had a shorter length of stay (9 vs 10 days, p=0.005)[231]. In a similar study, Cools et al. (n=3748) found that NAT patients were more likely to undergo a venous resection (36% vs 18%, p<0.001) or have a prolonged operation (413 vs 364 minutes, p<0.001), however, this group were less likely to develop grade C POPF (0.2% vs 1%, p<0.001)[232]. No difference in overall morbidity or perioperative mortality was observed[232]. Youngwirth et al. (n=18,243) reached similar conclusions[233]. In contrast, Aziz et al. (n=1445) found that NAT patients were more likely to have unplanned readmissions (18% vs 12%, p=0.02) or an unplanned return to theatre (2% vs 1%, p=0.03), however, no difference in perioperative mortality was observed[234]. The authors acknowledged that these differences might be as patients in the NAT group were more likely to have had advanced disease[234]. Teng et al. (n=5025) found that NAT was associated with longer

operation times, and increased rates of blood transfusion, vascular reconstruction and SSI (all p<0.05). However, perioperative mortality and major morbidity rates were not affected by NAT[235].

A recent MA by Kamarajah et al. (n=19,416, nineteen studies) found that NAT was associated with reduced rates of both overall POPF (OR: 0.6, p<0.001) and grade B/C POPF (OR, 0.6, p<0.001)[236]. Mangieri et al. (n=10,665) and Marchegiani et al. (n=455) reached the same conclusion[237]. The latter also found that NAT was associated with a reduced risk of PPH (9% vs 15%, p=0.02), but an increased risk of DGE (12% vs 3%, p=0.03)[238].

In summary, the use of NAT in the management of PDAC remains controversial. Emerging evidence suggests NAT offers a survival benefit and may help to identify the most appropriate PD candidates. NAT is also associated with a reduced length of stay, as well as reduced overall morbidity, POPF and PPH rates. NAT may increase DGE rates and is associated with increased rates of venous resection, but this likely reflects preoperative disease stage. Whether NAT affects unplanned readmission rates remains controversial.

Biliary stenting

This topic is well-studied but it remains controversial. UK national guidelines advise against routine PBS before PD as the associated risks are thought to outweigh the potential benefits[47]. Gong et al. recently carried out a MA (27 studies, n=10,445) and found PBS was associated with increased overall morbidity (OR: 1.2, p=0.01), DGE (OR: 1.2, p=0.02) and SSI (OR: 2.1, p<0.0001), but there was no difference in overall mortality or major morbidity[239]. The authors concluded that patients awaiting PD should not undergo PBS unless they have cholangitis or organ failure secondary to an obstructed biliary system[239]. In those who did undergo PBS, there was no difference in morbidity between the endoscopic and percutaneous drainage groups[239]. In another recent MA,

Scheufele et al. (25 studies, n=6214) also found that PBS was associated with increased overall morbidity (OR: 1.4, p<0.002)[240].

Numerous single/multicentre studies have investigated the impact of PBS on PD outcomes. Morris-Stiff et al. (n=280) found stenting did not significantly alter preoperative serum bilirubin, and that stented patients had higher overall morbidity (54% vs 41%, p=0.03), and rates of POPF (26% vs 18%, p=0.03) and intra-abdominal haemorrhage (13% vs 6%, p=0.03)[241]. Hamidi et al., who excluded NAT patients, matched 927 PD patients with obstructive jaundice who underwent PBS to 927 who did not. No significant difference in short-term outcomes was observed between the two groups[242]. The authors concluded that PBS is safe and that it does not need to be avoided[242]. De Pastena et al. (n=1500) found that major morbidity and mortality rates were not affected by PBS, but did argue that jaundiced patients with a serum bilirubin >7.5 mg/dL should be considered for PBS[243].

El Nakeeb et al. (n=588) found that PBS was associated with higher overall morbidity (33% vs 24%, p=0.03), POPF (19% vs 10%, p=0.002) and bile leak (11 vs 6%, p=0.04) rates. The mean length of stay was also longer in the drainage group (10 vs 8 days, p=0.01)[244]. Sahora et al. (n=1000) showed that SSI rates were higher in stented patients (19% vs 9%, p=0.001) but PBS did not affect overall morbidity or mortality[245]. In contrast, Bolm et al. matched 480 patients who underwent PBS to 480 who underwent upfront surgery (jaundiced and non-jaundiced patients were included) and found PBS was associated with increased major morbidity rates (27% vs 22%, p=0.03). However, this was not significant in PBS patients who presented with jaundice[246]. Gavazzi et al. (n=180) found PBS was associated with deep (14% vs 4%, 0.04), but not superficial, SSI[247]. Bhatti et al. (n=133) found that patients undergoing PBS were more likely to develop a SSI (23% vs 7%, p=0.01) or be readmitted (11% vs 0%, p=0.006), but that PBS did not affect rates of overall perioperative mortality or grade B/C POPF[248].

In summary, PBS appears to be associated with higher rates of overall morbidity, DGE, SSI, POPF, bile leak and unplanned readmissions. Stented patients may also have

a longer length of stay. Most authors argue that patients should only undergo PBS if there is a clear indication e.g., cholangitis or organ failure secondary to jaundice. It is important to consider that patients who undergo PBS may be in a worse premorbid state than those who undergo upfront surgery, and these patients may have higher morbidity rates regardless of their management. It is unknown whether PBS affects long-term PD outcomes.

Preoperative blood tests

Bilirubin

Multiple prior studies have investigated the impact of serum bilirubin levels on PD outcomes. Scheufele et al. (n=304) found that preoperative bilirubin did not affect overall morbidity or long-term survival[249]. Pamecha et al. (n=177) reached similar conclusions but found severe jaundice (≥15 mg/dL) was associated with increased intraoperative blood loss (650 vs 300 ml, $p<0.001$)[250]. Wang et al. also reached similar conclusions but found severe jaundice was associated with increased infective complications (57% vs 36%, $p<0.05$)[251]. Dolejs et al. (n=2556) found that preoperative bilirubin level did not affect overall morbidity, major morbidity, or perioperative mortality[252]. Yoon et al. (n=164) found that preoperative bilirubin was more likely to be ≥7 mg/dL in those who did not survive 60 months (44% vs 5%, $p=0.01$)[253].

C-reactive protein

Preoperative CRP levels are inversely proportional to survival in several cancers. Stevens et al. carried out a SR to investigate the role of preoperative CRP as a prognostic predictor in PDAC patients (n=485). Of the six studies which investigated the effect of high CRP on OS, whilst the cut-off value for high CRP varied, four suggested a correlation between high CRP and decreased OS. On multivariable analysis, three studies observed this finding. The authors concluded that there was insufficient evidence

to justify the use of CRP level in clinical decision making[254]. A more recent study by Mansukhani et al. (n=133), where CRP levels were taken 48 hours prior to surgery, found that CRP was a predictor of infective complications ($p<0.01$)[255]. However, this was not significant following a multivariable analysis.

Albumin

Serum albumin is often used as a crude indicator of nutritional status and hepatic synthetic function. Low levels are associated with poor surgical outcomes[256]. Rungsakulkij et al. (n=238) found low preoperative serum albumin was a risk factor for major morbidity (OR: 0.9, $p<0.05$)[256]. Other studies have also found this [257, 258]. Hendifar et al. (n=106) found that a low serum albumin was associated with increased postoperative transfusion rates ($p=0.02$) and reduced OS (HR: 0.5, $p=0.02$)[259].

C-reactive protein/albumin ratio

C-reactive protein/albumin ratio has been used as a marker for chronic inflammation and nutritional status. Few recent studies have investigated the impact of preoperative CAR on PD outcomes. Van Wijk et al. (n=163, HR: 1.7, $p=0.004$) and Haruki et al. (n=113, $p<0.05$), found that, independent of disease stage, high CAR was a risk factor for reduced OS among PDAC patients[260, 261]. No recent studies have investigated the impact of preoperative CAR on perioperative outcomes.

Neutrophil/lymphocyte ratio

A high preoperative neutrophil/lymphocyte ratio is associated with poor prognosis in cancer patients across a wide spectrum of diagnoses, stages of disease, and courses of treatment[262]. Although this is well described, the mechanisms behind this are poorly understood. Following a recent MA, Mowbray et al. (eight studies, n=1519) found high preoperative NLR was associated with reduced OS in PDAC patients (HR: 1.8,

p<0.001)[263]. The authors concluded that further studies are required to obtain a cut-off value which can be used for prognostic purposes[263]. Sun et al. (n=358) found that OS was lower in PDAC patients with a NLR >3.3 (HR: 1.6, p=0.01)[264].

Concerning perioperative outcomes, Arikan et al. (n=123) demonstrated that a high preoperative NLR was associated with increased overall morbidity (42% vs 15%, p=0.03)[265]. NLR had a high specificity but a low sensitivity for predicting POPF[265]. Other authors have also found this[266]. In addition, Ida et al. (n=208) found a high NLR was associated with increased overall morbidity (OR: 1.1, p=0.03), which contributed towards an increased length of stay in those who experienced a complication (19 vs 33 days, p=0.005)[267]. Huang et al. (n=223) also concluded that patients who experienced complications were more likely to have a NLR ≥3.8 (p=0.006)[268]. Shen et al. (n=835) found that NLR was significantly higher in those who experienced major morbidity (3.8 vs 3.0, p<0.001)[269].

Discussion

This review was carried out to consolidate the recent literature on preselected preoperative factors and their impact on PD outcomes. **Table 3.1** summaries the impact of each variable on selected outcomes. Appreciating the modifiable factors discussed may allow for patient optimisation before surgery. For example, a preoperative review of all patients with diabetes or COPD by a specialist nurse, or the use of CPET to plan perioperative care, may reduce morbidity rates. This, in turn, may increase the likelihood of patients starting and/or completing AC and have implications for OS. Routine assessment of preoperative CT imaging for sarcopenia and myosteatosis could prompt early dietetic input to reduce the preoperative catabolic state, which may reduce the risk of anastomotic failure. To our knowledge, no prior studies have investigated the impact of treating myosteatosis on PD outcomes. We argue a study is required where patients

with myosteatosis are randomised to either a specialised diet and exercise programme or standard care prior to surgery to investigate the impact on morbidity.

An appreciation for the non-modifiable factors discussed will assist the assessment of potential surgical candidates, allow clinicians to consider the appropriateness of PD, and result in more informed risk stratification and discussions with patients regarding risk and benefit. The influence of many of these factors on outcomes are limited to single centre retrospective analyses and may not account for all confounding variables. The limitations of this SR have been outlined in **Chapter 9**.

Conclusion

Despite improvements to patient selection, surgical techniques, and perioperative care, PD continues to be associated with considerable morbidity. Even in the absence of surgical complications, few patients achieve long-term survival due to cancer recurrence. A number of the variables discussed above affect PD outcomes. Some of these may be used as prognostic indicators to assist patient selection, optimise patients preoperatively and to guide risk/benefit discussions with potential surgical candidates. A robust study which considers confounding variables is required to investigate these further.

Post hoc comment

This SR did not include data from the Cochrane Library. Additional Cochrane Library searches were carried out to identify any additional relevant articles. The same search methods were used as described above. No additional relevant articles were identified.

Preoperative factor	Risk of POPF	Risk of SSI	Risk of DGE	Intra-op blood loss	Length of stay	Peri-op morbidity	Peri-op mortality	Disease-free survival	Overall survival
Demographic factors									
Advanced age (various thresholds)						↑	↑		
Male gender		↑		↑					
Pre-existing comorbidities									
Cardiac						↑	↑		
Respiratory						↑	↑		
Diabetes mellitus									
Nutritional status									
BMI ≤18.5 kg/m^2					↑	↑	↑		
BMI ≥25 kg/m^2	↑	↑	↑			↑			
BMI ≥30 kg/m^2		↑		↑	↑	↑			
BMI ≥40 kg/m^2							↑		
Sarcopenia	↑	↑	↑			↑			↓
Myosteatosis									↓
Preoperative imaging									
Heterogeneous tumour on CT								↓	
Hypoattenuating tumour on CT								↓	
Low enhancement change on dynamic contrast-enhanced CT								↓	↓
Rim-enhancement on MRI								↓	↓
Maximum standardised uptake value >3.5 on PET-CT								↓	↓
Metabolic tumour volume >3cm^3 on PET-CT								↓	↓
Total lesion glycolysis >10g on PET-CT								↓	↓
Preoperative treatment									
Biliary stenting	↑	↑	↑			↑			
Neoadjuvant chemotherapy	↓		↑		↓	↓			↑
Preoperative blood tests									
Bilirubin <7 mg/dL									↑
Bilirubin >20 mg/dL							↑		
Raised CRP (various thresholds)									↓
Albumin <35 g/L				↑		↑		↓	↓
CRP/albumin ratio (various thresholds)	↑					↑		↓	↓
Neutrophil/lymphocyte ratio (various thresholds)	↑				↑	↑			↓

Table 3.1: Selected preoperative factors and their impact on PD outcomes. Increased or decreased risk/survival compared to patients without the factor. References can be found within the main text.

3.2. Selected intraoperative factors: a narrative review

In this section, a narrative review is presented that provides an overview of the existing evidence relating to pre-selected intraoperative factors and their impact on PD outcomes.

Russell TB, Labib PL, Aroori S. Selected intraoperative factors which affect pancreatoduodenectomy outcomes: a narrative review. *Ann Pancreat Cancer* 2022. DOI: 10.21037/apc-21-16. Open access.

What is known:

- An appreciation for the intraoperative factors which affect PD outcomes will improve patient selection, guide risk/benefit discussions with patients and allow surgeons to consider their operative approach

What is new:

- ASA grade III patients are high-risk and soft pancreas texture, the absence of pancreatitis and a small calibre main pancreatic duct increase the risk of POPF
- A pylorus-preserving approach may reduce operation times and blood loss, whilst increasing rates of DGE
- Minimally invasive approaches have their advantages, but they are only available at certain units and are not appropriate for all patients
- A P-G may reduce blood loss and operation times whilst increasing the risk of postoperative bleeding
- The benefits of concomitant vascular resection remain controversial and transfused patients have poor outcomes, but this is difficult to quantify

Introduction

This section aimed to review the recent literature on selected intraoperative factors and their impact on short- and long-term PD outcomes (when performed for PDAC, AA or distal CC). Although many of the factors discussed are non-modifiable, an in-depth understanding of their impact will result in improved patient selection and guide

risk/benefit discussions. An appreciation for the modifiable factors discussed will allow surgeons to consider their operative technique and optimise their outcomes.

Method

The intra-operative factors included were chosen prior to carrying out the literature search. These were: pylorus-resecting vs. pylorus-preserving technique, open vs. minimally invasive technique, type of pancreatic anastomosis, concomitant vascular resection, pancreas texture, evidence of pancreatitis, dilatation of the main pancreatic duct, and perioperative blood transfusion. ASA grade was also included although this is not strictly an intraoperative factor. In the blood transfusion section, articles reporting on transfusions given in the intra- and early postoperative period were included.

A comprehensive online search of the English literature was carried out on June 14th, 2021. The PubMed database was searched using the terms ["factor in question", "pancreatoduodenectomy", AND "outcome"] from May 2011 through May 2021. The following articles were included: 1) English language, 2) human studies, 3) MAs, SRs and clinical studies reporting on outcomes of PD performed for suspected malignancy, 4) in terms of risk factors/associations, only statistically significant results were included ($p<0.05$).

Results

ASA grade

The ASA physical classification system, or ASA grade, has been in use for more than 60 years. It categorises a patient's preoperative physiological status to guide clinical decision making. The system alone cannot quantify risk since it does not consider the operation being performed or physical factors such as a difficult airway, or a patient's wish to refuse a blood transfusion. Furthermore, it is subjective and does not consider the impact of advancing age on physiological fitness. Nonetheless, it is a useful tool.

ASA grade I patients are healthy and grade II patients have mild systemic disease[270]. Grade III patients have a severe systemic disease and grade IV patients have a severe systemic disease which is a constant threat to life[270]. It is rare for patients with an ASA grade of IV or higher to be offered PD.

The impact of ASA grade on surgical outcomes is well documented[270]. Morbidity and mortality rates increase with ASA grade in both the elective and emergency settings[271]. Specific to PD, an increasing ASA grade has been shown to correlate with adverse outcomes. Eeson et al. (n=100) found that an ASA grade of III was associated with increased perioperative mortality (p=0.01)[272]. However, this was not significant after adjusting for increasing age[272]. The authors concluded that, whilst an age >80 years should not be an absolute contraindication, extreme caution should be used when considering PD in a patient of this age if they are ASA grade III[272]. Other authors have shown that ASA grade III patients have significantly increased major morbidity rates[167, 273]. Concerning long-term outcomes, the Eeson et al. study showed that increasing ASA grade correlated with reduced overall survival (OS). Compared with ASA grade I-II patients, median OS was significantly shorter in ASA grade III patients (12 vs. 20 months, p=0.04)[272].

In summary, ASA grade is a basic but useful tool for estimating risk. One should consider the additional risks when offering PD to ASA grade ≥III patients, especially if they are elderly. This group have higher perioperative morbidity and mortality rates, and reduced OS.

Pylorus resection vs pylorus preservation

The classic PD (**Figure 3.2**) refers to resection of the pancreatic head, gallbladder, bile duct, duodenum and distal stomach, before the formation of the three anastomoses. A modified approach is the pylorus-preserving pancreatoduodenectomy (PPPD) which, as the name suggests, does not involve resection of the distal stomach (**Figure 3.2**). The

PPPD was popularised by the American surgeons L. William Traverso and William Longmire in the late 1970s and was initially intended for the management of chronic pancreatitis[274]. Due to reports of shorter operation times, decreased intraoperative blood loss, and reduced incidence of dumping syndrome, it was proposed as an alternative to the classic approach for the management of periampullary malignancies[274].

Multiple MAs have compared the outcomes of the two procedures. Whilst there were initial concerns regarding the oncological outcomes of PPPD, it has been shown to be equivalent in terms of recurrence and long-term survival[275]. Following a review of eight RCTs, Hüttner et al. (n=512) found that opting for a pylorus-preserving technique did not affect morbidity, mortality or OS[276]. A less recent MA by Diener et al. reached similar conclusions[277]. A further MA by Yang et al. (eight RCTs, n=662), suggested the PPPD had short-term advantages, including reduced operation times (MD: 53 minutes, p=0.01) and reduced intraoperative blood loss (mean difference: 365 ml, p=0.006)[278]. However, a classic PD was associated with lower rates of DGE (RR: 2.4, p=0.04). Morbidity and mortality rates were similar, and OS was not studied[278]. A MA by Zhou et al. reached similar conclusions[279].

In summary, the classic PD and the PPPD are both acceptable approaches which have similar recurrence and survival rates. It may be that the PPPD is associated with shorter operation times and reduced intraoperative blood loss. A classic PD may be associated with reduced DGE rates.

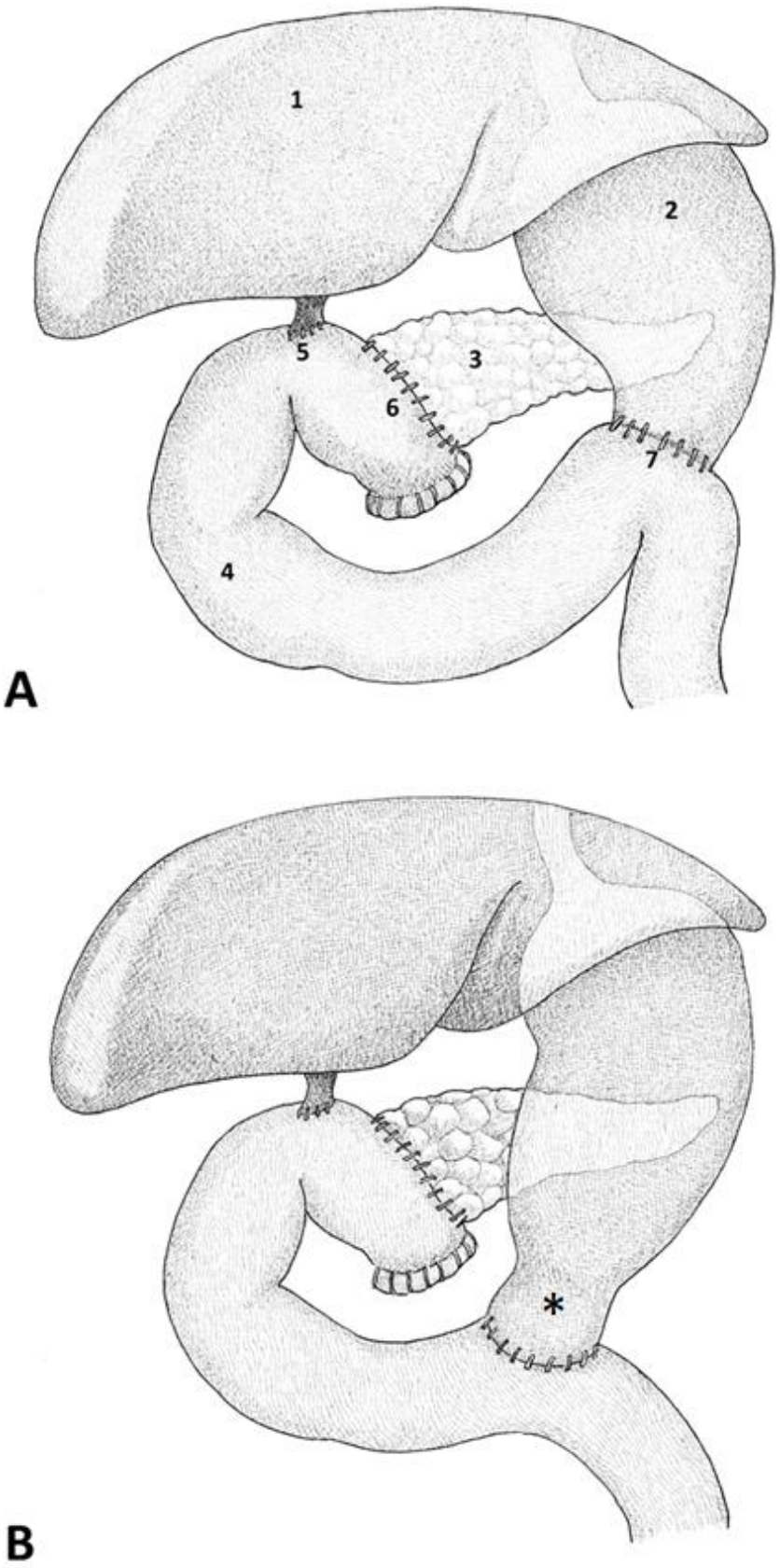


Figure 3.2: The classic (A) and pylorus-preserving (B) approaches. 1 = liver, 2 = stomach, 3 = remnant of pancreas, 4 = loop of jejunum, 5 = H-J, 6 = P-J, 7 = G-J, * = pylorus/proximal duodenum (Illustrations by John Peter Ovens).

Open vs minimally invasive techniques

In recent decades, minimally invasive surgical techniques have seen a meteoric rise. Many operations which were once performed open are now routinely performed laparoscopically or robotically. The first laparoscopic PD (LPD) was reported by Michel Gagner and Alfons Pomp in 1994. However, uptake has been slow due to the associated technical challenges of performing an oncological resection in a difficult-to-access anatomical location, and the need to perform the three anastomoses[280]. Not all PD patients are suitable for a laparoscopic resection; this includes those who are likely to require a concomitant vascular resection, are obese, or have previously had abdominal surgery or pancreatitis[281]. Unsurprisingly, a high proportion (up to 10%) of LPDs are converted to an open procedure[282]. Multiple studies, including MAs, have suggested that LPD is associated with longer operation times, a shorter length of stay and reduced intraoperative blood loss[281, 283-286]. No significant difference has been observed in morbidity, mortality, or oncological outcomes[282, 284, 287]. Despite this, some specialists have concerns regarding the risk of major morbidity following LPD. A recent RCT by van Hilst et al. was terminated early due to safety concerns as, although not significant due to the small sample size, LPD was associated with a higher number of complication-related deaths[288].

Laparoscopic surgery creates several issues for the surgeon, including two-dimensional imaging, poor ergonomics, restricted range of movement, and a long learning curve. Robotic PD (RPD) has been developed as an alternative which has become popular in certain units. RPD provides superior three-dimensional visualisation, instruments which mimic the surgeon's own hands, an articulating "wrist", and a greater range of motion. The feasibility of RPD was first described in 2003 by Giulianotti et al. who published a series of thirteen patients[289]. A recent MA by Da Dong et al. (24 studies, n=12,579) compared RPD to open surgery. RPD was associated with reduced intraoperative blood loss (MD: 191 ml, $p<0.001$) and longer operation times (MD: 75 minutes, $p<0.001$). There was a strong association toward increased complete (R0)

resection rate but this was not significant (16% vs 20%, p=0.05)[290]. The surgical approach did not impact on major morbidity or mortality rates, and long-term outcomes were not studied[290]. The survival outcomes of RPD are not well studied. Shyr et al., who compared the long-term outcomes of 85 RPDs and 81 open PDs, found that the former had improved one- (83% vs 64%), three- (45% vs 26%) and five-year (27% vs 17%) survival rates (p=0.004). However, these findings will have been heavily influenced by selection bias[291].

Aziz et al. (n= 11,218) compared the three approaches and found that the rates of SSI were lowest in LPD patients and highest in open patients (3% vs 6% vs 9%, p<0.01). Rates of respiratory tract infection were lowest in the RPD group, and highest in the open group (0.9% vs 3.6% vs 4.4%, p=0.04). Operation times were longest in the LPD group and shortest in the open group (482 vs 463 vs 354 minutes, p<0.001), and 30-day mortality was lowest in the open group and highest in the LPD group (2.3% vs 3.3% vs 3.6%, p=0.02)[292]. Long-term outcomes were not studied, and the authors concluded that smaller incisions did not improve outcomes. In a recent MA, Aiolfi et al. also compared the three approaches (41 studies, n=56,440). Perioperative mortality and major morbidity rates were similar[293]. Compared to an open approach, both LPD and RPD were associated with reduced perioperative blood loss and overall morbidity, shorter length of stay, and reduced rate of readmission[293]. The authors advised that the surgeon's skillset should guide the choice of approach but that minimally invasive approaches should be considered if feasible[293].

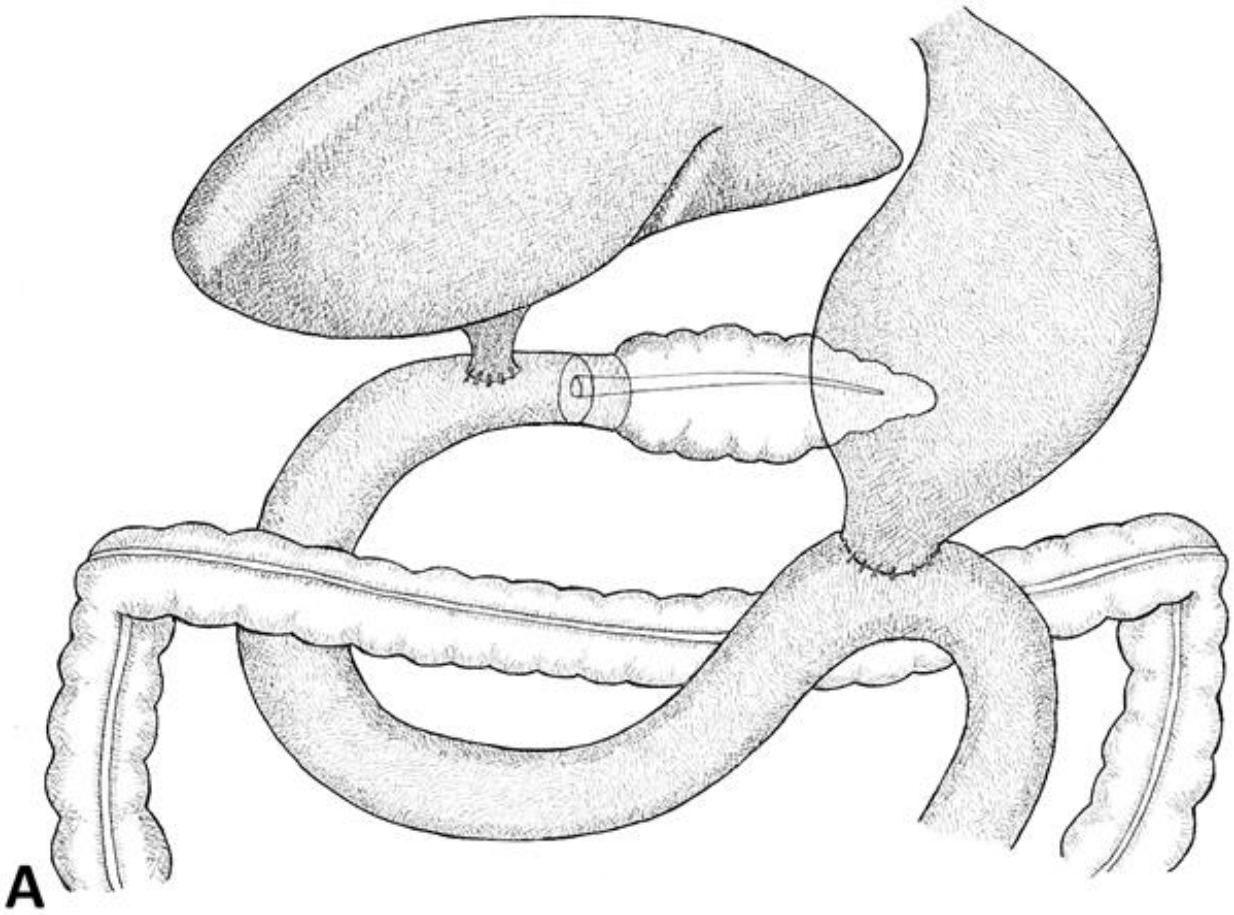
In conclusion, LPD has equivalent short- and long-term outcomes when compared with open PD. However, it is only possible in selected patients and, despite the long learning curve, benefits are likely to be modest. When compared with an open approach, it may be that RPD results in improved histopathological outcomes at the expense of longer operating times and increased financial cost. Whilst selected authors have safety concerns regarding minimally invasive approaches, it is important to remember that the

safety of these techniques is highly dependent on the expertise of the operating surgeon and the centre within which they work.

Pancreatic anastomosis

After resection of the pancreatic head and duodenum, it is necessary to anastomose the pancreatic remnant to a loop of small bowel or the stomach. Some surgeons prefer a pancreato-jejunostomy (P-J) whereas others prefer a pancreato-gastrostomy (P-G). Both are acceptable (**Figure 3.3**). Numerous P-J anastomotic techniques have been described. The most recent position statement by the International Study Group of Pancreatic Surgery (ISGPS) does not endorse any technique but advises an invaginating approach in patients with a soft pancreas[294]. This is supported by the findings of Cao et al. who found that invaginating techniques were associated with reduced rates of grade B/C POPF (7% vs 12%, p=0.006)[295]. P-G is a reasonable alternative. Whilst not backed by high quality evidence, some authors claim a P-G is preferable since pancreatic enzymes are not activated in the acidic stomach, the stomach has a rich blood supply to support the anastomosis, and the join itself is not put under tension[296]. Others argue that a P-G may be less technically challenging, especially in patients with a soft pancreas[297].

Multiple MAs have compared P-J and P-G outcomes. Some of these have come to conflicting conclusions, possibly due to the high degree of heterogeneity between the included studies. Menahem et al. (seven RCTs, n=1121) found a P-G reduced the risk of POPF (11% vs 19%, p=0.0003), but only four studies used the standardised ISGPS definition[298]. Zhou et al. (six RCTs, n=1005) reached the same conclusion (OR: 0.6, p=0.001)[299]. In contrast, Wang et al. (sixteen RCTs, n=2396), Daamen et al. (six RCTs, n=1086), and Jin et al. (eleven RCTs, n=1765) showed a P-G was not superior to a P-J in terms of POPF risk[300-302]. Ratnayake et al. (fifteen RCTs, n=2428), who compared and ranked five anastomosis techniques, found a P-G duct-to-mucosa approach was associated with the lowest rate of clinically-relevant POPF[296].



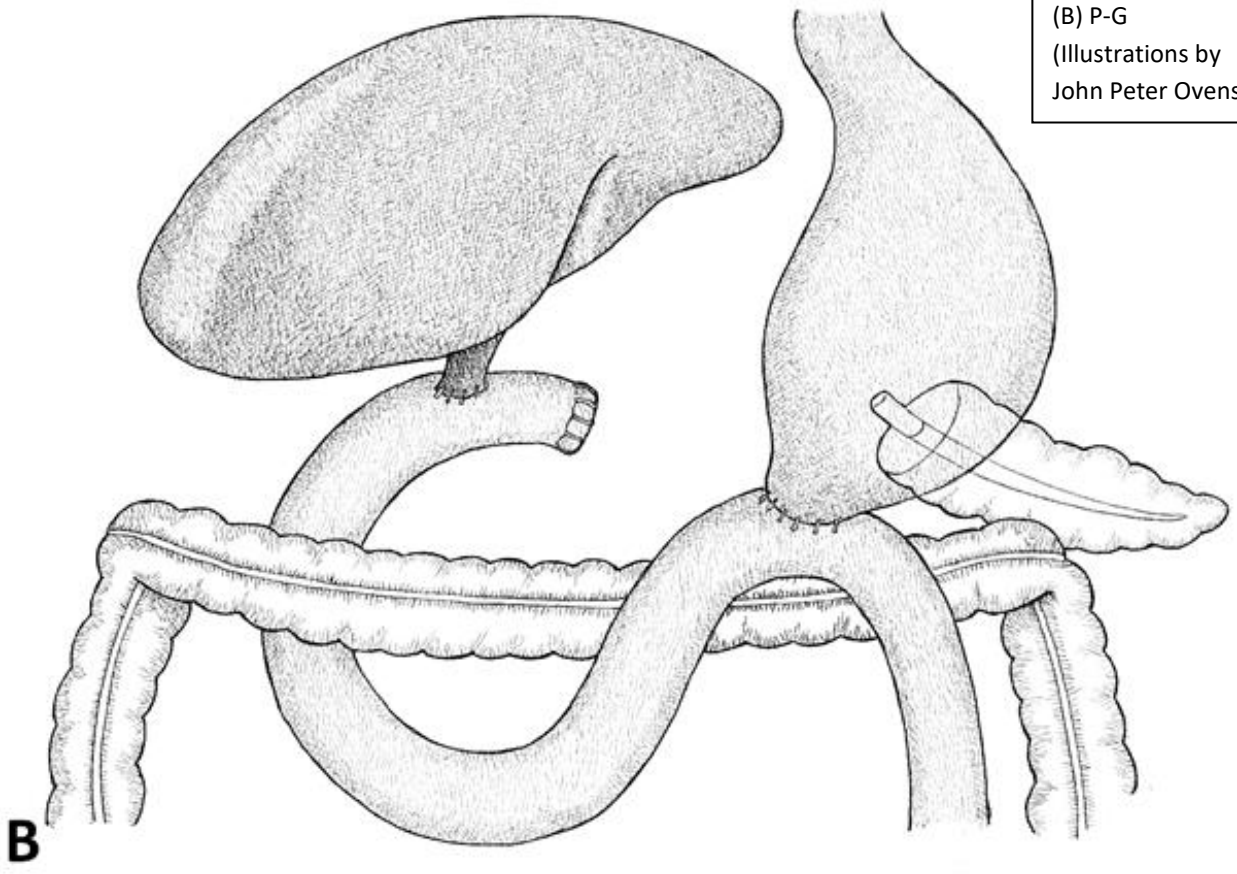


Figure 3.3: (A) P-J, (B) P-G (Illustrations by John Peter Ovens).

Concerning other perioperative outcomes, Ratnayake et al. found that a P-G duct-to-mucosa approach was associated with the lowest rates of intraoperative blood transfusion, DGE, and intra-abdominal collection[296]. This technique also correlated with the shortest operation times and length of stay, and the lowest overall morbidity and mortality rates[296]. Furthermore, Zhou et al. found intra-abdominal collections (OR: 0.4, p<0.001) and biliary fistulae (OR: 0.3, p=0.01) were less common in P-G patients[299]. However, Jin et al. found that P-G patients more commonly experienced postoperative haemorrhage (OR: 1.5, p=0.03)[302].

More recently, the Blumgart-style P-J has gained popularity. This technique utilises full-thickness transpancreatic sutures to invaginate the jejunum and encapsulate the pancreatic parenchyma. This is thought to reduce the tension on the anastomosis and reduce the risk of a capsule tear. Double sutures are placed at the six and twelve o'clock positions and single sutures are placed at the three and nine o'clock positions. A recent MA by Li et al. (eleven studies) compared the Blumgart-style P-J (n=1155) to the non-Blumgart P-J (n=1257) and found the former was associated with a reduced risk of grade B/C POPF (OR: 0.4, p=0.004)[303].

In conclusion, both P-J and P-G are safe and accepted techniques. A P-G is arguably less technically challenging and is associated with a reduced risk of POPF and increased risk of PPH. The impact of anastomosis type on long-term survival is unknown.

Concomitant vascular resection

PDAC can infiltrate into the PV and/or the SMV. Whilst this is no longer an absolute contraindication to PD, the benefits of venous resection (VR) remain controversial. In a recent MA, Wang et al. (41 studies, n=7567, arterial resection cases excluded) found that VR was associated with increased operation times (491 vs 399 minutes, p<0.0001), blood loss (929 vs 581 ml, p=0.0001), PPH (p<0.0001), DGE (p=0.03), and reoperation (12% vs 11%, p=0.008)[304]. Interestingly, VR was associated with a lower risk of POPF

(8% vs 11%, p=0.001) and similar overall morbidity rates[304]. 30-day mortality was marginally higher (3.8% vs 3.2%, p=0.03) in the VR group but 90-day mortality rates were similar[304]. Tumour size was significantly larger in the VR patients (35.7 vs 30.8 mm, p<0.0001), and reduced rate of R0 resection was observed in this group (61% vs 69%, p<0.0001)[304]. One- (RR: 0.9, p=0.0009) and five-year (RR: 0.6, p=0.004) survival were significantly shorter in the VR group[304]. The VR patients likely had more advanced disease, although this was not studied. The authors concluded that VR is safe and feasible, and, given the benefit of an R0 resection on OS, it may be necessary to achieve a radical resection.

In another recent MA, Peng et al. (30 studies, n=12,031) also found VR was associated with longer operation times (MD: 69 minutes, p<0.0001), increased intraoperative blood loss (MD: 202 ml, p<0.0001), larger tumour size (MD: 2.4 mm, p<0.0001), and a lower rate of R0 resection (OR: 0.6, p<0.0001)[305]. Overall morbidity rates, including POPF, were similar, but VR was associated with higher rates of bile leak (OR: 4.5, p=0.0003), reoperation (OR: 1.6, p=0.0001), DGE (OR: 1.4, p=0.02), and postoperative haemorrhage (OR: 2.2, p<0.0001)[305]. VR did not affect the length of stay but was associated with higher inpatient (OR: 1.7, p=0.01) and 30-day mortality (OR: 2.0, p<0.0001)[305]. The authors concluded that, because of the additional risks, VR is only indicated in selected cases. They also concluded that, although VR is associated with reduced OS, this likely reflects tumour, rather than intraoperative, factors[305]. Some authors have speculated that the length of resected vein is significant. Pan et al. (n=118) studied PD patients who underwent resection of a named vein (SMV or PV) and found VR did not affect OS[306]. However, patients with >3 cm of vein resected had worse OS (11 vs 18 months, p=0.02)[306].

Arterial resection (AR) is associated with significant additional risk. As such, most centres are reluctant to perform PD where there is arterial involvement since outcomes are poor. However, as NAT is now the standard of care in patients with borderline resectable disease, this may increase the number of potential surgical candidates in this

subgroup. In a recent MA, Rebelo et al. (31 studies, n=7111, VR cases excluded), showed AR (coeliac artery +/- superior mesenteric artery +/- common hepatic artery) was associated with higher rates of POPF (27% vs 14%, p<0.001), DGE (19% vs 13%, p<0.001), reoperation (11% vs 5%, p<0.001), and perioperative mortality (5% vs 1%, p<0.001)[307]. AR was also associated with a lower R0 resection rate (73% vs 80%, p<0.001) and reduced OS (22 vs 46 months, p=0.008) [307]. Again, the authors concluded that the impact on survival likely reflected tumour factors, and that the need for AR should not be an absolute contraindication to PD[307].

In summary, PD with concomitant vascular resection is associated with additional risk but this should not be an absolute contraindication to resection. The number of potential surgical candidates with vascular involvement will likely rise as the number of patients that receive NAT increases.

Pancreas texture

Intraoperatively, the surgeon will often characterise the texture of the pancreas as either “soft” or “hard”. This is subjective, but it can be a useful predictor of postoperative outcomes. Marchegiani et al. suggested that assessing pancreatic stiffness using a durometer may be more consistent than using an individual surgeon’s subjective assessment[308]. Martin et al. (n=9366) found that patients with a soft pancreas texture had significantly higher rates of POPF (37% vs 10%, p<0.001)[309]. These findings are supported by other recent studies[310-312]. This is likely due to the fragility of the parenchyma and the secretion of high volumes of pancreatic juice[313].

Although the association between a soft pancreas and POPF is well known, this can be difficult to assess preoperatively using non-invasive methods. Harada et al. (n=16) found liver fibrosis index correlated with pancreatic fibrosis (p=0.02) and POPF (p<0.05), and suggested real time tissue elastography evaluation of pancreatic stiffness may be a

useful predictor of POPF[314]. Shi et al. suggested that preoperative magnetic resonance imaging (MRI) findings may also be useful for this purpose[315].

Pancreatitis

Fibrosis associated with chronic pancreatitis results in a stiff parenchyma. As discussed above, a hard pancreas texture is associated with a reduced incidence of POPF[316]. Furthermore, chronic pancreatitis may be associated with duct dilatation which further aids the surgeon (see below). Schmidt et al. (n=510, all pathologies) found that those with a histological diagnosis of pancreatitis were significantly less likely to develop POPF than those with a malignancy (9% vs. 28%, p=0.02)[317].

Pancreatic duct dilatation

A dilated main pancreatic duct has long been associated with a reduced incidence of POPF. Martin et al. categorised patients by duct diameter (<3 mm, 3-6 mm, or >6 mm) and found those in the <3 mm group were highest risk, and those in the >6 mm group were lowest risk (36% vs 10%, p<0.0001)[309]. Di Martino et al. (n=107) found that patients who developed POPF had significantly smaller median duct diameters (2.8 vs 4.0 mm, p=0.01) [318].

As with pancreas texture, prior authors have attempted to identify predictors of POPF using preoperative imaging of the main pancreatic duct. Barbier et al. (n=186) found that the median duct size on preoperative computed tomography (CT) was significantly smaller in patients who developed a fistula (3 vs 5 mm, p<0.01)[319]. The ratio of pancreas body thickness to main pancreatic duct size was also higher in POPF patients (6 vs 3, p=0.04), and a value >3.8 was associated with increased rates of postoperative haemorrhage (OR: 4.3, p=0.01) and reintervention (OR: 3.4, p=0.02)[319].

Perioperative blood transfusion

Several studies have investigated for correlation between intraoperative blood transfusions and adverse perioperative outcomes. Dosch et al. (n=6869) found that patients who received an intra- or perioperative blood transfusion (within 72 hours of PD) were significantly more likely to experience infective complications (3% vs 27%, $p<0.001$)[320]. This included SSI, UTI, pneumonia, and sepsis. Zhang et al. (n=212) reached a similar conclusion (OR: 3.2, $p<0.01$)[321]. After the exclusion of patients with POPF, blood transfusion remained an independent risk factor for serious infection (OR: 5.8, $p<0.01$). The authors suggested that perioperative blood transfusion rate should be used as a quality indicator for the performance of PD[321]. Hallet et al. (n=17,523) reached similar conclusions. In this study, perioperative blood transfusion was associated with increased major morbidity (25% vs 11%, $p<0.0001$), length of stay (RR: 1.3, $p<0.0001$), and mortality (6% vs 1%, $p<0.0001$)[322].

The association between perioperative blood transfusion and infective complications is well documented. This phenomenon is known as transfusion-related immunomodulation; it was first described in the late 1980s when renal transplant patients were found to be less likely to reject recipient organs if they had received a perioperative transfusion. Whilst the exact underlying mechanism is unknown, it is thought the suppression of natural killer cells, T-cells, and neutrophils plays an important role[320]. Since PD is a high-risk operation and infective complications are common, further studies are required to investigate the factors which affect perioperative blood transfusion rates to minimise the number of transfusions given.

It has previously been hypothesised that immunosuppression induced by a perioperative blood transfusion may reduce the host response to tumour cells and affect OS. This is difficult to investigate due to confounding factors and remains controversial. Concerning long-term outcomes, Clark et al. (n=170, all pathologies) found perioperative blood transfusion was not a predictor of OS[323]. In contrast, Abe et al. (n=148, PDAC only) found patients who received a perioperative blood transfusion had reduced survival rates

at three (5% vs 46%) and five (0% vs 28%) years (p<0.001)[324]. However, the patients who did not receive a transfusion were younger (p=0.03), had higher preoperative haemoglobin levels (p<0.001), less advanced disease (p=0.001), shorter operation times (p<0.001), were less likely to a undergo concomitant vascular resection (p<0.001), and were more likely to achieve an R0 resection (p=0.03)[324]. Additional authors have reached similar conclusions[325, 326].

Perioperative blood transfusion rate is often considered non-modifiable, but it is arguably modifiable. For example, individual anaesthetists may have differing opinions on transfusion thresholds, and individual units may have differing transfusion protocols. It has been hypothesised that one of the reasons larger centres have superior PD outcomes is that these units have lower thresholds for transfusion and increased use of reserved blood units (relative to the number given). This was investigated by Lammi et al. (n=1337, total pancreatectomies also included) and no differences were observed between high-, medium-, and low-volume centres in terms of blood usage, transfusion trigger point, or use of reserved units. However, during the study period (2002-2011), the trigger points decreased (p=0.003) and the usage of reserved units increased (p<0.001) at high-volume centres relative to the other units[327].

Due to the potential impact of perioperative blood transfusion, several authors have investigated the effect of estimated intraoperative blood loss (EBL) on PD outcomes. EBL is known to be subjective and imprecise, so its use in studies is often criticised. Ghee et al. recently found that surgeons tend to underestimate EBL (p=0.009) whereas anaesthetists tend to overestimate (p=0.004)[328]. Seykora et al. (n=5323) categorised EBL into 0-300, 301-750, 751-1300 and >1300 ml, and found that the median EBL was 400 ml[329]. Intra- and postoperative transfusion rates were 16% and 25%, respectively. Progressive EBL corelated with intra- but not postoperative transfusion in a dose-dependent manner (p<0.0001) and was associated with poor perioperative outcomes[329]. Hence, the authors concluded that efforts should be made to minimise intraoperative blood loss and that there are gains to be made by targeting modifiable factors[329].

Furthermore, Casciani et al. (n=7706) matched 966 PD patients with EBL ≤700 ml to 966 with EBL >700 ml. The former had lower rates of clinically relevant POPF (19% vs 13%), major morbidity (28% vs 16%), transfusion (50% vs 14%), reoperation (9% vs 4%) and 90-day mortality (5% vs 2%, all $p<0.001$)[330]. The authors suggested that blood loss should be minimised by careful transection of the pancreatic neck using transfusion sutures to control the pancreatic arcades, using electrocautery to dissect the parenchyma, and to combat any pulsatile bleeding with sutures[330]. In addition, they advised an "artery first" approach when dissecting the pancreatic head from the mesenteric axis to allow early detection of gross vascular infiltration. They concluded that operative techniques associated with reduced EBL might be preferrable as this may reduce the need for transfusion e.g., a P-G rather than a P-J anastomosis, and the use of externalised transanastomotic stents, transperitoneal drainage, and prophylactic octreotide[330].

In conclusion, PD patients receiving perioperative blood transfusion appear to be high-risk for infective complications. Whether transfusion affects long-term outcomes remains controversial. Whilst it is difficult to account for confounding variables, a perioperative blood transfusion may be associated with reduced OS. Where suitable, preoperative anaemia should be corrected, and efforts should be made to minimise intraoperative blood loss.

Discussion

Myriad intraoperative factors are known to affect PD outcomes (**Table 3.2**). Whilst some are non-modifiable, an appreciation for these allows an informed assessment of potential surgical candidates and guides risk-benefit discussions. Patients with ASA grade III are high-risk and have poor short- and long-term outcomes. Patients should be optimised prior to surgery where possible and the appropriate members of the multidisciplinary team should be involved early so that the best possible outcome is achieved. Whilst

advanced age should never be an absolute contraindication to PD, one should be cautious when offering resection to a patient over 75 years-old with an ASA grade of III, as this sub-group have additional associated risks. These patients should be made aware of the additional risks they face. Further important non-modifiable factors include a soft pancreas texture, the absence of pancreatitis and a small main pancreatic duct. Each of these is associated with an increased risk of POPF. Surgeons may wish to adapt their practice in patients with these characteristics in an attempt to optimise their outcomes.

Many modifiable intraoperative risk factors relate to surgical technique and approach. A pylorus-preserving technique may reduce operation times and intraoperative blood loss, achieving comparable oncological outcomes. However, this likely results in higher rates of DGE. Minimally invasive techniques have become more popular in recent years, but an open approach remains the standard of care. Some studies have demonstrated superior outcomes following LPD and/or RPD but these will have been affected by selection bias and these procedures are only available in certain specialised units.

P-G and P-J are both acceptable and numerous studies have compared the two techniques. It may be that a P-G is associated with reduced blood transfusion rates and shorter operation times, at the expense of an increased risk of postoperative haemorrhage. As with any surgical technique, it is important to weigh this up against the expertise of the surgeon performing the procedure and the team within which they work.

Concomitant vascular resection remains controversial. This is associated with increased perioperative morbidity and evidence supporting improved long-term outcomes is lacking. Whilst those who undergo concomitant vascular resection have reduced OS, this likely reflects tumour, rather than operative, factors. The number of patients with vascular involvement who are appropriate surgical candidates is set to rise as the number of patients who receive NAT for borderline resectable disease is increasing.

Perioperative blood transfusion rate is arguably a modifiable factor. Those who receive a transfusion are more likely to experience an infective complication and may have worse long-term outcomes. Whilst these findings are likely influenced by confounding variables, some authors suggest perioperative transfusion rate should be a performance indicator for PD and argue surgeons should alter their approach where appropriate to minimise blood loss. Much of the evidence on the factors discussed is limited to small studies or those influenced by selection bias or confounding variables. The limitations of this review have been outlined in **Chapter 9**.

Conclusion

A number of intraoperative variables affect the short- and long-term outcomes of PD. Given the limitations of the current literature, a robust study is required. A greater understanding of these variables will improve patient selection, guide risk-benefit discussions and allow surgeons to adjust their own practice to optimise patient outcomes.

Intra-/perioperative factor	Risk of POPF	Risk of infection	Risk of DGE	Risk of postoperative haemorrhage	Operation time	Intra-op blood loss	Length of stay	Peri-op morbidity	Peri-op mortality	Overall survival
ASA grade III (vs ASA grade I-II)								↑	↑	↓
PPPD (vs classic Whipple)			↑		↓	↓				
Laparoscopic approach (vs open)					↑	↓	↓	↑		
Robotic approach (vs open)					↑	↓				↑
P-G anastomosis (vs P-J)	↓		↑	↑	↓		↓			
Concomitant venous resection	↓		↑	↑	↑	↑		↑	↑	
>3 cm of vein resected										↓
Concomitant arterial resection	↑		↑					↑	↑	↓
Soft pancreas texture	↑									
Evidence of pancreatitis	↓									
Main pancreatic duct >6 mm in diameter	↓									
Perioperative blood transfusion		↑					↑	↑	↑	↓

Table 3.2: Selected intra-/perioperative factors which affect PD outcomes. Increased or decreased risk/overall survival compared to patients without the factor. References within the main text.

Chapter 4: Methodology

Study set-up

This thesis centred on the findings of the Recurrence After Whipple's (RAW) study. Prior to the RAW study being carried out, a single centre preliminary study was carried out at University Hospitals Plymouth NHS Trust. This study included all patients who underwent PD for histologically-confirmed PDAC, AA or distal CC between September 1st, 2006 and May 31st, 2015. This smaller pilot study (the results of which are outlined in **Chapter 5**) used the same methods as the RAW study (see below). Following our single centre study, we set up a larger and more robust multicentre study in order to achieve our objectives. The RAW study was an international multicentre retrospective cohort study which was set up primarily to investigate the factors which affect disease recurrence in patients who undergo PD for malignancy (see **Supplementary Material** for full study details). The study was advertised on Twitter and by word-of-mouth at various meetings. All centres that expressed an interest were invited to join the study. Initially, 21 British centres and seven international centres declared an interest. Therefore, we estimated that a minimum of 2000 patients would be included. The follow-up duration was five years from the date of PD or the date of death, whichever was sooner.

Inclusion criteria:

- PD performed between June 1st, 2012 and May 31st, 2015 (inclusive)
- Postoperative histology confirmed PDAC, AA or CC
- Patient died within five-years of PD (and date of death known) or five-year follow-up data available

Exclusion criteria:

- Postoperative histology confirmed benign pathology, non-invasive neoplasia or a malignant tumour other than PDAC, AA or CC

- The primary procedure was distal pancreatectomy or total pancreatectomy (i.e., not PD)

The primary objective of the RAW study was to evaluate preoperative, perioperative and histological predictors of disease recurrence after PD for malignancy. The secondary objectives were to determine how morbidity, mortality, DFS, OS and specific patterns of recurrence were affected by the following: preoperative comorbidities, radiological staging, NAT, preoperative blood tests, type of pancreatic anastomosis, postoperative complications, the use of surgical drains, histological features (including resection margin status) and AC.

Methods

The study did not involve any patient contact and only used data which was already collected as part of routine hospital care. Therefore, participant and public involvement was not sought. The RAW study was approved by North West – Greater Manchester South Research Ethics Committee (20/NW/0397) and University Hospitals Plymouth NHS Trust. In addition, it was approved by the research and development departments of all the included centres and adhered to the standards laid down in the Declaration of Helsinki (2013).

The initially proposed study inclusion period was June 1st, 2010 to May 31st, 2015. This was decided as we expected most centres to perform 30-50 PDs per annum. Therefore, we estimated that we would have a final cohort of approximately 3000 cases. Using local figures, we estimated that 53%, 28% and 20% of the cohort would have PDAC, AA and CC, respectively. After consulting the findings of other studies, we estimated that 75% of the overall cohort would experience recurrence (highest among the PDAC group). Based on existing data, PDAC patients who experienced recurrence were estimated to comprise 40% of the entire cohort. In a one-sided test, assuming a minimal sample size of 2000 patients and testing a null risk risk of 75%, we expected to

detect an elevated risk of 82% among the PDAC cohort with 82% power (using Pearson's χ^2 test at the 5% significance level, and assuming a normal approximation to reasonable for a large sample from a binomial process). It was hoped that a high number of cases would allow the detection of small but significant differences in the studied variables.

To avoid overburdening the collaborating centres and to keep the study manageable, the start date was changed to June 1st, 2012 (reducing the study window from five years to three years). A further reason for this change was the introduction of the seventh edition of the UICC staging system. Having patients staged using two different systems would have made making comparisons impractical. The end date of June 2015 was chosen so that five-year follow-up data was available for all the included patients.

Data were collected by each participating centre using physical and electronic records. If not available locally, follow-up data were collected from referring hospitals to reduce attrition bias. A purpose-built electronic database was created using REDCap (v11.0.3, Nashville, TN) to collect and store the data. This was uploaded locally by the participating units. REDCap access was provided by University Hospitals Plymouth NHS Trust and data were stored on the Microsoft Azure web-based cloud service. Data on the following were collected: patient identification number (anonymised), demographics, comorbidities, preoperative imaging, NAT, preoperative blood tests, the PD procedure, postoperative complications (all defined using internationally agreed criteria and classified using the Clavien-Dindo (CD) classification system), histology details, adjuvant therapy, recurrence, palliative treatments, and survival. Prior to being included, patients were screened to ensure they met the inclusion criteria and did not fall into the exclusion categories. The clinical team at each participating unit was responsible for maintaining a password-protected database that linked the local patient hospital number to the anonymised participant identification number on REDCap.

Statistical methods

Once the data collection was complete, the dataset was reviewed and a "cleaning" process was undertaken. Records with spurious results or missing data were highlighted and sent back to the collaborating centres for review. Any errors were then corrected. Once a finalised dataset was obtained, the analysis was performed after consultation with a statistician. Categorical data were presented as frequency counts and associated percentages, and continuous data were presented as means, with standard deviation (SD), or medians, with interquartile range (IQR). When comparing groups, means were compared using Student's *t*-test and distributions were compared using the Mann Whitney *U* test. When testing for independence between two variables with multiple, mutually exclusive levels or categories, Fisher's exact test was used. Cases were excluded from the relevant sub-analyses if data were missing (the number of cases each sub-analysis included was always made clear). Where relevant, multivariable analyses were also performed (see results chapters for specific details). Kaplan-Meier curves were plotted to compare times to recurrence and times to death (in patients that experienced these outcomes), and the log-rank method was used to test for significant differences. For all analyses, a p-value <0.05 was considered significant. The analyses were performed using Microsoft Excel (v2103, Redmond, WA), GraphPad Prism (v9.3.1, San Diego, CA) and IBM SPSS Statistics (v25, Chicago, IL).

The RAW study generated a vast amount of data, far too much to be included in a single thesis. As such, the results section of this thesis focussed on nutritional assessment and management, perioperative outcomes, postoperative complications, and oncological outcomes in patients with AA. **Chapter 5** focussed on the preliminary single centre study. This included patients who were included in the RAW study and also those operated on between 2006 and 2012 (prior to the RAW study research period). **Chapter 5.1** outlined the surgical and oncological outcomes of the cohort and described the experience of a typical UK HPB centre. **Chapter 5.2** focussed on the perioperative outcomes of those with PDAC and investigated the impact of perioperative complications

on AC and OS (this smaller preliminary study was used as a template to plan the study described in **Chapter 7.2**). **Chapter 6** focussed on the entire RAW cohort and described the variations in the type of nutritional support provided after PD. **Chapter 7.1** focussed on the perioperative outcomes of the RAW study patients and considered how this data might be used to identify high-risk patients. **Chapter 7.2** described the impact of postoperative complications on adjuvant treatment and oncological outcomes. The final results chapter, **Chapter 8**, looked at the AA cohort in greater detail. This section examined recurrence patterns and explored the potential implications for future practice.

Definitions

Preoperative comorbidities

DM included type one and type two DM. Patients were deemed to have had a cardiovascular comorbidity if any of the following had been previously diagnosed: hypertension, atrial fibrillation (AF), cardiac arrythmia (other than AF), ischaemic heart disease, heart failure, PVD, or previous stroke/transient ischaemic attack. Patients were deemed to have had a respiratory comorbidity if any of the following had been previously diagnosed: asthma, COPD, pulmonary fibrosis or PE.

Postoperative complications

POPF (**Table S1**) was categorised as biochemical leak (formerly grade A POPF) or CR-POPF (grade B or grade C POPF) according to the ISGPS 2016 definitions[102]. BL (**Table S2**) was categorised as grades A, B and C per the ISGLS 2011 definitions[113]. PPH[123] (**Table S3**) and DGE[331] (**Table S4**) were defined as grades A, B and C per ISGPS 2007 definitions. Patients were considered to have had a chest infection if they were given antibiotics during their index admission for a clinically or radiologically diagnosed chest infection. Intra-abdominal collection was radiologically diagnosed (usually by CT). Ileus and SSI were clinically diagnosed. All complications were graded using the CD

classification of surgical complications (**Table S5**)[332]. An unplanned return to theatre included any unplanned operation within 30 days of the index procedure. An unplanned readmission included any presentation to hospital within 30 days of discharge which included at least one overnight stay.

Postoperative histology and recurrence

A positive resection margin included any resection margin where tumour cells were visible within 1.0 mm of the margin. A negative resection margin included all margins where no cancer cells were visible at the margin or within 1.0 mm of the margin. If not confirmed radiologically, cancer recurrence was assumed if a patient had a raised CA 19-9 and relevant signs/symptoms.

Chapter 5: Results - Peninsula HPB Centre

5.1. Pancreatoduodenectomy for malignancy: a complication profile and five-year outcomes

Russell TB, Labib PL, Aroori S. Five-year follow-up after pancreatoduodenectomy performed for malignancy: a single-centre study. *Ann Hepatobiliary Pancreat Surg* 2023. DOI: 10.14701/ahbps.22-039. Open access.

Introduction

This study aimed to describe the experience of a typical UK HPB centre by compiling a PD complication profile and investigating the impact (if any) of selected variables on short- and long-term outcomes of PD.

Method

See **Chapter 4** for a full description of the methods used. See **Supplementary Material** for a full list of the definitions used. When comparing patients by their histological diagnosis, distributions were compared using the Kruskal-Wallis test. Fisher's exact test was used to compare proportions of binary outcomes and independence of nominal data. This test was also used to investigate correlations between selected preoperative variables (age, BMI, comorbidities, ASA grade, serum albumin, serum bilirubin and NLR) and overall morbidity, major morbidity (CD grade I-II complications excluded), 90-day mortality, and five-year survival. Kaplan-Meier curves were plotted and compared (the data was not censored, i.e., full survival times until death or the end of follow-up, whichever was soonest, was used); the log-rank test was used to test for significant differences.

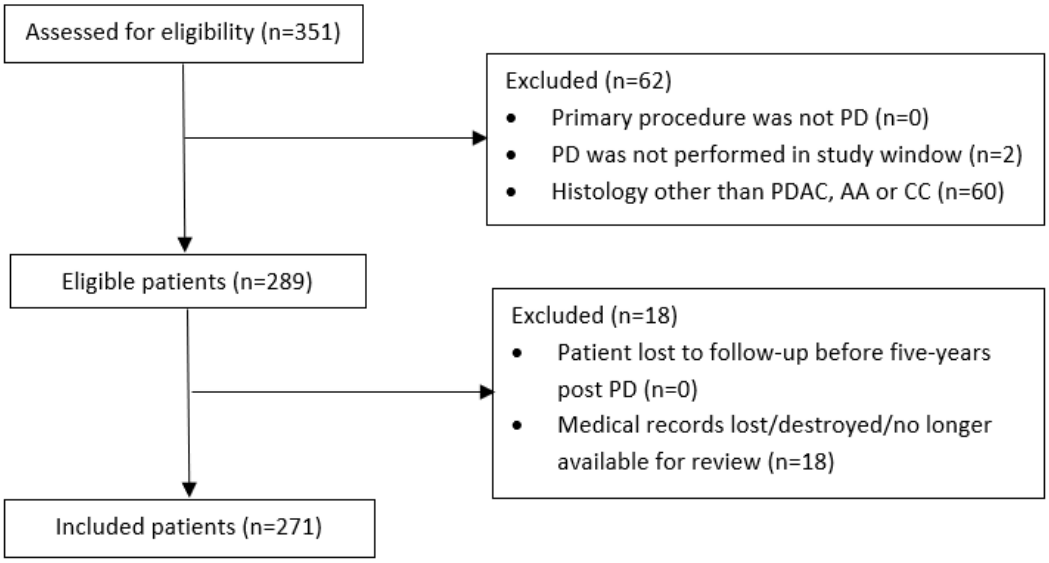


Figure 5.1: Cohort flow diagram.

Results

In total, 351 records were screened for eligibility. Eighty patients were excluded as they did not meet the inclusion criteria (**Figure 5.1**). The final analysis included 271 patients. Of these, 157 (58%) had a postoperative histological diagnosis of PDAC, 70 (26%) had an AA, and 44 (16%) had a distal CC (**Table 5.1**). The mean age was 66 years (SD: 9.2 years) and the mean BMI was 26.5 kg/m^2 (SD: 5.3 kg/m^2). Concerning comorbidities, 42 patients (16%) had a prior history of diabetes mellitus (DM), 104 (38%) had a cardiovascular comorbidity, and 46 (17%) had a respiratory comorbidity. DM was significantly more common in patients with PDAC (p=0.01). Respiratory comorbidities were more common in those with a CC (p<0.05). A total of 28 patients (10%) had a prior history of cancer (excluding the cancer being treated with PD). The decision was made to include these patients in the analyses as none died secondary to recurrence of their non-PD-related cancer. In addition, five-year survival rates were similar between those who had a prior cancer and those who did not (21% vs 23%, p=1.00). A total of 221 patients (82%) had received a preoperative biliary stent. Very few patients received NAC (1%) or radiotherapy (0.7%). A majority of patients (65%) were ASA grade I-II. Of all

patients, 72% received a P-G. A total of 35 patients (13%) underwent a concomitant venous resection and seven (3%) underwent a concomitant arterial resection. Venous resection was significantly more common in patients with PDAC (p<0.001).

	All (n=271)	PDAC (n=157)	AA (n=70)	CC (n=44)	p-value
Age in years (range)	66 (33-83)	67 (41-82)	66.5 (33-83)	65 (42-83)	0.871
Body mass index in kg/m^2 (range)	25.9 (16.4-53.4)	25.1 (16.4-53.3)	26.7 (19.2-41.6)	25.9 (16.6-36.9)	0.080
Comorbidities					
• Diabetes mellitus	42 (15.5%)	32 (20.4%)	7 (10.0%)	2 (4.5%)	**0.013***
• Cardiovascular	104 (38.4%)	64 (40.8%)	22 (31.4%)	18 (40.9%)	0.381
• Respiratory	46 (17.0%)	24 (15.3%)	9 (12.9%)	13 (29.5%)	**0.048***
Prior history of cancer	28 (10.3%)	20 (12.7%)	4 (5.7%)	4 (9.1%)	0.263
Pre-op treatment					
• Biliary stent	221 (81.5%)	124 (79.0%)	58 (82.9%)	39 (88.6%)	0.327
• Chemotherapy	3 (1.1%)	3 (1.9%)	0 (0.0%)	0 (0.0%)	-
• Radiotherapy	2 (0.74%)	2 (1.3%)	0 (0.0%)	0 (0.0%)	-
Pre-op blood tests (range)					
• Bilirubin in µmol/L	29 (3-916)	30 (3-916)	26 (4-288)	36.5 (6-277)	0.353
• Albumin in g/L	40 (12-51)	40 (21-51)	40.5 (21-48)	42 (22-49)	0.363
• Neutrophils (x10^9/L)	5.2 (1.6-29)	5.1 (1.6-29)	5.5 (2.6-20)	4.9 (2.2-14.2)	0.549
• Lymphocytes (x10^9/L)	1.8 (0.2-7.1)	1.8 (0.2-5.0)	1.7 (0.6-7.1)	1.9 (0.5-3.0)	0.780
• NLR	3.1 (0.5-28.4)	3.2 (0.9-28.4)	2.8 (0.5-22.8)	3.2 (1.4-28.4)	0.891
ASA grade I-II	177 (65.3%) Unknown: 9	102 (66.7%) Unknown: 4	50 (73.5%) Unknown: 2	24 (58.5%) Unknown: 3	0.266
Type of pancreatic anastomosis					
• Not performed	1 (0.4%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	-
• P-G	195 (72.0%)	121 (77.1%)	44 (62.9%)	30 (68.2%)	0.073
• P-J	75 (27.7%)	36 (22.9%)	25 (35.7%)	14 (31.2%)	0.110
Vascular resection performed					
• Venous	35 (12.9%)	32 (20.4%)	1 (1.4%)	2 (4.5%)	**0.001***
• Arterial	7 (2.6%)	6 (3.2%)	0 (0.0%)	1 (2.3%)	0.620
Intra-op blood transfusion received	32 (11.8%)	22 (14.0%)	8 (11.4%)	2 (4.5%)	0.323
Post-op destination					
• Critical care	197 (72.7%)	121 (77.1%)	50 (71.4%)	26 (59.1%)	0.059
• Surgical ward	74 (27.3%)	36 (22.9%)	20 (28.6%)	18 (40.9%)	0.059
Post-op nutritional support given	81 (29.9%)	42 (26.8%)	22 (31.4%)	17 (38.6%)	0.300
30-day return to theatre	15 (5.5%)	6 (3.8%)	6 (8.6%)	3 (6.8%)	0.324
Length of stay in days (range)	11 (3-102)	10 (3-69)	11 (3-102)	12 (5-50)	0.842
30-day readmission	18 (6.6%)	12 (7.6%)	4 (5.7%)	2 (4.5%)	0.732
90-day mortality	9 (3.3%)	6 (3.8%)	3 (4.3%)	0 (0.0%)	0.869
Tumour size in mm (range)	30 (5-130)	32 (12-130)	24 (5-80)	24.5 (10-50)	**0.001***
Resection margin (R) status					
• R0	101 (37.3%)	30 (19.1%)	53 (75.7%)	26 (59.1%)	**0.001***
• R1	166 (61.3%)	123 (78.3%)	17 (24.3%)	18 (40.9%)	**0.001***
• R2	4 (1.5%)	4 (2.5%)	0 (0.0%)	0 (0.0%)	-
Number of resected nodes	16 (1-38)	16 (1-34)	15 (2-33)	16 (4-38)	0.299
Number of involved nodes	2 (0-21)	4 (0-21)	1 (0-11)	2 (0-12)	**0.001***

Table 5.1: Key information on the patients who underwent PD for PDAC, AA or CC. Figures are medians unless otherwise specified. *Denotes statistical significance.

Complication and incidence	Number of cases by CD grade						
	I	II	IIIa	IIIb	IVa	IVb	V
Postoperative pancreatic fistula: 52 (19.2%) Biochemical leak: 30 (11.1%) Clinically-relevant: 22 (8.1%) • Grade B: 17 • Grade C: 5	25	14	6	3	0	4	0
Bile leak: 11 (4.1%) • Grade A: 6 • Grade B: 5 • Grade C: 0	7	2	1	1	0	0	0
Gastrojejunal anastomotic leak: 0 (0.0%) • Grade A: 0 • Grade B: 0 • Grade C: 0	0	0	0	0	0	0	0
Postpancreatectomy haemorrhage: 25 (9.2%) • Grade A: 3 • Grade B: 13 • Grade C: 9	2	7	4	6	4	1	1
Delayed gastric emptying: 54 (19.9%) • Grade A: 31 • Grade B: 13 • Grade C: 10	26	28	0	0	0	0	0
Acute kidney injury: 6 (2.2%)	1	3	0	0	1	1	0
Cardiac arrythmia: 16 (5.9%)	1	13	1	0	1	0	0
Chest infection: 45 (16.6%)	0	44	0	0	0	0	1
Cholangitis: 3 (1.1%)	0	2	0	0	1	0	0
Chyle leak: 12 (4.3%)	6	3	2	1	0	0	0
Clostridium difficile infection: 4 (1.5%)	0	4	0	0	0	0	0
Ileus: 26 (9.6%)	12	14	0	0	0	0	0
Intra-abdominal collection: 36 (13.3%)	1	14	12	7	0	2	0
Liver abscess: 2 (0.7%)	0	1	0	1	0	0	0
Myocardial infarction: 2 (0.7%)	0	2	0	0	0	0	0
Pancreatic necrosis: 0 (0.0%)	0	0	0	0	0	0	0
Pancreatitis: 3 (1.1%)	1	2	0	0	0	0	0
PV/SMV thrombosis: 2 (0.7%)	0	0	1	1	0	0	0
Sepsis of unknown origin: 5 (1.8%)	0	5	0	0	0	0	0
Splenic vein thrombosis: 1 (0.4%)	0	0	0	1	0	0	0
Surgical site infection: 59 (21.8%)	22	36	0	0	1	0	0
Urinary tract infection: 10 (3.7%)	0	10	0	0	0	0	0
Deep vein thrombosis: 3 (1.1%)	0	2	0	1	0	0	0
Pulmonary embolism: 2 (0.7%)	0	2	0	0	0	0	0
Other complication: 22 (8.1%)	5	6	1	2	1	3	4
Sum total of complications by CD grade	**109**	**214**	**28**	**24**	**9**	**11**	**6**

Table 5.2: Recorded complications.

The median length of stay was eleven days (range: 3-102 days). A total of eighteen patients (7%) were readmitted to hospital within 30 days of discharge. Nine patients (3%) died within 90 days of their index procedure. Two patients developed early disease

recurrence and died with disseminated disease (these patients may have had radiological occult metastases preoperatively). One died of intra-abdominal sepsis. One died with gastrointestinal haemorrhage. One died secondary to a splenic artery haemorrhage. One patient died secondary to hospital acquired pneumonia. One patient developed multiorgan failure secondary to faecal peritonitis caused by a stercoral perforation. In the remaining two cases, the cause of death was unclear. Both patients underwent a post-mortem examination. In one, the patient was found to have an infarcted liver but there were no other significant findings. In the other case, the cause of death was not identified.

The median tumour size was 30 mm (range: 5-130 mm). Patients with PDAC had significantly larger tumours ($p<0.001$). Concerning resection margins, 101 patients (37%) had no positive margins (R0), 166 (61%) had at least one positive margin (R1) and four patients (2%) had tumour left *in situ* (R2). An R0 resection was most common in those with AA ($p<0.001$). An R1 resection was most common in patients with PDAC ($p<0.001$). The median number of resected nodes was sixteen (range: 1-38). The median number of involved nodes was two (range: 0-21). The number of involved nodes was significantly higher in patients with PDAC ($p<0.001$).

One hundred and eighty-four patients (68%) experienced at least one postoperative complication and 47 (17%) experienced a CD grade ≥IIIa complication. A total of 401 postoperative complications were recorded (**Table 5.2**). Of these, 109 (27%) were CD grade I, 214 (53%) were grade II, 52 (13%) were grade III, 18 (4%) were grade IV, and six (2%) were grade V. CR-POPF affected 22 (8%) cases (17 grade B and five grade C). Bile leak affected eleven (4%) cases (six grade A and five grade B). No patients experienced a gastro-intestinal leak. PPH affected 25 (9%) patients (three grade A, thirteen grade B and ten grade C). Other commonly occurring complications included SSI (22%), chest infection (17%), intra-abdominal collection (13%) and ileus (10%). Other complications of note included cardiac arrythmia (6%) and chyle leak (4%).

	Morbidity	p-value	Major morbidity	p-value	90-day mortality	p-value	5-year survival	p-value
Age ≤66 years	69.1%	0.698	17.3%	1.00	2.2%	0.325	21.6%	0.772
Age >66 years	66.7%		17.4%		4.5%		24.2%	
BMI ≤25.9 kg/m^2	65.3%	0.579	20.3%	0.500	2.5%	0.500	21.2%	0.642
BMI >25.9 kg/m^2	69.5%		16.1%		5.1%		24.6%	
Pre-op comorbidity	70.7%	0.297	13.3%	0.055	2.7%	0.519	21.3%	0.662
No pre-op comorbidity	64.5%		22.3%		4.1%		24.0%	
ASA grade I-II	62.1%	**0.002***	13.0%	**0.009***	2.3%	0.155	24.3%	0.539
ASA grade III-IV	81.2%		27.1%		5.9%		18.8%	
Pre-op bilirubin ≤29 µmol/L	61.6%	**0.027***	11.6%	**0.016***	2.9%	0.746	26.8%	0.109
Pre-op bilirubin >29 µmol/L	74.4%		23.3%		3.8%		18.0%	
Pre-op albumin ≤40 g/l	68.4%	0.522	16.9%	0.874	2.9%	0.748	20.6%	0.470
Pre-op albumin >40 g/l	64.4%		17.8%		3.7%		24.4%	
NLR ≤3.1	61.8%	**0.037***	11.2%	**0.006***	2.2%	0.334	25.7%	0.245
NLR >3.1	74.1%		23.7%		4.4%		19.3%	

Table 5.3: Selected preoperative factors and their association with morbidity (any complication), major morbidity, 90-day mortality and five-year survival. "Comorbidity" refers to a preoperative diagnosis of DM, cardiovascular disease or respiratory disease. *Denotes statistical significance.

When patients aged ≥66 years (the median age) were compared to those aged <66 years, there was no significant difference in overall morbidity (69% vs. 67%, p=0.7), major morbidity (both 17%, p=1.0) or 90-day mortality (2% vs. 5%, p=0.3) (**Table 5.3**). The median was used as the cut-off so that two equal sized groups could be compared. The same pattern was observed concerning preoperative BMI and serum albumin. Patients with a preoperative bilirubin ≥29 µmol/L less often experienced morbidity (62% vs. 74%, p=0.03) and major morbidity (12% vs. 23%, p=0.02). However, 90-day mortality rates were similar (3% vs. 4%, p=0.7). Similarly, those with a preoperative NLR ≤3.1 had lower rates of morbidity (62% vs. 74%, p=0.04) and major morbidity (11% vs. 24%, p=0.01), but the difference in 90-day mortality was not significant (2% vs. 4%, p=0.3). Patients with a preoperative diagnosis of DM or cardiorespiratory disease had similar overall morbidity (71% vs. 65%, p=0.3), major morbidity (22% vs. 13%, p=0.06) and 90-day mortality (3% vs. 4%, p=0.5) to those without these conditions. In contrast, an ASA grade of III-IV correlated with higher overall morbidity (81% vs. 62%, p=0.002) and major morbidity (27% vs. 13%, p=0.009) rates, although the difference in 90-day mortality was

not significant (6% vs. 2%, p=0.2). The latter was likely not significant due to the small sample size.

A total of 151 patients (57%) received adjuvant chemotherapy (**Table 5.4**). The median number of cycles was six (range: 1-12). Of those who commenced adjuvant chemotherapy, 76% completed the planned course. Five-year cancer recurrence affected 68% of patients. Compared to patients with AA, recurrence was significantly more frequent among patients with PDAC (77% vs. 56%, p<0.001). Among those who developed recurrent disease, the median time to diagnosis was nine months (range: 0-58 months). This was shortest among patients with PDAC (p=0.02). Palliative chemotherapy was received by 31% of the patients that developed recurrent disease. Overall five-year survival was 23%. Five-year survival was lowest in PDAC patients (14% vs. 40%, p=0.001); this was not significantly affected by age, BMI, preoperative comorbidities, ASA grade or preoperative blood tests (**Table 5.4**). Estimated median time to recurrence (p<0.05) and estimated median overall survival (p=0.001) were significantly lower in PDAC patients (**Figure 5.2**).

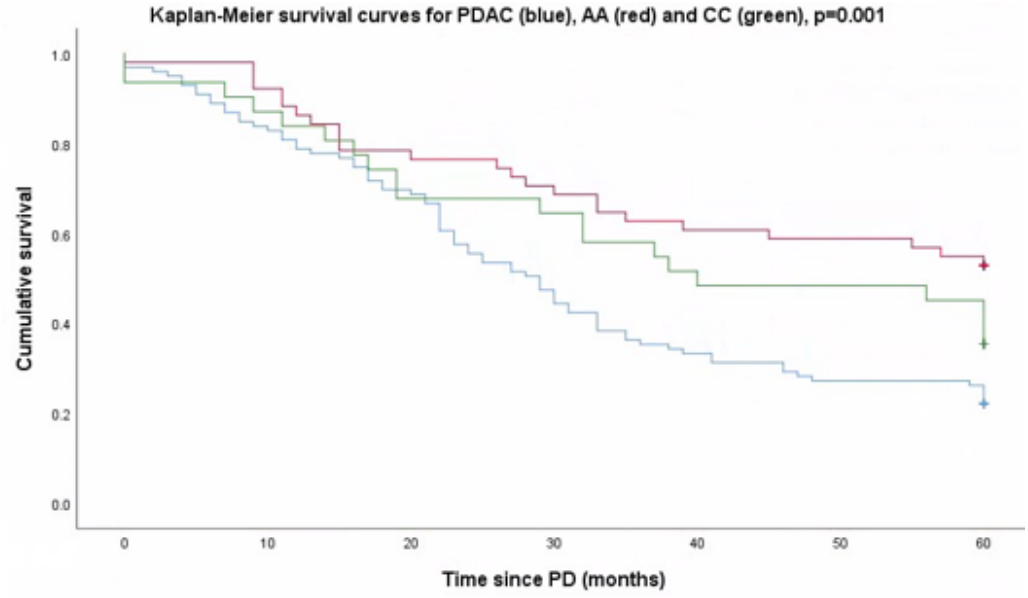
	All (n=271)	**PDAC (n=157)**	**AA (n=70)**	**CC (n=44)**	**p-value**
Adjuvant chemotherapy received	Yes: 151 (57.2%) Unknown: 7	Yes: 101 (65.6%) Unknown: 3	Yes: 24 (35.3%) Unknown: 2	Yes: 26 (61.9%) Unknown: 2	**0.001***
Completed planned course	Yes: 113 (75.8%) Unknown: 2	Yes: 73 (73.0%) Unknown: 1	Yes: 17 (73.9%) Unknown: 1	Yes: 23 (88.5%)	0.253
5-year cancer recurrence	185 (68.3%)	121 (77.1%)	39 (55.7%)	25 (56.8%)	**0.001***
Median time to recurrence in months (range)	9 (0-58)	7 (0-58)	16 (1-50)	11.5 (2-43)	**0.017***
Palliative chemotherapy received**	Yes: 58 (31.4%) Unknown: 7	Yes: 34 (28.0%) Unknown: 3	Yes: 15 (38.5%) Unknown: 2	Yes: 9 (36.0%) Unknown: 2	0.414
5-year survival	61 (22.5%)	22 (14.0%)	28 (40.0%)	11 (25.0%)	**0.001***

Table 5.4: Postoperative treatment, recurrence and survival statistics. *Denotes statistical significance. **Patients who did not develop recurrent disease excluded.

Discussion

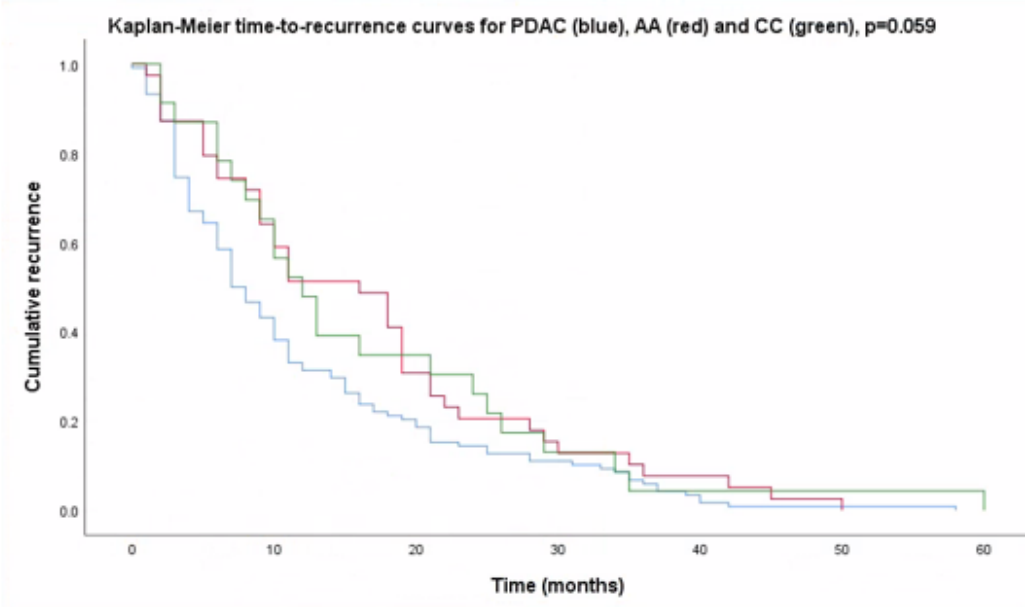
This section describes the short- and long-term outcomes of 271 patients who underwent PD for histologically-confirmed PDAC, AA or CC at a typical tertiary HPB unit in the UK between September 2006 and May 2015 (inclusive). Few prior articles have reported on both surgical and oncological outcomes. Our study could be compared to that of El Nakeeb et al. who studied PD cancer patients at an Egyptian centre between 1993 and 2017[333]. The median age was considerably higher in our study (66 vs. 54 years), which might reflect the more elderly population of the UK. However, the number of patients with preoperative DM was similar (16% vs. 15%). In our study, 82% of patients underwent PBD (vs. 51%). The median preoperative serum albumin was the same for both studies (40 g/L). However, the median bilirubin was higher in the Egyptian study (40 µmol/L vs. 29 µmol/L). Although similar numbers of patients received a P-G in the two studies, a considerably higher proportion of patients underwent a vascular resection in our study (13% vs. 1%). The median tumour size was the same in both studies. However, the median length of stay was considerably longer in our study (11 days vs. 8 days). This might be because healthcare is publicly funded in the UK. In our study, 8% of patients developed a clinically relevant (CR)-POPF (vs. 7%), 20% developed DGE (vs. 18%) and 7% developed a bile leak (vs. 4%). A similar number of patients in each study had an unplanned return to theatre, and five-year survival rates were also similar.

The incidence of CR-POPF was slightly lower in our study than the incidence reported in a recent SR (10-26%)[334]. This could be partly explained by the high proportion of patients who received a P-G. However, a recent randomised controlled trial did not suggest that a P-G was protective[297]. Our observed incidence rates for bile leak, PPH, cholangitis, chyle leak and DGE were similar to those described in the literature[334]. No patients in our study developed a gastro-jejunal anastomotic leak. A recent SR suggested that this complication affects 0.4-1% of PD patients[334].



A

Number at risk							
PDAC	99	83	69	47	33	27	15
AA	51	47	40	36	31	30	28
CC	31	27	21	20	16	15	14
Time (months)	0	10	20	30	40	50	60



B

Number at risk							
PDAC	118	51	24	13	4	1	
AA	39	25	12	6	3	1	
CC	23	15	8	3	1	1	1
Time (months)	0	10	20	30	40	50	60

Figure 5.2: Kaplan-Meier survival (A) and time-to-recurrence (B) curves by histology. (B) excludes those who did not experience five-year recurrence.

Prior studies have suggested that advanced age alone should not be an absolute contraindication to PD. Whilst some authors have suggested older patients are at increased risk of morbidity[164-166], others have shown that selected older patients have similar perioperative and survival outcomes to younger patients[163, 168]. Our dataset suggested older patients had similar overall morbidity, major morbidity and five-year survival to younger patients. Although the 90-day mortality rate was slightly higher in older patients, this difference was not significant. Whilst older patients should not be discriminated against if they are fit, they might be less inclined to opt for surgical management as there might be less of a perceived gain. Additionally, the favourable outcomes reported among older cohorts may reflect selection bias.

Obesity is associated with poor operative outcomes for a number of reasons. However, a high BMI should not be a contraindication to resection. Obese patients tend to have a reduced residual capacity and are high-risk for atelectasis and shunting[335]. These patients also have a high resting metabolic rate, work of breathing and minute oxygen demand[335]. In addition, being overweight is often associated with hypertension, increased cardiac workload and a prothrombotic state[336]. Finally, from a surgical point of view, access can be difficult, and a high amount of intra-abdominal adipose tissue can cause further challenges. However, in our series, being overweight did not appear to correlate with adverse outcomes. This finding was unexpected. It was not consistent with the results of other similar studies. Chen et al. suggested that a BMI >24 kg/m^2 resulted in an increased risk of perioperative morbidity[181]. Aoki et al. suggested a BMI >25 kg/m^2 correlated with grade C POPF and major morbidity[182]. El Nakeeb et al. found a BMI >25 kg/m^2 was associated with increased overall morbidity and perioperative mortality[184, 193, 194]. Del Chiaro et al. also found that a BMI >25 kg/m^2 was associated with increased intra-operative blood loss and an increased risk of POPF[185]. Greenblatt et al. concluded that a BMI >25 kg/m^2 was a predictor of overall morbidity, but not perioperative mortality[186]. Interestingly, some studies have shown that obese patients might have an advantage when it comes to long-term outcomes. Tsai et al. suggested that overweight

and obese patients have better five-year survival rates than those of a healthy weight[192]. However, other similar studies have not observed this.

In our study, patients with a preoperative comorbidity (DM, cardiovascular disease or respiratory disease) had similar short- and long-term outcomes to those without these conditions. The impact of DM on PD outcomes remains controversial. Deo et al. found that preoperative DM did not affect surgical outcomes, although five-year survival was lower among diabetics[337]. Since patients with DM are thought to have a soft pancreas with a high fat content (both risk factors for POPF), it has been suggested they have a higher risk of developing POPF. However, two recent meta-analyses have refuted this[208, 210]. Other studies have suggested that patients with DM are high-risk for developing DGE due to vagal neuropathy and hyperglycaemia-induced reduction of gastric emptying time[338], although this is also controversial. Additionally, since long-term hyperglycaemia is thought to impair immune function, some authors have suggested diabetics are at increased risk of infective complications[211]. A recent meta-analysis[208] has suggested this is not the case. The conclusions of this meta-analysis might reflect the greater degree of care often shown to patients who are perceived to be high risk (e.g., a surgeon may subconsciously pay more attention during a high-risk case or put pressure on the intensive care unit to keep hold of a patient rather than discharge them to the ward).

The impact of pre-existing cardiac disease on PD outcomes is more clear-cut. Ronnekleiv-Kelly et al. found that patients with a cardiac comorbidity were at increased risk of cardiac complications, major morbidity and mortality[213]. Other authors have reached similar conclusions[214, 215]. To the best of our knowledge, no studies have specifically investigated whether cardiac disease affects long-term survival in PD patients. Very few studies have investigated the impact of pre-existing respiratory comorbidities on PD outcomes. This is likely because few patients with a significant respiratory comorbidity would be offered a resection. Shia et al. found that patients with COPD had reduced 90-day survival after PD[216]. Aoki et al. found that patients with respiratory disease had higher rates of major morbidity and POPF[182].

In our study, ASA grade I-II patients were significantly less likely to experience morbidity or major morbidity. However, these patients had similar 90-day mortality and five-year survival rates to those with a high ASA grade. Similar findings have been reported in the literature. Eeson et al. found that ASA grade III patients had an increased risk of perioperative mortality. However, this was not significant once age was adjusted for[272]. Whilst Eeson et al. did not look at five-year survival, ASA grade III patients had shorter median OS than those with an ASA grade of I or II[272]. Other authors have also found that increasing ASA grade is correlated with additional morbidity risk[167, 273].

We found that patients with high preoperative serum bilirubin levels more often experienced morbidity or major morbidity. However, this did not affect 90-day mortality or five-year survival. Scheufele et al. found that bilirubin level did not affect overall morbidity or long-term survival[249]. Pamecha et al. reached similar conclusions, although severely jaundiced patients had increased intraoperative blood loss[250]. Wang et al. also found that bilirubin level did not affect long-term outcomes, although severely jaundiced patients had higher rates of infective complications[251]. A number of theories have been put forward to try and explain why this might be. Firstly, biliary stasis favours microbial proliferation in a normally sterile site. In addition, increased pressure within the biliary tree can lead to retrograde flow of bile and provide a route for organisms to enter the systemic circulation[55]. Further, the synthetic function of hepatocytes may be affected, resulting in impaired immune function[55].

Neutrophils are the most abundant type of lymphocyte. Neutrophilia has long been associated with poor outcomes for cancer patients. It is thought that neutrophilia along with sustained inflammation, may promote angiogenesis, tumorigenesis and metastasis, thus protecting cancer cells from immune-mediated destruction[339]. Lymphopenia occurs in patients with many cancer types. It is associated with an immunocompromised state. It is thought to correlate with poor outcomes due to an impaired response to tumour cells and an increased risk of infective complications[340]. Whilst the mechanisms behind this are poorly understood, a high NLR has been shown to correlate with poor short- and

long-term PD outcomes[263, 265], although the clinical implications of a high NLR are currently unknown. Our results showed that patients with a NLR >3.1 more often experienced morbidity and major morbidity. However, a NLR >3.1 did not affect 90-day mortality or five-year survival. Other authors have also observed this. Arikan et al. found that those with a high NLR had increased morbidity and POPF rates[265]. Other authors have reached similar conclusions[267-269]. Some prior studies have shown that a high NLR is associated with reduced overall survival[263]. We did not observe this. This may be because of the low number of patients that achieved five-year survival. The limitations of this study have been outlined in **Chapter 9**.

Conclusion

In our series, most PD patients developed at least one complication, however, few experienced major complications. Rates of CR-POPF, bile leak, gastro-jejunal leak, PPH and DGE were 8%, 4%, 0%, 9% and 20%, respectively. ASA grade III-IV patients and those with a high preoperative bilirubin and/or NLR more often experienced postoperative morbidity and/or major morbidity. Five-year recurrence and five-year survival rates were 68% and 23%, respectively. The preoperative variables analysed in this study did not affect five-year survival rates. Surgeons who perform PD should have a sound understanding of the figures quoted; this will guide patient selection and the consenting process.

5.2. Pancreatoduodenectomy for pancreatic cancer: do serious postoperative complications correlate with lower rates of adjuvant chemotherapy?

Russell TB, Labib PL, Bowles M, Aroori S. Serious complications of pancreatoduodenectomy correlate with lower rates of adjuvant chemotherapy: would high-risk patients benefit from neoadjuvant chemotherapy? *Eur J Surg Oncol* 2022. DOI: 10.1016/j.ejso.2022.08.032.

Introduction

In the UK, patients typically undergo PD prior to receiving AC, as AC has been shown to provide an additional survival benefit[341]. Unfortunately, up to 40% of patients develop disease recurrence and die within a year of PD[342]. Recent evidence suggests that, independent of histology, serious postoperative complications are associated with higher rates of disease recurrence[343]. This may partly be due to complications affecting the length of time to recover from surgery, resulting in delayed or omitted adjuvant treatment. It could be argued that a patient who is high-risk for developing a serious complication may benefit from NAT to ensure the delivery of systemic therapy. Although delaying resection, this can treat micrometastases and down-stage tumours, increasing the likelihood of a complete (R0) resection[344]. However, NAT is not currently recommended in patients with resectable disease. This study aimed to compare the outcomes of PD patients who received AC to those who did not, to investigate whether serious complications were more frequent in the latter. We also aimed to investigate whether selected complications correlated with a reduced number of patients receiving AC.

Method

See **Chapter 4** for a full description of the methods used. See **Supplementary Material** for a full list of the definitions used. Patients were included if they underwent PD for

histologically-confirmed PDAC at University Hospitals Plymouth NHS Trust between September 1st, 2006, and May 31st, 2015. Patients who died within 90-days of PD were excluded. Those who commenced AC were compared to those who did not; demographics, comorbidities and complication rates were compared. We decided to use the number of patients who commenced AC as opposed to the number who completed AC for two reasons. Firstly, due to the small sample size. If we excluded patients who did not complete AC this would reduce our sample size further. Secondly, because of the hypothesis being tested. We aimed to investigate whether a serious complication correlated with AC being delayed/omitted. After patients who died within 90-days were excluded, the Kaplan-Meier curves were plotted to compare survival between those who received AC and those who did not, and those who developed the studied complications and those who did not. The log-rank method was used to test for significant differences. When comparing the AC group to the no AC group, distributions were compared using the Mann-Whitney *U* test. Other comparisons were made using Fisher's exact test. The outcomes of patients who developed the studied complications were compared to those who did not using Fisher's exact test.

Results

During the study period, 175 patients underwent PD for histologically confirmed PDAC. Eighteen were excluded as their medical records were not available for review, leaving 157 eligible patients (90%) in the final cohort. All procedures were performed with an open, pylorus-resecting approach (classic PD). The pancreatic anastomosis fashioned was a P-G in most cases (77%) as our unit gradually switched from P-J to P-G as standard from 2009 onwards.

Patient demographics are outlined in **Table 5.5**. The mean age was 65.7 years (SD: 8.9) and 45% of patients were female. The mean BMI was 26.2 kg/m^2 (SD: 5.6), 64 patients (41%) had a preoperative cardiovascular comorbidity and 24 (15%) had a

preoperative respiratory comorbidity. Most patients (79%) underwent PBD and three (2%) received NAT. Most patients were either ASA grade II (57%) or III (29%). The median length of stay was ten days (range: 3-69). **Table 5.6** outlines the frequency and severity of the postoperative complications recorded. Nineteen patients (12%) developed a POPF, seven of which were clinically relevant (grade B or C). Four patients (3%) experienced a POPF which was CD grade ≥IIIa. Six patients (4%) developed a bile leak; one of these was CD grade ≥IIIa. Fifteen patients (10%) developed a PPH, with all but one being grade B or C. Ten of these (75%) were CD grade ≥IIIa. Thirty-two patients (20%) developed DGE; all were CD grade I-II. Twenty-eight patients (18%) developed a chest infection, thirteen (8%) developed an intra-abdominal collection and 29 (19%) developed a SSI.

Selected outcomes following discharge are outlined in **Table 5.7**. Twelve patients (8%) had an emergency readmission within 30-days. One of these had an intra-abdominal collection which was treated with antibiotics only, two had significant abdominal pain which required strong analgesia, two patients presented with bleeding which settled without intervention, two had a chyle leak which was managed nonoperatively, one had a SSI which was managed with antibiotics alone, two had severe vomiting which settled with antiemetics, and two had wound dehiscence. Six patients (4%) died within 90-days of PD. Two of these died with early cancer recurrence (these patients may have had radiologically occult disease at the time of PD), one died with respiratory failure secondary to chest sepsis, one died with renal failure and intra-abdominal sepsis secondary to a stercoral colonic perforation, one died of a PPH and in the final case the cause of death was unknown. This patient underwent a post-mortem examination and an infarcted liver was found but no other significant findings were observed.

Demographics	
Age (years)	Median: 67 (range: 41-82, IQR: 12)
Sex	Female: 71 (45.2%) Male: 86 (54.8%)
Body mass index (kg/m^2)	Median: 25.1 Range: 16.4-53.4 IQR: 5.5
Preoperative comorbidities	
Cardiovascular history	Yes: 64 (40.8%) • Hypertension: 48 (30.6%) • Atrial fibrillation/other arrythmia: 6 (3.8%) • Ischaemic heart disease: 11 (6.4%) • Previous cardiac surgery: 6 (3.8%) • Peripheral vascular disease: 3 (1.9%) • Stroke/transient ischaemic attack: 4 (2.6%) • Heart failure: 1 (0.6%) • Other: 3 (1.9%) No: 93 (59.2%)
Respiratory history	Yes: 24 (15.3%) • Asthma: 15 (9.6%) • COPD: 10 (6.4%) • Other: 4 (2.6%) No: 133 (84.7%)
Preoperative radiological stage*	
Tumour (T) stage	1: 16 (10.2%%) 2: 36 (22.9%) 3: 46 (29.3%) 4: 4 (2.6%) X: 55 (35%)
Node (N) stage	0: 105 (66.9%) 1: 52 (33.1%)
Treatment prior to pancreatoduodenectomy	
Preoperative biliary stent	Yes: 124 (79.0%) No: 33 (21.0%)
Neoadjuvant chemotherapy	Yes: 3 (1.9%) No: 154 (98.1%)
American Society of Anaesthesiologists (ASA) grade	
ASA grade	I: 13 (8.3%) II: 90 (57.3%) III: 46 (29.3%) IV: 4 (2.6%) Unknown/not recorded: 4 (2.6%)
Length of stay	
Length of stay (days)	Median: 10 (range: 4-69, IQR: 7.5)

Table 5.5: Patient demographics and selected preoperative details. *Patients imaged prior to January 1st, 2010, were staged using the 6th edition of the UICC TNM system and patients treated from 2010 onwards were staged using the 7th edition.

Postoperative complication	Clavien-Dindo grade						
	I	II	IIIa	IIIb	IVa	IVb	V
Postoperative pancreatic fistula: 19 (12.1%) Biochemical leak: 12 (7.6%) Clinically-relevant: 7 (4.5%) • Grade B: 5 (3.2%) • Grade C: 2 (1.3%)	8 (5.1%)	7 (4.5%)	1 (0.6%)	0 (0%)	1 (0.6%)	2 (1.3%)	0 (0%)
Bile leak: 6 (3.8%) • Grade A: 4 (2.5%) • Grade B: 2 (1.3%) • Grade C: 0 (0.0%)	5 (3.2%)	0 (0%)	0 (0%)	1 (0.6%)	0 (0%)	0 (0%)	0 (0%)
Gastro-jejunal anastomotic leak: 0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Post-pancreatectomy haemorrhage: 15 (9.6%) • Grade A: 1 (0.6%) • Grade B: 11 (7%) • Grade C: 3 (1.9%)	1 (0.6%)	4 (2.6%)	4 (2.6%)	4 (2.6%)	0 (0%)	1 (0.6%)	1 (0.6%)
Delayed gastric emptying: 32 (20.4%) • Grade A: 18 (11.5%) • Grade B: 7 (4.5%) • Grade C: 7 (4.5%)	15 (9.6%)	17 (10.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Chest infection: 28 (17.8%)	24 (15.3%)	0 (0%)	0 (0%)	0 (0%)	2 (1.3%)	1 (0.6%)	1 (0.6%)
Intra-abdominal collection: 13 (8.3%)	0 (0%)	7 (4.5%)	3 (1.9%)	2 (1.3%)	1 (0.6%)	0 (0%)	0 (0%)
Surgical site infection: 29 (18.5%)	10 (6.4%)	19 (12.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Other infective complications: 14 (9%) Urinary tract infection: 7 (4.5%) Sepsis of unknown origin: 3 (1.9%) *C. difficile* infection: 4 (2.6%)	0 (0%)	14 (8.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Table 5.6: Summary of the postoperative complications recorded.

Outcomes following discharge (n=157, all patients)	
Emergency readmission within 30 days	Yes: 12 (7.6%) No: 145 (92.4%)
90-day mortality	Yes: 6 (3.8%) No: 151 (96.2%)
Adjuvant chemotherapy (n=151, excluding patients who died within 90 days)	
Adjuvant chemotherapy commenced	Yes: 102 (68.5%) No: 47 (29.6%) Unknown: 2*
Patients who commenced adjuvant chemotherapy (n=102)	Median number of cycles: 6 Planned course completed? Yes: 71 (72.4%) No: 27 (27.6%) • Due to treatment toxicity: 15 (55.6%) • Due to disease progression: 11 (40.7%) • Other: 1 (3.7%) Unknown: 4*
Cancer recurrence and palliative chemotherapy (n=151, excluding patients who died within 90 days)	
Five-year cancer recurrence	Yes: 119 (78.8%) No: 32 (21.2%)
Palliative chemotherapy commenced (n=119, excluding patients who did not develop recurrence)	Yes: 34 (29.3%) No: 82 (70.7%) Unknown 3*
Patients who commenced palliative chemotherapy (n=34)	Median number of cycles: 3 Planned course completed? Yes: 11 (35.5%) No: 20 (64.5%) • Due to treatment toxicity: 5 (25%) • Due to disease progression: 12 (60%) • Other: 3 (15%) Unknown: 3*
Five-year overall survival (n=157, all patients)	
Alive five-years after date of resection	Yes: 22 (14%) No: 135 (86%)

Table 5.7: Selected outcomes, adjuvant and palliative chemotherapy. *Not included in percentages.

Of the 151 patients who did not die within 90 days, 102 (69%, two patients excluded due to missing data) commenced AC and 71 (72%) completed the planned course. The most common reasons for not completing AC were treatment toxicity (15, 56%) and disease progression (11, 41%). Excluding patients who died within 90 days, 119 patients (79%) developed cancer recurrence, 34 of which (29%) received palliative chemotherapy. Five-year overall survival was 14%. Using the Kaplan-Meier method (**Figure 5.3**), cumulative survival was significantly longer in patients who commenced AC (p=0.004). The studied complications (of any CD grade) did not significantly affect survival (whether AC was commenced or not). Five-year survival rates were unaffected by AC rates and postoperative complications.

The demographics and complication profile of patients who received AC are compared with those who did not in **Table 5.8a**. The two groups were similar in terms of age, gender, BMI, ASA grade and preoperative comorbidities. ASA grade I-II patients were no more likely to have received AC than ASA ≥III patients (68% vs 60%, p=0.4). Those in the AC group had less frequently experienced a postoperative chest infection (9% vs 34%, p=0.0003). No significant differences were observed between the two groups in terms of CR-POPF, bile leak, PPH, DGE, intra-abdominal collection and SSI. When the studied complications were combined and CD grade I complications were excluded, grade ≥II (29% vs 57%, p=0.002) and ≥III (7% vs 21%, p=0.02) postoperative complications were significantly less frequent in the AC group. **Table 5.8b** compares patients who developed the studied complications to those who did not. Only postoperative chest infection correlated with a lower rate of commencing AC (36% vs 75%, p=0.0003). Patients who experienced one of the studied complications which was CD grade ≥II (49% vs 93%, p=0.01) or ≥III (29% vs 70%, p=0.002) less frequently commenced AC.

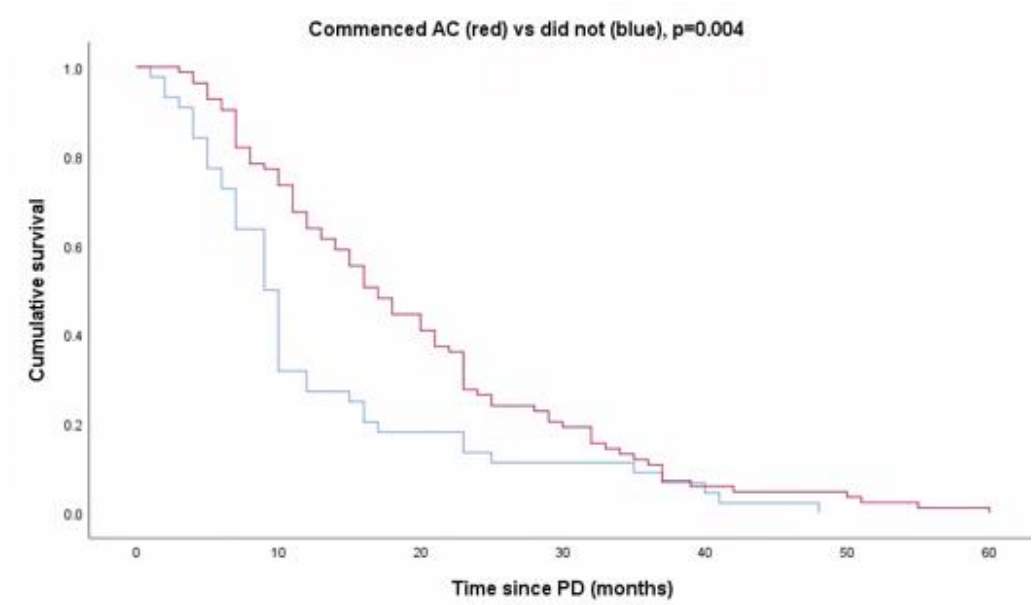
Variable	Commenced AC (n=102)	Did not commence AC (n=47)	p-value
Median age (years)	65.5 (range: 43-82, IQR: 10.8)	69 (range: 41-82, IQR: 12)	0.587
Female gender	48 (47.1%)	19 (43.2%)	0.483
Median BMI (kg/m^2)	25.4 (range: 16.4-53.4, IQR: 6.4)	24.9 (range: 18.0-35.0, IQR: 5)	0.144
Cardiac history	39 (38.2%)	24 (51%)	0.157
Respiratory history	14 (13.7%)	9 (19.1%)	0.466
ASA grade I-II	69 (69.7%)	30 (65.2%)	0.702
CR-POPF	2 (2%)	2 (4.3%)	0.591
Bile leak	3 (2.9%)	2 (4.3%)	0.651
PPH	6 (5.6%)	7 (14.9%)	0.114
DGE	18 (17.6%)	12 (25.5%)	0.278
Chest infection	9 (8.8%)	16 (34%)	**0.0003***
Intra-abdominal collection	7 (6.9%)	4 (8.5%)	0.742
SSI	16 (15.7%)	10 (21.3%)	0.487
Any ≥CD II complication	30 (29.4%)	27 (57.4%)	**0.002***
Any ≥CD III complication	7 (6.9%)	10 (21.3%)	**0.023***

A

Variable	(Present + commenced AC) / (present)	(Absent + commenced AC) / (absent)	p-value
CR-POPF	2/4 (50%)	100/145 (69%)	0.591
Bile leak	3/5 (60%)	99/144 (68.8%)	0.651
PPH	6/13 (46.2%)	96/136 (70.6%)	0.114
DGE	18/30 (60%)	84/119 (70.6%)	0.278
Chest infection	9/25 (36%)	93/124 (75%)	**0.0003***
Intra-abdominal collection	7/11 (63.6%)	95/138 (68.8%)	0.742
SSI	16/26 (61.5%)	86/123 (69.9%)	0.487
Any studied complication	48/78 (61.5%)	54/71 (76%)	0.0772
Any CD ≥II complication	30/55 (54.5%)	72/94 (76.6%)	**0.006***
Any CD ≥III complication	5/14 (35.7%)	97/135 (71.9%)	**0.012***

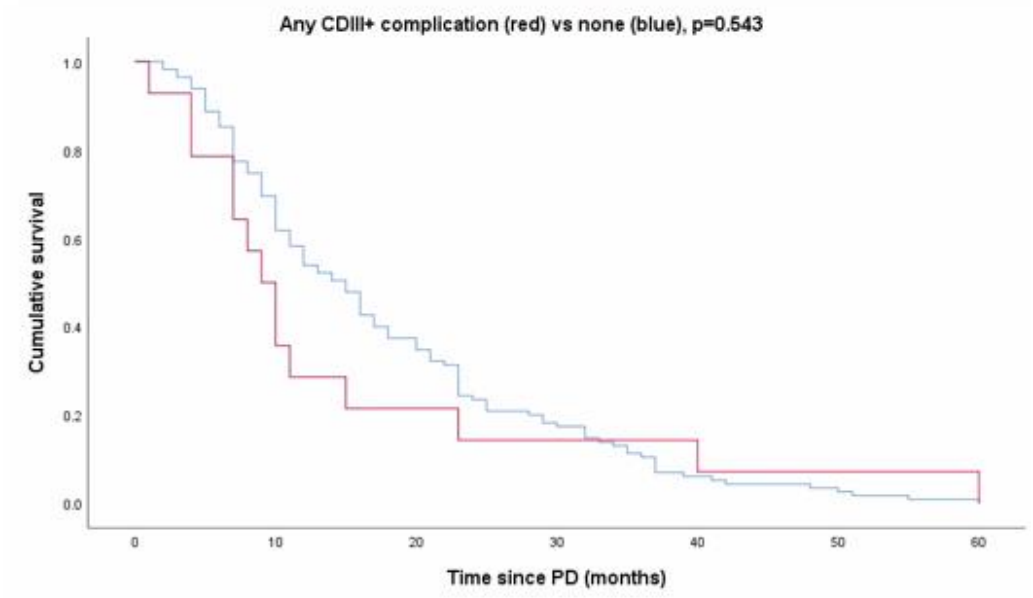
B

Table 5.8: (A) Comparing the patients who commenced AC to those who did not. (B) Selected outcomes and their association with commencing AC. Patients who died within 90 days of resection were excluded from all analyses. P-values obtained using Fisher's exact test. *Denotes statistical significance. AC data unavailable for two patients (excluded).



A

Number at risk							
AC	83	64	37	17	5	4	1
No AC	44	22	8	5	3		
Time (months)	0	10	20	30	40	50	60



B

Number at risk							
CDIII+ comp	14	7	3	2	2	1	1
None	115	80	43	21	7	4	1
Time (months)	0	10	20	30	40	50	60

Figure 5.3: Kaplan-Meier survival curves for (A) commenced AC vs none and (B) any studied CD grade ≥III complication vs none (patients who achieved five-year survival excluded). P-values obtained using the log-rank test. Patients who died within 90 days of PD were excluded from all analyses.

	Present 5-yr survival	Absent 5-yr survival	p-value
Commenced adjuvant chemotherapy	18/101 (17.8%)	4/48 (8.3%)	0.146
Any studied complication	10/81 (12.3%)	12/70 (17.1%)	0.490
Any ≥CD II complication	8/57 (14%)	14/94 (14.9%)	1.00
Any ≥CD III complication	1/15 (6.7%)	21/136 (15.4%)	0.698

Table 5.9: Five-year survival. P-values obtained using Fisher's exact test. Patients who died within 90 days of PD were excluded from all analyses.

Discussion

This study analysed the outcomes of 157 patients who underwent PD for histologically confirmed PDAC at our institution. Our patient demographics are comparable to those of a Japanese study by Yamashita et al. (n=174), where the median age was 67 years (vs 69) and 45% of patients were female (vs 47%)[345]. However, the median BMI was considerably higher in our series (25.1 vs 21.6 kg/m^2). This likely reflects the differences between Japanese and Western populations. In a similar German study of 405 PDs (all pathologies), the median age was 63 years, 39% of patients were female and the median BMI was 24.9 kg/m^2[167]. 57% of patients were ASA grade I-II (vs 66% in the present study) and 43% were ASA grade III-IV (vs 32%)[167]. These differences may be as the German study included all pathologies, whereas we only included patients with PDAC. The median length of stay in the Japanese study was 24 days, compared to ten days in our study, and eighteen days in the German study. In our series, 90-day mortality was 4%. In a recent American series of 551 PDs (all pathologies), Narayanan et al. found 90-day mortality was similar at 4%[124]. In our study, five-year cancer recurrence was 77% and actual five-year survival was 14%. A recent Taiwanese study (n=223, PDAC only) reported that five-year survival was 10%[157] and a recent German study (n=167, PDAC only) reported that this was 20%[346].

Recent studies have suggested the incidence of CR-POPF following PD (all pathologies) ranges from 10%[106] to 26%[311]. In the present series, just 5% of patients

developed CR-POPF. Our figures for bile leak[114], gastro-jejunal anastomotic leak[120], PPH[126], DGE[347] and SSI[348] were comparable to those described in the literature. In a large American series of 1090 PDs (all pathologies) by Nagle et al., 4% of patients developed pneumonia[349]. In our study, 18% developed a postoperative chest infection. Radiological evidence of pneumonia was required in the Nagle et al. series, this could partly explain the discrepancy. In our study, efforts were made to ensure intra-abdominal complications were not misdiagnosed as a chest infection. Of the 28 who were diagnosed with a chest infection, just four (14%) had a concomitant intra-abdominal complication.

In a recent Japanese series of 113 PDs (all pathologies) by Sato et al., 36% of patients developed a postoperative intra-abdominal collection[350]. In a larger Chinese series by Zhao et al. (n=2064) a figure of 15% was obtained[351]. In the present study, just 8% of patients experienced this complication. Again, this discrepancy is likely explained by diagnostic criteria differences. Both our study and that of Zhao et al. required confirmation of a collection using CT/ultrasound, whereas Sato et al. accepted positive drain cultures and associated signs/symptoms alone.

In our series, 69% of patients received AC. This is comparable to the figure of 59% obtained by Yamashita et al.[345]. Patients who received AC less frequently experienced a chest infection when compared to those who did not. The other studied complications were less frequent among the AC patients, but these differences were not significant. The small sample size might partly explain this. When CD grade I complications were excluded, the studied complications were significantly less frequent among those who received AC. This would suggest that, whilst minor complications likely do not affect whether a patient will receive AC or not, more serious complications might well do. Patients who developed a postoperative chest infection less commonly received AC. This effect was not observed with the other complications. Again, this may partly be explained by the small sample size. When CD grade I complications were excluded, patients who developed a complication less frequently commenced AC. Again, this would

suggest minor complications do not affect the likelihood of a patient commencing AC, whereas more serious complications might.

Until the 1990s, AC was not routinely given after resection for PDAC[64]. However, following the findings of studies such as the European Study Group of Pancreatic Cancer (ESPAC) study[352], AC has become the standard of care in suitable patients. Numerous trials have since demonstrated the survival benefit of combination chemotherapy after PD. In some cases, AC has been shown to improve median survival up to 54.4 months in selected patients[64]. In addition, numerous studies have shown that combination AC significantly increases the number of patients that achieve five-year survival[65]. The optimal timing for commencing AC is debated. Prior authors have argued that the completion of AC is more important than the timing[353]. However, Sung et al. (n=7548) demonstrated that patients who received their first dose between 28-59 days had the greatest survival advantage[354]. Whilst our study did not specifically study the timing of AC, it may be that those who had a serious complication had their first treatment dose delayed. Our results do suggest that those who have a serious complication are less likely to receive a first dose. This may be because of the significant deterioration in their performance status following the development of a serious postoperative complication, or because they develop recurrent disease by the time they are fit enough to commence AC.

We argue that future research should focus on developing models that can predict the likelihood of serious complications in individual patients. If a patient is deemed high-risk for a serious complication or early disease recurrence, it may be that they would benefit from NAT. This may increase the likelihood of them starting and completing at least one course of systemic treatment and have potential survival benefits. Prior studies have shown that almost 40% of PD patients with histologically confirmed PDAC develop cancer recurrence and die within one year of resection[342]. However, current UK guidelines do not support the use of NAT unless a patient has a borderline resectable tumour that involves named vessels[344]. Since early recurrence rates are so high,

considering NAT in high-risk patients may also aid patient selection. A positive response to NAT may help select patients with a chemosensitive tumour. Patients who have a poor response to NAT may also be poor candidates for PD[355]. These patients would arguably be better served by palliative therapy rather than an aggressive surgical resection which affects their quality of life considerably[159]. Further evidence from RCTs is required before NAT can be considered in patients with resectable disease[343]. The limitations of this study have been outlined in **Chapter 9**.

Conclusion

Patients who undergo PD for PDAC affecting the pancreatic head are at risk of developing serious postoperative complications which may affect their postoperative treatment. In our series, after patients who died in the perioperative period were excluded, those who had developed a serious complication commenced AC less frequently. The preoperative identification of patients who are high-risk for a serious complication may have implications for management planning.

Chapter 6: Results - RAW study: variations in nutritional practice

Russell TB, Labib PL, Murphy P, et al. Do some patients receive parenteral nutrition unnecessarily after pancreatoduodenectomy? Results from an international multicentre study. *Ann Hepatobiliary Pancreat Surg* 2023. DOI: 10.14701/ahbps.23-071. Open access.

Introduction

Although not supported by strong evidence, international guidelines recommend that patients should receive an oral diet in the early postoperative phase after PD, unless there is a contraindication[356]. They can then benefit from the potential gains of early enteral nutrition[357] without being exposed to the risks associated with more invasive forms of postoperative nutritional support (NS)[358]. Indeed, early enteral nutrition has been shown to correlate with a reduced length of hospital stay and reduced rates of DGE[359, 360]. However, the nutritional management of PD patients is known to be highly variable[361-363] and some centres still provide PN routinely.

A proportion of patients who receive PN experience serious complications[364] so it should only be provided when there is a clear indication. Using data from the RAW study, we aimed to determine the proportion of PD patients that received postoperative NS and describe the nature of this. In addition, we aimed to determine the number of patients that received PN and investigate whether receiving PN correlated with morbidity.

Method

See **Chapter 4** for a full description of the methods used. See **Supplementary Material** for a full list of the definitions used. For the purposes of this study, postoperative NS referred to either: “enteral nutrition (EN) only” (i.e., NG/nasojejunal (NJ) feeding or oral nutritional supplement drinks), “parenteral only” (PN), or “EN and PN”. Patients were

classified as having a “complication typically associated with a postoperative NS requirement” if they experienced any of the following: CR-POPF, BL, G-J leak, DGE, CL or ileus.

The patients were divided into binary groupings, and the proportion of patients in each that received postoperative NS was compared using Fisher’s exact test. Following this, the patients who received postoperative NS were compared to those who did not using univariate tests. For continuous outcomes where a normal distribution was assumed, Student’s *t*-test was used. Binary outcomes were compared using Fisher’s exact test, and the Mann-Whitney *U* test was used to compare the heavily skewed data from blood tests. Using the same methods, the patients were compared by the form of postoperative NS they received (if any). Finally, patients were divided into those who experienced a CD grade ≥IIIa complication and those who did not, and those who experienced a complication typically associated with a postoperative NS requirement, and those who did not. Comparisons were made using Fisher’s exact test.

Results

A total of 3705 patients were assessed for eligibility by the collaborating centres and 2212 were excluded as they did not meet the inclusion criteria (**Figure 6.1**). The lead centre removed nine cases as their entries were incomplete and a further 161 cases were excluded as their records did not include data on whether or not postoperative NS was provided. Therefore, the final analysis included 1323 patients. **Table 6.1** summarises the included patients' demographics and treatment details. The mean patient age was 66 years (SD: 9.8) and the mean BMI was 25.6 kg/m^2 (SD: 4.4). In total, 44% of patients were female and 35% were ASA grade >II. Concerning the surgical approach, 50% underwent a classic Whipple procedure and 50% underwent a pylorus-preserving PD. The median length of stay was 13 days (IQR: 10 days) and the 30-day

unplanned readmission rate was 10%. In all, 5% of patients had an unplanned return to theatre and the 90-day mortality rate was 4%.

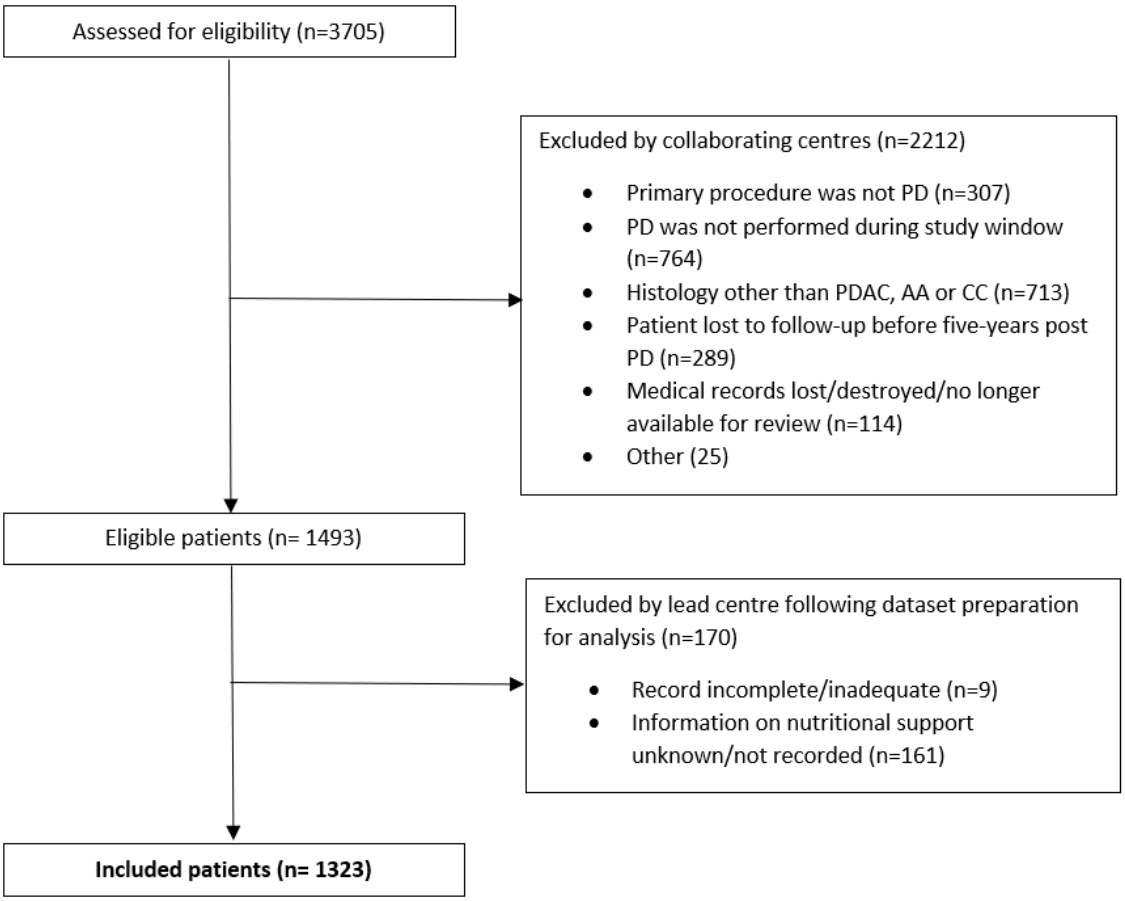


Figure 6.1: Cohort flow diagram.

In total, 601 patients (45%) received some form of postoperative NS. Of these, 44% received enteral-only support, 35% received parenteral-only support, and 21% received both enteral and parenteral support. The type of postoperative NS received was not recorded in one patient. Underweight patients (BMI <18.5 kg/m^2) more commonly received postoperative NS than patients with a normal BMI (18.5-24.9 kg/m^2, 70% vs 45%, p=0.03) (**Table 6.2**). Patients who underwent preoperative biliary stenting (PBS) received postoperative NS less often (43% vs 50%, p=0.009), as did those with a normal

preoperative serum albumin (≥36 g/L, 51% vs 43%, p=0.009). Patients who experienced POPF, DGE, an intra-abdominal collection or an unplanned return to theatre all received postoperative NS more often (all p<0.0001).

Table 6.3 compares the patients who received postoperative NS to those who did not. The former more frequently had a cardiovascular comorbidity (48% vs 41%, p=0.01) and had less often undergone PBS (61% vs 68%, p=0.008). POPF (26% vs 8%, p<0.0001), BL (5% vs 2%, p=0.0005), DGE (22% vs 5%, p<0.0001), PPH (9% vs 4%, p=0.002), an unplanned return to theatre (9% vs 3%, p<0.0001) and 30-day readmission (13% vs 8%, p=0.003) were all more common in patients that received postoperative NS.

Mean age (years)	66.0 (SD: 9.8)
Female sex	579 (43.8%)
Mean BMI (kg/m^2)	25.6 (SD: 4.4) Unknown/not recorded: 525 (39.7%)
Preoperative biliary stent	857 (64.8%)
Median preoperative serum bilirubin (μmol/L)	21 (IQR: 43)
Median preoperative serum albumin (g/L)	37 (IQR: 10) Unknown/not recorded: 75 (5.7%)
ASA grade >II	465 (35.1%) Unknown/not recorded: 1 (0.1%)
Type of PD performed	Classic Whipple: 660 (50.0%) Pylorus-preserving: 660 (50.0%) Unknown/not recorded: 3*
Received an intraoperative blood transfusion	164 (18.1%) Unknown/not recorded: 417*
Received postoperative NS	601 (45.4%) • Enteral only: 266 (44.3%) • Parenteral only: 211 (35.2%) • Enteral + parenteral: 123 (20.5%) • Unknown/not recorded: 1*
Median length of stay (days)	13 (IQR: 10) Unknown/not recorded: 65 (4.9%)
Unplanned return to theatre	71 (5.4%)
30-day readmission	134 (10.2%) Unknown/not recorded: 3 (0.2%)
90-day mortality	51 (3.9%)

Table 6.1: Summary of the 1323 patients who underwent PD and had information on their postoperative NS status available. *Not included in percentages.

Variable	Received post-op NS	p-value
Age (years) • <75 vs ≥75	44.2% vs 50.4%	0.081
Sex • Female vs male	43.4% vs 47.0%	0.182
Body mass index (kg/m^2) • Underweight (<18.5) vs ideal (18.5-24.9) • Ideal (18.5-24.9) vs overweight (≥25.0)	69.6% vs 45.2% 45.2% vs 51.0%	**0.030*** 0.114
Pre-op biliary stent • Yes vs no	42.7% vs 50.2%	**0.009***
Pre-op serum bilirubin (µmol/L) • <40 vs ≥40	44.1% vs 48.3%	0.154
Pre-op serum albumin (g/L) • <36 vs ≥36	50.9% vs 43.3%	**0.009***
American Society of Anesthesiologists grade • ≤II vs >II	44.1% vs 48.0%	0.184
Type of pancreatoduodenectomy • Classic vs pylorus-preserving	44.1% vs 46.7%	0.376
Intra-op blood transfusion • Yes vs no	51.2% vs 45.0%	0.166
Left theatre with a nasogastric tube *in situ* • Yes vs no	49.9% vs 30.4%	**0.0004***
Post-op pancreatic fistula • Yes vs no	74.2% vs 40.0%	**0.0001***
Delayed gastric emptying • Yes vs no	77.2% vs 40.8%	**0.0001***
Intra-abdominal collection • Yes vs no	68.8% vs 42.2%	**0.0001***
Unplanned return to theatre • Yes vs no	74.3% vs 43.7%	**0.0001***

Table 6.2: Selected variables and the number of patients that received postoperative NS. Comparisons made using Fisher's exact test.

Table 6.4 compares patients by the type of postoperative NS they received (if any). This table also compares patients who received EN only to those who received PN (with or without EN). Patients who received PN had more commonly experienced POPF (34% vs 15%, p<0.0001), an unplanned return to theatre (13% vs 5%, p=0.0003) or 90-day mortality (7% vs 2%, p=0.003). Length of stay and AC rates were similar. **Table 6.5** compares patients who experienced major morbidity (at least one CD grade ≥IIIa complication) to those who did not. The former were more likely to have received postoperative NS (70% vs 40%, p<0.00001). Both groups had a similar number of patients that received EN (17% vs 21%, p=0.3). A higher proportion of patients received PN (+/-EN) in the major morbidity group (50% vs 17%, p<0.00001). In total, 215 patients

(20%) who did not experience a major complication received PN. Similarly, 131 patients (15%) who did not develop a complication typically associated with a requirement for postoperative NS still received PN.

Variable	Post-op NS (n=601)	No post-op NS (n=722)	p-value
Mean age (years)	66.3 (SD: 9.9)	65.6 (SD: 9.7)	0.148
Female sex	251 (41.8%)	328 (45.4%)	0.182
Mean BMI (kg/m^2)	25.6 (SD: 4.5)	25.5 (SD: 4.3)	0.926
Pre-op diabetes	133 (22.2%)	141 (19.5%)	0.248
Pre-op cardiovascular comorbidity	291 (48.4%)	299 (41.4%)	**0.012***
Pre-op respiratory comorbidity	75 (12.5%)	66 (9.1%)	0.060
Preoperative biliary stent	366 (60.9%)	491 (68.0%)	**0.008***
Received neoadjuvant chemotherapy	21 (3.5%)	40 (5.5%)	0.087
Median pre-op bilirubin (µmol/L)	21.5 (IQR: 46)	20 (IQR: 40)	0.724
Median pre-op serum albumin (g/L)	37 (IQR: 11)	39 (IQR: 9)	**0.0003***
ASA grade >II	223 (37.1%)	242 (33.5%)	0.184
Venous resection performed	90 (15.0%)	114 (15.8%)	0.701
Intra-op blood transfusion	84 (20.1%)	80 (16.4%)	0.166
Left theatre with NG tube *in situ*	501 (94.7%)	504 (88.7%)	**0.0004***
Post-op pancreatic fistula	155 (25.8%)	54 (7.5%)	**0.0001***
Post-op bile leak	31 (5.2%)	12 (1.7%)	**0.0005***
Gastro-jejunal anastomotic leak	13 (2.2%)	7 (1.0%)	0.111
Post-pancreatectomy haemorrhage	52 (8.7%)	32 (4.4%)	**0.002***
Delayed gastric emptying	129 (21.5%)	38 (5.3%)	**0.0001***
Intra-abdominal collection	26 (4.3%)	50 (6.9%)	**0.044***
Unplanned return to theatre	55 (9.2%)	19 (2.6%)	**0.0001***
Median length of stay (days)	11 (IQR: 7)	12 (IQR: 6)	**0.017***
30-day readmission	77 (12.8%)	57 (7.9%)	**0.003***
90-day mortality	29 (4.8%)	22 (3.0%)	0.114
Commenced AC**	342 (59.8%)	451 (64.4%)	0.092

Table 6.3: Comparison of patients who did and did not receive postoperative NS after PD for PDAC, AA or CC. *Denotes statistical significance. **Excluding patients who died within 90 days of PD. Statistical methods: Student's *t*-test: age, BMI, Mann Whitney *U* test: blood tests, length of stay, Fisher's exact test: all other comparisons.

	Post-op nutritional support received			
	Enteral only	**Parenteral only**	**Enteral + parenteral**	**None**
Number of patients	266	211	123	722
Left theatre with NG tube *in situ*	208 (94.5%)	187 (94.9%)	106 (94.6%)	504 (88.7%)
Postoperative pancreatic fistula	40 (15.0%)	68 (32.2%)	47 (28.2%)	54 (7.5%)
Median length of stay (days)	11 (IQR: 7)	11 (IQR: 7)	11 (IQR: 7)	12 (IQR: 6)
Unplanned return to theatre	12 (4.5%)	21 (10.0%)	22 (17.9%)	19 (2.6%)
90-day mortality	5 (1.9%)	17 (8.1%)	7 (5.7%)	22 (3.0%)
Commenced AC**	159 (60.9%)	112 (57.7%)	71 (61.2%)	451 (64.4%)

	Post-op nutritional support received		
	Enteral only	**Parenteral +/- enteral**	**p-value**
Number of patients	266	334	-
Left theatre with NG tube *in situ*	208 (94.5%)	293 (94.8%)	1.00
Postoperative pancreatic fistula	40 (15.0%)	115 (34.4%)	**0.0001***
Median length of stay (days)	11 (IQR: 7)	11 (IQR: 6)	0.743
Unplanned return to theatre	12 (4.5%)	43 (12.9%)	**0.0003***
90-day mortality	5 (1.9%)	24 (7.2%)	**0.003***
Commenced AC**	159 (60.9%)	183 (59.0%)	0.669

Table 6.4: Postoperative NS and selected outcomes. *Denotes statistical significance. **Excludes patients who died within 90 days of PD. The type of nutritional support was unknown/not recorded in one patient (excluded from the above). Statistical methods: Mann Whitney *U* test: length of stay, Fisher's exact test: all other comparisons.

Discussion

This retrospective study describes the variations in nutritional support received by 1323 PD patients who had malignancy confirmed on their postoperative histology. Although not supported by strong evidence, international guidelines recommend that, postoperatively, PD patients receive an early oral diet unless this is contraindicated. However, over a quarter of the patients included in our study received PN. Additionally, considerable numbers received PN when they had not experienced a significant postoperative complication (CD grade ≥IIIa), or a complication typically associated with a requirement for NS. Although we do not know why individual patients were given PN, one can speculate and assume that there was a group that received PN without a strong indication, exposing these patients to avoidable risks such as line infection/sepsis, or DVT[365]. PN can also result in metabolic complications such as electrolyte imbalance, dysglycaemia, cholestasis, hypertriglyceridemia and deranged liver function[366]. As such,

PN should only be used when the gastrointestinal tract is either inaccessible or not functioning[367]. The involvement of qualified nutrition professionals in the early postoperative period is key to selecting which patients require PN as part of their management.

	Major complication	**No major complication**	**p-value**
Number of patients	226 (17.1%)	1097 (83.0%)	-
Received post-op NS	159 (70.4%)	442 (40.3%)	**0.00001***
Received EN only	39 (17.3%)	227 (20.7%)	0.274
Received PN (+/- EN)	112 (49.6%)	215 (19.6%)	**0.00001***
	Studied complication	**No studied complication**	**p-value**
Number of patients	454 (34.3%)	869 (65.7%)	-
Received post-op NS	297 (65.4%)	304 (35.0%)	**0.00001***
Received EN only	93 (20.5%)	173 (19.9%)	0.829
Received PN (+/- EN)	203 (44.7%)	131 (15.1%)	**0.00001***

Table 6.5: Comparing patients who experienced at least one CD grade ≥IIIa complication (major morbidity) to those who did not (top), and patients who experienced a complication typically associated with a NS requirement to those who did not (bottom). Comparisons made using Fisher's exact test. "Studied complications" included CR-POPF, BL, G-J leak, DGE, CL and ileus.

Traditionally, patients who underwent major gastrointestinal surgery were kept nil by mouth in the early postoperative phase and they were often routinely given PN or fed via the jejunal route. However, these artificial feeding methods are not without risk and guidelines now recommend allowing patients to take an oral diet as early as is feasible[368, 369]. Implementation of these guidelines has been shown to correlate with reduced length of stay and reduced incidence of DGE[359, 360]. If a patient cannot tolerate an oral diet or if oral intake is likely to be inadequate for more than seven days, EN via the jejunal route is advised[370]. To our knowledge, no recent studies have described the type of postoperative NS received by a large cohort of PD patients, as we have done. However, several authors have compared the outcomes of patients receiving different types of postoperative NS. Takagi et al. recently performed a SR of 20 RCTs where, compared to PN, the safety and tolerability of EN following PD was demonstrated[371]. Indeed, the

authors highlighted that early oral intake with systemic nutritional support is essential to the enhanced recovery after surgery (ERAS) concept[371]. Whilst patients who received EN had reduced length of stay compared to those who received PN (length of stay was similar in our study), the authors suggested that the effect of EN on postoperative complications was controversial. They concluded that postoperative EN should be selectively provided to PD patients and that preoperative EN should only be provided to patients who are severely malnourished[371].

Kapoor et al. recently conducted a retrospective analysis of 562 PDs from a single Indian institution and 19% received postoperative NS[372]. Whilst our figure of 45% was considerably higher, this included patients that received oral nutritional supplements only. In the Indian study, a tube jejunostomy was performed in 8% of patients, PN was provided for 15% and a NJ tube was placed in 5%. Increasing age, low preoperative serum albumin and high intraoperative blood loss were all independently associated with receiving postoperative NS. Low preoperative serum albumin and preoperative gastric outlet obstruction were predictors of requiring prolonged nutritional support[372]. The authors concluded that a pre-emptive jejunostomy should be considered in patients with these risk factors. This is particularly relevant to patients with preoperative gastric outlet obstruction as a chronically dilated stomach regains its tone gradually. Hence, patients with this condition are likely to have poor tolerance to oral diet in the early postoperative period. Indeed, preoperative gastric outlet obstruction has been shown to correlate with postoperative DGE[373]. This is also relevant in patients with very a low serum albumin, since this is associated with high morbidity rates and a prolonged admission[186].

In our study, patients who experienced serious morbidity received PN more often. However, a considerable proportion of those who did not develop a serious complication still received PN. This contrasts with current guidelines which suggest patients should take an oral diet at will unless this is contraindicated. Similarly, over 15% of those who did not develop a complication typically associated with a postoperative NS requirement received PN. Whilst we do not know why PN was provided in each case, one could

speculate and argue that this figure is too high. There were probably a group of patients that received PN inappropriately. These patients may have missed out on the potential benefits of early EN[357] whilst being subjected to the risks associated with an indwelling catheter and PN[358]. The limitations of this study are outlined in **Chapter 9**.

Conclusion

In conclusion, 45% of the included patients who underwent PD received some form of postoperative NS and most of these received PN. Being underweight, not undergoing PBS and having a low preoperative serum albumin all correlated with receiving postoperative NS. One-fifth of the patients who did not experience a serious postoperative complication received PN. It may be that some of these patients were given PN unnecessarily. PD patients should undergo pre- and early postoperative nutritional assessment and have a nutritional treatment plan agreed in advance of surgery. This will likely increase the proportion that receives the most appropriate form of NS and result in marginal gains to surgical outcomes.

Chapter 7: Results - RAW study: postoperative complications

7.1. Which patients develop serious complications and why is this important?

Russell TB, Labib PL, Streeter A, et al. Postoperative complications after pancreatoduodenectomy for malignancy: results from the Recurrence After Whipple's (RAW) study. *BJS Open* 2023. DOI: 10.1093/bjsopen/zrad106. Open access.

Introduction

Due to the complex nature of the PD, several general and procedure-specific complications may occur postoperatively. Surgeons must have a sound understanding of the incidence of these, as this will guide preoperative discussions with patients and the consenting process. Further, patients who develop serious complications may have their AC delayed or omitted as a result[374]. Hence, it is essential that surgeons aim to minimise morbidity wherever possible. Identifying high-risk patients preoperatively is helpful as this could aid patient selection and allow for preoperative patient optimisation. Multiple small studies[333, 375] have recently reported on the procedure-specific outcomes of PD, but no large studies have compiled a robust complication profile. Using data from the RAW study, we aimed to calculate the incidence and severity of all PD complications and identify risk factors for overall morbidity, major morbidity, CR-POPF, PPH and 90-day mortality.

Method

See **Chapter 4** for a full description of the methods used. See **Supplementary Material** for a full list of the definitions used. Specific data were collected on the following

complications: POPF, BL, G-J leak, PPH, DGE, acute kidney injury, cardiac arrythmia, chest infection, cholangitis, CL, *Clostridium difficile* infection, ileus, intra-abdominal collection, liver abscess, MI, pancreatic necrosis, pancreatitis, PV/SMV thrombosis, sepsis of unknown origin, splenic vein thrombosis, SSI, UTI, DVT, and PE.

The patients were compared according to two binary groupings: those who experienced complications versus no complications, those who experienced major morbidity (at least one CD grade ≥IIIa complication) versus those who did not, those who experienced CR-POPF versus those who did not, those who experienced PPH versus those who did not, and those who died within 90 days of PD versus those who did not. Means were compared using Student's *t*-test and distributions were compared using the Mann Whitney *U* test. When testing for independence between two variables, Fisher's exact test was used. Following the univariable tests, each of the outcomes in turn were fitted using logistic regression to all the key demographic variables (age, sex), baseline comorbidities (diabetes, cardiovascular disease, respiratory disease), key risk groups (ASA grade, preoperative nodes on CT) and salient procedural features (classic Whipple vs pylorus-preserving approach, anastomosis type). See table legends for specific details.

Results

A total of 3705 patient records were assessed for eligibility by the collaborating centres and 2212 were excluded as they did not meet the inclusion criteria (**Figure 7.1**). Nine records were removed as they were incomplete and 136 records were removed as they did not include data on complications (if any). Therefore, the final analysis included 1348 patients. **Table 7.1** displays the demographics, preoperative, intraoperative and postoperative details of those included. The mean patient age was 66 years (SD: 9.8 years), and 42% were female. The mean BMI was 25.5 kg/m^2 (SD: 4.4 kg/m^2) and the ASA grade was >II in 34% of cases. A classic Whipple was performed in 49% of patients and 51% underwent a pylorus-preserving (PPPD) approach. A P-J was fashioned in 81%

of patients and 19% received a P-G. The median length of stay was thirteen days (IQR: 10-20 days) and 6% of patients had an unplanned return to theatre. The 30-day readmission rate was 10% and the 90-day mortality rate was 4%. Regarding postoperative histology, 792 (59%), 363 (27%) and 192 (14%) patients had PDAC, AA and CC, respectively.

A total of 1340 complications were reported; 72% were CD grade I-II, 18% were grade III, 7% were grade IV, and 4% were grade V (**Table 7.2**). Clinically-relevant POPF, PPH, chyle leak, bile leak and G-J leak affected 8%, 6%, 4%, 3% and 2%, respectively. Other notable complications included intra-abdominal collection (12%), SSI (9%) and chest infection (7%). In total, 720 patients (53%) experienced at least one complication. When patients that experienced a complication were compared to those who did not (**Table 7.3**), mean BMI was higher in the former (25.9 vs 25.0 kg/m^2, p=0.003), as was the number of patients with preoperative cardiovascular disease (47% vs 40%, p=0.006) or an ASA grade >II (32% vs 24%, p=0.002). The median preoperative serum albumin was lower in those who experienced morbidity (38 vs 39 g/L, p=0.004). A higher proportion of patients who experienced complications had undergone a classic Whipple (vs PPPD, 53% vs 44%, p<0.0001) or a P-G (vs P-J, 21% vs 15%, p<0.0001). The histological diagnosis was similar between the groups that developed complications and the groups that did not; PDAC (54% vs 59%, p=0.06), AA (29% vs 27%, p=0.2) and CC (16% vs 14%, p=0.3).

A total of 228 patients (17%) experienced a CD grade ≥IIIa complication. This group were more often ASA grade >II (45% vs 36%, p=0.0006). Patients with CR-POPF were more often male (68% vs 55%, p=0.003) or ASA grade >II (38% vs 27%, p=0.02), and had a higher mean BMI (27.1 vs 25.3 kg/m^2, p=0.0002). Those who experienced PPH had a higher median preoperative serum bilirubin (34 vs 20 µmol/L, p=0.02), were more often ASA grade >II (44% vs 26%, p=0.002) and were more likely to have received a P-G (29% vs 18%, p=0.02). Patients who died within 90 days were significantly older (mean difference: 3.1 years, p=0.02) but no other risk factors were identified. Among the major

morbidity group, the number of patients with AA (33% vs 27%, p=0.07) and CC (18% vs 14%, p=0.1) were like that of the entire cohort. However, PDAC was less common among those who developed serious complications (49% vs 59%, p=0.04).

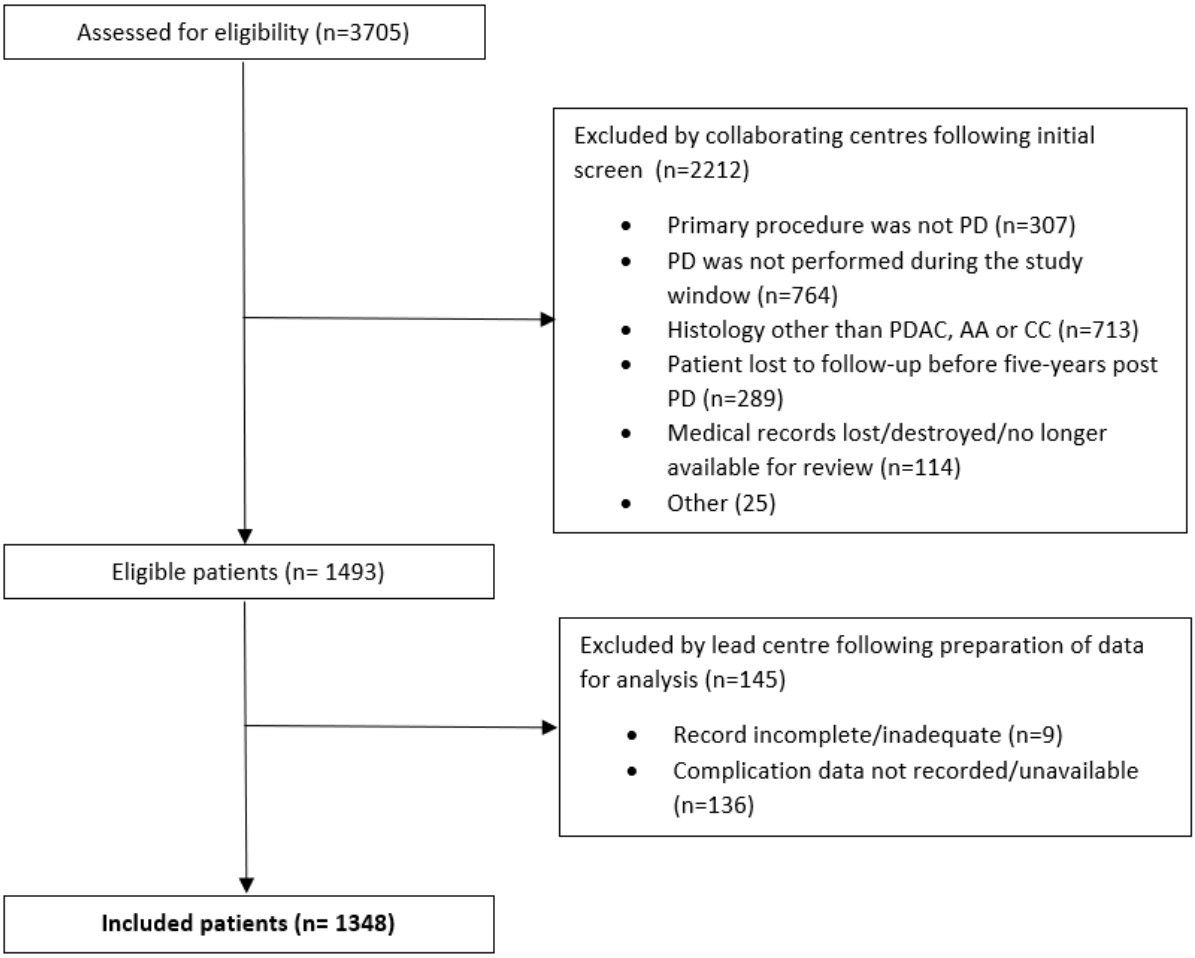


Figure 7.1: Cohort flow diagram.

Results from the multivariable analyses are displayed in **Table 7.4**. The following factors were associated with complications: increasing BMI (odds ratio (OR): 1.1, p=0.007), ASA grade >II (OR: 2.2, p<0.0001) and a classic Whipple procedure (OR: 1.2, p=0.01). However, only ASA grade >II correlated with major morbidity (OR: 2.2, p<0.0001) and only increasing BMI (OR: 1.1, p=0.001) correlated with CR-POPF. ASA

grade >II (OR: 2.5, p=0.002) and positive nodes on preoperative imaging (OR: 2.1, p=0.01) were associated with an increased risk of PPH. However, preoperative diabetes (OR: 0.4, p=0.045) and a P-J anastomosis (OR: 0.5, p=0.03) were associated with a decreased risk of PPH. Interestingly, none of the studied variables had a significant relationship with 90-day mortality.

Discussion

This study describes the complications experienced by a large cohort of patients who underwent PD for malignancy at one of the 29 participating centres. The procedure-specific complications of PD were classified using internationally recognised criteria, and all complications were classified using the CD system. Whilst prior multicentre studies have been carried out with similar patient numbers, few have used strict diagnostic criteria as we have done[334]. Further, unlike many prior studies, we have only included patients with histologically-confirmed PDAC, AA or CC[334]. Our study group's patient demographics and comorbidity profile are comparable to that of a Swedish study by Williamson et al. (2012-2017, n=1957)[179]. Similar to the Swedish study, a significant proportion of our patients underwent PBD (64% and 63%, respectively)[179]. The reoperation rate, CD grade ≥IIIa complication rate, median length of stay, and 90-day mortality rate we also all similar[179]. However, our study's overall morbidity rate (54% vs 47%) was higher. This may be because we included all postoperative complications whereas the Swedish study only included those that were deemed clinically-relevant. Furthermore, the Swedish study included patients with premalignant, duodenal and neuroendocrine tumours but we only included those with PDAC, AA or CC.

The incidence of CR-POPF in our study was eight per cent, slightly lower than the 10% observed in the Swedish study[179]**.** In a study of 170 consecutive patients that underwent PD for various indications, Ke et al. observed a CR-POPF rate of 26%[110]. In another study of 539 consecutive PDs, Fu et al. observed an incidence of 37%[111]. Our

lower observed incidence could be due to the exclusion of patients without histologically-confirmed malignancy. In addition, it could also be due to the higher number of PDAC patients, who tend to have a firmer pancreas compared to those with AA or CC[67, 103]. Similar to Lovasik et al., we observed that patients with a high BMI more often experienced CR-POPF. A pancreatic remnant with a higher parenchymal fat content may help to explain this. Interestingly, we did not observe a relationship between POPF and a P-J anastomosis, PBD or preoperative diabetes. Williamson et al. (n=2503) suggested a P-J was a risk factor and found that both PBD and preoperative diabetes were protective[106].

PPH is one of the most common causes of reoperation and death after PD[124]. The reported incidence is between 4% and 14%[334]. In our study, 6% of patients experienced PPH and 13% of these died as a result. The mortality rate of 13% from PPH is comparable to other published series[334]. PPH was the leading cause of perioperative death in our study. Twenty-one patients experienced PPH which was at least CD grade IV; this was higher than for any other complication. We found that high serum bilirubin and positive lymph nodes on preoperative imaging were significant risk factors for PPH, whereas preoperative diabetes was protective. In a recent study of 1169 pancreatic resections (all types), Izumo et al. also found that diabetes was protective[376]. Diabetes is associated with decreased pancreatic exocrine secretion and an atrophied and firm pancreas. A firm pancreatic gland is associated with a reduced incidence of POPF, which is a further risk factor for PPH[110, 377].

Similar to other published series, we found that patients who experienced morbidity had a significantly higher BMI. Patients with a high BMI are likely to have a worse baseline fitness level and have additional comorbidities. Also, obese patients can be challenging to ventilate, which can increase the risk of respiratory and anaesthetic complications. Thirdly, the obese patient presents surgical challenges. Surgical access is more difficult in patients with a thick layer of subcutaneous fat between the skin and the abdominal wall, and tissue planes can be more challenging to visualise. Furthermore,

a high BMI is associated with a high pancreatic fat content, which is associated with an increased risk of injury to the pancreatic capsule/parenchyma, ductal disruption, and an increased risk of POPF[111]. In a recent meta-analysis by You et al. (22 studies, n=8994), patients with a BMI ≥25 kg/m^2 were compared to those with a BMI <25 kg/m^2. The former were found to have longer operation times (mean increase: 15 minutes), increased intraoperative blood loss (mean difference: 271 ml), higher rates of POPF (OR: 2.0), DGE (OR: 1.6) and SSI (OR: 1.4), and longer hospital stays (mean difference: 2.9 days, all $p<0.05$)[187].

In our study, the median serum albumin was lower in the group that experienced complications. A low albumin is associated with increased third space losses, a higher anastomotic leak rate and reduced immunity[256]. Rungsakulkij et al. (n=238)[256], and others[257, 258], have found that lower preoperative serum albumin correlates with major morbidity (OR: 1.1, $p<0.05$)[256]. Hendifar et al. (n=106) also concluded that this was associated with an increased postoperative transfusion requirement ($p=0.02$) and reduced overall survival ($p=0.02$)[259].

The ASA physical classification system can be used to categorise a patient's preoperative physiological status. Its impact on surgical outcomes is well documented[270]. Specific to pancreatic resection, increasing ASA grade has been shown to correlate with adverse perioperative outcomes. As in our study, both Wiltberger et al. (n=405) and Braga et al. (n=700) showed patients with an ASA grade >II were more likely to experience postoperative complications[167, 273]. We found that ASA grade >II patients were more than twice as likely to develop complications, major morbidity or PPH. As such, one should consider the additional risks when offering PD to patients in this group, especially if they are elderly or have a high BMI.

We also examined the relationship between the type of PD and the risk of overall morbidity and major morbidity. We found that a classic PD was more common among those who experienced complications. A meta-analysis by Yang et al. (eight RCTs, n=662) suggested a PPPD had short-term advantages, including shorter operation times

(mean difference: 53 minutes, p=0.01) and reduced intraoperative blood loss (mean difference: 365 ml, p=0.006). However, a classic PD was associated with a lower rate of DGE (risk ratio (RR): 2.4, p=0.04) and similar morbidity/mortality rates[278]. Unlike our study and those discussed above, several studies have shown that the operative approach does not significantly affect perioperative outcomes[276, 277].

We examined for correlation between the type of pancreatic anastomosis and the studied outcomes. We found that a P-G anastomosis was associated with higher rates of overall morbidity and PPH. Multiple meta-analyses have compared P-J and P-G outcomes and these have come to conflicting conclusions, possibly due to high heterogeneity between the included studies. Menahem et al. (seven RCTs, n=1121) found a P-G correlated with a lower incidence of POPF (11% vs 19%, p=0.0003), but only four studies used the standardised ISGPS definition[298]. Zhou et al. (six RCTs, n=1005) reached the same conclusion (OR: 0.6, p=0.001)[299]. In contrast, a meta-analysis by Wang et al. (16 RCTs, n=2396) found that a P-G was not superior to a P-J in terms of POPF risk[300-302]. Ratnayake et al. (fifteen RCTs, n=2428), who compared and ranked five different techniques, found a P-G duct-to-mucosa approach was associated with the lowest rate of CR-POPF[296]. Concerning other short-term outcomes, Ratnayake et al. also found this technique was associated with the lowest rates of intraoperative blood transfusion, DGE, and intra-abdominal collection[296]. This method also correlated with the shortest median operation time, hospital stay, and rates of morbidity/mortality[296]. Furthermore, Zhou et al. found that intra-abdominal collection (OR: 0.4, p<0.001) and biliary fistulae (OR: 0.3, p=0.01) were less common among P-G patients[299]. In another recent meta-analysis, Jin et al. found that patients with a P-G more commonly experienced PPH (OR: 1.5, p=0.03)[302]. We also observed this.

In our study, when all complications were considered, cancer type did not appear to affect the risk of perioperative morbidity. However, relative to the entire cohort, fewer patients who experienced a serious complication had PDAC. In a single-centre study, Wiltberger et al. (n=225) found that PD patients with a distal CC were more likely to

develop a grade C POPF[378]. In a multicentre Japanese study, Aoki et al. (n=17,564) also found that distal CC was a risk factor for serious (CD grade ≥IV) complications (OR: 1.4, p=0.003) and grade C POPF (OR: 1.7, p<0.001)[182]. These findings are likely as, compared to patients with PDAC, those with a distal CC are more likely to have a soft pancreas with a non-fibrotic parenchyma[182]. The limitations of this study have been outlined in **Chapter 9**.

Conclusion

In our multicentre study of patients who underwent PD for malignancy, the overall morbidity rate was 53% and the perioperative mortality rate was 4%. Whilst minor complications were common, serious complications affected less than a fifth of patients. The most common cause of death was PPH, followed by POPF. A high BMI and an ASA grade >II were associated with the studied adverse outcomes. Patients who fall into these sub-groups should be made aware of the additional risks they face. Surgeons must have a sound understanding of the complication profile of PD as this will allow them to evaluate their performance and guide patient selection.

Mean age in years (SD)	66.0 (9.8)	
Female sex	587 (42.4%)	
Mean BMI in kg/m^2 (SD)	25.5 (4.4)	Unknown/not recorded: 561 (40.5%)
Preoperative comorbidities • Diabetes • Cardiovascular • Respiratory	 277 (20.6%) 590 (42.6%) 142 (10.5%)	 Unknown/not recorded: 38*
Preoperative biliary stent	875 (63.3%)	Unknown/not recorded: 2*
Neoadjuvant chemotherapy received	61 (4.6%)	
Median preoperative blood tests (IQR) • Bilirubin (µmol/L) • Albumin (g/L) • Neutrophils ($x10^9$/L) • Lymphocytes ($x10^9$/L)	 20 (42) 37.5 (10) 4.9 (2.8) 1.8 (1.2)	 Unknown/not recorded: 2 (0.1%) Unknown/not recorded: 100 (7.4%) Unknown/not recorded: 28 (2.1%) Unknown/not recorded: 28 (2.1%)
ASA grade >II	467 (33.7%)	Unknown/not recorded: 116*
Positive nodes on preoperative CT	324 (27.7%)	Unknown/not recorded: 177*
Type of PD performed	Classic Whipple: 660 (49.1%) Pylorus-preserving PD: 685 (50.9%)	Unknown/not recorded: 3*
Pancreatic anastomosis	P-J: 1064 (81.2%) P-G: 246 (18.8%)	Unknown/not recorded: 38*
Concomitant venous resection	205 (15.5%)	Unknown/not recorded: 28*
Concomitant arterial resection	25 (1.9%)	Unknown/not recorded: 29*
Intraoperative blood transfusion	164 (18.1%)	Unknown/not recorded: 442*
Unplanned return to theatre	74 (5.5%)	
Median length of stay in days (IQR)	13 (10)	Unknown/not recorded: 70 (5.2%)
30-day unplanned readmission	134 (10.0%)	Unknown/not recorded: 5 (0.4%)
90-day mortality	51 (4.0%)	
Postoperative histology • PDAC • AA • CC	 792 (58.8%) 364 (27.0%) 192 (14.2%)	

Table 7.1: Demographics, preoperative, operative and postoperative details. *Not included in percentages.

Postoperative complication and incidence	Incidence by CD grade						
	I	**II**	**IIIa**	**IIIb**	**IVa**	**IVb**	**V**
Postoperative pancreatic fistula: 210 (15.6%) Biochemical leak: 102 (7.6%) • Grade A: 101 Clinically-relevant: 108 (8.0%) • Grade B: 85 • Grade C: 23	68	91	22	14	5	5	5
Bile leak: 44 (3.3%) • Grade A: 13 • Grade B: 18 • Grade C: 13	12	9	8	7	3	2	3
Gastrojejunal leak: 20 (1.5%) • Grade A: 6 • Grade B: 8 • Grade C: 6	2	8	2	5	1	0	2
Post-pancreatectomy haemorrhage: 84 (6.2%) • Grade A: 17 • Grade B: 40 • Grade C: 27	11	21	14	17	7	3	11
Delayed gastric emptying: 167 (12.4%) • Grade A: 73 • Grade B: 59 • Grade C: 35	50	97	8	9	0	2	1
Acute kidney injury: 33 (2.4%)	10	9	0	0	8	2	4
Cardiac arrythmia: 32 (2.4%)	8	19	0	1	3	0	1
Chest infection: 96 (7.1%)	10	70	3	0	11	1	1
Cholangitis: 6 (0.4%)	0	5	0	0	1	0	0
Chyle leak: 47 (3.5%)	24	17	6	0	0	0	0
Clostridium difficile infection: 9 (0.7%)	0	9	0	0	0	0	0
Ileus: 37 (2.7%)	15	20	0	2	0	0	0
Intra-abdominal collection: 160 (11.9%)	21	64	52	16	2	1	4
Liver abscess: 13 (1.0%)	1	6	6	0	0	0	0
Myocardial infarction: 3 (0.2%)	0	2	0	0	1	0	0
Pancreatic necrosis: 2 (0.1%)	1	0	0	0	1	0	0
Pancreatitis: 5 (0.4%)	2	2	0	0	1	0	0
PV/SMV thrombosis: 16 (1.2%)	1	6	1	3	1	0	4
Sepsis of unknown origin: 19 (1.4%)	1	13	0	0	4	0	1
Splenic vein thrombosis: 3 (0.2%)	0	2	0	0	0	0	1
Surgical site infection: 115 (8.5%)	52	57	4	1	1	0	0
Urinary tract infection: 20 (1.5%)	1	19	0	0	0	0	0
Deep vein thrombosis: 6 (0.4%)	0	5	0	1	0	0	0
Pulmonary embolism: 15 (1.1%)	4	10	0	0	0	0	1
Other complication: 177 (13.1%)	34	79	16	21	9	4	14
Sum of complications (n=1340) by CD grade	**328 (24.5%)**	**640 (47.8%)**	**142 (10.6%)**	**98 (7.3%)**	**59 (4.4%)**	**20 (1.5%)**	**53 (4.0%)**

Table 7.2: The postoperative complications recorded classified by their CD grade.

Variable	Any complication (n=720)	No complication (n=628)	p-value
Mean age in years (SD)	66.4 (9.6)	65.5 (10.1)	0.103
Age ≥80 years	46 (6.4%)	36 (5.7%)	0.649
Female sex	301 (41.8%)	286 (45.5%)	0.169
Mean BMI in kg/m^2 (SD)	25.9 (4.5)	25.0 (4.2)	**0.0028***
BMI ≥30 kg/m^2	82 (17.7%)	40 (11.1%)	**0.010***
Preoperative comorbidities			
• Diabetes	144 (20.0%)	133 (21.2%)	0.593
• Cardiovascular	340 (47.2%)	250 (39.8%)	**0.006***
• Respiratory	86 (11.9%)	56 (8.9%)	0.071
Preoperative biliary stent	471 (65.4%)	404 (64.3%)	0.700
Median preoperative blood tests (IQR)			
• Bilirubin (µmol/L)	20 (44)	21 (41)	0.800
• Albumin (g/L)	38 (12)	39 (9)	**0.004***
• Neutrophils (x10^9/L)	4.9 (2.7)	4.9 (3.0)	0.649
• Lymphocytes (x10^9/L)	1.8 (1.2)	1.8 (1.1)	0.298
ASA grade >II	214 (32.3%)	138 (24.2%)	**0.002***
Positive nodes on preoperative CT	176 (27.5%)	148 (27.8%)	0.948
Classic Whipple (vs PPPD)	382 (53.1%)	278 (44.3%)	**0.0015***
P-J anastomosis (vs P-G)	553 (76.2%)	511 (81.4%)	**0.004***
Variable	**Major morbidity (n=228)**	**No major morbidity (n=1120)**	**p-value**
Mean age in years (SD)	66.0 (9.6)	66.0 (9.9)	0.905
Age ≥80 years	13 (5.7%)	69 (6.2%)	0.880
Female sex	96 (42.1%)	491 (43.8%)	0.660
Mean BMI in kg/m^2 (SD)	25.5 (3.9)	25.5 (4.9)	0.990
BMI ≥30 kg/m^2	21 (13.8%)	100 (14.9%)	0.801
Preoperative comorbidities			
• Diabetes	46 (20.2%)	231 (20.6%)	0.929
• Cardiovascular	101 (44.3%)	489 (43.7%)	0.884
• Respiratory	21 (9.2%)	121 (10.8%)	0.554
Preoperative biliary stent	141 (61.8%)	734 (65.5%)	0.288
Median preoperative blood tests (IQR)			
• Bilirubin (µmol/L)	19 (52)	21 (41)	0.573
• Albumin (g/L)	37 (13)	38 (10)	0.456
• Neutrophils (x10^9/L)	5.0 (2.7)	4.9 (2.9)	0.650
• Lymphocytes (x10^9/L)	1.8 (1.4)	1.8 (1.1)	0.463
ASA grade >II	81 (39.3%)	271 (26.4%)	**0.0003***
Positive nodes on preoperative CT	56 (27.9%)	268 (27.6%)	0.931
Classic Whipple (vs PPPD)	123 (54.0%)	537 (47.9%)	0.110
P-J anastomosis (vs P-G)	176 (77.2%)	888 (79.3%)	0.477
Variable	**CR-POPF (n=142)**	**No CR-POPF (n=1206)**	**p-value**
Mean age in years (SD)	65.6 (10.5)	66.0 (9.8)	0.595
Age ≥80 years	11 (7.7%)	71 (5.9%)	0.355
Female sex	45 (31.7%)	542 (44.9%)	**0.003***
Mean BMI in kg/m^2 (SD)	27.1 (4.5)	25.3 (4.3)	**0.0002***
BMI ≥30 kg/m^2	21 (20.1%)	100 (13.8%)	0.070
Preoperative comorbidities			
• Diabetes	23 (16.2%)	254 (21.1%)	0.119
• Cardiovascular	71 (50.0%)	519 (43.0%)	0.128
• Respiratory	21 (14.8%)	121 (10.0%)	0.084
Preoperative biliary stent	95 (66.9%)	780 (64.7%)	0.643
Median preoperative blood tests (IQR)			
• Bilirubin (µmol/L)	19 (54)	21 (42)	0.992
• Albumin (g/L)	37 (11)	38 (10)	0.828
• Neutrophils (x10^9/L)	4.9 (3.1)	4.9 (2.7)	0.831
• Lymphocytes (x10^9/L)	1.9 (1.35)	1.8 (1.35)	0.195

ASA grade >II	51 (37.8%)	301 (27.4%)	**0.0152***
Positive nodes on preoperative CT	35 (27.3%)	289 (27.7%)	1.00
Classic Whipple (vs PPPD)	76 (53.5%)	584 (48.5%)	0.287
P-J anastomosis (vs P-G)	111 (78.7%)	953 (81.5%)	0.425
Variable	**PPH (n=84)**	**No PPH (n=1264)**	**p-value**
Mean age in years (SD)	65.0 (10.0)	66.0 (9.8)	0.330
Age ≥80 years	3 (3.6%)	79 (6.3%)	0.477
Female sex	36 (42.9%)	551 (43.6%)	0.910
Mean BMI in kg/m^2 (SD)	25.5 (3.9)	25.5 (4.4)	0.898
BMI ≥30 kg/m^2	9 (14.5%)	112 (14.7%)	1.00
Preoperative comorbidities			
• Diabetes	11 (13.1%)	266 (21.1%)	0.094
• Cardiovascular	30 (35.7%)	560 (44.3%)	0.140
• Respiratory	6 (7.1%)	136 (10.8%)	0.361
Preoperative biliary stent	48 (57.1%)	827 (65.5%)	0.125
Median preoperative blood tests (IQR)			
• Bilirubin (µmol/L)	33.5 (122.5)	20 (40)	**0.0219***
• Albumin (g/L)	36 (11.5)	38 (10)	0.474
• Neutrophils (x10^9/L)	5.0 (2.7)	4.9 (2.8)	0.707
• Lymphocytes (x10^9/L)	1.8 (1.4)	1.8 (1.1)	0.985
ASA grade >II	35 (44.3%)	317 (27.5%)	**0.002***
Positive nodes on preoperative CT	30 (37.5%)	294 (26.9%)	0.0515
Classic Whipple (vs PPPD)	48 (57.8%)	612 (48.5%)	0.113
P-J anastomosis (vs P-G)	60 (71.4%)	1004 (81.9%)	**0.0211***
Variable	**90-day mortality (n=51)**	**Alive at 90 days (n=1297)**	**p-value**
Mean age in years (SD)	69.0 (10.6)	65.8 (9.8)	**0.0219***
Age ≥80 years	6 (11.8%)	76 (5.9%)	0.122
Female sex	22 (43.1%)	565 (43.6%)	1.00
Mean BMI in kg/m^2 (SD)	25.5 (5.0)	25.5 (4.4)	0.929
BMI ≥30 kg/m^2	6 (11.8%)	115 (14.5%)	0.452
Preoperative comorbidities			
• Diabetes	15 (29.4%)	262 (20.2%)	0.114
• Cardiovascular	26 (51.0%)	564 (43.5%)	0.315
• Respiratory	2 (3.9%)	140 (10.8%)	0.160
Preoperative biliary stent	31 (60.8%)	844 (65.2%)	0.551
Median preoperative blood tests (IQR)			
• Bilirubin (µmol/L)	17 (39)	21 (43)	0.287
• Albumin (g/L)	35 (11)	38 (10)	0.233
• Neutrophils (x10^9/L)	5.1 (3.5)	4.9 (2.7)	0.706
• Lymphocytes (x10^9/L)	1.8 (0.8)	1.8 (1.2)	0.896
ASA grade >II	18 (40.0%)	334 (28.2%)	0.093
Positive nodes on preoperative CT	16 (35.6%)	308 (27.4%)	0.236
Classic Whipple (vs PPPD)	25 (49.0%)	635 (49.1%)	1.00
P-J anastomosis (vs P-G)	43 (89.6%)	1021 (80.9%)	0.185

Table 7.3: Univariable analysis: comparing patients by selected outcomes. Major morbidity includes any Clavien-Dindo grade ≥IIIa complication. *Denotes statistical significance. Statistical methods: Student's *t*-test: age, BMI, Fisher's exact test: sex, comorbidities, preoperative biliary stent, ASA grade, positive nodes on preoperative CT, classic Whipple vs PPPD, P-J vs P-G, Mann Whitney *U* test: blood tests. Where data were missing (Table 7.1), patients were excluded from the relevant sub-analysis.

Variable	Any complication OR (SD)	p-value
Age	1.009 (0.008)	0.261
Female sex (vs male)	0.918 (0.146)	0.589
BMI	1.054 (0.020)	**0.007***
Preoperative diabetes	0.772 (0.157)	0.203
Preoperative cardiovascular disease	1.017 (0.170)	0.918
Preoperative respiratory disease	1.596 (0.449)	0.097
ASA grade >II	2.208 (0.404)	**0.00001***
Positive nodes on preoperative CT	0.835 (0.149)	0.313
Classic Whipple (vs PPPD)	1.589 (0.259)	**0.005***
P-J anastomosis (vs P-G)	0.742 (0.154)	0.150
Variable	**Major morbidity OR (SD)**	**p-value**
Age	0.991 (0.010)	0.385
Female sex (vs male)	1.036 (0.202)	0.856
BMI	1.005 (0.023)	0.826
Preoperative diabetes	0.972 (0.238)	0.907
Preoperative cardiovascular disease	0.839 (0.180)	0.412
Preoperative respiratory disease	0.544 (0.188)	0.079
ASA grade >II	2.159 (0.429)	**0.00001***
Positive nodes on preoperative CT	1.220 (0.269)	0.365
Classic Whipple (vs PPPD)	1.245 (0.258)	0.290
P-J anastomosis (vs P-G)	1.155 (0.280)	0.552
Variable	**CR-POPF OR (SD)**	**p-value**
Age	1.005 (0.013)	0.671
Female sex (vs male)	0.763 (0.181)	0.255
BMI	1.093 (0.028)	**0.001***
Preoperative diabetes	0.611 (0.189)	0.111
Preoperative cardiovascular disease	1.087 (0.274)	0.739
Preoperative respiratory disease	1.269 (0.428)	0.480
ASA grade >II	1.096 (0.273)	0.712
Positive nodes on preoperative CT	1.600 (0.401)	0.061
Classic Whipple (vs PPPD)	0.819 (0.201)	0.414
P-J anastomosis (vs P-G)	1.072 (0.315)	0.813
Variable	**PPH OR (SD)**	**p-value**
Age	0.983 (0.014)	0.224
Female sex (vs male)	1.032 (0.291)	0.911
BMI	1.002 (0.032)	0.954
Preoperative diabetes	0.397 (0.183)	**0.045***
Preoperative cardiovascular disease	0.638 (0.203)	0.158
Preoperative respiratory disease	0.392 (0.242)	0.129
ASA grade >II	2.470 (0.709)	**0.002***
Positive nodes on preoperative CT	2.065 (0.603)	**0.013***
Classic Whipple (vs PPPD)	1.718 (0.511)	0.069
P-J anastomosis (vs P-G)	0.510 (0.155)	**0.027***
Variable	**90-day mortality OR (SD)**	**p-value**
Age	1.029 (0.025)	0.242
Female sex (vs male)	1.436 (0.608)	0.393
BMI	1.007 (0.049)	0.889
Preoperative diabetes	1.307 (0.636)	0.583
Preoperative cardiovascular disease	1.140 (0.519)	0.774
Preoperative respiratory disease	0.317 (0.329)	0.268
ASA grade >II	1.043 (0.470)	0.925
Positive nodes on preoperative CT	1.969 (0.863)	0.122
Classic Whipple (vs PPPD)	1.193 (0.523)	0.687
P-J anastomosis (vs P-G)	2.488 (1.626)	0.163

Table 7.4: Multivariable analysis: comparing patients by selected outcomes. Major morbidity includes any Clavien-Dindo grade ≥IIIa complication. *Denotes statistical significance. Where data were missing (Table 7.1), patients were excluded from the relevant sub-analysis.

7.2. Pancreatoduodenectomy for pancreatic cancer: do serious postoperative complications correlate with lower rates of adjuvant chemotherapy?

Russell TB, Labib PL, Ausania F, et al. The impact of serious postoperative complications on adjuvant treatment following pancreatoduodenectomy for pancreatic cancer: an international multicentre retrospective cohort study. *Eur J Surg Oncol* 2023. DOI: 10.1016/j.ejso.2023.04.018. Reproduced with written permission from Elsevier.

Introduction

Pancreatoduodenectomy followed by AC is recommended in fit patients with a resectable PDAC of the pancreatic head. PD remains the only curative-intent treatment option for this group and AC has been shown to provide a significant survival benefit[65, 379]. Around half of the patients who undergo PD experience at least one postoperative complication[380]. Those who develop no complications, or only minor complications, are likely to make a full and timely recovery. However, patients who develop a serious complication may have a prolonged recovery and some do not recover to their preoperative baseline level of fitness. This can affect their suitability for AC, which might have implications for their OS[381, 382]. This study aimed to investigate the impact of serious PD complications on AC rates, disease recurrence and OS. This information will guide patient selection and the consenting process, and could have a role in identifying patients that might benefit from NAT.

Method

See **Chapter 4** for a full description of the methods used. See **Supplementary Material** for a full list of the definitions used. AC was defined as any chemotherapy received postoperatively within 120 days of PD which was intended to treat PDAC, where recurrent disease/metastases had not been diagnosed/were not suspected. After

patients who died within 90-days of PD were excluded (from all analyses), the Kaplan-Meier method was used to compare survival between those who commenced AC and those who did not, those who completed AC and those who did not (including those who did not commence AC), and those who developed a serious (CD grade ≥IIIa) complication and those who did not. If patients did not have data available on their postoperative complications (if any), they were excluded from the latter only (**Table 7.5**). P-values were obtained using the log-rank test. Univariable tests were then performed to compare these groups. Means were compared using Student's *t*-test and distributions were compared using the Mann Whitney *U* test. Testing for independence between two variables was carried out using Fisher's exact test. Following the univariable tests, the Holm and Hochberg step methods were used to adjust for error from multiple testing.

Results

A total of 3705 records were screened by the collaborating centres and 2212 were excluded as they did not meet the inclusion criteria, leaving 1493 records. A further 685 cases were excluded by the lead centre. This included 599 patients who did not have histologically-confirmed PDAC, nine records which were incomplete, 38 patients who died within 90-days of PD, and 39 patients who did not have AC data available (if any). Therefore, the final analysis included 808 patients. The mean patient age was 66.6 years (SD: 9.4), 47% were female and the mean BMI was 25.4 kg/m^2 (SD: 4.6). A total of 64.7% had received a preoperative biliary stent and 5.7% had received NAT (**Table 7.5**). The vast majority of patients (94%) were ASA grade I-II and 47% underwent a classic Whipple procedure, with the remainder undergoing a pylorus-preserving PD. The median length of stay was thirteen days (IQR: 9) and 11% of the patients had an unplanned readmission within 30 days of discharge. CR-POPF, PPH and DGE affected 6%, 5% and 13% of patients, respectively. Concerning major morbidity, 12% of patients experienced a serious complication (CD grade ≥IIIa). Five-year recurrence (actual) was 69% and five-year survival (actual) was 24%.

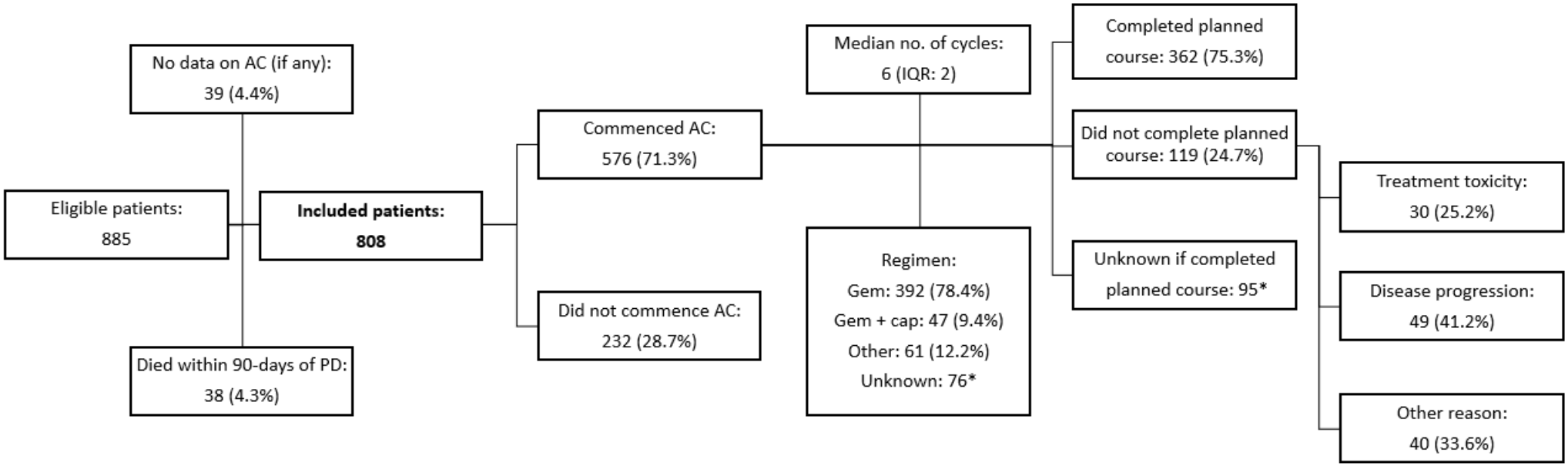


Figure 7.2: AC flow diagram. Cap = capecitabine, Gem = gemcitabine. *Excluded from percentages.

Mean age in years (SD)	66.6 (9.4)
Female sex	383 (47.4%)
Mean BMI in kg/m^2 (SD)	25.4 (4.6) Unknown: 268 (33.2%)
Preoperative diabetes	176 (27.8%) Unknown: 87*
Preoperative cardiovascular comorbidity	320 (39.7%) Unknown: 1
Preoperative respiratory comorbidity	83 (10.3%)
Median tumour size on pre-op CT in mm (IQR)	26 (13) Unable to assess/unknown: 324 (40.1%)
Radiological T stage	T1: 148 (21.0%) T2: 239 (33.9%) T3: 187 (26.5%) T4: 22 (3.1%) TX: 110 (27.1%) Unknown: 102*
Radiological N stage	N0: 439 (61.9%) N1: 205 (28.9%) NX: 65 (9.2%) Unknown: 99*
Preoperative biliary stent	522 (64.7%) Unknown: 1
Neoadjuvant chemotherapy received	46 (5.7%)
Median preoperative serum bilirubin in µmol/L (IQR)	21 (48) Unknown: 1 (0.1%)
Median preoperative serum albumin in g/L (IQR)	38 (IQR: 10) Unknown: 141 (17.5%)
Median preoperative serum neutrophils in $x10^9/L$ (IQR)	4.7 (2.9) Unknown: 99 (12.3%)
Median preoperative serum lymphocytes in $x10^9/L$ (IQR)	1.7 (1.3) Unknown: 99 (12.3%)
ASA grade I-II	536 (94.1%) Unknown: 48*
Surgical approach	Classic Whipple: 375 (46.5%) PPPD: 432 (53.5%) Unknown: 1*
Pancreatic anastomosis	P-J: 655 (82.9%) P-G: 135 (17.1%) Not performed/unknown: 18*
Concomitant venous resection	165 (22.9%) Unknown: 86*
Concomitant arterial resection	19 (2.6%) Unknown: 86*
Median length of stay in days (IQR)	13 (9) Unknown: 20 (2.5%)
30-day readmission	76 (10.6%) Unknown: 88*
CR-POPF**	41 (5.7%)
Post-pancreatectomy haemorrhage**	39 (5.4%)
Delayed gastric emptying**	93 (12.9%)
Any Clavien-Dindo grade ≥IIIa complication**	88 (12.2%)
Median tumour size on histology in mm (IQR)	30 (13) Unknown: 81 (10.0%)
Histological T stage	T1: 51 (6.3%) T2: 81 (10.0%) T3: 648 (80.5%)

	T4: 21 (2.6%) TX: 4 (0.5%) Unknown: 3*
Histological N stage	N0: 188 (23.4%) N1: 615 (76.2%) NX: 4 (0.5%) Unknown: 1*
Resection margin status	R0: 368 (48.1%) R1: 374 (48.9%) R2: 23 (3.0%) Unknown: 43*
Median number of positive nodes (IQR)	2 (4) Unknown: 27 (3.3%)
Median number of resected nodes (IQR)	17 (10.5) Unknown: 27 (3.3%)
Commenced adjuvant chemotherapy	576 (71.3%)
Completed planned adjuvant chemotherapy course	362 (44.8%)
Five-year recurrence (actual)	560 (69.3%) Of these, 226 (40.4%) received palliative chemotherapy
Five-year survival (actual)	193 (23.9%)

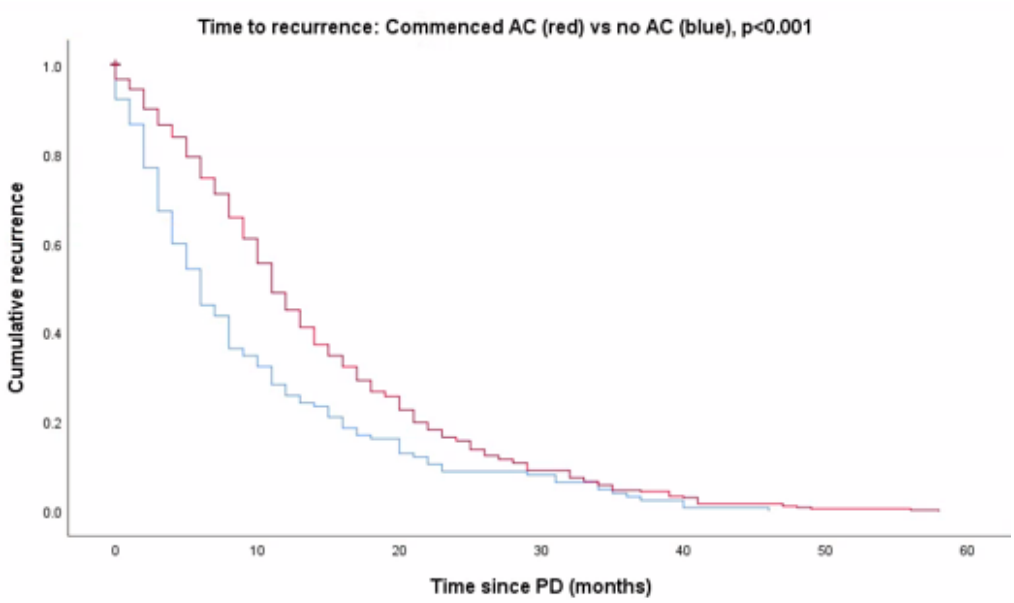
Table 7.5: Key information on the included patients. *Not included in percentages. **Data on postoperative complications unknown/not recorded in 88 cases (excluded from relevant sub-analyses).

In total, 71% of patients commenced AC; the median number of cycles was six (IQR: 2) and the majority of patients (78%) received gemcitabine only (**Figure 7.2**). Of those who commenced AC, 63% completed the planned course. The median time to administration (TTA) of the first AC dose was 69 days (IQR: 35). Those who completed the planned course had a shorter median TTA (66 days, IQR: 32) than those who did not (77 days, IQR: 30, p=0.006). Among those who received AC, patients who developed a serious postoperative complication had a longer median TTA of the first AC dose (73 days, IQR: 49) than those who did not (69 days, IQR: 34) but this difference was not significant (p=0.4).

Among the patients that died within five years of PD, the median OS was 19 months. Among those who developed recurrence within five years, the median time to recurrence was 11 months. Patients who commenced AC had longer disease-free survival (DFS, MD: 6 months, p=0.001) and OS (MD: 7 months, p<0.0001) than those who did not (**Figure 7.3**). The same pattern was observed when patients who completed AC were

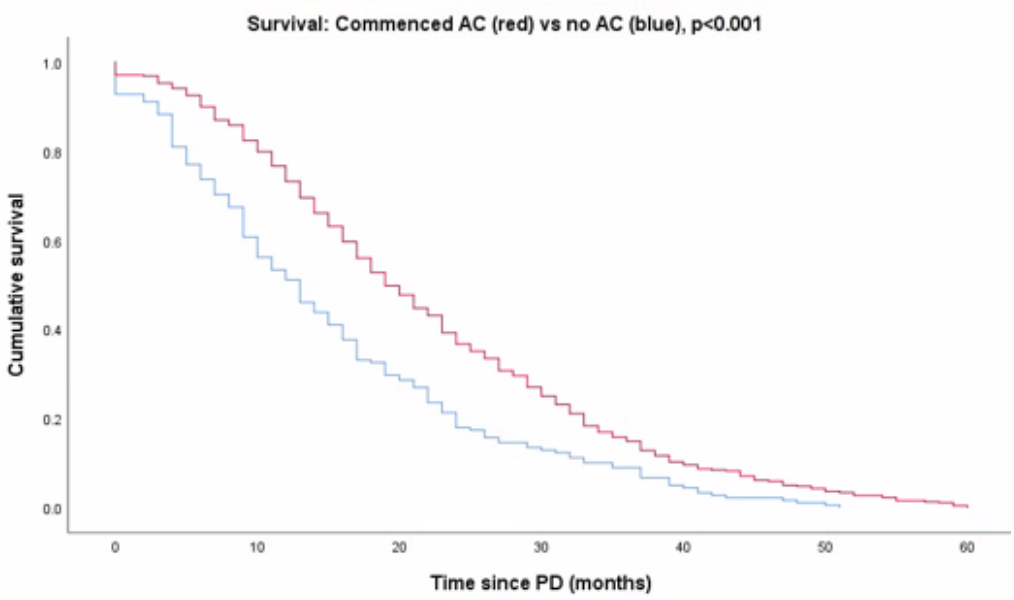
compared to those who did not. Patients who experienced a serious postoperative complication had similar DFS (MD: 1 month, p=0.5) and OS (MD: 2 months, p=0.3) to those who did not. The univariable tests (**Table 7.6**) demonstrated that the patients who commenced AC were younger (MD: 3 years, p=0.0002) and more often ASA grade I-II (74% vs 63%, p=0.004). In addition, these patients had less often experienced PPH (4% vs 9%, p=0.02), a serious complication (10% vs 18%, p=0.002), or readmission (9% vs 14%, p=0.04). Those who completed AC were younger (MD: 2 years, p=0.0009), less often had positive nodes on preoperative imaging (33% vs 42%, p=0.01) and were more often ASA grade I-II (76% vs 66%, p=0.003). In addition, CR-POPF (4% vs 8%, p=0.047) and an unplanned readmission (8% vs 14%, p=0.03) were less common in this group.

The patients who experienced a serious complication were less often ASA I-II (52% vs 73%, p=0.0004), and more frequently experienced readmission (24% vs 9%, p<0.0001). Those who experienced a serious complication commenced AC less frequently (58% vs 74%, p=0.002). Following the application of the Holm and Hochberg step methods (**Table 7.7**), only younger age was a significant association of commencing (MD: 3 years) and completing (MD: 2 years) AC. Serious complications correlated with readmission (OR: 3.3). Patients who experienced a serious postoperative complication were less often ASA I-II (OR: 0.4) and commenced AC less frequently (OR: 0.5).



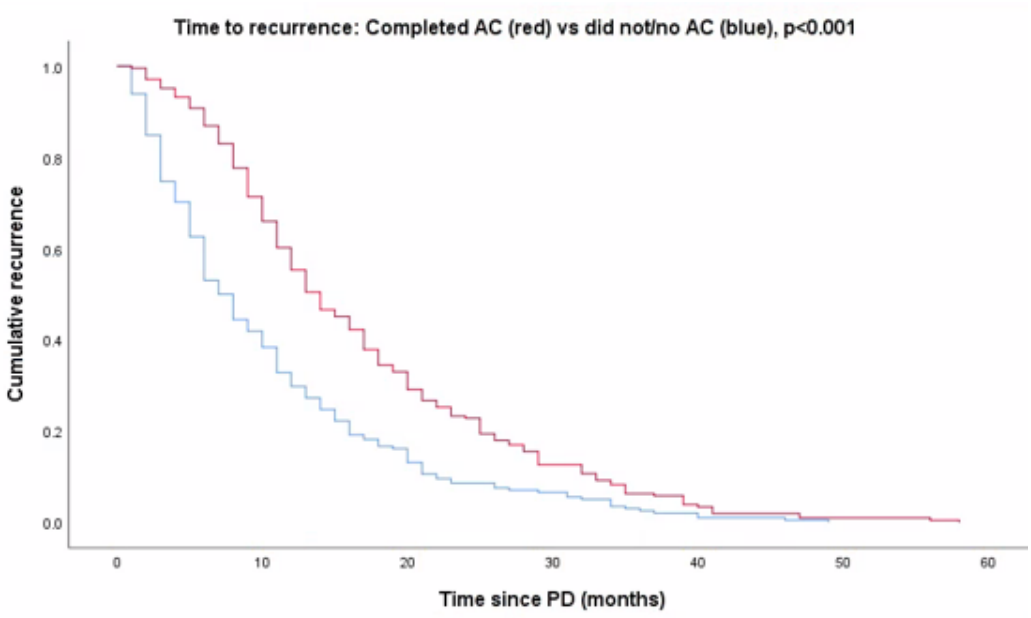
A

Number at risk							
AC	436	359	217	118	45	19	2
No AC	178	108	53	24	9	2	
Time (months)	0	10	20	30	40	50	60



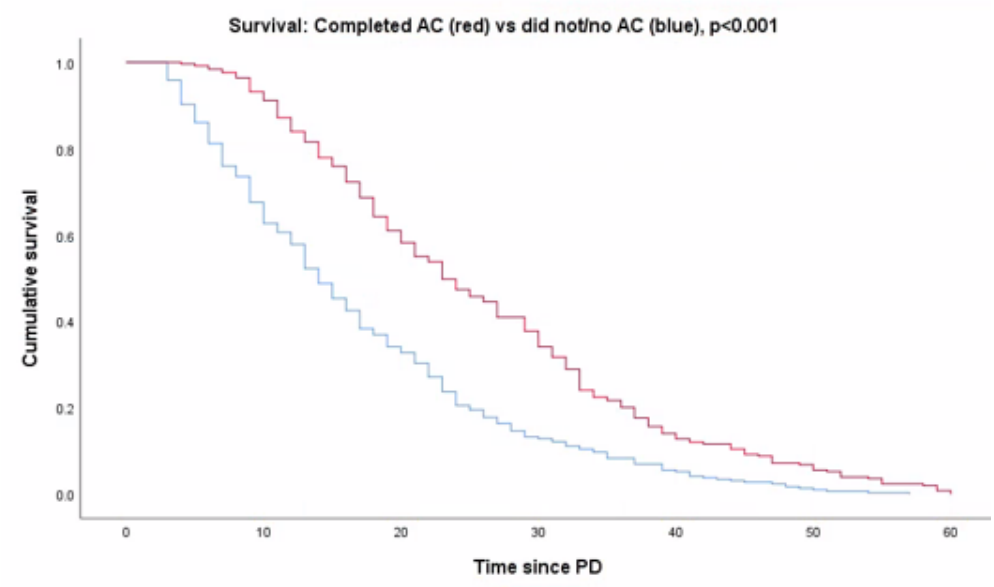
B

Number at risk							
AC	367	221	93	33	12	2	
No AC	130	43	20	10	3		
Time (months)	0	10	20	30	40	50	60



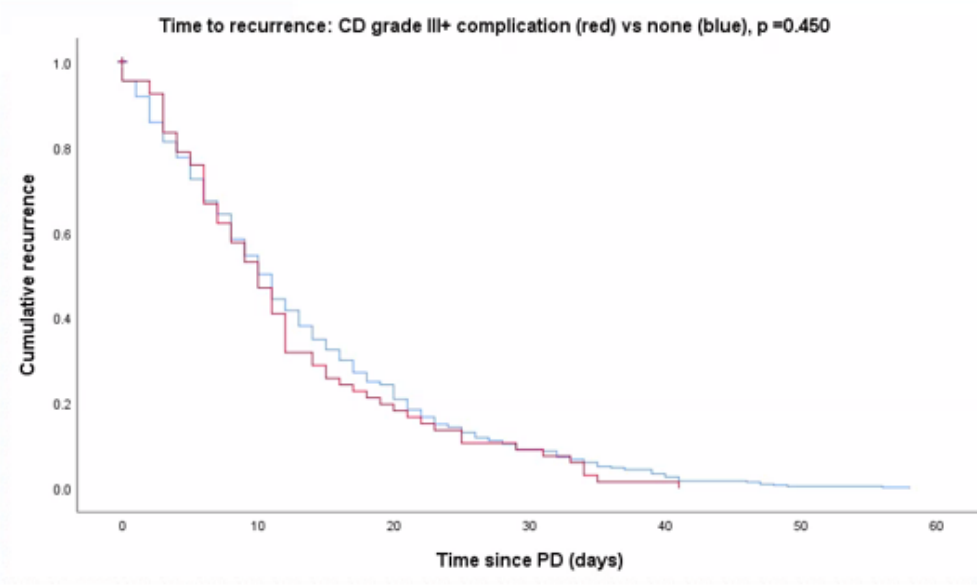
C

Number at risk							
Comp AC	206	147	68	26	8	2	
Did not/no AC	198	83	32	13	4		
Time (months)	0	10	20	30	40	50	60



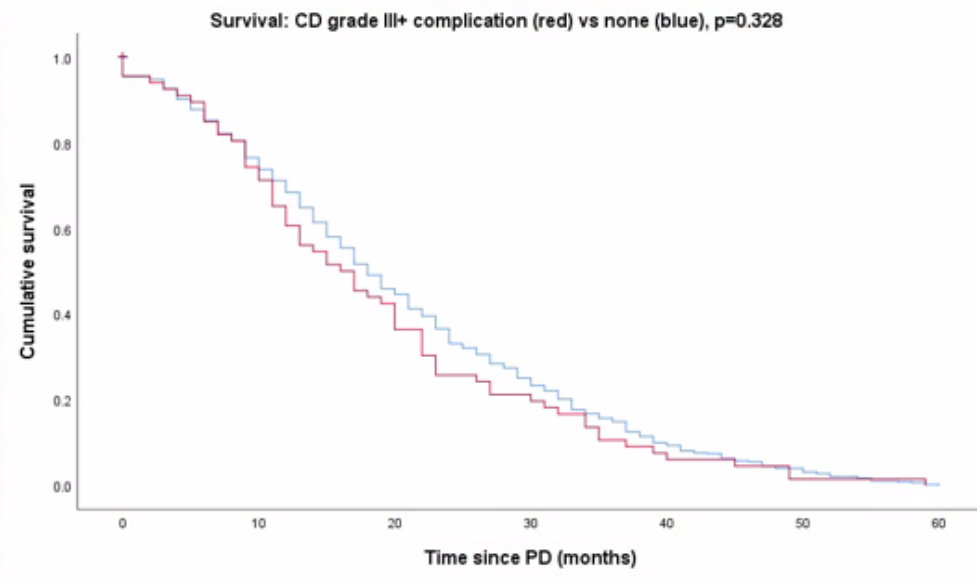
D

Number at risk							
Comp AC	249	232	152	94	35	17	2
Did not/no AC	287	194	98	38	16	4	
Time (months)	0	10	20	30	40	50	60



E

Number at risk							
CD III+ comp	67	35	13	6	1		
None	423	225	100	37	14	2	
Time (months)	0	10	20	30	40	50	60



F

Number at risk							
CD III+ comp	67	49	28	14	5	1	
None	478	360	216	118	47	19	1
Time (months)	0	10	20	30	40	50	60

Figure 7.3: Kaplan-Meier curves: commenced AC vs did not: time to recurrence (A) and time to death (B), completed AC vs did not/no AC: time to recurrence (C) and time to death (D), experienced major morbidity vs did not: time to recurrence (E) and time to death (F). Patients who did not experience recurrence/death were excluded from the relevant sub-analyses.

Variable	Commenced AC (n=576)	Did not commence AC (n=232)	p-value
Mean age in years (SD)	65.8 (9.5)	68.5 (8.9)	**0.0002***
Female sex	266 (46.2%)	117 (50.4%)	0.274
Mean BMI in kg/m^2 (SD)	25.6 (4.5)	24.8 (4.6)	0.078
Preoperative diabetes	129 (25.0%)	47 (23.0%)	0.590
Preoperative cardiovascular comorbidity	221 (38.4%)	99 (42.9%)	0.239
Preoperative respiratory comorbidity	58 (11.2%)	25 (10.8%)	0.765
Median tumour size on pre-op CT in mm (IQR)	27 (13.5)	25 (13)	0.595
Radiological T stage I-II	284 (56.0%)	103 (51.8%)	0.307
No regional lymph nodes on preoperative CT	326 (69.5%)	113 (64.6%)	0.231
Preoperative biliary stent	384 (66.8%)	138 (59.7%)	0.058
Median pre-op serum bilirubin in µmol/L (IQR)	22 (51)	20 (39)	0.592
Median pre-op serum albumin in g/L (IQR)	37 (9)	39 (11)	0.119
Median pre-op serum neutrophils in x10^9/L (IQR)	4.7 (2.9)	4.9 (2.7)	0.513
Median pre-op serum lymphocytes in x10^9/L (IQR)	1.8 (1.3)	1.6 (1.4)	0.092
ASA grade I-II	400 (73.5%)	136 (63.0%)	**0.004***
Classic Whipple (vs PPPD)	262 (45.5%)	113 (48.9%)	0.406
P-J anastomosis (vs P-G)	479 (84.5%)	176 (78.9%)	0.062
Concomitant venous resection	123 (23.7%)	42 (20.8%)	0.676
Concomitant arterial resection	10 (1.9%)	10 (5.0%)	**0.040***
CR-POPF**	25 (4.8%)	16 (7.9%)	0.158
Post-pancreatectomy haemorrhage**	21 (4.1%)	18 (8.9%)	**0.016***
Delayed gastric emptying**	63 (12.2%)	30 (14.9%)	0.326
Any Clavien-Dindo grade ≥IIIa complication	51 (9.8%)	37 (18.3%)	**0.002***
Median length of stay in days (IQR)	13 (9)	14 (10)	0.092
30-day readmission	47 (9.1%)	29 (14.4%)	**0.043***
Five-year recurrence	416 (72.2%)	144 (62.1%)	**0.005***
Five-year survival	139 (24.1%)	54 (23.3%)	0.796
Variable	**Completed AC (n=362)**	**Did not complete AC or no AC (n=380)**	**p-value**
Mean age in years (SD)	65.5 (9.2)	67.7 (9.3)	**0.0009***
Female sex	179 (49.4%)	178 (46.8%)	0.478
Mean BMI in kg/m^2 (SD)	25.6 (4.4)	25.1 (4.7)	0.246
Preoperative diabetes	81 (24.7%)	82 (24.4%)	0.931
Preoperative cardiovascular comorbidity	133 (36.7%)	163 (43.0%)	0.082
Preoperative respiratory comorbidity	36 (9.9%)	40 (10.5%)	0.794
Median tumour size on pre-op CT in mm (IQR)	26 (12)	26 (13)	0.939
Radiological T stage I-II	188 (58.6%)	169 (51.2%)	0.059
No regional lymph nodes on preoperative CT	218 (67.5%)	191 (57.7%)	**0.010***
Preoperative biliary stent	232 (64.2%)	242 (63.9%)	0.907
Median pre-op serum bilirubin in µmol/L (IQR)	24 (50)	22 (50)	0.468
Median pre-op serum albumin in g/L (IQR)	37 (10)	38 (10)	0.245
Median pre-op serum neutrophils in x10^9/L (IQR)	4.6 (2.8)	4.9 (3.0)	0.182
Median pre-op serum lymphocytes in x10^9/L (IQR)	1.6 (1.2)	1.8 (1.5)	0.467
ASA grade I-II	260 (75.8%)	234 (65.5%)	**0.003***
Classic Whipple (vs PPPD)	177 (48.9%)	180 (47.5%)	0.703
P-J anastomosis (vs P-G)	296 (82.7%)	304 (82.4%)	0.916
Concomitant venous resection	72 (21.8%)	81 (24.3%)	0.444
Concomitant arterial resection	6 (1.8%)	13 (3.9%)	0.161
CR-POPF**	13 (4.0%)	26 (7.8%)	**0.047***
Post-pancreatectomy haemorrhage**	13 (4.0%)	24 (7.2%)	0.090
Delayed gastric emptying**	47 (14.3%)	44 (13.2%)	0.666
Any Clavien-Dindo grade ≥IIIa complication	34 (10.4%)	51 (15.3%)	0.079
Median length of stay in days (IQR)	13 (10)	13 (10)	0.973
30-day readmission	27 (8.2%)	46 (13.7%)	**0.026***

Median time to first AC dose in days (IQR)	66 (32)	77 (30)	**0.006***
Five-year recurrence	256 (70.7%)	260 (68.4%)	0.497
Five-year survival	107 (29.6%)	71 (18.7%)	**0.0005***
Variable	**CD ≥IIIa comp. (n=88)**	**No CD ≥IIIa comp. (n=632)**	**p-value**
Mean age in years (SD)	65.8 (9.6)	66.5 (9.5)	0.518
Female sex	42 (47.4%)	294 (46.5%)	0.831
Mean BMI in kg/m^2 (SD)	25.5 (4.0)	25.3 (4.5)	0.737
Preoperative diabetes	17 (19.3%)	159 (25.2%)	0.289
Preoperative cardiovascular comorbidity	33 (37.5%)	287 (45.4%)	0.171
Preoperative respiratory comorbidity	7 (8.0%)	76 (12.0%)	0.372
Median tumour size on pre-op CT in mm (IQR)	24.5 (17)	27 (12.5)	0.274
Radiological T stage I-II	51 (89.5%)	336 (54.3%)	0.446
No regional lymph nodes on preoperative CT	57 (65.5%)	382 (61.4%)	0.460
Preoperative biliary stent	51 (58.0%)	398 (63.0%)	0.343
Median pre-op serum bilirubin in µmol/L (IQR)	23.5 (73)	22 (48)	0.402
Median pre-op serum albumin in g/L (IQR)	36 (11.5)	38 (10)	0.547
Median pre-op serum neutrophils in x10^9/L (IQR)	4.5 (2.6)	4.8 (2.9)	0.183
Median pre-op serum lymphocytes in x10^9/L (IQR)	1.8 (1.6)	1.7 (1.2)	0.804
ASA grade I-II	43 (52.4%)	434 (73.4%)	**0.0004***
Classic Whipple (vs PPPD)	48 (54.5%)	327 (51.8%)	0.632
P-J anastomosis (vs P-G)	65 (75.6%)	502 (81.5%)	0.193
Concomitant venous resection	23 (26.4%)	142 (22.9%)	0.471
Concomitant arterial resection	4 (4.6%)	16 (2.6%)	0.295
Median length of stay in days (IQR)	14 (12)	12 (9)	0.611
30-day readmission	21 (23.9%)	55 (8.7%)	**0.0001***
Commenced AC	51 (58.0%)	467 (73.9%)	**0.002***
Completed AC	34 (40%)	294 (50.9%)	0.061
Median time to first AC dose in days (IQR)	73 (49)	69 (34)	0.359
Five-year recurrence	69 (78.4%)	437 (69.1%)	0.075
Five-year survival	22 (25.0%)	160 (25.3%)	1.00

Table 7.6: Comparing patients who commenced AC to those who did not, those who completed AC to those who did not, and those who developed a CD grade >IIIa complication to those who did not. Patients who died within 90-days of PD were excluded from all analyses. *Denotes statistical significance. **Data on postoperative complications unknown/not recorded in 88 cases (excluded from the relevant sub-analyses). Statistical methods: means were compared using Student's *t*-test and distributions were compared using the Mann Whitney *U* test. Fisher's exact test was used to compare proportions of binary outcomes and independence of nominal data.

Discussion

In our multicentre study of PD patients with histologically-confirmed PDAC, those who commenced AC had improved DFS and OS compared to those who did not. Patients who commenced AC were younger, were more likely to be ASA grade I-II and had less often experienced a serious postoperative complication. Whilst serious complications correlated inversely with commencing AC, a serious complication alone did not significantly affect DFS or OS (when patients who died within 90 days of PD were

excluded). Our study is comparable to that of Wu et al. (n=1144) who studied PD outcomes at a single Chinese institution (PDAC only). The median age was 68 years (vs mean: 67 years in our study), 48% of patients were female (vs 47%), and 19% developed a complication which was CD grade ≥IIIa (vs 12%)[383]. Overall, 54% of patients received AC (vs 71%) and the median TTA was 60 days (vs 69 days)[383]. In the Chinese study, age >68 years (p<0.001) and length of stay >9 days (p=0.002) both correlated with not receiving AC[383]. Whilst the presence of any complication correlated with not receiving AC, this effect did not increase with increasing complication grade[383]. Unlike in our study, those who experienced a complication had reduced survival compared to those who did not (16 vs 20 months, p=0.001)[383]. The authors found that patients who did not experience a complication and received AC survived longer than those who experienced a complication and received no AC (23 vs 11 months, p<0.001)[383]. Both complications (HR: 1.2, p=0.02) and AC (HR: 0.7, p<0.001) were independently related to survival[383]. The authors concluded that both complications and a lack of AC are common following PD for PDAC, and that patients who experience a serious complication have increased TTA of the first AC dose, and are less likely to receive multimodal treatment.

Our study can also be compared to that of Mackay et al. (n=1306) which used Dutch national data. In the overall cohort, the median age was 67 years, 45% of patients were female and 24% developed a complication which was CD grade ≥IIIa[384]. A total of 67% received AC and the median TTA was 48 days[384]. Among other factors, major complications were shown to be an independent predictor of not receiving AC (OR: 0.4, p<0.001)[384]. Unlike in the Chinese study, patients with major complications received AC less frequently (52% vs 27%, p<0.001) and the median TTA was also longer in this group (56 vs 47 days, p<0.001)[384]. The authors concluded that serious complications were the most important factor in patients not receiving AC.

In a smaller Norwegian study which also included patients who had undergone distal pancreatectomy (median age: 67 years, 47% females), Labori et al. (n=203) found that 20% of patients experienced a serious postoperative complication[380]. A total of 62%

commenced AC and 33% of these did not complete the planned course[380]. The primary reasons for not initiating AC were recurrent disease (35%), postoperative complications/poor performance status (32%) and advanced age (25%)[380]. OS was significantly longer in those who completed AC (25 vs 12 months, p<0.001). Patients who experienced serious complications (CD grade ≥IIIa) were less likely to commence AC (p<0.001), less likely to complete AC (p=0.007) and had reduced OS (11 months vs 19 months, p=0.03)[380]. The authors argued that strategies are required to improve patient selection and reduce surgical morbidity as early recurrence, major postoperative complications and poor postoperative performance status together result in more than a third of patients not completing their planned adjuvant treatment[380].

Commenced AC vs did not	
Age	Mean difference: 2.7 years
Completed AC vs did not (or did not commence AC)	
Age	Mean difference: 2.2 years
Major complication (Clavien-Dindo grade ≥IIIa) vs none	
30-day readmission	OR: 3.3 (95% CI: 1.9-5.8)
American Society of Anesthesiologists grade I-II	OR: 0.4 (95% CI: 0.2-0.6)
Commenced adjuvant chemotherapy	OR: 0.5 (95% CI: 0.3-0.8)

Table 7.7: Adjusting for multiple testing: the Holm and Hochberg step methods. CI = confidence interval, OR = odds ratio.

Postoperative AC has been offered to fit PD patients with PDAC since the 1990s[64]. The findings of studies such as the European Study Group of Pancreatic Cancer (ESPAC) studies have confirmed that AC can provide a significant survival benefit so this is now the standard of care[65]. Our study would support the benefits of AC with time to recurrence and time to death being significantly longer in those who commenced AC (**Figure 7.3**). Time to recurrence and time to death were also significantly longer in those who completed AC. Whilst DFS and OS were longer in those who did not experience a serious complication, these differences were not significant (patients who died within 90

days of PD were excluded). A recent RCT showed that combination AC could increase median OS to 54.4 months in selected patients[385]. Other studies[65] have also shown that AC correlates with increased five-year survival, but our data did not suggest this. This may be due to the relatively small number of patients that achieved five-year survival and the fact that patients who died within 90 days of PD were excluded.

Our results suggest patients are less likely to receive AC if they are older, are ASA grade ≥III, or if they experience a serious postoperative complication. It may be that some patients who experienced a serious complication had a prolonged recovery as a result. Some of these patients might not have returned to their preoperative baseline level of fitness, or a level of fitness which is required to undergo AC. Further, they may have developed early disease recurrence during their prolonged recovery and missed their window of opportunity to commence AC. However, we acknowledge that some patients diagnosed with early recurrence will likely have had radiographically occult or persistent disease. Postoperative complications (of any grade) did not affect whether patients completed AC or not. This is likely as, whilst a prolonged recovery might affect commencing AC, it is unlikely to result in treatment being terminated. The optimal timing for AC is debated and some authors argue that it is the completion of AC which is more important[353]. However, Sung et al. (n=7548) found patients who started AC before 60 days post-PD had the greatest survival advantage[354].

In our study, patients who experienced a serious postoperative complication less often commenced AC. They also completed AC less often, but this difference was not significant, possibly due to the low number of patients in this group. Currently, there are no models which can accurately predict which PD patients are likely to develop serious complications. This information would be useful as those who are high-risk may benefit from NAT. These patients would then complete a course of systemic therapy and undergo repeat imaging. Those with a good response would likely have a chemosensitive tumour and be appropriate surgical candidates. Those who do not have a good response, or those who develop metastases, may not have been appropriate

candidates[355]. These patients would arguably have a better quality of life if they received palliative chemotherapy rather than an aggressive surgical resection[159]. This is particularly relevant in older patients, those with positive nodes on preoperative imaging and those who are not ASA grade I-II. Whilst neoadjuvant therapy is often given to patients with resectable disease in the USA[386], guidelines from many other countries do not advise this[343]. Future research which focusses on developing predictive models could be very helpful for patient selection. The limitations of this study have been outlined in **Chapter 9**.

Conclusion

In our multicentre study of patients who underwent PD for PDAC, both commencing and completing AC correlated with a significant survival advantage. Patients who commenced AC had less often experienced a serious postoperative complication. Although a serious complication alone did not affect OS (patients who died within 90 days of PD were excluded), patients in this group were less likely to commence AC. The preoperative identification of patients who are high-risk for a serious complication may have implications for management planning. Selected older patients who are not ASA grade I-II might benefit from NAT. Future studies should investigate this.

Chapter 8: Results - RAW Study: patterns of recurrence after pancreatoduodenectomy for ampullary adenocarcinoma

Russell TB, Labib PL, Denson J, et al. Predictors of actual five-year recurrence and survival after pancreatoduodenectomy for ampullary adenocarcinoma: an international multicentre cohort study. *HPB (Oxford)* 2023. DOI: 10.1016/j.hpb.2023.03.010. Reproduced with written permission from John Wiley & Sons, Inc.

Introduction

Ampullary adenocarcinomas are uncommon; they account for less than ten per cent of all periampullary malignancies[80]. Overall age-adjusted incidence is 0.59 per 100,000 per year and the median age at diagnosis is around seventy years[83]. In the absence of distant metastases, PD is recommended in fit patients with resectable disease. Although morbidity rates are high and the risk of perioperative mortality is significant, PD remains the only curative-intent treatment option. After resection, up to half of all patients develop recurrent disease[387, 388] and five-year survival is in the region of 40%[389].

Many of the recent studies that have reported on the long-term outcomes of PD in patients with AA have included less than 100 cases and are therefore underpowered for detailed prognostic analyses[390, 391]. There is also a lack of data on predictors of recurrence and possible sites of recurrence after PD for AA. Therefore, we conducted a retrospective multicentre cohort study which included the five-year outcomes of almost 400 patients. The study aimed to identify predictors of five-year recurrence/survival and reduced time to recurrence/death.

Method

See **Chapter 4** for a full description of the methods used. See **Supplementary Material** for a full list of the definitions used. For this study, we only included patients with AA. Patients who developed recurrent disease within five-years were compared to those who did not. Means were compared using Student's *t*-test and distributions were compared using the Mann Whitney *U* test. When testing for independence between two variables with multiple, mutually exclusive levels or categories, Fisher's exact test was used. See table legends for specific details. Cases were excluded from the relevant sub-analysis if data were unavailable. The group that achieved five-year survival was compared to the group that did not, and the group that developed local recurrence was compared to the group that developed distant (+/- local) recurrence, using the same methods. Following the univariable tests, the Holm and Hochberg step methods were used to adjust for error from multiple testing. Kaplan-Meier curves were plotted to compare times to recurrence (excluding patients who did not develop recurrence within five years of PD) and times to death (excluding those who achieved five-year survival). P-values were obtained using the log-rank method.

Results

In total, 3705 records were screened for eligibility (entire RAW study) by the collaborating centres and 2212 were excluded as they did not meet the inclusion criteria. A further 1090 patients with PDAC or CC were excluded. Therefore, 394 patients with confirmed AA were included in the final analysis. The mean patient age was 64.8 years (SD: 10.6 years), 43% were female and 71% were ASA grade I-II. Preoperative treatment and operative details can be found in **Table 8.1**.

Perioperative outcomes

In total, 24% of patients developed a POPF. Of these, 51% were biochemical leaks. Fifteen patients (4%) experienced a PPH and 6% had an unplanned return to theatre. Of those who returned to theatre, three patients underwent a completion pancreatectomy +/- splenectomy and a further three patients required reoperation to control haemorrhage (+/- revision of the pancreatic anastomosis). Two patients required a gastroscopy, one underwent a bowel resection, one underwent drainage of an intra-abdominal collection, and one underwent omentectomy. Seven patients underwent re-laparotomy where no further details were provided. The reason for the return to theatre was not provided in three patient records.

The median length of stay was fourteen days (IQR: 10-23 days) and 9% of the patients had an unplanned readmission within 30 days of discharge. Six patients returned with an abdominal infection/collection, four presented with sepsis with no obvious source, three had a leaking drain site/wound, three had vomiting, two had bowel obstruction/ileus, two had an intestinal fistula, two had venous thrombosis, and two had an anastomotic leak. One patient represented with each of the following: abdominal pain, bleeding, chyle leak, gastro-jejunostomy stricture, SSI, fever, constipation and chest infection. The reason for readmission was unrecorded in two patients. Twelve patients (3%) died within 90 days of PD. Four died with intra-abdominal sepsis, three died as a result of haemorrhage, two had multiorgan failure and one had chest sepsis. The cause of death was not provided in two patients.

Postoperative histology

Most of the patients had a moderately differentiated (52%) or poorly differentiated (23%) tumour, and the median tumour size was 21 mm (IQR: 15-30 mm). Concerning histological staging, 33%, 33% and 22% of patients were T stages I, II and III, respectively, and 39%, 61% and 0.3% were N stages 0, I and II, respectively. In total,

81% of the patients had an R0 resection and 19% had an R1 resection. The most commonly involved resection margin was the superior mesenteric artery/posterior margin (59%) and 24% of those with at least one involved margin had multiple positive margins.

Adjuvant therapy

In total, 59% of patients commenced AC, the majority of whom (54%) received gemcitabine only. The median time from PD to the first AC dose was 71 days (IQR: 58-90 days) and the median number of cycles was six (IQR: 5-6). Of those who commenced AC, 76% completed the planned course (39% of the total). Adjuvant radiotherapy was received by 2% of patients, all of which completed the planned course.

Recurrence

Actual five-year recurrence was 45% and the median time to recurrence was 14 months (IQR: 7-21 months). Of those with recurrent disease, 20% had local only recurrence, 23% had local and distant recurrence, and 55% had distant only recurrence. In those with recurrence, the most common sites were the liver (32%), locoregional lymph nodes (14%), lung/pleura/mediastinum (13%), distant lymph nodes (7%), omentum/peritoneum (6%), the superior mesenteric artery area (6%) and the superior mesenteric vein area (6%). Patients who commenced AC experienced recurrence more often than those who did not (55% vs 30%, $p<0.0001$). Of those who developed recurrence, 57% commenced palliative chemotherapy. The median number of cycles was six (IQR: 3-6) and 41% completed the planned course. Palliative radiotherapy was received by sixteen patients, all of whom completed the planned course.

When the group who developed recurrence was compared to the group that did not, the following were found to correlate with recurrence after univariable tests: ASA grade I-II (87% vs 72%, $p=0.0008$), higher preoperative serum bilirubin (MD: 7.5 µmol/L,

p=0.003), larger histological tumour size (MD: 5 mm, p<0.0001), poorly differentiated tumour (28% vs 18%, p=0.04), ≥1 positive resection margin (27% vs 13%, p=0.001), higher number of positive resected nodes (MD: 2, p<0.0001), peripancreatic fat invasion (PPFI, 51% vs 27%, p=0.0003), perineural invasion (PNI, 59% vs 28%, p=0.0001), microvascular invasion (MVI, 59% vs 33%, p<0.0001) and lymphatic invasion (LI, 73% vs 48%, p<0.0001) (**Table 8.2**). The patients who developed recurrence were also more likely to have commenced AC (72% vs 48%, p<0.0001) but, if AC was initiated, this group were less likely to have completed the planned course (68% vs 89%, p=0.01). Actual five-year survival was 21% in those with recurrence and 80% in those without (p<0.0001). With the exception of serum bilirubin and poor tumour differentiation, all of these were significant following multivariable testing (**Table 8.3**).

When the group that developed local only recurrence was compared to the group that developed distant (+/- local) recurrence, no significant differences were observed in terms of age, sex, BMI, comorbidities, ASA grade, preoperative imaging, preoperative blood tests, postoperative complications, histology or adjuvant treatment.

Five-year survival

The actual five-year survival rate was 54%. When the group that achieved five-year survival was compared to the group that did not, the following correlated with survival after the univariable tests: younger age (MD: 2.5 years, p=0.02), lower preoperative bilirubin (MD: 6.5 µmol/L, p=0.007), lower preoperative neutrophils (MD: 0.4 x 10^9/L, p=0.003), smaller histological tumour size (MD: 3 mm, p=0.03), histological T stage I-II (58% vs 31%, p<0.0001), and completion of AC in those that received a first dose (87% vs 64%, p=0.0002). The following correlated inversely: preoperative respiratory disease (11% vs 5%, p=0.02), poorly differentiated tumour (28% vs 18%, p=0.02), ≥1 positive resection margin (29% vs 11%, p<0.0001), number of positive resected nodes (MD: 2, p<0.0001), PPFI (54% vs 22%, p<0.0001), PNI (59% vs 35%, p<0.0001), MVI (55% vs

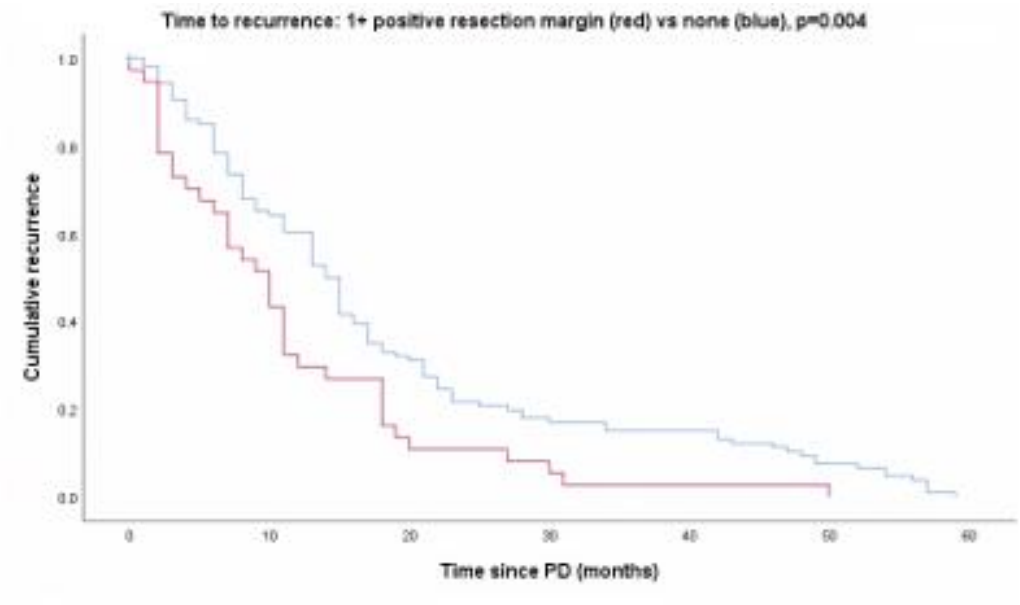
37%, p=0.002), LI (69% vs 49%, p=0.0005) and AA recurrence (77% vs 17%, p<0.0001). The following were significant after multivariable testing: histological T stage I-II (OR: 0.3), ≥1 positive margin (OR: 0.3), number of positive resected nodes (OR: 0.2), PPFI (OR: 0.2), PNI (OR: 0.4), completion of AC (OR: 3.6) and LI (OR: 0.4).

Time to first recurrence/death

The following were predictors of reduced time to recurrence: ≥1 positive resection margin (MD: 5 months, p=0.005), PPFI (MD: 7 months, p=0.004) and PNI (MD: 4 months, p=0.006) (**Figure 8.1**). Preoperative biliary stenting (MD: 4 months, p=0.004), histological T-stage >II (MD: 8 months, p<0.0001), histological N stage >0 (MD: 7 months, p=0.004), PPFI (MD: 10 months, p=0.007) and PNI (MD: 8 months, p<0.0001) were predictors of reduced time to death.

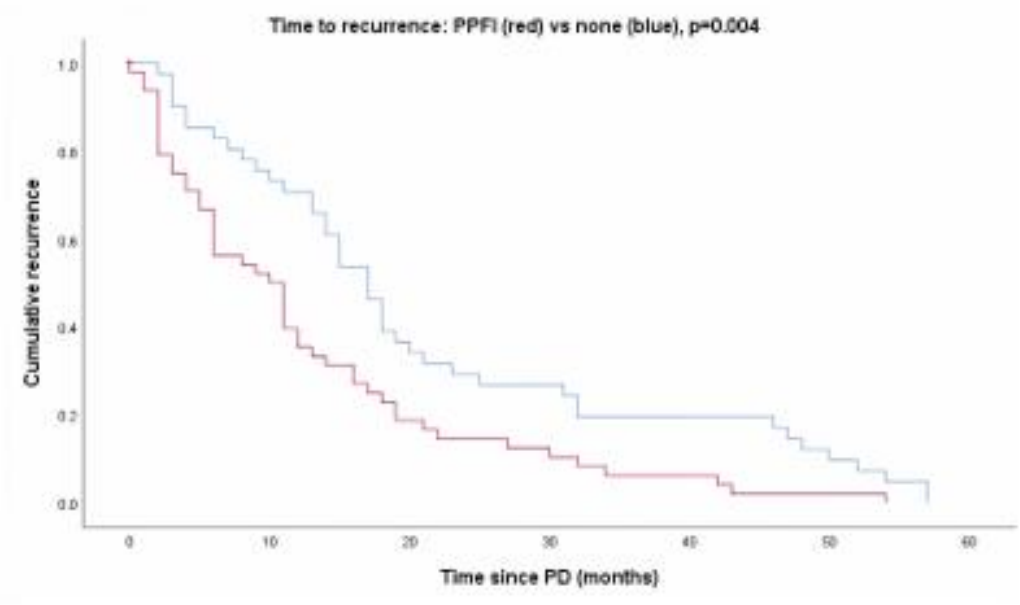
Discussion

This multicentre study aimed to identify factors associated with five-year recurrence/survival in a large cohort of PD patients with AA. In addition, we aimed to identify predictors of reduced time to recurrence/death in those that experienced these outcomes. Our results are compared to those of other recent studies in **Table 8.4**. Whilst several studies have aimed to identify factors associated with long-term survival, few multicentre studies have studied recurrence patterns in any level of detail, as we have done.



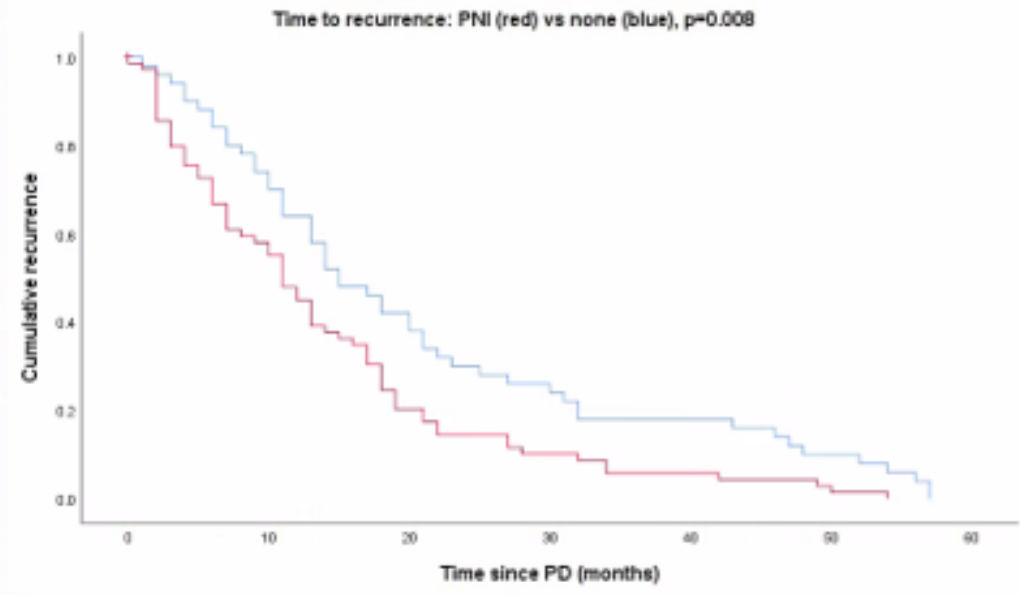
A

Number at risk							
1+ pos margin	37	19	5	3	1	1	
None	107	69	34	19	16	8	
Time (months)	0	10	20	30	40	50	60



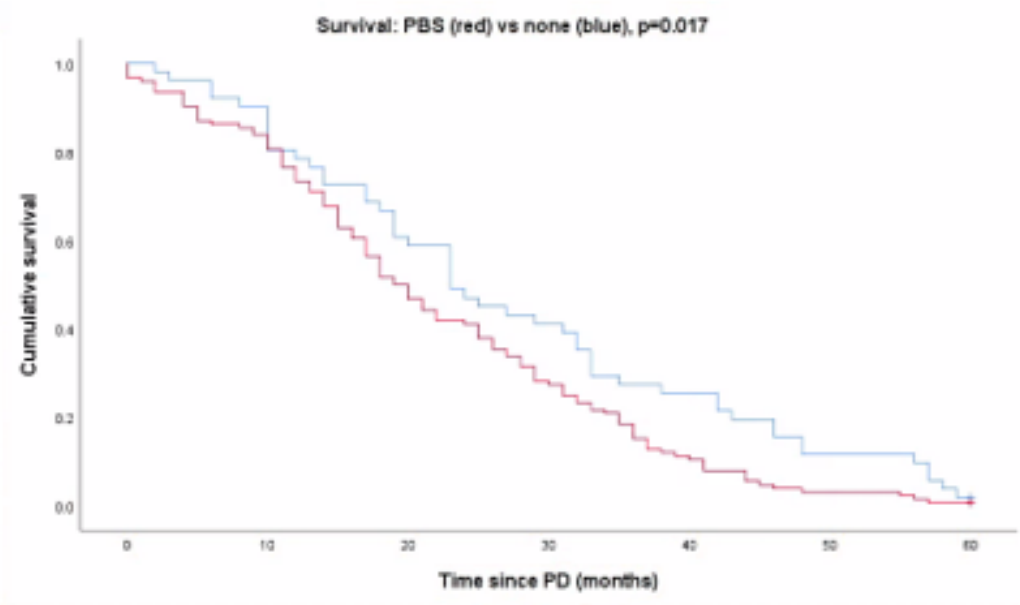
B

Number at risk							
PPFI	49	25	9	6	3	1	
None	41	31	15	11	8	5	
Time (months)	0	10	20	30	40	50	60



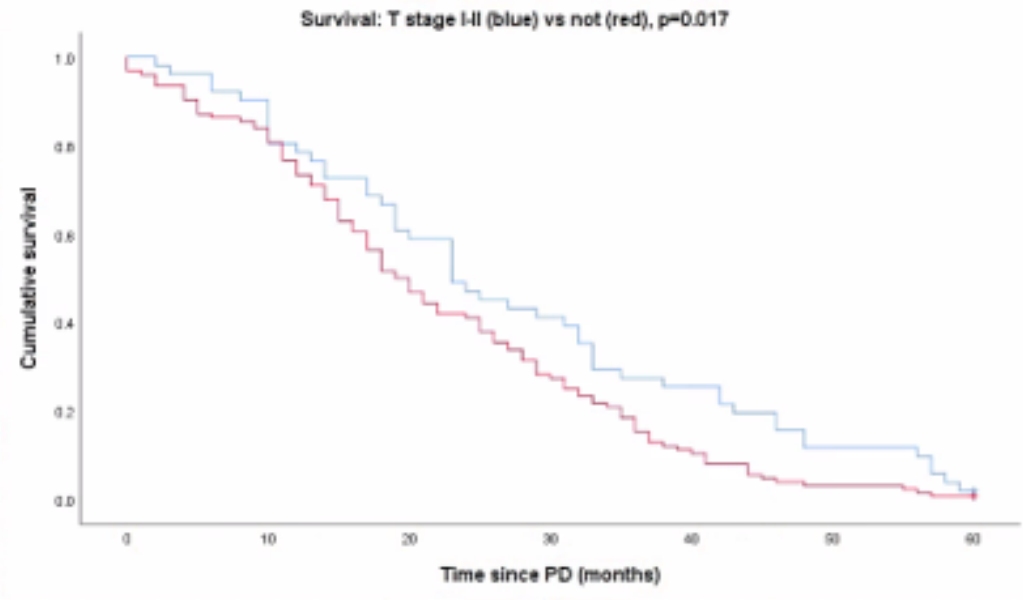
C

Number at risk							
PNI	70	40	14	7	4	2	
None	50	37	21	13	9	5	
Time (months)	0	10	20	30	40	50	60



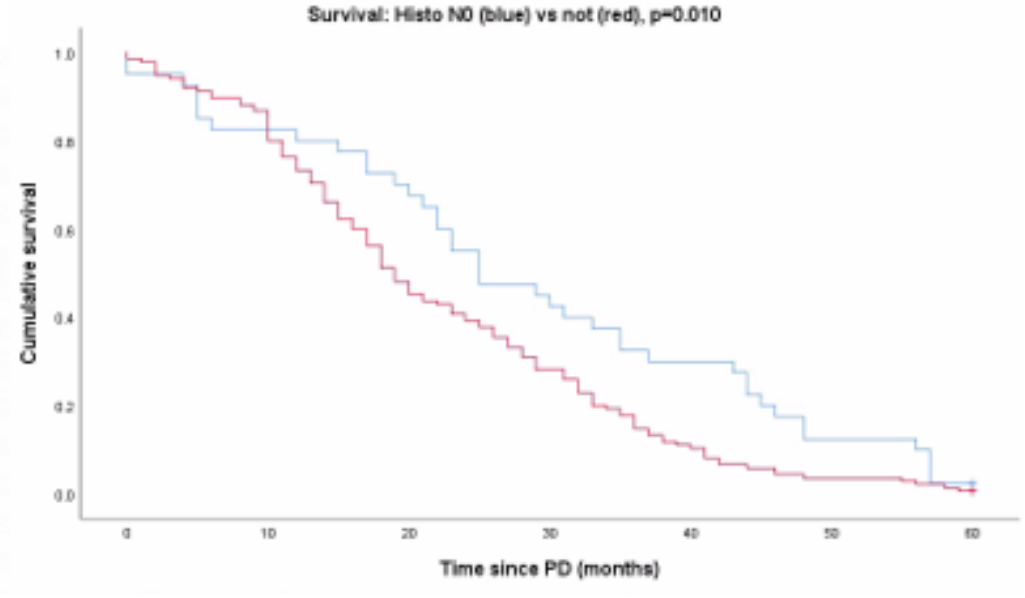
D

Number at risk							
PBS	124	104	62	35	13	4	1
None	51	46	31	21	13	6	1
Time (months)	0	10	20	30	40	50	60



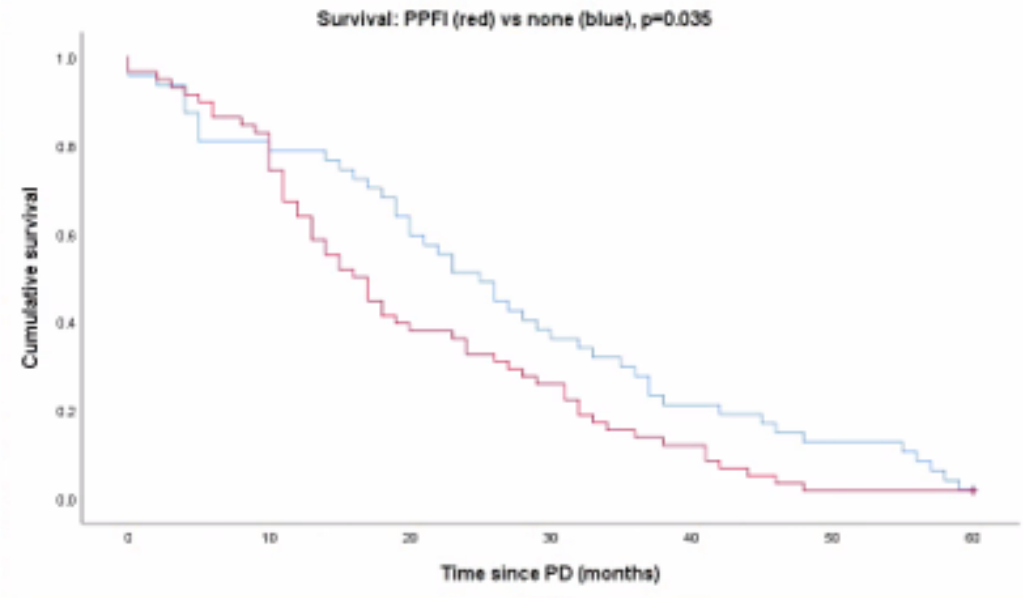
E

Number at risk							
T stage I-II	124	104	62	35	14	4	1
Not	51	46	31	21	13	6	1
Time (months)	0	10	20	30	40	50	60



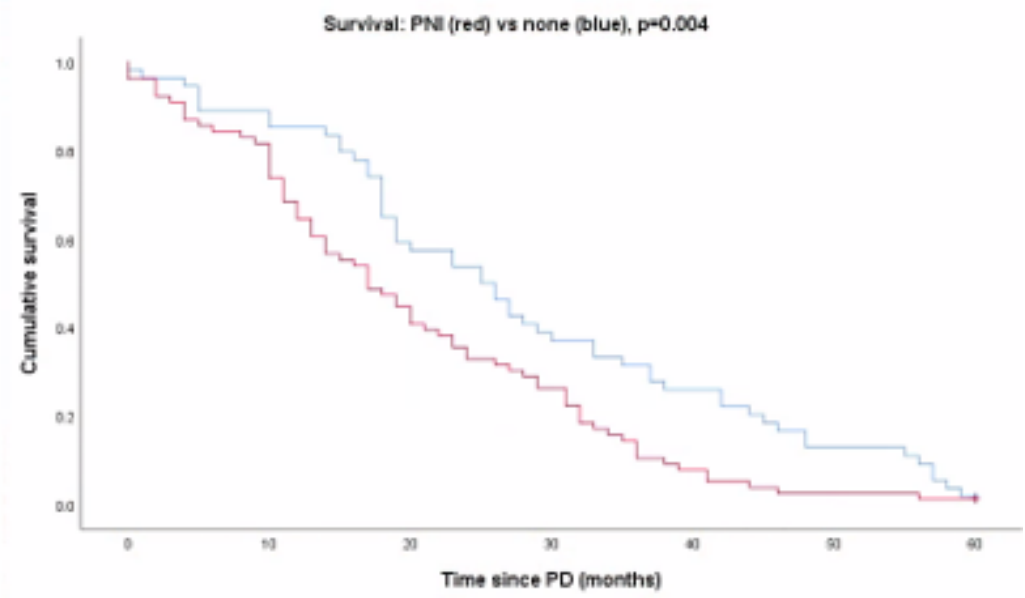
F

Number at risk							
Histo. N0	135	117	65	38	15	5	1
Not	40	33	28	18	12	5	1
Time (months)	0	10	20	30	40	50	60



G

Number at risk							
PPFI	58	48	23	15	7	1	1
None	47	38	30	18	10	6	1
Time (months)	0	10	20	30	40	50	60



H

Number at risk							
PNI	76	62	34	20	6	2	1
None	54	48	32	21	15	7	1
Time (months)	0	10	20	30	40	50	60

Figure 8.1: Significant variables associated with (A-C) reduced time to recurrence (TTR, days) and (D-H) reduced time to death (TTD, days) in those who experienced five-year recurrence/death. P-values obtained using the log-rank test.

Preoperative patient details		
Mean age (years)	64.8 (SD: 10.6)	
Female sex	171 (43.4%)	
Mean BMI (kg/m^2)	25.9 (SD: 4.7)	Unknown: 157*
Comorbidities/functional status		
Diabetes	51 (13.9%)	Unknown: 26*
Cardiovascular disease	148 (37.7%)	Unknown: 1*
Respiratory disease	30 (7.6%)	
ASA grade	I-II: 252 (71.4%) III-IV: 101 (28.6%)	Unknown: 41*
Preoperative investigations		
Median time from CT to PD (days)	39 (IQR: 40)	Unknown in 11 cases*
MRI performed	101 (25.6%)	
Median time from MRI to PD (days)	52 (IQR: 64.5)	
PET-CT performed	26 (6.6%)	
Median time from PET-CT to PD (days)	28.5 (IQR: 37)	
EUS performed	111 (28.2%)	
Median time from EUS to PD (days)	35 (IQR: 49)	
EUS cytology	Diagnostic/suspicious for malignancy: 64 (59.8%) Sample inadequate for diagnosis of malignancy: 22 (20.6%) No cytology/biopsy taken: 21 (19.6%) Unknown: 4*	
Staging laparoscopy performed	23 (5.8%)	
Median time from staging laparoscopy to PD (days)	15 (IQR: 18)	
Tumour site on CT	Head of pancreas: 67 (17.0%) Ampulla: 307 (77.9%) Distal bile duct: 20 (5.1%)	
Median tumour diameter on CT (mm)	20 (IQR: 10)	Unknown in 244 cases*
Radiological T stage	I: 116 (33.8%) II: 79 (23.0%) III: 41 (12.0%)	IV: 9 (2.6%) X: 98 (28.6%) Unknown: 51*
Radiological N stage	0: 232 (68.0%) I: 70 (20.5%)	X: 39 (11.4%) Unknown: 53*
Preoperative treatment		
Biliary stent	266 (67.5%)	
Neoadjuvant chemotherapy	11 (2.8%)	
Median preoperative blood tests		
Bilirubin (µmol/L)	15 (IQR: 30)	Unknown in 1 case*
Albumin (g/L)	38 (IQR: 11)	Unknown in 57 cases*
Neutrophils (x10^9/L)	5.0 (IQR: 2.6)	Unknown in 43 cases*
Lymphocytes (x10^9/L)	1.8 (IQR: 0.9)	Unknown in 43 cases*
Operation details		
Type of PD performed	Classic Whipple: 164 (41.7%) Pylorus-preserving: 229 (58.3%)	Unknown: 1*
Pancreatic anastomosis	P-J: 329 (85.9%) P-G: 54 (14.1%)	Unknown: 11*
Concomitant procedure	19 (4.9%)	Unknown: 5*
Concomitant venous resection	7 (1.9%)	Unknown: 25*
Concomitant arterial resection	2 (0.5%)	Unknown: 24*
Intraoperative blood transfusion	31 (13.6%)	Unknown: 166*
Postoperative hospital stay		
POPF	86 (23.6%)	Unknown: 30*

• Biochemical leak • Clinically relevant POPF	• 44 (12.1%) • 42 (11.5%)	
Median time to POPF diagnosis (days)	5 (IQR: 5)	
Post-pancreatectomy haemorrhage	15 (4.1%)	Unknown: 31*
Unplanned return to theatre	21 (5.8%)	Unknown: 31*
Median time to unplanned return to theatre (days)	10 (IQR: 11)	
Median length of stay (days)	14 (IQR: 13)	Unknown: 2*
30-day unplanned readmission	34 (9.3%)	Unknown: 30*
90-day mortality	12 (3.0%)	
Postoperative histology		
AA phenotype	Intestinal: 64 (46.4%) Pancreatobiliary: 61 (44.2%)	Mixed: 13 (9.4%) Unknown: 156*
Tumour differentiation	Well: 27 (8.2%) Well/moderate: 11 (3.3%) Moderate: 172 (52.0%)	Moderate/poor: 46 (13.9%) Poor: 75 (22.7%) Unknown: 63*
Median histological tumour diameter (mm)	21 (IQR: 15)	Unknown in 59 cases*
Histological T stage	I: 46 (11.7%) II: 131 (33.2%) III: 130 (33.0%)	IV: 86 (21.8%) X: 1 (0.3%)
Histological N stage	0: 154 (39.1%) I: 239 (60.6%)	II: 1 (0.3%)
Resection margin status	R0: 294 (80.8%) R1: 70 (19.2%)	R2: 0 (0.0%) Unknown: 30*
Involved margins	Multiple: 16 (24.2%) Anterior surface only: 3 (4.5%) Pancreatic transection only: 4 (6.1%) Periductal circumferential only: 1 (1.5%) SMA/posterior only: 39 (59.1%) SMV groove only: 3 (4.5%) Unknown: 4*	
Median total positive lymph nodes resected	1 (IQR: 3)	Unknown in 9 cases*
Median total lymph nodes resected	16 (IQR: 12)	Unknown in 11 cases*
Peripancreatic fat invasion	85 (37.8%)	Unknown in 169 cases*
Perineural invasion	136 (46.1%)	Unknown in 99 cases*
Microvascular invasion	128 (45.2%)	Unknown in 111 cases*
Lymphatic invasion	170 (58.6%)	Unknown in 104 cases*
Adjuvant treatment		
Adjuvant chemotherapy commenced	220 (58.7%)	Unknown: 19*
Adjuvant chemotherapy received	Gemcitabine: 119 (54.1%) Gemcitabine and capecitabine: 30 (13.6%) 5-Fluorouracil: 7 (3.2%) Gemcitabine and cisplatin: 7 (3.2%) FOLFIRINOX: 6 (2.7%) Capecitabine: 6 (2.7%) Capecitabine and oxaliplatin: 6 (2.7%) Other: 9 (4.1%) Unknown: 30*	
Median time to first dose of AC (days)	71 (IQR: 29)	Unknown in 107 cases*
Median number of AC cycles	6 (IQR: 1)	Unknown in 46 cases*
Completed planned AC course	154 (75.5%)	Unknown in 16 cases*
Adjuvant radiotherapy commenced	9 (2.4%)	Unknown in 24 cases*
Adjuvant radiotherapy completed	9 (100%)	
AA recurrence		

Five-year recurrence (actual)	176 (44.7%)	
Median time to recurrence (days)	412 (IQR: 449)	
Sites of recurrence	Local only: 34 (20.0%) Local and distant: 41 (23.3%)	Distant only: 94 (55.3%) Unknown: 7*
Palliative chemotherapy commenced	86 (57.0% of those with recurrence)	Unknown: 25*
Palliative chemotherapy received	Gemcitabine and capecitabine: 14 (18.7%) Gemcitabine: 10 (13.3%) Capecitabine and FOLFIRINOX: 10 (13.3%) FOLFIRINOX: 9 (12.0%) Gemcitabine and abraxane: 7 (9.3%) FOLFOX: 5 (6.7%) Capecitabine: 3 (4.0%) Other: 17 (22.7%) Unknown: 11*	
Median number of palliative chemotherapy cycles	6 (IQR: 3)	
Palliative chemotherapy completed	30 (41.1%)	Unknown: 43*
Palliative radiotherapy commenced	16 (9.1% of those with recurrence)	
Palliative radiotherapy completed	16 (100%)	
Five-year survival (actual)	**211 (53.6%)**	

Table 8.1: Key information on the patients who underwent PD for AA. *Not included in percentages.

In our study, the proportion of patients who were ASA grade I-II was significantly higher among those who developed recurrence. This is probably because these patients less often died of non-malignant causes. Indeed, when the group who were alive at five years was compared to the group that were not, ASA grade I-II patients were more numerous in the former, however, this was not quite significant. Bolm et al. also found that ASA grade I-II patients survived longer (p=0.002) but they did not study recurrence patterns[392].

We found that median preoperative serum bilirubin was significantly higher among patients with recurrence. In a single-centre Korean study, Kim et al. also observed this[393]. This may be because those who develop recurrence have more advanced disease (at the time of PD) or a larger tumour, which can contribute to biliary obstruction. Indeed, in our study, the patients who developed recurrence had histologically larger tumours, were more often T stage >II and were more likely to have a poorly differentiated tumour. However, these differences were not apparent preoperatively, as the two groups were similar in terms of radiological tumour size and preoperative staging. Further studies are required to investigate the utilisation of preoperative serum bilirubin as a prognostic indicator.

Variable	5yr recurrence (n=176)	No 5yr recurrence (n=218)	p-value
Preoperative patient details			
Mean age in years (SD)	65.1 (10.2)	64.6 (11.0)	0.680
Female sex	78 (44.3%)	93 (42.7%)	0.741
Mean BMI in kg/m^2 (SD)	25.4 (4.9)	26.3 (4.5)	0.149
Comorbidities/functional status			
Diabetes	21 (12.8%)	30 (14.7%)	0.651
Cardiovascular disease	56 (31.8%)	90 (41.5%)	0.053
Respiratory disease	17 (9.7%)	13 (6.0%)	0.186
ASA grade I-II	140 (87.0%)	139 (72.4%)	**0.00082***
Preoperative imaging			
Median tumour size in mm (IQR)	20 (10)	20 (10)	0.722
Radiological T stage I-II	81 (77.9%)	114 (82.6%)	0.183
No regional lymph nodes on pre-op CT	103 (74.6%)	129 (78.7%)	0.409
Preoperative treatment			
Biliary stent	122 (69.3%)	144 (66.1%)	0.492
Neoadjuvant chemotherapy	5 (2.8%)	6 (2.9%)	1.00
Median preoperative blood tests			
Bilirubin in µmol/L (IQR)	21.5 (41.5)	14 (26)	**0.0030***
Albumin in g/L (IQR)	38 (11)	38 (13.5)	0.532
Neutrophils in x10^9/L (IQR)	5.2 (3.1)	4.9 (2.4)	0.096
Lymphocytes in x10^9/L (IQR)	1.7 (0.8)	1.8 (1.1)	0.224
Operation details			
Classic Whipple (vs PPPD)	72 (40.9%)	92 (42.4%)	0.767
P-J anastomosis (vs P-G)	142 (83.0%)	187 (88.2%)	0.149
Concomitant procedure	9 (5.2%)	10 (4.6%)	0.817
Concomitant venous resection	3 (1.8%)	4 (1.9%)	1.00
Concomitant arterial resection	1 (0.6%)	1 (0.5%)	1.00
Postoperative hospital stay			
POPF	33 (20.4%)	53 (26.2%)	0.215
CR-POPF	15 (9.3%)	27 (13.4%)	0.251
Post-pancreatectomy haemorrhage	6 (3.7%)	9 (4.6%)	0.796
Unplanned return to theatre	6 (3.7%)	15 (7.4%)	0.175
Median length of stay in days (IQR)	14 (12)	14.5 (15)	0.184
30-day readmission	9 (5.6%)	12 (5.5%)	1.00
Postoperative histology			
Median tumour size in mm (IQR)	25 (20)	20 (11)	**0.000040***
Histological T stage I-II	51 (29.0%)	91 (58.1%)	**0.000015***
Poorly differentiated tumour	42 (28.0%)	33 (18.2%)	**0.035***
Pancreatobiliary subtype AA	28 (49.1%)	33 (40.7%)	0.385
≥1 positive resection margin	44 (26.7%)	26 (13.1%)	**0.0013***
Median positive resected nodes (IQR)	2 (4)	0 (2)	**0.00001***
Median total resected nodes (IQR)	16 (11)	15 (12)	0.357
Peripancreatic fat invasion	50 (51.0%)	35 (27.6%)	**0.00032***
Perineural invasion	77 (58.8%)	59 (36.0%)	**0.000095***
Microvascular invasion	77 (58.8)	51 (33.3%)	**0.000017***
Lymphatic invasion	93 (72.7%)	77 (47.5%)	**0.000016***
Postoperative treatment			
Commenced adjuvant chemotherapy	121 (72.0%)	99 (47.8%)	**0.00001***
Completed adjuvant chemotherapy‡	77 (68.1%)	77 (88.7%)	**0.010***
Received adjuvant radiotherapy	3 (1.8%)	6 (2.9%)	0.737
Long-term survival			
Five-year survival	36 (20.5%)	175 (80.3%)	**0.00001***
Variable	**Alive at 5 years (n=211)**	**Dead at 5 years (n=183)**	**p-value**
Preoperative patient details			
Mean age in years (SD)	63.7 (10.5)	66.2 (10.7)	**0.020***
Female sex	100 (47.4%)	71 (38.8%)	0.086
Mean BMI in kg/m^2 (SD)	26.1 (4.7)	25.6 (4.7)	0.438
Comorbidities/functional status			
Diabetes	21 (10.7%)	30 (17.5%)	0.069
Cardiovascular disease	80 (37.9%)	66 (32.3%)	0.736
Respiratory disease	10 (4.7%)	20 (10.9%)	**0.023***
ASA grade I-II	139 (75.1%)	113 (67.3%)	0.102

Preoperative imaging			
Median tumour size in mm (IQR)	20 (11)	20 (9)	0.162
Radiological T stage I-II	26 (19.0%)	24 (22.2%)	0.632
No regional lymph nodes on pre-op CT	30 (18.9%)	40 (28.0%)	0.061
Preoperative treatment			
Biliary stent	137 (64.9%)	129 (70.5%)	0.240
Neoadjuvant chemotherapy	6 (2.8%)	5 (2.7%)	1.00
Median preoperative blood tests			
Bilirubin in µmol/L (IQR)	14 (26)	20.5 (37)	**0.0071***
Albumin in g/L (IQR)	38 (12)	38 (11)	0.994
Neutrophils in $x10^9$/L (IQR)	4.9 (2.5)	5.3 (3.2)	**0.032***
Lymphocytes in $x10^9$/L (IQR)	1.8 (1.0)	1.8 (0.9)	0.853
Operation details			
Classic Whipple (vs PPPD)	87 (41.2%)	77 (42.3%)	0.838
P-J anastomosis (vs P-G)	180 (87.4%)	149 (84.2%)	0.370
Concomitant procedure	12 (5.7%)	7 (3.9%)	0.482
Concomitant venous resection	4 (2.0%)	3 (1.8%)	1.00
Concomitant arterial resection	1 (0.5%)	1 (0.6%)	1.00
Postoperative hospital stay			
POPF	45 (23.0%)	41 (24.4%)	0.746
CR-POPF	18 (9.2%)	24 (14.3%)	0.129
Post-pancreatectomy haemorrhage	5 (2.6%)	10 (6.0%)	0.101
Unplanned return to theatre	8 (4.3%)	13 (7.8%)	0.176
Median length of stay in days (IQR)	14 (12)	14 (12.5)	0.925
30-day readmission	22 (11.2%)	12 (7.2%)	0.210
Postoperative histology			
Median tumour size in mm (IQR)	20 (14)	23 (17)	**0.031***
Histological T stage I-II	121 (57.6%)	56 (30.6%)	**0.00001***
Poorly differentiated tumour	31 (17.6%)	44 (28.4%)	**0.019***
Pancreatobiliary subtype AA	32 (41.0%)	29 (48.3%)	0.489
≥1 positive resection margin	21 (10.8%)	49 (29.0%)	**0.00001***
Median positive resected nodes (IQR)	0 (2)	2 (4)	**0.00001***
Median total resected nodes (IQR)	15 (10)	16 (12)	0.083
Peripancreatic fat invasion	25 (22.1%)	60 (53.6%)	**0.00001***
Perineural invasion	55 (34.8%)	81 (59.1%)	**0.000029***
Microvascular invasion	55 (36.7%)	73 (54.9%)	**0.0021***
Lymphatic invasion	75 (49.0%)	95 (69.3%)	**0.00045***
Postoperative treatment			
Commenced adjuvant chemotherapy	110 (54.5%)	110 (63.6%)	0.074
Completed adjuvant chemotherapy‡	90 (86.5%)	64 (64.0%)	**0.00018***
Received adjuvant radiotherapy	6 (3.0%)	3 (1.8%)	0.514
AA recurrence			
Five-year recurrence	36 (17.1%)	140 (76.5%)	**0.00001***

Table 8.2: Univariable analysis: five-year recurrence and five-year survival in PD patients with AA. *Denotes statistical significance. ‡Includes only those who commenced AC. Statistical methods: means were compared using Student's *t*-test and distributions were compared using the Mann Whitney *U* test. Fisher's exact test was used to compare proportions of binary outcomes and independence of nominal data. Percentages may appear incorrect as cases were excluded from sub-analyses if data were unavailable (see Table 8.1).

Five-year disease recurrence	
Median number of positive resected nodes	Median difference: 2
Commenced adjuvant chemotherapy	OR: 2.8 (95% CI: 1.8-4.3)
Histological T stage I-II	OR: 0.3 (95% CI: 0.2-0.4)
Lymphatic invasion	OR: 2.9 (95% CI: 1.8-4.8)
Microvascular invasion	OR: 2.9 (95% CI: 1.8-4.7)
Median histological tumour size	Median difference: 5 mm
Perineural invasion	OR: 2.6 (95% CI: 1.6-4.2)
Peripancreatic fat invasion	OR: 2.7 (95% CI: 1.6-4.8)
American Society of Anesthesiologists grade I-II	OR: 1.2 (95% CI: 0.7-1.9)
≥1 positive resection margin	OR: 2.4 (95% CI: 1.4-4.1)
Five-year survival	
Histological T stage I-II	OR: 0.3 (95% CI: 0.2-0.5)
≥1 positive resection margin	OR: 0.3 (95% CI: 0.2-0.5)
Median number of positive resected nodes	Median difference: 2
Peripancreatic fat invasion	OR: 0.2 (95% CI: 0.1-0.4)
Perineural invasion	OR: 0.4 (95% CI: 0.2-0.6)
Completed adjuvant chemotherapy	OR 3.6 (95% CI: 1.8-7.2)
Lymphatic invasion	OR 0.4 (95% CI: 0.3-0.7)

Table 8.3: Adjusting for multiple testing: the Holm and Hochberg step methods. CI = confidence interval, OR = odds ratio.

In our study, more patients from the group that developed recurrence were commenced on AC. In addition, the patients who received AC also survived longer due to their baseline level of fitness, as well as the treatment they received. Indeed, the patients who were commenced on AC were a median of 4.5 years younger at the time of PD (64.5 vs 69 years, p<0.0001) and were more often ASA grade I-II (76% vs 66%, p=0.048). Among those who commenced AC, the group who completed the planned course were less likely to develop recurrence and more likely to achieve five-year survival. Bolm et al. studied the role of AC in 214 PD patients with AA. Patients with pancreatobiliary subtype AA who received AC had improved median survival (85 vs 65 months, p=0.005), but this effect was not observed in those with intestinal subtype AA[392]. Results from several recent studies[79, 394, 395] have suggested that pancreatobiliary subtype tumours behave more aggressively. We were unable to investigate this due to the unavailability of phenotype data.

The remaining variables which had a significant association with AA recurrence and reduced time to recurrence were all histological features. Hence, we argue histopathology reports must contain information on all these variables. Patients deemed high-risk for recurrence may benefit from earlier and more intensive surveillance, however, this is not supported by evidence. Additionally, it may be that adjuvant treatment is more relevant in this group. This is also an assumption and needs to be investigated by further trials.

The only other recent multicentre study which has studied predictors of recurrence in resected AA patients is that of Moekotte et al.[160]. Whilst our study had a smaller sample size, it considered more histological and non-histological variables. For example, in addition to the factors identified by Moekotte et al.[160] (**Table 8.4**), ≥1 positive resection margin, a higher number of positive nodes, higher preoperative serum bilirubin, larger histological tumour size and PPFI also correlated with AA recurrence in our study.

When the patients alive at five years were compared to those who were not, the latter were older (median) at the time of PD and had a higher prevalence of preoperative respiratory disease. These patients will have been more likely to die from other causes (not related to AA). As with recurrence, the median preoperative serum bilirubin was higher among those who died. Again, this is likely as these patients had more advanced disease, which is more likely to result in biliary obstruction. Whilst the alive and dead groups were similar in terms of preoperative staging, the latter had more histologically advanced disease. Kim et al. found that patients with preoperative serum bilirubin >1.5 mg/dL were less likely to achieve long-term survival[393].

In addition, median preoperative serum neutrophils were significantly higher in those who were dead at five years. Several other studies have suggested that a high neutrophil/lymphocyte ratio (NLR) correlates with adverse outcomes. Demirci et al. found that a NLR ≥3.0 was associated with reduced OS and argued this should be considered a biomarker for poor prognosis[396]. The authors hypothesised that patients with an elevated NLR have a relative lymphocytopenia and a decreased leukocyte response[397].

However, among our patients, whilst median neutrophils were higher among those who died, a NLR <3.0 did not correlate with improved five-year survival (56% vs 51%, p=0.4).

When the group who survived were compared to those who did not, the former had more often completed a course of AC, if this was commenced. Whilst several recent studies[388] have shown that receiving AC can benefit selected patients, no recent studies have specifically investigated the relative importance of completing the planned course. Jin et al.[398], Kamarajah et al.[388] and Moekotte et al.[160] all observed a correlation between receiving AC and long-term survival. The other studies listed in **Table 8.4** either did not observe this or did not investigate this. Whilst the benefits of AC in patients with PDAC are undeniable[374], the picture is less evident in those with AA. A stage-matched analysis of chemotherapy outcomes would shed light on this.

The remaining variables which had a significant association with five-year survival were all histological features. Whilst many of the other studies included in **Table 8.4** also identified histological predictors of five-year survival, apart from Kamarajah et al.[388], few considered as many variables as our study did. Excluding preoperative biliary stenting, the variables associated with reduced time to death were also all histological features.

Our study suggests that patients who undergo PD for AA have better long-term outcomes than those with PDAC[399]. However, a significant number develop recurrent disease within five years, and this, as one would expect, correlates with reduced five-year survival. Identifying variables associated with recurrence is crucial as it allows clinicians to estimate the likelihood of recurrent disease in individuals. A tailored management plan can then be considered. For example, if a patient has several histological predictors of recurrence, they should arguably undergo earlier and more regular surveillance. In turn, this may result in recurrence being diagnosed earlier and have implications for management planning and overall survival. Patients who have recurrence diagnosed earlier may be more likely to receive and complete palliative chemotherapy, which could result in prolonged survival or improved quality of life. In addition, it may be more important to consider adjuvant treatment in patients with

predictors of recurrence. Future trials should investigate this as recent reports on the use of adjuvant therapy for resected AAs are rare[400].

Bakkevold et al. demonstrated that AC delayed the incidence of recurrence in the first two years following PD, but this was not associated with an increased cure rate[401]. Others have found that radiation therapy, in addition to AC, can contribute to local disease control, but this does not correlate with improved OS[402, 403]. Similarly, Sikora et al. found that chemoradiotherapy did not improve OS[404]. A prospective randomised study based on histopathologic and clinical predictors of recurrence is warranted to study the impact of adjuvant therapy in high-risk patients. Whilst the potential benefits of adjuvant therapy in all resected AA patients can be debated, there may be a sub-group who would benefit from a tailored, rather than a generic, treatment approach. The limitations of this study have been outlined in **Chapter 9**.

Conclusion

In our multicentre study of patients with resected AA, 45% developed recurrent disease within five years of PD and 54% achieved five-year survival. Multiple predictors of recurrence and reduced time to recurrence were identified, most of these were histopathological features which should be included in all histopathology reports. Patients with predictors of recurrence should arguably undergo earlier and more intensive surveillance. Additionally, it may be that this group would benefit from individualised adjuvant therapy regimens. Future studies are warranted to investigate the role of surveillance and AC in patients with high-risk features for recurrence.

Study	Study type	AA recurrence	Associated with recurrence	Survival	Associated with reduced survival
Bolm et al. 2020[392] n=214	Retrospective, multicentre	-	-	Median OS: 137 months	*ASA III-IV (MD: 67 months, p=0.002) *Hist. N stage >0 (MD: 49 months, p=0.001) ≥1 positive resection margin (MD: 98 months, p=0.03) Hist. T stage III-VI (MD: 65 months, p=0.001) Moderate/poor differentiation (MD: 32 months, p=0.03) PB/mixed subtype (MD: 38 months, p=0.03) Pre-op CA19-9 >40 IU (MD: 36 months, p=0.04) Pre-op CEA >0.5 ng/ml (MD: 66 months, p=0.01)
Chen et al. 2013[405] n=253	Retrospective, single centre	-	-	Median OS: 144 months Five-year survival: 33%	*Hist. N stage >0 (OR: 0.3, p=0.02) *Jaundice at presentation (OR: 0.8, p=0.002) *Poor cell differentiation (OR: 0.0, p=0.03) *Post-op intra-abdominal collection (OR: 1.3, p=0.009) *Tumour size >20 mm (OR: 0.4, p=0.006) High intra-op blood loss (MD: 225 ml, p=0.005) Larger tumour size (MD: 5 mm, p=0.02) Male sex (18% vs 33%, p=0.001) Perineural invasion (10% vs 25%, p=0.001) Post-pancreatectomy haemorrhage (p=0.007) Pre-op diabetes (p=0.02) Pylorus resecting PD (25% vs 32%, p<0.05) Nb Associated with reduced 5YS (includes patients with PDAC/CC)
Doepker et al. 2016[406] n=106	Retrospective, single centre	Median DFS: 27 months Five-year recurrence: 64%	*≤12 lymph nodes resected (HR: 4.5, p=0.001) *Hist. N stage >0 (HR: 1.7, p=0.001) *Moderate/poor differentiation (HR: 23, p=0.002) *PB subtype (HR: 2.1, p=0.04) Increasing age (HR: 1.1, p=0.002) Perineural invasion (HR: 1.8, p=0.007)	Median OS: 49 months Five-year survival: 43%	*≤12 lymph nodes resected (HR: 5.0, p=0.001) *Hist. N stage >0 (HR: 1.2, p=0.007) *Moderate/poor differentiation (HR: 29, p=0.007) *PB subtype (HR: 2.8, p=0.01) Increasing age (HR: 1.1, p=0.001) Lymph node ratio ≥0.1 (p=0.001) Lymphovascular invasion (HR: 1.9, p=0.04) Perineural invasion (HR: 1.9, p=0.04)
Jin et al. 2018[398] n=121	Retrospective, single centre	Median DFS: 66 months Five-year recurrence: 48%	-	Median OS: 92 months Five-year OS: 58%	*Higher comorbidity score (HR: 2.9, p=0.001) *Initial disease stage ≥IIb (HR: 4.8, p=0.001) *No AC (stage ≥IIb patients only) (HR: 2.0, p=0.04) Age ≥70 years (p=0.006) Hist. N stage >0 (p=0.001) Increasing Hist. T stage (p=0.006)

					Lymph node ratio >0.06 (p=0.001)
Kamarajah et al. 2021[388] n=7358	Retrospective, multicentre	-	-	Median OS: 40 months Five-year survival: 40%	*≥1 positive resection margin (HR: 1.7, p=0.001) *Higher comorbidity score (HR: 1.2, p=0.001) *Increasing age (p=0.001) *Increasing Hist. N stage (p<0.05) *Increasing Hist. T stage (p=0.001) *Lower education level (p=0.02) *Lower median income (p=0.001) *Male sex (HR: 1.1, p=0.001) *Moderate/poor/anaplastic differentiation (p=0.001) *No AC (HR: 1.2, p=0.001) *No adjuvant radiotherapy (HR: 1.1, p=0.001) *No health insurance (p=0.001)
Kamarajah et al. 2018[407] n=1106	Retrospective, multicentre	Median CSS: 37 months	No ARad. (Hist. N2 patients only) (MD: 8 months, p=0.004) Nb CSS	Median OS: 31 months	No AR (Hist. N2 patients only) (MD: 6 months, p=0.009)
Klein et al. 2014[408] n=143	Retrospective, single centre	-	-	Median OS: 37 months Five-year survival: 40%	*Intra-op blood transfusion (OR: 2.0, p=0.008) *Lymphatic invasion (OR: 4.0, p=0.001) *Raised pre-op CA 19-9 (OR: 1.8, p=0.02) ≥1 positive resection margin (p=0.02) High comorbidity score (p=0.008) Hist. N stage >0 (p=0.001) Increasing Hist. T stage (p=0.001) Microvascular invasion (p=0.008) Moderate/poor differentiation (p=0.001) Postoperative pancreatic fistula (p=0.01) Pre-op jaundice (p=0.04)
Kim et al. 2011[393] n=181	Retrospective, single centre	Five-year recurrence: 49%	*Hist. N stage >0 (HR: 2.4, p=0.008) *Pre-op bilirubin >1.5 mg/dL (HR: 4.1, p=0.003) *Pre-op CEA >5.0 ng/ml (HR: 4.0, p=0.001) Increasing Hist. T stage (p=0.001) Pre-op CA19-9 >35 IU/ml (p=0.001) Pylorus-resecting PD (5YS: 58.7% vs 38.9%, p<0.05)	Median OS: 29.7 Five-year survival: 61.9%**	*Hist. N stage >0 (HR 3.0, p=0.006) *Pre-op CEA >5.0 ng/ml (HR: 7.9, p=0.001) Increasing Hist. T stage (p=0.001) Pre-op bilirubin >1.5 mg/dL (p=0.003) Pre-op CA19-9 >35 IU/ml (p=0.04) Pylorus-resecting PD (5YS: 44.5% vs 74.0, p=0.002)
Lothe et al. 2019[394] n=109	Retrospective, single centre	Median DFS: 29 (PB) and 31 (Int.) months	-	Median OS: 44 (PB) and 75 (Int.) months	*Hist. stage III disease (vs stage I-II, HR: 2.4, p=0.03) ≥1 positive resection margin (HR: 4.9, p=0.001) Hist. N stage >0 (HR: 3.5, p=0.001)

				Five-year survival: 36% (PB) and 56% (Int.)	Hist. T stage III-IV (HR: 3.7, p=0.001) Larger tumour diameter (HR: 1.2, p<0.05) PB subtype (HR: 1.8, p=0.04) Perineural invasion (HR: 2.7, p=0.001) Vascular involvement (HR: 2.2, p=0.003)
Moekotte et al. 2020[160] n=887	Retrospective, multicentre	-	*Hist. N stage >0 (HR: 2.7, p<0.05) Increasing Hist. T stage (p<0.05) Lymphovascular invasion (p<0.05) Moderate/poor differentiation (p<0.05) No AC (p<0.05) PB subtype (p<0.05) Perineural invasion (p<0.05)	Median OS: 64 months Five-year survival: 52%	*Hist. N stage >0 (HR: 3.3, p<0.05) *No AC (HR: 1.4, p<0.05) *Perineural invasion (HR: 1.5, p<0.05) Increasing Hist. T stage (p<0.05) Lymphovascular invasion (p<0.05) Moderate/poor cell differentiation (p<0.05) PB subtype (p<0.05)
Present study 2022 n=394	Retrospective, multicentre	Five-year recurrence: 44.7%	*≥1 positive resection margin (OR: 2.4, p=0.01) *ASA I-II (OR: 1.2, p=0.001) *Commenced AC (OR: 2.8, p=0.001) Completed AC (p=0.01) *Higher no. of positive resected nodes (MD: 2, p=0.001) Higher pre-op bilirubin (MD: 7.5 µmol/L, p=0.003) *Hist. T stage I-II (OR: 0.3, p=0.001) *Larger Hist. tumour size (MD: 5 mm, p=0.001) *Lymphatic invasion (OR: 2.9, p=0.001) *Microvascular invasion (OR: 2.9, p=0.001) *Perineural invasion (OR: 2.6, p=0.001) *Peripancreatic fat invasion (OR: 2.7, p=0.001) Poor cell differentiation (p=0.04) Nb A/W 5YR ≥1 positive resection margin (MD: 144 days, p=0.0005) Peripancreatic fat invasion (MD: 214 days, p=0.004) Perineural invasion (MD: 124 days, p=0.006) Nb A/W reduced median time to recurrence (5YR patients only)	Five-year survival: 53.6%	*≥1 positive resection margin (OR: 0.3, p=0.001) *Did not complete AC (OR: 3.6, p=0.0002) *Higher no. of positive resected nodes (MD: 2, p=0.001) Higher pre-op bilirubin (MD: 6.5 µmol/L, p=0.01) Higher pre-op neutrophils (MD: 0.4x10^9/L, p=0.03) *Hist. T stage >II (OR: 0.3, p<0.001) Increasing age (MD: 2.5 years, p=0.02) Larger Hist. tumour size (MD: 3 mm, p=0.03) *Lymphatic invasion (OR: 0.4, p=0.001) Microvascular invasion (p=0.002) *Perineural invasion (OR: 0.4, p=0.001) *Peripancreatic fat invasion (OR: 0.2, p=0.001) Poor cell differentiation (p=0.02) Pre-op respiratory disease (p=0.02) Nb A/W reduced 5YS Pre-op biliary stent (MD: 119 days, p=0.004) Hist. T stage >II (MD: 228, p=0.0001) Hist. N stage >0 (MD: 196, p=0.0001) Peripancreatic fat invasion (MD: 287 days, p=0.007) Perineural invasion (MD: 241 days, p=0.0001) Nb A/W reduced median time to death (5YS patients excluded)

Table 8.4: Recent studies which have reported on the long-term outcomes of PD performed for AA. *Independent predictor/significant following multivariable analysis. **Patients who died of causes other than AA or secondary to PD-related complications excluded. 5YR = five-year recurrence, 5YS = five-year survival, A/W = associated with.

Chapter 9: Summary

9.1. Reflection

Prior to being offered the opportunity to carry out this piece of work, I had not planned to obtain a postgraduate research degree. I was aware that I would have to be involved in research to some extent in order to become a well-informed clinician who practices evidence-based medicine, but I had not considered taking time out of my training to complete a doctorate. However, the challenge and the prospect of learning new skills persuaded me to take on the project.

One of the first issues I faced was managing the RAW study collaborators' expectations regarding the workload, as the data collection process was labour intensive. This was not a problem for me (collecting the Plymouth data) as I had the time and motivation to get this done. However, I was concerned that the other centres, although initially enthusiastic, would not be able to put in the work that was required due to their clinical commitments. With the benefit of hindsight, we should not have asked for quite so much information on each included patient. Although the robustness of our study may have been affected as a result, this likely would have improved collaborator engagement and patient numbers. My fears materialised when some units failed to make progress as they were not able to invest the time they had planned. This was not helped by the coronavirus pandemic. Understandably, many research and development departments were not prepared to authorise new projects since hospitals were put under enormous pressure. In addition, many clinicians were redeployed to other departments or were not able to complete the planned work due to new commitments. Whilst the pandemic undoubtedly had an impact on the RAW study, this was not something that could have been foreseen.

I feel my research skills have developed considerably through the process of submitting my work to peer-reviewed journals. With the help of others, I was able to get several review articles and several original research articles published. When I submitted each article, I felt each was my best work but the comments I received from the reviewers highlighted that it was perhaps not quite the standard I had hoped. Although the constructive criticism I received was sometimes difficult to take, it unquestionably helped me develop my data analysis and writing skills. I began to appreciate that the often harsh peer review process was necessary in order to produce quality articles which help shape future practice and research.

Over the last two years I have gained an appreciation for just how much work goes into research projects. I felt that the project I had undertaken could quite easily be completed in the time available. However, even accounting for possible delays, everything took significantly longer than I expected. Even once I had a finalised dataset, although I was able to analyse the data and produce drafts reasonably quickly, transforming these into submission-worthy articles was another challenge entirely. If I were to repeat my research period, I would approach it with more realistic aims.

9.2. Limitations

Literature reviews

All the literature reviews in this thesis only considered English-language articles from the PubMed database and unpublished data were not considered (the originally submitted version of this thesis did not contain data from the Cochrane Library). Further, only statistically significant results were considered; this is a further potential source of bias. Also, only studies reporting on open PD outcomes were included and sensitivity analyses, reporting bias and certainty assessments were not carried out for each included study. Finally, only one reviewer performed the database extractions.

Chapter 2.3.2: I did not consider all the procedure-specific complications of PD. No data were available from RCTs and there was a high degree of heterogeneity between the included studies. Chapter 3.1: due to the number of topics covered, certain sections were very concise. Not all essential preoperative variables were considered and studies with less than 100 cases were not included. A MA was not performed due to the large number of variables. Chapter 3.2: I did not consider all intraoperative factors which might affect PD outcomes and, whilst I attempted to summarise the most important studies, I did not include all relevant studies.

Preliminary single centre study

This study was a single centre, retrospective study with a relatively small sample size. It had a long procurement period (some cases were performed as far back as 2006), and practice likely evolved during the study window. This, along with the definitions used, might help to explain the relatively high number of PDAC patients with a positive resection margin status. Patient selection and surgical techniques have likely improved considerably since 2006. When investigating the impact of the selected variables on perioperative and oncological outcomes, we were not able to consider all relevant variables, or the impact of confounding factors. We were unable to perform independent analyses due to the small sample size. Our study was also affected by the fact that a relatively low number of patients achieved five-year survival.

Chapter 5.2: we did not consider all possible complications and risk factors. Our results suggested there was a correlation between serious complications and not receiving AC, but this did not demonstrate causation. We accept that patients who did not receive AC may have represented a more comorbid cohort. However, their age, BMI, ASA grade and cardiorespiratory comorbidities were similar to those who received AC. We acknowledge that there are other factors, aside from postoperative complications,

which can affect whether patients receive AC. Two patients had to be excluded from the AC vs no AC analysis due to missing data.

RAW study

The RAW study had several limitations. Firstly, it was retrospective, so both recall bias and inadequate clinical documentation may have affected our findings. Although, after initial screening, a large proportion of patients were excluded, almost all were removed for a valid reason (see cohort flow diagrams). Further, standard practice will likely have differed between the included units. As our data is historic, we accept that practice will have evolved. Whilst we have compiled a robust dataset, it was not 100% complete. Wherever data were missing, we have clearly stated the number of patients this involved and excluded these from the relevant sub-analyses. Also, as is inevitable with large multicentre studies, the larger high-volume centres provided more cases than the smaller low-volume centres.

Prior to centres being included in the study, an online induction took place with a core member of the RAW study team. However, physical site visits did not take place as this would have been impractical due to the geographical location of the centres. The RAW team had to assume that data were entered correctly and that all data collectors acted in an appropriate manner. Whilst a data checking and cleaning process did take place, the study relied heavily on the trustworthiness of the original data collectors. With hindsight, it may have been reasonable to ask the local principal investigator at each site to perform “spot checks”. The RAW data set was vast so it would not have been practical for a core member of the team to collect all of the data. In any case, the core RAW team would not have been authorised to access the medical records of patients from the collaborating centres. All data collectors were listed as collaborating authors on all of the papers which came out of the RAW study. One would hope this would have incentivised them to enter the data correctly.

Chapter 6: whether or not NS was provided, and how this was provided, was entirely at the discretion of the treating team and no patients were included/excluded due to variations in practice. Also, we did not know the preoperative nutritional status of the included patients, or the reason NS was provided to individuals (i.e., whether this was routine practice or due to preoperative malnutrition or postoperative complications). As such, we were only able comment on the patterns of NS and could not identify risk factors for requiring NS. Our dataset did not contain the specific details on the NS provided e.g., timing, dosing, or length of treatment. In addition, because of the way the data were collected, patients who were given oral nutritional supplements only were categorised as receiving NS. We could not distinguish these patients from those who were fed via the NG/NJ route. Further, we could not determine which complications resulted from NS. Therefore, we were unable to quantify the risks associated with NS.

Chapter 7.1: only the procedure-specific complications of PD were graded using internationally recognised criteria; the remainder were diagnosed clinically. Due to missing data, the multivariable analysis did not include the entire patient cohort. Chapter 7.2: patients who died within 90 days of PD were excluded but some of these may have already commenced AC. It is likely that practice evolved during the research period e.g., most patients that commenced AC received gemcitabine only, whereas multimodal therapy is now the standard of care. Whilst our results suggested there was an inverse relationship between serious complications and commencing AC, this did not demonstrate causation. Although we accept that the patients who commenced (and completed) AC may have represented a less comorbid cohort than those who did not, the groups were similar in terms of sex, BMI, preoperative comorbidities, staging, preoperative treatment and preoperative blood tests. We acknowledge that other factors, aside from postoperative complications, can affect whether a patient receives AC or not.

Chapter 8: whilst most of the identified prognostic features were histological, a second review of the histology reports did not take place (the original reports were assumed to be correct). Due to limited data, we were not able to accurately investigate

the impact of the AA subtype on long-term outcomes. Although we collected data on preoperative blood tests, we did not consider serum CEA and CA 19-9, as some other studies have done.

Statistical methods

The originally submitted version of this thesis contained some minor statistical errors that were pointed out at the time of the viva voce examination. Firstly, the Kaplan-Meier plots did not include tables outlining the numbers at risk. These have now been included. Secondly, it was noted that the multivariable analysis in Chapter 6 had included variables that were not significant following the univariable analysis. Strictly speaking, this analysis should have only included the variables which were significant following the univariable analysis.

9.3. Conclusions

Key findings:

1. In total, 45% of the RAW cohort received some form of postoperative NS
    I. This was “enteral only”, “parenteral only” and “enteral and parenteral” in 44%, 35% and 21%, respectively
2. Among the RAW patients that had a relatively uneventful postoperative recovery, 20% received postoperative PN
3. Among the RAW cohort, overall morbidity, major morbidity and 90-day mortality rates were 53%, 17% and 4%, respectively
    I. CR-POPF, PPH, chyle leak, bile leak and gastro-jejunal anastomotic leak affected 8%, 6%, 4%, 3% and 2%, respectively

II. A high BMI and a high ASA grade were predictors of the adverse perioperative outcomes studied

4. Among the RAW PDAC cohort, those who experienced a serious postoperative complication commenced AC less frequently
    I. The survival benefit of AC was demonstrated
5. Among the RAW AA cohort, numerous predictors of actual five-year recurrence/survival were identified
    I. Most of these were histopathological features
    II. The patients that developed local only recurrence were statistically similar to the group that developed distant (+/- local) recurrence

Implications for future practice/research

Findings 1 and 2 highlight that a considerable number of patients received PN when this may not have been the most appropriate feeding method. PN is not risk-free so surgeons should only provide it when it is clinically indicated. Nutrition professionals should be involved preoperatively to ensure perioperative outcomes are optimised and unnecessary risks are avoided.

Finding 3 can be used to guide patient selection and the consenting process. Patients should only be offered PD if they are an appropriate surgical candidate and if there is a realistic chance of them obtaining a favourable long-term outcome. Patients should also have a clear understanding of the risks they face as the decision to opt for a PD is huge and should be a well-informed one. Finding 3 will also be of use to pancreatic surgeons who should regularly carry out audits to benchmark their own complication rates. They may wish to adapt their practice if they find their patients are outliers in any particular category.

Finding 4 highlighted the need for a study which aims to produce a model that can accurately predict which PD patients are likely to experience serious postoperative

complications. A serious complication can affect a patient's suitability for AC, which can significantly prolong OS. As such, the potential complication risk should arguably influence the decision to offer PD or NAC (not currently recommended in patients with resectable disease in the UK). Further, if high-risk patients can be identified preoperatively, this group can be targeted with preoperative optimisation strategies.

Finding 5 highlighted that AA patients with certain histopathological features are more likely to experience disease recurrence and less likely to achieve five-year survival. This information can be used to predict individual patient outcomes. Patients with these features are high-risk and arguably should be considered for trials involving AC and/or earlier/more intensive surveillance. The latter might result in the earlier diagnosis of recurrence and have implications for further treatment or QoL. The fact that the patients who developed local only recurrence were statistically similar to those that developed distant (+/- local) recurrence highlights the difficulties clinicians face when attempting to tailor treatment to individuals.

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Supplementary material

Supplementary tables

Criterion	Biochemical leak (formerly grade A POPF)	Grade B POPF	Grade C POPF
Drain amylase three times the upper limit of the normal serum value	Yes	Yes	Yes
Persisting pancreatic drainage for more than three weeks	No	Yes	Yes
Clinically relevant* change to patient management	No	Yes	Yes
Percutaneous or endoscopic treatment for a POPF-related collection	No	Yes	Yes
Angiographic procedure for POPF-related bleeding	No	Yes	Yes
Reoperation for POPF	No	No	Yes
Signs of infection related to POPF	No	Yes (without organ failure)	Yes (with organ failure)
POPF-related organ failure**	No	Yes	Yes
POPF-related death	No	No	Yes

Table S1: Classification of POPF. In the text Grade B and Grade C POPF have collectively been referred to as CR-POPF. *Suggests prolongation of hospital/critical care stay, includes the use of therapeutic agents specifically employed for fistula management or its consequences (includes somatostatin analogues, parenteral nutrition, blood products and other medications). **Postoperative organ failure is defined as the need for reintubation, haemodyalysis and/or inotropic agents for more than 24 hours for respiratory, renal or cardiac insufficiency, respectively. Definitions according to the 2016 ISGPS.

Criterion	Grade A bile leak	Grade B bile leak	Grade C bile leak
Clinical condition	Mildly impaired	Moderately impaired	Severely impaired
Symptoms/signs	Commonly none	Abdominal pain +/- signs of infection	Life-threatening condition +/- organ failure +/- biliary peritonitis
Persistent biliary leakage for more than one week	No*	Commonly yes	Yes
Need for diagnostic assessment	No	Commonly yes	Yes
Positive radiological findings (e.g., biloma, abscess or leak)	Possibly yes	Commonly yes	Commonly yes
Relaparotomy required	No	No	Yes
Prolonged hospital stay	Commonly no	Commonly yes	Yes

Table S2: Classification of postoperative bile leak (BL). *Patients with a Grade A BL persisting for more than one week are diagnosed with Grade B leakage regardless of the need for therapeutic intervention. Definitions according to the 2011 ISGLS.

Criterion	Grade A PPH	Grade B PPH	Grade C PPH
Time of onset, location, severity and clinical impact of bleeding	Early, intra- or extraluminal, mild	Early, intra- or extraluminal, severe Late, intra- or extraluminal, mild	Late, intra- or extraluminal, severe
Clinical condition	Well	Often well/intermediate, very rarely life-threatening	Severely impaired, life-threatening
Diagnostic consequence	Observation, blood count, USS +/- CT	Observation, blood count, USS, CT angiogram, endoscopy if bleeding is intra-luminal	CT angiogram, endoscopy if bleeding is intraluminal
Therapeutic consequence	None	Transfusion of fluid/blood, high level or critical care bed, therapeutic endoscopy if intraluminal, embolisation, relaparotomy for early PPH	CT angiography and embolisation, endoscopy if intraluminal or relaparotomy and intensive care stay

Table S3: Classification of PPH. Timing: early: within 24 hours of the index operation, late: more than 24 hours after the index operation. Severity: mild: small/medium volume blood loss, decrease in haemoglobin concentration <30g/L, maximum treatment required is volume resuscitation or blood transfusion, no need for reoperation or angiographic treatment, severe: large volume blood loss, haemoglobin decrease >30g/L, clinically significant signs of blood loss, need for three or more units of blood, need for angiographic treatment or relaparotomy. Definitions according to the 2007 ISGPS.

Criterion	Grade A DGE	Grade B DGE	Grade C DGE
NG tube required	4-7 days OR reinsertion >3d post-op	8-14 days OR reinsertion >7d post-op	>14 days OR reinsertion >14d post-op
Unable to tolerate solid oral intake by post-op day	7	14	21
Vomiting/gastric distension	Possibly	Yes	Yes
Use of prokinetics	Possibly	Yes	Yes

Table S4: Classification of DGE. Definitions according to the 2007 ISGPS.

Grade	Definition
1	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic or radiological interventions. Allowed therapeutic regimens are: antiemetics, antipyretics, analgesics, diuretics, electrolytes and physiotherapy.
2	Requiring pharmacological treatment with drugs other than such allowed for grade 1 complications. Blood transfusions and parenteral nutrition are also included.
3a	Requiring surgical, endoscopic or radiological intervention under local or regional anaesthesia
3b	Requiring surgical, endoscopic or radiological intervention under general anaesthesia
4a	Life-threatening complication requiring critical care management (single organ failure)
4b	Life-threatening complication requiring critical care management (multiorgan failure)
5	Death of patient

Table S5: CD classification of surgical complications.

RAW study details

ClinicalTrials.gov identifier:
NCT04596865

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Collaborator:
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Approved by:
North West – Greater Manchester South Research Ethics Committee (20/NW/0397)
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University Hospitals Plymouth NHS Trust

RAW study protocol

Recurrence After Whipple's (RAW)

An international multicentre retrospective cohort study investigating factors affecting cancer recurrence following pancreaticoduodenectomy for pancreatic ductal adenocarcinoma, ampullary adenocarcinoma and distal bile duct cholangiocarcinoma

Version 1.4: 15th July 2021

IRAS Number: 280423

REC Reference: 20/PR/0464

SPONSORS Number: 20/GAS/413

FUNDERS Number: N/A

This protocol describes the study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the NHS UK Policy Framework for Health and Social Care Research (2017). It will be conducted in compliance with the protocol, the Data Protection Act (2018) and other regulatory requirements as appropriate.

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University Hospitals Plymouth NHS Trust

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

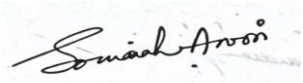
For and on behalf of the Study Sponsor:

Signature:  Date: 15/07/2021

Name (please print): Christopher Rollinson

Position: Research Governance Manager

Chief Investigator:

Signature:  Date: 15/07/2021

Name (please print): Somaiah Aroori

University Hospitals Plymouth NHS Trust

GLOSSARY OF ABBREVIATIONS

AA	Ampullary Adenocarcinoma
CI	Chief Investigator
CA	Coeliac Artery
CBD	Common Bile Duct
CT	Computed Tomography
DBCC	Distal Bile duct Cholangiocarcinoma
DFS	Disease Free Survival
FFPE	Formalin Fixed Paraffin Embedded Tissue
GDPR	General Data Protection Regulation
HA	Hepatic Artery
HPB	Hepatopancreaticobiliary
HRA	Health Research Authority
MI-LAP UK	Minimally Invasive Liver and Pancreatic Surgical Society UK
NHS	National Health Service
NRES	National Research Ethics Service
OS	Overall Survival
PD	Pancreaticoduodenectomy
PDAC	Pancreatic ductal adenocarcinoma
PHM	Pancreatic Head Malignancy
PI	Principal Investigator
PIMS	Patient Information Management System
PV	Portal Vein
R&D	NHS Trust R&D Department
RD&I	Research Development & Innovation
REC	Research Ethics Committee
SMA	Superior Mesenteric Artery
SMV	Superior Mesenteric Vein
SOP	Standard Operating Procedure
TNM	Tumour Node Metastasis
UHPNT	University Hospitals Plymouth NHS Trust
UICC	Union for International Cancer Control

KEY WORDS	Pancreatic cancer Ampullary cancer Cholangiocarcinoma Pancreaticoduodenectomy Cancer recurrence

University Hospitals Plymouth NHS Trust

STUDY SUMMARY

Study Title	Recurrence After Whipple's (RAW): An international multicentre retrospective cohort study investigating factors affecting cancer recurrence following pancreaticoduodenectomy for pancreatic ductal adenocarcinoma, ampullary adenocarcinoma and distal bile duct cholangiocarcinoma
Study Design	Multicentre Cohort study (retrospective observational)
Study Participants	Patients who underwent pancreaticoduodenectomy (PD) between 01/06/2010* and 31/05/2015 for histologically-confirmed adenocarcinoma of the pancreatic head, ampullary region, and distal portion of the common bile duct (hereafter collectively referred to as pancreatic head malignancy (PHM)) (*01/05/2006 for Plymouth sub-study)
Eligibility Criteria	Inclusion Criteria: 1. Patients who underwent PD for pancreatic head malignancy. 2. Date of surgery from 01/06/2010* to 31/05/2015 inclusive (*01/05/2006 for Plymouth sub-study). 3. Post-operative surgical histology confirmed pancreatic ductal adenocarcinoma (PDAC), ampullary adenocarcinoma (AA) or distal bile duct cholangiocarcinoma (DBCC). Exclusion Criteria: 1. Postoperative surgical histology confirmed benign pathology, non-invasive neoplasia or malignant tumours other than adenocarcinoma of pancreatic, ampullary or biliary origin. 2. Patients who underwent distal pancreatectomy or total pancreatectomy as their primary procedure. 3. Patients in whom five-year follow up data is not available.
Planned Sample Size	276 local patients with contributions from 19 other centres in the UK and 12 international centres (minimum 3000 patients expected).
Follow-up Duration	Five years from date of surgery or date of death, whichever is sooner.

Planned Study Period01/06/2010* – 31/05/2020 (*01/05/2006 for Plymouth sub-study).

Primary Objective To evaluate pre-operative, peri-operative and histological predictors of patterns of disease recurrence following pancreaticoduodenectomy (PD) for pancreatic ductal adenocarcinoma (PDAC), ampullary adenocarcinoma (AA) and distal bile duct cholangiocarcinoma (DBCC)

Secondary Objectives Determine if/how morbidity, mortality, disease free survival (DFS) and overall survival (OS) following PD for pancreatic head malignancy are affected by the following factors:

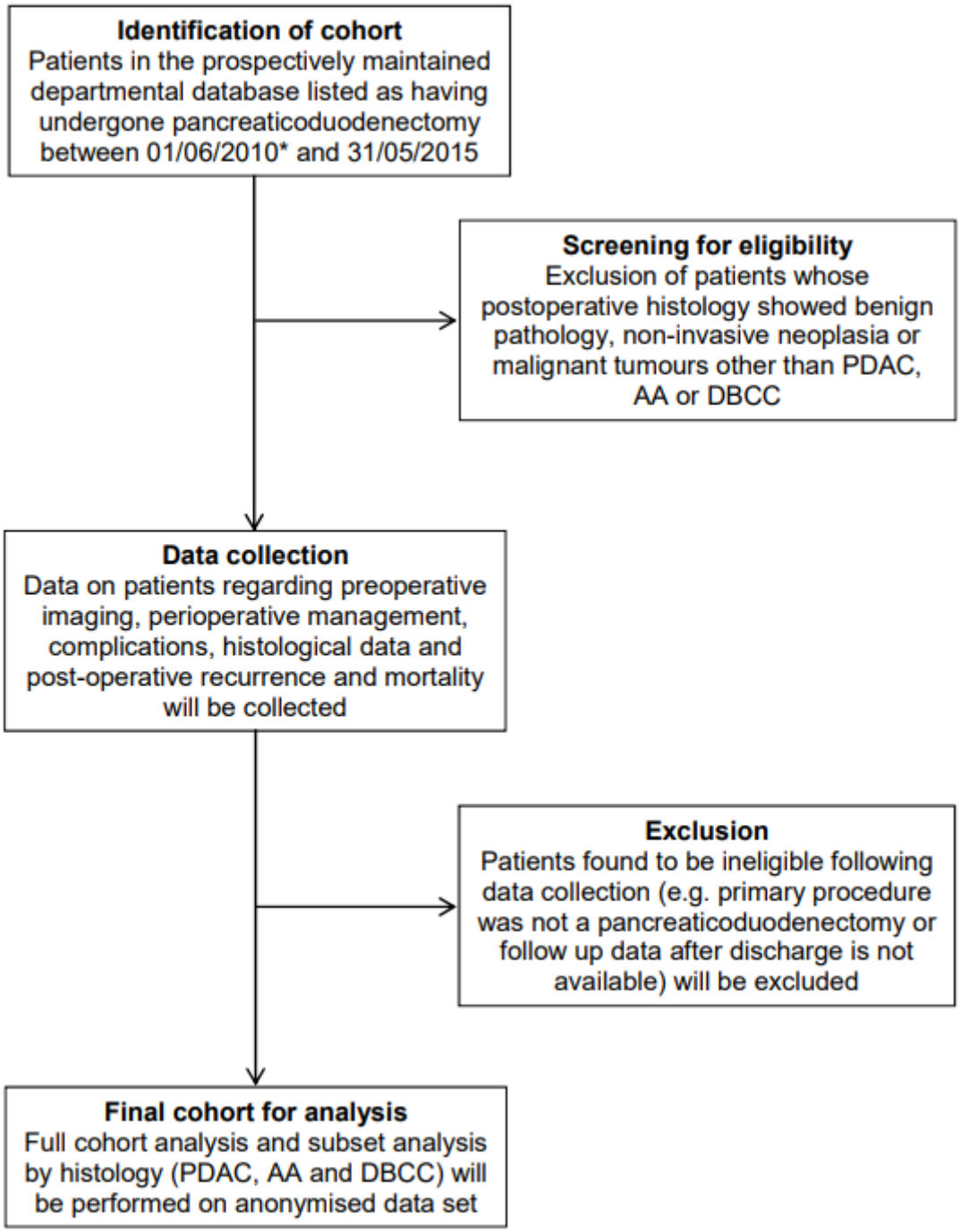
- The use of pre-operative endoscopic or percutaneous biliary stenting.
- Pre-operative systemic comorbidities.
- Pre-operative diagnosis of diabetes.
- Pre-operative radiological UICC Tumour Node Metastasis (TNM) staging.
- Named vessel involvement on pre-operative imaging.
- Sarcopenia or myosteatosis present on pre-operative imaging.*
- The use of neoadjuvant chemotherapy/radiotherapy.
- Pre-operative serum bilirubin.
- Portal Vein (PV) / Superior Mesenteric Vein (SMV) resection.
- Hepatic Artery (HA) / Superior Mesenteric (SMA) / Coeliac Artery (CA) resection
- Need for peri-operative blood transfusion.
- Type of pancreatic anastomosis [pancreatico-gastric (PG) vs. pancreatico-jejunal (PJ)].
- Post-operative complications.
- The use and number of post-operative drains.
- Histological factors:
    - Primary tumour site (pancreas, ampulla or distal common bile duct (CBD))
    - Primary tumour size (mm)
    - Pathological TNM stage
    - Resection margin status, distance from tumour to margin and whether an involved margin in involved directly by tumour, by an involved node, by perineural invasion and / or by lymphovascular invasion.
    - Lympho-vascular invasion
    - Perineural invasion
    - Differentiation
- The use of adjuvant chemotherapy.
- The use of palliative chemotherapy.

Determine if/how specific patterns of recurrence (local only, distant only, synchronous local and distant) following PD are affected by the following factors:

- Preoperative TNM staging.
- Named vessel involvement on preoperative imaging.
- The use of neoadjuvant chemotherapy/radiotherapy.
- PV/SMV resection.
- HA/SMA/CA resection.
- Histological factors
    - Primary tumour site (pancreas, ampulla or distal common bile duct (CBD))
    - Primary tumour size (mm)
    - Pathological TNM stage
    - Resection margin status, distance from tumour to margin and whether an involved margin in involved directly by tumour, by an involved node, by perineural invasion and / or by lymphovascular invasion.
    - Lympho-vascular invasion
    - Perineural invasion
    - Differentiation
- The use of adjuvant chemotherapy.
- The use of palliative chemotherapy.

*Plymouth sub-study only

STUDY FLOW CHART



PDAC = pancreatic ductal adenocarcinoma
AA = ampullary adenocarcinoma
DBCC = distal bile duct cholangiocarcinoma

*01/05/2006 for Plymouth sub-study

1. INTRODUCTION

1.1 Lay summary

Pancreatic cancers are aggressive cancers that are often inoperable when they are diagnosed. In the ~20% of patients who are diagnosed when the disease is still operable, surgery is the only treatment that can provide a chance of cure. Unfortunately, up to 75% of patients undergoing surgery will have the cancer come back (recur). One of the reasons for this is the challenge of removing the whole tumour with some surrounding normal tissue to ensure that every tumour cell has been removed. This is difficult because there are many structures very close to the pancreas (such as the blood vessels that supply the intestines) that cannot be removed. A recent review study of >1700 patients who had a Whipple's operation (the cancer operation that is performed to remove the head of pancreas) and found that whilst the majority of patients had cancer recurrence in distant sites (like the liver) that would not be affected by how the operation was performed, 12% of patients had the cancer recur just at the site of where the operation had been (so-called 'local' recurrence). This suggests that a small amount of cancer was not removed at the time of surgery in these patients. Very few studies have looked at the relationship between the Computed Tomography (CT) scan before surgery and the histology results (information about the tumour after it has been examined under the microscope) and whether this can predict exactly where the tumour recurs. If we can find predictors of local cancer recurrence, we may be able to offer improved surgical techniques or other therapies during or immediately after the operation, hopefully leading to improved cure rates.

1.2 Background

Pancreatic head resection is indicated for the treatment of malignancy arising from the proximal pancreatic duct, distal common bile duct, ampulla of Vater and the peri-ampullary duodenum. Cancers arising from these sites often cause obstruction of the distal common bile duct within the pancreatic head leading to a similar presentation with obstructive jaundice. Usually the histological diagnosis is made after resection.

Pancreatic ductal adenocarcinoma (PDAC) is a cancer arising from the pancreatic ductal epithelial cells and carries a poor prognosis. It is the 10th most common cancer in the United Kingdom with an incidence of around 10,300 cases per year.[1] The overall five-year survival rate is 3%[1] which increases to 15-25% in the subgroup able to undergo pancreatic resection.[2] Current evidence suggests that only 13-22% of pancreatic cancers are eligible for resectional surgery.[2]

Ampullary adenocarcinoma (AA) arises from the epithelium of the Ampulla of Vater, into which the common bile duct and pancreatic duct drain. Ampullary tumours are usually diagnosed at an earlier stage than PDAC due to causing visible jaundice early in the disease process. They have a less aggressive clinical course with an overall five-year survival rate of 37-64%.[3]

Cholangiocarcinomas arise from the bile duct epithelium. These may occur within the intra-pancreatic portion of the distal common bile duct and mimic pancreatic cancer. Survival following treatment of these lesions is intermediate between that of PDAC and ampullary cancer.[4] Only distal bile duct cholangiocarcinoma (DBCC) is treated by a Whipple's operation, with more proximal disease being treated by excision of the bile duct and/or liver depending on the site of disease.

Due to the late onset of specific symptoms, only 13-22% of patients with PDAC, AA or DBCC (hereafter collectively referred to as pancreatic head malignancy (PHM)) undergo curative-intent surgery.[2] Should surgery be feasible, the most commonly performed procedure for PHM is pancreaticoduodenectomy (PD). Unfortunately, the majority of patients who undergo surgery will develop postoperative disease recurrence. A recent systematic review of patients undergoing PD for PDAC (23 studies, n=3815) found that 47-92% of patients developed recurrence.[5] In the 11 studies that reported on the site of recurrence (n=1713), 12% of resected patients developed local recurrence at the resection site with no distant metastases. A large retrospective study from John Hopkins Hospital (n=692) investigated patterns of recurrence following resection for PDAC and found that after a median follow up of 25.3 months, 531 patients (76.7%) developed disease recurrence (**Table 1**).[6]

Table 1 Site of recurrence following curative-intent pancreatic cancer surgery for PDAC

Site	Frequency (n)	Percentage (%)
No recurrence	161	23.3
Multiple site	176	25.4
Liver only	134	19.4
Local only	126	18.2
Lung only	78	11.3
Other	17	2.4

Adapted from Groot et al.[6]

It is likely that patients who develop isolated distal recurrence (e.g. liver, lung) in the absence of local disease recurrence (i.e. pancreatic bed) had early systemic dissemination of their cancer that was not radiologically or clinically apparent at the time of surgery. In this cohort, it is unlikely that any further enhancement to operative techniques will reduce recurrence rates. Similarly, patients who recur with local and distal recurrence simultaneously are likely to have had aggressive tumour biology with early systemic disease dissemination that would not achieve higher cure rates from changes to surgical techniques. However, in the cohort who develop isolated local recurrence, this pattern suggests a favourable tumour biology (less capable of early systemic dissemination) but a small volume of residual tumour that was not identified during resection. This cohort of patients are the most likely to benefit from enhancements to current surgical techniques and practice, such as intraoperative or adjuvant locoregional therapies. However, it is not currently known how to identify this cohort of patients.

1.3 Rationale for current study

To understand how to best tailor treatment to improve cure rates, both the patterns of recurrence and the factors that influence the likelihood of recurrence need to be fully understood. The outcomes of surgery, post-operative complications and associated mortality following PD for PHM have been investigated by many centres. Mortality is an easily measured and reliable end-point, which usually

occurs as a result of post-operative complications or as a consequence of tumour recurrence. Long-term survival is well described for the three tumour types under investigation, both in case-matched studies[7,8] and in unselected populations[4,9,10] undergoing surgery. However, the most likely site of tumour recurrence (local, regional or distant), has only recently been investigated.[5,6] The relative prognostic significance of first recurrence at the most common sites (local, nodal, hepatic or pulmonary) is also not well described. There is potentially a role for liver resection in the event of isolated hepatic metastases from ampullary and cholangiocarcinoma, but this is rarely undertaken. Assessment of recurrence patterns may demonstrate the frequency of this occurrence and provide a rationale for resection of isolated metastases in selected cases.

In addition, there are many known factors that influence the likelihood of recurrence, such as the use of pre-operative or adjuvant chemotherapy, the proximity of the tumour to the surgical margin ('R' status), and whether or not there was evidence of lymphovascular or perineural involvement in the surgical specimen, as well as tumour size. Furthermore, the width of uninvolved resection margin required to fulfil the criteria for tumour involvement varies in different staging systems. The Royal College of Pathologists dataset states that 1mm of uninvolved tissue must be present, whereas the American College state only that the margin itself must be uninvolved, and do not stipulate a margin thickness. Correlation of recurrence patterns with resection margin status may reveal if there is a requirement for a minimum thickness of uninvolved margin. In addition, the potential association of other pathological staging elements with recurrence pattern has not been performed. The finding of nodal involvement at the time of surgery may influence the likelihood of developing locoregional rather than distant metastases.

There are also a number of other factors which may influence likelihood of recurrence that have not been fully explored yet. For example, detailed information on whether the specific site of local recurrence is more closely related to the specific tumour site within the pancreas (e.g. medial, overlying or lateral to the superior mesenteric vessels). There is also some evidence that suggests sarcopenia and myosteatosis (low bone density and fat deposition in the muscle that can be objectively quantified using the preoperative CT)[11] may indicate a higher risk of postoperative complications, although whether or not this leads to a reduced disease-free survival (DFS) or overall survival (OS) is not yet established.[12] To draw conclusions on the influence of histology on the patterns of local recurrence, these other factors need to be taken into account as confounding variables that influence DFS and OS.

1.4 Participant and Public Involvement

This retrospective cohort study does not involve any patient contact and uses data already collected as part of routine hospital care. Participant and public involvement have not been sought for this study.

2. STUDY OBJECTIVES

2.1 Primary objectives

To evaluate pre-operative, peri-operative and histological predictors of patterns of disease recurrence following pancreaticoduodenectomy (PD) for pancreatic ductal adenocarcinoma (PDAC), ampullary adenocarcinoma (AA) and distal bile duct cholangiocarcinoma (DBCC).

2.2 Secondary objectives

- Determine if/how morbidity, mortality, disease free survival (DFS) and overall survival (OS) following PD for pancreatic head malignancy are affected by the following factors:
    - The use of pre-operative endoscopic or percutaneous biliary stenting.
    - Pre-operative systemic comorbidities.
    - Pre-operative diagnosis of diabetes.
    - Pre-operative radiological UICC Tumour Node Metastasis (TNM) staging.
    - Named vessel involvement on pre-operative imaging.
    - Sarcopenia or myosteatosis present on pre-operative imaging.*
    - The use of neoadjuvant chemotherapy/radiotherapy.
    - Portal Vein (PV) / Superior Mesenteric Vein (SMV) resection.
    - Hepatic Artery (HA) / Superior Mesenteric (SMA) / Coeliac Artery (CA) resection
    - Need for peri-operative blood transfusion.
    - Type of pancreatic anastomosis [pancreatico-gastric (PG) vs. pancreatico-jejunal (PJ)].
    - Post-operative complications.
    - The use and number of post-operative drains.
    - Histological factors:
        - Primary tumour site (pancreas, ampulla or distal common bile duct (CBD))
        - Primary tumour size (mm)
        - Pathological TNM stage
        - Resection margin status, distance from tumour to margin and whether an involved margin in involved directly by tumour, by an involved node, by perineural invasion and / or by lymphovascular invasion.
        - Lympho-vascular invasion
        - Perineural invasion
        - Differentiation
    - The use of adjuvant chemotherapy.
    - The use of palliative chemotherapy.
- Determine if/how specific patterns of recurrence (local only, distant only, synchronous local and distant) following PD are affected by the following factors:
    - Preoperative TNM staging.
    - Named vessel involvement on preoperative imaging.
    - The use of neoadjuvant chemotherapy/radiotherapy.

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    - Lympho-vascular invasion
    - Perineural invasion
    - Differentiation
- The use of adjuvant chemotherapy.
- The use of palliative chemotherapy.

*Plymouth sub-study only

2.3 Outcome measures

- Disease free survival
- Overall survival
- Sites of cancer recurrence

3. STUDY DESIGN AND METHODS

3.1 Research window

This retrospective observational cohort study will investigate the outcomes of patients who underwent pancreaticoduodenectomy at 32 HPB units in the UK and abroad between 01/06/2010 and 31/05/2015. These dates were chosen because:

- Most HPB units would expect to see 30-50 patients undergoing PD per annum. Based on our unit's prospectively maintained database of consecutive patients, 310 patients underwent PD during this window (benign and malignant). A five year research window would provide a large number of patients that is appropriate for subset analysis. This is especially important in DBCC, which is less commonly treated with PD compared to PDAC and AA. Even if all centres only provided 100 patients (20 per annum), this would provide a cohort of ~3000 patients. This number of cases will have greater resolution to detect small but significant statistical differences in studied variables. For example, if a post-operative wound infection causes a very small increase in the rate of cancer recurrence then this may not reach statistical significance amongst our unit's patients, but might be apparent using the multi-centre cohort.
- The amount of data available on patient records reduces with chronicity, in part due to a heavier reliance on paper rather than digital records. In addition, other reporting standards (e.g. TNM staging and histology reporting) change over time. 2010 was selected as a starting year as the 7th edition of the UICC TNM staging came into effect that year.
- An end date of June 2015 allows the study to collect full five-year follow up data on all patients to June 2020, thus providing a complete data set.

11.6 Data collection

Data will be collected by each participating centre on a purpose-built RedCap database. RedCap is a well-established secure web-based data collection tool that is frequently used in medical research involving several centres. Advantages include:

- Real-time collection of data from all centres visible to the research team.
- Guaranteed anonymity of patients as only anonymised data will be collected.
- In-built data validation (e.g. set limits on expected ranges of values) to reduce poor quality/erroneous data collection.
- Easy download of data into a format suitable for processing on an appropriate statistical software package (e.g. SPSS).
- The ability to display or hide questions based on previous responses to tailor data collection to each record.

RedCap access is provided through University Hospitals Plymouth NHS Trust (UHPNT). Data is stored on the Microsoft Azure web-based cloud service. Servers are based in the EU and are GDPR compliant. RedCap access will be provided to all participating centres (one user per centre) for data collection.

Data collected falls into the following categories (examples given after each category are not exhaustive):

- Participant ID number (anonymised).
- Demographics: Age, sex, body mass index.
- Comorbidities: Diabetes, cardiovascular disease, respiratory disease, previous history of cancer.
- Pre-operative imaging: Dates, modalities, maximum tumour size, radiological TNM stage.
- Pre-operative biliary drainage: Approach, stent type.
- Neoadjuvant therapies: Type, duration.
- Pre-operative bilirubin.
- Surgery: Date, type, ASA grade, intraoperative procedures and findings.
- Post-operative complications: Types, date of occurrence, Clavien-Dindo grade, treatment, 30-day readmission, 90-day mortality and cause of death.
- Histology: Cancer type, differentiation, tumour size, pathological TNM stage, R status, involved margins and distance, total and involved number of resected lymph nodes, perineural, microvascular and named vessel invasion.
- Adjuvant therapies: Type, duration.
- Recurrence: Date of recurrence, site(s) of recurrence.
- Palliative therapies: Type, duration.
- Survival: DFS and OS.

11.6 Screening of eligible patients

Patients will be screened to ensure that they meet the inclusion and exclusion criteria (see below). Each unit will be responsible for screening patients for eligibility. All participating units have confirmed that they already have an existing list of consecutive patients who underwent PD during the research window. The clinical team at each participating unit will be responsible for maintaining a password- protected participant look up database that links the local patient hospital number to the anonymised participant ID number on RedCap. This is so that the local team can know which patient is represented by each RedCap record. The research team in Plymouth will not have access to the look up databases of other participating centres. The password for the look-up databases will only be known to local investigators who need this information to link hospital and RedCap data records.

Once data from all centres is uploaded onto RedCap, data analysis will be performed as per the statistics section below.

The sources of data will vary depending on the participating centre. In the UK, centres are likely to collect data from the following sources:

- Perioperative data, complications and 30-day outcomes will be collected from electronic and physical patient records by the HPB clinical team.
- Chemotherapy data and date of death will be collected from electronic and physical patient records and PIMS by the HPB clinical team or a cancer pathway co-ordinator.

- Histology data will be collected by the HPB or histopathology clinical teams. For the majority of patients, this will only require review of electronic histology reports.
- Pre-operative radiological staging and anatomical sites of cancer recurrence will be determined from CT / PET-CT imaging as recorded by the clinical team (HPB and radiology). This will be acquired through the local and regional radiology viewing program (InSightWeb, also known as PACS). In cases where recurrence is suggested but inconclusive, we will record the initial date that recurrence was suspected, only if this was subsequently confirmed on following scans. We will also record the CT reports suggesting abnormal soft tissue in the pancreatic resection to find out the whether the incidence of this being true recurrence versus simply scar tissue. If the imaging is not locally available, the clinical team will contact the relevant hospital via their cancer network to digitally import the images for local review. If the post-operative surveillance scans cannot be reviewed for any reason, then the patient will be excluded from analysis. This is because the primary outcome requires detailed information on the pattern of disease recurrence.

11.6 Plymouth sub-study on sarcopenia and myosteatosis

As stated above, there is evidence that sarcopenia and myosteatosis may indicate a higher risk of postoperative complications, although its impact on DFS and OS is not yet established.[12] Patients entered into the study from Plymouth will also have their pre-operative CT scan reviewed by a member of the research team trained in sarcopenia and myosteatosis estimation (an academic radiology trainee). For the evaluation of sarcopenia, a cross-sectional area of the muscle at the level of L3 vertebral body will be measured. Applying previously validated boundaries of −190 to −30 HU for fat tissue and −29 to 150 HU for skeletal muscle,[11] the total abdominal muscle area (cm^2), intramuscular fat area (cm^2), visceral fat area (cm^2), and subcutaneous fat area (cm^2) will be assessed. The total abdominal muscle area (cm^2) will be normalised for height (m^2) and reported as lumbar SMI. The clinicians taking the measurements will be unaware of any outcomes or complications.

This is not being extended to other centres for the following reasons:

- Normal values of tissue attenuation are specific to local populations due to the variation in morphology of patients and the HU cut-offs in one country are not applicable to other countries. It would therefore not be possible to pool data on myosteatosis and sarcopenia from multiple countries.
- As the measurement relies on pre-operative CT imaging, and CT scanners and protocols vary between hospitals and change over time, it is difficult to retrospectively pool such data from multiple sites and maintain meaningful data. Using a single centre provides more robust data for analysis.
- We will be using an inbuilt software package that is part of Plymouth's InSightWeb. This package may not be available in other centres.

As this reduces the number of patients in the cohort, Plymouth will extend its research window to 01/05/2006. This date was chosen as it is the beginning of our prospectively maintained database. This provides a pre-screened population of 365 patients who underwent PD at our unit, with a predicted 276 patients for analysis (see **6.2**).

11. STUDY PARTICIPANTS

4.1 Screening procedures

Patients on locally maintained patient databases that were recorded as having undergone a pancreaticoduodenectomy between 01/06/2010* and 31/05/2015 will be screened by the clinical team for eligibility (*01/05/2006 in Plymouth).

4.2 Inclusion Criteria

Participants will be included in the study if they meet ALL of the following criteria:

Inclusion Criterion 1: Patients who underwent PD for suspected PHM.

Justification: This research is focusing on outcomes for the most commonly performed procedure for operable PHM. Pylorus-preserving or classic PD are both eligible for inclusion.

Inclusion Criterion 2: Date of surgery from 01/06/2010* to 31/05/2015 inclusive (*01/05/2006 in Plymouth).

Justification: Five years of follow up is already available for patients operated on during these dates.

Inclusion criterion 3: Postoperative surgical histology confirmed PDAC (including large duct pattern, clear cell pattern and cystic papillary pattern adenocarcinomas), ampullary adenocarcinoma, NOS and distal bile duct cholangiocarcinoma, adenocarcinoma NOS.

Justification: PDAC, AA, and DBCC are the three most common cancers for which PD is performed. The number of patients for each of these histological subtypes will allow for analysis of cancer subtypes and will be the most clinically relevant.

4.3 Exclusion criteria

The participant may not enter the study if ANY of the following apply:

Exclusion criterion 1: Postoperative surgical histology confirmed benign pathology, non-invasive neoplasia, malignant tumours other than adenocarcinoma of pancreatic ductal, ampullary or distal bile duct origin, uncommon histological variants of PDAC, ampullary adenocarcinoma or distal bile duct cholangiocarcinoma (such as adenosquamous carcinoma) or mixed tumours (such as mixed neuroendocrine neoplasm-adenocarcinoma).

Justification: As the primary objective for the study is to determine factors affecting location

of cancer recurrence, patients with benign/non-invasive pathology on histology will be excluded. Patients with rare cancers (e.g. pancreatic neuroendocrine tumours, metastases to the pancreas, and uncommon histological variants of adenocarcinoma) will be a low number of cases and may follow different clinical courses postoperatively.

Exclusion Criterion 2: Patients who underwent distal pancreatectomy or total pancreatectomy as their primary procedure. However, patients who required total completion pancreatectomy following complications from pancreaticoduodenectomy are eligible.

Justification: This study is focused on identifying factors that influence recurrence following pancreaticoduodenectomy.

Exclusion Criterion 3: Patients in whom follow up data is not available.

Justification: Follow up to identify cancer recurrence and OS is necessary to identify which factors influence these outcomes.

11. STUDY PROCEDURES AND INTERVENTIONS

5.1 Recruitment

Relevant participants will be identified from the existing HPB databases at each participating centre and eligibility confirmed by review of electronic and physical patient records. No patients will be contacted for this study.

5.2 Consent

All data to be collected has already been recorded as part of routine hospital care and participants will not be contacted at any point during the study. Data will be collected by the clinical team in each participating centre and entered into a purpose-built database on RedCap that does not collect any patient identifiable information. Local principle investigators will maintain a password-protected look up database linking local hospital ID and RedCap ID. These will be stored on hospital computers according to local hospital data security protocols. All published data will be anonymised with no patient identifiable information used. Therefore, participant consent is not required.

5.3 Study assessments/ interventions

The intervention of PD occurred between 01/06/2010* and 31/05/2015. No new interventions or patient assessments will be conducted during this study (*01/05/2006 in Plymouth).

5.4 Definition of End of Study

The last data collection point is 31/05/2020 (five years after the last PD was performed). The investigators envisage that data collection and analysis will take twelve months from the date of ethical approval for the study.

6. STATISTICS AND DATA ANALYSIS

6.1 Analysis of endpoints

Exploratory analysis of the associations between the binary outcome of recurrent and potential categorical and continuous explanatory variables shall be conducted through logistic regression modelling. Exploratory analysis of the association between survival outcomes and potential explanatory variables shall be conducted using Cox regression models. Associations from the fitted models shall be deemed statistically significant at the 5% level with results presented with their 95% confidence interval.

Having a large number of variables in this study, machine learning and feature selection (branches of artificial intelligence) shall be performed to identify influential and meaningful historical factors which are predictive for disease recurrence, and explore how these factors affect the recurrence of disease. The published studies on journals, such as Nature, Lancet, New England Journal of Medicine, JAMA[13- 17] have demonstrated that machine learning holds the promises of analyse complex health datasets to unravel hidden information, such as rules and patterns related to patient activities, heath behaviours, life styles etc. to support medical decision making and improve health outcomes. For this study, machine learning driven predictive models shall be developed and used to predict recurrence of disease following PD by the identified factors. The blinded samples will be used to evaluate the model performance in terms of multiple measures – sensitivity, specificity, positive predictive values, negative predictive values, F_β score and AUC (area under the curve). Because the data in this study is extremely imbalanced, resampling and bagging techniques will be used in machine learning led data analysis.

6.2 The number of participants

The existing HPB database estimates that of the 365 patients that underwent a pancreaticoduodenectomy during the research window, 145 cases were PDAC, 55 cases were cholangiocarcinoma and 76 cases were ampullary cancer. We acknowledge these figures will change slightly once histology data is reviewed by the clinical team. However, additional data will be provided by other centres. This should afford greater power to detect associations in our analysis and improve the generalisability of the results.

We would expect 75% of the overall cohort to have a recurrence of cancer. This is likely to be elevated among the PDAC group. Based on existing HPB data, this can be seen to comprise approximately 40% of patients. Assuming a minimum sample size of 2000 patients and testing a null risk of 75%, we could expect to detect an elevated risk of 80% among the PDAC group with 82% power, using a chi- square test at the 5% significance level. The power calculations were performed in Stata version 14.2.

7. ETHICAL AND REGULATORY COMPLIANCE

7.1 Ethics and HRA approval

The Chief Investigator has obtained approval from the UK Health Research Authority (HRA) and Research Ethics Committee (REC). The Investigators will ensure that this study is conducted in full conformity with relevant regulations and with the UK Policy Framework for Health and Social Care Research (2017), which have their basis in the Declaration of Helsinki.

7.2 Confidentiality

To comply with the Data Protection legislation information will be collected and used fairly, stored safely and not disclosed to any unauthorised person. This applies to both manual and electronically held data.

The Chief Investigator will preserve the confidentiality of participants taking part in the study and ensure the EU General Data Protection Regulation (GDPR) in conjunction with the UK Data Protection Act 2018, which sets out the statutory requirements for the processing of personal data, is adhered to.

Only anonymised patient data will be collected on RedCap. The Plymouth RedCap is hosted on the Microsoft Azure cloud server. The servers are based in the European Union and comply with GDPR regulations. Patient identifiable information in the look-up tables will be password protected, stored on the hospital computers of participating centres, and be only accessible to the local clinical team at a participating unit. The research team will never ask for access to these databases.

RedCap will have a recording of the names, e-mail addresses and affiliations of contributors to the project. As these data are stored on the Microsoft Azure cloud server, they require the consent of the contributor to be stored. Consent will be presumed based on the fact that the contributors will be entering their details themselves. An appropriate privacy notice will be displayed on the collaborator entry page on RedCap.

7.3 Indemnity

This is an NHS-sponsored research study. If an individual suffers negligent harm as a result of participating in the study, NHS indemnity covers NHS staff and those people responsible for conducting the trial who have honorary contracts with the relevant NHS Trust. In the case of non- negligent harm, the NHS is unable to agree in advance to pay compensation, but an *ex-gratia* payment may be considered in the event of a claim.

7.4 Sponsor

UHPNT will act as the main sponsor for this study assuming overall responsibility for the initiation and management of the trial. Delegated responsibilities maybe assigned to other relevant parties taking part in this study and appropriately documented.

7.5 Funding

Funding has been provided by MI-LAPS (Minimally Invasive Liver and Pancreatic Surgical Society UK) charitable fund. Further funding has been requested from the Liver and Pancreatic R&D Cancer Charity, although MI-LAPS have stated that they are able to cover all associated research costs for this study if no further funding becomes available. Clinical research staff (Mr Matthew Browning and Mr Peter Labib) are salaried employees of the trust and will donate any time outside working hours for free. This is also the case for our radiology colleagues Dr Mark Puckett and Dr Andrew McCormick. A clinical research fellow undertaking an MD (Thomas Russell) is also joining the research team in April 2021, whose projects will include data collection for this study. His academic fees and salary are already covered elsewhere. Funding covers the cost of the statistician, one computer, open access publication fees for two articles and a contribution to conference fees/transport for research dissemination. There are no costs for other participating centres as RedCap access is provided for free. It is agreed that data will be collected at other centres by clinical research staff who are otherwise salaried and will be contributing data for free in exchange for appropriate recognition in the research output of the study.

7.6 Monitoring

The study will be subject to monitoring by UHPNT under their remit as sponsor to ensure adherence to the UK Policy Framework for Health and Social Care Research (2017). All UHPNT studies will be initially monitored at 25 days (+/- 7 days) after R&D capability and capacity has been given. The subsequent level of monitoring will be determined by a risk assessment, or on a for cause basis. The study may also be audited/ inspected by regulatory bodies to ensure compliance with national regulations.

8. STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated by the CI.

9. PUBLICATION POLICY

Final results of the study will be disseminated via presentations at appropriate scientific meetings and conferences and publication in appropriate peer-reviewed journals. Authorship will involve named individuals and the collaborative authorship model based on contributions to individual publications.

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