IMPROVING OUTCOMES IN PATIENTS WITH A DIAGNOSIS OF PANCREATIC CANCER

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Abbreviations

ACE - Adult Comorbidity Evaluation Score

AEs - Adverse Events

ASCO - American Society of Clinical Oncology

ATM - Ataxia Telangiectasia Mutated

ATR - Ataxia Telangiectasia And Rad3-Related Protein

BMI - body mass index

BRAF - B-Raf Proto-Oncogene, Serine/Threonine Kinase

BRCA1 - Breast Cancer 1

BRCA2 - Breast Cancer 2

BSA - body surface area

CA19-9 - Cancer antigen 19-9

CBR - Clinical Benefit Response

CDKN2A/P16 - Cyclin-Dependent Kinase Inhibitor 2A

cfDNA - Cell-Free DNA

CI - confidence intervals

CNV - Copy number variation

CPCR - Christie Patient Centred Research

CRUK MI - Cancer Research UK Manchester Institute

CT - Computed Tomography

DDR - DNA Damage Repair

DM - Diabetes Mellitus

DNA - Deoxyribonucleic Acid

ECOG PS- Eastern Cooperative Oncology Group Performance Status

EN - enteral nutrition

EOL - end of life

EORTC - European Organization for Research and Treatment of Cancer

ESMO- European Society for Medical Oncology

ESMO-MCBS - ESMO Magnitude of Clinical Benefit Scale

FBG - fasting blood glucose

FDA - US Food and Drug Administration

FNA - Fine Needle Aspiration

FOLFIRINOX- 5-Fluorouracil, Leucovorin, Irinotecan and Oxaliplatin combination chemotherapy

FPC - Familiar Pancreatic Cancer

gBRCA - Germline BRCA Mutation

GlucMax- the highest plasma glucose measured per patient ever- including baseline and during treatment

GlucMin - the lowest plasma glucose measured per patient ever- including baseline and during treatment

GP - General Practitioner

HbA1c - glycated haemoglobin

HBOC - Hereditary Breast and Ovarian Cancer

HCRW - Health and Care Research Wales

HHS - hyperosmolar hyperglycaemic state

HPB - Hepato-Pancreato-Biliary

HR - Hazard Ratio

HRA - Health Research Authority

HRQoL - health related quality of life

ICF - Informed Consent Form

ICM - irinotecan, cisplatin and mitomycin-C combination chemotherapy

IDMC - Independent Data Monitoring Committee

KRAS - KRAS proto-oncogene, GTPase

MCRC - Manchester Cancer Research Centre

MLH1 - Mutl Homolog 1

MLH3 - MutL Homolog 3

MMR - Mismatch Repair

MRI - Magnetic Resonance Imaging

MSH2 - Muts Protein Homolog 2

MSH6 - Muts Protein Homolog 6

NA - not available

NGS - Next Generation Sequencing

NHS - National Health Service

NICE - National Institute for Health and Care Excellence

NTRK - Neurotrophic Receptor Tyrosine Kinase

ORR - Overall Response Rate

OS - Overall Survival

OxMDG - 5-Fluorouracil, Leucovorin and Oxaliplatin combination chemotherapy

PALB2 - Partner and Localiser of BRCA2

PARP - Poly (ADP-Ribose) Polymerase

PARPi - PARP inhibitor

PDAC - Pancreatic Ductal Adenocarcinoma

PD-L1 - Programmed death-ligand 1

PEXG - Cisplatin, Epirubicin, Capecitabine and Gemcitabine combination chemotherapy

PFS- Progression Free Survival

PIS - Patient Information Sheet

PJS - Peutz-Jeghers Syndrome

PN - parenteral nutrition

PNI - Perineural invasion

PR - Partial Response

PROMs - Patient Reported Outcome Measures

QLQ-C30 - EORTC Quality-Of-Life Core Questionnaire

QLQ-C30- PAN26 - QLQ-C30 Pancreatic Cancer Module

QoL - Quality Of Life

RCT - Randomised Controlled Trial

REC - Research Ethics Committee

RECIST - Response Evaluation Criteria In Solid Tumours

RNF43 - ring finger protein 43

RR - Risk Ratio

SD- Stable Disease

SMAD4 - SMAD Family Member 4

SNVs - Single Nucleotide Variants

T1- Time-Point 1

T2- Time-Point 2

T3- Time-Point 3

T2DM - type 2 Diabetes Mellitus

T3cDM - type 3c Diabetes Mellitus

TNM - The Tumour Node Metastasis Classification of Malignant Tumours

TP53 - Tumour Protein P53

TRK - Tropomyosin Receptor Kinases

UK - United Kingdom

US - United States

WES - Whole Exome Sequencing

WGS - Whole Genome Sequencing

WHO - World Health Organisation

Abstract

Pancreatic ductal adenocarcinoma (PDAC) has a dismal prognosis with high resistance to chemotherapy. Many clinical trials with novel treatment combinations have failed to increase survival for patients with advanced disease, and consequently, it is currently one of the deadliest cancers globally. This PhD thesis aimed to identify areas within the management framework of PDAC that, with appropriate interventions, could lead to improved patient outcomes. As such, I addressed two clinical entities highly prevalent but often overlooked in patients with PDAC, to determine whether improvements in these areas could lead to improved outcomes.

A specifically-designed and populated large retrospective data collection of patients with PDAC (all stages), demonstrated for the first time that high GlucMin (defined as the lowest plasma glucose measured per patient ever) confers a worse OS; and that antidiabetic treatment use in patients with high baseline glucose leads to better OS. Thus, these results give the first signal that better antidiabetic control in patients with PDAC could lead to longer OS. Whilst confirmation and validation of these results are needed from prospective studies, I also showed that hyperglycaemia is a widespread issue in patients with PDAC, with almost 2/3 of patients having abnormal glucose levels, but only 29% were known to be diabetic.

Conventional survival-based outcomes were then challenged by assessing clinician and patient perceptions on “clinically-meaningful” outcomes in the setting of a poor-prognosis malignancy, with modestly-effective treatment options. For this purpose, a prospective investigator-designed longitudinal questionnaire study was developed comprising of purposely built survey; and two validated tools measuring quality of life. Results from this study revealed that there is a mismatch between patient and physician views about the aims, priorities and expected benefit from the treatment of advanced PDAC. The main findings were that patients significantly overestimated the expected length of time extension that chemotherapy would offer, and when making decisions about treatment options: patients prioritised length of survival, while physicians thought that patients would prioritise the best balance between side-effects and survival. Overall, patients in this study had significantly higher hopes for treatment leading to life extension, compared to their physicians, and also had a lot of fear and worry about the future and poor symptom scores and quality of life.

These findings highlight that there are currently some important improvements that could be made in management of hyperglycaemia and diabetes, quality of life and symptoms, and patient expectations in patients with PDAC. Given the poor outcomes in PDAC, these potential advancements should not be overlooked.

Declaration

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

Copyright statement

This thesis is dedicated to my father

Arvo Pihlak

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Chapter 1: Introduction

This chapter contains text modified from the following articles that I wrote or co-wrote as part of this PhD:

- *Pihlak R, Valle JW, McNamara MG. Germline mutations in pancreatic cancer and potential new therapeutic options* [1].
- *Pihlak R, Weaver J MJ, Valle JW and McNamara MG. Advances in molecular profiling and categorisation of pancreatic adenocarcinoma and the implications for therapy* [2].
- *Lewis AR, Pihlak R and McNamara MG. The importance of quality of life management in patients with advanced pancreatic cancer ductal adenocarcinoma* [3].

1.1. Pancreatic ductal adenocarcinoma incidence, survival and treatment options

Pancreatic ductal adenocarcinoma (PDAC) is the 11th most common cancer in the United Kingdom (UK) (2016) [4] and United States (US) (2017) [5] and it is also one of the deadliest cancers [6] with a 5-year overall survival (OS) for all stages around 8% in the US [5] and 3% in the UK [4]. Around 50% of patients have metastatic disease at presentation, 35% locally advanced and only 15% have potentially resectable disease [7]. Adjuvant chemotherapy is recommended for all patients who have had potentially curative surgery, where appropriate, and in recent years there have been multiple trials assessing different chemotherapy combinations in this setting [8-10]. Recent reported data from the phase III randomised PRODIGE24/CCTG PA.6 trial reported that even in patients who receive "aggressive" adjuvant chemotherapy with modified 5-fluorouracil and leucovorin, irinotecan and oxaliplatin combination (mFOLFIRINOX), the median OS is just 54.4 months [11]. A previous trial in the adjuvant setting reported an OS of 28.0 months with the combination regimen of gemcitabine and capecitabine [12]. Prior to these two published trials, the standard of care in the adjuvant setting was single agent gemcitabine [13], and it is still in use in the adjuvant setting for patients who have poorer performance status or who have comorbidities precluding combination chemotherapy. The use of mFOLFIRINOX in the adjuvant setting can be especially challenging, as this combination is associated with high number of treatment-related adverse events [11] and thus, the choice of chemotherapy depends very much on patients' performance status and if they have recovered from surgery.

Locally advanced PDAC is stage III disease and classified as a cancer that involves the celiac axis or superior mesenteric artery, but without metastatic disease [14, 15], and depending on the degree of vascular involvement, it can be further divided in to 2 surgical categories: borderline resectable and locally advanced unresectable [16]. There are currently no phase III trials demonstrating a benefit of neoadjuvant treatment prior to surgery in patients with resectable PDAC thus, currently if the disease is suitable for resection, best evidence supports surgery followed by adjuvant chemotherapy. However, due to high recurrence rates after surgery, many ongoing phase III trials are investigating the benefit of neoadjuvant chemotherapy or chemoradiotherapy, prior to surgery, for both resectable and borderline resectable disease. Some ongoing clinical trials have shown early mixed results regarding the benefit of neoadjuvant chemoradiotherapy [17, 18] for resectable and borderline resectable disease, with the final analysis showing no benefit on survival [18]. A small phase II trial has also reported a benefit of neoadjuvant FOLFIRINOX chemotherapy followed by chemoradiotherapy in patients with borderline resectable disease [9]. Similarly a phase II feasibility study, ESPAC-5F which compared immediate surgery (32 patients) with neoadjuvant gemcitabine plus capecitabine (20 patients) or FOLFIRINOX (20 patients) or chemoradiotherapy (16 patients) in borderline resectable disease, showed no difference in resection rates; however neoadjuvant therapy had a significant one year survival benefit with a Hazard Ratio (HR) = 0.28 [19]. Multiple trials are currently ongoing in this setting assessing the benefit of various combinations as pre- or perioperative treatment [20-22] and phase III trial results are awaited as some centres have already adopted neoadjuvant treatment [23], whilst others are still waiting for more convincing evidence [24]. Currently, for locally advanced PDAC that is not resectable, the choice of chemotherapy is usually based on evidence from the metastatic setting, as the majority of large phase III trials with chemotherapy have only included patients with metastatic disease [7].

In advanced PDAC, the Phase III ACCORD [25] and MPACT [26] combination chemotherapy trials have been the only studies which reported clinically-meaningful significant extensions in median OS in the first line setting in the recent decade. The FOLFIRINOX regimen from the ACCORD trial has resulted in the longest-reported median OS for patients with metastatic PDAC; 11.1 months compared to 6.8 months with single-agent gemcitabine [25]. The MPACT trial resulted in a median OS of 8.5 months in the

gemcitabine plus nab-paclitaxel arm, compared to 6.7 months in the gemcitabine alone arm [26] in patients with metastatic pancreatic cancer and thus, this combination is another option for first line treatment. Unfortunately, multiple other clinical trials with either chemotherapy combinations or novel agents have failed to demonstrate a significant OS improvement [27-30]. Figure 1.1 shows current treatment options based on performance status in patients with advanced PDAC.

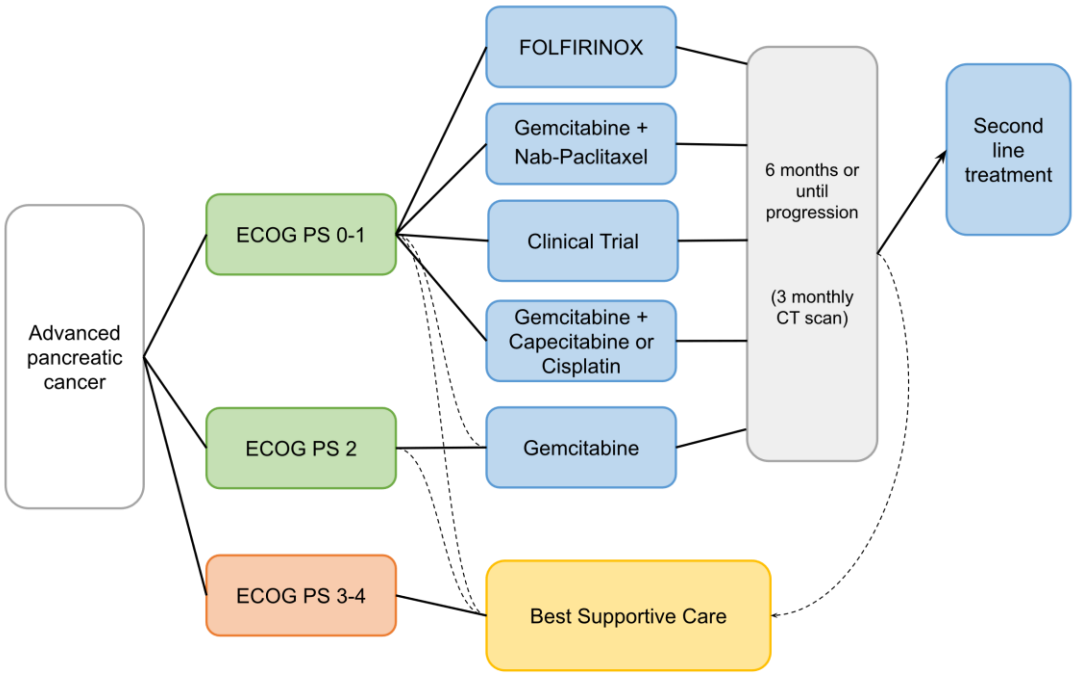


Figure 1.1: First line treatment options for patients with advanced PDAC based on performance status. ECOG PS: Eastern Cooperative Oncology Group performance status. FOLFIRINOX: 5-fluorouracil, leucovorin, irinotecan and oxaliplatin, CT: Computerised tomography. Dotted lines show decline in performance status that leads to change in treatment.

In 2019 the POLO trial [31] showed benefit in progression free survival (PFS) in the maintenance setting with a poly (ADP-ribose) polymerase (PARP) inhibitor olaparib in patients with germline BReast CAncer gene 1/2 (*BRCA)*-mutated PDAC, after at least 16 weeks of first-line platinum-based chemotherapy and no radiological progression. There was a significant difference in PFS between the olaparib- and placebo-treated groups (7.4 vs. 3.8 months; HR 0.53; p=0.004), and this is the first phase III trial to report efficacy of maintenance treatment and targeted therapies in patients with PDAC. It was also reported that 3315 patients with metastatic pancreatic cancer were screened and of those, 7.5% harboured germline BRCA 1/2 mutations [31].

Second-line chemotherapy options are also limited in patients with pancreatic cancer with the longest median OS reported in the phase III NAPOLI-1 trial combining 5-FU, folic acid with liposomal irinotecan, achieving a median OS of 6.1 months versus liposomal irinotecan monotherapy (4.9 months) or 5-FU/folinic acid (4.2 months) [32]. Unfortunately, liposomal irinotecan is not funded in many countries, and thus second line treatment options are based on earlier trials with 5-FU, folic acid and oxaliplatin [33], smaller phase II trials with irinotecan [34] or gemcitabine given after FOLFIRINOX [35].

The poor outcomes of patients with PDAC have been previously proposed to be due to various cancer related factors like aggressive biology [36], late presentation [37], difficult anatomical location (unresectability due to vascular involvement) [38], early micrometastatic disease and limited treatment options targeting the dominant driver mutation (KRAS) [39]. Therefore, due to poor prognosis and limited improvement in survival, PDAC is a major cause of cancer death, and it is estimated that it will become the 2nd leading cause of cancer-related death in the US by 2030 [40]; being 3rd [5] and 5th [4] currently in the US and UK respectively.

Currently the predictive factors to identify patients most likely to benefit from any of the standard of care treatments is limited. However, the POLO trial [31] has opened up the possibility of precision medicine in patients with advanced PDAC.

1.1.1 Targeted and other novel therapies in pancreatic cancer

Due to the poor outcomes of patients with pancreatic cancer, the need for new treatment options is crucial, even if it only benefits a subgroup of patients. The published data suggests that depending on the family history of cancer, there may be varying levels of both germline and sporadic mutations in patients with pancreatic cancer.

It has previously been reported that around 5-10% of pancreatic cancers arise in the presence of a family history of this diagnosis [41]. Multiple syndromes and diseases [42-44] have been associated with an increased risk of developing pancreatic cancer, including familial atypical multiple mole melanoma (FAMMM)[45, 46], Peutz-Jeghers syndrome (PJS) [47, 48], hereditary pancreatitis [49], hereditary nonpolyposis colorectal carcinoma (HNPCC) [50], hereditary breast and ovarian cancer (HBOC) [51], and familial

adenomatous polyposis [52, 53]. Although the numbers are small, the most common germline mutations in pancreatic cancer related to these syndromes are *BRCA*1/2, partner and localiser of *BRCA*2 (*PALB2*), cyclin-dependent kinase inhibitor 2A (*CDKN2A*), ataxia telangiectasia mutated (*ATM*), tumour protein p53 (*TP53*) and mismatch repair genes mutL homolog 1 (*MLH1)*, mutS homolog 2 (*MSH2)* and mutS homolog 6 (*MSH6)* (Figure 1.2).

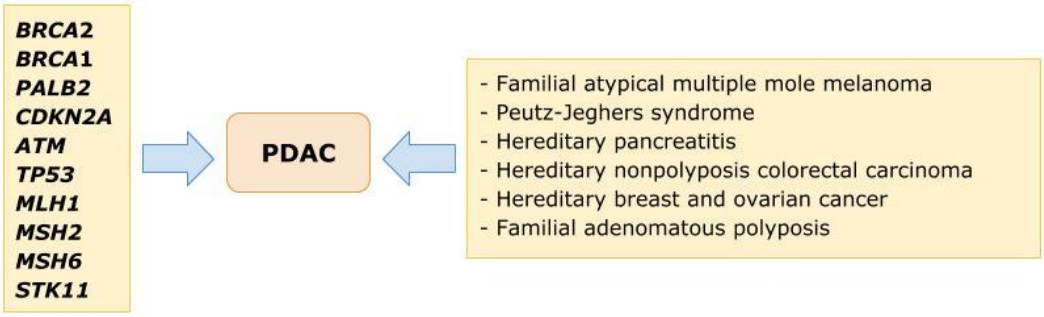
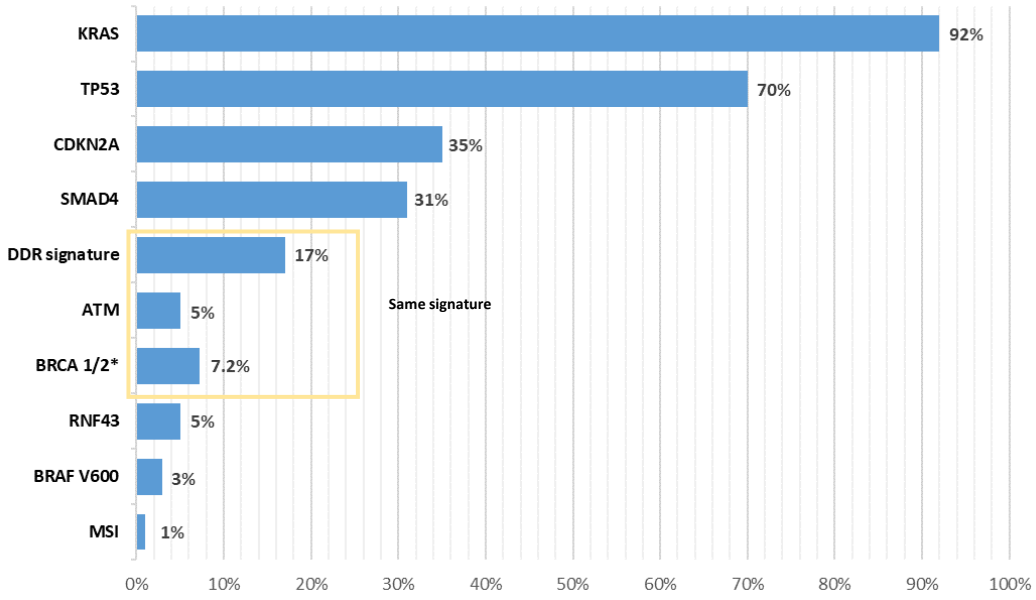


Figure 1.2. Most common germline mutations and syndromes associated with increased risk of developing PDAC. *BRCA2*-breast cancer 2, *BRCA1*-breast cancer 1, *PALB2*-partner and localiser of BRCA2, *CDKN2A*-cyclin-dependent kinase inhibitor 2A, *ATM*-ataxia telangiectasia mutated, *TP53*-tumour protein p53, *MLH1*-mutL homolog 1, *MSH2*-mutS homolog 2, *MSH6*-mutS homolog 6.

Over the past 3 decades, multiple studies have looked at the number of different potentially targetable mutations in patients with PDAC. The largest whole genome sequencing (WGS) and whole exome sequencing (WES) studies have shown prevalent mutations in PDAC to be: KRAS proto-oncogene, GTPase (KRAS); Tumour protein p53 (TP53); cyclin-dependent kinase inhibitor 2A (CDKN2A); SMAD Family Member 4 (SMAD4); DNA damage repair (DDR) pathway mutations (signature); ATM; BRCA1/2, ring finger protein 43 (RNF43); B-Raf proto-oncogene, serine/threonine kinase (BRAF); microsatellite instability (MSI) [54-56] (Figure 1.3).

Currently there is only phase III trial evidence about the efficacy of targeting germline *BRCA*1/2 variants present around 7% of patients with PDAC however, many of these other mutations are being investigated in various basket trials [57-59] also including patients with PDAC and may be possible targets for future treatment in these patients.



	KRAS	TP53	CDKN2A	SMAD4	DDR signature	ATM	BRCA 1/2*	RNF43	BRAF V600	MSI
Patients	456	100	100	100	456	150	2206	456	150	385
Platforms	WGS & WES	WGS & CNV	WGS & CNV	WGS & CNV	WGS & WES	WES	NGS & CNV	WGS & WES	WES	WGS & WES
Ref	[54]	[55]	[55]	[55]	[54]	[56]	[60]	[54]	[56]	[61]

Figure 1.3. Prevalence of common mutations found in PDAC, with patient numbers and platforms used. KRAS—KRAS proto-oncogene, GTPase; TP53—tumour protein p53; CDKN2A—cyclin-dependent kinase inhibitor 2A; SMAD4—SMAD Family Member 4; DDR—DNA damage repair signature; ATM—Ataxia Telangiectasia Mutated; BRCA1/2—BReast CAncer gene 1/2; RNF43—ring finger protein 43; BRAF—B-Raf proto-oncogene, serine/threonine kinase; MSI—microsatellite instability. WGS - Whole Genome Sequencing; WES - Whole Exome Sequencing; CNV- Copy number variation; NGS- Next generation sequencing. Yellow box indicating mutations part of the same signature. *-germline mutations. Ref-reference.

Increasing research in recent decades has improved our understanding of the biology of pancreatic cancer, and this has led to new clinical trials aiming to determine if changes in these tumours are targetable. Whilst whole genome sequencing has provided strong evidence that there are multiple germline and somatic changes in these tumours [55], it is not yet known whether these are targetable by the same novel therapeutics, and so future studies should attempt to address this dilemma in clinical trials.

The PARP and ATM/Ataxia Telangiectasia And Rad3-Related Protein (ATR) inhibitors are currently promising novel agents undergoing investigation in these solid tumours, as in addition to 7.5% of patients with PDAC having germline BRCA mutations, up to 24% of patients seem to have DDR deficiency [62]. Whilst the POLO trial reported positive

results [31], previous trials in PDAC have shown limited effects of PARP inhibitors as monotherapy after disease progression [63, 64]. Further research into different combinations of cytotoxic and targeted therapies is obligatory in pancreatic ductal adenocarcinoma. At this time, treatment with platinum agents is considered the standard of care for patients with germline-mutated PDAC [65], and updated guidelines recommend genomic testing for all patients with pancreatic cancer [66].

The use of immunotherapy as a therapeutic option has also been researched in patients with PDAC, with disappointing results in the initial single agent trials [67-69]. A recently-presented randomised phase II trial [70] investigated first-line gemcitabine and nab-paclitaxel with or without durvalumab (Programmed death-ligand 1 - PD-L1 inhibitor) and tremelimumab (anti-cytotoxic T-lymphocyte-associated protein 4 - CTLA-4) in patients with metastatic PDAC. The results demonstrated that even the addition of dual immune checkpoint inhibitors to standard chemotherapy did not result in a significant improvement in overall response rate (ORR), PFS or OS [70].

However, MSI, found in 1% [61] of patients with PDAC, has been shown to predict response to immunotherapy [71], and the PD-L1 inhibitor pembrolizumab has been licenced in the US for the treatment of patients with any MSI-high advanced cancer [72]. Although MSI is rare in PDAC, there have been promising results in studies of novel treatments with immunotherapy in solid tumours (including PDAC) [59, 71], and thus mutational testing for this deficiency in patients with PDAC could also be considered.

Whilst the outcomes of patients with PDAC are dismal, and recent trials have shown only modest survival improvements, this raises the question as to whether addressing other aspects of the patient pathway and implementing changes, even if small, would result in greater improvements in quality of life or survival.

1.2. Influencing the current standard of care

1.2.1. Diabetes and hyperglycaemia in patients with PDAC

More than 25 years ago, Fisher *et al* demonstrated a link between a diagnosis of diabetes and increased growth of pancreatic cancer cells *in vivo* [73]; this led to multiple studies investigating this interaction.

Compared to other common cancers, the incidence of diabetes is much higher in patients with PDAC [74]. In a study by Aggarwal *et al*, diabetes was found in 14.8-20.7% of patients with prostate, colon, breast, lung cancers and 23.5% healthy controls compared to 68% of patients with PDAC (age matched) [74].

In a study by Pannala *et al*, they recorded fasting glucose levels of 512 patients with recently-diagnosed PDAC within 30 days of diagnosis and found that only 14% of patients had normal values, 47% had diabetes levels and 38% had abnormal levels that did not yet meet the diagnostic criteria [75].

This and other previous studies that screened patients with PDAC for diabetes [75-77] showed significantly higher rates of diabetes compared to studies that relied on medical notes [78-80], and this highlights the issue that around a third of diabetes cases in patients with PDAC is unrecognised [81].

Diabetes also increases the risk of development of pancreatic cancer [82-84] and it is also one of the foremost risk factors. In a meta-analysis conducted by Huxley *et al* in 2005, it was reported that the pancreatic cancer risk ratio (RR) was negatively associated with the duration of diabetes and thus, showed a modest causal association between type-II diabetes (T2DM) and PDAC [85]. Gullo *et al* reported that in 40% of patients with pancreatic cancer, diabetes was diagnosed at the same time as the cancer, and in approximately 16%, within two years before the diagnosis of cancer [86]. The previously mentioned study by Pannala *et al* reported that approximately 74% of the new cases of diabetes diagnosed in patients with pancreatic cancer was new onset (defined as a diagnosis <2 years previous) [75].

A recent study [87] found that there were 3 phases of metabolic or soft tissue changes seen in patients prior to the diagnosis of PDAC (compared to healthy controls): 1) Hyperglycaemia, 18-30 months prior to diagnosis without any other changes; 2) Pre-cachexia, 6-18 months before diagnosis- significant decreases in serum lipids, body weight, abdominal subcutaneous fat with increases of hyperglycaemia; 3) Cachexia, 0-6 months before diagnosis- hyperglycaemia with significant reductions in all serum lipids, abdominal subcutaneous fat, visceral adipose tissue and muscle [87].

These data support the hypothesis that new onset diabetes can be a sign of early pancreatic cancer, although the pathogenesis and mechanisms for this are still largely

unknown [88]. Due to the previous evidence of weight loss and diabetes preceding the diagnosis of PDAC by many months, studies are currently ongoing to understand if these symptoms together or with additional biomarkers or investigations could be used for earlier detection of PDAC [87, 89, 90]. Even in patients with long-standing T2DM, if there is new onset of worsening glycaemic control and weight loss, these features are atypical for T2DM and should alert the clinician to think about possible pancreatic malignancy [89].

1.2.2. Evidence from preclinical studies

In preclinical studies, both *in vivo* and *in vitro* models have shown the effect of PDAC on β-cell dysfunction [91-94]. Additionally, conditioned medium from PDAC cell lines has been shown to generate insulin resistance in cultured hepatocytes [95] and myoblasts [96]. Insulin resistance has also been shown *in vitro* in skeletal muscle tissue obtained from patients with PDAC (compared to healthy controls)[88, 97, 98].

The effect of diabetes and hyperglycaemia on cancer cells has also been investigated in preclinical studies. These have reported that glucose plays a crucial role in the growth of tumour cells [99], as malignant tissues use more glucose [100-102], and it can also promote pancreatic cancer cells metastatic potential [103], and protect cancer cells from cytochrome C-mediated apoptosis [104].

More recently, Hu *et al* reported that hyperglycaemia could also induce *KRAS* mutations in pancreatic cells, leading to initiation of pancreatic cancer [105]. However, as discussed in the previous section, hyperglycaemia seems to be an early sign of PDAC rather than causing the cancer. Thus, the results from this last study are difficult to interpret.

1.2.3. Causes of hyperglycaemia in patients with PDAC

On diagnosis of pancreatic cancer, approximately half of the patients have metastatic disease and another 35% have locally advanced disease, therefore, only around 15% of these cancers are resectable [7]. Patients with operable disease may be suitable for a Whipple's procedure or other types of pancreatic surgery, if appropriate, resulting in reduction of the total functioning pancreas. This can affect glucose control in the body, as the residual pancreas may produce less insulin than required [106]. The same can happen even if the patient does not have surgery, if there is a significant bulk of disease

in the pancreas or pancreatic atrophy due to pancreatic duct obstruction. However, all diabetes cases in these patients are not associated with bulky disease or operation, and, as mentioned before, diagnosis of new onset diabetes precedes the diagnosis of pancreatic cancer, even in the early stages [107].

Multiple studies have now shown that the diabetes seen in patients with PDAC could instead be a paraneoplastic phenomenon caused by the cancer and similarly to T2DM, β-cell dysfunction and peripheral insulin resistance are also seen [87-89, 108]. Pancreatogenic diabetes, secondary to pancreatic exocrine disease, is classified as type 3c diabetes (T3cDM)[89] and the diagnostic criteria requires 1) pancreatic exocrine insufficiency, 2) pancreatic pathology 3) absence of type 1 diabetes associated autoimmune markers [89]. Compared to other diseases (like chronic pancreatitis) causing T3cDM, pancreatic cancer induced diabetes does not always follow the clinical and laboratory findings of T3cDM [109] and further studies are required to understand these differences [88].

As a distinct difference from T2DM, in T3cDM caused by PDAC, glucose control significantly worsens at the same time of ongoing, often extreme weight loss [88], and these two symptoms together come many months before the cancer-specific symptoms [87, 108].

The paraneoplastic phenomenon caused by PDAC is due to factors induced by the cancer interfering with insulin secretion or action and thus leads to diabetes. The study by Pannala *et al* [75] showed this in a subgroup of patients who underwent pancreatic cancer resection and where 57% of patients had a resolution of the new-onset of diabetes postoperatively, whilst this was not seen in any of the patients with long-standing diabetes [75]. One way of distinguishing between T3cDM and T2DM is by measuring secretory defects of pancreatic polypeptide (PP), incretin or insulin [89], as unlike other diabetes types, the islet loss in T3cDM involves not only β-cells, but also PP cells early in the course of the disease [89, 110]. However, when deficient PP response was measured in two studies on patients with PDAC and healthy controls, these showed mixed results [111, 112]. The first smaller study by Hart *et al* showed significantly decreased meal-stimulated PP release in patients with PDAC and T3cDM compared to patients with T2DM without PDAC [111], whilst the second larger study by the same group with multiple comparative controls with or without T2DM, T3cDM (other causes)

or PDAC showed no significant difference between the groups in meal-stimulated PP release [112]. Thus, currently the role of PP in diagnosing PDAC-related T3cDM is unclear, but studies are ongoing where various potential biomarkers (including PP) are used to distinguish between T2DM and PDAC-related T3cDM in order to inform screening tool development for PDAC [113, 114].

Thus, the mechanisms behind the paraneoplastic phenomenon caused by PDAC and ways to assess it are still unknown, and further studies are awaited to better understand the interaction between PDAC and diabetes.

1.2.4. Diabetes and PDAC outcomes

As mentioned earlier, around 85% of patients with PDAC have impaired glucose tolerance or even diabetes [75, 103]. In patients with early stage PDAC, a negative effect of diabetes on survival has been shown following resection [115]. Patients with pre-existing diabetes who underwent resection had worse survival outcomes, increased tumour size and increased disease recurrence [116]. Perineural invasion (PNI), that is associated with aggressive tumour behaviour and worse clinical outcomes [117], is increased in patients with pancreatic cancer and hyperglycaemia [118] or diabetes [117], compared to patients with normal glucose levels.

There have been multiple studies looking at the effect of diabetes on survival outcomes in patients with advanced pancreatic cancer, and they have shown mixed results; some had shorter survival [119] and in others there was no effect [120]. In one of the largest and most recent studies, Jeon *et al* have reported that in 2792 patients with all stages of PDAC, there was no effect of either long-term or recently diagnosed diabetes mellitus (DM) on survival [120]. They did however find that in patients with resectable PDAC, long-term diabetes (>3 years prior to PDAC diagnosis) was associated with worse survival [120].

Similarly, Yuan *et al* [119] reported in 2014 that long-standing diabetes was associated with decreased survival among 1392 patients with PDAC enrolled onto three longitudinal studies. However, they did not find any effect of recent-onset diabetes (<4 years) on survival nor any differences between stages of disease [119].

In an older study, Wakasugi *et al* [121] reported similar results among 401 patients with PDAC (all stages) where survival was significantly shorter in patients with diabetes,

compared with patients without diabetes, and they also reported that the diabetic angiopathies were not usually seen in these patients, as the survival period was so short. They also found glucose control to be difficult to achieve with insulin, but it was absolutely necessary when treating patients with PDAC [121].

In a meta-analysis that consisted of more than 16,000 patients, Shen *et al* [122] reported that patients with diabetes and PDAC had a worse OS than those without DM. They reported that both long-standing and recent-onset diabetes was associated with worse survival, although this distinction based on the length of diabetes was not analysed in all the studies included. Interestingly, in the non-surgical setting, only one of the included studies based the diagnosis of diabetes on blood tests; all the rest were based on medical records or self-reporting by the patients. Nevertheless, their pooled analysis demonstrated that patients with DM and PDAC had worse survival with a HR of 1.19 (95% confidence interval [CI]: 1.07–1.32) [122].

In a large meta-analysis published this year, including more than 32 million people with various cancers, the authors showed again an effect of DM to survival of patients with PDAC and a HR of 1.67 for death (compared to patients with PDAC and no DM) [84].

One of the reasons why these results [119-122] are conflicting might be the heterogeneity of patient data analysed, and that the glucose levels themselves or glucose control were not reviewed in the majority of the studies.

1.2.5. Metformin and PDAC outcomes

Besides antidiabetic effects, metformin has been proposed to have anticancer molecular action mainly through the inhibition of the mammalian target of rapamycin complex 1 (mTORC1) and by the reduction of circulating level of insulin and insulin-like growth factor 1 (IGF-1) [123]. Due to this, it has been researched in many settings as both antidiabetic and anticancer medication, with mixed results.

One of the largest randomised controlled trials (RCTs) to assess metformin in the context of pancreatic cancer, was a randomised phase II study [124] in 2015 that allocated patients with advanced PDAC between arm A: gemcitabine, erlotinib and metformin and arm B: gemcitabine, erlotinib and placebo. In total, 121 patients were randomised (10-13% in both arms were known diabetics) and there was no difference in any of the survival outcomes (PFS or OS at 6 months) between the two arms. The authors

concluded that there was no survival benefit of metformin in combination with standard treatment in patients with advanced PDAC.

Another randomised phase II trial [125] published around the same time reported similar results when metformin was added to systemic therapy with cisplatin, epirubicin, capecitabine and gemcitabine (PEXG) in patients with metastatic PDAC. Sixty patients were randomised prior to the Independent Data Monitoring Committee (IDMC) ending the study early due to futility at the preplanned interim analysis. There was no difference in PFS or OS survival between the two arms [125]. Thus, RCTs have not shown any benefit of metformin administration in patients with advanced PDAC (with or without diabetes) [124, 125].

Interestingly, two meta-analyses based on observational studies and one which also included the 2 RCTs described above, have reported that there is a survival benefit of using metformin in patients with PDAC, but only in the subgroup of patients who also have diabetes [126, 127]. This may indicate that the benefit lies with better control of diabetes with treatment (metformin) rather than metformin having an anticancer effect. Thus, research into the effects of metformin treatment on survival in patients with pancreatic cancer (with or without diabetes) [124-126], to date is inconclusive.

1.2.6. Multiple interactions between diabetes and PDAC

From epidemiological studies, conditions that cause hyperglycaemia, like DM, obesity, pancreatitis, and chronic stress are likely to be associated with tumour genesis or tumour progression [128-130], hinting that this interaction between diabetes and cancer can also be multifactorial (Figure 1.4). As mentioned previously, malnutrition and pancreatic exocrine insufficiency are significant problems for patients with pancreatic cancer, that in turn also impact on blood glucose levels.

Hyperglycaemia is also associated with increased chemotherapy toxicity in all cancers [131] and is predictive of early stopping of chemotherapy [132]. Interestingly, whilst in clinical practice, corticosteroids are often used for chemotherapy toxicities and to relieve symptoms of pancreatic cancer, like fatigue and appetite loss, steroids also increase blood glucose levels and have been shown to cause steroid-induced diabetes in around 20% of patients who received antiemetic doses of dexamethasone [133]. In a recent study, Bergandi *et al* reported that in colon cancer cells, hyperglycaemia impaired

the effectiveness and promoted resistance to chemotherapy [134] thus, demonstrated a potential negative impact on treatment success.

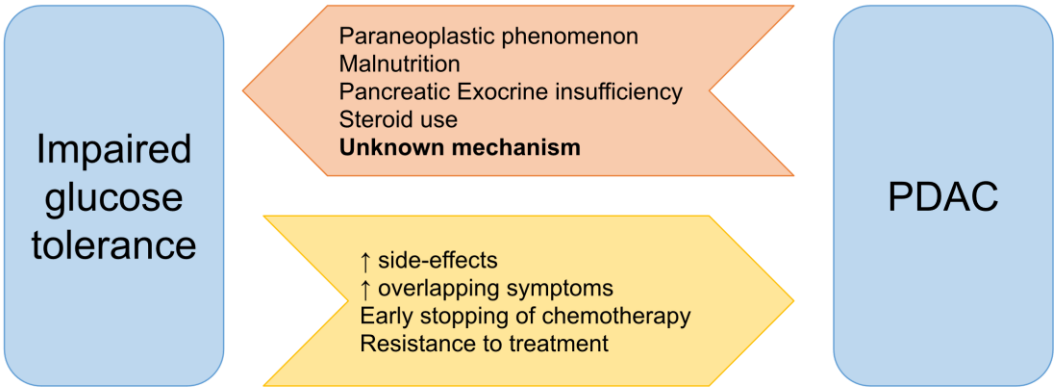


Figure 1.4. Interactions between impaired glucose tolerance and PDAC.

Whilst more information is accumulating about PDAC causing hyperglycaemia or diabetes, it is still not known why the cancer needs to produce this. One previous hypothesis is that PDAC induces hyperglycaemia, lipolysis and weight loss in order to enhance its survival, proliferation and tumorigenesis and potentially carcinogenicity [88]. As PDAC is a very aggressive cancer with high proliferation rate and invasiveness but is in a very hostile microenvironment with poor vasculature and a lot of hypoxia, producing hyperglycaemia might be a mechanism of cell survival [88]. However, currently there is no clear evidence behind this hypothesis and future studies are awaited.

Thus, these afore-mentioned studies all provide evidence that there is an interaction between PDAC and glucose levels with approximately 85% of patients diagnosed with pancreatic cancer having impaired glucose tolerance or even diabetes [103]. Whilst the exact cause is not known, it is known that hyperglycaemia can have an impact on treatment toxicities, but how it affects patient outcomes is unclear. For this reason, in the second chapter of this thesis, I explore how baseline plasma glucose and glucose control during chemotherapy treatment for patients with PDAC (all stages) influences survival outcomes.

1.3. Symptomatic burden and quality of life in patients with PDAC

Diagnosing pancreatic cancer can prove challenging, as early stage disease may be asymptomatic, and even in cases of advanced disease, the typical symptoms are vague abdominal pain and possibly weight loss. In the case of obstructive jaundice, patients are more likely to seek medical help [135]. A significant proportion may also present with non-specific symptoms, such as diabetes mellitus or impaired glucose tolerance [75].

A study investigating patient presentations with symptoms suspicious of pancreatic cancer to different UK centres (of whom 30% had a diagnosis of pancreatic cancer, 12% had other cancers and 58% no cancer), did not identify any first symptom that was reported more frequently in the group with pancreatic cancer, compared to other groups [136]. Most patients presented with multiple symptoms. Jaundice, change in urine or stool colour, fatigue, change in bowel habit, weight loss, decreased appetite, and feeling different, were more frequently reported as subsequent symptoms in people diagnosed with pancreatic cancer than in those with no cancer [136]. This is relevant, as worse symptoms at baseline have been reported to be associated with worse survival [137] and earlier cessation of chemotherapy [138].

Malnutrition caused by decreased dietary intake and weight loss is another major problem in patients with pancreatic cancer. More than 80% of patients with pancreatic cancer report significant weight loss at the time of diagnosis [139]. In patients not receiving any treatment, Wigmore *et al* [140] reported that all patients with PDAC will lose a median 24% of their body weight by the time of their death. Furthermore, up to 70-80% will show signs of cachexia, with pathological weight loss due to skeletal muscle wasting and loss of adipose tissue [141]. Cancer cachexia has been demonstrated to have deleterious effects on prognosis, quality of life [142], and to increase the risks of post-operative complications in those with resectable disease [142, 143].

Decreased dietary intake is often due to multiple different symptoms like appetite loss, pain, nausea, early satiety, anxiety or depression [144]. Additionally, multi-drug chemotherapy combinations like FOLFIRINOX are associated with toxicities like nausea/vomiting and diarrhoea that can cause further problems with malnutrition [145]. Nutritional state can be further complicated in patients with advanced pancreatic cancer due to the presence of diabetes mellitus and impaired glucose tolerance [75],

pancreatic exocrine insufficiency [146] and the effects of pancreaticoduodenectomy in those with recurrent disease after surgery [139, 147].

On the other hand, weight stabilisation in patients with pancreatic cancer has been associated with improved OS and quality of life [148]. Where nutritional therapy is required, enteral nutrition (EN) has demonstrated greater benefits to nutritional status than parenteral nutrition (PN), with fewer associated complications [149], however this may not always be appropriate.

1.3.1. Assessing quality of life in patients with PDAC

For patients with pancreatic cancer, there are two questionnaires used predominantly for assessment of health-related quality of life (HRQoL) in clinical trials: the European Organisation for Research and Treatment of Cancer (EORTC) quality of life core questionnaire (QLQ-C30) with the Pancreatic cancer module (PAN26) [150] and the Functional Assessment of Cancer Therapy - Hepatobiliary (FACT-HEP) [151]. Both are validated tools that have been used in various clinical trials and research studies including patients with pancreatic cancer [152-155]. The FACT-HEP questionnaire is for all hepatopancreaticobiliary (HPB) cancers and consists of 45 questions [151], whilst the QLQ-C30+PAN26 consists of 30 core questions (for all cancers) and 26 questions specifically for pancreatic cancer [150]. Thus, the QLQ-C30+PAN26 is more specific to pancreatic cancer, but also 11 questions longer than the FACT-HEP. There does not seem to be any specific differences in the quality or results of the two questionnaires and the choice between the two seems to depend on the continent the study is run on, where the QLQ-C30+PAN26 is used more in Europe and FACT-HEP in US [156], but the two are also sometimes used together in trials [157, 158].

A systematic review investigated survival and HRQoL amongst patients with different stages of pancreatic cancer collated data from 5 clinical trials; both prospective and retrospective [159]. They reported that patients with pancreatic cancer had significantly worse scores on the EORTC QLQ-C30 scales than the general population. The highest symptom scores (indicating worse symptomatology) across all studies were for pain, fatigue, appetite loss and insomnia [159]. This indicates that patients with pancreatic

cancer have a higher symptomatic burden compared to other malignancies and that treatment of all of these can be very complex.

The recently presented QOLIXANE study gathered real life HRQoL and efficacy data of patients with metastatic pancreatic cancer, who started 1st line treatment with gemcitabine and nab-paclitaxel in 95 centres in Germany [160]. In total, 600 patients were recruited to the study and were asked to complete a QLQ-C30 questionnaire at baseline and every month during their treatment. The results of the study reported that 61% and 41% of patients maintained their baseline QoL at 3 and 6 months, respectively. The worse (lowest) scores for function scales were for role functioning (53.2 points[p]) and best for cognitive functioning (78.2p), whilst on symptom scales, the worst (highest) were fatigue (51.4p) and best nausea and vomiting (15.7p). They also showed that in univariate analysis, all baseline scales predicted survival, whilst in multivariable analysis, the physical functioning and nausea and vomiting scales had the most significant effect on OS [160]. In that study, whilst 98% filled in the baseline survey, 80% filled one other survey, 49% baseline and month 3, 28% baseline and month 6 and only 23% baseline, month 3 and 6. This study highlights the significant symptom burden of patients with metastatic pancreatic cancer and how it can impact on survival. Equally it demonstrates that patients deteriorate rapidly, and the drop-out rates are high for the subsequent questionnaires.

1.3.2. Mood disorders in patients with pancreatic cancer

In addition to quality of life issues, it is well recognised that a diagnosis of cancer is associated with high rates of mental health disorder [161]. There has long been an association between PDAC and mood changes, including reports of patients developing mood changes before the development of other symptoms of the disease [162]. It is often quoted that rates of depression are higher in patients with PDAC than in patients with other malignancies [163-165]. For example, Massie *et al* [166] quote the prevalence of depression among patients with advanced PDAC as 33%-50%. Another study by Jia *et al* [167] of 262 patients with cancer of the gastrointestinal (GI) tract, including 50 patients with PDAC, reported that patients with PDAC had the highest incidence of depression with a rate of 78%. This study also found that patients with depression had worse QoL, role-, emotional- and social functioning and worse fatigue, pain and appetite loss than patients without depression [167].

A prospective Japanese study of 110 patients with PDAC (15% resectable, the remainder either locally advanced or metastatic) reported rates of depression and anxiety of 13.6% at baseline, and 16.5% at 1 month after commencement of anticancer therapy [168]. A retrospective study of surveillance, epidemiology and end-results data reported that suicide rates among patients with a diagnosis of PDAC (all ages) were 11 times higher than the US average for people aged 65-74 years, which was the commonest age group of patients with PDAC within the study [169].

Interestingly, the association between pancreatic cancer and depression has been previously described as possibly caused by paraneoplastic syndrome and the dysregulation of inflammatory cytokines, especially IL-6 [170-172]. Thus, whilst the true prevalence of mood disorders among patients with PDAC compared to other malignancies is not clear, there seems to be both cancer worry and anxiety; and biological factors behind it.

In conclusion, problems with HRQoL and mood disorders are prevalent among patients with pancreatic cancer. Unlike most other malignancies, long-term survival rates for these patients have not improved significantly over the last 20 years, and although work is ongoing in many aspects of pancreatic cancer to develop new treatments with the aim of improving survival, definitive improvements remain elusive. In view of this, survival should not be the only focus for studies in patients with pancreas cancer and more effort should be put into improving all aspects of care including quality of life of these patients.

1.3.3. The impact of improving quality of life

A prospective randomised trial by Basch *et al* [173] compared HRQoL in 766 patients with solid tumours undergoing chemotherapy, allocated to either standard of care with physician-led symptom monitoring or self-reporting via tablet computer (intervention arm). They reported an improvement in HRQoL in 34% of patients in the intervention arm, compared with 18% in the standard of care arm. Similarly, there was a worsening of HRQoL in 38% of those in the interventional arm, compared with 53% in the standard of care arm ($p<0.01$). Patients in the interventional arm received chemotherapy for longer (8.2 months vs 6.3 months, $p=0.002$). Later an analysis of OS of this study reported an OS in the interventional arm was 31.2 months compared with 26 months in the standard of care arm ($p=0.03$). The authors proposed that this 5-month difference

in OS might have come from early responsiveness to patient symptoms or that the patients in the intervention arm were able to continue on chemotherapy longer [174]. An improvement of survival by 5 months was seen in patients who self-reported their symptoms (with nurses responding to alerts), which is more than has been achieved in the majority of clinical trials with novel agents in patients with advanced disease. These results have led to new trials being developed around the world focusing on patient reported outcomes and the use electronic devices for patients to self-monitor symptoms and quality of life [175-177].

In addition to measuring HRQoL, it has been reported that the integration of early supportive care into the clinical management of patients with PDAC has demonstrated improvements in survival outcomes [178, 179]. In a retrospective analysis of 5381 patients with PDAC, early palliative care consultations were associated with less aggressive care at the end of life [178]. Similar results have also been reported in a meta-analysis [180], and in a RCT of different advanced cancers (including 32-40% of patients with PDAC) [179]. This RCT revealed that quality of life was significantly higher in the patient group who received early and systematic integration of palliative care, compared to palliative care consultations on demand [179]. Thus, there is strong evidence of the benefit of measuring QoL and dealing with patient symptoms early in their treatment pathway that can impact QoL, treatment decisions and survival of these patients.

1.4. Clinically meaningful outcomes in pancreatic cancer

Another difficulty with advanced pancreatic cancer is that, with a median survival of 6 months [181], little is known about how patients perceive these outcomes; and what they and their clinicians would consider to be a clinically meaningful benefit from treatment. In light of recent large phase III trials in patients with advanced pancreas cancer showing only modest improvements in OS, and with the most effective chemotherapy combinations causing a large amount of side-effects [25], it is important to define what would be a clinically and personally meaningful benefit for patients.

1.4.1. Meaningful benefit defined by oncology organisations

In 2014, the American Society of Clinical Oncology (ASCO) defined clinically meaningful improvement in pancreatic cancer outcomes as at least 3-5 month extension of PFS or

OS over the current standard of care [182], indicating that this is the bar that future trials would need to pass in order to show meaningful benefit. These estimations meant that for very fit patients who are eligible for FOLFIRINOX treatment, the improvement in PFS or OS of a novel agent combination would need to be at least 4-5 months, and the 1-year survival rate would need to increase from 48% to 63%. Similarly, in patients who are eligible for gemcitabine or gemcitabine/nab-paclitaxel, a new combination would need to result in a 3-4 month benefit in PFS/OS and a 35% to 50% improvement in 1-year survival [182].

The European Society for Medical Oncology (ESMO) approached this from a slightly different angle and stratified the magnitude of clinical benefit of anti-cancer therapies from existing phase III trials or meta-analysis [183]. The ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS) was first published in 2015 [183] and for pancreatic cancer, showed the greatest clinical benefit for FOLFIRINOX [25] that was graded as 5 (maximum) out of the 5 point scale in the non-curative setting. Combining gemcitabine and nab-paclitaxel was graded 3 out of 5 and gemcitabine and erlotinib combination as 1 (limited clinical benefit). Interestingly, in the updated version 1.1 published in 2017, the benefit of the gemcitabine and nab-paclitaxel combination was downgraded to 2, as it was thought to be very unlikely that the 2-year survival gain of 5%–10% in the tail of the curve was statistically significant [184]. The ESMO-MCBS scale is based mainly on HRs and length of PFS/OS gain, and in the case of advanced pancreatic cancer where the control arm OS is less than 12 months, the expected HR needed to be ≤ 0.65 and the gain in length of OS ≥ 3 months. As FOLFIRINOX is currently the only combination that has fulfilled both of these criteria in patients with PDAC, it is the highest graded treatment option for these patients. This scale has subsequently been used to show which novel anti-cancer therapies should be funded as a priority and the version 1.1 also added or deducted points on the clinical benefit scale depending on impact on quality of life [184].

Both the ASCO and ESMO definitions of clinical benefit are mainly based on survival length. However, it does not answer the question as to how to achieve these aspirational efficacy goals with novel treatments and whether these would be similarly meaningful to patients.

1.4.2. Defining clinical benefit in clinical trials

The concept of clinical benefit was first introduced in a phase II clinical trial of second line treatment with gemcitabine in patients with metastatic pancreatic cancer in 1996 by Rothenberg *et al* [185]. Based on the observation that even in the absence of a radiological response to treatment patients fared better symptomatically with improved fitness, they defined "Clinical Benefit Response" (CBR) as a combination of alteration of three elements: pain, performance status and weight. A year later they reported similar results in a study of first-line treatment of patients with metastatic pancreatic cancer, where the CBR and survival was better with gemcitabine treatment compared to 5-FU [186], making gemcitabine the new standard of care at that time. In the latter decades, the definition of clinical benefit became more unclear and included anything from stable disease rate, to overall survival benefit, to sustained quality of life [187]. In 2009, there was a call for clarity in the reporting of these outcomes by Booth *et al* to unify the way of wording benefit, rather than defining different endpoints as one single entity [187]. They proposed that clinical benefit should only be used to describe patient-centred outcomes and not tumour-centred outcomes, like response rate and survival. They defined patient-centred benefit as changes in symptom burden or quality of life [188] and interestingly, it did not include patients' views or opinions.

1.4.3. Patients views on treatment benefit

Combination chemotherapy regimens used in the treatment of patients with pancreas cancer result in improved survival, but at the expense of treatment-related toxicities [25] that does not always translate into worse quality of life. When making their initial decisions regarding therapeutic management of their disease, patients may choose to receive treatments that will potentially result in better survival outcomes prior to experiencing the side effects. There is little evidence to show if patients would have made a different choice after experiencing the common side effects of the treatment, with the possible associated decrease in quality of life. Currently, patients' views vary greatly [189], and the reasons for this are unknown. It may be based on their previous contact with chemotherapy, either from a personal or family member perspective. Some patients are not willing to receive chemotherapy because they wish to continue experiencing the quality of life they currently have and not risk it with chemotherapy-induced adverse events.

One of the largest reviews in relation to how patients make decisions about treatment, conducted by Matsuyama *et al*, reports that patients with cancer would choose chemotherapy, even with small survival benefits [190]. However, the majority of studies on this topic have conducted interviews or surveys only at baseline or when starting new lines of treatment, and have not assessed changes throughout treatment. Interestingly, compared to healthy volunteers, medical professionals or other groups, patients with cancer were found to always accept a lower chance of benefit, even with more toxicities [191, 192]. Visser *et al* reported in their prospective cohort study assessing patients satisfaction with platinum-based chemotherapy for advanced lung cancer that 86% of patients would probably or definitely choose the same treatment again, irrespective of whether their quality of life deteriorated or improved, and if they had a large or small amount of treatment side-effects [193].

Understanding the potential benefit also depends on understanding the aim of treatment. According to Weeks at al [194], in a study of 1193 patients with stage IV colorectal or lung cancer, around 70-80% of patients had unrealistic expectations about the likelihood of chemotherapy curing their cancer, when they were receiving palliative chemotherapy. They also reported in one of their previous studies [195] that patients who thought they were going to live for at least 6 months were more likely to favour life-extending therapies compared to comfort care, and in turn were more likely to undergo aggressive treatment. In this study, there was no difference in 6-month survival between patients who had aggressive treatment and those who opted for comfort care. In a later study, it was also shown that less aggressive measures near death were associated with early end of life (EOL) care discussions [196], demonstrating that EOL discussions and understanding of prognosis really effect patient decisions about treatment. Especially, as studies have shown that chemotherapy use in the last months of life do not improve quality of life near death, and in some cases even worsen it [197].

As the median survival in patients with advanced pancreas cancer is around 6 months [181], many patients are already in their last months of life when they are first seen by an Oncologist. McCarthy *et al* reported that patients at the end of life with different solid tumours preferred comfort care over life-extending therapies [198], but that is probably only true if patients are aware of their poor prognosis.

Furthermore, treating physicians often have different views than patients on choosing between treatments [199], adverse events and quality of life. Physicians may either under- or over-estimate [200] the potential for treatment benefit and adverse events, and it is not known how these match up with the views of the patients.

It is important also to note that patient preferences, communication, and emotional support are also integral part of patient-centred care [201, 202]. Patient-centred care is defined by ensuring that patients views guide all clinical decisions and care is responsive and respectful to individual patient preferences, needs and values. This was first defined by Gerteis *et al* in 1993 and comprised of six dimensions: respect for patients' values, preferences, and expressed needs; coordination and integration of care; information, communication, and education; physical comfort; emotional support—relieving fear and anxiety; and involvement of family and friends [201, 202]. These dimensions have since been used to evaluate patient-centeredness in healthcare [203]. Therefore, understanding patients views about treatment is not only beneficial for that patient, but is also used to measure the quality of care.

1.4.4. Prognosis discussion and hope

Knowing and understanding their cancer prognosis has previously been shown to allow patients to make informed treatment decisions [204-206] and prepare for end of life [207]. Most patients with advanced cancer want to be given information about their prognosis and expected outcome of their treatment [204, 208, 209]. Not knowing or understanding prognosis has been associated with more aggressive anticancer treatment [195, 210, 211] and life-sustaining measures at the end of life [204, 212], whilst accurate understanding of prognosis is associated with improved QoL [213, 214], patient engagement in care planning [212, 215] and preference for supportive care [195, 216]. Additionally, patients who become aware of their terminal status by their worsening condition, or by chance, have been found to have lower QoL [214], which again highlights the need for early open discussions.

Interestingly, in patients with advanced cancer receiving palliative radiotherapy, physicians' inaccurate survival predictions were associated with aggressive end-of-life care [217]. Furthermore, in another study, it was found that one of the main reasons why patients have unrealistic expectations is due to oncologists reluctance to disclose

realistic prognostic information [218]. It is also important to note that patients who overestimate their prognosis do not actually live longer [195].

Physicians' reluctance to discuss prognosis with patients has been linked to worries about impacting patient psychological wellbeing [215], patient-physician relationship [206], taking away hope [219] or originating from personal fears or discomfort [204]. It is reassuring that there are no reported negative associations found between these worries and most research done on these topics have revealed the opposite, with either no or positive associations between prognostic discussion and psychological wellbeing [216, 220, 221]. Interestingly, the study by Shin *et al* [221] showed that patients who reported more frequent prognosis discussions over time, had significantly less depression [221]. Various studies have again shown positive associations between prognosis discussion and patient-physician relationships, especially on care preference conversations [222-224].

In terms of hope, there are studies assessing the association between hope and prognosis. Smith *et al* showed in patients with various advanced cancers that when patients are given honest prognostic information, hope is maintained even when the news is bad [225]. Hagerty *et al* [219] investigated hope-giving behaviours in patients with metastatic cancer. Giving the most up to date treatment (90%), knowing everything about the patient's cancer (87%), and stating that pain will be managed (87%) were rated highest by patients. When discussing prognosis, 98% wanted the physician to be realistic, open to questions and acknowledge the patient as an individual. Realism, individualised care and positive-collaborative-expert styles were endorsed most strongly by patients as the most hope-giving [219].

Using the worst, typical and best-case scenarios to explain the prognosis (compared to using median survival time) is another strategy that patients have rated as highly useful and would improve their understanding of life expectancy, be helpful, would help family or carers and would support the making of future plans [204, 226, 227]. Van Vliet *et al* [228] showed that giving explicit prognostic information, together with reassurance about non-abandonment, significantly reduced patient uncertainty and anxiety, and increased self-efficacy and satisfaction. Reassurance about non-abandonment was also viewed as a hope-giving trait while remaining realistic [228, 229].

The research shows that besides medical information, patients have other sources that can increase hope, such as faith, dignity, inner peace, meaningful life events, relationships, and humour [228, 230].

Contrary to physician worries, giving prognosis information in a realistic, open way, that is tailored to the individual, can be viewed as hope-giving by patients. It is important to note that in all studies, there was still a small group of patients who did not want to discuss prognosis thus, patient individual information preferences should always be checked. An understanding of prognosis and treatment outcomes has been linked to patient views about various aspects of their treatment and life plans and so, these are important to monitor and discuss.

1.4.5. Understanding views about treatment outcomes in patients' with pancreatic cancer

There is very little understanding about how patients and their clinicians view poor pancreatic cancer survival outcomes. Whilst large international oncology organisations like ASCO and ESMO define benefit based on length of PFS/OS and hazard ratios [182, 183], it is not known what patients and their clinicians treating them think of these. This is especially important in advanced pancreatic cancer, as it is one of the most aggressive cancers and has a median survival of only around 6 months [181]. It has been previously shown that the majority of patients with advanced cancers had unrealistic expectations about cure [194] and that this impacts on their decision-making about treatment [195].

Compared to a well person or their treating medical team, patients with cancer were always more willing to receive treatment for small benefits [190, 231], even if the physicians presented the results pessimistically [232]. A study by Slevin *et al* [231] done now more than 30 years ago, compared views in 100 patients with metastatic cancer to healthy controls and oncology professionals (medical oncologist, radiotherapist and oncology nurses), and asked what amount of time or percentage chance of cure or palliation of symptoms would make chemotherapy worthwhile using two hypothetical regimens. The majority of patients were willing to accept intensive chemotherapy for a small chance of benefit, whilst oncology professionals were less likely to accept radical treatment for minimal benefit. Half of the patients completed the questionnaire on a second occasion, and there were no differences seen in the responses [231].

The most recent study by Loh *et al* [233] among 524 patients with advanced cancers, had the primary aim of assessing the effect of standardised geriatric assessment on communication, but the questionnaire part of this study reported that there was still around 5% who thought that there is a 100% chance that their cancer would be cured, and these patients were more willing to trade off QoL for longer survival [233].

Patient choice between length and quality of life is also a topic that has revealed mixed results in previous studies [234]. There has been a large number of studies throughout the years looking at different aspects associated with the trade-offs of length and quality of life. One of the earlier studies by Silvestri *et al* [189] in 1998 reported that in the second-line setting of metastatic lung cancer, patients willingness to accept treatment varied greatly, and some patients (6%) were willing to take treatment with a survival benefit of 1 additional week, whilst others (11%) were not willing to take it, even for a 24 month gain, and favoured QoL instead [189]. DiBonaventura *et al* [235] reported that among 181 survey responders with metastatic breast cancer, OS was of primary importance to these patients, followed by side-effects. In contrast, Danson *et al* [236] reported that among 202 patients with advanced lung cancer, patients favoured treatments that would enhance QoL rather that length of life. Meropol *et al* [237] reported that among 459 patients with a variety of advanced cancers who answered their survey, 55% valued QoL and length of life equally, 27% prioritised QoL and 18% preferred length of life. Other studies have investigated if there are specific subgroups of patients that would rate survival time over QoL, and have found that younger patients and those with a shorter history of cancer, favoured length of life, whilst patients who were older and more tired were opting for QoL [238]. These studies have shown that there is a great deal of variation in patient preferences, and their views about their treatment. Patients seem to view both longevity and QoL as important, but prioritising one over the other seems to depend on many other factors.

No studies investigating patient views or priorities have been performed in patients with advanced PDAC, hence the need to investigate this in light of the known short survival outcomes, poor quality of life and high symptomatic burden. Thus, due to discrepancies between defining meaningful benefit for patients and clinicians; physician opinions not matching patients'; patients unrealistic views about treatment outcomes and the impact it can have on their decision making; and mixed results shown in choosing between QoL

and length of life; I developed an observational questionnaire study to explore these dilemmas as part of this PhD.

RELEVANT study: Patient and physician perspectives on clinically-meaningful outcomes in advanced pancreatic cancer.

The purpose of this study is to explore and describe a specific population of patients recently diagnosed with advanced pancreatic cancer, starting their first line chemotherapy treatment. In this study, I will evaluate patient and physician views on advanced pancreatic cancer diagnosis, treatment received, and patient's goals, in an effort to understand what would be a meaningful outcome from treatment for these patients and what would be considered meaningful for physicians.

Chapter 3: RELEVANT study development and methods.

Chapter 4: RELEVANT study results and discussion.

Aims of this PhD

The overall focus of this PhD thesis is to identify areas within the management framework of PDAC that, with appropriate interventions, could lead to improved patient outcomes. As large numbers of clinical trials with novel anti-cancer therapies have failed to show any improvements in outcomes for patients with advanced PDAC, I addressed two clinical entities highly prevalent but often overlooked in patients with PDAC, to determine whether improvements in these areas could lead to improved outcomes.

Firstly, I specifically designed and populated a large, detailed patient database for this thesis, to assess the role of hyperglycaemia and glycaemic control, which is known to be altered in patients with pancreatic cancer, on patient outcomes. This aimed to assess the effect of baseline and on-treatment glucose levels on OS and to determine if any other variables impacting these levels could be confounding factors.

Secondly, I then challenged conventional survival-based outcomes by assessing clinician and patient perceptions on "clinically-meaningful" outcomes in the setting of a poor-prognosis malignancy with modestly-effective treatment options. For this aim, a prospective investigator-designed questionnaire study was developed comprising a purposely-built survey assessing patients' and physicians' views about outcomes in conjunction with two validated tools measuring quality of life.

Chapter 2: Effects of glucose levels on the outcomes of patients with PDAC

As part of this PhD, I have presented portions of the work in this chapter in an abstract and poster format:

- *Pihlak R, Almond R, Srivastava P, Raja H, Broadbent R, Hopewell L, Higham C, Lamarca A, Hubner RA, Valle JW, McNamara MG (2018). Effects of random glucose levels on outcomes of patients with pancreatic ductal adenocarcinoma [239].*

2.1 Introduction

As discussed in chapter one, the interaction between glucose and pancreatic cancer and its impact on survival is uncertain. Whilst previous research has shown that hyperglycaemia could be a paraneoplastic phenomenon caused by PDAC [88] and preclinical studies have shown that hyperglycaemia can have negative effects on pancreatic cancer outcomes, the clinical evidence in patients with pancreatic cancer is not convincing, likely due to other confounding factors that make the assessment of interaction more difficult.

Diagnosing diabetes [240] is also complicated by the fact that usually at least two abnormal blood measurements are needed, and patients need to be fasting. Unfortunately, a lot of patients with pancreatic cancer have a high symptomatic burden from their cancer, poor performance status and short prognosis; thus, treating diabetes is not always prioritised among other problems [81, 241]. This has also been shown in previous studies [242] where blood glucose was measured for all patients with pancreatic cancer who were going for resection and in patients who self-reported not to have any diabetes; 39% were found to have a diabetes level fasting blood glucose (FBG level >126 mg/dL). Therefore, these patients had diabetes, but the diagnosis had not been made until that time [242]. This could also explain why most studies have not found a difference in PDAC survival between patients with or without diabetes, as the majority of these studies have based the diabetes diagnosis on patients self-reporting or clinical records, rather than measured blood glucose levels.

Based on previous literature, it is known that diabetes is a risk factor for PDAC [82, 83]; new onset of hyperglycaemia could be an early sign of PDAC [87]; patients with pre-existing diabetes undergoing resection of pancreatic cancer had worse outcomes [75];

in preclinical models, hyperglycaemia is associated with greater metastatic potential of PDAC [243] and more resistance to chemotherapy[134]; and in large observational studies, the effect of diabetes on outcomes of patients with PDAC has been mixed [84, 119-121].

Due to the overwhelming evidence that diabetes or hyperglycaemia is a problem for patients with pancreatic cancer and the lack of evidence on how this affects their outcomes, I developed a retrospective study as part of this PhD.

Using a retrospective cohort of patients with PDAC seen in The Christie NHS Foundation Trust during a 5.5-year period, I investigated the relationship between plasma glucose levels and clinical outcomes.

Objectives: The purpose of this study was to determine whether plasma glucose levels in patients with pancreatic ductal adenocarcinoma either at baseline or during treatment have any relationship with the OS of these patients.

Hypothesis: The overarching (alternative) hypothesis was that hyperglycaemia at baseline or during treatment is associated with shorter overall survival in patients with pancreatic ductal adenocarcinoma.

Null hypotheses:

- There is no difference in OS between patients with baseline hyperglycaemia and normo-glycaemic patients.
- There is no difference in OS between patients with a high minimum glucose (GluMin) compared to low GlucMin.
- Hyperglycaemia at the time of disease progression does not correlate with OS.

Other variables known to be associated with glucose levels in patients with PDAC were also assessed (for example, corticosteroid treatment, weight loss, antidiabetic treatment). Details of these are described in the *Candidate variables examined* section below.

The layout of this chapter is based on the Reporting recommendations for tumour marker prognostic studies (REMARK) [244] guidelines, and the final checklist, based on the results of this study, is presented at the end of the chapter in Table 2.13.

2.2 Methods

2.2.1 Study methods

Patients

All consecutive patients with a diagnosis of pancreatic cancer seen in The Christie NHS Foundation Trust HPB new patient clinic between January 2012 and July 2017 were identified retrospectively, based on hospital electronic records using the Clinical Outcomes Form. Patients with all stages of PDAC were included in this study. The only exclusion criteria were patients with another histological subtype (not adenocarcinoma) or high proportion of missing critical clinical data. Other histological subtypes were excluded due to potentially different tumour biology and behaviour. Patients who had no plasma glucose measured ever, were included in the study population if they otherwise had all critical clinical data available.

Treatments received

Patients were treated in an adjuvant, neoadjuvant or palliative setting with standard of care chemotherapy and phase II-III clinical trials recruiting at the time. Treatment protocols varied over time, but in general patients were either treated with monotherapy (gemcitabine), doublet chemotherapy (gemcitabine with nab-paclitaxel, capecitabine or cisplatin; or 5FU with oxaliplatin) or triple chemotherapy (FOLFIRINOX). Some patients were treated as part of a phase II-III clinical trial with combination treatment of chemotherapy with novel agents, however, as these trials showed no benefit in overall survival [245-247] of the treatment arms, patients were categorised based on the backbone chemotherapy regimen used (e.g. patients who were treated with gemcitabine, nab-paclitaxel and ibrutinib were categorised as having received doublet treatment).

Specimen characteristics

Glucose values used in the study were all peripheral venous samples where the plasma glucose levels were analysed in The Christie biochemistry laboratory with the standardised Glucose Hexokinase assay (© 2012 Siemens Healthcare Diagnostics) [248,

249]. All values used were from the results of standard plasma analysis done with patients' regular bloods; no samples were re-analysed for the purpose of the study.

Glucose values were firstly used as continuous variables in analysis and then three additional thresholds were referenced, based on local guidelines for management of patients with diabetes or at risk of developing diabetes. These were: >8 mmol/L (requiring monitoring), ≥14 mmol/L (requiring closer monitoring and potentially antidiabetic treatment), and ≥11.1 mmol/L on 2 occasions (fulfilling World Health Organisation [WHO] diabetes criteria [240], if not previously known to have diabetes). The National Institute for Health and Care Excellence (NICE) Type 2 diabetes in adults guideline [250] was referenced for the glycated haemoglobin (HbA1c) cut-off of ≤48 mmol/mol (for patients with type 2 diabetes managed by lifestyle and diet). All glucose levels recorded in this study were random (i.e. non-fasted); GlucMin was defined as the lowest plasma glucose measured per patient ever, including baseline and during treatment and GlucMax was the highest plasma glucose measured per patient.

Study design

Patients with PDAC seen in The Christie between January 2012 and July 2017 were identified retrospectively through a search of the hospital electronic records. All sequential patients with PDAC seen within the time period who fulfilled the inclusion and exclusion criteria were included in the study and was therefore an unselected group of patients. The patients were all referred for chemotherapy either with adjuvant, neoadjuvant or palliative aim. Pre-defined clinical and laboratory data were collected from the patient's electronic hospital records and national death records and inputted into a study-specific electronic database that was developed as part of this work. The follow-up period for each patient ranged from first clinic visit to death, and the interval of data collection from first clinic visit to data cut-off ranged from 6 months (last patient) to 5.5 years (first patient).

The study was approved as a clinical audit by The Christie NHS Foundation Trust Clinical Audit Committee on 07/Dec/2016 (reference number: 16/1812).

Clinical endpoint examined

All univariate and multivariable analysis were assessed based on the effect on OS. Overall survival was defined as the period of time in weeks from the date of diagnosis to the date of death, patients were considered censored if they died after 31/01/2018.

Candidate variables examined

Survival analyses were performed to examine the prognostic effect of categorical and continuous variables: gender (male v female), stage (1-2 v 3-4), ECOG performance status (PS) (0-1 v 2, 3-4), Adult Comorbidity Evaluation (ACE) score (0 [none] v 1, 2, 3 [severe]), treatment intent (adjuvant-neoadjuvant v palliative), diabetic status at baseline (no diabetes v diabetic), antidiabetic medication (no v yes), weight loss at baseline (no v yes), regimen for adjuvant/neoadjuvant treatment (monotherapy v doublet, triple), regimen of first line treatment (none v monotherapy, doublet, triple), second line chemotherapy (no v yes), third line chemotherapy (no v yes), corticosteroids treatment ever (no v yes), status at data cut-off (alive v dead), glucose >8 mmol/l at baseline (no v yes), glucose ≥14 at baseline (no v yes), glucose >8 ever (no v yes), glucose ≥14 ever (no v yes), glucose ≥11.1 ever (no v yes), glucose ≥11.1 twice (no v yes), serum Carbohydrate Antigen (CA)19-9 baseline (U/mL), baseline albumin (g/L), glucose baseline (mmol/L), GlucMin (mmol/L), GlucMax (mmol/L), glucose when last seen (mmol/L), HbA1c ever (mmol/L), age, and body mass index (BMI; in kilograms per square meter).

Various glucose time points (baseline, GlucMin, GlucMax, when last seen) were included in order to understand which would be the most significant to take forward in the following prospective validation study.

Sample size

The sample size of 640 patients was based on the number of patients seen during the time period that had critical clinical data available, and were histologically adenocarcinomas. As this was a retrospective signal searching study, no sample size calculations were done and positive findings from this analysis need to be validated in a prospective patient population.

2.2.2 Statistical analysis

Preliminary data preparation

Graphical representation (histograms) and skewness analysis of continuous variables was carried out to check for distribution, if values were found to be skewed, these were log2 transformed in order to include them in parametric Cox-regression analysis. Continuous variables that were normally distributed were used for analysis in their original form.

Association between variables

The association analysis of all variables going into multivariable analysis was done using Pearson's Chi-Squared independence analysis, where the p-value of <0.05 indicates that there is a significant association between the two variables. For this analysis, all continuous variables were dichotomised using the median variable as a cut-off.

Similarly, for other association analysis between baseline glucose and antidiabetic treatment given and glucose levels and corticosteroids treatment, Pearson's Chi-Square analysis with dichotomised variables were used.

Methods to evaluate the association between each clinical variable and clinical outcome

Median survival time for all patients included were estimated using the Kaplan-Meier log-rank test. Univariate associations between survival time and covariables were examined using Cox proportional hazard regression model. Continuous variables, including the 4 glucose variables (baseline, GlucMin, GlucMax, when last seen), were used in their continuous form initially and proportionality was checked. Continuous variables were transformed or categorised if evidence of non-proportionality was observed. Categorical variables were used in their original categories (see Candidate variables examined section).

Multivariable analyses and variable selection

A Cox regression multivariable model was used to assess the effect of glucose on OS as the outcome. All variables found to be statistically significant in the univariate analysis with a p-value of <0.05 were included in the multivariable analysis. Some variables of interest that were thought to be important to assess in the context of others, like antidiabetic treatment, was included in the multivariable analysis, regardless of univariate results. Backward elimination likelihood ratio (LR) [251] method was used to

form the final model. Backward elimination starts with all candidate variables and tests the deletion of each variable and eliminates step by step variables whose loss gives the most statistically insignificant deterioration of the model fit. It automatically repeats this process until no further variables can be deleted [251] and the final model is formed.

Internal validation

The multivariable model was subject to an internal validation using a bootstrap resampling procedure [252, 253]. This is a statistical procedure that resamples the study dataset with replacement to create many (1000 in this study) simulated samples [254]. The method has an equal probability of randomly drawing each original data point for inclusion, creates resampled datasets that are the same size as the original dataset, and ends up with many different combinations of the values from the original dataset [252]. Bootstrapping is used to assess the internal validity of the model and to determine if the results could be driven by a small proportion of outliers [255-257].

Missing data

Forty-five patients (7%) had no glucose levels measured at any time, 48 patients had no baseline glucose measured and 137 patients had no glucose measured when last seen. These patients were still included in the survival analysis, as their other clinical data was available, but for each of those variables, they were marked as missing. Thus, in uni- and multivariable analysis if the variable was missing, these patients were excluded from the analysis, but if the analysis was for another variable that they did have (for example stage or CA19-9) the patients were included in that analysis. No imputing methods were used. Details of all missing values for variables are further detailed in Table 2.1 and 2.2.

Handling of marker values

All glucose values were log transformed to account for skewness. Hazard ratios and 95% CIs for the 4 glucose values were estimated using Cox proportional hazards.

For the baseline glucose variable, the clinically defined cut-off points (>8 and ≥14 mmol/L) were used to divide the patients to two or three groups, when categorical values were used (e.g. Kaplan-Meier analysis). The GlucMin variable had no clinically important threshold as it is the lowest over time (retrospectively) thus, in order to categorise this variable, the median and 25^{th}/75^{th} percentile were used.

Analysis process

The data analysis followed the REMARK guidelines [244] and the IBM SPSS Statistics software (version 23) was used for analysis.

2.3 Results

2.3.1 Flow of patients through the study

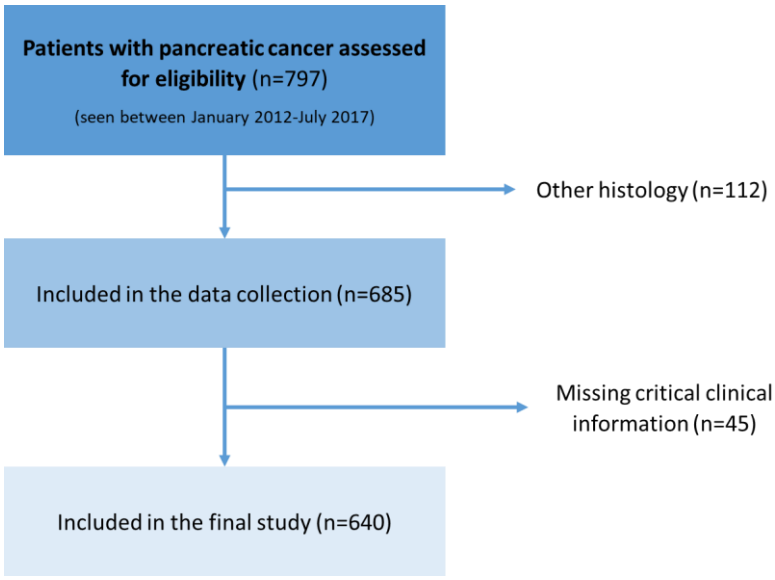


Figure 2.1. Patients flow through the study.

Between January 2012 and July 2017, 797 new patients with pancreatic primaries were seen in the HPB clinic at The Christie NHS Foundation Trust. Of those, 112 were excluded due to having other histological subtypes and 685 patients were included in the data collection.

A further 45 patients were excluded due to missing critical baseline information and the final 640 were eligible for analysis.

2.3.2 Variable preparation

Baseline CA19-9, glucose baseline, GlucMin, GlucMax and glucose when last seen (figure 2.2 A, B, C, D) showed that these values were positively skewed and thus, these covariates were log transformed in order to include them in a parametric analysis. Other continuous variables like age, BMI, HbA1c and baseline albumin were all normally distributed and were used for analysis in their original form.

2.3.3 Basic demographic characteristics

Patient baseline characteristics are further described in Table 2.1 and glucose-related characteristics in Table 2.2.

Second- and third-line chemotherapy variable is only available for patients where treatment was possible, and this was defined as patient being alive at least 180 days after the start of previous line of treatment and no mention of declining performance status as the reason for stopping previous line of treatment. Thus, this included 225 patients for second-line treatment and 50 patients for third-line treatment.

Of 640 patients, 428 (67%) received chemotherapy, 102 (16%) were for best supportive care (BSC) from initial consultation and 110 (17%) did not receive chemotherapy for other reasons (for example, patients declined treatment, presented or recovered too late for adjuvant treatment, emergency admissions). Eighty-five (13.3%) patients received adjuvant or neo-

Table 2.1. Patient baseline characteristics

Baseline characteristics	Number	Percentage
Gender		
Male	338	52.8%
Female	302	47.2%
Age		
(median, range)	68.0	(25-92)
Stage		
1-2	169	26.4%
3-4	471	73.6%
ECOG PS		
0-1	409	63.9%
2	142	22.2%
3-4	89	13.9%
ACE score		
0	229	35.8%
1	261	40.8%
2	114	17.8%
3	36	5.6%
Treatment Intent		
Adjuvant- neoadjuvant	117	18.3%
Palliative	523	81.7%
Weight loss at baseline		
No	90	14.1%
Yes	408	63.8%
Missing	142	22.2%
BMI		
kg/m^2 (mean, SD)	24.3	4.7
Albumin		
g/L Baseline (mean, SD)	39.6	4.6
CA19-9		
U/ml Baseline (median, IQR)	1372.5	69.8-7283.5
Regimen of adjuvant /neoadjuvant		
Monotherapy	49	57.6%*
Doublet	26	30.6%*
Triple	10	11.8%*
Total	85	13.3%
Regimen of first-line chemotherapy		
Monotherapy	129	34.4%*
Doublet	161	42.9%*
Triple	85	22.7%*
Total	375	58.6%
No treatment	265	41.4%
Second-line chemotherapy		
Given	85	13.3%
Not given	140	21.9%
Not possible	415	64.8%
Third-line chemotherapy		
Given	12	1.9%
Not given	38	5.9%
Not possible	590	92.2%

ACE- Adult Comorbidity Evaluation, SD- standard deviation, IQR- interquartile range, *- including only patients who had treatment.

adjuvant chemotherapy. First-line palliative chemotherapy was received by 375 (58.6%), second-line treatment by 85 (13.3%) and third-line treatment by 12 (1.9%) patients.

As shown in Table 2.1, 64% of patients had reported weight loss at baseline and of the 228 patients (36%) who had information available on amount of weight loss, the median loss was 10.5 kg (range 1-60kg: 412 missing). The median baseline body surface area (BSA) was 1.77 m^2 (range 1.25-2.57, 49 missing) and the median body mass index (BMI) was 24.3 kg/m^2 (range 13-42 kg/m2, 49 missing).

Baseline blood results are also shown in Table 2.1 revealing as expected, high median tumour marker CA19-9 of 1372.5 U/ml (range 5 to >70000 U/ml [the upper limit of titration]) and normal mean albumin of 39.6 g/L (range 21-51g/L).

Table 2.2. Glucose related characteristics

Glucose related variables	Number	Percentage
Glucose baseline		
mmol/L (median, IQR)	7.3	6.0-10.4
missing	48	
Glucose min (GlucMin)		
mmol/L (median, IQR)	5.8	5.0-7.4
missing	45	
Glucose max		
mmol/L (median, IQR)	9.3	7.3-13.8
missing	45	
Glucose when last seen		
mmol/L (median, IQR)	7.3	5.9-9.9
missing	137	
HbA1c (ever)		
mmol/mol (median, IQR)	44.5	39-56
missing	536	
Diabetic status at baseline		
No diabetes	457	71.4%
Diabetic	183	28.6%
Antidiabetic medication		
No	441	68.9%
Yes (started or previously on)	199	31.1%
Corticosteroids ever		
No	196	30.6%
Yes	368	57.5%
Missing	76	11.9%
Glucose >8 mmol/L baseline		
No	360	60.8%*
Yes	232	39.2%*
Glucose ≥14 mmol/L baseline		
No	515	87.0%*
Yes	77	13.0%*
Glucose >8 mmol/L ever		
No	218	36.6%*
Yes	377	63.4%*
Glucose ≥14 mmol/L ever		
No	450	75.6%*
Yes	145	24.4%*
Glucose ≥11.1 mmol/L ever		
No	390	65.5%*
Yes	205	34.5%*
Glucose ≥11.1 mmol/L twice		
No	471	79.2%*
Yes	124	20.8%*

IQR- interquartile range. *- out of the patients who had glucose measured (595 patients ever, 592 baseline)

The median values of the various plasma glucose levels that were used in the study are shown in Table 2.2. The frequency of these plasma glucose levels are shown as histograms on Figure 2.2 A-D. Seven percent (45 patients) had no glucose measured at any time. Either at baseline or during treatment, 377 (63.4%) and 145 (24.4%) patients had random plasma glucose levels

>8mmol/L and ≥14 mmol/L, respectively. Based on the WHO diabetes diagnosis criteria [240], 205 patients (34.5%) had plasma glucose values ≥11.1 mmol/L and 124 (20.8%) had it on 2 occasions (fulfilling the diagnosis criteria [240]), of whom only 81 were previously known to have diabetes. Thus, there were 43 new diagnoses of diabetes. Of the 205 patients, there were a further 34 patients who had glucose levels ≥11.1 mmol/L once, but did not have a second reading, thus their diabetes status is not known.

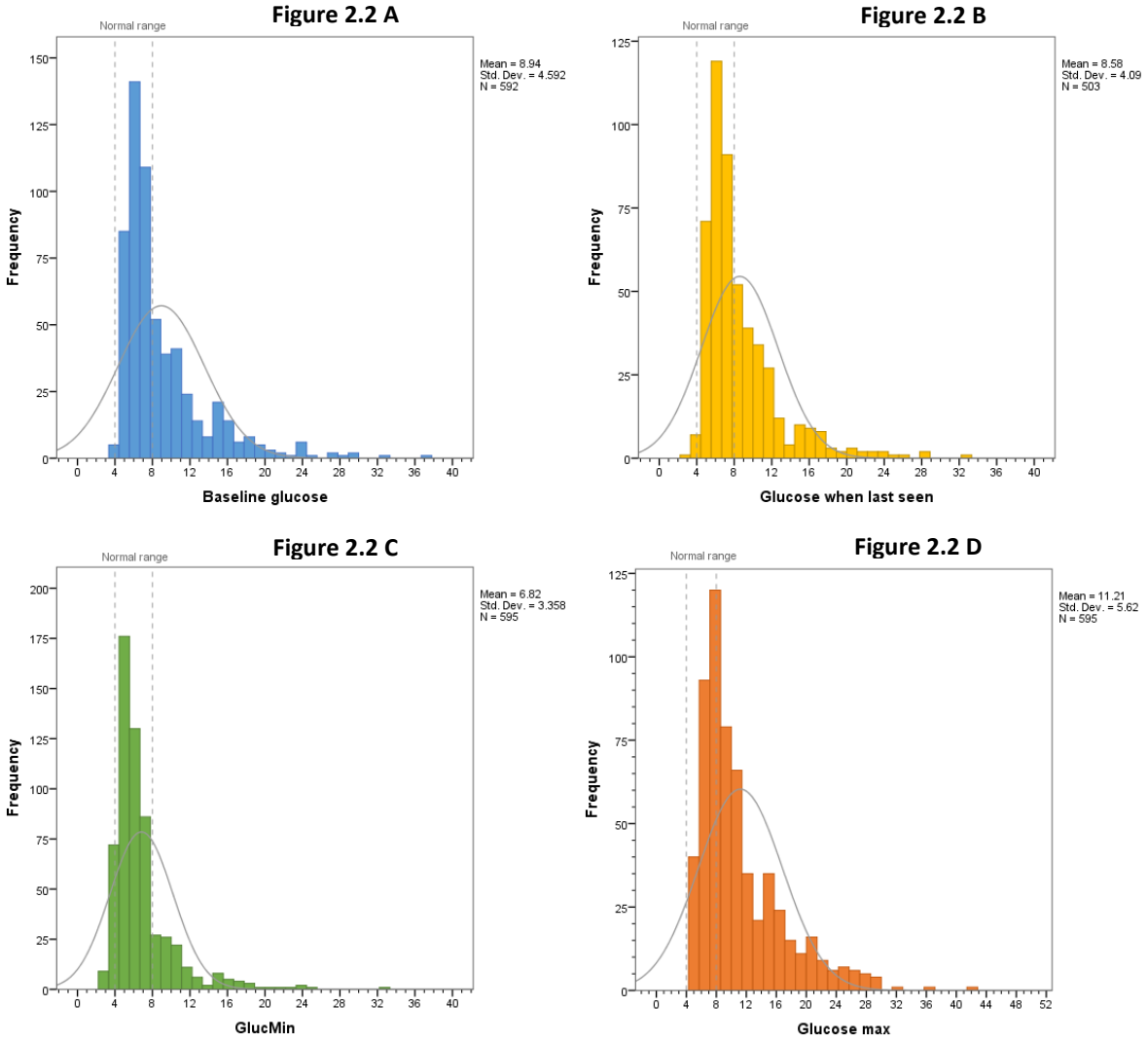


Figure 2.2 A, B, C, D. Histograms of patients' plasma glucose level frequencies at baseline (A), when last seen (B), GlucMin (C), Glucose max (D) (grey line shows normal plasma glucose reference 4-8 mmol/l).

Measuring HbA1c levels was not systematically performed at the time at the treating institution in patients with PDAC and was only measured in 16% of patients. The median

HbA1c was 44.5 mmol/mol (range 30-103 mmol/mol, 535 missing). Of those 104 who had HbA1c measured, it was >48 mmol/mol in 38% of patients, indicating inadequate glucose control [250]. However, HbA1c was measured at different time-points for these patients (baseline, during treatment, or when there was a clinical need), and thus it is not possible to link these with the outcomes of patients.

Twenty-nine percent of patients had a previous diabetes diagnosis; 199 (31%) were already on antidiabetic treatment or had treatment started at the treating institution. The type of antidiabetic treatment is further described in Figure 2.3.

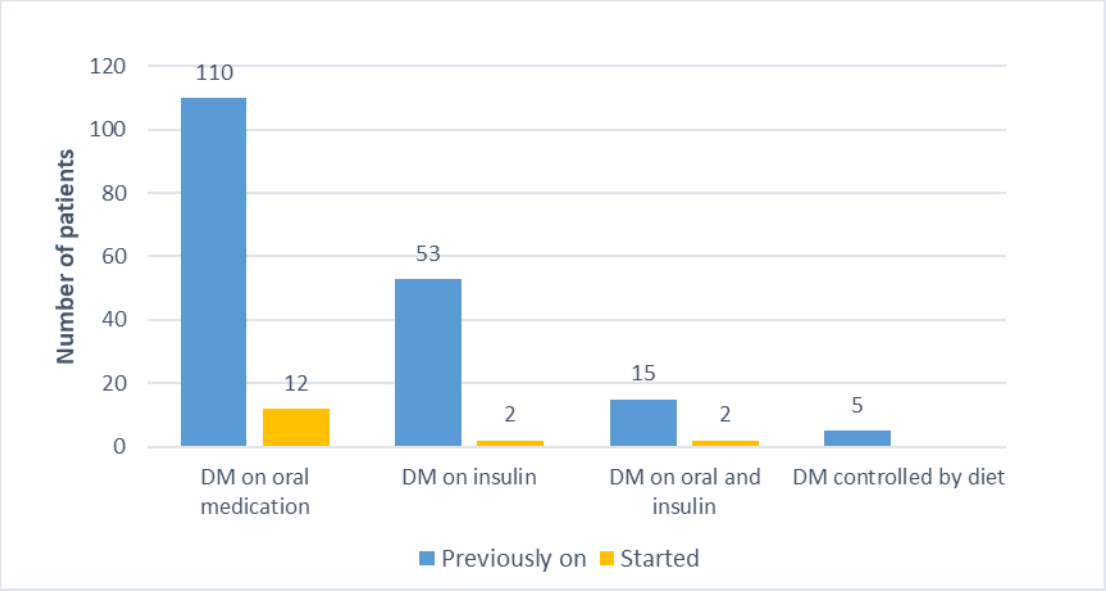


Figure 2.3. Bar charts of 199 patients who were already on antidiabetic treatment (blue bars) **or had treatment started at the treating institution** (yellow), illustrating type of antidiabetic treatment used. DM- Diabetes Mellitus.

As discussed in chapter one, corticosteroids are often used as supportive medications to help with symptom control in patients with pancreatic cancer (fatigue, loss of appetite, chemotherapy toxicities) and are also associated with increases in plasma glucose levels. Thus, the use of this medication was also recorded. However, as the timing and duration of this medication was very variable, it was only recorded as a binary (yes/no) variable. At baseline or during treatment 369 (58%) patients received corticosteroids, 196 (31%) did not, and 75 (12%) had missing information.

As demonstrated in the methods section, one of the hypotheses of the study was to also assess the correlation between hyperglycaemia at the time of disease progression and OS. However, during data collection, it was discovered that most patients did not have glucose measured at progression (or close to that time), and as patients deteriorated quickly after progression, often did not have another glucose measured. Thus, it was not possible to address that aspect of the research question, due to lack of data.

2.3.4 Correlation between glucose and standard prognostic variables

The Pearson's Chi-Squared independence analysis was performed (with all variables to be included in the multivariable analysis) to investigate known significant associations between variables (e.g. CA19-9 and stage/treatment intent) and to understand the relationship between each pair of variables. The absence of expected associations may imply biases or errors in the dataset that will need to be taken into account in further analysis.

Results of the independence analysis are shown in Table 2.3 where p-value of <0.05 indicates a significant association between the two variables.

As demonstrated in Table 2.3, the glucose values, especially GlucMin is significantly (p value between <0.001 and 0.003) associated with almost all variables and key markers of poor prognosis (CA19-9, stage, albumin, treatment intent, ECOG PS). In addition, the various glucose variables are highly dependent on each other and known associations between variables was also confirmed (e.g. CA19-9 and stage/treatment intent).

Table 2.3. Association between variables for planned inclusion in the initial multivariable analysis.

Pearson Chi-Square of independence													
	ACE score	CA19-9	Glucose baseline	GlucMin	Albumin baseline	Weight loss	1st line chemotherapy	2nd line chemotherapy	Glucose last	Stage	ECOG PS	Treatment intent	Antidiabetic treatment
ACE score	X	0.09	**<0.001**	**<0.001**	**<0.001**	0.05	**<0.001**	0.92	**0.01**	0.77	**<0.001**	0.27	**<0.001**
CA19-9	0.09	X	**<0.001**	**<0.001**	0.55	**0.01**	0.53	0.30	**<0.001**	**<0.001**	0.05	**<0.001**	0.09
Glucose baseline	**<0.001**	**<0.001**	X	**<0.001**	0.10	0.17	0.37	0.89	**<0.001**	**<0.001**	**0.01**	**<0.001**	**<0.001**
GlucMin	**<0.001**	**<0.001**	**<0.001**	X	**<0.001**	0.38	**<0.001**	0.50	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Albumin baseline	**<0.001**	0.55	0.10	**<0.001**	X	**<0.001**	**<0.001**	0.57	0.18	0.19	**<0.001**	0.29	0.42
Weight loss	0.05	**0.01**	0.17	0.38	**<0.001**	X	0.17	**0.03**	0.42	0.52	**<0.001**	**0.01**	0.09
1st line chemotherapy	**<0.001**	0.53	0.37	**<0.001**	**<0.001**	0.17	X	**0.01**	0.26	0.14	**<0.001**	0.30	0.19
2nd line chemotherapy	0.92	0.30	0.89	0.50	0.57	**0.03**	**0.01**	X	0.82	0.69	**0.02**	0.60	0.42
Glucose last	**0.01**	**<0.001**	**<0.001**	**<0.001**	0.18	0.42	0.26	0.82	X	**<0.001**	**0.02**	**<0.001**	**<0.001**
Stage	0.77	**<0.001**	**<0.001**	**<0.001**	0.19	0.52	0.14	0.69	**<0.001**	X	**<0.001**	**<0.001**	0.20
ECOG PS	**<0.001**	0.05	**0.01**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**0.02**	**0.02**	**<0.001**	X	**<0.001**	0.15
Treatment intent	0.27	**<0.001**	**<0.001**	**<0.001**	0.29	**0.01**	0.30	0.60	**<0.001**	**<0.001**	**<0.001**	X	0.33
Antidiabetic treatment	**<0.001**	0.09	**<0.001**	**<0.001**	0.42	0.09	0.19	0.42	**<0.001**	0.20	0.15	0.33	X

ACE- Adult Comorbidity Evaluation.

Statistically significant ($p<0.05$) associations are highlighted in yellow.

A separate association analysis was done to understand if corticosteroids impacted glucose values in this data set. This was done by using a t-test to compare the mean glucose values in patients with or without corticosteroid use. This analysis showed that there was no significant difference in baseline glucose (p=0.07), GlucMin (p=0.06), GlucMax (p=0.21) or glucose when last seen (p=0.56) between patients who had corticosteroids and who did not.

2.3.5 Univariate analysis

All variables were evaluated for effect on OS using the univariate Cox-regression analysis and results are shown in Table 2.4 for general variables and Table 2.5 for glucose-related variables.

Table 2.4. Cox regression univariate analysis results of general variables effect on OS.

Variables	Variable type	p-value	HR	95% CI	
				Lower	Upper
Gender (men/women)	cat	0.671	0.96	0.81	1.14
ACE score- 0	cat	0.115			
ACE score- 1	cat	0.066	1.20	0.99	1.46
ACE score- 2	cat	0.145	1.20	0.94	1.54
ACE score- 3	cat	**0.049**	1.44	1.00	2.08
Weight loss (yes/no)	cat	**0.004**	1.48	1.14	1.92
Regimen of adjuvant/neo-adjuvant treatment- mono	cat	0.881			
Regimen of adjuvant/neo-adjuvant treatment- doublet	cat	0.687	0.80	0.28	2.33
Regimen of adjuvant/neo-adjuvant treatment - triple	cat	0.897	0.93	0.29	2.99
Regimen of first-line chemotherapy	cat	**<0.001**			
Regimen of first-line chemotherapy- mono	cat	0.952	0.99	0.80	1.24
Regimen of first-line chemotherapy -doublet	cat	**<0.001**	0.58	0.47	0.72
Regimen of first-line chemotherapy- triple	cat	**<0.001**	0.43	0.32	0.57
Second-line chemotherapy (yes/no)	cat	**0.002**	0.60	0.43	0.83
Third-line chemotherapy (yes/no)	cat	0.444	1.36	0.62	2.96
Stage binary (late v early)	cat	**<0.001**	3.03	2.43	3.77
ECOG PS 0-1	cat	**<0.001**			
ECOG PS 2	cat	**<0.001**	2.16	1.76	2.65
ECOG PS 3-4	cat	**<0.001**	3.42	2.68	4.35
Treatment intent (palliative v adjuvant/neo-adjuvant)	cat	**<0.001**	4.58	3.46	6.07
Age at diagnosis	con	0.071	1.01	1.00	1.02
Albumin baseline	con	**<0.001**	0.94	0.93	0.96
BMI baseline	con	0.650	1.00	0.98	1.02
CA19-9 baseline (log)	con	**<0.001**	1.16	1.13	1.19

HR- hazard ratio. cat- categorical variable, con-continuous variable. Log- variable was log-transformed for the cox-regression analysis. ACE- Adult Comorbidity Evaluation.

The known prognostic factors were confirmed to be significant for OS in this dataset: late stage compared to early stage (p<0.001, HR 3.03); ECOG PS 2 (p<0.001, HR 2.16) and ECOG PS 3-4 (p<0.001, HR 3.42) compared to ECOG PS 0-1; low baseline albumin compared to higher (p<0.001, HR 0.94); high CA19-9 (p<0.001, HR 1.16); and palliative treatment aim (p<0.001, HR 4.58).

A statistically significant higher risk of death was also seen in patients with differing ACE comorbidities; comparing score 3 to 0 (p=0.049, HR 1.44) and baseline weight loss compared to no weight loss (p=0.004, HR 1.48), but no difference was seen in BMI (p=0.65, HR 1.0), age at diagnosis (p=0.07, HR 1.01) or gender (p=0.67, HR 0.96).

Regarding anticancer treatment, there was a beneficial effect on OS in giving doublet (n=161 patients; p<0.001, HR 0.58) or triple (n=85; p<0.001, HR 0.43) treatment, but no difference in single agent (n=129; p=0.95, HR 0.99) first-line chemotherapy compared to not giving treatment (n=265). Similarly, there was a benefit of giving second-line chemotherapy (p=0.002, HR 0.60), but no benefit in giving third-line treatment (p=0.44, HR 1.36), although these analyses included 225 for second-line and only 50 patients for third-line. The benefit of giving second-line treatment can be related to survivor bias in this retrospective data set, as only patients who were alive or fit at the end of first-line treatment, could go on the have further treatment and thus, have longer OS.

Table 2.5. Cox regression univariate analysis results of glucose related variables.

Glucose related variables	Variable type	p-value	HR	95% CI	
				Lower	Upper
Diabetic status at baseline (yes/no)	cat	0.251	1.12	0.93	1.34
Antidiabetic medication (yes/no)	cat	0.502	1.06	0.89	1.28
Corticosteroids ever (yes/no)	cat	0.578	1.06	0.87	1.28
Glucose >8 mmol/L baseline (yes/no)	cat	**0.002**	1.33	1.11	1.60
Glucose ≥14 mmol/L baseline (yes/no)	cat	**0.001**	1.52	1.17	1.96
Glucose >8 mmol/L ever (yes/no)	cat	0.536	0.94	0.78	1.13
Glucose ≥14 mmol/L ever (yes/no)	cat	0.651	0.95	0.77	1.17
Glucose ≥11.1 mmol/L ever (yes/no)	cat	0.360	0.92	0.76	1.10
Glucose ≥11.1 mmol/L twice (yes/no)	cat	**0.011**	0.75	0.60	0.93
HbA1c ever	con	0.625	1.00	0.98	1.01
Glucose baseline (log)	con	**<0.001**	1.36	1.17	1.57
GlucMax (log)	con	0.521	0.95	0.82	1.10
GlucMin (log)	con	**<0.001**	2.14	1.85	2.48
Glucose last (log)	con	**<0.001**	1.42	1.20	1.68

HR- hazard ratio. cat- categorical variable, con-continuous variable. Log- variable was log-transformed for the cox-regression analysis.

As demonstrated in Table 2.5, there were various glucose-related variables that statistically significantly affected the overall survival of these patients. Baseline glucose both as a continuous variable (p<0.001, HR 1.36) and with cut-off levels higher than the two thresholds >8 mmol/L (p=0.002, HR 1.33) and ≥14 mmol/L (p=0.001, HR 1.52) were associated with worse OS. The highest risk of death was associated with the continuous GlucMin variable (p<0.001, HR 2.14). Glucose when last seen was also significant (p<0.001, HR 1.42) as a continuous variable.

The diabetes diagnosis criteria of ≥11.1 mmol/L twice, was statistically significant (p=0.011, HR 0.75) however, it was associated with improved OS (not worse). The Kaplan-Meier analysis of this variable showed that the survival curves cross (Figure 2.4) and thus, the proportional hazard assumption is violated [258] and the effect of this variable on survival is not clear.

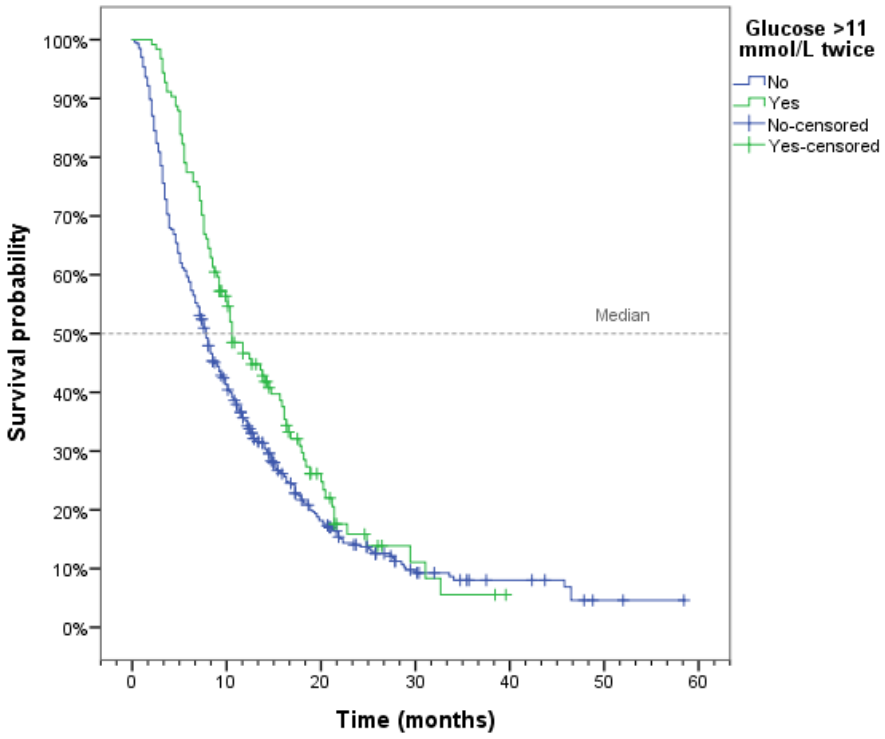


Figure 2.4. Kaplan-Meier graphics illustrating overall survival by measured glucose values ≥11.1 mmol/L on at least two occasions (p=0.01).

Diabetic status at baseline (p=0.25), antidiabetic treatment (p=0.5) and corticosteroids (p= 0.58) did not have a statistically significant effect on OS in univariate analysis. Similarly, levels of hyperglycaemia above >8 mmol/L (p=0.54) and ≥14 mmol/L ever (p=0.65) or ≥11.1 mmol/L once (p=0.36), did not have a significant impact on OS.

Univariate survival length

In order to illustrate the impact of variables on the length of OS the Kaplan-Meier and log-rank analysis was used.

Median PFS and OS for all stages were 6.7 (95%CI 6.1-7.2) and 8.1 (95%CI 7.3-8.8) months respectively. Median OS for early stage disease (1/2): 17.5 months (95%CI 15.6-19.9), advanced stage disease (3/4): 6.2 months (95%CI 5.4-7.0) (Figure 2.5).

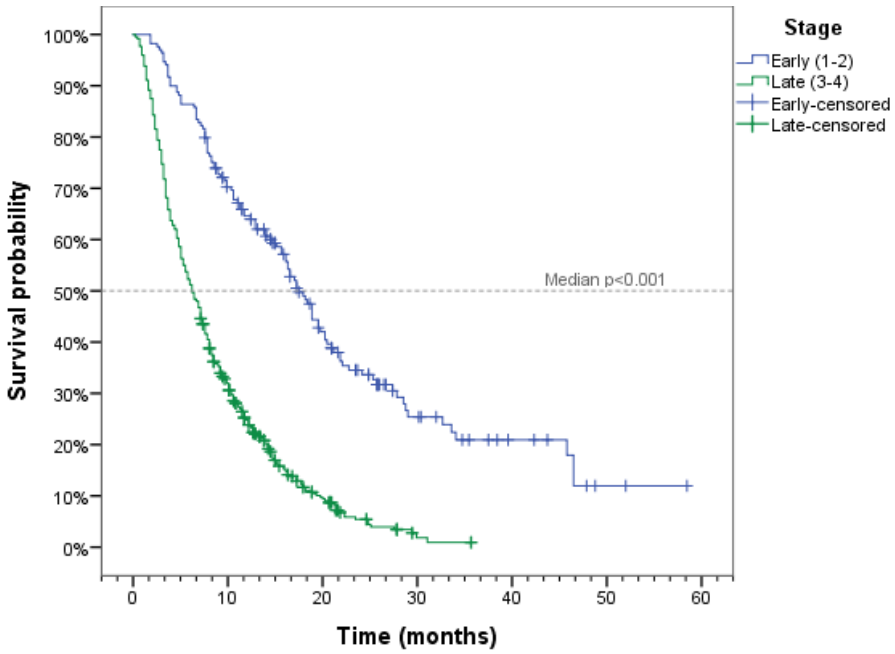


Figure 2.5. Kaplan-Meier graphics illustrating overall survival by stage of disease (p<0.001).

Median OS based on ECOG PS was 11 months (95% CI 9.8-12.3) for ECOG PS 0-1; 4.8 months (95% CI 3.9-5.8) for ECOG PS 2 and 3 months (95% CI 2.4-3.6) for those with and ECOG PS of 3-4 (Figure 2.6).

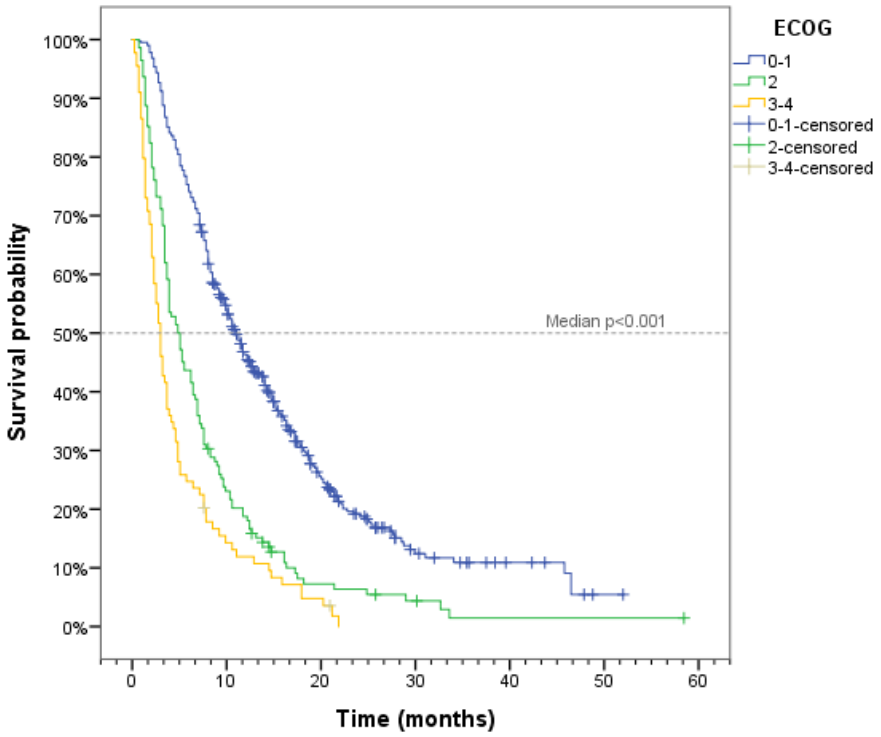


Figure 2.6. Kaplan-Meier graphics illustrating overall survival by ECOG performance status (p<0.001).

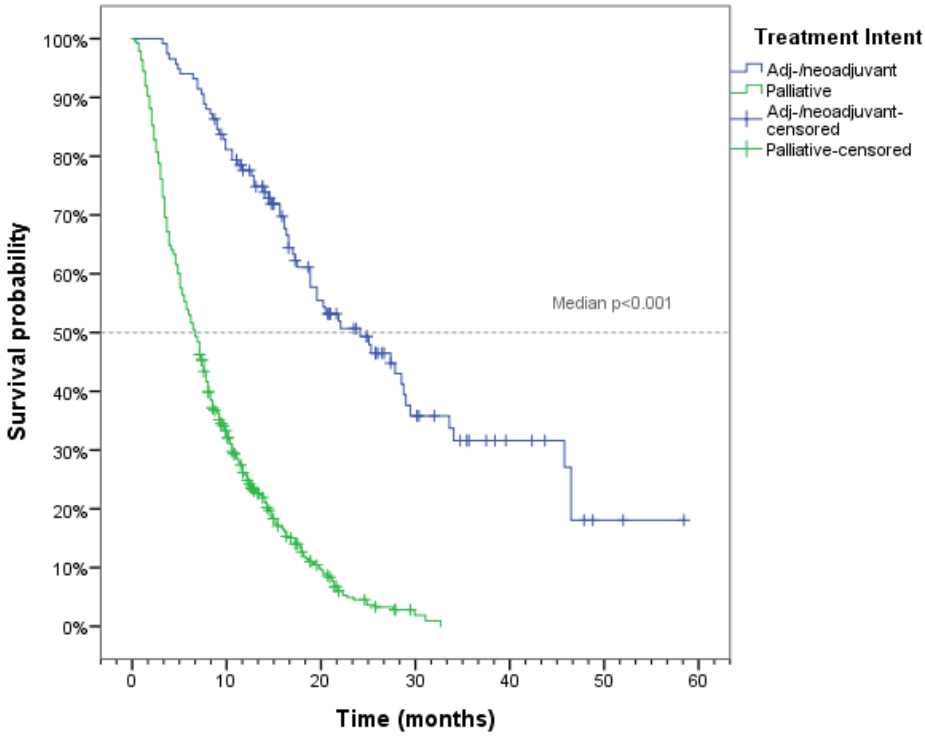


Figure 2.7. Kaplan-Meier graphics illustrating overall survival by treatment intent (p<0.001).

As expected, there was a statistical significant (p<0.001) effect on OS, depending on the aim of treatment, where patients with a palliative aim of treatment had a median OS of 6.7 months (95%CI 5.9-7.4) and those receiving adjuvant-or neoadjuvant treatment had a median OS of 24.2 months (95%CI 16.8-31.5, Figure 2.7).

On reviewing the patients with a palliative aim of treatment, there was a statistically significant difference (p<0.001) in median OS based on first line palliative treatment: no treatment 3.0 months (95%CI 2.6-3.4), monotherapy 6.4 months (95%CI 5.4-7.5), doublet 10.4 months (95%CI 8.6-12.1) and triple 14.3 months (95%CI 12.1-16.4, Figure 2.8).

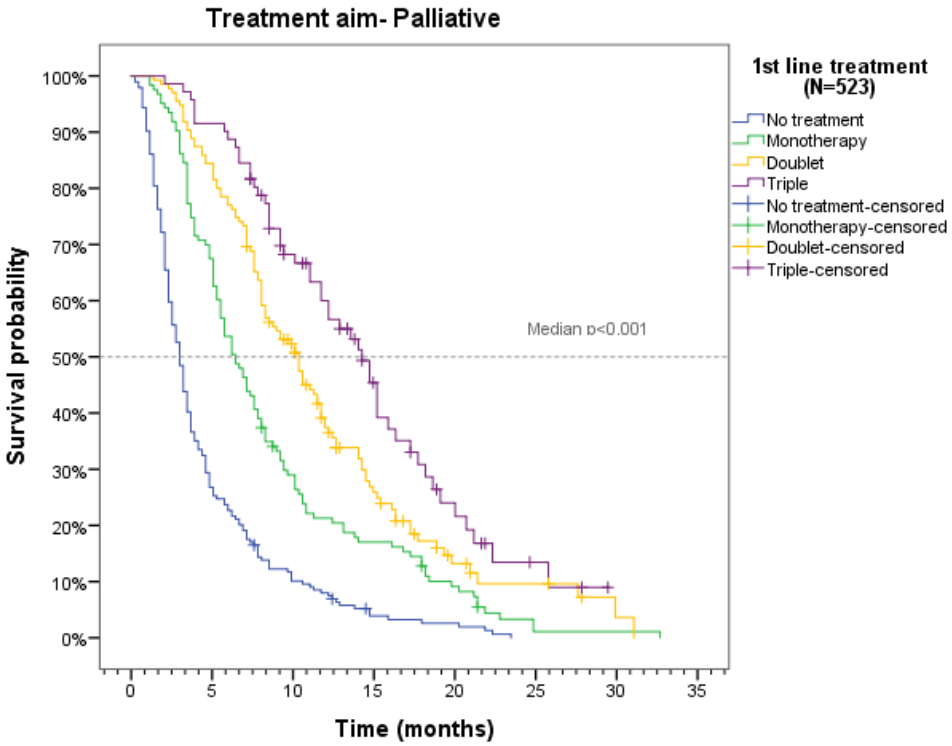


Figure 2.8. Kaplan-Meier graphics illustrating overall survival by first line palliative treatment (p<0.001), including only the patients where the aim was palliative.

As seen in Table 2.6 baseline plasma glucose levels (>8mmol/L and ≥14 mmol/L) significantly impacted on OS in all patients (Figure 2.9 and 2.10). When further divided into subgroups, the stratified Kaplan-Meier log-rank analysis testing equality of survival distributions according to the baseline glucose analysis adjusted for the intent of treatment showed a statistically significant difference only in the palliative </≥14

mmol/L group, but not in the others. This seems to be mostly due to overlapping confidence intervals in the ≤/>8 mmol/L group, whilst the </≥14 mmol/L palliative patients group has a larger OS difference. The results of these variables in a multivariable analysis when adjusted for other factors is shown in the next section.

Table 2.6. Overall survival in patients with PDAC according to baseline plasma glucose levels (Kaplan-Meier log-rank analysis).

Patients	All	Overall Survival (95%-Confidence Interval) months									
		N	≤8 mmol/L	N	>8 mmol/L	P value	N	<14 mmol/L	N	≥14 mmol/L	P value
Stage 1-4	640	360	9.7 (8.2-11.1)	232	7.1 (5.9-8.4)	**0.002**	515	8.5 (7.5-9.6)	77	7.1 (5.2-9.1)	**0.001**
Palliative	519	274	7.6 (6.8-8.4)	201	6.2 (5.3-7.2)	**0.48**	408	7.1 (6.4-7.9)	67	5.3 (3.6-7.0)	**<0.001**
Curative	115	83	27.4 (20.8-34.0)	29	18.9 (11.1-24.7)	**0.26**	103	27.8 (23.2-32.5)	9	12.9 (8.2-17.6)	**0.2**

N - Number of patients

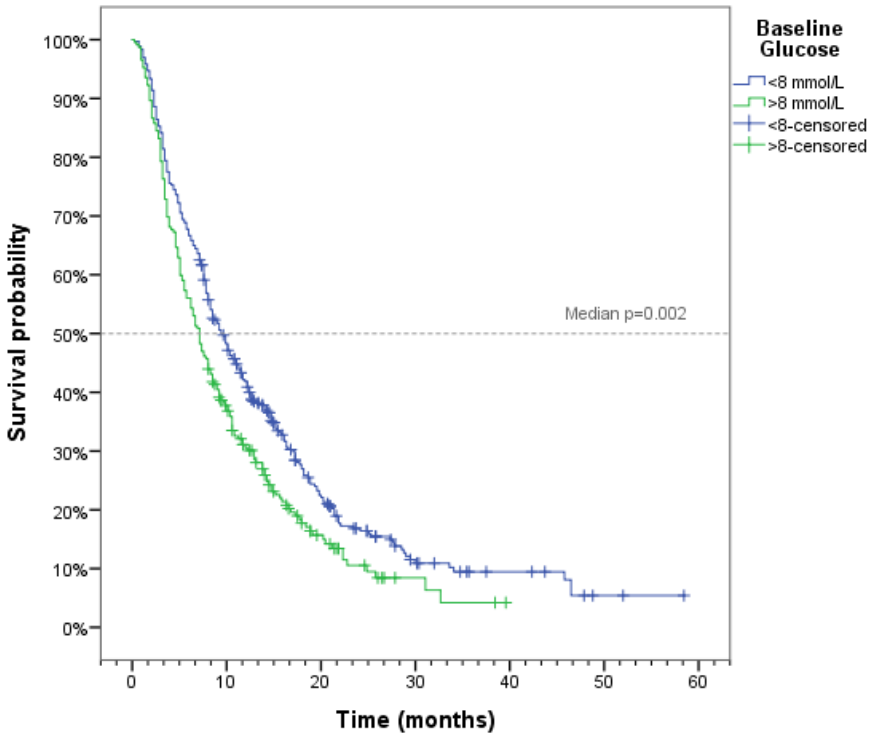


Figure 2.9. Kaplan-Meier graphics illustrating overall survival by baseline glucose values >8mmol/L.

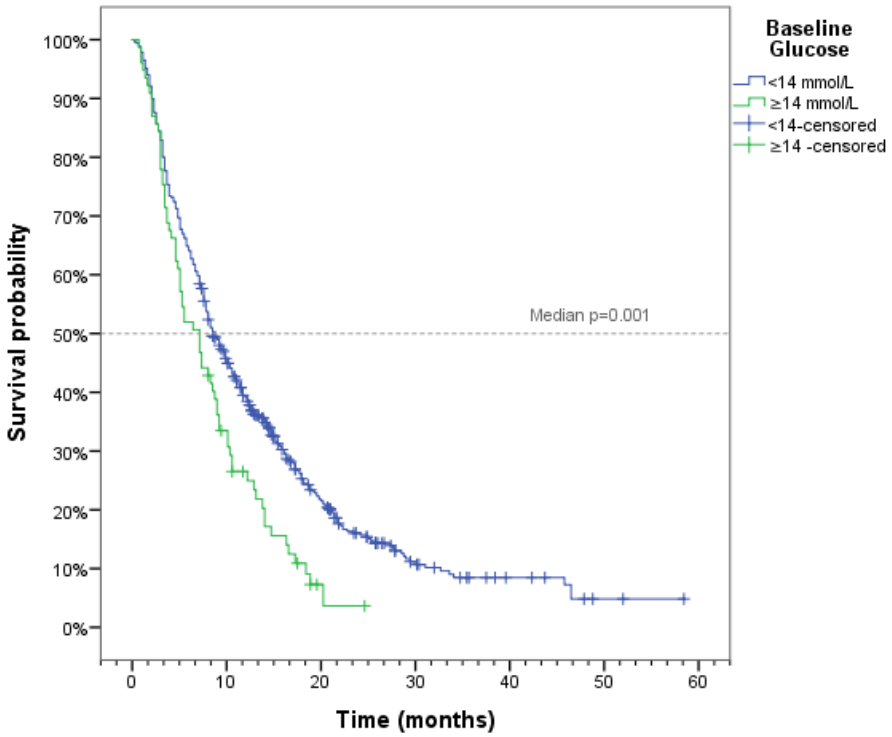


Figure 2.10. Kaplan-Meier graphics illustrating overall survival by baseline glucose values ≥14 mmol/L.

To illustrate the effect of GlucMin (continuous variable) on OS, the dichotomised form based on the median (5.8 mmol/L) was used. Based on the dichotomised variable, the median OS in the higher group (>5.8 mmol/L) was 5.1 months (95%CI 4.3- 5.9) and in the lower than median group was 12.7 months (95%CI 10.7-14.6, p<0.001, Figure 2.11).

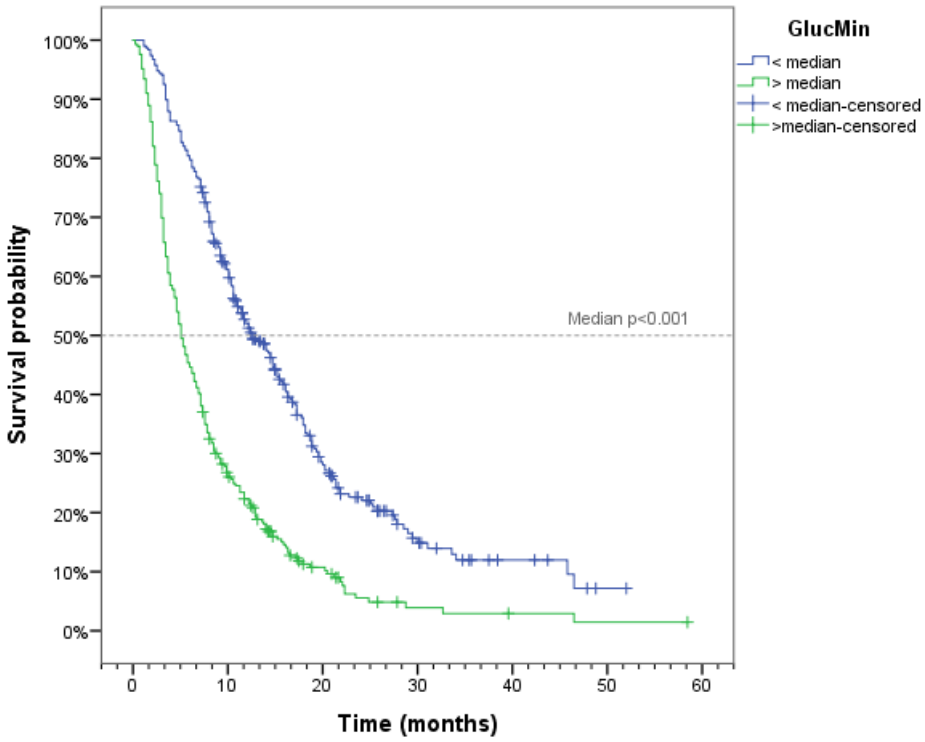


Figure 2.11. Kaplan-Meier graphics illustrating overall survival by GlucMin values above or below the median.

2.3.6 Multivariable analysis

All variables with p-values <0.05 on univariate analysis and additionally the antidiabetic treatment variable, were included in the Cox multivariable analysis. The backwards likelihood ratio stepwise elimination was used to build the final model, which starts with all variables and eliminating the variables that were not significant, step by step.

The final model included antidiabetic medication, regimen of 1st line chemotherapy, stage of disease, treatment intent, baseline albumin, baseline CA19-9, baseline glucose, GlucMin.

The Cox multivariable analysis final model results are presented in Table 2.7 and Figure 2.12. All final variables were significantly associated with poor OS, including the previously known prognostic variables like late stage (p=0.01, HR 1.54 95%CI 1.107-2.148), low albumin (p=0.03, HR 0.97 95%CI 0.952-0.997 [benefit of higher v lower]), high baseline CA19-9 (p<0.001, HR 1.12 95%CI 1.084-1.159), palliative treatment aim (p<0.001, HR 3.7 95%CI 2.337-5.862) and no first line chemotherapy (p<0.001; HR 0.52

95%CI 0.384-0.716- monotherapy, HR 0.41 95%CI 0.295-0.559 doublet, HR 0.26 95%CI 0.175-0.383 triple benefit).

Table 2.7. Multivariable Cox regression results for prognostic effects on OS in patients with pancreatic ductal adenocarcinoma.

Variables	Variable type	p-value	HR	95% CI	
				Lower	Upper
Antidiabetic medication (yes/no)	cat	**0.04**	0.75	0.573	0.986
Glucose baseline (log)	con	**<0.001**	0.62	0.465	0.840
GlucMin (log)	con	**<0.001**	2.04	1.499	2.764
Regimen of 1st line chemotherapy	cat	**<0.001**			
Regimen of 1st line chemotherapy- **mono**		**<0.001**	0.52	0.384	0.716
Regimen of 1st line chemotherapy -**doublet**		**<0.001**	0.41	0.295	0.559
Regimen of 1st line chemotherapy- **triple**		**<0.001**	0.26	0.175	0.383
Stage binary (late v early)	cat	**0.01**	1.54	1.107	2.148
Albumin baseline	con	**0.03**	0.97	0.952	0.997
CA19-9 baseline (log)	con	**<0.001**	1.12	1.084	1.159
Treatment intent (palliative v adjuvant/neo-adjuvant)	cat	**<0.001**	3.70	2.337	5.862

HR- hazard ratio. cat- categorical variable, con-continuous variable. Log- variable was log-transformed for the cox-regression analysis.

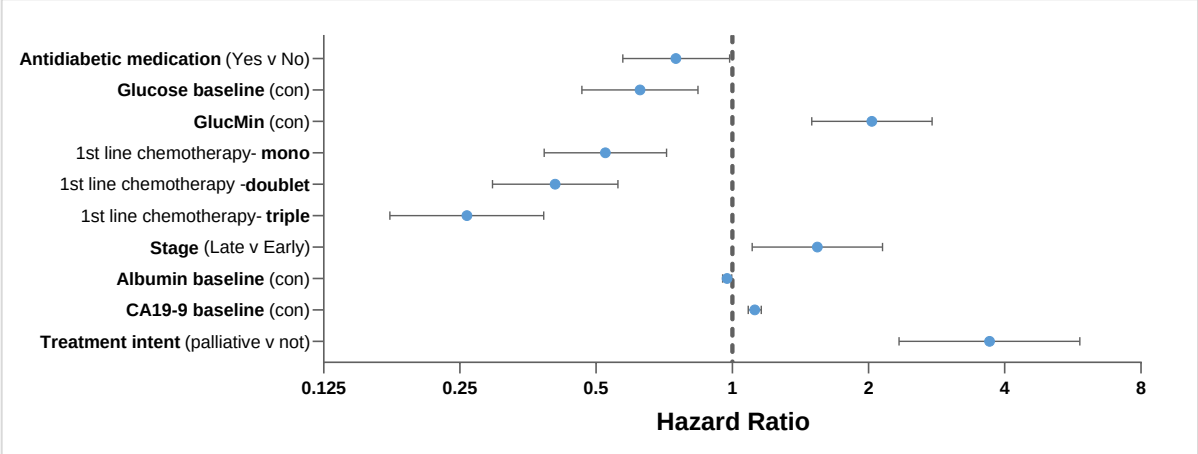


Figure 2.12. Forest plot illustrating the multivariable cox-regression analysis hazard ratio for death results. Con: continuous variable (going higher).

From the glucose-related variables left in the model, a significant two-fold risk was seen with high GlucMin (continuous variable); associated with worse prognosis (p <0.001, HR 2.04). The analysis also showed benefit of being on antidiabetic medication (p=0.04, HR 0.75), although as previously shown, this variable was not statistically significant in the univariable analysis. Somewhat counter-intuitively, a higher baseline glucose (continuous variable) indicated a reduced risk of death (p <0.001, HR 0.62), whilst it showed increased risk of death in univariate analysis (p<0.001, HR 1.36). The other baseline glucose thresholds (>8, ≥14 and ≥11.1 mmol/L twice) were not found to be significant in multivariate analysis and were eliminated from the model.

Thus, higher glucose levels have been found to be associated with increased survival at one point (baseline), but associated with decreased survival at another (GlucMin). Additionally, some variables differed from the univariate results (antidiabetic treatment, glucose baseline), whilst as seen in the previously shown independence analysis (Table 2.3) were highly dependent on each other. In order to understand these associations, further analysis was performed between these variables.

2.3.7 Additional analysis

2.3.7.1 Association between baseline glucose and antidiabetic treatment.

Pearson's Chi-Square analysis was used to understand the association between baseline glucose and antidiabetic treatment variables, and as seen in Table 2.8 there was a significant association (p<0.001) between the baseline glucose (grouped) and being on antidiabetic treatment. This shows that majority (89.6%) of patients with baseline glucose ≥14 mmol/L were either on or given antidiabetic medication, whilst only 12.9% of patients with baseline glucose <8 mmol/L needed this medication.

Table 2.8. Association analysis between baseline glucose levels and use of antidiabetic treatment.

Baseline glucose	Antidiabetic medication		Total	Pearson's Chi-Square
	No	Yes		
≤8 mmol/L	316 (87.1%)	**47 (12.9%)**	363	**p<0.001**
8.1-13.9 mmol/L	87 (57.2%)	**65 (42.8%)**	152	
≥14 mmol/L	8 (10.4%)	**69 (89.6%)**	77	
Total	411 (69.4%)	181 (30.6%)	592	

The majority of patients with higher baseline glucose levels were on or started on antidiabetic treatment and this could explain why the baseline glucose variable was switched from detrimental to OS in the univariate analysis to beneficial in the multivariable analysis when adjusted for antidiabetic treatment, as this could be the beneficial effect of the two variables together.

Additionally, the baseline glucose only captures the starting timepoint, whilst the presence of antidiabetic treatment was assessed over time, and similarly the GlucMin variable was retrospectively assessed over time. Thus, patients with high glucose at baseline are more likely to receive antidiabetic treatment, and the effect of the use of antidiabetic treatment may be driving the benefit in OS.

However, given the retrospective dataset this could also be a spurious result, representing the need for prospective study to collect info about and adjust for many other covariates that could be the cause of the differences seen in variable effect on OS.

2.3.7.2 The effect of antidiabetic treatment on GlucMin

As use of antidiabetic treatment has been shown to be associated with improved OS and high GlucMin with worse OS, a stratified Kaplan-Meier analysis was done to understand how the antidiabetic treatment effects outcomes of patients with high or low GlucMin (dichotomised form).

The stratified log-rank analysis that tests equality of survival distributions for the different levels of GlucMin adjusted for presence or absence of antidiabetic medication showed a statistically significant difference ($p<0.001$, Table 2.9). It is also shown that there is a large difference in OS between these sub-groups of patients, especially in the GlucMin high compared to low groups, in both the patients who were on antidiabetic treatments (14.04 months compared to 6.44 months, Figure 2.14) and who were not (12.43 months compared to 4.37 months, Figure 2.13). Numerical extension in OS can be seen when comparing the patients with or without antidiabetic treatment use both in the GlucMin high or low groups, where the longest OS is seen in patients with GlucMin low and on antidiabetic treatment (14.04 months). This hints to patients who receive antidiabetic treatment and have hyperglycemia well controlled having longer OS even compared to patients who are normoglycemic and not on antidiabetic medication. However, the 95% confidence intervals clearly overlap between these groups. This is

especially interesting as the group of patients receiving antidiabetic treatment and GlucMin low was relatively small (55 patients), but might suggest the benefit of tightly controlling glucose in these patients. However, again given the retrospective dataset, other variables could be the reason for differences found and a prospective study is needed to adjust and measure alls variables.

Table 2.9. Kaplan-Meier log-rank analysis showing survival stratified by the presence or absence of antidiabetic medication use in the GlucMin high or low groups.

		N of patients	**Median OS** (months)	**95% Confidence Interval** Lower	Upper	**p-value**
Not on antidiabetic medication	GlucMin < median	251	**12.43**	10.31	14.54	**p<0.001**
	GlucMin > median	162	**4.37**	3.51	5.23	
On antidiabetic medication	GlucMin < median	55	**14.04**	7.71	20.37	
	GlucMin > median	127	**6.44**	4.92	7.97	

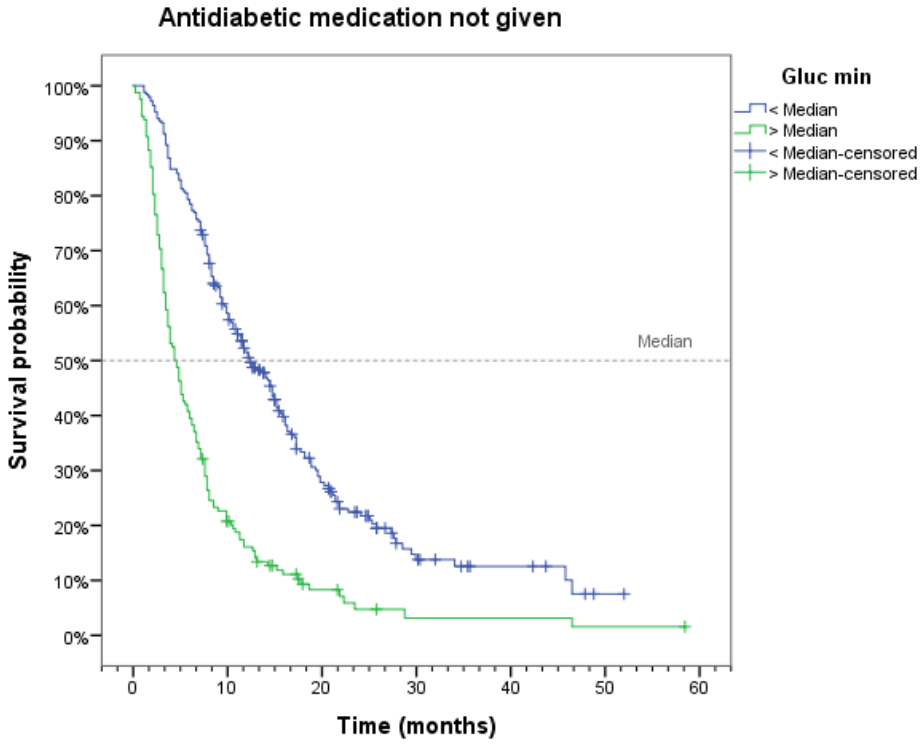


Figure 2.13. Kaplan-Meier graphics illustrating overall survival by GlucMin values above or below the median in the subgroup of patients without antidiabetic treatment

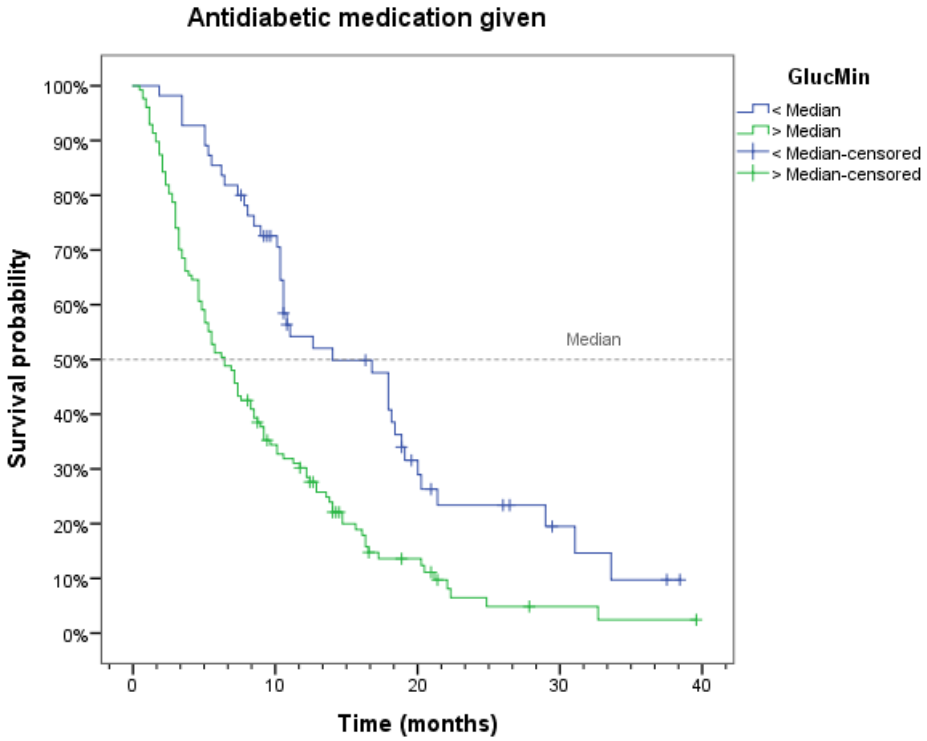


Figure 2.14. Kaplan-Meier graphics illustrating overall survival by GlucMin values above or below the median in the subgroup of patients using antidiabetic treatment.

In this previous analysis, the dichotomised median based GlucMin was used, but in order to analyse further how the extreme values of GlucMin impact on OS, the <25th and >75th percentile values were used. As seen in Table 2.10, there was more than a 4-fold difference between the <25th percentile group (17.25 months) compared to the >75th percentile (3.91 months, p<0.001, Figure 2.15) in OS.

Table 2.10. Kaplan-Meier log-rank analysis showing median OS in the GlucMin highest (>75th percentile) compared to lowest (<25th percentile) group.

GlucMin	N of patients	**Median OS** (months)	95% Confidence Interval		**p-value**
			Lower	Upper	
< 25th percentile	162	**17.26**	15.19	19.33	**p<0.001**
>75th percentile	195	**3.91**	3.20	4.63	

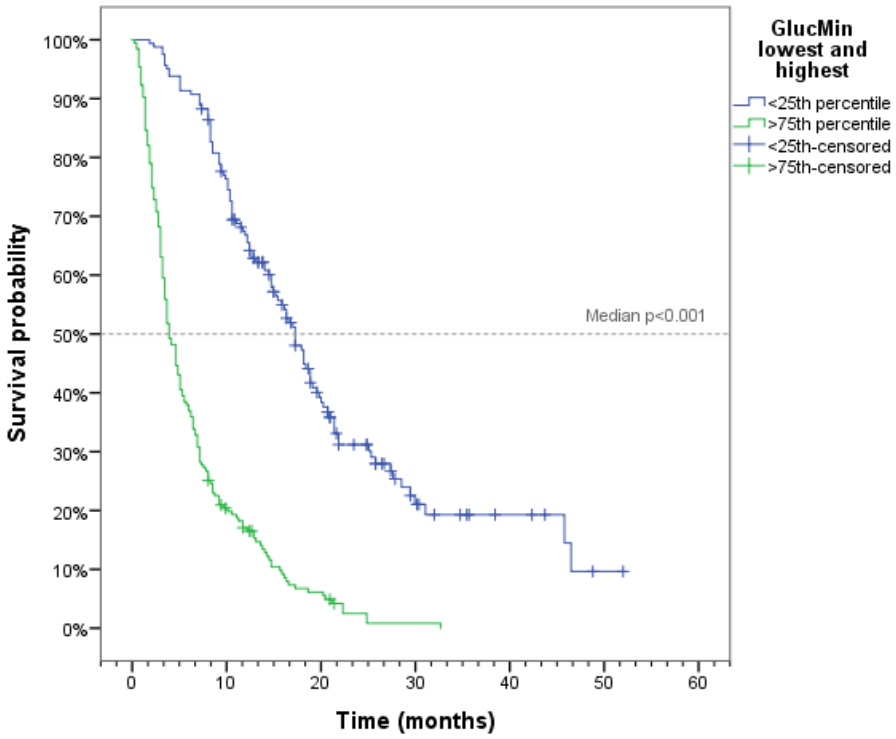


Figure 2.15. Kaplan-Meier graphics illustrating overall survival by GlucMin values in the highest (>75th percentile) compared to lowest (<25th percentile) group.

Similar results were also seen when the analysis was stratified based on presence or absence of antidiabetic treatment, as illustrated in Table 2.11 and Figure 2.16-2.17.

Table 2.11. Kaplan-Meier log-rank analysis showing survival stratified by the presence or absence of antidiabetic medication use in the GlucMin highest (>75th percentile) compared to lowest (<25th percentile) groups.

	GlucMin	N of patients	**Median OS** (months)	95% Confidence Interval		**p-value**
				Lower	Upper	
Not on antidiabetic medication	< 25th percentile	131	**16.57**	14.41	18.73	**p<0.001**
	>75th percentile	90	**3.45**	2.98	3.93	
On antidiabetic medication	< 25th percentile	31	**18.41**	16.98	19.84	
	>75th percentile	105	**5.29**	3.93	6.65	

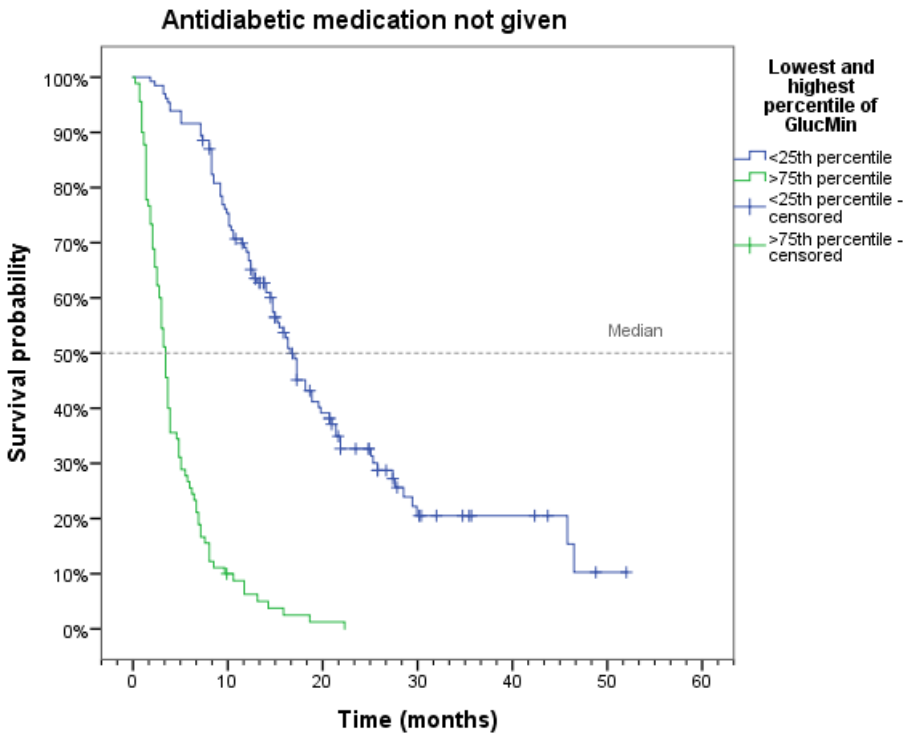


Figure 2.16. Kaplan-Meier graphics illustrating overall survival by GlucMin values in the highest (>75th percentile) compared to lowest (<25th percentile) group in the subgroup of patients not receiving antidiabetic treatment.

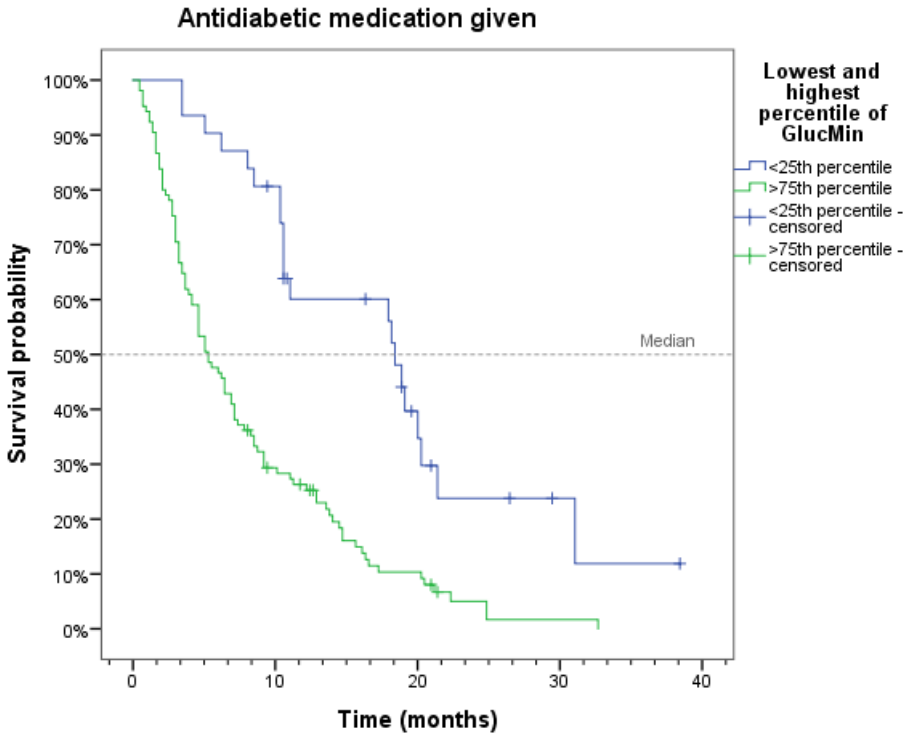


Figure 2.17. Kaplan-Meier graphics illustrating overall survival by GlucMin values in the highest (>75th percentile) compared to lowest (<25th percentile) group in the subgroup of patients with antidiabetic treatment use.

The subgroup analysis of patients with or without antidiabetic treatment use showed again the longest OS (18.41 months) in patients who were on antidiabetic treatment and had GlucMin <25th percentile, even compared to patients who were not on antidiabetic treatment and had GlucMin <25th percentile (16.57 months). However, the confidence intervals were overlapping and the main 3-4-fold benefit in OS was seen when comparing low levels of GlucMin to higher. This indicates that of these two variables that were statistically significant on multivariable analysis, the main prognostic effect seems to be from the GlucMin variable and that the antidiabetic treatment effect could be spurious.

2.3.7.3 Association between baseline glucose and GlucMin

To understand what happens to patients with high glucose at baseline and how GlucMin effects their OS, a further subgroup analysis was done. As seen in Table 2.12, there was again at least 2-fold difference in median OS between the GlucMin high and low groups.

Table 2.12. Kaplan-Meier log-rank analysis showing survival, stratified by the baseline glucose values in the GlucMin low or high groups.

Baseline glucose	GlucMin	N of patients	**Median OS** (months)	95% Confidence Interval		**p-value**
				Lower	Upper	
≤8 mmol/L	GlucMin < median	249	12.66	10.35	14.96	
	GlucMin > median	114	4.60	3.23	5.98	
8.1-13.9 mmol/L	GlucMin < median	39	14.50	10.22	18.78	**p<0.001**
	GlucMin > median	113	5.52	4.32	6.72	
≥14 mmol/L	GlucMin < median	16	10.36	8.25	12.46	
	GlucMin > median	61	5.29	3.28	7.30	

There was also some difference seen between the three baseline glucose groups showing longest OS (14.5 months, 95%CI 10.22- 18.78) in patients with baseline glucose between 8-13.9 mmol/L and GlucMin lower than median. However, as the OS confidence intervals between the three groups with GlucMin lower than median, largely overlap, it can be concluded that there is no significant difference between these groups. The 55 patients who had high (>8 or ≥14 mmol/L) baseline glucose, but had a

lower than median GlucMin had a much longer OS than those where the GlucMin was high, suggesting the detrimental effect on OS coming from having constantly high glucose.

Thus, the beneficial effect of high baseline glucose on OS seen in the multivariable analysis might have been driven by the group of patients where GlucMin was lower and as previously discussed, potentially where patients were given antidiabetic treatment.

2.3.7.4 Internal validation

As described in the methods section, the bootstrapping method [252, 253] was used to internally validate the multivariable model. The bootstrap analysis included 1000 resampled datasets from the original data and assessed if the results could be driven by a small proportion of outliers [259]. The results are provided in Table 2.13.

Table 2.13. Bootstrap internal validation of model variables (based on 1000 resampled datasets).

Variables	p-value	HR	95% Confidence Interval	
			Lower	Upper
Antidiabetic medication (yes/no)	0.021	0.74	0.57	0.97
Glucose min (log)	0.001	1.77	1.37	2.47
Glucose baseline (log)	0.003	0.68	0.51	0.88
Regimen of 1st line chemotherapy- **mono**	0.010	0.66	0.47	0.87
Regimen of 1st line chemotherapy -**doublet**	0.001	0.51	0.37	0.66
Regimen of 1st line chemotherapy- **triple**	0.001	0.32	0.21	0.44
Stage binary (late v early)	0.007	1.49	1.13	1.96
Albumin baseline	0.003	0.96	0.93	0.99
CA19-9 baseline (log)	0.001	1.12	1.08	1.16
Treatment intent (palliative v adjuvant/neo-adjuvant)	0.001	3.14	2.28	4.74

The results of the bootstrap resampling confirmed the significance of all variables present in the model, indicating that the model did not contain significant bias or was driven by outliers. Thus, the results validate the model internally.

Naturally, this does not validate the clinical value of the results, which still needs to be assessed in a prospective validation study and is further described in a later section.

2.4 Discussion

2.4.1 Discussion of study findings

This was a retrospective analysis of 640 patients with PDAC investigating the association between plasma glucose levels and survival outcomes.

Besides the known prognostic factors, this study found that a high GlucMin is independently associated with a two-fold increase in the risk of death; and in patients with a high baseline glucose receiving antidiabetic treatment can lead to better OS.

Diabetes or hyperglycaemia

The previous studies on this topic have primarily looked at the impact of a diagnosis of diabetes on survival, and not specifically at the effect of hyperglycaemia. Similar studies in breast cancer have shown that hyperglycaemia can be a more important prognostic factor than a diagnosis of diabetes [260]. This is especially important in pancreatic cancer, where there has been substantial preclinical work published on glucose levels and its impact on tumour cell aggressiveness [103, 115]. It has been reported as a potentially paraneoplastic phenomenon caused by the cancer [88]. However, clinical translation of this effect is still unknown, but hyperglycaemia is still much more prevalent in pancreatic cancer than in other cancer types [74]. High prevalence was also seen in this study with 63.4% of patients having abnormal glucose levels (>8 mmol/L) and only 28.9% known to be diabetic.

Diagnosis of diabetes

In this current study, the diabetes diagnosis itself did not have an impact on patients' outcomes. As discussed in the first chapter, other studies have shown mixed results concerning the impact of diabetes on patient survival outcomes. Whilst some large

retrospective studies showed that there was no effect of either long-term or recently diagnosed DM on survival [120], others reported that long-standing diabetes was associated with decreased survival [119]. The largest pooled meta-analysis assessing the association between diabetes and cancer, concluded that patients with DM and PDAC had worse OS than those without DM (HR 1.67) [84]. These conflicting results [84, 119-122] might be due to the heterogeneity of patient data analysed, and that the diagnosis of diabetes was based on patients self-reporting or clinical records, and the glucose levels themselves or glucose control were not reviewed. In the current study, it was not possible to distinguish between long-term or recently-diagnosed diabetes, as the diabetes diagnosis was based on clinical records and the aim of my work was to look specifically at the glucose levels rather than diabetes.

New diagnosis of diabetes

I did show however, that based on the WHO criteria [240], there were 43 new diagnoses of diabetes in our database, based on random glucose levels, and an additional 34 patients who had readings ≥11.1 mmol/L once, but glucose levels were not measured again, and thus it is not known if these patients would have ended up matching the diagnostic criteria. Of the 205 patients who had glucose ≥11.1 mmol/L, 47 patients had it measured again and it was not above that level the second time. However, we do not have information if these patients had further glucose monitoring as these values would require home glucose monitoring to determine their risk of diabetes.

Similarly, there were 145 (24.4%) patients with glucose ≥14 mmol/L and 377 (63.4%) >8 mmol/L either at baseline or during treatment. Of the 145 that had glucose ≥14 mmol/L, 114 were on antidiabetic medication and 31 (21%) were not, whilst out of the 377 that had glucose >8 mmol/L, 44% (166) were on antidiabetic treatment and 211 (56%) were not. Based on local guidelines, these 211 (who went >8 or >14 and not on antidiabetic treatment) patients should have regular glucose monitoring and potentially also antidiabetic treatment, if diabetes confirmed, but it is not known if this was actioned. In contrast, there were also 18 patients who were known to be diabetic but had no glucose measurement at The Christie. Thus, no information about their glucose control is available. This illustrates that glucose monitoring was not done regularly and similarly to previous research [75, 81], some patients with diabetes were potentially missed. It also highlights that the patients with DM did not have regular recorded glucose

monitoring, and some patients might have needed increased antidiabetic treatment to control their glucose levels. Equally, it is not known if patients had any regular glucose monitoring done outside The Christie.

In the general population (non-cancer), the high-risk group for developing diabetes are those with a 1 in 4 risk of developing diabetes in the next 10 years [261]. As in the current study 24.4% of patients had glucose >14mmol/L and 20.8% had glucose levels >11 mmol/L recorded twice (diabetes diagnosis criteria) thus, these are close to the 1:4 odds, especially if we take into account that the median OS was 8.1 months in this group (compared to risk over 10 years as in the guidelines). This once again highlights that patients with PDAC might benefit from regular monitoring of glucose to diagnose diabetes. According to the national guidelines on type 2 diabetes prevention in people at high risk [261], patients in the high risk group should be offered a blood test at least once a year (fasting glucose and HbA1c).

Baseline glucose levels (first hypothesis)

The current data indicates that baseline plasma glucose above institutional guidelines-based thresholds (>8 mmol/L or ≥14 mmol/L) conferred worse outcomes on univariate analysis. However, when adjusted for other prognostic factors, antidiabetic treatment and GlucMin in the multivariable analysis, there was a beneficial effect of high baseline glucose on OS. As discussed in the additional analysis section, this phenomenon seemed to be due to the combination of antidiabetic treatment given and GlucMin, where patients whose baseline glucose was high were more likely to be given antidiabetic treatment and only if their GlucMin was then lower, they had a longer OS. The beneficial effect of high baseline glucose on OS was not seen in patients whose GlucMin was high.

To the best of my knowledge there have been no other studies in patients with PDAC looking at these interactions between baseline glucose levels and survival. The previously-mentioned RCT on the effect of adding metformin to gemcitabine and erlotinib chemotherapy by Kordes *et al* [124] mentioned that baseline glucose concentrations were neither prognostic nor predictive for OS in their study. However, they did not provide any further information about that, and the study only included 121 patients [124]. It is not clear how they assessed the glucose levels and whether the lack of patient numbers contributed to the lack of prognostic/predictive effect.

Antidiabetic treatment

In the current study, there was no benefit of antidiabetic treatment seen in the univariate analysis, but when adjusted for baseline glucose, GlucMin and other prognostic variables, giving antidiabetic treatment had a significant positive impact on OS. As discussed previously, the beneficial effect could be from glucose control and this was best evidenced by the additional Kaplan-Meier log-rank analysis stratified by the presence or absence of antidiabetic medication in the GlucMin high or low groups, that showed that in the group treated with antidiabetic medication, the benefit was mainly in the group with GlucMin low. This indicates that it was the antidiabetic treatment controlling the GlucMin that led to better OS and patients on antidiabetic treatment whose GlucMin was still high, did not have this beneficial effect on OS. However, given the fact that the variable switched between univariate and multivariable analysis, this could also be a spurious result that will need to be further investigated in the prospective study.

As described in the introduction, metformin as an antidiabetic medication has been proposed to also have anticancer effects, but RCTs [124, 125] have not confirmed this. Unfortunately, I was not able to distinguish between different oral antidiabetic treatments in this data, thus, the true effect of metformin could not be analysed. Similarly, in clinical practice, metformin is only used in patients with diabetes and so we did not have any patients on metformin who were not diabetic, as previous RCTs have not shown any benefit of adding metformin to standard chemotherapy in all patients with PDAC [124, 125]. The previously mentioned meta-analyses [126, 127] have shown some slight benefit of metformin in OS of patients with pancreatic cancer and diabetes. In my study, there were 122 patients who were on oral antidiabetic treatments. However, in the clinical context, diabetes treatment is usually based on glucose control and in order to achieve that, multiple medications are often used in combination, thus, these 122 patients probably had a mix of antidiabetic medications, and so the individual effect of one medication cannot be concluded. Ultimately, these previous meta-analyses may also indicate that similarly to my results, better control of diabetes with treatment (rather than metformin per se) may be responsible for better survival.

Glucose during treatment

Plasma glucose levels during treatment (after baseline) above the two thresholds (>8 mmol/L or ≥14 mmol/L) did not have a significant impact on patient outcomes in the current database, whilst ≥11.1 mmol/L twice (fulfilling diabetes criteria) showed inconclusive results (violating proportional hazard assumption). This lack of effect of hyperglycaemia during treatment is potentially due to missing data and different systemic treatments and treatment effects. As the OS in patients with PDAC is very short, after baseline, the amount of available data decreased, as many patients rapidly progressed or died. Nevertheless, the last glucose measured per patient was found to have a significant impact on OS on univariate analysis, demonstrating that patients with higher last glucose had shorter OS. A previous study by Karlin *et al* [262] analysed the effect of diabetes on pancreatic cancer outcomes, and showed that in their cohort of 92 patients with diabetes and PDAC (paired with 92 patients without diabetes), glucose and HbA1c decreased over time, but insulin use was doubled. It seems that more patients needed insulin to keep their hyperglycaemia under control, and it is likely that they had lower blood glucose levels because of insulin.

GlucMin (second hypothesis)

The multivariable analysis showed that of the glucose variables, the GlucMin, defined as lowest plasma glucose level measured per patient during treatment, had the most significant impact on patient survival outcome. This indicates that if the glucose is constantly high and does not return or fluctuate back to normal levels during treatment, then these patients have worse survival outcomes. This was best illustrated in the subgroups of patients with the highest (>75th percentile) and lowest (<25th percentile) GlucMin, where the difference in OS was more than 4-fold (17.26 months compared to 3.91 months, $p<0.001$). As seen in the glucose related baseline characteristics Table 2.2, the cut-offs for the 25th and 75th percentiles were 5.0 mmol/L and 7.4 mmol/L, respectively. This demonstrates that the per-patient lowest glucose does not need to be out of the normal range to have a significant impact on OS.

Compared to baseline values, GlucMin shows the glucose fluctuations longer term, over the treatment period, and for this reason, it could also be one of the markers for poor glucose control during treatment. As hyperglycaemia has been hypothesised to be a

paraneoplastic phenomenon caused by PDAC [88], this result could also suggest that the patients with higher GlucMin had worse OS because they had more aggressive cancer. However, the reason behind hyperglycaemia in PDAC is still not clear and thus, it is not known how PDAC influences the glucose levels exactly. As seen in the association table (Table 2.3), GlucMin was significantly associated with all other poor prognostic factors (CA19-9, stage, albumin, treatment intent, ECOG PS), which does suggest that there is a link between hyperglycaemia and aggressiveness of the cancer.

Other prognostic factors

Previously-known poor prognosis factors like high serum CA19-9, late stage, low albumin [263], choice of first-line chemotherapy and palliative treatment aim were found to be similarly prognostic in this current thesis. Equally, the baseline characteristics displayed in Table 2.1 show results similar to previously published averages of patients with PDAC: ¾ of patients have late stage disease compared to a quarter with early disease, equal split between men and women, median age 68 years, two thirds ECOG PS 0-1, a fifth ECOG PS 2. Taking into account that these patients were all referred for chemotherapy, we did see 14% of patients who were ECOG PS 3-4 and not fit enough for treatment (by the time of the appointment). This is a common problem described in chapter 1, patients deteriorate fast and have a high symptom burden due to the underlying malignancy [159]. Thus, these data demonstrate that the patient cohort seen in this study does represent everyday clinical practice patients with PDAC, reviewed at a tertiary hospital Medical Oncology clinic.

Internal validation

Internal validation of the model was also carried out using the bootstrap method. This confirmed the significance of all variables present in the model, and did not identify any significant bias in the dataset.

To validate the results internally, additional ways of using the current large dataset were also considered. One method would be “Split-sample validation” [259, 264], where the dataset is split in half and the first part is used as a “training” set and the second half as a “validation” set [265]. We assessed the possibility of this with our data, where the 640 patients’ data was split into two sets of 320, and reanalysed with the same multivariate model. However, splitting the data this way would mean that only the first 320 is used

for the general analysis, and the "validation" set is only used to validate the single GlucMin variable. The results of this analysis illustrated that GlucMin was still statistically significant in the training and validation set (HR 1.7 and 2.2, respectively). However, the dataset was retrospective (with its limitations and missing data), and splitting the data did not provide any additional results in relation to improvements in clinical practice, whilst leaving the model less statistically powered. Similar conclusions have been previously made about the split-sample validation in the literature [259, 264, 265], advising against this, due to suboptimal performance of the model and lack of additional results, other than of the first half of the sample [259, 266]. It has also been proposed that split-sample validation should not be used with sample sizes less than 20 000 [259]. Thus, as this analysis provided no additional results and the sample size was only 640, the split-sample validation method was not pursued further.

Nevertheless, the internal validation of the model was confirmed with the bootstrap resampling method, whilst the clinical value of these results will still need to be validated in a prospective study.

2.4.2 Patients with extreme hypo- or hyperglycaemia

It has previously been shown that extreme levels of plasma glucose are dangerous and have a high mortality rate [267, 268]. Both hypoglycaemia and hyperglycaemia are known to have detrimental effects on patients' wellbeing and health. A hyperglycaemia level of >33 mmol/L is a symptom of hyperosmolar hyperglycaemic state (HHS), and is associated with mortality rates of 5–20% [267]. Similarly, hypoglycaemia <3.9 mmol/L is also associated with 3.4-fold higher mortality compared to patients with no hypoglycaemia (in patients with diabetes) [268]. To investigate if these extreme levels could be confounding the effects found in this study, I reinvestigated those patients' data.

As illustrated in the histogram (Figure 2.2A), in our cohort of 640 patients, at baseline, only 1 patient had glucose <4 mmol/L (3.8 mmol/L) and the patient was known to have diabetes on insulin treatment. One patient had glucose >33 mmol/L (37.1 mmol/L) at baseline, and the patient was similarly known to have diabetes and was originally on oral medication and was switched to insulin. Twenty-five patients (3.9%) were found to

have glucose levels <3.9 mmol/L as their lowest glucose measured during treatment (GlucMin, Figure 2.2C); 9 of those patients were known diabetics on antidiabetic treatments. Two patients (0.3%) had glucose levels >33 mmol/L as their highest ever measured (GlucMax, Figure 2.2D); both of these patients were known diabetics on insulin. As patient numbers with extreme hypo- and hyperglycaemia are very low in this study, it is not possible to analyse how these affected their outcomes compared to other patients. I was however able to go back and calculate these patients OS. All 3 patients who had glucose >33 mmol/L either at baseline or GluMax, had metastatic PDAC and had OS 7-9 months, which is similar to the median OS in this study for patients with advanced disease. The 25 patients found to have hypoglycaemia were a more heterogeneous group, with 6 patients having adjuvant treatment and 19 palliative. However, just focusing on the palliative group, the median OS was 11 months. As previously mentioned, it is impossible to correctly statistically compare these small number of patients, nevertheless it is noteworthy to see that their median OS is similar to the overall OS in this study, and therefore these extremes probably did not bias the overall results.

2.4.3 Study limitations

This was a retrospective data collection and we relied on the information that was available in the electronic patient records and the blood tests that were done. I excluded 45 patients with missing critical clinical information. Additionally, not all patients had blood glucose measured regularly and 45 (7%) had no glucose measured at any time. There were also huge variations of the amount of times glucose was measured per patient, ranging from 0 to almost all clinic appointments. As discussed in the methods and results sections, I also planned to assess hyperglycaemia at the time of disease progression (on any line of treatment), but during data collection, it was discovered that most patients did not have glucose measured at those time-points and I had to abandon that part of the research question, due to lack of data.

One of the other limitations of this current retrospective data collection is that the patients were not actively screened for diabetes. The diagnosis of DM is based on clinical record annotations of previous medical history, and interestingly 43 new patients were found retrospectively in this study who matched the WHO diabetes criteria.

Additionally, there is no information about the date of diabetes diagnosis in this study. Previously, it has been reported that pancreatic cancer-associated diabetes develops as recent-onset diabetes, usually up to 5 years prior to a pancreatic cancer diagnosis [85]. Unfortunately, in this study it is not possible to differentiate between recent-onset and long-standing diabetes, as the patients' clinical records did not have that information.

Another limitation of this study is that the plasma glucose levels recorded were drawn at the same time as the patients' normal blood tests, and thus these are random and not fasting glucose measurements. This complicates the interpretation of some of the normal glucose thresholds, for example between 6-8mmol/L. However, glucose levels above 8 or 14 mmol/L would still need monitoring and potentially antidiabetic treatment if they continued to be high. Non-fasting glucose levels also make the diabetes diagnosis difficult, as that would usually require fasting glucose or as explained, a twice measured glucose level ≥11.1 mmol/L.

Nonetheless, even in this retrospective data set, these results demonstrate that higher GlucMin is a poor prognostic factor and that if patients with high baseline glucose receive antidiabetic treatment that controls hyperglycaemia, their survival could be longer.

2.4.4 Clinical relevance

This study provides further information about the association between pancreatic cancer and plasma glucose levels. It also gives a signal that this risk could be modifiable by antidiabetic medication, but this will need to be prospectively evaluated in future studies. A study by Karlin *et al* reported that glucose control was not affected by the presence of pancreatic cancer or its treatment, [262] thus, this could be achieved with standard antidiabetic treatment. Good glucose control in patients without cancer has previously been shown to improve survival outcomes [269], therefore one hypothesises is that good glucose control in patients with PDAC could produce similar effects. This is especially interesting in pancreatic cancer where the hyperglycaemia is hypothesised to be caused by PDAC in order to grow and progress faster [88], thus, more tightly controlling hyperglycaemia with antidiabetic medication, may also help control pancreatic cancer. However, this correlation is still hypothetical and more research is

needed to understand why PDAC is causing hyperglycaemia and how it affects patient outcomes.

Tight glucose control

In patients without cancer, tighter glucose control for type 2 diabetes has previously been shown to lead to less vascular complications and rates of death [270, 271]. With the aim of preventing diabetes complications, tight control is an intensive diabetes management method that requires maintaining glucose levels as close as possible to normal, without causing frequent hypoglycaemia [272]. This is achieved by having lower fasting glucose and HbA1c targets, and earlier and more adaptable treatment, usually using a combination of antidiabetic agents [271, 273]. Thus, this is a method already used in diabetes care that could also be employed in management of patients with PDAC, should tighter control be found to be beneficial.

Prospective clinical studies are needed to evaluate whether improved treatment of diabetes, leading to better glycaemic control in patients with PDAC, results in more favourable survival outcomes. As diabetes treatment has evolved rapidly over the past decades, optimal glycaemic control is possible to achieve in the majority of patients (with or without cancer), and thus may also lead to improved survival outcomes in patients with PDAC.

2.4.5 Conclusions of the study

In this retrospective data collection of patients with PDAC (all stages), I demonstrated for the first time that high GlucMin confers significantly worse survival outcomes. I also showed that antidiabetic treatment in patients with high baseline glucose could lead to better outcomes and thus gives the first signal that better antidiabetic control in patients with PDAC could lead to longer OS. Importantly, I found that 24.4% patients had glucose levels above ≥14 mmol/L and 63.4% >8 mmol/L (either at baseline or during treatment) which highlights that hyperglycaemia is common in these patients and that monitoring patients' plasma glucose levels during active systemic treatment is essential. However, results of this retrospective study will need to be prospectively confirmed in order to further describe the effect of hyperglycaemia and its treatment on the outcomes of patients with PDAC.

2.5 Implications of the data for future work and the clinic

These results demonstrate an important association between glucose levels and outcomes of patients with pancreatic cancer, that needs to be prospectively confirmed and validated.

2.5.1 Change in clinical practice

Whilst collecting data for this study, I noticed that measuring glucose for patients with PDAC was not done regularly at The Christie and so, I was not able to collect some of the data that I originally planned. Also, HbA1c was rarely done for any patients with PDAC and usually only when there was a diabetes treatment-related need. Furthermore, when glucose levels were high, they were not always acted on, as this was expected to be a known complication of the cancer. Similar problems with monitoring and treating patients with hyperglycaemia or diabetes have been published previously by other centres [75, 274]. As a result of inconsistencies in practice, I highlighted this to the HPB disease group, and it was decided that practice would be altered to improve monitoring of plasma glucose levels in patients with PDAC. It was decided that all new patients seen in clinic with pancreatic cancer would have random plasma glucose and HbA1c measured at baseline and plasma glucose levels measured every time they come to clinic. In addition, collaboration with the diabetes services in The Christie was increased and regular referrals of all patients who had abnormal plasma glucose levels was instituted, so that home monitoring and potential treatment could be organised.

2.5.2 Positive effects of controlled glucose

This study showed that there are three glucose-related variables that have a significant effect on the outcomes of patients with PDAC. However, this study did not aim to understand what the cause of hyperglycaemia in PDAC is and thus, whilst these results highlight there is a connection, the reasons behind this remain unknown. As previously explained, one hypothesis is that PDAC induces hyperglycaemia, lipolysis and weight loss in order to enhance its survival, proliferation and tumorigenesis and potentially carcinogenicity [88], whilst the second hypothesis is that hyperglycaemia is a side-product of the disease growth in the pancreas causing β-cell dysfunction [89]. This

indicates that whilst the cause of hyperglycaemia is not known, we also do not know if controlling hyperglycaemia could also help to control the cancer or not.

There are two possible thoughts on how controlling hyperglycaemia could control PDAC:

1) If hyperglycaemia is needed for cancer proliferation and tumorigenesis, then when (aggressively) normalising the glucose, the growth of cancer could also be controlled. As previously mentioned, due to the increase of novel antidiabetic treatments, glucose control is achievable in the majority of patients. So, based on this theory, the antidiabetic medication could then work also as anticancer treatment, but only if the glucose is controlled. This theory has some evidence from previous literature where hyperglycaemia has been linked with more aggressive features of PDAC [103, 116, 117], but obviously the question remains, if the glucose is controlled does that ease the aggressiveness of the cancer as well.

2) Symptomatic effect. If hyperglycaemia is a side-product of the effect of PDAC in the pancreas, then by controlling glucose it probably will not directly impact the cancer growth, but could improve patient symptoms like fatigue and weight loss, that are usually associated with both PDAC and uncontrolled diabetes. The side-effects from chemotherapy may also be lessened, as hyperglycaemia is associated with more chemotherapy side-effects [241] and thus, patients may potentially stay on chemotherapy longer. The previously mentioned study by Basch *et al* [174] showed that monitoring patient side-effects and dealing with them early, allowed patients to stay on chemotherapy longer and achieve better OS. Similarly, the hypothesis could be that if we were able to achieve good glucose control in these patients and lessen their side-effects, their outcomes could be improved by keeping them on treatment longer.

2.5.3 GlucMin as a biomarker

In this study, higher GlucMin was prognostic on multivariable analysis and could be thus, considered as a prognostic biomarker. However, as GlucMin is a retrospective marker that is only available when the patient has died (or the study period has ended), it would not be a good marker for glucose control or prognosis. Another problem with GlucMin

is that it is only one value and does not give any information about the range or variability of glucose. This means that future studies should use more advanced tools to assess glucose control. For example, HbA1c assesses how well glucose has been controlled over a period of about 3 months [275], which could be a more sustained way of assessing glucose over time.

Interestingly, in the last decades, there has been a rapid increase in the number of novel blood glucose measurement tools that can now continuously monitor blood glucose, and whilst the evidence for the benefit of their use is compelling in diabetes [276], they do not seem to have been researched in patients with cancer. In patients without cancer, it has already been shown that increased glycaemic variability, measured by continuous glucose monitoring, was associated with increased diabetes complications, like diabetic peripheral neuropathy [277]. Thus, there are validated ways of analysing the continuous monitoring values, that would be potentially a better marker for glucose control than GlucMin.

2.5.4 Cancer Research UK biomarker development

Cancer Research UK (CRUK) has created a Prognostic/Predictive Biomarker Roadmap and defined different stages of biomarker development [278] (Figure 2.18).

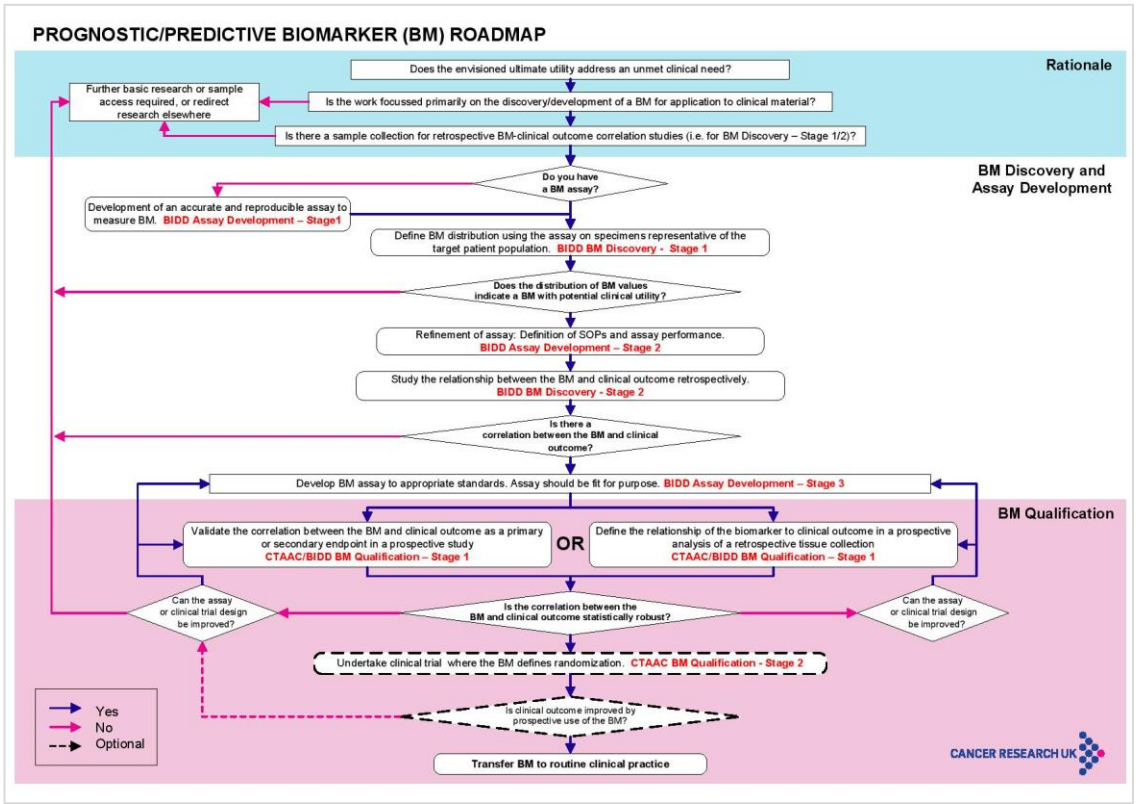


Figure 2.18. Cancer Research UK Prognostic/Predictive Biomarker Roadmap [278].

The data from the current study has shown important correlations between the biomarker and clinical outcome, but as discussed above, GlucMin will not be a good biomarker to take forward prospectively. Nevertheless, there are potential others that could act as a surrogate or even an improvement on GlucMin. Importantly, as all glucose variables (fasting, random, HbA1c and continuous monitoring) have been in standard use for decades, and have been heavily researched also in patients with cancer, there would be no need to re-validate the assays or ways how these are measured. Thus, these potential biomarkers can be analysed in a standard way in patients with PDAC, but their effect on the outcomes of these patients are not known.

This means that with the results of this study, GlucMin has gone through the Biomarker Discovery and Assay Development (BIDD) stage of the CRUK roadmap [278], and the next step would need to validate the correlation between the biomarker and clinical outcome as a primary or secondary endpoint in a prospective study [278]. This next biomarker qualification stage will need to show if there is a statistically robust correlation between the biomarker and clinical outcome before it can be used in clinical practise [278].

Interestingly, the results from the current study raise two questions that need to be addressed in this validation study, as our results have shown the first signal that glucose levels during treatment could have an impact on the patients OS. Based on this, I propose the need for two phases of studies to test this hypothesis according to the CRUK roadmap.

First phase: Pure observational study with HbA1c as a surrogate for GlucMin (as GlucMin is not an appropriate biomarker for prospective study). This phase would aim to confirm the validity of using HbA1c as a surrogate for GlucMin, assess patients HbA1c levels throughout treatment and how these affect the OS. If the validation study confirms this to be a prognostic marker, then the next phase study could be done.

Second phase: Prospective randomised interventional study, where patients are randomised between SOC glucose management and tighter glucose management. This would address whether the prognostic marker is modifiable with tighter glucose control.

Thus, the first phase would aim to initially validate HbA1c as a surrogate prognostic biomarker for GlucMin. The prospective validation study proposal is now described.

2.5.5 Proposed validation study to confirm the prognostic effect of hyperglycaemia.

A validation study proposal was developed based on the CRUK biomarker roadmap [278] and the REMARK [244] guidelines items 1-9 (Table 2.13). Other items from the checklist (Table 2.13) were not included, as these are about reporting or analysing the data once it is collected. This study could be run as a prospective observational study or as part of another phase II-III clinical trial.

Below, the items 1-9 are further described in detail for the prospective study.

<u>Item 1.</u> State the marker examined, the study objectives, and any pre-specified hypotheses [244].

Background

Baseline hyperglycaemia had a statistically significant impact in the current study on OS, but changed directions between univariate and multivariable analysis. Also, the data collected was retrospective and did not include all diabetes-related variables, so it would need to be assessed prospectively with at least fasting glucose and HbA1c included. This would allow an understanding of whether baseline hyperglycaemia could be a prognostic marker and if it is related to the aggressiveness of the cancer.

I have shown that an elevated GlucMin is associated with a worse patient survival; however, GlucMin would not be a good biomarker as it would always be applied retrospectively and only includes one variable, not showing the range. Instead 3-monthly HbA1c levels would be used as a surrogate, especially as testing for this is now readily available in the community [275, 279, 280], and could be easily implemented in the future, should this be prognostic. Continuous glucose monitors would potentially be another way of analysing glucose fluctuations and variability over time.

Thus, I would plan to include 3 ways of measuring glucose throughout the patients treatment: 1) fasting glucose (every visit), 2) HbA1c (every 3 months), 3) continuous

glucose monitors (constant measurement). This would allow the maximum data available about these patients' glucose levels, as glucose is a changeable variable, affected by various other factors (food, treatment, weight loss). Ultimately one of these ways of measuring glucose is expected to be the most beneficial, but including all three for this study would allow the most informative one to be chosen in the end. As HbA1c is the most longitudinal of these three variables and potentially most straightforward surrogate of GlucMin, the study sample size calculation (described later) will be based on this.

Hypotheses of the validation study:

1) Patients with high baseline HbA1c have worse OS.
2) Longitudinal poor glucose control* is a poor prognostic marker leading to worse OS.

* defined based on HbA1c, fasting glucose or continuous glucose monitoring levels.

HbA1c levels will be assessed as means over time. Additionally, changes between levels (as absolute numbers and percentage) will be recorded to determine if there is a threshold associated with increased risk. This could then be used to enable development and sample size calculation of the second phase interventional study.

<u>Item 2.</u> Describe the characteristics of the study patients, including their source and inclusion and exclusion criteria [244].

Patients with newly-diagnosed advanced (unresectable) PDAC would be recruited to the study prior to starting palliative standard of care chemotherapy. I would exclude patients with early stage disease because they would need to be seen prior to surgery to assess how blood glucose changes with surgery, recovery and adjuvant treatment. Also, there are multiple trials ongoing assessing hyperglycaemia as a screening tool for early PDAC, and thus I would not include these patients.

Inclusion criteria: patients with advanced PDAC due to start first-line chemotherapy and willing to have additional blood tests at clinic visits, and willing to wear a continuous glucose monitor.

Exclusion criteria: patients with a known diagnosis of type 1 diabetes mellitus.

Item 3. Describe treatments received and how chosen (for example, randomised or rule-based) [244].

All patients would be treated with standard of care chemotherapy. Patients hyperglycaemia or diabetes management would also follow the local treatment guidelines and no additional hyperglycaemia treatment would be offered.

Item 4. Describe type of biological material used. Item 5. Specify the assay method used [244].

Standard plasma glucose analysis will be done, including fasting glucose and HbA1c (every 3 months) following the local Standard Operating Procedures (SOPs).

Item 6. State the method of case selection, including whether prospective or retrospective and whether stratification or matching was used [244].

Patients will be prospectively recruited to the study and will be stratified based on previous diagnosis of diabetes (type 1 excluded), to ensure comparable numbers of patients with or without diabetes on the study. No stratification will be done based on plasma glucose levels to include a various range.

Study design: patients would be prospectively consented and asked to have additional bloods taken for fasted glucose (every clinic visit), albumin (every clinic visit), CA19-9 (once a month) and HbA1c (once every 3 months) during their normal clinic visits. They will also be asked to wear the continuous glucose monitor during their whole treatment period. Patients would also need to fill in a short quality of life and chemotherapy side-effects questionnaires, to assess treatment toxicities and QoL. All patients would have access to standard of care diabetes services.

Patients will be on the study until they continue SOC treatment, including further lines of chemotherapy (if given), and will be asked to return the continuous monitor, if no additional treatment is planned. Follow-up survival data will be gathered from electronic patient records.

Item 7. Precisely define all clinical endpoints examined [244].

Overall survival will be the primary endpoint, and this will be defined as the period of time from cycle 1 day 1 of chemotherapy to the date of death.

<u>Item 8.</u> List all candidate variables initially examined or considered for inclusion in models [244].

Standard prognostic variables will be collected for each patient, including but not limited to stage, CA19-9, Albumin, ECOG PS, type of first line treatment (as found in this study). Additionally, information about diabetes-related variables will be collected from all patients at baseline and regularly during treatment; this would include any antidiabetic treatment and diabetes-related investigations they have had.

<u>Item 9.</u> Give rationale for sample size; if the study was designed to detect a specified effect size, give the target power and effect size [244].

Whilst GlucMin was the highly significant in the current study, it would not be a good biomarker for a prospective study, and HbA1c could be used as a surrogate. Thus, for the sample size calculation, it is assumed that HbA1c will result in a similar overall HR as was found for GlucMin in the current study.

I intended to detect this hazard ratio (for death) using the "Time to event data with Cox-regression (2-sided)" sample size calculator.

The inputted variables for this calculation were:

- HR of 1.7, based on dichotomised GlucMin (</>median, repeated MV analysis)
- Overall probability of event 0.8 (535/640=0.84 had died at the time of analysis)
- Proportion of sample in groups 0.5 (dichotomised data)
- Power 80%
- Type I error rate α 5%.

Based on these variables, the sample size for this study would need to be 140 patients.

We also would include a contingency of 10% (14 patients) to account for possible drop-out rate, and therefore the overall required number for this prospective validation study would be 154 patients.

2.5.6 Future steps and questions

Based on the CRUK roadmap, this first phase proposed validation study will answer the Biomarker qualification stage 1 question [278] about correlation between hyperglycaemia and outcomes of these patients. According to the roadmap, the optional

stage 2 after this step would be a prospective study where the biomarker defines the randomisation to understand if the clinical outcome is improved by the prospective use of the biomarker [278]. In the case of hyperglycaemia, this would probably not be a good randomisation variable, as the aim would be to see how the glucose levels change throughout the treatment, and for this reason the optional stage 2 might not be needed.

However, as highlighted previously, a separate question remains about tightly controlling glucose and if that would lead to better OS. This question could be answered in the second phase either in a separate study or as an additional part to the described validation study after the results of the initial validation study are available. However, as that study would need to also assess treatment related toxicities (as potentially a secondary endpoint), it will probably need to be separate from the first validation study. For this second phase study patients would need to be randomised between standard of care glucose management and more tight glucose control potentially with more proactive diabetes team input. This could then answer the question if this is a modifiable biomarker.

After the first phase validation study, if the correlation between hyperglycaemia either at baseline or longitudinal poor glucose control and patient outcomes has been shown, only then the final step of transferring the biomarker to routine clinical practice can be done based on the CRUK roadmap [278].

Table 2.13. Reporting recommendations for tumour marker prognostic studies (REMARK) [244] checklist with the page numbers of where these steps are presented in my study (chapter 2).

	Item to be reported	Page no.
INTRODUCTION		
1	State the marker examined, the study objectives, and any pre-specified hypotheses.	**46**
MATERIALS AND METHODS		
Patients		
2	Describe the characteristics (e.g., disease stage or co-morbidities) of the study patients, including their source and inclusion and exclusion criteria.	**47**
3	Describe treatments received and how chosen (e.g., randomized or rule-based).	**47**
Specimen characteristics		
4	Describe type of biological material used (including control samples) and methods of preservation and storage.	**47-48**
Assay methods		
5	Specify the assay method used and provide (or reference) a detailed protocol, including specific reagents or kits used, quality control procedures, reproducibility assessments, quantitation methods, and scoring and reporting protocols. Specify whether and how assays were performed blinded to the study endpoint.	**48**
Study design		
6	State the method of case selection, including whether prospective or retrospective and whether stratification or matching (e.g., by stage of disease or age) was used. Specify the time period from which cases were taken, the end of the follow-up period, and the median follow-up time.	**48**
7	Precisely define all clinical endpoints examined.	**49**
8	List all candidate variables initially examined or considered for inclusion in models.	**49**
9	Give rationale for sample size; if the study was designed to detect a specified effect size, give the target power and effect size.	**49**
Statistical analysis methods		
10	Specify all statistical methods, including details of any variable selection procedures and other model-building issues, how model assumptions were verified, and how missing data were handled.	**49-51**
11	Clarify how marker values were handled in the analyses; if relevant, describe methods used for cutpoint determination.	**51**
RESULTS		
Data		
12	Describe the flow of patients through the study, including the number of patients included in each stage of the analysis (a diagram may be helpful) and reasons for dropout. Specifically, both overall and for each subgroup extensively examined report the numbers of patients and the number of events.	**52**
13	Report distributions of basic demographic characteristics (at least age and sex), standard (disease-specific) prognostic variables, and tumor marker, including numbers of missing values.	**53-55**
Analysis and presentation		
14	Show the relation of the marker to standard prognostic variables.	**58**
15	Present univariable analyses showing the relation between the marker and outcome, with the estimated effect (e.g., hazard ratio and survival probability). Preferably provide similar analyses for all other variables being analyzed. For the effect of a tumor marker on a time-to-event outcome, a Kaplan-Meier plot is recommended.	**59-67**
16	For key multivariable analyses, report estimated effects (e.g., hazard ratio) with confidence intervals for the marker and, at least for the final model, all other variables in the model.	**67-69**
17	Among reported results, provide estimated effects with confidence intervals from an analysis in which the marker and standard prognostic variables are included, regardless of their statistical significance.	**67-69**
18	If done, report results of further investigations, such as checking assumptions, sensitivity analyses, and internal validation.	**69-77**
DISCUSSION		
19	Interpret the results in the context of the pre-specified hypotheses and other relevant studies; include a discussion of limitations of the study.	**77-85**
20	Discuss implications for future research and clinical value.	**85-95**

2.6 Chapter Summary

In this chapter, I have reported on the impact of random plasma glucose levels on outcomes of patients with PDAC. The data in this study reveal that patients with high GlucMin have worse OS, antidiabetic treatment use in patients with high baseline glucose could lead to better outcomes and thus, gives the first signal that better antidiabetic control in patients with PDAC could lead to longer OS.

Whilst confirmation and validation of these results are needed from prospective studies, I also showed that hyperglycaemia is indeed a widespread issue in patients with PDAC, with almost 2/3 of patients having abnormal glucose levels, either at baseline or during treatment, but only 29% were known to be diabetic. This further highlights the importance of regular glucose monitoring in patients with PDAC.

The rationales as to why controlling hyperglycaemia might improve patient outcomes are two fold: patients might get improvements in hyperglycaemia-related symptoms that might in turn improve quality of life in patients who already have high disease-related symptomatic burden [159]. Secondly, if the hypothesis that hyperglycaemia is a paraneoplastic phenomenon caused by PDAC [88] is true, then controlling glucose might also help to control the cancer.

Additionally, I have proposed a prospective clinical study concept that could confirm and validate the results from this data, and hopefully give some clarity about how to best help patients who are in desperate need for some improvements in outcomes. Antidiabetic medications are relatively cheap and accessible compared to anticancer drugs. If controlling blood glucose levels could improve patient survival, this would be a relatively inexpensive and effective way to achieve this.

Chapter 3: RELEVANT study development, process, and methods

RELEVANT study: Patient and physician perspectives on clinically-meaningful outcomes in advanced pancreatic cancer.

3.1 Survey design theory

According to Groves *et al* [281] there are two main perspectives to a survey study, the design and the process, and these incorporate various elements involved in designing and running a survey. The two main components to both of these perspectives are measurement and representation, where measurement covers "how" and "what" you want to measure (questions and the mode) and representation deals with the "who" - target population and sampling.

Design perspective

As shown in figure 3.1 [281], the four steps of measurement consist of construct, measurement, response, and edited response. The *construct* consists of the elements of information that researchers are interested in measuring. The *measurement* is the more concrete and usually the actual question being asked from the respondents, with the aim of gathering information about the constructs. Thus, the aim of "measurement" is to design a question that perfectly reflects the construct that researchers are trying to measure. The *response* recorded from the respondents is then provided through the survey measurements, usually by respondents answering verbally or marking on paper/electronic questionnaires. After the initial response has been provided, this is then reviewed prior to moving on to the next step. This is to check for errors both at the individual respondent level and in the full data set. The *edited*

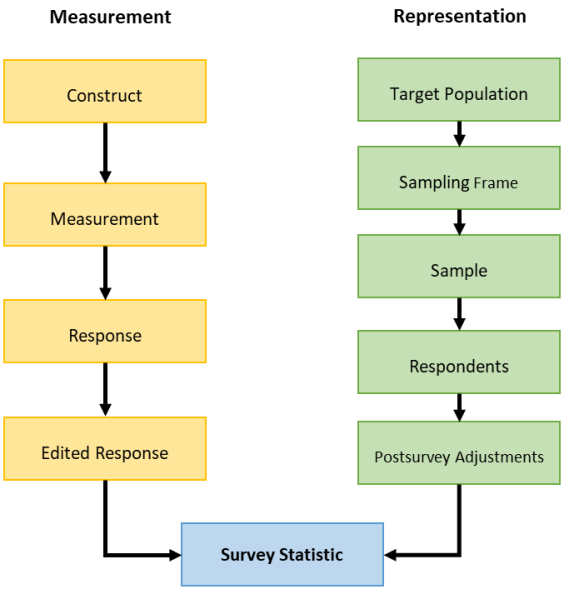


Figure 3.1. Survey lifecycle from a design perspective according to Groves *et al* [281].

responses will then allow inference regarding the values of the construct for each of the individual respondents [281, 282].

"Representation" has five steps moving from the abstract to the concrete: target population, sampling frame, sample, respondents and postsurvey adjustments. The *target population* is the set of units that you wish to study in the most abstract sense. The *sampling frame* then includes the members of the target population that have a chance to be selected for inclusion in the survey sample, listing all units in the target population. The *sample* is then selected from the sampling frame, usually only consisting of a very small fraction of the sampling frame (e.g. 1: 5000 for population studies). The *respondents* are then those from the sample who were successfully measured, as measuring the selected sample does not always achieve full success. Similarly, to "measurement", *postsurvey adjustments* are done after all data is collected, to improve the quality of the estimates [281, 282].

Process perspective

The process perspective (figure 3.2 according to Groves *et al* [281]) of a survey helps to understand the steps needed prior to recruitment and measurement. Based on the research objectives, decisions are again made about the sample and measurement process.

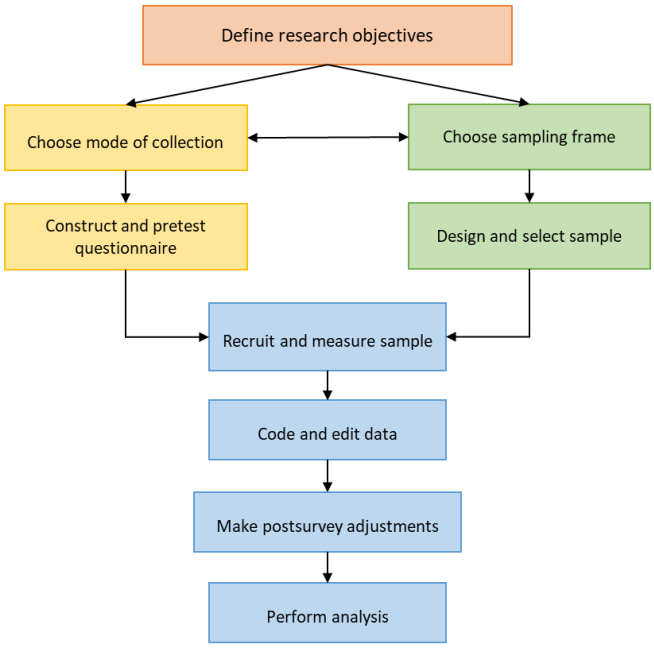


Figure 3.2. Survey lifecycle from a process perspective, according to Groves *et al* [281]

<u>Mode</u>

For "measurement", the mode of data collection is a particularly important step to determine how the instrument is shaped. The survey mode refers to the medium and agent used for survey data collection [281, 282]. The medium could be a voice, text on screen, text on paper or video. The agent can be an interviewer or respondent (self-administration). The traditional modes of data collection are face-to-face interviewing, telephone interviewing and mail interviewing.

Table 3.1 illustrates examples of modes of data collection, dependent on the medium and agent used.

Table 3.1. Examples of modes of data collection according to various authors [281-284].

		Medium	
		Paper	**Computer**
Agent	**Self**	Mail-out questionnaire, Self-Administered Questionnaire (SAQ)	Web-surveys, Touchtone Data Entry (TDE) Interactive Voice Response (IVR) Computer Assisted Self Interviewing (CASI) Audio Computer-Assisted Self Interviewing (ACASI)
	Interviewer	Telephone, Face to face/Personal visit	Computer-Assisted Telephone Interviewing (CATI), Computer-Assisted Personal Interviewing (CAPI)

There are important dimensions of data collection methods to consider when choosing a mode: degree of interviewer involvement (interviewer vs self-administered); degree of contact with respondent (direct vs indirect); channels of communication (audio vs visual); degree of privacy (low vs high privacy needed) [281, 282, 284, 285]. Thus, the choice of a mode for a study depends on various factors, in addition to constraints, such as costs, time and mix of personnel involved [282].

The next step after choosing the mode, is the construction and pretesting of the questionnaire. This will again depend on the objectives and mode decision and will, in the end, produce a final survey instrument for use in the study. Some general rules for designing and pretesting questionnaires are further explained later (see *Constructing the questionnaire and pretesting* on page 106).

Sample

In “representation”, the sampling frame is based on the research objectives and leads into designing and selecting a sample based on the objectives [281].

It is not possible to measure all units/people in a target population. Sampling is done to identify a representative sample to measure and to permit inference. The aim of sampling is to identify sample units that represent a microcosm of the target population. Sampling usually refers to samples that have some kind of probability mechanism of

being selected for inclusion. There are various ways of sampling to make sure that each element of the sample has the same probability of being selected, so that the results can be generalisable to the population from which they were chosen [281, 282].

Various probability and nonprobability sampling methods can be used depending on the study population, mode and restrictions like time, resources and people involved (Table 3.2). Probability sampling is any method that uses any form of random selection whilst nonprobability sampling does not. In large population studies, randomisation is used to make sure different units of population would have equal probabilities of being chosen [281, 282, 286].

Table 3.2. Examples of probability and non-probability sampling methods [287].

Probability sampling methods	Non-probability sampling methods
Simple random sampling	Convenience sampling
Cluster sampling	Judgemental or purposive sampling
Systematic sampling	Snowball sampling
Stratified random sampling	Quota sampling

For example, in country census surveys, a sampling frame could be the list of citizens of that country with contact information (how to contact them), and then random sampling is used to draw a representative sample from that list. Nonprobability sampling is about accidentally or purposively choosing the sample from the people who are available to sample or by simply recruiting volunteers. An example of non-probability sampling would be recruiting volunteers from one university, patients seen in clinic or researcher choosing the participants based on prior knowledge about them [287]. Probability sampling is usually used for large surveys to ensure inference from the respondent answer level to the target population follows clear randomisation rules, and thus would be more likely to represent the true population [282, 288]. However, that does not necessarily mean that the nonprobability samples are not representative of the population, as that depends on the population under study. There are various advantages and disadvantages to both [288] (Table 3.3). Probability samples are a significant challenge to execute with large sample size, cost, time, and effort associated, but results are more likely to be unbiased and generalisable. Nonprobability samples on

the other hand are easier to execute, cheap and efficient, with the key disadvantage being the unknown generalisability of the results to the whole population. The most common nonprobability sampling is convenience sampling, where the sample is selected based on accessibility to the research or researchers [286].

Table 3.3. Strengths and weaknesses of probability and non-probability sampling depending on the purpose of the study [287].

	Non-probability Sampling	**Probability Sampling**
Research has an exploratory purpose	Strength	Weakness
Need for quick result/decision	Strength	Weakness
Need to target specific elements of the population	Strength	Weakness
Need for a representative sample	Weakness	Strength
Need to make statistical inferences from the sample	Weakness	Strength
Need to minimise selection bias	Weakness	Strength

Data collection and adjustments

In the recruitment and measuring of the sample step, the measurement and representation aspects are included with the final survey instrument being used in the survey sample. Data collection procedures depend on the mode and the survey instrument being used and usually follow rules based on those [285]. This is the field work part of the study where the data collection is formed based on the pre-planned study design [281, 282].

After all the data has been collected for all units in the sample, the data is then coded and edited and goes though postsurvey adjustments to remove errors prior to performing the survey analysis [281]. As the survey is a fallible instrument, the aim of the adjustments is to improve the quality of the estimates made from the study [282]. This part will assess nonresponse in the unit (responder) and item (question) level and can improve estimates by replacing the missing data by weighing or imputation, if needed. Microediting is data editing at the level of the individual, while macroediting

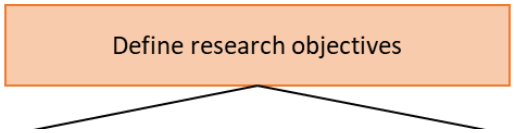
takes place at the level of all available data [282]. During the data collection process, the interchange between respondents and SAQ forms are a source of errors that could be controlled or reduced during the data editing process [281, 282].

After adjustments, the clean data is then analysed and assessed for quality.

3.2 RELEVANT survey process

For the RELEVANT study, the general survey study process by Groves *et al* [281] was followed as shown in Figure 3.2. The measurement and development process consisted of defining the research objective, choosing the mode, constructing the questionnaire and pretesting [281, 282]. The sample decision process consisted of choosing the sampling frame and then designing and selecting the sample [281, 282]. Each individual component will now be described separately.

Defining the research objective



The purpose of the study was to explore and describe a specific population of patients with advanced pancreatic cancer. The research objective was then defined as understanding these patients' views on their treatment outcomes, seeing how these changed over time during treatment, and how these compared to the physicians' views about those same patients. As discussed in the introduction section of the thesis, most of the previous literature consisted of single time-point surveys of different patients with advanced cancer [189, 194, 195, 231, 233] and did not take into account the poor prognosis of PDAC, nor how the patients' views changed over time. There has been previous research conducted comparing patient and physicians' views about treatment choices [190, 231]. However, this again was mainly conducted at one timepoint, asked one focused question and did not include other views about treatment effect or side-effects. The most influential studies informing the development of this survey, in terms of topics we wanted to cover, were: Weeks *et al* [194]; publication about patients views on the likelihood of cure while having advanced cancer; Slevin *et al* [231] study; which explored the difference between patient and physicians views about chemotherapy; Silvestri *et al* [189]; which assessed

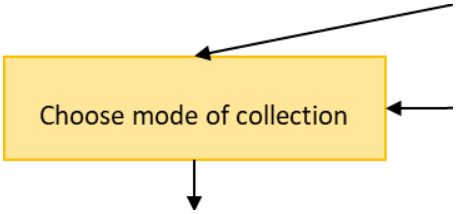
patients willingness to accept a trade-off between treatment toxicities and survival benefit; and Loh *et al* [233]; which looked at beliefs about curability in patients with advanced cancer, and how that impacted their decision making.

Based on the aims of this thesis and the previous literature, the study objectives shown in Table 3.4 were defined.

Table 3.4. RELEVANT study objectives.

Study Objectives
• Primary objective: To evaluate patients' and physicians' views on pancreatic cancer diagnosis, treatments given, patient's goals and meaningful outcomes.
• Secondary objective: To provide a descriptive analysis of the change in these views in relation to treatment response, side effects and changes over time.

Choosing the mode of data collection



As explained earlier (see page 99), there are various parts to consider when choosing the mode of data collection, and this also depends on constraints like funding, time and mix of personnel involved [281, 282, 285].

I chose the self-administered questionnaire (SAQ) as a mode for this study based on a number of reasons. Firstly, as the aim of this study was to compare the differences between patients' and physicians' views and changes over time, I had to choose a mode that was easy to use for all participants (both patients and physicians) and that could be re-administered consistently at multiple time-points. Secondly, the study was intended to include sensitive questions about prognosis and patients' views about treatment effect, thus, it was important to ensure that the mode would help capture this. Interviewer presence can be considered threatening to some respondents and thus, their absence is known to increase the respondent's likelihood of answering sensitive questions [281, 282, 284]. Thirdly, the ease of use for the respondents was also important, as some of these patients are known to have significant symptomatology and

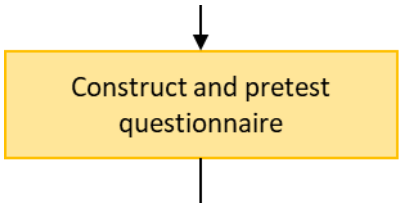
this is known to influence respondent's likelihood of answering [282]. Thus, a time was chosen where patients would be attending routine clinics and, so they could complete the questionnaire during this time. Previous questionnaire studies have shown that this approach of answering surveys at the time of outpatient clinics has been acceptable to patients with cancer and resulted in high response rates [289, 290]. It also allowed patients to ask their physicians questions if they felt confused or upset after completing the questionnaire. The distress policy was developed so that the participants would have a person to contact directly after completing the survey, in case they were upset by the sensitive questions. Previously, mail surveys have been associated with consent forms that were difficult to understand and high drop-out rates [282], and for this reason, all participants were consented in person, allowing them the time to ask direct questions, if required.

Face to face interviews were not chosen due to the need for professional interviewers with experience of asking sensitive questions, the decreased likelihood of respondents answering sensitive questions in the presence of an interviewer, the increased time needed for each survey administration, and the high costs of this mode [282, 284].

There are also some potential drawbacks to SAQs that were considered. Firstly, SAQs are often sent to respondents by post and thus, response rates to mail surveys have been found to be low, especially if they include sensitive questions that respondents do not want to answer [281, 282, 284, 285]. In this current study, the questionnaires were given to the patient in clinic personally or by another health care professional (who was not a physician participant). Secondly, paper SAQ put high demands on the design of the paper questionnaire [282, 291] (e.g. format, clarity, position and order of questions) and this issue was highlighted in the pretesting phase of the study (described in the next section) to make sure it was easily understandable to all participants. Thirdly, the absence of an interviewer can be disadvantageous, as additional explanation is not possible if the respondents get confused [282]. This aspect was also highlighted in the pretesting stage where the questionnaire was reviewed by patient representatives to ensure that the questions were understandable to all.

Constructing the questionnaire and pretesting

Constructing the questionnaire



Based on the research objectives, exploration of patient views on various aspects were identified as necessary. These included: background information about cancer, patient understanding of aims of treatment, disease and treatment impact on patient life, patients' personal goals, their views on treatment outcomes, their quality of life. Additionally, the aim was that the topics included in the physicians' survey would be comparable to the patient survey. Based on the literature, the tools and questions used in previous studies and the outlined topics of interest, the first survey questions were developed.

Most questions were aimed to be nonfactual, addressing subjective attitudes and opinions of the responder, where there is no true value. There were some factual questions included to allow an understanding of the patients' background understanding about their cancer and chemotherapy. These were not checked or compared to the true value.

General question text guidelines highlighted by Bethlehem [282] were followed: using familiar wording, avoiding ambiguous questions, avoiding long question texts, avoiding recall questions as much as possible, avoiding leading questions, avoiding asking things respondents don't know, avoiding sensitive questions as much as possible, avoiding double-barrelled questions, avoiding negative questions, and avoiding hypothetical questions as much as possible [282]. One of the aims of this study was to include sensitive and hypothetical questions, thus, guidance from previous studies [282, 284, 292] that is explained next, was followed in order to make these easier for respondents to answer.

One way of increasing the likelihood of response to sensitive questions is to include the question in a series of less sensitive questions [282, 292]. Another way is to ask the respondent select a range of values instead of writing an exact value [282]. These principles were followed in this questionnaire in relation to sensitive questions, where ranges were given for time (prognosis) questions, and Likert scales for likelihood of treatment benefit questions, which were included at the end of the questionnaire.

Hypothetical questions can be difficult to answer [281, 282], and little is known about how patients decide on an answer and thus it is not clear if these questions really measure what you want them to measure [282]. However, hypothetical questions are still used to get more insight into attitudes and opinions about certain issues.

Open questions were avoided due to the known issues with those – for example, respondents might overlook a certain answer, answers might be very vague and unclear, and problems with processing and analysis of the answers to open questions can lead to errors [281, 282].

There were 2 simple routing questions included where responders were asked to answer "yes/no" to the first question and if "yes" was answered, they would then need to answer the subsequent sub-question. The routing was done as a simple sub-question format, so responders who answered "no" could just continue with the next question, hopefully not causing any routing errors.

The question order is also an important part when developing the survey [281, 282]. Ideally, the early questions in a survey should be easy and pleasant to answer and encourage respondents to continue the survey. Difficult and sensitive questions should be asked at the end of the questionnaire. If responders stop answering the questions then, most other questions will already have been answered [281, 282, 292]. This rule was followed in my survey, with easier background and impact questions posed at the beginning, and more sensitive questions at the end.

I also collaborated with the Christie Patient Centred Research team in the development phase of the questionnaire, and they assisted in building more structure to the different parts of the survey, emphasising the order of the questions and the natural flow.

Survey questions format

The questions in the survey were in a variety of formats (see the full survey in Appendix 4): multiple-choice questions with one expected answer; yes/no questions; ranking questions (asked to rank in order of importance/acceptability); Likert scale questions based on likelihood, with 5 response options (not at all, slightly, moderately, very,

completely likely); time questions with 5 response options (1-2 months, 3-6 months, 6 months- 1 year, 1-5 years, more than 5 years).

EORTC QLQ-C30 and PAN26

The previously established QLQ-C30 [293, 294] and its supplementary pancreatic cancer module PAN26 [150, 294] were used in this study to assess patient's health related quality of life and symptomatic burden, to determine how these could impact their responses to the study survey developed.

As discussed in the introduction chapter, the QLQ-C30 and its supplementary modules were established by the EORTC [294] to measure the health-related quality of life of patients with cancer and to have a unified way of comparing this within international clinical trials. The core questionnaire was first released in 1993 and has gone through 3 major versions, 3.0 being the latest version, which was used in this study.

The QLQ-C30 and PAN26 are both composed of multi-item scales and single-item measures. The QLQ-C30 consists of 5 functional scales, 3 symptom scales, 1 global health status/QoL scale and 6 single symptom items. The PAN26 questionnaire consists of 2 functional scales, 6 symptom scales and 10 single symptom items (see table 3.5). In both questionnaires, the scale/item score ranges from 0 to 100, where higher scores represent high levels of functioning for functional scales and higher levels of symptomatology for symptom scales and items. Thus, the results of the functional scales and symptom scales are reversed.

Table 3.5. EORTC QLQ-C30 and PAN26 scales [294].

QLQ-C30		PAN26	
QL	Global health status/QL scale	**Functional scales**	
		HC	Satisfaction with health care
Functional Scales		SX	Sexuality
PF	physical functioning scale,		
RF	role functioning scale,	**Symptom scales**	
EF	emotional functioning scale	PP	Pancreatic pain
CF	cognitive functioning scale	BL	Bloating
SF	social functioning scale	DI	Digestive symptoms
		TL	Taste
Symptom scales/items		IN	Indigestion
FA	fatigue	FL	Flatulence
NV	nausea and vomiting	WE	Weight loss

PA	pain	WL	Weakness arms and legs
DY	dyspnoea	DM	Dry mouth
SL	insomnia	HE	Hepatic symptoms
AP	appetite loss	AB	Altered bowel habit
CO	constipation	BI	Body image
DI	diarrhoea	SE	Troubled with side-effects
FI	financial difficulties	FH	Future Worries
		FP	Planning of activities

Permission to use these questionnaires for my study was requested from the EORTC on 16/03/2018 and granted on 27/03/2018. The analysis of the questionnaires was based on the EORTC scoring and reference manuals [294, 295].

Pretesting

Pretesting is used in questionnaire design before data can be collected in order to remove essential errors [281, 282]. Two main errors that could be corrected with pretesting are problems with validity and measurement error. Validity is about seeing if the question measures what the researcher wants to measure; does the question mean the same to all respondents (explained in detail later in *Validity and Reliability of the questionnaire* section) [282, 296, 297]. A measurement error happens when the respondents do not understand the question or do not want to give the answer.

Simple errors in questionnaires may also cause some questions to be incorrectly skipped or answered and most importantly lead to errors in answers [282].

Thus the reason to pretest a questionnaire is to identify and reduce various sources of error: specification error (decomposition), operationalisation error (questions not measuring construct, variability across respondents/interviews/times), measurement error (question characteristics leading to response error, respondent processing issues leading to response error, instrument features leading to response error) [281, 282, 285]. There are various tools for pretesting, such as expert reviews, focus groups, cognitive interviews, statistical models, and field testing [281, 282]. Pretesting is qualitative in nature and rather than providing quantifiable results, it guides on changes in wording or layout of the questionnaire [281].

My survey was pretested by multiple expert reviews, field testing and ethics committee review. The expert reviews were from multiple angles; survey methodology expert, subject matter experts and funding body representatives with a special interest in the subject (Pancreatic Cancer UK). The field test was run among patient representatives. Patients from clinics were not used as part of the pretesting, due to the lack of ethical committee approval for this and the sensitive nature of the surveys, thus, patient representatives were included instead.

Expert reviews

Survey methodology expert review was by Prof Janelle Yorke (Christie Patient Centred Research Group lead). As mentioned in the previous section, more structure was built into the questionnaire in collaboration with Prof Yorke. In the pretesting part, the whole questionnaire was reviewed, and some changes were added about the wording and order of answer options to questions. One question was added about the patient's involvement in decision making, to determine if this may be influencing their views about treatment as proposed by previous research studies in other cancers [196, 216].

Subject matter expert review was performed by Medical Oncology consultants. Pretesting was performed by three experts and the main feedback was in relation to the need for wording changes to make questions more easily understandable to patients. There was also a recommendation to add the section titles to ease the flow of the questionnaire. Some wording change recommendations were added to the physicians' questionnaire. As financial toxicity has been previously shown to impact patients decision making in various advanced cancers [298-300], one question was added about the financial implications of the treatment as a potential issue that could influence patient answers and was of interest to track throughout the patient journey. Based on this, question 12 (see patient survey in appendix) was added to the patient questionnaire.

The funding body representative with a special interest in the subject, the Pancreatic Cancer UK (PCUK) charity, which provided funding for the PhD programme applicant salary (no funding specifically for this study) also pretested the questionnaire. Their main aim in pretesting was to review this from a "layman" perspective to ensure that it was understandable. Additionally, PCUK was conducting their own patient survey about

the diagnosis pathway experience of patients with pancreas cancer, and this allowed them to evaluate if there were any areas of overlap between both questionnaires. Based on this pretesting, minor wording changes were implemented, and some extra information was added to the patient information sheet (PIS).

Field test

As previously mentioned, field testing was done by patient representatives from the PCUK charity, due to the lack of ethical approval to pretest this on patients in clinic. For the field test, the study PIS, Informed Consent Form (ICF) and patient survey were sent to patient representatives and reviewed by two of them. The representatives were not from Manchester and face to face meeting was therefore not possible. They were sent the study documents by email and were asked to comment directly on those documents. The main comments were about wording and personal struggles with some of the issues raised in the survey. This enabled improvements to the wording and also highlighted which of the questions were more sensitive and could upset patients. The comments from these patients were quite substantial, but mainly emphasised the struggles patients face when going through their cancer journey and in coming to terms with their diagnosis. The feedback also highlighted the importance of doing this research, as the patients mentioned that they would very much like to know the results of this study and that it could be helpful for both patients and physicians.

After this final field test, the survey documents were finalised and submitted to the North West Greater Manchester East Research Ethics Committee (REC; reference 18/NW/0293).

Research Ethics Committee review

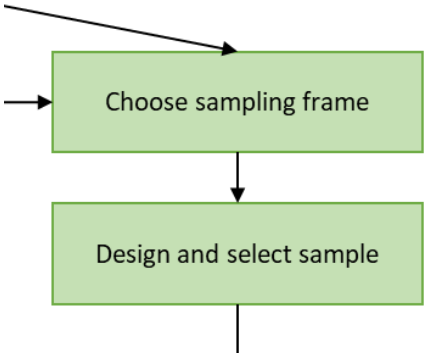
Although not a clear part of pretesting, the REC also reviewed all the study documents and resulting queries were addressed in a face to face meeting. During the meeting, the steps of the study and the questionnaires were reviewed, and some potential wording changes were highlighted in the patient and physician PIS. These were more about clarifications of which of the physicians will be asked to fill in the physician's questionnaire and to highlight the support services available if the patient gets upset as a consequence of this study. After the feedback was received, some wording changes

were made to the PIS, ICF and the surveys. These were mainly about clarifications; no major content changes were required.

Final survey instrument

Based on the pretesting results, firm items were identified for the final survey instrument. No questions were deemed "not useful" for the instrument and two extra questions of interest were added by the content experts about patient's involvement in decision making and financial implications of treatment. Multiple wording changes were instituted based on feedback from pretesting, to ensure that it was understandable to all. The final questionnaire was re-reviewed by the REC (which includes lay people). The final survey instrument consisted of 27 questions and 56 quality of life items (QLQ-C30 and PAN26) for patients and 14 questions for physicians.

Representation and sampling



The target population for this study was newly diagnosed patients with advanced pancreatic cancer due to start first line chemotherapy treatment in the UK. Detailed inclusion and exclusion criteria are described later in the methods section of the study. Due to the restrictions of funding and lack of expertise in the random sampling theory [282, 301], it was decided to choose nonprobability sampling and convenience sampling as the sampling method. Another type of nonprobability sampling technique is total population sampling [302], where the entire population with a particular set of characteristics can be examined. However, in this study, that would require the need to include all patients with advanced pancreatic cancer in the UK. Therefore, due to the lack of access to these patients, and the resources needed for this much larger study [303], convenience sampling was chosen. Moreover, the assumption was made that the patients seen at The Christie NHS Foundation Trust during a one-year period, fulfilling the inclusion/exclusion criteria, would not differ in a significant way from patients treated in other centres. As all sequential eligible patients would be offered participation in the study during the one-year time frame, the otherwise random referral of patients would minimise the bias that can be otherwise seen in convenience sampling. As The

Christie NHS Foundation Trust is a tertiary referral centre, it was assumed that these patients would not significantly differ from the overall UK population. Thus, based on the convenience sampling method [301, 303], all consecutive patients who fulfilled the inclusion/exclusion criteria were asked to participate in the study and were recruited.

Therefore, a sample size was not set beforehand as the aim was not to assess survival, and convenience sampling was used to collect all patients during a specific timeframe [282, 303].

3.3 The study development timeline

The study was approved by the Health Research Authority (HRA) and Health and Care Research Wales (HCRW) on the 16/05/2018. The full study timeline can be seen on Figure 3.3.

Study documents developed:

- Protocol*
- Patient PIS*
- Patient ICF*
- Patient Survey*
- Physician PIS
- Physician ICF
- Physician Survey*
- GP Letter
- Distress Policy
- Schedule of Events
- Statement of activities
- Pan-Manchester R&D Notification Form (PANMAN)
- Insurance form
- EORTC application for QLQ-C30/PAN26 usage
- Capacity and capability

*- see full documents in Appendix 1-5

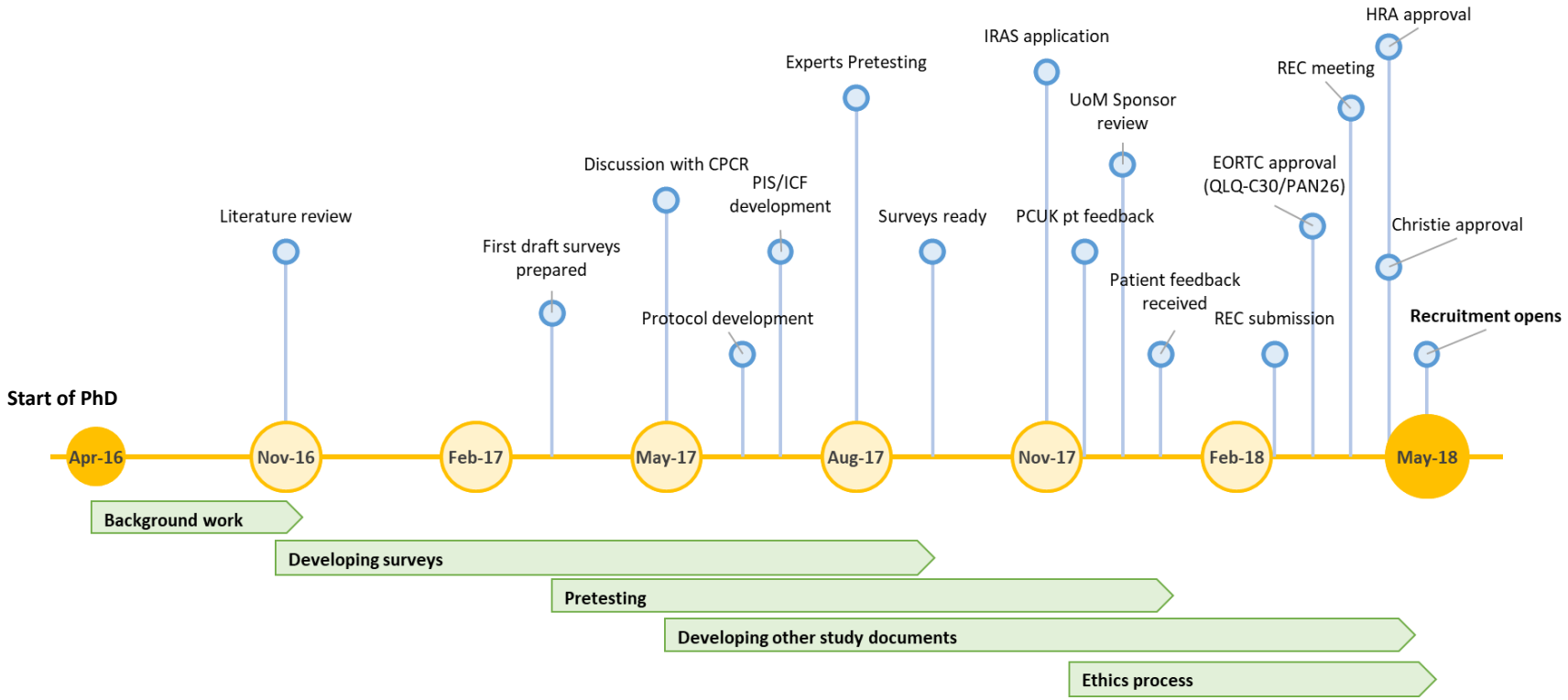
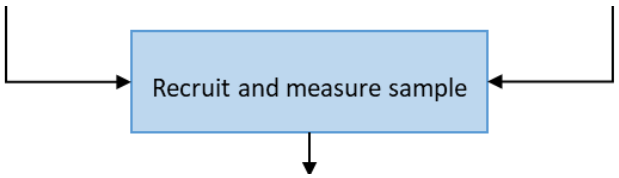


Figure 3.3. RELEVANT Study development timeline.

CPCR- The Christie Patient Centred Research Group, PIS- Patient Information Sheet, ICF- Informed Consent Form, IRAS- Integrated Research Application System, PCUK- Pancreatic Cancer UK charity, UoM- The University of Manchester, REC- Research Ethics Committee, HRA- The Health Research Authority

3.4 Study Design



This was a prospective investigator-designed longitudinal questionnaire study which aimed to evaluate patient and physician views on pancreatic cancer diagnosis, treatments received and patient goals, with the ultimate aim being to determine what aspects were considered meaningful to patients. The full study protocol, ICF, PIS and patient/physician surveys can be found in Appendices 1-5.

Patient participant inclusion criteria

Patients with newly-diagnosed advanced pancreatic cancers who were seen at The Christie NHS Foundation Trust in the HPB new patient clinic were eligible. Advanced pancreatic cancer in this setting signified all patients with unresectable pancreatic cancer, where the treatment aim was palliative. Satisfactory English language skills were required in order to fill in the study questionnaire by the participant themselves (translators were not used).

Physician inclusion criteria

Physicians or nurse clinicians who saw patients in the HPB clinic at The Christie NHS Foundation Trust during the study period were eligible.

Patient participant exclusion criteria

Patients who were not fit enough for anticancer treatment, or where surveillance was planned instead of anticancer treatment, were excluded.

Demographics and disease details

During informed consent, patients consented for clinical information to be retrieved from their electronic hospital records by the researchers (see full informed consent form in Appendix 4). The following clinical information was collected to understand the demographics of patients involved: date of birth, date of death (if died during the study period), age, gender, stage of disease, ECOG performance status at baseline, chemotherapy received (monotherapy/dual/triple), treatment received as part of clinical trial (yes/no), outcomes of the first treatment CT (progression, stable disease,

partial response), documented discussion about prognosis (yes/no, limited to the first month after initial visit).

3.5 Study process

Patients were given study information in the HPB new patient clinic and consented during the follow-up visit. After consent, patients were invited to complete the study survey and two quality of life questionnaires, EORTC QLQ-C30 and PAN26, at three time points (Figure 3.4):

- Time-point 1 (T1): Before starting palliative chemotherapy treatment
- Time-point 2 (T2): After starting, and before first on-treatment CT scan (at least one dose of chemotherapy, ideally after 2-3 months)
- Time-point 3 (T3): After the first CT scan (after the patient has received the results of the CT scan).

A paired survey was completed by their corresponding physician at each of these three time points.

If the patients had to stop treatment early (due to intolerance or progression or patient decision) and were not having a mid-treatment scan, they were also asked to complete these forms as time point 3.

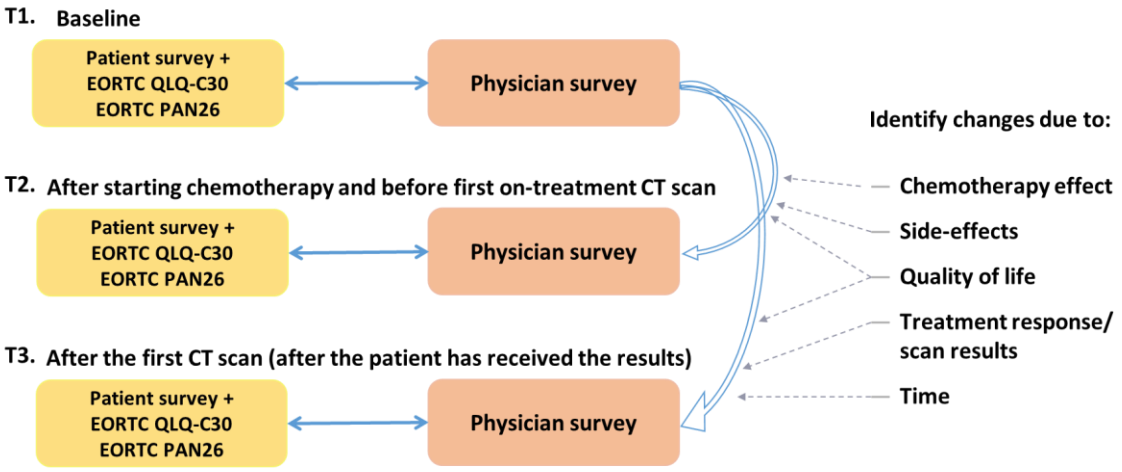


Figure 3.4. RELEVANT study outline

Study Amendments

During the study period, two non-substantial amendments were submitted to the HRA and subsequently approved. In November 2018, the first amendment was a change in the wording of the three time-points, as patients deteriorated on treatment and either did not have a new CT done, or had it done earlier than three months. Thus, the second time point was changed from needing at least 3 months of treatment to after starting chemotherapy, and before the first scan. An additional clause was added that if patients had to stop treatment early, and were not having a CT scan, they were to be asked to complete the last survey as time-point 3.

The second amendment in January 2019 was to alter the study closure date from the originally planned 28/02/2019 to 31/08/2019.

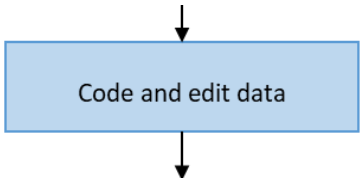
Recruitment

The study was opened in May 2018 and was closed to recruitment in May 2019 and follow up was completed in August 2019. During this one-year recruitment period, 106 patients were approached to take part in this study and 71 consented. All twelve physician participants who were eligible for inclusion were also approached and subsequently all consented.

Online survey

To validate the physicians' views and to test whether there was any institutional bias, I developed a separate online survey for distribution to physicians treating pancreas cancer in the UK. This survey consisted of the same questions that were used in the RELEVANT physician survey and asked Medical Oncologists to base their answers on a recent patient with metastatic pancreatic cancer that they had seen in their new patient clinic. To ensure data consistency, they were asked to assume patients had a good performance status (ECOG 0-1) and were due to start FOLFIRINOX chemotherapy [25]. The online survey was developed on the surveymonkey internet platform (www.surveymonkey.com) and was sent by email to 23 Medical Oncologists working in different Oncology centres in the UK who are known to regularly treat patients with pancreatic cancer.

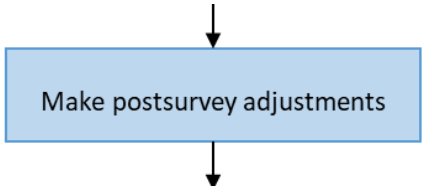
3.6 Data collection and analysis



Baseline demographic data from electronic patient records and the data from the surveys and quality of life questionnaires were entered into a purpose-built electronic database. All study documents were pseudoanonymised: personal data was recorded on the consent forms (name), together with a unique study ID. All other documents only used the unique ID.

All data from surveys and QLQ-C30/PAN26 questionnaires were coded and added to the electronic database. In order to limit any coding errors, this was done manually by me.

Postsurvey adjustments

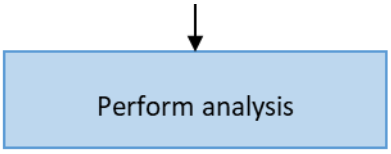


In order to clean the data for analysis, some minor postsurvey adjustments were instituted. In the patient survey ranking questions there were clear issues where patients did not fill these in correctly (often using the same number multiple times). It was decided in consultation with Prof Janelle Yorke, that if there was an understandable number present, even if it was not correctly ranked, it was still included in the analysis as it highlights the level of importance to the patient.

For the QLQ-C30/PAN26 questionnaires, the data was cleaned using procedures outlined in the EORTC analysis manual [294]. Based on this, if a scale uses multiple answers and at least half of those are filled in, the rest can be imputed to analyse the scale.

Further details of the postsurvey adjustments and the impact of these on the results of the study are described in Chapter 4 under the *Discussion and limitations of the developed study questionnaire* section on page 155.

3.7 Statistical Methods



The data were analysed from multiple different viewpoints: Patient survey responses at baseline; responses at time points 2 and 3 were compared to baseline; patient responses were compared to the physician responses; changes in quality of life questionnaires were compared between the time points. Summary statistics were provided for patient demographics.

Categorical variables were summarised by the number and percentage of patients in each category. Continuous variables were summarised by the statistical mean and standard deviation (for normally distributed data) or median and range (for non-normally distributed, skewed data). Changes in patient responses between time points were examined using paired statistical tests. Changes in categorical variables with a binary scale and unordered categories were examined using the Fishers paired exact test. This was preferred to the McNemar's test, due to the relatively small numbers of responses in some categories [304-306]. Changes in ordinal categorical variables and variables with a Likert scale were assessed using the Wilcoxon matched-pairs test to allow for the order of the category [304, 306]. The QLQ scores were more continuous in nature. Changes in these scores between time points were found to be approximately normally distributed, and thus analysed using the paired t-test [294]. A final set of analyses compared the responses of clinicians and patients at all three time points. The clinician responses were matched to individual patients, so the data was paired in nature, and the same statistical methods were used to those utilised to compare changes in patient responses between time points [306]. The results from the online survey were compared to the physicians results in this study using the Mann-Whitney U test as these data were not matched [306]. The internal reliability of the questionnaire was measured using the Cronbach's alpha test [307].

Statistically significant results were defined as having a p-value <0.05. The IBM SPSS Statistics software package (version 23) was used for data analysis.

The sample size of this study was not based on statistical power as it was not aimed at analysing survival differences. All sequential eligible patients were approached to avoid

bias. The planned number of subjects for inclusion was decided by the projected numbers of patients that would be seen in clinic over the specified time period; it as determined that this would address the heterogeneity (age, gender, performance status, disease stage, etc.) of “real-life” patients.

3.8 Validity and Reliability of the questionnaire

In addition to developing the questionnaire, it is also important to assess its quality before and after data collection. One way of doing this is to look at validity and reliability of the questionnaire [296]. There are various ways of analysing both (described below) and depending on the type of a questionnaire developed, different measures can be applied [281, 296].

Validity

Validity is the extent to which the question measures the underlying construct that the researcher wants to measure [281, 282]. Although, it is not always simple to assess question validity in practice due to needing extra time, resources and experts in the field to do this [282]. The first step is to ensure that the respondent and researcher interpret the question similarly. Previous research has shown that respondents can change the meaning of the question if they don’t understand it [282]. The second aspect is to check if questions allow sufficient variation in answer options. If not, the question is probably not very interesting for the research and some important details about the population might be missed [282].

In general, assessing validity can be divided into three parts: face validity, content validity and criterion validity [296]. Face validity refers to the appearance of the questionnaire and evaluates the readability, feasibility, layout/style and clarity of wording. Content validity is assessing whether the domain has been adequately covered and all questions are relevant to the domain. Criterion validity compares the new questionnaire to a previous gold standard or validated questionnaire (if these exist) and assesses its accuracy compared to the previous. Some questionnaires cannot be validated by such means because of the absence of an external criterion [296].

Reliability

Reliability or "response variance" refers to the reproducibility of the questionnaire and aims to demonstrate consistency [281, 296]. In general, there are three ways to assess the reliability of questionnaires and depending on the study, one or all of them could be used.

Firstly, test-retest reliability of the questionnaire is assessed by administering the questionnaire to the same person on two occasions. Importantly, this would need to measure concepts that are stable in time [296]. For this reason there are some possible disadvantage to this assessment: practice effect (respondents might remember what they answered last time and just copy that), too short interval (respondent answers from memory) and some traits may still change in time [296]. The scores between the two timepoints for the respondents are then compared and calculated using the Pearson correlation coefficient matrix and Cronbach's alpha [308, 309].

Secondly, one could examine interobserver reliability if the same subject is assessed by two interviewers using the same questionnaire. Obviously, this would only be needed when there are interviewers involved and interobserver reliability could be an issue [296].

Thirdly, one could examine the internal consistency of the questionnaire and the degree to which the subjects answer similar questions in a similar way [296]. This can be used in homogeneous questionnaires by the split-half method where even- and odd-numbered questions are separated and analysed to see if equivalent answers are seen in both halves. The split-half method cannot be used when questionnaires are heterogeneous as these will not give similar answers [296]. In those cases however, questions measuring the same concept could be analysed using Cronbach's Alpha to see if the respondents answer these in a similar way.

Following assessment of validity and reliability, questions can be removed, added or rewritten for future studies.

As some aspects of validity and reliability analysis are based on the responses gathered from the participants, these assessments for the RELEVANT study are further discussed in Chapter 4 (page 155).

Chapter 4: RELEVANT Study Results and Discussion

4.1 Study accrual

During the one-year study timeline, 106 patients were approached to take part in this study and given the PIS. Of those, 71 patients consented and 35 declined study entry or decided not to start chemotherapy, and thus did not fulfil the inclusion criteria. Full accrual and each patient's length on study are illustrated in Figure 4.1.

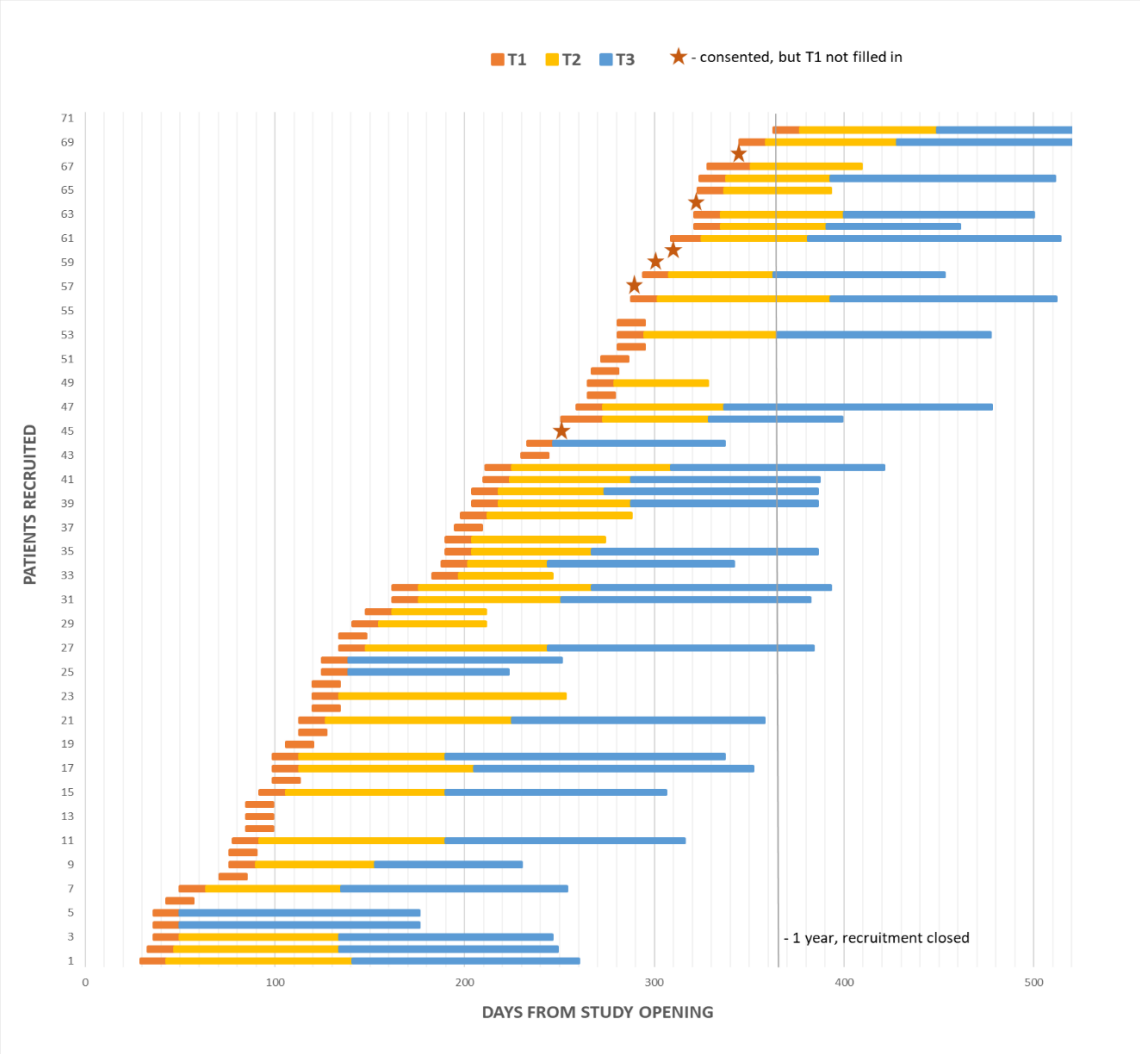


Figure 4.1. Study accrual over 1-year recruitment period, including patient length on study (T2 and T3 questionnaires were filled in at the end of the yellow and blue bars).

4.2 Study baseline characteristics

Survey compliance (Figure 4.2)

Time-point 1: Of the 71 consented patients, 65 filled in the T1 (baseline) survey, including the 2 validated questionnaires (EORTC QLQ-C30 and PAN26). Reasons for not filling in the time-point 1 questionnaire, after consent, were deterioration or death in 3 patients and 3 patients declined answering the survey after seeing the questions. All the 71 baseline physician surveys were filled in.

Time-point 2: Of the 65 patients who filled in T1, 39 (60%) filled in the T2 survey. Six patients missed T2 due to having a CT scan early because of acute hospital admission, suspicion of disease progression or as a clinical trial requirement. A study amendment was approved in November 2018 to enable patients to fill in T2 surveys after starting chemotherapy, and before the first scan. Prior to that amendment, they needed to have at least 3 months of chemotherapy first. Twenty patients deteriorated or died between T1 and T2 and did not fill in the survey beyond T1. The T2 physician survey was completed for 41 patients.

Time-point 3: Of the 39 patients who filled in T2 and the 6 patients who missed T2 for various reasons, 36 patients filled in the T3 survey. Nine patients deteriorated or died between T2 and T3 and did not complete the surveys. The T3 physician survey was returned for 38 patients.

The discrepancy between the number of T2 and T3 completed surveys for patients' and physicians' was due to some patients being too unwell to fill in their survey in clinic, whilst the physician survey was completed.

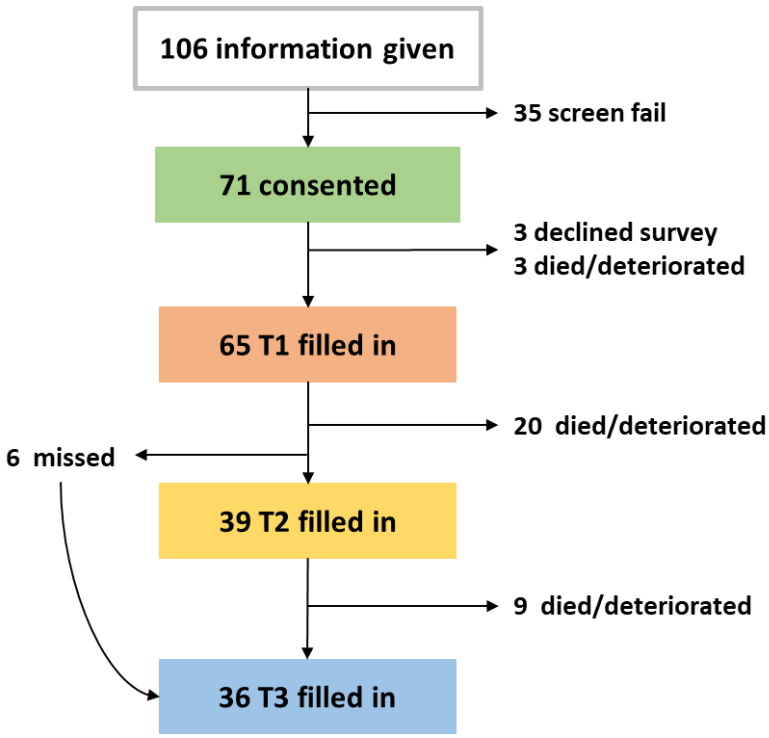


Figure 4.2. CONSORT diagram of patients included in the RELEVANT study.

Patient characteristics

At baseline, of the 71 patients who were consented, the median age was 65 years (range 43-83), 52% were male and 48% female. Ninety-three percent had stage III-IV disease, 7% had stage I-II unresectable disease, and all patients had treatment with palliative intent (inclusion criteria). Fifty-four patients (76%) had ECOG performance status 0-1, 24% were ECOG 2. All patients were planned to start chemotherapy, 23% started monotherapy, 38% started doublet chemotherapy and 32% started triple chemotherapy, 5 patients (7%) did not start treatment due to rapid deterioration. In the case of 15 patients (21%), treatment was given as part of a clinical trial. Around half (51%) of all consented patients had a prognosis discussion documented at their first visit, or during the first month of treatment.

Physician characteristics

Twelve clinicians were consented for the physicians' part of this study; all worked in the Medical Oncology HPB clinic at The Christie NHS Foundation Trust. Four were medical

oncology consultants, 6 junior doctors (fellows and specialist registrars), 1 nurse clinician and 1 GP with a special interest in HPB medical oncology.

Interval between time points

There was an average of 71 days (2.3 months) between T1 and T2, 112 days (3.7 months) between T1 and T3 and 40 days (1.3 months) between T2 and T3. To assess later described changes between T1 - T2 and T1 -T3, only the 39 patients who filled in both surveys for T2 and the 36 patients for T3 were included in the analysis.

4.3 Survey findings

4.3.1 Involvement in decision making

As illustrated in Figure 4.3, when asked about the extent to which patients wish to be involved in decisions regarding their treatment, 48% of patients answered at T1 that they preferred that they share responsibility with their doctor regarding decisions about which treatment was best for them. The second most chosen option (30%) was that patients preferred to make the final decision about their treatment after seriously considering their doctors opinion. There was no change in these top two choices over time: 54% and 17% at T2 and 53% and 33% at T3, respectively. Physicians were not asked this question in their survey.

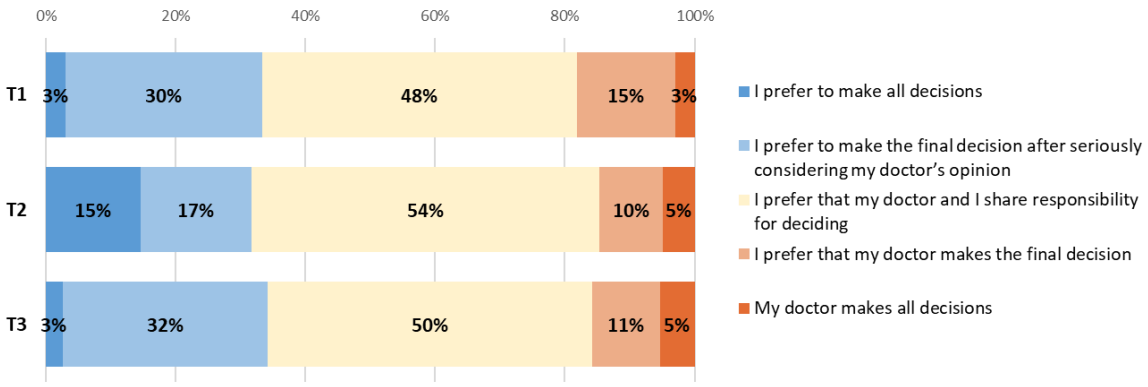


Figure 4.3. Changes in patient views about involvement in decision making between T1, T2 and T3.

4.3.2 Impact of treatment on patient's everyday lives

For 68% of patients it took up to 1 hour to come to The Christie for treatment (one way), for 26% it took 1-2 hours. The majority (79%) had to come 2-3 times a month and most (95%) drove themselves or had others drive them. Patients were asked how the treatment has affected them financially (Figure 4.4) and 29% of patients were a little or a lot out of pocket at T1, this increased to 41% at T2 (p=0.036) and 42% at T3 (p=0.034). Interestingly, the QLQ C30 question 28 also asks about treatment or physical condition causing financial difficulties and the results of these were 18 points (p)/100 at T1 and T2 and 16p/100 at T3 (lower scores better), which at T1/T2 was worse than the EORTC thresholds for clinical importance (17p) [310].

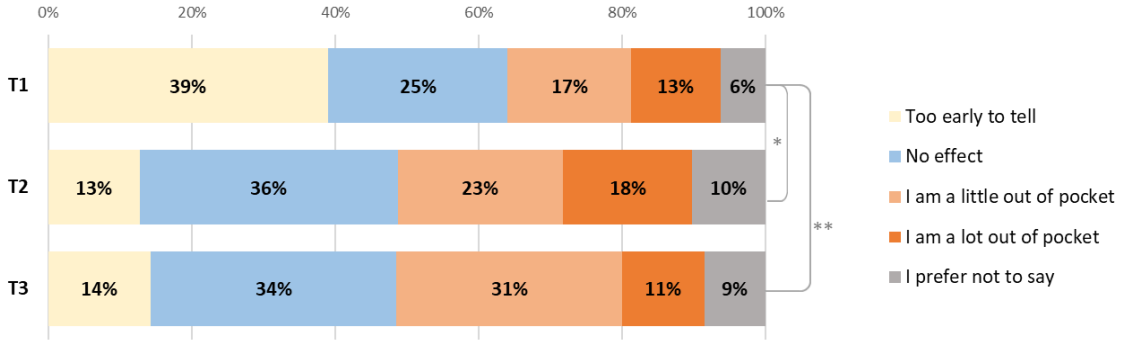


Figure 4.4. Changes in the financial impact of diagnosis or treatment on patients between T1, T2 (*p=0.036) and T3 (**p=0.034).

4.3.3 Aim of treatment

Of the 65 patients who filled in the T1 survey, 2 (3%) thought that the aim of their treatment was to cure the cancer, 13 (15%) thought that it was to shrink the cancer to make it surgically resectable (including 9 patients with metastatic and 4 with locally advanced PDAC) and 82% thought that it was to keep the cancer under control and manage symptoms or end-of-life treatment. Three patients (4%) answered that they did not know what the aim was or that they had not had a discussion about that (Figure 4.5).

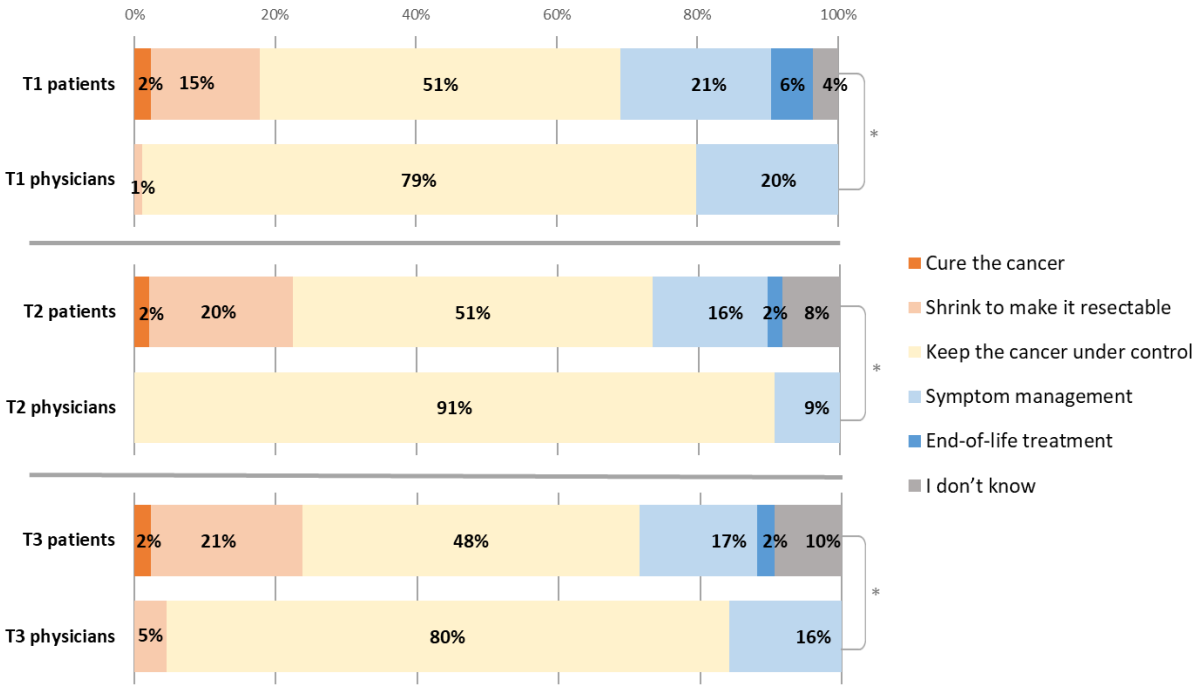


Figure 4.5. Changes in the patient and physician views about aims of treatment between T1, T2 and T3. * all p<0.001

Compared to physicians, there was a statistically significant difference (p<0.001) in this question, where 99% of physicians responded that the goal of treatment was to control the cancer and manage symptoms, and similarly more patients thought that the aim would be to shrink the cancer in order to make it surgically resectable (15% of patients compared to 1% of physicians, p<0.001).

There was no significant change between the timepoints in patients' or physicians' views.

4.3.4 Chemotherapy effect on wellbeing and symptoms

Patients were asked about how they expect the chemotherapy to affect their wellbeing and as illustrated in Figure 4.6, at baseline, 39% expected the treatment to improve their wellbeing (a lot or somewhat) and 25% expected it to worsen (a lot or somewhat). There was a change between the timepoints in the answers, that was mainly due to less patients answering "I don't know" over time.

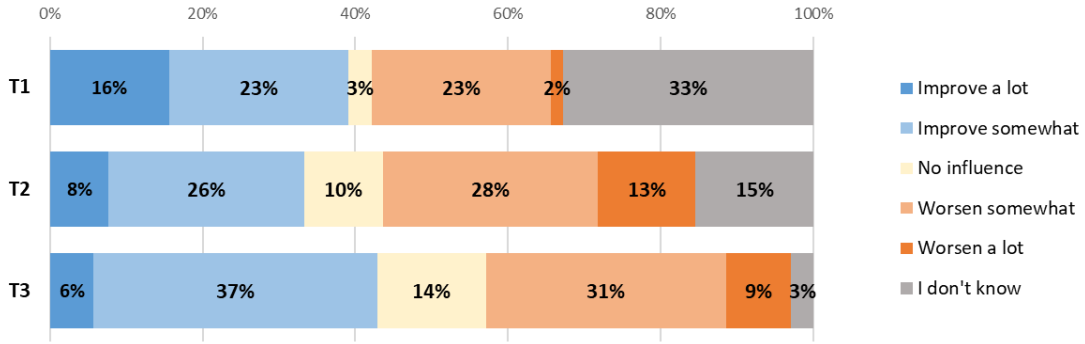


Figure 4.6. Changes in the patients' views about the impact of treatment on their wellbeing between T1, T2 and T3.

Patients were then asked about the percentage of patients they think will have serious (life-threatening or requiring hospitalisation) side effects with the same type of chemotherapy they are starting, and 32.3% expected it to be 6-10%, 21.5% expected 1-5%, 20% expected 11-20% and 18.5% expected >20%.

When asked about the likelihood of chemotherapy reducing their current cancer symptoms (Figure 4.7), 40% answered that this was very or completely likely, 35% thought it would be moderately likely and 26% thought that it would be slightly or not at all likely. There was no significant change between the timepoints in this question (p=0.95).

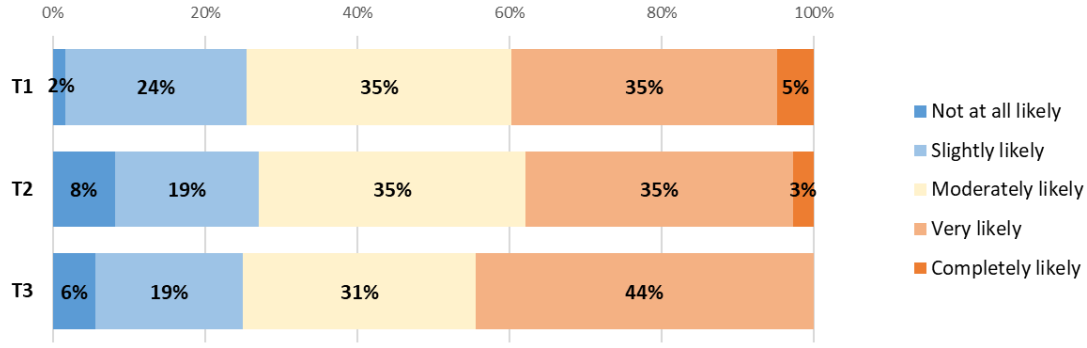


Figure 4.7. Changes in the patients' views about the likelihood chemotherapy reducing their current symptoms between T1, T2 and T3.

4.3.5 Response to treatment

Most patients (58%) were aware that chemotherapy was not at all likely to cure the cancer, 17% thought that it was slightly likely and 8% moderately likely to lead to cure (Figure 4.8). Around a third of patients (39%) responded that chemotherapy was very or completely likely to respond to chemotherapy, whilst 14% thought that it was not at all or slightly likely (Figure 4.9).

Compared to physicians, patients felt that there was a higher likelihood of chemotherapy curing the cancer, when 94% of clinicians reported that it was not at all likely, compared to 58% of patients (p=0.02). Additionally, patients were more optimistic about cancer responding to chemotherapy (39% compared to 6% completely or very likely, p=0.001) and prolonging their life (45% compared to 9% very or completely likely, p<0.001). There was no significant change in these views between the timepoints.

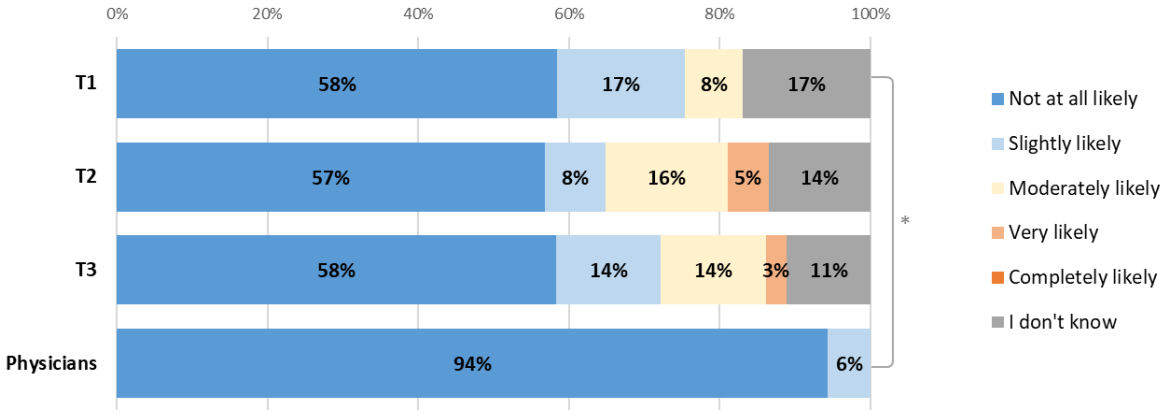


Figure 4.8. Changes in the patients' views about the likelihood of the treatment to cure the cancer between T1, T2 and T3 (compared to physician baseline views). *p=0.02

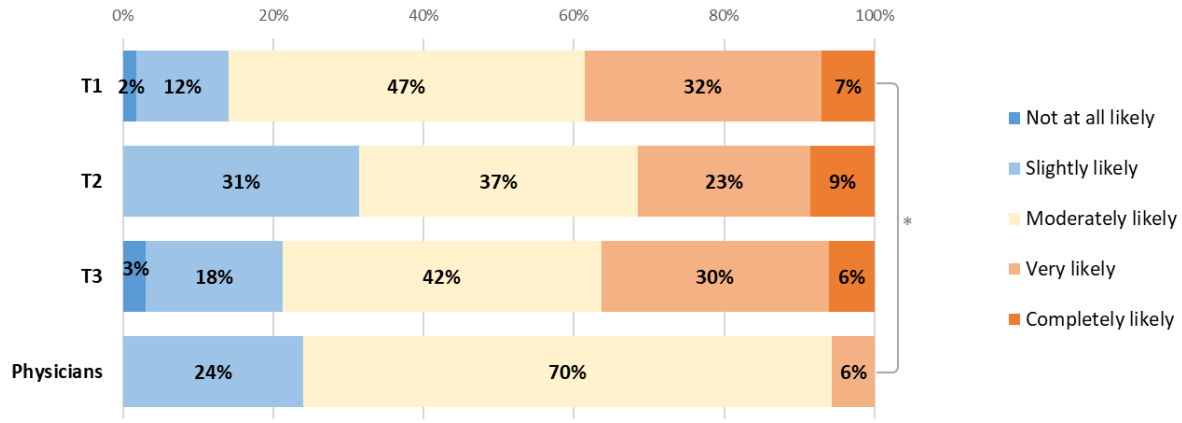


Figure 4.9. Changes in the patients' views about the likelihood of the cancer to respond to chemotherapy between T1, T2 and T3 (compared to physician baseline views). *p=0.001

4.3.6 Patient goals and priorities

The majority (86%) of patients answered that they have personal or family goals that they would like to reach with the help of treatment. Spending time with family, self-care as long as possible and being able to socialise were ranked as the top 3 priorities for patients, respectively. Being able to work and do one's own shopping were ranked as least important (Figure 4.10).

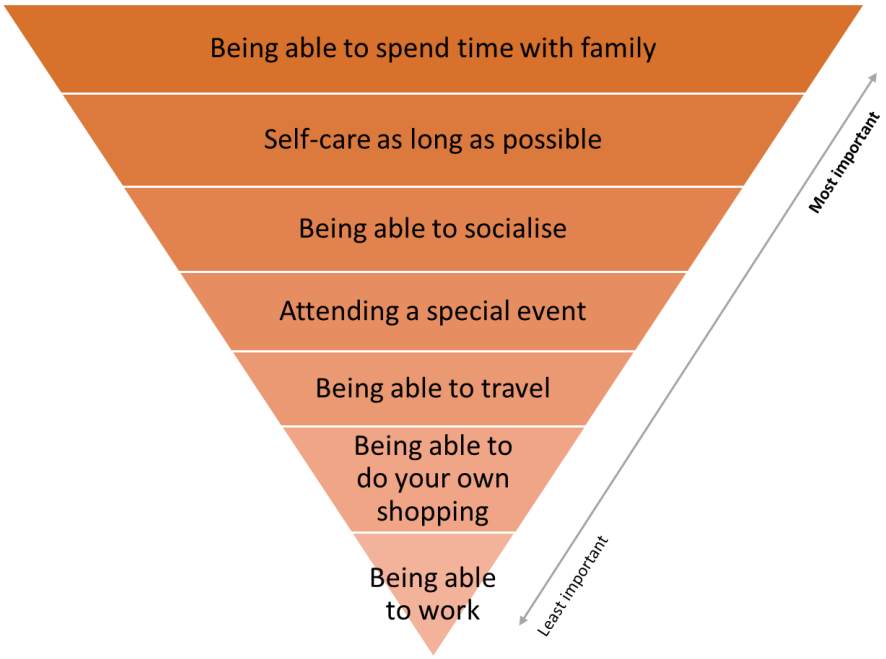


Figure 4.10. Patients priorities ranked from most important (nr 1) to least (nr 7) important (baseline).

The only statistically significant change between T1 and T3 was that spending time with family became more important to patients, mean score was 2.3 at T1 and 1.5 at T3 (p=0.02, details about analysis can be found in the methods section, page 119).

Compared to physicians, there was a significant difference in patients' personal goals. Eighty six percent of patients indicated that they had goals, whilst only 12% of clinicians were aware of these ($p<0.001$). The importance of some goals varied between the two groups (patients and physicians). Being able to travel (mean 3.7 compared to 5.1, for clinicians and patients, respectively, $p<0.001$), spending time with family (mean 1.4 compared to 2.4, $p<0.001$) and special events (mean 3.2 compared to 4.7, $p<0.001$) were all rated as significantly more important by patients than clinicians.

There was an increase in patients prioritising spending time with family between T1 and T3 (+0.7 points), whilst physicians views about this priority stayed the same over time or even decreased slightly (-0.3 points, $p=0.01$).

4.3.7 Choosing between treatment options

Most (54%) patients ranked longest survival as their main priority when making decisions about different treatment options, 26% prioritised the best balance between side-effects and survival, 15% could not choose their top choice and 5% prioritised controlling symptoms of cancer (Figure 4.11).

There were no statistically significant changes between timepoints. However, numerically slightly more patients (26% to 38%, $p=0.4$) favoured balance between survival and side-effects as the main priority when choosing between treatment options at T2, compared to T1. But only minimal change was seen between T1 and T3 (26% compared to 30%, $p=0.5$).

Over half (59%) of clinicians indicated that the balance between side effects and survival would be the main priority for the patient when choosing between treatment options, whilst longest survival was the most common response from patients (54%, $p<0.001$, Figure 4.11).

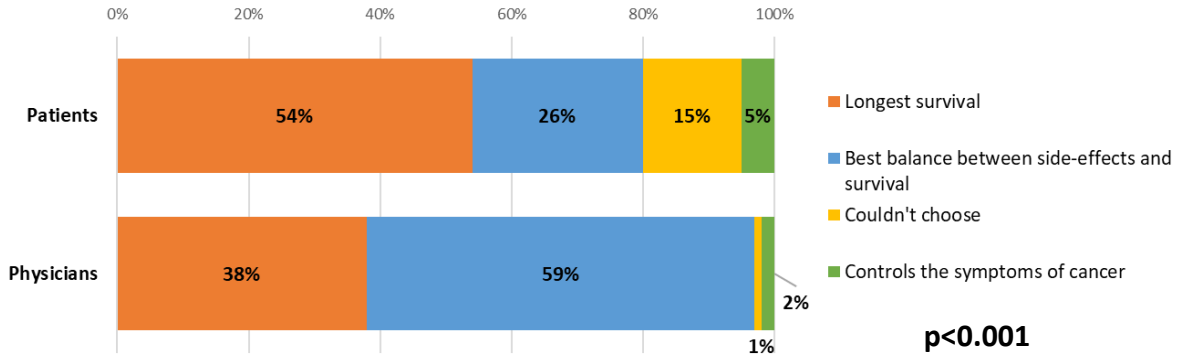


Figure 4.11. Differences between patients' and physicians' views about patient priorities when choosing between treatment options.

4.3.7.1 Patients who prioritised survival

Patients who prioritised survival over balance had higher symptomatic burden (p=0.03), more issues with constipation (p=0.03), more appetite loss (p=0.01) and borderline significantly worse role functioning (p=0.058) at baseline. There was no statistical difference in QoL or other functioning scales, no difference in worries about the future and no difference between time points.

Comparing patients groups based on their top choice in this question at T1, there was also a significant difference in overall survival (p=0.01), where patients who prioritised symptom control, lived an average of 2.8 months from T1, patients who prioritised survival 6.4 months, couldn't choose 8.7 months and who prioritised balance lived 9.2 months.

4.3.8 Acceptability of side-effects

On average, patients ranked altered taste, alopecia and tiredness (1st, 2nd and 3rd respectively) as the most acceptable chemotherapy side-effects, and infection with fever, nausea and vomiting (NV) and diarrhoea as the least acceptable (10th, 9th and 8th respectively, out of a possible 10, Figure 4.12).

Comparing changes between T1 and T2, patients responded that tiredness was the less acceptable (+0.9 points at T2, p=0.15) and alopecia was more acceptable side-effect (-

1.0 points at T2, p=0.12), but both of these findings were not statistically significant (Figure 4.12). Between T1 and T3, a borderline significant change was seen in tiredness becoming a less acceptable side-effect of treatment (+1.0 points at T3, p=0.05, Figure 4.12).

Compared to physicians, alopecia and skin rash were more acceptable to patients than physicians thought (both p=0.004), and diarrhoea was less acceptable to patients (p<0.001).

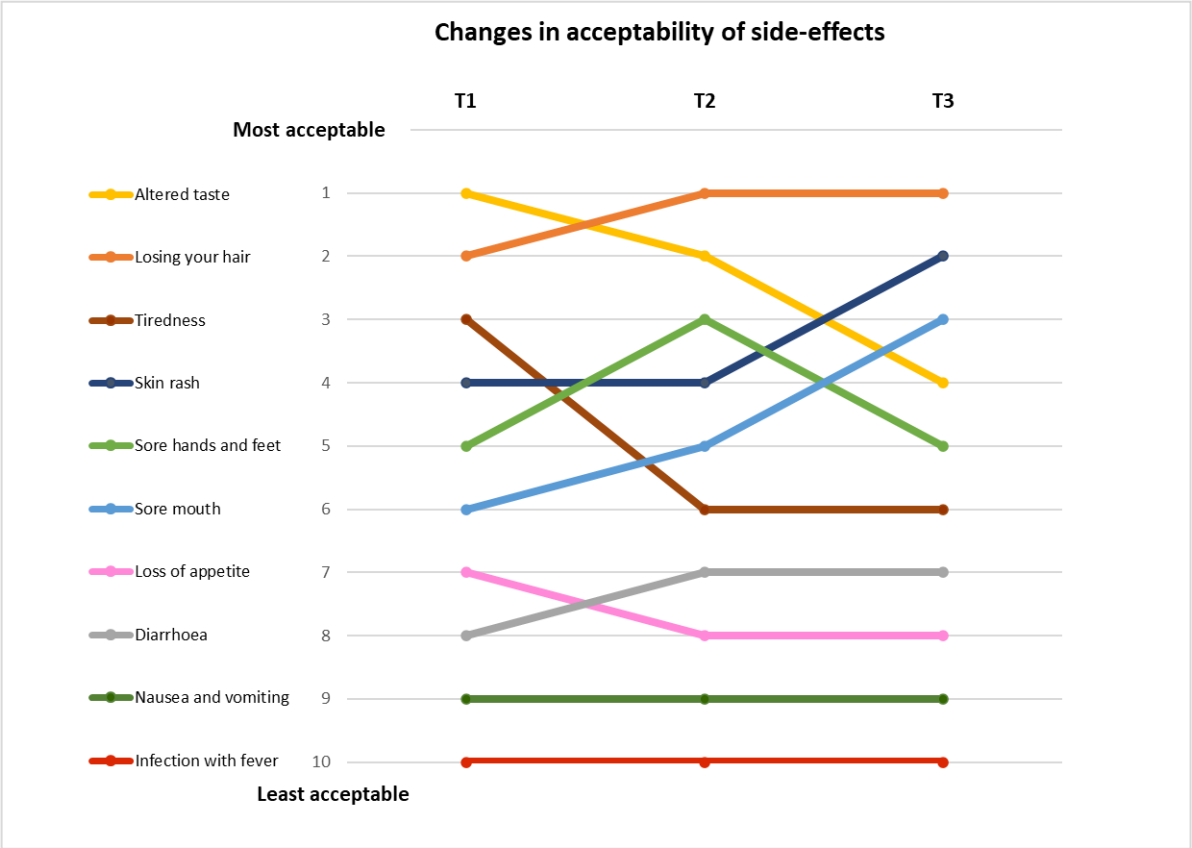


Figure 4.12. Changes in patients ranking of side-effect acceptability between T1, T2 and T3: 1 being very acceptable, 10 not acceptable at all. Not all changes were statistically significant, please see details under each section of this chapter.

4.3.8.1 Acceptability and QoL answers

On matching acceptability of side-effects with the QLQ-C30 and PAN26 responses, some symptoms that patients were already struggling with were also ranked as less acceptable. Nausea and vomiting, ranked by patients as one of the least acceptable side-effects (ranked 9/10), was a significant problem for patients (QLQ-C30 46/100p, higher

numbers indicating worse symptoms) and worsened at T2 (+12p, p=0.11). Diarrhoea was worse at all time points compared to the EORTC threshold for clinical importance and was ranked as one of the least acceptable side-effects by patients (8/10). Fatigue became less acceptable between T1 and T3 (p=0.05). Whilst there was no change in fatigue in the QLQ-C30 questionnaire, it was constantly worse than the EORTC threshold for clinical importance, and also physical functioning worsened between T1 and T2 (-10p, p=0.11). Appetite loss was much worse compared to EORTC threshold and worsened at T2 (+10p, p=0.3) and was constantly ranked not very acceptable (7-8/10) by patients.

4.3.9 Important time

Thirty-three patients (58%) expected the chemotherapy to extend their life by 1-5 or more than 5 years (46% and 12%, respectively), 17 (30%) patients expected this to be between 6 months and 1 year and 7 (12%) patients between 3 and 6 months (8 did not answer) at baseline. Similarly, when asked what would be the minimal extra time that would be important to them (with 5 options provided), 24 (43%) answered 1-5 or >5 years (32% and 11%, respectively), 22 (39%) responded 6 months to 1 year and 10 (18%) 3 to 6 months (9 did not answer).

Comparing T2 answers to T1, more patients (37% to 54%) reported 1-5 or >5 years as the minimally important time acceptable, but this was not statistically significant (p=0.66). Between T1 and T3, there was also a slight increase in the time patients expected the chemotherapy to extend their life by (63% compared to 74% of patients expecting 1-5 or >5 years). However, this result did not reach statistical significance (p=0.06).

There were significant differences between patient and physician responses regarding the length of time chemotherapy was expected to extend patients' lives (p<0.001); 81% of physicians and only 12% of patients thought that this would be between 1-2 or 3-6 months, whilst 58% of patients and none of physicians thought that this would be by 1-5 or >5 years (Figure 4.13). Detailed per participant patients' and physicians' responses comparison is shown on Figure 4.15.

Similarly, the minimal extra time (survival gain) patients would consider to be important was statistically different from the physician responses (p<0.001). Three-quarters of

physicians and only 18% of patients thought that the minimal survival time gain would be 1-2 or 3-6 months, whilst 43% of patients and none of the physicians thought that it would be 1-5 or >5 years (Figure 4.14 and detailed in Figure 4.16).

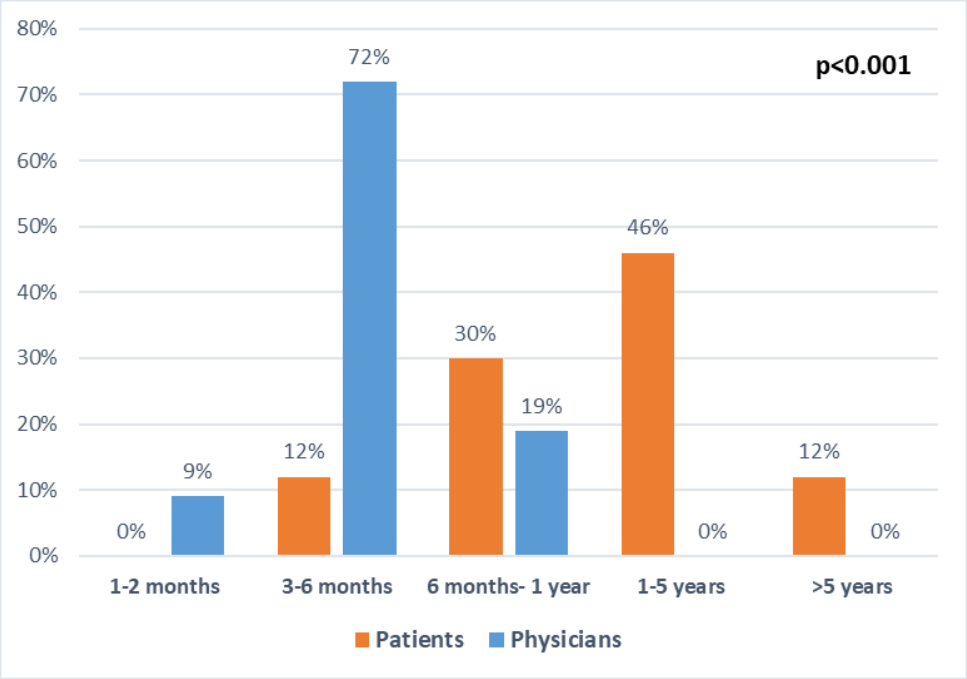


Figure 4.13. Comparison between patient and physician expectations (p<0.001) about chemotherapy extending patient survival at baseline.

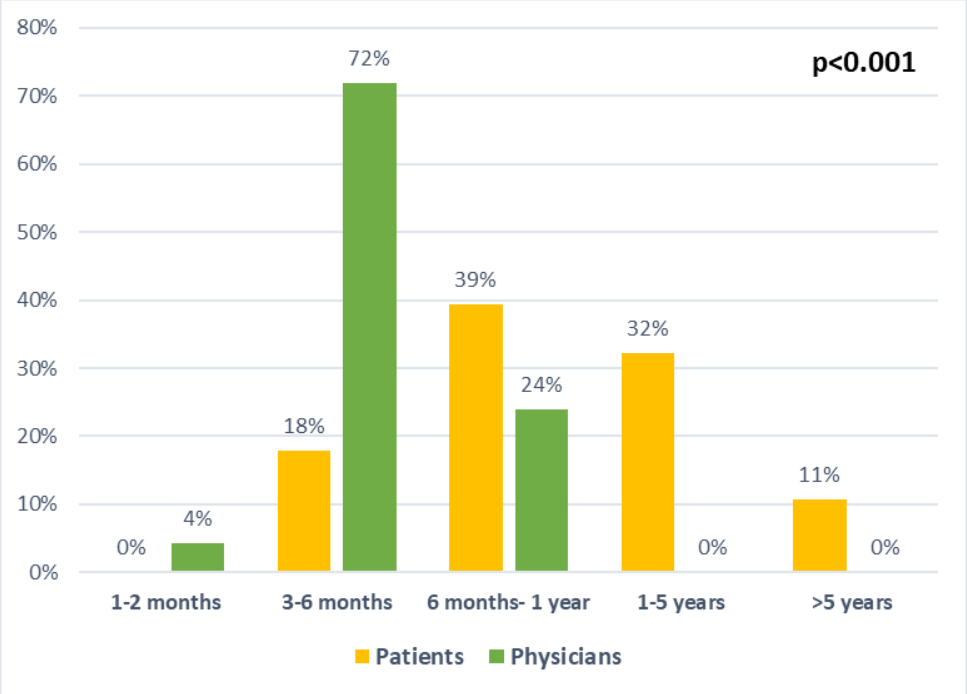


Figure 4.14. Comparison between minimal extra survival time that patients and physicians (p<0.001) thought would be important to patients at baseline.

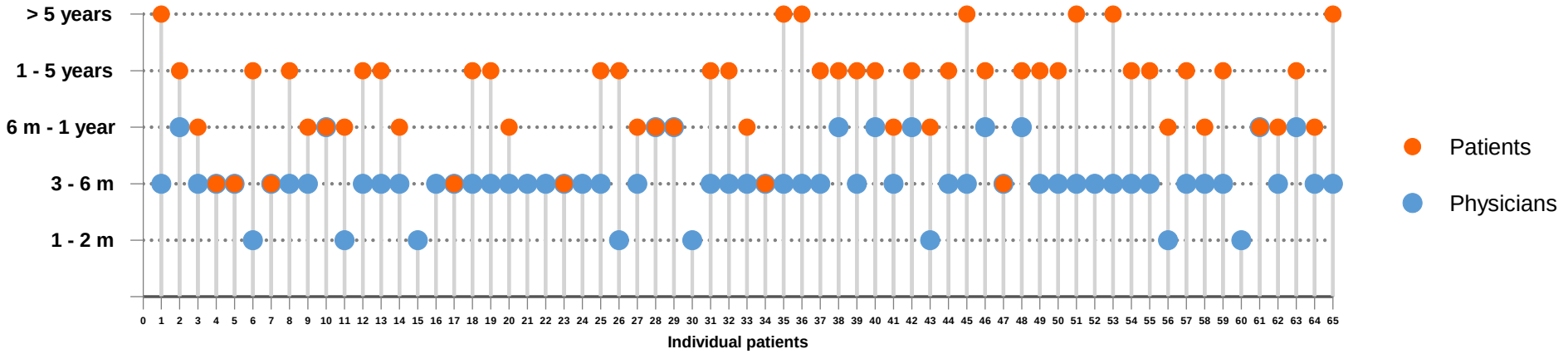


Figure 4.15. Detailed per participant comparison between patient and physician expectations (p<0.001) about chemotherapy extending patient survival at baseline. m-months

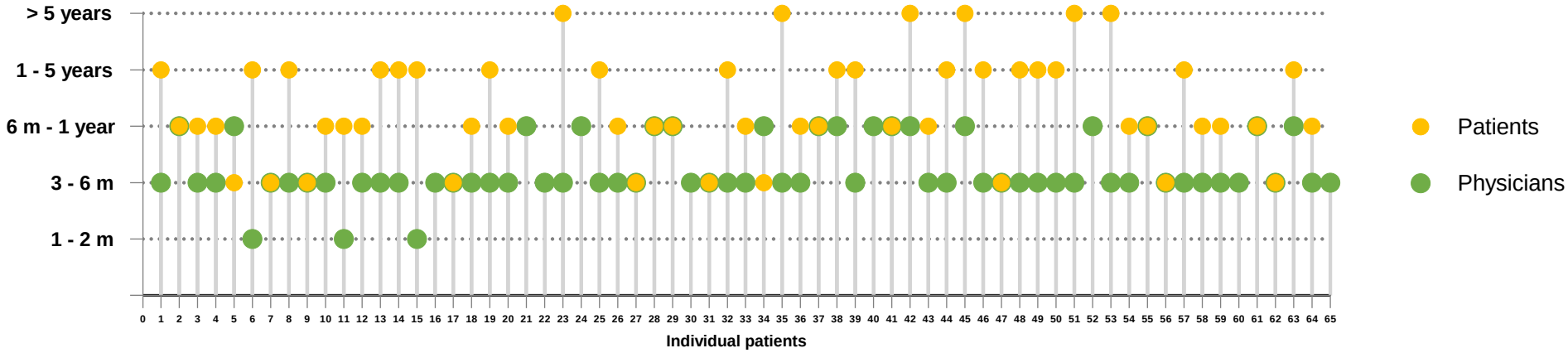


Figure 4.16. Detailed per participant comparison between patient and physician expectations (p<0.001) about minimal extra survival time that patients and physicians thought would be important to patients at baseline. m-months

There was no difference when comparing changes from T1 to T3 between patients and physicians' answers to these questions; these decreased or increased similarly between the two groups. For example, 22% of both patients and physicians had an increase in the expected time chemotherapy will extend patients life (between T1 and T3) whilst, 19% of physicians and 4% of patients had a decrease in this view (p=0.42). However, in physicians the increase was mainly from 3-6 months to the next category (6 months to 1 year), whereas in patients this was from the lower categories (3-6 months or 6 months to 1 year) to higher categories (1-5 and >5 year). Similarly, the minimal extra important time increased through time in 28% and 31% and decreased in 10% and 17% of patients and physicians respectively (p=0.83).

4.3.9.1 Patients who expected >5 years survival

There were 12 (18%) separate patients who at any time point expected chemotherapy to extend their lives by >5 years or who answered that >5 years would be the minimally important time for them.

Compared to other patients, these 12 had less problems with nausea and vomiting on the QLQ-C30 scale (p=0.006) and borderline significantly (p=0.05) higher summary score indicating less symptomatic burden. They were also more likely to choose survival length over balance between side-effects and survival as their main priority when choosing between treatment options (Q16), but this was borderline significant (p=0.054). There was no difference in willingness to accept large amounts of side-effects between these patient groups and no significant difference in overall survival.

4.3.10 Trading off side-effects for time

When asked how many side-effects patients were willing to trade off for this minimally important time, almost all of them were willing to take small or medium amount of side-effects (defined as taking oral medication for side-effects at home) whilst, 57% were not willing to experience large amounts of side-effects (8 did not answer). If the minimally important time was doubled, more patients were willing to take large amounts of side-

effects (47% increased to 60%). Two-thirds (67%) of patients were willing to accept chemotherapy if it controlled symptoms of their cancer, but did not extend survival.

Between the timepoints, the only statistically significant change was a decrease from 70% to 43% (p=0.04) of patients who would be willing to accept chemotherapy with a large amount of side-effects if the minimally significant survival time was doubled (between T1 and T2).

Comparing patients and physicians answers (Figure 4.17), there was a statistically significant difference in patients willingness to accept chemotherapy with medium and large amounts of side-effects as a trade-off for minimal important time gain (100% compared to 88% for medium (p=0.02) and 47% compared to 9% for large amount (p<0.001), patients and physicians respectively). However, given the fact that 43% of patients expected this minimal time to be 1-5 or >5 years, it is difficult to interpret if they would have made the same choice considering the timeframe physicians thought to be important.

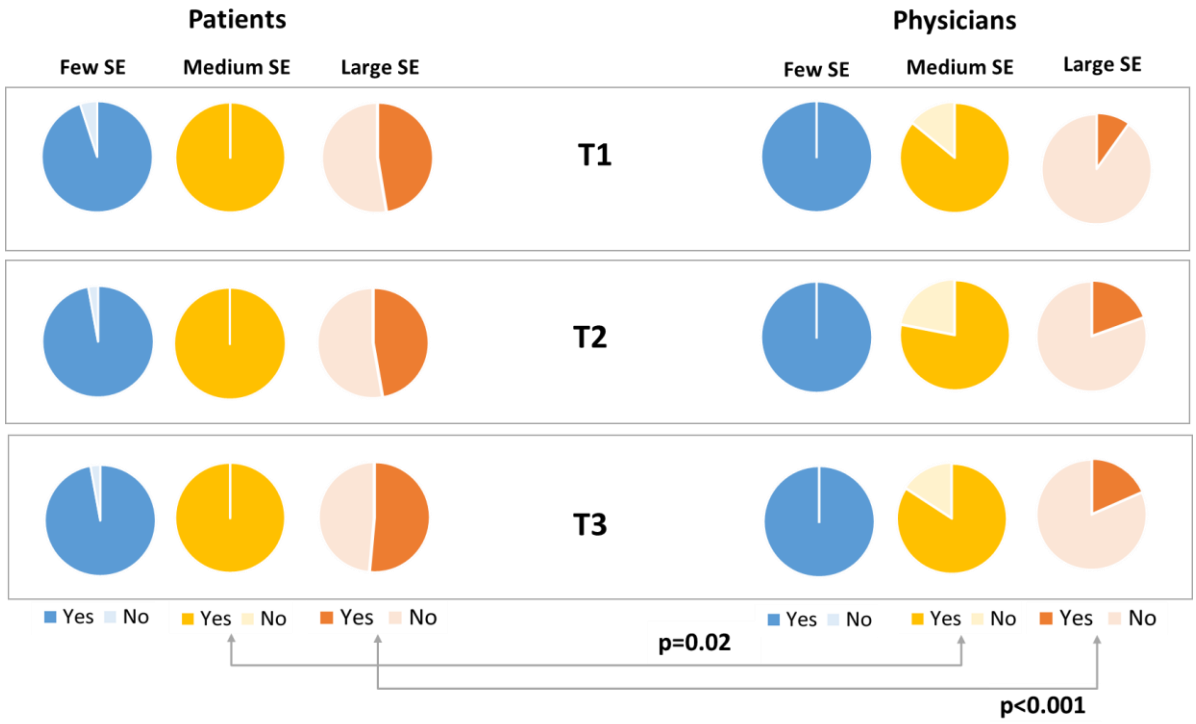


Figure 4.17. Differences between patients' and physicians' views about patient's willingness to accept few-, medium- or large amounts of side-effects at T1, T2 and T3. SE- side-effects

Physicians underestimated the amount of patients willing to accept chemotherapy if it controlled symptoms of cancer, but did not extend survival (67% patients compared to 46% physicians, p=0.05).

4.3.11 EORTC QLQ-C30 and PAN26

Of a possible 100 points, Table 4.1 details all the mean results from the QLQ-C30 and PAN26 scales at baseline and changes between the time points, these are further illustrated on figures 4.18 and 4.19.

The baseline symptom and functional scale values were compared to the EORTC reference manual averaged scores for HPB cancers [295] and recently updated EORTC Quality of Life Group thresholds for clinical importance [310].

Compared to the average scores for HPB cancers in the EORTC reference manual [295], scale scores with at least 10p difference from the reference were highlighted. At T1, patients had worse: pain (44p vs 29.6p), appetite loss (47p vs 32.3p) and constipation (30p vs 20p, current study compared to manual, lower scores indicating less symptoms). At T2, patients on the current study had worse: role functioning (50 vs 65.2, higher better functioning), social functioning (55 vs 69, higher better), fatigue (52 vs 41.2, higher worse symptoms), nausea and vomiting (30 vs 12.4, higher worse), pain (39 vs 29, higher worse), insomnia (43 vs 32, higher worse), appetite loss (56 vs 32.3, higher worse), diarrhoea (30 vs 11.1, higher worse, current study compared to manual respectively). At T3, patients on the current study had worse diarrhoea (21 vs 11, current study compared to manual respectively, higher worse).

Compared to EORTC thresholds for clinical importance [310], patients in the current study had worse physical functioning (72.7, 65.5, 70.5 compared to 83), fatigue (45.8, 51.9, 44.6 compared to 39), pain (44.4, 38.9, 26.3 compared to 25), nausea and vomiting (18.6, 29.8, 15.6 compared to 8) and diarrhoea (23.2, 30.2, 21.4 compared to 17) in all 3 time points (T1, T2, T3 respectively). At T2, they also had worse role functioning (50.0 compared to 58), social functioning (54 compared to 58), emotional functioning (67 compared to 71), appetite loss (55.6 compared to 50), dyspnoea (20.2 at T2 and 18.3 at T3 compared to 17) and financial difficulties (18.1 at T1 and 18.2 at T2 compared to 17).

There are no standardised thresholds for PAN26, however, compared to a previous clinical trial [152] and psychometric validation study [311] that have both used PAN26 in patients with advanced pancreatic cancer (historical control), patients on the current study seemed to have numerically worse pancreatic pain, worse digestive symptoms, worse altered bowel movements, worse body image, worse worries about the future and worse future activity planning. At baseline, the lowest (best) symptom scales were hepatic symptoms (10p), indigestion (21p) and worries about side-effects (21p), whilst the highest (worst) scales were worries about the future (58p), future activity planning (56p) and digestive symptoms (45p).

Changes between time points

Based on previous research [312], 10 point changes in the QLQ-C30 have been found to be clinically meaningful and corresponding to supportive care needs. There has been previous efforts to identify significant changes in each scale separately [313] and dividing these in to small, medium and large deteriorations or improvements. However, all thresholds for medium change are still around 10 points, and previous clinical trials in pancreatic cancer [157, 314, 315] have similarly used the 10p change, thus, this cut-off was also used in the current study.

At least 10p changes between T1 and T2: physical functioning worsened (-10 p, p=0.11), role functioning worsened (-17p, p=0.039), nausea and vomiting worsened (+12p, p=0.11), appetite loss worsened (+10p, p=0.29), pancreatic pain improved (-11p, p=0.05), altered bowel habit worsened (+13p, p=0.05), body image worsened (+18p, p=0.01), taste worsened (+25p, p=0.002), weakness in limbs worsened (+11p, p=0.09), dry mouth worsened (+12p, p=0.1), worries about side-effects worsened (+25p, p<0.0001).

At least 10p changes between T1 and T3: pain improved (-16p, p=0.04), constipation improved (-14p, p=0.06), pancreatic pain improved (-23p, p<0.0001), digestive symptoms improved (-10p, p=0.18), bloating improved (-20p, p=0.002), taste loss worsened (+16p, p=0.023), weight loss improved (-11p, p=0.154), worries about side-effects worsened (+17p, p=0.008).

Table 4.1. Average scores (out of 100) and changes between time points of QLQ-C30 and PAN26 scales of all patients.

		T1 Mean, 95% CI	T2 Mean, 95% CI	Change T1-T2*	p-value*	T3 Mean, 95% CI	Change T1-T3*	p-value*
Global health status/QL (higher better)								
C30	Global health status/QL scale	57.3 (52.0-62.7)	48.7 (40.2-57.2)	-9	0.11	63.6 (55.5-71.8)	2	0.71
Functional Scales (higher better)								
C30	physical functioning	72.7 (67.0-78.3)	65.5 (56.1-75.8)	**-10**↓	0.11	70.5 (62.6-78.4)	-9	0.09
	role functioning scale	63.8 (55.6-72.1)	50.0 (38.5-61.5)	**-17**↓	**0.039**	61.3 (49.5-73.0)	-6	0.47
	emotional functioning scale	72.7 (66.8-78.7)	67.4 (56.9-78.0)	-2	0.76	74.4 (65.6-83.3)	4	0.45
	cognitive functioning scale	77.1 (71.8-82.4)	77.6 (66.6-88.6)	-2	0.796	76.7 (66.9-86.4)	-2	0.76
	social functioning scale	62.7 (55.3-70.1)	54.7 (43.6-65.8)	-7	0.316	62.9 (53.2-72.6)	-3	0.7
PAN26	Satisfaction with health care	73.9 (66.2-81.5)	65.3 (54.5-76.0)	-9	0.192	74.5 (63.9-85.1)	1	0.9
	Sexuality	42.4 (30.3-54.4)	38.2 (25.0-51.3)	-4	0.635	33.3 (19.5-47.2)	-9	0.32
Symptom scales/items (lower better)								
C30	fatigue	45.8 (38.9-52.6)	51.9 (42.0-61.7)	9	0.197	44.6 (35.7-53.6)	4	0.55
	nausea and vomiting	18.6 (12.2-25.1)	29.8 (18.0-41.6)	**12**↓	0.11	15.6 (7.6-23.6)	1	0.93
	pain	44.4 (35.9-52.8)	38.9 (25.9-51.9)	-6	0.51	26.3 (15.9-36.8)	**-16**↑	**0.039**
	dyspnoea	17.5 (11.6-23.4)	20.2 (8.8-31.6)	3	0.67	18.3 (10.0-26.5)	2	0.72
	insomnia	35.0 (27.1-43.0)	43.4 (30.7-56.1)	9	0.26	34.4 (20.8-48.0)	-3	0.69
	appetite loss	46.9 (37.8-56.0)	55.6 (41.5-69.6)	**10**↓	0.29	33.3 (21.5-45.1)	-5	0.52
	constipation	29.9 (21.8-38.1)	26.3 (14.9-37.6)	0	1	18.3 (8.4-28.2)	**-14**↑	0.06
	diarrhoea	23.2 (15.4-30.9)	30.2 (19.5-40.9)	4	0.61	21.1 (10.5-31.7)	-3	0.73
	financial difficulties	18.1 (11.4-24.8)	18.2 (8.3-28.0)	3	0.63	16.1 (7.3-25.0)	0	1
PAN 26	Pancreatic pain	45.2 (38.5-52.0)	33.9 (24.3-43.4)	**-11** ↑	0.054	22.0 (14.7-29.3)	**-23**↑	**<0.001**
	Bloating	41.2 (33.0-49.5)	37.8 (26.4-49.3)	-3	0.628	21.1 (11.6-30.6)	**-20**↑	**0.002**
	Digestive symptoms	44.9 (36.5-53.3)	42.6 (32.5-52.7)	-2	0.723	34.9 (22.7-47.2)	**-10**↑	0.179
	Taste	29.9 (21.3-38.3)	55.0 (42.1-67.8)	**25**↓	**0.002**	46.2 (35.0-57.5)	**16**↓	**0.023**
	Indigestion	20.7 (14.2-27.2)	26.9 (15.5-38.2)	6	0.346	18.3 (9.4-27.1)	-2	0.658
	Flatulence	45.2 (36.9-53.5)	46.7 (33.0-60.3)	1	0.853	40.9 (28.3-53.4)	-4	0.561

	Weight loss	37.9 (28.7-47.0)	47.2 (36.0-58.5)	9	0.197	26.9 (14.5-39.3)	**-11**↑	0.154
	Weakness arms and legs	33.3 (26.3-40.4)	44.4 (33.0-55.9)	**11**↓	0.099	32.3 (23.6-40.9)	-1	0.846
	Dry mouth	35.6 (27.9-43.3)	47.7 (35.0-60.5)	**12**↓	0.103	26.9 (16.7-37.1)	-9	0.172
	Hepatic symptoms	9.6 (6.2-13.0)	9.3 (4.3-14.2)	0	0.908	5.4 (1.7-9.0)	-4	0.093
	Altered bowel habit	31.9 (24.8-39.1)	44.4 (33.6-55.3)	**13**↓	**0.056**	38.2 (28.3-48.1)	6	0.302
	Body image	25.7 (18.4-33.0)	44.0 (32.1-55.9)	**18**↓	**0.010**	29.8 (19.0-40.6)	4	0.528
	Troubled with side-effects	20.9 (13.0-28.9)	46.1 (35.7-56.4)	**25**↓	**<0.001**	38.4 (28.1-48.7)	**17**↓	**0.008**
	Future Worries	57.9 (48.8-67.0)	64.8 (53.4-76.2)	7	0.341	53.1 (41.0-65.3)	-5	0.526
	Planning of activities	56.3 (46.7-65.9)	60.0 (48.6-71.4)	4	0.619	49.0 (36.0-61.9)	-7	0.358

* Changes calculated only between patients who filled in both questionnaires (39 patients T1-T2, 36 patients T1-T3). Time point means include all patients who filled in the questionnaire at that time point (65 patients at T1, 39 patients at T2, 36 patients at T3).

CI- confidence interval

↑- clinically significant improvement by at least 10 points

↓- clinically significant worsening by at least 10 points

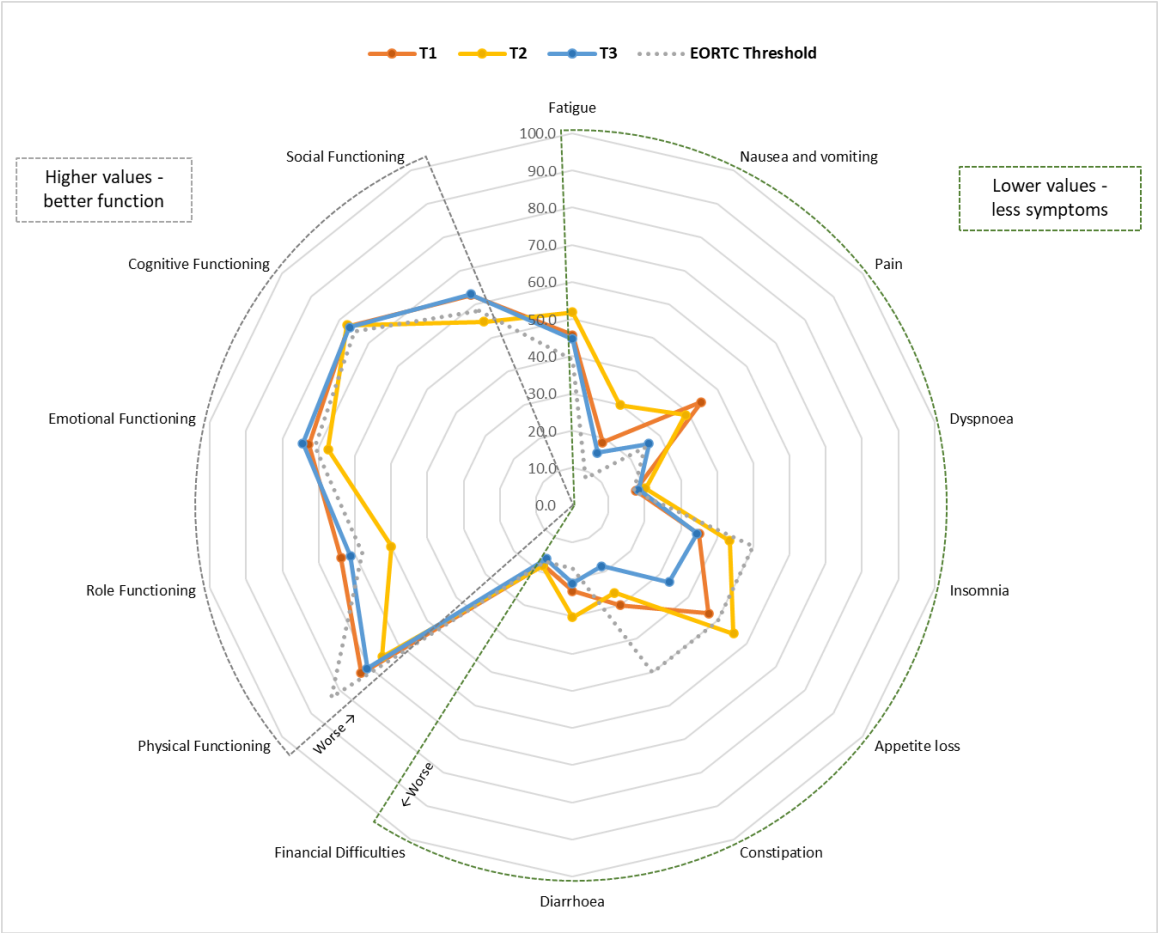


Figure 4.18. Average QLQ-C30 scale scores at T1, T2, T3 compared to the EORTC Threshold for clinical importance. Details of the values and changes between time points are described in Table 4.1.

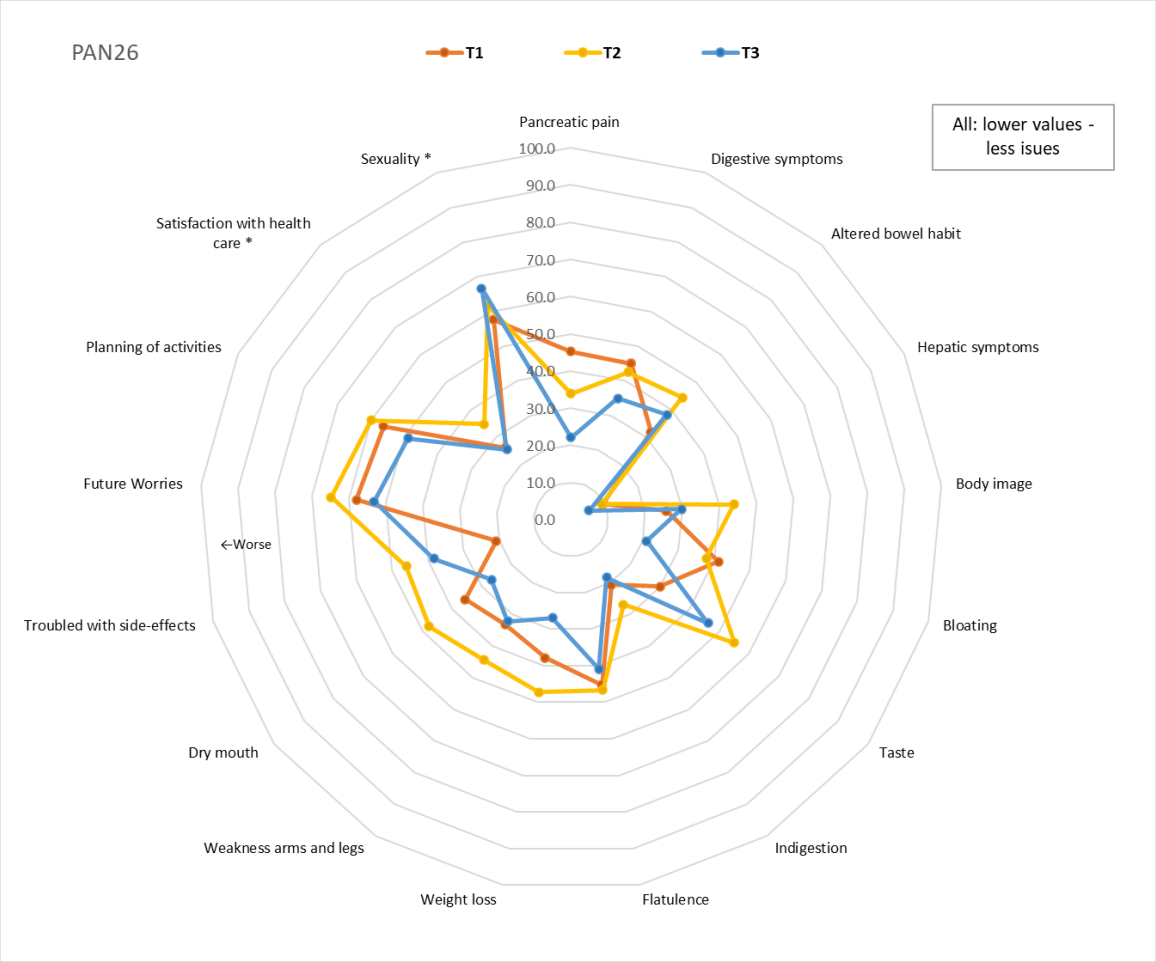


Figure 4.19. Average PAN26 scale scores at T1, T2, T3. Details of the values and changes between time points are described in Table 4.1. *- function scales were switched for all scales to have the same direction.

4.3.12 Patient survival outcomes

Assessing patient survival outcomes was not the main aim of this study. However, to give a general overview of how patients did in real world compared to their expectations, some survival data was collected. Forty-three (61%) patients died during the study timeframe; for those patients, the median OS from T1 was 3 months (range 0-13 months). At the time of final analysis 93% of patients had died, the median OS for all patients was 7.39 months (95% CI 5.3-9.5 months).

Of the 36 patients who reached T3, the CT (first on-treatment scan) showed stable disease (SD) in 29 patients and partial response (PR) in 7 patients.

4.3.13 Online survey results

An online survey was sent to 23 medical oncologists working in different centres in the UK who are known to treat patients with PDAC; 8 (34%) responses were received (5 reminders were sent to maximise response). On average, respondents ranked nausea and vomiting as the least accepted chemotherapy side-effect, followed by getting an infection and loss of appetite; the presumed most acceptable side-effect was altered taste, skin rash and alopecia.

"Spending time with family" followed by "being able to socialise" was ranked as the presumed most important priority for patients and "doing their own shopping" and "being able to travel" as least important. When choosing between different types of chemotherapy, 62% of responders ranked the balance between side-effects and survival and 38% longest survival as the top presumed priority for patients. The majority (62%) of responders expected the life extension from chemotherapy to be around 3-6 months and 38% expected it to be 6 months to 1 year. Similarly, 62% thought the minimal extra time a patient would think is important was 3-6 months; 25% thought it would be 6 months-1year and 13% 1-2 months. All expected the patients to take chemotherapy with few or medium amount of side effects, irrespective of extra time, and 38% of respondents expected the patients to take chemotherapy with a large amount of side-effects, irrespective of expected minimal time or if this would be doubled. Three quarters of physicians thought that patients would take chemotherapy even if it controlled symptoms of cancer only, and would not extend survival. As the online survey only consisted of 8 respondents, it is difficult to analyse statistical difference with the physician baseline results of this study (71 respondents) however, given the limitations of the small sample, no significant difference was seen between the online and current study responses. The percentage differences compared to The Christie physicians are illustrated on Figure 4.20.

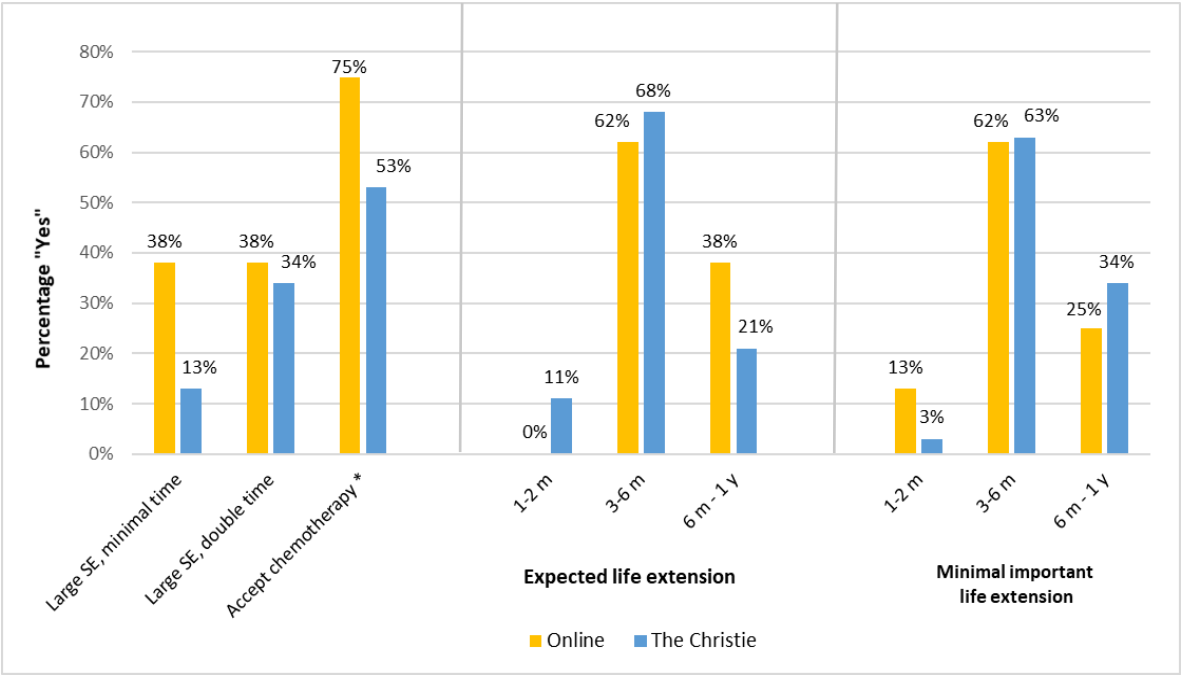


Figure 4.20. Comparison of selected results between The Christie and online physicians' responses (% of responders who answered 'Yes' to these questions). * if it controlled symptoms only and did not extend survival. SE- side-effects, m-months, y-years.

4.4 Discussion

4.4.1 Discussion of survey findings

This was an observational questionnaire study aiming to evaluate patients' and physicians' views on outcomes of pancreatic cancer. The purpose of the study was to explore and describe a specific population of patients recently diagnosed with advanced pancreatic cancer starting their first line chemotherapy. This is the first study of its kind specifically looking at patients and physicians views in PDAC, but previous studies in other advanced cancers on similar topics have reported mixed results in relation to these questions.

Similarly to previous research [316-318], patients in the current study wanted to be involved in decision making about their treatment and this did not change over time. The diagnosis of cancer and treatment had a significant impact on patients everyday lives, due to the need to travel for treatment and the burden of financial toxicities which significantly worsened over time. The patients most important goals were spending time with family and self-care for as long as possible (at all time points). A significant decline in role functioning became evident at later time points. This highlights that patients

might not be able to do things that are most important to them because of their symptoms and their cancer treatment.

Compared to the previously-described study by Weeks *et al* (2012) [194] that showed that a majority (69-81%) of patients with metastatic lung or colorectal cancers were not aware that chemotherapy is unlikely to cure their cancer, the current study illustrated that 58% of the patients were aware of this, whilst 17% thought it would be slightly likely and 8% moderately likely. There were still 2% of patients who thought that the aim of treatment would be to cure the cancer, which is similar to 5% reported in another study by Loh *et al* [233].

There were mixed views from patients about the expected effect of treatment on their wellbeing, as around half expected it to improve and half to worsen. This was probably attributable to patients already experiencing large amounts of symptoms from the cancer, whilst also been told about additional potential side-effects from treatment. Most patients (53.8%) expected <10% of patients to experience serious side-effects from their treatment (requiring hospitalisation). All treatment regimens that these patients received produced >10% Grade 3-4 side-effects in previous clinical trials [25, 26] (gemcitabine, gemcitabine and nab-paclitaxel, FOLFIRINOX). Compared to physicians, patients were also significantly more optimistic about the effectiveness of treatment.

This study also found that the majority of patients had personal or family goals that they wanted to reach with the help of treatment. Only a small number of physicians were aware of these. These patient goals also remained throughout the treatment, with no difference seen between T1 and T3. This difference seen between patients and physicians could be due to patients not always communicating this to their physicians, as sometimes these can be more personal, or this could also be a result of a lack of communication between the two parts and the time pressures associated with busy oncology clinics. However, these might be actually very important to discuss with the physician as previous research has shown that meaningful life events and relationships are sources of hope for patients [204] and patients who reach their goals have less anxiety [319]. Spending time with family became even more important to patients between these time points. Overall, patient priorities were ranked similarly by patients and physicians, but family, special events and being able to travel were more important to patients.

One of the main differences between physician and patient expectations in this study was that whilst the majority of patients indicated OS as their main priority when choosing between chemotherapies, physicians thought that the patients would prioritise the balance between OS and side-effects. This discrepancy between priorities is especially interesting as most patients still answered in a later question that they were willing to undergo treatment if it controlled symptoms of cancer but did not lead to longer survival. It was found that the patients who prioritised survival seemed to be the ones that were already struggling significantly worse symptoms and had a significantly worse overall survival compared to patients who prioritised balance between side-effects and survival. This could be due to patients already feeling worse at baseline and desperately wanting more time.

As discussed earlier, research into patients' choice between length of life and quality of life revealed mixed results [234] and could be related to age, symptom burden or other factors. It is particularly interesting as the question in this study had also two other answer options- *least amount of side-effects* and *controls the symptoms of my cancer*, which were all together chosen only by 5% of patients. Whilst previous research [190, 234, 237, 320] has shown that most patients thought both survival and QoL as important, in the current study the option *best balance between side effects and survival* should have been chosen as the main priority. Thus, even given the option of choosing both survival and QoL, patients still prioritised length of life over it. This could be due to the fact that for these patients, the expected average prognosis would be measured in months and highlights the fear that patients have of running out of time. Taking into account that patients wanted to be an equal partner in decision making, the results from this question indicate that physicians and patients have different priorities in mind (for the patients) with one side favouring length of life and the other, the best balance between survival and QoL.

The results of this study also highlight that overall, the acceptability of chemotherapy side-effects was similar between patients and physicians. However, skin rash and alopecia were more acceptable and diarrhoea less acceptable to patients. This could be a reflection of the physicians previous experience with these side-effects, or the previously shown negative impact of diarrhoea on patient social activities [321]. Interestingly, the diarrhoea symptom scale showed worse levels compared to the EORTC

clinically important thresholds at all time points [310], indicating that most of patients had problems with this symptom, and symptoms that patients were already struggling were observed to be rated as less acceptable. Both physicians and patients ranked infection, with fever, as the least acceptable side-effect at all time-points.

The second main finding of this study is the differences between patient and physician views in relation to prognosis and minimal important survival time gain. Whilst half of the patients had had discussions about prognosis, this did not seem to have an impact on their expectations from chemotherapy. The majority of patients still expected life extension to be 1-5 or >5 years. Physicians who are more aware of the prognosis averages from previous clinical trials or from their own clinical experience, all expected the extension of life to be less than 1 year (Figures 4.13 and 4.15). This discrepancy between patients' and physicians' expectations could have implications for patient decision making. In the study by Weeks *et al* [195], patients who expected their survival to be more than 6 months favoured life-extending therapy over best supportive care and were more likely to undergo aggressive treatment, but their 6-month survival was not actually longer. The patients most likely to choose life-extending therapy were the ones where the mismatch between physicians and patients expectations of length of survival was the widest [195]. In the current study, 81% of physicians' answers expected the life extension from chemotherapy to be up to 6 months, and only 12% of patients responded similarly. There were 12 (18%) patients in the current study who expected treatment to prolong their survival by >5 years or that the minimally important time for them would be >5 years and there was a borderline significant difference in these patients being more likely to choose survival as their primary aim, but there was no difference in willingness to accept large amounts of side-effects or in overall survival. Thus, similarly to the Weeks at al [195] study, patients with the widest mismatch in expected length of life did not live longer, but were more likely to choose survival as their treatment priority.

A previous study in patients with advanced ovarian cancer has also reported that patients were more likely to experience anxiety and depression if there was a large discrepancy between expectations of benefit and experienced benefit [319]. In the current study, the QLQ-C30 does not clearly measure anxiety and depression, but has an *emotional function* scale that was worse than the clinically important threshold [310]

at T2, and on PAN26 the *future worries* and *future planning* scales were scored highest (worst) at all time points. This highlights that on average most patients in the current study had issues with emotions and worry and taking this together with the mentioned significant differences in expectations about prognosis, this association between expectations and emotional state can be seen for almost all patients in the current study.

The authors of the previously mentioned study of patients with advanced ovarian cancer proposed that a solution would be for clinicians to encourage realistic hope, targeted toward achievable goals [319]. As depression has been shown to be a major problem and present in 33-50% of patients with PDAC [166], it might be important to have candid conversations with patients rather than give false hope that could in turn lead to further psychological harm. As previously discussed, research has shown that giving prognostic information in a realistic and open way, tailored to the individual, can be actually viewed as hope-giving by patients [219] and that when patients are given honest prognostic information, hope is maintained even when the news is bad [225]. Thus, physicians should not worry about taking away hope with these conversations and instead use the strategies highlighted by patients to maintain realistic hope. In the current study I found that only around half of patients had documented prognosis discussions within the first month of their palliative treatment. Whilst we do not know if this was done but just not documented, it does highlight the need to remind the clinicians the importance of prognostic discussions, especially as patients deteriorate quickly and patients who become aware of their terminal status by worsening condition or by chance have been previously found to have worse QoL [214].

As discussed in the introduction section, previous research has shown that patients with cancer are willing to undergo treatment for very small benefit, even with major toxicities [190], and similar results were found in the current study. Most patients were willing to accept a large amount of side-effects if their minimally important extension of time was doubled at T1, but compared to T2 there was a significant reduction in the number of patients who were willing to accept this trade-off. One of the reasons for this could be that at T1, patients had not had any chemotherapy yet and as seen in the QLQ-C30 answers, many of the function and symptom scales worsened over time, indicating that some of these could be treatment side-effects that patients experienced and were not

willing to accept over time. A similar phenomenon was seen when comparing QoL data to the acceptability of side-effects, where the more patients were already struggling with a particular symptom, the less acceptable it was in their answers. Physicians in this study underestimated the number of patients who would be willing to accept large amounts of side-effects and the patients who would accept treatment if it did not extend survival. This could be due to physicians being more aware of the risks and mortality associated with potential side-effects and witness these more often, whilst for patients, these might be more hypothetical.

At all time points, patients in the study had significant issues with symptoms, functions, and quality of life. As seen in Table 4.1, there were also significant changes over time, especially at T2 where physical- and role functioning worsened, and also symptoms like altered bowel habits, taste, nausea and vomiting and appetite loss all worsened. There were improvements in pain, constipation, digestive symptoms and weight loss at T3, but worsening of other symptoms like taste loss and worries about side-effects. These results indicate the high symptomatic burden of patients recently diagnosed with advanced PDAC and how these worsen during first line treatment. Recent studies have also shown that baseline PF and nausea and vomiting scales are predictive of OS in patients with PDAC [160, 322] and both of these scales deteriorated over time and were worse than the EORTC threshold also in the current study. As >10 p changes in any scales have previously been associated with increased supportive care needs [312], the study also shows that most patients require involvement of specialist supportive care services, but we do not have data of how many actual had that. Early and systematic integration of supportive care into the clinical management of patients with PDAC has demonstrated improvements in survival outcomes, compared to consultations 'on demand' [178, 179]. Thus, monitoring patients QoL scales continuously and integration of early supportive care might pick up more subtle, but significant over time, symptoms that need more systematic management. Ultimately these symptoms have significant impact on QoL and survival of these patients and thus, monitoring and managing these needs to be emphasised in routine care of these patients.

Besides being the first study to assess patients' and physicians' views on patients on treatment outcomes in PDAC, to the best of our knowledge, this is also the first to link patients QoL scores with their views about treatment. As described in the results

section, the patients who prioritised OS over balance between QoL and OS, had worse symptomatic burden, constipation, appetite loss and borderline worse role functioning. However, these patients ended up having, on average, a shorter OS than the patients who prioritised balance. Taken together with the previously highlighted prognostic value of baseline PF and NV scales on OS of patients with PDAC, this highlights that baseline QoL questionnaires could be used also to help decision making and in guiding discussions with patients about treatment aims.

Although survival analysis was not the main aim of the current study, 61% of patients died during the study with a median OS of 3 months and the overall median OS at the time of final analysis was 7.39 months (95% CI 5.3-9.5 months). In contrast, the majority of patients expected their survival to be 1-5 or >5 years, indicating that the expected survival was longer than the actual survival. The mismatch between patients' expectations of survival length and actual survival has been shown in a previous study with a variety of different advanced cancers [323], but the actual survival of patients in that study was still 19-30 months depending on the type of cancer. As the average survival is so short in the current study, it is not known if "urgency" plays an additional role in patient decision making.

In order to assess possible institutional bias (this study was run in only one centre), we compared baseline physician responses from the current study to the results from the online survey of physicians treating PDAC in other centres in the UK. There were similar results in relation to expected life extension, minimal perceived important survival time, and the balance between side-effects and OS. In the online survey there was a higher number of physicians assuming patients would accept treatment if it would control symptoms of cancer, but would not extend survival (75% online, 46% in physicians T1) and this was more similar to the patients answers in T1 (67%- yes).

Previous research has shown that patients with advanced cancers might be able to cope with realism more over time [219], but it is not known how long this time would need to be. In the current study, no significant reductions were noted in patients' views about their prognosis. On the contrary, there was a trend towards patients expecting the chemotherapy to extend their life longer in the last survey (T3) than in the first one (T1). This could reflect the positive bias in our results, as only 51% of patients reached the third time point and all of them had SD or PR on CT imaging. Thus, they had received

positive results about the treatment effect and were potentially more hopeful about the continuation of this. Equally, it could highlight that patients get more desperate and want more time as time is passing by. The 46 patients who died during the study had a median OS (from T1) of 3 months indicating rapid disease progression prior to reaching the third survey (T3) that was on average 3.7 months from T1. As previously discussed, this highlights the normal clinical behaviour of PDAC which is known to be a very aggressive disease and resistant to treatment.

I also aimed to assess if there was a change in patients views due to treatment response in this study, but unfortunately this was not possible, as patients who deteriorated faster did not fill in the second or third surveys and patients who did, all had SD or PR on mid-treatment CT. Therefore, the effect of treatment response could have on patients' views about current and future treatment remains unknown.

Change in patient views due to time was however assessed, and in general, there were not many significant changes between different time points. Comparable results have been shown in one of the earliest studies, performed more than 30 years ago, assessing patients' attitudes towards chemotherapy (Slevin *et al* [231]), where 50% of patients who had a second survey after 3 months of palliative chemotherapy had no significant change in their views and were as likely to accept treatment, even with small chances of benefit. In the current study at each time point, around half of the patients were willing to accept large amounts of side-effects for minimal extra time and 67-78% were willing to accept treatment when it would control their symptoms, but would not extend their survival. Thus, our results are comparable to the previous research showing patients willingness to undergo treatment with small chances of benefit, after experiencing the effects of the treatment in question [190].

As described in chapter 1, large international oncology organisations such as ASCO [182] and ESMO [184] have defined clinically meaningful extension of survival as being at least 3 months in patients with advanced PDAC. In the results of the current study, only 18% of patients considered an extension of life by 3-6 months as important. Of course these numbers are not directly comparable, as the ASCO/ESMO expectations are looking at extension beyond current standard of care and reflect recommendations made by physicians, not patients, but this does highlight that patients expect much more than the current established treatments can deliver.

4.4.2 Discussion and limitations of the developed study questionnaire

As detailed in the methods chapter, the aim of this study was to explore and describe the views of patients with advanced pancreatic cancer and their physicians. As no previous studies have been undertaken in this specific topic, questions and themes from studies in other advanced cancers were used to formulate the basis of this questionnaire. Thus, in order to cover a wide variety of patient views and include comparable themes from previous studies, a wide range of questions were developed, and additional quality of life tools were used to capture both their views and how their quality of life can impact on those.

To limit the number of questions and topics in a survey, explorative qualitative studies are sometimes conducted to explore the patient experience first and then to develop the questionnaire based on those results. However, this step was not undertaken due to limited resources and lack of expertise in running qualitative research in the team. Instead, the study captured a wide range of topics that could later be selected for more specific studies to take forward.

4.4.2.1 Quality of the questionnaire

As discussed in the methods section, the quality of a questionnaire can be measured by looking at validity and reliability of the questionnaire. The standardised ways of measuring validity have been described in the methods section and can be divided into three parts: face validity, content validity and criterion validity [296].

RELEVANT study validity

During the pretesting phase of the study development, the face validity of the questionnaire was assessed by subject matter and survey methodology experts, patient representatives, funding body representatives and the research ethics committee. Details of the changes to the questionnaire based on pretesting findings can be found in the pretesting section under methods.

Content validity assessment for these types of questionnaires can be performed by content experts assessing the relevance of each question to the overall construct and then Content Validity Index (CVI), also known as proportion agreement method, is used

to analyse the average of all questions that were ranked as high level relevance (usually 3-4 on a Likert scale) [4, 5]. No formal content validity assessment was done in the development phase of this study, as the questionnaire went through multiple revisions during pretesting, and so relevance of the questions was assessed informally. If future studies are planned with this questionnaire, formal assessment and calculation of content validity should be built into the survey improvement plans (discussed in detail later in the *Future development of the questionnaire* section).

Criterion validity assessment for this questionnaire was not possible as no prior questionnaires on this specific topic were available. Additionally, as developing a validated tool was not the aim of this study, assessing criterion validity at this time was not deemed necessary, but could be looked at in the future development of the questionnaire.

RELEVANT study reliability

As this study did not have interviewers administering the questionnaire, analysis of interobserver reliability was not required. The questionnaire was administered to participants at three timepoints. Thus, test-retest reliability could be measured for the study. However, as one of the aims of the study was to see how patients' views change over the course of treatment, the baseline assumption was that there would be a change in answers. For this reason, this method was not used to analyse the internal reliability.

The questionnaire constructed for this study is heterogeneous, consisting of different questions about a patient's previous experience, current effect on everyday life and views about treatment outcomes. Thus, the internal reliability of the questionnaire cannot be measured using the split-half method, but it could be analysed by assessing questions that are asking about the same concept and have similar answer options [296], as described below.

For example, when I analysed reliability of the whole questionnaire using Cronbach's Alpha method, the alpha (α) = -.018; a negative value due to a negative average covariance among items, as this questionnaire violates reliability model assumptions. The assumptions for using reliability analysis are: 1) normality; 2) cardinality; 3) Tau-equivalence (unidimensionality of the scale items) [324, 325]. Thus, in order to analyse

internal reliability of this questionnaire, only questions that are measuring the same concept and have the same scale answer options can be used [307].

For this reason, only questions 20-22 from the patient questionnaires (*20. As far as you understand, how likely is your treatment to cure the cancer? 21. How likely is your cancer to respond to chemotherapy? 22. How likely is chemotherapy to give you a longer life?)* could be used for the analysis, as these ask about similar concepts and were all in the same 5 point Likert scale (*not at all likely, slightly likely, moderately likely, very likely, completely likely*). In general, it is recommended that α should be higher than 0.70 when used for research settings, >0.80 for applied settings and >0.90 for high-stake clinical or diagnostic purposes [326].

The reliability analysis using Cronbach's Alpha on these three items show α = 0.546. Interestingly, as shown in table 4.2 below, if question 20 was removed, then the α would be higher at 0.811. This is potentially due to the fact that Q20 asks about the likelihood of cure, whilst Q21 and Q22 ask about the likelihood of treatment response, which is a slightly different concept. The difference in answers can also be seen in the mean score and SD of the items, where Q20 has lower mean and SD (indicating lower likelihood and higher variability) than the other two questions.

Table 4.2. Item statistics for reliability analysis of questions 20-22.

Questions	N	Mean	Standard Deviation	Cronbach's Alpha if item deleted
Q20	57	2.14	1.797	0.811
Q21	57	3.30	0.844	0.291
Q22	57	3.40	0.842	0.412

N-number, Q-question.

The QLQ-C30 questionnaire [293] used to assess quality of life in this study, is already a validated tool and has gone through the full 4 level international validation. Thus, it was expected that reliability of this questionnaire would be high. To assess this, I similarly analysed the QLQ-C30 answers from the study patients (baseline) with the Cronbach's Alpha method and removed questions 29-30 as these are on a 7 point scale not a 4 point scale as the other questions [294]. For the 28 items on the QLQ-C30, the α = 0.938 indicating high reliability of this tool for clinical purposes.

In conclusion, an internal reliability analysis was carried out on this developed questionnaire that showed that when analysing all items, the items violate the reliability analysis assumptions. When the analysis included only the 3 similar items, the questionnaire did not reach acceptable (α >0.7) reliability. However, if item 20 was removed, this could increase the α to 0.811 and reach acceptable reliability. As such, if validation of this questionnaire is planned in the future, the item Q20 could be removed or re-worded. Similarly, in order to validate the whole questionnaire, the questions would need to be put in similar format and scale (e.g. 5-point Likert scale) with unidimensional answers. As expected, the QLQ-C30 showed high internal reliability as a validated tool.

4.4.2.2 Item nonresponse

As highlighted in the study development chapter, self-administered questionnaires can have issues with missing answers and responders deliberately (because they do not wish to answer) or accidently not filling in the questionnaire correctly. To understand the impact missing answers could have on the current study, any question that was missed by >10% of respondents at any time point was reviewed. In the physician questionnaires, there were no questions that were missed for >10% of the respondents thus, data about physician questionnaires are not included here.

Table 4.3. Questions with at least 10% missing answers at T1, T2, T3.

	Missing answers	Questions
T1 (65 patients)	Q 21=8 (12.3%) Q 23=8 (12.3%) Q 24=9 (13.8%) Q 25C=8 (12.3%) Q 26C=7 (10.8%)	**Q21.** How likely is your cancer to respond to chemotherapy? **Q23.** How long do you expect chemotherapy to extend your life by? **Q24.** What minimal extra time would you consider to be important for you? **Q25C.** Based on the answer you gave to question number 24, we would like to know if you would be willing to accept large amount of side-effects as a trade-off for that amount of extra time? **Q26C.** Based on the answer you gave to question number 24, if that time was doubled, would be willing to accept large amount of side-effects as a trade-off for that amount of extra time? **Q27.** Would you accept chemotherapy if it controlled symptoms but did not extend your survival?
T2 (39 patients)	Q 23=6 (15.4%) Q 24= 6 (15.4%) Q 26C=6 (15.4%) Q 27=5 (12.8%).	
T3 (36 patients)	Q 23=7 (19.4%) Q 24= 4 (11.1%) Q 26C=4 (11.1%)	

As seen in Table 4.3, at T1 there were a maximum of 9 patients who did not answer the question about minimal extra time; at T2 the least answered questions were 23, 24 and 26C asking about time and trading off large amount of side-effects for time; and at T3 the least answered question was about the length of life extension. This shows that the most missed questions were the sensitive ones (inquiring about a sensitive topic like prognosis), especially Q23-24 asking about the expected or minimally important time (missed by >10% at each time point) that patients probably did not want to answer. As discussed in the methods chapter, this is a common problem with sensitive questions [282, 292, 327]. In general, SAQ are more confidential and respondents are more likely to give answers to sensitive questions [327], but previous research has also shown that there are a couple of ways to improve respondents willingness to answer sensitive questions in surveys. One possibility would be to have the sensitive questions later in the questionnaire [282], so that the respondents are more motivated by the easier questions in the beginning and if they still do not want to answer the sensitive questions, at least the first part of the survey is filled in. This method was already used in the development phase of this study and all sensitive questions were placed at the end of the questionnaire. Another approach is to increase the respondents' trust by making the method as confidential as possible [327], in the current study this could have been done by respondents sealing the questionnaire in an envelope or using computer-assisted techniques. Envelopes were used in this study occasionally if the study team was not in clinic and patients had to leave the filled questionnaires in a specific clinic area. However, we did not assess if this increased their likelihood of answering the sensitive questions. Computer-assisted versions of the questionnaire were not used, as this would have required more resources and potentially complicated data collection, but definitely this is an area that could be evaluated in the future as it would allow us to make questions mandatory and potentially have less issues with item nonresponse. However, this could also increase the number of questionnaires that are not finished [282], and data from earlier questions being lost if patients really do not want to answer these questions.

Impact of item nonresponse to the results

It is not possible to know the actual impact that item nonresponse can have on the study results. It is interesting that the questions most missed (Q23-24) were about prognosis and time, highlighting that this is potentially something patients do not want to think about or answer which could be a sign that they are more worried about it. As discussed earlier in the results section, there was an increase of patients opinions about the minimally important time (at T2) and the expected time (at T3) whilst 15.4% and 19.4% of patients did not answer those questions at those time points, respectively. It is not known if these patients who did not answer questions had different views, but we can see that there were continuously around 6-9 patients at any time point who did not want to answer these questions.

Imputing

In the case of item nonresponse, an imputation procedure could also be carried out where the missing value would be replaced by a synthetic value [282]. The new value is calculated based on an imputing technique or model using all the available information from other questions. At times, a reasonable approximation of the correct value can be determined by the imputation procedure, but other times it is not possible to impute the value based on answers to other questions, and the value is just replaced with "unknown"[281, 282].

In the data cleaning stage of the current study, imputation was used only in the analysis of QLQ-C30 and PAN26, based on the standardised guidance from the EORTC QLQ-C30 Scoring Manual [294]. Based on this, individual nonresponse items could be imputed if these were part of a multi-item scale and at least half of the items from the scale had been answered. A simple imputing technique of averaging the other items that were filled in for that respondent for that scale [294], was used to impute the synthetic value in these validated questionnaires.

Imputing items of nonresponse for the developed survey was not thought to be appropriate in this study, as very few questions asked about similar topics, and there was no indication of which answers to previous questions could be used for imputation. Furthermore, there was no clear need for imputing missing data, as this was an exploratory study.

Questions not answered correctly

There were also some questions in the developed questionnaire that were not filled in correctly. These were mainly the questions where patients were asked to rank options (Q14, 16 and 19) and were often answered incorrectly using the same number multiple times (e.g. instead of ranking from 1-10, patients ranked multiple items as 1). This was picked up during the study accrual and based on the discussion with survey development expert (Prof Janelle Yorke), the wording of these questions was amended (non-substantial amendment 1) to include all ranking options. In the data cleaning process, we included all data that was indicative of the intent or importance (e.g. if multiple items were ranked as 1 but others as 10, this was indicative that 1 was more important to the patient than 10).

There could be various ways of improving these questions in the future, for example, patients could be asked importance of each side-effect based on a 5-point scale, rather than ranking them all from 1-10. Or if this questionnaire was computer-assisted, it would visually be easier to make the ranking task more understandable to patients. Thus, these options could be used in the future to make these questions more clear for patients.

4.4.2.3 Missing patients

As discussed in the results section, only 55% of the patients who consented to the trial filled in T2 and 51% the T3 questionnaire. This showed that there were a large number of patients who deteriorated or died, mainly between T1 and T2. This drop-out rate could be causing an inherent positive bias in the study results, as patients whose disease progressed, often did not return to clinic to fill in the surveys, whilst patients who were doing better filled in the survey at other timepoints. To understand if the patients who deteriorated or died before filling in another survey were different from the patients who made it to another time point, I compared their baseline quality of life, performance status and treatment received.

Patients who filled in at least one other questionnaire had higher (better) physical functioning at baseline (76.5 compared to 64.6p, p=0.037) compared to patients who did not reach T2/T3. There was also a statistically significant difference (p=0.0001) between treatments received by these two groups: patients who did not fill in T2/T3 had on average less aggressive treatment (monotherapy=34.6%, dual=34.61%, triple=11.5%,

none=19.2%) compared to the group who did make it to the other timepoints (mono=15.6%, dual=40%, triple=44.4%). No difference in ECOG performance status was found between the groups (p=0.164), and patients who did not fill in T2/T3 had an average survival of 2.17 months from T1 (T2 was on average 2.3 months from T1 for patients who filled it in). This highlights that these patients were potentially worse off in the beginning. It is especially interesting that they had less aggressive treatment and worse PF, but no difference in ECOG which could mean that whilst their performance status was still good, their functioning was deteriorating and potentially influenced the decision to give less aggressive treatment. A recent study by Mackay *et al* showed similarly that in their cohort of 109 patients with advanced (unresectable) PDAC or peri-ampullary cancer, lower PF score at baseline was associated with worse OS [322].

In a recent presentation, the large prospective registry study QOLIXANE showed similar drop-out rates in their cohort of 600 patients with metastatic pancreatic cancer who started first line chemotherapy with Gemcitabine and Nab-Paclitaxel in 95 centres in Germany [160]. Patients in this study were asked to fill in QLQ-C30 at baseline and every month during their treatment. The results showed that whilst 80% filled baseline and one other time point, only 49% patients filled in the baseline and at 3 months, and 28% the baseline and 6 month questionnaire. This again demonstrates the potential for rapid deterioration of these patients and highlights the challenges to achieving questionnaire completion at later time points.

Around 45% of the patients in the current study did not fill in the subsequent questionnaire and it is unclear if anything could have been done to improve that. Options would be to choose another mode of study when patients do not return to clinic- telephone or by post (mixed-mode). However, as discussed earlier in the methods chapter, one of the main issues with sensitive questions is that respondents are less likely to answer these if there is an interviewer present [281, 284, 327] and equally in the case of this study it would be worrying to ask questions about prognosis from patients who are too unwell to come to clinic, as this might upset them and we would not be able to support them at home with this extra distress. Equally, it was shown that the patients who did not make it to T2 died prior to the average time other patients filled in the T2 questionnaire (2.17 compared to 2.3 months). In addition to these issues,

sending the questionnaire by post would have additional issues with low response rates, especially if these included sensitive questions [282].

Another option would be to ask their caregiver or next of kin to fill in the questionnaire instead of the patient. However, it has previously been shown that patients and their caregivers have different views about treatment and prognosis [190, 211, 328]. Including caregivers would thus introduce a third variable when assessing views about treatment, and as the study was aimed at comparing the views of patients and physicians at the same time point, this approach was not used. Additionally, when the study was initially designed, we did not expect this drop-out rate prior to 3 months as the median OS of these patients should be around 6-11 months and it was expected that at T3 (around 3 months from start of treatment) there would be a higher rate of patients filling in the questionnaire. Thus, we did not take into account the possibility of having to contact patients by other modes or their caregivers, and did not write this option into the study protocol or ethics application. One option to improve this in the future would be to ask patients to fill in these questions more frequently and continue this for a longer period (until disease progression or death), to asses if there is anything specific about the views of patients who live longer and have better treatment responses.

In conclusion, drop-out is a common problem in the setting of advanced pancreatic cancer due to patients rapidly deteriorating [160], and similar results were seen in this study with just over half of the patients reaching another time point. Patients who did not reach another time point in this study had worse physical functioning and less aggressive treatment at baseline. Future studies could include shorter intervals between surveys and potentially introduce a caregiver view from the beginning.

4.4.3 Additional general study limitations

Limitations have been discussed in previous sections; in addition, another potential limitation of this prospective questionnaire study was that it included 83 questions (27 from the developed survey and 56 from QLQ-C30/PAN26) and this amount of questions might lead to questionnaire fatigue [281, 282], especially if patients need to fill this in at multiple time points. One of the reasons for this was that no studies had been done on this patient group of advanced pancreatic cancer and thus, we aimed to cover a wide range of topics and patient views in this exploratory study, to describe this patient group. Nevertheless, we did not take into account that it could lead to questionnaire

fatigue and impact on patents willingness to fill in the surveys. In future studies, the questions should be limited to include only the relevant areas from this survey that we would like to investigate further, especially as the general wellbeing of respondents can also impact on their willingness to fill in surveys, and we showed in this study that the symptom burden was high in this patient group.

Another potential limitation of the study was using nonprobability sampling instead of probability sampling (explained more in detail under the study development chapter) that has an unknown effect on the generalisability of the results. As discussed earlier, probability sampling would have been a challenge to execute as these require much larger sample sizes, cost, time and resources. Additionally, we would have needed to acquire a full sampling frame of all patients recently diagnosed with advanced pancreatic cancer in the UK and their contact information, which would be almost impossible to get in a timely manner. We hoped to reduce the potential institutional bias by recruiting all patients recently diagnosed with advanced pancreas cancer seen in the Christie over a one year period, and by comparing our physician answers to physicians treating patients with PDAC in other centres in the UK. There were no significant differences between The Christie and online survey physicians' answers. In other studies, non-probability sampling is often more time-efficient and cost-effective, does not show any significant differences between respondents [301] and is often used when assessing cancer patients views [329, 330].

Nonetheless, the results of this study demonstrate that there is a mismatch between patient and physician views about the aims, priorities and expected benefit from the treatment of PDAC.

4.4.4 Future development of the questionnaire

As discussed in previous sections, there were some areas where the developed questionnaire could be improved. These included the length and breadth of the study, answer scales, ranking questions, frequency of the follow up surveys and the drop-out rates.

Length and breadth of the study

Based on the results of the current study, we are now able to remove some of the wider questions that were included to describe the patient group, but were not focused on

views about outcomes. This would help to avoid questionnaire fatigue in these patients, especially as their wellbeing turned out to be quite poor and that can put extra limitations on their willingness to take part in these types of studies. Thus, some of the questions about the background (Q 2, 3, 4,5, 6, 7) and impact on patients' daily life (9, 10, 11, 15) could be removed, as this study already gathered that information. Equally, it would also be important to see if all QLQ-C30 and PAN26 questions are necessary to include. Based on the results of the study, the main important aspects worth keeping would be around physical functioning, QoL and future worries. These questionnaires are not good at measuring anxiety or depression thus, it might be worth including other relevant questions rather than all the questions about symptom scales. One of the options would be to include the Hospital Anxiety and Depression Scale (HADS) [331] that has been used in pancreatic cancer [332] to measure anxiety and depression specifically. To limit the general quality of life questions, it might be worth including the EORTC QLQ-C15-PAL which is a 15 item shortened version of QLQ-C30 aimed at measuring QoL in the palliative care setting, but includes the main questions from QLQ-C30 [333]. One of the more recent developments from the EORTC Quality of Life Group (QLG) is the Item Library [334], which allows to add missing questions about specific symptoms or problems from the item library to the modules. This way researchers could pick the additional questions they want to include, instead of using the whole tool, and that way limit the number of additional questions.

Question format

The questionnaire development of this study did not take into account the need for formal testing of validity and reliability. The results have shown important differences between patient and physician views. The future development of the questionnaire should also include question and answer formats that could ease the assessment of the quality of the survey. Thus, the questions and answers should be altered to have similar format and answer scales (e.g. 5-point Likert) with unidimensional answers (e.g. from *not at all likely* to *very likely*). This way the correlation between questions and the reliability could be more easily calculated. The ranking questions could also be transformed to a Likert scale to ease the analysis and interpretation.

Mode of the questionnaire

To improve patient retention, other modes could be used or added (mixed-mode) in the next stage to avoid the dropout rate. The pros and cons of using SAQ and computer-assisted questionnaires (CAQ) has been discussed earlier. The most important aspect of this questionnaire is the sensitive questions thus, the mode needs to be the one most supportive of that, and probably not include interviewers. The obvious additional difference between SAQ and CAQ are the resources needed, including the technology (laptop, tablet) and technical support (available if patients unable to fill these in). Whilst CAQ could be more easily also sent to patients, it does not always improve the response rates in questionnaires [282]. Thus, the decision between using SAQ or CAQ could be based on the resources available at the start of the study.

The other aspect of the mode is whether interviews or other qualitative methods could be used to gather more in-depth results of the reasons behind the differences in patients' and physicians' views. A qualitative approach could also be used in order to understand what the potential solutions or next steps would be, both from the patients' perspective and physicians. For example, focus groups could be used to map out what the two groups think could help mitigate the differences that the study found. The clinical relevance of the study is further described in the next section, but it would also be useful to check if the planned solutions would truly be useful for patients. Thus, one option would be to conduct focus groups with both patients and physicians, present the results of the current study and then have a structured discussion about the potential solutions. This approach would need involvement of additional researchers with expertise in running qualitative studies, but could give valuable data for the future steps.

Regardless of the mode used, the frequency of the follow-up surveys should probably be increased to have more regular mapping of changes and potentially lose less patients to follow-up. The QOLIXANE [160] study showed that even monthly questionnaires had quite high drop-out rates, but around 80% of patients filled in one other questionnaire thus, having more frequent and longer term (past 3 months) follow-up surveys might help capture the data better.

4.5 Study conclusions and clinical relevance

In this prospective questionnaire study, over 1 year period, I recruited 71 patients with 39 patients reaching the T2 time point and 36 patients the T3. The patient and physician answers showed important differences between their views about treatment and expected outcomes.

In general, there were similar views between patients and physicians in the acceptability of chemotherapy side-effects and prioritising patients' goals. However, most patients had personal goals that they wanted to reach with the help of treatment, but majority of physicians were not aware of these. Patients were more optimistic about the likelihood of chemotherapy prolonging their life or curing their cancer.

One of the main significant findings of this study is that patients largely overestimated the length of time chemotherapy is expected to extend their life by, and there was very little overlap in this time compared to physician expectations ($p<0.001$). This was further highlighted in the minimal extra survival time that patients thought would be meaningful to them. Instead of having a more realistic understanding of prognosis over time, the patients' life extension expectations increased over time, as seen at the third time point. This could indicate both hope for the continued success of chemotherapy and fear of running out of time and wanting more. Similar to previous research that has shown that unrealistic views about prognosis can lead to depression, anxiety and more aggressive decisions about further treatment, it was shown in this study that the patients are already very worried about the future. Worries about side-effects significantly worsened over time and emotional functioning was worse than the clinically significant threshold at T2. As discussed in the introduction, giving prognostic information in an open and realistic way whilst assuring patient about non-abandonment significantly reduced patients uncertainty and anxiety. Importantly in the current study only around half of patients had documented prognosis discussions within the first month of their palliative treatment. Thus, whilst worry and unrealistic views were present in most of the patients, the results highlight the importance of improving communication about prognosis and other difficult topics with patients, giving realistic hope and offer psychosocial support where needed.

Another significant finding ($p<0.001$) observed between patients and physicians views was that when making decisions about treatment options, patients prioritised length of survival, while physicians thought patients would prioritise the best balance between side-effects and survival. This discrepancy could lead to problems, as the majority of patients wanted to be an equal partner in the decision-making process about treatment, but both sides seem to have a different priority in mind. In clinical practice, this means that there needs to be more candid conversations about the aims and priorities of treatment so that there is better understanding between both sides. As previous research has shown, patients with cancer will probably always accept treatment with lower chances of benefit, compared to any other group, and interestingly in this study patients prioritised length of survival even over balancing of side-effects and survival. This may suggest that they are worried about running out of time and might benefit from psychosocial support services. Nevertheless, there should be more emphasis on discussing quality of life and offering symptom management support to all patients with advanced pancreatic cancer, as this study demonstrated significant issues for patients with symptoms and side-effects, and offering the support services available to patients might at least highlight to patients that this is of equal importance.

Trying to bridge the gap between patient and physician views with regards to treatment aims and expectations, and taking into account patient worries and goals, are also essential to ensure the delivery of patient-centred care [201, 202].

In conclusion, in this study, patients with advanced pancreatic cancer can be described as having significantly higher hopes for treatment and life extension compared to their physicians, and they also have a lot of fear and worry about the future and poor symptoms and quality of life. As a solution, there should be more candid discussions about prognosis, outcomes and patients' goals and easier access to psychosocial support services.

Future topics

There were some topics that emerged from this study and the literature around it, that would be interesting to explore in the future:

- **Treatment effect impact on patients' views**. We were unable to assess the effect of treatment success/failure on patients' views as all the patients who reached

T3 in our study had SD or PR on CT. This still remains an interesting topic for future research, as there is a need to understand if patients' views become more realistic or not. Knowing this would help physicians tailor their discussions with patients at those important time-points or lead to potentially offering additional support services (for example, physiological or palliative care).

- **Patients view on "was treatment worth it".** Visser *et at* [193] published a study in 2018 using the Cancer Therapy Satisfaction Questionnaire in patients with advanced lung cancer, highlighting interesting results about the majority of patients thinking chemotherapy was worth it, even if they had large amount of side-effects or their QoL deteriorated. This would be an interesting topic to assess in patients with advanced PDAC, in light of the results of the current study, where we showed that patients functioning and symptoms deteriorated between the time points. Additionally, FOLFIRINOX chemotherapy is associated with large amount of toxicities and patients with PDAC can progress very rapidly, leaving physicians often thinking if it was worth giving patients "aggressive" treatment. Knowing what patients think of this would better inform discussions about treatment options between physicians and patients.

- **Does "urgency" play a role in patients' decision making?** The majority of previous research on patients' views about treatment has been in various other advanced cancers where the prognosis is still limited but is considerably longer than in patients with PDAC. Thus, it would be fascinating to see if there is a difference in patient decision making abilities or their views about treatment outcomes, due to this "urgency". For example, a survey could be developed for assessing this in two newly diagnosed cancer groups: 1) patients with advanced colorectal or lung cancer (known to have longer prognosis compared to PDAC), 2) patients with advanced PDAC (or also other cancers with short prognosis). The aim would be to see if there is something specific about patients' views in the latter group. As discussed earlier, it is not known if longer time is needed for patients to become more realistic about their prognosis or how the acceptance of treatment side-effects changes when patients have been on treatment for longer.

4.6 Chapter conclusion

In conclusion, the results of this study demonstrate that while most patients are aware that chemotherapy is unlikely to cure their cancer, there are discrepancies between patient and physicians' views about the aims, priorities and expected extension of life. The findings of this study will educate the treating clinical community as to the importance of establishing patients' goals of care and priorities at the beginning and during their treatment. It also highlights the need of offering psychosocial support and candid conversations as patients were found to have a lot of worry and fear about the future and high symptomatic burden. Future studies may explore the best strategies to overcome these challenges and barriers and help find solutions that the patients would value the most. As these discrepancies between patients and physicians' views can have clinical implications, highlighting these and dealing with them early on, would be another marginal change whereby patients' outcomes could be improved.

Chapter 5: Final Discussion

5.1 Improving outcomes in patients with a diagnosis of pancreatic cancer

In the US and UK, PDAC is the 3rd [5] and 5th [4] leading cause of cancer-related death, respectively, and is projected to become the 2nd by 2030 [40]. The management of patients with PDAC is complex and challenging as the majority are still diagnosed late and have a prognosis measured in months [181]. Even for the small subgroup of patients treated as early-stage disease, the risk of relapse after curative surgery and aggressive adjuvant treatment remains very high [11].

Intensive clinical and translational research are in progress to develop strategies aiming to provide clinically meaningful gain in survival outcomes for patients with PDAC. Most of such efforts are focused on identifying therapeutically exploitable molecular targets and novel matched compounds. However, complementary approaches aimed at optimising control on cancer-related systemic alterations (e.g. biochemical/hormonal imbalances, cachexia, pain, fatigue), which have proven to positively impact on cancer patient outcomes - both QoL and OS [142, 174], have been less extensively explored in PDAC. Furthermore, other aspects of patient-centred care such as patients views on treatment, prognostic communication and emotional support are similarly known to affect outcomes [195, 213, 214], and yet only marginally investigated in PDAC. This is particularly important in patients with PDAC who are known to have high disease burden and short survival, making it crucial to adequately address patient holistic needs in addition to extending OS duration.

In this thesis, I investigated two areas where progress could be made (Figure 5.1): uncontrolled hyperglycaemia, and unmet patient expectations; both of which have a significant impact on QoL and survival in patients with PDAC. These present opportunities for medical interventions that can be easily implemented in clinical practice alongside the delivery of anti-cancer treatment and ultimately lead to meaningful improvement in survival outcomes in patients with PDAC.

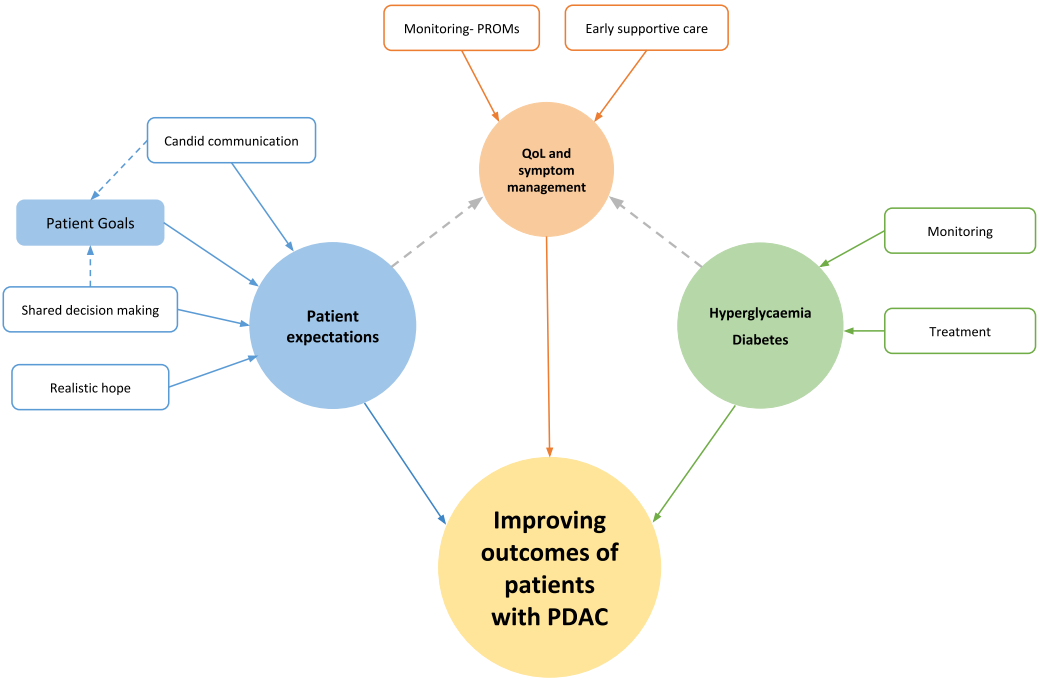


Figure 5.1. Proposed areas where progress could be made to improve outcomes of patients with PDAC.

5.2 Hyperglycaemia as a potential prognostic biomarker in patients with PDAC

Hyperglycaemia in patients with PDAC is hypothesised to be of paraneoplastic origin [88]. There are two theories as to how a better glucose control could lead to improved outcomes in patients with PDAC. Firstly, less hyperglycaemia-related symptoms favourably impact on the QoL of these patients who already have high disease-related symptomatic burden [159], and therefore provides a better chance for them to continue on anticancer treatment for longer. Secondly, if hyperglycaemia is needed for PDAC proliferation and growth, then a better glucose control might also lead to improved cancer control [88].

In chapter 2 of this thesis, I presented results about the interaction between hyperglycaemia and patient outcomes that indicated that high GlucMin (the lowest plasma glucose measured per patient ever, including baseline and during treatment) is significantly associated with shorter OS, and that antidiabetic treatment in patients with high baseline glucose is associated with longer OS. This is especially important as I demonstrated that hyperglycaemia is indeed a widespread issue in patients with PDAC,

with around 63% of patients having abnormal glucose levels (>8mmol/L), in line with previous research [103].

To the best of our knowledge, this study provides the first signal that a better glucose control in patients with PDAC in a real-life setting could lead to longer OS. The next step will be to validate these findings in a prospective observational study and a trial concept was proposed for this in chapter 2. This will allow a more thorough and consistent evaluation of glucose control-related parameters (fasting glucose, HbA1c, albumin etc), determine the use of HbA1c as a surrogate for GlucMin and a more rigorous collection of clinical data, including anti-diabetic treatment. If proven to be a prognostic biomarker in this validation study, glucose monitoring and associated management could be routinely instituted in clinical practice. The second important question to come from this data is to understand if tighter glucose control would lead to improved survival of these patients and similarly, ideas for this randomised future study, were discussed in chapter 2. Compared to novel anticancer treatments, it is important to also note that antidiabetic treatment is relatively easy and inexpensive, and there is a lot of experience in treating diabetes in the community. The development and clinical use of continuous glucose monitors is another area where technological advances could improve our knowledge of how hyperglycaemia impacts on quality of life and survival of these patients and for this reason, I proposed that these could to be part of the future validation study.

In conclusion, I have demonstrated in chapter 2 that hyperglycaemia has a negative impact on patient survival outcomes, and whilst these results need validation in a prospective study, monitoring glucose levels could be readily implemented in clinical practice. Additionally, there is a signal that the use of antidiabetic treatment may result in better outcomes through better glucose control, either by less associated symptoms and better quality of life, or by inhibiting the proliferation of the tumour.

5.3 Symptomatic burden and quality of life of patients with PDAC

In chapter 3-4, I showed the development and results of the RELEVANT study, a prospective longitudinal questionnaire study with the primary objective of evaluating patients' and physicians' views on pancreatic cancer diagnosis, treatments given,

patient's goals and meaningful outcomes. This is the first study in patients with PDAC trying to understand what the known short survival outcomes mean to patients, how they make decisions about treatments and what is important to them. Patients views were compared to their physicians to understand if the two sides have any important differences in views and the study also monitored patients QoL and for the first time linked QoL with patients' decisions about treatment.

The RELEVANT study is a prospective investigator-designed questionnaire study comprising a purposely built survey assessing patients' and physicians' views about outcomes in conjunction with two validated tools measuring quality of life.

At the pre-determined study endpoint at 1 year, I had recruited 71 patients (36 patients reached the complete follow-up at T3) and 12 physicians. From the two validated QoL tools used in this study (QLQ-C30 + PAN26), I found that most patients had significant issues with symptoms, functions, and quality of life. The Global Health Status/QoL scale was constantly low indicating poor quality of life for most patients (57.3, 48.7 and 63.6 out of 100 at time-points T1, T2 and T3 respectively; higher scores being indicative of better quality of life). In accordance to the previously defined EORTC thresholds for clinical importance [310], results in my study indicated significant problems with physical functioning, fatigue, pain, nausea and vomiting and diarrhoea at all 3 time-points. In particular, at T2, patients also had worse role functioning, social functioning, emotional functioning, appetite loss, dyspnoea and financial difficulties. Additionally, the PAN26 questionnaire results revealed that our cohort of patients had worse pancreatic pain, digestive symptoms, altered bowel movements, body image, worries about the future and future activity planning, compared to a previous clinical trial [152] and psychometric validation study [311] of PAN26.

The worst scores throughout the time-points were for *worries about the future* (58, 65 and 53 out of 100; lower scores indicating less worry) and *future activity planning* (56, 60 and 49, out of 100; lower scores indicating less worry), indicating that these patients have high levels of fear and worry about the future. Previous research has shown that a change of at least 10-points between time-points corresponded to increased supportive care needs [312]. In this RELEVANT study, patients have indeed reported worsening of many of the symptom scales over time. This provides strong data to propose a system whereby closer monitoring of patients' self-reported QoL scales can

be done, thus allowing their care team to notice more subtle changes which may become significant over time and trigger the need for interventions.

Several studies have provided concordant evidence that the integration of early supportive care into the clinical management of patients with PDAC resulted in improvements in survival outcomes and less aggressive care towards the end of life [178-180]. Taken together, these studies reported that quality of life was significantly higher in patients who received early and systematic integration of palliative care, compared to palliative care consultations 'on demand'. Therefore, in order to manage the complex symptoms in patients with PDAC effectively, there needs to be a system for reliable and regular monitoring. As discussed in chapter 1, a previous study [174] with electronic monitoring of PROMs reported an improvement of OS by 5 months due to reporting of symptoms in real time and timely responses from nurses to address care needs [174]. Additionally, whilst the RELEVANT study showed that QoL scales were associated with patients' decisions about treatment and baseline QoL scales have previously been found to have prognostic effect on OS in patients with PDAC [160, 322], these questionnaires could be further used as a decision tool and to guide discussions with patients about treatment aims. Therefore, the results of the RELEVANT study provide further support for the implementation of (electronic) PROMs in routine clinical practice.

In summary, in chapter 4, the validated tools from the RELEVANT study provided systematically collected comprehensive longitudinal QoL data showing that patients with PDAC report consistently poor quality of life, and have significant symptoms and worry about the future. This provides an opportunity for close monitoring and early supportive care that could potentially lead to significant improvements in patient outcomes and help guide discussions between patients and physicians.

5.4 Patient expectations

The purposely-built survey of the RELEVANT study assessing patients' and physicians' views on treatment outcomes highlighted an important mismatch between patient and physician views regarding the aims, priorities and expected benefit from the treatment for advanced PDAC.

In general, patients and physicians had similar views about the acceptability of chemotherapy side-effects. However, patients in the study reported significant issues with symptoms, functions, and quality of life at all time points, and the symptoms they were already struggling with were ranked less acceptable by them. Of note, the need to travel for treatment and financial toxicities (that significantly worsened over time) also had a considerable impact on patients' everyday life. Whilst patients and physicians held similar views about patient priorities, most patients had personal or family goals that they wanted to reach with the help of treatment of which only a small number of physicians were aware of.

This discrepancy between patient and physicians views may have a deleterious effect, as previous research has shown in patients with various chronic diseases, that treatment adherence could be negatively impacted if patients and physicians goals do not align [335, 336]. Additionally, patients who achieve their goals have less anxiety and depression [319]. Previous studies have also shown that meaningful life events and relationships are sources of hope for patients with cancer [204]. The RELEVANT study also uncovered a significant mismatch in relation to patients and physicians having different priorities when making decisions about treatment; patients prioritised length of survival, while physicians thought patients would prioritise the best balance between side-effects and survival. The majority of patients wanted to be an equal partner in the decision-making process about treatment, but both sides seem to have a different priority in mind for these patients. Previous studies on this topic have asked physicians about what they would choose for themselves in similar situations [234], but in this study they were asked about what they think these individual patients would choose. This highlights that physicians may not be able to reliably predict what patients would choose as their main aim of treatment, revealing a difference in the understanding of the overall treatment goal. I also showed that the patients who prioritised survival (over balance between OS and QoL) were the ones who had worse symptoms and, in the end, had shorter survival indicating potentially how fear and worry about "running out of time" impacts their decisions about treatment aims.

Communicating prognosis and treatment information to a patient who has been recently diagnosed with PDAC, whilst remaining hopeful about the treatment is a challenge. The difference in aims in this aspect of patient care could lead to additional

communication and possibly compliance issues. Other studies have shown that there is something very specific about patients with cancer and their decision making that is different from their caregivers or people without cancer [189, 190]. Patients with cancer seem always more likely to be willing to undergo treatment with very small odds of benefit [190]. Interestingly, this was even true in patients who had had curative treatment for their cancer and were on follow-up. This suggests that the fear and worry that are associated with a cancer diagnosis and treatment, potentially have long-term psychological effects on people. This phenomenon was also reported when patients were asked if treatment was worth it, on completion [193], and even in patients who had more AEs and worse QoL, the majority would be willing to do it again [193]. Similar results were seen in the RELEVANT study where patients had high levels of worry about the future and compared to physicians, patients were more willing to accept large amounts of side-effects and undergo treatment, if it only controlled symptoms and did not extend survival.

One of the key findings from my study was that patients largely overestimated the expected life extension achievable with chemotherapy, and there was very little overlap in this predicted time compared to physician expectations. A similar mismatch was seen in the minimal extra survival time that patients thought would be meaningful to them. Of note, patients' expectations about prognosis did not become more realistic over time, but instead an increase in expected time was seen in the last time-point (T3). This could be both an indication of increased hope of continued success of treatment and a fear of running out of time. The mismatch regarding the expected life extension between patients and physicians could impact on patient decision making [195], and this was also observed in my study where patients who expected the chemotherapy to extend their life >5 years were more likely to choose length of survival as their primary aim of treatment. However, similarly to this previous study [195], patients with the widest mismatch in expected length of life did not actually end up living longer. Likewise, unrealistic views about prognosis have been previously linked to higher levels of depression and anxiety [319], both of which were also potentially present in my study where most patients had high levels of worry and large mismatch in expectations.

In clinical practice, there needs to be more candid conversations about prognosis, and the aims and priorities of treatment so that there is better understanding between

physicians and patients. The results of the RELEVANT study could also educate the treating community about the importance of communication between patients and physicians about encouraging realistic hope, targeted toward achievable goals [319]. In addition to depression, that is a significant problem in patients with PDAC [166], the current study has shown also significant worry and anxiety thus, it is important to have these conversations with patients about aims of treatment and their goals, as honest prognostic information has been shown to maintain hope even when the news is bad [225] and achieving personal goals is perceived as a source of hope by patients [204]. Additionally previous research has shown ways of giving prognostic information in a realistic and open way, tailored to the individual, is actually viewed as hope-giving by patients [219]. Thus, using these methods to deliver candid prognostic information and discuss achievable patient goals could result in less anxiety and worry, and improved QoL of patients. Because worry was so prevalent among patients included in this study, they might also benefit from psychosocial support services.

There should be more emphasis on discussing quality of life and offering early symptom management support to all patients with advanced pancreatic cancer, as this study demonstrated significant issues for patients with symptoms and side-effects, and offering the support services available to patients might at least highlight to patients that this is of equal importance.

In conclusion, differences were found between patient and physician views related to aims, priorities and expected extension of life in chapter 4 that could have implications on the patient decision-making process, quality of life and treatment compliance. Patients with cancer will probably always accept treatment with lower chances of benefit [190], compared to any other group and so coordinated efforts to improve communication and discussions about hope and achievable goals may lead to better QoL, more patient-centred care, better choices about treatment, better relationships with the medical team, and ultimately potentially better survival for these patients.

5.5 Putting the pieces together - future directions

Treatment of patients with advanced PDAC can be particularly complicated due to the presence of multiple simultaneous issues that need managing. Patients with PDAC may

experience weight loss/malnutrition, high symptomatic burden (including pain, nausea and appetite loss), impaired glucose tolerance, pancreatic exocrine insufficiency and other disease-related complications like jaundice and ascites. They are then given information about limited prognosis, complex treatment regimens and potential side-effects of treatment. Consequently, physicians may end up prioritising the cancer treatment and potentially neglect other co-existing problems, as has been shown previously in relation to diabetes [75, 274]. However, what was shown in this thesis and previous research is that the majority of these issues can have a negative impact on patients QoL and length of survival and thus, these should be similarly prioritised. This is especially important in patients with PDAC, as life-expectancy can be very short and symptom burden high.

One of the aims of the RELEVANT study (chapters 3-4) was to determine what is important to patients with PDAC during their treatment journey, and to enable a better understanding of the human aspect of this disease. It is important to note that spending time with family, less fatigue and added time are what patients valued most. Physicians perceived that patients would be more worried about side-effects of treatment, in addition to survival length, probably due to the detrimental effect these could have on patients QoL. Obviously, none of us can truly know what it feels like to face this devastating disease unless diagnosed with it, but it is comforting to observe that patients' and physicians' views aligned in some of the important priorities, like spending time with one's family or being able to socialise.

This thesis investigated often overlooked changes, that are clinically relevant, which could potentially lead to improvements in quality of life, or survival outcomes of patients with advanced PDAC. As illustrated in Figure 5.1, I propose that there are improvements that could be instituted quickly and effectively which I believe when adopted within standard of care management could lead to meaningful improvements in patient outcomes.

The research undertaken in this thesis highlights that there are currently some important shortcomings in management of these three elements in daily practice: QoL and symptoms, hyperglycaemia and diabetes, and evaluation and management of patient expectations. Whilst the results of the impact of hyperglycaemia on patient outcomes still needs to be prospectively validated, with the recommendations that I

proposed to all of these areas, there are clinically relevant changes that can be made for patients with PDAC more immediately. Physicians could improve communication about prognosis, promote achievable goals and explain priorities of treatment on a regular basis in a hope-giving way; all patients could have their blood glucose checked as a high risk group for developing diabetes and potentially more tightly controlled; and all patients symptoms would be dealt with early in their treatment journey; then I propose that these patients may have a better quality of life and potentially even longer survival.

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Appendices

Appendix 1: RELEVANT study protocol

Appendix 2: RELEVANT study Patient Information Sheet

Appendix 3: RELEVANT study Patients Informed Consent Form

Appendix 4: RELEVANT study patient survey

Appendix 5: RELEVANT study physician survey

Appendix 6: Pihlak R, Valle JW, McNamara MG (2017). Germline mutations in pancreatic cancer and potential new therapeutic options.

Appendix 7: Pihlak R, Weaver J MJ, Valle JW and McNamara MG (2018). Advances in molecular profiling and categorisation of pancreatic adenocarcinoma and the implications for therapy.

Appendix 8: Effects of random glucose levels on outcomes of patients with pancreatic ductal adenocarcinoma (poster).

Appendix 9: RELEVANT study: Patient and physician views on meaningful outcomes in advanced pancreatic ductal adenocarcinoma (poster).

Appendix 1: RELEVANT study protocol

RELEVANT study: Patient and physician perspectives on clinically-meaningful outcomes in advanced pancreatic cancer.

SPONSOR – The University of Manchester

REC number: 18/NW/0293

Christie study reference: 18_DOG03_442

Protocol

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This document describes the project and provides information about procedures.

The project will be conducted in compliance with the protocol, the Data Protection Act (DPA Z6364106), the Declaration of Helsinki, the Research Governance Framework (2005) and other regulatory requirements as appropriate.

Protocol Authorised by:

Name & Role	Site	Signature	Date
Dr Mairéad McNamara (Chief Investigator)	The Christie NHS Trust		
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List of Abbreviations

ECOG - Eastern Cooperative Oncology Group Performance Status

EORTC - European Organisation for Research and Treatment of Cancer

ESPAC-4 - European Study Group for Pancreatic Cancer 4 trial

FOLFIRI - 5-fluorouracil, leucovorin and irinotecan chemotherapy

FOLFIRINOX - 5-fluorouracil, leucovorin, irinotecan and oxaliplatin combination chemotherapy

GCP - Good Clinical Practice

GP - General Practitioner

HPB - Hepato- Pancreatico- Biliary

ICF - Informed Consent Form

OS - Overall survival

PARP - poly (ADP-ribose) polymerase

PDAC - Pancreatic Ductal Adenocarcinoma

PFS – Progression-Free Survival

PIS - Patient Information Sheet

PROMs - Patient-Reported Outcome Measures

REC - Research Ethics Committee

R&D - Research and Development

QoL - Quality of Life

QLQ-C30 - EORTC quality-of-life core questionnaire

QLQ-PAN26 - QLQ-C30 pancreatic cancer module

Project Summary

Title:	RELEVANT study: Patient and physician perspectives on clinically-meaningful outcomes in advanced pancreatic cancer.
Acronym:	RELEVANT
Design:	Observational questionnaire
Objectives:	To evaluate the views of patients' and physicians' on pancreatic cancer diagnosis, treatment, patient goals and meaningful outcomes. Views in relation to treatment response, side effects and changes over time will also be assessed.
Eligibility:	Patients: Patients with newly diagnosed advanced pancreatic ductal adenocarcinoma defined as unresectable cancer, seen at the Christie NHS Foundation Trust in the HPB new patient clinic. Satisfactory English language skills are required. Physicians: Physicians and nurse clinicians working in the hepatopancreaticobiliary new patient clinic at the Christie NHS Foundation Trust.
Planned sample size:	Approximately 150 patients (with paired physician responses) and approximately 10-12 physicians.
Project methods:	Patients will be given information in the HPB new patient clinic and will be consented during the following clinic visit. After consent, patients will be asked to complete the study survey and 2 validated quality of life questionnaires. A paired similar survey will also be given to their physician to complete in relation to the patient they have just seen. Patient participants will be requested to complete the survey and questionnaires again during treatment; following starting treatment (ideally after 2-3 months) and prior to their first treatment scan, and during the next clinic visit after their first scan. Physicians who see these patients in clinic on those time points are also asked to fill in the paired physician survey in clinic.
Project duration per participant:	For patients: Survey and questionnaires will take 10-15 minutes to complete at 3 different time points (before patient starts treatment, after the patient has started treatment (ideally after 2-3 months) prior to their first treatment scan, and after their first scan) and the time taken for completion of the survey by the physicians who see the patients will be 10 minutes at each time point. Each patient participant will remain in the study for approximately 4 months. Physicians can answer surveys in relation to different patient participants during the whole duration of the study.
Estimated total project duration:	9- 12 months

Background

Pancreatic cancer is the 10th most common cancer in the United Kingdom (UK) (2013) and 12th most common cancer in the United States (US) [4, 337]. Unfortunately, pancreatic ductal adenocarcinoma (PDAC) has also been shown to be the most lethal human malignancy with the worst 5-year overall survival (OS) compared to other types of cancer [6]. The 5-year OS of all stages is around 7.7% in the US [337], and 3% in England and Wales (2010-2011) [4]. Even for patients who have had potentially curative surgery who receive adjuvant chemotherapy (gemcitabine and capecitabine), the 5 year OS is 28.8% according to the most recently-reported data from the phase III randomised ESPAC-4 trial [10]. The longest OS reported for patients with metastatic disease was in the ACCORD clinical trial, where patients receiving the 5-fluorouracil and leucovorin, irinotecan, and oxaliplatin combination (FOLFIRINOX) had a median OS of 11.1 months [25]. In the MPACT clinical trial, the median OS for patients who received gemcitabine and nab-paclitaxel was 8.5 months [26]. Sadly, the majority of clinical trials recruiting patients with advanced pancreatic cancer over the past 5 years have failed to demonstrate a more significant clinically-meaningful benefit [27].

The prognosis for patients with pancreatic cancer is dismal. Due to short-lived treatment responses, pancreatic cancer is the 3rd and 5th most common cause of cancer death in the US and UK (2012) respectively, accounting for more than 5% of all deaths from cancer [4, 337], and is projected to become the second leading cause of cancer-related death by 2030 [40].

Some of the aggressive chemotherapy regimens used in the treatment of patients with pancreas cancer result in improved survival but at the expense of increased treatment-related toxicities [25]. When making their initial decisions regarding therapeutic management of their disease, patients may choose to receive treatments that will potentially result in better survival outcomes prior to experiencing the side effects. It is not known if patients may have made a different choice after experiencing the common side effects of the treatment, with the possible associated decreased quality of life.

Currently, patients' views vary greatly [189], and the reasons for this are unknown, it may be based on their previous contact with chemotherapy, either from a personal or family member perspective. Some patients are not willing to receive chemotherapy because they wish to continue experiencing the quality of life they currently have and not risk it with chemotherapy-induced adverse events.

Physicians often have different views on adverse events and quality of life than patients. Physicians may view treatment differently, possibly either under or over-estimating the potential for treatment benefit and adverse events.

According to Weeks at al [194], in a study of 1193 patients with stage IV colorectal or lung cancer, around 70-80% of patients had unrealistic expectations about the likelihood of chemotherapy curing their cancer, when they were receiving palliative chemotherapy. They also reported in one of their previous studies [195] that patients who thought they were going to live for at least 6 months were more likely to favour life-extending therapies compared to comfort care, and in turn were more likely to undergo aggressive treatment. In this study, there was no difference in 6 month survival between patients who had aggressive treatment and those who opted for comfort care.

While some patients may have unrealistic perceptions of prognosis, it is still not known what difference in survival would be meaningful to them. In pancreatic cancer, the median survival of all patients with advanced pancreas cancer is around 6 months [181], therefore many patients are already in their last months of life when they are first seen by an oncologist. McCarthy et al reported that patients at the end of life with different solid tumours rightfully preferred comfort care over life-extending therapies [198], but that is probably only true if patients are aware of their poor prognosis.

In this study, it is planned to evaluate patients' and physicians' views on pancreatic cancer diagnosis, treatment received and patient's goals, in an effort to understand what would be a meaningful outcome from treatment for these patients. Views in relation to treatment response, side effects and changes over time will also be assessed in addition to discrepancies between patient and physician responses.

Project Objectives

- Primary objective: To evaluate patients' and physicians' views on pancreatic cancer diagnosis, treatments given, patient's goals and meaningful outcomes.

- Secondary objective: To provide a descriptive analysis of the change in these views in relation to treatment response, side effects and changes over time.

Project Design

This is a non-commercial questionnaire project which aims to evaluate patient and physician views on pancreatic cancer diagnosis, treatments received and patient's goals, with the ultimate aim being to determine what is meaningful to patients.
Patients will be given information in the HPB new patient clinic and consented during the following visit. After consent, patients will be requested to complete the study survey and 2 validated quality of life questionnaires (EORTC QLQ-C30 and PAN26). A similar survey will also be given to a physician who has seen them in clinic during that same visit for completion. The same process will be repeated after the patient has started treatment (at least one dose of chemotherapy, ideally after 2-3 months) prior to their first treatment scan, and after their first scan, for both patient and physician participants. If the patients have to stop treatment early and are not having a scan, they are also asked to complete these forms as time point 3.

Patient Participant inclusion criteria

- Patients with newly diagnosed advanced pancreatic cancers seen at the Christie NHS Foundation Trust in the HPB new patients' clinic.
- Advanced pancreatic cancer in this setting means all patients with unresectable pancreatic cancer whose treatment aim is palliative.
- Satisfactory English language skills are required.

Physician inclusion criteria

Physician or nurse clinician who sees patients in the Hepatopancreaticobiliary clinic in the Christie NHS Foundation Trust.

Patient Participant exclusion criteria

- Patients who are not fit enough for anticancer treatment.
- Patients where surveillance is planned instead of anticancer treatment.

Project procedure

For patients:

Potentially eligible patients will be approached in the HPB new patient clinic by a member of the clinical team and informed about the study. They will be given the patient information sheet (PIS) and informed consent form (ICF) to review. One of the research team members will be available to answer their questions. Patients who are interested in taking part in this study will be consented during their next clinic visit and assigned a study ID number. After consent, patient participants will be given the first study pack containing the survey (developed for the purposes of this study) and 2 quality of life questionnaires (EORTC QLQ-C30 and PAN26) and they will be asked to fill this in. A paired similar physician's survey will be given to the physician, who is seeing the patient in clinic, to complete, on the same day as the patient, to enable correlation of the patient and physician views.

Once patients have started chemotherapy (ideally after 2-3 months) , but before the first treatment scan, they will be requested to complete the same pack of questionnaires. The attending physician will also be asked to fill in the survey on the same day. The third set of questionnaires will be completed once the patient has had their first treatment scan and they have been informed of the results. If the patients have to stop treatment early and are not having a scan, they are also asked to complete these forms as time point 3.These second and third time points will determine how time, treatment response and side-effects influence the patient's views.

For physicians:

All physicians and nurse clinicians who work in the HPB clinic in the Christie Hospital will be approached to attend a study induction meeting where the study, necessary procedures and aims will be explained. They will be given a physician information sheet and informed consent forms to review. Once information has been given and potential participant's questions have been answered, physicians can be consented during or after that meeting. After consent, physician participants will be given the physician survey in clinic if they have seen a patient participant during that clinic. They will only be asked to fill in this survey if the patient they have just seen in clinic is also taking part in this study. Physicians are asked to answer the survey in the clinic on the same day they saw the patient. Physicians can answer surveys about different patients during the whole duration of the study.

Consenting Participants

Patients:

The patient's consent to participate in the study will be obtained after a full explanation has been given. Patients should be given sufficient time after being given the study patient

information sheet to consider and discuss participation in the study with friends and family. However, consent may be obtained on the day the patient is first approached regarding participation, if that is their preference. If patients wish to take information home, they will meet one of the members of the research team during their next clinic visit and can consent then. A contact number will be given to the patient should they wish to discuss any aspect of the study at a later stage.

One ICF is used for all 3 time points, but patients are free to withdraw consent at any time.

Physicians:

All eligible physicians and nurse clinicians are invited to the study induction meeting where study rationale, aims and procedure will be explained. After adequate time has been given (same day consent is permitted), all queries have been addressed and the research team is confident that the participant understands the study and all requirements, they will be consented to participate. If they wish to take the information home, one of the research team members can meet them at a later time to answer any questions and take consent. Consent will be taken by a member of the study team who is Good Clinical Practice (GCP) trained and who has been delegated by the investigators to undertake this activity (and this delegation is clearly documented on the delegation log). One signed consent form per physician is required to take part in the study and to fill in physician surveys for different patients.

Patients and physicians will be consented prior to any study-related activities being undertaken.

The original, signed copy of the patient information sheet and consent form(s) should be retained in the Investigator Site File and preferably an original will be kept in the patient notes. Copies will be given to the participants.

The participants' data (patients and physicians) will be inputted under a unique ID, such that individual participants will not be identifiable on the database. Any personal data recorded will be regarded as confidential, and any information which would allow individual participants to be identified will not be released into the public domain. The project team will maintain the project ID log and all other project documents (including participants' written consent forms), which will be held securely at the Christie NHS Foundation Trust. The chief investigator will ensure that participants' confidentiality is maintained.

Discontinuation/withdrawal of participants

Participants can withdraw from the study at any time without giving a reason and without any consequences to their current or future treatment. No further data will be collected from the moment they withdraw consent, although data collected to that point may be used unless they specifically request otherwise.

Participants who lose capacity

Should the participant lose capacity during the study, no further data will be collected about them. Data that has been already collected will be retained and used in the study.

Capacity would be assessed by:

- Physical capacity: patients whose physical capacity worsens based on Eastern Cooperative Oncology Group (ECOG) performance score.

- Mental capacity: patients whose mental capacity worsens based on the Mini–Mental State Examination.

End of project

The project team will notify the REC and local R&D of the end of the project once they have analysed the results.

Data collection and analysis

Information from surveys and quality of life questionnaires will be inserted in to study-specific electronic databases.

The data will be analysed from multiple different viewpoints: Patient survey responses at baseline will be reported. Responses at the three time points will also be compared to each other, and changes in these will evaluated; patients responses will also be compared to the physicians responses and differences will be evaluated; changes in quality of life questionnaires will be correlated with the changes in the relevant survey questions. Summary statistics will be provided for patient demographics and these will also be correlated with the survey responses.

Number of Participants

Approximately 150 participants will be approached and consented to take part.

Data Management

- Baseline data will be collected about patient demographics from patient's electronic records.
- Data from the surveys and quality of life questionnaires will be entered in to a purpose built database.
- Signed ICFs will be kept in the Department of Medical Oncology, Christie NHS Foundation Trust (locked filing cabinet, with swipe card access required in to the Department of Medical Oncology).

A random, Quality Assurance (QA) check of the data collected will be performed to ensure its accuracy and validity. An audit can also be requested via the Research and Development office at The Christie NHS Foundation Trust.

Data will be managed according to The Christie NHS Foundation Trusts Standard Operating Procedures and the Medical Research Council's 'Good research practice: Principles and guidelines'.

All study documents will be pseudoanonymised: personal data will be recorded on the consent forms (name), together with a unique ID. All other documents will only use the unique ID. The consent forms will be kept in a secure, locked filing cabinet accessible only to members of the research team. The other documents will be stored in a separate filing cabinet.

All sensitive data stored on NHS Trust computers will be encrypted using prescribed software. Person-identifying data or confidential information will not be stored on desktop machines but will be kept on the NHS Trusts secure network drives.

The research team will have access to the personal data collected in the frame of the study. Informed consent will be obtained for this. Study data and material may be looked at by individuals from regulatory authorities or from the NHS Trust, for monitoring and auditing purposes and this may well include access to personal information. Data will be retained for a period of 15 years in line with the Trust Data Retention Policy and the University of Manchester policy.

Quality Assurance Procedures

The project will be conducted in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

Ethical and Regulatory Requirements

The study will be conducted in accordance with the principles of GCP.

The project team will ensure that the project protocol, PIS, ICF, GP letter and submitted supporting documents have been approved by the appropriate regulatory bodies and research ethics committee prior to any patient recruitment and will ensure the project is run and closed according to requirements.

Any agreed substantial amendments will also be submitted for ethical approval prior to implementation.

Declaration of Helsinki: The Investigator will ensure that this project is conducted in accordance with the principles of the Declaration of Helsinki.

Approvals: The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee and host institutions for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents. All substantial amendments will also be reviewed by the University of Manchester Faculty of Biology, Medicine and Health (FBMH) Research Governance Office to obtain Sponsor approval.

Reporting: The CI will submit an Annual Progress Report to the REC, host organisation and Sponsor at the end of the project, or on request.

Participant Confidentiality: The project staff will ensure that the participants' anonymity is maintained. The participants will be identified only by project ID number on any electronic database. All documents will be stored securely and only accessible by project staff and authorised personnel. The project will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so.

Sponsorship and Indemnity: The University of Manchester will act as the sponsor for this project. Delegated responsibilities will be assigned to the research team to manage the project.

Finance and Insurance

Funding: This project is not funded, but Dr Pihlak is funded by the Collins PhD clinical fellowship fund and by Pancreatic Cancer UK.

Insurance: The project team has submitted an insurance assessment form to the sponsor and the sponsor has ensured insurance is in place.

Publication Policy

The main project results will be published in the name of the project in a peer-reviewed journal, on behalf of all collaborators. No investigator may present or attempt to publish data relating to the project without prior permission from the project team.

Project Record Retention and Archiving

Essential documents are documents that individually and collectively permit evaluation of the conduct of the project and substantiate the quality of the data collected. Essential documents will be maintained at the Christie Hospital NHS Foundation Trust in a way that will facilitate the management of the project, audit and inspection. They should be retained for a sufficient period (at least 5 years) for possible audit or inspection. Documents should be securely stored and access restricted to authorised personnel.

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RELEVANT study: Patient and physician perspectives on clinically-meaningful outcomes in advanced pancreatic cancer.

Patient Information Sheet

This PIS should be read in conjunction with **The University privacy notice** (http://documents.manchester.ac.uk/display.aspx?DocID=37095)

Introduction

We would like you to help us with this research study which is explained below.

You have been invited to take part in this study because you have been diagnosed with a cancer of the pancreas that is being treated with chemotherapy and you are attending The Christie to receive treatment for your cancer. The research involves the completion of one survey and two questionnaires at three different time points:

(1) Before you start treatment.

(2) After starting chemotherapy, and before your first scan (ideally after 2-3 months of treatment).

(3) After your first scan following starting treatment*.

* if you have to stop treatment early, and you are not having your scan, we will also ask you to complete these forms.

The first survey has been designed specifically for use in this study to help doctors learn more about what you consider to be the most important goal(s) of treatment, as you receive drugs (chemotherapy) to treat your cancer.

You will also be asked to complete two other previously developed and well-tested questionnaires called the European Organisation for Research and Treatment Quality of Life Questionnaire-C30 (EORTC QLQ-C30) and QLQ-PAN26 questionnaires, which will ask you other questions about your quality of life. We will also ask your hospital doctor or nurse to complete a similar paired survey (developed for the purposes of this study) after seeing you at these three time points.

Before you decide whether to take part in this research study, we would like you to understand why the research is being done and what it would involve for you. Take time to read this information sheet and to talk with others, e.g. your family or friends, about the research study if you wish.

One of the doctors or nurses will go through the information sheet with you, and answer any questions you have.

What is the purpose of the study?

This survey, along with the two questionnaires that you will complete, will help us to understand better what patients like you think about the cancer diagnosis, treatments offered and goals of treatment. This survey is conducted at three different time points to see if your views change over time, due to treatment response or side effects or other events.

Why have I been invited to take part in this study?

You are being invited to take part, as you have been diagnosed with cancer of the pancreas, and are due to start treatment at The Christie NHS Foundation Trust.

Do I have to take part?

No, you do not have to take part in this study if you do not want to. It is up to you to decide whether or not to take part. If you do decide to take part, you will be given this information sheet to keep and you will also be asked to sign a consent form. Your decision to participate in this study will not affect the treatment that you are receiving now or in the future. If you decide to take part, you are free to withdraw at any time, without giving a reason, and without any consequences to your current or future treatment. If you choose not to take part, your care and treatment will not be affected.

What will taking part involve?

Should you decide to participate, you will be asked to complete a survey in addition to two other questionnaires, at three different time points during your clinic visits (as part of your normal clinic appointments):

(1) Before starting chemotherapy.
(2) After starting chemotherapy, and before your first scan (ideally after 2-3 months of treatment).
(3) After your first scan following starting treatment*

* if you have to stop treatment early, and you are not having your scan, we will also ask you to complete these forms.

A similar survey will be given to your doctor to complete on those three time points. Relevant information from your hospital records about your diagnosis and treatment will also be collected.

What are the possible disadvantages and risks of taking part?

Answering this survey will not affect your treatment in any way. Filling in this survey and the other two questionnaires will probably take around 10-15 minutes.

What are the possible benefits of taking part?

We cannot guarantee that the research will help you, but the information may generate new knowledge regarding patients and doctors perspectives on treatment which may benefit future patients.

How is confidentiality maintained?

Any information collected about you during this study will be kept strictly confidential. Data from the survey and questionnaires and any additional data that is collected about your treatment will be anonymised by using a patient number only. You will not be identified at any stage of the data collection, nor in any resulting publications. All researchers are appropriately trained and data collected will be stored on computers in the Department of Medical Oncology, The Christie NHS Foundation Trust, and they will be encrypted so that it can only be accessed using the correct password, to ensure that only the research group can access the data. The computers are stored in a locked office in the department of Medical Oncology, which requires swipe card access. Data from the study will be kept for a minimum of 5 years after the date of any publication resulting from the study, or for 10 years after data is collected, whichever is greater, to follow recommended good practice guidelines for research. Data will then be destroyed.

What will happen to my personal information?

The University of Manchester, as Data Controller for this project, takes responsibility for the protection of the personal information that this study is collecting about you. In order to comply with the legal obligations to protect your personal data the University has safeguards in place such as policies and procedures.

Individuals from the University of Manchester, NHS Trust or regulatory authorities may need to look at the data collected for this study to make sure the project is being carried out as planned. This may involve looking at identifiable data but all individuals involved in auditing and monitoring the study, will have a strict duty of confidentiality to you as research participants.

We are collecting and storing this personal information in accordance with the General Data Protection Regulation (GDPR) and Data Protection Act 2018 which legislate to protect your personal information. The legal basis upon which we are using your personal information is "public interest task" and "for research purposes" if sensitive information is collected. For more information about the way we process your personal information and comply with data protection law please see our Privacy Notice for Research Participants (http://documents.manchester.ac.uk/display.aspx?DocID=37095).

You have a number of rights under data protection law regarding your personal information. For example you can request a copy of the information we hold about you. This is known as a Subject Access Request. If you would like to know more about your different rights, please consult our privacy notice for research (link above) and if you wish to contact us about your data protection rights, please email dataprotection@manchester.ac.uk or write to The Information Governance Office, Christie Building, University of Manchester, Oxford Road, M13 9PL. at the University and we will guide you through the process of exercising your rights.

You also have a right to complain to the Information Commissioner's Office, Tel 0303 123 1113

Contacting your General Practitioner (GP)

With your consent, your GP will be informed that you are taking part in this study. This is standard practice and will ensure that your GP continues to be involved in your care.

What will happen if I do not want to carry on with the study?

You can withdraw from the study at any time without giving a reason and without any consequences for your current or future treatment. No further data will be collected from the moment you withdraw consent, although data collected to that point may be used unless you specifically request otherwise.

Should you lose capacity during the study; no further data will be collected about you. Data that has been already collected will be used in the study.

What will happen to the results of the study?

The information and data obtained will be analysed and summarised in the form of research articles, which will be published in medical journals or as conference abstracts. Results will also be shared with the Pancreatic Cancer UK Charity, and they may make this summarised information available on their website. Should you like a summary of the results this would be available through your regular clinic appointments.

Who will conduct the research?

Dr Rille Pihlak, Prof Janelle Yorke, Prof Juan Valle, Dr Mairéad McNamara from the Division of Cancer Sciences in The University of Manchester (M13 9PL, Manchester, UK) and the Department of Medical Oncology in The Christie NHS Foundation Trust (M20 4BX, Manchester, UK).

Who is legally responsible for the study?

This study is being conducted by researchers employed by The University of Manchester and who work at The Christie NHS Foundation Trust. The University of Manchester is the legal sponsor of the study.

Who is funding the research?

The researchers, who are employees of The University of Manchester and The Christie NHS Foundation Trust, are not being paid to conduct this research. Dr Pihlak is funded by the Collins Clinical Research fellowship and by Pancreatic Cancer UK.

Expenses and Payments

Unfortunately, we are unable to give you money for your travel expenses and your time for taking part in this study; you will be asked to complete the questionnaires during your normal appointments at the hospital.

Who reviewed and approved this study?

The NHS REC (North West – Greater Manchester East Research Ethics Committee) and the HRA have reviewed and approved this study.

Who to contact if you feel in distress?

If you become distressed due to the information you read here, or you are worried about your diagnosis of pancreatic cancer, you can contact your key worker (Specialist nurse: Natalie Roberts – Tel: 0161 446 7965 , pancreatic cancer support groups, Pancreatic Cancer UK Support Line or Macmillan Cancer Support. See below for contact details.

Pancreatic Cancer UK is a registered charity, whose aim is to inform patients and their family members, healthcare providers and the wider community about dealing with pancreatic cancer, treatments, current research, awareness, funding and fundraising. You can access the charity's website for contact details and information at http://www.pancreaticcancer.org.uk/.

Pancreatic Cancer UK Support line: 0808 801 0707. The Support Line is free to call and is open Monday - Friday 10am-4pm.
Details on Pancreatic Cancer Support groups are available at: www.pancreaticcancer.org.uk/information-and-support/get-support/support-groups/ or you can call the support line.

Macmillan Cancer Support is a registered charity providing information about all aspects of cancer for cancer patients and their families. They have published several useful booklets on different types of cancer, chemotherapy, radiotherapy, and clinical trials in general. These booklets may be requested from Macmillan Cancer Support, 89 Albert Embankment, London SE1 7UQ. Alternatively, you may view the contents of these booklets on their website (www.macmillan.org).

In addition, Macmillan Cancer Support also provides advice from specialist cancer nurses on: Freephone 0808 808 0000 (9am to 8pm, Monday to Friday, excluding Bank Holidays).

The contact number and information of your key worker is found on the chemotherapy information sheet that will be given to you by the nurse or doctor who sees you in clinic at The Christie for the first time.

Complaints

If you have a minor complaint then you need to contact the researcher(s) in the first instance by contacting Dr Rille Pihlak by telephoning 0161 446 8106 (secretary).

If you wish to make a formal complaint, or if you are not satisfied with the response you have gained from the researchers in the first instance, then please contact the Research Governance and Integrity Manager, Research Office, Christie Building, University of Manchester, Oxford Road, Manchester, M13 9PL, by emailing: research.complaints@manchester.ac.uk or by telephoning 0161 275 2674 or 275 2046.

Whom can I contact for further information?

If you have any questions, or require any additional information about this research project, please do not hesitate to contact Dr Rille Pihlak (at 0161 446 8106 [secretary]).

If you have any questions about your rights as a research patient, or concerns or complaints about the study, you may contact your local Patient Advisory Liaison Service (PALS) at

Tel: 0161 446 8217 between 10:00 – 16:00.

Email: pals@christie.nhs.uk

Address: Patient Advice and Liaison Service, The Christie NHS Foundation Trust, Wilmslow Road, Manchester, M20 4BX

Thank you for taking the time to read this information sheet and for considering taking part in this study.

Appendix 3: RELEVANT study Informed Consent Form

Informed Consent Form

RELEVANT study: Patient and physician perspectives on clinically-meaningful outcomes in advanced pancreatic cancer.

Investigators: Dr Rille Pihlak, Prof Janelle Yorke, Prof Juan Valle, Dr Mairéad McNamara.

Patient Study ID Number:

	Initial box
1. I confirm that I have read and understand the Participant Information Sheet dated 02/11/2018 for the above study and I have had the opportunity to consider the information.	
2. I confirm that I have had the opportunity to ask questions about the study and that these questions have been answered satisfactorily.	
3. I understand that my participation is completely voluntary and that I am free to withdraw at any time, without giving a reason (no further data will be collected from the moment you withdraw consent, although data collected to that point may be used, unless you specifically request otherwise). I understand that it will not be possible to remove my data from the project once it has been anonymised and forms part of the data set.	
4. I understand that the data collected may be published as part of a research project (my identity will not be revealed in any publication).	
5. I understand that relevant sections of my clinical records will be accessed by the research team, in order to collect data as part of the study.	
6. I understand that relevant sections of my clinical records and data collected during the study may be looked at by responsible individuals from the University of Manchester, from regulatory authorities, or from the NHS Trust, where it is relevant to my taking part in the research. I give permission for these individuals to have access to my data.	
7. I confirm that I am happy to fill in the necessary surveys and questionnaires as part of this study.	
8. I agree to my GP being informed of my participation in this study.	
9. I agree to take part in the above study.	

Data Protection

The personal information we collect and use to conduct this research will be processed in accordance with data protection law as explained in the Participant Information Sheet and the Privacy Notice for Research Participants (http://documents.manchester.ac.uk/display.aspx?DocID=37095).

Name of Participant: _____

Signature of participant: _____ Date: _____

Name of Researcher: _____

Signature of researcher: _____ Date: _____

When completed: one copy for the participant, one original for the site file.

NHS
The Christie
NHS Foundation Trust

MANCHESTER
1824

RELEVANT study: Patient Survey

Patient ID number:

Date:

Time point (1/2/3):

You have been diagnosed with a cancer of the pancreas and are attending The Christie hospital to receive treatment for your cancer.

This survey has been designed to help doctors learn more about what you, as a patient, consider to be the most important goal, as you receive chemotherapy to treat your cancer.

You will be asked to complete this survey at three different times:

(1) Before you start treatment.

(2) After starting chemotherapy, and before your first scan (ideally after 2-3 months of treatment).

(3) After your first scan following starting treatment*.

* if you have to stop treatment early, and you are not having your scan, we will also ask you to complete these forms.

You will also be asked to complete two other questionnaires called the European Organisation for Research and Treatment Quality of Life Questionnaire-C30 (EORTC QLQ-C30) and QLQ-PAN26 questionnaires, which will ask you other questions about your quality of life.

Please read the questions below and answer by ticking the appropriate box. We would also be very grateful if you could complete the other two quality of life questionnaires attached (the EORTC QLQ-C30 and QLQ-PAN26 questionnaires).

Thank you for taking part in this study.

NHS
The Christie
NHS Foundation Trust

MANCHESTER
1824

Background

1. **Please select the response which best represents to what extent you wish to be involved in decisions regarding your treatment.**

   - ☐ I prefer to make all decisions regarding my treatment
   - ☐ I prefer to make the final decision about my treatment after seriously considering my doctor's opinion
   - ☐ I prefer that my doctor and I share responsibility for deciding which treatment is best for me
   - ☐ I prefer that my doctor makes the final decision about which treatment will be used, but seriously considers my opinion
   - ☐ I prefer to leave all decisions regarding my treatment to my doctor

2. **Which healthcare professional told you that you had cancer?**

   - ☐ General practitioner (GP)
   - ☐ Surgeon
   - ☐ Nurse
   - ☐ Gastroenterologist
   - ☐ Oncologist
   - ☐ Other: _____

3. **How satisfied are you with the speed and organisation of the tests that were performed so that a diagnosis could be made?**

   - ☐ Completely satisfied
   - ☐ Mostly satisfied
   - ☐ Somewhat satisfied
   - ☐ Neither satisfied nor dissatisfied
   - ☐ Somewhat dissatisfied
   - ☐ Mostly dissatisfied
   - ☐ Completely dissatisfied

   Any comment:

   _____

4. **Have you had chemotherapy (drug used to treat any cancer) before?**

   - ☐ Yes
   - ☐ No

5. Has anyone you know had chemotherapy before?

☐ No

☐ Yes

If 'Yes'- as far as you are aware was this person's experience of chemotherapy:

☐ Very good

☐ Good

☐ Neither good nor bad

☐ Bad

☐ Very bad

6. Have you read or received information in addition to that provided by the Christie about the possible treatments for your cancer?

☐ Yes

☐ No

7. If yes, then where did you get the information? *Tick all that apply*

☐ I searched on the internet

☐ I was given information to read from a healthcare professional

☐ I have heard about it from friends

☐ I have joined support groups

☐ Other (please specify below)

If other, please specify:

_____

<u>Understanding the aims of treatment</u>

8. What have you been told about the goal of your treatment? *Tick all that apply*

The goal of my treatment is to:

☐ Cure the cancer

☐ Shrink the cancer to make it surgically removable

☐ Keep the cancer under control

☐ Manage my symptoms only

☐ End-of-life treatment

☐ I haven't had a discussion about this

☐ I don't know

Impact on your life

9. How long would it usually take for you to come to The Christie for treatment (one way)?

- ☐ Up to 30 minutes
- ☐ 30 minutes to 1 hour
- ☐ 1-2 hours
- ☐ More than 2 hours

10. What mode of transport do you take to get to The Christie?

- ☐ Public transport
- ☐ I drive myself
- ☐ A relative or friend drives me
- ☐ Christie-arranged transport
- ☐ Walk or cycle

11. How often are you expected to come for treatment for your cancer?

- ☐ Once a month
- ☐ Twice a month
- ☐ Three times a month
- ☐ Four times a month
- ☐ More than four times a month
- ☐ As often as needed

12. How has the diagnosis or treatment affected you financially?

- ☐ Too early to tell
- ☐ No effect
- ☐ I am a little out of pocket
- ☐ I am a lot out of pocket
- ☐ I prefer not to say

13. How would you expect the chemotherapy to affect your wellbeing (how you feel)?

- ☐ Improve my wellbeing a lot
- ☐ Improve my wellbeing somewhat
- ☐ Not influence my wellbeing either way
- ☐ Worsen my wellbeing somewhat
- ☐ Worsen my wellbeing a lot
- ☐ I don't know

14. **We would like to know which chemotherapy side-effects are acceptable to you. Please rate <u>each of these from 1-10</u> based on your acceptance: 1 being very acceptable and 10 being not acceptable at all.**

    __ Altered taste
    __ Sore hands and feet
    __ Diarrhoea
    __ Sore mouth
    __ Tiredness
    __ Losing your hair
    __ Skin rash
    __ Getting an infection with fever
    __ Nausea and vomiting
    __ Loss of appetite

15. **What do you think - how many people who are treated with this type of chemotherapy have serious (i.e. life-threatening or requiring hospitalisation) side-effects?**

    ☐ 1-5%
    ☐ 6-10%
    ☐ 11-20%
    ☐ >20%

16. **How would you choose between different types of chemotherapy?**

    Please rate these in the order of priority from 1 to 4, with 1 being the most important and 4 being the least important to you

    __ Gives the longest survival (length of life)
    __ Has the least amount of side-effects
    __ Has the best balance between side effects and survival
    __ Controls the symptoms of my cancer (such as pain, or feeling like getting sick)

17. **How likely, do you think, is chemotherapy to reduce your current symptoms?**

    ☐ Not at all likely
    ☐ Slightly likely
    ☐ Moderately likely
    ☐ Very likely
    ☐ Completely likely

Your goals

18. **Do you have personal or family goals that you would like to reach with the help of this treatment?** *Like holidays, concerts, weddings, birthdays, graduations, birth of children, or grandchildren or other milestones or important events to you*.

- ☐ Yes
- ☐ No
- ☐ I haven't thought about it
- ☐ I don't know

If Yes, have you discussed these with your doctor?

☐Yes

☐No

If Yes, were these taken into account when making treatment decisions?

☐Yes

☐No

19. **We know that patients have their own goals and priorities in mind. Please rate these in order of importance to you from 1-7: 1 being the most important and 7 the least.**

- __ Self-care as long as possible
- __ Being able to do your own shopping
- __ Being able to work
- __ Being able to socialise
- __ Being able to travel
- __ Being able to spend time with family
- __ Attending a special event (birthday, anniversary, wedding etc)

Treatment outcome

20. **As far as you understand, how likely is your treatment to cure the cancer?**

- ☐ Not at all likely
- ☐ Slightly likely
- ☐ Moderately likely
- ☐ Very likely
- ☐ Completely likely
- ☐ I don't know

21. How likely is your cancer to respond to chemotherapy (control the disease for a period of time)?

- ☐ Not at all likely
- ☐ Slightly likely
- ☐ Moderately likely
- ☐ Very likely
- ☐ Completely likely

22. How likely is chemotherapy to give you a longer life?

- ☐ Not at all likely
- ☐ Slightly likely
- ☐ Moderately likely
- ☐ Very likely
- ☐ Completely likely

23. How long do you expect chemotherapy to extend your life by?

- ☐ 1-2 months
- ☐ 3-6 months
- ☐ Between 6 months and 1 year
- ☐ Between 1 and 5 years
- ☐ More than 5 years

24. What <u>minimal</u> extra time would you consider to be important for you while receiving chemotherapy compared to managing symptoms alone, without chemotherapy?

- ☐ 1-2 months
- ☐ 3-6 months
- ☐ Between 6 months and 1 year
- ☐ Between 1 and 5 years
- ☐ More than 5 years

25. Based on the answer you gave to question number 24, we would like to know how many side effects you would be willing to accept as a trade-off for that amount of extra time:

a. If you had few side effects with that amount of extra time, would you take chemotherapy?

- ☐ Yes
- ☐ No

b. If you had a medium amount of side effects (management of side effects possible at home, with oral tablets, if needed) with that amount of extra time, would you take chemotherapy?

- ☐ Yes
- ☐ No

c. If you had a large amount of side effects (needing any hospitalisations) with that amount of extra time, would you take chemotherapy?

☐ Yes

☐ No

26. Based on the answer you gave to question number 24, if the minimal amount you said here <u>was doubled,</u> how many side effects would you be willing to accept as a trade-off for that amount of extra time (see below questions).

a. If you had few side effects with that amount of extra time, would you take chemotherapy?

☐ Yes

☐ No

b. If you had a medium amount of side effects (management of side effects possible at home, with oral tablets, if needed) with that amount of extra time, would you take chemotherapy?

☐ Yes

☐ No

c. If you had a large amount of side effects (needing any hospitalisations) with that amount of extra time, would you take chemotherapy?

☐ Yes

☐ No

27. Would you accept chemotherapy if it controlled symptoms of your cancer (like pain or the feeling that you are going to get sick) but did not extend your survival (length of life)?

☐ Yes

☐ No

Thank you for taking part in the study, please also fill in the two other questionnaires called the EORTC QLQ-C30 and QLQ-PAN26.

RELEVANT study: Physician Survey

Appendix 5: RELEVANT study physician survey

Physician ID number:

Patient ID number:

Date:

Time point (1/2/3):

Please answer the following questions about this patient that you have just seen in clinic with advanced pancreatic cancer.

Understanding the aims of treatment

1. **What is the treatment intent for this patient?** Tick all that apply

Aim of treatment is to:

- ☐ Cure the cancer
- ☐ Shrink the cancer to make it resectable
- ☐ Keep the cancer under control
- ☐ Symptom management only
- ☐ End-of-life treatment
- ☐ I don't know

Impact on patient's life

2. **How often is the patient expected to come for treatment?**

- ☐ Once a month
- ☐ Twice a month
- ☐ Three times a month
- ☐ Four times a month
- ☐ More than four times a month
- ☐ I don't know

3. **We would like to know which chemotherapy side-effects you think would be acceptable to this patient. Please rate these from 1-10 based on what you think this patient would accept: 1 being the most acceptable and 10 being the least acceptable.**

- __ Altered taste
- __ Sore hands and feet
- __ Diarrhoea
- __ Sore mouth
- __ Tiredness
- __ Losing hair
- __ Skin rash
- __ Getting an infection with fever

__ Nausea and vomiting
__ Loss of appetite

4. What do you think about how the patient would choose between different types of chemotherapy?

Please rate these in the order of priority from 1 to 4, with 1 being the most important and 4 being the least important for the patient:

__ Gives the longest survival (length of life)
__ Has the least amount of side-effects
__ Has the best balance between side effects and survival
__ Controls the symptoms of their cancer (such as pain, or feeling like getting sick)

<u>Patient goals</u>

5. Are you aware if the patient has personal or family goals that they would like to reach with the help of this treatment*? Like holidays, concerts, weddings, birthdays, graduations, birth of children, or grandchildren or other milestones or important events to them.*

☐ Yes
☐ No

If yes, were these goals taken into account when making decisions regarding treatment offered?

☐ Yes
☐ No

6. We know that patients have their own goals and priorities in mind. Please rate these as you would think your patient would rate them based on importance to them from 1-7: 1 being the most important and 7 the least.

__ Self-care as long as possible
__ Being able to do their own shopping
__ Being able to work
__ Being able to socialise
__ Being able to travel
__ Being able to spend time with family
__ Attending a special event (birthday, anniversary, wedding etc)

<u>Treatment outcome</u>

7. As far as you understand, how likely is this treatment to cure the cancer?

☐ Not at all likely
☐ Slightly likely
☐ Moderately likely
☐ Very likely
☐ Completely likely
☐ I don't know

8. **How likely is this patient's cancer to respond to chemotherapy (control the disease for a period of time)?**

- ☐ Not at all likely
- ☐ Slightly likely
- ☐ Moderately likely
- ☐ Very likely
- ☐ Completely likely

9. **How likely is chemotherapy to give the patient a longer life?**

- ☐ Not at all likely
- ☐ Slightly likely
- ☐ Moderately likely
- ☐ Very likely
- ☐ Completely likely

10. **How long do you actually expect the chemotherapy to extend the patient's life by, if at all?**

- ☐ 1-2 months
- ☐ 3-6 months
- ☐ Between 6 months and 1 year
- ☐ Between 1 and 5 years
- ☐ More than 5 years

11. **What <u>minimal</u> extra time would you consider that the patient thought was important while receiving chemotherapy versus managing symptoms alone, without chemotherapy?**

- ☐ 1-2 months
- ☐ 3-6 months
- ☐ Between 6 months and 1 year
- ☐ Between 1 and 5 years
- ☐ More than 5 years

12. Based on the answer you gave to question number 11, we would like to know how many treatment side effects you think the patient would be willing to accept as a trade-off for that amount of extra time:

a. If they had few side effects with that amount of extra time, would they take chemotherapy?

☐ Yes
☐ No

b. If they had a medium amount of side effects (management of side effects possible at home, with oral tablets, if needed) with that amount of extra time, would they take chemotherapy?

☐ Yes
☐ No

c. If they had a large amount of side effects (needing any hospitalisations) with that amount of extra time, would they take chemotherapy?

☐ Yes
☐ No

13. Based on the answer you gave to the question number 11, if the minimal amount you said <u>was doubled,</u> how much treatment side effects do you think the patient would be willing to accept as a trade-off for that amount of extra time:

a. If they had a few side effects with that amount of extra time, would they take chemotherapy?

☐ Yes
☐ No

b. If they had a medium amount of side effects (management of side effects possible at home, with oral tablets, if needed) with that amount of extra time, would they take chemotherapy?

☐ Yes
☐ No

d. If they had a large amount of side effects (needing any hospitalisations) with that amount of extra time, would they take chemotherapy?

☐ Yes
☐ No

14. **Do you think that the patient would accept chemotherapy if it just controlled symptoms of their cancer and did not extend their survival?**

☐ Yes
☐ No

Thank you for filling in this survey.

Appendix 6: Germline mutations in pancreatic cancer and potential new therapeutic options.

Pihlak, R., J.W. Valle, and M.G. McNamara, Germline mutations in pancreatic cancer and potential new therapeutic options. Oncotarget, 2017. 8(42): p. 73240-73257.

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Germline mutations in pancreatic cancer and potential new therapeutic options

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ABSTRACT

Due to short-lived treatment responses in unresectable disease, pancreatic ductal adenocarcinoma (PDAC) continues to be one of the deadliest cancers. There is availability of new information about germline and sporadic mutations in the deoxyribonucleic acid (DNA) damage repair pathway in PDAC in recent decades and the expectation is that novel targeted therapies will thus be developed. A variety of germline mutations (*BRCA2*, BRCA*1*, *PALB2*, *CDKN2A*, *ATM*, *TP53* and mismatch repair genes *MLH1*, *MSH2*, *MSH6*) have been reported in these patients with the highest prevalence being *BRCA1/2*. Positive results have been reported with the use of targeted therapies, particularly poly (ADP-ribose) polymerase inhibitors in *BRCA*-mutated ovarian and breast cancers, and their use is currently being investigated in germline-mutated pancreatic cancer. The aim of this review is to provide an outline of germline DNA damage repair mutations in pancreatic cancer and their effect on the incidence, outcomes and responses to different therapeutic options.

INTRODUCTION

Pancreatic cancer is the 10th most common cancer in the UK (2013) and 12th most common cancer in the US [1, 2]. Unfortunately, pancreatic ductal adenocarcinoma (PDAC) has also been shown to be the most lethal human malignancy with the worst 5-year overall survival (OS) compared to other types of cancer [3]. The 5-year OS of all stages is around 7.7% in the US [1], and 3% in England and Wales (2010–2011) [2]. Even for patients who have had potentially curative surgery who receive adjuvant chemotherapy (gemcitabine and capecitabine), the 5 year overall survival is 28.8% according to the most recently-published data from the phase III randomised ESPAC-4 trial [4]. The longest overall survival reported for patients with metastatic disease was in the ACCORD trial where patients receiving the oxaliplatin, irinotecan, 5-fluorouracil and leucovorin combination (FOLFIRINOX) had a median overall survival of 11.1 months [5]. In the MPACT trial, the median OS for patients who received gemcitabine and nab-paclitaxel was 8.5 months [6]. In both of these studies, there are hints of possible subsets of patients that may be deriving significant benefit from the treatment, with tails observed in the Kaplan-Meier curves, and better characterisation of these patient subgroups is necessary to guide future therapeutic options. Sadly, the majority of clinical trials recruiting patients with advanced pancreatic cancer over the past 5 years have failed to demonstrate a more significant clinically meaningful benefit [7].

Due to short-lived treatment responses, pancreatic cancer is the 3rd and 5th most common cause of cancer death in the US and UK (2012) respectively, accounting for more than 5% of all deaths from cancer [1, 2], and is projected to become the second leading cause of cancer-related death by 2030 [8].

Most of the cases of pancreatic adenocarcinoma are thought to be sporadic, however approximately 5% to 10% occur in the presence of a family history of the disease [9].

Multiple syndromes and diseases [10–12] have been associated with an increased risk of developing pancreatic cancer, including familial atypical multiple mole melanoma (FAMMM) [13, 14], Peutz-Jeghers syndrome (PJS) [15, 16], hereditary pancreatitis [17], hereditary nonpolyposis colorectal carcinoma (HNPCC) [18], hereditary breast and ovarian cancer (HBOC) [19], and familial adenomatous polyposis [20, 21]. Although the numbers are small, the most common germline mutations in pancreatic cancer related to these syndromes are breast

Appendix 7. Advances in Molecular Profiling and Categorisation of Pancreatic Adenocarcinoma and the Implications for Therapy.

Pihlak, R., et al., Advances in Molecular Profiling and Categorisation of Pancreatic Adenocarcinoma and the Implications for Therapy. Cancers (Basel), 2018. 10(1).

cancers

MDPI

Review

Advances in Molecular Profiling and Categorisation of Pancreatic Adenocarcinoma and the Implications for Therapy

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Abstract: Pancreatic ductal adenocarcinoma (PDAC) continues to be a disease with poor outcomes and short-lived treatment responses. New information is emerging from genome sequencing identifying potential subgroups based on somatic and germline mutations. A variety of different mutations and mutational signatures have been identified; the driver mutation in around 93% of PDAC is *KRAS*, with other recorded alterations being *SMAD4* and *CDKN2A*. Mutations in the deoxyribonucleic acid (DNA) damage repair pathway have also been investigated in PDAC and multiple clinical trials are ongoing with DNA-damaging agents. Rare mutations in *BRAF* and microsatellite instability (MSI) have been reported in about 1–3% of patients with PDAC, and agents used in other cancers to target these have also shown some promise. Immunotherapy is a developing field, but has failed to demonstrate benefits in PDAC to date. While many trials have failed to improve outcomes in this deadly disease, there is optimism that by developing a better understanding of the translational aspects of this cancer, future informed therapeutic strategies may prove more successful.

Keywords: pancreatic adenocarcinoma; mutations; molecular profiling; clinical implications

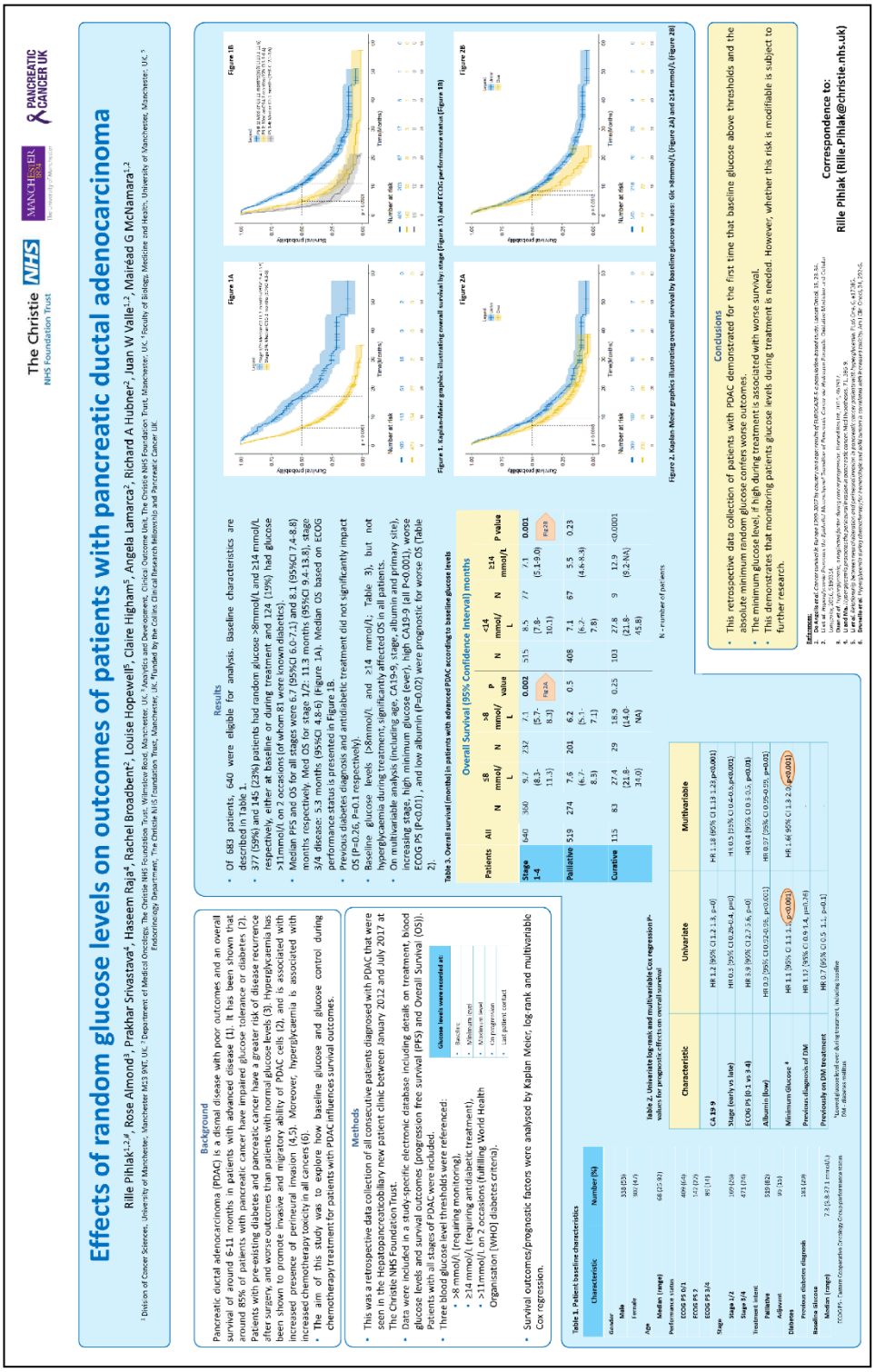
1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the deadliest cancers [1] with a five-year overall survival (OS) for all stages of around 8% in the United States (US) [2] and 3% in the United Kingdom (UK) [3]. Even in patients who had potentially curative surgery followed by adjuvant chemotherapy with gemcitabine and capecitabine, the five-year OS was still only 28.8% in the recently reported phase III randomised ESPAC-4 trial [4]. The Phase III ACCORD [5] and MPACT [6] combination chemotherapy trials in patients with advanced PDAC have been the only studies which reported clinically meaningful significant extensions in median OS in the recent decade. Currently, the combination of 5-fluorouracil, oxaliplatin, irinotecan and leucovorin (FOLFIRINOX) from the ACCORD trial has resulted in the longest-reported OS for patients with metastatic PDAC; median OS was 11.1 months compared to 6.8 months with single-agent gemcitabine [5]. Unfortunately, multiple other clinical trials with either chemotherapy combinations or novel agents have failed to demonstrate a significant OS improvement [7–10]. Due to poor prognosis and very little improvement in survival, PDAC is a major cause of cancer death and it is estimated that it will become the 2nd leading cause of cancer-related death in the US by 2030 [11], being 3rd [2] and 5th [3] currently in the US and UK, respectively.

It has been reported that around 5–10% of pancreatic cancers arise in the presence of a family history of this diagnosis [12]. Hereditary breast and ovarian cancer (HBOC) [13], Peutz-Jeghers

Appendix 8. Effects of random glucose levels on outcomes of patients with pancreatic ductal adenocarcinoma (poster).

Pihlak R, Almond R, Srivastava P, Raja H, Broadbent R, Hopewell L, Higham C, Lamarca A, Hubner RA, Valle JW, McNamara MG (2018). Effects of random glucose levels on outcomes of patients with pancreatic ductal adenocarcinoma. Presented in ESMO 2018, Munich, Germany.



Appendix 9. RELEVANT study: Patient and physician views on meaningful outcomes in advanced pancreatic ductal adenocarcinoma (poster).

Pihlak R, Frizziero M, Mak SYG, Nuttall C, Lamarca A, Hubner R, Yorke J, Valle J, McNamara M (2020). RELEVANT study: Patient and physician perspectives on clinically-meaningful outcomes in advanced pancreatic ductal adenocarcinoma (poster).

The ASCO Quality Care Symposium, October 2020.