THE EPIDEMIOLOGY OF ABDOMINAL PAIN IN INOPERABLE PANCREATIC CANCER AND THE POTENTIAL ROLE OF EARLY ENDOSCOPIC ULTRASOUND-GUIDED COELIAC PLEXUS NEUROLYSIS

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Doctor of Medicine (MD)

DECLARATION

This dissertation and the work presented in it are my own and have been generated by me as the result of my own original research.

I confirm that:

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2. This work has not been submitted for a degree, diploma, or any other qualification at this University or any other institution;
3. Where I have consulted the published work of others, this is always clearly attributed;
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Dr Andreas Koulouris

THESIS ABSTRACT

Abdominal pain commonly affects patients with inoperable pancreatic cancer. Its management relies mainly on strong opioid analgesia which is often ineffective, requires dose escalation and risks significant side-effects. Endoscopic ultrasound-guided coeliac plexus neurolysis (EUS-CPN) involves injecting a neurolytic agent into and/or around the coeliac plexus. It is often reserved for the latter stages of the patient's treatment pathway when opioids have failed to control pain or their side-effects are unacceptable. It is unclear whether early EUS-CPN could prevent severe pain and reduce opiate burden in this patient group.

This research aims to explore the rationale, feasibility and design considerations of a clinical trial of early versus on demand EUS-CPN in patients with advanced pancreatic cancer.

The first chapter reviews the anatomy and physiology of the normal pancreas, the clinical aspects of pancreatic cancer, the aetiopathogenesis of pain and its management.

The second chapter presents the results of a systematic review and meta-analysis of the efficacy of EUS-CPN in patients with pancreatic cancer-related abdominal pain. In addition, it estimates the individual efficacy of the three main technique variations of EUS-CPN: the central injection, the bilateral injection and the ganglia injection and provides a rationale for its use in clinical practice and in a future trial. The safety profile of EUS-CPN is also explored.

The third chapter reports a prospective observational study (The BAC-PAC study) where patients with newly diagnosed inoperable pancreatic cancer were followed up monthly with questionnaires on their pain levels, morphine use, quality of life and use of medical resources. This study provided data on pain-related and health economic parameters which would be assessed in a future trial. It also provides information on the methods of identification, recruitment and follow-up of patients in a future trial. Recruitment was hindered in part due to the COVID19 pandemic, and a separate study was developed to address this (chapter 5).

The fourth chapter presents the views of patients, their carers and pancreato-biliary endoscopists towards pain and endoscopic analgesia. Thematic analysis of interviews with an inductive and deductive approach was adopted. The experience of pain was found to be diverse among the patients and the intensity of pain is often under-reported. Low dose opioids are well-tolerated. The role of opioids is multi-dimensional: hypnotic, anxiolytic and soothing of the chemotherapy constitutional side-effects, such as generalised aches and myalgia. These properties may not be alleviated by EUS-CPN. Patients were sceptical towards pain-preventative endoscopies because their emphasis is placed

on imminent concerns, such as managing emotional distress or chemotherapy side-effects, rather than the potential for poorly-controlled pain in the future. The conduct and design of a future trial of early EUS-CPN requires effective communication with patients and their families, and strong Patient and Public Involvement (PPI) from the outset.

The fifth chapter details a longitudinal retrospective cohort study of 383 patients on the epidemiology of pain in patients with pancreatic cancer (PREDICT-PANC). This study was developed to meet key objectives of the BAC-PAC study given poor recruitment due to the COVID-19 pandemic. Pancreatic pain is prevalent in approximately 40% of patients in the first year of diagnosis. In 77% of the patients with pain, medical performance status was between 0 and 2, and should not be prohibitive of an endoscopic intervention, such as EUS-CPN. The median survival of those on opioids is 5.9 months. Clinical and radiological parameters at diagnosis are associated with the use of opioids at three months. A clinical model predictive of opioid use was constructed with good discrimination and calibration.

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ACKNOWLEDGEMENTS

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ABBREVIATIONS

AEC	Absolute Enhancement Change
Ach	Acetylcholine
APD	Accessory Pancreatic Duct
BAC-PAC	Best Analgesia Control in Pancreatic adenocarcinoma
BIT	Bilateral Injection Technique
BMI	Body mass index
CA 19-9	Cancer Antigen 19-9
CCK	Cholecystokinin
CFTR	Cystic Fibrosis Transmembrane Conductance Regulator
CI	Confidence Interval
CIT	Central Injection Technique
CITL	Calibration-in-the-large
COVID19	Corona Virus Disease 2019
CP	Coeliac Plexus
CT	Computerised Tomography
CTRC	Chymotrypsin C
E:O	Expected-to-Observed (refers to calibration plot)
ERCP	Endoscopic Retrograde Cholangio-Pancreatography
EUS-CPN	Endoscopic Ultrasound-guided Coeliac Plexus Neurolysis
EUS-FNA	EUS-Fine Needle Aspiration
EUS-FNB	EUS-Fine Needle Biopsy
FAMMM	Familial Atypical Multiple Mole Melanoma
FDR	First Degree Relative
GRP	Gastrin Releasing Peptide
ICD-10	International Classification of Diseases- version 10
IMMPACT	Initiative on Methods, Measurement and Pain Assessment in Clinical Trials
IPMN	Intraductal Papillary Mucinous Neoplasm
IQR	Inter Quartile Range
LCRF	Luminal CCK-releasing factor
MCN	Mucinous Cystic Neoplasm
MMC	Migrating Myenteric Complex
MMR	Mismatch Repair
MPD	Main Pancreatic Duct
MRCP	Magnetic Resonance Cholangio-Pancreatography
NPV	Negative Predictive Value
PP	Pancreatic Polypeptide
PPV	Positive Predictive Value
PRSS	Serine Protease
PSSRU	Personal Social Services Research Unit
PTC	Percutaneous Transhepatic Cholangiogram
REC	Relative Enhancement Change
QoL	Quality of Life
SEER	Surveillance Epidemiology and End Result Registry
SCR	Somerset Cancer Registry
SIR	Standardised Incidence Ratio
SPINK1	Serine Peptidase Inhibitor Kazal type 1

T2DM	Type 2 Diabetes Mellitus
VIP	Vasoactive Intestinal Polypeptide
WHO	World Health Organisation

CHAPTER 1 - General Introduction

THE NORMAL PANCREAS

Anatomy

The pancreas is a 12 to 20 cm elongated gland located in the retroperitoneal abdominal space[1]. The gland is surrounded by a fine layer of connective tissue which separates it from adjacent structures[1]. It is divided in five main anatomical portions the: head, neck, body, tail and a projection of the lower end of the head towards the midline, called the uncinate process (**Figure 1**). Embryologically, the pancreas arises from two outgrowths of the foregut, called buds or anlagen, which appear at the fifth week of gestation[2]. These both are located at the level of the foregut which later forms the duodenum. One outgrowth develops ventrally and the other dorsally. The ventral outgrowth gives rise to the biliary system, liver and part of the head of pancreas and the uncinate body. The dorsal outgrowth develops into the rest of the pancreatic head, the neck, the body and the tail. At the seventh week of gestation, the dorsal outgrowth rotates medially around the duodenum and fuses with the ventral bud, to form the pancreas (**Figure 2**). The ventral outgrowth gives rise to the proximal portion of the main pancreatic duct (MPD) or Duct of Wirsung and the dorsal system gives rise to the distal portion of the Main Pancreatic Duct as well as the entire Accessory Pancreatic Duct (APD) or Duct of Santorini.

The following anatomical relationships are relevant to the symptoms of pancreatic cancer, management options and prognosis. The head of the pancreas anteriorly is surrounded by the pylorus superiorly and the second and third parts of the duodenum laterally and inferiorly, respectively. Posteriorly, it borders the inferior vena cava, the hilum of the right kidney and its renal vessels. The common bile duct crosses posteriorly to the head of pancreas in its distal end before draining into the second part of the duodenum. The uncinate process abuts the abdominal aorta, the inferior vena cava and the superior mesenteric arteries. The neck of the pancreas lies anteriorly to the confluence of the portal vein with the superior mesenteric and the splenic veins and posteriorly to the pylorus and the peritoneum. The body of the pancreas lies anteriorly to the abdominal aorta and the origin of the superior mesenteric arteries. Anteriorly it is covered by the omental bursa which separates it from the body of the stomach and its antrum. The tail of the pancreas projects into the hilum of the spleen and posteriorly abuts the left kidney and the left adrenal gland. The splenic vein runs along the superior border of the body and tail before entering the spleen[2].

Figure 1. The gross anatomy of the pancreas and the anatomical relationship with the neighbouring organs. Adapted from Pancreapedia: Exocrine Pancreas Knowledge Base (2021).

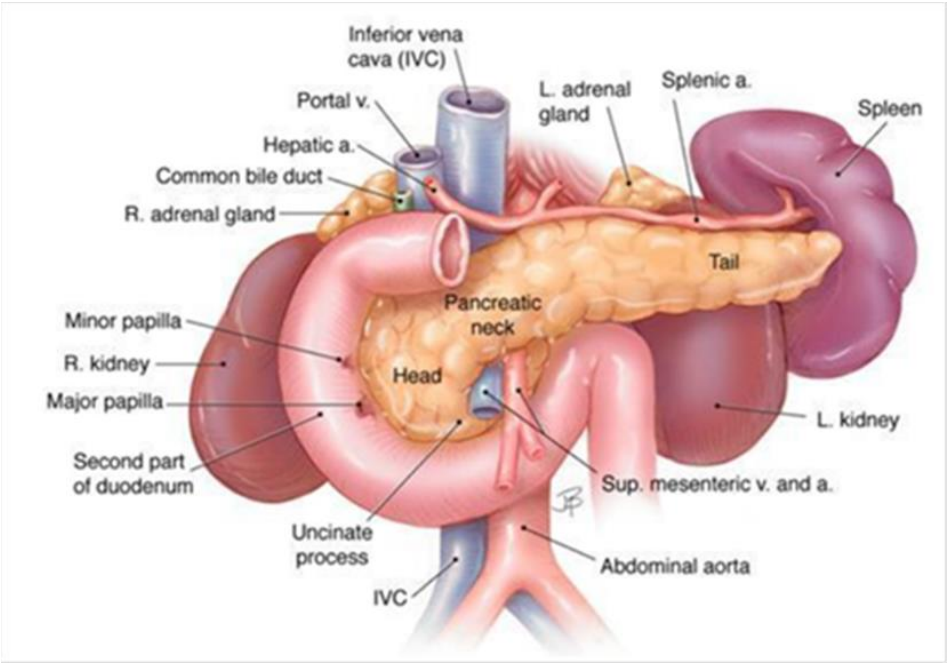
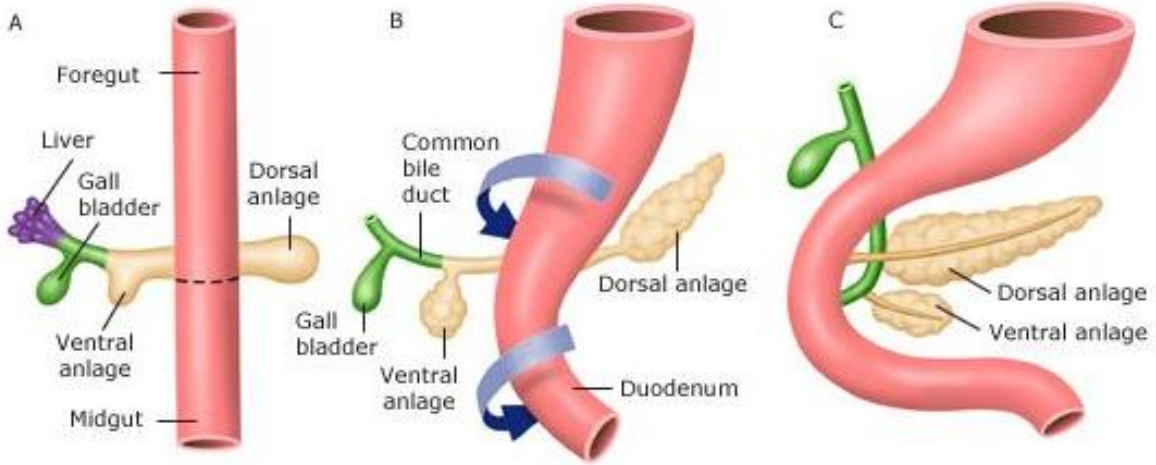


Figure 2. Embryonic development of the pancreas. Adapted from Sleisenger and Fordtran's Gastrointestinal and Liver Disease E-Book (2020).



Pancreatic Ductal System

The pancreatic ductal system consists of a network of ductules throughout the pancreatic parenchyma which join to form two larger ducts, the Main Pancreatic Duct (MPD) and the Accessory Pancreatic Duct (APD) [1]. These transport the exocrine pancreatic secretions from the acinar cells, where these are synthesized, to the duodenum to enable digestion. The Main Pancreatic Duct or Duct of Wirsung arises in the tail of pancreas and runs a downstream course through the entire gland to drain into the small bowel through the duodenal papilla (Papilla of Vater). Small ductules draining the lobules of the gland join the MPD throughout its course[1]. In approximately three quarters of individuals, the MPD drains into the major duodenal papilla through a common channel with the common bile duct (**Figure 3**). In the remaining quarter these two ducts are divided by a thin layer of connective tissue.

The Accessory Pancreatic Duct or Duct of Santorini is located in the superior aspect of the pancreatic head and neck and runs a horizontal course caudally to the MPD. Several anatomical variants of the APD are described based on Endoscopic Retrograde Cholangio Pancreatograms (ERCP) and surgical specimens: a. in approximately 30% of the general population APD lacks continuity with the duodenum and is non-functional (A), b. in 60% it drains into the duodenum through the minor papilla (B), c. in 4.1 to 17.9%, it fails to merge with the MPD, giving rise to a Pancreas Divisum (**Figure 4**)[3].

The diameter of the MPD in healthy individuals increases with the age. Below the age of fifty it measures on average 3.3 (SD 1.2) mm in the head, 2.3 (SD 0.7) in the body and 1.6 (SD 0.4) in the tail[4]. From the age of seventy the MPD increases on average by 1mm every 10 years. Pancreatic ductal adenocarcinoma arises from the ductal cells, thus commonly causes MPD obstruction.

Figure 3. The anatomical variants of the Ampulla of Vater: A. Main Pancreatic Duct and Common Bile Duct drain through a common channel, B. The Main Pancreatic Duct and the Common Bile Ducts drain through separate openings. Adapted from Pancreapedia: Exocrine Pancreas Knowledge Base (2021).

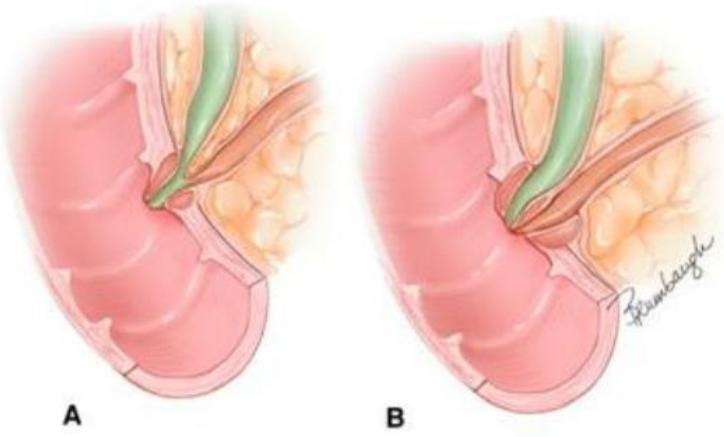
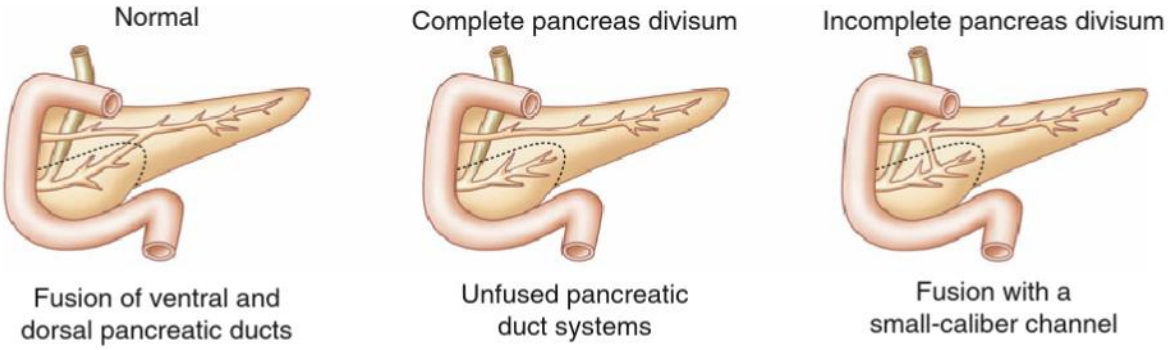


Figure 4. Images illustrate the normal pancreatic ductal system and the complete and incomplete pancreas divisum. Adapted from Pancreapedia: Exocrine Pancreas Knowledge Base (2021).



Histology and Ultrastructure

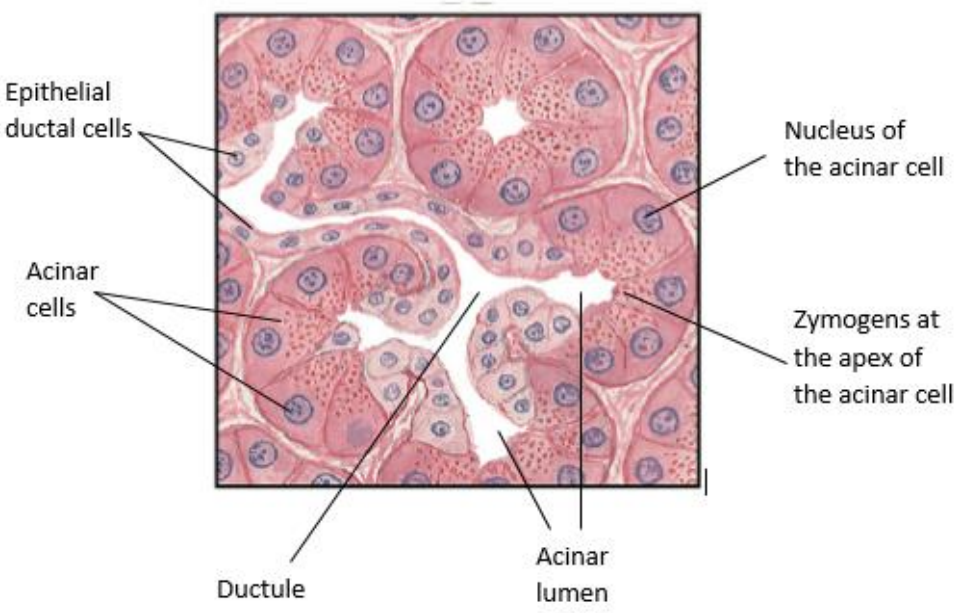
The pancreas is composed of exocrine cells (99%) and endocrine cells (1%)[5]. The former synthesizes the pancreatic juices and the latter the endocrine hormones. The exocrine secretory subunit of the pancreas is called acinus. A fine layer of connective tissue surrounds the pancreas. This connective tissue projects inwards to form septa which divide the gland into its lobules[5]. These septa accommodate all the vascular structures, including veins, arteries and lymphatics, nerves as well as the larger ductules[1].

The exocrine pancreas consists of three main types of cells: acinar, ductal and centroacinar cells[1]. Acinus is a latin word which translates into “clusters of grapes”. This term describes how the acinar and the epithelial cells are arranged to form the secretory subunit of the pancreas. The grapes resemble the acinar cells, where the digestive enzymes are produced, and the branches of the grape-tree resemble the ductules which allow the flow of the digestive enzymes towards the main ducts of the pancreas.

The acinar cells have a pyramidal shape with a broad base, apex and two sides (**Figure 5**)[5]. Each acinar cell lines up with its adjacent neighbouring acinar cells. Their apical surfaces face inwards and their broad bases face outwards. These form a spherical structure with a lumen in the middle. This lumen is connected with a goblet-shaped neck lined up by columnar cells, which form the epithelium of the pancreatic ductules[5]. The cytoplasm of the acinar cells is polarised, with the nucleus and the rough endoplasmic reticulum located in the base where synthesis of digestive enzymes takes place. The apex is occupied by the enzyme-containing zymogens where these are stored, ready to be secreted into the acinar lumen when appropriate hormonal stimulation occurs[5].

The ductal epithelial cells produce and secrete bicabonate and mix them with the digestive enzymes from the acinar cells. This mixture is then drained into the larger calibre ducts and eventually to the duodenum. The centroacinar cells are located mainly in the transition area of the acinar-ductal cells in the neck of the acinus. They are thought to contribute to the bicarbonate secretion, however their function has not been fully elucidated. The endocrine portion of the pancreas is organised in islets of cells, called islets of Langerhans, which are scattered among the acini[1, 6].

Figure 5. High resolution microscopy of the pancreatic acinus. The pyramidally-shaped acinar cells line up with their zymogens in their apex, facing the lumen and their nucleous resting in their broad base. Adapted from Motta *et al* (1997).

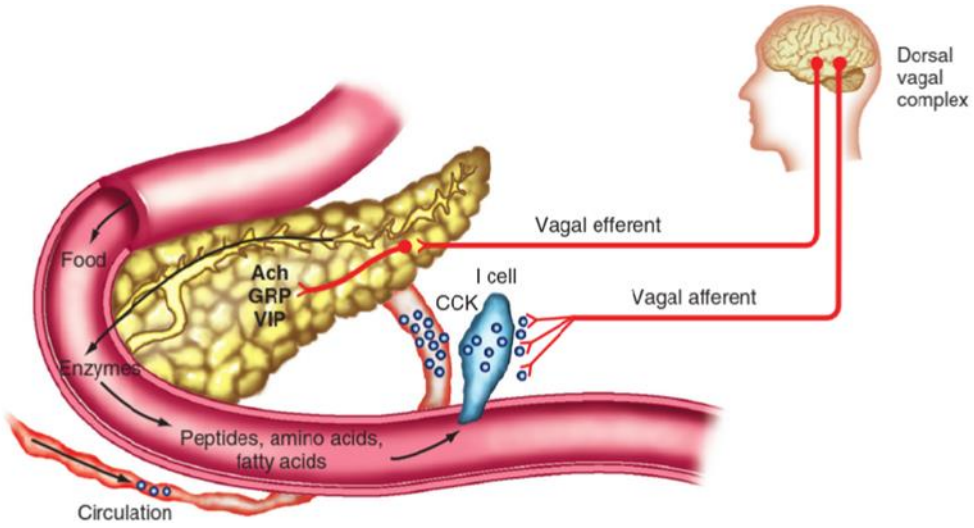


Exocrine Function

The exocrine pancreatic secretion consists of both enzymes and electrolytes. On average the pancreas secretes 20g of enzymes and 2.5L of bicarbonate per day[7]. The composition and volume of this secretion is proportional to the composition and volume of the macro- and micro-nutrients in the duodenal lumen. The pancreas secretes at a basal rate during fasting and reaches a secretory peak in response to food ingestion[7]. Mechanical and chemical receptors, lining the upper gastrointestinal tract, are stimulated by mechanical distention and the presence of acid, proteins, fats and carbohydrates. This leads to the release of hormones by enteroendocrine cells which stimulate the pancreatic parenchyma, either directly or through activation of the parasympathetic system in the form of gastro- and entero-pancreatic reflexes[1, 7]. The most important entero-endocrine cells are the S cells which secrete Secretin and the I cells which secrete Cholecystokinin (CCK). Secretin is released into the blood stream in response to a low pH or the presence of intraluminal fats and proteins and binds directly to the ductal cells to stimulate secretion of bicarbonate. Cholecystokinin (CCK) is released locally in the duodenal lumen in response to the presence of intraluminal fat and proteins.

This hormone stimulates the parasympathetic afferent vagal neurons innervating the duodenum, transmitting the digestion signals to the central nervous system, and specifically to dorsal vagal complex at the medulla. From there, the digestion signals return to the pancreas through the efferent vagal neurons, which eventually synapse with neurons within the pancreatic ganglia to release Acetylcholine (Ach), Gastrin Releasing Peptide (GRP) and Vasoactive Intestinal Polypeptide (VIP). Ach, GRP and VIP bind on receptors at the pancreatic parenchyma to stimulate pancreatic secretion (**Figure 6**).

Figure 6. The stimulation of the pancreatic secretion through activation of the parasympathetic nervous system in response to CCK. Adapted from Sleisenger and Fordtran's Gastrointestinal and Liver Disease E-Book (2020).



Pancreatic Ductal Cell Secretion

The pancreatic ductal cells are responsible for producing and secreting inorganic constituents, consisting of water, bicarbonate, potassium, cloride and sodium[1]. These are essential for the functioning of the organic constituents, i.e. enzymes and proenzymes, firstly to flow through the ductal tree into the duodenum and secondly they form a pH-neutral environment for proenzymes to be activated. The inorganic constituents are secreted both post-prandially as well as during fasting. Their basal flow rate is estimated at 0.2 to 0.3 ml/min, and increases to 4.0 ml/min after meals[1].

The bicarbonate secretion into the acinar lumen is regulated by two hormones: secretin and acetylcholine. The flow rate and consistency of the inorganic secretions varies depending on the level of hormonal stimulation of the ductal cells from secretin and acetylcholine which are secreted in response to food intake. Other transporters contribute to a lesser degree to further electrolyte

secretion and are responsible for maintaining the electrical gradient and the hydrostatic and osmotic pressures between the capillaries, the ductal cell and the acinar lumen. Sodium and water are transported following the osmotic and electrical gradients[1].

Pancreatic Acinar Cell Secretion

The pancreatic acinar cells are responsible for the synthesis, storage and secretion of the organic components of the pancreatic juice which consists of proteolytic, lipolytic and amylolytic enzymes[1].

Pancreatic Secretion during fasting

The exocytosis of digestive enzymes occurs both in fasting and upon meal stimulation. In the fasting state, there are short bursts of pancreatic secretion which are repeated every 60 to 120 minutes. These cycles are regulated by the parasympathetic nervous system. Release of motilin increases the volume of the pancreatic secretion and reduces the interval between the cycles. The pancreatic polypeptide (PP) has inhibitory control over this secretory activity during fasting. This cyclical pattern is synchronised with the motor activity of the stomach and duodenum, as part of the migrating myenteric complex (MMC), which is believed to have the role of clearing the alimentary track of food and chime residue in preparation for digestion[1].

Pancreatic secretion during digestion

The pancreatic secretion during digestion has three phases, similar to the gastric secretion: the cephalic, the gastric and the intestinal. The cephalic phase of pancreatic secretion is initiated by the sight, smell, thought or taste of food. The gastric phase of pancreatic secretion is initiated in response to mechanical distention when nutrients enter the stomach. The amount of this secretion accounts for 10% of the total pancreatic secretion[8, 9].

The intestinal phase begins with the food bolus mixed with the gastric secretions entering the duodenum. This represents 50-80% of the total pancreatic secretion. The presence of fats and fatty acids in the duodenal lumen stimulates the release of pancreatic enzymes, water and bicarbonates[1, 7]. Experiments where fat emulsions were instilled in rats' duodenum led to CCK and secretin spikes, indicating that both acinar and ductal cell secretion is needed for their digestion[10]. In other experiments, the intravenous administration of fats did not lead to pancreatic secretion, indicating that these hormones that the stimulation of the pancreas requires intraluminal activation of entero-endocrine cells[11, 12]. The digestion of proteins, peptides and aminoacids is very similar to those of fats, being mediated by the CCK and Secretin pathways[1, 7]. The volume of pancreatic secretion depends on the composition of the amino acids[13]. The acid content of the food bolus stimulates the release of secretin from the S cells of the duodenum into the blood which binds receptors on the ductal cells and drives the secretion of bicarbonates[1] .

Endocrine Function

The endocrine pancreas consists of clusters of cells, the islets of Langerhans, dispersed within the pancreatic parenchyma, and it is the main organ regulating glucose homeostasis[14]. The islets of Langerhans are made of insulin-secreting beta cells (75%), the glucagon-secreting alpha cells (20%) and somatostatin-secreting delta cells (3-5%)[14]. F cells consist the remaining 1-2% and secrete Pancreatic Polypeptide (PP)[14]. The islets of Langerhans are surrounded by capillaries, and through these the absorbed glucose reaches the beta cells. The GLUT2 transporters on the beta cell membrane permit the transportation of glucose intracellularly. This leads the intracellular signalling pathways to be activated and calcium to spike within the beta cells, causing insulin to be released into the blood stream[14]. Similar events occur in response to amino acid absorption[14]. Gastric Inhibitory Peptide (GIP) and Glucagon-like Peptide 1(GLP-1), are released by neuroendocrine cells in jejunum and ileum in response to food digestion, and contribute to insulin release[14]. Glucagon is an antagonist to insulin, being released in response to low serum glucose and triggers glycogenolysis and gluconeogenesis in the liver and peripheral tissues[14].

GENERAL CONSIDERATIONS IN PANCREATIC CANCER

Anatomy in pancreatic cancer

In total, 56% of the cancers arise from the head, 18% body and tail whilst the rest 26% involve more than one portion of the pancreas[15, 16]. Data from the US Surveillance, Epidemiology and End Results (SEER) registry reported annual incidence of pancreatic head cancers of 5.6 (95% CI, 5.5 to 5.6) per 100,000 population, versus with 1.6 (95% CI, 1.6 to 1.6) for the body and tail[15]. Disparities are also observed in the resectability rates with tumour located in the head being resectable in 29.9% versus 16.1% in tumours of the body or tail ($p<0.01$). Typically, distant metastases are present at diagnosis, but this is far more common in body and tail tumours (67.1%) versus the head tumours (35.5%) ($p<0.01$)[16]. This difference is likely to be attributed to the fact that tumours affecting the head are more likely to cause symptoms, due to firstly, its anatomical association with the common bile duct, causing obstructive jaundice, and secondly involving the distal portion of the main pancreatic duct through which the digestive enzymes pass into the duodenum, causing exocrine insufficiency or, less commonly, acute pancreatitis. Cancers of the neck, body or tail are more likely to give symptoms due to extensive local growth or distant metastases, rather than due to distorting the pancreatic parenchyma itself[1].

Exocrine function in pancreatic cancer

The exocrine function in pancreatic cancer was mainly researched in the mid to late 1970's with very limited research being conducted in the recent years. Intravenous administration of CCK and secretin

in 17 patients with pancreatic adenocarcinoma resulted in impaired secretion of trypsin, lipase and bicarbonate[17]. The same study reported that 60% of the Main Pancreatic Duct had to be occluded for exocrine insufficiency to be detected[17]. A more recent clinical study showed that 50% of patients with pancreatic cancer have normal exocrine function, defined as faecal elastase > 200 micrograms/g, 11% have moderate (100-200 micrograms/g), 14% severe (20-100 micrograms/g) and 25% extremely severe (<20 micrograms/g) and of those only 10% had steatorrhea[18]. Interestingly, the vast majority (95.8%) of those who had extreme exocrine insufficiency their tumour was located at the head of pancreas[18].

Pancreatic Carcinogenesis

Pancreatic carcinogenesis is a stepwise process where pancreatic ductal epithelial cells accumulate genetic defects over time. The combination of genetic defects are unique to each tumour. These genetic defects are mutations in tumour suppressor genes and proto-oncogenes, shortening of telomeres and overexpression of growth factors[19].

Tumour Suppressor Genes

Tumour suppressor genes inhibit cell proliferation, should a genetic defect occur[19]. Mutations in tumour suppressor genes may lead to loss of their functions and, hence, contribute carcinogenesis, allowing abundant proliferation of genetically defective cells. These mutations are usually autosomal recessive. They are found in sporadic cases, where both alleles undergo mutations during the individual's lifetime, or one mutated allele is inherited and the other one undergoes mutations later in the patient's life[19]. Several mutations of tumour suppressor genes are found in pancreatic adenocarcinoma, indicating that these hold a fundamental role in pancreatic carcinogenesis. Specifically, p161NK4A/CDKN2A is found in 85%, p53 in 50-75% and SMAD4/DPC4 in 55% of patients with pancreatic adenocarcinoma[19].

Formation of Oncogenes

Proto-oncogenes are responsible for the regulation of cell proliferation in response to growth signals[20]. Mutations of these genes can transform them to oncogenes which activate cell proliferation pathways in the absence of growth signals, leading to the development of cancer. In contrast to the tumour suppressor genes, only one mutated allele is sufficient to promote carcinogenesis [19]. K-RAS is the most commonly found oncogene in pancreatic adenocarcinoma, being identified in 90% of patients[21], whilst mutations in gene components of the phosphoinositide 3-kinase (PI3K) and the Notch signalling pathways are the next most common[19].

Shortening of Telomeres

Telomeres are repetitive DNA sequences at the end of chromosomes, preventing their fusion with other chromosomes [19]. Genetic analysis of pancreatic adenocarcinoma specimens revealed significant

shortening of the telomeres and it is believed that this is a contributing factor to pancreatic carcinogenesis[22].

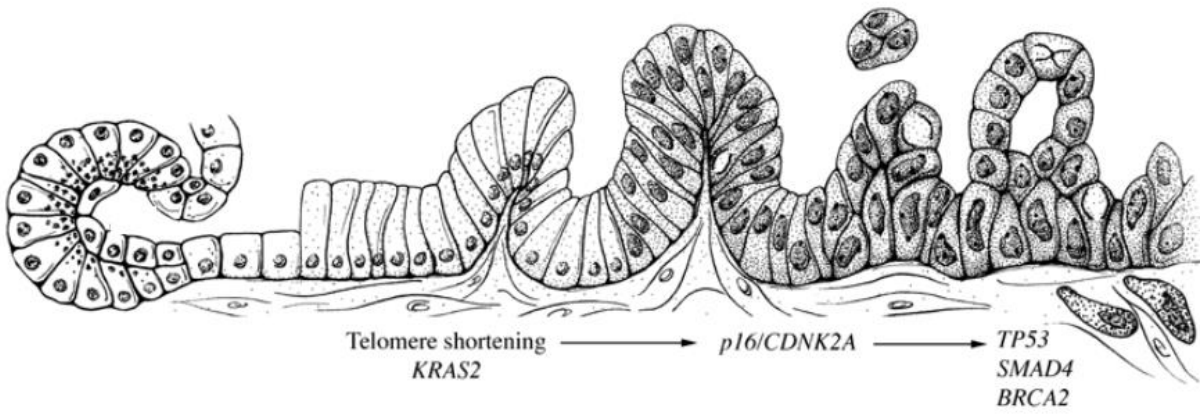
Abundant Expression of Growth Factors

Overexpression of growth factors, namely Epidermal Growth Factor (EGF), Insulin-like Growth Factor (IGF) and Vascular Endothelial Growth Factor (VEGF), as well as their receptors, has been identified in specimens of patients with pancreatic adenocarcinoma, and most likely have a cancer promoting effect[23].

The Precursors of pancreatic adenocarcinoma

Pancreatic adenocarcinoma evolves following the sequence of metaplasia- dysplasia- carcinoma *in situ*- invasive adenocarcinoma (**Figure 7**)[20]. The majority of pancreatic adenocarcinomas arise from microscopic intraepithelial lesions, called Pancreatic Intraepithelial Neoplasias (PanINs). PanIN-1 is characterised by mucinous hyperplasia of the ductal epithelium but with lack of cytological atypia[20]. Telomere shortening and KRAS mutation are the typical genetic defects found at this stage[20]. PanIN - 2 is characterised by atypia, crowding and nuclear enlargement and typically is affected by a mutated p161NK4A/CDKN2A tumour suppressor gene[20]. Finally, PanIN- 3 ductal cells exhibit complete loss of their cytoplasmic polarity, equivalent to high grade dysplasia/ carcinoma in situ and they are positive for SMAD4 and TP53 mutations[20]. A small proportion of pancreatic adenocarcinomas arise from macroscopically visible, cystic-forming epithelial lesions, the Intraductal Papillary Mucinous Neoplasms (IPMNs) and the Mucinous Cystic Neoplasms (MCNs)[20]. KRAS and p53 are the most commonly found mutations whilst SMAD4 mutation is usually found in IPMNs and MCNs which have transformed to invasive tumours[24-26].

Figure 7. Stages of Pancreatic Carcinogenesis and the associated genetic mutations Adapted from Macgregor-Das *et al* (2013).



Histological Differentiation of Pancreatic Cancer

Pancreatic adenocarcinoma is a gland-forming tumour with surrounding dense desmoplastic response, rich in fibroblasts and collagen[27]. Different degrees of tumour differentiation are observed and are associated with different biological behaviours. Well-differentiated tumours have regular round glands. Moderately-differentiated tumours are characterised by variability in size and shape of the glands. Poorly-differentiated tumours are those where glandular structures cannot be appreciated. Other histological subtypes include: adenosquamous pancreatic carcinomas (3-4%)[28], acinar cell carcinomas 1-2%[29], signet ring carcinomas[30], anaplastic carcinomas[31], colloid pancreatic carcinomas[32] and medullary pancreatic carcinomas[33]. All these subtypes have not been extensively studied due to their rarity, however, evidence from case reports and small case series suggest that their biological behaviour is either similar or more aggressive to classical pancreatic adeocarcinoma[27].

A large proportion of tumours display such heterogeneity that cannot be classified into one of the categories mentioned above[27]. For this reason, in cases where surgical specimens are not to be obtained and the management relies on biopsy alone, it is strongly advised that multiple samples are taken; the final verdict is based on the collective assessment of those samples. Immunohistochemistry, i.e. assessment of the localisation, distribution and expression of specific antigens, is utilised to assist the visual assessment of the biopsy specimens[34]. In total, 76 immunohistochemical biomarkers have been identified[35]. Ki-67, p27, p53, transforming growth factor β1, Bcl-2, endothelial growth factor, CD34, S100A4 are the most commonly used in diagnosis[35].

The grade of tumour differentiation, apart from its diagnostic value, is also associated with survival. An epidemiological study based on USA SEER data of 7,627 patients with histologically confirmed pancreatic cancer from 17 different geographic regions, reported a 40% higher survival rate in patients with well-differentiated (low grade) tumours compared to those which were undifferentiated (high grade) (HR= 1.40, 95% CI, 1.31 to 1.48, $p<0.001$)[36]. A similar survival benefit was detected in the analysis stratified by age and the cancer Tumour Node Metastasis (TNM) stage[36]. Similarly, patients with tumours arising from mucinous cystic neoplasms (MCNs) demonstrate improved survival in comparison to classical adenocarcinomas (HR= 0.88, 95% CI, 0.84 to 0.91, $p<0.05$)[37].

Epidemiological Considerations in Pancreatic Ductal Adenocarcinoma

Descriptive Epidemiology

Worldwide pancreatic cancer is the 12th commonest malignancy, with 495,773 cases diagnosed in 2020[38]. Most patients are diagnosed between the ages of 60-80 years with the incidence increasing with age[39]. There is a marginal gender preference for men, with an incidence of 5.5 per 100 000 per year, in comparison to women which is 4.0 cases per 100,000 per year[39, 40]. The average lifetime risk

for pancreatic cancer is approximately 1 in 64, although the individual lifetime risk is highly dependent on the exposure to modifiable and non-modifiable risk factors[41]. Variation is observed in the geographical distribution, with pancreatic cancer being more prevalent in industrial regions, such as Europe, North America, Australia and New Zealand, whilst it is lower in South Central Asia and Africa (**Figure 8**)[38].

In the UK, 10,452 new cases were diagnosed on an annual average in 2016-2018 in UK[40, 41]. The age-standardised incidence rates have increased from 14 per 100,000 in early 90's to 17 per 100,00 in late 10's and it is anticipated to climb to 21 cases per 100,000 in 2035[41]. The incidence varies depending on the different standards of living; 20% higher incidence rates are observed in the areas of the highest quintile of social deprivation in comparison to those in the lowest quintile[41].

Pancreatic cancer has the worst prognosis of any tumour, with the mortality nearly equal to its incidence; with 466,003 pancreatic cancer-related deaths in 2020 worldwide and 9,263 in 2016 in UK[40] making it the sixth most common cause of cancer-related death, with a mortality/incidence ratio of 94% (**Figure 9**)[40]. Newer chemotherapeutic agents in recent decades are responsible for the increase in one-year survival from 10% to 21%, however, the five year survival has been unaffected at 5% based on UK data (**Figure 10**)[38, 41].

Figure 8. A map of the age-standardized incidence of pancreatic cancer worldwide in 2018. Images adapted from Bray *et al* (2018).

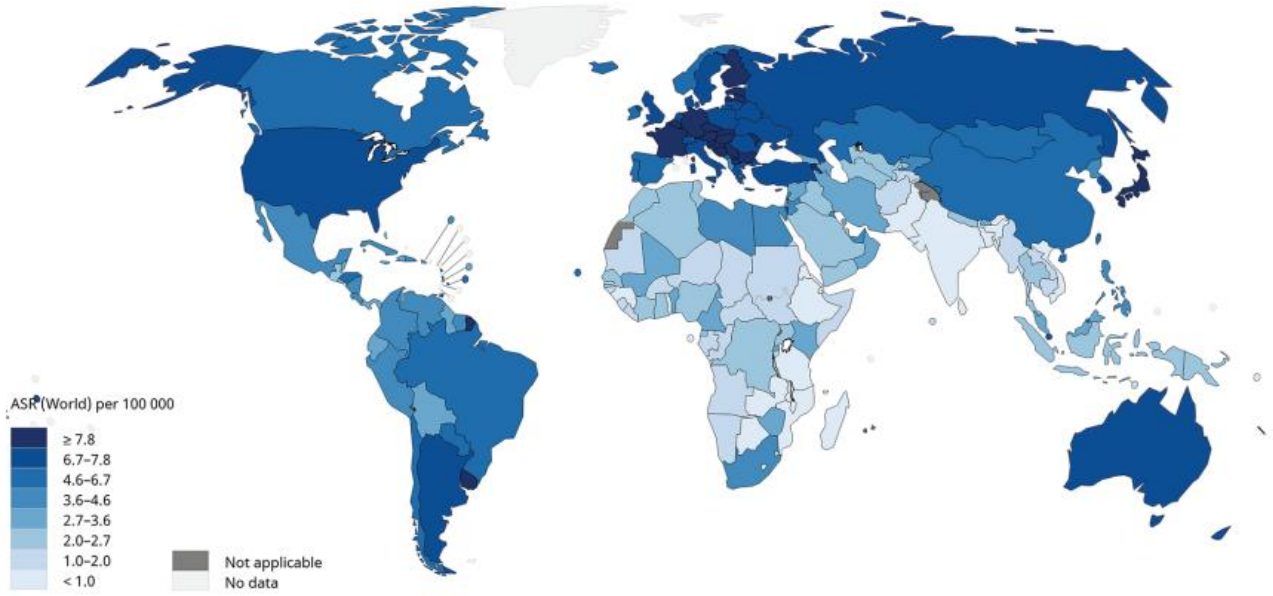


Figure 9. Bar chart demonstrating the incidence and mortality from pancreatic cancer per region Images are adapted from Bray *et al* (2018).

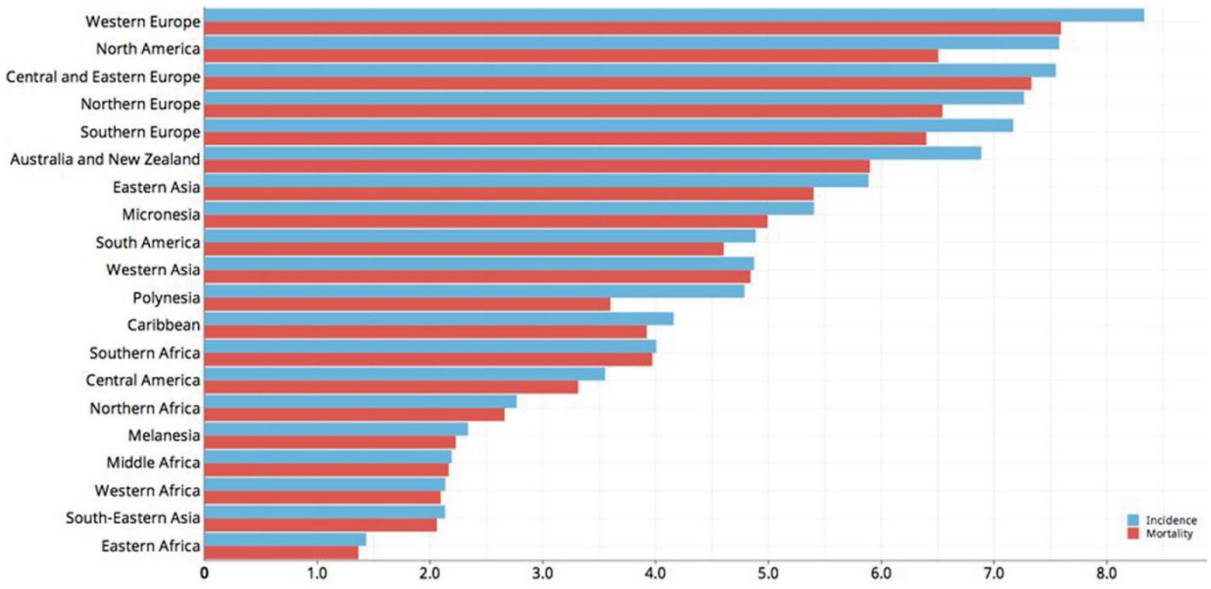
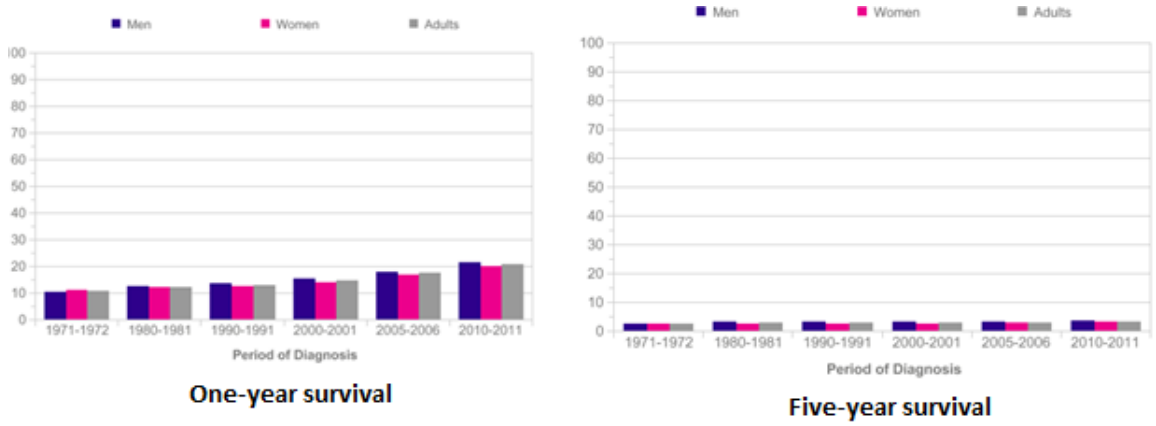


Figure 10. Histogram of one (left) and five (right) year survival in both sexes from 1971 to 2011 in the UK. Images are adapted from Cancer Research UK (2017).



Risk Factors

Current evidence suggests that the interaction of several factors are necessary for the development of the pancreatic cancer phenotype, including: environmental (smoking, diet), metabolic (insulin resistance, adiposity), inflammatory (*Helicobacter Pylori*, infections) and genetic[42]. However, the relative contribution of each is not yet fully defined.

Smoking

Smoking is the most well-known risk factor for the development of pancreatic cancer. The association of cigarette smoking with the risk of developing pancreatic cancer has been demonstrated in a meta-analysis of 47 case-control and 35 cohort studies which reported relative risk of 1.74 (95% CI, 1.61 to 1.87, p<0.001)[42]. Overall, 21.9% of the cases of pancreatic cancer in UK are considered to be attributed to smoking[43]. Further analysis of pooled data shown a dose- and duration- response relationship between smoking and pancreatic cancer (OR for 25–30 cig/day compared to non-smokers: 1.28, 95% CI, 0.88 to 1.88, OR for ≥30 cig/day compared to non-smokers: 1.75, 95% CI, 1.27 to 2.42, OR for smoking >50 years compared to non-smokers= 2.13, 95% CI, 1.25 to 3.62)[44]. Finally, those who ceased smoking for less than 10 years remain at risk, compared to those who never smoked (OR: 2.19, 95% CI, 1.25 to 3.83), whilst association with pancreatic cancer was attenuated for those who stopped smoking more than 15 years (OR = 1.24, 95% CI, 0.78 to 1.98)[44].

Chronic Pancreatitis

Approximately 5% of patients with chronic pancreatitis develop pancreatic cancer[45]. Increased oxidative stress, impaired autophagy and chronic activation of inflammatory pathways caused by chronic pancreatic injury, all contribute to DNA damage and accumulation of genetic mutations, namely KRAS, p53 and p16, all of which are found in both pancreatic cancer and chronic pancreatitis, implying that a common causal mechanism may exist[46]. A meta-analysis of four case–control and nine cohort studies evaluated the risk of pancreatic cancer in patients with chronic pancreatitis versus those without[47]. The odd ratio for developing pancreatic cancer were 7.90 (95% CI, 4.26 to 14.66) for those with a diagnosis of chronic pancreatitis of five years. However, limitations in this meta-analysis should be highlighted: chronic pancreatitis shares many clinical (weight loss, diarrhoea) and radiologic features (hypoattenuation) with pancreatic cancer, leading to misclassification bias (e.g. cancers being erroneously reported as chronic pancreatitis at baseline) which may inflate the estimated OR at 5 years. To rectify this problem authors excluded patients with a diagnosis of pancreatic cancer made within 2 years from the onset of chronic pancreatitis from their analysis. The OR from this sensitivity analysis was 6.09 (95% CI, 3.79 to 9.79). Another methodological limitation is not taking into account

the influence of confounding factors, such as smoking, diabetes and anthropometry, which was reported only in limited number of the included studies[47].

Type 2 Diabetes Mellitus

It is estimated that 1-16% of the cases of pancreatic cancer are attributed to Type 2 Diabetes Melitus (T2DM)[42]. Insulin resistance in T2DM leads to compensatory hyperinsulinaemia and increased circulating Insulin-like Growth Factor-1 (IGF-1), which is mitogenic and anti-apoptotic[48]. Furthermore, 71% of patients with pancreatic cancer develop reduced insulin sensitivity in peripheral tissues due to release of diabetogenic molecules from the pancreatic cancer, which improves following curative resection[49]. These two observations imply that insulin resistance is likely to be both a risk factor for, as well as a manifestation of pancreatic cancer. This point should be taken into consideration when the associations between these two conditions is examined.

A meta-analysis of 35 cohort studies reported a two-fold risk for pancreatic cancer in those with T2DM [Relative Risk (RR) of 1.94, 95% CI, 1.66 to 2.27], although substantial heterogeneity was detected (P< 0.001, I^2 = 93.6%)[50]. The estimated risk was significantly raised in patients who were diagnosed with T2DM within less than a year from the diagnosis of pancreatic cancer (RR: 5.38, 95% CI, 3.49–8.30) compared to those diagnosed more than one and less than four years (RR: 1.95, 95% CI, 1.65–2.31)[50]. In the former group with T2DM the reported RR is probably inflated by the cases were T2DM was a manifestation rather than a risk factor for pancreatic cancer. Certain limitations of this meta-analysis should be highlighted. Firstly, DM is not distinguished in type 1 and type 2; knowing that the former is not associated with pancreatic cancer, the risk is most likely underestimated[51]. Secondly, most of the included studies did not adjust for confounders, such as smoking, bodyweight and glycaemic control.

Anthropometry

Obesity is responsible for 3-16% of the cases of pancreatic cancer[42]. Visceral adipose tissue is responsible for the release of leptin and adiponectin, which activate intracellular pathways involved in pancreatic carcinogenesis[52]. The risk of pancreatic cancer in obese populations was summarised in a meta-analysis of 6 case-control studies with 6,391 cases[53]. This reported a 2% additional risk for every unit increase in body mass index (BMI) (summary RR per unit of BMI: 1.02, 95% CI, 1.01–1.03). Obese subjects (BMI≥ 30 kg m^{-2}) were at a 19% higher risk than non-obese (BMI<30) (RR 1.19, 95% CI 1.10–1.29)[53].

Family history of pancreatic cancer

Familial cases account for 3-7% of all the cases of pancreatic cancer[42]. Cancer syndromes namely: Peutz-Jeghers, Hereditary Breast and Ovarian Cancer Syndrome, Familial Atypical Mole Melanoma,

Ataxia Telangiectasia and Lynch Syndrome, account for 10-20% of these familial cases. The remaining 80-90% are attributed to germline mutations which are yet to be identified[54]. The most comprehensive work assessing the risk of individuals with a positive family history of pancreatic cancer was conducted by Klein *et al*[54]. In total, 5,179 individuals from 838 families were identified from the National Familial Pancreatic Tumour Registry in the USA, 370 of which with two or more affected members with first degree relation between them (FDRs) and 468 with one affected member. In total, 3,904 individuals had family history of pancreatic cancer in one or more FDRs, 906 with one non-FDR with a history of pancreatic adenocarcinoma and 369 individuals with no family history of pancreatic cancer. The cohort was followed-up for a total of 14,128 person-years. Individuals with three FDRs had a Standardised Incidence Ratio (SIR) of 32 (95% CI, 10.2 to 74.7) for developing pancreatic cancer. Those with two FDRs had a SIR of 6.4 (95% CI, 1.8 to 16.4). A family history of one affected FDR and a family history of one affected non-FDR were not associated with increased risk [SIR: 4.6 (95% CI, 0.5 to 16.4) and (SIR: 1.8, 95% CI, 0.22 to 6.4) respectively][54].

Lynch syndrome

Hereditary Non-Polyposis Colorectal Cancer Syndrome, or Lynch Syndrome, is an autosomal dominant condition with incomplete penetrance, associated with both intestinal and extra-intestinal tumours, due to mutation in the Mismatch Repair (MMR) genes[55]. Analysis of data from a USA cancer registry demonstrated a 8.6-fold (95% CI, 4.7 to 15.7) increased risk of pancreatic cancer among families with pathogenic MMR gene mutations compared to the general population[55].

Peutz-Jeghers Syndrome

Peutz-Jeghers Syndrome is an autosomal dominant disorder due to mutations in the STK11/LKB1 (Serine Threonin Kinase 1) tumour suppression gene, associated with both hamartomatous gastrointestinal polyps and mucocutaneous pigmentation[56]. A cohort study of 131 patients with total follow-up duration of 4430 person-years, which was conducted in Netherlands, reported a RR of 76 (95% CI, 36 to 160; $p<0.001$) for developing pancreatic cancer in patients with Peutz-Jeghers Syndrome compared to the general population[56].

Breast Cancer-Associated Gene mutations

There is an association between the Breast Cancer-Associated Gene 2 (BRCA-2) and the development of pancreatic cancer but it is equivocal for BRCA-1. The BRCA-2 carriers have a RR of 4.1 (95% CI, 1.9 to 7.8) for developing pancreatic cancer[57].

Familial Atypical Mole Melanoma

Familial atypical multiple mole melanoma (FAMMM or familial dysplastic nevus syndrome) is an autosomal dominant condition, due to a germline mutation in the p16 (CDKN2A) gene, and presents

as malignant melanomas of the skin in combination with multiple precursor nevi[58]. Affected individuals have an increased risk for non-skin cancers, including pancreatic, liver lung, brain and breast. The estimated cumulative risk in putative mutation carriers by age 75 years is 17% (95% CI, 1.4 to 27.2)[58].

Ataxia Telangiectasia

Ataxia telangiectasia (AT) is an autosomal recessive condition, affecting the central nervous and the immune systems, and characterised by vascular malformations which affect any organ[59]. AT is associated with increased incidence of several cancers namely: pancreatic, breast, lung, ovarian, stomach and urinary bladder[60]. Genetic testing of individuals who belonged to families with significant pancreatic adenocarcinoma history, where three or more incident cases were observed, revealed unusually increased prevalence of AT heterogeneity, suggesting a possible association, however, large epidemiological studies are lacking due to the rarity of the disease[59].

Hereditary Pancreatitis

Hereditary pancreatitis is a clinical syndrome requiring the following three characteristics: a. presents either with acute recurrent or chronic pancreatitis, b. develops in the absence of any other precipitant factors (e.g. alcohol, gallstones, drugs etc.) and c. two first- or second-degree relatives are affected[61]. Hereditary Pancreatitis is associated with four mutations: PRSS (Serine Protease) -1 & -2, SPINK1 (Serine Peptidase Inhibitor Kazal type 1), CFTR (Cystic Fibrosis Transmembrane Conductance Regulator) and CTRC (chymotrypsin C). These either cause disordered trypsinogen activation or electrolyte transportation, both leading to chronic necro-inflammatory and fibrotic changes which may predispose to carcinogenesis.

Two studies evaluated the associations between the hereditary pancreatitis and the risk of pancreatic cancer. In the first, a cohort of 200 patients from France, with a total follow-up time of 6,673 person-years and reported SIR for pancreatic cancer of 87 (95% CI, 42 to 113) compared to the general population[62]. The second one was a multicentre study of 246 patients with clinical diagnosis of hereditary pancreatitis from the USA, Europe and Japan, who were surveyed for a total of 8,531 person-years and reported a SIR for pancreatic cancer of 53 (95% CI, 23-105)[63].

Miscellaneous

Several other genetic and environmental factors have been investigated for associations with pancreatic cancer. The incidence of pancreatic cancer varies among patients belonging to different ABO blood groups, with Group A, AB and B being at higher risk compared to those with Blood Group 0[64]. A meta-analysis of eight case-control studies reported associations between *Helicobacter Pylori*

infection and development of pancreatic cancer[65]. Other studies have shown occupational exposure to chlorinated hydrocarbon and nickel compounds to increase the overall risk for pancreatic cancer[66].

Clinical presentation

Patients with pancreatic cancer usually present at an advanced stage[67]. Tumours affecting the head are more likely to cause symptoms due their anatomical association with the common bile duct, causing obstructive jaundice. Cancers of the neck, body or tail may develop symptoms due to extensive local growth or distant metastases, rather than distorting the pancreatic parenchyma itself[1]. Several studies have attempted to document the most common symptoms patients with pancreatic cancer present with[67-69]. Porta *et al*[67] recruited 185 patients from five different hospitals across Spain, soon after diagnosis and asked them to recall their symptoms. The mean age at diagnosis was 66.8 years, 59% were men and 63% were at stage III and IV (American Joint Committee of Cancer [AJCC] cancer staging) at diagnosis. The main complaints were constitutional symptoms: asthenia (86%), weight loss (85%) and reduced appetite (83%). Abdominal Pain was reported by 79% of patients at diagnosis. The majority had pain in the epigastric area (71%), 59% in the right upper quadrant, 49% in the lumbar region and 45% the left upper quadrant. Other symptoms were jaundice (56%) nausea (51%), vomiting (33%), pruritus (32%), steatorrhea (25%) and thrombophlebitis (3%). For clinical signs, 32% had palpable hepatosplenomegaly, 27% palpable abdominal mass, 13% were cachexic or had Courvoisier's sign (the combination of jaundice with a palpable non-tender gallbladder)[70].

Work up and Diagnosis

The diagnosis of pancreatic cancer relies mainly on the appropriate clinical context in combination with CT imaging and biopsies. The tumour markers, carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA), have a limited diagnostic yield but they have a role in prognostication[71].

Carbohydrate Antigen 19-9 (CA19-9)

CA19-9, is a glycoprotein expressed on the tumour's surface in response to tumour-related hypoxia[72]. It is a ligand for the adhesion molecule E-selectin, assisting the attachment of cancer cells to the endothelium and, consequently, favouring the development of distant haematogenous metastases[73]. 7-10% of the patients with pancreatic cancer do not harbour a functional Lewis enzyme, hence in those CA19-9 is not expressed[74]. In addition, CA19-9 is not specific to pancreatic cancer, but instead, it may be raised in other gastrointestinal malignancies (colorectal cancers and cholangiocarcinoma) as well as non-malignant gastrointestinal conditions, such as cholestatic jaundice, chronic liver disease, liver abscesses, liver cysts, acute and chronic pancreatitis[74]. CA19-9 has limited role in detecting

pancreatic cancer in general population (positive predictive value 0.5-0.9%)[75]. However, it is useful for prognostication as it correlates with the clinical stage, overall survival, response to chemotherapy and the maintenance of remission following pancreatectomy[75, 76].

Staging

The staging of pancreatic cancer is based on the AJCC Tumour/Nodes/Metastasis (TNM) system. However, for practical reasons the cancer stages can be divided into resectable (stage I and II), borderline resectable (stage III), locally advanced (Stage III) and metastatic (stage IV). The resectability of stage III tumours mainly relies upon the degree of vascular involvement[77].

Figure 11. American Joint Cancer Committee (AJCC) TNM system for Pancreatic Cancer Staging. Table adapted from Court M *et al* (2018).

AJCC Stage	Stage grouping	Stage description*
0	$T_{is}N_0M_0$	Cancer confined in the ductal epithelium, not invading deeper tissues. No nodal involvement. No distant metastases.
IA	$T_1N_0M_0$	Cancer confined within the pancreas, no bigger than 2cm. No nodal involvement. No distant metastases.
IB	$T_2N_0M_0$	Cancer confined within the pancreas, bigger than 2cm but less than 4cm. No nodal involvement. No distant metastases.
IIA	$T_3N_0M_0$	Cancer confined within the pancreas, bigger than 4cm. No nodal involvement. No distant metastases.
IIB	T_1 or T_2 or T_3 N_1M_0	Involvement of 3 or less regional nodes. No distant metastases.
III	T_1 or T_2 or T_3 N_2M_0	Involvement of 4 or more regional nodes. No distant metastasis.
	Or	
	$T_4N_xM_0$	Cancer extending outside the pancreas, into the nearby vessels with or without nodal involvement. No distant metastasis.
IV	$T_xN_xM_1$	Distant metastasis with any T or N status

Radiological Assessment and Resectability

The objectives of the radiological assessment of pancreatic cancer are: 1. differentiate pancreatic adenocarcinoma from other mass-forming pancreatic lesions (IPMNs, MCNs, NETs, inflammatory masses, pseudopapilary tumours, lymphomas and sarcomas), 2. assessment of distant metastases and 3. assessment of the vascular involvement which is the main determinant of resectability in locally advanced cancers. The main diagnostic and staging modality in pancreatic cancer is Computerised Tomography (CT). Pancreas-specific scanning protocols have been developed to best characterise pancreatic masses[78]. Pancreatic adenocarcinoma is surrounded by a desmoplastic stroma, compressing the intra-parenchymal blood vessels in the pancreas[77]. As result, on CT scans, upon administration of intravenous contrast, the tumour acquires hypo-attenuating appearances, making it distinct from the unaffected pancreatic parenchyma which has normal arterial perfusion[78]. Moreover, this hypoattenuation may assist the differentiation from other mass lesions in the pancreas with different histological characteristics, such as neuroendocrine tumours which are hypervascular[78]. In addition, intravenous contrast helps to delineate the wall of the major vessels, namely inferior vena cava, coeliac trunk, hepatic artery, portal vein, superior mesenteric artery and superior mesenteric vein, and permits the assessment of their invasion[78]. The oral administration of contrast allows delineation of the duodenal loops and the duodenal papilla around the head of pancreas to aid assessment of the degree of involvement of those structures[78].

Portal and superior mesenteric vein invasion, if limited, may be amenable to resection and reconstruction. Tumours abutting less than 180° of the vein's circumference on CT have 40% probability of invading the vessel wall[77]. In these patients, curative surgical resection is indicated. In contrast, tumour encasing more than 180° have 80% probability of invading the wall vessel and curative resection is unlikely to be successful (**Figure 12 and Figure 13**)[77]. Other radiological predictors of resectability include: unilateral narrowing of the portal or superior mesenteric veins and less than 12mm length of longitudinal encasement[77]. Formation of collateral channels, namely short gastric varices, gastrohepatic ligament varices and gastroepiploic to gastrocolic vessels are strongly predictive of the superior mesenteric vein involvement[78]. Similar principles apply in the assessment of the arterial involvement. Involvement of the coeliac artery is considered non-resectable, whilst hepatic and superior mesenteric arteries can be reconstructed if their involvement is confined in a short segment[77].

Radial Endoscopic Ultrasound (EUS) following staging CT can increase the accuracy of the assessment of vascular involvement. Based on a Cochrane review of 34 patients from two retrospective studies, preoperative EUS has a pooled sensitivity of 87% (95% CI, 54% to 97%) and specificity of 80% (95% CI, 40% to 96%) in predicting resectability in respect to vascular involvement[79]. Positron Emission

Tomography (PET) CT has not been evaluated as a staging method, however, it can be used in surgical candidates to rule out distant metastases which may have been missed on standard CT. Magnetic Resonance Imaging (MRI) is not superior to CT in the diagnosis of pancreatic cancer, however, it has a role in the characterisation of indeterminate liver lesions, differentiating incidental benign nodules from metastatic. Despite advances in preoperative imaging assessment, approximately 12% of patients who attend surgery with curative intent are discovered to have significant involvement of the vasculature intra-operatively and the resection is abandoned[79, 80].

Figure 12. Hypo-attenuating mass in the head of pancreas, abutting <180° of the circumference of the superior mesenteric artery (arrow). Adapted from Casadei *et al* (2009).

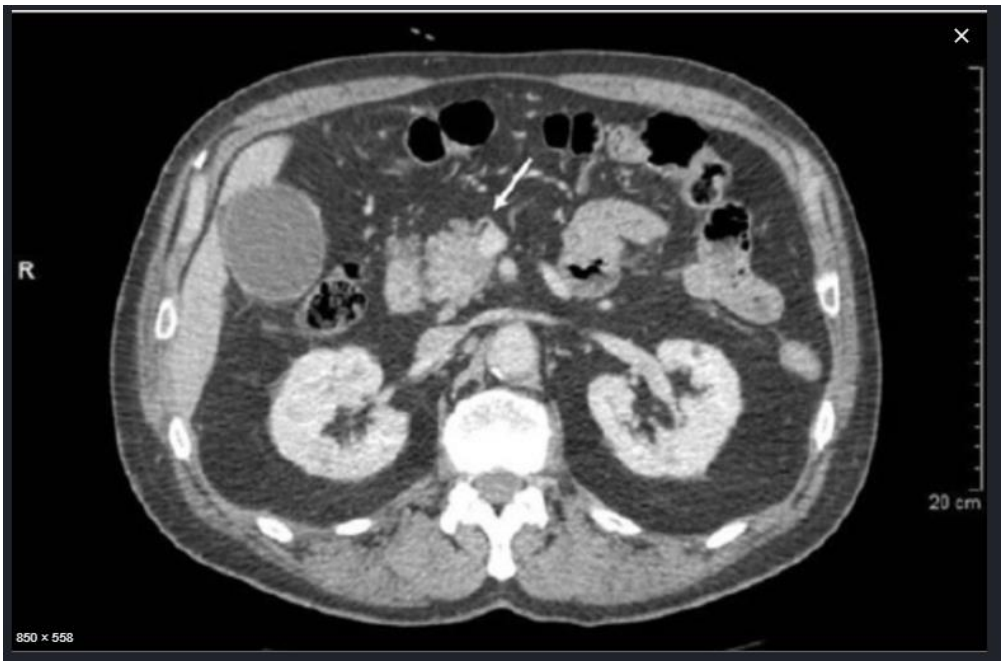
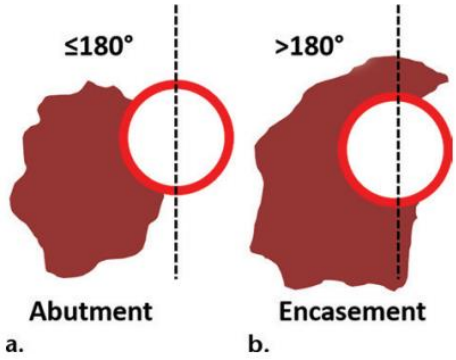


Figure 13. Radiological assessment of tumour's resectability. a. Pancreatic mass abutting less than 50% of the venous circumference and it is likely amenable to curative resection, b. pancreatic tumour encasing more than 50% of the vessel circumference and therefore resectablility is unlikely. Adapted from Zaky *et al* (2017).



Tissue Diagnosis

Tissue biopsy is highly recommended in patients where oncological or surgical treatments are considered. The specimen can be in the form of scattered cells (cytology) or preserved organised tissue (histology), depending on the mode of acquisition and the diameter of the needle. Cytology can become available with brushings obtained with Endoscopic Retrograde Cholangio Pancreatography (ERCP), percutaneous transhepatic cholangiopraphy or with EUS-Fine Needle Aspiration (FNA). Histology can be obtained with percutaneous ultrasound-guided biopsy of liver lesions and EUS- Fine Needle Biopsy (EUS-FNB). Rarely, tissue is obtained from extra-abdominal lesions, such as inguinal lymph nodes. All methods have advantages and disadvantages and the choice is decided on a case-by-case basis, depending on the location, size and stage of the tumour.

Management and Prognosis

The management options in pancreatic adenocarcinoma include curative surgery followed by adjuvant chemotherapy, neoadjuvant chemotherapy followed by resection for borderline resectable disease, palliative chemotherapy for non-resectable disease and supportive care alone for those with impaired general health. FOLFIRINOX (combination of FOLinic acid (leucovorin), Fluorouracil, IRinotecan and OXaliplatin) has been established in the last decade as the most effective chemotherapeutic agent, however, its use is limited by increased toxicity, hence is only suitable for patients with performance status of 0 to 1 and well-preserved liver synthetic function[74]. Each cycle is administered every two weeks and can be repeated up to twelve times. Gemcitabine monotherapy is less effective, although it has a more favourable toxicity profile and can be used in patients with performance status of 2 as well as those with moderate jaundice[74]. Each cycle is given every 21 to 28 days and can be given up to

six times. Gemcitabine combined with other cytotoxic agents such as cisplatin, marimastat, axitinib, mytomicin and others, have been evaluated in phase two and three trials but without additional benefit to gemcitabine monotherapy[81]. Modified courses of FOLFIRINOX or gemcitabine, consisting of reduced number of cycles, are often given depending on individual circumstances. Overall, prognosis is influenced by cancer stage, patient demographics, co-morbidities and medical performance status at diagnosis[82].

Resectable Disease

15-20% of patients present at a resectable stage (stage I, II and III with limited vascular involvement)[74]. The surgical options are either: pancreatoduodenectomy (Whipple's procedure), distal pancreatectomy or a total pancreatectomy, depending on the size, anatomical location and the proximity of the lesion with other organs. Based on US nationwide data, pancreatectomy carries an in-hospital mortality rate of 5.3%, hence careful patient selection is needed[83]. A pre-pancreatectomy clinical score has been developed, using demographic, co-morbidity and procedural specifics (type of operation, lymphadenectomy, preservation of the pylorus and others) to calculate the risk of peri-operative morbidity and mortality for each surgical candidate[83]. Based on the systematic review by Conroy *et al*[84], the median survival in patients treated with surgery alone is 15 to 20 months. Several adjuvant chemotherapy schemes have shown a survival benefit in the context of clinical trials with the most effective being FOLFIRINOX with overall median survival of 54.4 months (95% CI, 41.8 to upper bound not reached) and overall survival rate at 3 years of 63.4% (95% CI, 55.7 to 70.1)[85]. Other regimes with gemcitabine or 5-Fluorouracil have been shown to prolong survival by 2 to 6 months in comparison to surgery alone[84, 85]. In contrast, trial data demonstrated a lack of survival benefit from adjuvant chemoradiotherapy[84, 86-88].

Borderline Resectable Disease

In total, 20-40% of patients present with borderline resectable disease[74]. Several phase III clinical trials are currently in progress examining the effect of neoadjuvant treatments versus upfront surgery. In the interim, the European Society of Medical Oncology suggests consideration of FOLFIRINOX or combined gemcitabine and paclitaxel regime, with intent to down-stage such patients[74].

Unresectable Locally Advanced Disease

The chemotherapy options for this patient group consist of either gemcitabine (median survival 16.5 months, 95% CI, 14.5 to 18.5 months)[89] or FOLFIRINOX (median overall survival 24.2 months, 95% CI, 21.7 to 26.8 months)[90]. In contrast, radiotherapy did not add any survival benefit when was given in addition to gemcitabine (median overall survival 15.2 months, 95% CI, 13.9 to 17.3 months)[89].

Metastatic Disease

Approximately 60% of patients with pancreatic cancer present with metastatic disease[74]. Those with health performance status of 0 or 1 have a median survival of 11.1 months (95% CI, 9.0 to 13.1) with FOLFIRINOX [91]. Those with health performance status of 2 are more likely to tolerate gemcitabine and their median survival is reduced to 6.8 months (95% CI, 5.5 to 7.6)[91]. The 6-, 12- and 18- month survival was 76%, 48%, and 19%, respectively, in the FOLFIRINOX group, compared with 58%, 21%, and 6%, respectively, in the gemcitabine group ($p<0.05$)[91].

Supportive care

A large proportion of patients do not meet the fitness criteria for surgery or chemotherapy and therefore receive supportive care alone. There is no recent survival data specific to this patient group. Early clinical trials from the 1980's and 1990's where the control group was not receiving chemotherapy, reported survival limited to 2 to 4 months[74]. The care focuses on optimisation of their nutritional status with pancreatic enzyme supplementation, supportive treatment for the gastroparesis with probiotics and antiacids, prescription of nutritional supplements to address cachexia and management of depression[92]. Finally, frequently occurring complications such as obstructive jaundice or gastric outlet obstruction are addressed with the insertion of expandable metal stents via ERCP or percutaneous transhepatic drainage[92].

PAIN IN PANCREATIC CANCER

Pancreatic Innervation

The pancreas receives external innervation via both sympathetic and parasympathetic nerve fibers, which transmit the efferent autonomic signals from the central nervous system into the gland, as well as the afferent sensory signals to the opposite direction[93]. In addition, it possesses intrinsic ganglia within its parenchyma which contribute to its neurohumoral control[94].

The sympathetic efferent nerve fibers

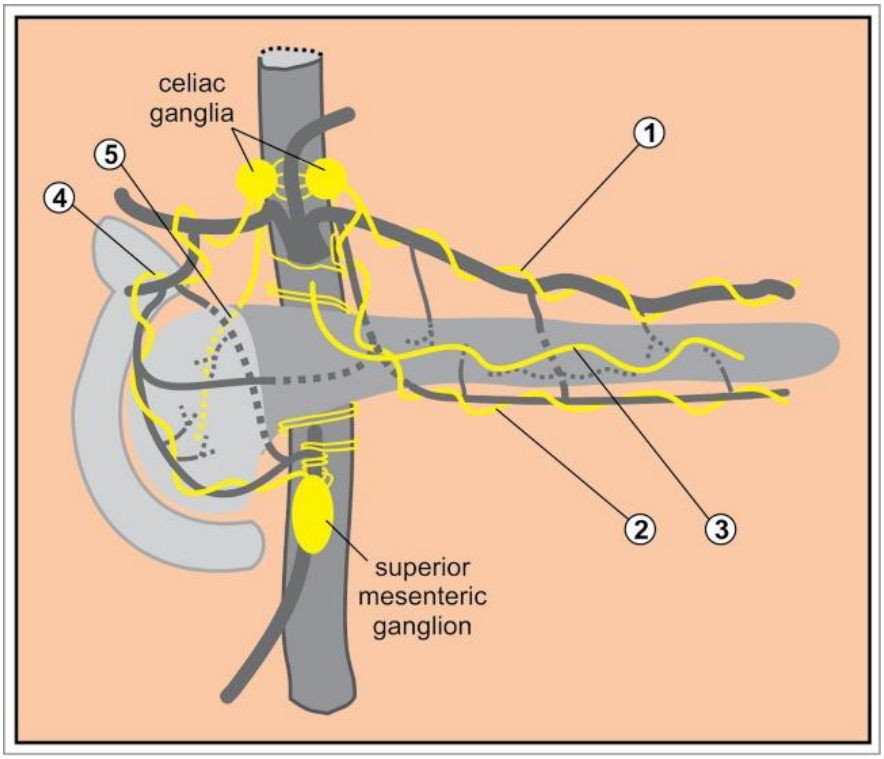
The cell bodies of the sympathetic nerves reside within the grey matter of the spinal cord, at the C6-L1 levels[95]. Their axons exit the spinal cord through its lateral horns, to form the greater, lesser and least splachnic nerves. These are the pre-ganglionic sympathetic nerves which after a short course synapse with post-ganglionic neurons at the coeliac and the superior mesenteric ganglia[93]. The celiac ganglia are located in the retroperitoneum, laterally and slightly inferiorly to the root of the celiac artery at the T12-L2 level[95]. Inferior to the celiac artery is the superior mesenteric ganglion, adjacent to the superior border of the superior mesenteric artery[95]. The post-ganglionic neurons project from the ganglia into the pancreatic parenchyma where they synapse with the intra-pancreatic ganglia and

release neurotransmitters, norepinephrine and neuropeptide Y, which regulate the responses of the islet, acinar and ductal cells, as well as the muscle layers of the local blood vessels[94, 95].

The coeliac plexus

The post-ganglionic nerve fibers from the sympathetic ganglia project into different sections of the pancreas. A group of the post-ganglionic nerve fibers of the coeliac ganglia travel circumferentially to the splenic and the transverse pancreatic arteries and innervate the body and tail (**Figure 14**)[95]. A second group runs across the common hepatic artery and the portal vein and innervate the head and a third one across the main pancreatic duct[95]. Nerve fibers originating in the superior mesenteric ganglion, travel cephalically, along the inferior pancreatico-duodenal artery and innervate the uncinate process[95]. Numerous interconnections exist between the coeliac, the superior mesenteric and other sympathetic ganglia of the upper abdomen, namely the left and right aorticorenal and the renal ganglia, as well as with the myenteric plexus of Auerbach and the submucosal plexus of Meissner[96, 97]. This complex of ganglia with their interconnecting nerve fibers which innervate the pancreas consist the coeliac plexus. Like most structures, the exact anatomy of the coeliac ganglia is variable among individuals. A study of 20 human adult cadavers showed that there is variation in the shape, size and number of the coeliac ganglia[98]. 85% of the examined ganglia had a longitudinal, 10% a round and 5% a sickle-shape. The number of ganglia varied between 1 and 5 and the diameter 20.02 ± 10.13 mm[98].

Figure 14. The distribution of post-ganglionic sympathetic nerve fibers: 1) across the splenic artery, 2) across the transverse pancreatic artery, 3) across the main pancreatic duct, 4) across the hepatic artery and 5) across portal vein. Adapted from Dolenšek *et al* (2015).

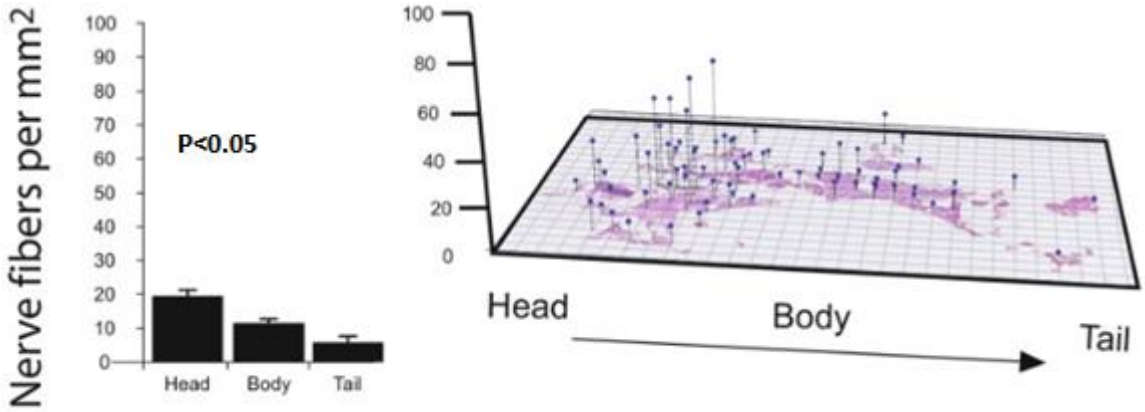


The afferent sensory fibres

Sympathetic and parasympathetic afferent nerve fibres provide sensory innervation to the pancreas[96]. Cell bodies located in the sympathetic dorsal root ganglia at T6-L2 level in spinal cord, transverse the splachnic nerves and the coeliac ganglia and synapse into the pancreatic parenchyma. The cell bodies of the afferent parasympathetic nerves are located in the nodose ganglia and synapse in the pancreatic parenchyma. Substance P (SP) and calcitonin gene-related peptide (CGRP) are neurotransmitters involved in the conduction of the afferent sensory signals[96].

The distribution of sensory nerve fibres varies in the different anatomical sections of the pancreas, as has been demonstrated in animal models (**Figure 15**)[99]. In pancreas specimens from mice, the sensory fibres were identified with immunohistochemistry staining antibodies against CGRP, and showed that nerve density is highest in the head of pancreas, with lower density in the body and the lowest density in the tail[99].

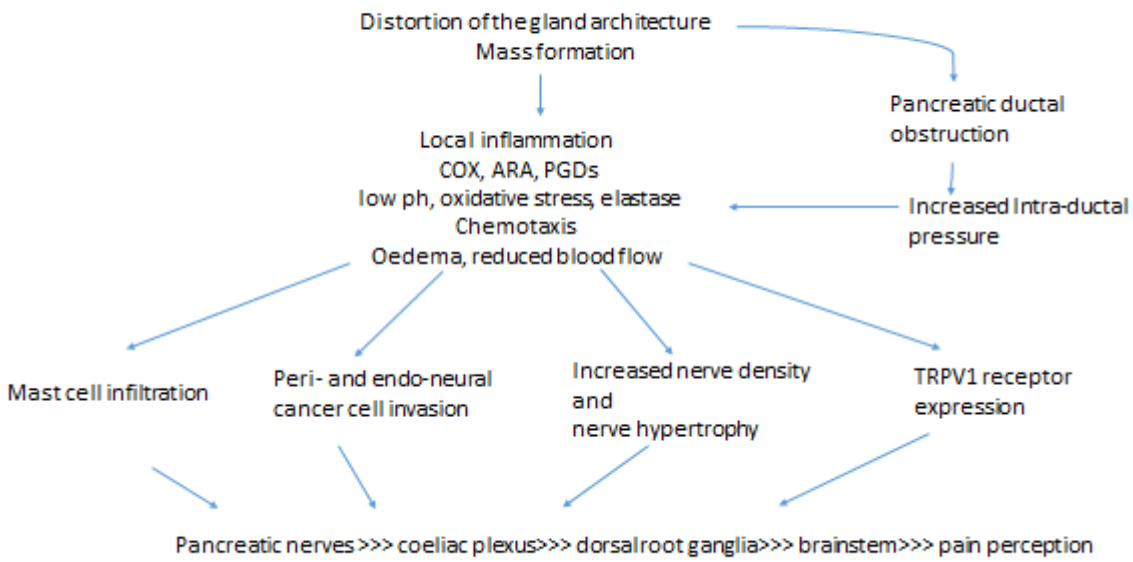
Figure 15. Graphs illustrating the nerve density in different anatomical portions of the pancreas. Adapted from Lindsay *et al* (2006).



The aetiopathogenesis of pain

Histological and mechanical phenomena contribute to the generation of pancreatic pain. The natural history of pain begins with the abundant and chaotic proliferation of the pancreatic ductal cells leading to the distortion of the normal pancreatic architecture[100]. Consequently, the local inflammatory response results in the release of arachidonic acid, prostaglandins and cycloxygenase and causing further cell damage, local oedema and vasodilatation, formation of free oxygen radicals and low pH, like any inflammatory response[100]. Although the exact aetiopathogenesis of pancreatic cancer related abdominal pain is unclear, previous literature describes its associations with the following histopathological features (**Figure 16**): i) peri- and endo- neural cancer cell invasion, ii) increased nerve density and nerve hypertrophy of the intra-parenchymal nerves, iii) over-expression of the vanilloid cation channel receptors, iv) domination of the peri-tumoural inflammation by mast cells and v) expression of neurotrophic growth factors which are undetectable in the normal pancreas and vi) the mechanical obstruction of the pancreatic ductal system. Below, we summarise the key clinical studies contributing to the current knowledge on the aetiology of pancreatic cancer pain and provide the appropriate information needed to justify the selection of radiological and cytological characteristics to be examined in subsequent chapters.

Figure 16. Simplified graphical representation of the events leading to pain generation in pancreatic cancer.



*** COX: CYCLOOXYGENASE, ARA: ARACHIDONIC, PGDS: PROSTAGLANDINS**

Perineural Invasion (PNI)

Perineurium is the connective tissue that surrounds and supports the neurons. Pancreatic cancer is known to invade the perineurium due to its increased affinity for the neurons[101]. This is attributed to the specific cytokines secreted by the tumour cells and the fibroblasts and include the following molecules: epidermal growth factor (EGF), transforming growth factor-a (TGF-a) and the Nerve growth Factor (NGF) and Glial-cell Derived Neurotrophic Factor (GDNF) families. In addition to this increased affinity for neurons, those cytokines are involved in three other histopathological processes: 1. chronic inflammatory response leading to a desmoplastic reaction, 2. growth signalling and 3. tumour neovascularisation. These cytokines are known to increase the metastatic potential of the primary tumour and contribute to a more aggressive biological behaviour. It is plausible that perineural invasion causes ongoing nerve cell damage and leads to pain generation. Ceyhan *et al.* examined this hypothesis in a case series of 149 specimens from patients with pancreatic adenocarcinoma, 73 Intraductal Papillary Mucinous Neoplasm (IPMNs) and 52 Neuroendoscrine Tumours (NETs)[102]. Perineural invasion was detected in 79% of pancreatic adenocarcinomas, 50% of NETs and 35% of

IPMNs[102]. In adenocarcinoma, the invasion was typically more extensive than in the other neoplasms as it can also involve the endoneurium, axons and Schwann cells. In NETS and IPMNs cancer cell invasion was restricted to the perineurium. In the above series the severity of neural invasion was classified as either: i) no invasion= 0, ii) perineural invasion=1 or iii) endoneural invasion=3 and the frequency as i) absent=0. ii) low= 1, iii) frequent= 2 and iv) excessive= 3. The multiple of those two was the neural cancer cell invasion score. Patients reporting severe pain had nearly twice neural cancer cell invasion score compared to those with no pain ($p< 0.05$) and mild pain ($p<0.001$)[102] (scores were 3.8 and 2 respectively).

Nerve Growth Factor

Another important molecule in the nociceptive pathway is Nerve Growth Factor (NGF). This is a neuropeptide, normally undetectable in the healthy pancreas but secreted by fibroblasts, immune, pancreatic and Schwann cells in response to neural injury to promote repair and regeneration[103]. NGF is a pro-inflammatory cytokine, promoting chemotaxis and further release of SP and CGRP. This peptide binds to the TrkA receptor (Tropomyocin kinase receptor), which promotes cancer cell proliferation in the perineural spaces[104]. NGF and TrkA mRNA levels were increased 2.7-fold ($p < 0.05$) and 5.6-fold ($p < 0.05$), in pancreatic cancer compared to healthy pancreatic tissue and were associated with higher pain scores ($r=0.63$ and 0.64) ($p<0.01$)[104].

Nerve Hypertrophy and Increased Nerve Density

Abdominal pain is associated with an increase in the number of nerve endings per unit area (nerve density) in the pancreas and increase in the total nerve tissue per unit area (nerve hypertrophy). Ceyhan *et al* recorded the pre-operative pain score of 149 patients with resectable pancreatic cancer. Patients reported their pain intensity (0=none, 1= mild, 2= moderate, 3= strong) and frequency (3=daily, 2= weekly, 1= monthly) and the multiple of the two was the registered pain score. Examination of their surgical specimens detected nerve density and hypertrophy increased by 14 and 2 times respectively, compared to that in non-cancerous tissue obtained from organ donors ($p<0.01$) [102]. Patients with pancreatic cancer who reported severe pain had a threefold greater nerve hypertrophy compared to those with mild pain ($P<0.0001$) or those pain free ($P<0.0001$)[102].

Mast Cell Infiltration

Immune cells including mast cells, T-lymphocytes and macrophages populate the microenvironment of pancreatic tumours, whilst eosinophils, B-lymphocytes and plasma cells, are rarely present[105]. A clinical study of 20 patients with resectable pancreatic cancer investigated the association between pre-operative pain and the presence of specific types of immune cells in their resection specimens. Patients who reported pain had pancreatic tissue infiltrated predominantly by mast cells, as opposed

to those without pain with infiltration predominantly by T-lymphocytes ($p < 0.05$)[105]. This observation, in addition to the fact that SP, CGRP and Nerve Growth Factors (NGF) bind to mast cells receptors and promote their degranulation supports a link between the pre-tumoural immune reaction and the activation of nerves[103] in the generation of pancreatic cancer pain[105].

Transient Receptor Potential Vanilloid-1 (TRPV1)

Transient Receptor Potential Vanilloid-1 (TRPV1) is a cation channel that conducts sodium and calcium influx into the neurons and facilitates the generation of action potentials[103]. This releases Substance P (SP) and Calcitonin Gene- Related Peptide (CGRP), two neurotransmitters which conduct pain signals from the parenchyma to the dorsal root ganglia[100]. In addition, SP and CGRP are also well known for being involved in chemotactic processes, such as release of pro-inflammatory molecules namely TNF-a, IL1,-2,-6,-8 and consequent neutrophil extravasation, macrophage activation, mast cell degranulation and eventually to the development of fibrosis[102, 103]. This has also been shown in several human tissues with painful disorders, such as synovial fluid in patients with arthritis or in the uterus of patients with endometriosis[106, 107]. The pain scores of 32 patients prior to Whipple's surgery were measured and classified into one of three groups (1= no pain, 2= controlled pain with non-steroidal anti- inflammatory drugs, 3= use of opioid analgesics). Post-operative real time polymerase chain reaction (PCR) and immunohistochemistry quantified and localised TVPR1 in the resected pancreas and also in 19 organ donor controls. There was a positive linear association between TVRP1 mRNA levels and the intensity of pain reported ($p<0.0001$). Controls expressed the TVRP1 only in acinar cells, whilst in the pancreatic cancer patients this cation channel was also detected in ductal and nerve cells (16). Based on the above observation, it is assumed that TVRP1 is over-expressed in response to the original tissue damage caused by the cancer. This over-expression facilitates the influx of cations into the nociceptive neurons and lowers the threshold for generating action potentials leading to hyperalgesia (a weak stimulant perceived as strong) and hyperexcitability.

Cytokines released by the tumour or by the cellular component of the desmoplastic stroma (fibroblasts and immune cells), depending on their genetic defect determine the biological behaviour of the tumour, and as part of this biological behaviour they do or do not lead to the development of pain. In subsequent chapters we investigate whether PNI in its extreme form (ganglia invasion), the radical distortion of the pancreas by large-sized tumours, the development of tumours in the nerve-dense head of pancreas, the density of the desmoplastic reaction as this is reflected on the CT intensity and degree of histological distortion (poor, moderately or well differentiated) are associated with the development of pancreatic cancer pain requiring opiates.

Pancreatic Ductal Obstruction

The Main Pancreatic Duct (MPD) or Duct of Wirsung arises in the tail of pancreas and runs a downstream course through the entire gland to drain into the small bowel through the duodenal papilla (Papilla of Vater)[1]. Small ductules draining the lobules of the gland join the MPD throughout its course. Pancreatic adenocarcinoma arises from the ductal epithelium and as it increases in size it obstructs the normal flow of pancreatic secretions[19]. Dilatation of the MPD more than 3mm is observed in 76.8% of the patients with pancreatic adenocarcinoma[108]. This percentage is variable depending on the tumour location (87% for head tumours, 86% for neck, 81% for body, 65% for uncinate process and 23% for tail)[108]. The pancreas has a basal secretion rate of 0.2 to 0.3 ml/min during fasting which gradually increases during the cephalic and gastric phase of the digestion to reach its peak of 4.0 ml/min in the intestinal phase[7]. The secretion is produced by the pancreatic acinar cells and flows through the small ductules into the main and the accessory pancreatic ducts before it reaches the duodenum[7]. It has been postulated that the pain caused by pancreatic ductal obstruction occurs in the post-prandial period and resembles that of the biliary colic. Pancreatic ductal manometry in patients with MPD dilatation secondary to chronic pancreatitis showed increased ductal and interstitial pressures, as well as reduced blood flow within the parenchyma[109]. It is believed that these changes lead to “pancreatic compartment syndrome” and generation of pain. Based on the assumption that a similar phenomenon may be applicable to pancreatic cancer, case series offered pancreatic ductal stenting in patients with biliary-type abdominal pain and dilated main pancreatic duct confirmed on CT. These reported total pain resolution between 41% to 87% of patients, however this has not been examined in randomised controlled trials[110-113].

The stimulation and inhibition of pancreatic secretion depends on the presence of either deficit or surplus of active proteases, respectively, in the upper intestinal lumen in the post-prandial period[7]. In animal models, the diversion of the pancreatico-biliary secretion away from the intestinal lumen after eating led to an increase in pancreatic secretion[114]. In the same animal experiments, this was followed by instillation of a mixture of pancreatico-biliary juices containing trypsin and chemotrypsin, into the upper intestinal lumen and resulted in suppression of the pancreatic secretion. In the last phase of this experiment trypsin inhibitors were infused into the upper small bowel leading to a second increase in the exocrine pancreatic secretion[114]. Along the same lines, other animal experiments showed that instillation of trypsin inhibitors into the small intestine as well as diversion of the pancreatic juices caused spikes in the serum CCK in rats[115]. These observations led to the conclusion that is the presence of active trypsin and chemotrypsin in the upper intestinal lumen which provides negative feedback regulation of pancreatic exocrine secretion, and similarly, the lack of those have the opposite effect. It is plausible that Pancreatic Enzyme Replacement Treatment (PERT) in patients

with pancreatic cancer may reduce the inherent pancreatic secretion through the negative feedback regulation and consequently the intra-ductal pressures and parenchymal oedema.

MANAGEMENT OF PANCREATIC CANCER PAIN

Opioid treatment

The management of pancreatic cancer pain relies mainly on pharmacotherapy. The selection of the appropriate agent is informed by the World Health Organisation (WHO) analgesic ladder, starting with simple painkillers, such as paracetamol or non-steroid anti-inflammatory drugs, progressing to moderate-strength opioids (codeine or tramadol) before the prescription of stronger, morphine-based medications[116]. Alfentanyl is used in patients with renal impairment, as it does not accumulate systemically like other opioid analgesics. Combinations of oxycodone and the opioid antagonist naloxone minimise opioid-related side effects, particularly constipation[117]. Methadone and ketamine, two NMDA (N-methyl-D –aspartate) receptor antagonists are given when opioids are ineffective. Transdermal morphine formulations are available for those heavily affected by nausea. Continuous subcutaneous pumps, known as syringe drivers, are given towards the end of life. Tricyclic antidepressants and gabapentinoids are known to reduce the release of nociceptive neurotransmitters such as the substance P (SP) and the calcitonin gene-related peptide (CGRP) and can be used to treat neuropathic pain in addition to the standard analgesics[118].

A previous retrospective cohort study estimated that patients with pancreatic cancer require a mean opioid dose of 55.9 (SD 53.8) mg at the early stages of their disease whilst in their last month of their life their doses increased to a mean of 162.8 (SD 131.6) mg[119]. These doses indicate substantial exposure to opioid-related side effects. To give a measure of the opioid burden in those patients, it is worth noting that the risk of respiratory depression is nearly three-fold (RR 3.09, 95% CI, 1.84 to 5.18, $p<0.001$) for those receiving 50-100 mg daily in comparison to those using less than 50mg[120] and, similarly, patients receiving 90mg or more per day have 2.12 times higher odds of developing delirium (95% CI, 1.09 to 4.13, $p=0.032$)[121]. The mean duration of the opioid-free period for patients were 97 (SD 234) days whilst the mean survival from the first opioid prescription was 187 (SD 212) days. There is an inverse association between the initial dose of opioids and survival (coefficient= −0.18; $P < 0.01$)[119].

This suggests pain worsens towards the end of life, and escalating morphine doses could adversely impact quality of life and wellbeing and alternative approaches are necessary.

Coeliac Plexus Neurolysis; technique, efficacy and limitations in the current literature

Coeliac Plexus Neurolysis (CPN) is the injection of the coeliac ganglia with absolute alcohol (or similar caustic agent) in order to ablate them and disrupt the nociceptive signals ascending to the central nervous system[122]. Different techniques have been used historically to approach and chemically ablate the coeliac ganglia. These are: surgical, fluoroscopic-guided, CT-guided, percutaneous ultrasound-guided and endoscopic ultrasound guided (EUS). The latter is now the preferred technique as it allows the endoscopist to distinguish the coeliac ganglia from other structures, like lymph nodes or vasculature, with high accuracy (sensitivity= 93.3%, specificity= 93.7%, positive predictive value (PPV)= 96.2% and negative predictive value (NPV)= 89.2%)[123]. In addition, it is less invasive than surgery and there is less interference of other organs and structures in comparison to percutaneous radiological techniques. EUS-guided Coeliac Plexus Neurolysis (EUS-CPN) is a day-case procedure which can be carried out either under sedation or general anaesthetic. An ultrasound probe, incorporated into the tip of the endoscope (echoendoscope), is placed against the lesser curvature of the stomach enabling the endoscopist to visualise the coeliac ganglia. A 22- or 25- gauge needle is used firstly to aspirate, to ensure no vessel has been punctured, and then to inject absolute alcohol. Mild and short-lived adverse effects are common and include diarrhoea, postural hypotension and pain exacerbation. Some authors associate the EUS-CPN with the risk of spinal stroke and visceral ischaemia, although the evidence on these is very scarce[124].

The evidence in the efficacy of the EUS-CPN is limited, with only a select number of randomised controlled clinical trials meeting high quality design standards[125, 126]. Wyse *et al*. offered EUS-CPN at diagnosis versus opioids alone to patients with non-metastatic pancreatic cancers. The patients in the EUS-CPN group (n=54) had 60% (95% CI, 26% to 87%) lower pain scores in the Likert pain scale at three months compared to the controls (n=54) (p=0.01). The mean morphine consumption in the EUS-CPN group was 49 mg (95% CI, 7 to 127mg) less than in the controls, although this difference reached only borderline statistical significance (p=0.10)[126]. In addition, this trial showed that the morphine dose plateaued between the months one and three in the EUS-CPN group, whilst for participants in the control group it continued to increase. This trial demonstrated the efficacy of the EUS-CPN in locally advanced pancreatic cancer at diagnosis but despite its methodological rigor, several uncertainties remain, including whether EUS-CPN is effective in stage IV disease and whether it is effective if given to those who develop pain at a later time.

Kanno *et al.* conducted a randomised control trial where EUS-CPN was administered in 24 patients versus an equally sized morphine-alone control group[127]. 58% of the participants had metastatic disease, although their outcomes were not stratified by staging, so the efficacy of the EUS-CPN in

metastatic disease is unclear. There were no statistically significant differences either in the mean VAS pain scores (1.3 vs 2.3, p=0.10) or in the mean morphine consumption between the two arms at four weeks (62 (SD 2.5) vs 35 (SD 2.0) mg daily, p=0.14). The timing of administration of the EUS-CPN (i.e. at diagnosis versus on demand) was not detailed in the manuscript. This trial ran from 2011 to 2018 and recruited only 48 (26%) out of the 179 eligible patients in that time period.

Levy *et al* compared the efficacy of two different EUS-CPN techniques given at diagnosis (described in detail in chapter 2) to patients with locally advanced and metastatic disease and provided data on pain relief and opioid consumption before and after neurolysis: 40% of participants had at least a 30% drop in their pain score. Similar to Wyse *et al*, the median morphine dose plateaued in the months following the procedure [pre-treatment: 45mg (IQR: 18-90 mg), month one: 90mg (IQR: 45-150 mg), month two: 90mg (IQR: 45 to 135 mg), month three: 93mg (IQR: 64 to 150 mg)][125].

Another uncertainty of administration of EUS-CPN is related to the method of injection. The classical EUS-CPN involves a single injection adjacent to the base of the coeliac artery[122]. However, it has been debated that two injections, each one given laterally to the coeliac artery may have a better spread of the injectate and therefore a more potent neurolytic effect[122]. A third approach involves advancement of the tip of the needle into the ganglia[122]. For ease, in this document we refer to these three techniques as the central injection technique (CIT), bilateral injection technique (BIT) and coeliac ganglia injection (CGN). Currently, in the absence of robust evidence EUS-CPN is administered based on the endoscopist's individual preferences with CIT and BIT being the most commonly used techniques.

A key uncertainty is whether EUS-CPN should be used as a first line treatment when the pain first occurs (i.e. "early EUS-CPN") or if it should be reserved as an option after opioids have failed ("on demand EUS-CPN"). In their most recent guidance NICE recommends that a trial comparing early versus on demand EUS-CPN is needed[128].

Radiotherapy and Pain Relief

As discussed earlier, radiotherapy has a debatable role in the management of pancreatic cancer. Low dose radiotherapy has been used to promote analgesia, however this is based on secondary outcome data (the primary outcome in those studies was survival). A systematic review and meta-analysis of four phase I and II clinical trials and ten retrospective cohort studies, with a total of 469 patients, attempted to summarise the analgesic effect of radiotherapy[129]. Complete pain resolution was reported in 54% (95% CI, 41% to 67%, I^2 =77%, P=0.013). Reduction in analgesic use was observed in 69% of the patients (95% CI, 59% to 78%, I^2=86%, P<0.001). The very high heterogeneity among the

studies in this meta-analysis probably reflects the variation in; the study designs; the radiotherapy doses used; and the heterogeneity of the treated population in terms of their pain intensity, cancer stage and the applied radiotherapy technique (robotic radiosurgery vs stereotactic radiotherapy vs external beam radiotherapy). The median radiation dose was 27.8 Gy (16.5 to 45) and the median number of fractions were 3.5 (1 to 6). In 11 of those studies, the pre-radiation pain was mild (Visual analogue score 2 or less). The treated patients received either palliative or neoadjuvant radiotherapy. Although radiotherapy may have an analgesic role in patients with otherwise good health, its use is hampered in those with lower fitness. Gastric outlet obstruction, bleeding duodenal ulcer and perforation are reported in 3.3% to 18%, as a result of heat injury[129]. Therefore, in contrast to EUS-CPN, radiotherapy requires preserved physiological reserves, so the adjacent tissue can heal upon exposure to therapeutic doses of radiation. This probably explains why patients with reduced fitness may experience a deterioration of their pain following radiotherapy.

Chemotherapy and Pain Relief

The primary outcome measure in chemotherapy trials is survival, with pain relief examined as a secondary outcome, usually as one of the dimensions in health-related quality of life questionnaires. Kristensen *et al.* conducted a systematic review of the analgesic effect of chemotherapy in patients with inoperable pancreatic cancer, using data from all the historic clinical trials administering regimes which either became later standard care, such as single-agent gemcitabine, or regimes which were abandoned due to lack of survival benefit over the standard care (e.g. marimastat, gemcitabine/cisplatin, gemcitabine/exatecan and other combination schemes)[81]. Here we summarise the results related to the analgesic effect of single-agent gemcitabine chemotherapy which is currently used in clinical practice. Data on the analgesic efficacy of FOLFIRINOX is not available. Three trials administer single-agent gemcitabine in their standard care group and reported pain relief in the form of proportion of patients with a 50% reduction in their pain scores. These reported that pain relief was achieved in 15%, 21% and 24%, respectively[130-132]. Other studies reported pain outcomes as the proportion of those with a 5% drop in their pain levels[133], 10% drop in their pain levels[134] or as a binary outcome (pain improvement versus pain deterioration) without quantification of the improvement[135]. Overall, gemcitabine appeared to have a positive effect on pain control, however, as none of these studies reported the pre- and post-treatment pain levels, the magnitude of this change remains unclear. It is plausible that chemotherapy suppresses the neuro-inflammatory changes in the tumour's microenvironment which are involved in the generation of pain. However, the analgesic effect of chemotherapy should be considered in view of its probable limitations; patients who are included in chemotherapy trials are likely to have preserved general health and mild pain (otherwise they would

be unable to tolerate chemotherapy or their chemotherapy would be postponed until their pain is under control with opioids); several cycles are required to be administer (i.e. at least 1-2 months) for an analgesic effect to become apparent; an initial deterioration of the patient's general health with constitutional symptoms is usually observed after the first few chemotherapy cycles.

Pain management in pancreatic cancer; the summary

In summary, pain is a common complaint in patients with pancreatic cancer affecting approximately 60-80% of the patients at diagnosis. Overall, the main analgesic modality for managing pain in patients with pancreatic cancer is opioid therapy, which may be associated with severe side-effects. The evidence supports the use of EUS-CPN in locally advanced pancreatic cancer, however, it is uncertain if it is effective patients in metastatic disease and if it can prevent dose escalation if given the outset of pain in those whose pain starts the months after diagnosis. Radiotherapy can be used to treat pain, although it has associated toxicity and it is suitable only in those with adequately preserved health. Patients who respond to chemotherapy are likely to have pain improvement and decrease in their opioid requirements, however, this analgesic effect has a slow onset and pain is likely to recur once the tumour stops being sensitive to the chemotherapy.

AIMS OF THIS THESIS

The two overarching aims of this research are to determine the rationale, feasibility and design considerations of a future trial of EUS-CPN versus standard care and develop a multivariable model predictive of opiate use in patients with pancreatic cancer.

Objectives

In patients with inoperable pancreatic cancer:

a) Summarise the current evidence on the mechanisms of pancreatic cancer pain.
b) Determine the efficacy of endoscopic neurolysis for the treatment of pain based on previously published research.
c) Estimate the logistics and assess the feasibility of a randomised trial of early EUS-CPN for the prevention of pain.
d) Explore patient's and carers' lived experiences of pain and their attitude towards endoscopic treatments during terminal illness.
e) Determine the proportion of patients requiring opioids, their health performance status and their absolute and relative survival.

f) Investigate associations between clinical, radiological and cytological tumour characteristics and pain.

g) Develop a multivariable model predictive of severe pain requiring high dose opiates.

CHAPTER 2 - Endoscopic Ultrasound-guided Coeliac Plexus Neurolysis (EUS-CPN) Technique, Analgesic Efficacy and Safety in Patients with Pancreatic Cancer: a Systematic Review and Meta-analysis.

ABSTRACT

Background. Endoscopic Ultrasound-guided Coeliac Plexus Neurolysis (EUS-CPN) for the treatment of abdominal pain in pancreatic cancer can be administered using three different injection methods, depending on the site of needle insertion: central injection technique (CIT), bilateral injection technique (BIT) and coeliac ganglia neurolysis (CGN). This meta-analysis aimed to (1) estimate the overall efficacy of the EUS-CPN; (2) compare the efficacy of each of the three techniques; and (3) investigate demographic (age, gender) and disease characteristics (tumour located in the head of pancreas, stage IV disease and baseline pain score) as potential predictors of analgesic response.

Methods. We searched MEDLINE and EMBASE for studies that reported the proportion of treatment responders to EUS-CPN overall, and according to the technique used. We performed a random effects meta-analysis of proportions, and meta-regression was used to estimate the association between technique and clinical characteristics with treatment response. The safety profile was reviewed through narrative synthesis.

Results. In total, seventeen studies of 727 patients were included in the meta-analysis. Overall response rate to EUS-CPN was 68% (95% CI, 61% to 74%) at week two and 53% (95% CI, 45% to 62%) at week four. There was no evidence of a significant difference in the efficacy between the three techniques. Demographics and disease characteristics were not associated with treatment response. Serious complications have been reported for BIT and CGN but not for CIT. Moderate to high risk of bias of included studies was observed.

Discussion. EUS-CPN is a useful addition to opioids in the management of pain. There is no evidence of a difference in the efficacy among the three techniques, however, CIT is probably the safest. The appropriate timing of EUS-CPN administration (early versus on demand) and randomised comparison to establish the comparative efficacy of each technique needs to be evaluated in future research.

INTRODUCTION

Nearly 58-78% of patients with pancreatic cancer suffer from abdominal pain[67]. The management of pain relies mainly on the prescription of opioid-based medications. These are frequently poorly tolerated due to side-effects such as lethargy, constipation, memory impairment and delayed gastric emptying[136]. Endoscopic ultrasound-guided coeliac plexus neurolysis (EUS-CPN) causes irreversible destruction of the coeliac plexus and it is indicated when opioids fail to control pain or related side effects are not tolerated[137].

Several variations of the EUS-CPN technique are reported in the literature. The central injection (CIT) technique for EUS-CPN involves a single injection of absolute alcohol into the peritoneal space, immediately anteriorly to the root of the coeliac artery. The bilateral injection (BIT) technique involves administration of the same volume of injectate, divided in two and injected bilaterally at the root of the coeliac artery[126]. More recent reports describe advancement of the tip of the needle deep into the middle of the coeliac ganglia and injection until resistance is felt on the syringe which is attached at the proximal end of channel of the echoendoscope. This procedure is usually referred to as Coeliac Ganglia Neurolysis (CGN). This can be combined with an extra injection in the free retroperitoneal space (Combined CGN). Injection at the area of the superior mesenteric ganglion, at the root of the superior mesenteric artery is a fourth technique frequently refer to as Broad Plexus Neurolysis (BPN) but this has only been examined in one pilot study[138]. All these different techniques have evolved historically over the past 25 years with an intention to achieve a better spread of the injectate and a more radical ablation of the nerve tissue of the ganglia, to optimise the neurolytic effect.

A series of clinical studies have assessed the analgesic efficacy and safety profile of the different EUS-CPN approaches in patients with pancreatic cancer, however considerable uncertainties remain. The comparative effectiveness and safety of each injection techniques is unclear. Previous meta-analyses comparing CIT versus BIT reported contradictory results with one finding no difference[139] whilst the other reporting substantially higher efficacy of the BIT technique[140]. The efficacy of EUS-CGN has not been assessed in any meta-analysis. It is also not clear whether clinical characteristics influence analgesic response. Therefore, this systematic review aimed to determine (i) the comparative analgesic efficacy of each technique; (ii) the independent clinical predictors of treatment response; (iii) the safety profile of each approach; and (iv) the risk of bias of included clinical studies. Establishing the comparative efficacy and safety of those techniques may help to inform the current clinical practice as well as the most appropriate one to be adopted in a potential future clinical trial of early versus on demand EUS-CPN.

METHODS

Eligibility Criteria

The eligibility criteria for the meta-analysis of the efficacy of the EUS-CPN were: 1. Studies managing patients with pancreatic cancer, 2. Studies using EUS-guided methods, 3. Clinical trials of any design, including randomised, non-randomised or single-arm trials. The exclusion criteria were: 1. method of guidance other than EUS (percutaneous ultrasound, CT, surgical or fluoroscopic) and 2. studies investigating a mixed population of patients with pancreatic cancer, chronic pancreatitis and/or other upper gastrointestinal cancers. We propose such conditions have different biological behaviour, may differ in their response to treatment, and hence should be studied separately to pancreatic cancer.

Literature Search

The literature search was conducted in the Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, MEDLINE, ClinicalTrials.gov and Google Scholar, from inception until December 6th 2020. Search terms were: “pancreatic cancer”, “endoscopic ultrasound”, “coeliac plexus neurolysis”, “coeliac ganglia neurolysis”, and “broad plexus neurolysis”. A detailed search strategy on OVID MEDLINE is displayed **Appendix 1.** A manual search for additional articles was conducted by reviewing the reference lists of the retrieved publications. The number of identified, screened, included and excluded studies is illustrated on the PRISMA chart.

Statistical Analysis

For each trial arm, data on the number of the treatment responders and total number of participants were pooled. Treatment responders were classed as those with *“at least 3-point drop in their 0-10 visual analogue scale”* (VAS). The primary outcome was the summary proportion of treatment responders to endoscopic neurolysis, regardless the performed endoscopic technique. Subsequently, a meta-analysis stratified by the type of the performed technique (CIT, BIT and CGN) was conducted and pooled proportions of treatment responders were calculated for each technique. We used *metaprop*[141], to perform a meta-analysis of proportions extracted from each study. Confidence intervals for individual studies were calculated using the binomial exact method[142]. Proportions were transformed to stabilize their variances using Freeman-Tukey double arcsine transformation[143], prior to calculation of pooled estimates using the random effects model proposed by DeSimonian and Laird[144]. Confidence intervals for the pooled estimates were calculated using the Wald method.

Heterogeneity between studies was assessed with x^2 test (Cochrane Q statistic) and quantified with the I^2 statistic. Heterogeneity was classified as low, moderate and high with cut-off values of 25%, 50%

and 75%. Publication bias was assessed by examining the visual symmetry of funnel plots, performing Egger's regression test and by using the "Trim and Fill Method" [145,146].

A meta-regression analysis investigated the association between each technique and overall treatment response, and estimated the relative efficacy of each technique[147]. This model was built in the form of univariate logistic (meta-) regression. The outcome variable was the probability of treatment response, the performed technique was the categorical moderator variable and the CIT group was the reference category. The relative effect of the one technique over the others was reported as the absolute difference in the proportion of pain responders. In addition, the relationship of treatment response with other explanatory variables: age, gender, tumour located in the head of pancreas, stage IV disease and baseline pain score, was examined with the same methodology (i.e. logistic regression with forward selection). A sensitivity analysis based on quality of studies was not possible due to their small number. The analysis was conducted on the STATA 16.0 software (StataCorp LP, College Station, Texas, USA)[148, 149].

Adverse Events

Adverse events were assessed through a systematic review of the published clinical trials. However, because the life-threatening events have been described solely in case reports, a narrative analysis of those was also conducted.

Risk of Bias Assessment and GRADE Quality of Evidence Assessment

Risk of bias assessment was carried out using the Cochrane's Collaboration Tool for randomised clinical trials and the Risk of Bias Assessment Tool for Non-Randomized Studies (RoBANS)[150,151]. The quality of the evidence was assessed using the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) approach[152].

RESULTS

In total, 136 reports were identified through the database searches (**Figure 17**). Upon removal of duplicates, there were 54 remaining records. Overall, 28 publications were dismissed as irrelevant, based on their titles and abstracts. A full-text review was undertaken in the remaining 26 reports. Nine reports were excluded based on the eligibility criteria; six abstracts, some of which were included in later publications[153-158]; two administered EUS-CPN in patients with chronic pancreatitis[159, 160]; one study offered two different EUS-CPN techniques, however, the pain responses were reported cumulatively[161]. In total, seventeen studies of 727 patients were included in the systematic review (**Table 1**). These consisted of: five parallel group randomised trials[125-127, 162, 163], three two-arm non-

randomised trials[138, 164, 165] and eight single arm phase II trials with a case series design[166-172]. Four studies contributed to the narrative synthesis but not the quantitative synthesis because they did not report the proportion of treatment responders. Instead, their outcome was reported as the mean difference[126, 127, 138, 162].

Figure 17. PRISMA flow chart for the meta-analysis of the efficacy of the EUS-CPN

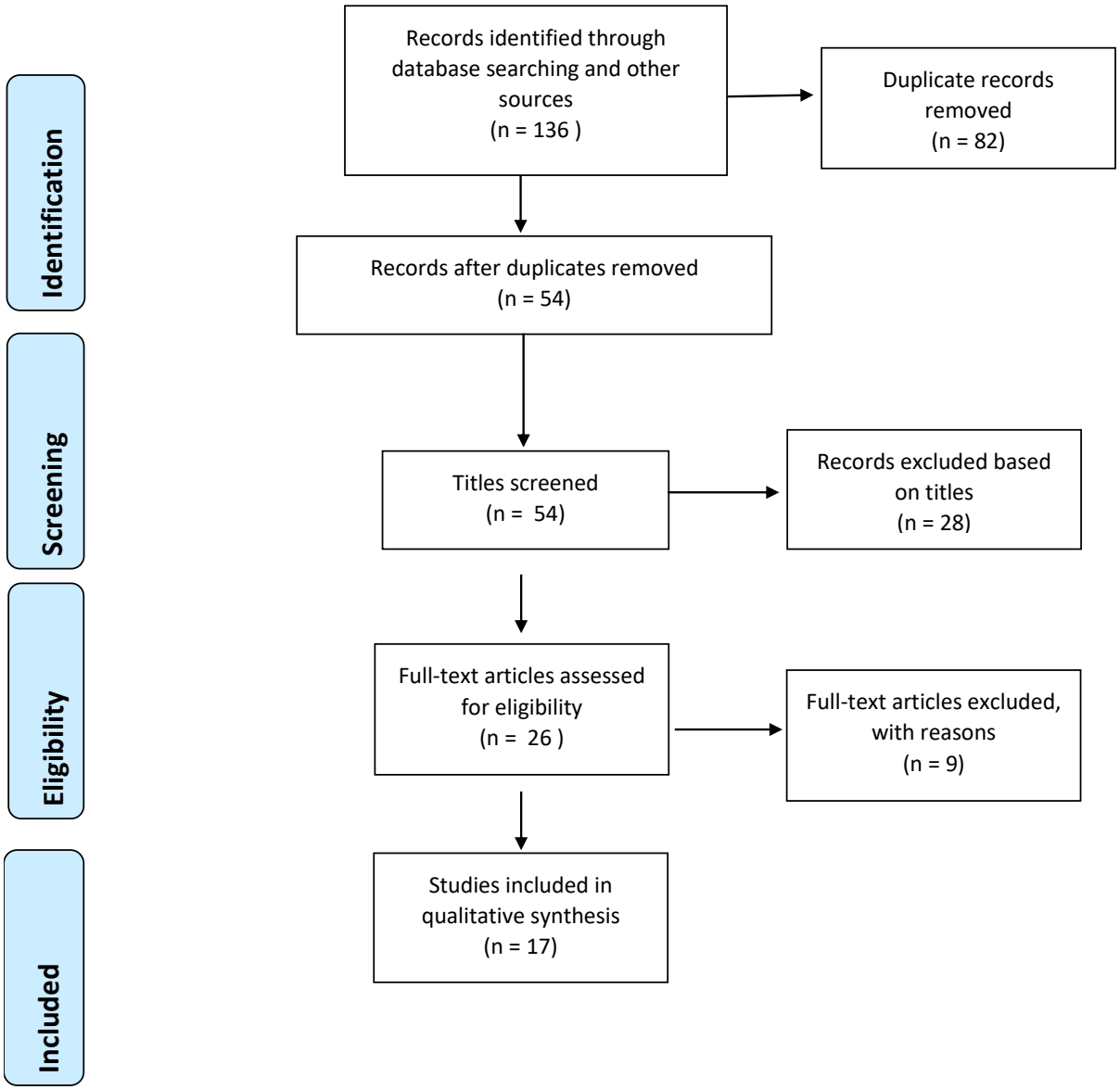


Table 1. Effect sizes of the reporting "proportion of pain responders" post- EUS-guided neurolysis".

Author	Number of participants per trial arm	Week 1-2	Week 4	Week 8	Week 12
Central Injection Technique					
LeBlanc *et al* [156]	21	69.0%	-	-	-
Tellez-Avila *et al* [164]	21	62.0%	47.6%	-	-
Doi *et al* [163]	33	45.5%	39.2%	33.3%	33.3%
Levy *et al* [125]	60	-	48.1%	39.6%	40.4%
Iwata *et al* [167]	47	61.8%	-	-	-
Facciorusso *et al* [173]	58	70.7%	-	-	-
Seican *et al* [174]	32	87.5%	-	-	-
Bilateral Injection Technique					
LeBlanc *et al* [156]	29	81.0%	-	-	-
Tellez-Avila *et al* [23]	32	59.4%	56.3%	-	-
Wiechovwska *et al* [171]	29	59.0%	-	56%	-
Wieserma *et al* [169]	29	54.0%	-	-	-
Gunaratnam *et al* [170]	58	54.0%			
Coeliac Ganglia Neurolysis					
Minanga *et al* [172]	112	77.7%	67.9%	-	-
Doi *et al* [163]	34	73.5%	64.7%	58.8%	47.0%
Levy *et al* [125]	50	-	52.3%	55.9%	46.2%
Si-Jie *et al* [168]	42	80.4%	-	-	60.9%
Ascuse *et al* [166]	40	65.0%	50.0%	-	-

Proportion of Treatment Responders

The estimated summary proportion of treatment responders to endoscopic neurolysis, regardless of the exact technique, was 68% (95% CI, 61% to 74%) (I^2 = 68.0%, P=0.01) at week two (**Table 2**), and 53% (95% CI, 45% to 62%) (I^2 = 60.3%, P=0.01) at week four (**Table 3**).

Central Injection Technique (CIT)

At week two and four, the proportions of patients with analgesic response were 67% (95% CI, 56% to 79%) (I^2= 72.4%, P=0.01) and 46% (95% CI, 36% to 55%) (I^2=0, P=0) (**Table 2 and Table 3**). Three parallel group randomised controlled trials provided direct comparison between CIT and BIT techniques[156, 164, 165]. All of them showed higher response rates in their bilateral injection groups but none of them reached statistical significance. Only one used double blind randomisation design[156]. Two randomised trials directly compared between CIT and CGN[125, 163]. The one trial delivered EUS-CGN as an endoscopic monotherapy, showing higher response rates in the EUS-CGN group compared to CIT (73.5% vs 45.5%, p=0.026)[163]. The second trial administered CGN and when resistance was felt on the syringe the left-over volume of the neurolytic agent was injected in the free peritoneal space anteriorly to the root of the coeliac trunk, in a CIT fashion. The difference in the proportion of pain responders was only marginal between the two trial arms at month one, two and three in favour of the CGN and the difference, in contrast to the previous trial, was statistically non-significant (46.2% vs 40.4% at 12 weeks, p>0.05) [exact p-value not provided][125].

Bilateral Injection Technique (BIT)

At week two the proportion reporting analgesic response after BIT was 62% (95% CI, 50% to 73%, I^2=64.3%, P=0.01) (**Table 2**). A meta-analysis of the BIT Technique was not possible for other follow up time-points due to insufficient data. Two randomised clinical trials investigated the effect of the BIT technique versus opioids alone, both of which reported higher drop in mean pain scores in the EUS-CPN groups[126, 127]. The one with the greatest methodological rigor reported 60.7% more reduction in the EUS-CPN group (95% CI, 25.5% to 86.6%, p= 0.01) at 12 weeks[126]. The other randomised trial showed higher drop in the pain scores in the EUS-CPN group at week four, too, but the difference was not statistically significant (VAS pain score 1.3 vs 2.3, p=0.10)[127].

Coeliac Ganglia Neurolysis (CGN)

At week two and four the proportion reporting analgesic response after EUS-CGN was 76% (95% CI, 71% to 82%, I^2 = 0%, P=0) and 58% (95% CI, 48% to 69%, I^2 = 65.0%, P=0), respectively. Only two studies

were randomised trials, comparing CIT versus CGN and reported respond rates between 46.2% and 73.5% in their CGN arms, respectively[163],[125]. Three delivered EUS-CPN as main therapy, and CGN was performed as an additional manoeuvre, if ganglia were identifiable endosonographically[166, 168, 172]. The group of patients who received CGN was not reported separately.

Table 2. Summary proportion of Treatment Responders at the first two weeks post-EUS-guided neurolysis and individual pooled proportions for: a. Central Injection, b. Bilateral Injection and c. Coeliac Ganglia Neurolysis.

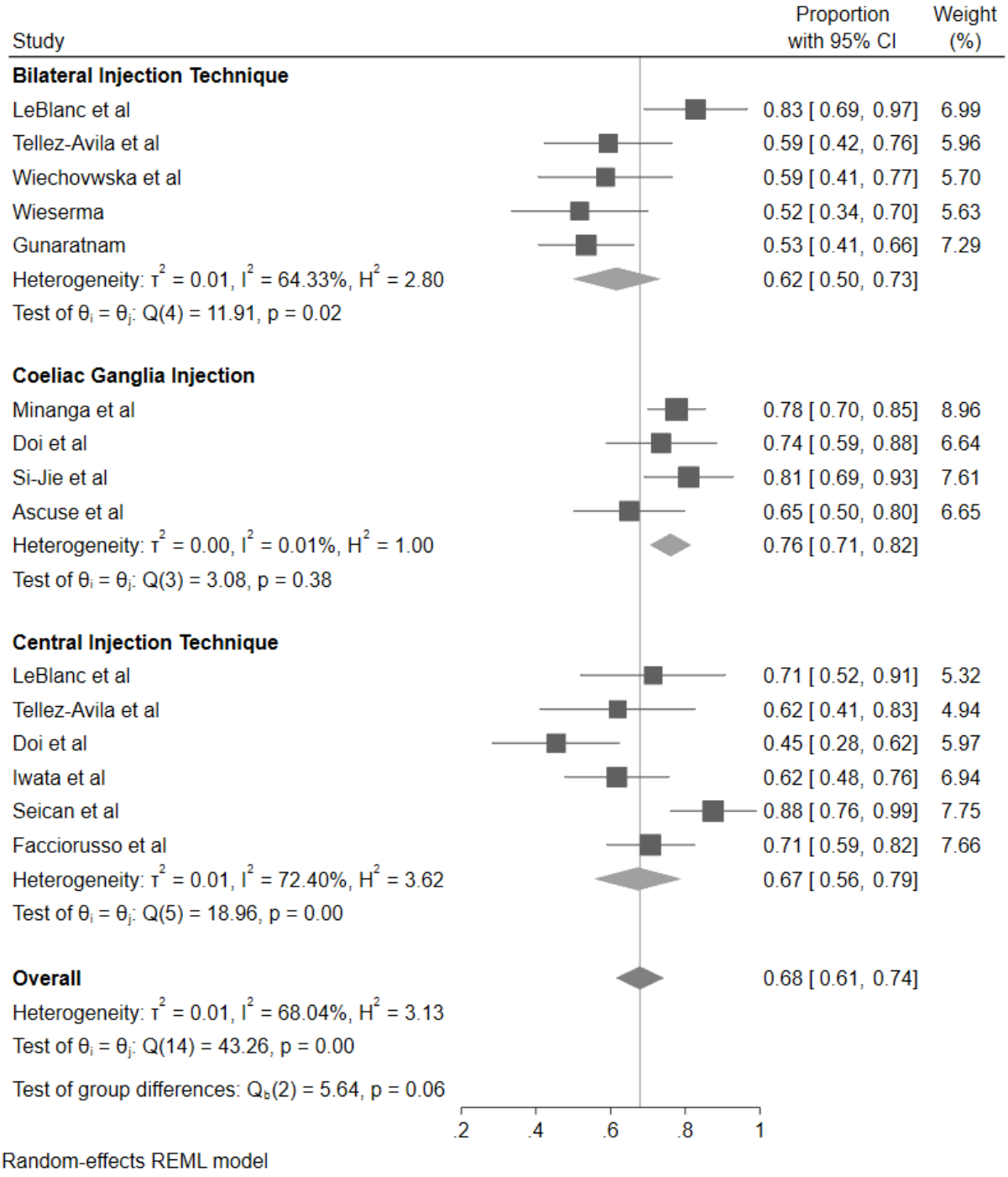
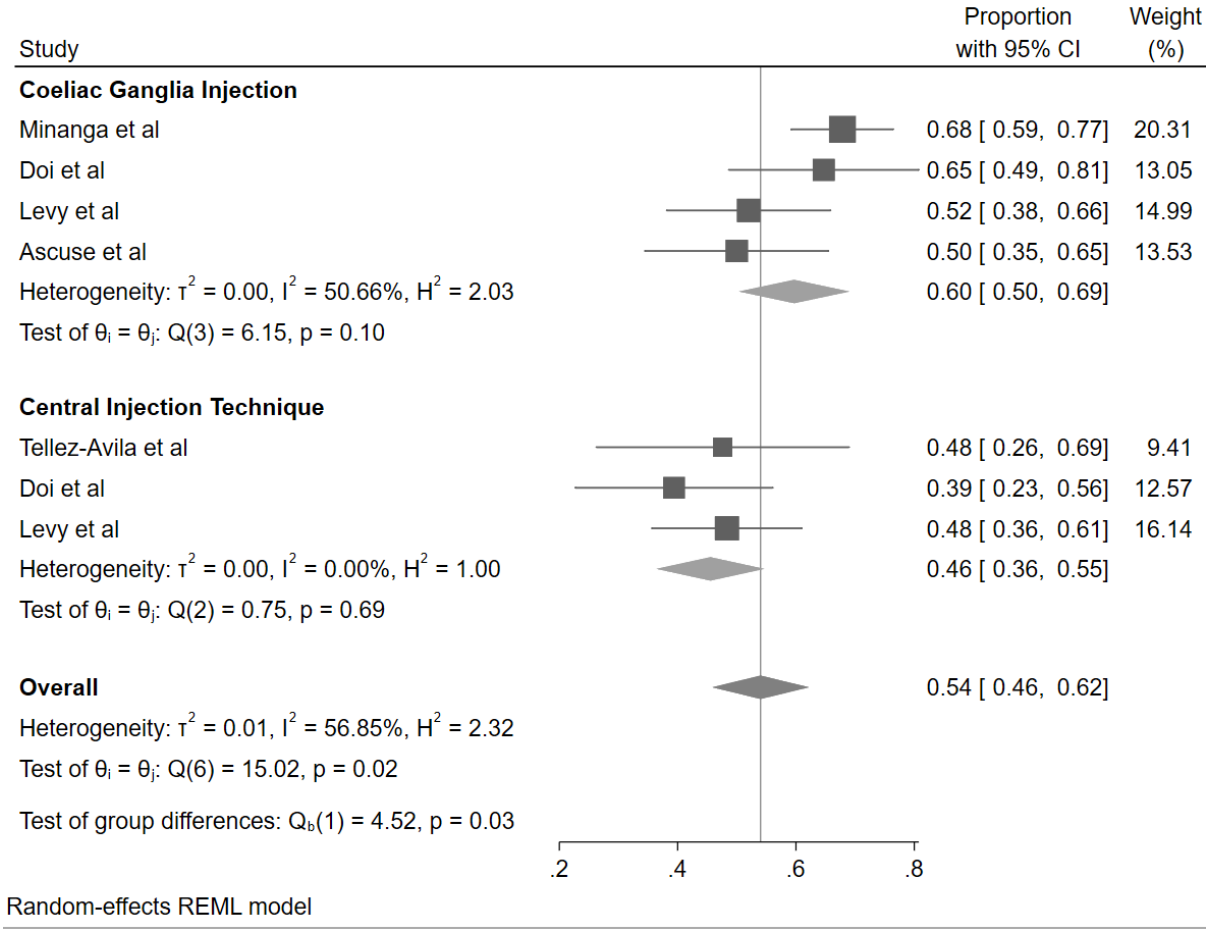


Table 3. Summary pooled proportion of Pain Responders at week four post-EUS-guided neurolysis and individual pooled proportions for: a. Central Injection and b. Coeliac Ganglia Neurolysis. Pooled proportion for Bilateral Injection was not possible due to insufficient data.



Putative Predictors of Treatment Response

Meta-regression analysis using the individual technique as moderator variable, showed that there was no evidence of difference in the efficacy of the three techniques at week two and week 4 **(Table 4).** In addition, there was no evidence that age, male gender, tumour located in the head of pancreas, TNM stage IV disease and baseline pain score are associated with the efficacy of the EUS-CPN.

Table 4. Exploration of within the studies heterogeneity with meta-regression analysis: none of the examined co-variates moderates the treatment response.

Week 2	**Difference in proportion of treatment responders**	**95% CI**	**p-value**
Central l injection	reference category	-	-
Bilateral Injection	6%	[-13% to 26%]	0.34
Coeliac Ganglia Injection	15%	[- 4% to 35%]	0.51
Every year of age	-0.9%	[-3% to 1%]	0.45
Gender (male)	<0.01%	*	0.38
Head of Pancreas Tumour	<0.01%	*	0.68
Every unit of VAS at baseline	0.3%	[-6 % to 11 %]	0.51
Tumour stage IV	<0.01%	*	0.88
Week 4	**Difference in proportion of treatment responders**	**95% CI**	**p-value**
Central Injection	reference category	-	-
Coeliac Ganglia Injection	15%	[-37 % to 68 %]	0.17
Every year of age	0.6%	[-4 % to 9 %]	0.73
Male gender	<0.01%	*	0.80
Head of Pancreas Tumour	<0.01%	*	0.88
Every unit of VAS at baseline	0.3%	[-3 % to 9 %]	0.43
Tumour stage IV	<0.01%	*	0.67

*values < 0.001% were omitted from the table.

Adverse Events of EUS-CPN

Search through Ovid Medline detected a total of 16 studies (871 participants) where adverse events were reported (**Table 5**). Four of those did not report the incidences of benign, spontaneously resolved adverse events but instead reported absence of morbidity or mortality[126, 127, 156, 167, 174]. In the remaining 12 studies, diarrhoea (9%), temporary pain exacerbation (8%) and hypotension (6%) were the most observed. Their frequencies were similar among the three techniques. Inebriation due to the injected alcohol was specific only to Japanese studies. Gastric bleeding requiring mechanical haemostasis was observed in one patient who was on anticoagulants and received EUS-CGN (the paper did not specify if the anticoagulant was reversed prior to the procedure)[163].

Of all the patients who participated in clinical trials, spinal stroke was observed twice (0.2%), both in patients who received EUS-CGN (albeit, one technically had a failed CGN which was converted into EUS-BPN intra-procedurally)[125, 172]. Another three case-reports have reported similar events (**Table 5**), although, there duplications are very possible, considering the clinical details, hospital location, authorship and year of publication of those reports (two patients have been reported by Minaga *et al* in 2016[172, 175], whilst Mittal[176], Fuji[177] and Levy all reported in Mayo Clinic, Rochester, Minesota, with overlapping dates (2010-2014)) (**Table 6**). One of those used epinephrine alongside alcohol and local anaesthetic[176]. Importantly, these patients received either EUS-CGN combined with injection in the free retroperitoneal space, BIT or EUS-BPN and the dose of injected alcohol was 20ml or above.

Gastric ischaemia in pancreatic cancer has been reported only once[178]. This patient had undergone ERCP and stent exchange during the same time of the EUS-CPN which was complicated by gastric bleeding requiring adrenaline injection or haemostasis. Another patient who underwent EUS-FNA and EUS-CPN for mass-forming chronic pancreatitis pain developed extensive (hepatic, renal, pancreatic) visceral ischaemia within 24 hours[179]. This patient had undergone EUS-CPN 13 times in total. Of relevance, is that this patient had retroperitoneal fibrosis involving segments of his aorta. This could be assumed to be the long-term result of the sclerotic effect of alcohol. A third case report described a patient with alcohol-related chronic pancreatitis who was admitted with abdominal pain and received EUS-CPN[180]. Four days later a CT showed splenic infarcts. A fourth case-report described the case of a 57 year old patient with idiopathic recurrent acute pancreatitis who developed complete thrombotic occlusion of the coeliac artery post EUS-CPN[181]. Overall, those case reports describing thromboembolic events contain significant gaps, therefore, aetiological links with the EUS-CPN are not possible.

Figure 18. PRISMA flow chart for the systematic review of adverse events to EUS-CPN

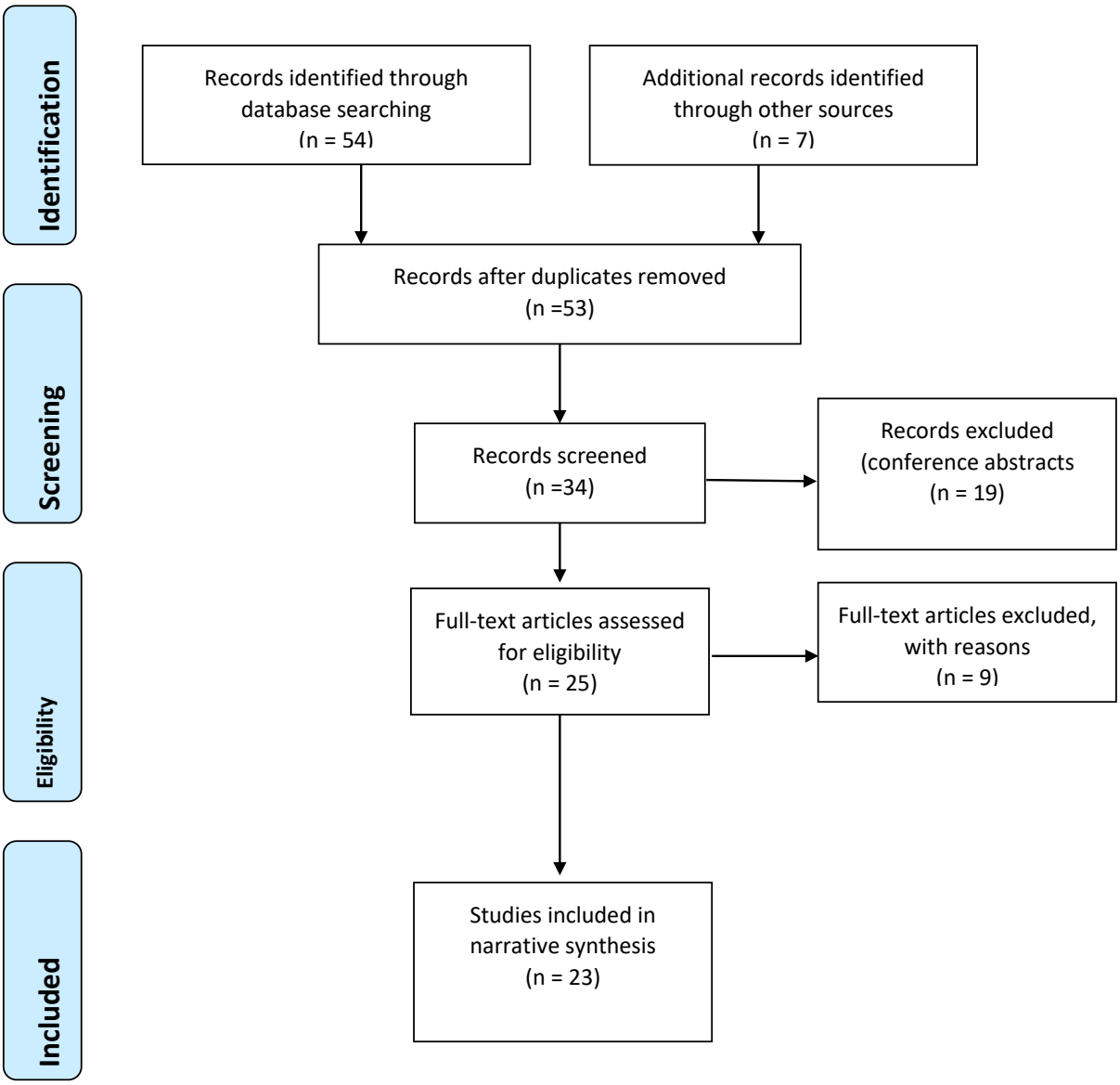


Table 5. Adverse events following EUS-CPN; Spinal stroke observed twice in a total of 817 patients. The two cases were associated with EUS-CGN and EUS-BPN, respectively.

Study	Total number of participants	Diarrhoea	Hypotension	Pain	GI Bleed	inebriation	Spinal Stroke
Central Injection							
LeBlanc *et al* [156]	21	not reported	not reported	not reported	not reported	not reported	0
Tellez-Avila *et al* [164]	21	0	0	0	0	0	0
Doi *et al* [163]	33	3	2	7	0	1	0
Iwata *et al* [167]	47	11	8	0	0	4	0
Seican *et al* [174]	32	not reported	not reported	not reported	not reported	not reported	0
Sahai *et al* [159]	30	0	0	0	0	0	0
Wyse *et al* [126]	49	not reported	not reported	not reported	0	not reported	0
Kanno *et al* [127]	23	not reported	not reported	not reported	not reported	not reported	0
Levy *et al* [125]	60	6	10	5	0	0	0
Facciorusso *et al* [173]	58	14	not reported	20	0	0	0
% of affected participants in the CI group		14%	4%	11%	0	0	0
Bilateral Injection							
LeBlanc *et al* [156]	29	not reported	not reported	not reported	not reported	not reported	0
Tellez-Avila *et al* [164]	32	0	0	1	0	0	0
Wiechovwska *et al* [171]	29	3	1	2	0	0	0
Wieserma *et al* [169]	29	3	0	0	0	0	0
Sahai *et al* [159]	42	0	0	0	0	0	0
Gunaratnam *et al* [170]	58	9	11	0	0	0	0
% of affected participants in the BIT group		10%	8%	2%	0	0	0

Table continues in the next page

Coeliac Ganglia Injection							
Levy *et al* [125]	50	6	7	22	0	0	1
Minanga *et al* [172]	112	4	5	4	0	9	1
Doi *et al* [163]	34	2	1	10	1	1	0
Si-Jie *et al* [168]	42	0	2	0	0	0	0
Ascuse *et al* [166]	40	15	1	1	0	0	0
% of affected participants in the BIT group		11%	7%	15%	0.4%	4%	0.4%
Total number of events	871	76	48	72	1	15	2
Percentage of affected participants	-	9%	6%	8%	0.1%	2%	0.1%

* Patient received EUS-BPN

Table 6. Characteristics of patients who experienced spinal stroke. Two of them received EUS-CPN in the context of a clinical trial. Another three were published as case-reports.

Author	Year	Country	Age	Technique	Anaesthetic support	Volume of alcohol	Needle diameter	Survival
Minanga *et al* [175]	2016	Japan	73	BIT*	sedation	20 ml	25G	>90 days
Minanga *et al* [172]	2016	Japan	Not reported	BPN	not reported	40 ml	25G	not reported
Koker *et al* [182]	2017	Turkey	74	BIT*	edation	20 ml	22G	60 days
Fuji *et al* [177]	2012	USA (Mayo)	76	Combined CGN	general anaesthetic	24 ml	22G	24 days
Mittal *et al* [176]	2012	USA (Mayo)	76	Combined CGN	not reported	24 ml	22G	not reported
Levy *et al*[125]	2010-2014	USA (Mayo)	66±10	Combined CGN	not reported	21±4.5 ml	22G	not reported

***Although author, location and year match in these two reports, there is discrepancy in the description of the technique and the patient's characteristics. Overall, the reports on adverse events are of low quality standards.**

Heterogeneity

The following methodological and clinical sources of diversity were detected, which may account for the observed heterogeneity (**Appendix 2, Table 34**); the study designs consisted of randomised, non-randomised and single arm clinical trials; the definition of "treatment response" was variable, as the volume of the neurolytic agent and the proportion of patients with concurrent opioid and chemoradiotherapy treatments; in some CGN studies, the ganglia injection was combined with injection of neurolytic agent at the free retroperitoneal space; the pre-treatment mean pain scores ranged between 3.6 and 9.5.

Risk of Bias Assessment

The following sources of bias were classified as "high risk" in non-randomised trials: a. recruitment of non-consecutive cases, b. co-variates, especially chemotherapy treatment and dose of opioid analgesic drugs, not being considered (except two single arm trials[169, 170]), c. addressing missing values (it is likely that patients do not complete follow-up assessments due to their declining health status, who plausibly have higher pain levels) and d. selective reporting (usually arising from the use of a single cut-off value in the definition of treatment response). Instead, proportions at several cut-off points (3-,4- and -5 points drop from baseline) as well as mean differences in VAS scores before and after the procedure should have been reported. Regarding randomised trials, three of them met good quality standards[125, 126, 162]. In two[156, 163] we detected selection reporting of moderate significance. The risk of bias tables are provided in **Appendix 3.**

Publication Bias

Review of the grey literature revealed 16 unpublished studies. Of these, 10 were published as conference proceedings but not as full publications and 6 were registered with ClinicalTrials.gov **Appendix 4.** Funnel plots for weeks 2 and 4 were constructed, plotting effect sizes, expressed as logit proportions on the horizontal axis and standard error on the vertical (**Figure 19** and **Figure 20**). Subjective visual assessment of the plots showed symmetrical distribution of the effect sizes of the included studies. The Egger's regression test did not detect evidence of publication bias either at week two (p=0.17) or week four (p=0.16). The application of the "Trim and Fill" method demonstrated that a small degree of asymmetry was attributed to two studies at week two which were removed and replaced by their counterparts and the modified summary effect size remained almost the same (pooled proportion of treatment responders: 68%, 95% CI, 60% to 74%, I^2=58.9%, P=0.02). Similarly,

there was one study “trimmed and filled” at week four with no effect on the summary effect size (pooled proportion of treatment responders: 53%, 95% CI, 45% to 64%, I^2= 54.2%, P=0.032). Based on the above assessments, we concluded that publication bias is an unlikely explanation for our findings.

Figure 19. Funnel plot of effect sizes at week two, demonstrating low likelihood of publication bias. Empty dots represent the effect sizes of the “filled-in” studies by the “trim and fill method”.

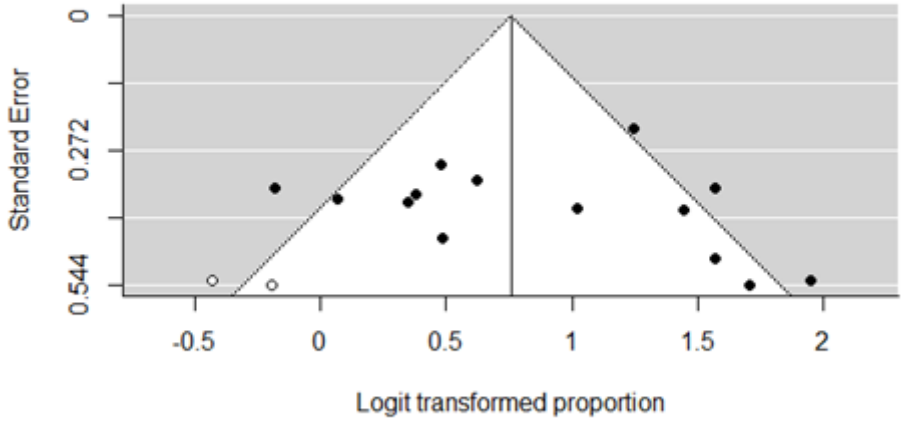
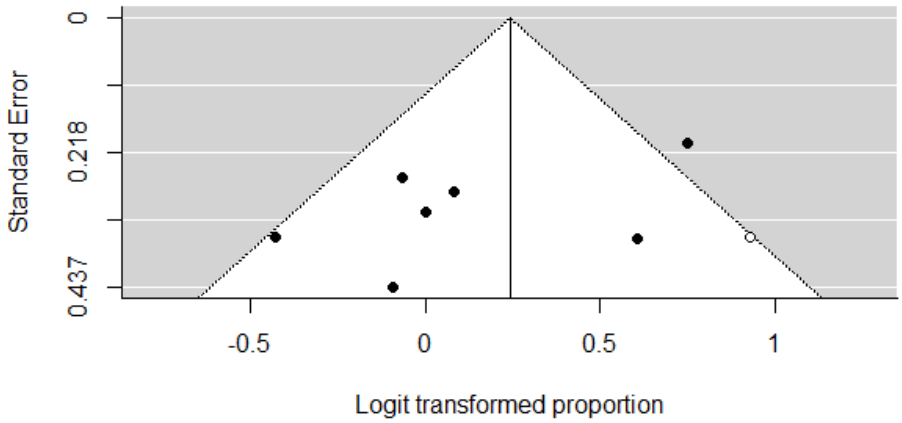


Figure 20. Funnel plot of effect sizes at week four, demonstrating low likelihood of publication bias. Empty dots represent the effect sizes of the “filled-in” studies by the “trim and fill method



GRADE Quality of Evidence Assessment

The quality of the evidence is summarised in **Table 7.**

Table 7. GRADE (Grades of Recommendation, Assessment, Evaluation, Development and Evaluation) Quality of Evidence Assessment

	Result of GRADE ASSESSMENT	**COMMENT**
Risk of bias	High	Recruitment of non-consecutive cases, confounders not considered, selective reporting (see risk of bias assessment section).
Inconsistency	Moderate	Inconsistency is likely to be attributed to the clinical and methodological heterogeneity (see heterogeneity section).
Indirectness	Moderate	Studies use different comparators, such as morphine, central injection, bilateral injection, CGN or BPN.
Imprecision	Moderate	The majority of the studies reporting proportion of pain responders do not report standard error and confidence intervals, hence precision is questionable
Publication Bias	Low	Symmetrical funnel plots and negative statistic tests (see publication bias section).

DISCUSSION

Main findings

This systematic review and meta-analysis showed that the endoscopic denervation, using either CIT, BIT or CGN technique, reduce pain scores in two thirds of patients with pancreatic cancer at week two. This pain remission is sustained by week four in approximately half of those patients. The pain relief outcomes were similar among the three techniques at week two, however, CIT is the only one not linked to serious adverse events. Moreover, demographics (age, gender) and disease characteristics (cancer stage, tumour at the head of pancreas and pain score at baseline) are not associated with treatment response.

Strengths and weaknesses

This systematic review has several strengths, including a systematic search strategy, strict eligibility criteria focusing only on those with pancreatic cancer, appropriate methods of pooling proportions and comprehensive risk of bias assessment. However, it is also impacted by several weaknesses which may have affected the estimation of treatment efficacy. The definition of treatment response varied between the studies, ranging from 3 to 5 point drop in VAS. This may have introduced a misclassification of cases as "successes" or "failures". Our risk of bias assessment demonstrated that all three study subgroups are subjected to bias and the overall literature on EUS-CPN is of moderate quality.

Comparison with previous studies

Previous meta-analyses in the field report conflicting results. The first published in 2009[140], reported overall treatment response in 63.3% (95% CI, 57.8% to 68.7%) in a total of 283 patients who were treated with EUS-CPN regardless the technique, whilst for those treated with CIT it was 46% (95% CI, 37.3% to 54.8%) and BIT was 84.5% (95% CI, 72.2% to 93.8%). However, this meta-analysis inappropriately combined pain outcomes measured at different time-points post-procedure; as we have shown analgesic effect of the EUS-CPN declines over time. Another previous meta-analysis of 437 patients reported no evidence of difference in the analgesic efficacy between CIT and BIT (standardised mean difference of the VAS pain scores of 0.31, 95% CI, -0.20 to 0.81, p=0.97)[139]. However, several limitations should be noted: the two largest studies, weighting 24.7% and 19.9%, treated patients with chronic pancreatitis[159, 160, 183]; one study, weighing 25.9%, used percutaneous EUS-guidance[183]; and another one administered CGN[166]. Nagels *et al* (2013)[184] conducted a meta-analysis of studies reporting difference in the mean pain scores before and after EUS-CPN and showed

that patients with baseline VAS pain score of 6-7 have on average a 4-point reduction sustained until week eight ($p<0.001$). However, it did not provide comparisons between the techniques.

Implications for the administration of the EUS-CPN

Sufficient data exists demonstrating the safety of EUS-CPN. The only well-recognised major complication is spinal stroke. However, this occurs very rarely (0.2%) and it is associated with the more invasive forms of neurolysis; BI, CGN and the combined CGN, but not with the CIT. Moreover, the incident cases received high doses of absolute alcohol, varying from 20 to 40 ml. Even more scarce is the evidence in visceral ischaemia, with case-reports providing very limited information on the exact circumstances leading up to these events. Overall, ischaemic events either in the spinal cord or other internal organs, although not implausible, are highly unlikely to be merely related to the alcohol injection in the context of an EUS-CPN, considering that these organs have at least dual arterial supply. For example, the lumbar portion of the spinal cord is supplied by one anterior and two posterolateral arterial branches[185]. Previous experiments in mammals clamped on of these branches at a time, with no neurological deficits being observed, leading to the conclusion that the unclamped branches could compensate the flow in the arterial network of the spinal cord[186]. Equally, dually supplied are the liver (portal vein, hepatic artery) and the pancreas (coeliac artery, superior mesenteric artery) whilst the stomach is supplied by branches of the coeliac artery which has a large diameter of 0.8 cm and a short length (nearly 1.0 cm), hence the blood flow is unlikely to be severely diminished in response to the vasoconstrictive effect of the alcohol[187]. Therefore, we suggest that for ischaemic events to occur, a combination of factors to act synergistically is possibly required such as atherosclerosis with impaired endothelial function, systemic hypovolaemia and very high doses of injected alcohol.

Appropriate patient selection, technique selection and peri-procedural care should be considered to minimise the risk of ischaemic events. Any evidence of arteriopathy and endothelial damage, such as history of heavy smoking, previous thromboembolic events, ischaemic strokes, peripheral vascular disease, uncontrolled diabetes with end-organ damage or excessive calcifications in the aorta should be regarded as a relative contraindications. Overall, CIT should be the technique of choice in those cases. Pre-hydration and continuous blood pressure monitoring during the procedure to ensure euvolaemia and normotension is maintained throughout is advisable. Sedation should be preferred over general anaesthesia as the latter may mask neurological events occurring intra-procedurally. Instillation of alcohol should be given in small increments of 1-2 ml with pauses in between to permit detection of early neurological signs and discontinuation of the procedure.

Conclusion

Our findings overall demonstrate EUS-CPN is a useful additive to analgesics when patients are carefully selected. CIT is probably the most attractive option considering that it has similar efficacy to the other two and it is not linked with ischaemic events. However, this meta-analysis leaves certain questions unanswered. Further research should focus on disease characteristics predisposing to success or failure. In addition, the exact timing of EUS-CPN should be explored; it is unknown if it should be given as a first line treatment or if it should be reserved as a rescue therapy.

CHAPTER 3 - Best Analgesia Control in Pancreatic Adenocarcinoma Study: Justification and feasibility of a randomised trial of early EUS-CPN versus standard care - a prospective observational study (The BAC-PAC study)

ABSTRACT

Background. Severe abdominal pain is a common symptom in patients with unresectable pancreatic cancer and is associated with poor quality of life (QoL) and reduced survival. Strong opiates are commonly prescribed to manage pain, however dose escalation is frequently required and side-effects are common. Endoscopic Ultrasound-guided Coeliac Plexus Neurolysis (EUS-CPN) can be considered in patients with opiate refractory pain, however it is not known whether it is effective if administered early. The National Institute for Health and Care Excellence (NICE) have recommended a randomised trial be undertaken in patients with unresectable pancreatic cancer comparing early versus on-demand EUS-CPN.

Aims. This study aimed to assess the feasibility, justification and establish the design considerations of a randomised trial of early EUS-CPN versus standard care.

Objectives. To assess medical performance status at time of pain onset; median survival after pain onset; characteristics of participants versus those who declined participation; quality of life (QoL) in (unpaid) carers; questionnaire completion rates; time from diagnosis to first opioid prescription; standard error of possible outcome measures of a future trial; associations between radiological signs and the development of pain; and feasibility of data collection to allow a health economic evaluation in a future trial.

Methods. This was a prospective observational study. Patients with inoperable pancreatic adenocarcinoma with an Eastern Co-operative Oncology Group (ECOG) performance status of 0-3 and expected survival of at least one month were eligible. Data were collected at baseline and every month until death, withdrawal or the data collection end (whichever came first). Patients were asked to complete questionnaires on their performance status, pain levels (using a visual analogue scale from 0 (none) to 10 (worst possible pain), analgesic use, QoL (European Organisation for Research and Treatment of Cancer-30 [EORTC-30] and EuroQoL EQ-5D-5L) and healthcare resource use. Patient carers, which were relatives or close friends, were asked to complete the EQ-5D-5L questionnaire on a monthly basis.

Results. The recruitment was conducted in two instalments, with a pause in between due to the COVID-19 pandemic. Over a total period of twelve months 143 patients were screened for eligibility, of which 56 met eligibility criteria. In total, 12 (21%) patients were recruited. Medical performance status ranged between 0 and 2 for those in pain. The median survival from the first record of pain was 5.2 (IQR 2.46-5.9) months. There was no statistically significant differences in the characteristics (age, sex, cancer stage) between participants and those who declined participation. The QoL of carers was moderately impaired at all time points (EQ-5D-5L summary index scores 0.86-0.89). In total, 80% of the questionnaires were completed and returned. The median Visual Analogue Score for pain was 2.6 (0.8-5.1) and the median daily morphine dose was 36 (20-48) mg. The cost of resources per patient was estimated at £1,258 and 1,771, at months one and two, respectively. The median QALYs were 0.073 (0.062-0.076) between month one and two and 0.054 (0.020-0.076) between month two and three. The medical resource data collection tool requires refinement to capture the disease-specific expenditure. Associations between radiological signs and development of pain was not examined due insufficient data.

Discussion. Recruitment rates remained low throughout this study. Therefore, estimates of key outcomes were imprecise for: fitness for endoscopy at the time of the pain onset; survival time after the pain onset; time from diagnosis to first opioid prescription; and the descriptive statistics of the possible outcome measures of a future trial (pain scores, opioid doses and QoL scales). Despite these limitations, overall this study supports the justification of trial administering endoscopic analgesia. However, uncertainties remain with regards to its feasibility. In a future trial, data collection procedures should minimise burden to patients. Further observational research with sufficient sample size and follow-up is required to further inform the design and feasibility of a future trial of early EUS-CPN vs. standard care.

INTRODUCTION

Pancreatic cancer has the worst prognosis of any other cancer, with only 21% of the patients surviving beyond a year [85]. Patients can be divided in those who are surgical candidates, those eligible for chemotherapy and those eligible only for supportive, palliative and end of life care. In patients with unresectable disease, FOLFIRINOX (FOLinic acid, Fluorouracil, IRINotecan, OXaplatinin) is the most potent, but less well tolerated palliative chemotherapeutic regime with median survival of 11.1 months (95% CI, 9.0 to 13.1) [91]. Gemcitabine is an alternative to FOLFIRINOX with lower toxicity profile but also a lower median survival of 6.8 months (95% CI, 5.5 to 7.6) [91, 131]. Most patients who receive supportive care alone survive between two to six months [91, 131]. Previous studies have shown that 58-78% of patients develop abdominal pain of pancreatic origin either at diagnosis or during the course of their disease [119, 188]. Over time, opiate doses required for its control need to escalate from a mean of 55.9 mg (SD 53.8) at diagnosis to 162.8 mg (SD 131.6) towards the end of life [119, 136]. These doses may lead to serious side-effects such as gastroparesis, constipation, lethargy and cognitive decline [136].

Extrapolating from research conducted in patients with other malignancies, pain impacts wider quality of life (QoL). In a previous paper patient provided the following statements regarding pain's implications: "Pain is more than a physical symptom; it is spiritual and social as well" and "Pain is my biggest fear because it blocks out… it puts me in a darkness and a lack of will to go forward and a desire to die" [189]. The distress and devastation of poorly controlled symptoms, including pain, often extend to the families or others close to the patient responsible for providing care and support; in a previous qualitative study a caregivers quoted: "his pain is my pain" and "watching hurts" to describe their detriment caused by living with suffering patients [190, 191].

Endoscopic Ultrasound-guided Coeliac Plexus Neurolysis (EUS-CPN) is an endoscopic procedure which causes chemical ablation of the coeliac ganglia and disrupts efferent pain signalling [137]. EUS-CPN is usually reserved as a second line analgesic option when opioids have failed to control pain. For ease, in this document the EUS-CPN given as a second line analgesic treatment will be referred as "on demand", in line with the NICE position statement for the management of pancreatic cancer. There is limited evidence on whether early EUS-CPN may have a role in preventing severe pain and reducing opiate burden.

In total, 17 clinical studies have assessed the efficacy and safety of EUS-CPN in the past 25 years [124]. Of those, ten were phase II trials which compared pain levels in the same participants before and after the procedure [138, 166-174]. Five studies had two treatments arms, each one offering variations of the EUS-CPN technique, differing by injection location (central vs bilateral vs within the ganglia) or the volume or type of neurolytic agent or method (alcohol vs phenol vs radiofrequency ablation) [125, 156,

[162-164]. Only one phase III randomised controlled trial by Wyse *et al.* has investigated the efficacy of standard EUS-CPN (with absolute alcohol used as the neurolytic agent injected around the ganglia) versus opioids alone [126]. The included patients had locally advanced cancer and each arm included 54 patients. Between baseline and three months, the control group mean pain score increased by 12% (95% CI, -19% to 36%), in contrast to the EUS-CPN group where it decreased by 49% (95% CI, 38% to 61%). The difference in the mean percent changes of the pain scores between the two groups at three months showed a greater drop in the EUS-CPN group by 60.7% (95% CI, 25.5% to 86.6%, P=0.01).

Differences were also observed in the opioid consumption between the two groups. The control group was using a mean of 36 (SD 62) mg of opioids at baseline. This figure increased by 54 mg (95% CI, 20 to 96) from baseline to month one and continued to increase over time, so between baseline and month three the mean dose increased by 100 mg (95% CI, 49 to 180). The intervention group started from 42 (SD 71) mg at baseline, increased their consumption by 53mg (95% CI, 28 to 89) at month one but their opioid requirements had plateaued by month three, so the recorded increase from baseline to three months was only 50 mg (95% CI, 28 to 79). The paper did not report the mean opioid doses at each time point but from the above it can be inferred that the control group was using approximately 90mg at month one and 136 mg at month three, whilst the intervention group was using 94mg at month one and 91 mg at month three. The mean opioid consumption was 49mg less (95% CI, -7.0 to 127.0) in the EUS-CPN group at 3 months, but this difference was not statistically significant (p=0.10). This trial only included patients with pain at diagnosis who had locally advanced disease. Consequently, recruitment was limited to 10% of the overall cohort with inoperable pancreatic cancer.

Kanno *et al*. conducted a clinical trial of 48 patients with advanced pancreatic cancer were randomised to EUS-CPN versus morphine in a 1:1 ratio [127]. In total, 58% of the participants had metastatic disease, but their outcomes were not reported separately to the ones with locally advanced disease. At four weeks, the mean pain score for the EUS-CPN group was 1.3 (SD 1.3) versus 2.3 (SD 2.3) in the control group and their difference did not reach statistical significance (p=0.10). The mean opioid dose in the EUS-CPN group was 62mg (SD 2.5) versus 35mg (SD 2.0) in the control group (p=0.14). Inferences from this study were limited by substantial imbalances in baseline characteristics (insert mean opiate dose comparison) and a small sample size.

Furthermore, QoL benefits in association with the costs to the National Health System (NHS) and personal social services (PSS), incurring as a result of the two different approaches to pain management, have yet to be explored. If early EUS-CPN improves pain control and keeps opioids to a lower level, then its recipients are less likely to have opioid toxicity and therefore are more likely to

maintain a preserved health status for longer. In contrast, patients treated with opioids alone may be more prone to decline faster due to side-effects (lethargy, nausea etc) and therefore have a greater impairment in their QoL in comparison. However, using EUS-CPN as a first line analgesic measure, and therefore being applicable to a larger number of patients, is likely be more costly (in terms of upfront costs) compared to EUS-CPN on demand. Therefore, a cost-utility analysis can be used to establish if QoL is improved by using EUS-CPN as a first-line measure compared to current treatment and if there are QoL gains, how costs to the NHS&PSS are impacted

Rationale

The optimal timing of delivering EUS-CPN is unclear: in particular whether it is better delivered early (as soon as pain develops) or whether it should only be reserved for those with opioid-refractory pain or opioid toxicity. It is plausible that offering early EUS-CPN may prevent opioid dose escalating and preserve QoL for longer. NICE, in its latest position statement, supports the conduct of a randomised trial of early EUS-CPN versus standard care (i.e. opioids +/- on demand EUS-CPN) [128]. However, further research is necessary to first establish the design, logistics and feasibility of such a trial.

Aim

The overarching aim of the BAC-PAC study is to determine the rationale, feasibility and refine the design considerations of a future trial of early EUS-CPN versus standard care.

Objectives

Specific objectives are to determine:

1. Medical performance status at the onset of pain. It is important to estimate the proportion of all patients with inoperable pancreatic cancer who are potentially fit enough for an EUS-CPN to assess the magnitude of this clinical problem and plan the number of centres required for a future trial.

2. Median survival after pain first develops. This will inform whether survival after pain onset is sufficient to justify assessing early EUS-CPN in a future trial.

3. Characteristics of participants versus those who refused participation. We will compare demographic and clinical characteristics between patients who accept and decline participation to assess generalizability of our estimates to the total population eligible for the study.

4. The QoL of carers of pancreatic cancer patients at monthly intervals. If QoL is severely impaired, this may further justify assessing EUS-CPN to improve QoL in patients which could consequently enhance that of their carers.

5. The proportions of patients who complete questionnaires on: medical performance status, QoL, pain scores and health resource use to assess the feasibility of conducting the randomised controlled trial, including a health economic analysis.

6. Measure time from diagnosis to first opioid prescription. This will inform the timescales for reviewing and approaching patients for randomization into a future trial.

7. The descriptive statistics of the QoL scores, abdominal pain score and opioid doses. This will aid estimating sample sizes for a future trial.

8. Estimate associations between radiological findings and pain occurrence. These radiological changes include i) cancer invading the coeliac plexus and ii) pancreatic duct dilatation. Significant associations may suggest sub-populations at higher risk of developing pain on whom future research should focus, for example to inform eligibility criteria for a future trial.

The following objectives were set as part of BAC-PAC, but as these were explored through qualitative interviews they are addressed in chapter four:

9. Patient experiences of previous endoscopic tests used to diagnose pancreatic cancer. Qualitative interviews with a purposive sub-sample of patients will explore: their previous experiences of endoscopic procedures for diagnosing pancreatic cancer, and willingness to undergo a second endoscopy to enable better pain control if this was offered in a future clinical trial. We will ascertain patient experiences of pain and side-effects related to opioids, plus perceptions of the relative benefits and adverse effects of opioids and EUS-CPN, and their preferences for EUS-CPN versus pharmacotherapy. Identified concerns could be addressed to enhance future trial recruitment.

10. Carers' views of patients' experiences of pain, drug-related side-effects, diagnostic endoscopic tests and proposed therapeutic EUS-CPN. Any concerns identified may be addressed to enhance future recruitment into a clinical trial.

11. Clinicians' willingness to use EUS-CPN. Qualitative interviews will be conducted with clinicians treating pancreatic cancer patients to assess their decision-making process for referring patients for an EUS-CPN, the delivery of this service and how the clinical experience of patients could be improved.

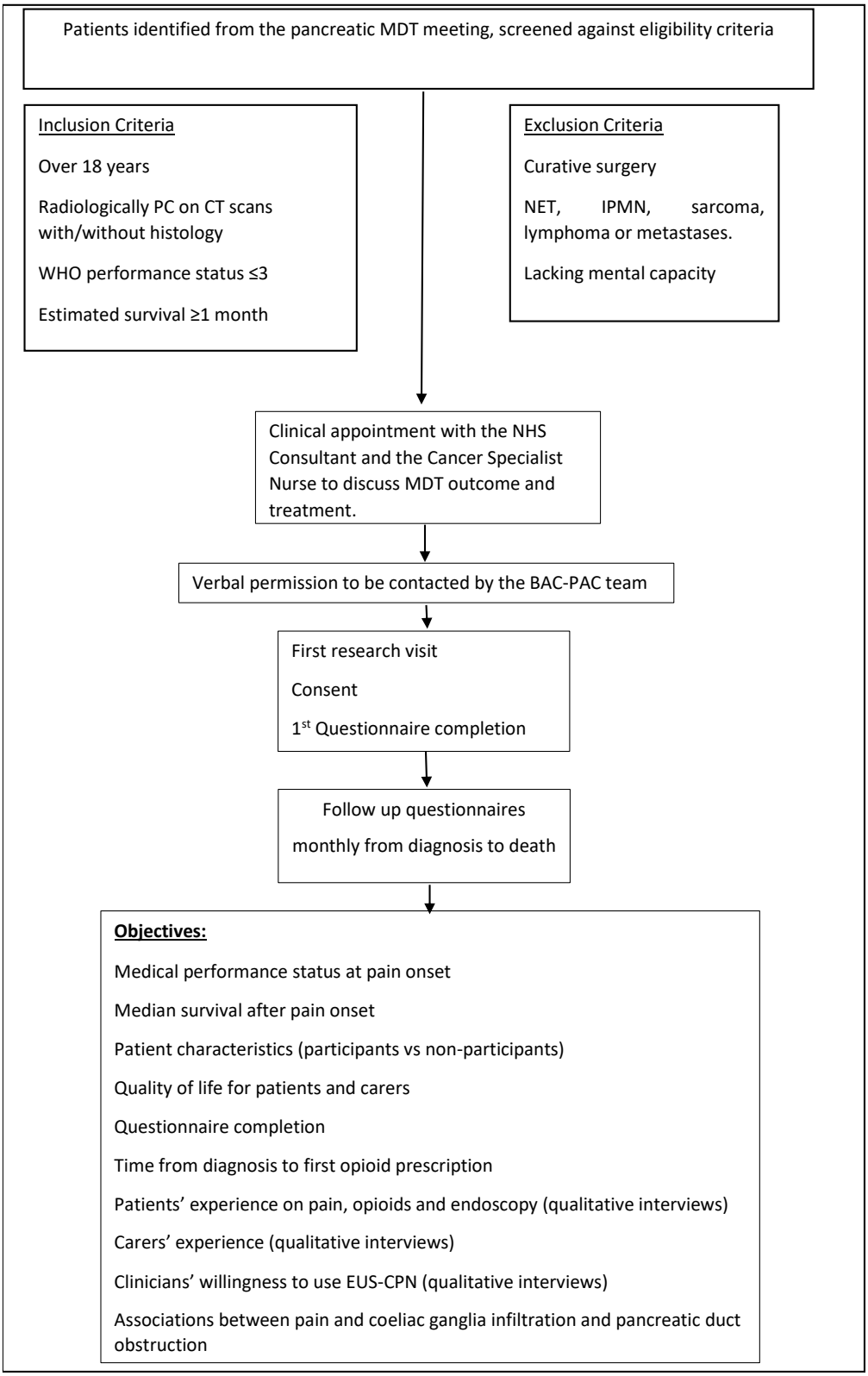
Objectives 1 to 4 will provide further evidence to justify a future trial of early EUS-CPN. Objectives 5 to 11 will inform the feasibility and enable planning for a future trial.

METHODS

Study Design

This prospective cohort study explored the rationale, feasibility and design considerations of a future phase III trial investigating the effectiveness of early EUS-CPN versus standard care (opioids alone with or without on demand EUS-CPN). The study design is summarised in **Figure 21.** Patients with inoperable pancreatic cancer were identified through the weekly multi-disciplinary pancreatic cancer team meetings at the Norfolk and Norwich and James Paget University Hospitals. Patients were monitored for pancreatic pain and other relevant clinical outcomes, including opioid use, QoL and medical resource use, from diagnosis to death, through monthly self-completed questionnaires. In addition, their primary (unpaid) caregiver, usually partner or other close relative, was asked to complete QoL questionnaires at the same time points. The study was approved by the East Midlands-Leicester Central Research Ethics Committee (**Appendix 5**)**.**

Figure 21. Summary of the Best Analgesia Control in Pancreatic Adenocarcinoma (BAC-PAC) study design.



Research Setting and delivery

This study was conducted at the Norfolk and Norwich University NHS Foundation Trust (NNUH) and the James Paget University Hospital (JPUH). The research was hosted within the gastroenterology departments at each NHS trust. The University of East Anglia (UEA) sponsored the study. The study was adopted by the UK Cancer Research Network[192]. The recruitment period in NNUH lasted for a total of twelve months in two instalments: from 11th of October 2019 to 6th of March 2020 and 22nd of July 2020 to 28th of February 2021. The recruitment in JPUH was open from 2nd of September 2019 to 6th of March 2020. The gap in the recruitment period was due to the COVID-19 pandemic when the Heath Research Authority suspended all the non-essential research and clinical academic personnel were deployed to support clinical services.

Study Participants

Patients with radiologically and/or cytologically confirmed diagnosis of inoperable pancreatic adenocarcinoma at the NNUH and JPUH who fulfil the following eligibility criteria:

Inclusion criteria for patients

I. individuals over 18 years of age.
II. diagnosis of pancreatic cancer as confirmed by the pancreatic Multi-Disciplinary Team.
III. patients with pancreatic adenocarcinoma treated with chemotherapy or palliative care alone.
IV. East Co-operative Oncology Group (ECOG) performance status ≤3.
V. estimated survival time since patient informed of diagnosis >1 month.

Exclusion criteria for patients

I. patients undergoing potentially curative surgery.
II. non-adenocarcinoma neoplasms (neuroendocrine tumours (NETS), Intra-ductal Papillary Mucinous Neoplasms (IPMNs), sarcomas, lymphomas or metastases).
III. lack of mental capacity.

Inclusion criteria for carers

I. individuals over 18 years of age.
II. individuals with mental capacity.
III. person of patient's choice.

Exclusion criteria for carers

I. professional carer who is not a relative or close friend.

Protocol Procedures

This is an observational study involving completion of questionnaires and qualitative interviews without any clinical interventions. The study procedures are summarised in **Table 8**.

Table 8. Study activities/measures at baseline and follow up.

Study activity	Screening Date of diagnosis	Visit 1 1-2 weeks after patient information leaflet	Postal follow up Monthly until death
Eligibility assessment	✓		
Clinical note review	✓	✓	✓
Demographics	✓		
Informed consent		✓	
Medical history		✓	
Baseline information		✓	
Telephone prompts for questionnaire completion and return			✓
Medical performance status		✓	✓
Concomitant medications		✓	✓
Opioid use		✓	✓
EORTC-QLQ30		✓	✓
EQ-5D-5L		✓	✓
Resource use		✓	✓
Carer EQ-5D-5L		✓	✓
Assessment of questionnaire completion		✓	✓

Screening and Eligibility

Consecutive patients were identified at the local pancreatic cancer multi-disciplinary team (MDT) meetings at each NHS site. Further eligibility assessment against the inclusion and exclusion criteria was undertaken through review of medical notes and liaison with the responsible NHS clinician, including the consultant and the specialist nurse who were directly responsible for the care of the patient.

Initial Approach to Potential Participants

Patients typically attend an initial outpatient appointment where the responsible clinician and the cancer specialist nurse discuss the MDT outcome. During this appointment or in subsequent ones eligible patients were given a Patient Information Leaflet (PIL) and were asked to provide verbal permission for the research team to contact them regarding participation to the BAC-PAC. The timing of the initial information-giving about the research was at the discretion of the lead clinician and the cancer specialist nurse and was adjusted depending on the patient's individual circumstances. A similar approach was used with patients who were diagnosed during an inpatient admission.

Recruitment and First research visit

Eligible patients were contacted by the research team to discuss participation in BAC-PAC. A minimum of 24 hours was allowed from the time the PIL was handed to the patient until the contact from the research team. The first research visit was arranged by a member of the research team, so the patient and the carer (if participating) were taken through the study in more depth and their questions were addressed. Written informed consent was obtained from the patient and their carer. The patient and carer completed for the first time the questionnaires with the assistance of the research specialist nurse. Research appointments were originally face-to-face, but from commencement of the COVID-19 pandemic, subsequent research appointments were held via telephone or via video-conferencing.

Informed Consent and Withdrawal

The research specialist nurse or the research fellow/MD candidate were responsible for taking informed consent which took place during the first research visit. Each patient and carer was taken through the information sheet, all the study activities were explained, queries were addressed before written informed consent was sought. Each participant personally signed and dated the Informed Consent Form which was observed and countersigned by a member of the research team before any further research activities took place. The participant was free to withdraw from the study at any time for any reason without prejudice to their future care, and with no obligation to give reasons for withdrawal. Their data up to the point of withdrawal were kept, unless the participant wished otherwise.

Collection of baseline documentation

Baseline Documentation collection took place through note review soon after the first research visit and included recording of:

i) demographics (age and gender)

ii) significant co-morbidities (cardiac, respiratory, renal, hepatic and endocrine)

iii) smoking

iv) cancer stage on diagnostic CT scan (American Joint Committee of Cancer TNM classification)[193].

Patient Questionnaire

Every patient completed the study questionnaire at the first research visit under the supervision of the research specialist nurse. Thereafter, patients were invited to complete a questionnaire at the same day every month.

This questionnaire included:

i) Eastern Cooperative Oncology Group (ECOG) medical performance status (Scale 0-5).

ii) Visual analogue score (VAS) for pain.

iii) Current analgesic and non-analgesic drug use.

iv) QoL questionnaires (EORTC 30 and EuroQol EQ-5D-5L)[194, 195].

v) Use of health care resources over the last month, as described above[196].

Carer Questionnaire

Carers completed the EQ-5D-5L questionnaire. They completed the first questionnaire during the first research visit and the same questionnaire on a monthly basis thereafter, on the same date as the patient.

Follow-up assessments and withdrawal of participants

Patients were given a telephone reminder call a few days before questionnaire completion was due. If the questionnaire was not returned there was a second reminder a few days after that. If despite these two reminder calls a questionnaire was not returned, further contacts were ceased, and it was assumed the patient intended to withdraw from the study. Further contacts were avoided to limit the intrusiveness of the study, patients' health is expected to decline over time.

Statistical Analysis

Continuous variables were described using either means or medians according to their distributions. Categorical variables, including WHO medical performance status, were reported as frequencies and percentages. Kaplan-Meier analyses was conducted to estimate survival from diagnosis to the first opioid prescription and separately the survival time from pain onset. The differences in the characteristics between recruited participants and those who declined to participate were examined with Fisher's exact test for the categorical variables (age and cancer stage) and Wilcoxon test for age. The difference in the EQ-5D-5L QoL scores over time were examined with the Friedman test for ordinal variables. Associations between radiological signs (coeliac plexus infiltration and pancreatic duct obstruction) and pain were planned to be estimated using logistic regression. All the parameters were analysed for each month from the entry to the study and up to six months. Some patients were recruited less than six months before the study completed and their outcomes were censored at the last date of follow-up.

Scoring and reporting of the quality-of-life scores

The EQ-5D-5L is a generic measure of health status consisting of two sections. The first section evaluates health in five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). Each dimension has five levels of response (no problems, slight problems, moderate problems, severe problems, extreme problems). Each health state is assigned a summary index score based on societal preference weights for the health state. Index scores range from less than 0 to 1, where 0 is the value of a health state equivalent to death, negative values representing health states considered worse than death and the value of 1 representing perfect health. The second part of the questionnaire consists of a visual analogue scale on which the patients rate their perceived health from 0 (the worst possible health) to 100 (the perfect health). For each dimension (mobility, self-care etc.), means and standard deviations (SD) were calculated by visit. A summary index score was calculated from individual health profiles using specific value set for England[197]. The EQ VAS score (between 0 and 100) was summarised using mean and SD by visit. A Friedman test was conducted to investigate changes by visit. Scoring and reporting was conducted in accordance with the EQ-5D-5L user guide[194].

The EORTC-QLQ30 is a cancer-specific, QoL assessment tool. It comprises 30 items (questions) which are scored on a 4-point scale from 1 to 4, except for the last two questions which are scored from 1 to 7. These 30 items can be used to calculate 16 parameters, each one representing a dimension of QoL. Five of these parameters are functional scales (physical, role, cognitive, emotional, and social), three are symptoms (fatigue, pain, and nausea and vomiting), one is a global health status / QoL scale,

and a number of single items assessing additional symptoms commonly reported by patients with cancer (dyspnoea, loss of appetite, insomnia, constipation and diarrhoea) and perceived financial impact of the disease . All of the scales and single-item measures range in score from 0 to 100. For the functional scales 0 represents the greatest degree of impairment and 100 represents perfect health. In contrast, for the symptoms and the single items 0 represents absence and 100 represents the highest level of disturbance. The raw average of each item contributing to each scale was calculated and then it was linearly transformed to the 0-100 scale. The EORTC-QLQ30 scoring and reporting were in line with the relevant EORTC manuals[198] [195].

Health economic analysis

Earlier use of EUS-CPN is likely to be a more expensive treatment compared to opioids because of the infrastructure it requires (e.g. endoscopy equipment and highly trained staff). However, it may convey a higher health benefit through side-effect free- pain control, and these health benefits may reduce other costs (e.g. fewer clinic attendances for pain control). Given uncertainty around the financial implications, a future trial could explore the impacts on quality life and the associated costs through a health economic analysis (specifically, a cost-utility analysis). If early use of EUS-CPN is beneficial and leads to reduced costs to the health system, it would be preferred to standard care (in health economic terms there is 'domination'[199]). However, should costs of EUS-CPN be greater, an 'incremental cost-effectiveness ratio' (ICER) "is calculated by dividing the difference in total costs (incremental cost) by the difference in the chosen measure of health outcome or effect (incremental effect) to provide a ratio of 'extra cost per extra unit of health effect'[200]. Use of a QoL measure such as the EuroQol EQ-5D-5L allows utilities to be calculated, from which the 'health effect' can be quantified as quality adjusted life years (QALYs) which are "designed to combine the impact of gains in QoL and in quantity of life (i.e. life expectancy) associated with an intervention"[201]. Thus, if early EUS-CPN use leads to better outcomes but increased costs, the ICER can be compared to a pre-determined threshold to determine if the benefits are considered cost-effective: for example, NICE generally considers the threshold to be between £20-30K/QALY[202]. Accordingly, the feasibility of a health economic (cost-utility) analysis in a future trial is determined based on the feasibility of data collection to estimate resource use (and thus costs to the care system) and QoL. A study-specific health care cost questionnaire was adapted from the UK Cancer Costs Questionnaire (UKCC) Version 2.0[196]. This questionnaire asks patients about their use of NHS, personal social services and "out of pocket" expenses (travel costs, parking and others) in the last month. Associated costs to the NHS and PSS (the NICE preferred costing perspective[202]) of this resource use were determined from Personal Social Services Research Unit's (PSSRU's) "Unit Costs of Health and Social Care 2020"[203] and NHS Reference

costs[204]. The costing year was 2020, the latest for which costing resources were available (NHS reference costs were adjusted to 2020 values through appropriate use of the NHS cost inflation index (NHSCII))[203]. QoL utilities were calculated from the EQ-5D-5L value set, using the value set for England[205]. Where a patient was known to have died, we gave them a utility value of 0 for all future QoL assessments. QALYs were calculated from the utilities by calculating the area under the curve with linear interpolation[206]. Completion rates of the resource use questionnaire and QoL measures were used to gauge the feasibility of a future economic evaluation. Patterns of missingness and feedback to data collectors were considered to see if they suggested questionnaire refinements that might optimise future data collection.

Sample size considerations

A formal sample size calculation was not needed as this was an observational study to plan a future definitive randomised trial of early EUS-CPN vs standard care: as such, it did not have a particular primary outcome. However, based on cancer registry data, a total of approximately 90 patients in NNUH and JPUH are diagnosed with pancreatic cancer over an 18-month period, our intended duration of recruitment. Assuming that 25-30% of the patients would be ineligible on the basis of the poor general health or decline participation based on their choice, we aimed to recruit 65 patients.

Patient and Public Involvement

Pancreatic Cancer UK information and Norfolk Together Against Cancer Organisation were actively involved in the design of BAC-PAC study. The groups revised the questionnaires and gave advice about the content and length, they made recommendations about the timing potential participants should be approached and they were the main advocates for carer involvement. Upon patient group recommendations, the pancreatic module of the EORTC, the EORTC-PAN26, was removed as it was deemed to have intrusive questions which were unacceptable to patients (e.g. questions about sexual life and body image).

Funding

The NIHR Research and Design Service of East of England contributed to study design [207]. This study was funded by NIHR Research Capability Funding (RCN) and the NIHR Research for Patient Benefit (RfPB) scheme (reference number: PB-PG-0817-20028).

Expansion of BAC-PAC to other UK tertiary centres

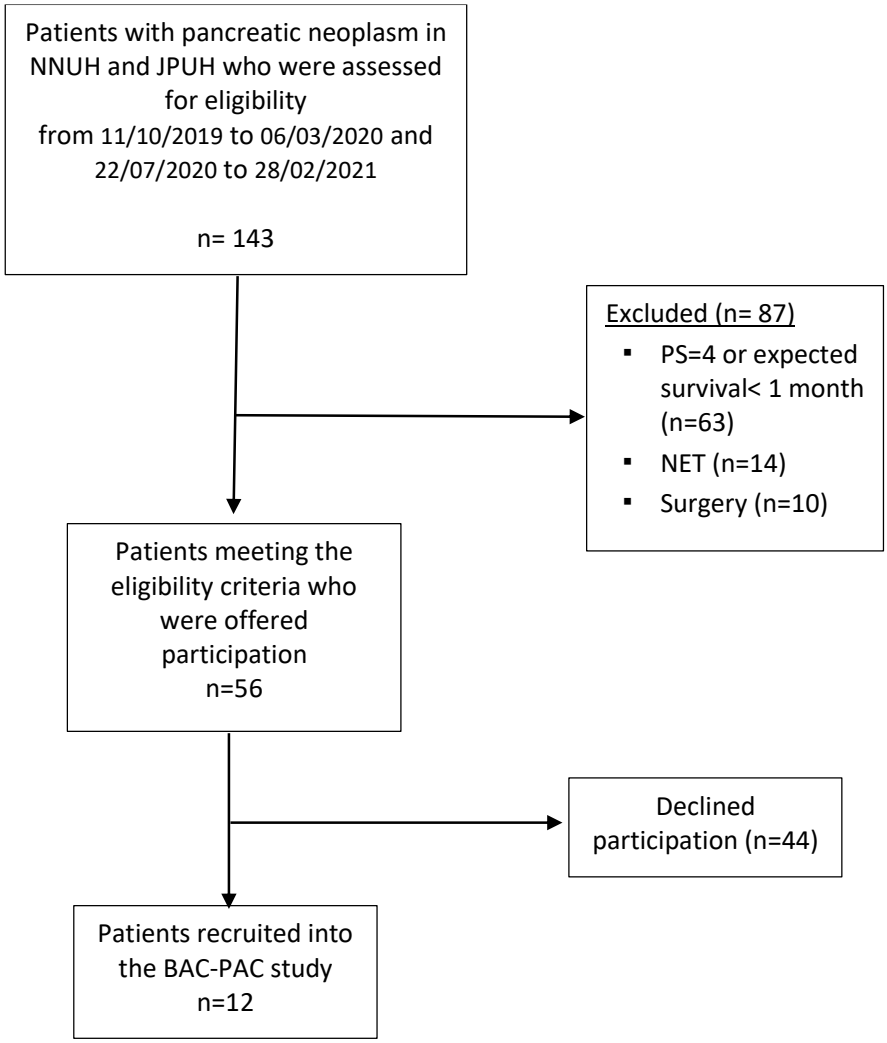
Due to low recruitment rates, which were exacerbated by the first COVID-19 wave, the research team decided to expand recruitment to another five tertiary centres. Those centres were: Leeds Teaching Hospitals NHS Trust, Dudley Group NHS Foundation Trust and the Newcastle Upon Tyne Hospitals, University of North Tees and Sheffield Teaching Hospitals NHS Foundation Trust. The expansion obtained approval from the Health Research Authority (HRA) however site opening coincided with the second COVID-19 wave in November 2020 and was never realised.

RESULTS

Recruitment

During the recruitment period, from October 11th 2019 to March 6th 2020 and from July 22nd 2020 to February 28th 2021, 143 patients were diagnosed with pancreatic cancer and assessed for eligibility (**Figure 22**). In total, 87 (61%) patients were excluded due to not meeting the eligibility criteria (63 (44%) were excluded on the basis of a very poor medical performance status and limited expected survival, 14 (10%) with NETs and 10 (7%) who underwent surgery). The remaining 56 patients were offered participation, of whom 12 (21%) eventually were recruited.

Figure 22. STROBE flow chart of the study participants.



Demographics and Clinical Characteristics

The demographics and clinical characteristics of the 12 patients who were recruited are summarised in **Table 9**. The mean age at diagnosis was 71 (SD 9.9) years. Eight (66.7%) of the respondents were males. Out of the 12 patients, one (8.3%) had stage II, six (50%) had stage III and five (41.7%) had stage

IV cancer. Chemotherapy was administered in nine (75%) of the participants. The median survival was 5.9 (IQR 4.8-11.0) months. The mean time from diagnosis to the first questionnaire completion was 39 (SD 16) days.

Table 9. Demographic and clinical characteristics of recruited patients.

Number of recruited patients	12
Number of recruited carers	8
Patients' Age in years (mean, SD)	71 (9.9)
Male patients (n, %)	8 (66.7%)
Time from diagnosis to the first questionnaire completion in days (mean, SD)	39 (16)
Cancer Stage (n, %)	
II	1 (8.3%)
III	6 (50.0%)
IV	5 (41.7%)
Chemotherapy	9 (75.0%)
Survival in months (median, IQR)	5.9 (4.8-11.0)
Major Co-morbidities	
Heart	6 (50%)
Lung	3 (25%)
Liver	1 (8.3%)
Kidney	5 (45.5%)
Diabetes	3 (25%)
Smoking History	
Non-smoker	9 (75%)
Ex-smoker	2 16.7%)
Current-smoker	1 (8.3%)

SD: standard deviation, IQR: inter-quartile range.

Medical performance status at the pain onset

The medical performance status of those respondents who reported pain is detailed in **Table 10**. In total, seven (58%) out of the twelve of the respondents were affected by pain by the time of their entry to the study. Their performance status varied between 0 and 2. One patient developed pain at month two and had performance status of 0 and another one developed pain at month three with a performance status of 2. The remaining three patients did not report pain during follow-up.

Table 10. Medical performance status of patients reporting pain.

Months	1	2	3	4	5	6
Patients at risk (n)	12	10	8	4	4	3
Patients returning questionnaires (n)	12	10	6	2	2	1
Patients reporting pain (n,%)	7 (58%)	5 (50%)	1 (17%)	0	0	0
Patients whose completion was censored[1] due to end of study (n)	0	0	1	4	4	5
Performance status[2] (n,%)						
0	1 (14%)	3 (60%)	-	-	-	-
1	3 (43%)	1 (20%)	-	-	-	-
2	3 (43%)	1 (20%)	1	-	-	-
3 or 4	-	-	-	-	-	-

[1]Censored are the patients whose follow up was ceased due to end of the study.

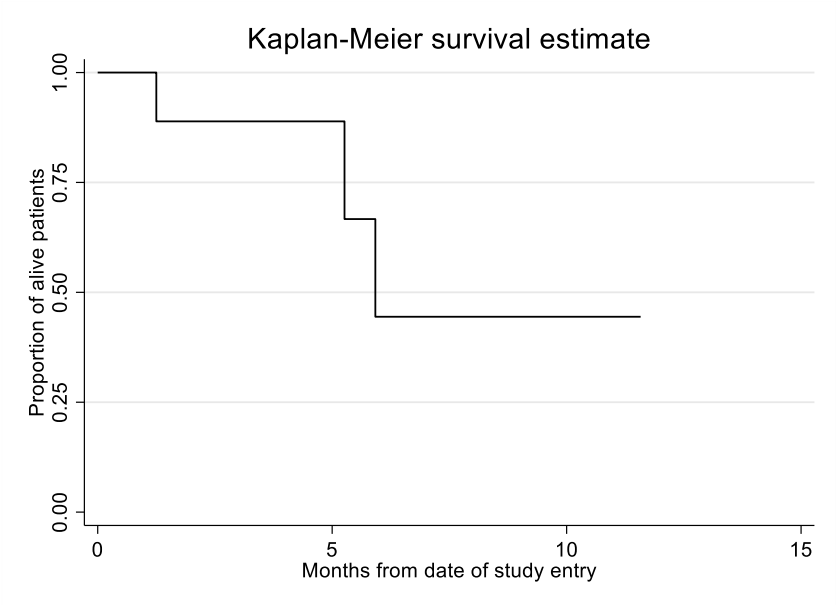
[2]The displayed performance status refers only to patients with pain, who therefore would be EUS-CPN candidates, if a clinical trial was running.

Median survival after pain onset

Seven out of twelve (58%) patients reported pain requiring opioids by the time of entry to the study. The exact onset of their pain is unknown as it preceded the completion of their first questionnaire. For the purpose of this survival analysis, it was assumed that their pain started at the time they completed their first questionnaire. Another two patients developed pain, one a month after their study entry and the other two months after their study entry. Overall, three patients out of nine (33%) who had pain were alive by the date of the study close. The total analysis time at risk was 39.1 months.

The median survival from pain onset was 5.2 (IQR 2.46-5.9) months. A Kaplan-Meier plot is shown in **Figure 23**.

Figure 23. Kaplan-Meier plot demonstrating mortality over time since pain onset. Overall, nine out of the twelve patients (75%) developed pain either at baseline or follow-up.



Characteristics of participants versus those who declined participation

Out of a total of 56 patients, 44 (79%) refused participation (**Table 11**). Although some differences in the proportion of males (54% vs 67%) and the cancer stage IV (65% vs 47%) were observed, these differences were not statistically significant. Overall, 19 (52%) of those who declined participation, reported doing so because of severe emotional distress, 12 (31%) were not interested in participating in research, whilst four (11%) had an initial intention to participate, but developed chemotherapy complications and decided against participation.

Table 11. Demographic and clinical characteristics of patients who declined participation to BAC-PAC. The observed differences did not reach statistical significance.

	Non-participants	Participants	p-value
Number of patients	44	12	
Age in years (median, IQR)	72 (59.9-78.5)	75 (65.9- 80.4)	0.604
Male patients (n, %)	23 (53.5%)	8 (66.7%)	0.516
Cancer Stage (n, %)			
II	5 (11.6%)	1 (8.3%)	
III	10 (23.3%)	6 (50.0%)	0.267
IV	28 (65.1%)	5 (41.7%)	

The QoL of carers of pancreatic cancer patients

In total, eight out of the twelve patients (75%) participated in the study were accompanied by a carer. The number of the participating carers diminished as the patients deceased or dropped out from the study. The mean EQ-5D-5L scores for the first three months of the study follow up are displayed in **Table 12 and Appendix 6**. The global health VAS score and the summary index score demonstrate a static impairment of the QoL throughout the first three months. The differences across the months were not statistically significant.

Table 12. QoL scores in carers calculated based on the EQ-5D-5L QoL questionnaire.

	Month 1	Month 2	Month 3	p-value
Number of participating carers (n)	8	6	5	
Mobility (mean, SD)	1.13 (0.35)	1.50 (0.55)	1.40 (0.54)	0.532
Self-care (mean, SD)	1.13 (0.35)	1.00 (0.00)	1.00 (0.00)	1.00
Usual activities (mean, SD)	1.50 (0.92)	1.33 (0.51)	1.20 (0.44)	0.494
Pain/discomfort (mean, SD)	1.50 (1.00)	1.50 (0.83)	1.40 (0.54)	0.494
Anxiety/depression (mean, SD)	2.00 (0.53)	1.83 (0.75)	1.60 (0.54)	0.187
Summary Index score (mean, SD)	0.86 (0.16)	0.87 (0.13)	0.89 (0.11)	0.098
Global health VAS score (mean, SD)	76.9 (25.5)	88.3 (10.3)	84.0 (13.8)	0.127

Figures in the five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) represent mean values in a 5-point scale from 1 to 5 where 1 is perfect health and 5 highest degree of impairment.
Only one carer participated beyond month three, therefore descriptive statistics were not calculated.

Questionnaire completion rates

Questionnaire completion at each time point was assessed based on those who returned their questionnaires as a proportion of those who were alive and were expected to complete questionnaires. Dropouts refer to those who did not return their questionnaires, although they were still alive. Some patients had a reduced follow up time, as they started participating three months before the study's end date; their questionnaire completion was therefore censored. Overall, 33 (80%) questionnaires were returned from a total of 41 which were expected. The completion rates were 100% in the first two months and gradually reduced to 33% at six months. The missing questionnaires were from two out of the twelve patients who dropped out at month three. Their missing questionnaires account for 20% of the questionnaires expected to be returned. The completion rates

at each time point are detailed in **Table 13**. Where questionnaires were returned, completion of the different questionnaire sections was very high: only one patient declined to complete medication use.

Table 13. Questionnaire completion rates in BAC-PAC participants.

Month	1	2	3	4	5	6	Total
Expected questionnaires from alive patients (n)	12	10	8	4	4	3	41
Returned questionnaires (n)	12	10	6	2	2	1	33
Completion rate[1] (%)	100%	100%	75%	50%	50%	33%	80%
Dropouts[2] (n,%)	0 (0%)	0 (0%)	2 (25%)	2 (50%)	2 (50%)	2 (76%)	20%
Deceased patients (n)	0	2	3	4	4	4	-
Patients whose completion was censored due to end of study[3] (n)	0	0	1	4	4	5	-

[1]Completion rate is estimated as the number of returned questionnaires divided by the number of alive patients expected to return a questionnaire at each time-point.

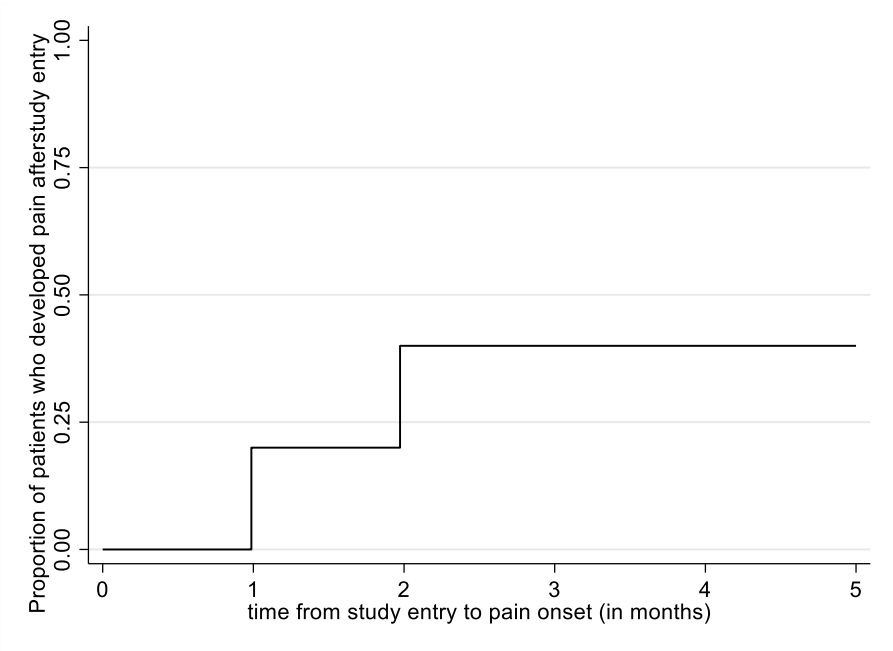
[2]Dropouts refer to the proportion of patients who did not return their questionnaire despite being alive and are calculated for each time point.

[3] The completion rate was censored for patients who were recruited less than six months from the end of the study.

Time from diagnosis to first opioid prescription

In total, seven out of the twelve (58%) patients reported pain by the time of their study entry. Of the remaining five patients, one reported pain one month after their entry, another one after two months from their entry and three patients (25%) did not develop pain during follow-up. The median time from study entry to pain onset could not be calculated, as more than 50% of the patients experienced the pain before the study entry. A Kaplan-Meier plot is shown in **Figure 24.**

Figure 24. Kaplan-Meier plot: time from study entry to pain onset. Five out of twelve (42%) patients were pain-free at their entry, of whom two (40%) developed pain in the first two months.



The mean/median QoL, abdominal pain score and opioid dose

Analysis was limited to the first three months of follow-up, as beyond this point data were available for two or fewer patients. The EQ-5D-5L scores showed a gradual impairment of the global health VAS score, however the differences between month one, two and three were not statistically significant (p=0.185) (**Table 14 and Appendix 7**). All the other elements of the EQ-5D-5L (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) as well as the summary index score were relatively static. Analysis of the EORTC-QLQ30 score also demonstrated stable impairment of all the functioning scales (role, emotional, cognitive, social and cognitive) (**Table 15 and Appendix 7**). A relatively static impairment was also noted for fatigue, dyspnoea, diarrhoea and appetite loss. In contrast, pain, constipation and insomnia showed a trend for improvement. Nausea was the only symptom with a trajectory of deterioration. Financial difficulties remained zero throughout. The median VAS pain score was 2.9 (IQR 0.8 to 5.1) and 1.7 (IQR 1.0 to 1.9) at month one and two, respectively. The median daily morphine dose equivalents were 36 (IQR 20 to 48) at month one and 28 (IQR 6.8 to 70) at month two (**Table 16**). Only one out of the six (17%) respondents reported pain in month three.

Table 14. EQ-5D-5L QoL scores for patients.

	Month 1	Month 2	Month 3	p-value
Number of participating patients (n)	12	10	6	
Mobility (mean, SD)	1.4 (0.79)	1.3 (0.48)	1.8 (0.83)	0.237
Self-care (mean, SD)	1.1 (0.29)	1 (0)	1.2 (0.45)	0.955
Usual activities (mean, SD)	2.3 (1.21)	1.8 (0.92)	2.6 (1.52)	0.209
Pain/discomfort (mean, SD)	1.9 (0.90)	1.9 (0.88)	2.0 (1.0)	0.143
Anxiety/depression (mean, SD)	1.4 (0.79)	1.4 (0.51)	1.8 (0.83)	0.129
EQ-5D-5L index value (mean, SD)	0.86 (0.12)	0.87 (0.12)	0.78 (0.20)	0.102
Global health VAS score (mean, SD)	71.3 (21.3)	67 (18.2)	51 (15.1)	0.185
Only two patients participated beyond month three, therefore descriptive statistics were not calculated.				

Table 15. Table of the function scores and symptoms of the EORTC-QLQ30 over time.

Month	1	2	3
Participants	**n=12**	**n=10**	**n=6**
	Mean (SD)	**Mean (SD)**	**Mean (SD)**
Global health status[1]	53 (22.0)	58 (22.0)	56.7(27.9)
Physical functioning[1]	74 (21.7)	78 (21.8)	70.7 (29.3)
Role functioning[1]	72 (30.4)	78 (23.6)	63.3 (44.7)
Emotional functioning[1]	69 (22.6)	70 (24.3)	71.7 (32.6)
Cognitive functioning[1]	81 (30.0)	85 (14.6)	83.3 (23.6)
Social functioning[1]	64 (24.4)	70 (24.6)	73.3 (25.4)
Fatigue[2]	44 (31.9)	43 (31.2)	55.6 (35.1)
Nausea and vomiting[2]	13 (22.6)	18 (21.4)	33.3 (23.6)
Pain[2]	33 (36.2)	18 (19.9)	13.3 (29.8)
Dyspnea[2]	19 (30.0)	20 (35.8)	20 (29.8)
Insomnia[2]	36 (30.0)	23 (22.5)	13.3 (29.8)
Appetite loss[2]	50 (41.4)	53 (39.1)	53.3 (29.8)
Constipation[2]	39 (37.2)	10 (16.1)	6.7 (14.9)
Diarrhea[2]	36 (38.8)	33 (47.1)	46.7 (38.0)
Financial difficulties[2]	0 (0)	0 (0)	0 (0)

[1]Functioning scores in EORTC-QLQ30 are scaled from 0 to 100. 0 represents worst possible functioning and 100 represents perfect health.

[2]Symptom scores in EORTC-QLQ30 are scaled from 0 to 100. In contrast to the functioning scores, 0 represents absence of a symptom whilst 100 represents the highest level of impairment in the QoL due to the examined symptom.

Table 16. Visual analogue pain scores and morphine dose equivalents.

Month	1	2	3	4	5	6
Number of patients completing questionnaires (n)	12	10	6	2	2	1
Number of patients reporting pain (n, %)	7 (58%)	5 (50%)	1 (17%)	0	0	0
Number of patients alive (n)	12	10	9	8	6	5
VAS score (Median, IQR)	2.9 (0.8-5.1)	1.7 (1.0-1.9)	7.8	N/A[1]	N/A[1]	N/A[1]
Morphine dose equivalent in mg (median, IQR)	36 (20-48)	28 (6.8-70)	78	N/A[1]	N/A[1]	N/A[1]

[1]After month three two data were available for two or less patients, hence descriptive statistics were not calculated.

Associations between two radiological signs of pancreatic cancer and pain occurrence

This objective required a minimum of 52 patients to be met. Due to insufficient recruitment, this objective was not assessed.

Health economic analysis

Analysis of the resource use identified 17 types of expenditure. The estimated unit costs per resource and the assumptions made for the estimation of those costs are shown in **Table 17.** The mean NHS and PSS expenditure per patient was estimated at £1,491 per month. A detailed breakdown of the expenditure per resource is shown in **Table 18.** The estimated median QALY were 0.073 (IQR 0.062 to 0.076) between month one and two and dropped to a median of 0.054 (IQR 0.020 to 0.076) between month two and month three **Table 19**.

A narrative assessment, in terms of completeness, relevance and quality of the collected data was undertaken based on informal feedback from patients and members of the research team involved in data collection. This revealed that patients' pattern of medical resource use consists of elective attendances for planning, consent and delivery of chemotherapy treatments as well as non-elective attendances to emergency services. However, it also revealed that our data collection instrument was not specific enough to capture the purpose of patients' elective and non-elective attendances and the specific hospital department involved and the medical activities that were undertaken during those. For example, the number of non-elective attendances were questioned but it did not specify if this was for a cancer-related or a general medical problem. Similarly, if a patient attended for a chemotherapy infusion, we did not capture whether they were seen by the consultant or the specialist nurse during the same event. Imprecisions as such may have lead to significant cost misestimations. In terms of the completeness, one patient did not complete his drug record because he felt it was too time-consuming as it contained many items.

Table 17. Unit costs per medical resource or other health-related expenditure.

Resource	Unit Cost	Reference	Assumption
Hospital-based resources			
Hospital admission	£ 447.00	PSSRU (2020) section 7.1, NHS reference costs for hospital services, p87.	Patients receive palliative care and chemotherapy side-effect treatments
Non-elective attendance to A&E or similar	£ 382.00	National schedule of NHS cost 2018/2019, code SB97Z, tab: non-elective short stay (NES).	A&E attendances are be related to chemotherapy or procedure complications or due to poorly controlled symptoms attributed to cancer progression. Co-incidental illnesses rarely led to admission in patients with pancreatic cancer, hence are not considered in the costings [208, 209].
Delivery of parenteral chemotherapy at first attendance	£ 307.58	National schedule of NHS cost 2018/2019, code SB13Z.	Costs reflect delivery of complex chemotherapeutic schemes, such as FOLFIRINOX, but not single agent chemotherapy such as gemcitabine or capecitabine. Costs adjusted for inflation.
Delivery of subsequent elements of a chemotherapy cycle	£ 332.83	National schedule of NHS cost 2018/2019, code SB15Z.	Costs reflect delivery of complex chemotherapeutic schemes, such as FOLFIRINOX, but not single agent chemotherapy such as gemcitabine or capecitabine. Costs adjusted for inflation.
Radiotherapy	£ 142.88	National schedule of NHS cost 2018/2019, code 800, tab: total outpatient attendance.	No assumptions made. Costs adjusted for inflation.
Consultant: medical	£ 59.50	PSSRU (2020) section 14, hospital-based doctors, p159.	Consultant cost per working hour £119. Appointment length 30 mins (incorporating administrative tasks).
Dietician appointment	£ 25.00	PSSRU (2020) section 12, hospital-based scientific and professional staff, p151	NHS band 6 dietician, with cost per working hour 50. Appointment length 30 mins (incorporating administrative tasks)
Occupational health appointment	£ 25.00	PSSRU (2020) section 12, hospital-based scientific and professional staff, p151	NHS band 6 occupational therapist, with cost per working hour 50. Appointment length 30 mins (incorporating administrative tasks)
Specialist nurse appointments	£ 25.00	PSSRU (2020) section 12, hospital-based nurses, p155.	NHS band 6 nurse, with cost per working hour £50. Appointment length 30 mins (incorporating administrative tasks)

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Resource	Unit Cost	Reference	Assumption
Community-based resources			
GP surgery consultations	£ 39.23	PSSRU (2020) section 10.3b, community-based health care staff-general practitioner, p126.	This unit cost is calculated based on the average duration of GP contact per patient, lasting 9.22 minutes.
GP telephone call	£ 8.41	PSSRU (2020) section 10.4, the cost of online consultations, p128.	This unit cost represents telephone contacts for following up tests or treatments that were decided during a GP surgery consultation.
Primary care nurse appointment	£ 24.50	PSSRU (2020) section 10.1, the cost of online consultations-nurses, p123.	NHS band 6 nurse, with cost per working hour 49. Appointment length 30 mins (incorporating administrative tasks)
Primary care nurse home visits	£ 23.00	PSSRU (2020) section 10.2, GP practice nurse, p124.	NHS band 6 primary care nurse, with cost per working hour 42 plus an average of 10 miles stuff travel per visit. Appointment length 30 mins (incorporating administrative tasks)
Community equipment (stairlift)	£ 654.00	PSSRU (2020) section 7.3, equipment and adaptations, p90.	No assumptions made.
Medical prescriptions			
Medical prescriptions		British National Formulary, URL: https://bnf.nice.org.uk/drug/, accessed on: 05/08/2021.	Costs were estimated based on the medication use the patients recorded on their self-completed questionnaires.
"Out of pocket" expenses			
Travel for medical appointments (in miles)	£ 0.15	AA motor insurance company, mileage calculator, URL: https://www.theaa.com/driving/mileage-calculator.jsp, accessed on: 30/07/21	Approximate fuel cost £1.40 per litre and engine performance rate of 40 miles per gallon.
Car parking expenditure	n/a	Costs directly reported by patients on self-completed medical resource questionnaire	No assumptions made.

Table 18. Units of medical resource used and actual expenditure per resource.

	Month 1 (12 participants)			Month 2 (10 participants)			Mean expenditure over the first two months
	units used	total expenditure per resource	average expenditure per patient	units used	total expenditure per resource	average expenditure per patient	
Hospital-based resources							
Days in-hospital stay	21	£9,387	£782	11	£4,917	£492	£7,152
Non-elective attendance to A&E or similar	1	£382	£32	3	£1,146	£115	£764
Delivery of parenteral chemotherapy at first attendance	9	£2,768	£231	0	-	-	£1,384
Delivery of subsequent elements of a chemotherapy cycle	0	-	-	27	£2,663	£266	£1,331
Radiotherapy	0	-	-	5	£714	£71	£357
Consultant appointments	11	£655	£55	8	£476	£48	£565
Specialist nurse appointments	21	£525	£44	44	£1,100	£110	£813
Community-based resources							
GP appointments	7	£275	£23	2	£78	£8	£177
GP telephone call	2	£17	£1	6	£50	£5	£4
Primary care nurse appointment	6	£147	£12	4	£92	£9	£120
Primary care nurse home visits	5	£115	£10	0	-	-	£58
Dietician appointment	2	£50	£4	3	£75	£8	£63
Occupational health appointment	1	£25	£2	0	-	-	£13
Community equipment (stairlift)	1	£654	£55	0	-	-	£327
Appointments with other health professionals	4	£100	£8	3	£75	£8	£88
Total costs		**£15,099**	**£1,258**		**£17,711**	**£1,771**	**£16,405***
Medical prescriptions	-	£384	£35	-	£208	£20	
Out of pocket expenses							

Travel for medical appointments (in miles)	887	£133	£11	1972	£296	£30	£214
Car parking expenditure	-	£46	£4	-	£72	£7	£59

*Mean expenditure per patient for the first two months was £1,491.

Table 19. Table of QALYs per month.

Month intervals	1st to 2nd	2nd to 3rd	3rd to 4th	4th to 5th	5th to 6th
Total number of patients in the cohort (n)	12	12	12	12	12
Alive patients contributing utility values at the start and the end of the month (n)	10	6	2	2	1
Deceased patients at each time interval[1] (n)	2	3	4	4	4
Patients with missing data due to dropouts (n)	0	2	2	2	2
Patients with censored data[2] (n)	0	1	4	4	5
Quality Adjusted Life Years (QALY)[3] (median, IQR)	0.073 (0.062-0.076)	0.054 (0.020-0.076)	0[3] (0.000-0.033)	0[3] (0.000-0.083)	0[3] (0.000-0.083)

[1]Deceased patients contributed with "0" utilities at the end of the month they died and for the subsequent months.

[2]Some patients entered the study less than six months before its closure. Their utility values from three to six months were censored

[3]As this represents a QALY score from a month, the maximum QALY, at full health would be 0.083 (e.g. 1/12).

DISCUSSION

Main findings

Overall, twelve out of the 56 eligible patients (21%) were recruited to the BAC-PAC study. There was no statistically significant difference in the age, gender and cancer stage between the recruited participants and those who declined participation; however, a lack of statistical significance may reflect the small sample size. Questionnaire completion rate was 80%. Completeness of the provided data was high overall . The medical performance status of those in pain varied between 0 and 2. The median survival from pain onset was 5.2 (IQR 2.5-5.9) months. Seven out of the twelve patients (58%) reported pain at baseline and another two developed in the subsequent months. Consequently, the median time from diagnosis to the pain onset could not be assessed; less than 50% of patients who were pain-free at diagnosis develop pain upon their entry to the study. The QoL was consistently impaired in the first three months based on the functioning scales of EORTC-QLQ30 and the summary index score deriving from the ED-5Q-5L. The median VAS pain score was 2.9 (IQR 0.8-5.1) at month one and 1.7 (IQR 1.0-1.9) at month two. The median daily morphine dose equivalents were 36 (IQR 20-48) and 28 (IQR 6.8-70) at months one and two, respectively. The associations between CT signs and the risk for developing pain could not be assessed due to lack of sufficient data. In total, eight out of twelve carers (75%) participated in the study. Their QoL was impaired based on the EQ-5D-5L QoL questionnaire. Overall, 17 different types of expenditure were identified, including hospital-based care, community-based care, medical prescription costs and “out of pocket” expenses. The mean NHS and PSS expenditure per patient was £1,491 per month. The estimated median QALY were 0.073 (IQR 0.062 to 0.076) between month one and two and dropped to a median of 0.054 (IQR 0.020 to 0.076) between month two and month three. The health economic data collection instrument needs to be more specific about the purpose of the attendances and the specific activities undertaken during those and supplemented with medical record review.

Interpretation

Assessment of study objectives was limited by poor recruitment. This was the result of two waves of the COVID-19 pandemic but also lower than expected recruitment rates as a proportion of eligible patients. This resulted in imprecise estimates for most objectives, or in the case of objective 8, it was not possible to estimate the radiological associations with pain. We intended to record performance status at the time of pain onset, so that we could estimate how fitness for endoscopy may affect eligibility for early EUS-CPN in a future trial. The medical performance status of those with pain ranged from normal (performance status 0) to mildly impaired (performance status 2) and therefore, these

patients' general health should not preclude EUS-CPN. We showed that the median survival from pain onset is 5.2 (IQR 2.46-5.9) months. This is likely to be an underestimate, considering that patients were typically recruited 6 weeks after diagnosis and onset of pain preceded this time point in the majority of them (seven out of nine). Nevertheless, this is a meaningful period of survival time (i.e. at least three months) and they could potentially benefit from an early EUS-CPN. However, in view of limited study recruitment, it is unclear if this estimated survival can be generalised to all patients with inoperable pancreatic cancer. We aimed to compare the characteristics of those who participated versus those who refused in order to evaluate the generalisability of our results. Age, gender and cancer stage were numerically similar and there were no statistically significant differences between the two groups. This is important as recruitment to a prospective observational study is likely to differ to that of a randomised controlled trial (participants may derive direct benefit if allocated to the intervention which may alter decisions around participation). We therefore have some indirect evidence to conclude that inferences from this research could be applied to a future trial.

We hypothesized that carers' QoL declines as a result of patients' uncontrolled pain and we aimed to explore if QoL in carers could be a secondary outcome in a future trial. Indeed, aspects of their life, such as mood, ability to attend usual activities and global health were adversely affected. However, QoL is multidimensional, and it is unclear whether improving pain when all other negative cancer consequences persist (reduced survival, frequent chemotherapy complications, cachexia etc) can produce any detectable QoL benefits for carers in the context of a clinical study. To determine this, the effect of early EUS-CPN on domains of QoL would need to be evaluated as a secondary outcome in a future RCT. The questionnaire completion rate was 100% in the first two months of follow-up, however completion rates fell to 75% by month three and continued to decline in subsequent months. Informal feedback from participants revealed that the burden of study activities was prohibitive for their adherence to follow-up. Consideration for this in a future study is needed, for example, questionnaires could be completed jointly with members of the research team (rather than self-reporting) and efforts to reduce the overall volume of data collected may improve retention.

This study intended to measure several fundamental parameters to inform the logistics of a future trial. Firstly, recording the time from diagnosis to the first opioid prescription was considered an important element, as this is when randomisation in a future trial could happen. Herein we showed that most patients presented with pain and therefore they would be randomised soon after diagnosis. Moreover, we calculated the descriptive statistics for the QoL scores, VAS pain scores and daily morphine consumption, one of which could reasonably serve as the primary outcome of a future trial. However, given the small sample it is unlikely these estimates can be relied upon and further assumptions are likely to be required in order to plan and design a future trial (particularly estimates

of recruitment, retention and parameters on which to base a sample size calculation). We were unable to estimate the associations between radiological signs and the development of pain; and further research will be required to do this.

In this work we assessed the feasibility of collecting the data needed for the calculation of the costs of the medical care and the health effect, expressed in QALYs. These would be necessary for the estimation of the incremental cost effectiveness ratio (ICER) measured in costs per additional QALY in a future clinical trial (assuming EUS-CPN is shown to be more beneficial, but leads to greater costs). We showed that it is feasible to calculate QALYs, however, the capture of medical care costs may require input from the researchers to ensure better accuracy of the exact resources used.

Comparison with previous literature

Two previous retrospective cohort studies have comprehensively assessed the epidemiological characteristics of pain in patients with inoperable pancreatic cancer[119, 188]. In those the prevalence of pain was estimated between 58-78%[119, 188]. Our estimate of 58%, falls within the lower end of this range and this is possibly because our study may not have included patients with the most severe pain who could not engage with study procedures, such as questionnaire completion. The previously reported mean daily opioid dose of 55.9 (SD 53.8) mg at diagnosis [119] is higher than our estimate of 39 (SD 25) mg (in the results section we reported the median values to reflect their skewed distribution, but here we report mean to facilitate direct comparison with previous literature). This discrepancy, similar to the prevalence of pain, probably reflects that our study, due to the method of data collection, recruited patients with preserved general health who are less likely to use high dose opioids. The same previous paper estimated a mean period of 3.2 (SD 7.7) months from diagnosis to the first opioid prescription [119]. In our study this figure was not measurable, as 58% of the patients already had pain by the time they entered the study, so a median time is not informative. The mean survival time from the pain onset was 6.2 (SD 6.9) months which is similar to our findings (median survival 5.2, IQR 2.46 to 5.9).

Several studies have reported QoL scores in pancreatic cancer. These studies were conducted either for questionnaire validation or measuring QoL outcomes in the context of chemotherapy. We have chosen four of them for comparison with our results, based on their relevance, rigor and contemporality[210-214]. Two studies have reported the EORTC-QLQ30 in patients with inoperable pancreatic cancer[210,211]. One prospective cohort study of 116 patients undergoing chemotherapy reported EORTC-QLQ30 global health scores for month one, two and three of 50.8%, 46.8% and 48.4%, respectively (SD not provided)[210]. These were broadly similar to our results, which were 53% (SD 22), 58% (SD 22) and 57% (SD 28) at the same time points. The EORTC group defines clinically meaningful

results as any difference in excess of ≥ 10%[198]. Similarly, pain, fatigue, sleep disturbance and loss of appetite scores were the most affected quality of life dimensions with a score around 40 (scale 0 to 100) which are very similar to our results. Four studies, one from United States, Canada, Norway and Japan, reported EQ-5D-5L scores; the summary index ranged from 0.62 to 0.82 at month one and 0.64 to 0.69 at month two[211-214]. These values are lower than our estimates; 0.86 (0.12), 0.87 (0.12) at months one and two. Three reasons may explain this disparity. Firstly, the EQ-5D-5L is a generic instrument, not specifically designed to capture cancer-related impairment. Secondly, it is validated against societal preferences for given health states which, by definition, are variable among ethnicities[194]. Thirdly, only 41% of our participants had metastatic disease, whilst in the above studies this percentage was 70% and above.

The poor recruitment rate in observational studies targeting patients with newly diagnosed pancreatic cancer is not unique to our study; a multicentre, questionnaire-based, prospective observational study, aiming to investigate the predictive value of common presenting symptoms (jaundice, nausea, weight loss etc) with the risk of pancreatic cancer in patients newly referred from the primary care to the relevant cancer pathway in seven UK and Australian hospitals, recruited only 24% of the eligible patient population[69]. Similar low participation rates were observed in studies with a prospective design in patients with lung and colorectal cancer[215, 216]. This is likely to be attributed to the psychological and physical effects a cancer diagnosis places on patients.

To the best of our knowledge, there is no previous literature with which to compare on the performance status and the associations of the radiological features with the development of pain. Overall, our results, including prevalence of pain, opioid doses and QoL, are indicative of patients with a better general health in comparison to those in previous studies; this suggests that questionnaire self-completion is probably prohibitive for the participation of the more unwell patients.

Strengths and limitations

It is unlikely that eligible cases were missed: there was a systematic screening on a weekly basis of the cancer registry, review of the MDT notes and other medical records and liaison with the direct clinical team to ensure all cases were identified and eligibility was accurately evaluated. The prospective design of this study enabled to capture real-time patient reported outcomes. In addition, the conduct of this study, informed by PPI groups, sought to minimise burden and impact on this very vulnerable group the study was conducted in. For example, there were occasions understandably when patients and their carers were struggling to process their diagnosis and prognosis due to emotional distress. In those cases, the time to approach patients was carefully considered in consultation with the direct care team. Similarly, to avoid intrusiveness, contacts with patients were discontinued when patients

were repeatedly not returning their questionnaires despite gentle reminders from the research team. Although these considerations were hindering for the recruitment, they revealed the fragile psychology of this patient's group which is relevant to the design of a trial of early EUS-CPN. On the other hand, the study suffered several limitations mainly related to the small number of participants, limiting assessment of objectives with resulting imprecision. Involvement of other centres was attempted to rectify poor recruitment, in part, however site setup unfortunately coincided with the second wave of the COVID-19 pandemic and this plan unfortunately never materialised. Unfortunately, the use of self-completed questionnaires (which were informally viewed as burdensome) likely had a negative impact on recruitment.

Implications for future research

Our study, being exploratory in nature, has revealed important aspects relevant to a future trial of early EUS-CPN versus standard care. We have demonstrated that pain has a high prevalence among patients with inoperable pancreatic cancer; the need of opioids is frequently observed; QoL of both patients and carers is impaired, with pain being one of the contributors to this impairment. All these findings support the rationale for a future trial of early EUS-CPN. In addition, the patients' performance status and the survival after the pain onset lend further support for feasibility. However, given the limitations of this study, further information is required to determine the specific design of a future trial. Robust estimates of the prevalence of pain, opiate burden and related adverse events are needed over time in this population to better inform justification. Another finding with implications for a future trial were low recruitment rates, and barriers to recruitment would need to be addressed. Attention to recruitment and retention procedures in a trial are important and will require extensive PPI to develop and implement. In the next chapter the patients' and carers' perspectives on the barriers to participation in research are explored through in-depth qualitative interviews. Furthermore, informal feedback from patients and carers suggested that questionnaire completion may be perceived as a laborious task during one's terminal illness. Therefore, greater reliance on routinely collected clinical data is needed, to minimise the burden placed on patients. For example, medication use could be ascertained using routinely collected data from primary and secondary care. The conduct of a health economic analysis is feasible, however refinement of the data collection instrument is needed, so the exact use of medical resource is captured, and this resource is directly related to pain management. Finally, the small number of patients who were eligible for the BAC-PAC and the even smaller of those who suffered from pain, indicates that a future multi-centre feasibility trial is required to ensure adequate recruitment.

Conclusion

Pain is prevalent in 58% of the patients with advanced pancreatic cancer at diagnosis. Survival is likely sufficient (median survival time: 5.2, IQR 2.46 to 5.9) months) to permit endoscopic analgesia. However, further research is needed to provide more precise estimates of the prevalence of pain, the doses of opioids and survival to improve the assessment of the justification and planning of a future trial. Careful attention to enablers and barriers to recruitment need to be considered in this patient population.

CHAPTER 4- Patients', carers' and clinicians' beliefs and ideas towards endoscopic analgesia for unresectable pancreatic cancer: a qualitative study using semi-structured interviews

ABSTRACT

Background. Patients with pancreatic cancer are often affected by severe abdominal pain. The pain is treated with morphine-based preparations, the dosage of which are often escalated as the cancer progresses. Morphine in high doses can be responsible for debilitating side-effects. Endoscopic ultrasound-guided coeliac plexus neurolysis (EUS-CPN) disrupts pain signals and improves pain. However, its exact role is uncertain due to a lack of clinical trial data. At present, it is administered as a rescue therapy when opioids have failed. Theoretically, if it is given early at pain onset, it may minimise opiate burden. This study sought to investigate patients' perspectives on their pain burden, explore aspects of morphine treatment, discuss the appropriateness of an early endoscopic intervention and gather qualitative data related to the feasibility of a clinical trial of an early EUS-CPN versus standard care.

Methods. Patients with inoperable pancreatic cancer, and their respected carers, underwent semi-structured in-depth interviews at least three months after their diagnosis. Also, the perspectives of pancreato-biliary endoscopists, who are the ones responsible for delivering the procedure, were explored. This qualitative study was nested within the Best Analgesia Control in Patient with Pancreatic Adenocarcinoma (BAC-PAC) prospective cohort study. Data were analysed using deductive and inductive thematic analysis.

Results. In total, four patients, their four partners and two pancreato-biliary endoscopists, attended one qualitative interview each. The patient and partner interviews were conducted three months after diagnosis. The patients' characteristics were: 50% females, age range: 61-82 years, cancer stages II to IV, three treated with chemotherapy and one with radiotherapy. Three of the patients had ongoing pain requiring small to moderate doses of morphine. Five themes and 16 sub-themes were identified. The main finding is that morphine has acceptable efficacy-toxicity profile in moderate doses and patients would consider endoscopic analgesia as a second choice, if morphine stops working. Overlaying gastrointestinal problems, such as constipation and irritable bowel syndrome (IBS) may complicate the clinical picture. Pain may contribute to malnutrition, but other factors are also involved in weight loss. People are hesitant to initiate morphine treatments, however, they are more accepting

once they experience their analgesic benefit. Patients experience insomnia or daytime somnolence, but neither are attributable to pain or morphine toxicity. Morphine has a positive impact on sleep disturbance due to its sedative effect. Overall, patients were satisfied with the endoscopic treatment they received and although an unpleasant experience, they would undertake a second procedure if necessary. Patients believe that better pain relief methods need developing, however, they suggested that they would consider participation into a trial only if their pain was severe enough to justify an endoscopy. Chemotherapy causes physical and emotional distress and may limit trial participation.

Conclusion. Herein, we interviewed patients with moderate pain, at a stage a few months ahead of the terminal illness diagnosis, and whose symptoms were well-controlled with low morphine doses. Consequently, pain was a lower priority compared to other issues, such as the chemotherapy side-effects and the psychological burden of the poor life expectancy. A future trial design should take into account the following challenges: a. endoscopic analgesia is more likely to be acceptable to patients with significant pain, rather than those with mild pain who improve with small doses of morphine, b. allocating participants to the control group as part of the randomisation could potentially lead to high dropout rates and c. patients prioritise chemotherapy, the administration of which is demanding and challenging, and in turn may act as a barrier to recruitment to a trial of an endoscopic analgesic intervention.

INTRODUCTION

Background

Every day, 28 new patients are diagnosed with pancreatic cancer in UK[40] . Its related prognosis is so poor that its incidence nearly matches its mortality: out of the 10,257 new cases diagnosed in 2017 there were 9,421 deaths in the following year (mortality/incidence ratio of 94%)[40]. Of those diagnosed with pancreatic cancer only 15-20% are eligible for potentially curative resection and they survive for a median of 30 months (95% CI, 27 to 33)[74, 217]. For the rest with unresectable disease, chemotherapy may be given. The survival for those with metastases who receive chemotherapy is limited to a median of 11.1 months (95% CI, 9.0 to 13.1)[91]. Those few with unresectable disease who are diagnosed before their disease is disseminated (metastatic) and receive chemotherapy can survive approximately 2 years (median overall survival 24.2 months, 95% CI, 21.7 to 26.8)[90]. A significant limitation of chemotherapy is its severe toxicity which causes many patients to not be able to complete their course or to choose to not pursue it at all. Those patients who are too frail to receive chemotherapy survive for a maximum of six months[40].

Abdominal pain affects 58-78% of patients with pancreatic cancer[119, 188]. Morphine has a central role as a treatment modality, although it is notorious for the serious side-effects it causes, which include lethargy, cognitive impairment, constipation and gastroparesis and other[136]. Endoscopic Ultrasound-guided Coeliac Plexus Neurolysis (EUS-CPN) is an endoscopic intervention which disrupts the pain signalling pathways to the central nervous system and promotes analgesia. EUS-CPN is usually offered as a rescue therapy when opioids have failed to control pain. It is plausible that if is given early, at pain onset, it may prevent patients from requiring high dose of opioids and reduce associated toxicity. However, robust trial data to inform the most appropriate timing of administration of EUS-CPN is lacking, so the clinicians use it based on their own personal experience and expertise. Further research including clinical trials are needed to elucidate its exact role. However, this is a physically and emotionally vulnerable patient group with poor prognosis. Therefore, there are several important practical and emotional factors we need more information on when the application of endoscopic analgesia is discussed in the context of a clinical trial.

Rationale

The burden of pain on patients and their carers is poorly documented in the current literature. In addition, complex reasons related to the nature of the disease, the delivery of endoscopic procedures or other factors that researchers were not aware of prior to this study may be relevant to the application of EUS-CPN. Exploring patients', carers' and endoscopist's perspectives, may be useful to

inform the role of endoscopic analgesia in routine practice and also any barriers to the delivery of EUS-CPN in the context of a future trial.

Aims

To assess the burden of pain in patients and their carers and whether endoscopic analgesia is acceptable during the terminal illness. Moreover, this study is aimed to explore if a future clinical trial of endoscopic analgesia is justifiable and feasible based on patients', their carers' and clinicians' perspectives.

Objectives

To use semi-structured qualitative research interviews to explore the patient and carer's: 1. experience of the impact of pain, 2. use of morphine, 3. experience of endoscopic procedures and 4. attitudes towards randomised research trials. The same areas were to be explored from the perspective of clinicians involved in decision making with such patients. The research questions include:

How much burden does pain place on the study participants (patients and carers)?

What are the implications of morphine use, including its efficacy and side-effects?

What are the wider implications of pain and morphine use, for example in food intake, energy levels, sleep or social life?

What was their experience of attending endoscopy, either themselves or people who they know of?

What are participants views on the acceptability of offering a similar endoscopic procedure for the purpose of analgesia?

What thoughts or concerns would participants have if a trial of endoscopic analgesia was offered to them?

What is the endoscopist's personal experience in assessing eligibility, explaining and delivering EUS-CPN to patients?

How an invasive procedure can fit in the care of patients with poor life expectancy and frailty?

METHODS

Study Design

One-to-one in-depth interviews with patients and their carers were conducted in order to generate language data with regards to the magnitude of pain and opioid use in pancreatic cancer and explore peoples' views on endoscopic analgesia. Moreover, the reasons behind recruitment difficulties to clinical trials in this area were explored. These interviews were designed to supplement the quantitative data generated by the BAC-PAC study. The face-to-face interaction in the context of an interview was hypothesised to be able to give us a better understanding of patients' and carers' thoughts and perceptions and more importantly to explore potential barriers in the recruitment of a future trial, which cannot be captured by the quantitative research. The subject was also explored from the endoscopists' perspective who are responsible for assessing patients for eligibility, discuss risks and benefits and deliver the EUS-CPN.

Patients and their carers were offered interviews separately to each other, assuming that they may have discordant perspectives on the same topics which could not be explored if they were attending jointly. On occasions, the two participants were interviewed together according to their wish. The discussion was semi-structured, guided by prompts recorded in topic guides. These topic guides were formulated in advance and modified depending on findings of previous literature and individual circumstances (i.e. chemotherapy, radiotherapy, endoscopy experience, socioeconomic status, home circumstances etc). The topic guides were modified before each interview, based on the participants' responses in the BAC-PAC questionnaires (detailed in chapter 3). For example, patients who were not on morphine at the time of the interview were asked if they have come across other patients treated with opioids during their terminal illness and what thoughts they had about these. Equally, some patients did not have endoscopic therapies, hence they were asked what is their understanding about endoscopy and what they would be concerned about, if they needed to have one. The generic topic guides are provided in **Appendix 8.**

Research Setting, Recruitment and Study participants

The qualitative interviews were nested within the BAC-PAC prospective observational study. Chapter three described the research setting, identification and recruitment of newly diagnosed patients with unresectable pancreatic cancer. Written information about the qualitative interviews were provided in a section of the BAC-PAC patient information leaflet and were further explained by the research specialist nurse during the first research visit. Informed consent specific for the qualitative interviews was obtained during the first research visit for the BAC-PAC study and it was documented in a separate

designated section of the generic BAC-PAC consent form. The interviews were designed to be conducted at a convenient time at least three months from the diagnosis. This three-month period was deemed necessary for two main reasons: firstly, it is sufficient time for the participants to experience cancer-related symptoms and reflect upon them and secondly, it is on average before their general health becomes very poor. On the day of the interview, the researcher confirmed with the participants that their consent was still valid and reiterated their right to withdraw it anytime, if they wished. The pancreato-biliary endoscopists who were interviewed were identified through their membership in the Pancreas Committee of the British Society of Gastroenterology (BSG)[218].

Sample size and sampling methods

In our original research plan, a purposive sample of 20 participants, 10 patients and 10 carers, with diverse demographic and disease characteristics, such as pain levels, cancer stage, age, gender, education status and estimated survival, was intended to be recruited to the qualitative interviews. The target of 20 was deemed as an appropriate figure to allow sufficient volume of data to be generated within the given time constraints. However, due to the small number of participants recruited to the BAC-PAC study, a purposive sample was not possible, hence, all BAC-PAC participants were invited for a qualitative interview. The invitation was given by the research fellow over the phone. An assessment of the appropriateness of an interview was undertaken during the same phone call, such as the health and emotional status or the social circumstances. The participants' ability to communicate effectively and their access to teleconference technology (Zoom and Skype), were de facto inclusion criteria for qualitative interviews, in addition to the generic eligibility criteria for the BAC-PAC study. Similarly, we intended to interview 10 clinicians from different disciplines (oncology, palliative care and pancreato-biliary endoscopists).

Researcher characteristics

The interviews were carried out by two investigators: a male gastroenterology physician (AK), who was the primary interviewer and a female senior qualitative researcher who had a supervisory role (CS). The clinician is a gastroenterology trainee with a special interest in pancreatic diseases who, having completed 50% of his clinical training, ran this project as part of his MD (Doctor of Medicine) degree. He had prior experience in sensitive conversations as part of his medical training and his day-to-day clinical practice with vulnerable patients and also attended a qualitative interview course as part of his MD training. The qualitative researcher is an honorary Senior Lecturer in Health and Communication, tutor in communication skills and experienced in qualitative research in patients with chronic illnesses. The clinicians' interviews were conducted by AK alone.

Reflexivity

Among the other topics, patients were asked to discuss the overall care they received, rate the endoscopy service and share views on participation to research. At the same time, the main interviewer (AK) had a triple role; a gastroenterology doctor (involved in the care of some of them), endoscopist and researcher. This relationship between interviewer and interviewee had both advantages and disadvantages. It was beneficial in terms of understanding the clinical events the participants described, however, it may have also inhibited them from criticising the service, so they can stay in good terms with the "doctor-interviewer" who they may see again in a future clinic. The same may apply to questions revolving around participation to future research were patients may have been somewhat reluctant to criticise the idea of an early EUS-CPN over opioids.

Data collection instruments and technologies

Interviews were conducted throughout the duration of the BAC-PAC study (11th of October 2019 to 6th of March 2020 and 22nd of July 2020 to 28th of February 2021). The first two interviews were conducted face-to-face in a hospital meeting room. However, due to the COVID-19 pandemic and in line with the guidance from the Health Research Authority (HRA) the following ones were carried out using video-conferencing technologies including Zoom and Skype, to avoid non-essential patient exposure to the hospital environment. Therefore, participants were in the familiarity of their own home and not in a clinical environment. Audio recordings were obtained and field notes made before and after each interview. Interviews were transcribed verbatim using a combination of the researcher, otter.ai software and a professional transcription company. The transcripts were transferred into Excel spreadsheets where each line from the transcript was accommodated into a separate row which was numbered and tagged with the audio timing to facilitate retrieval of particular lines when the dataset was re-assessed.

Data Analysis

The qualitative data was analysed using a thematic approach. The two investigators examined the dataset of each interview blindly to each other. The data was assessed for recurrent and common themes [219]. The transcripts were supplemented by field notes and the analysis was both inductive and deductive as certain areas for investigation were already known. This supported the analysis of the key areas already known to the research team as well as the emergence of new themes. Recordings were listened to and transcripts were read and re-read by the investigators to ensure familiarity before transcripts were coded and linked between and across interviews. Borrowing from the principles of framework analysis, codes were mapped and interpreted across the whole dataset to look at the

relationship between codes and the implications for the study findings[220]. Emphasis was given to evaluate the different perspectives in the same topics between the patients and their carers. To enhance trustworthiness and credibility of the data analysis, the independent analysis by the two investigators was compared and contrasted and discussed at supervision meetings. Anonymised verbatim extracts were used in the results and discussion sections of this report.

Ethics

The study was approved by the East Midlands- Leicester Central Research Ethics Committee as part of the BAC-PAC study. Ethical considerations were made based on the principles of autonomy, beneficence and non-maleficence (justice does not apply to this situation) [221]. The participants reserved the right to withdraw consent at any point, they were able to refuse discussion on specific subjects, if they wished, or to bring up their own topics for discussion. No justification for their decisions was needed. The patients were always interviewed prior to their carers, so verbal permission from the patient was obtained with regards to the topics for discussion with the carer. In view of how vulnerable this patient group is, breaks or early discontinuation was to be offered. If unaddressed medical problems were revealed during the interviews or when participants were seeking medical advice from the researcher clinician, the latter would suggest they discuss those with their responsible clinicians. The possibility of emotional distress during the discussion was acknowledged among the investigators from the stage of the research protocol development. Hence, the researchers were aware of high-risk features, such as evidence of self-neglect or self-harm, the interviews could potentially reveal. In this case, the researchers were prepared to breach confidentiality and refer the patient to their general practitioner to prevent occurrence of any harmful events.

Patient and Public Involvement

Extensive Patient and Public Involvement activities (PPI) were undertaken throughout this study. Mr Gerald Coteman, founder and Director of The Elizabeth Coteman Fund (URL: ecfund.org)[222], a charity whose mission is to raise awareness of pancreatic cancer, provide support for patients and families living with a diagnosis of pancreatic cancer, and to encourage and support research into the disease, undertook an advisory role in the design, monitoring and reporting of our qualitative interviews. A husband, himself, of a patient deceased with pancreatic cancer, was the one who recommended carer involvement in the interviews, implemented amendments in the patient information leaflet and commented on the researchers' interpretation of the qualitative data. In addition, Gerald is a patient representative on the Anglia Cancer Network pancreatic cancer site-specific group and a PPI adviser to the Cambridge Pancreatic Cancer Centre (http://www.cambridge-pcc.org/engagement.html)[223].

In addition, other patients and carers of the Research Information Network (RIN) of Pancreatic Cancer UK, the UK's largest charity for pancreatic cancer, patients registered with an East of England regional online support group and the Norfolk–Together Against Cancer - a local organization which comments on service provision for patients were asked to comment on our patient information leaflet and our topic guides. All the groups stated this research question is extremely important as anxiety of having uncontrolled pain is a major concern and that adequate pain control is vital for maintaining their quality of life and dignity.

RESULTS

Characteristics of the study participants

In total, ten qualitative interviews were recorded with four patients, their carers/partners and two pancreato-biliary endoscopists. The characteristics of the interviewees are detailed in **Table 20**. The patients were aged between 61 and 82 years, two were females. The cancer stages varied from stage II to stage IV. All the patients were receiving oncological treatments at the time of the interview. Three were using low-to-moderate doses of morphine at the time of the interview whilst one was using only paracetamol and non-steroidal anti-inflammatory drugs on an occasional basis. The rest of the BAC-PAC cohort patients were considered for interviews, however, this was not possible for several reasons which are illustrated in **Table 21**. The most common reason was rapid deterioration, including unexpectedly early death, either due to chemotherapy complications or because of the disease itself. A few patients deceased or deteriorated during the period when the study was halted during the COVID-19 pandemic. The four carers were the patients' marital partners who were accompanying them in the clinic appointments when the research team approached them to offer the study information. Their age varied between 65 and 74 years, two of them had a personal experience of endoscopic investigations and another two had a health care background (nurse and paramedic) (***Table 20***). The two clinicians were both specialised in pancreatic endoscopy and had over 10 years of experience working in tertiary UK centres.

Table 20. Demographic, clinical and other relevant characteristics of the participants.

	Patient 1	Patient 2	Patient 3	Patient 4
Patients' characteristics				
Age	63	61	82	77
Gender	Female	Female	Male	Male
Cancer Stage	III	IV	II	IV
Morphine use at the time of the interview	10 mg liquid morphine as required	Simple painkillers as required	10 mg morphine three times a day	20 mg morphine twice a day & 10mg liquid morphine as required
Time from diagnosis to the interview (in months)	3.5	3.5	3.3	3.0
Personal endoscopy experience	Colonoscopy	EUS and ERCP	EUS and gastroscopy	EUS and gastroscopy
Other treatments	chemotherapy	chemotherapy	radiotherapy	chemotherapy
Previous occupation	housewife	office worker	scientist	restaurant manager
Carer's characteristics				
Age	66	65	75	74
Carer's occupation	paramedic	construction manager	nurse	hospitality worker
Carers' personal endoscopy experience	none	gastroscopy	none	EUS

Table continues from previous page

	Discipline	Type of Hospital	Population of the catchment area	Years of experience
Endoscopist 1	Pancreatic-biliary endoscopy	Tertiary Centre	1 650 000	18
Endoscopist 2	Pancreatic-biliary endoscopy	Tertiary Centre	450 000	11

Table 21. Demographic and clinical characteristics of the BAC-PAC participants who did not attend qualitative interviews.

Age	Sex	Chemotherapy	Cancer Stage	ERCP	EUS	Daily morphine use at two to three months	Reason for not attending interview
73	M	No	4	Yes	No	20 mg	Withdrew due to deterioration at month two
52	F	Yes	4	Yes	Yes	48 mg	Withdrew due to chemotherapy complications
67	M	Yes	4	No	No	36 mg	Withdrew due to chemotherapy complications
57	M	Yes	3	No	Yes	6.8 mg	Unwilling to attend interview due to emotional distress
81	M	No	3	No	No	40 mg	Unexpectedly early death
78	M	Yes	4	No	Yes	0	Memory decline and COVID-19[1]
82	M	Yes	3	No	Yes	0	Deceased during COVID-19 pause[1]
77	M	Yes	4	No	Yes	70 mg	Deceased during COVID-19 pause[1]

[1] During the COVID-19 pandemic all the non-essential research studies were paused and research staff was deployed into clinical services. Patients who were already recruited with deceased or deteriorated prior to the study's resumption, hence their interviews were not conducted.

Findings

Overall, five themes and 16 subthemes emerged from the interviews. These are summarised in **Table 22**. Due to the relatively small amount of data, the findings from the patients' and carers' interviews are interwoven in each theme.

Table 22. List of the themes and sub-themes emerged from the thematic analysis.

Theme 1	**THE EXPERIENCE OF PAIN**
	The onset of pain is variable
	Diagnostic challenges can be distressing
	Lack of appetite is not solely due to pain
	Pain is under-reported as part of a coping mechanism
Theme 2	**THE EXPERIENCE OF MORPHINE USE**
	Prejudice over morphine
	Altered sleeping patterns and the use of morphine as a hypnotic
	Lethargy is not directly associated with morphine
Theme 3	**THE EXPERIENCE OF ENDOSCOPY**
	Patient apprehension
	The sedation
	Difficult intubation
	Critique of the overall endoscopy service provision
Theme 4	**VIEWS ON CLINICAL TRIALS OF ENDOSCOPIC ANALGESIA**
	Participation is motivated by the severity of pain
	Endoscopy may jeopardise chemotherapy
Theme 5	**THE EUS-CPN FROM THE ENDOSCOPIST'S PERSPECTIVE**
	The use of EUS-CPN
	Patients' reluctance to undergo endoscopy
	Frailty and poor life expectancy

Theme one: the experience of pain

Three out of the four patients had ongoing problems with pain. The onset, the frequency and the character of the pain were variable among them, whilst their symptoms were commonly indistinguishable from other co-incidental pathologies, posing diagnostic and treatment difficulties. Oral nutrition was invariably poor and on occasions, but not always, was caused by the pain. Patients appeared with a tendency to downplay their true pain levels, and pretend that their health is better than it actually was.

The onset of pain is variable

The onset, the description and the frequency of the abdominal pain were diverse among the patients. The pain typically had an intermittent onset which, over time, intensifies and leads the patient to seek medical help. Patient four described a non-specific, constant abdominal discomfort which evolved insidiously for a few months before a CT scan was undertaken and the diagnosis of metastatic pancreatic cancer was made:

> "*I would say the current situation of pain started early, early summer, last summer (patient was diagnosed in the following December). And it usually, usually came about through after eating anything. I was suffering from a, a build up of, of wind I was burping an awful lot and, and, and as just a just, just a feeling of bloatedness and all and everything like that".* (Patient four).

In contrast, patient one sought medical help due to the recent onset of constipation, hence her first investigation was a colonoscopy rather than a CT pancreas. This patient, who had a very large 10cm non-metastatic pancreatic mass, described complete lack of pain up to one week after her diagnosis. Her pain was more sporadic, short-lived but intense and was involving the epigastric and the lumbar regions:

> *"I didn't have any pain before I was diagnosed, you see, all I went to the doctors with was constipation and that's how they discovered it, so I didn't have any pain as such then, all the pain happened after it was diagnosed. I was diagnosed, one, one week and then the next week, it, you know, all the pain and everything started, which was quite incredible actually because I would have thought that I would have, you know, felt something prior to that…I don't all, get it every day, but when I do get it, it's quite intense and it starts off obviously here (patient points at the epigastric area), and then it goes to the back".* (Patient one).

Patient three had a small 2cm tumour which was discovered incidentally. This remained completely asymptomatic for the first two months, likely due to its small size until he received a five-day course

of palliative radiotherapy. Several weeks later he developed a bleeding duodenal ulcer. He received endoscopic treatment and was then discharged home. His first abdominal pain appeared soon after his return to his home which became much more frequent in the weeks to come:

> *"So I came home and there was, there was no pain really, odd, odd little bits but not, not anything and then suddenly it started to kick in my, my tummy, I got abdominal pains in my tummy".* (Patient three).

Diagnostic challenges can be distressing

Co-incidental abdominal problems, such as constipation, peptic ulcer disease or irritable bowel syndrome, may complicate the clinical picture by mimicking pancreatic symptoms. This is a challenging problem for the doctor who has no clear explanation to provide to the patient and may have to do several "trial and error" attempts to manage the symptom. Oral antacid drugs, laxatives, pancreatic enzyme replacement tablets and painkillers are often prescribed. Some of them may have a competing effect to each other, for example painkillers may aggravate constipation. From the patients' perspective these diagnostic and therapeutic conundrums are perceived as signs of severity and refractoriness and, in combination with their fragile psychology, they may cause significant distress, adding to the overall climate of uncertainty. We see this in patient's three description of his team, including GP and oncologists, discerning the cause of his pain and discomfort:

> *"I reported it and the GP thought it might just be constipation and the (University Town) (in the clinical trials unit) people thought that it was multi-factorial. It could be the, the tumour returning, of course, or it could be constipation or it could be something to do with duodenal ulcer and I forget what the other thing was but there were four things that were possibly causing it".* (Patient three).

Patient four in addition to his pancreatic cancer, he also suffered from chronic pancreatitis and chronic gastritis due to alcohol excess. His doctor tried to address the entire array of symptoms that he was experiencing, advising the use of hot water bottle and anti-acids and even irritable bowel syndrome was considered as an alternative explanation for his symptoms. This lack of effective symptom control was distressing to the patient. When we asked him to give a description and how he manages it he gave a particularly graphic description of how he would literally physically manipulate his abdomen and use a hot water bottle to try and alleviate the pain. In describing the difficult nature of his diagnosis in relation to his past medical history he also highlights how any previous treatment 'didn't even seem to touch' this new pain:

"I was advised by one of the doctors that I spoke to, when I've actually got talking to the doctors to use a hot water bottle on my stomach to try and alleviate if you like, but I found I was, kind of seem to be if I manipulated my stomach area could actually move, move the pain around if you like it seemed like there was pockets of pain or lumps of pain around in the in the in the stomach area….I've been taking for years Gaviscon. And before that it was Zantac….these didn't even seem to touch it really… And they were talking about irritable bowel syndrome and all that sort of stuff". (Patient four)

Lack of appetite is not solely due to pain

One way or another appetite was mentioned by all four patients. Whilst for some pain was directly linked to eating and therefore appetite, for others the link was less clear cut. Patient four reported aggravation of pain in direct response to eating, stating:

"A*s soon as I take anything inside me like this morning after breakfast I felt quite uncomfortable and bloated but then I haven't been eating a great deal so that was just too much if you like in in one day, I don't know. My porridge this morning was really quite uncomfortable to, to live with for a little while...I'm also scared of eating because of what it does to me. See what I mean? Although it's not stopping me from eating. I'm certainly not eating as much as I should be eating anyway. Yeah. But the weight loss is obviously there".* (Patient four)

On the other hand, the other patients suggested that their lack of appetite was not directly attributed to pain. Patient two who did not have any pain said they now 'feel full up a lot quicker… I am forcing myself to eat but I'm not enjoying it'. Patient one associated the lack of appetite with the emotional instability at the time leading up to chemotherapy, whereas patient three saw the relationship between eating and pain as more complicated and seemed to feel it was more coincidental than directly relatable:

"I didn't have an appetite, I felt sick the whole time, but I think that, what it was, when I first started the chemo, because I wasn't, I didn't know what to expect and I just felt sick all the time, not in pain, just felt sick and just the thought of food actually made me feel so sick, I couldn't even look at food". (Patient one)

> "It doesn't correlate with that (eating), I wouldn't say that I'm go, that I'm eating and I'm going to get pain, I'm not, I don't associate the two things but it, it's so, as it happens, it is to do when I eat, you know, too. I mean, I, I did have some breakfast this morning, I had porridge of course, yeah, and but other, other times when I've eaten, it hasn't returned the pain, the morphine seems to sort it". (Patient three)

Herein, we hypothesized that pain is aggravated by eating and patients reduce their food intake in order to prevent pain. This phenomenon was observed in the above analysis, however, other factors other than pain, seem to be contributing to the lack of appetite, too.

Pain is under-reported as part of a coping mechanism

Patients are not always transparent about their pain. Knowing that their survival is limited to a few months, they have a tendency to under-report their true pain levels in order to convince themselves and their relatives that they are not affected much by the cancer. This denial appears to be a coping strategy they unconsciously develop in order to maintain their optimism and get through this difficult time. Such a concept becomes apparent by reading patient one's statement:

> *"I only take two Paracetamol in the morning and, and that sees me through all whole day, whether it's a mindset or not, I don't know, because I am actually trying to be very positive about this and, as far as I'm concerned, I haven't got it and I'm treating life as I did in the past, so whether it's, as I say".* (Patient one)

This behaviour pattern, though, cannot remain unnoticed by the carers who identify patient's discomfort through their mannerisms and body language. This can create additional concern to the carer who cannot judge the exact seriousness of the patient's condition. Carer three admitted that: "It's really difficult to judge… I would say that, noticing his demeanour, I would say that the pain comes and goes." Similarly, carer one expressed his concern for his partner being in pain saying:

> *'From my point of view, you, you, you absolutely have a worry because you don't know how much pain they're (the patient) actually in, although she says, oh well, you know, sort of, oh it's, sometimes it's just a niggly pain, and then sometimes it's, it's, it's a bit more and it's uncomfort, you know, it is uncomfortable, so you, there, there's no real way that you can know just how much pain she's in, she is in, so that, you've, that, you know, you obviously find worrying and if, if she's in, if she's in more pain, I obviously, the way, the only way I actually know is because then she'll turn round and actually take the morphine, which she doesn't in general, so that's the only way that sort of I can really judge how much pain she's, she's, she*

might be in. So it is, it is awkward to actually really, to realise how much pain she would be in, you know.' (Carer one)

Theme two: The experience of morphine use

There is a general prejudice against morphine from non-medical individuals, either because it is perceived as a last resort or because people associate it with addiction. However, in this small sample of individuals, this prejudice was overcome rapidly as soon as moderate-to-low dose opioids were given and the pain subsided without side-effects. Further analysis revealed that morphine has a positive effect over the patients' state of anxiety and was also helpful as a hypnotic. In contrast, the fatigue and lethargy that all the patients suffered from did not seem to be directly associated with the morphine use but it was more associated with the systemic effects of chemotherapy and the burden of the disease itself.

Prejudice over morphine

The prospect of the morphine use was a matter of concern for most interviewees. According to them, this concern appears to be bi-dimensional; firstly, to them, morphine signifies terminal illness and secondly it is associated with the risk of addiction. Patient three had an extensive family history of cancer and many of his relatives had to have morphine during the terminal phase of their illness. Inevitably, it was a shock to him when doctor announced that he needs morphine himself:

"Well my association with it (i.e. morphine) has always been the terminal stages, you know, my father had cancer, my mother had cancer, my brother had cancer, so I mean I've always associating them (i.e. morphine preparations) with the, the, the, the pain and so on". (Patient three).

Patient two did not have to have morphine so far, however, her in-laws had morphine in the past, during their terminal illnesses and she talked about these experiences. Her father-in-law had cancer and he was suffering severe pain for which he used to take high doses of morphine which was causing him serious side-effects. Her mother-in-law died of pulmonary oedema and during that terminal event she was requiring high dose opioids to comfort her dyspnoea and chest heaviness. According to the patient, the mother-in-law was resisting morphine while she was remaining conscious because of her husband's previous bad experience. She eventually had morphine herself only when she lost consciousness at the very last days of her illness and her next of kin gave consent on her behalf for a syringe driver. Although we cannot be sure whether these symptoms were truly due to morphine or

due to the end-of-life itself, it is a fact that these had led patient two to develop a substantial fear over the use of morphine:

> *"She'd been in hospital a while before they started administering the morphine. And they did that towards the end of her life. And in fact, she wasn't actually able to give her consent to it. My husband actually gave his consent for her to have it because she was in so much pain. And also she'd seen her husband die with morphine. So she knew the side effects. And she resisted having it... it's, it's a last resort, I think, rather than actually a good thing".* (Patient two)

Finally, the fear of addiction to opioids was reported by patient three when he said:

> *"I had been a bit worried about the addiction problem with morphine but that's just a prejudice…It was just sheer prejudice because Ian Jury, the singer, used to, when he was singing, at concerts, take it all the time and I kind of knew him in London, when he was fighting his cancer but he was still singing, you know".* (Patient three)

Despite his original reservations, patient three reported a good effect from his morphine saying his doctor *'put me on it and it certainly helped, you know'.* Carer four reported that after some initial adjustment to the morphine dose and type the patient could eventually feel a clear analgesic benefit with no side-effects. Further discussions uncovered another dimension of morphine use: chemotherapy is a systemic treatment which causes constitutional symptoms, among which are generalised discomfort and pain. Therefore, morphine becomes even more important to patients on chemotherapy. Carer four flagged this matter up with the following statement:

> *"You (patient four) started on liquid morphine and you seem to have no effect whatsoever. Then you changed on to the zomorph with the paracetamol and that's when the pain subsided. But since then, because he's still suffering he was well, he was after the first chemo still suffering quite bad stomach pains… it certainly seems to have helped with the bloating and the pain".* (Carer four).

Altered sleeping patterns and the use of morphine as a hypnotic

Sleeping disturbances were reported invariably by the four patients, although the way their sleeping pattern is affected was different. Difficulty to fall asleep or awaking up in the middle of the night was reported by patients one and two but this was due to anxiety and the use of steroid treatments rather

than the impact of pain. Patient four faced sleeping issues mainly due to the profound diarrhoea caused by the chemotherapy and again pain was not in any obvious way associated with his insomnia. Patient three reported having several daytime sleeps to fight his general exhaustion. Carer one admitted his wife's erratic sleep has an impact on him, too:

> *"Yeah, she's having trouble sleeping, it's, and so I think, to a, generally, we're, we're probably both kind of erratic sleepers now, because if she's, she gets up".* (Carer one).

No doubt, the enormity of the diagnosis poses a significant psychological burden. Patients described how they time their morphine administration so they benefit from its relaxant and hypnotic effect. Patient one characteristically stated that:

> *"The reason why I take that at night is because I'm thinking that it is helping me sleep, even if it is only for an hour or two hours, it is helping me sleep".* (Patient one).

Patient three said about his use of morphine that he *'would take, take some, a small amount 1.5 ml or something and then go to bed and sleep it off and it was fine'.* Overall, the analysis cannot support the hypotheses that patients in this small sample remain awake as a result of intractable pain, neither that they sleep in excess due to the sedative effect of morphine. Instead, lack of sleep appears to be the result of a state of anxiety which morphine helps to address due to its anxiolytic effect.

Lethargy is not directly associated with morphine

We attempted to explore the levels of fatigue the patients experience and whether the fatigue may be caused by morphine. Indeed, all the patients reported general weakness and lack of energy and they had to step down from tasks that they used to do in their pre-morbid life. These tasks are, from now on, taken up by their carers. The fatigue seemed to be the result of the general health decline, rather than a direct consequence of either the pain or the morphine use. Patient four, for example, reported extreme lethargy, however, according to him this mostly coincided with starting chemotherapy rather than morphine.

> *"It's not so much pain now. I think what I'm what I'm what I'm feeling generally is just totally tired and drained and weak, very, very weak. It seems as though I can hardly do anything sort of physically start to feel very tired very quickly... So I feel a general a general tiredness lethargic weakness. Since I've since I started chemo".* (Patient four).

This was confirmed by his wife's statement on the subject:

> *"Well, as I'm having to do the cleaning and the garden there. He said, he would just do a bit of vacuuming. And within half an hour, he just had to stop. He just he was just shattered. So really, he can't do those sorts of things… So I can't link the tiredness with the morphine because the morphine was done. Started that three weeks before. And he didn't have any indication of the tiredness".* (Carer four).

Similar descriptions regarding the activity levels were obtained from other patients and carers, although the degree of decline was variable. The psychological component of fatigue was also highlighted alongside the day-to-day impact on carers:

> *"There was a decline in activity, decline in energy levels, decline in psychological I think, I mean psychologically there was a fairly rapid decline as you come to terms with the diagnosis. So, and she's not been able to do much, I do all the housework, I do pretty much everything really, it's not because she doesn't want to do it it's purely due to her physical inability to be able to do it, so she's never been lazy ever and she's always be highly active and in fact on her seeing somebody now who's or at the beginning pretty moribund really, but as time's gone on she's become more come out of herself a lot more and she's been engaging more with sort of life generally. Christmas we had our family with us and I think that helped an awful lot, and she does try and do things if I go out walking the dog I might come back and she's hoovered or something but, which is kind of like a bit of a big deal for her I think at the moment so from my point of view, I'm expecting her to do nothing but leaving her to do whatever she feels she can do".* (Carer three).

> "*Bits and pieces, yeah, bits and pieces, I do but generally, she'll, if I'm doing something, which I don't normally do, if she's not feeling well, she's, won't have a problem with it, but if, if she's feeling alright, she'll turn round and say, oh well don't, you know, what you doing that for, don't do that, so she's, she's been amazing quite honestly with it. So I a little bit, a little bit but no, not massively so, just in small, in small ways, in, just in small ways".* (Carer one).

Theme three: The experience of endoscopy

All four patients and some of the carers had endoscopic investigations as part of their cancer investigations or for previous illnesses. Those included gastroscopy, colonoscopy, Endoscopic

Ultrasound (EUS) and Endoscopic Retrograde Cholangio-Pancreatography (ERCP). The most common concern was the fear of what the findings may be, whereas physical discomfort was only ascribed to intubation of the upper gastrointestinal track. Besides this, all patients stated that they received the correct amount of sedation which kept them comfortable during the procedure. Praise was also given to the service for the pre-and post-procedure explanation of the risks, benefits and findings, respectively.

Patient apprehension

Patient two had an ERCP. She described how she was feared of the unknown and was also concerning of what the findings might be. On the other hand, she described the actual service provision with very positive words:

> *"It was okay, I was very nervous when I went in, but obviously with the sedatives that they give you, I was aware and I could hear the nurses and the doctor talking but it wasn't painful at all, I didn't feel it… The unknown really, you know, having a tube put down your throat and totally unknown… The thought of having a tube fitted down my throat and the thought of fishing around inside my body was a bit alien, but I was completely out of it, so I didn't feel it at all".* (Patient three).

The sedation

Patient four had a gastroscopy under local anaesthetic followed by an EUS under sedation. He has very sensitive gag reflex, making intubation very uncomfortable. He explained how big difference the sedation made in his second endoscopy. Despite the discomfort, he admits that he would endure another procedure if that was for a justified reason:

> *"It certainly wasn't the most pleasant experience of my life. The first one (diagnostic gastroscopy), the first one was very very uncomfortable. I found it very very uncomfortable. But I choose I chose not to have the the injection (means sedation) or whatever it is that I chose just to have the (anaesthetic) spray down the throat that was very, very uncomfortable. The second one (diagnostic EUS with biopsies) was less uncomfortable but it wasn't anywhere near as long either. I think they would just aim down there to specifically look at the tumour and get a biopsy. But it was it's not a comfortable experience… So it's a bit embarrassing (being in discomfort), but you know, you have to go through these things… I'll go through it obviously I'd have to go through it but i mean you know it I wouldn't it be looking forward to*". (Patient four).

His wife confirmed that she would support him towards a second endoscopy, if needed:

> *"(My husband) was alright, with it (endoscopy), really, he would have another one if, you know, needed".* (Carer four).

Patient three stated that the sedation was wearing off but even then she did not feel any discomfort:

> *"There was one slight hiccup where I coughed and the doctor had to give me more anaesthetic so obviously the anaesthetic was wearing off, was wearing thin and I started to cough and he obviously didn't want me to cough at that time, you know, but I didn't feel a thing".* (Patient three).

Difficult intubation

Two participants (one patient and one carer) described intubation as the most uncomfortable part of the procedure due to the gag reflex. Patient four said:

> *"The biggest fear is even when I, you know, go for a COVID test or swab. Anybody who goes anywhere near me mouth on the nose, and I start gagging. I just I just, it's just a natural thing with me, I'll just gag".* (Patient four).

Care one said:

> *"They numb, numb the throat and then you're, you're trying to swallow and yeah, not the most pleasant thing but I don't know".* (Carer one).

The rest of the participants did not report any other complaints when they were asked about the procedure itself.

Critique of the overall endoscopy service provision

Patients were asked their opinions on the strengths and weaknesses of the endoscopy care they received. The patients were given appointments on time and they were satisfied with the explanation they were given before and after the procedure.

> *"Alright, I had no, no problem with it (the overall service), didn't wait very long, it was, it was alright… Yes, oh yes, I didn't feel anything*". (Patient one).

> *"The scan was brought forward because I was in the hospital, they obviously fitted me in when they could do and I think the endoscopy was done quicker as well than my original appointment because I was there already…He (i.e. the endoscopist) came down to see me*

before the endoscopy and explained what would happen and there would be nothing to worry about". (Patient three).

"*I've got no, I've got no problem with, with what was explained to me. And what they were looking for what they were gonna do. Now, yes, I think it was fine. Now. The risks were explained to me and I'm quite happy with them".* (Patient four).

Theme four: Views on clinical trials of endoscopic analgesia

The patients were asked to share their thoughts on a clinical trial of endoscopic analgesia, if participation was offered to them at the time around the interviews. Their views were that pain controlled by small doses of morphine is acceptable and therefore an endoscopic procedure in this setting is not justified. Due to the nature of the disease, the patients were more focused on imminent problems, such as their chemotherapy side-effects, and they could not see the risk of pain deterioration and morphine dose escalation in the months to come. Participation in a trial was seen as an opportunity to receive a more advanced treatment, if pain becomes intractable, rather than a preventative measure. Moreover, participation in an endoscopic trial around this time would coincide with cycles of chemotherapy. This can be overwhelming for patients and, if a complication occurs such as a bleed or infection, may interrupt their chemotherapy.

Participation is motivated by the severity of pain

Patients stated that such a trial would not appeal to them unless their pain was becoming intractable:

"*If the pain was that intense, but the way the pain is at the moment, it's manageable with Paracetamol and the Oramorph but no, it's so, no, I'd, I wouldn't but if, if the pain was really intense, then yes, of course, you, you do anything, don't you, to relieve pain".* (Patient one).

But the above quote also reveals another important methodological issue; participation to a trial is seen as an opportunity to receive the procedure. This raises the question of whether patients would accept randomised treatment allocation to the intervention and control groups and if they would remain engaged with research follow-up if they were allocated to the latter. We explored this question with the patients whose answers mainly imply that drop-outs should be expected. The following conversation was retrieved as a characteristic example:

Interviewer: "At some point, we want to do a trial where half of the people get endoscopy for pain relief, and half of the people they will get no endoscopy, so they will rely on morphine. Do you think this might be a problem to patients?"

Patient two: "With me no. I want to try anything really"

Carer two: "What he is saying is that you might get placebo or you might not get the endoscopy. Like just hang up on a comparison. "

Patient two: "Okay, I'd go for the endoscopy first."

Carer two: "You may not have a choice."

Patient two: "Okay, yeah. I don't know."

Endoscopy may jeopardise chemotherapy

Another issue is that such a trial could interfere with chemotherapy. The patients and their families are well-aware that chemotherapy is the main life-prolonging treatment but, at the same time, it requires an enormous amount of resilience to get through. It involves frequent journeys to the hospital, interval scans, care for a semi-permanent venous access line and severe side-effects after each cycle which make people feel very unwell and, in general, is a both emotionally and physically demanding period for them. During this time, they live with the constant fear that chemotherapy may at any point be discontinued for a series of reasons. For example, a patient whose endoscopic procedure is complicated by a perforation, a thrombosis or a gastrointestinal bleed will have to either temporarily suspend or terminate indefinitely their chemotherapy. They also described how fragile their psychology was with the prospect of any unfortunate changes to their care plan which may indicate an even shorter life expectancy. All these factors make patients wary of potential new therapeutic options which might not have imminent benefit.

"The doctor has assured me that it it will buy me time... I want to carry on with the world. Before I, I think they haven't gone so far, I don't think I want to be messed about anymore if you like. I've got a, I've got to give what I'm having. I've got to give it enough and give it a chance. I don't really want to change anything at this stage…I had discussions with, with my wife and the doctors that were prescribing me originally for this chemotherapy. I'm gonna have to put my faith in them. That's what I want to do". (Patient four).

"There's just so much, we spend most of our time up and down at A(road)… I know if I understand with chemotherapy. Well, this particular one, you know, some people suffer badly to start with some people, or some people later on some people not at all. And we obviously don't know what what you fall into on that one, anyhow, but they, it's very much a learning game for us… you know, assuming one is guaranteed that the process could not cause any other side effects." (Carer four).

On the other hand, carer four did admit that her and her husband have an overall positive attitude towards clinical trials and they would reconsider their position if they achieve a feeling of stability with the chemotherapy at a later stage and if the need for better analgesia was becoming more prominent:

> *"Maybe if he can get through the next couple of chemos, he would be up for that kind of thing (i.e. endoscopy trial). But as he says at the moment, he's not, you know, suffering. I don't think it's this sort of right now: No, no, I wouldn't under any circumstances! But he's suffering quite a bit (i.e. with chemotherapy side-effects) at the moment that really just taking on anything else."* (Carer four).

Theme five: the EUS-CPN from the endoscopist's perspective

The interviews with the clinicians directly involved in the delivery of the EUS-CPN, revealed that the procedure is currently used as a rescue therapy when opioids have failed. The many patients who develop severe pain after being discharged from the hospital may never be offered the option of having the procedure. Early EUS-CPN may be justifiable as a method of prevention for high dose opioid consumption. However, it is important to look at each patient's pain trajectory to decide who is likely to benefit from an early procedure. The poor survival and frailty are not absolute contraindications, but a matter of a case by case fitness for endoscopy assessment.

The use of EUS-CPN

The referrals for EUS-CPN arise from various sources. Most commonly, they are patients who are referred from the primary care with pancreatic symptoms and need investigations for pancreatic cancer. For those who have severe pain at diagnosis, CPN can be administered at the same time of the diagnostic EUS. An alternative scenario is that patients develop pain at a later stage, while they are under the care of the oncologist or the palliative care physician, and are referred to the pancreatic clinic because opioids have failed to control pain. This group of patients are very keen to undergo an endoscopy, regardless the general state of their health, as they have long been suffering from uncontrolled pain:

> *"We clearly get referred those who are finding it intolerable with their medication or the pain isn't well enough controlled, so they're a bit desperate and therefore will take anything".* (Endoscopist one).

Some patients are never offered the option of an EUS-CPN, because by the time they develop pain they are discharged from the hospital and they are managed by the community palliative care:

"As you know, most of these patients, I think personally, they're given opioids and are discharged to community palliative. I don't think all are giving the option to have the CPN." (Endoscopist two).

However, the clinicians recognise that a better use of EUS-CPN may be to administer it at an earlier stage, before high dose opioids are instituted. If EUS-CPN is delayed, the patient may already be very dependent on opioids and this dependency may not be reversible. In addition, their general health may decline due to cancer progression or they may be deconditioned as a result of the chemotherapy, so their fitness for an endoscopic procedure may be reduced:

"I guess, once you're under opioid, it's really hard to get off them, but actually if someone has a really good response from CPN, they may actually only be on ten milligrams, twice a day, or something like that, of MST, whereas the other patients tend to escalate up to sixty, seventy…The effect of a CPN not just, it makes the pain better but it stops them having more side effects from the drugs that they're taking or that's the, that's the, the, the hypothesis anyway, that's what we're going to help… so preventing someone getting on to a high dose, I think would be a good thing…If you get them early when they're still fittish, you know, or are fittest when you first met them, you know, if you wait for a while, all that's going to happen is they're going to deteriorate and deteriorate because they may get chemotherapy and often de, chemotherapy even de-conditions people further, so you, you want to catch them earlier on, whether, you know, there's going to be other things." (Endoscopist one).

Patients' reluctance to undergo endoscopy

The scepticism of patients towards an early EUS-CPN, was brought up for discussion with the clinicians. It was acknowledged that many patients with mild pain will probably avoid the option of an endoscopy. Endoscopist one suggested that this can only be addressed if we try and see the trajectory of each patient and their individual likelihood of requiring higher doses of opioids in the coming months when other parameters, such as nutrition or response to chemotherapy, will have changed. In addition, all the disciplines involved in the care of these patients will have to be aware of the option of an early EUS-CPN and make a collective effort to encourage selected patients in this direction:

"Educating CNS (cancer nurse specialist), educating the palliative team, educating oncologists, then they say, Okay, yeah, there is another option of treating the pain." (Endoscopist two).

However, the most important consideration to be made is to explain to the patients that higher doses of opioids will probably be needed in the near future and that EUS-CPN may help to prevent this from happening, although its success is not guaranteed:

> *"It's largely based on their symptoms and their expectations on what we think we're going to be able to deliver and the quality of life, because again, some people turn up thinking we're going to do some magic where, you know, we're, we're really going to be treating their pain and that's really what it's for."* (Endoscopist one).

Frailty and poor life expectancy

As many of the patients are approaching their end of life, their general health is severely impaired. The endoscopists' perspective was that the EUS-CPN is by definition a palliative procedure and therefore, the poor performance status or the limited survival is not a contraindication *per se*, but a more individualised approach is necessary:

> *"If someone's performance status three or four, well certainly four, I don't think we'd want to consider it (i.e. EUS-CPN), they're, they're very much at the end of life… the other thing, sometimes stops us from doing an endoscopy is about the actual practicalities, some patients, you know, they're, they're too breathless or they're too, they're clearly too frail, we do have to make this assessment, so we have our patients turn up, we think, you know, we've made the wrong, or someone has not appreciated what it means to undergo this, it's not a nothing procedure, it's still got some risks and what have you, you've still got to get through it."* (Endoscopist one).

Poor life expectancy, even if it is as short as one month, is not an absolute contraindication itself, but indeed EUS-CPN is not indicated for those who have end of life symptoms:

> *"The main worry I have is sometimes you get referred somebody who's clearly, you know, pretty much dying and the last thing you want to have is someone to die on the end of your scope, that's, that's not good and I could justify someone dying within a month of having a CPN, if it made their pain relief perfect for the last month, I think that's fine". (*Endoscopist one).

DISCUSSION

Main Findings

To the best of our knowledge, this is the first qualitative study to investigate the impact of pain in patients with inoperable pancreatic cancer. The main finding is that mild to moderate pain that is well-controlled with lower doses of morphine is acceptable to patients and endoscopic analgesia, from a patient's perspective, is not justified. The benefit of morphine is not limited to the relief of the pancreatic pain, but instead it has broader effect, including relief of the systemic discomfort caused by the chemotherapy as well as anxiolytic and hypnotic effects. Overlaying gastrointestinal symptoms, such as constipation or IBS, may complicate the clinical picture and add to the overall psychological burden of the disease. Pain may affect eating to some degree but cachexia is not solely attributed to pain. The exact magnitude of pain is difficult to ascertain as the patients under-report their symptom as part of a defence mechanism, similar to concept of denial[224]. People associate morphine with terminal illness and are reluctant to use it, however this perspective alters when they start experiencing the analgesic benefit of it. Endoscopy is unpleasant but people are willing to repeat it if it is necessary. Clinical trials of endoscopic analgesia versus opioids alone may face three main methodological challenges; patients with mild to moderate pain may be unwilling to attend, participation to a trial is mainly seen as the opportunity to receive an advanced intervention, so it is unknown how well people will engage with the trial activities if are allocated to the control group, and, finally, patients are more likely to avoid other activities, such as an endoscopic trial, which may risk suspension or termination of their chemotherapy. From the endoscopist's perspective, early EUS-CPN is a justified approach to prevent escalation of opioid doses. Looking at each patient's trajectory, i.e. who is likely to need high doses, is essential for appropriate patient selection and may help discussions with patients who are hesitant to undergo an endoscopy before their pain becomes severe. Poor life expectancy or the frailty are not absolute contraindications and it is the matter of case-by-case decision making.

Interpretation

Overall, patients have the tendency to emphasize their imminent clinical concerns such as chemotherapy side-effects (diarrhoea, fatigue, stomach upset) and the anxiety of their inevitable premature death. Hence well-controlled pain features lower in their list of priorities. This became very apparent in the interviews where patients were steering the conversation away from the pain and endoscopic analgesia and they were more proactive in talking about their most imminent concerns. From previous research, as well as clinical practice, it is known that the opioid doses tend to increase

over the months and nearly triple from diagnosis to end of life[119]. However, patients in the first few months of their illness do not view future pain as a pressing issue in the present, whilst concerns such as the chemotherapy side-effects dominate their thinking[119, 188]. This study has not answered whether patients might change their views if deterioration occurs in the months to come. This could be answered if follow-up interviews were undertaken towards the end of their life. Unfortunately, this was not possible partly due to research capacity issues as well as due to COVID-19 restrictions which prohibited face-to-face contact. Another important finding was the multi-dimensional role of morphine: analgesic, anxiolytic/hypnotic and soothing the chemotherapy discomfort. Therefore, even if endoscopic analgesia could be used to address the organic component of pain, it could not replace morphine's multi-dimensional effect. Recruiting patients for a clinical trial of an early EUS-CPN versus opioids may have several challenges. These patients are recently being told that they have only a few months to live and they see themselves declining day-by-day. The psychological burden they have to deal with is so significant they may not have the mindset to discuss participation in research activities. In addition, the chemotherapy, which is their main hope for a longer survival, is an emotionally and physically demanding process, leaving very little room for other activity (such a trial of endoscopic therapy).

Strengths

This study had the benefit of including patients from a representative for the condition age group, ranging from 63 to 77 years of age[39]. Their cancer stages covered a wide spectrum, from potentially operable (Stage II) to locally advanced (Stage III) and metastatic (Stage IV). Previous research in this field has shown that patients tend to hide the true magnitude of their symptoms[225], therefore interviewing partners opened an opportunity to explore the real severity of pain from a different perspective. The timing of the interview gave the opportunity to the participants to accrue experiences of the disease and reflect on them but also it is representative of the timing they would normally be invited to participate into a clinical trial.

Limitations

Attention should be paid to the limitations of the study when the results are interpreted. Firstly, theme saturation is unlikely to have been achieved due to the small number of participants: therefore, theses findings are unlikely to be broadly generalisable despite providing helpful insights. Secondly, all these patients had mild to moderate pain levels and their symptom were under reasonable control with moderate doses of morphine. As a result, pain was not at the top of their treatment priority, whilst none of them had significant morphine toxicity due to the use of moderate doses. It is plausible that

their views and opinions could be seriously affected if they were suffering from excruciating pain. Ideally, follow-up interviews at later stages could have been helpful to answer this question, however, this was not possible due to time constraints brought about by the COVID19 pandemic. Attempts to interview patients with more severely impaired health status were made, however, video-conferencing with them was impractical and was abandoned. It would be very helpful if these interviews could be conducted face-to-face with the researchers vising hospices or patients' place of residence, but this was not allowed due to the COVID-19 pandemic.

Relevance with existing literature

There is no previous qualitative research exploring pain specifically in pancreatic cancer, however, similarities and differences can be found in studies exploring cancer symptoms in general. Previous research confirmed that pain has multiple facets and is not always easy to define or describe. In a previous paper a patient stated: *"Pain is more than a physical symptom; it is spiritual and social as well"* [189]. In line with our findings, this quote implies that the physical suffering is inseparable from the emotional or the spiritual suffering. Some patients went even further to suggest that: "*physical pain is the lesser of two evils*". Therefore, although the EUS-CPN may be the remedy to the somatic component of the pain, pain relief cannot be achieved if the emotional part remains unaddressed. Another qualitative study showed how the anticipation of physical symptoms can be more distressing than the symptom itself: *"Sometimes I get anxiety attacks over it, I don't want ever to go back to being in pain again"*[226]. Coyle *et al* conducted semi-structured interviews in patients with various cancers, including lung, prostate and hemopoietic, exploring the experience of pain and opioid use. In contrast to our study, these patients were at the terminal phase of their illness, hence they articulate different thoughts and experiences to our participants[227]. These patients stated that their pain was so intense that they were *"losing their will to live"* and that the thought of dying was causing them agony:

> *"Pain is my biggest fear because it blocks out… it puts me in a darkness and a lack of will to go forward and a desire to die…the, the pain wants me to have a vehicle to just, just to stop my life. If I could press a button, take a pill, I'd do anything. I just don't want to exist anymore having the pain… I just want to stop it, I want it to be over with…the pain has a finality to it that I want to stop right there…no matter how much good there is left, no matter how much I could enjoy the… I wanna go… I want to be out of this body…You can't find it (inner peace) in that darkness of pain… I can't emphasize that the pain blinds you to all of that, blinds you to all that's positive. I mean the real bad pain… it just closes you down. You just can't get through it…it's an iron door and it's one thing you don't wanna go through it you just wanna, wanna stop"*[227].

A similarity with our study was that patients associated opioids with side-effects with one of them specifically referring to the cognitive disturbance the opioids can cause with these words: *"I was worried I would lose myself"*. However, as death came closer, analgesia became uppermost in their minds and the opioids were described as "*a welcome means of hastening death"*[227]. Another contrasting finding to ours is that patients associated the lack of energy and the low mood with the presence of severe pain: "My moods really depend on how this feels… when it feels better I function and when it feels worse I don't. So it's like the physical dictating our moods…". Another mutual finding to our theme that Coyle *et al* identified was the patients' fear over the chemotherapy discontinuation and the concern that withholding chemotherapy may result in *"valuable time being lost"*[227]. The determination to continue chemotherapy was so strong, that one of the patients was hiding his symptoms from his care team, so the treatment was not withheld:

> *"I accepted the pain because I wanted to receive it (chemotherapy)… from Friday to Saturday to Monday I waited (in pain) because I figured that if they treated me for pain I wouldn't be eligible for the drug (meaning the chemotherapy)"*[227].

Overall, the comparison to the previous literature reveals that some perceptions remain the same during the course of cancer, such as the reluctance to initiate opioids or the keen interest to continue chemotherapy at any costs, but it also demonstrates that patients priorities change dramatically depending on which symptom is the most dominant at each stage of their disease.

Implications for research and practice

Pain in patients with inoperable pancreatic cancer has organic, emotional and spiritual components. Morphine despite its side-effects has a multi-dimensional role, including anxiolytic and hypnotic effects, in addition to relieving constitutional effects of chemotherapy. Patients are more likely to want to avoid an early EUS-CPN if their pain is well-controlled. Extrapolating from other cancers, it is possible that this attitude may change when pain deteriorates in the later phases of the disease when patients are willing to try anything to get rid of the pain. This is because the time after diagnosis is a very emotional period with many physical, psychological and practical challenges which they need to overcome. The patients' mindset is more focused on addressing imminent concerns rather than thinking to the future. Offering an early EUS-CPN may be medically justified for the prevention of the opioid dose escalation, however, this may be contrary to the patients' agenda. In relation to the design of a clinical trial of early EUS-CPN versus standard care, patients may resist an endoscopic intervention while they are on chemotherapy, either due to overwhelming fatigue or because they fear complications which can lead to discontinuation of their treatment. A major conclusion drawn from this work is that a future trial of early EUS-CPN will need to be designed taking into account all the

above factors- emotional, physical, practical and behavioural-. Therefore, PPI involvement will be required from the outset and effective communication around treatment allocation processes will be critical to ensure successful recruitment.

CHAPTER 5- The burden of abdominal pain in patients with inoperable pancreatic cancer and the prediction of opiate use based on clinical, radiological and cytological characteristics: a retrospective cohort study (The PREDICT- PANC study).

ABSTRACT

Background. The epidemiology and aetiology of pancreatic cancer-related abdominal pain are not well understood. Patients who are treated with opioids may experience serious side-effects. The role of the endoscopic analgesia in the form of the Endoscopic Ultrasound-guided Coeliac Plexus Neurolysis (EUS-CPN) remains unclear in terms of patient selection and timing of administration.

Objectives. For patients with inoperable pancreatic cancer we sought to estimate (1) the prevalence of pain requiring opiate use; (2) the absolute and relative survival in opiate users compared with those not taking opiates; (3) the health performance status of patients using opiates; (4) the association between demographic, clinical, radiological and cytological characteristics with opiate use by three months in patients with pancreatic cancer; and (5) the performance of a multivariable model predictive of pain.

Methods. This was a single-centre retrospective cohort study of patients with unresectable pancreatic adenocarcinoma with a minimum survival of three months. Prevalence of opiate use was estimated at three monthly intervals following diagnosis. Kaplan-Meier curves and Cox proportional hazard regression estimated the absolute and relative survival of patients according to opiate use at three months. Logistic regression estimated the association between clinical, biochemical, histocytological and radiological variables for the outcome of opiate use by three months. Model performance was assessed with ROC (Receiver Operator Characteristic) analysis, a calibration plot and the Hosmer-Lameshow test. The model was internally validated with bootstrap resampling. Sensitivity analysis was undertaken to assess the ability of the model to predict use of ≥60mg of opioids per day.

Results. Overall, 383 patients were included in the analysis**,** of whom 146 (38%) had available radiological data. Prevalence of pain at 0, 3-, 6-, 9- and 12-months was 37%, 47%, 46%, 46% and 39%, respectively. Patients requiring opiates at three months had shorter survival times than non-opiate users (median overall survival 5.9 (IQR 4.4 to 8.8) months in

opiate users vs. 9.3 (IQR 6.6 to 14.0) months in non-users, hazard ratio for all-cause mortality = 1.83 (95% CI, 1.14 to 2.95, p=0.012). In total, 77% of the opioid users had a performance status between 0 and 2. Age (odds ratio [OR] per year 0.97, 95% CI, 0.94 to 0.99, p<0.001), pain at presentation (OR 9.57, 95% CI, 5.78 to 15.85, p<0.001), performance status of 3 (OR 2.57, 95% CI, 1.32 to 5.00, p = 0.006), tumour distance from the right ganglion (OR per mm of distance: 0.96, 95% CI, 0.94 to 0.9, p=0.004), the anterior-posterior (OR 0.94, 95% CI, 0.89 to 0.99, p= 0.042) and the latero-lateral tumour dimensions (OR 1.04, 95% CI, 1.00 to 1.08 , p= 0.048) were independent risk factors for the opioid use at three months. The C-statistic for the prediction model including clinical and radiological characteristics was 0.84. Sensitivity 78.9%, specificity 69.2%, positive and negative predictive values were 73.7% and 75.0%, respectively. The prediction model arising from the sensitivity analysis was subject to overfitting and therefore unsuitable to predict use of high dose of opioid use.

Conclusions. Nearly 40% of patients with inoperable pancreatic cancer use opiates by three months, and their use at this timepoint is associated with reduced survival. Health performance status in such opiate users should not preclude most patients from EUS-CPN. Age, pain at presentation, health performance status, tumours of the body and distance of the tumour from the right coeliac ganglion are associated with opioid use at three months. External validation of this predictive model is required.

INTRODUCTION

Clinical Problem

Pancreatic Cancer has the worst prognosis of any malignancy and there has been little improvement in survival in the last three decades[41]. Worldwide, pancreatic cancer is the 12th commonest malignancy, with 458,918 cases diagnosed in 2018[39]. In the UK between 2015-2017 there were 10,257 new cases and 9,421 associated deaths per year[40]. Most patients are diagnosed between the ages of 60-80 years with similar distribution between men and women[228]. Only 15% present with surgically resectable disease, and the remainder with locally advanced or metastatic disease[229]. Consequently, the overall 5-year survival rate of all patients is less than 5%[229]. Pancreatic cancer-related abdominal pain is a common and difficult to treat symptom. Previous research has demonstrated that 60-80% of the patients have moderate to severe abdominal pain during their illness[119, 188, 230]. The management of severe pain consists mainly of strong opioid analgesic drugs which have debilitating adverse effects[136]. Over time, the doses required to control these patients' symptoms require escalation which may lead to worsening side-effects[119]. High doses of opioids are inversely associated with survival[119, 230].

Endoscopic analgesia and limitations in the current literature

Endoscopic Ultrasound-guided Coeliac Plexus Neurolysis (EUS-CPN) is an endoscopic modality which provides analgesia by causing chemical ablation of the coeliac plexus[137]. It is effective in preventing the escalation of morphine requirements in locally advanced disease, whilst serious adverse events are rare[124, 126]. However, uncertainties remain regarding the optimal timing of its administration (i.e. soon after the onset of pain or after failure of opioids to control the pain) and its role in patients with metastatic disease. A statistical model predictive of pain could be helpful for the early identification of patients at high risk of intractable pain who could then be selected for EUS-CPN before their opioid doses are escalated.

Knowledge gap in the natural history and aetiopathogenesis of pain

Although common in patients with pancreatic cancer, the burden and pathophysiology of the abdominal pain remain poorly understood. Further research investigating its natural history is necessary to assist clinicians and their patients in decision-making with regards to pain management. Exploring aetiological associations of pain with other clinical

characteristics may lead to a better understanding of the causal mechanisms and establish more individualised treatment approaches. Such aetiological associations may enable the early identification of patients at risk of developing intractable and opioid-refractory symptoms. Early identification of those at high risk may help clinicians to offer an EUS-CPN soon after diagnosis and potentially before opioid doses are required or escalated. Similarly, a risk prediction tool could inform the inclusion criteria of a future clinical trial of EUS-CPN given at diagnosis or when the pain first occurs before opioids are prescribed.

Rationale

NICE suggests that a clinical trial of early versus on demand EUS-CPN is needed[231]. Such a trial would establish whether early administration of EUS-CPN has a role in the prevention of high dose opioid consumption in patients with inoperable pancreatic cancer. The BAC-PAC prospective cohort study, which was reported in the previous chapter, was intended to explore the justification and the logistics of a trial, by investigating the prevalence of pain, the time from diagnosis to the first opioid prescription, the survival after the pain onset as well as the means/medians and dispersions of the pain score, opioid dose and quality of life scales which may serve as trial outcomes. All these parameters are necessary to inform the design of a trial. The poor recruitment, which was partly due to the COVID19 pandemic but also due to the nature of the disease, did not allow the BAC-PAC study to estimate these parameters with accuracy. The present study intends to calculate the similar parameters as per the BAC-PAC study but with better precision, taking advantage of its retrospective design which can ensure availability of the appropriate volume of data. In addition, it intends to develop a pain prediction model to identify those patients who are at risk of requiring opioids at three months post-diagnosis which could be useful for the identification of those at higher risk of pain who would benefit the most from an early EUS-CPN.

AIMS AND OBJECTIVES

This study aims to (1) estimate opiate burden, the health performance status and the absolute and relative survival in patients with inoperable pancreatic cancer and (2) develop a multivariable model predictive of opiate use.

The objectives for the first aim are to estimate:

1. The prevalence of opioid use at baseline, three, six, nine and twelve months.
2. The incidence of opioid use at baseline, three, six, nine and twelve months.

3. The patients' fitness for interventional analgesia based on their health performance status.
4. The absolute and relative survival of patients with pain requiring opiates, compared with those not requiring opiates.

The objectives for the second aim are:

5. Estimate the association between demographic, clinical, radiological and cytological characteristics with opiate use in patients with pancreatic cancer.
6. Derive and estimate performance of a multivariable model predictive of pain.

Due to the preliminary nature of this research and study feasibility, this second aim is limited to a derivation study, with intended future external validation if appropriate, dependent on model performance.

METHODS

Study Design and Setting

This is a single-centre, retrospective cohort study, conducted in the Gastroenterology Department at the Norfolk and Norwich University Hospital (NNUH) Foundation Trust, Norwich, United Kingdom. The subjects were identified through the Somerset Cancer Register (SCR) from January 2010 to December 2020[232]. The SCR is the national cancer database of the National Health System (NHS) England where every cancer patient is registered at diagnosis. The SCR records the dates of diagnosis and death, patient demographics, results of diagnostic tests, cancer stage and treatment decisions determined at the hepato-pancreatico-biliary (HPB) multi-disciplinary team (MDT) meetings. The remaining clinical, radiological and histological data were retrieved from the patients' medical notes. The study was conducted in accordance with the guidelines of the Declaration of Helsinki and the principles of good clinical practice. The study was approved via proportionate review by the West Midlands - Black Country Research Ethics Committee on 29 March 2021 (REC reference: 21/WM/0092).

Study Population

Inclusion Criteria:

i. men and women over 18 years.
ii. radiological and/or histo-cytological diagnosis of pancreatic adenocarcinoma, confirmed by the HPB MDT.
iii. patient treated with either chemotherapy or best supportive care or both.
iv. patients who survived for a minimum of 90 days from diagnosis.

Exclusion Criteria:

i. patients who underwent potentially curative surgery.
ii. patients with chronic pain syndromes using morphine prior to diagnosis of pancreatic cancer.
iii. patients with incomplete medical record whose opioid prescriptions could not be retrieved.

Eligibility was restricted to those with at least 90 day's follow-up to enable capture of opiate burden and permit generalisability to the population who may be eligible for EUS-CPN (and would be expected to survive this period of time as a minimum).

Outcomes

Outcomes for each of the study objectives are as follows:

Objectives 1 and 2: opioid use for pancreatic cancer pain at baseline, three, six, nine and twelve months.

Objective 3: performance status at baseline.

Objective 4: all-cause mortality.

Objectives 5 and 6: opioid use at three months.

Opioid use was defined as receipt of opioid medications for the treatment of pancreatic cancer-related pain. The prevalence of opioid use at each time-point was defined as the fraction of opioid users to the total number of at risk (alive) subjects without missing data regarding their opioid use. The incidence was the proportion of patients with a new opioid prescription to the total number of patients who were alive and opioid-free in the previous three-month period. Fitness for endoscopy was determined based on the health performance status recorded in patients' notes assuming that scores 0 to 2 represented definitive fitness, scores of 3 represented borderline fitness, and scores of 4 represented lack of fitness. Other indirect measures of the fitness for endoscopy were diagnostic or therapeutic endoscopies performed at diagnosis and the administration of chemotherapy.

Case Ascertainment and Clinical Measurements

A medical gastroenterologist reviewed each set of case notes to ascertain the prescribed opioids and dose, and confirm that the pain described in patients' correspondence letters was likely to be pancreatic in origin. This was essential as other painful cancer complications may also occur, such as gastric outlet obstruction. Likewise, patients with spinal or rib metastases as well as those who were using opioids for other non-malignant reasons, such as osteoarthritis or spondylosis, were excluded. Patients were typically prescribed a fixed, basal opioid dose, as well as additional, *pro re nata* (PRN) doses for breakthrough pain. The clinic letters were reviewed to search for statements declaring the exact amount of the PRN prescription used. If a clear statement was not included in the clinic letter, it was

assumed that the patient was using 50% of the maximum PRN dose. The doses were converted into morphine dose equivalents[233].

Exposures

The following variables were assessed for their association with morphine use at three months: pancreatic duct diameter (continuous variable; mm), distance of the tumour from the left coeliac ganglion (continuous variable; mm), distance of the tumour from the right coeliac ganglion (continuous variable; mm), volume of the pancreatic tumour (continuous variable, cm^3), the latero-lateral, anterio-posterior and craniocaudal dimensions of the tumour (continuous variables; mm), the location of the pancreatic tumour (categorical variable; head, body, tail), the tumour intensity values on CT (continuous variable, Housefield Units [HU]), the grade of WHO Histological Classification (categorical variable; poorly differentiated, moderately differentiated, well-differentiated, other WHO variants), the baseline levels of the CA19-9 tumour marker and the prescription of pancreatic enzyme supplements at diagnosis.

Covariates

Age, gender, abdominal pain at presentation, cancer stage, chemotherapy treatments and major co-morbidities were recorded as plausible confounding factors. The prescription of anti-depressant, hypnotic, anxiolytic and anti-psychotic medications were recorded as a surrogate marker of anxiety and/or depression which may confound the association of the above exposures with pancreatic pain.

Radiological Measurements

The tumour location was identified through the CT reports and the International Classification of Diseases version 10 (ICD-10)[234]. The rest of the radiological data were obtained through manual measurements carried out by a specialised gastrointestinal radiologist with over 10 years clinical experience in pancreato-biliary radiology. The radiologist was blind to opioid use and the other clinical data. Tumour volume was estimated, as the multiple of their latero-lateral, antero-posterior and cephalocaudal dimensions.

The CT attenuation measurements were obtained following the methodology previously described by Zhu *et al*[235]. A circular region-of-interest (ROI) was placed within the tumour, allowing at least 1mm distance from the tumour margin. Areas of necrosis, vasculature and

ductal structures were excluded. A similar-size ROI was engraved in the parenchyma. For each ROI, CT enhancement values in Housefield Units (HU) were obtained at the portal, the arterial and the unenhanced phases for both the tumour and the parenchyma. Tumour contrast enhancement in the arterial and portal venues phases were calculated by subtraction of the tumour attenuation value on non-enhanced images. One concern was that the ROI may not correspond to the same tumour section when the images were switched from the unenhanced to the portal and then to the arterial phase images. For this reason, the relative positions of the other abdominal organs and the CT slice number were used to ensure the ROI is appropriately located and applied to the same tumour section. In addition, the absolute (AEC) and relative enhancement changes (REC) were calculated[235]. The formulas for AEC and REC are provided in **Appendix 9.**

Statistical Analysis

Descriptive analysis was undertaken with the categorical variables reported as frequencies and proportions. Continuous variables were described either as means (and standard deviation) or medians (and interquartile range) depending on their distributions. Confidence intervals for prevalence and incidence were estimated using the Binomial exact test (objectives 1 and 2)[236]. Kaplan Meier survival curves were plotted to compare those with and without severe pain requiring opiates at three months and statistical significance was examined with log-rank test (objective 4)[236, 237]. Associations between demographic, clinical, radiological and cytological characteristics and the opioid use were estimated by a logistic regression model (objective 5). Both unadjusted and adjusted models are presented. Stepwise selection was used for the construction of the multivariable models. A significance level of 0.25 was used for the selection of the variables for entry into the multivariable model, whilst a significance level of 0.05 was used for elimination from the final model. Calculations were conducted using Stata software (Version 16, StataCorp LP, College Station, Texas, USA).

Development of predictive models and evaluation of their performance

We sought to develop a clinical prediction model incorporating all the clinical parameters that a clinician could estimate during an outpatient consultation, in addition to a radio-clinical prediction model, incorporating imaging measurements which require radiological expertise. Discrimination of the two models (i.e. ability to distinguish individuals who did versus those who did not experience the outcome) was measured using the concordance

statistic (c-statistic)[238]. The c-statistic is equivalent to the area under the receiver operating characteristic (ROC) curve for models with binary primary outcome[239]. In addition, sensitivity, specificity and positive and negative predictive values were reported. Calibration of the derived model (i.e. how well the predicted probabilities agree with the observed probabilities) was evaluated by visual assessment of a calibration plot, in conjunction with the estimation of the relevant metrics expressing the degree of discordance between observed and expected probabilities[240]. These metrics were: a. the calibration slope (i.e. odd ratio of the mean predicted and the mean observed probability), b. the ratio of expected to observed events (E:O) and c. the calibration-in-large (CITL) (i.e. a one-sample t-test of the difference between the mean predicted and the mean observed probability). We also applied the Hosmer-Lemeshow test, which is the statistical analogue of the calibration plot[241]. The Hosmer-Lemeshow test is a chi-squared test examining the difference in the proportion of patients with outcome versus the proportion of patients expected to develop the outcome. The null hypothesis is that the two proportions are equal, so if the model is well-calibrated a p-value > 0.05 is expected.

Model optimism (i.e. a decrease in model performance if model applied to a different dataset) was assessed with bootstrap resampling[240]. Bootstrapping draws 500 random subsets from the original dataset. It uses one for derivation and compares this 499 times with the remaining random subsets, by performing a chi-squared test[240]. The null hypothesis is that all these subsets they fit the model identically, so we expect a p-value < 0.05 to conclude that there is no optimism. Bootstrap resampling was also used for bias correction (objective 6)[240]. Our derivation cohort may hypothetically fit differently in a different (external) dataset due to sampling bias. As for this study an external dataset was not available, we performed bootstrapping to correct for such bias. We estimated the OR alongside its distributions, expressed as CIs and SD for each subset and we calculated mean OR of the bootstrap samples. The difference between the mean OR and the OR calculated from the original dataset it is believed to be due to sampling bias, in the context of the internal validation of a prediction model[240].

Sample Size Calculation

The sample size was calculated using the method described by Riley *et al*[242] for clinical prediction models. The study was designed to assesses 18 parameters, including exposures and confounding factors. Based on data from a local audit, we expected “events”, i.e. morphine prescription for pancreatic cancer-related abdominal pain, to occur in 50% of the

cohort. The anticipated model performance, expressed as R-squared (R_{cs}^2), was estimated 0.375. The formula : $R_{cs}^2 = (R_{Neglerkerge} \times Max(R_{cs}^2))$ was used for this calculation, where the $R_{Neglerkerge}$ was defaulted at 0.5 for direct measurements in the absence of existing data[242]. Therefore, a sample size of 385 participants (193 events, 10.69 events per parameter) was deemed sufficient to avoid overfitting and optimism in the development of our predictive model. Unfortunately, due to unexpected and unavoidable issues with research capacity the radiological data was limited to 142 patients.

Sensitivity Analysis

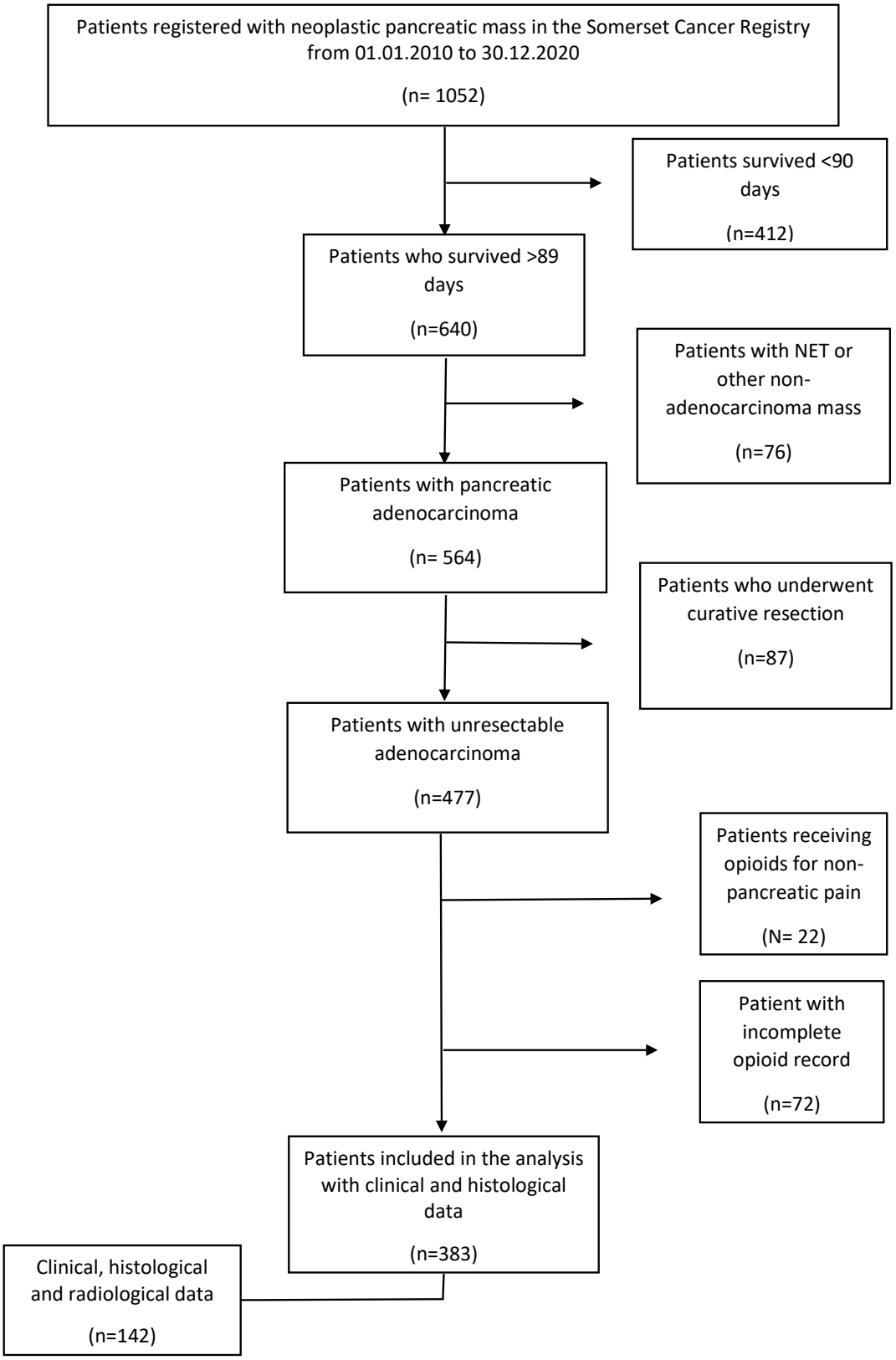
It is possible that morphine is well-tolerated if given in small doses. Therefore, endoscopic analgesia may be more suitable for those at risk of requiring higher doses. For this reason, *post-hoc* sensitivity analysis was undertaken defining as outcome the use of 60 mg of morphine or more.

RESULTS

Study Participants

In total, 1052 patients were identified from the Somerset Cancer Register (SCR) with pancreatic neoplasms (**Figure 25**). From these, 412 (39%) patients were excluded due to survival of 89 days or less, 76 (7%) excluded due to having neuroendocrine and other non-adenocarcinoma tumours (pseudopapillary, pancreatic cysts under surveillance, intraductal papillary neoplasms), 87 (8%) underwent curative pancreatic resection, 22 (2%) were using morphine for pain due to causes other than pancreatic cancer and 72 (7%) had insufficient records to ascertain opioid use (follow-up by community palliative care team, relocation or participating in chemotherapy clinical trials in the neighbouring Cambridge University Hospital). The study cohort was comprised of the remaining 383 (36%) patients who had complete clinical and histological data. Radiological assessment was undertaken in 142 patients. Subjects were followed from their date of diagnosis for a median period of 7.5 months (IQR 5.1 to 11), representing a total follow-up period of 301 years.

Figure 25. Flow chart of study participants.



Clinical Characteristics

Baseline characteristics of study participants are summarised in **Table 23**. The mean age was 70.8 years (SD 10.4) and 198 (52%) were male. Cardiovascular disease and Type II Diabetes Mellitus were the most common co-morbidities with prevalence of 45% and 24%, respectively. At diagnosis, 184 (48%) patients were affected by weight loss and lack of appetite. Abdominal pain or discomfort was reported by 165 (43%) patients. Jaundice was the third more common symptom at presentation, affecting 155 (42%) patients. In total, 198 (52%) presented with metastatic and 128 (33%) with locally advanced disease. Chemotherapy was administered in 231 (60%) of the patients. Several variables were affected by missing values. The tumour histological differentiation was not available in 241 (63%) patients. Of those, 83 (22%) did not have a histological diagnosis, 111 (29%) had ERCP brushings and 3 (1%) had ascitic or pleural fluid cytology. Of a total of 146 (38%) who underwent EUS- fine needle aspiration or biopsy (FNA or FNB), 49 (12%) had an inconclusive record of the degree of differentiation despite having definitive histological features of adenocarcinoma and another 22 (6%) reports were not available. Smoking history was missing from the clinical notes in 96 (24%) patients. Finally, missing values of the CA19-9 was observed in 111 (29%) patients. These missing values were either due to patients being deceased in the early 2010's, so their biochemistry record has been erased from the electronic systems, or because there was no plan for oncological treatments and therefore CA19-9 monitoring was not indicated.

Table 23. Clinical characteristics of the cohorts.

	Total (n=383)	Cases with missing values
Age (mean, SD)	70.8 (10.4)	-
Gender (n, %)		-
Male	198 (51.7%)	-
Female	185 (48.3%)	-
Major Co-morbidities (n, %)		17 (4.4%)
Neurological	45 (12%)	-
Cardiovascular	127 (35%)	-
Respiratory	25 (7%)	-
Type 2 Diabetes Mellitus	86 (24%)	-
Renal Disease	20 (5%)	-
Presenting Symptoms (n, %)		-
Jaundice	155 (42%)	13 (3.4%)
Abdominal Pain[1]	165 (43%)	-
Weight Loss or Anorexia	184 (48%)	13 (3.4%)
Nausea or Vomiting	46 (12%)	13 (3.4%)
Diarrhoea or Steatorrhea	50 (13%)	13 (3.4%)
Incidental	44 (12%)	13 (3.4%)
Other[2]	21 (6%)	13 (3.4%)
Health Performance Status(n, %)		17 (4.4%)
0	119 (32%)	-
1	111 (30%)	-
2	61 (17%)	-
3	62 (17%)	-
4	13 (3%)	-
Smoking History (n, %)		96 (25%)
Current smokers	44 (15%)	-
Ex- smokers	57 (20%)	-
Never smoked	186 (65%)	-
CA19-9 (media, IQR)	503 (95, 2476)	111 (28.9%)
Cancer Stage (n,%)		4 (1.0%)
I	22 (7%)	-
II	31 (8%)	-
III	128 (33%)	-
IV	198 (52%)	-
T stage		11 (2.9%)
T_1	5 (1.5%)	-
T_2	54 (15%)	-
T_3	68 (18%)	-
T_4	245 (66%)	-
N stage		5 (1.3%)
N_o	176 (46%)	-
N_1	202 (54%)	-
M stage		4 (1.0%)
M_o	181 (48%)	-
M_1	198 (52%)	-
Histological Differentiation (n, %)		141 (39%)
Poorly- differentiated	35 (10%)	-
Moderately- differentiated	48 (13%)	-
Well-differentiated	10 (3%)	-
Adeno-squamous differentiation	6 (2%)	-
Acinar differentiation	3 (0.8%)	-
Mucinous differentiation	22 (6%)	-
Unclassified	100 (27%)	-
Biopsy not available	141 (39%)	-
Chemotherapy Treatment (n,%)		13 (3.4%)
No chemotherapy	152 (41%)	-
FOLFIRINOX	103 (28%)	-
Gemcitabine	94 (25%)	-
Other	21 (5%)	-
Chronic Pancreatitis (n, %)	24 (6%)	10 (2.6%)
Pancreatic Enzyme Therapy (n, %)		11 (2.9%)
Prescribed	243 (65%)	-
Not prescribed	129 (35%)	-
Depression or Anxiety (n,%)	102 (27%)	11 (2.9%)

[1] This refers to abdominal pain or discomfort which may be controlled with or without opioids.

[2] Thromboembolic events, acute pancreatitis, haematuria, ascites, new onset diabetes, breathlessness.

Radiological Characteristics

Radiological assessment was undertaken in 142 (38%) sequential patients, diagnosed between 2014 and 2018. The generic radiological characteristics illustrated in **Table 24**. The CT attenuation values were available in 142 patients, however, of those only 79 had triple-phase CT (therefore AEC and REC were available only for these individuals), with the rest having dual phase or other protocols (for example colonography, kidney-ureter-bladder or non-contrast CTs). The CT attenuation values are demonstrated in **Table 25**. In total, 256 (67%) tumours were located in the proximal portion of the pancreas (head, neck and uncinate process), 74 (19%) in the body and 49 (13%) in the tail. The mean distance of the tumour from the left coeliac ganglion was 26.9 (SD 21.3) mm and from the right 25.7 (SD 21.3) mm. Tumours of the body were more proximal to the ganglia, with mean distances of 5.7 (SD 9.1) mm from the left and 8.1 (SD 11.3) from the right. Out of the 142 patients, in 29 (20%) the coeliac ganglia was directly infiltrated bilaterally by the primary tumour. Unilateral infiltration was observed 8 (6%) on the left and 5 (4%) on the right. The mean diameter of the main pancreatic duct was 5.95 (SD 3.08) mm and the mean tumour volume 4.9 (SD 6.5) cm^3. The mean absolute tumour enhancement change (AEC) between the arterial and the portal phase was 34.9 HU (SD 29.0) and the mean relative attenuation change (REC) was 1.19 HU (SD 7.07).

Table 24. Radiological characteristics of the pancreatic tumours.

Radiological Characteristics	Total
Tumour location (n, %)	
Head/Neck/Uncinate Process	256 (67%)
Body	74 (19%)
Tail	49 (13%)
Unclassified or unavailable	4 (1%)
Main Pancreatic Duct Diameter in mm (mean, SD)[1]	5.95 (3.08)
Tumour Dimensions in mm (mean, SD) [1]	
Anterior-posterior	32.4 (12.8)
Latero-lateral	34.9 (15.6)
Cephalo-caudal	32.4(11.4)
Tumour Total Volume cm^3 (mean, SD) [1]	4.9 (6.5)
Distance from the Left Coeliac Ganglion in mm (mean, SD) [1]	
Overall	26.9 (21.4)
Head/neck/uncinate process tumours	31.7 (20.5)
Body tumours	5.7 (9.1)
Tail tumours	23.2 (20.9)
Distance from the Right Coeliac Ganglion in mm (mean, SD) [1]	
Overall	25.7 (21.3)
Head/neck/uncinate process tumours	27.0 (19.7)
Body tumours	8.1 (11.3)
Tail tumours	40.6 (26.6)

[1]The radiological characteristics were available for 142 patients who were diagnosed between 2014 to 2018.

Table 25. Computerised tomography (CT) attenuation values of the tumour and the unaffected parenchyma in the portal, the arterial and the unenhanced phases.

Tumour (mean, SD)	**Attenuation values**	**Number of observations**
Attenuation on non-enhanced	39.6 (22.5)	79
Arterial Phase	38.1 (21.7)	77
Portal Vein Phase	68.5 (39.2)	137
Parenchyma (mean, SD)		
Attenuation on non-enhanced	40.5 (23.3)	80
Arterial Phase	38.6 (21.9)	77
Portal Vein Phase	67.9 (38.9)	136
Absolute Enhancement Change (AEC) [1] (mean, SD)	34.9 (29.0)	76
Relative Enhancement Change (REC)[2] (mean, SD)	1.19 (7.07)	76
All the values represent Hounsfield units (HU).		

Only 76 patients had triple phase CT. The rest had dual phase or other protocols (CT colonography, CT kidney-ureter-bladder etc), therefore AEC and REC could not be estimated.

[1] AEC= tumour attenuation at the PV phase – tumour attenuation at the arterial phase.

[2] REC= (tumour attenuation at the PV phase- tumour attenuation at the arterial phase)/ (parenchymal attenuation at the PV phase- parenchymal attenuation at the arterial phase).

Prevalence and Incidence of Pain Requiring Opioid Treatment

The prevalence, incidence and daily morphine doses are displayed in **Table 26** and **Appendix 10**. Opioid use was prevalent in 37% among the newly diagnosed patients with unresectable pancreatic cancer. The prevalence remained almost constant throughout the first year from the diagnosis, ranging from 37%-47%. Of a total of 241 opioid-free patients at month one, 46 (19%) were opioid users (i.e. became incident cases) by month three. The incidence continued to raise until the end of the first year but at a slower rate. The mean daily morphine dose started from 54 (SD 44) mg at baseline to climb progressively to 126mg (SD 125) by the end of the first year from diagnosis **(Appendix 11)**. Five patients were using morphine at small doses at diagnosis which they then discontinued in their subsequent follow-up. The absolute number of patients using opioids at NNUH in the first three months after diagnosis averaged at 17 (SD 3) patients per year **(Appendix 12)**.

Table 26. Time-point prevalence, incidence and daily morphine doses

Follow-up	Total number of alive patients at risk[1] (n)	Absolute number of patients on opioids[1] (n)	Time-point prevalence (%, CI)	Absolute number of new opioid-recipients (n)	Incidence[2] (%, CI)	Missing data (n)	Daily morphine dose in mg (mean, SD)
Month 1	383	142	37% (32%-42%)	-	-	-	54 (44)
Month 3	383	183	47% (43%-53%)	46	19% (14%-25%)	-	90 (84)
Month 6	238	111	46% (40%-53%)	24	12% (8%-17%)	36	105 (83)
Month 9	137	63	46% (37%-55%)	15	12% (7%-19%)	51	114 (128)
Month 12	88	34	39% (29%-50%)	2	3% (0.3%-9%)	45	126 (125)

[1]The figures represent the alive population who has no missing values.

[2]Incident cases are defined as the subjects in receipt of new opioid prescription, who were opioid-free in their previous three-month follow-up period.

Fitness for Endoscopic Analgesia

Of a total of 176 opioid users with recorded performance status at diagnosis, definitive fitness for EUS-CPN (defined as performance status scores of 0 to 2) was observed in 137 (77%). Borderline fitness, with a score of 3, was observed in 36 (20%) whilst lack of fitness was only observed in 3 (1.7%) of the patients (**Table 29**- **see performance status in opioid users**). In total, 125 (67%) of the opioid users pursued diagnostic (EUS or gastroscopy) or therapeutic endoscopy (ERCP) in the days to weeks following diagnosis, therefore, their fitness for endoscopy is evident. Finally, chemotherapy was administered in 107 (58.5%) of the opioid users.

Survival Analysis stratified by opioid use at three months

Overall, median survival was 7.5 (IQR 5.1 to 11) months. In total, 33 out of 383 patients were alive by the end of the study. The median survival was shorter in patients treated with opioids [median survival 5.9 (IQR 4.3 to 8.8) versus 9.3 (IQR 6.6 to 14) months, log rank test p<0.001] (**Figure 26**). The following covariates were associated with survival at a significance level of 0.250 in the univariable analysis and therefore included in the multivariable model: age, cardiovascular and renal co-morbidities, health performance status, CA19-9, cancer stage, chemotherapy, total tumour volume and location (**Table 27**). The multivariable analysis showed that patients on opioids were at 83% higher risk of death overall in comparison to those who were opioid-free (HR 1.83, 95% CI, 1.14 to 2.95, p=0.012). Retained variables independently associated with mortality were: chemotherapy treatment (HR 0.44, 95% CI, 0.26 to 0.76, p=0.003), the total tumour volume per cm^3 (HR 27.29, 95% CI, 2.06 to 360.86, p=0.012) and cancer stage (HR for trend across categories 1.40, 95% CI, 1.01 to 1.95, p=0.001).

Figure 26. Kaplan-Meier survival curves of the patients with inoperable pancreatic cancer stratified by their opioid use.

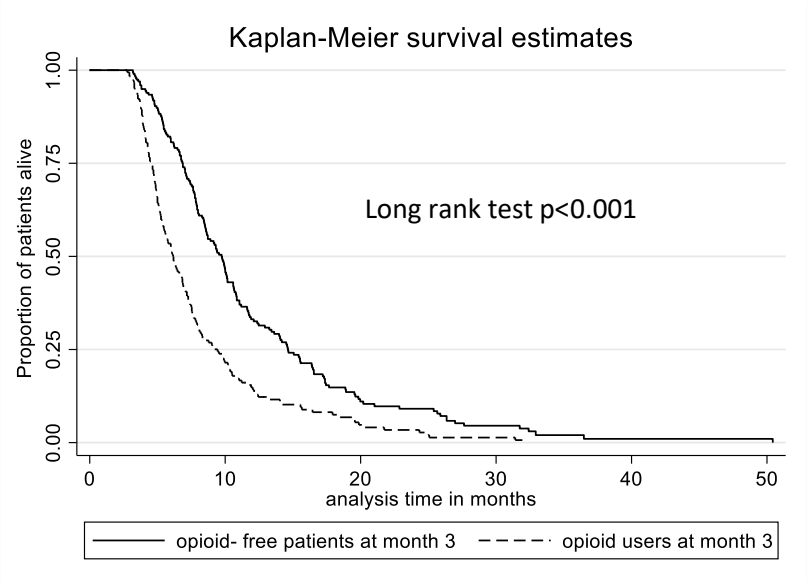


Table 27. Univariate associations between demographic, clinical, radiological characteristics and all-cause mortality.

Characteristics	Hazard Ratio (95% CI)	P-value
Opioid use (Y/N)	1.89 (1.53–2.34)	**<0.001**[1]
Age per year	1.02 (1.01–1.03)	**<0.001**[1]
Sex (male)	0.99 (0.81–1.23)	0.952
Major Co-morbidities (Y/N)		
Neurological	0.95 (0.69–1.32)	0.760
Cardiovascular	1.44 (1.15–1.80)	**0.002**[1]
Respiratory	1.18 (0.77–1.80)	0.457
Diabetes Mellitus Type 2	0.92 (0.70–1.19)	0.512
Renal	1.86 (1.18–2.93)	**0.007**[1]
Health Performance Status[2]	1.32 (1.21–1.44)	**<0.001**[1]
Smoking History[2]	1.09 (0.93–1.29)	0.285
CA19-9 per 1000 units/mm	1.02 (1.01–1.04)	**<0.001**[1]
Cancer Stage[2]	1.31 (1.13–1.51)	**<0.001**[1]
Histological Differentiation[2]	0.93 (0.81–1.06)	0.77
Chemotherapy Treatment (Y/N)	0.50 (0.408–0.62)	**<0.001**[1]
Pancreatic Enzyme Therapy (Y/N)	1.13 (0.90–1.41)	0.299
Depression or Anxiety (Y/N)	1.12 (0.89–1.42)	0.341
Total tumour volume per cm^3	11.36 (1.73–74.80)	**0.011**[1]
Tumour location	1.16 (0.99–1.35)	**0.052**[1]
Absolute Enhancement Change (AEC) per HU	1.00 (0.99-1.01)	0.839
Relative Enhancement Change (REC) per HU	1.01 (0.98–1.04)	0.373

[1]**Covariates included in the multivariable analysis**
[2]**Variables analysed as trends across categories.**

Table 28. Multivariable associations between demographic, clinical, radiological characteristics and all-cause mortality.

Characteristics	Hazard Ratio (95% CI)	P-value
Opioid use	1.83 (1.14–2.95)	0.012
Chemotherapy Treatment	0.44 (0.26–0.76)	0.003
Total tumour volume per cm^3	27.29 (2.06–360.86)	0.012
Cancer Stage[1]	1.40 (1.01–1.95)	0.001

[1]**Variable analysed as trends across categories.**

Association between clinical characteristics with opiate use at three months

Univariate analysis determined eight clinical variables (age, gender, pain at presentation, type 2 diabetes mellitus, health performance status, cancer stage, smoking history and anxiety/depression) and six radiological variables (pancreatic duct diameter, the anterioposterior and laterolateral tumour dimensions, tumour location, tumour distance from left and right ganglia) which were associated with opioid use at three months at a significance level of 0.250 (**Table 29** and **Table 30**). In contrast, there was no evidence of association with CA19-9 levels, grade of histological differentiation, use of pancreatic enzyme therapy, chronic pancreatitis, chemotherapy, total tumour volume, cephalocaudal tumour dimension and CT attenuation values. Due to high missing value rates, smoking history and anxiety/depression was not included in the multivariable model.

The multivariable analysis of the clinical parameters included 366 patients and revealed the following three associations: age was inversely associated (OR per year of age: 0.97 95% CI, 0.94 to 0.99, p<0.001) with the risk of requiring opioids at here months, a performance status of 3 had a 2.5-fold times higher odds (OR: 2.57, 95% CI, 1.32 to 5.00, p = 0.006) for requiring opioids in comparison to those with a scores between 0 and 2, and patients who presented with pain in their first clinic appointment had 9.57 (95% CI, 5.78 to 15.85, p<0.001) higher odds for requiring opioids at three months (**Table 31**). The model combining clinical and radiological variables was examined in a total of 138 patients. In addition to the associations with the age, performance status and pain at presentation, it also revealed an association of opioid use with the latero-lateral tumour dimension (OR 1.04, 95% CI, 1.00 to 1.08 , p= 0.048), as well as inverse associations with the anterior-posterior dimension (OR 0.94, 95% CI, 0.89 to 0.99, p= 0.042) and the tumour distance from the right ganglion (OR per mm of distance: 0.96, 95% CI, 0.94 to 0.9, p=0.004) (**Table 31**).

Table 29. Univariate analysis of clinical parameters predictive of opioid use at three months.

	Patients on opioids at 3 months (n=183)	Patients not on opioid at 3 months (n=200)	Odd Ratio (95% CI)	P-value
Age (mean, SD)	68.5 (10.6)	73.0 (9.7)	0.96 (0.94–0.98)	**<0.001[1]**
Gender (n,%)				
Male	87 (47.5%)	111 (55.5%)	1.00	-
Female	96 (52.4%)	89 (44.5%)	0.73 (0.49–1.09)	**0.120[1]**
Abdominal Pain at diagnosis (n/%)				
Yes	129 (70.5%)	164 (82%)	10.89 (6.73-17.6)	**<0.001[1]**
No	54 (29.5%)	36 (18%)	1.00	
Major Co-morbidities (n,%)				
Neurological	21 (11%)	24 (14%)	1.29 (0.69–2.40)	0.430
Cardiovascular	58 (33%)	69 (36%)	0.88 (0.57–1.35)	0.549
Respiratory	14 (8%)	11 (6%)	1.42 (0.63–3.22)	0.398
Diabetes Mellitus Type 2	36 (21%)	50 (27%)	0.84 (0.66–1.08)	**0.169[1]**
Renal	9 (5%)	11 (6%)	0.89 (0.36–2.19)	0.796
Health Performance Status (n,%)			1.16 (0.98–1.39)	**0.086[1]**
0	44 (25%)	75 (39%)	1.00	-
1	60 (34%)	51 (27%)	2.01 (1.18–3.40)	**0.010[1]**
2	33 (19%)	28 (15%)	2.01 (1.07–3.76)	**0.029[1]**
3	36 (20%)	26 (14%)	2.36 (1.26–4.42)	**0.007[1]**
4	3 (1.7%)	10(5%)	0.51 (0.13–1.96)	0.328
Smoking History (n,%)			1.27 (0.93–1.75)	**0.123[2]**
Current smokers	24 (17%)	20 (13%)	1.52 (0.79–2.95)	**0.212[2]**
Ex- smokers	31 (23%)	26 (17%)	1.51 (0.83–2.74)	**0.174[2]**
Never smoked	82 (60%)	104 (69%)	1.00	-
CA19-9 per 1000 units (mean, SD)	12745 (88536)	4042 (13258)	1.02 (0.98–1.05)	0.342
Cancer Stage (n,%)			1.29 (1.01–1.64)	**0.039[1]**
I	7 (4%)	15 (7%)	1.00	-
II	13 (7%)	18 (9%)	1.55 (0.49–4.87)	0.455
III	58 (32%)	70 (35%)	1.78 (0.68–4.65)	**0.242[1]**
IV	103 (57%)	95 (48%)	2.32 (0.91–5.94)	**0.079[1]**
Histological Differentiation (n,%)			0.89 (0.70–1.13)	0.345
Poorly- differentiated	19 (11%)	16 (8%)	1.00	-
Moderately- differentiated	27 (15%)	21 (11%)	1.08 (0.45–2.60)	0.859
Well-differentiated	5 (3%)	5 (3%)	0.84 (0.20–3.43)	0.811
Adeno-squamous differentiation	2 (1%)	4 (2%)	0.42 (0.07–2.61)	0.985
Acinar differentiation	1 (0.5%)	2 (1%)	0.42 (0.03–5.08)	0.496
Mucinous differentiation	12 (7%)	10 (5%)	1.01 (0.35–2.94)	0.985
Unclassified	42 (24%)	58 (31%)	-	-
Biopsy not available	67 (38%)	74 (39%)	-	-
Pancreatic Enzyme Therapy (n,%)				
Not prescribed at the 1st month	65 (36%)	64 (33%)	1.00	-
Prescribed at the 1st month	115 (64%)	128 (67%)	0.89 (0.58–1.36)	0.574
Anti-depressant or anxiolytic (n,%)				
Not prescribed	120 (66%)	150 (78%)	1.00	-
Prescribed	59 (34%)	43 (22%)	1.72 (1.08–2.72)	**0.022[2]**
Chronic Pancreatitis (n,%)				
No	167 (94%)	182 (93%)	1.00	-
Yes	10 (5%)	14 (7%)	0.78 (0.33-1.80)	0.558
Chemotherapy Treatment (n,%)				
No chemotherapy	76 (43%)	76 (39%)	1.00	-
FOLFIRINOX	45 (25%)	58 (30%)	0.78 (0.47 – 1.28)	0.322
Gemcitabine	45 (25%)	49 (25%)	0.92 (0.55- 1.54)	0.675
Other	11 (6%)	10 (5%)	-	-

[1]Covariates included in the multivariable analysis based on significance level of 0.250.

[2]Smoking history and Anxiety/depression were not included in the multivariable model due to high missing value rates.

Table 30. Univariate analysis of radiological parameters predictive of opioid use at three months post-diagnosis.

Radiological Characteristic	Patients on opioids at 3 months	Patients not on opioids at 3 months	Odd Ratio	P-value
Pancreatic Duct Diameter mm (mean, SD)	5.66 (3.09)	6.26 (3.07)	0.94 (0.84–1.04)	**0.238**[1]
Total tumour volume in cm^3	5.3 (4.8)	4.6 (7.9)	5.1 (0.02-1083)	0.548
Tumour Dimensions in mm (mean, SD)				
Anterior-posterior	33.9 (11.9)	30.9 (13.4)	1.02 (0.99–1.05)	**0.159**[1]
Latero-lateral	37.5 (14.9)	32.1 (16.0)	1.03 (1.00–1.05)	**0.044**[1]
Cephalo-caudal	33.1 (11.0)	31.7 (11.9)	1.01 (0.98–1.04)	0.453
Tumour location (n, %)				
Head tumours	114 (62%)	142 (71%)	0.67 (0.44–1.03)	**0.071**[1]
Body tumours	44 (24%)	30 (15%)	1.79 (1.07–3.00)	**0.026**[1]
Tail tumours	21 (11%)	28 (14%)	0.79 (0.43–1.45)	0.461
Unclassified or unavailable	4 (2%)	-	-	-
Distance from the Right Coeliac Ganglion in	22.2 (21.0)	31.7 (20.7)	0.96 (0.95–0.98)	**0.001**[1]
Distance from the Left Coeliac Ganglion in mm (mean, SD)	19.6 (19.8)	32.0 (21.2)	0.97 (0.96–0.99)	**0.008**[1]
Tumour CT attenuation values				
Non-enhanced phase	38.1 (22.0)	40.9 (23.1)	0.99 (0.97–1.01)	0.570
Arterial Phase	35.2 (23.6)	40.6 (19.9)	0.99 (0.96–1.01)	0.273
Portal Vein (PV) Phase	66.9 (37.7)	70.1 (41.1)	1.00 (0.99–1.01)	0.623
Parenchyma CT attenuation values				
Non-enhanced phase	30.9 (17.2)	38.4 (21.8)	0.98 (0.96–1.00)	0.070
Arterial phase	35.5 (21.5)	41.3 (22.2)	0.99 (0.97–1.01)	0.246
Portal vein phase	69.9 (38.7)	65.7 (39.5)	1.00 (0.99–1.01)	0.521
Absolute Enhancement Change (AEC)	31.6 (21.7)	38.1 (34.3)	0.99 (0.98-1.01)	0.331
Relative Enhancement Change (REC)	0.93 (5.1)	0.35 (2.8)	1.06 (0.95-1.17)	0.321

[1]Covariates included in the multivariable analysis based on significance level of 0.250.

Table 31. Multivariable logistic regression analysis of the clinical and the radiological predictors of opioid use at three months post-diagnosis.

Clinical model		
Characteristics	**Odd Ratio (95% CI)**	**P-value**
Age in years	0.97 (0.94-0.99)	<0.001
Presentation with Abdominal Pain	9.57 (5.78-15.85)	<0.001
Performance status 3	2.57 (1.32-5.00)	0.006
***The clinical parameters were analysed in a total of 366 patients**		

Radio-clinical model		
Characteristics	**Odd Ratio (95% CI)**	**P-value**
Age in years	0.94 (0.89-0.99)	0.008
Presentation with Abdominal Pain	8.33 (3.36-20.66)	<0.001
Performance status 3	5.42 (1.50-19.79)	0.010
Anterior-posterior tumour dimension in mm	0.94 (0.89-0.99)	0.042
Latero-lateral tumour dimension in mm	1.04 (1.00-1.08)	0.048
Tumour distance from the right ganglion in mm	0.96 (0.93-0.98)	0.001
***The radio-clinical model was developed in a summary of 138 patients.**		

Model Discrimination

The discriminatory ability of the two models, as this was assessed based on their AUC, was estimated at 0.81 (95% CI 0.76 to 0.85) and 0.84 (95% CI 0.78 to 0.92), for the clinical and the radio-clinical models, respectively (**Figure 27** and **Figure 28**). Sensitivities, specificities, PPVs and NPVs remained at moderate levels (**Table 32**).

Figure 27. Receiver Operator Curve (ROC) analysis for the clinical prediction model.

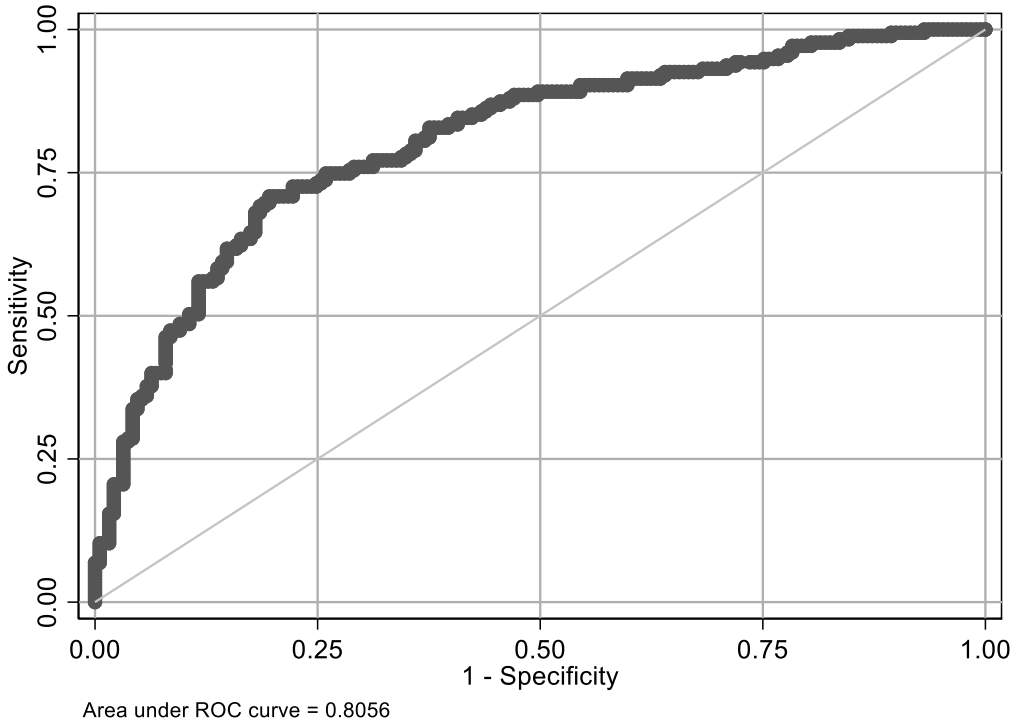


Figure 28. Receiver Operator Curve (ROC) analysis for the radio- clinical prediction model

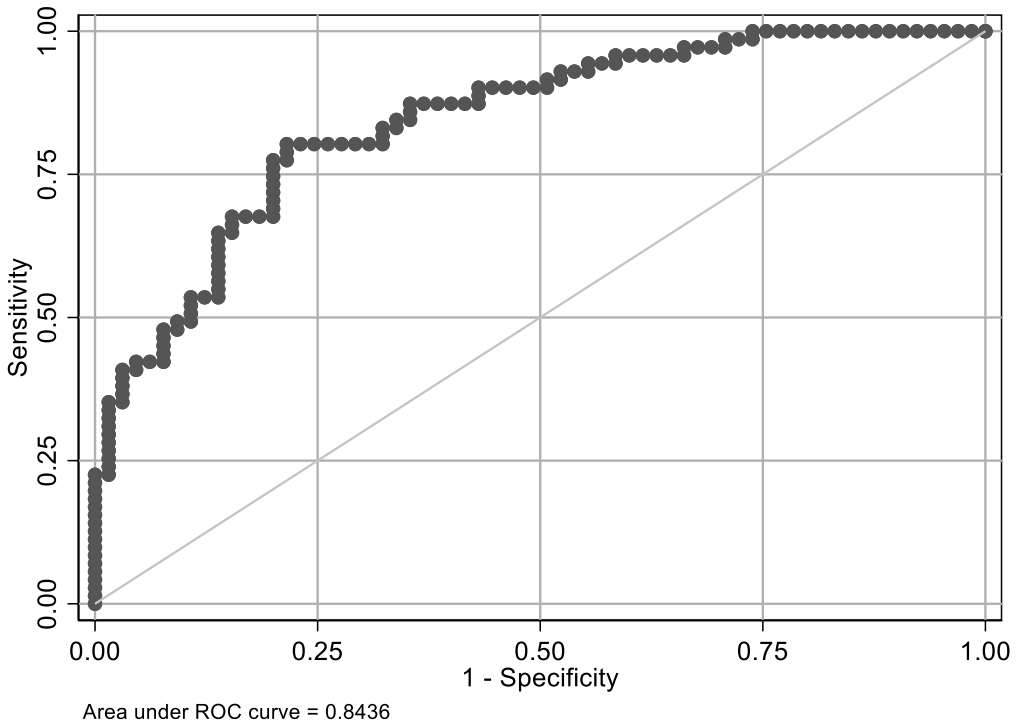


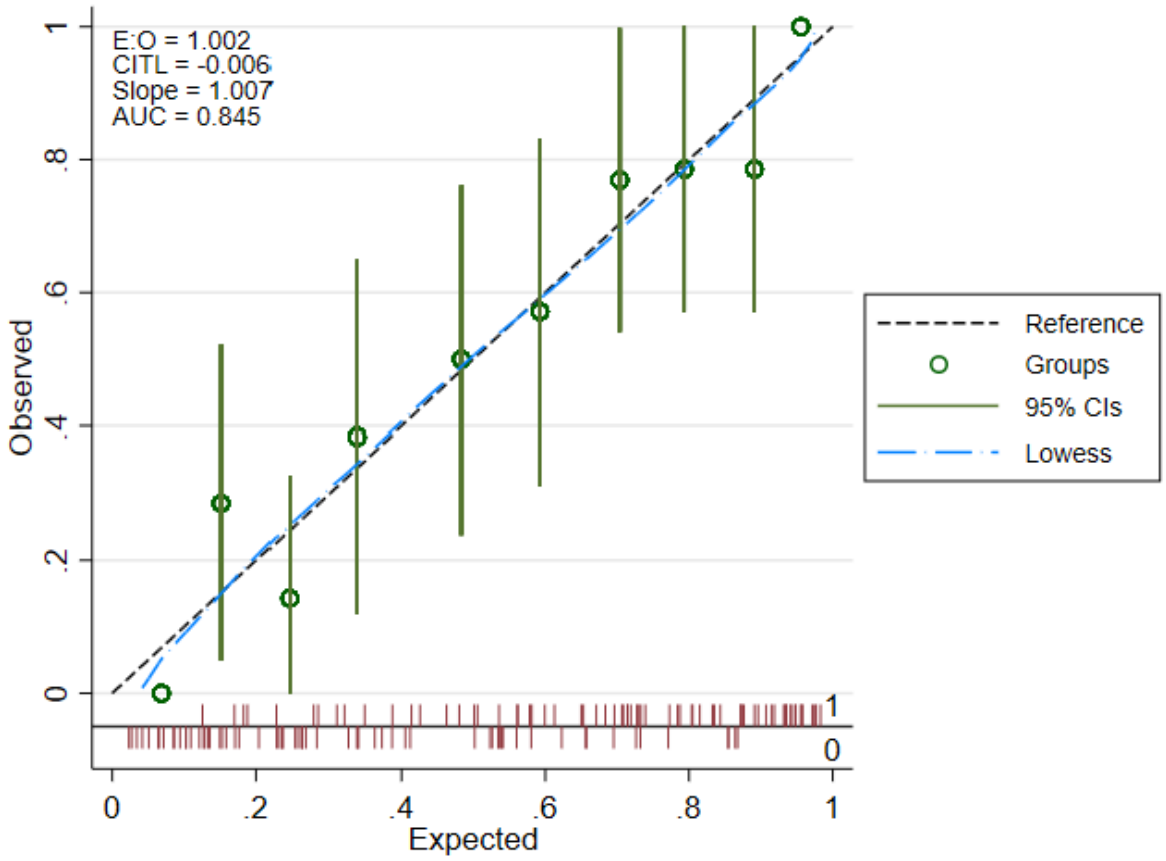
Table 32. Predictive performance of the clinical and the radio-clinical models at a cut off probability of 50%.

Model Discrimination	Clinical Model	Radio-clinical Model
Sensitivity	70.9%	78.9%
Specificity	80.4%	69.2%
Positive predictive value	77.0%	73.7%
Negative predictive value	74.9%	75.0%

Model Calibration

The calibration plot showed evidence of goodness-of-fit for the radio-clinical model based on the following assessments: the Lowess smoother line (light blue on the graph) approaches very closely to the diagonal line (**Figure 29**), the calibration slope was 1.007, the ratio of expected to observed events (E:O) was 1.002 and the CITL equalled -0.006. A detailed explanation of the construction and interpretation of the calibration plot is provided in **Appendix 13.** Further calibration assessment with the goodness-of-fit Hosmer-Lemeshow statistical test confirmed the good calibration (p=0.636).

Figure 29. Calibration plot for prediction of opioid use at three months. The diagonal line represents the ideal calibration, the light blue line (known as Lowess curve) represents the actual predictions and the green circles are the outcomes by deciles of risk. Visual assessment of the plot indicates that Lowess curve runs close to the diagonal line, hence the model is well-calibrated.



Internal validation

Bootstrapping revealed low level of sampling bias proportionally to the estimated effect sizes (**Table 33**). For example, patients who present with abdominal pain have 10.05 higher odds to require opioids at three months and the only 2.489 of these odds are due to bias. Also, bootstrap resampling revealed low probability of model optimism (p=0.003).

Table 33. Bias estimation and correction, using bootstrap resampling technique

	Observed Odds Ratio	Bias	Bias-corrected 95% CI	p-value
Age in years	0.93	-0.010	0.88–0.99	0.019
Presentation with Abdominal Pain	10.05	2.489	4.03-37.8	<0.001
Performance Status 3	11.46	4.012	1.41–83.96	0.012
Latero-lateral tumour dimension	1.05	0.017	0.99-1.11	0.211
Anterior-posterior tumour dimension	0.94	-0.012	0.88-1.02	0.087
Distance of the Tumour from the Right Ganglion in mm	0.96	-0.004	0.93–0.98	0.029

Case Examples

A 70 year old patient is presenting with a health performance less than three, with no pain at diagnosis. His tumour is located 5mm away from the right coeliac ganglion, it has an anterior-posterior dimension of 20mm and a latero-lateral dimension of 20mm. This patient has a 44% probability (95% CI 22% to 66%, p<0.001) to require opioids. If the same patient had a 30 mm latero-lateral tumour dimension his probability increases to 55% (95% CI 0.33 to 0.77, p<0.001) and if this dimension increased to 40 mm his probability climbs to 65% (95% CI 41% to 89%, p<0.001).

Sensitivity Analysis

The sensitivity analysis revealed associations between 11 radio-clinical variables with the outcome of using 60mg or more of morphine daily at three months post-diagnosis, at a significance level of 0.250 (**Table 35**, **Appendix 14**). The multivariable analysis of the clinical model, in a total of 357 patients, demonstrated that age, pain at presentation and depression or anxiety are independent risk factors for use of ≥ 60mg of morphine daily (**Table 36**, **Appendix 14**). A radio-clinical model was not constructed in the context of the sensitivity analysis because only 51 patients of those with radiological data experienced the outcome. The AUC for the clinical model was 0.81 but it was poorly calibrated **(Figure 32 and Figure 33, Appendix 14).** The sensitivity, specificity, PPV and NPV 57.3%, 84.6%, 62.4% and 81.6%, respectively. In contrast to the original models, the patients' performance status was not retained whilst a new association with anxiety and depression was detected.

DISCUSSION

Main Findings

This retrospective single-centre cohort study demonstrated that opioid use is prevalent in 37% to 47% of patients with pancreatic cancer during the first year of their diagnosis. Opiate use at three months is associated with reduced survival (HR for death 1.83, 95% CI, 1.14 to 2.95, p=0.012). The mean daily morphine dose starts at a relatively low daily dose (mean 54 mg, SD 44) and gradually escalates to higher dose use (mean 126 mg, SD 125) towards the end of the first year. We sought to develop predictive models based on clinical and radiological characteristics to identify patients at risk of pain requiring opiates. Such patients may benefit from an early EUS-CPN and a prediction model could serve to identify a cohort at higher risk of pain suitable for an RCT of early EUS-CPN vs. standard care. We investigated a series of candidate predictors of opioid use at three months. Based on those associations, we firstly developed a predictive model based exclusively on clinical parameters. Age, presentation with pain and health performance status were the three parameters retained in this clinical model. The discrimination between predicted and observed cases of opioid use was optimal (AUC: 0.81; sensitivity: 70.9%; specificity: 80.4%; PPV: 77.0%; NPV: 74.9%). We then added a series of radiological parameters, of which the distance of the tumour from the right ganglion, the latero-lateral and the anterior-posterior tumour dimensions reached statistical significance. The discrimination ability of this radio-clinical model improved (AUC: 0.84, sensitivity: 78.9%, specificity: 69.2%, PPV: 73.7%, NPV: 75.0%). A sensitivity analysis, using as 60mg of morphine or above as the outcome showed sufficient discrimination (AUC 0.81) but poor calibration.

Due to the scarcity of evidence in the use of early EUS-CPN, we also generated data specific to the feasibility of a randomised trial of this technique versus standard care (opiates +/- on demand EUS CPN). In our trust, it was estimated that an average of 17 (SD 3) new patients present with painful pancreatic cancer every year, requiring opioid analgesia. Based on their reported health performance status, 77% of these patients meet the fitness criteria for endoscopic analgesia whilst 20% have borderline fitness. Overall, 67% of the patients who were suffering with pain at three months underwent an endoscopic procedure (ERCP, EUS or gastroscopy) in the first month of their diagnosis, a figure implying that the majority of these patients could have had EUS-CPN during the same session, if the intractability of their symptom in the future could be accurately predicted.

Interpretation

Opioid use is frequent in patients with inoperable pancreatic cancer. The opioid dose typically escalates to 125mg per day in the first year from the diagnosis[188]. A previous meta-analysis

investigating the risk of unintentional opioid overdose showed that doses ≥50mg per day have nearly a four-fold (RR 3.87, 95% CI, 2.36 to 6.33, p<0.001) risk to lead to overdoses in comparison to doses of ≤50mg[120]. This indicates that the opioid doses used by patients with pancreatic cancer consist a substantial exposure to opioid-related risks. This would support the rationale for a future trial of early EUS-CPN. Two thirds of the opioid users undertake endoscopies as part of their diagnostic or therapeutic work up. If their risk of requiring high dose opioids could be predicted, these patients could benefit from EUS-CPN during the same session of the diagnostic endoscopy or soon after. We developed such a model predictive of opioids, using plausible clinical and radiological parameters which achieved good performance. As opioids in small to moderate doses may be well-tolerated, we examined the model's performance at predicting the use of ≥ 60mg of opioids per day. This model that arose from the sensitivity analysis confirmed the predictive value of the age and pain at presentation. In contrast, performance status was not retained, whilst associations with anxiety and depression were revealed. Given that the sensitivity analysis was conducted with fewer events per parameter (because high dose opioid use is less prevalent than any opioid use), the differences from the original model may be spurious, resulting from model overfitting.

In relation to the feasibility of a future randomised trial of early EUS-CPN, we showed that the expected number of eligible patients, based on survival, opioid use and fitness for endoscopy, is approximately 17 per year, so a single-centre would likely recruit ~ 50 patients over three years for a trust the size of NNUH. Such estimates could help determine the number (and size) of sites for a future trial.

Strengths

This research has a number of strengths. To the best of our knowledge, this is the first clinical study to evaluate associations between clinical and radiological parameters with opioid use in patients with advanced pancreatic cancer. The study was conducted in a large UK tertiary centre and covered a period of 10 years. The cases were identified from the national cancer registry, so missing cancer cases are highly unlikely. It is likely our results are representative of the general population of patients with pancreatic cancer, as demonstrated by the representative epidemiology of this cohort (for example the mean age in this cohort is 71 years and 52% of them are males which match exactly the UK cancer statistics[41]). A medical gastroenterologist reviewed one-by-one all the case notes in order to minimise the classification bias for the outcome of opioid use. Based on previous literature and clinical experience, we selected a plausible list of candidate predictors. A sample size calculation was determined *a priori*, based on previous audit data to ensure sufficient events per parameter were

included. In that way, we tried to address the risk of model over and under fitting , i.e. selecting spurious predictors or failing to include important predictors, respectively.

Limitations

This study has several weaknesses that deserve consideration. The retrospective nature of this study, which was reliant on case note review to ascertain opiate use, may have introduced measurement error: we were unable to fully establish the exact opioid doses administered, especially when PRN prescriptions were issued. Nevertheless, this does not detract from the key findings that burden of opiate use in the cohort is substantial and increases over time. Furthermore, the primary outcome for the risk prediction model (opiate use at three months in patients with pain due to pancreatic cancer) is unlikely to be influenced by this source of measurement error. Missing values may have accounted for loss of statistical power of several variables with a plausible role in the aetiopathogenesis of pain. The pattern of missing data differed by variable and mechanism. The most characteristic example is the availability of radiological data which was limited to a subset of 138 patients due to unforeseen issues with research capacity, which were unfortunate, but unavoidable. If a full radiological dataset was available, perhaps variables eliminated on the basis of the borderline significance, such as stage ($p= 0.142$), could have been retained and contribute to the predictive ability of the model. Another example, the histological differentiation was missing in 63% of the cohort participants, reflecting clinical practice: either because invasive tests were not clinically indicated or cytology specimen, rather than histology, was used for diagnosis. Pancreatic tumours commonly develop heterogenous degrees of differentiation across their different sections. Consequently, these tumours cannot categorically be classified based on the WHO Histological Classification[243]. This problem could only be addressed with specimens showing the fully organised ultrastructure of the tumour, i.e. liver core biopsies and wide bore FNAs, rather than cytology aspirates. Use of histology in a future predictive model is therefore unlikely to be applicable. Diagnosis of chronic pancreatitis is likely to be under reported due to the known high rates of underdiagnosis of this condition and the 6% of patients affected in this cohort is a probable underestimate of the true prevalence of this variable[47]. The main role of CA19-9 is monitoring of the response to chemotherapy. Its values were commonly missing, probably because these patients did not have a plan for oncological treatment. In respect to the prevalence and incidence of pain at six, nine and twelve months, there were patients who did not have hospital follow up. The majority of those patients were discharged to the community palliative care, to which access of the notes was not possible. It is likely that most of them deteriorated and potentially required opioids towards the end of their life, therefore, their missing values are likely to have led to underestimation of the true prevalence of opioid use.

Comparison to previous research studies

The prevalence of pain and opioid use has been reported in three previous studies [119, 188, 230]. A previous retrospective cohort study included 103 patients with stage IV pancreatic cancer who underwent chemotherapy[188]. Overall, 78% of the patients received opioids at baseline, of whom 66% were on doses exceeding 5mg per day. Morphine was associated with reduced survival; patients on less than 5mg/daily of morphine equivalents survived longer than those on doses greater than 5mg/daily (median survival: 315 versus 150 days, p<0.01, HR= 1.79; 95% CI, 1.13 to 2.84) which is similar to the association demonstrated in our study (HR= 1.83; 95% CI, 1.14 to 2.95, p=0.012)[188]. A second retrospective cohort study examined 566 patients with stage III and IV inoperable pancreatic cancer. Only 9.7% of the patients treated with chemotherapy. The mean opioid dose at their first opioid prescription was 55.9 (SD 53.8) mg whilst the mean opioid dose in their last month of their life was 162.8 (SD 131.6) mg. These figures approximate our results, where mean daily morphine dose at the start was 54 mg (SD 44) and gradually escalated to 125 mg (SD 126) at twelve months. The mean survival time from diagnosis was 284 (SD 328) days. The mean duration of the opioid-free period for patients were 97 (SD 234) days whilst the mean survival from the first opioid prescription was 187 (SD 212) days. There was an inverse correlation between the initial dose of opioids and survival (coefficient= −0.18, p< 0.01)[119]. A third retrospective cohort study depicted 109 male patients with adenocarcinoma and non-adenocarcinoma tumours which were identified from a US army veterans' registry[230]. In total, 58% of them had pain at diagnosis. The primary outcome of the study was early death, defined as death in the first six months post diagnosis. Patients with abdominal pain had a 6.77-fold (p<0.01) higher odds for early death in comparison to those who were pain free (95%CI not provided by the authors)[230].

The prevalence of opioid use in our study was lower (37-47%) in comparison to the ones reported by Steel et al[188] (76%) and Kim et al[230] (58%). Methodological reasons, related to the research aims and data collection, could explain this discrepancy. Firstly, in our study we excluded patients with very short survival (<three months) who were likely to have high pain levels and likely required opiates. This exclusion happened because these patients were unlikely to be candidates for endoscopic treatments, so outside our target group, and also their data could not contribute to the development of a prediction model as they were deceased before the primary outcome was assessed. In any case, such patients in our region are managed by the community palliative care team and their clinical data were not available to us on this instance. Secondly, the aim of the other two studies was to investigate the associations between opioid use and survival, and therefore the origin of pain was not in their main focus. In contrast, our study was aiming to inform an intervention for a very specific type of pain. Consequently, in our study the pain data were extracted from clinic letter review and the type of pain

was ascertained based on the symptom descriptions, contrary to the other studies where opioid data were retrieved from drug charts and prescriptions. Indicative of this difference is that we excluded 72 patients who were using opioids for non-pancreatic pain, whereas the other studies did not; if these exclusions were not applied, our estimated prevalence would be 69% and would fall much closer to the other papers. Overall, the retrospective nature of all these studies, the particular research aims of each one of them, the method of data collection and the different in the target subgroups of patients with pancreatic cancer may justify some discrepancy in the estimated pain and opioid use prevalence.

In addition, our study had a radiomic component. Radiomics is an emerging method of image analysis that translates images into quantitative values to enable phenotypic profiling of tumours[244]. Pancreatic cancer is characterised by the development of a strong desmoplastic stromal reaction in its microenvironment which determines the overall tumour texture[245]. The stroma compresses the arterioles within the tumour and restricts the perfusion of contrast into them, giving the tumour a hypo-attenuating appearance on the CT images in comparison to the unaffected portion of the parenchyma. The stroma is believed to play a significant role in the tumour's broader biological behaviour, such as cellular proliferation rates and invasiveness, due to the release of cytokines from its cellular components[245]. Previous studies have evaluated the associations of the tumour enhancement values on CT with the tumour's biological behaviour in terms of response to chemotherapy, post-operative recurrence and overall survival[235, 246-248]. As pain appears to be part of this overall biological behaviour[117], we hypothesised the intensity signal the tumour exhibits on the CT images may be predictive of pain. Herein we used the most primitive method of measuring the tumour enhancement values, adjusted for the values of the unaffected parenchyma[235]. This method has the advantage of not requiring additional image processing and reconstruction, however, it has several limitations; the obtained values may have been affected by the position of the patient, the timing the different images were captured in the arterial and the portal phases and more importantly, our radiomic analysis was retrospective rather than prospective, where many of these factors (position, radiation dose, timing, breathing artefact) can be controlled. Nevertheless, tumour enhancement was not associated with opiate use at three months.

Research Implications

Overall, this study provides the rationale and feasibility estimates to plan a future randomised controlled trial of early EUS-CPN versus standard care. In addition, it has demonstrated preliminary evidence of the predictive value of using clinical and radiological parameters to identify patients with pancreatic cancer who will require opioids in the medium term. This risk prediction model once externally validated, could be used to inform eligibility for the above trial.

Conclusion

Opiate burden at three months is high and associated with worse prognosis. Age, performance status tumour distance from the right coeliac ganglion, the latero-lateral and anterior-posterior tumour dimensions are independently associated with opiate use at three months. Expansion of the derivation cohort and external validation of this predictive model should be sought in a validation cohort. These findings support the rationale for a clinical trial of early EUS-CPN versus standard care where eligible patients are identified from the above model.

CHAPTER 6- Final Discussion

EUS-CPN is currently indicated in patients with inoperable pancreatic cancer whose pain remains poorly controlled despite increasing doses of opioids or with intolerable opioid-related side effects[128]. The research detailed in this thesis investigated the rationale, feasibility and design considerations of a clinical trial of early, versus on-demand EUS-CPN. From a systematic review of the literature, we established the current evidence base regarding the efficacy and safety of the EUS-CPN, as well as the technical considerations which could be adopted in a future clinical trial. Specific procedural considerations were made to minimise the risk of spinal stroke, a rare but serious complication. Through prospective observational work, we followed patients with inoperable pancreatic cancer through their clinical pathway from diagnosis. This gave us the opportunity to map the clinical pathways through which potential candidates of a future trial are managed (and therefore when and where to seek their participation in such a trial), obtain an estimate of eligible participants for a trial, identify real-time barriers and challenges related to the nature of their disease and, finally, assess the feasibility of obtaining pain-related data through self-completed questionnaires. We reinforced these observations by conducting in-depth qualitative interviews with patients and their carers to obtain their views on a trial of early EUS-CPN and the willingness of patients to engage with trial activities. We substantiated our evidence on the burden of opioids and therefore the justification of a trial by retrospectively reviewing the prevalence of opioid use; opioid consumption in the first year following diagnosis; health performance status and the main diagnostic modality (these two were used as surrogate markers of fitness for endoscopy); and the survival of those on opioids (specifically whether patients could survive long enough to potentially justify an invasive procedure). Finally, we developed a clinical model predictive of the need for opioids at three months following diagnosis. This model, once if externally validated could be used for the selection of patients at high risk of opiate use who may be more likely to benefit from early EUS-CPN in a future trial.

Appropriate method of delivery of EUS-CPN

Based on a systematic review and meta-analysis, 68% of patients with pancreatic cancer report pain improvement two weeks after EUS-CPN[124]. The proportion of patients reporting pain improvement drops to 53% at four weeks post-procedure. Three technique variations of the EUS-CPN are described in the literature, differing by site of injection - central injection, bilateral injection and the ganglia injection. These variations have been developed based on the hypothesis that better spread of the injectate or more targeted instillation into the ganglia may enhance the analgesic effect of the

procedure. We demonstrated no significant difference in the analgesic efficacy among these three variations in technique. However, a key consideration is that the central injection, which is the less invasive, appears to be the safest of the three. Neither age, gender, tumours located in the head of pancreas, VAS pain score at baseline and tumour stage IV appeared to influence its analgesic effect.

Overall, EUS-CPN is a relatively safe procedure. The most commonly observed side-effects of EUS-CPN are associated with the unopposed activity of the parasympathetic autonomic nervous system and consist of diarrhoea (9%), temporary pain exacerbation (8%) and hypotension (6%). These resolve spontaneously within a few days, once the equilibrium between the sympathetic and parasympathetic activity is restored. Spinal stroke is the most concerning complication of EUS-CPN. It occurs in 0.2% of cases and can lead to permanent paraplegia. The evidence on EUS-CPN -related spinal stroke derives mainly from a few case reports and it is believed to be caused by the vasoconstrictive effect of alcohol. It has been observed in patients who received bilateral injection or ganglia injection but not in those who received central injection and in patients who received doses of absolute alcohol exceeding the 20mls. Although speculative, atherosclerosis could plausibly contribute to risk of spinal stroke considering the spinal cord receives arterial supply from three arterial branches and obstruction of more than two of those is required to cause a spinal stroke[185]. In view of this, caution should be taken when patients with excessive atherosclerotic burden are evaluated for eligibility into the future trial.

Justification of an EUS-CPN trial

We assessed the justification of a trial of early EUS-CPN based on the proportion of patients suffering from pain, opioid burden, survival and the fitness for endoscopy of those with pain. PREDICT-PANC showed that pancreatic cancer -related pain is highly prevalent, observed in 47% of those patients at three months post diagnosis. Over time, more patients develop pain; every three months approximately 12% of non-opioid users initiate opioid treatments to manage their pain. Extrapolating this data more widely, we estimate 4,000 patients with advanced pancreatic cancer suffer from pancreatic pain, per year nationally. The opioid requirements increase sharply from 54 (SD 44) mg at baseline to 126 (SD 125) mg by the end of the first year. Opioids can cause side-effects at any dose, however the risk of toxicity increases with higher doses. For example, the risk of respiratory depression is nearly three-fold (RR 3.09, 95% CI, 1.84 to 5.18, p<0.001) for those receiving 50-100 mg daily in comparison to those using less than 50mg [120]. Similarly, patients receiving 90mg or more per day have 2.12 times higher odds of developing delirium (95% CI, 1.09 to 4.13, p=0.032) [121]. This indicates the opioid doses prescribed to patients with pancreatic cancer may expose them to substantial opioid-related risks and therefore opioid-sparing treatment strategies are needed. Sufficient survival is essential to judge whether an endoscopic intervention is justified; we showed the

median survival of patients with advanced pancreatic cancer on opiates to be six months (IQR 4.3 to 8.8). In total, 77% of the patients with pain appeared to have performance status of 0 to 2, whilst another 20% a performance status of 3. Although performance status score is not a definitive measure of fitness, it is likely that the majority of those patients would be fit enough to undergo EUS-CPN. Overall, our results support that a trial of early EUS-CPN is justified based on the prevalence of pain, opioid exposure, survival and fitness for endoscopy in this population.

Identification and recruitment of patients in a future trial

From conducting prospective observational research (The BAC-PAC Study), we concluded that one of the most significant barriers hindering research participation in the early weeks following diagnosis is the emotional distress patients experience. This is the consequence of a very abrupt psychological transition from "normal health" to "incurable cancer", which occurs within a few weeks and leaves a very short time period for patients and their caregivers to adapt[191]. In addition, chemotherapy treatments, which usually start at this time, can be arduous, leading to severe constitutional symptoms, frequent complications requiring hospitalisation, long day-case admissions for blood tests and infusions, central line care and interval imaging. Overall, the weeks after diagnosis consist an emotionally and physically demanding period which may steer patients' mindsets away from involvement in research activities, especially if those activities do not convey a visible benefit to them in their foreseeable future (this is a key difference with chemotherapy trials where patients are keen to participate, incentivised by the prospect of potentially longer survival). A reluctance to engage with observational research in patients with incurable cancer is reflected in the low participation rates seen in other observational studies in this patient group[69] as well as in patients with lung and colorectal cancers[215, 216]. Careful attention must be paid to trial design to minimise intrusiveness and the burden of study procedures.

The multi-disciplinary team meetings and the Somerset Cancer Registry provide reliable sources for the identification of patients who are managed through the non-surgical pancreatic cancer pathways and are potential candidates for a future trial. Some further clinical assessment, in liaison with the parent clinical team is needed to exclude those who are moribund with very poor life expectancy, and therefore ineligible for a trial. Nearly 40% of patients present with pain requiring opioids and therefore will have to be approached for participation into the trial very soon after diagnosis. We estimated that approximately 67% of these patients undergo endoscopies for diagnostic or therapeutic purposes. If these patients were to agree to participate in the trial at the time of diagnosis, their EUS-CPN could be combined in the same session with the endoscopic procedure they undertake, and they could therefore avoid the burden of a separate procedure at another date, as has previously been

suggested[122]. The remaining will require monitoring for the development of pain. We estimate that of those who are pain-free at diagnosis, 12% become opioid users every three months. These patients are either managed by the oncology team or in the community by palliative care services or general practitioners. The fact that these patients are looked after by different services (that are also likely to be geographically dispersed), makes their identification and recruitment to a trial challenging. Collaboration with all clinical teams involved in the care of those patients will be required, so these patients are flagged to the research team. Also, sufficient trial information could be provided to patients at an early stage in their pathway soon after diagnosis, to enable them to notify the trial team when their pain first occurs.

Design considerations for a future trial

Patients with inoperable pancreatic cancer who suffer from pancreatic pain (or are at high risk of needing high dose opiates) would be eligible for a future trial. The diagnosis of pancreatic cancer - related abdominal pain may be challenging as there are no well-defined criteria and there are many other types of pain mimicking it, therefore the eligibility of patients will have to be determined by an experienced clinician. Patients who receive neo-adjuvant chemotherapy with the prospect of downstaging to potentially resectable disease should be excluded: the injected alcohol may cause fibrotic tissue around the coeliac artery and preclude resection[179]. Exclusions should also apply to patients with pain attributable to chronic pain syndromes, or non-pancreatic cancer pain, such as bone metastasis. As discussed above, spinal stroke is a recognised serious complication of EUS-CPN. It is assumed to be attributed to the vasoconstrictive effect of the injected alcohol, however, the exact causal mechanism is poorly understood. Atherosclerosis may be contributory by preventing the homeostatic auto-regulation of the blood flow in the arterial network supplying the spinal cord. To ameliorate this risk, patients with excessive atherosclerotic burden may have to be excluded, such as those with extensive vascular calcifications or other extensive vascular complications.

A future clinical trial will need to be a multicentre study for reasons outlined below (see sample size considerations). Central, web-based randomisation with variable block size will be needed to preserve allocation concealment and maintain an equal number of participants in both arms. Patients assigned to the intervention group would receive EUS-CPN at the earliest opportunity, soon after their pain first occurs, using central injection of 10-20 ml of absolute alcohol. These technique specifications are shown to be safe and effective in previous literature[124]. Those assigned to the control group will receive standard care, i.e. opioid-based medications with or without on demand EUS-CPN. Blinding of participants would likely be very difficult in the setting of a trial assessing endoscopic versus non-endoscopic pain management; and a sham procedure could be difficult to justify. Therefore, an open-

label design would most likely be required. Such a design could introduce detection and performance bias and this needs to be taken into account when the outcome measures of analgesia are selected, e.g. objective measures (changes in opioid doses) versus self-reported outcomes (pain or patient satisfaction scales). Most importantly an outcome assessor blinded to allocation would be required.

Careful consideration should be made regarding the selection of the primary outcome measure in a future trial. Assessing the analgesic effect of an analgesic intervention is associated with challenges related to the validity and reproducibility of the measurement[249]. Pain is a very personal experience and there is no external gold standard to compare it against. Also, pain relief is a multidimensional concept, incorporating aspects of pain's intensity, quality and interference with daily living. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT), a professional organisation producing consensus recommendations specific to pain trials, suggests five principals to be considered in the selection of pain outcome measures[249]. These include: appropriate content validity (i.e. is the actual concept of interest assessed?), test re-test reliability, construct validity (is there a relationship between the selected outcome measure and other measures or patient characteristics that are in accordance with our priori hypotheses? For example, relationship between pain levels and doses of opioid usage?), assay sensitivity (does the outcome measure capture changes over time?) and interpretability[249].

In view of the above, we suggest that the change in the dose of opioids is the most objective measure of the pain status and could be the primary outcome in a future trial. However, it also has two disadvantages; firstly is one dimensional and secondly, a clinical assessment will be required to ensure the opioids are not taken due to non-pancreatic pain. The EORTC-QLQ30 quality of life score is a useful tool to measure changes in a broad range of aspects (emotional, physical, social etc) and also includes scales assessing symptoms such as pain, nausea, fatigue and constipation which are directly relevant to opioid treatments. The EORTC-QLQ30 could be assessed as a secondary outcome. However, pancreatic cancer itself and related treatments diminish quality of life through a number of mechanisms which are not necessarily related to pain (weight loss, malaise, depression etc), and even if pain is addressed with EUS-CPN but the other emotional and physical impairments remain, differences in the global quality of life scores between groups may not be detectable in the context of a trial. The visual analogue score or its numerical equivalent, the numerical rating score, may be falsely low, if the patient receives high doses of analgesia at expense of greater analgesia-associated side-effects. In addition, these scores have the disadvantage that their anchor points (0 for no pain, 5 for moderate pain, 10 for worst possible pain) are poorly defined and subjective, open to individuals' interpretations with moderate test re-test validity[249]. A future trial would need to rationalise the number of timepoints the clinical outcomes are measured to minimise attrition. Another lesson learnt

from the BAC-PAC study was that lengthy questionnaires are burdensome to patients and may be prohibitive to their involvement to research. Hence, the patients should be assigned to complete only patient-reported outcomes. All the other clinical data, such as the medical resource use and the dose of opioids, could be collected directly by the research team.

Sample size considerations in a future trial

In our retrospective cohort study, PREDICT-PANC, we showed that patients receiving standard care (i.e. predominantly opioids alone with a minority having on-demand EUS-CPN) require 54 mg (SD 44) of opioids daily at the first month and their requirements progress to 90 mg (SD 84) at three months. We assumed that with the administration of EUS-CPN opioid doses will remain the same or increase slightly, so the intervention group will require 60 mg (SD 44) at three months. This assumption is in line with the findings of the trial conducted by Wyse *et al*[126], where the opioid doses of patients in receipt of EUS-CPN were plateaued. Based on these observations and assumptions, 158 patients in total with 79 patient at each arm (randomised in a 1:1 ratio) would be sufficient to detect a 30mg difference in the mean opioid doses, with statistical power of 80% and alpha of 0.05. On average, in NNUH, with a catchment area of approximately 800 000, we diagnose 17 (SD 3) patients with painful pancreatic cancer per year whilst, based on our observed three monthly incidence rates, we estimate that another seven patients develop delayed-onset pain, within the first year of their diagnosis (24 patients in total). Assuming 50% of these patients consent to trial participation, 12 patients would potentially be recruited per year. Assuming recruitment runs over three years, a single centre equivalent in size could recruit 36 patients. A multi-centre trial with at least 5 centres (of equivalent size) which offer EUS-CPN would be required to ensure recruitment within three years.

The role of a predictive model of opioid use in a future clinical trial

A strategy of offering early EUS-CPN to all eligible patients with advanced pancreatic cancer may expose a number of patients to an invasive procedure, with associated risks, who may not be expected to derive benefit. A clinical risk prediction model could enable risk stratification to identify those at highest risk of requiring high dose opiates, who may be the most likely to benefit from early EUS-CPN, and could be used to determine eligibility in a future trial. In this research we developed a preliminary clinical prediction model (PREDICT-PANC). As there was no previous literature on the risk factors associated with the opioid use, we explored a number of plausible predictors. Age, medical performance status, pain at diagnosis, distance of the tumour from the right ganglion and tumours located in the body were shown to be associated with the need of opioids at three months. The model demonstrated good performance (AUC= 0.84, sensitivity 78.9%, specificity 69.2%, PPV 73.7% and NPV

75.0%). To improve generalisability and its potential future application, this preliminary data should be combined with other external cohorts to inform a larger derivation cohort and ultimately externally validated.

Future research

The research presented in this thesis contributes to the evidence supporting the rationale, feasibility and design considerations for a future clinical trial of early versus on demand EUS-CPN in patients with advanced pancreatic cancer. However, uncertainties remain regarding its feasibility, and robust estimates of recruitment and retention, and the acceptability of trial -related procedures to participants are required. Before proceeding to a phase III trial, we would recommend either a standalone feasibility/pilot study with an embedded phase III randomised controlled design or alternatively a phase III trial with an internal pilot. This trial will need to be carefully developed with all stakeholders, including extensive PPI input, an experienced clinical trials unit, clinical academics and specialist societies (such as the pancreatic section of the BSG) to ensure its success. If effective, early EUS-CPN could represent a major advance in the management of patients with advanced pancreatic cancer, benefiting patients and the NHS.

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APPENDIX

Appendix 1. Search Strategies on MEDLINE.

Search for clinical trials

1. pancrea$.mp.
2. (cancer or carcinoma or adenocarcinoma or tumour).mp. or Neoplasms/
3. (EUS or endoscopic ultrasound).mp.
4. (coeliac plexus neurolysis or coeliac plexus neurolysis or CPN or coeliac ganglia neurolysis or coeliac ganglia neurolysis or broad plexus neurolysis or radiofrequency ablation or RFA).mp.
5. (randomi$ed controlled or RCT or trial).mp. or Randomized Controlled Trials as Topic/
6. 1 and 2 and 3 and 4
7. 6 not (case report or review).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
8. remove duplicates from 7

Search for adverse events

1. pancreatic cancer.mp.
2. (complication* or side effect* or adverse event*).mp.
3. (coeliac plexus neurolysis or coeliac plexus neurolysis or CPN or coeliac ganglia neurolysis or coeliac ganglia neurolysis or broad plexus neurolysis).mp.
4. 1 and 2 and 3
5. 5 limit 4 to original articles
6. 5 not review*.mp.
7. 6 not abstract.mp.
8. 7 not chronic pancreatitis.mp.
9. (endoscopic ultrasound or EUS).mp.
10. 8 and 9
11. remove duplicates from 10
12. 11 not editorial*.mp.
13. 12 not conference abstract.mp.
14. 13 not conference proceeding*.mp.

Appendix 2. Sources of heterogeneity

Table 34. Methodological characteristics which account for heterogeneity in the effect sizes of the pooled studies.

Author	Year	Country	Study Design	Alcohol dose	ıseline VAS	Definition of treatment response	Opioid users (%)	Mean opioid dose (mg)	Chemo- or radiotherapy (%)	Risk of Bias
Central Injection										
LeBlanc *et al* [156]	2011	USA	randomised	20	-	≥40%	-	-	-	Moderate
Tellez-Avila *et al* [164]	2013	Mexico	non-randomised	10	9.5 (6-10)	≥50%	-	-	-	High
Doi *et al* [163]	2013	Japan	randomised	20	6.1 (1.7)	≥30%	32%	-	11%	Moderate
Levy *et al* [125]	2019	USA	randomised	10	3.6 (2.5)	≥30%	81%	45	87%	Low
Iwata *et al* [167]	2011	Japan	single arm	20	6 (5-9)	≥30%	38%	60		High
Facciorusso *et al* [173]	2016	Italy	single arm	20		≥30%	86%	-	100%	High
Seican *et al* [174]	2012	Romania	single arm	10-15	-	≥30%	100%	-	0%	High
Bilateral Injection										
LeBlanc *et al* [156]	2011	USA	randomised	20	-	≥40%	-	-	-	Moderate
Tellez-Avila *et al* [23]	2013	Mexico	non-randomised	20	9.0 (5-10)	≥50%	-	-	-	High
Wiechovwska *et al* [171]	2012	Poland	single arm	20	7.9 (6-10)	≥30%	100%	-	38%	High
Wieserma *et al* [169]	2001	USA	single arm		6.6 (2.2)	≥30%	100%	95	52%	Moderate
Gunaratnam *et al* [170]	1996	USA	single arm		5.8 (2.7)	≥30%	100%	24	30%	Moderate
Coeliac Ganglia Injection										
Minanga *et al* [172]	2016	Japan	single arm	20-40	7.3 (3-10)	≥30%	-	12	-	High
Doi *et al* [163]	2013	Japan	randomised	10-20	6.1 (1.9)	≥30%	29%	-	9%	Moderate
Levy *et al* [125]	2019	USA	randomised	21±4.5	3.7 (2.1)	≥30%	82%	41	76%	Low
Si-Jie *et al* [168]	2014	China	single arm	20	7.4 (5-10)	≥30%	-	-	-	High
Ascuse *et al* [166]	2011	USA	single arm	20	6.4 (2.0)	≥20%	-	-	-	High

The (-) symbol signifies that the relevant variable was not reported in the original study.

Appendix 3. Risk of bias assessment

Risk of Bias in non-Randomised Studies using ROBINS-I								
Author	**Bias Due to Confounding Factors**	**Bias in Selection of Participants**	**Bias In Measurement of Exposure**	**Bias in Blinding of Outcome Assessment**	**Bias Due to Missing Data**	**Bias in Measurement of Outcomes**	**Bias due to Selective Reporting**	**Overall Judgement**
Si-Jie *et al*[168],2014.	HIGH	SOME CONCERN	LOW	LOW	SOME CONCERN	LOW	HIGH	HIGH
Ascuse *et al*[166], 2011.	HIGH	SOME CONCERN	LOW	LOW	HIGH	LOW	HIGH	HIGH
Tellez-Avila *et al*[164], 2013.	HIGH	SOME CONCERN	LOW	LOW	SOME CONCERN	LOW	HIGH	HIGH
Seican *et al*[174]	HIGH	SOME CONCERN	LOW	LOW	SOME CONCERN	LOW	HIGH	HIGH
Minanga *et al*, 2016	HIGH	SOME CONCERN	LOW	LOW	HIGH	LOW	HIGH	HIGH
Wiechovwska *et al*[171], 2012.	HIGH	HIGH	LOW	LOW	LOW	LOW	SOME CONCERN	HIGH
Gunaratnam *et al*[170], 2001.	LOW	SOME CONCERN	LOW	LOW	SOME CONCERN	LOW	LOW	SOME CONCERN
Wiesema *et al*[169], 1996.	LOW	SOME CONCERN	LOW	LOW	SOME CONCERN	LOW	LOW	SOME CONCERN
Iwata *et al*[167], 2011.	HIGH	HIGH	LOW	LOW	SOME CONCERN	LOW	HIGH	HIGH
Facciorusson *et al* [173], 2017	HIGH	HIGH	LOW	LOW	SOME CONCERN	LOW	HIGH	HIGH

Risk of Bias in Randomised Trials using RoB 2.0 Tool						
	Potential Sources of Bias					
Author	**Randomisation Process**	**Deviation from Intended Intervention**	**Missing Outcome Data**	**Measurement of the Outcome**	**Selection of Reported Result**	**Overall Judgement**
Kanno *et al*[127], 2020.	**SOME CONCERN**	**LOW**	**HIGH**	**LOW**	**HIGH**	**HIGH**
Wyse *et al*[126], 2011.	**LOW**	**LOW**	**LOW**	**LOW**	**LOW**	**LOW**
Doi *et al*[163], 2013.	**SOME CONCERN**	**LOW**	**LOW**	**LOW**	**SOME CONCERN**	**SOME CONCERN**
Levy *et al*[125], 2019.	**LOW**	**LOW**	**LOW**	**LOW**	**LOW**	**LOW**
LeBlanc *et al*[156], 2011.	**LOW**	**LOW**	**LOW**	**SOME CONCERN**	**SOME CONCERN**	**SOME CONCERN**

Appendix 4. Grey Literature

List of studies registered in ClinicalTrials.gov, which remain unpublished upon completion.

Study 1:

Title:	EUS-guided CGN for Inoperable Cancer
Status:	Terminated
Study Results:	No Results Available
Locations:	Chinese University of Hong Kong, Hong Kong, Hong Kong, China
URL:	https://ClinicalTrials.gov/show/NCT02356640

Study 2:

Title:	Randomized, Controlled Trial of Endoscopic Ultrasound-Guided Bilateral Coeliac Plexus Neurolysis vs Coeliac Ganglia Neurolysis to Control Pain in Inoperable Pancreatic Cancer Patients with Inadequate Pain Control by Pain Killer
Status:	unknown status
Study Results:	No Results Available
Locations:	Unknown
URL:	https://ClinicalTrials.gov/show/NCT02220062

Study 3:

Title:	Evaluation of Injection Techniques in Coeliac Plexus Neurolysis
Status:	Completed
Study Results:	No Results Available
Locations:	Florida Hospital, Orlando, Florida, United States
URL:	https://ClinicalTrials.gov/show/NCT02068677

Study 4:

Title:	Trial Comparing Two Techniques of Coeliac Plexus Neurolysis for Treatment of Pain in Carcinoma Pancreas
Status:	Unknown status
Study Results:	No Results Available
Locations:	Asian Institute of Gastroenterology, Hyderabad, Andhra pradesh, India
URL:	https://ClinicalTrials.gov/show/NCT01182831

Study 5:

Title:	Endoscopic Ultrasound (EUS) Guided-Coeliac Plexus Neurolysis (CPN) in Unresectable Pancreatic Cancer
Status:	Completed
Study Results:	No Results Available
Locations:	University of Alabama at Birmingham, United States
URL:	https://ClinicalTrials.gov/show/NCT00968175

Study 6:

Title:	Randomized Trial of EUS Neurolysis in Pancreas Cancer
Status:	Completed
Study Results:	No Results Available
Locations:	Mayo Clinic Scottsdale, Scottsdale, Arizona, United States
URL:	https://ClinicalTrials.gov/show/NCT00279292

List of Studies which have been published only as Conference Proceedings.

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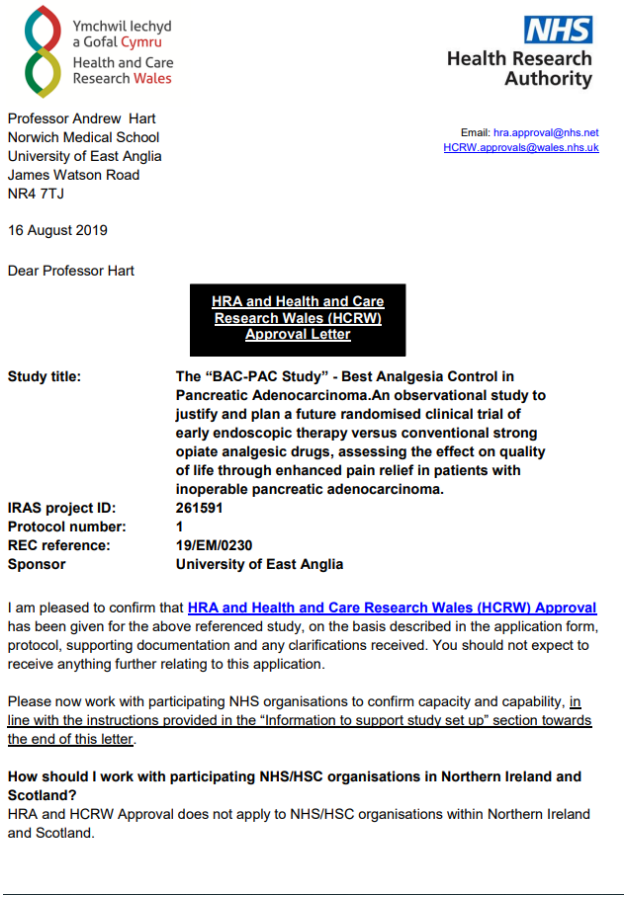
Appendix 5. HRA approval for BAC-PAC study



Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Professor Andrew Hart
Norwich Medical School
University of East Anglia
James Watson Road
NR4 7TJ

Email: hra.approval@nhs.net
HCRW.approvals@wales.nhs.uk

16 August 2019

Dear Professor Hart

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**The "BAC-PAC Study" - Best Analgesia Control in Pancreatic Adenocarcinoma.An observational study to justify and plan a future randomised clinical trial of early endoscopic therapy versus conventional strong opiate analgesic drugs, assessing the effect on quality of life through enhanced pain relief in patients with inoperable pancreatic adenocarcinoma.**
IRAS project ID:	**261591**
Protocol number:	**1**
REC reference:	**19/EM/0230**
Sponsor	**University of East Anglia**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?

The document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **261591**. Please quote this on all correspondence.

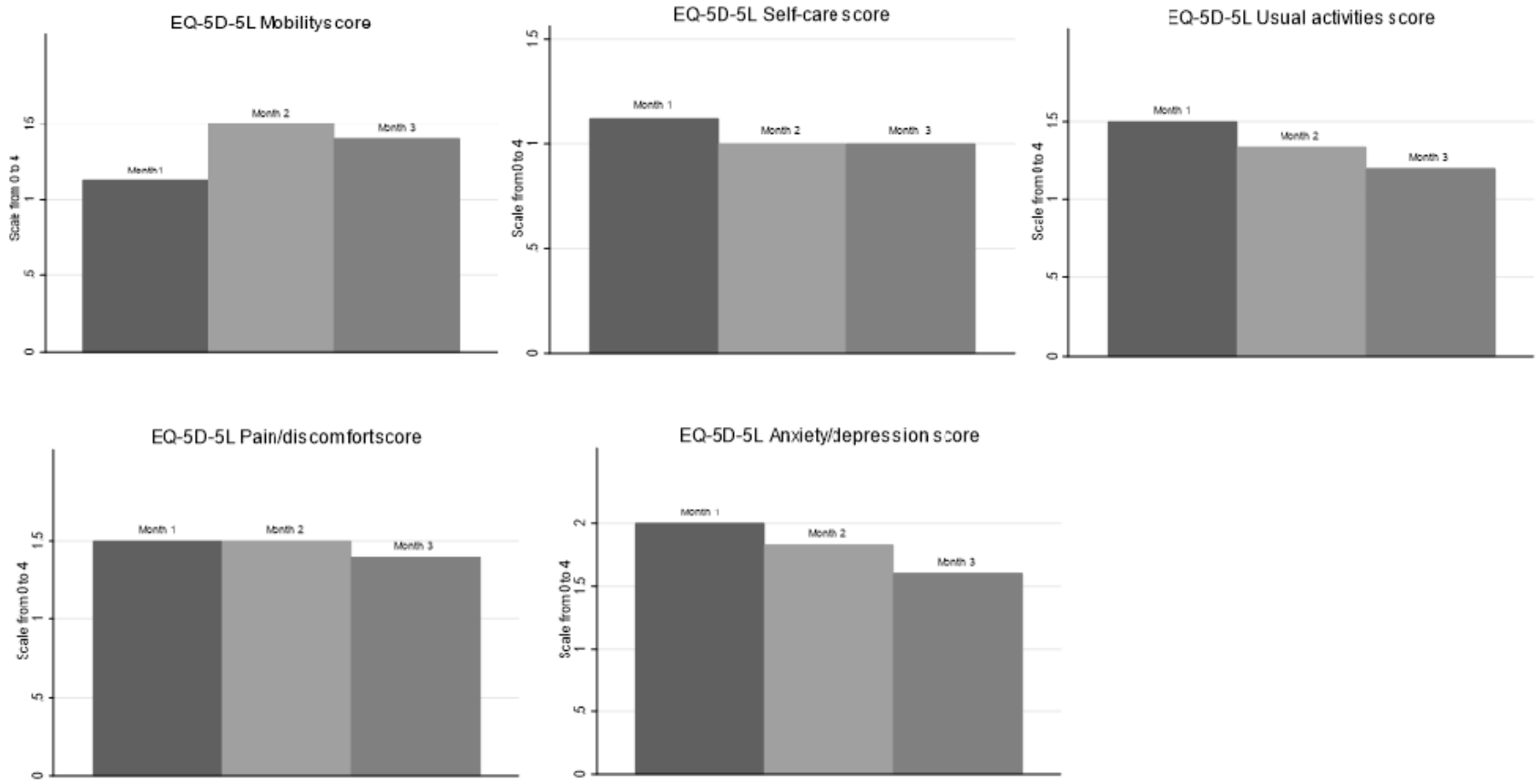
Yours sincerely,
Barbara Cuddon

Approvals Specialist

Email: hra.approval@nhs.net

Appendix 6. Graphical representation of the EQ-5D-5L scores for carers.

EQ-5D-5L quality of life mean scores of carers in the first three months of the study: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.



Appendix 7. Graphical representation of the EORTC-QLQ30 and EQ-5D-5L scores for patients.

Figure 30. EQ-5D-5L quality of life mean scores of patients in the first three months of the study.

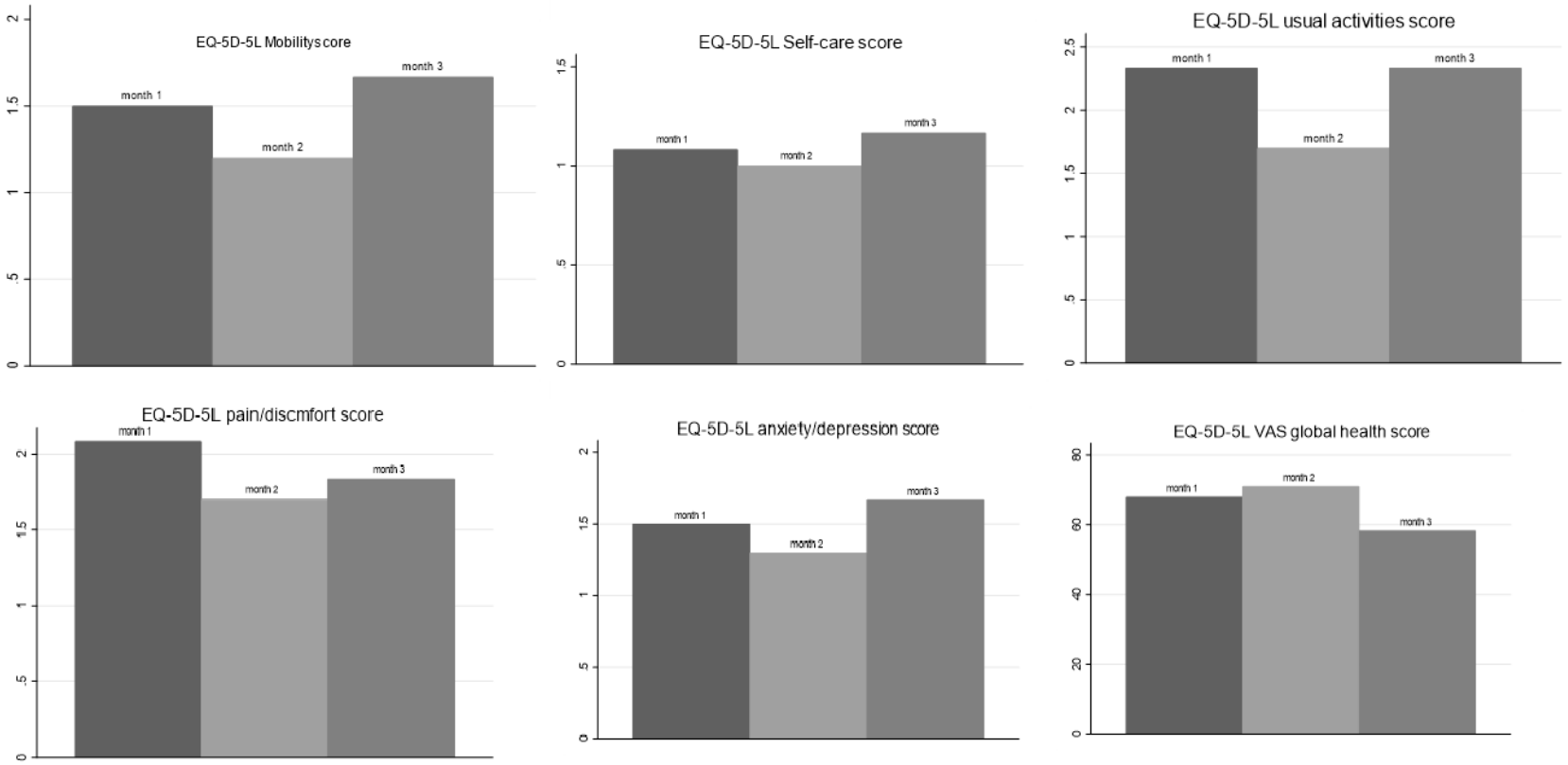
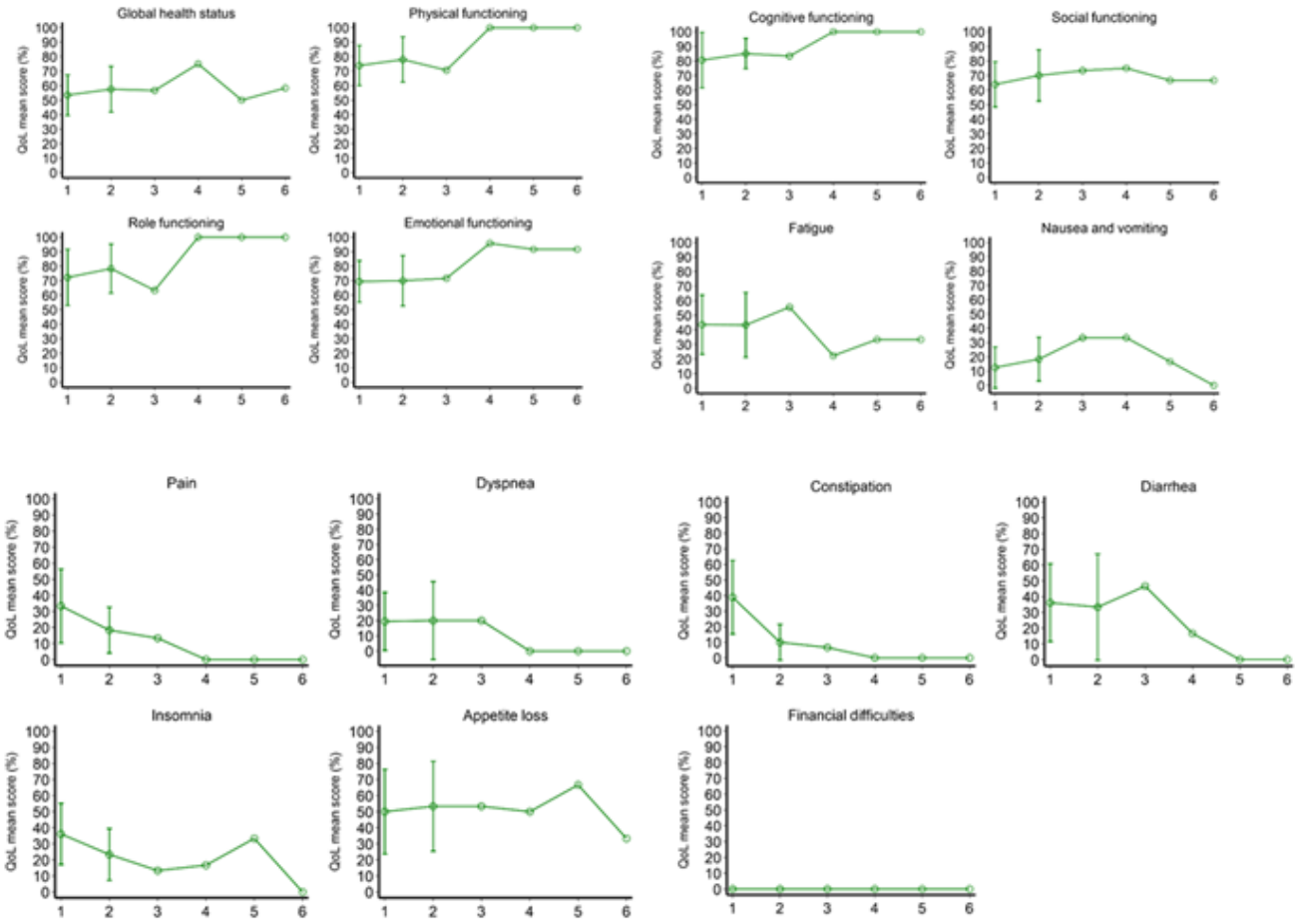


Figure 31. Graphical representation of the EORTC-QLQ30 scores over the first six months of follow up.



Appendix 8. Topic guides

Topic Guide for semi-structured interviews of patients with inoperable pancreatic cancer

Introductions

Explain main 4 themes (pain, treatments, endoscopy, and involvement in future RCT)

Confidentiality

Consent form signed

A. Pain

- Opening question: have you experienced any abdominal pain, so far and if yes how severe has it been?
- How does pain affect your wellbeing (including mood, sleep, appetite, energy levels, mobility)?
- How pain affects daily living activities (shopping, cleaning, cooking, dressing up)?
- Have you made any changes in your day-to day life since the pain started (change house, buy equipment, stopped activities)?
- Do you have any help from your close environment?
- Has pain affected your roles in the family? What about your social and professional roles, as well?
- Any other ways the pain has affected you?

B. Pain-treatments

- Opening question: have you received any pain treatments so far?
- How did you find them?
- Did you get any morphine?
- Did you get any side effects from it?
- Is the morphine effective?
- Do you feel the abdominal pain in pancreatic cancer is treatable with tablets?
- Is it easy to get appointments and prescriptions?
- Does the way your pain is being treated, give you security?
- Have you used or thought about using any private services to alleviate your pain (acupuncture, hypnotherapy?)Have you had any chemotherapy?
- Has your pain affected your chemotherapy treatment?
- What is your overall experience of having abdominal pain and being treated for pain

C. Endoscopy experience

Opening question: have you had any endoscopic procedures?

What is your experience of this test?

Perception of EUS

- Where you nervous about it in the preceding days?
- Did you have long waiting time?

Experience of having an EUS

- Were you feeling comfortable in the waiting room beforehand?
- How did you find staff behaviours? (receptionist, nurses in the room, nurses in the recovery area and doctor)
- Did you get enough sedation?
- Did you experience any pain/discomfort/ claustrophobia?

Patient attitudes towards endoscopy

- What you think should be done differently/better?
- What was done well? What could be done better?
- What was the most unpleasant part of the procedure?
- Are they overall satisfied?

D. Involvement in Research

- Would you be willing to have a second endoscopy as part of a research study?
- The allocation of treatments in an RCT are allocated through a system of randomisation. If the study was currently in progress, would you be willing your treatment to be randomly allocated, i.e. to get either endoscopy or morphine?
- Would the side-effects of morphine affect your decision?

Summarise and close the interview

Thank participant for their time and contribution.

Topic Guide for semi-structured interviews of carers with inoperable pancreatic cancer

Introductions

Explain main 4 themes (pain, treatments, endoscopy, and involvement in future RCT)

Confidentiality

Consent form signed

Opening questions:

How things have been since you found out about his/her illness?

Are you related to Mr X?

Did you have to go to the clinics and test with him/her?

A. Pain

- Has he/she been in pain?
- Has pain been a serious problem?
- Of all the symptoms Mr X has been experiencing, how high would you say is the pain in the list?
- Has he/she needed any support so far?
- Has this been just only emotional or physical, as well?
- How this has affected you?
- Have you had to make any changes to your day-to day life (for example give up family tasks, stop leisure activities, take time-off work, travel from where you normally live etc.)

B. Pain treatment

- Has morphine made any difference to his/her symptoms?
- Do you think he/she needs more support since morphine was prescribed?
- Does he/she do less since morphine was started? Does he stay in bed more?
- Is he/she more confused or forgetful? Has it been more difficult to co-op at home with him/her?
- Has morphine affected his/her mood?
- Do you think abdominal pain is treatable with morphine?

C. Endoscopy experience

- Did you go with him/her for the endoscopy?
- Where you worried about him/her having an endoscopy?
- What was your concern about the endoscopy? Was it the risks of complications, was the result of the biopsy or anything else?
- Did you see anything in the endoscopy unit that you didn't like?
- Is there anything we could do to make things better?

D. Involvement in research

- Would you encourage your relative to come for a second endoscopy as part of a research study or would you rather not?
- If not, what would be the reason?
- Is there anything that we could do to make you re-think about it? For example if we would explain better the procedure, if your appointment was first in the morning so you don't have to wait?
- What would make people more willing to have a second endoscopy for treating pain?

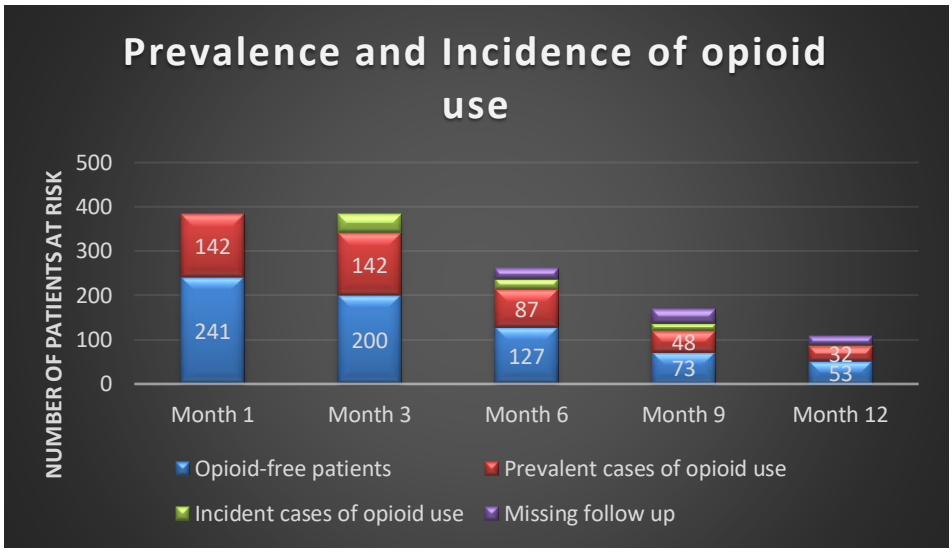
Summarise and close the interview

Appendix 9. Formulas for the estimation of the CT enhancement patterns

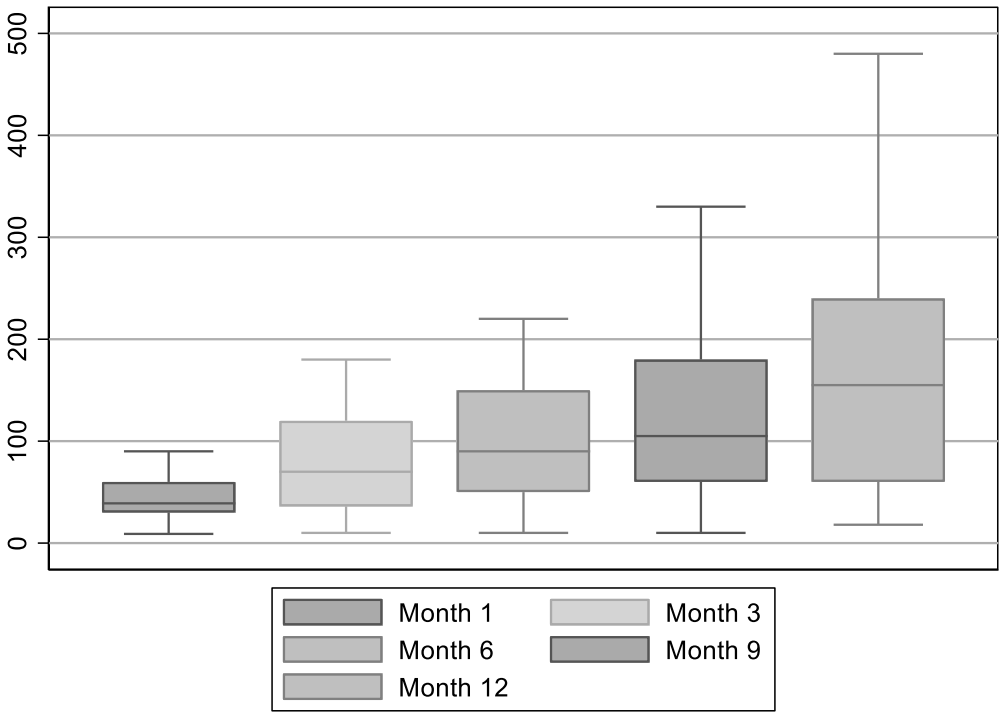
AEC= (tumour attenuation at the portal venous phase) – tumour attenuation at the arterial phase.

REC= (tumour attenuation at the portal venous phase- tumour attenuation at the arterial phase)/ (parenchymal attenuation at the portal venous phase- parenchymal attenuation at the arterial phase)

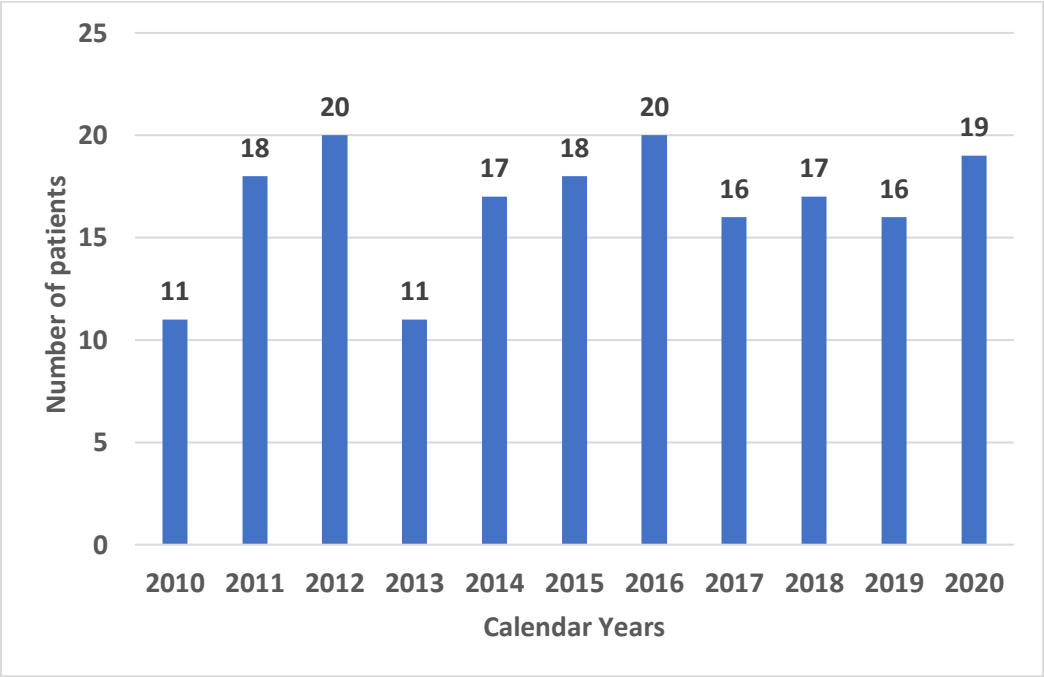
Appendix 10. Graphical illustration of the prevalence, incidence and missing follow up



Appendix 11. Box plot of the daily morphine requirements over time. Values expressed in mg.



Appendix 12. Graphical illustration of the number of patients with pancreatic cancer requiring opioids at three months diagnosed in NNUH, for the period 2010 to 2020.



Appendix 13. Construction and interpretation of the calibration plot

In this calibration graph we ranked the probabilities from 0 to 1 and divided them into 10 deciles. We created a scatter plot with the mean values of each decile, plotting the observed probabilities in the y-axis and the predicted probabilities in the x-axis. In general, the model is relatively well-calibrated for most of the deciles of probability. For example, in our plot in the 9th decile of probabilities the mean value (green circle) is almost on the diagonal line, therefore the probability calculated by the model equals the one that was observed. In contrast, the model is less calibrated for probabilities in the 6th decile, where the expected probability is 59% but the observed is 70%. Overall, there is no systematic deviation, i.e. the observed values being constantly lower or constantly higher than the expected. Finally, we constructed a Lowess smoother (light blue line), which is the regression line fitting the mean probabilities of each decile. The Lowess smoother approximates the diagonal line, implying that the model is likely to be well-calibrated.

Appendix 14. The sensitivity analysis model

Table 35. Univariate analysis of parameters predictive of >60 mg of opioids at three months post-diagnosis.

	Patients on ≥ 60mg of opioids at 3 months (n=116)	Patients on <60 mg of opioid at 3 months (n=267)	Odd Ratio (95% CI)	P-value
Age in years (mean, SD)	66.5 (0.6)	72.8 (9.8)	0.94 (0.92-0.96)	<0.001
Abdominal Pain at diagnosis (n,%)	91 (78%)	74 (28%)	9.49 (5.66-15.93)	<0.001
Health Performance Status (n,%)				
0	28 (25%)	91 (36%)	1.00	
1	41 (37%)	70 (28%)	1.90 (1.07-3.38)	0.028
2	24 (21%)	37 (15%)	2.11 (1.08-4.10)	0.028
3	17 (15%)	45 (18%)	2.03 (0.95-4.33)	0.067
4	2 (2%)	11 (4%)	0.96 (0.19-4.88)	0.970
Cancer Stage (n,%)				
I	4 (3%)	18 (7%)	2.14 (0.57-8.02)	-
II	10 (9%)	21 (8%)	1.83 (0.58-5.77)	0.258
III	37 (32%)	91 (34%)	2.15 (0.70-6.61)	0.303
IV	64 (56%)	134 (51%)	2.15 (0.70-6.61)	0.182
Anti-depressant or anxiolytic (n,%)	43 (37%)	59 (23%)	2.00 (1.2-3.23)	0.004
Pancreatic duct diameter in mm (SD)	5.56 (3.1)	6.16 (3.1)	0.94 (0.83-1.05)	0.262
Distance of the tumour from the right ganglion in mm (SD)	17 (16)	30 (22)	0.96 (0.94-98)	0.001
Distance of the tumour from the left ganglion in mm (SD)	19 (18)	31 (21)	0.97 (0.95-0.99)	0.002
Anterior-posterior tumour dimension in mm (SD)	34.6 (11.4)	31.3 (13.3)	1.02 (0.99-1.04)	0.146
Latero-lateral tumour dimension in mm (SD)	37.6 (14.1)	33.4 (16.3)	1.01 (0.99-1.04)	0.132
Cephalocaudal tumour dimension in mm (SD)	34.5 (11.5)	31.3 (11.3)	1.02 (0.99-1.05)	0.105

Table 36. Multivariable logistic regression analysis of the clinical predictors of ≥ 60mg daily opioid use at three months post-diagnosis. The clinical parameters were analysed in a total of 357 patients.

	OR	95% CI	p-value
Age in years	0.96	(0.94-0.99)	0.003
Abdominal Pain at diagnosis	8.24	(4.77-14.23)	<0.001
Anxiety or depression	2.11	(1.15-3.87)	0.017

Figure 32. Receiver Operator Curve (ROC) analysis the clinical prediction model in the sensitivity analysis for predicting ≥60 mg of opioids daily.

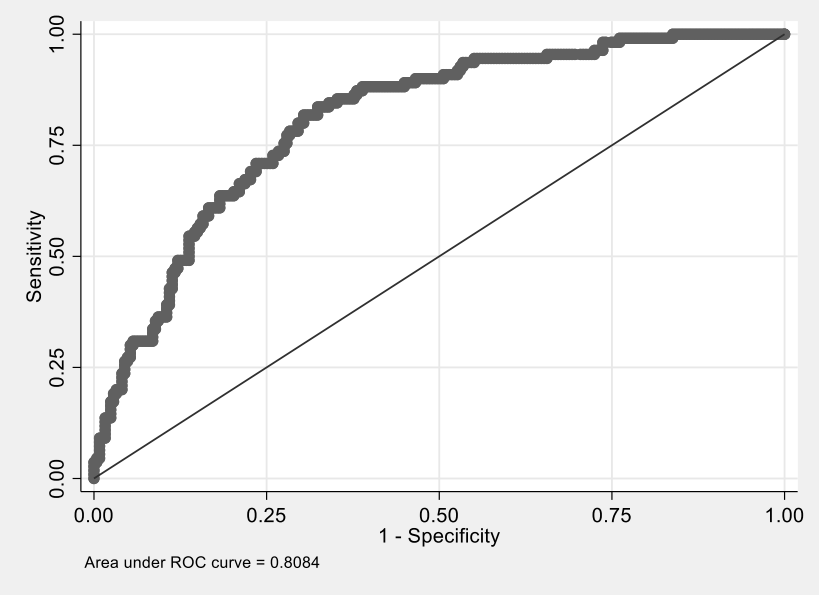


Figure 33. Calibration plot for the clinical prediction model in the sensitivity analysis for predicting ≥60 mg of opioids daily.