Optimisation of radiotherapy for pancreatic cancer

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Abstract

Background

Pancreatic ductal adenocarcinoma (PDAC) remains a cancer of unmet need, with modest improvement in overall survival (OS) being realised over the past few decades. State of the art RT technology has advanced treatment protocols for PDAC, increasing the ability to deliver sophisticated RT that exploits the therapeutic ratio and overcomes the innate radioresistance. PDAC is a disease that requires optimised multi-modality protocols. This can facilitate delivery of dose escalated radiotherapy (RT) of high-quality that can be investigated in studies to determine if clear benefits can be established.

Uncertainties continue to be problematic in the planning and delivery of RT for PDAC, with many challenges present in the multi-factorial chain. By considering the relationship between pathway components and the impact they have on the delivery of safe, precise, and accurate treatment, RT can be improved.

Aim

To optimise components of the RT planning and delivery pathway using a linear accelerator (linac)-based treatment platform to improve safety, accuracy, and precision of stereotactic ablative RT for PDAC.

Methods

I. A retrospective study evaluated dosimetric and clinical outcomes for patients treated for PDAC with conventionally fractionated VMAT. This was to describe clinical outcomes with standard of care treatment, which would provide a baseline measurement.

II. A survey methodology was used to understand the views of clinical oncologists (CO) and clinical oncology trainees (COtrain), to determine

the importance and priorities of areas that required optimisation of PDAC RT.

III. The volumetric impact of introducing MR-CT fusion to RT planning for pancreatic cancer was evaluated for CO and COtrain delineations. Volumes were quantified with and with and without MR, and concordance of volumes were compared to gold standard (GS) volumes.

IV. Image quality scoring criteria was developed and used to evaluate if breath-hold (BH) imaging could improve subjective image quality, visualisation of structures and confidence in decision making, using a comparison of CBCT images acquired in exhale breath-hold (CBCT_EBH) and free-breathing (CBCT_FB). This was carried out for expert (EXP) and clinical observers (OBS).

V. Planning and delivery of stereotactic ablative RT (SABR) to PDAC patients was compared using two methodologies. These were i) a motion encompassing technique which used 4DCT in free-breathing (4DCT_FB) to plan with an ITV approach, with CBCT_FB verification; and an individualised EBH technique using a 3D-contrast enhanced CT in EBH (3D-CECT_EBH) data set and the exhale phase of the 4DCT acquired in free-breathing (FB) (4DCT_EXHALE) for planning, with CBCT_EBH verification.

Results

Thirty-six patients were evaluated with clinically acceptable plans being created and delivered successfully for all patients. The maximum acute toxicity experienced was a grade 2 for anorexia (3 patients), diarrhoea (1 patient), nausea (6 patients) and pain (2 patients). The median OS for potentially operable patients was 16 months (95%CI 11-27) and for inoperable was 14 months (95%CI 6-17).

CO and COtrain respondents described PDAC delineation was challenging, and they agreed that optimisation of the pathway was important. Optimisation of

planning images; peer review of volumes and plans with a multi-disciplinary team (MDT); and improving tumour delineation by reducing inter-observer variability (IOV) were ranked as the most important.

Volumes of GS structures were smaller than mean observer structures. Across the population, MR volumes were smaller than those created with CT only (GTV_3D). The highest magnitude of mean difference was observed directly between volumes with and without MR. Using MR and CT for delineation showed an increase in dice-similarity coefficient (DSC).

Image quality scores were improved for EXP and OBS in CBCT_EBH images and was statistically significant. An improvement in mean standard deviation (SD) scores for celiac artery (CA), superior mesenteric artery (SMA) and superior mesenteric vessel (SMV), duodenum, GTV/ITV and PTV were shown for EXP and OBS. Increased confidence was observed for the EXP and OBS groups.

Clinically acceptable plans were created using both methodologies. Similar planning target volume (PTV) coverage were achieved for PTV_FB and PTV_BH, with OAR dose reduction being shown in the PTV_BH plans. CBCT_EBH significantly improved image quality, visualisation of structures and confidence in decision making. The assessment of PTV_BH resulted in 97% of scores, there was confidence in verifying coverage, significantly more than in CBCT_FB at 26%.

Conclusions

In conclusion, the evaluation of thirty-six patients in the initial retrospective study showed that VMAT plans resulted in acceptable acute toxicity. No grade $\geq$3 toxicity reported, and grade 2 symptoms being reported in a small percentage of cases. The median overall survival for both potentially operable and inoperable patients were reported. This formed a baseline for conducting the next stages of the thesis.

The survey carried out highlighted the challenges in delineating pancreatic cancer (PDAC) and emphasised the collective desire to optimise the pathway when developing SABR. Various strategies, including peer review, improved imaging, and reducing inter-observer variability, were identified as crucial in this context.

The delineation study demonstrated that IOV was high across volumes using MR alone, CT alone, and registered images. MR imaging alone resulted in smaller target volumes, but more agreement was shown in volumes delineated with an ITV approach which used MR and CT.

CBCT image quality scores assessed using scoring criteria developed within this thesis showed improvements with CBCT_EBH. This was shown for EXP and OBS groups when compared to CBCT_FB scores. This enhanced visualisation of structures and improved confidence in decision-making.

A comparison of plans for PTV_FB and PTV_EBH showed both methodologies were effective in generating clinically acceptable plans, with BH resulting in similar PTV outcomes and reduced dose to normal tissue. A clear and important advantage of a BH SABR technique was that CBCT_EBH offered superior image quality and increased confidence in verifying target coverage. This demonstrated that CBCT_EBH is superior to CBCT_FB in delivering PDAC SABR and should be considered a necessary method for linac-based RT.

This thesis has investigated a number of processes within the PDAC SABR pathway, identifying uncertainties which can be minimised, allowing protocols to be optimised. These findings contribute to the ongoing effort to optimise techniques that can be implemented in clinical trials going forward, with an aim to improve outcomes for pancreatic cancer patients.

Table of Contents

Description of tables and figures

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Authors declaration

I declare that I am the sole author of this thesis. The work presented here is my own, unless otherwise acknowledged. This thesis has not been submitted for consideration of another degree in this or any other university.

List of abbreviations

3D- conformal RT (3D-CRT)

3D- contrast enhanced CT (3D-CECT)

3D- contrast enhanced CT in exhale breath hold (3D-CECT_EBH)

4DCT exhale bin of 4DCT_FB (4DCT_exhale)

4DCT inhale bin of 4DCT_FB (4DCT_inhale)

4DCT acquired in free-breathing (4DCT_FB)

6 degrees of freedom (6-DOF) Adaptive RT (ART)

Abdominal compression (AC)
Advisory Committee for Radiation Oncology (ACROP)

Age standardised incidence rate (ASR)

American Association of Physicists in Medicine (AAPM)

American Joint Committee on Cancer (AJCC)

American Society for Radiation Oncology (ASTRO)

Anisotropic Analytical Algorithm (AAA)

Apparent diffusion coefficient (ADC)

Artificial intelligence (AI)
Biologically effective dose (BED)
Borderline resectable pancreatic cancer (BRPC)

Breath-hold (BH)

Celiac artery (CA)

Chemoradiotherapy (CRT)

Clear resection margins (R0)

Clinical target volume (CTV)

Chemoradiotherapy (CRT)

Clinical nurse specialist (CNS)

Clinical Oncologists (CO)

Clinical Oncology trainees (COtrain)

Cone-beam CT (CBCT)

Cone-beam CT in exhale breath hold (CBCT_EBH)
Cone-beam CT in free-breathing (CBCT_FB)
CO and COtrain observer structures (All OBS)

Common Terminology Criteria for Adverse Events (CTCAE)
Consultant radiologist (COrad)

Deep-inspiration BH (DIBH)

Diabetes mellitus (DM)

Dice similarity coefficient (DSC)

Diffusion-weighted imaging (DWI)

Dose limiting toxicities (DLT)

Dynamic contrast-enhanced MRI (DCE-MRI)
Exhale BH (EBH)

Endoscopic ultrasound (EUS)

Endoscopic retrograde cholangiopancreatography (ERCP)

European Society for Radiotherapy and Oncology (ESTRO)

Fast imaging employing steady state acquisition (FIESTA)

Fat-saturation (FS)

Fluorodeoxyglucose -positron emission tomography (FDG-PET)

FOLFIRINOX (FFX).

Free-breathing (FB)

Gastro-intestinal (GI)

General practitioner (GP)

Glasgow resectability criteria (GRC)
Gold standard (GS)

Gross tumour volume (GTV)

Gross tumour volume delineated on 3D CECT_EBH (GTV_3D)

Gross tumour volume delineated on exhale phase of 4DCT (GTV_exhale)

Gross tumour volume delineated on inhale phase of 4DCT (GTV_inhale)

Gross tumour volume delineated on MR (GTV_MR)

Gross tumour volume delineated on MR and CT registered images (GTV_MR-CT)

High dose kidney (HK)
Internal GTV (iGTV)

Internal target volume on 3D and 4DCT (ITV_CT)

Internal target volume on 3D and 4DCT registered with MR (ITV_MR)

Image-guided radiotherapy (IGRT)

Image registration (IR)

Intensity modulated RT (IMRT)

Inter-disciplinary team (IDT)
Inter-observer variability (IOV)

Internal target volume (ITV)

Inter-quartile range (IQR)

International Commission on Radiation Units and Measurements (ICRU)

Intra-venous (IV)

Intra-voxel incoherent motion (IVIM)

Linear accelerator (linac)

Locally advanced pancreatic cancer (LAPC)

Low dose kidney (LK)
Magnetic resonance cholangiopancreatography (MRCP)

Master test case (MC)
Maximum tolerable dose (MTD)

Mid-ventilation (Mid-v)

Monitor units (MU)

Motion management (MM)

MR-guided linear accelerator (MR-Linac)

Multi-disciplinary team (MDT)

National Comprehensive Cancer Network (NCCN)

Neoadjuvant therapy (NAT),

National Institute for Health and Care Excellence (NICE)

Normal tissue control probability (NTCP)

Not completed (NC)Radiotherapy (RT)

Obstructive jaundice (OJ)

Organs at risk (OAR)

Overall image quality (OQ)
Overall image quality in exhale breath hold (OQ_BH)

Overall image quality in exhale breath hold with abdominal compression

(OQ_BH_AC)

Overall image quality in free-breathing (OQ_FB)

Overall image quality in free-breathing with abdominal compression (OQ_FB_AC)

Overall survival (OS)

Peer review (PR)Positive resection margin (R1)

Pancreatic cancer (PC).

Pancreatic ductal adenocarcinoma (PDAC)

Pancreatic intraepithelial neoplasia (PanIN)

Patient and public involvement (PPI)

Positron emission tomography CT (PET-CT)
Photon Optimiser (PO)

Planning target volume (PTV)
Progression free survival (PFS)

Progressive Resolution Optimiser (PRO3)
Quality assurance (QA)

Radiotherapy (RT)

Radiotherapy Trials Quality Assurance (RTTQA)
Region of interest (ROI)

Respiratory motion (RM)

Respiratory patient management system (RPM)

Royal College of Radiologists (RCR)

Simultaneous integrated boost (SIB)
Standard Deviation (SD)

Standard of care (SOC)

Stereotactic ablative RT (SABR)

Stereotactic body RT (SBRT)
Superior mesenteric artery (SMA)

Superior mesenteric vein (SMV)

Surface guided-RT (SGRT)
Systematic error (SE)

Treatment planning system (TPS)Tumour in situ, no nodal involvement, and no metastases (TisN0M0)
Tumour, node, metastasis (TNM)

Twice daily (BD)
Volumetric arc therapy (VMAT)

Chapter 1 Introduction

1.1 Anatomy of the pancreas

The pancreas is an elongated digestive glandular organ that lies transversely across the posterior abdominal wall, posterior to the stomach. The organ can be split into sections which include the head, neck, body, and the tail. Their positioning in the abdomen is described in relation to differing neighbouring structures, with the head of the pancreas situated on the right side of the organ, in the curve of the duodenum (Mahadevan, 2019). It has a prolongation called the uncinate process that extends superiorly and to the left and lies posterior to the superior mesenteric vessels. The body and tail of the pancreas extends to the left side of the abdomen, narrowing towards the tail which is situated beside the spleen. The pancreatic duct joins the common bile duct (which produces bile) just before it enters the second part of the duodenum. Predominantly, the pancreas is an exocrine gland (where digestive enzyme secretions enter the duodenum via the pancreatic duct); another role is important endocrine functions, where glucagon and insulin enter the blood.

Blood supply of the pancreas includes the pancreatic-duodenal, gastroduodenal, splenic, and superior mesenteric arteries (SMA). Its relationship to the arteries and veins are illustrated in figure 1.1. The location of the pancreas and the interrelation of GI, arterial and venous structures make it challenging to treat with both surgery and radiotherapy as illustrated in figure 1.1 by Shi and Liu (2014). Above the pancreas, the celiac axis branches from the aorta. The SMA and superior mesenteric vein (SMV) are closely related to the neck of the pancreas; with the splenic vein beginning close to the tail (Russell and Aroori, 2022).

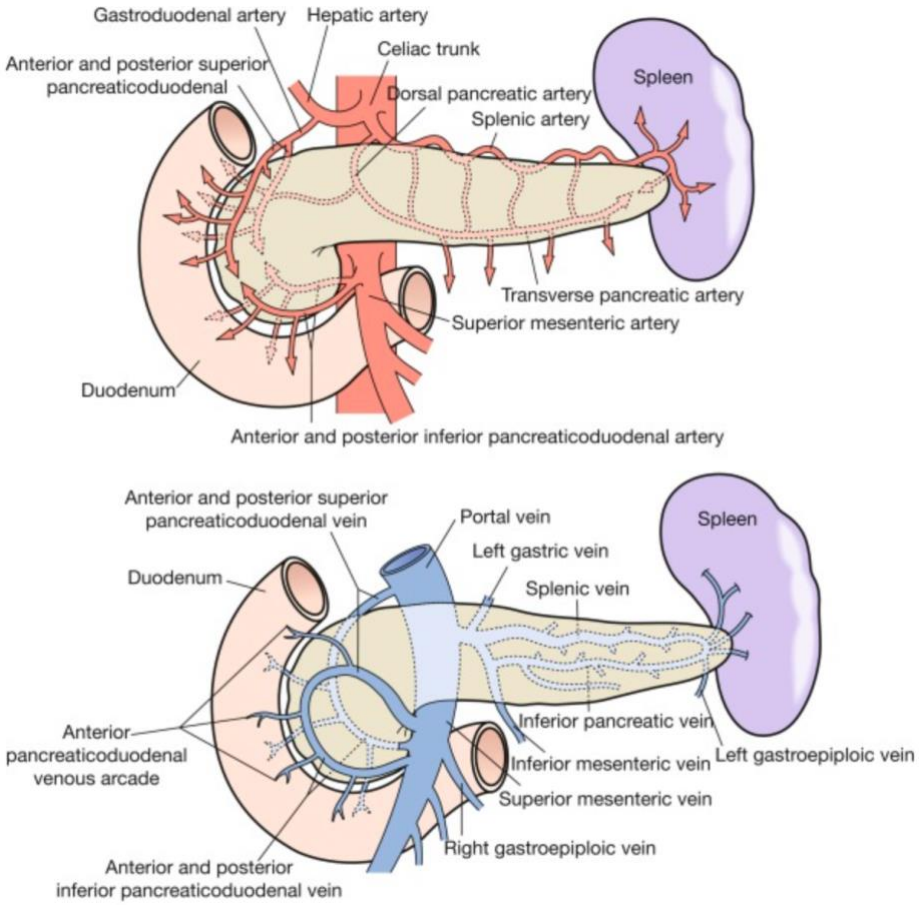


Figure 1.1 The pancreas is supplied by multiple branches from the celiac and superior mesenteric arteries and is drained by the portal, inferior, and superior mesenteric veins (Shi and Liu, 2014).

The anatomical location and relationships of the pancreas play a key role in the complexities of surgical resection and delivering targeted RT treatment for pancreatic cancer. Involvement of adjacent veins and arteries are described in criteria by the National Comprehensive Cancer Network (NCCN) (Tempero et al., 2017), where levels of involvement often deem the patient as unresectable i.e. locally advanced pancreatic cancer (LAPC) and metastatic PC; or, resectable PC and borderline resectable pancreatic cancer (BRPC), the latter reflecting the likelihood of surgery being technically challenging and unlikely to result in clear margins (R0). Close proximity of these structures also present challenges in delivering effective doses or RT without delivering unacceptable doses to the adjacent normal tissues. The GI tract including duodenum, stomach and bowel are dose-limiting structures, at risk of toxicity through exposure to radiation, this will be discussed in more detail in a later section.

The location of pancreas and its relationship to surrounding organs are indicative of the challenges in surgical resection and delivering targeted radiotherapy (RT). An understanding of this is key to addressing the challenges faced in optimising treatment (Sabater et al., 2018).

1.2 Pancreatic ductal adenocarcinoma

1.2.1 Epidemiology

Pancreatic cancer is a malignant and treatment resistant disease which results in a poor prognosis for the majority of patients. This is reflected in the mortality rates associated with the disease, with 5-year survival rates being around 7 %; and 10-year survival 5%, based on data from England (CRUK, 2023); and with the clear illustration that the number of deaths in 1 year is close to matching the number of new diagnoses i.e. 9,600 patients died annually between 2017-2019 from pancreatic cancer, with 10,500 being diagnosed. Patients are faced with the inauspicious evidence that there has been no improvement in UK survival in the last four decades (CRUK, 2023), although USA statistics report an improvement in 5-year overall survival (OS) to 11% for combined stages (Siegel et al., 2022). Even with moderate progress made in some areas, the overall landscape demonstrates that more investment is required to achieve a clinically significant improvement in outcomes.

Pancreatic cancer has the lowest one-year survival of any cancer in the UK (CRUK, 2023); this further illustrates the poor outlook suffered by patients. Other worrying factors in pancreatic cancer survival are the disparity and inequalities across geographical areas, which may suggest variation in disease management throughout the UK (PHE, 2020). This is reflected by the differences in estimations of OS reported across different regions in England. When coupled with the worst 1 year survival, this demonstrates the need for further investigation, with UK initiatives on understanding the variation and reducing the gap described by the UK charity Pancreatic Cancer UK (PCUK, 2020). When

compared to other similar countries, the UK OS figures for pancreatic cancer are substandard, ranking 29th out of 33 countries with comparable data between 2000-2014 (Allemani et al., 2018). Pancreatic cancer is a global problem and according to worldwide cancer statistics, it is the 7th top cause of cancer death (Bray et al., 2018).

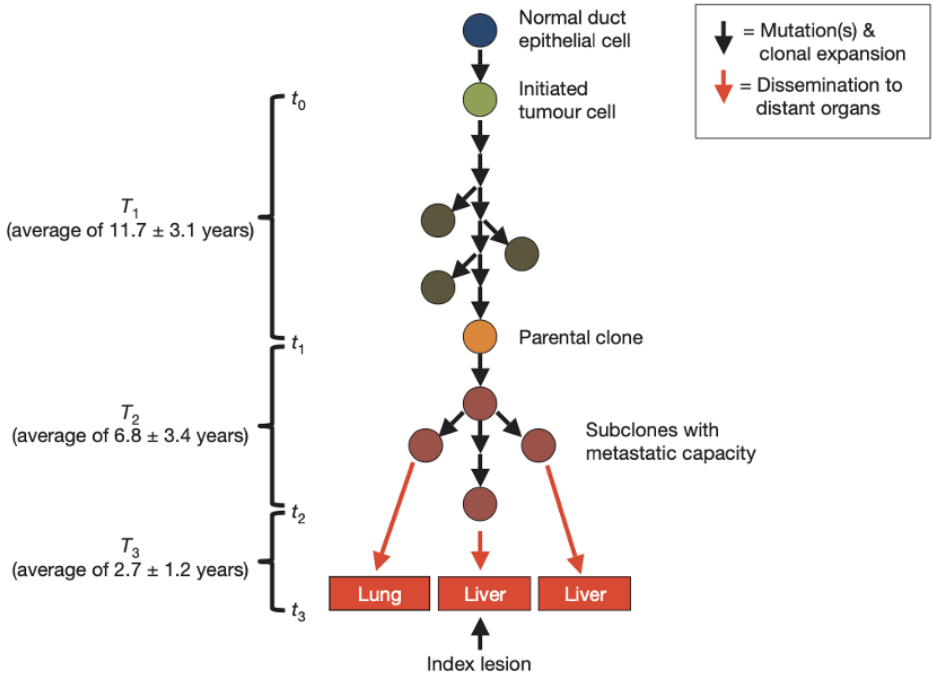
There are notable differences in the incidence of pancreatic cancers across different regions worldwide, with Europe and North America having the highest age standardised incidence rate (ASR), significantly more than less developed regions e.g. Eastern Africa and South-East Asia. The incidence is higher in men than women for most regions, which is illustrated by Bray et al. (2018). Worldwide, 5-year survival rates have shown modest improvement between 2014 and 2018.

1.2.2 Risk factors

Although there are no concrete answers as to why these geographical and gender incidences vary so much, it could be down to environmental factors and exposure to them. Another consideration is that global variations in diagnostic capacity and resources may lead to under-diagnosis or under-reporting of cases. Attributing factors can be classified into non-modifiable and modifiable risk factors (Midha et al., 2016). The former includes familial genetic factors that cannot be changed and demographics e.g. gender, age, ethnicity, and diabetes mellitus (DM). Modifiable examples include environmental risk factors e.g. diet, smoking history, alcohol intake, and exposure to harmful substances, all of which are described in detail by Rawla et al. (2019). Even where risks are non-modifiable, the addition of modifiable ones may exacerbate an individual's risk. For example, alcohol abuse or smoking history could exacerbate the risk of pancreatic cancer for someone with a non-O type blood group (non-modifiable); or obesity (modifiable) that leads to DM could also increase risk, with DM being a risk factor as well as a symptom of PDAC.

1.2.3 Molecular features

Most pancreatic cancers are defined as PDAC. These tumours are formed as a malignancy in the exocrine pancreas, originating in the duct responsible for transporting digestive enzymes. They often begin as precancerous lesions, known as pancreatic intraepithelial neoplasia (PanIN). Subsequent genetic alterations that accumulate gradually with time, are associated with an increase in severity of dysplasia (Mizrahi et al., 2020; Wang et al., 2021). Progression from low (PanIN1), through moderate (PanIN2) to high grade (PanIN3) histology is described by Hruben et al., (2004) in their classification system, and illustrated by Yachida et al., (2010) in figure 2. The characterisation of the genetic evolution of pancreatic cancer shows that slow progression to invasive cancer and metastatic disease could provide possibilities for earlier diagnosis. As shown in figure 1.2, most patients are diagnosed at time interval 3, at which tumour cells have already infiltrated organs beyond the pancreas.



Tumorigenesis begins with an initiating mutation in a normal cell that confers a selective growth advantage. Successive waves of clonal expansion occur in association with the acquisition of additional mutations, corresponding to the progression model of pancreatic intraepithelial neoplasia (PanIN) and time T_1. One founder cell within a PanIN lesion will seed the parental clone and hence initiate an infiltrating carcinoma (end of T_1 and beginning of T_2). Eventually, the cell that will give rise to the index lesion will appear (end of T_2 and beginning of T_3). Unfortunately, most patients are not diagnosed until well into time interval T_3 when cells of these metastatic subclones have already escaped the pancreas and started to grow within distant organs. The average time for intervals T_1, T_2 and T_3 for all seven patients is indicated in the parentheses at left

Figure 1.2. Schema of the genetic evolution of pancreatic cancer (Yachida et al., 2010).

Dynamic evolution and application of sequencing technologies have allowed researchers to understand more about the genetic and epigenetic factors associated with the disease. Molecular subtypes have been identified, which are detailed in an international consortium study published by Waddell et al. (2015). Genomic data for 100 patients were studied and four main subtypes identified. Structural variation events ranged from less than or equal to 50 in stage 1 (stable subtype) through to the subtype four which exhibited >200 structural variations (unstable subtype).

Although providing exciting opportunities to develop personalised treatment approaches, the complexity of these genomic discoveries makes them difficult to translate into clinical practice. In recent years, clinical research groups have been motivated to build platform studies that ensures the right trial is available for the right patient, allowing patients to be assigned to treatment protocols based on genomic characterisation of their disease (Froeling et al., 2021).

1.2.4 Clinical presentation

The known challenges in diagnosing upper GI cancers and early-stage pancreatic cancer have been described by authors MacDonald et al. (2006). They found late presentation at their general practitioner (GP), delayed awareness of symptom seriousness, and waiting times for diagnosis to be contributing factors to delays in diagnosis. Patients often present with symptoms such as back pain, nausea, jaundice, change in appetite, bowel habits and weight loss, which are described as non-specific symptoms. For many patients, this contributes to a failure to diagnose in a timely manner.

More specifically, work by Gullo et al. (2001) interviewed pancreatic cancer patients at least twice using an interview methodology. They questioned patients on whether they had experienced disease related symptoms up to five years prior to diagnosis. They reported that in a proportion of patients (15%) there were early indicators of suspected cancer i.e. non-specific symptoms were

suffered by some patients more than 6 months before pain and jaundice. Most frequently, symptoms experienced were anorexia, early satiety, and physical weakness (Gullo et al., 2001). Data from NHS England shows that although the number of patients diagnosed through emergency presentation has shown a decreasing trend from 50% in 2007 to 43% in 2018, these numbers remain high (NHS, 2018).

1.3 Diagnosis and staging

1.3.1 Imaging for diagnosis

The diagnosis of pancreatic cancer often occurs after the disease has sufficiently spread enough to be classified as LAPC or metastatic i.e. not suitable for surgical resection. A clear standardised approach to diagnosis and staging has been published in the UK National Institute for Health and Care Excellence (NICE) guidelines (NICE, 2018; O'Reilly et al., 2018). These provide recommendations on the optimal pathways to be applied to patients with suspected pancreatic cancer (PC). The aim of these guidelines was to reduce variations in the standard of care procedures, creating a positive impact on patient care.

Whether patients have suspected PC with or without obstructive jaundice (OJ), the first recommendation is to offer a pancreatic CT protocol, followed if required by a fluorodeoxyglucose -positron emission tomography (FDG-PET) -CT. For patients with OJ, an endoscopic retrograde cholangiopancreatography (ERCP) is indicated to enable insertion of a stent to relieve jaundice and providing an opportunity to obtain brushings or biopsies for cytology or histology to confirm diagnosis. If OJ is not present and ERCP not required, endoscopic ultrasound (EUS) may be required to obtain tissue.

A lack of high-quality evidence is acknowledged throughout the evidence base, with expert consensus approaches being important in guideline development (NICE, 2018; O'Reilley et al., 2018). EUS was reported as high sensitivity and low

specificity in the moderate/high quality literature, but with high availability and low invasiveness CT is recommended; where CT and EUS tissue sampling is acquired, this provides greater sensitivity and specificity. Recommendations differ for those with pancreatic cysts, where a CT protocol or a magnetic resonance cholangiopancreatography (MRCP) may be offered. These patients may then by evaluated for surgical resection, or in the instance where more information is required EUS (with fine needle aspiration) should be proposed.

Evidence for diagnostic imaging of pancreatic cancer using MRI has been discussed in a Cochrane meta-analysis by Best et al. (2017). This review showed that individual studies comparing imaging modalities were generally of low quality, recruited low patient numbers, and employed poor methodologies. These limiting factors highlight concerns that conclusions from such studies could result in false assumptions. Further to this, sensitivity and specificity evaluation of the different modalities failed to demonstrate adequate diagnostic quality, precluding definition of a gold standard modality. These issues are reflected throughout the guidelines where a consensus has generally been reached based on experience rather than definitive evidence (NICE, 2018; O'Reilley et al., 2018).

MRI plays an important role in tumour characterisation, as detailed in the NICE guidelines report (O'Reilley et al., 2018). Evidence supports the use of T1 and T2-weighted imaging (Toft et al., 2017); and functional imaging (primarily diffusion-weighted imaging (DWI)) which is of increasing interest, with evidence emerging that shows functional changes in tissue may be detected earlier than morphological changes. Research into functional imaging approaches is increasing, with an important gap being the differentiation of fibrotic and tumour tissue following therapies.

In a study conducted by Ferrone et al. (2015) that included 188 patients, 40 of which had undergone systemic neoadjuvant therapy (NAT), surgical exploration saw disagreement of restaging outcome when compared to radiological

assessments. This study highlighted the limitations of restaging using current techniques, with 92% of patients post- FOLFIRINOX (FFX) being defined as unresectable with imaging, but in fact, successful R0 margins were reported following surgical exploration. High accuracy, sensitivity and specificity of DWI have been reported as by Messina et al., (2020), demonstrating the additional benefit of adding such sequences to pancreatic protocols. More complex imaging protocols e.g. intra-voxel incoherent motion (IVIM) have potential to improve characterisation further, although there are limitations on the adoption into clinical practice routinely (De Robertis et al., 2015).

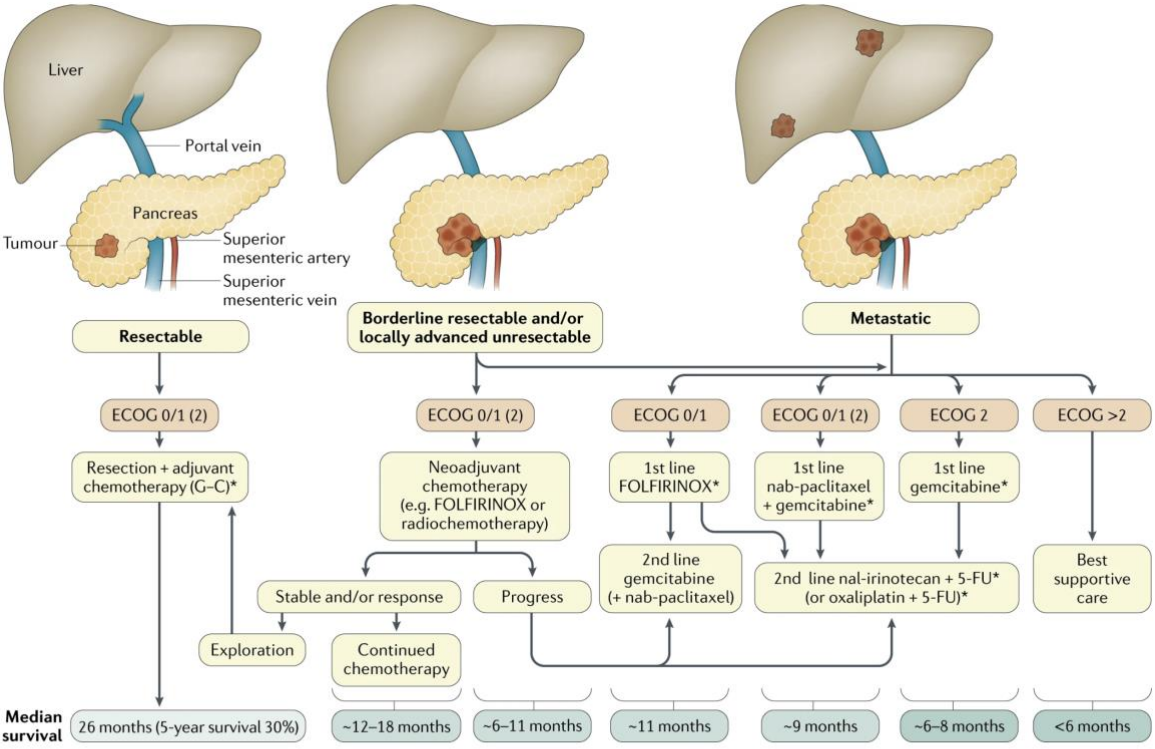
1.3.2 Staging

As described above, UK recommendations were made to support the use of a pancreatic protocol CT scan, as a minimum for either suspected or confirmed disease in the UK (NICE, 2018; O'Reilley et al., 2018). Where treatment is recommended for localised disease, an FDG-PET should also be performed, since this has been determined to increase the accuracy of staging and prevent unnecessary surgical resection. According to NICE, FDG PET/CT in diagnosing PDAC was supported by higher quality evidence. Results from a multi-centre study that implemented a robust methodology demonstrated that imaging results could change disease staging, therefore changing any management plan (Ghaneh et al., 2018). Additional information from an MRI is useful to rule out progression to the liver and is recommended to confirm the absence of metastases (Motosugi et al., 2011). Although most data on the staging of disease was deemed to be of low quality, there were high quality data allowing recommendation of CT, EUS and MRI for tumour, node, metastasis (TNM) staging; and FDG-PET.

Disease staging can be described in several ways. There is the stage of the cancer which refers to how advanced the disease is i.e. stage 1 is early disease which is operable; in stage 2 spread may include nearby lymph nodes; stage 3 is LAPC or BRPC; and stage 4 is advanced metastatic disease (American Cancer Society, 2023). The American Joint Committee on Cancer (AJCC) TNM system, 8th edition (Amin et al., 2017; AJCC, 2023), which requires the size and extent of the disease, lymph node involvement and the detection of metastases. Examples of classifications include stage 0, which would be tumour in situ, no nodal involvement, and no metastases (TisN0M0), through to the most advanced stage where metastases are present ($M \geq 1$). Such staging descriptions are updated when new evidence allows it e.g. an update from the 7th to the 8th edition included a greater emphasis to be placed on the size of the tumour rather than just the description. New editions aim to refine the classification system by utilising a more personalised approach.

Considering that appropriate disease management relies on diagnostic information concerning the stage of disease, the National Comprehensive Cancer Network (NCCN) resectability criteria is used to guide clinical decisions (Tempero et al., 2019). This criterion gives the treating clinician explicit radiological reporting on the factors that affect resectability e.g. detailed descriptions of the involvement of veins and arteries. These descriptions of vein and artery involvement allow comprehensive assessment of the suitability to attempt surgery. The NCCN also provides comprehensive disease management guidelines for multi-modality management.

An example of patient stratification as recommended by an expert consensus group (informed by evidence-based studies) is shown in figure 1.3 (Neoptolemos et al., 2018). This demonstrates the importance of using staging alongside performance status when disease management approaches are being considered.



Patients are stratified according to tumour stage (resectable, borderline resectable and locally advanced unresectable, metastatic) and performance status (defined by the Eastern Cooperative Oncology Group (ECOG) score). Median survival values are) estimates from published data, mainly from small, single-arm or retrospective trials. In the metastatic setting, survival data are from trials of first-line therapy. This treatment algorithm represents the expert opinion of the authors. 5-FU, 5-fluorouracil; FOLFIRINOX, folinic acid, fluorouracil, irinotecan and oxaliplatin; G–C, gemcitabine–capecitabine; nab, nanoparticle albumin-bound; nal, nanoliposomal. *Approaches are based on evidence from RCTs. Other depicted treatment algorithms are current approaches, but they are not evidence based and are not standard of care worldwide.

Figure 1.3. Suggested treatment algorithm for patients with pancreatic cancer (Neoptolemos et al., 2018).

1.4 Multi-modality treatment for PDAC

Discussion of patients in a multi-disciplinary team (MDT) setting is required to ensure patients get the optimal care and is recommended as the gold standard in the UK NICE guidance (NICE, 2018). Treatment requires specialist care across departments, so MDT working is essential in achieving that for a group of patients that have multiple unmet needs. Patients should receive the appropriate clinical investigations, have access to MDT specialists, and be included in discussions with the MDT regarding their management plan.

1.4.1 Surgery for PDAC

A lack of recognised symptoms prevents the diagnosis of early-stage tumours, with most patients presenting with unresectable disease (CRUK, 2023). Surgical intervention is known to be the only chance of delivering a "curative" treatment, however only the minority are given this opportunity due to the challenges in detecting small tumours with limited progression and no detectable metastases. Those who have resectable disease and proceed to surgery, still face the possibility of poor outcomes, where those with positive resection margins (R1) have similar outcomes to those with more advanced disease (Ghaneh et al., 2019).

Diverse R1 resection rates i.e. evidence of cancer cells within 1mm were described in a meta-analysis by Chandrasegaram et al. (2015), where studies reported between 28 and 71% of R1 rates. R1 rates are a prognostic variable linked to poorer outcomes (Howard et al., 2006; Strobel et al., 2017). However, the large variations reported may be due to confounding factors e.g. patient selection, margin interpretation, and pathological assessments. The importance of R status being important in terms of OS is reinforced in the published results of the ESPAC-3 trial (Valle et al., 2014), with resectable patients now being more likely to undergo NAT before proceeding to surgery.

The risk of mortality from surgery has reduced over the past 2 decades and is discussed in a review by Strobel et al. (2017). This reduction has been reported in high volume centres where specialist MDT care is available. These outcomes are more likely to improve where there are highly experienced staff, who are employing optimal patient selection strategies which consider both patient and disease factors in the process. As mortality rates have improved, the indications for surgery have evolved e.g. attempting surgery in LAPC and applying more aggressive approaches. However, post-surgery morbidity remains a great concern, with hugely complicated surgeries that require resection and reconstruction of arteries.

1.4.2 Neo-adjuvant therapy

For patients where surgery may be an option i.e. resectable or BRPC (around 20%), there has been a clear drive forward in using systemic NAT, with an aim of downstaging tumour and increasing the likelihood of clear resection margins (R0). Traction gained over the past few years using a NAT approach has provided an opportunity to deliver an upfront treatment for a disease that is at high risk of quick progression. Another benefit is that it allows the selection of patients with more favourable biology, as staging imaging pre/post-therapy can determine if disease is stable, or has progressed. The period where therapy is delivered followed by imaging and restaging gives clinicians the opportunity to select the best candidates for surgery, reducing the numbers of patients where there is a likelihood of no benefit.

A systematic review and meta-analysis of randomised data reported by van Dam et al. (2022) showed a benefit in OS when NAT was used in the BRPC group. A large number of patients were included in the pooled results (n=938), none of which had been treated with FFX. The heterogeneity of treatment protocols and the variation in staging of disease were limiting factors, leading to a conclusion that further evidence was required. Janssen et al. (2021) investigated the benefit of NAT (first line) using FFX in patients who were staged as BRPC and

found improved median OS. However, they also highlighted the need for further evidence to support a standardised regimen.

Despite this contradictory information and only moderate level evidence, American Society for Radiation Oncology (ASTRO) consensus guidelines strongly recommended that for BRPC and LAPC, definitive RT should be delivered following systemic therapy (Palta et al., 2019). High agreement was reached in the group (92% for BRPC and 85% for LAPC). In the LAPC group following NAT, improved OS was reported when compared to gemcitabine (24.2 months v. 6-13 months) was reported in a systematic review and meta-analysis (Suker et al., 2016). The authors reported a clear benefit in OS and progression free survival (PFS), and although a lack of randomised phase 3 data was included in the analysis, PRODIGE-29 (NEOPAN) have since confirmed the benefits of FFX in a phase 3 randomised trial (Ducreux et al., 2022).

1.4.3 Role of radiotherapy

The rationale for using RT as part of the disease management plan is to prevent, or at least delay progression i.e. maintain local control in LAPC; in cases where symptoms are caused by obstruction, RT is intended to alleviate these symptoms; or, RT is used to treat the microscopic disease before surgical resection, to improve R0 resection rates. The latter approach is much less studied and has quite different considerations from the former. Authors Hall et al. (2021a) provide a detailed explanation of the narrative that has been formed around RT for PDAC, and some of the much-discussed controversies that exist.

The publication of trial data from over three decades ago highlighted the benefits of RT when added to chemotherapy (Moertel et al., 1981). In later years, the role of RT in the treatment of pancreatic cancer became increasingly controversial due to a lack of clear, unambiguous, and high-quality data that shows improvement in OS. Conflicting evidence reported modestly improved outcomes with RT (Loehrer et al.,2011); and less efficacy with more toxicity reported by others (Chauffert et al.,2008). One prominent study impacting mixed opinions in the community, is down to the published randomised trial data, where they reported no significant benefit in OS with chemoradiotherapy (CRT) compared to chemotherapy alone (Hammel et al., 2016). A benefit that was reported in the study was that CRT patients had longer progression free survival 6.1 months versus 3.7 months, which showed potential of giving patients time off active treatment.

Standard of care RT for pancreatic cancer has been conventional fractionated RT for the past few decades, with outcomes from conventionally fractionated RT reported in trials (Hammel et al., 2016; Mukherjee et al., 2013). These used a dose of 50.4Gy delivered over 28 fractions. The delivery of these trials included less sophisticated RT than is now available, and although data showed the improvements that could be made with IMRT, these were not commonplace at the time (Bittner et al., 2015). These fractionated protocols delivered over a

number of weeks were designed to allow healthy tissue to recover between fractions. In this setting, less focus was required on precision and accuracy, with large margins and less frequent image-guided RT (IGRT) protocols being employed.

Conventionally fractionated RT did not produce the improved survival outcomes that were so much needed for PDAC, although these long fractionations remained as standard of care in the UK until the Covid-19 pandemic. An interest in higher dose RT has been reported over the years e.g. in 2002 using a rapid-fractionated RT protocol of 3Gy per fraction (Pisters et al., 2002). This study showed that 30Gy over 10 fractions resulted in 46% of patients experiencing grade 3 toxicity, although this was using paclitaxel and a 4-field RT technique that would have caused collateral damage to normal tissue. A large retrospective study of 119 patients reported by Reyngold et al., (2021) showed a significant improvement in 2-year OS was achieved using ablative techniques. This study was carried out using a biologically effective dose (BED) of >97Gy delivered in a 15 or 25 fraction schedule depending on how close to GI structures the tumour was situated (75Gy in 25 fractions when within 1cm, or 67.5Gy in 15 fractions when >1cm).

Progressive moves towards increasing dose and reducing fractionation have since been continuous, gaining even more traction since the advent of the MR-guided linear accelerator (MR-Linac) based RT (Pollard et al., 2017; Winkel et al., 2019). Modern RT techniques have since enabled a reduced dose to dose-limiting structures, where the necessary employment of optimal treatment strategies are required. These include improved set-up and immobilisation and motion mitigation, all used in conjunction with daily IGRT protocols (Heerkens et al., 2014).

The radioresistance of pancreatic cancer and the increased availability of more sophisticated treatments have led to much interest in delivering hypofractionated RT to the pancreas, where higher doses are required to

improve the therapeutic ratio (Brunner et al., 2015). Adoption of SABR for pancreas in the UK has been a slow process, which was somewhat accelerated in response to the Covid-19 pandemic. Hypo and moderately fractionated protocols were developed and implemented to reduce hospital visits in 2020, with a consensus approach used to publish contingency guidelines (RCR, 2020).

In the UK, patient and professional opinions have helped to drive SABR development and implementation forward, following work which entailed a survey of pancreatic clinical oncologists, in conjunction with a patient and public involvement (PPI) workshop (Brocklehurst et al., 2021). This saw the 2 groups reach agreement regarding the potential to improve quality of life with SABR. Several challenges were identified regarding implementation, which were raised by the professional group. A national programme was designed to provide the relevant guidance and support for departments through the UK SABR consortium and the Royal College of Radiologists (RCR).

Hypofractionation requires multiple additional considerations to be applied to the pathway. Immobilisation, positioning, and reproducible set-ups are key to delivering safe and accurate treatment; whilst optimal planning images (preferably multi-modality with additional support from a radiologist) are required in the delineation stage, to increase the precision of treatment (UK SABR consortium, 2019). With SABR being delivered in fewer sessions with a high dose per fraction, there are less opportunities to make changes, meriting more emphasis on safety, accuracy, and precision (Lo et al., 2010)

There are a diverse range of treatment protocols used within studies e.g. dose and fractionation, heterogeneous diagnosis of patients, and quality of RT. When used sequentially with NAT treatment, results have again been contradictory. This is demonstrated by different prospective trial outcomes, with long term results of the phase 3 PREOPANC study showing improved OS with CRT, whilst phase 2 Alliance A021501 trial closed the SABR arm early, reporting inferior OS when SABR was added to FFX (Katz et al., 2021; Versteijne et al., 2022).

With different study methodologies and reporting methods in the literature, combining data is a challenge. Dose escalation delivered using high precision RT i.e. SABR, is being investigated throughout different stages of disease, with much anticipation that clinical outcomes will improve for this cancer of unmet need. Benefits have been described in multiple settings, including assessment of high dose RT delivered to the tumour vessel interface, resulting in good R0 outcomes and locoregional control (Mellon et al., 2015); improved organ at risk sparing and target coverage using MR-Linac (Bohoudi et al., 2017); and improved local control (Parikh et al.,2022). This has been accelerated by constant evolution of planning and delivery technologies, motion mitigation strategies and IGRT. There have been consistent data capturing improved progression free survival, using these advancing technologies; adaptive protocols and ablative techniques; increasing with experience and the development of high-quality studies.

1.5 Radiotherapy for different stages of disease

1.5.1 Borderline resectable pancreatic cancer

Rationale for treating BRPC with NAT +/- RT is to reduce the risk of positive margins by treating microscopic disease, whilst observing a patient's response to treatment. Results following NAT for BRPC have been shown to be similar to that of resectable patients (Tang et al., 2016). Optimal RT protocols are less well defined for this group of patients. Katz et al. (2013) described a large cohort of BRPC patients who received neo-adjuvant chemotherapy and chemoradiation. The group reported a large percentage of patients successfully completing surgery with R0 resections (94%), of which the majority of the group had received chemoradiation (95%). RT was delivered in these cases using a conventional dose and fractionation of 50.4Gy in 28 fractions.

A hypofractionated BRPC study investigated dose escalation to a margin intensive region, with an aim to improve the R0 resection rates (Holyoake et al.,

2021). However this phase 1 trial closed early due to recruitment figures not being met, not meeting the primary endpoint of finding the maximum tolerable dose (MTD) using SABR. The PREOPANC trial presented positive findings where chemoradiation in the pre-operative patients compared to immediate surgery resulted in higher R0 resections, 71% and 40% respectively; and significantly improved PFS in comparison to surgery and chemotherapy (adjuvant). CRT in this study was of a low dose, over moderate hypofractionation i.e. 36Gy in 15 fractions (Versteijne et al., 2020).

1.5.2 Locally advanced pancreatic cancer

The rationale for RT to treat LAPC is different from BRPC, with the intent of this treatment being survival, local control, and control of symptoms. There are different considerations for LAPC than BRPC, where there is no dose-escalation required to arterial and vasculature structures that may prove challenging to reconstruct during technically challenging operations. That being said, there are LAPC patients who undergo neoadjuvant treatment and convert to being candidates for surgery. Hackert et al., (2016) reported that resection rates for LAPC following FFX and gemcitabine + RT were 50.8% and 46% respectively.

For LAPC the real concern is over local progression that may become symptomatic, with RT being an important option for those patients. Results from an autopsy study that investigated patterns of failure for 76 patients illustrated the importance of treating local disease (Iacobuzio-Donahue et al., 2009). They found that the cause of death for 30% of patients was caused by complications of local progression. Good results reported across studies have highlighted the benefit for SABR in LAPC, which include reduced treatment times for patients, improved outcomes including local control rates and survival (Petrelli et al., 2017). As with much of the evidence base around pancreatic cancer treatments, data is from non-randomised studies where the effects of treatment may be under-reported, and bias affecting results. A phase 1 dose escalation study investigating a 3-fraction protocol, successfully reached the highest dose level of

33Gy in 3 fractions with no dose-limiting toxicities (DLT) being reported in the 90 days following RT (Reyngold et al., 2021b).

1.6 Treatment resistance

1.6.1 Radiobiology of PDAC

In the context of PDAC, radiobiology plays a crucial role in understanding how radiation affects tumour cells and normal tissues, as well as in optimising treatment strategies. Optimisation of RT protocols for pancreatic cancer require knowledge of the radiobiological aspects. PDAC is known to be radioresistant, with several factors playing a role in this. Examples of such mechanisms are DNA damage and repair; changes to cell cycle pathway that result in either cell death or cell survival; and the complex microenvironment. With the limited progress in outcomes reported with conventional RT doses, higher radiation doses are required to overcome this (Seshacharyulu et al., 2017).

How well the tumour responds can be an effect of how much radiation is delivered, and over how many fractions, with both affecting the BED. Optimal dose and fractionation schedules require careful consideration of the impact to normal tissue, ensuring increased dose doesn't result in unacceptable toxicities. As well as radiosensitisers, different types of radioprotectors may play a role in future dose escalation, where higher doses are at risk of causing permanent damage to nearby tissue (Koukourakis et al., 2012). The effects of a standard conventionally fractionated regime have different implications to a dose-escalated hypofractionated regime, with limitations in how well the effects can be predicted. This requires further development and conduct of well-designed research studies.

1.6.2 Tumour micro-environment

Although outside the scope of this thesis, understanding the pancreatic cancer microenvironment is important in understanding tumour progression and response to treatment. The complexity of this is detailed by Fokas et al. (2015), where the authors describe the multiple factors associated with this aggressive disease. Many genetic and epigenetic mutations are responsible for the aggressive observable traits seen in PDAC. Radioresistance may be partially

attributed to desmoplasia, in the form of abnormal stroma tissue that makes up a major component of the disease. The relevance to RT and other treatment modalities, is that its dense and fibrous texture and consistency results in heterogeneous tissue that is deprived of oxygen and nutrients, which inhibits the ability for treatment to reach cancerous cells. Anti-stromal treatments may have promise in helping to break down this tissue and improve access of treatment to cancer cells, especially when combined with the correct cytotoxic drugs, but this work is still under investigation.

1.6.3 Radiosensitisers

Using radiosensitisers to target tumour cells which are known to be heterogeneous and resistant to treatment is an active area of research. Well known radiosensitisers have been studied in randomised controlled trials, for example Mukherjee et al. (2013) reported that a relatively low dose of gemcitabine compared to capecitabine was more toxic and resulted in worse survival outcomes. Another study showed the benefit of gemcitabine with RT to improve survival, compared to gemcitabine alone (Loehrer 2011); whilst OS was not improved in others (Chauffert et al., 2008; Hammel et al., 2016). As with all pancreatic literature, the limitations of such studies and the method of reporting must be interpreted with caution, especially where RT regimens were particularly toxic to normal tissue, or timing of delivery not being optimal.

Given the heterogeneous nature of pancreas tumours that have proven to be difficult to treat, exploration of further targeted therapies including molecular targets and radiosensitisers are attractive, especially in combination with novel RT protocols (Wardman et al., 2007). Tolerability of inhibitors such as erlotinib and gefitinib were tested in clinical studies to inform DLT and MTD (Strimpakos et al., 2008); continuing to be explored in patient datasets from randomised studies (Hoyer et al., 2021). As with anti-stromal therapy, these chemical agents must be assessed systematically to ensure normal tissue toxicity remains acceptable whilst investigating any benefits they may reap. Treatment and drug

combinations with the optimal timing and dose could have potential to improve outcomes.

1.7 Stereotactic ablative RT for PDAC

1.7.1 Implementation of stereotactic ablative radiotherapy in the UK

Advanced planning technologies teamed with improved IGRT and motion mitigation have been key to the development of PDAC RT. This has enabled the ability to treat pancreatic cancer with dose escalated RT using SABR for pancreatic cancer. SABR studies have not compared the difference between SABR and conventional treatments directly, being built on the basis that conventional doses failed to produce adequate improvements. SABR has recently been deemed as an appropriate national development in the UK, with creation of national guidelines and an education strategy being delivered through the RCR and UK SABR consortium in 2022, in response to a commissioning process (NHS England, 2020). These guidelines were to support the development of SABR protocols for non-metastatic LAPC. Although this is the case, SABR has been more readily adopted in the US, with the evidence from prospective and retrospective studies conducted for BRPC and LAPC showing good PFS (Ng et al., 2018), although with cautions on the incidence of grade ≥3 GI toxicity e.g. duodenal perforations and ulcers. Promising outcomes have since provided a backdrop for further investigation of higher BED, in excess of 100Gy.

1.8 CT imaging for radiotherapy planning

1.8.1 Pre-treatment imaging – 3DCT

3DCT has been the standard of care used to plan RT for many years now (Webb et al., 2006). In pancreatic cancer patients, planning images require a 3D contrast-enhanced CT (3D-CECT) as a minimum to be used for target delineation (Brunner et al., 2021). These images provide 3D soft tissue detail which are used

for delineation of target volumes and organs at risk (OAR), and calculation of dose.

Acquisition of CT for RT planning requires optimised set-up and reproducibility, which are essential for achieving high quality RT. This includes the use of immobilisation equipment to ensure comfort and prevent unnecessary motion; and appropriate discussion with the patient to allow gated or breath hold images to be acquired. The practicalities of acquiring images that are representative of the patients' daily treatment should be addressed and any uncertainties should be used to individualise the patients planning target volume (PTV) margin. Failure to consider these points may lead to major inaccuracies in the treatment planning and delivery. Patient preparation reduces the impact of stomach filling, with 2 or more hours fasting prior to planning and treatment recommended. Oral contrast is often given before scanning to help visualise the GI tract. This is mentioned in guidelines, but in practice has variable success (Chu et al., 2015).

ASTRO guideline development used a strong consensus methodology to make recommendations for RT (Palta et al., 2019). Strong recommendations were made for the following CT simulation aspects: 4DCT is necessary in the absence of breath-hold (BH) CT (for conventional and SABR fractionation); motion management to be required for SABR; daily IGRT required for both conventional and SABR, with fiducials and volumetric imaging recommended in the latter; and IV contrast should be used for planning CT, unless contraindications. The group were unanimous on all of these "strong recommendations", with high-level evidence supporting all. The European Society for Radiotherapy and Oncology (ESTRO)-Advisory Committee for Radiation Oncology (ACROP) guidelines also acknowledge the benefit of using fiducials in the SABR setting, which also still has limitations where soft tissue visualisation is not sufficient for identifying target volume and OAR (Brunner et al., 2021).

1.8.2 Pre-treatment imaging - 4DCT

The motion of pancreatic volumes can be measured and accounted for on a planning 4DCT, acquired in treatment position. Strategies for the use of 4DCT in the planning of pancreatic cancer have been implemented to deal with respiration induced motion of the target volumes. The addition of 4DCT and the optimal protocols are well established (Cattaneo et al., 2010; Mancosu et al., 2008; Tai et al., 2013).

Quantified motion data has been reported in several studies (Tai et al.,2013; Shiinoki et al., 2011), with agreement that superior-inferior motion is of the highest magnitude (Bussels et al., 2003; Feng et al., 2009). When using the internal target volume (ITV) method this motion is included in the volume, however it must be acknowledged that there are limitations of using just one 4DCT to plan for a course of RT, where motion from that planning session may not be representative of the full treatment course. Lens et al. (2014) studied the reliability and reproducibility of 4DCT and highlighted that the magnitude of motion detected between 4DCT and CBCT was significantly different, with motion magnitude being larger in 4DCT. This further supports the findings of Minn et al. (2009). Another limitation of 4DCT is that motion information comes at the cost of image quality, with the acquisition of high-quality images becoming a complex issue that requires detailed processes (Keall, 2004).

1.9 Multi-modality imaging

1.9.1 Multi-modality imaging for radiotherapy planning

Pivotal to the success of newly implemented RT techniques is the ability to incorporate multi-modality imaging in the RT pathway. Historically CT imaging has been the preferred choice for staging and diagnosis, especially where optimal acquisition techniques are applied (Callery et al., 2009). Despite CT being standard practice in defining areas of inclusion for RT treatment planning, the potential for MRI to further improve tumour definition is now commanding

more attention. This is better established for other disease-specific groups with benefits described for head and neck cancer and prostate cancer (Rasch et al., 1997; Rasch et al., 1999).

1.9.2 MRI acquisition

For MRI, the optimal techniques and their integration are still evolving. Within the studies described, there are technical descriptions of the sequences used for image acquisition and post-processing. One of the important factors not well described in publications are patient set-up and reproducibility, which could indicate that subjects weren't scanned in treatment position. There are also considerations required before standard implementation of MRI into the RT pathway, where studies have reported that MRI underestimates actual tumour volume on T1 imaging with contrast (Hall et al., 2013), although this is not unique to MR, with CT also known to underestimate volume size (Arvold et al., 2011).

When defining RT planning volumes it is essential to generate high quality MR images with superior spatial resolution. Abdominal organ motion is one of the biggest challenges to be overcome in producing high quality images to aid delineation of target volumes. MRI acquisition techniques in the presence of abdominal organ motion present challenges and optimisation of this is required to improve image quality and tumour characterisation. In the literature there is wide variation on techniques and patient preparation to reduce motion artefacts. Novel 4D-MRI techniques that can provide additional patient specific motion are reported (Deng et al., 2016; Liu et al., 2014; Stemkens et al., 2015; van de Lindt et al., 2016). Early investigations described lengthy patient scanning times and produced less than optimal image quality, such factors may add uncertainty to the RT process. This requires further investigation in patient studies, not just in healthy human subjects. It is also essential to consider the impact lengthy, and often uncomfortable scanning methods have on patients. Where the patient is on the couch for extended periods of time discomfort can lead to movement and involuntary internal motion can occur.

The feasibility study by Liu et al described a novel 4D-DWI technique that sought to improve tumour definition for RT (Liu et al., 2014). This study was conducted using a digital phantom and healthy volunteers. The authors describe the potential of this method in improving visualisation of tumours in the pancreas, as well as the possibility of extracting more features. This would require substantial follow up in the relevant patient group.

1.9.3 Diffusion Weighted MRI

There are many reasons DWI is an attractive imaging method. It is a non-invasive procedure, does not rely on IV contrast, and is known to determine tissue characteristics (Padhani et al., 2009). Even more attractive is the benefit of a non-ionising radiation imaging modality that could allow increased monitoring of functional changes during RT, providing information on the biological characteristics of tissue. Recent data shows promise in the prediction of treatment outcome using apparent diffusion coefficient (ADC) measured at different time points in RT (Dalah et al., 2018). Although its use in RT planning for pancreas is not well established, it is promising, and early data captured during MR-Linac delivery of RT has been published to show changes to tissue throughout a course of treatment (Banla et al., 2019).

1.9.4 Image registration for multi-modality imaging

Image registration (IR) should be a 'local registration' in the abdomen, where the IR should be focussed using a region of interest (ROI), placed around the site of disease. This differs from a "global" match, where more emphasis is placed on the whole image (Brock et al., 2017; Rong et al., 2021). Abdominal RT is recognised as challenging to plan and treat, which is exasperated by many factors, including differences in positioning when protocols require acquisition of multiple RT planning images. These positional differences may occur when acquisition set-up is performed on more than one scanner; and inter and intrafraction motion caused by respiration, stomach filling and peristalsis causes uncertainties. To minimise risk of poor registration, the task of IR must be completed by staff who are trained and competent in the process, which affect the accuracy of volume delineation and could introduce a systematic error.

MR and CT fusion in the RT pathway comes with challenges. IR is performed at the stage of treatment planning, so any uncertainties or errors at this point will lead to systematic error throughout the full RT course. Where multiple factors can result in images that are dissimilar in many ways, further backing up why a

local registration is required. Large differences in the same anatomy result in increased difficulty in achieving a good registration. The success of a rigid-IR is based on several steps being performed and checked by the person taking responsibility for assessing the outcome i.e. visually checking on all planes that automatic or manual adjustments result in a correct alignment. The importance of clinical trial QA is described by Rong et al. (2021) where credentialing is necessary for confirming the validity of registrations, with the registration process following a prospective protocol. Although, the high number of commercial systems require that departments take responsibility for their self-evaluation. Figure 1.4 provides a visual overview of the complex workflow in utilising RT images throughout the RT pathway, with areas where guidelines should be considered highlighted throughout.

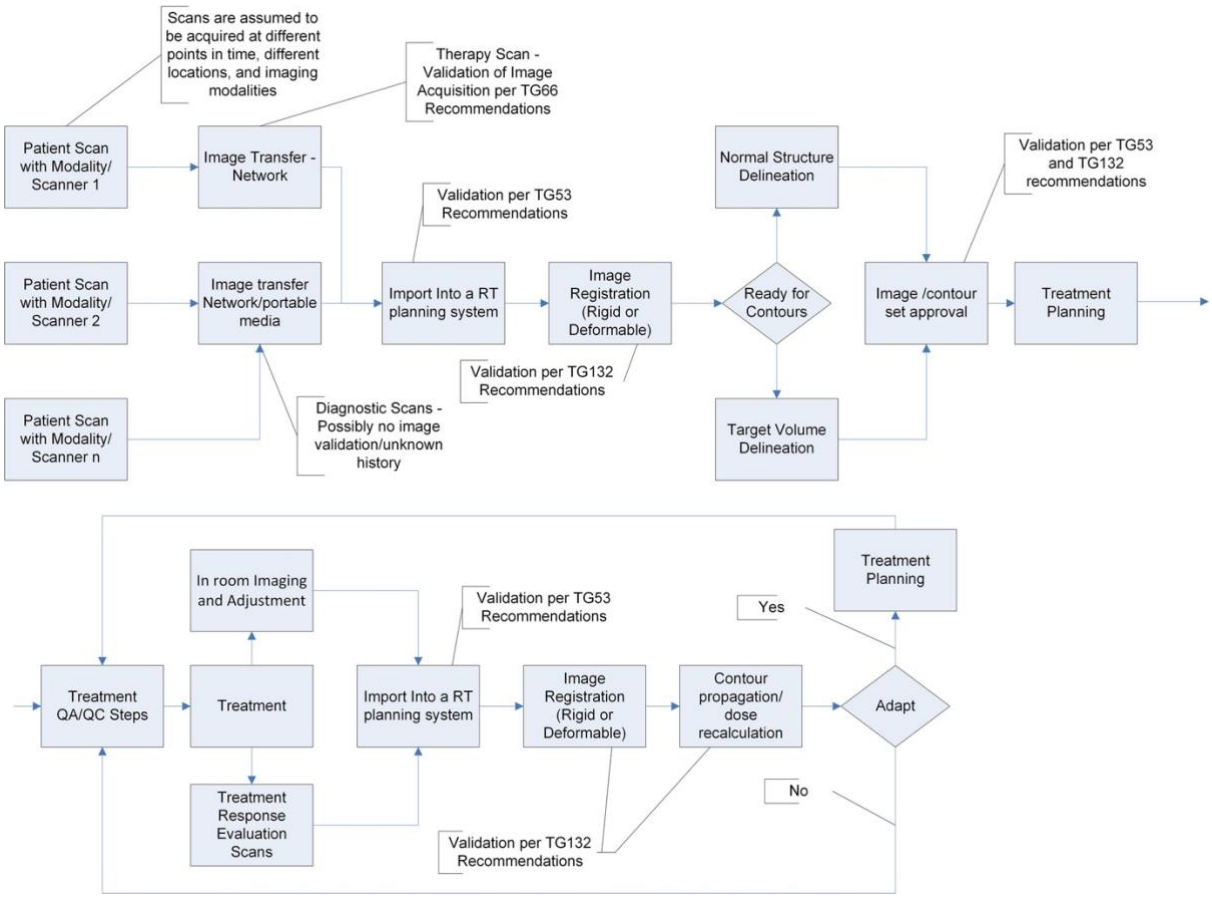


Figure 1.4. Diagram showing complexity of image data and processing workflow for the RT pathway (Brock et al., 2017).

1.10 Radiotherapy target volumes

1.10.1 Definition of target volumes for RT

As with treatment for all disease sites, adherence to the correct volume definitions is required for RT planning and reporting. Definitions for intensity modulated RT (IMRT) and SABR are described in the International Commission on Radiation Units and Measurements (ICRU) Report 83 (ICRU, 2010) and Report 91 (ICRU, 2014), where standardised nomenclature for planning structures are defined, including gross tumour volume (GTV) which refers to the "gross demonstrable extent and location of the tumour", although different clinical scenarios will result in different approaches to this. A fundamental difference between hypo-fractionated treatments and conventional, are the smaller PTV margin applied to target volumes. In pancreas 3-5mm is commonly used, although the PTV concept may not be entirely optimal for SABR treatments as it is very much a geometric concept that is grown irrespective of adjacent tissue. Confidence in planning and delivery systems must be considered during implementation to ensure that local techniques allow safe and accurate delivery of these volumes.

Additional SABR specific features are described in more detail in the ICRU 91 report (ICRU, 2014), which builds on previous publications. Standardisation of techniques throughout institutions can help to facilitate constant improvements; whilst allowing the progressive field to be assessed and optimised over time (Wilke et al., 2019). With the complexities of delivering SABR for pancreatic cancer, the application of multi-modality imaging; minimising uncertainties; and using a standardised method for dose prescribing are key.

ASTRO made strong recommendations that for SABR, patients with BRPC and LAPC that a GTV and small margin should be used for treatment. Evidence was deemed high level, and almost complete agreement throughout the group. ESTRO-ACROP guidelines do describe a method for adding a clinical target volume (CTV) depending on multiple criteria, but state it is not relevant in the SABR setting. A CTV in SABR is often not relevant, as it will be encompassed by

the ITV (Brunner et al., 2021). However, in BH margin strategies it is not explicitly clear whether a CTV method should be considered.

1.10.2 Internal target volume

The concept of an ITV strategy which accounts for motion throughout the breathing cycle was described by Wolthaus et al. (2008). They described this in relation to alternative strategies, based on lung RT. The ITV approach requires a volume to be created that includes the target volume and its full extent of motion. Delineation of target volumes using 4DCT allows additional structure volumes to be included in the delineation of the primary volume using 10 bins of data that corresponds to different phases of the breathing cycle. This allows an individualised volume to be created, based on the motion of the patient's tumour. Delineation on all bins is time consuming, therefore an approach commonly applied is to volume the 3D-CECT and the maximum inhale and exhale bins to create a composite volume, followed by a check to ensure the full tumour trajectory is included in the target volume (Brandner et al., 2017; ICRU report 62, 1999).

Another approach is mid-ventilation (Mid-v), which does offer dosimetric advantages, as described by Lens et al. (2015). They reported that Mid-v reduced the volume of stomach and duodenum irradiated. These factors are not clinically insignificant due to the impact of radiation induced side effects, where reaching dose thresholds to GI structures can result in grade $\geq$ 3 toxicity (Nakamura et al., 2012). Although thresholds were recommended based on longer conventionally fractionated treatments and less sophisticated techniques than are now available, they must still be considered with caution. The importance of understanding the delineation and margin concepts applied at each stage is vital in ensuring safe and accurate RT is planned.

1.10.3 Planning target volume

An additional PTV margin to account for uncertainties e.g. set-up, and delineation is required. A PTV created from an ITV results in the largest volume to be irradiated when compared to other strategies such as conventional 3D-CRT, gated, and Mid-v (Wolthaus et al., 2008). This is the result of including tumour motion as systematic error, although it is known that the tumour will only be in the extreme positions for some of the time. Guidelines have recommended the use of anisotropic margins of 5-10mm circumferentially, 15mm antero-posteriorly and up to 2cm craniocaudally in conventional fractionations, and with SABR it is typically 3-5mm (Brunner et al., 2021; UK SABR Consortium, 2022). Large margins that account for all motion do increase the planned/delivered dose to normal tissue, and so SABR is only feasible with these smaller margins. The margin recipe by Van Herk et al., (2000) requires a calculation of all uncertainties and such a calculation may result in exceeding these SABR values, however the premise of high dose hypo-fractionated RT is that accuracy and precision are essential components, so high uncertainty should call into question whether it is feasible or not to deliver.

1.10.4 Breath-hold volumes

Breath-hold volumes require a 3D-CECT planning image to be acquired in BH, used for volume delineation of target volume. Another approach would be to use the exhale phase of the 4DCT (4DCT_EXHALE), however better image quality is achieved using a 3D-contrast enhanced CT in exhale BH (3D-CECT_EBH). The GTV structure delineated on the BH scan or exhale phase then has a margin applied to create the PTV.

It has been indicated that when treating abdominal tumours in BH, exhale is recommended due to organs being in that position for the longest (Heerkens et al., 2014). Reports of both end-exhale BH (EBH) and deep-inspiration BH (DIBH) protocols are published in treatment of stereotactic RT for PDAC (Nakamura et al., 2011; Placidi et al., 2020; Reyngold et al., 2019), with concern on duodenum dose being higher when DIBH approach is used (Taniguchi et al., 2013).

1.11 Normal tissue toxicity

1.11.1 Dose limiting structures

The OAR of most concern for pancreatic RT treatments are the organs that make up the GI tract including stomach, duodenum, jejunum, and bowel. Liver and kidneys are also OAR but are less likely to be dose-limiting and have proven to be less of a concern with IMRT and volumetric modulated arc therapy (VMAT) (Ali et al., 2012; Milano et al., 2004). The highest risk structures will be affected by the position of the target volume e.g. a head of pancreas tumour position will increase the risk to duodenum, whereas a tail tumour may have higher risk to the stomach and bowel, whilst meeting duodenal constraints (Goldsmith et al., 2016). Level of risk also increases with the delivery of SABR dose, with high dose per fraction doses increasing the risk of causing damage to the GI tract. This reinforces the need to improve delineation of structures, ensuring that dose constraints are effectively reporting the planned dose to each structure.

1.11.2 Radiation induced toxicity

Treatment related side effects are caused by the irradiation of normal tissue, causing acute and late toxicity. The most experienced toxicities following PDAC RT are nausea, vomiting, and diarrhoea. Bittner et al. (2015) described a significant reduction in acute treatment related toxicity grade $\geq$3 using IMRT compared to 3D-conformal RT (3DCRT). This was assessing acute toxicity in 2 categories including nausea and vomiting; and diarrhoea. For late GI toxicity, this was also higher in the 3DCRT group 10.6% compared to 5% in IMRT (not found to be statistically significant).

Early reports of toxicity following SABR treatments were published by Hoyer et al. (2005), with poor outcomes and unacceptable toxicity being experienced by patients who received up to 45Gy in 3 fractions. This investigation of SABR for

pancreas was undertaken with little informative data and using conventional techniques that included static multi-field beam arrangement, 4mm CT slices, large margins, and portal films for verification. Several patients experienced grade 3 GI related toxicity, with many deteriorating rapidly after treatment. Further caution was recommended by Murphy et al. (2010) where single high dose RT i.e. 25Gy in 1 fraction resulted in a high incidence of late toxicity, which included 5 (33%) patients with grade 2 toxicity who required a medical intervention to treat ulceration; a stricture was categorised as grade 3 toxicity (n=1) and required placement of a duodenal stent. A duodenal perforation was experienced by 1 patient, where surgical intervention was necessary.

Reports of these outcomes provided essential learned lessons in progressing SABR, applying the necessary caution to less ablative doses in future protocols that resulted in acceptable toxicity levels (Herman et al., 2015; Lin et al., 2015). Most recently, a publication of a prospective multi-centre study has reported on 50Gy in 5 fractions using the MR-Linac, where adaptive RT (ART) with an optimal treatment delivery approach resulted in minimal grade $\geq$ 3 toxicity (Parikh et al., 2022).

1.12 Radiotherapy planning

1.12.1 Intensity modulated RT and volumetric arc therapy

Although conventional static field RT presented important benefits over historical 2D techniques, the implementation of IMRT and VMAT have been transformational in treating intra-abdominal tumours. IMRT and VMAT enable high dose conformity to target volumes and normal tissue dose to be minimised, especially important where complex shaped target volumes and abdominal OAR tissue interfaces exist. Assessment of dosimetric improvements include the ability to spare surrounding healthy tissue and deliver a homogeneous dose to the target volume, whilst meeting planning criteria and OAR constraints. This was initially shown in planning studies, with reports that VMAT also allowed shorter treatment times and required less monitor units (MU) compared to IMRT

(Ali et al., 2012; Nabavizadeh et al., 2014). The benefit of IMRT has been supported by clinical outcome data for many years, where Ben-Josef et al. (2004) reported acceptable outcomes of IMRT with radiosensitisation; with the benefits of IMRT being discussed in a systematic review by Bittner et al. (2015), where improved clinical toxicity data was reported.

1.12.2 SABR planning

Current guidance in the UK advises 33-40Gy as a range of doses to be considered for SABR treatments (UK SABR consortium, 2022). Factors that will affect the suitability of a higher dose prescription is the location of target volume in relation to the nearby OAR. With structures that overlap with PTV, a recommended method of achieving a clinically acceptable plan is to use an inhomogeneous PTV dose, where a dose reduction would be acceptable in the PTV where mandatory constraints are to be achieved. Dose escalated SABR for pancreas is often delivered using a dose painting method where the whole target volume will receive a minimum dose e.g. 33-35Gy and areas will be escalated to 40-50Gy (Chuong et al., 2013; Mellon et al., 2015). Dose escalation, steep dose gradients and complex motion requires high accuracy and precision RT to deliver these plans, and departments delivering these treatments must have confidence in their technique.

1.13 Pancreatic motion

1.13.1 Motion in RT

Motion is a major factor causing challenges and uncertainties when treating pancreatic tumours, with respiration and non-respiration motion being recognised for some time (Feng et al., 2009; Horst et al., 2002; Ozhasoglu and Murphy, 2002). Respiration induced motion is not insignificant, with cranio-caudal motion being over 2cm (Bussels et al., 2003). Motion in the abdomen causes inter and intrafraction uncertainties due to organ deformations and positional changes, which are often unpredictable. Liu et al., (2012) reported substantial changes were detected through multiple fractions of RT, supporting

an argument for ART. Other published data quantified the differential motion between soft tissue and bony anatomy, recommending large PTV margins in conventional RT (Jayachandran et al., 2010). A less reported problem associated with motion is that it affects image quality in RT planning and treatment images.

1.13.2 Motion management

Respiratory motion (RM) can be dealt with using several methods and are well defined in the American Association of Physicists in Medicine (AAPM) Task group 76 report (Keall et al., 2006). Methods that account for RM include incorporation at planning CT stage to determine motion of target volume, which is categorised as a motion encompassing method e.g. ITV approach and Mid-v. Such techniques are passive, and do not require on-treatment intervention. Respiratory gated techniques are active techniques that are applied at planning and delivery of RT by interrupting free-breathing (FB) image acquisition or treatment delivery when outside a certain phase of the breathing cycle. Other active techniques include real-time tracking where motion of target volume is tracked using fiducials, and BH techniques where the planned volumes are based on BH images and treatment delivery is executed in that same BH phase i.e. EBH or DIBH.

BH techniques were identified as feasible, initially for lung RT but have later provided valuable alternatives for treating pancreatic and abdominal tumours (Keall et al., 2006). Similar results have been reported between gating and BH techniques when comparing residual motion and efficiency (Zeng et al., 2021). With the addition of MRI for delineation, motion management to mimic that of CT is required; as well as consideration of how BH can be achieved with limitations on compatibility of equipment, patient set-up, preparation, and acquisition settings. For multi-modality imaging, BH techniques fit into the RT pathway and require optimal processes to ensure data captured throughout is reproducible and can be maintained over the course. There are many sources of uncertainty that can be introduced through RM management, where their

implementation at CT planning and treatment requires optimal processes and decision-making expertise (Dhont et al., 2020).

The use of abdominal compression (forced shallow breathing) is another passive motion mitigation method, which may reduce more than just breathing motion due to the way pressure is applied to the abdomen. This not only restricts respiratory motion, but will compress internal structures, affecting other sources of motion. Abdominal compression devices have the benefit of not requiring the patient to successfully carry out BH instructions, but they will have to endure the device whilst they maintain a regular treatment position. Such devices have varied success and results are patient dependant, with most motion limiting effect seen on the cranio-caudal direction, having a lesser effect on other directions (Heerkens et al., 2017a).

1.14 Image guided RT for PDAC

1.14.1 Cone-Beam CT

The benefit of improved IGRT using on-treatment MRI cannot be left unmentioned, given the momentous improvements in soft tissue visualisation when treating pancreas tumours that have otherwise presented significant challenges in online visualisation (Boldrini et al., 2019; Hall et al., 2021b). As the work presented in this thesis is related to linac-based RT, the focus of this section will be on CBCT.

Treatment of complex target volumes that are planned with VMAT/IMRT, require volumetric imaging to localise and verify treatment. This is to ensure delivery of dose to the planned target volume; and to confirm the avoidance of GI luminal structures, to be maintained throughout fractions. CBCT has limitations in the abdomen, where free-breathing scans display motion artefacts, blurring, and streaking that affect image quality. Improved image quality with BH techniques have been acknowledged for pancreas (Reyngold et al., 2019), with quantified data being published for lung cancer RT (Josipovic et al., 2016). As visualisation

of abdominal structures can be difficult many reports are based on CBCT with fiducial markers. There are limitations to the use of fiducial markers for correction, with concerns of under or overdosage to PTV and OAR when using them for alignment (Niedzieleski et al., 2021).

With SABR treatments, a homogeneous dose to PTV may not have been achieved at planning. The aim in these cases is to deliver as high a dose to as much of the PTV as possible, accepting that in areas that interface the GI OAR structures i.e. jejunum, duodenum, stomach and bowel, there will be reduced PTV dose. This requires CBCT to allow adequate visualisation of soft tissue structures, especially target volume and any dose-limiting OAR that may fall in the high dose region. The use of isodose structures to guide treatment decisions are recommended as an additional check at each fraction (Reyngold et al., 2019; UK SABR Consortium, 2022).

1.14.2 Surrogates for matching

Due to the poor image quality on CBCT, pancreatic target volumes have been notoriously challenging to verify, with surrogates such as diaphragm and abdominal wall having poor correlation (Feng et al., 2009); fiducials and stent being deemed acceptable (Huguet et al., 2015); and contradictory results reporting stent as having limited use, although being better than bony anatomy (Van der Horst et al., 2014). Fiducial free solutions have been proposed by Kaderka et al. (2017), who investigated adjacent organ motion as a surrogate for pancreatic tumour motion. The benefit of fiducial free RT is that patients do not have to attend for the implantation of markers through invasive methods such as EUS-guided, or percutaneously through MR guidance. Although deemed safe and feasible, these procedures carry risk and may contribute to significantly longer pathways (Park et al., 2010). Fiducials have other limitations in they don't provide information on target borders and where the high dose region is in relation to OAR.

1.14.3 Role of the radiographer

There has been much development in the role and responsibilities of therapeutic radiographer in the UK, with imaging aspects having been a major development for this staff group (Duffton et al., 2020; Joyce et al., 2022). Role development in this area requires appropriate training and competence on the optimal process required to treat SABR (RCR, 2021), and has often relied on AP or consultant radiographers optimising the online decision-making process. As complex planning techniques have evolved, the online IGRT process has reflected these which commands additional site-specific training and competencies for the MDT (RCR, 2021; Tsang and Routsis, 2021). Where high doses of RT are to be delivered to target volumes and dose minimised to OAR, a multiplex of decision making is required to ensure the optimal registration of imaging datasets (Daly et al., 2021). With the increasing availability of the MR-Linac and its utilisation for abdominal RT, radiographers are also faced with increased responsibilities in making decisions on ART (Gaya et al., 2021; Hales et al., 2022; McNair et al., 2020).

For linac-based treatment, achieving the best registration and to minimise inter-observer uncertainties, high-quality images are required. Reproducibility of the treatment position from CT simulator is essential, with the radiographers being responsible for ensuring patient preparation and positioning is optimised and is as planned. For pancreas SABR, registration of the planned CT dataset to CBCT requires adequate anatomical knowledge of the abdomen, target area and OAR. Contours used for RT planning will be available, however it is important that the correct structures are used to inform the analysis, especially where isodose structures are used to determine the treatability of that fraction and visualise any high dose region that would be detrimental to the patient's outcome. Relative positioning of GI tract and knowledge of the impact of exceeding dose limitations are required. Decision making criteria are useful, but limited for pancreas (Daly et al., 2021).

Increasing responsibilities in online registration and decision making requires good communication throughout the full patient pathway. Multi-disciplinary peer review meetings allow discussion of the target volumes, planning outcomes and treatment concerns, which are an important opportunity to ensure the delivery aspects are sufficient to match the complexity of treatment (RCR, 2022).

Chapter 2 Thesis aims and objectives

2.1 Background

Pancreatic ductal adenocarcinoma (PDAC) remains a cancer of unmet need, with little improvement in survival being realised over the past few decades. State of the art RT technology has advanced treatment protocols for PDAC, increasing the ability to deliver sophisticated RT that exploits the therapeutic ratio and overcomes the innate radioresistance. In PDAC this is particularly important due to historical controversies that have undermined the benefit of RT in combination with other modalities. Improvements in overall survival (OS) have been modest over the past few decades, with neither modality alone resulting in significant gains. PDAC is a disease that requires optimised multi-modality protocols. This can facilitate delivery of dose escalated RT of high-quality, that can be investigated in studies to determine if clear benefits can be established.

Njeh (2008) wrote that tumour delineation was "the weakest link". They used a simplistic diagram to illustrate the complex RT process and how each factor interacts in the chain. Uncertainties continue to be problematic in RT for PDAC, with many challenges in all aspects of the multi-factorial chain. By considering the relationship between pathway components and the impact they have on the delivery of safe, precise, and accurate treatment, RT can be improved. Njeh (2008) also highlighted a quote by a famous medical physicist, which conveys the importance of optimising RT.

"If you can't see it, you can't hit it and if you can't hit it you can't cure it"

Harold Johns (4 July 1915 – 23 August 1998)

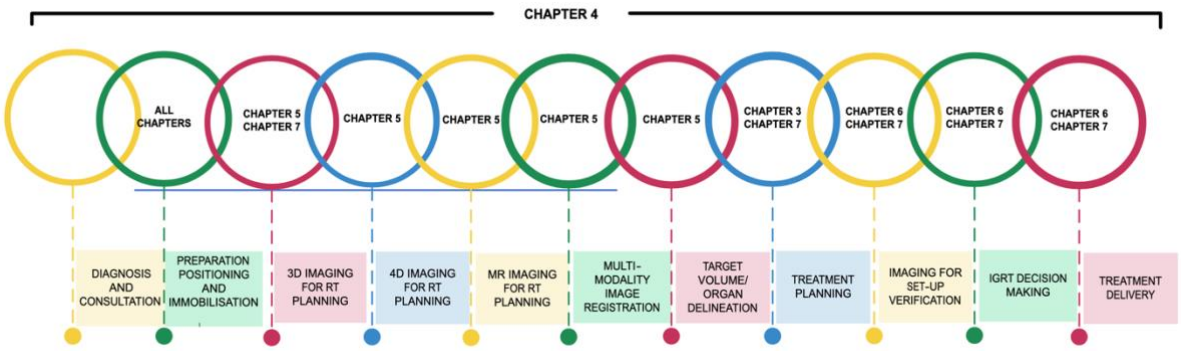


Figure 2.1 Components of the RT pathway that demonstrate the interaction of all components in the chain and where there are opportunities to introduce systematic and random errors. This figure is adapted from Njeh (2008).

2.2 Overall aim of thesis

Chapters throughout this work address uncertainties and limitations in RT planning and delivery of pancreatic tumours and highlight areas that require optimisation. By addressing these at each part of the process, the potential for improving personalised RT treatments using a linear accelerator can be reached. The overall aim of this thesis was the optimisation of different components of the RT planning and delivery pathway using a linac-based treatment platform, to improve safety, accuracy, and precision of stereotactic ablative RT for PDAC.

2.2.1 Aims and objectives of chapter 3

Title: Clinical and dosimetric outcomes in pancreatic ductal adenocarcinoma patients undergoing chemo-radiotherapy (CRT) with volumetric arc therapy (VMAT)

The aim of this retrospective study was to evaluate dosimetric and clinical outcomes for patients treated for pancreatic cancer with conventionally fractionated VMAT at our institute. This was to describe clinical outcomes with standard of care treatment.

Objectives

- Report dosimetric outcomes for VMAT plans created for pancreatic cancer patients treated with RT.
- Quantify incidence and grades of acute toxicity experienced by pancreatic cancer patients treated with VMAT.
- Report overall survival in locally advanced pancreatic cancer (LAPC) and borderline resectable pancreatic cancer (BRPC) following treatment with CRT-VMAT.

2.2.2 Aims and objectives of chapter 4

Title: Views of GI Clinical oncologists and Clinical Oncology trainees in optimising linac-based RT

Summary: There are a number of challenges in treating pancreatic cancer with high quality linac-based RT. The survey in this chapter was conducted to understand the views of GI Clinical Oncologists and Clinical Oncology trainees in optimising linac-based RT. This was used to provide a local understanding and consensus of the specific factors that required optimisation i.e. are recognised as a problem and could be prioritised due to there being a collective ambition. The aim of this survey was to understand where clinical oncologists (CO) and clinical oncology trainees (COtrain) would prioritise the optimisation of pancreatic radiotherapy.

Objectives

- Capture the views of CO and COtrain on the challenges experienced when treating PDAC.
- Quantify the level of difficulty experienced throughout aspects of the pathway.
- Prioritise areas that require optimisation.

2.2.3 Aims and objectives of chapter 5

Title: Multi-modality imaging in radiotherapy target volume definition for pancreatic cancer

Summary: Delineation of pancreatic cancer for RT is challenging and variation between observers can create high uncertainty in RT volumes. The use of co-registered multi-modality planning images acquired on the same day have not been investigated for PDAC but may reduce uncertainty. This study assessed the impact of MRI in the delineation process for pancreatic cancer tumour volumes for CO and COtrain observers. The hypothesis was that using these MR and CT imaging datasets together i.e. registered images, would result in smaller target volumes, and improve agreement between observers.

The aim of this chapter was to investigate the impact of introducing MR/CT fusion to RT planning for pancreatic cancer by addressing the following questions:

What is the volumetric impact of MR/CT fusion have on the delineation of gross tumour volumes between observers when compared to CT only GTV?
Does MR/CT fusion compared to CT only reduce inter-observer variability in delineation of gross target volume?

Objectives

- Measure gross tumour volume (GTV) and internal target volume (ITV) volumes (cm^3) for all CT only delineations and CT/MR registered delineations, for all individual observers.
- Report volumetric mean (cm^3), standard deviation (SD) for all volumes and all observers.
- Define volume difference between individual observer volumes and the GS, for all patients.
- Calculate the percentage of overlap in all observer volumes and GS volume.

. Describe the similarity of all observer volumes to GS volumes using dice similarity coefficient (DSC).
. Evaluate variation across all observers.
. Group observers into either CO or COtrain and compare DSC with GS volume for each group.
. Determine if uncertainties are reduced more in either group.

2.2.4 Aims and objectives of chapter 6

Title: Improved image quality with breath-hold CBCT for pancreatic cancer

Summary: Breath-hold cone-beam CT (CBCT_EBH) image acquisition has the potential to improve image quality used for IGRT. This has not been quantified or reported for pancreas patients, with most emphasis being placed on volume reduction, rather than the benefits of improved on-treatment image quality. Here we hypothesise that acquiring verification images in breath hold can improve on-treatment image quality for pancreatic RT and improve confidence in image registration and decision making.

The aim was to evaluate if EBH imaging could improve subjective image quality using a comparison of images acquired in breath-hold (CBCT_EBH) and free-breathing (CBCT_FB).

Objectives

. Develop scoring criteria to allow quantification of image quality, structure visualisation and confidence in assessing planning target volume coverage.
. Quantify the difference between CBCT_EBH and CBCT_FB scores for a group of expert radiographer observers and several groups of clinical radiographer observers.
. Assess if image quality improves confidence in radiographer IGRT decision making.

2.2.5 Aims and objectives of chapter 7

Title: Deliverability end exhale breath hold (EBH) RT using an external surrogate for motion

Summary: CBCT images acquired on a Varian Truebeam use an external surrogate to verify BH i.e. the RPM system. This system allows CBCT acquisition and treatment delivery to be executed in the same way as the CT planning acquisition, by verifying this against the planned breathing trace. Here we hypothesise that CBCT image quality improves when using a EBH approach, which allows localisation and verification of target volumes and relevant structures, thus improving confidence in image registration for pancreatic SABR. The aim of the work reported in this chapter was to assess the feasibility of planning and delivering SABR to PDAC patients using two methodologies. These were i) a motion encompassing technique i.e. an ITV approach in free-breathing; and ii) an individualised BH technique using a 3D-CECT_EBH data set and the exhale phase of the 4DCT acquired in FB (4DCT_EXHALE).

Objectives

- Calculate the volumetric difference between individualised PTV_BH and PTV_FB volumes created from GTV_BH and ITV_FB and using a breath hold and free-breathing approach.
- Compare the dosimetric outcomes of plans generated using PTV_BH and PTV_FB.
- Quantify image quality, structure visualisation and confidence in decision making for FB and BH CBCT acquisitions.
- Verify that volumes created for PTV_BH and PTV_FB approaches can be delivered using CBCT imaging at each fraction.

Chapter 3 Clinical and dosimetric outcomes in pancreatic ductal adenocarcinoma patients undergoing chemo-radiotherapy (CRT) with volumetric arc therapy (VMAT)

3.1 Aim and objectives

The aim of this retrospective study was to evaluate dosimetric and clinical outcomes for patients treated for pancreatic cancer with conventionally fractionated VMAT chemo-radiotherapy (CRT) at our institute which could act as a baseline review of outcomes and be used in future comparisons of new protocols implemented during this thesis.

Objectives

- Report dosimetric outcomes for VMAT plans created for pancreatic cancer patients treated with RT
- Evaluate number and grades of radiation induced toxicity experienced by pancreatic cancer patients treated with VMAT
- Report overall survival in locally advanced pancreatic cancer (LAPC) and borderline resectable pancreatic cancer (BRPC)

3.2 Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the leading causes of cancer deaths in the UK, with the number of deaths resembling the number of new cases each year (CRUK, 2020). Suitability for RT treatment is based on a combination of clinical diagnosis, comorbidities, and performance status. Pre-operative staging precludes surgery for the majority of patients; or may only be achievable once down staging has occurred e.g. following neo-adjuvant chemotherapy (NCCN, 2020). Even for those with a favourable diagnosis who complete surgery, recurrence or metastatic spread is still a high risk (Kanda et al., 2011).

The majority of cases which are localised75 are either BRPC or inoperable at diagnosis I.e. LAPC, and as such are reliant on neo-adjuvant or induction chemotherapy potentially followed by CRT. One controversial aspect in BRPC is that potentially resectable disease may progress in the neo-adjuvant phase, rendering them inoperable, and therefore unable to proceed with potentially curable treatment. The perceived benefit in the neo-adjuvant approach is that patients are given systemic treatment early to down stage them to resectable and improve chances of R0 resection (Katz et al., 2008; Katz et al., 2013). On the other hand, those who are chemo and radioresistant are not subjected to further invasive treatment. One fundamental issue is that current evidence lacks definitive answers to the optimal regimens and their timings (Bergquist et al., 2017; Mokdad et al., 2016; Zhan et al., 2017). Studies investigating which patients will respond well to treatment are essential in future trial design (Collisson et al., 2019; Dreyer et al., 2017).

In the UK, capecitabine was adopted as the choice of radiation sensitiser following publication of more favourable outcomes from SCALOP trial, (Mukherjee et al., 2013). There have, however, been contradictory results when comparing chemotherapy and CRT for locally advanced pancreatic cancer (LAPC) within randomised controlled trials (Mokdad et al., 2016; Zhan et al., 2017). In particular, through the results of a randomised trial which compared the survival benefit of CRT in LAPC (Hammel et al., 2016). Trial design was not optimal with concerns being expressed that timing of treatment interventions had led to undermining the benefit of radiotherapy (RT). Assessing trial methodology and interpreting results requires caution in clinical practice, especially as treatment choice is vital for those who have limited options.

State of the art technology has allowed significant advancements in RT imaging, planning and delivery to be achieved (Garibaldi et al., 2017). Advanced technologies increase the possibility of planning and delivering highly conformal treatment plans that allow delivery of high doses of ionising radiation to the target volume, whilst sparing normal tissue, including dose-limiting structures. Techniques such as intensity modulated RT (IMRT) and volumetric modulated arc therapy (VMAT) have become more widely available and have provided an

opportunity to reduce dose to normal tissue compared to 3D-conformal RT (3DCRT). This increases the possibility of delivering a tumoricidal dose to the desired target volume whilst minimising unwanted dose to adjacent organs at risk (OAR). As duodenum, stomach and bowel lie in close proximity to pancreas, gastrointestinal toxicity is the main concern. A review of a small number of studies, which included a small numbers of patients, demonstrated the benefit of IMRT in reducing toxicity (Bittner et al., 2015). A further benefit of VMAT is that treatment delivery can be performed within a short time frame, using an automated gantry rotation of 1-2 minutes.

In a specialty that has evolved at a rapid pace, such advancements are implemented clinically with expectations of improved outcomes, often not described in the literature. Much discussion on future RT treatment options for pancreatic cancer was forced due to Covid-19 infection (Jones et al., 2020; Tchelebi et al., 2020). The infection has continued to cause morbidity and mortality worldwide and has affected not only cancer patients and professionals, but the whole population. A clear need to individualise and hypo-fractionate treatments was recognised, with reduced hospital visits being highly recommended (RCR, 2020).

With many changes to standard of care treatment planned through this thesis and in response to Covid-19, the clinical outcomes reported here were to act as a baseline for future comparisons. The aim of this retrospective study was to evaluate dosimetric and clinical outcomes for patients treated for pancreatic cancer with VMAT chemoradiotherapy at our institute, which could be used in future comparisons of new strategies implemented during this thesis.

3.3 Methods

3.3.1 Patient selection

Following trust approval, an interrogation of the patient management system highlighted all patients treated for pancreatic cancer who were planned using VMAT and had electronically recorded on-treatment review data. Figure 3.1 shows a consort diagram of disease management for these patients. Patient records were reviewed to confirm patient demographics, initial diagnosis, dosimetric data and outcomes. We identified 36 patients with a confirmed diagnosis of PDAC who were treated with chemo-RT between 22nd June 2016-18th January 2018, and prescribed VMAT dose of 50.4Gy delivered in 28 treatments (Table 3.1a and b). We excluded patients with other pathology e.g. pancreatic neuroendocrine tumour and those treated using stereotactic body RT (SBRT) or reduced fractionation. Staging had been determined by a multi-disciplinary team including surgeons and clinical oncologists (CO) using the Glasgow resectability criteria (Figure 3.2).

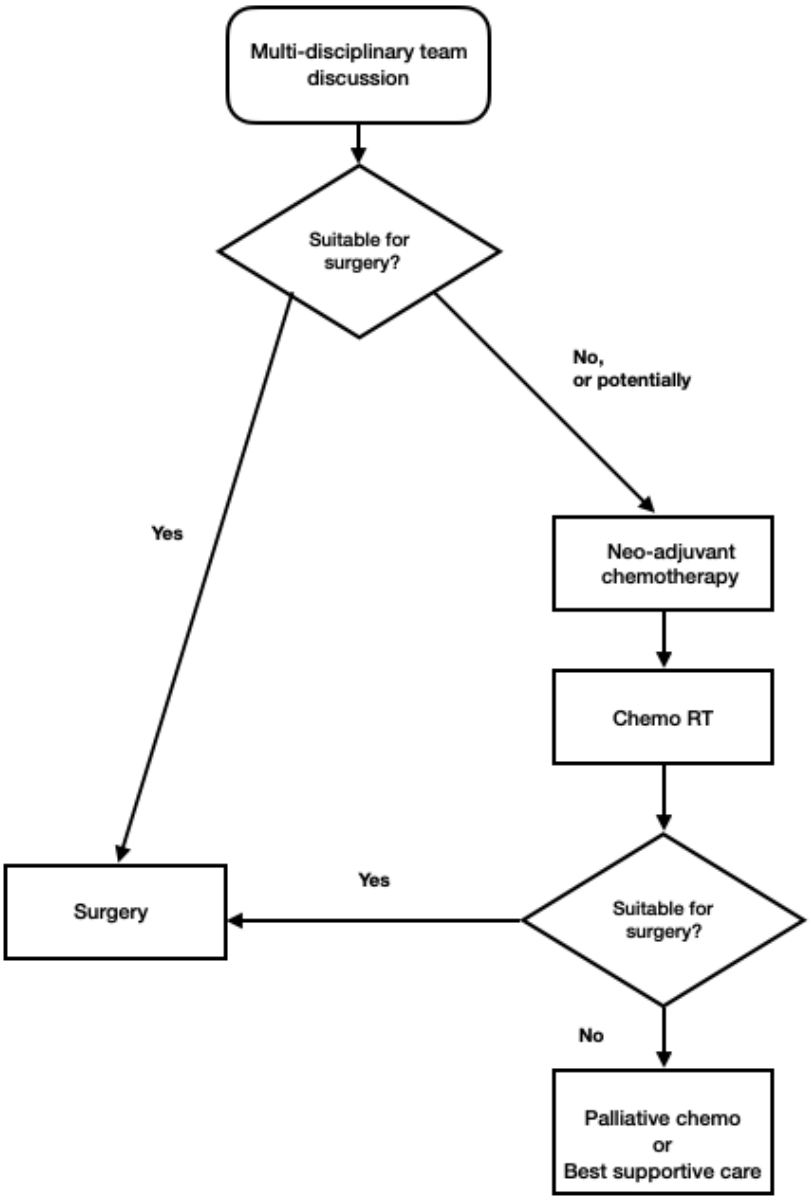


Figure 3.1 Consort diagram showing patient management.

Age	Med (IQR)	
	69 (50-77)	
Sex	n	%
Male	15	42
Female	21	58
Tumour location		
Head	20	55.6
Body	5	13.9
Body/Tail	3	8.3
Tail	2	5.6
Uncinate	6	16.7
Glasgow Resectability Criteria		
B	20	55.6
C	3	8.3
D1	11	30.6
D2	1	2.8
E	1	2.8
Chemotherapy regimen * n		
Gem/Cap	22	61
FFX	14	39

Table 3.1a. Patient characteristics showing number and percentage (%) of each category. Age is expressed as median and inter-quartile range (IQR). * induction/neo-adjuvant is detailed in table 3.1b.

Regime	
Gem/Cap (28-day cycle)	Gemcitabine 1000mg/m^2 d1, 8, 15 Capecitabine 830mg/m^2 BD d1-21
FFX (14 day)	Oxaliplatin 85mg/m^2 d1 Irinotecan 180mg/m2 d1 Fluorouracil 400mg/m2 d1 Fluorouracil 2400mg/m2 46hr infusion

Table 3.1b. Prescribed neo-adjuvant chemotherapy regimens detailing agent and dose (mg/m^2), delivered once (d) or twice daily (BD).

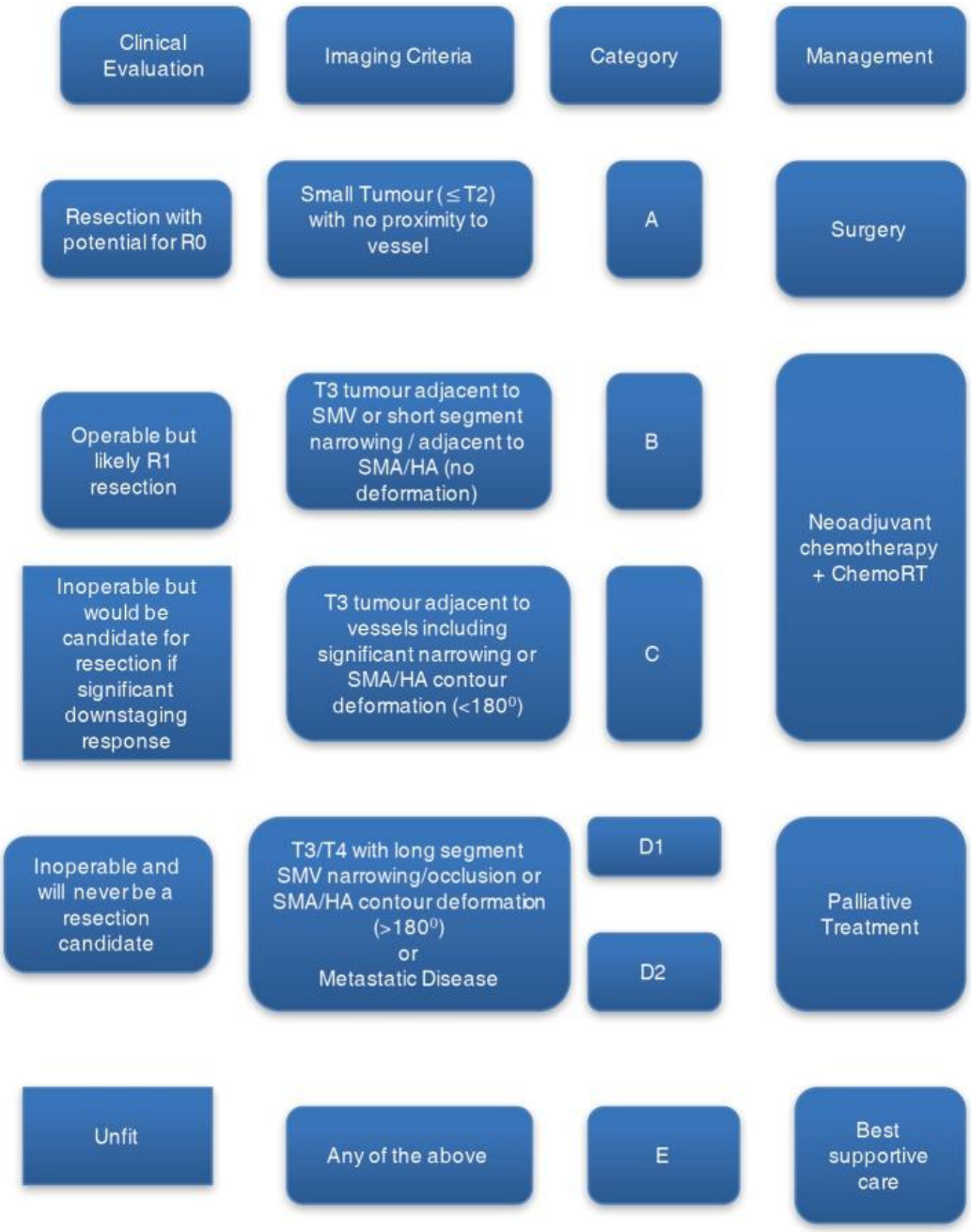


Figure 3.2 Glasgow resectability criteria (GRC) used by multi-disciplinary team to aid decision making (Grose et al., 2017).

3.3.2 Immobilisation and pre-treatment imaging

Patients were immobilised using a supine, arms up technique with a knee support for comfort. A 3DCECT scan and a 4DCT_FB were acquired on either a LightSpeed 16 CT (GE Healthcare, United Kingdom) or a Philips Brilliance Big Bore CT (Philips Healthcare, Cleveland, Ohio) with RPM (Varian Medical systems, Palo Alto, CA) in treatment position. Dilute oral contrast was given prior to scanning (10ml Gastrografin ®/250ml water).

3.3.3 Delineation

Gross target volume (GTV) was delineated by the CO using all bins of the 4DCT dataset to capture target motion, creating an internal target volume (ITV). A previously acquired staging MRI was used alongside CT to visualise disease, with input from a consultant radiologist. A 1cm margin was applied around the ITV to encompass any uncertainties, creating a planning target volume (PTV). Liver, kidneys, and duodenum were delineated and checked by the CO.

3.3.4 Planning

VMAT (RapidArc™) treatments were planned using Eclipse v10 to v13 (Varian Medical Systems, Palo Alto, CA), on a Varian Truebeam linear accelerator. Plans were optimised using the inverse planning Progressive Resolution Optimiser (PRO3) or the Photon Optimiser (PO) and the final dose calculation was performed using Anisotropic Analytical Algorithm (AAA) 10.0.28 with a calculation grid size of 1.25 mm.

The planning criteria applied were: Optimal dose to 99% of PTV should be equal or greater than 95% i.e. D99%$\geq$95%; and optimal dose to 95% of PTV was to be equal or greater than 97% i.e. D95%$\geq$ 97%. Dose constraints for OAR were: Volume of high dose kidney receiving 20Gy should be equal or less than 40% i.e. V20Gy$\leq$40% (optimal) and V20Gy$\leq$45% (acceptable), for low dose kidney the

volume receiving 5Gy should be 0% (optimal), acceptable not defined. Acceptable volume of liver receiving 30Gy should be equal or less than 30% i.e. V30Gy ≤30%. Maximum dose to 0.1cc of duodenum should be equal to or less than 48Gy i.e. Dmax (0.1cc) ≤48Gy (optimal), Dmax (0.1cc) ≤54Gy (acceptable); optimal volume of duodenum receiving 50Gy should be equal to or less than 10cc i.e. V50Gy≤10cc and V15Gy≤60cc. Constraints were based on those used in SCALOP (12). Each plan used two full arcs with a collimator offset between the two arcs of 30° degrees.

3.3.5 Chemotherapy and chemo-RT

Induction chemotherapy protocol i.e. doublet or triplet therapy, was determined by assessing age and fitness. Suitable patients for FOLFIRINOX (FFX) were those under 70 years of age with good performance status (0/1).
Following 12 weeks of neo-adjuvant chemotherapy, a CT of the chest, abdomen and pelvis was acquired to confirm stability of disease. This allowed patients to be selected for CRT (Figure 1 and 2). Concurrent capecitabine was given with VMAT, delivering 50.4 Gy in 28 fractions over 5.5 weeks, consistent with SCALOP (Mukherjee et al., 2013).

3.3.6 On-treatment verification and review

All patients had on-treatment verification using CBCT (Varian medical systems, Palo Alto, CA), acquired immediately before treatment fractions 1, 2, 3 and weekly. These were analysed for any mismatch to reference CT, with all shifts being applied. Surrogate anatomy was used for registration, and OAR position was assessed.

Patients were reviewed at start of RT treatment by clinical nurse specialist (CNS), and weekly throughout treatment. Acute gastrointestinal toxicities were recorded electronically on ARIA (Varian medical systems, Palo Alto) using Common Terminology Criteria for Adverse Events version 4.03 (CTCAE V 4.03) scoring criteria.

On completion of chemo-RT, patients were evaluated for surgical intervention by multi-disciplinary assessment. This assessment included radiological response to treatment defined by 2 radiologists.

3.3.7 Statistical analysis

Patient characteristics were summarised as proportions or means (with standard deviations) as appropriate. Follow-up and survival statistics were calculated from the start of radiotherapy treatment until death or the censor date (16/01/2020), whichever came first. Median follow-up time and median overall survival were estimated using Kaplan–Meier methodology. The log rank test was used to test for differences in survival between patients classified as potentially suitable for surgery (GRC B or C) compared to those deemed inoperable (GRC D or E), and to test whether there was a difference in survival between those who had received surgery and those who had not. All tests were two-sided and a p-value less than 0.05 was considered statistically significant. Data analysis was carried out using Stata Statistical Software: Release 14 (TX: StataCorp LP).

3.4 Results

3.4.1 Patient characteristics

Thirty-six patients were included in the analysis (Table 3.1a). Median age (IQR) was 69 years (50-77), 58% of which were female. At initial diagnosis, 23 (64%) were classified B or C (potentially operable with down staging) using GRC. The majority (56%) of tumours were located in the head of the pancreas.

Neo-adjuvant/induction chemotherapy was delivered using different regimens (Table 1b) including 22 patients (61%) receiving gemcitabine and capecitabine (Gem/Cap) and 14 (39%) FFX (Table 3.1a). Three patients (8%) stopped

chemotherapy early, and 16 (43%) had dose reductions.

3.4.2 Chemo-RT

Thirty-two patients (89%) completed the full course of RT in a mean of 38 (1.9 SD) days. The 4 (11%) patients who did not complete were recorded as "too ill to attend", with 1 patient stopping after 3 fractions, and 3 completing 25-27 fractions.

3.4.3 Planning and Dosimetric outcomes

The mean ITV, PTV and duodenum volume were 50.4 cm^3 (39.4 SD), 200.9 cm^3 (97.9 SD) and 133cm^3 (54.5 SD) respectively. Clinically acceptable VMAT plans that achieved planning criteria were produced for all patients (Table 3.2). Optimal PTV criteria of D99% $\geq$ 95% and D95%$\geq$ 97% were achieved i.e. 95.7% (0.9 SD) across the group, and 98.3% (0.6 SD) respectively.

PTV planning criteria					
	Criteria	Optimal	Acceptable	Achieved	
				Dose % (SD)	Dose Gy (SD)
PTV	D99%	≥95%	≥90%	95.8 (0.85)	48.28 (4.3)
	D95%	≥97%	≥95%	98.3 (0.62)	49.54 (3.1)
	Dmax (0.1cc) %	≤105%	≤107%	106.2 (0.74)	53.52 (3.7)

Table 3.2. Planning target volume planning criteria and outcomes for all patients expressed as percentage dose (%) and standard deviation, or absolute dose (Gy) and SD.

For the high dose kidney (HK) the mean V20Gy was 13% (11 SD), with the optimal constraint being V20Gy≤ 40%. For low dose kidney (LK) the mean V5Gy was 2.6% (9 SD) which is slightly above the optimal and aspirational constraint of V5Gy=0%. Acceptable liver constraints of volume receiving 30Gy being less than 30% (V30Gy < 30%) were achieved for all patients i.e. 2% (2.9 SD). Duodenum Dmax (0.1cc) was 53.1 Gy (3.5), within the acceptable constraint of ≤54Gy (Table 3).

OAR constraints	Constraint	Optimal	Acceptable	Achieved (SD)
High Dose Kidney	V20Gy	≤40%	≤45%	12.43% (11.1)
Low Dose Kidney	V5Gy	≤0%	Not defined	2.55% (6.0)
Liver	V30Gy	Not defined	≤30%	1.97% (2.9)
	Mean	≤28Gy	≤30Gy	5.65Gy (3.0)
Duodenum	Dmax (0.1cc)	≤48Gy	≤54Gy	53.1 Gy (3.5)
	V50Gy	≤10cc	Not defined	21.3cc (22.7)
	V15Gy	≤60cc	Not defined	80.8 cc (45.7)

Table 3.3 PTV dosimetric outcomes for all patients in either percentage (%) or absolute dose (Gy) and standard deviation (SD).

3.4.4 Acute toxicity

All 36 patients were reviewed weekly whilst on CRT. Maximum of grade 2 toxicity was recorded for anorexia, diarrhoea, nausea, and pain in 3, 1, 6 and 2 patients respectively. No grade ≥3 toxicity was reported (Table 3.4).

Toxicity grade	0	1	2	Total
Anorexia	21	12	3	36
Anxiety	34	2	0	36
Constipation	33	3	0	36
Dermatitis radiation	35	1	0	36
Diarrhoea	32	3	1	36
Dry skin	35	1	0	36
Nausea	21	9	6	36
Pain	22	12	2	36
Vomiting	32	4	0	36
Weight loss	31	5	0	36
Wheezing	35	1	0	36

Table 3.4. Maximum toxicity score recorded for all patients, for each toxicity recorded as more than 0 (for any patient) using CTCAE 4.03. Where toxicities were recorded as grade 0 for all patients throughout treatment course, these are not included in table.

3.4.5 Surgery

At initial diagnosis 23 (64%) patients were potentially resectable and 13 (36%) were defined as LAPC, i.e. inoperable. Following CRT, 7 (19%) patients had surgery and 29 (81%) patients did not. Of those having surgery, 6 were initially staged as GRC B, and 1 was GRC D1.

3.4.6 Survival

Median follow up was 15.3 months and median OS was 15 (95%CI 11-20%) months. Among patients who were identified as being potentially suitable for surgery at baseline (GRC B or C, n=23) median survival was 16 (95%CI 11-27) months (Figure 3.3). Among those deemed inoperable (GRC D or E, n=13) median survival was 14 months, (95%CI 6-17). Although median survival was longer in the potentially operable group by 2 months this difference was not statistically significant (p=0.16). At 24 months survival was estimated as 33% (95%CI 15-53%) and 23% (95%CI 6-47%) among the potentially operable and inoperable groups respectively.

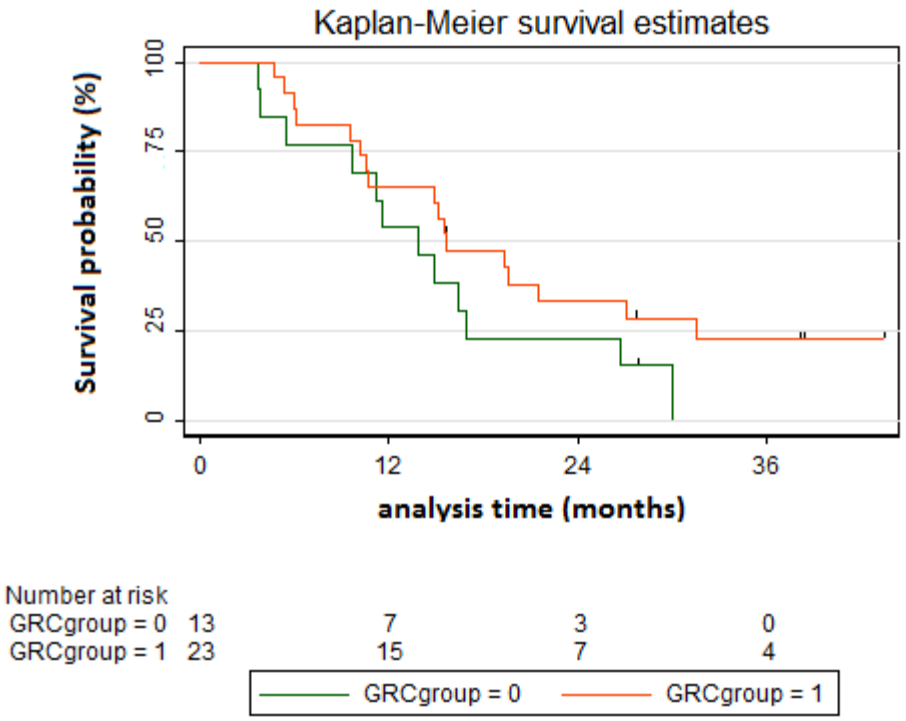


Figure 3.3. Kaplan Meier survival estimate grouped by their initial GRC diagnosis where patients who were GRC B or C i.e. operable/potentially operable are represented in group 1; and patients who were GRC D or E i.e. inoperable are represented in group 0.

Patients who received surgery (n=7) had a median survival of 27 months (95%CI not available) compared to 15.1 months (95%CI 11-19) months among patients who did not receive surgery (p= 0.28) (Figure 3.4). (p=>0.05). At 24 months, the estimate of OS was 57% (95%CI 17.2-83.7%) among those who had surgery and 22.4% (95%CI 9.3-39) among those who did not receive surgery.

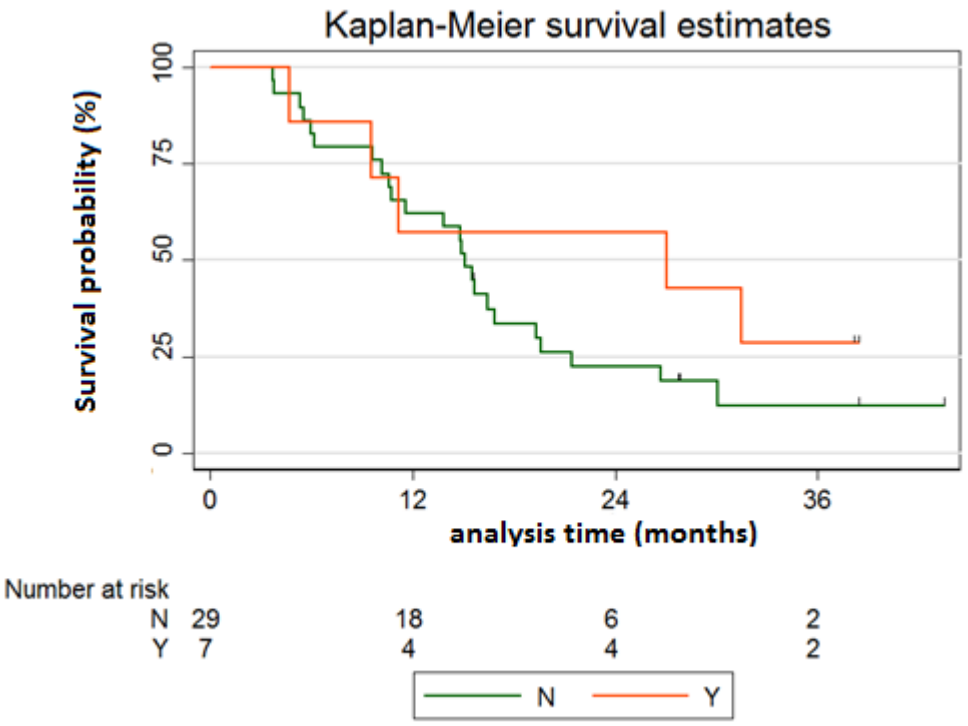


Figure 3.4. Kaplan Meier survival estimate grouped by patient who had surgery (Y) and patients who did not have surgery (N)

3.5 Discussion

All patients in this analysis were treated with VMAT, with a clear definition of delineation, planning and delivery methods. We report good tolerance of patients to CRT with only 4/36 (11%) patients being unable to complete their full course of RT, 3 of those still completing at least 25 fractions. Previous reports by the SCALOP study showed a higher rate of patients failing to complete, around 30% in both investigational groups (Mukherjee et al., 2013). Advancements in RT planning, online verification and delivery may be partially responsible for the higher completion rates compared to SCALOP. Within our cohort, there was heterogeneity in the chemotherapy regime used, which was down to fitness, performance status and diagnosis. Reassuringly the addition of FFX did not result in patients failing to complete.

RT protocols do differ between studies. We applied a different method of target volume contouring to SCALOP, by using an internal target volume (ITV) approach

which included 1cm margin isotropically. This differs from SCALOP guidelines which were GTV plus 1.5-2.0cm margin. Without quantifying the difference in approaches for each patient, we cannot compare volumes, or OAR overlap. It is commonly known that an ITV approach can overestimate volume, where adding 1.5-2cm margin would also result in large PTV. Both methods have potential to over-estimate the PTV.

Here we report the dosimetric outcomes for all patients who were treated with VMAT alongside acute toxicity. Given that Covid-19 strategies are pushing the UK and Europe towards reduced fractionation, this work can be used as a comparison for these adopted protocols, and any dose escalation in the future (Jones et al., 2020; Tchelebi et al., 2020).

High variation in duodenum volume was observed across all patients, demonstrating how this organ differs between individuals. Achieving acceptable dose constraints can be an issue when treating and delivering high doses of RT in tumours that are adjacent to this structure e.g. head of pancreas (figure 3.5). Structure volume variation is not only present at planning, but is also evident in patients between fractions, which has a dosimetric impact on OAR delivered dose (Bohoudi et al., 2017; Loi et al., 2019). Being the main dose-limiting structure associated with pancreatic RT, more uncertainty in volume, shape and location amplifies RT challenges. There is evidence of a relationship in volume of duodenum receiving a high dose and increased toxicity. In particular, V25-V55Gy parameters have been identified in studies (Cattaneo et al., 2013; Huang et al., 2012; Kelly et al., 2013; Verma et al., 2014; Yoon et al., 2013). This illustrates the challenges of dose escalating in close proximity to this structure.

Dose response relationships for gastro-intestinal toxicity can be difficult to interpret due to a lack of uniformity in the way they are reported. Groups have used data to inform normal tissue control probability (NTCP) models but are again restricted by the availability of data (Holyoake et al., 2017). Our data, although only meeting acceptable duodenal constraints in most patients, showed that acute toxicity was never greater than grade 2 and allowed most patients to

complete treatment. Dose parameters achieved were variable between patients, due to the geographical location of disease within the pancreas. Location of tumour should be considered when stratifying patients suitable for dose escalation or ablative treatment.

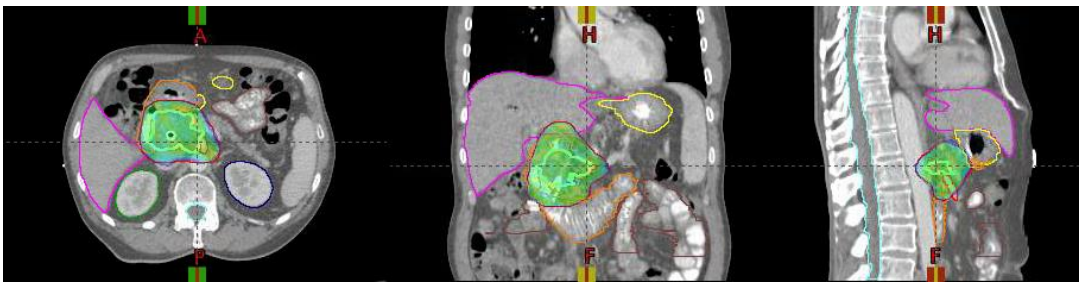


Figure 3.5. 95% dose colour wash for 1 patient showing high dose region covering ITV (cyan) and PTV (red). OAR structures close to ITV e.g. duodenum (orange) overlaps with PTV. OAR volumes shown above i.e. liver (magenta), stomach (yellow), bowel (brown).

Within this cohort of patients, there were 12 patients who reported maximum grade 2 toxicity. Here we show that liver dose is low using a VMAT technique and may have prevented the incidence of grade 3 nausea. Nausea is a known radiation induced toxicity associated with dose delivered to the liver (Miften et al., 2018). No prospective studies comparing clinical outcomes of IMRT/VMAT versus 3DCRT are available for pancreas. Of the IMRT studies discussed by Bittner, a reduction in the number of patients experiencing grade 3 toxicity was observed (Bittner et al., 2015). Our results support that IMRT/VMAT treatments achieve acceptable acute toxicity, beneficial to the patient by allowing completion of intended RT dose.

OS from similar studies showed no significant improvement between IMRT and 3D conformal studies, reported as between 7.7 - 11.6 months (IMRT) and 8.6 - 15.2 months (3D) for non-resected, and between 10.8 - 32 months (IMRT) and 16.9-25 months (3D) for resected patients (Bittner et al., 2015). Our median OS for all patients, non-resected and resected patients was 15, 15.1 and 27 months respectively. Our OS is consistent with these findings, although there may be variation on where the analysis time starts within studies.

Modern planning techniques such as VMAT can allow conformal treatment to irregular shaped PTVs whilst constraining dose to abdominal OARs. This is particularly important when duodenum is curved around head of pancreas. As the delivery is rotational and modulated, it is possible to spare adjacent normal tissue. One of the benefits associated with VMAT is the fast delivery time, each of the two treatment arcs taking approximately 1 minute to deliver. Fast delivery can reduce the opportunity for intra-fractional motion, and potentially improve patient comfort/experience. This provides an opportunity for additional methods of planning and delivery techniques to be implemented e.g. breath-hold protocols, which can reduce PTV and improve on-treatment verification (Boda-Heggemann et al., 2013).

Disease staging for pancreatic cancer is challenging and for this group we used GRC to determine patient management. Although this is not internationally validated criteria, it does include clinical and imaging factors similar to NCCN guidelines validated for clinical trials. It should be acknowledged that using unvalidated criteria for diagnosis could deliver differential results, and uniformity should be considered in future trial design. Systematic reviews and meta-analysis also describe common limitations, e.g. low numbers of high-quality studies, small patient numbers, and heterogeneity of patients and/or treatment schedule (Holyoake et al., 2017; Miften et al., 2018). This has progressively led to current/future studies ensuring they learn as much from every patient as possible.

The limited prospective nature of pancreatic cancer research is of ongoing concern, partially due to low incidence. Results from clinical trials informing practice are based on relatively low numbers of participants. New trials going forward are being designed to ensure that comprehensive patient data is captured along the way, allowing better stratification for future patients. Incorporating this principle into early trial design development should help facilitate this. Our local research group have generated and developed research studies with this in mind (Grose et al., 2019; Valle et al., 2019).

One of the major problems in delivering curative RT is caused by the complexity in delivering RT to the abdominal area. Such problems are poor visualisation on radiological images; targeting moving volumes (due to respiratory cycle, peristalsis, and heartbeat motion); and dose limiting structures overlapping with PTV. Although Chapman et al (Petrelli et al., 2017) indicated that complex 3DCRT plans could achieve constraints similar to VMAT, here we have shown that VMAT has also achieved better clinical results.

The recent introduction of MR-guided RT treatments into clinical practice will also seek to improve target visualisation and daily adaption for this patient group, with functional imaging under investigation (Banla et al., 2019; Boldrini et al., 2019). Great promise in overcoming some of the complex issues in delivering RT to the abdominal area has been described. Dedicated research teams are publishing their outcomes, and demonstrating the ability to visualise disease/organs, and verify treatment. However, this technology is still in the early stages of development and is not routinely available. We believe the linac-based technology we have readily available could be optimised to allow superior identification of target volumes and limit geometric uncertainties in the process. Although MR-linacs provide a promising solution to this, we should continue to progress linac-based treatment.

SBRT has also been investigated within studies, pre-dominantly in the LAPC patients. The benefit is that a biologically equivalent dose can be delivered using a high precision technique, with fewer hospital visits. In a review of 19 studies of SBRT for LAPC, there was no survival benefit over that of conventional fractionation (Petrelli et al., 2017). This systematic review highlights the limitations of pancreatic research so far, with majority of studies being retrospective, small heterogeneous groups, different dose/fractionation, and still no definitive randomised data to support it as standard of care. Grade 3 and 4 acute toxicities were reported in the majority of included series, although this is deemed “generally acceptable” by authors. There have been attempts to dose escalate for BRPC (Holyoake et al., 2016), however there is concern that

increasing dose could result in surgical complications. This is a reason where the benefit may lie in LAPC.

3.5.1 Strengths and limitations

This was a retrospective study of patient outcomes. It is possible that the retrospective nature could have resulted in toxicity data being under-reported. The planning aspects were carried out by different observers and were not prospectively reviewed, this provides an opportunity for inter-observer variation (IOV). Although retrospective, this was an important part of designing the thesis and ensuring that baseline data was captured. Given the poor outcomes associated with PDAC, patient's quality of life following diagnosis is of utmost importance, and outcome data should be captured before implementation of new techniques. The effect of modern RT solutions and treatment related toxicity should be understood so that joint informed decision making is part of the consent process and relevant to local standard of care. Understanding tolerance to treatment will allow honest conversations about disease management with patients, enhancing the consent process. This work will be repeated in the SABR setting, in future work using a prospective approach.

3.6 Conclusion

Treatment with VMAT is well tolerated for most patients with no patients experiencing grade 3 toxicity during treatment; and low numbers failing to complete. Although the role of CRT has also been controversial for this patient group, it still plays an important role in disease management. Due to the relatively small improvements seen in pancreatic cancer outcomes, any opportunity to explore hypo fractionation and dose escalation is desirable, especially in response to the current Covid-19 pandemic. Work in this thesis will ensure optimal RT protocols are adopted and optimised according to new recommendations, for implementation within clinical trials.

Whilst MR-linac research is much anticipated, further optimisation of linac based treatment protocols can provide many opportunities for dose escalation to

target volume, whilst maintaining safe dose to normal tissue. Reducing other sources of uncertainty e.g. tumour motion, inter-observer variability is now possible, and will be addressed in our future studies, alongside standardised prescribing, reporting, and optimising methodology.

Chapter 4 Views of GI Clinical Oncologists and Clinical Oncology trainees in optimising linac-based RT

4.1 Background – Aim and objectives

Summary: There are a number of challenges in treating pancreatic cancer with high quality linear accelerator (linac)-based radiotherapy (RT). The survey in this chapter was conducted to understand the views of gastro-intestinal (GI) Clinical Oncologists (CO) and Clinical Oncology trainees (COtrain) in optimising linac-based RT. This was used to provide a local understanding and consensus of the specific factors that required optimisation i.e. are recognised as a problem and could be prioritised due to there being a collective ambition.

Aim

The overall aim of this survey was to understand where CO and clinical COtrain would prioritise the optimisation of pancreatic ductal adenocarcinoma (PDAC) RT.

Objectives

- Capture the views of CO and COtrain on the challenges experienced when treating PDAC.
- Quantify the level of difficulty experienced throughout aspects of the pathway.
- Prioritise areas that require optimisation.

4.2 Introduction

Radiotherapy advancements such as imaging technology, planning systems, and treatment platforms have allowed significant progress to be made over the past few decades. As highlighted in chapter 1, the benefit of RT in treating pancreatic cancer remains under scrutiny, with no definitive high-quality evidence to demonstrate significant improvement. It is possible that further

optimisation of key aspects of the RT pathway could enable higher doses of stereotactic ablative RT (SABR) to be delivered safely and provide an opportunity to explore the benefits of a modern RT protocols. For linac-based PDAC treatment there are still aspects where inherent problems and challenges have not been sufficiently addressed.

Although many authors have stated the importance of improving different aspects of the RT protocol e.g. motion mitigation, delineation, multi-modality imaging, there is no evidence that describes how this would be prioritised by experts. The concept of using consensus research techniques to formalise a strategy is not new, with references to the different methodologies employed being described (Fink et al., 1984). Important aspects of guidelines in RT are standardised using such methodologies e.g. in organ at risk (OAR) delineation (Mir et al., 2020); volume delineation for pancreatic cancer (Goodman et al., 2012); and recommendations in how to treat patients in response to Covid-19 (Jones et al., 2020).

Surveys are a well-known method of capturing quantitative primary data from those working in healthcare, with survey methodology being well described within this setting (McColl et al., 2001), and more specifically in RT disciplines (Harris et al., 2012). The appeal of using surveys as a research method is to allow efficient contact with participants, data collection, and analysis of results. Quality of survey results can be affected by poor survey methodology, leaving them open to criticism. Carefully considered and reported methods should be applied to ensure results are meaningful.

Obtaining reliable and valid data depends on the survey being well designed, and if this is the case can be an effective data collection method. Likewise, poor application of survey methodology can affect data quality, and interpretation of results should be done with caution. Survey methods are commonly employed when aiming to understand the views of healthcare staff, though there are many steps that can be poorly applied in what needs to be a well thought out process. New surveys should include explicit detail on the development and piloting

stages to ensure that best practice has been followed. Good and bad practice is described by many authors and includes topics such as sampling, question definition, and piloting (Draugalis et al., 2008; Sullivan and Artino, 2017). These authors highlight the many frustrations experienced by peer reviewers when poor methodology has been applied and offer suggestions on how to, or how not to design surveys. To improve the quality of such studies going forward guidance should be adhered to when designing a valid and reliable tool.

4.3 Methodology

4.3.1 Previously reported data collection

Preceding the development of this survey a literature search was used to determine if any published evidence described a relevant survey that could investigate the views of clinical staff, in this area. Ideally a validated and relevant survey could have been used in this work. Following a scoping search of the literature, no studies were identified using a similar survey, and creation of a new survey was required.

This study used published survey methodology described by several authors, which was applied throughout all stages to ensure optimal design (Bowling, 2014; Oppenheim, 2000; Thomas, 2018). The survey was deliberately timed so that results were available before carrying out the investigations detailed in subsequent chapters i.e. prior to investigating chapters 5-7, a survey was developed to capture the views of these two groups.

4.3.2 Sample and data collection

The sample population included a local group of upper gastrointestinal (GI) CO and COtrain working at a single centre, with respondents being encouraged to complete before any optimisation studies had been undertaken. The study design aimed to capture the views of professionals who had experience of treating the anatomical disease site i.e. pancreatic cancer. Clinical oncologists from other disease sites, or trainees who had not completed a placement with

the upper GI team were excluded/not approached. No personal details were captured, and the anonymity of questionnaires was guaranteed to allow honest answers to be provided, reduce prestige bias, and ensure every respondent could contribute.

The survey preceded the MR-CT delineation study (Chapter 5), with respondents being invited to complete the survey before they commenced on the delineation study. On verbal agreement to participate, they were then sent the finalised electronic survey which was accompanied by a covering letter clearly detailing the background information. A deadline for completion was given, followed by an electronic reminder 1 week before the deadline.

4.3.3 Survey construction

The study used a single centre cross sectional survey methodology, with data being captured at one timepoint. A tightly structured original survey was designed to capture the answers to a written series of questions and allow supplementary information to be added, if required. This provided quantitative data and an option to include descriptive information, where volunteered. Answers to the survey were used to provide descriptive measures of their views, as described by (Moser and Kalton, 2017). To describe the phenomenon a descriptive study was used, with variables such as different disease classifications (BRPC and LAPC). As the intention was to understand attitudes, no right or wrong answers were defined for any of the questions.

4.3.4 Question design and order

The methodology chosen for this aspect was an original survey design which gave the option to answer each closed-ended question using a numerical scale that would provide quantitative data i.e. a Likert scale. This provided a way of quantifying whether the respondent agreed with the statement, and to what degree. The survey used a mixture of 4- and 5-point scales to capture ordinal data, with ordering of choices matching a changing degree of response e.g. 1 – Not at all important, 2 – Slightly important, 3 – Moderately important, 4 – Very important 5 – Extremely important. Questions were written so to prevent leading the respondent. For example, instead of using "how challenging" the participant was asked "what level of difficulty". Latter questions asked the importance of optimising each component along the RT pathway; and for 1 question respondents were asked to rank answers according to what they felt was most important. This was to understand how they would prioritise factors, indicating which were of more importance to them i.e. their preferential judgement. The questions were set out in the order of the pathway they were being asked about e.g. in RT for pancreatic cancer, the delineation comes first, followed by planning and delivery. This was to think logically along the process they were familiar with and identify where they believed the biggest challenges were.

The questions were mostly set out so that respondents could rate their answer using pre-defined criteria, using the Likert scale tool (Batterton and Hale, 2017). This would illustrate to what degree each person agreed with any statement. For one question, respondents were asked to rank answers according to which they were in most to least agreement with. This was to understand how they would prioritise answers, indicating preferential judgement. Additional comments were welcomed after each question where answers could be expanded on. Each question was followed by a free text option, so participants could raise anything of importance, related to the questions.

4.3.5 Piloting

Stage 1: Piloting was used to determine if questions were appropriate, readable, unambiguous, and answers were representative of the question being addressed. This process was also used to ensure clarity and precision of the questions, so that responses were well understood and complete. Four experienced abdominal RT experts (1 CO, 1 COtrain and 2 radiographers) were asked to complete the questionnaire and indicate any problems interpreting the questions e.g. ambiguity; comment on clarity; and check for overlap in questions.

Stage 2: Following feedback, the questionnaire was refined to address ambiguity in understanding the questions and duplication of questions. The process was repeated 3 weeks later (retested), this ensured all comments were addressed to a sufficient level and the survey was deemed appropriate for use.
Face and construct validity were used as described by Taherdoost et al (2016) to ensure the questionnaire design was going to successfully capture the data required to measure the intended outcomes. Reliability was tested alongside validity and was determined by looking at the agreement between repeat testing of the piloted group.

4.3.6 Data collection and survey analysis

The survey was created on web based WEBROPOL (https://webropol.com) survey and reporting, with final design included in appendix 1. A link was sent to all members of staff who met the inclusion criteria, with a cover letter explaining the survey. Data analysis used descriptive statistics and frequency analysis in IBM SPSS Statistics (Version 28.0.0.0). To rank priorities, the mean score across all respondents was calculated and ranked in order of lowest to highest. Standard deviation (SD) was reported to show variation. No qualitative analysis was performed on the free text due to only one respondent providing a limited repsonse.

4.4 Results

4.4.1 Survey respondents

Nine potential survey participants were identified and approached, including 5 CO and 4 COtrain. All 9 gave a verbal agreement to being sent the survey and agreed to their participation. Eight participants completed the survey, including 4 CO (2-10 years of experience) and 4 COtrain.

4.4.2 Difficulty of delineation of PDAC

All respondents answered either “difficult” or “very difficult” when describing level of difficulty in delineating BRPC or LAPC tumour volumes using 3D and 4DCT alone (Figure 4.1a and b). COtrain indicated a higher level of difficulty for LAPC than BRPC, with all CO respondents answering “difficult” for both.

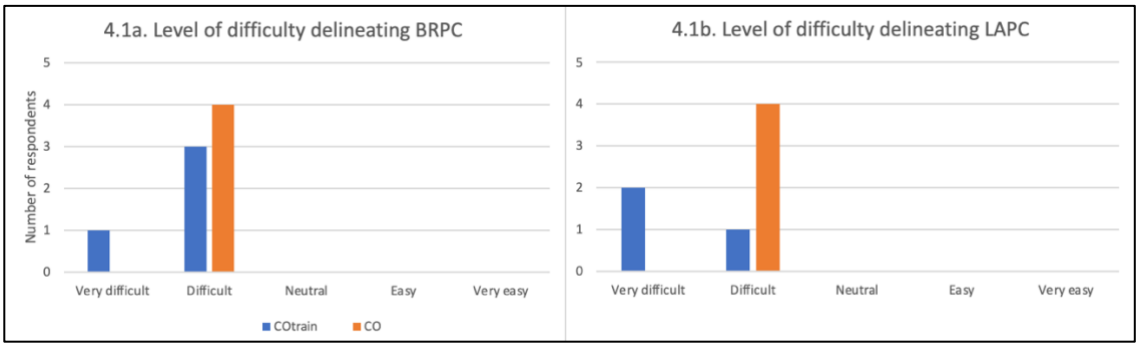


Figure 4.1a-b. Number of respondents indicating each level of difficulty in delineating BRPC (a) and LAPC (b), categorised by CO or COtrain.

4.4.3 Perceived impact of MRI to reduce IOV

For CO respondents, they thought the addition of MRI in the RT planning pathway would reduce the IOV compared to CT alone by 1 level of difficulty i.e. answering major (1) and moderate (3) without MRI; to moderate (1) to minor (3) with MRI. A shift was also seen with the trainees indicating less perceived IOV with MRI (Figure 4.2a-b). The impact which MRI would have on gross tumour

volume (GTV) was scored higher by the CO, with moderate (3) and major (1) variation being indicated compared to COtrain who answered minor (3) and moderate (1). Dosimetric impact of MRI volumes were thought to be less, with CO responding minor (2) and moderate (2), and for COtrain minor (3) and moderate (1) (Figure 2b-c).

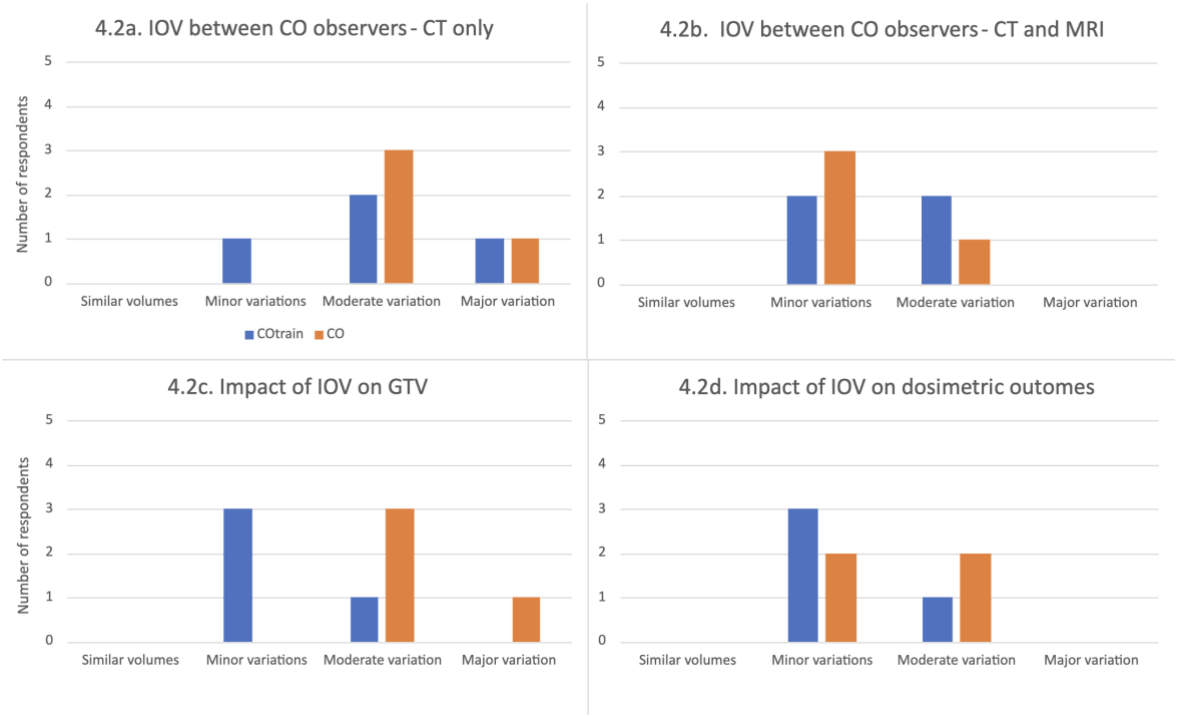


Figure 4.2a-d. Perceived IOV between consultant GI Clinical Oncologist observers when using CT alone (a) CT and MRI (b). Impact of IOV on GTV (c); and impact of dosimetric outcomes (d) by number of respondents.

4.4.4 Importance of optimising factors

The importance of improving delineation by reducing IOV by was rated high by CO respondents with all indicating “very” or “extremely” important. The majority of COtrain respondents also answered “very” or “extremely”, with only 1 answering slightly (Figure 4.3a). Respondents all agreed on a high importance in optimising planning images to provide better visualisation of volumes, with all indicating “very” or “extremely” (Figure 4.3b). Results showed less importance in optimising on-treatment images to improve soft tissue visualisation for IGRT matching protocols for the COtrain group, with 50% answering “moderately” (Figure 4.3c). Improving motion management techniques and strategies were

deemed “moderately” to “extremely” for all respondents (Figure 3d). Most variation in answers were observed for importance of delivering a standardised education package to junior clinicians on delineation. For this topic, answers were spread throughout 4 levels of importance including “slightly” to “extremely” (Figure 4.3e). The topic with the highest level of agreement and importance was the importance of peer reviewing volumes and plans with representation from a multi-disciplinary team (Figure 6f). “Extremely” important was answered most frequently across both group (7/8), with lowest importance expressed being “very” important (1).

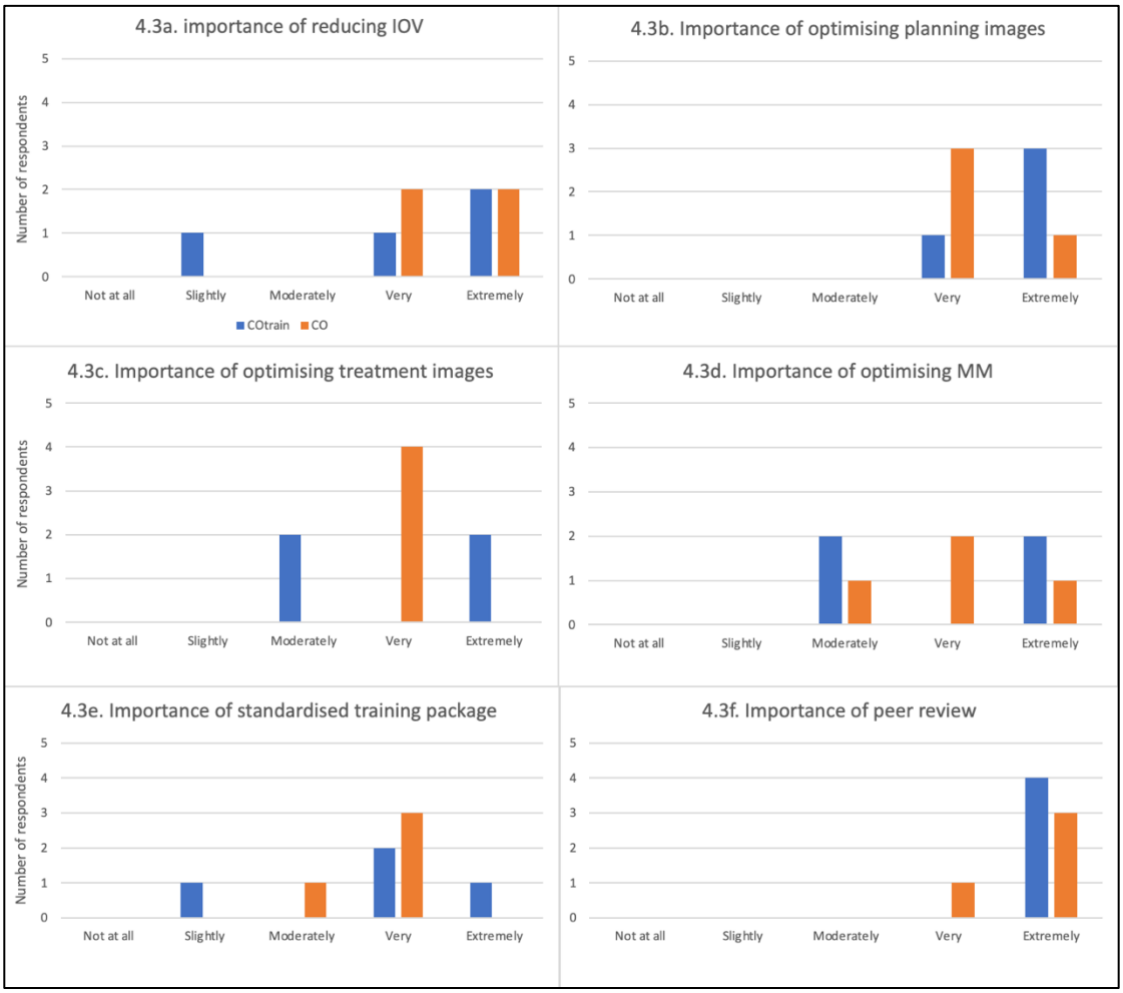


Figure 4.3 a-f. Number of respondents indicating each level of importance for optimising different aspects of the RT pathway including: reducing IOV (a), pre-treatment images (b), on treatment images for verification (c), motion management (MM) (d), standardising training packages for trainees (e) and peer review of volumes and plans within MDT (f).

When the topics reported in Figure 4a-f were ranked, optimising planning images was ranked first position and delivering a standardised education package was ranked last position (Table 4.1). In the least and most important topics (SD), the highest level of agreement was seen by all observers (SD 0.76, 0.46 respectively).

Ranked position	Topic	Mean	SD
1	Optimise the quality of planning images to give better visualisation of tumour volume and organs at risk	2.00	0.76
2	Peer review volumes and plans with representation from a multi-disciplinary team	2.38	1.30
3	Improve tumour delineation by reducing variation between consultant Clinical Oncologists	2.75	1.83
4	Improve motion management techniques and strategies	4.00	1.51
5	Optimise on-treatment images to improve soft tissue visualisation for IGRT matching protocols	4.13	0.83
6	Deliver a standardised education package to junior clinicians on delineation	5.75	0.46

Table 4.1. Ranked positions of most important topics to improve RT for pancreatic cancer, with 1 being determined as most important, through to 6 being least importance

When questioned about whether standard of care (SOC) prescribed dose was adequate in treating BRPC and LAPC, no respondents strongly agreed or disagreed, 2 (50%) of CO agreed it was adequate and 1 (25%) disagreeing that prescribed dose was adequate for BRPC and LAPC. For COtrain, no respondents indicated that UK doses were adequate in treating PDAC, whether BRPC or LAPC.

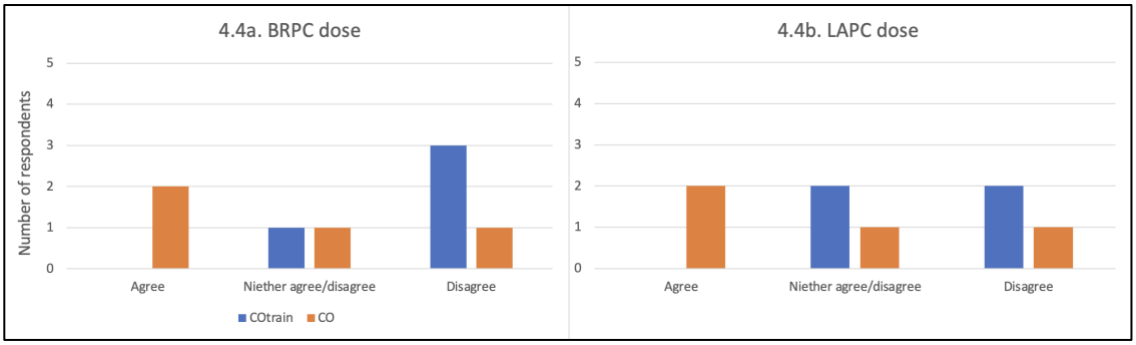


Figure 4.4 a-b. Number of respondents indicating each level of agreement with standard of care prescribed dose in the UK being adequate in treating BRPC (a) and LAPC (b).

CO train answers were spread from “slightly” to “extremely” when asked the importance of improving imaging to assess response, whereas all CO respondents indicated “moderately” or “very important”.

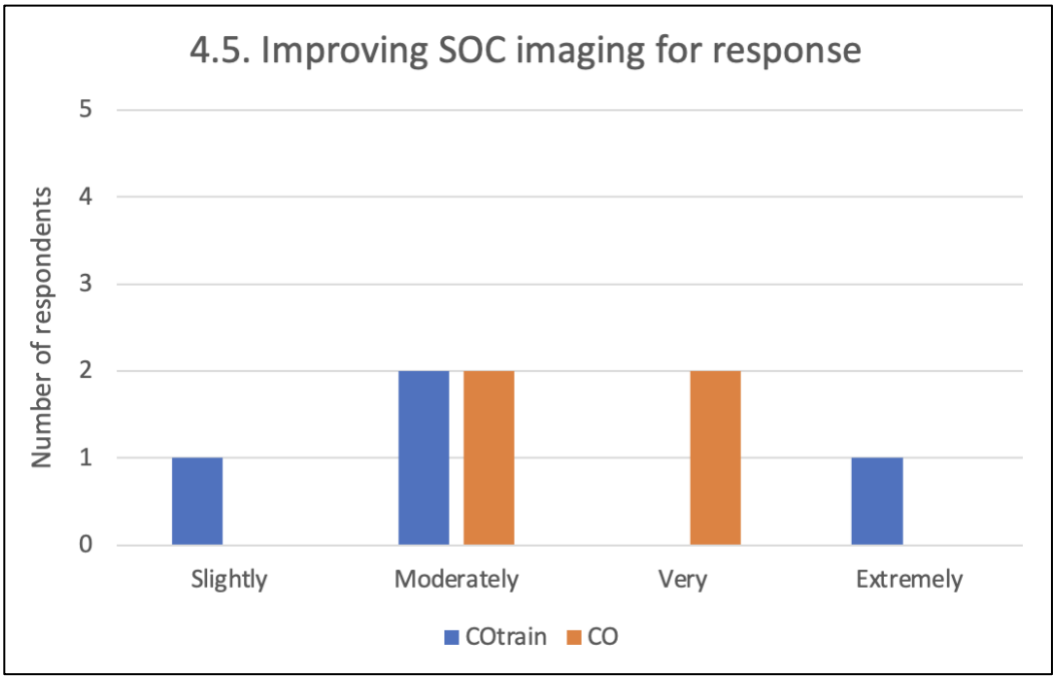


Figure 4.5. Number of respondents indicating each level of importance on how important it is to improve standard of care imaging to assess treatment response before and after radiotherapy.

4.5 Discussion

The aim of this survey was to capture the views of CO and COtrain in the optimisation of RT for PDAC. Understanding the priorities of the sampled group has guided further work within subsequent chapters, by providing a basis for an optimisation strategy. The survey identified that CO and COtrain recognised the importance of optimising each part of the RT process for pancreas and were motivated to improve these for future patients. Given the number of challenges faced in delivering safe and accurate abdominal RT, obtaining these views were important to understand the collective desire to improve techniques.

Consensus guidelines already describe the optimal methods for delineating, planning, and treating pancreas (Brunner et al., 2021). These documents make valuable recommendations on best practice, but do not specifically address areas where uncertainties could be improved or state which of these offers most potential to improve safety and accuracy of RT. Many uncertainties are addressed generally in On Target 2 IGRT guidance (RCR, 2021), which provides clear strategies on quantifying and reducing them. Individual PDAC studies may report on individual uncertainties, within a particular patient sample. However, in national/international efforts to drive advancements in PDAC RT there is no statement of consensus on optimisation of linac-based RT for abdominal sites, although UK SABR guidelines will be published for non-metastatic LAPC (UK SABR Consortium, 2022).

The reason for selecting expert and trainee respondents with upper GI experience was to ensure that an appropriate level of experience would give a better understanding of site-specific uncertainties that exist in treating complex abdominal RT. By making the survey anonymous respondents could answer the questions without any judgement and were reassured that their views were valued rather than providing answers that were expected.

When assessing the importance of improving different components, there were no areas where any respondent answered, “not at all”, indicating that all were

relevant areas in optimising RT. As would be expected, CO trainees indicated a higher level of difficulty (compared to CO) for delineating LAPC and BRPC. It is well known that delineation in pancreatic cancer is challenging even for practicing clinicians (Versteijne et al., 2017). Two COtrain respondents indicated "very difficult" for LAPC delineation, which may be in part due to the disease involvement around arteries and veins. In a study where diagnostic MRI was used alongside CT for delineation, LAPC cases showed more IOV (Caravatta et al., 2019). Although these challenges are also evident in the CO responses, more experience is likely to bring increased confidence. This also raises the question of such complex cases being treated at high volume centres, with adequate training and education in place.

The concept of using MRI in the delineation process is welcomed across tumour specific sites and the improved soft tissue definition makes it an attractive addition to the PDAC planning process. Views of both CO and COtrain showed that the expectation was that MRI and CT would reduce IOV, with major variations being indicated when using CT alone, thus identifying this as an area for further investigation.

For the CO, there were only 2 topics that were rated less than "very", including developing standardised training package, and improving motion management. However, these were still scored moderately. For COtrain, there was much more variation across all answers of the levels of importance. This could be a result of them having less involvement in later parts of the pathway, with COtrain being trained in the delineation stages early on but not on-treatment verification. This could be the reason that improving planning images and peer review process scored "very" or "extremely" important, as they rely on this method of feedback. Although being ranked in last position, there may still be a desire to explore the how standardised education packages may help to improve delineation. The benefits of different learning approaches have been demonstrated in different studies, which are discussed in a systematic review by Cacicedo et al. (2020). Even with such heterogeneous data they recommend that delineation skills could be improved by implementing an education program.

It is also worthwhile noting, that these results are based on CO and COtrain only and prioritisation may differ between different groups of staff. For example, a radiographer may not have the same knowledge and experience of the dose and fractionation used within this patient group, so by default prioritisation would be of on-treatment image optimisation. IGRT can be the full responsibility of the radiographer, so likewise, the CO or physicist may not prioritise these aspects due to less interaction with these processes. Specific involvement for each discipline will result in higher prioritisation of specific factors. Survey results ranked optimising the quality of planning images to give better visualisation of tumour volume and organs at risk as the most important factor, whereas optimising on-treatment images to improve soft tissue visualisation for IGRT matching protocols was ranked 4th. This may have been quite different if other professional groups had been included. The importance of acquiring high quality images for RT planning is well documented and can require quite complex processes with patient compliance (Mancuso et al., 2008; Godfrey et al., 2017). For RT delivery, the MR-Linac has allowed superior soft tissue for on-treatment visualisation, however given that the majority of patients cannot access this, linac-based treatments still require CBCT optimisation.

To ensure construct validity, participants were asked to rate questions then prioritise. This ensured that views expressed were representative and consistent, as described by Moser and Kalton (2017). For example, participants were asked to rate how much IOV there would be, then asked the importance of reducing IOV, and finally how they ranked this in terms of importance. Although face validity has been described as a weaker method of testing validity (Taherdoost et al., 2016) it was felt appropriate within the context of this survey, where quantified data was used to present a narrative description of healthcare experts views. Piloting allowed experts to determine whether the questions were relevant, feasible to answer, not ambiguous and of sufficient clarity. Especially since the desire was to report outcomes of the local team. Future studies to determine the views of a population would include steps to assess content validity in more detail, or potentially a more robust method e.g. Delphi consensus or nominal group technique would be used.

Strengths and limitations

This strength of this survey was that it quantified the views of medical professionals involved in RT for PDAC on the importance of optimising RT for this disease site. This confirmed the importance of optimising linac-based RT and engaging them in a strategy to do so. A limitation of this survey is that views expressed come from a single centre, where training and development of clinicians and trainees may result in similar practice and local protocols may influence views. The intention had been to survey UK experts from diverse geographical areas, however this survey was conducted at the time of the Covid-19 pandemic, where staff were dealing with a crisis period. Even with the single-centre approach, this work helped understand where there was ambition locally to address the themes of concern, with results demonstrating that most of those presented were important to optimise. Generalisation of results would only be possible by extending the survey using a multi-centre approach. This would ensure results had further implications within the expert community.

Conclusion and future work

Treating PDAC with RT remains challenging, and there is much work to do in optimising RT for future treatment and trial protocols. RT is a multi-disciplinary service where several disciplines optimise and streamline processes within their area of expertise. Future work will aim to understand the views of other key disciplines, by adapting this survey to capture discipline specific views within those areas i.e. medical physicists and radiographers. For these reasons, the MDT approach is even more important, where uncertainties at each part of the pathway are addressed. For the next chapter in this thesis, the optimisation of multi-modality imaging for RT planning will be the focus.

Chapter 5 Multi-modality imaging in radiotherapy target volume definition for pancreatic cancer

5.1 Background

The aim of this chapter was to investigate the impact of introducing MR/CT fusion to RT planning for pancreatic cancer. This study assessed the impact of using co-registered CT and MR images for the delineation of pancreatic cancer tumour volumes by clinical oncologist (CO) and clinical oncology trainee (COtrain) observers.

5.2 Hypotheses and research questions

The hypothesis was that using these MR and CT imaging datasets together i.e. registered images, would result in smaller target volumes, and improve agreement between observers.

1. What is the volumetric impact of MR-CT fusion have on the delineation of target volumes between observers when compared to CT only volumes

Objectives

- Measure gross tumour volume (GTV) and internal target volume (ITV) volumes (cm^3) for all CT only delineations and CT-MR registered delineations, for all individual observers.
- Report volumetric mean (cm^3), standard deviation (SD) for all volumes and all observers.
- Define volume difference between individual observer volumes and the gold standard (GS), for all patients
- Calculate the percentage of overlap in all observer volumes of GS volume included.
- Describe the similarity of all observer volumes to GS volumes using dice similarity coefficient (DSC).

2. Does MR-CT fusion compared to CT only reduce inter-observer variability in delineation of GTV?

Objectives

- Evaluate variation across all observers

- Group staff into either CO or COtrain and compare DSC between groups when calculated for each observer and GS.
- Determine if uncertainties are reduced in less experienced staff

5.3 Introduction

MR is an attractive modality for aiding the delineation of target volumes required for planning RT (Brock et al., 2014; Van der Heide et al., 2019). It's integration in the planning pathway must be executed with care, paying attention to developing the optimal protocols, including the registration process. When implementing MRI for RT planning, the optimal use of technology should be considered whilst being guided by the available scanning recommendations from experts in the field (Paulson et al., 2016; Speight et al., 2021). This is necessary to ensure that additional multi-modality imaging is introduced safely, providing a benefit to the outcome rather than introducing uncertainty.

Multi-modality imaging has the potential to improve the visualisation of pancreatic disease and nearby structures, which are often difficult to define on CT alone (Raman et al., 2012; Saisho et al., 2004). In the RT pathway this requires co-registration to be accurate around disease. This relies on the appropriate region of interest being applied i.e. target area and nearby surrogates. In the abdomen, structures susceptible to motion and deformation require careful consideration in this process.

Historical randomised studies that investigated treatment of PDAC with RT used less conformal techniques than available today (Hammel et al., 2016; Mukherjee et al., 2013). By using IMRT and VMAT techniques dose escalation in PDAC RT is feasible with acceptable levels of toxicity reported when delivered with motion management strategies, improved IGRT protocols, and advanced imaging for RT planning (Colbert et l., 2017; Krishnan et al., 2016). More recently, studies have investigated hypofractionated dose escalation, made possible by improving the accuracy and precision of planning and delivery. This has been described on

linac-based and MR guided platforms (Chuong et al., 2022; Courtney et al., 2021) with doses up to 50Gy being delivered in 5 fractions. Accurate delineation becomes even more important in such settings, where highly conformal plans with steep dose gradients are utilised.

Delineation uncertainty is well investigated across many disease sites since the introduction of conformal planning, with few studies investigating pancreatic target volumes using CT (Cattaneo et al., 2010; Versteijne et al., 2017; Yamazaki et al., 2007); and CT with staging MR (Caravatta et al., 2014). Inaccurate delineation of target volumes in RT results in the introduction of systematic error (SE), which can lead to a geographic miss, underdosing of the tumour, overdosing of organs at risk (Njeh, 2008; van Herk et al., 2000; van Herk, 2004). Unlike random error, SE affects each fraction of RT, with a high risk of going undetected. When SE is introduced at the delineation stage, this becomes the planned treatment and daily IGRT is based on a new reference, failing to recognise and correct for it.

Delineation of pancreatic lesions are challenging, with structure definition being hampered by low tissue contrast. Target volumes in pancreatic radiotherapy are known to be susceptible to inter-observer variation (IOV), with previous work in CT delineation for pancreas demonstrating the impact on clinical outcomes (Abrams et al., 2012; Fokas et al., 2016). Similar literature based on pancreatic cancer delineation using MRI is not so well established, with only a few publications addressing the impact of MRI in planning volumes for RT (Caravatta et al., 2019; Dalah et al., 2014; Gurney-Champion et al., 2017; Hall et al., 2018). Three of these publications described using co-registered images, with little or no detail on MR set-up and timing of corresponding CT (Dalah et al., 2014; Hall et al., 2018); have used differing acquisition/registration methodologies, with no detail on IOV (Heerkens et al., 2017); and only 1 pancreas specific study (Caravatta et al., 2019) was included in a recent systematic review that included publications between 2018-2021 (Guzene et al., 2022).

Studies that investigated delineation uncertainties using MRI in the RT process, have generally included small numbers of observers or patient cases and were mostly retrospective. A number of metrics that assess interobserver variability have been described across studies, as reported in review papers (Guzene et al., 2022; Hanna et al., 2010; Vinod et al., 2016). Heterogeneous methodologies have included volume and centre of mass comparisons through to the reporting of more detailed indices that assesses the relationship between volumes. The lack of standardised and uniform methodologies throughout studies being highlighted by most as a common theme, making comparisons a challenge. The delineation process was deemed the weakest link by Njeh (2008) and limitations in delineation/interobserver study methodologies are still being critiqued in review articles 15 years on, suggesting it has failed to lose that reputation (Guzene et al., 2022). This is even the case across even the more straightforward disease sites.

This is the first study to quantify IOV using co-registered MR and CT RT planning scans acquired on the same day in the delineation pancreatic RT volumes for cancer patients. Published data who have co-registered these scans, have used scans acquired on different days, have not quantified IOV or, have not explicitly detailed the scanning methodology sufficiently to determine this.

5.4 Methods

5.4.1 Patient datasets

Patients treated with RT for borderline resectable pancreatic cancer (BRPC) and locally advanced pancreatic cancer (LAPC) who had MR and CT for RT planning were included. From May 2020 in response to the covid-19 pandemic, moderate hypofractionation and hypofractionation protocols were implemented in our department as per the UK recommendations in response to the Covid-19 pandemic (RCR, 2020). All treatment courses were completed using this new standard of care, and datasets were analysed retrospectively. There was no change or intervention to patients' treatment.

5.4.2 Patient preparation and imaging datasets

Patients were in a fasted state for 2 hours prior to pre-treatment scanning, this was to ensure an empty stomach at each appointment. Dilute oral contrast (Gastrografin ®, 5-10ml in 125-250ml H_2O) was administered 10 minutes before scanning, with volume/concentration recorded to ensure reproducibility at treatment appointments. Patients were prepared for the acquisition of CT and MR images in breath-hold by providing them with additional verbal information a week before their scanning visit, immediately before their scanning appointment and throughout their appointment. This included a telephone appointment prior to the scan, which included an in-depth explanation of the procedure and a run-through of the proposed protocol, with recommendations on home practice. This was then repeated immediately before the CT appointment to ensure the exhale breath-hold was clear and feasible. The effects of intra-venous (IV) contrast e.g. flushing was also given to the patient in preparation for a successful breath hold acquisition.

Contrast enhanced exhale breath hold CT (3D-CECT_EBH) had been acquired in a supine treatment position on either a LightSpeed 16 CT (GE Healthcare, United Kingdom) or a Philips Brilliance Big Bore CT (Philips Healthcare, Cleveland, Ohio)

with RPM (Varian Medical systems, Palo Alto, CA) in treatment position. Immobilisation was used to support arms above head i.e. an indexed wing board, vacuum bag, and indexed knee rest to improve comfort. Reference points were marked externally on the patient's skin to aid set-up at MRI and treatment. Immediately following 3-CECT_EBH acquisition, a 4DCT was acquired in free-breathing (4DCT_FB), both datasets were acquired using respiratory patient management system (RPM) (Varian Medical Systems, Palo Alto, CA).

An MRI scan was acquired with the same immobilisation as CT and in treatment position. This was immediately following CT, so that preparation was consistent for all scans. MR sequences were all acquired in breath hold. Sequences were acquired on a GE Signa HDxt 1.5T (HD23.0_VOL_1210a) (GE Medical Systems) and included an Axial fast imaging employing steady state acquisition (FIESTA) 4mm and Axial FIESTA 4mm fat-saturation (FS) sequence.

5.4.3 Creation of test patients and structure sets

A library of test patients was created in Eclipse V15 (Varian Medical Systems, Palo Alto). This was done by exporting CT and MR datasets from already treated patients i.e. patients where a planning MR and CT had been acquired as standard of care. Datasets were anonymised, with no identifiable information available to observers. All GTV, ITV and PTV structures were deleted so that each observer was blinded to previous target volumes (Table 5.1).

	Test patient 1	Test patient 2	Test patient 3	Test patient 5	Test patient 8
MC	ZZ_Pan_P01	ZZ_Pan_P02	ZZ_Pan_P03	ZZ_Pan_P05	ZZ_Pan_P08
GS	ZZ_PanP1Ob00	ZZ_PanP2Ob00	ZZ_PanP3Ob00	ZZ_PanP5Ob00	ZZ_PanP8Ob00
NC	ZZ_PanP1Ob10	ZZ_PanP2Ob10	ZZ_PanP3Ob10	ZZ_PanP5Ob10	ZZ_PanP8Ob10
CO	ZZ_PanP1Ob21	ZZ_PanP2Ob21	ZZ_PanP3Ob21	ZZ_PanP5Ob21	ZZ_PanP8Ob21
NC	ZZ_PanP1Ob32	ZZ_PanP2Ob32	ZZ_PanP3Ob32	ZZ_PanP5Ob32	ZZ_PanP8Ob32
COtrain	ZZ_PanP1Ob43	ZZ_PanP2Ob43	ZZ_PanP3Ob43	ZZ_PanP5Ob43	ZZ_PanP8Ob43
COtrain	ZZ_PanP1Ob54	ZZ_PanP2Ob54	ZZ_PanP3Ob54	ZZ_PanP5Ob54	ZZ_PanP8Ob54
CO	ZZ_PanP1Ob65	ZZ_PanP2Ob65	ZZ_PanP3Ob65	ZZ_PanP5Ob65	ZZ_PanP8Ob65

Table 5.1. Naming of test patient ID. Master test case (MC) where all observer volumes were imported for analysis. Gold standard (GS) volumes were delineated by expert CO and consultant radiologist (COrad). Where cases were not completed (NC) and completed cases by CO or COtrain.

Each dataset had a pre-defined study structure set attached to ensure that correct and standardised nomenclature was used for all structures throughout the study (Table 5.2). Inter-observer variation in OAR was beyond the scope of this study, and so predefined OAR were available at the delineation stage, except duodenum. Differentiating border of duodenum and pancreas can be challenging and previous duodenal volumes could affect the GTV being delineated by observers. For this reason, the duodenum structure was removed on each dataset to ensure it was not used to aid observer volume delineation. Test patients were created for 8 consecutive patients, followed by an assessment to remove any that were not suitable for assessment i.e. tumour diffusivity. No access to previously acquired diagnostic imaging and reports were included, with a limited amount of information from the clinical history made available for each case (Table 5.3).

Volume	3DCECT-BH	4DCT-FB	MR-BH	Summary description
GTV_3D	X			GTV i.e. visible disease delineated on 3DCT only
GTV_inhale		X		GTV delineated on maximum inhalation bin of 4DCT
GTV_exhale		X		GTV delineated on maximum exhalation bin of 4DCT
ITV_CT	X	X	X	GTV_3D + GTV_inhale + GTV_exhale
GTV_MR			X	Visible disease delineated on MR only
GTV_MR_CT	X		X	GTV_3D with amendments based on information from MR
ITV_MR	X	X	X	GTV_MR_CT + motion from inhale/exhale

Table 5.2. Summary of delineated volumes by each observer detailing which datasets were used.

	Clinical information provided to each observer
ZZ_PanP1	eus - large mass in uncinate CT - mass lesion in the uncinate process of pancreas now measuring 26 mm. Reduced narrowing of the SMV, but persistent SMA encasement
ZZ_PanP2	CT - head of pancreas mass around 1.6 cm . Persistent circumferential encasement of the common hepatic artery and unchanged tight focal narrowing of the portal vein. Accessory right hepatic artery arising from the SMA has apparent soft tissue contact anteriorly, but no encasement.
ZZ_PanP3	eus - 25mm mass in head of pancreas -Mass clear of SMV/PV ct - head of pancreas mass measuring 30 mm . Contact with the SMV but no narrowing
ZZ_PanP5	eus - Body of pancreas lesion Close to coeliac, involving splenic A ct - large body of pancreas mass encasing the common hepatic artery, and in contact with the coeliac axis and SMA. DJ flexure also involved.
ZZ_PanP8	ct HOP mass measures 32 x 20mm -Atrophy of pancreatic body and tail -<180 degree encasement of SMA -SMVl occluded with large collaterals

Table 5.3. Clinical information available to observers on each test case

5.4.4 Observers

The GI team CO were approached and given information on the study protocol and an invitation to participate, explaining the rationale, methodology, expectations and timelines. Experienced COtrain of the GI team were also identified and invited. Where observers agreed to participate, they were given an observer number which was used alongside the ID of each patient to access their individual datasets. By each observer delineating on a separate dataset, uniquely named with their observer number, there was no opportunity for observers to view each other's structure set. This was intentional to reduce bias and ensure observers were blinded to other delineations. Anonymisation prevented any observer from accessing study patients' clinical records or their treated structures and planning outcomes. Observers were deliberately given a

unique non-consecutive observer number to reduce the likelihood of opening another observer's patient i.e. Observer 1, 2, 3, 4, 5, 6 was named Observer 10, 21, 32, 43, 54, 65 (Table 5.1). These were given to potential observers in confidence, with only the researcher knowing numbers, and whether they were assigned to a CO or COtrain.

5.4.5 Stage 1 – Delineation with CT only

All GTV and ITV delineations were added to each test patient by individual observers according to stage 1 instructions (table 5.4). This was standardised across all cases to allow volumes to be evaluated individually, and to allow comparisons between observers.

Each observer delineated all the GTV and ITV on the 3D-CECT_EBH radiotherapy planning scans only, for each test case (MRI scans were not accessed at this point). The 3D-CECT_EBH dataset had all OAR finalised, with the exception of duodenum. Standardised structure sets with standardised nomenclature were attached, as detailed in table 5.4 for GTV and ITV.

Descriptions of each volume were included in the instructions, detailing what should be delineated using each imaging dataset (appendix 2). The inhale (4DCT_inhale) and exhale (4DCT_exhale) bin of the 4DCT_FB was used to assess and delineate disease and motion by each observer i.e. 4DCT_inhale for GTV_inhale, and 4DCT_exhale for GTV_exhale. This was then copied onto the 3D dataset, where an ITV was created using a Boolean operator, and by amending throughout each slice to ensure all disease was included throughout all phases. All structures were saved on the 3D-CECT_EBH dataset.

Stage 1 requires delineation to be performed on the CT_1 (3D-CECT breath hold) dataset and the relevant 4DCT images i.e. CT_RP_00 and CT_RP_60 (inhale and exhale). **N.B. MRI should not be viewed until stage 2 and should not be completed within the same session to ensure reliability and validity of results**.
Using the 3D CECT and 4DCT delineate the following structures:
GTV_3D – This should include pancreatic tumour visible on image
GTV_inhale – On the maximum inhale bin of the 4DCT delineate GTV
GTV_exhale - On the maximum exhale bin of the 4DCT delineate GTV
ITV_CT -On the 3D-CECT create the ITV using Boolean operators to produce a union of GTV_3D, GTV_ inhale and GTV_ exhale
Once ITV_CT is created, verify that involved disease is adequately covered on all phases of 4DCT

Table 5.4. Stage 1 delineation instructions for CT only delineations

Once all observers had completed delineation, RT MR images were co-registered to the relevant 3D dataset using a mutual information match based on an individualised region of interest (ROI) around the disease and vessels.

5.4.6 Stage 2 – Delineation of MR only and final MRCT volumes

Observers delineated a GTV_MR on the MR image dataset only, this was only to include disease as visualised on MR (Table 5.5). A copy of the GTV_MR target volume was copied over to the CT dataset named GTV_MR_CT then was adjusted to account for any additional anatomical information visualised on the multi-modality images i.e. the result being a GTV structure to include disease identified on the registered CT and/or adapted using MR images.

Stage 2: Now using registered 3DCT, 4DCT and MR images
GTV_MR - delineate disease visualised on MR only
GTV_MR_CT – This will be your GTV_3D amended using registered MR and CT scan
ITV_MR – This is your GTV_MR_CT and any motion from GTV_inhale* and GTV_exhale*
***** may need amended, based on information from MR, please create copy of these structures if necessary and name MR_CT_inhale and MR_CT_exhale**) i.e. using MR and all 3D/4D information.

Table 5.5. Stage 2 delineation instructions for MR only, and MR/CT registered delineations.

5.4.7 Gold standard volumes

Delineation of GS cases were completed by an experienced CO with >10 years of experience in treating upper GI cancers and an expert in abdominal MR imaging radiologist with >10 years of experience. Accreditation for contouring pancreas tumours for treatment with SABR was obtained through the Radiotherapy Trials Quality Assurance (RTTQA) group for the GS CO.

5.4.8 Import to Master Case

On completion of all observer volumes, each GTV and ITV were given the observer numbers as a prefix e.g. observer 21 volumes were named 21_GTV_3D, 21_GTV_Inhale, 21_GTV_Exhale etc. All structure sets were then imported into the individual MC i.e. ZZ_Pancreas_P01, 02 etc, and compiled onto one final CT dataset. This allowed all volumes to be visualised, measured and calculations to be performed.

5.4.9 Validity and reliability for MR

To reduce the risk of bias, anonymisation prevented observers from identifying patients and viewing clinical structures. Observer numbers were not given consecutively to prevent access to other observers test patient. Observers did not have access to the RT planning MR images when completing their first delineations on CT only. This was to prevent any visualisation of soft tissue

changes apparent on MR that would affect results. Quality assurance (QA) was carried out on all imaging modalities to ensure consistent and reliable results were obtained from the datasets.

5.4.10 Statistical analysis

Volume (cm^3) data was extracted from the Varian Eclipse treatment planning system (Varian Medical Systems, Palo Alto, CA; Version 16.1) for all structure delineations created with CT alone, MR alone and registered MR and CT were recorded for each patient and each observer. Comparisons in volume and concordance were calculated between the GS and other observers. All volumes were assessed together to provide means and standard deviation for all observers, and the patients with and without the GS included. Non-parametric Wilcoxon signed rank tests were used to test for significance ($p=<0.05$). Overlap of all volumes for all observers and GS, were calculated using Boolean operators on the treatment planning system (TPS) e.g. “AND” for all structures were used to and measure area of overlap.

In conjunction with difference in volume, a similarity indice, was used to further describe the similarity between volumes, by utilising spatial information. This included DSC, as calculated on Eclipse. DSC results were categorised according to score i.e. 0-0.2 very poor, 0.21-0.4 poor, 0.41-0.6 moderate, 0.61-0.8 very good, 0.81-1.0 excellent. Descriptive statistics and data analysis were carried out using IBM SPSS Statistics (Version 28.0.0.0).

5.5 Results

5.5.1 Patients

Eight consecutive patients with the MR and CT planning protocol were anonymised and assessed for inclusion in the study. Three of the 8 patients selected for this delineation study were excluded before delineation commenced, this was due to the diffuse appearance of tumour on their RT planning images. A total of 5 patients with LAPC and BRPC were included in the final analysis (patient, 1, 2, 3, 5 and 8).

5.5.2 Observers

Six observers agreed to participate, including 4 CO and 2 COtrain. Four observers completed structure volumes for all test cases, and were included in the final analysis, 2 didn't complete. This included 2 CO observers one with 2 and, and one with >10 years of experience; and 2 COtrain with the upper GI experience of pancreas delineation. One CO and 1 COrad delineated all structures jointly for all 5 test patients to create the full GS dataset.

5.5.3 Volumes for each observer

A total of 175 volumes were analysed i.e. 7 volumes for each patient (GTV_3D, GTV_exhale, GTV_inhale, GTV_MR, GTV_MRCT, ITV_CT, ITV_MR), completed by 5 observers i.e. CO, COtrain and GS. All GTV structures delineated by all observers are shown for patient 1 in figure 5.1. These are shown for all delineated volumes, and overlap.

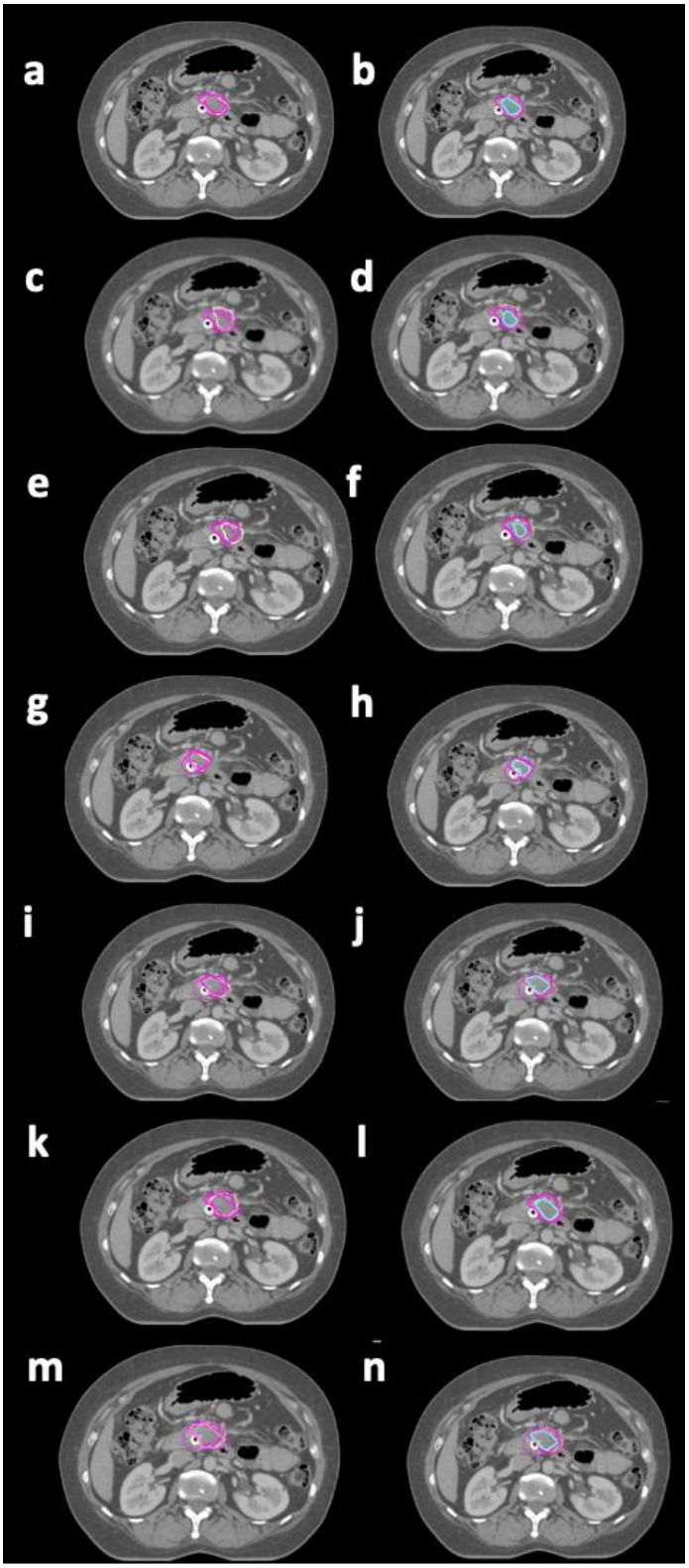


Figure 5.1 a-n. One slice of 3D-CECT_EBH showing all gold standard (yellow) observer structures (magenta) and overlap (cyan) for patient 1. GTV_3D (a) and overlap (b), GTV_exhale (c) and overlap (d), GTV_inhale (e) and overlap (f), GTV_MR (g) and overlap (h), GTV_MRCT (i) and overlap (j), ITV_CT (k) and overlap (l), ITV_MR (m) and overlap (n).

5.5.4 Mean structure volumes for individual patients

Mean (SD) structure volumes and individual observer volumes for individual patients are shown in figure 5.2. The mean GTV_MR structures were smaller than GTV_3D for 4/5 patients i.e. GTV_3D and GTV_MR for patient 1 were 10.4 and 12.3 cm^3 respectively (difference +18% i.e. GTV_MR was larger) for patient 1; 7.5 and 6.5cm^3 for patient 2 (-13%, i.e. GTV_MR was smaller); 35.0 and 33.5 cm^3 (-4%) for patient 3; 19.0 and 11.9 cm^3 (-37%) for patient 5; and 15.9 and 7.4 (-53%) for patient 8. GTV_MRCT showed an increase in GTV_3D volume of 49%, 65%, 26%, < 1% for patients 1,2,3 and 5; with a 11% decrease for patient 8. ITV volumes created using CT only (ITV_CT), and MR and CT (ITV_MR) were either the same, or similar.

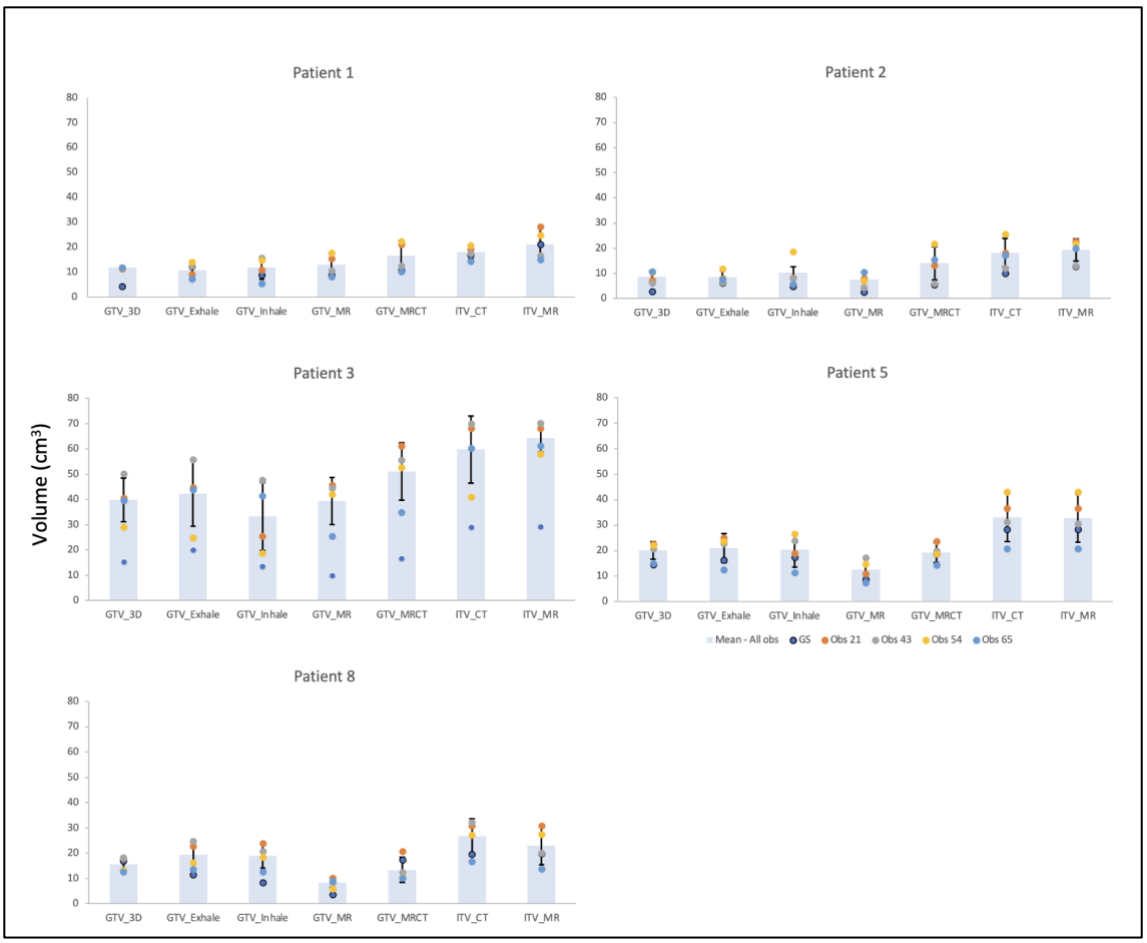


Figure 5.2. Mean observer volumes represented by bar (cm^3) and SD displayed as error bars for GTV_3D, GTV_exhale, GTV_inhale, GTV_MR, GTV_MRCT, ITV_CT, ITV_MR for each individual patient. Individual observer and GS volumes are plotted as per legend.

5.5.5 Mean structure volume all patients

Mean calculated volumes for all structures, all patients and all observers (i.e. across the population) are highlighted in figure 5.3. These showed that across the population, MR volumes were smaller than GTV_3D. The highest magnitude of mean difference was observed directly between volumes with and without MR i.e. (i) GTV_MR and GTV_3D and (ii) GTV_3D and GTV_MRCT. A 3cm^3 difference in means was observed between mean GTV_MR and GTV_3D across the population volumes for all observers, showing MR volume alone was smaller than 3D-CECT_EBH alone and was statistically significant (p=0.048). The mean GTV_MRCT to GTV_3D difference was -3.7cm^3 (p= 0.145). When mean across all observers including GS volumes were compared, the magnitude of the difference in means between GTV_MR and GTV_3D increased to 3.22cm^3 (GTV_MR smaller volumes); and the mean difference was -3.53cm^3 for GTV_MRCT (reduced difference in mean, but still larger volumes than 3D_GTV). When GS volumes were included in the analysis, they were statistically significant i.e. with GS p=0.019 and p=0.040 for GTV_MR compared to GTV_3D and GTV_MRCT respectively.

Mean observer volumes were larger across all structures compared to GS volumes (Figure 5.3). Mean difference in volume between GTV_3D and GTV_inhale and GTV_exhale showed that these were volumetrically similar. Paired t-tests for GTV_3D compared to GTV_exhale and GTV_inhale showed no significance p = 0.121, 0.904 respectively, and GTV_MR was statistically significant p = 0.048.

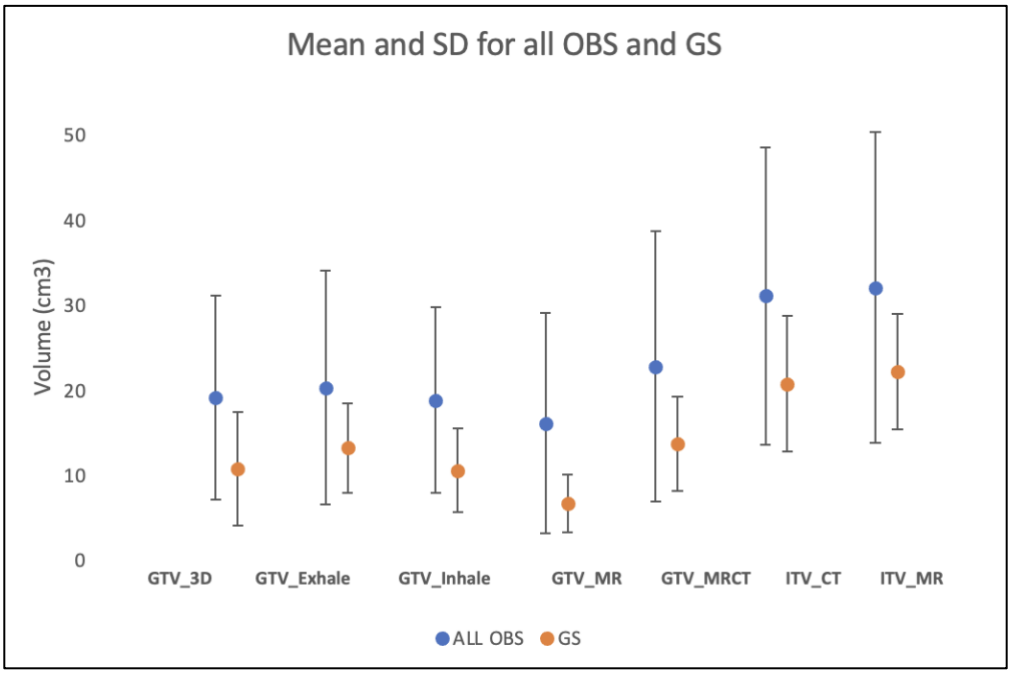


Figure 5.3. Mean volume (cm^3) for all CO and COtrain observer structures (All OBS) and SD shown as error bars, with mean volume of all gold standard (GS) structures with SD shown as error bars.

5.5.6 CO and COtrain volumes comparison

For CO and COtrain, the mean GTV_MR were smallest volumes 15.1 and 17.3 cm^3 respectively. Between the 2 groups highest mean values were observed for COtrain, with lower but similar values for CO (Figure 5.4, 5.5 and 5.6). The variation around the CO and COtrain means were similar i.e. difference in SD between 2 groups were $\leq$1 cm^3 for GTV_3D, GTV_exhale, GTV_inhale and ITV_MR. CO variation was lower for GTV_MR and GTV_MRCT i.e. SD was 2.5 and 1.6 cm^3 less than COtrain (Figure 5.6). The only variation that was smaller in the COtrain group was ITV_CT (difference of 2.7 cm^3). Median, IQR and outliers are presented in figures 5.4 and 5.5. No statistical significance was found in the difference between groups for each volume (GTV_3D p= 0.80, GTV_exhale p= 0.51, GTV_inhale p= 0.23, GTV_MR 0.38, GTV_MRCT p= 0.81, ITV_CT p= 0.62 and ITV_MR p=0.82).

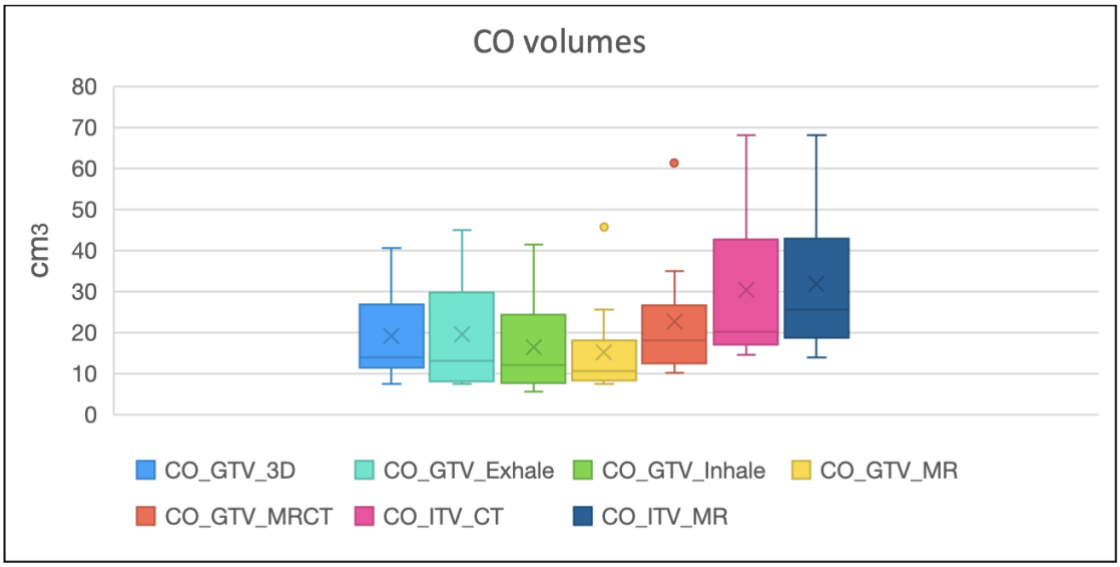


Figure 5.4. Box and whisker of CO volumes. Box includes IQR (I.e. Q1-3), cross is the mean of all volumes, median is represented by line, error bars showing minimum and maximum, and dots are outliers.

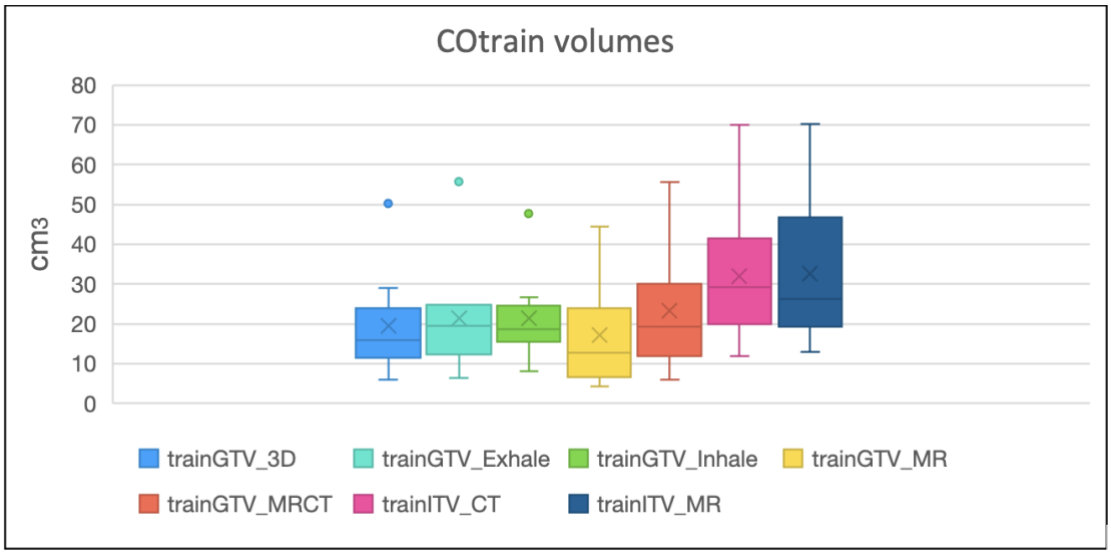


Figure 5.5. Box and whisker of COtrain volumes. Box includes IQR (Q1-3), cross is the mean of all volumes, median is represented by line, error bars showing minimum and maximum, and dots are outliers.

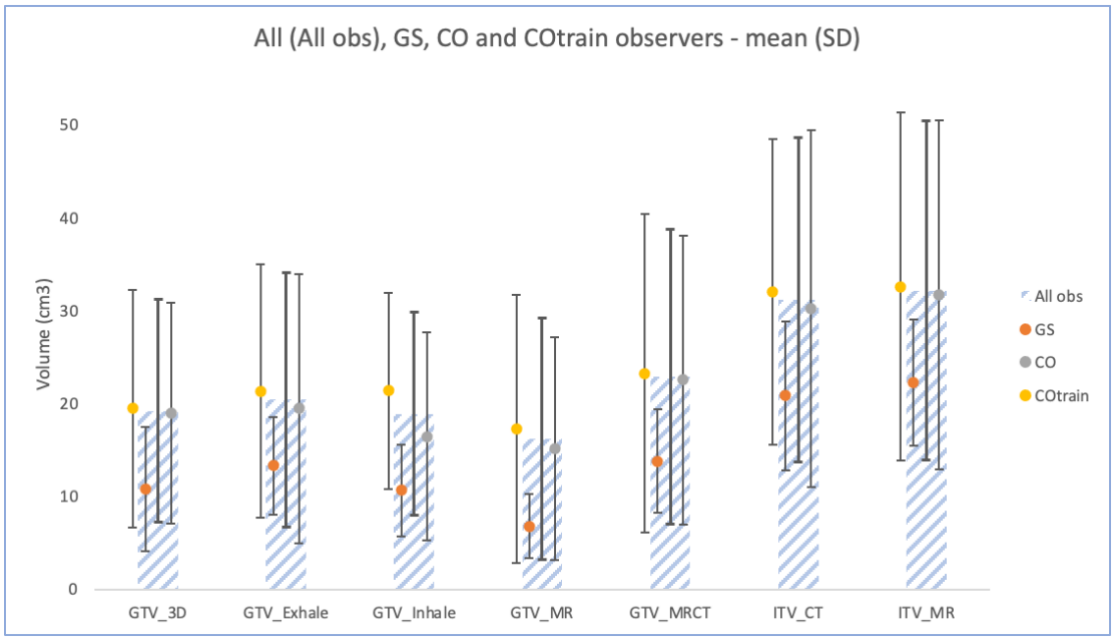


Figure 5.6. Bar showing each volume mean and SD (error bars) for all observers (All OBS), CO and COtrain, for all patients.

5.5.7 Overlap of volumes with GS

Percentage overlap of each structure, for each individual patient is shown in figures 5.7-5.11. Percentage overlap was ≥50% in 3/5 GTV_3D volumes, 1/5 GTV_exhale, 1/5 GTV_inhale, 3/5 GTV_MR, 2/5 GTV_MRCT, 2/5 ITV_CT and 2/5 ITV_MR.

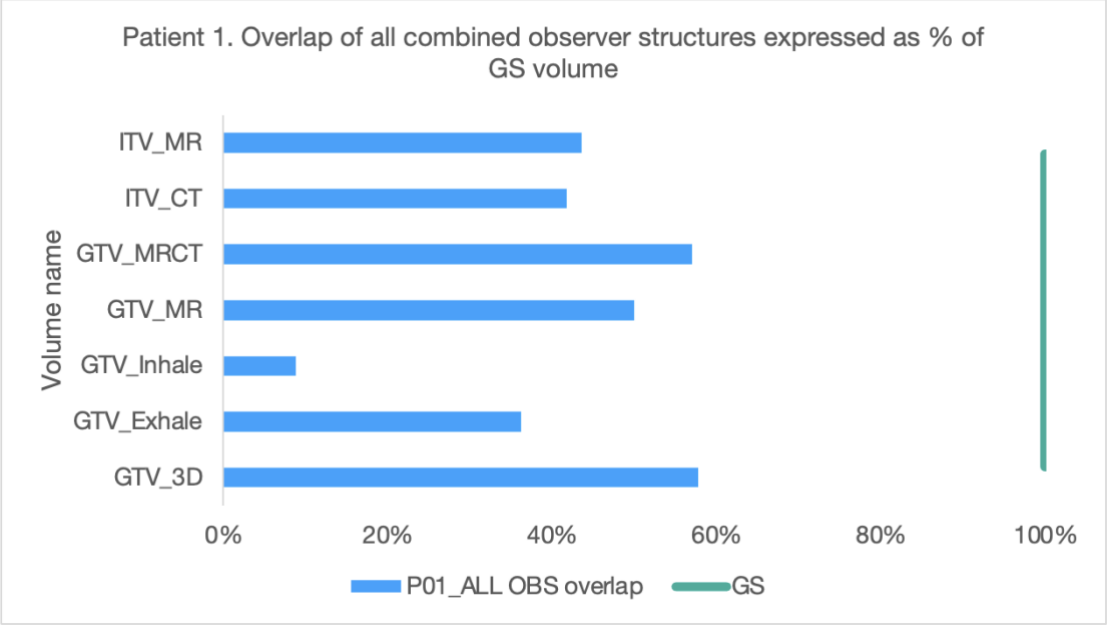


Figure 5.7. Bar showing overlap volume of all combined observer structures for patient 1, expressed as a percentage (%) of GS volume i.e. overlap volume divided by GS volume. This represents the common area delineated by all observers.

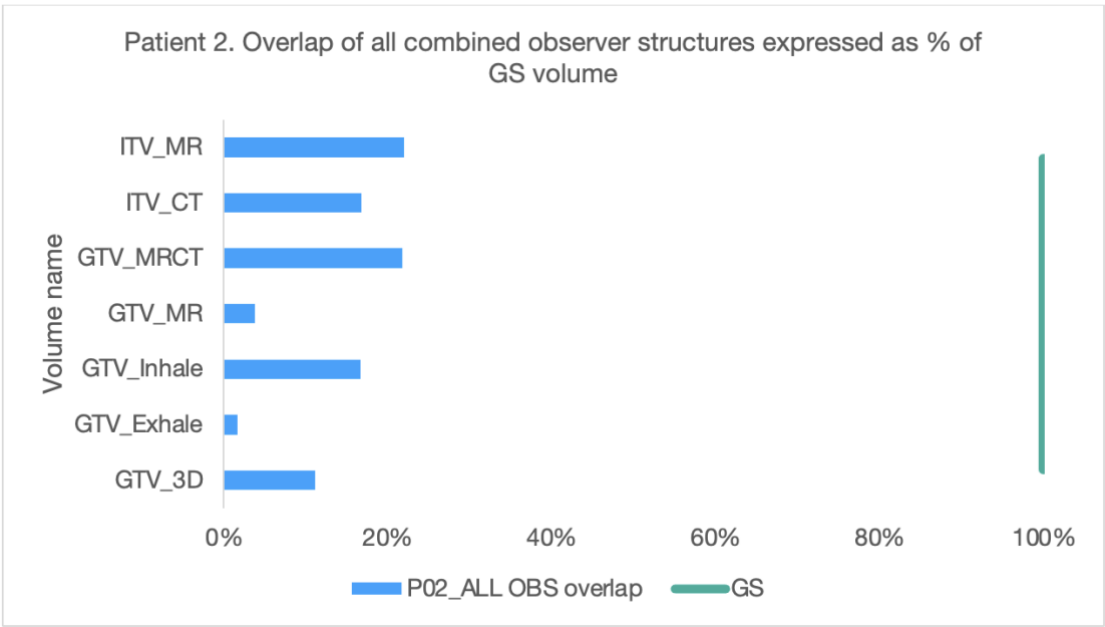


Figure 5.8. Bar showing overlap volume of all combined observer structures for patient 2, expressed as a percentage (%) of gold standard (GS) volume i.e. overlap volume divided by GS volume. This represents the common area delineated by all observers.

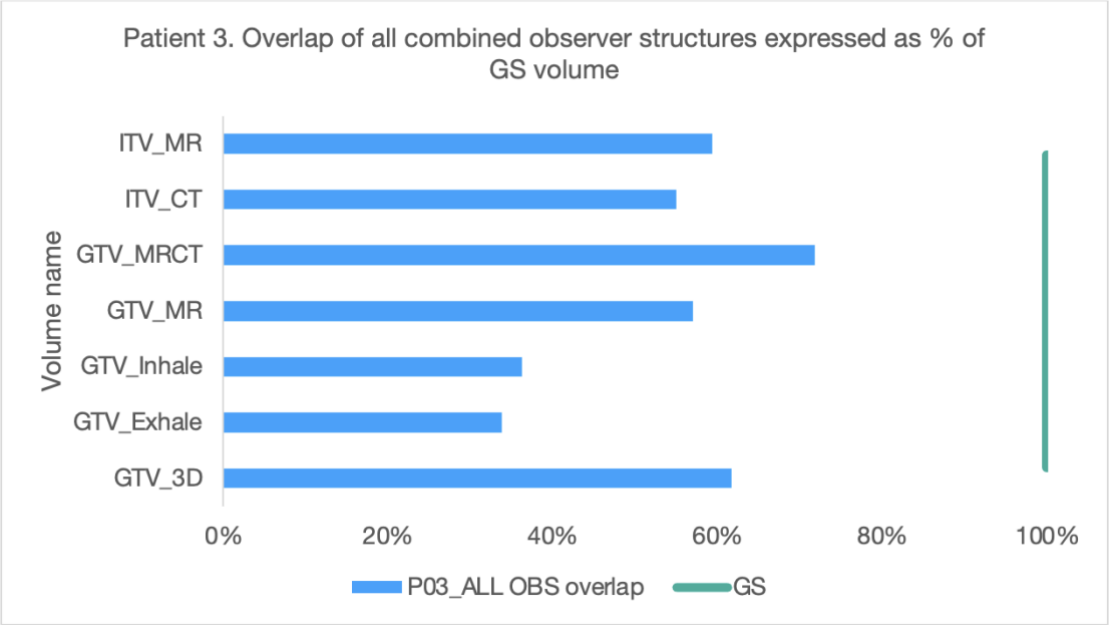


Figure 5.9. Bar showing overlap volume of all combined observer structures for patient 3, expressed as a percentage (%) of GS volume i.e. overlap volume divided by GS volume. This represents the common area delineated by all observers.

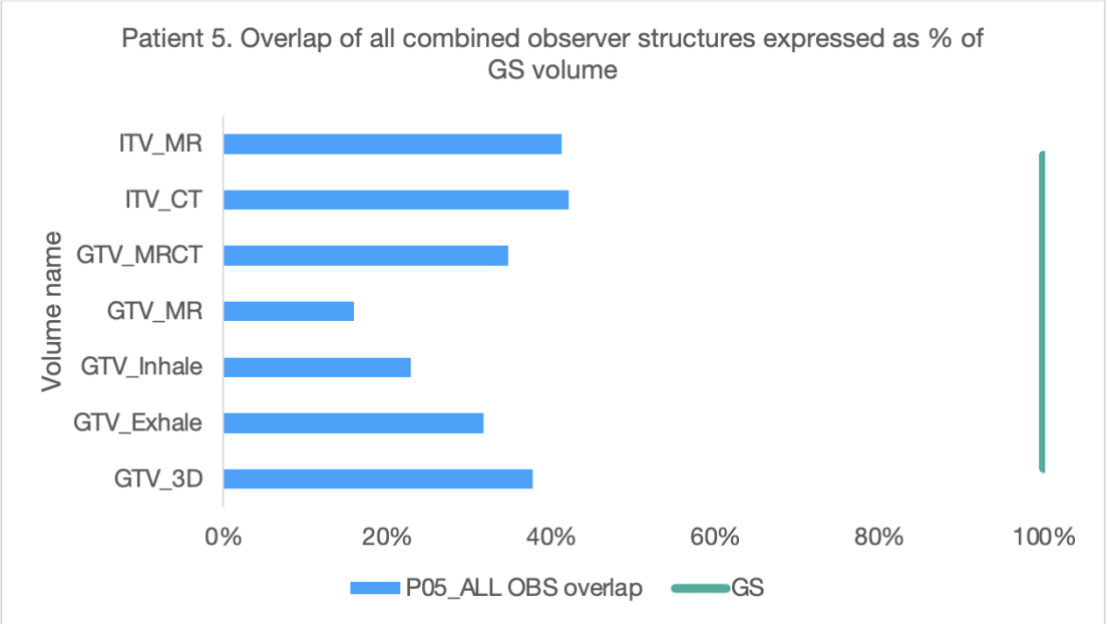


Figure 5.10. Bar showing overlap volume of all combined observer structures for patient 5, expressed as a percentage (%) of gold standard (GS) volume i.e. overlap volume divided by GS volume. This represents the common area delineated by all observers.

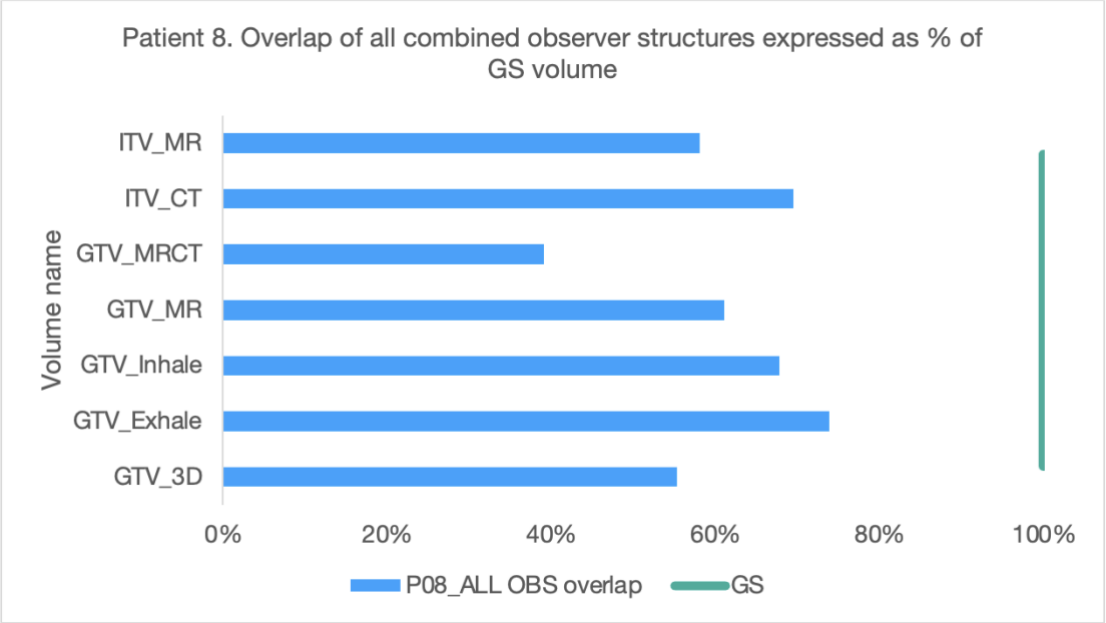


Figure 5.11. Bar showing overlap volume of all combined observer structures for patient 8, expressed as a percentage (%) of GS volume i.e. overlap volume divided by GS volume. This represents the common area delineated by all observers.

5.5.8 ITV_CT and ITV_MR

For all CO and COtrain observers combined, mean volume (SD) between ITV created with CT only (ITV_CT) and ITV with CT plus MR (ITV_MR) were 31.1 (17.5) and 32.2 (18.3) cm^3 (p=0.34) respectively. Mean volumes (SD) between ITV_CT and ITV_MR for all observers and including GS were similar 29.1 (16.4) and 30.1 (17.0) cm^3 (p=0.28), not statistically significant.

5.5.9 Dice Similarity Coefficient

Five of 140 volumes were categorised as having very poor agreement with the GS. Twenty-eight had poor, 53 moderate, 50 very good and 4 were excellent (Figure 5.12). As additional datasets were utilised for delineation, DSC increased i.e. for each observer there was a trend toward higher DSC for GTV_MRCT (using 3DCT and MR), ITV_CT (using 3DCT and 4DCT) and ITV_MR (using 3DCT, 4DCT and MR).

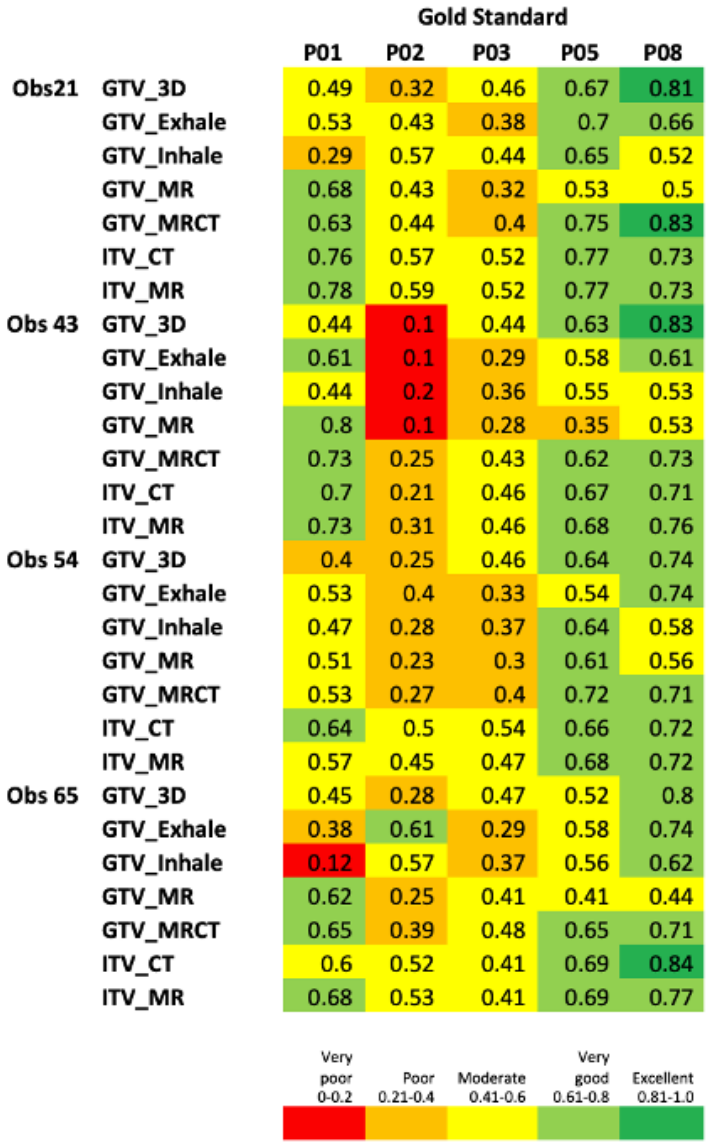


Figure 5.12. Heatmap categorising agreement between each individual observer and GS, for each structure and patient.

Dice similarity coefficient (DSC) was lowest for GTV_MR, which was the smallest volume for all observers and for GS. Largest volumes for all observers and GS were ITV_CT and ITV_MR, with DSC being similar for these volumes which used all available CT datasets (i.e. either with or without MR.

Structure	Mean volume (cm^3) and SD							
	GS Vol	SD	OBS vol	SD	Vol change	SD	DICE	SD
GTV_3D	10.8	6.2	19.2	12.0	-8.4	9.7	0.51	0.20
GTV_Exhale	13.3	4.9	20.4	13.7	-6.6	10.7	0.50	0.17
GTV_Inhale	10.6	4.5	18.9	10.9	-8.3	9.6	0.46	0.15
GTV_MR	6.8	3.1	16.2	13.0	-9.4	11.3	0.44	0.17
GTV_MRCT	13.8	5.1	22.9	15.9	-9.1	15.1	0.57	0.17
ITV_CT	20.8	7.3	31.2	17.5	-10.4	13.1	0.61	0.15
ITV_MR	22.3	6.3	32.3	18.3	-10.1	14.5	0.62	0.14

Table 5.6. Mean GS volume (cm^3) and standard deviation (SD), mean observer volume (SD) and volume difference (delta) between GS and mean observer (OBS) volumes (SD), for all structures. Mean dice similarity coefficient (DSC) and (SD) for all observers compared to GS.

When split into groups of CO and COtrain, DSC were greater for CO across all structures, and variation was less for CO in all structures except for 1 (GTV_inhale). There were no statistical significance found between CO and COtrain DSC (Table 5.7). When comparing volumes created with CT and MRI i.e. GTV_3D and GTV_MR, there were no statistical difference between groups for CO and COtrain p = 0.28 and 0.31 respectively. Comparison of CT alone and CT with additional MRI created GTV i.e. GTV_3D and GTV_MRCT showed no significance for COtrain (p=0.12), or CO, although a mean DSC improvement of 0.07 was close to significance in the latter group (p=0.05).

	Mean DSC (SD)						
Structure	GTV_3D	GTV_Exhale	GTV_Inhale	GTV_MR	GTV_MRCT	ITV_CT _	ITV_MR
CO	0.53 (0.18)	0.53 (0.15)	0.47 (0.17)	0.46 (0.13)	0.59 (0.16)	0.64 (0.14)	0.65 (0.13)
Cotrain	0.49 (0.22)	0.47 (0.19)	0.44 (0.14)	0.43 (0.21)	0.56 (0.17)	0.58 (0.16)	0.58 (0.16)
P value	0.23	0.23	0.67	0.54	0.31	0.17	0.06

Table 5.7. Mean DSC (SD) split by CO and COtrain for all patients, for each structure and p- values of CO and COtrain.

5.6 Discussion

This study assessed the impact of MRI in the delineation process for pancreatic cancer tumour volumes for clinical oncologist (CO) and clinical oncology trainee (COtrain) observers. Here we investigated the impact of using MR and CT co-registered images at the delineation stage, which we hypothesised would reduce variation. Results showed there were:

- A large difference in volumes delineated using CT alone; MR alone; and registered MR-CT images, by different observers.
- The high level of IOV in the delineation of PDAC volumes by CO and COtrain groups highlights the challenges in target volume definition for pancreas RT.
- As CT remains the gold standard dataset for planning RT, the ability to reduce volumes requires particular care in registration and clear processes for use.
- Although recommendations have been made for integrating MRI, the benefits are not clearly defined.

This study reports that delineation of disease on MR resulted in smaller volumes for the majority of patients, this is consistent with other published work (Gurney-Champion et al., 2017; Hall et al., 2018). However, the variation in these volumes and the increase in size of MRCT volumes, shows there is more work required to understand how these smaller volumes don't result in significantly smaller volumes later in the process. The similarity between ITV_CT and ITV_MR shows that when using the ITV approach in pancreatic RT, additional information gained from the MR dataset may not have much impact on final treatment volumes when accounting for motion using a 4DCT dataset. These larger volumes are expected with this method of target volume creation, and other approaches may have more impact on volume size (Wolthaus et al., 2008).

In a comparison between 3D and 4DCT, data has shown there to be "considerable IOV" (Versteijne et al., 2017), demonstrating the need to think

carefully about what and how additional datasets are used and determine the optimal protocol for PTV definition.

Studies specifically investigating MRI for delineation have included 8 – 31 observers, and a small number of patients i.e. 2-5, with a diagnosed pancreatic lesion It may be suggested that further studies should look at investigating a homogeneous group rather than mixed staging. Alternatively, more could be understood by increasing the number of different cases who are diagnosed with different stages of disease, as highlighted by Caravatta et al. (2019), who saw a difference in agreement between BRPC and LAPC. This would allow the exploration of different disease management strategies, with an example being whether dose escalation becomes possible for particular stages e.g. LAPC to improve progression free survival, or BRPC to improve R0 margins at surgery.

Our study failed to demonstrate the noticeable reduction in variation reported by most others. This could be due to the small number of observers, the inclusion of trainees and differences in methodology e.g. sequences used. There are known limitations in the conduct of delineation studies applying robust methodology.

The multi-centre study by Gurney-Champion et al. (2017), used the MR images "alongside" CT which were not acquired for RT purposes. They found a reduction in the majority of internal GTV (iGTV); decreased local variation; and increased precision when using MRI alongside CT. There were several delineations performed on each patient within this study and like ours, there were a planned number of weeks between each session. The use of non-registered images is sub-optimal, with error being introduced due to positional inaccuracies, as demonstrated in the treatment of glioma (Cattaneo et al., 2006).

Within the studies described, technical data is discussed regarding the sequences used for image acquisition and post-processing, however one of the important factors not well described is patient set-up and reproducibility. Patient positioning and immobilisation were not described in detail for most, e.g. Caravatta et al., 2019; Hall et al., 2018; Gurney-Champion et al., 2017) or highlighted as problematic at the registration process (Heerkens et al., 2017).

Dalah et al. (2014) co-registered images, however these were acquired on different days/sessions which may have allowed for changes in abdominal anatomy. They confirmed that MR resulted in smaller volumes, having studied the difference in volumes generated using different modalities which included: diffusion weighted imaging MR (DWI-MR), positron emission CT (PET-CT) and dynamic contrast enhanced MR (DCE-MR). This study included 19 patients who each were imaged using all modalities. Results showed that DCE-MR underestimated tumour, where diffusion resulted in a larger volume than that of T1 and T2 sequences. Although differences were clearly identified in the GTV delineated on a variety of image data sets, the study could not make any recommendations on which imaging modality results in the true definition of disease. For the definition of RT target volumes, further studies need to correlate pathological specimens to GTV defined on RT planning scans to inform future practice, with previous work indicating 4-7mm underestimation of tumour on CT and MR (Arvold et al., 2011; Hall et al., 2013).

Optimal RT specific images require a reproducible set-up and preparation of the patient, as well as the selection of the optimal sequences to be acquired for each specific disease site. CT only data from these patients had previously been presented in another publication by the same group, identifying large inter-observer variability between GTV on 3D and 4D CT, showing a larger SD in 4DCT volumes (Versteijne et al., 2017). The large SD in 4DCT generated volumes may be a result of reduced image quality on 4DCT, increasing the margin required to compensate for set-up uncertainties. This highlights the importance of evaluating multi-modality image techniques to ensure that any benefit gained from additional information is not negated by increasing uncertainties. Work by Hall et al. (2018), (similar authorship to that of Heerkens et al., 2017), went on to make a comparison between CT and MR delineations. This group of international experts highlighted the complexity of using MR and described detailed steps to guide contouring of structures. Their study described a significant decrease in SD in inter-observer variability using MR, however observers had access to diagnostic imaging which was not available in this study. It was also not clear from the methodology if MRI and CT acquisition had been performed under the same conditions, on the same day.

Similarity

The work presented here showed similar DSC between volumes with and without MR, which was also reported by Hall et al. (2018), who found DSC between CT and MRI to be 0.73 and 0.72 respectively. Although results in this chapter showed lower DSC, there was differences in the methodology applied. For example, in their study delineations were performed in conjunction with a tumour board approach which provided teaching on cases by an experienced radiologist; and there were no trainees included as observers.

Results here also showed that DSC was lowest for GTV_MR, (smallest volume for all observers and GS), which highlights how important it is to improve precision where there is potential to reduce target volumes using different motion or treatment strategies. The opposite was true for the ITV_CT and ITV_MR in this work. These were the largest volumes for all observers and GS, with best agreement between observers and GS i.e. 0.61 and 0.62 respectively and had slightly less variation. These delineations were completed using 3D and 4D datasets +/- MR.

Discussion of methods

Observers in the study were provided with step-by-step instructions on how to delineate each volume throughout the process. Although attempts had been made to ensure this provided a clear and standardised approach, there may have been different interpretations. These volumes were created by observers using minimal clinical history and with no access to previously acquired diagnostic scans and full radiology reports. The variation shown here indicates there is a heavy reliance on these when delineating disease, consistent with guideline recommendations that state that when delineating targets, all available diagnostic information should be used to inform volumes (Brunner et al., 2021). It does raise the question of whether RT planning scans are of optimal quality for delineating a GTV or informed heavily by previous images and reports. It is acknowledged that using contouring guidelines could improve standardisation of

target volumes and clarify definitions (Cacicedo et al., 2020), with other studies acknowledging the benefit, or providing detailed instructions (Hall et al., 2018). This has been somewhat addressed through robust clinical trial QA in the UK and the UK SABR pancreatic RT guidelines (Holyoake et al., 2021, UK SABR Consortium, 2022). Some aspects do remain equivocal, e.g. the appropriate use of CTV.

In clinical practice

The volumes created in this study showed large variation in volume and agreement. These results are not representative of what would happen in a clinical scenario i.e. didn't replicate final treatment volumes that would be used for RT, with (i) no peer review (PR) process in this methodology; and (ii) no additional diagnostic MR or CT was available and only limited detail on each patient's diagnosis was provided. Standard of care practice requires that volumes are subjected to the peer review process, where any amendments can be made using a consensus approach. Peer review in the UK (RCR, 2022) has been formally recommended, with guidance aiming to reduce variation between clinicians; and to improve standards. In pancreatic RT, where challenges are evident PR is invaluable. Other benefits include the opportunity to discuss challenging cases with peers, which includes other disciplines e.g. radiologists. This is the standard of care process used in our department.

In clinical practice, it is difficult to separate the benefit of adding MR for tumour definition from other confounding factors, such as additional discussion on patient cases with a radiologist; peer review; and improving competencies by gaining experience. Hall et al., (2018) completed their contouring exercise following discussion on cases with an expert radiologist, whereas our study aimed to understand more the impact RT planning scans alone made to volumes created. Evidence still lacks definition of the optimal sequences and validation of MRI techniques, with different sequences recommended for delineation of organ at risk (OAR) and GTV (Heerkens et al., 2017). Even though these gaps exist, new evidence emerging from MR-Linac based work is constantly verifying the need for MR images in RT (Banla et al., 2019; Boldrini et al., 2019).

5.6.1 Strengths and limitations

As the aim of this thesis was to optimise the RT pathway, this work has successfully highlighted many factors which could be acknowledged and implemented. These results have informed the process of using multi-modality imaging for delineation and have been used to further develop the optimal process required to improve standard of care for all pancreas patients. They have also aided the development of protocols and applications of MRI for more novel studies in our department. This includes clarification of structure definitions; training of all staff, maintenance of competencies etc and a review of margin strategies to be applied. As discussed earlier (Chapter 3), the question of whether RT improves outcomes for patients with PDAC remains controversial and attempts to undertake high quality studies have failed to provide clear definitive results.

A limitation of this study was small patient and observer numbers, however this was severely impacted by Covid-19 and staff resources following this period. In our department, there was no option to acquire contrast enhanced scans for RT planning purposes, so for this work T2 weighted imaging was used. Expert consensus recommendations on MR based delineation for pancreatic tumours were used to determine optimal sequences within our limitations (Heerkens et al., 2017). This expert group made several recommendations based on experience and visual assessment of sequences to be used in the definition of tumour and OAR, highlighting concern on missing full extent of tumour through non-contrast imaging. Also, the MR imaging data in this work was acquired using an older scanner (approx. 15-year-old) which required some customisations to allow RT planning scans. This included an in-house developed flat couch top and a small-bore size, which provided challenges in patient positioning and reproducibility e.g. making minor adjustments necessary to arm position due to small bore causing collision. Appointment slots could be lengthy, increasing the likelihood of patient and organ motion.

5.7 Conclusion

Introducing MR into the planning process for linac-based treatments results in high variation between observers and is subject to many sources of uncertainty. This requires consideration of multiple factors in the implementation process. These include optimising MR sequences; improving immobilisation, set-up, and preparation; competencies in abdominal image registration; and appropriate education and competencies for CO and COtrain in using MR. Future work will repeat a study to assess the impact of planning scans using actual clinical scenarios following implementation from the recommendations from this work.

Chapter 6 Improved image quality with breath-hold CBCT for pancreatic cancer

6.1 Background

Breath-hold cone-beam CT (CBCT_EBH) image acquisition has the potential to improve image quality. This has not been quantified or reported for pancreas patients, with most emphasis being placed on volume reduction, rather than the benefits of improved image quality. Here we hypothesise that acquiring verification images in breath hold can improve on-treatment image quality for pancreatic RT and improve confidence in image registration and decision making.

The aim was to evaluate if EBH imaging could improve subjective image quality using a comparison of images acquired in breath hold i.e. CBCT_EBH and free-breathing (CBCT_FB).

Objectives

- Develop scoring criteria to allow quantification of image quality, structure visualisation and confidence in assessing planning target volume coverage
- Quantify the difference between CBCT_EBH and CBCT_FB scores for a group of expert radiographer observers and several groups of clinical radiographer observers
- Assess if image quality improves confidence in radiographer IGRT decision making

6.2 Introduction

Image-guided radiotherapy (IGRT) protocols have advanced over the past decade, accompanying the increased complexity of radiotherapy (RT) techniques for abdominal RT (Jaoude et al., 2020; IMRT working group, 2001). The absence of clear data on the benefits of conventionally fractionated RT for pancreatic cancer continues to leave uncertainty of the optimal treatment strategy (Hammel et al., 2016). This underpins the need for optimal RT that harnesses

new technology and fractionations within studies, where there has been limited improvements in overall survival (OS) past 2 years. There is increasing interest in optimising advanced RT techniques and hypo-fractionated dose escalation protocols i.e. stereotactic ablative RT (SABR) (Choung et al., 2013; Tchelebi et al., 2020), which is progressively being implemented in the UK (UK SABR Consortium, 2022). Studies have shown a dosimetric benefit for pancreatic cancer patients using different methods of advanced planning techniques, with superior sparing of organs at risk (OAR) than traditional techniques (Jin et al., 2016), however IGRT has remained challenging for this site (Aznar et al., 2023; RCR, 2021).

To treat 3D target volumes of irregular shapes safely and effectively with highly conformal treatment plans on a linear accelerator (linac) e.g. intensity modulated RT (IMRT)/ volumetric arc therapy (VMAT), 3D volumetric imaging is essential to localise and verify target volume coverage; and ensure avoidance of dose limiting OAR (RCR, 2021). With such inverse planned treatments, daily volumetric images should be registered to planning reference images, verifying treatment to be consistent with planned. Verification of target volumes and OAR relies on adequate visualisation of soft tissue, or surrogates which can be problematic in in the abdomen. This is to allow registration of relevant structures between the planning scan (reference image) and the on-treatment image. In linac-based treatments, delivery of volumetric plans routinely use 3D-cone beam CT (CBCT) images to detect daily variations in patient set-up. In the abdomen, the success of this method of treatment verification is impacted by poor soft tissue contrast and without adequate visualisation, any benefit of treating “sculpted” volumes may be negated by poor set-up and localisation (RCR, 2021). Consequently, optimisation of image quality is crucial in enabling radiographer decision making using an online IGRT protocol.

CBCT image quality has been shown to be inferior to planning CT (Stock et al., 2009). Specifically for pancreas, this is amplified by poor contrast, motion and gas and stent artefacts (Liu et al., 2008; Shah et al., 2018). Multiple sources of motion and inferior quality have an impact on the observer’s ability to perform on-treatment matching, by either causing deformations in structures that do not

match planned; or by introducing artefacts which degrade image quality (Weiss et al., 2010). Such factors inhibit soft tissue matching prior to delivery and may have an impact on decision making. Solutions such as 4D-CBCT and MR guided platforms may improve this, but these technologies are not widely available. (Boldrini et al., 2019; Keiper et al., 2020; Trakul et al., 2014)

Where pancreatic target volumes are difficult to identify, the use of surrogate structures can be considered for matching purposes. Surrogates can provide improvement on that of a bony registration. In these cases, it is necessary to understand how well surrogates correlate to target volume, with caution applied accordingly. For pancreas, there have been investigations into the suitability of bony anatomy, diaphragm, fiducial markers, and biliary stent, with authors agreeing that bony anatomy is a poor surrogate for pancreatic motion, and others should be used with careful consideration (Goldstein et al., 2010; Feng et al., 2009; Van der Horst et al., 2014). Correlation of stents to GTV have been reported by a group as superior to bony anatomy and RPM marker block (Huguet et al., 2014), however they are not a reliable method due to migration and deformation warranting consideration of a larger margins (Van der Horst et al., 2014; Huguet et al., 2014; Chu et al., 2015). Fiducials are the most reliable surrogate so far, with safety, feasibility and efficacy well documented and minimal migration reported, although several clinical disadvantages have been reported (Coronel et al., 2019; Patel et al., 2020). The invasive placement procedure may lead to complications such as pain, infections, and bleeding, which may lead to hospitalisation that incurs associated healthcare costs. Additionally, the placement of fiducials require dedicated resources, including specialised equipment and trained personnel, further adding to resources burden.

Motion management strategies have been compared for pancreatic cancer RT with a gated technique being the most effective in reducing motion when compared to no mitigation and abdominal compression (Campbell et al., 2017). Such studies often focus on the planning aspects, whereas deliverability is of utmost importance and requires optimal IGRT. Subjective assessment of image quality and visibility of structures have not been investigated for pancreatic RT

using linac based breath hold techniques, although data suggests improvements in matching abdominal tumours when motion is restricted by abdominal compression (Chu et al., 2019). Studies have demonstrated improved image quality from using breath hold techniques for other sites e.g. lung radiotherapy with deep-inspiration breath hold, where image quality improved using this EBH technique (Josipovic et al., 2016; Boda-Heggemann et al., 2016). Lung specific criteria was described by Sweeney et al. (2012) who used a score from 1-3 to indicate image quality when comparing 3D-4D CBCT. Their criteria led to development of more detailed lung specific criteria used by Josipovic et al. (2016). The improvement in image quality with these techniques have not been reported for pancreas patients, with most emphasis being placed on volume reduction, rather than the benefits of improved image quality.

Here we hypothesise that acquiring verification images in breath hold can improve on-treatment image quality for pancreatic RT and improve confidence in image registration and decision making. The aim was to evaluate if EBH imaging could improve subjective image quality using a comparison of images acquired with CBCT_EBH and CBCT_FB.

6.3 Methodology

6.3.1 Patient and image selection

Patients who had completed RT treatment for pancreatic ductal carcinoma (PDAC) were included. RT had been planned and delivered using a VMAT technique. Paired image datasets were randomly selected from six consecutive patients who had CBCT_EBH and CBCT_FB images, for inclusion by an independent radiographer. Two sessions for each patient were selected randomly to ensure there was no bias in selecting “better” images. The selection included paired EBH and FB CBCT datasets from 1 session at the start of treatment (in first 50%) and 1 session from the end of treatment (last 50%). All scans were performed as per standard of care protocol, with no additional dose

to patients. All data were anonymised, and stored in password protected files. Local approvals were obtained.

6.3.2 Acquisition of images

Images were acquired on a Varian Truebeam linear accelerator (Varian Medical Systems, Palo Alto, CA) using CBCT exposure settings of 45mA, 125 kV, 805mAs. End exhale CBCT was acquired using the Real Time Position Management (RPM) System (Varian Medical Systems, Palo Alto, CA)) to verify EBH. An EBH threshold was defined using the parameters from acquisition of the planning CT. This was set to include a +/- 2mm threshold. Any deviation from this exhale CBCT resulted in the CBCT being interrupted, resuming once the same EBH was achieved again. Free-breathing CBCT was acquired using a single continuous rotation of the gantry. This included the full breathing cycle, with no interruptions. Dilute oral contrast (Gastrographin ®, Bayer pharmaceuticals, UK) 5-10ml diluted in 125/250ml water was administered before imaging, consistent with planning.

6.3.3 CT-CBCT Registration

CBCT images had previously been registered to the planning CT with online corrections for set-up error having been applied at time of treatment. Registration was performed using a rigid registration with 6 degrees of freedom (6-DOF) couch to correct for patient positioning using a pre-defined region of interest (ROI) which included bony anatomy around the PTV. Radiographers used the position of nearby vessels and arteries celiac artery (CA), superior mesenteric artery (SMA), superior mesenteric vein (SMV) to aid the registration check. Manual adjustments based on soft tissue were made taking into consideration all information. This was followed by a visual check of all transversal slices to verify full coverage of internal target volume, and position of OAR. A check on the sagittal, coronal, and transversal plane were confirmed by treatment radiographers to ensure agreement of final match.

6.3.4 Radiographer assessment – Image quality (retrospective)

The study was designed to evaluate image pairs i.e. FB and EBH images from the same patient and same session. These were presented to observers in a random order to eliminate any direct comparison between each method within any given patient, and to blind observers to which acquisition method. Images were randomly presented by an independent radiographer to the observers to ensure the acquisition method was unknown. The images were split over multiple sessions to reduce any familiarity with volumes and confounding factors. The random assignment of datasets was to reduce bias, by blinding observers to acquisition method and to prevent direct comparisons between the same patient. Observers had access to the planning scan, with scans being presented with an online registration between treatment and planning image. At each assessment, conditions were kept the same i.e. automatic window level settings were used throughout the study, with the same viewing terminal and lighting conditions. This was scheduled at times where each observer had no clinical commitments, to prevent interruptions and distractions.

6.3.5 Observers – expert (EXP)

Two radiographers with specialist knowledge (>10 years) in abdominal imaging for RT assessed the images together (to replicate the online analysis), with final score based on a consensus. A training image was used at the outset to ensure scoring criteria was descriptive and reproducible. Definitions were provided to ensure consistency.

6.3.6 Observers – clinical (OBS)

Clinical radiographer volunteers with experience of treating intra-abdominal lesions replied to a call which requested their input to the study. Once participation was agreed, a training session and example case (different patient to those analysed in this work) was presented and discussed to ensure that the scoring criteria was understood, and the process required to score the datasets was clear. They were then allocated into groups of 2. This was to reflect similar partnerships that would have provided the correct skill mix in a clinical setting.

6.3.7 Scoring criteria

Image quality was scored by each observer using the below scoring criteria (Table 6.1). No pancreas specific image quality criteria had been described in the literature, so the development of the scoring criteria used in this study was based on modifications of published criteria reported for assessment of lung IGRT for SABR patients (Sweeney et al., 2012; Josipovic et al., 2016).

Overall image quality assessed according to streaks and artefacts around the PTV	Structures
1. No artefacts 2. Minor 3. Moderate 4. Major	Assessment of streaks and artefacts in the PTV region. Defined as PTV+1cm.
Assessment of surrogate structures, GTV/ITV and duodenum	
1. I can clearly identify this structure and could confidently use it to manually adjust the match 2. I can identify this structure and could use it as a guide but would not be confident to manually adjust the match 3. I can vaguely see this structure and would not be confident to use as a guide or for manually adjusting the match 4. I cannot see this structure at all	Assessment of below structures Celiac artery Superior mesenteric artery Superior mesenteric vein Gross target volume/internal target volume Duodenum
How confident are you that soft tissue visualisation allows assessment of PTV coverage and avoidance of OAR?	
1. Extremely confident that target volume can be verified in relation to the PTV 2. Fairly confident 3. Not very confident 4. Not at all confident	Assessment of GTV/ITV coverage with PTV and avoidance of OAR

Table 6.1. Scoring criteria used to assess image quality

6.3.8 Overall image quality

This was assessed by categorising whether streaks and artefacts were present in the transversal slices at the level of PTV + 1cm superior/inferior. Details of all scoring criteria are shown in table 6.1, with lower scores indicating better quality of images e.g. 1 = no artefacts. Higher scores indicated worse image quality e.g. 4 = major artefacts (Table 6.1).

6.3.9 Structures – surrogate, target volume and duodenum

Each of the following structures were assessed using the developed scoring criteria (Table 6.1) for each image dataset: CA, SMA, SMV, GTV/ITV and duodenum (DUO). These were scored according to how clearly they could be visualised; and confidence to use them as a matching structure. The lower scores indicated better visualisation of the structures i.e. 1 = I can clearly identify this structure and could confidently use it to manually adjust the match. Higher scores indicated poor/no visualization of the structure i.e. 4 = I cannot see this structure at all. For example, by scoring a 1-2, this would indicate that structures could be visualised and used to some degree for matching purposes. A score of 3-4 demonstrate that image quality would not be good enough to allow decision making in the registration process. The 4-point scale was used to assess any subtle differences that may have an impact on matching, but also ensure that scoring categories demonstrated what could/couldn't be used to aid manual adjustment with no middle score allowing the observer to be neutral. Examples of paired images are shown in figure 6.1 a-j.

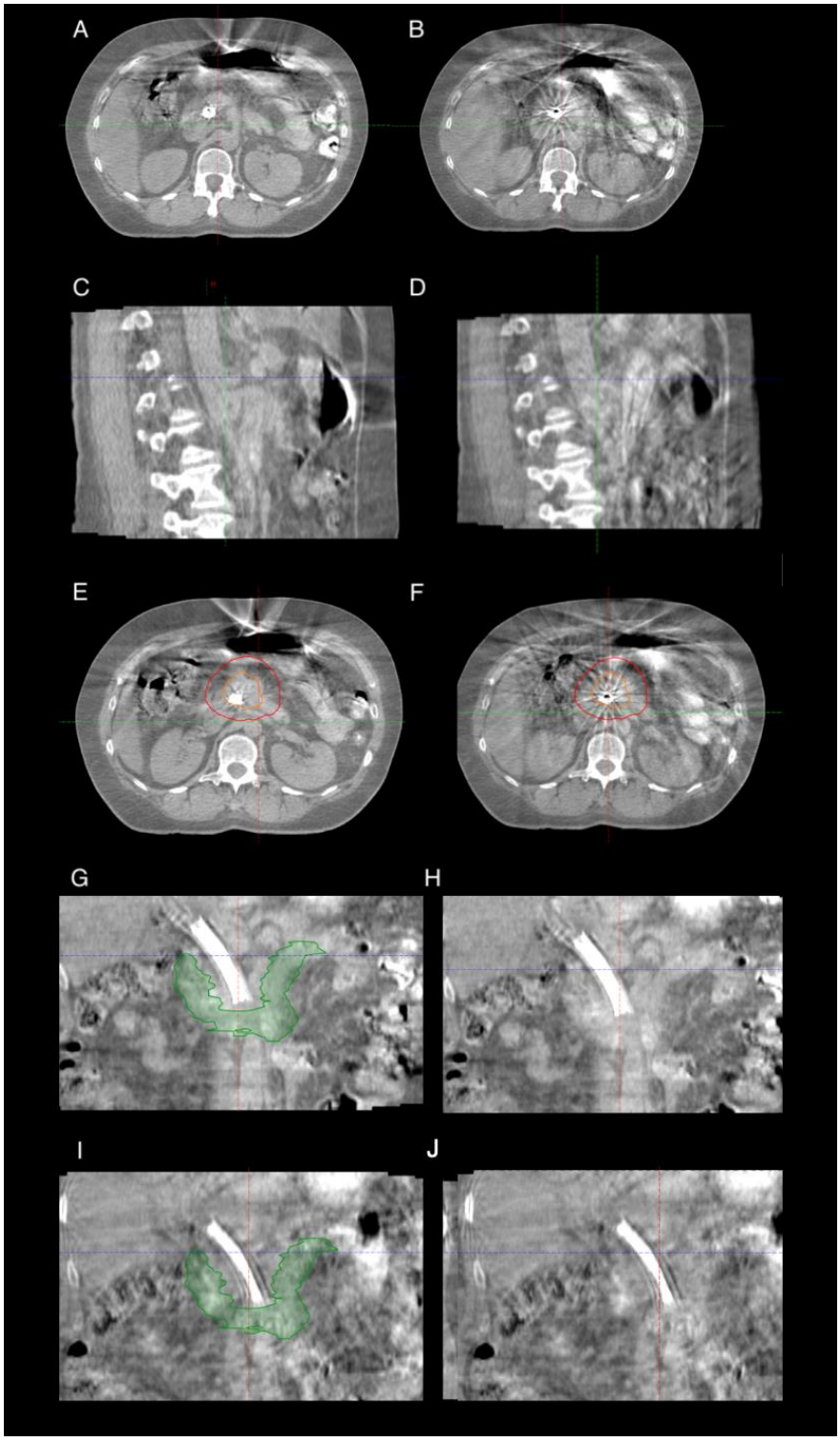


Figure 6.1. EBH and FB images showing difference in scores for assessing image quality, with image A showing an image quality scored as minor artefacts (score 2), B showing major artefacts (score 4). Image C shows sagittal of CA and SMA, clearly visualised (score 1) and D showing these structures obstructed by streaking and artefacts. Image E shows good soft tissue visualisation of target volumes allowing observers to be extremely confident in using for decision making (score 1); and F showing poorly defined soft tissue that reduces confidence in matching to "not very confident" (score 3). Images G and H are sagittal images that show duodenum with and without the planning contour on. They show duodenum can be visualised, with contrast enhancing the structure. Images I and J show poor image quality that resulted in duodenum borders not being visualised (score 4).

6.3.10 Planning target volume (PTV)

Assessment of the PTV coverage was made by asking the observers how confident they were in checking the GTV/ITV was encompassed by the PTV and avoidance of any dose-limiting OAR (Table 6.1). A low score indicated higher confidence i.e. 1 = extremely confident that target volume can be verified in relation to the PTV. Higher scores indicated decreasing confidence i.e. 4 = no confidence at all.

6.3.11 Statistical analysis

Frequency of scores were reported for image quality, structures and PTV assessment. Mean, standard deviation (SD), median and interquartile range (IQR) were used to illustrate variation in the data. All OQ, CA, SMA, SMV, GTV/ITV, duo and PTV cover scores from the EBH and FB images were summed to create an overall score and percentage change. This sum was calculated to illustrate the difference in image quality, structure visualisation and target coverage using the 2 acquisition techniques. To allow a comparison between the expert observer group (EXP) and clinical observer group (OBS), the OBS group scores were summed and divided by 3 i.e. to provide average summed score. As set out *a-priori*, a 25% improvement in the overall sum of image quality scores would indicate improved imaging with EBH.

Statistical tests were carried out on IBM SPSS Statistics (Version 28.0.0.0). Paired t-tests were used to test for statistical significance, with a threshold of $p \leq 0.01$. This level was selected to ensure that a high level of significance was achieved.

6.4 Results

Six patients, with 2 imaging time points during their RT were included in the blinded assessment. This included 12 EBH and 12 FB matched datasets with both one EBH and one FB dataset acquired within the same treatment session, immediately after one another. In total 4 observer groups completed the scoring

criteria assessment, which included an expert observer group (EXP) and 3 clinical observer groups (OBS1, OBS2, OBS3), with each group consisting of 2 radiographers. Observer groups evaluated 24 imaging datasets i.e. EBH and FB datasets acquired in 12 treatment sessions, resulting in 96 image datasets assessed.

6.4.1 Overall image quality – expert

All paired datasets showed an improved score using EBH image (Figure 6.2). Eleven of twelve (92%) EBH images were rated as having “no artefacts” or “minor artefacts” with a score of 1 -2 for overall image quality, with one score (8%) being 3. For the FB images the majority i.e. 11/12 (92%) were rated a 3 or 4. The mean (SD) overall image quality for EBH and FB images were 1.5 (0.67) and 3.33 (0.78) respectively (Table 6.2). The difference between these repeated measurements were significant ($p<0.001$). The sum of all OQ scores were 18 for EBH, and 41 for FB, showing an improvement of 56.1% using EBH when scored by EXP (Table 6.3).

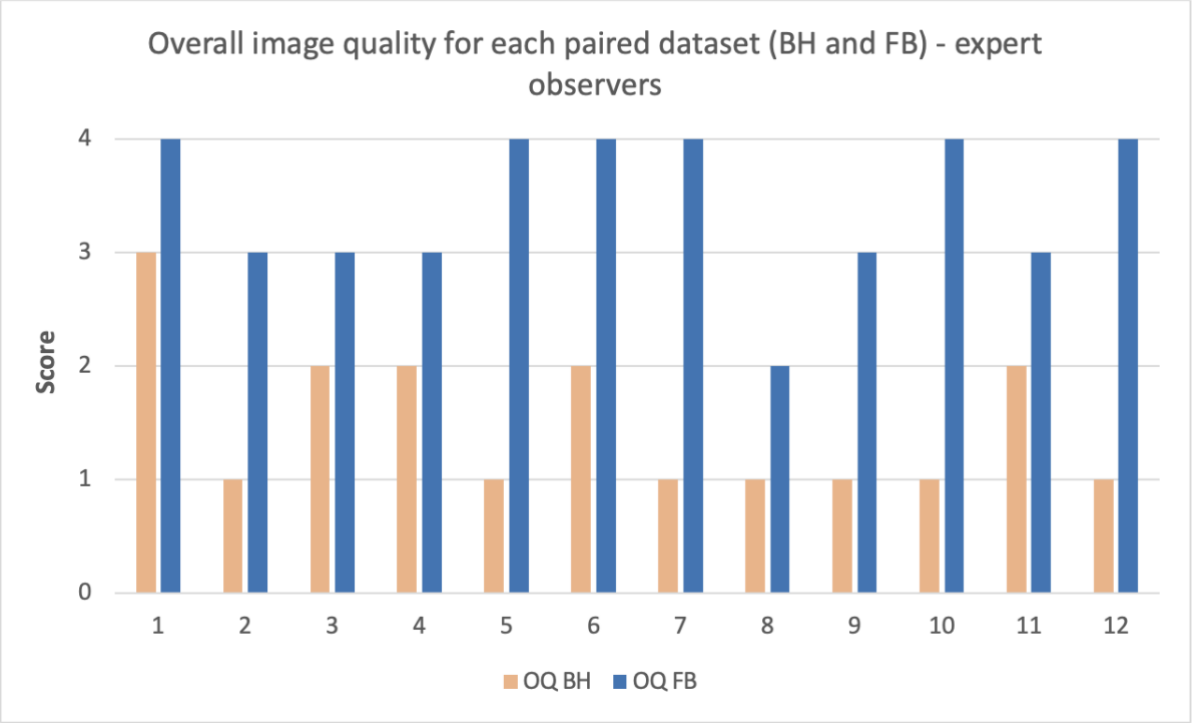


Figure 6.2. Bar chart displaying overall image quality scores for paired EBH and FB datasets, scored by expert observer group.

	BH		FB		
EXPERT OBS	**Mean**	**SD**	**Mean**	**SD**	**P value**
OQ	1.5	0.67	3.33	0.78	<0.001
CA	1.25	0.62	2.92	0.67	<0.001
SMA	1.17	0.39	3.17	0.58	<0.001
SMV	1.92	1.08	3.75	0.45	<0.001
GTV/ITV	1.33	0.49	3.50	0.52	<0.001
Duo	2.17	0.72	3.00	0.85	0.001
PTV Cover	1.67	0.78	2.33	0.78	0.006
CLINICAL OBS					
OQ	2.11	0.57	3.64	0.54	<0.001
CA	1.44	0.77	2.25	0.73	<0.001
SMA	1.58	0.69	2.61	0.69	<0.001
SMV	2.25	0.87	3.31	0.67	<0.001
GTV/ITV	1.81	0.75	2.78	0.54	<0.001
Duo	1.92	0.84	2.72	0.70	<0.001
PTV Cover	1.69	0.71	2.53	0.65	<0.001

Table 6.2. Mean (SD) expert and observer scores for overall image quality (OQ) and for each structure in EBH and FB. Paired t-test used to test for significance, with statistical significance set at $p \leq 0.01$.

Expert	BH	FB	% improvement	p value
OQ	18	41	56.1%	<0.001
CA	15	35	57.1%	<0.001
SMA	14	38	63.2%	<0.001
SMV	23	45	48.9%	<0.001
Duo	26	36	27.8%	0.001
GTV/ITV	16	42	61.9%	<0.001
PTV Cover	20	28	28.6%	0.006
All	**132.0**	**265.0**	**50.2%**	
Observers	**BH**	**FB**	**% improvement**	**p value**
OQ	25.3	43.7	42.0%	<0.001
CA	17.3	27.0	35.8%	<0.001
SMA	19.0	31.3	39.4%	<0.001
SMV	27.0	39.7	31.9%	<0.001
Duo	23.0	32.7	29.6%	<0.001
GTV/ITV	21.7	33.3	35.0%	<0.001
PTV Cover	20.3	30.3	33.0%	<0.001
All	**153.7**	**238.0**	**35.4%**	

Table 6.3. Sum of all scores, percentage improvement (%) and p value for overall quality (OQ) and each individual structure (CA, SMA, SMV, Duo, GTV/ITV and PTV) for all EBH and FB datasets. For OBS groups, the average sum and % is presented.

6.4.2 Overall image quality – observers

The clinical observer groups overall image quality score for EBH images were between 1-2 for the majority of datasets (28/36, 78%), whereas the FB images were scored 3-4 in most cases (35/36, 97%) (Figure 6.3). The mean (SD) for the EBH and FB datasets were 2.11 (0.57) and 3.64 (0.54) respectively (Table 6.2). Thirty-two of 36 (89%) datasets showed an improved score in EBH, and 4/36 (11%) datasets were scored the same. The difference between these repeated

scores were significant (p<0.001) (Table 6.2). An improvement of 42% was observed between FB and BH acquisition (Table 6.3).

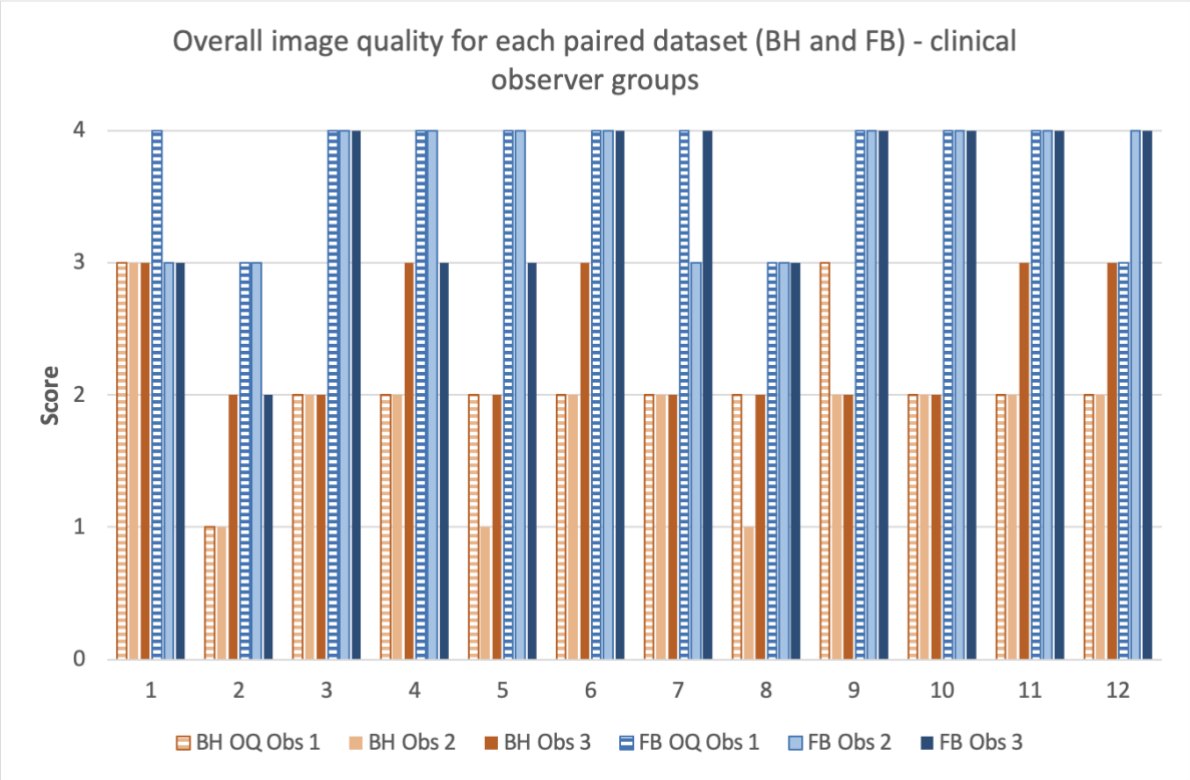


Figure 6.3. Overall image quality (OQ) scores for each paired dataset e.g. EBH Obs 1 and FB Obs 1 are paired datasets for one group of observers. These are shown for all three observer groups (EBH and FB Obs 1, EBH and FB Obs 2 and EBH and FB Obs 3).

6.4.3 Summary of overall image quality

A summary of all overall image quality measurements are presented in figure 6.4, which includes all data from EXP observers and OBS plotted as pairs. Variation in the data is presented in figure 6.5, which shows the mean EBH, median, IQR, minimum and maximum for EXP and OBS groups. Overall image quality in EBH was scored lower in the EXP (i.e. better image quality was observed) with a mean and SD of 1.5 (0.67) compared to OBS 2.11 (0.57). The mean and SD in FB image quality were slightly lower in FB for EXP compared to OBS with mean (SD) of 3.3 (0.78) and 3.6 (0.54), both groups demonstrating a significant improvement in image quality (p=<0.001) (Table 6.2).

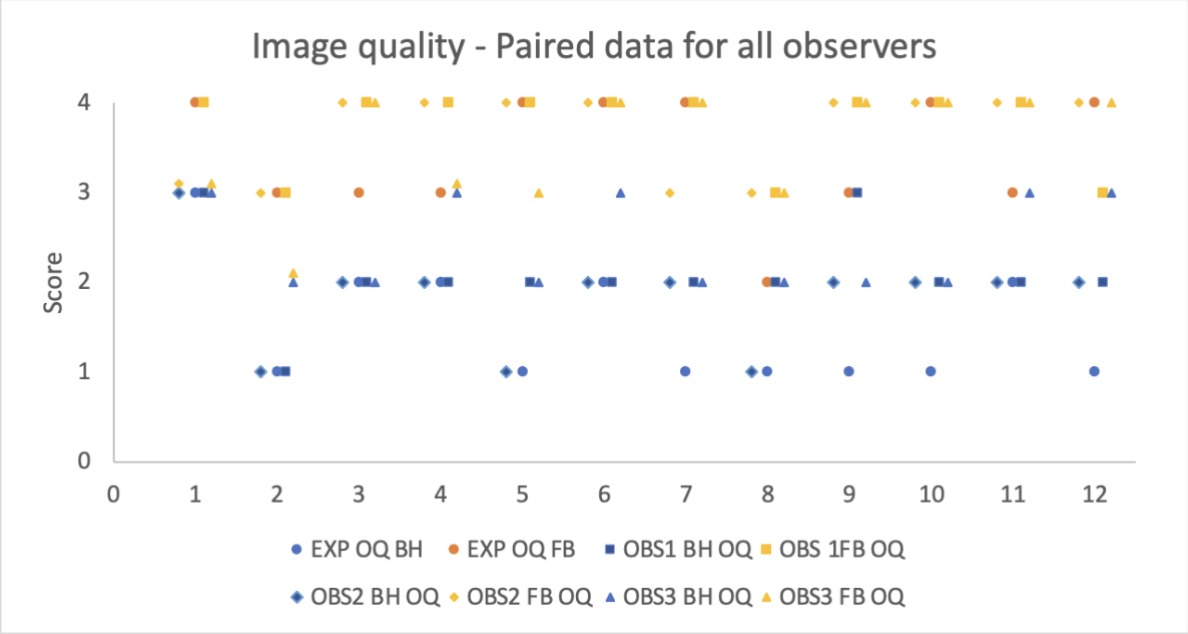


Figure 6.4. Overall image quality for paired EBH and FB scores for each observer groups i.e. EXP, OBS1, OBS2 and OBS3.

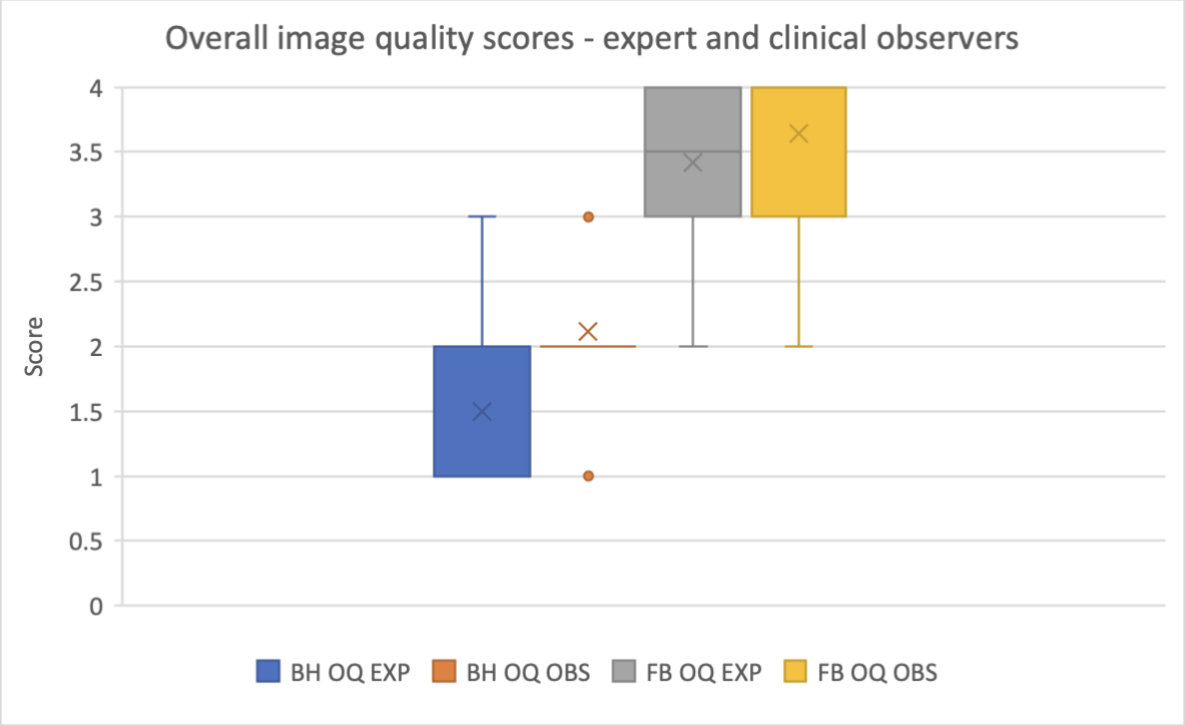


Figure 6.5. Box and whisker plot showing overall image quality for EXP and OBS groups. Box represents IQR i.e. quartile 1(Q1) -quartile 3 (Q3), mean is represented by a cross, whiskers are minimum and maximum.

6.4.4 Structures – expert

For CA, the majority of assessments on EBH images (10/12, 83%) scores showed the structure was clearly identified and could be used as a matching structure, with confidence (Figure 6.6). One score (8%) indicated that the structure couldn't be used confidently. In FB assessments the majority (9/12, 75%) were scored a 3 or a 4, showing no confidence in using to guide or adjust the registration. Mean (SD) for EBH and FB were 1.25 (0.62) and 2.92 (0.67) respectively, difference between EBH and FB were statistically significant for CA (Table 6.2). SMA was scored a 1 or 2 for all EBH images (100%) reflecting confidence in use for registration purposes. On FB images 11/12 (92%) were rated a 3 or 4 showing no confidence (Figure 6.6). Mean (SD) for BH and FB were 1.17 (0.39) and 3.17 (0.58), and the difference between EBH and FB were statistically significant (Table 6.2). The SMV was scored between 1-2 for the majority (10/12, 83%) of observations on EBH images (Figure 6.6). No patients scored 3, and 2 patients were scored 4. On FB images, the SMV scored 3 or 4 for

all patients. Mean (SD) for EBH was 1.92 (1.08) and for FB was 3.75 (0.45) (Table 3). Duodenum 1-2 scores in EBH were 67% for EXP, reducing to 33% in FB. An improvement in scores were observed in EBH compared to FB (Figure 6.6).

6.4.5 Target volumes – expert

For GTV/ITV (Figure 6.11), EXP BH scores indicated 100% of datasets allowed confidence in assessing this structure and using them for soft tissue adjustments i.e. scoring 1-2 (67% scored 1, 33% scored 2), with 100% being scored 3-4 (50% scored 3, 50% scored 4) in FB indicating “not very” or “not at all confident”. The mean (SD) score for all BH observations were 1.33 (0.49) and for FB images 3.50 (0.52). Planning target volume coverage assessment for EXP and OBS in EBH showed the majority of scores indicated high confidence (scores 1-2) in decision making, with 83% and 86% respectively. This reduced to 67% and 50% in FB datasets respectively (Figure 6.6).

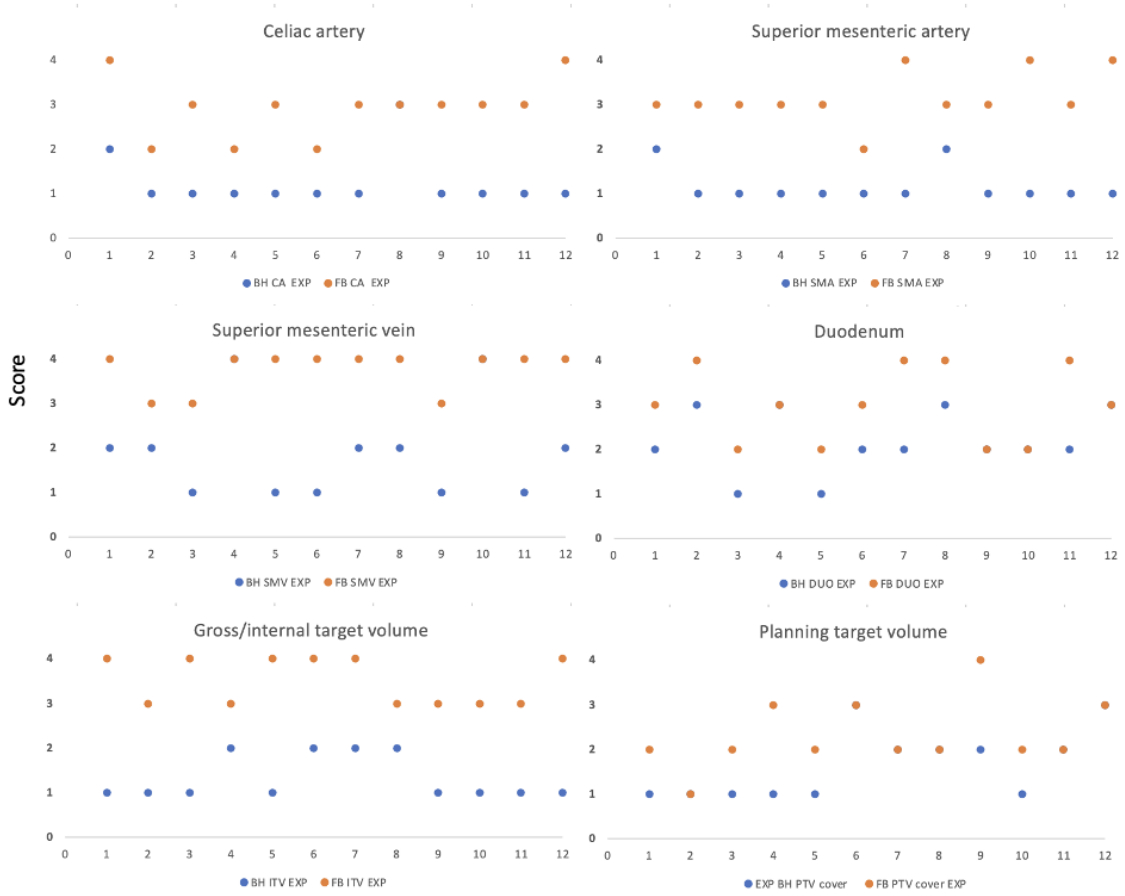


Figure 6.6. Plot showing scores for image datasets to illustrate the difference between paired scores for BH and FB by EXP observers.

6.4.6 All structures for expert and clinical observers

A summary of all structure scores is presented in figures 6.7 – 6.12, which includes all paired data from EXP and OBS. Variation in the data is presented in figures A3.6.13 – A3.6.18 (appendix 3), which shows the mean EBH, median, IQR, minimum and maximum for EXP and OBS groups. In EBH images, an improvement in mean (SD) scores for CA, SMA and SMV, duodenum, GTV/ITV and PTV were shown for expert and clinical observers (Table 6.2). The difference between EBH and FB scores were statistically significant, reaching the threshold of $p \leq 0.01$.

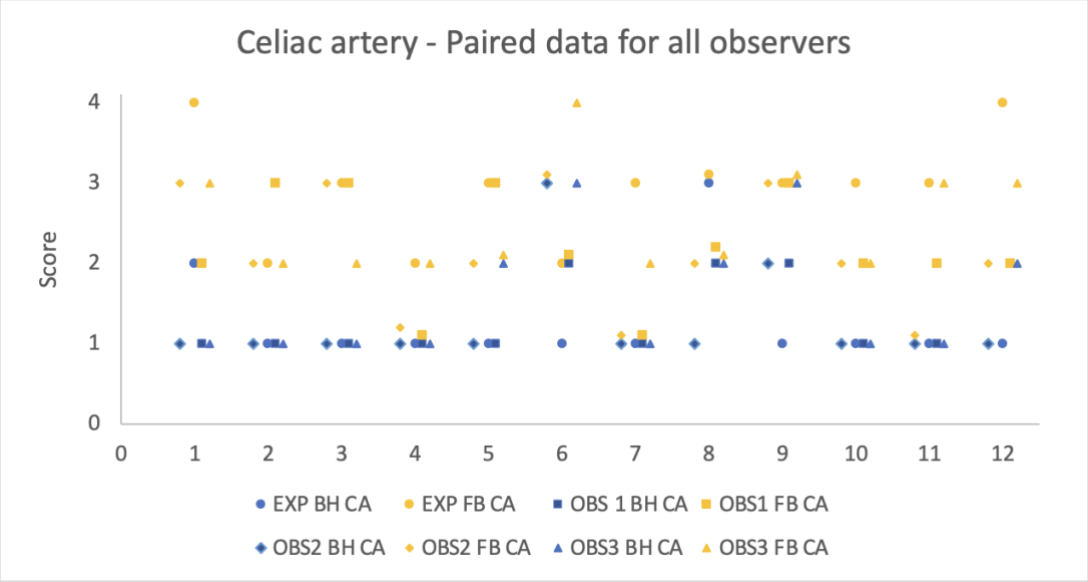


Figure 6.7. Celiac artery scores plotted for EXP observers and OBS groups to illustrate difference between paired scores for EBH and FB datasets, for EXP and individual observer groups (OBS1, OBS2 and OBS3).

Figure 6.8. Superior mesenteric artery scores plotted for EXP observers and OBS groups to illustrate difference between paired scores for EBH and FB datasets, for EXP and individual observer groups (OBS1, OBS2 and OBS3).

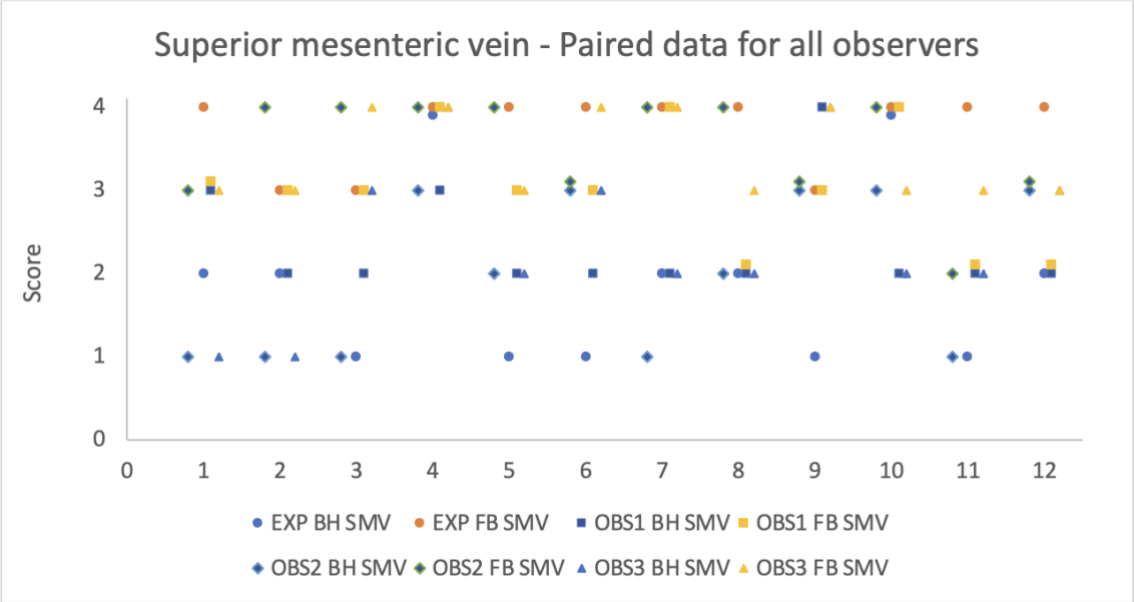


Figure 6.9. Superior mesenteric vein scores plotted for EXP observers and OBS groups to illustrate difference between paired scores for EBH and FB datasets, for EXP and individual observer groups (OBS1, OBS2 and OBS3).

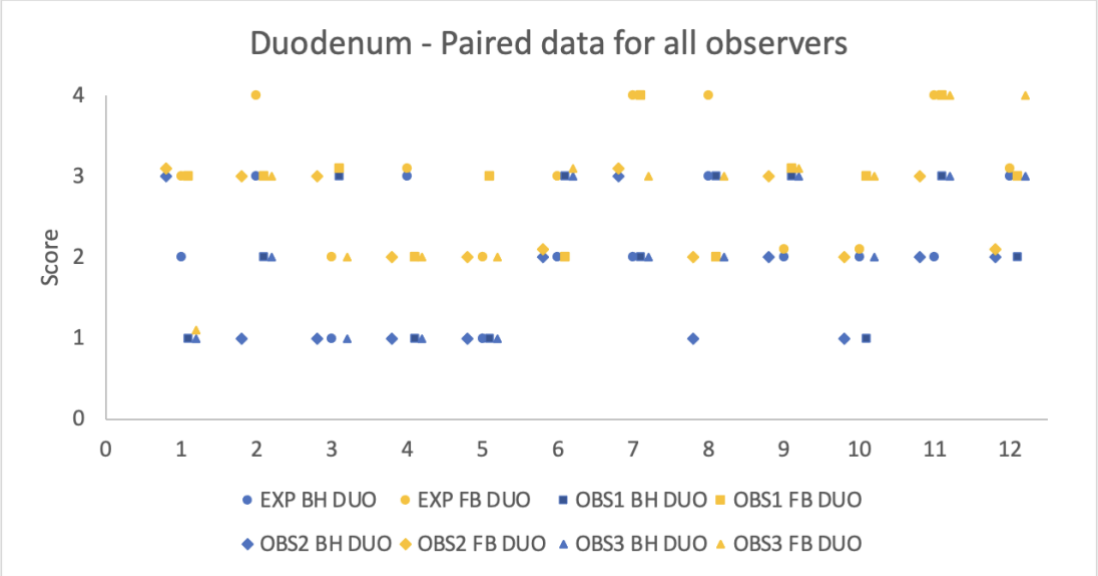


Figure 6.10. Duodenum scores plotted for EXP observers and OBS groups to illustrate difference between paired scores for EBH and FB datasets, for EXP and individual observer groups (OBS1, OBS2 and OBS3).

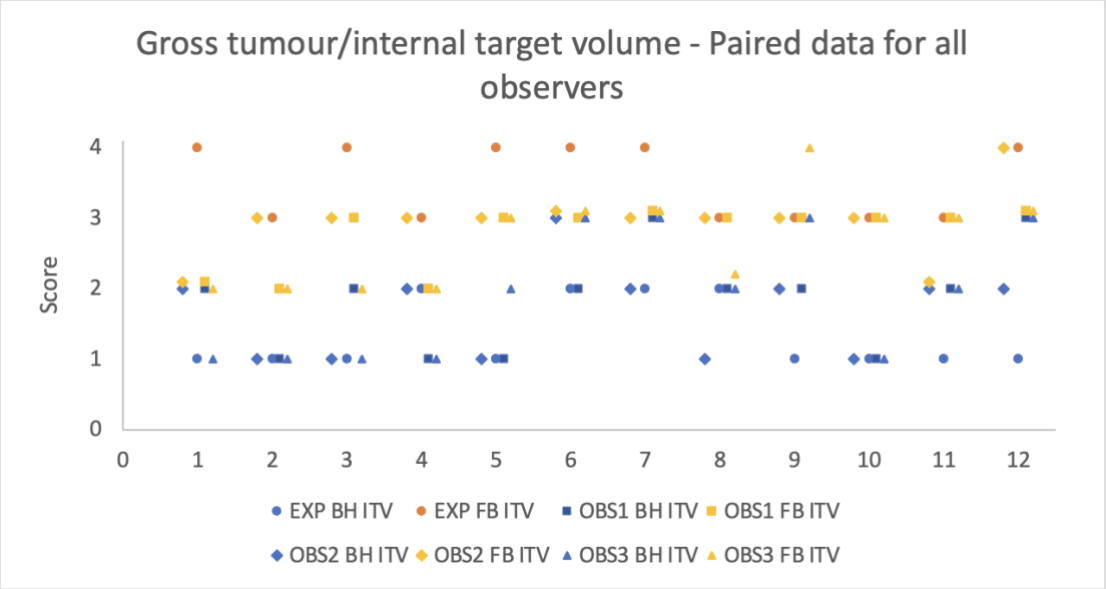


Figure 6.11. Gross tumour volume/internal target volume scores plotted for EXP observers and OBS groups to illustrate difference between paired scores for EBH and FB datasets, for EXP and individual observer groups (OBS1, OBS2 and OBS3).

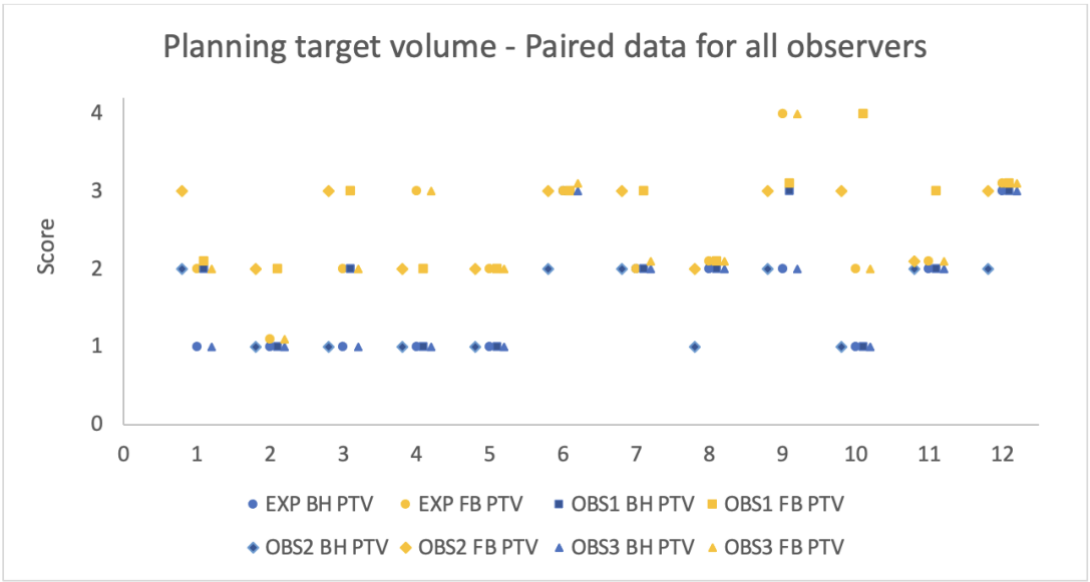


Figure 6.12. Planning target volume scores plotted for EXP observers and OBS groups to illustrate difference between paired scores for EBH and FB datasets, for EXP and individual observer groups (OBS1, OBS2 and OBS3).

6.4.7 Structures – clinical observers

The OBS CA scores indicated 92% of scores 1-2 in EBH, with 36.1% scoring 3 and above (Figure 6.7). Superior mesenteric artery (Figure 6.8), OBS scored 1-2 in 89% of cases in EBH, reducing to 39% in FB. The SMV (Figure 6.9), OBS scores were 1-2 in 64% of EBH cases, with FB scores of 1-2 reducing to 11%. Duodenum (Figure 6.10), 1-2 scores in EBH were 69% for OBS, reducing to 36% in FB.

6.4.8 Target volumes – clinical observers

For GTV/ITV (Figure 6.11), confidence in assessing this structure i.e. scoring 1-2, was 81% for OBS in EBH, and in FB 1-2 scores were observed in 28%. Planning target volume coverage (Figure 6.12) assessment for OBS in EBH showed the majority of scores indicated high confidence (scores 1-2) in decision making for 86% of scores. This reduced to 50% in FB datasets, with 50% being scored 3-4.

6.4.9 Summary of improvements for all scores – expert and clinical observers

For all evaluations made by experts and clinical observers, there was a clear improvement in quality, visualisation, and confidence in registration for EBH images, all improvements being greater than 28.6%. A higher percentage improvement was shown in the expert group for most structures. The exception was duodenum which was 27.8% for EXP and 29.6% for OBS; and PTV cover 28.6 and 33% respectively (Table 6.3). The EXP group results across all summed scores showed a 50.2% improvement and the OBS group showed 35.4%. Both groups showed a statistically significant improvement for all structures ($p=<0.001$ except for the expert group duodenum and PTV coverage where $p=0.001$ and 0.006 respectively) (Table 6.3).

6.5 Discussion

The aim of this study was to determine if image quality improvements in CBCT_EBH imaging could improve confidence in IGRT image registration, compared to CBCT_FB. Pancreas specific scoring criteria was developed for observers to score image quality, visualisation of structures and confidence in GTV/ITV and PTV assessment. The a-priori expectation was that a 25% change would indicate image quality improvement, with a p value threshold of <0.01 testing for statistical significance. The results demonstrate a significant improvement in image quality was achieved using the EBH acquisition technique, scored by multiple observers who included experts and clinical staff. Overall image quality and structure visualisation significantly improved for all observers, with a 50.2% improvement reported by EXP and 35.4% for OBS when using the mean sum of all scores.

This is the first study to investigate improved radiographer confidence in image registration and decision making between EBH and FB images. EBH resulted in improved visualisation of nearby soft tissue structures and higher confidence in using them for matching purposes. An improvement in most individual structures across all patients were observed for EXP and OBS, confirmed by the increased number of 1-2 scores when using CBCT_EBH datasets.

The main clinical application of CBCT is the correction of set-up error before delivery of high doses of RT, especially important in a hypofractionated schedule. With artefacts affecting the clear visualisation of soft tissue, poorly defined tumour/OAR borders may compromise the safety of high dose delivery. Radiographers have become increasingly responsible for IGRT across many sites and play a key role in the development of imaging protocols, for both linac-based and MR-Linac RT (Daly et al., 2021; Duffton, 2020; Gaya et al., 2021). If complex plans are to be executed in an accurate and precise manner, improved IGRT protocols that correspond with rapidly evolving planning and delivery systems are vital. The confidence of the radiographer in carrying out image registration and approvals should be addressed, especially in the abdominal sites, where decision making is challenging.

There is a lack of evidence showing the impact of improvements in subjective CBCT image quality have on the treatment of pancreatic cancer. A study by Hadley et al. (2013) conducted a study where radiation oncologists scored similar structures including CA, renal vessels and SMA using CBCT_EBH. This was not a comparison between different acquisition methods like evaluated in this work, but an evaluation of the difference between an automatic and manual match performed on one imaging dataset. Limited information on the methodology was available, with this being published in abstract format rather than a full paper. The surrogates evaluated in our study were chosen due to being in close proximity to the pancreas and are structures commonly used in the staging of pancreatic cancer (NCCN), where there may be interest in dose escalating to achieve improved R0 resection rates (Holyoake et al., 2016).

The duodenum is a dose limiting structure which should be avoided as much as possible, however its proximity to PTV means there is a risk of causing severe toxicity where high doses are delivered (Holyoake et al., 2019). This historically has been a significant limiting factor in overcoming radio resistance in this group of patients, with dose escalation requiring caution. This chapter results showed that duodenum visualisation could be improved by 28-30% using EBH imaging, which is important in assessing high dose regions on the PTV and duodenum interface.

The administration of oral contrast delivered before images were acquired did enhance the duodenum and improve visualisation. There was no way to separate any change in scoring based on timing delay of image acquisition and transit of contrast. Although visualisation of hard to see structures can be improved with the use of oral contrast, any dose implications must be considered (Kavanagh et al., 2010). The density of contrast agents will affect the Hounsfield units, so implications from this should be considered by the clinical oncologist.

Inter-observer variation and image quality assessments between DIBH, FB and 4D-CBCT have been compared for lung cancer treatments (Josipovic et al., 2016;

Sweeney et al., 2012). These studies showed significantly improved image quality and reduced IOV (Boda-Heggeman et al., 2016; Josipovic et al., 2016). Although this data is useful in lung, it is not directly transferrable to pancreas due to key differences in the ability to discriminate tumour in contrast to nearby structures being more challenging in the abdominal region; and the necessity of visualising dose-limiting structures with little or without contrast. These factors affect decision making protocols in abdominal RT with different prioritisation of OAR necessary compared to that of lung.

The benefits of improving soft tissue contrast in the abdomen could allow expansion of hypofractionated treatments, and dose escalating in future studies. The metrics used to quantify improvement in this work were designed to capture the potential benefits these would make to clinical practice. Although here we chose a subjective methodology, this was designed to be the best method to reflect the impact these would have on the specific task of decision making for RT. By applying scoring criteria relevant to abdominal structures which could be used for pancreatic radiotherapy. This work demonstrates an improvement in the confidence radiographers have in the matching process. In the abdomen, the identification of target volume remains challenging due to poor soft tissue contrast not being addressed; and identification of dose-limiting structures such as duodenum remaining poor.

Although soft tissue definition is a known problem that hinders dose-escalation and increases the necessity for motion management techniques to compensate, there is still a lack of literature that quantifies the difference in image quality identified by radiographers who are using these methods to deliver treatment. Such improvements have potential to reduce inter and intra observer uncertainty in the matching protocols applied at daily treatments, with the potential to deliver a more accurate and precise treatment. The impact of image quality is not well described for all aspects of pancreatic RT, although the benefit of reducing PTV with BH methods have been reported (Yang et al., 2014); as have the impact of 4DCT image artifacts on patient outcomes (Sentker et al., 2020). The latter study reported that following SBRT, there were 14/62 local failures,

involving 17 metastases. Severe artifacts on the 4D planning CT, and longer breathing periods were associated with higher risk.

There are many reports of fiducial markers placed in the target volume to act as a surrogate for the purposes of IGRT, as published in systematic reviews and meta-analysis (Coronel et al., 2019; Patel et al., 2020). The pooled data did demonstrate a high success rate (98%), low level of complications (4%) and minimal migration (3%) (Coronal et al., 2019). This was similarly reported by a second review (Patel 2020). The majority of studies are safety and feasibility studies that investigate the success rate of implantation. However, the limitation of included studies is the wide range of techniques employed i.e. heterogenous datasets and the lack of high-quality studies published that shows the impact fiducials have on clinical outcomes. There is also little data to illustrate what would be the preferred patient choice when faced with additional time for BH, or implantation of fiducials.

The work reported here did not use FMs, due to the limited EUS resource. There are other negatives of FM which include: they are invasive and require additional intervention, i.e. placement by an interventional radiologist under CT guidance, or EUS placement by a surgeon; EUS appointments and FM are costly; additional patient visits are required. FM are useful in identifying motion to an extent i.e. acting as a surrogate for matching, tracking, and verifying the reproducibility of BH (Han-Oh et al., 2021). One disadvantage is they do not provide information on the relativity of the target volume to nearby normal tissue. Although they can be justified where there is clear patient benefit, non-invasive techniques that improve image registration are attractive in e.g. improving image quality could improve target volume/OAR visualisation and may be preferred by the patient.

However, the ability to visualise them, along with the GTV/ITV and PTV allows improved radiographer confidence who are using them to aid decision making. This work cannot recommend prioritising them over target volume, although these structures may have potential in dose escalation strategies. The results showed that PTV encompassing the target volume could be checked with

significantly increased confidence using soft tissue visualised in the EBH scans. This is an area that has not been previously well described in pancreas RT. Further work will investigate the correlation of surrogates to pancreas.

It could be expected that GTV/ITV visualisation and PTV coverage would show similar improvements in confidence, however the increased visualisation and confidence in the GTV/ITV when assessed by experts as a stand-alone evaluation was much higher than the for the PTV coverage and OAR avoidance. This is because when assessing PTV coverage and OAR avoidance, there are multiple factors to be considered. which require additional knowledge, experience, and competence, allowing complex decision making.

Kincaid et al. (2013), demonstrated a benefit from acquiring respiratory correlated CBCT with an improvement in contrast to noise ratio and calculating the optimised normalised cross-correlation following CBCT-to-respiratory correlated rigid registrations. These were objective measurements and did not include any assessment of how well treatment radiographers could visualise structures. In their study 4 pancreas patients were included in the analysis, although the sample was reduced further to demonstrate significance by excluding one patient. Images were acquired with the patient FB i.e. the image acquisition switched on and off when the patient moved outside the defined threshold. In our study, images were acquired in breath hold to further limit any motion. This group went on to investigate the benefit of a respiratory motion corrected CBCT (acquired at end exhale) to improve the localisation of abdominal organs and soft tissue visualisation for a small number of patients (Kincaid 2018). Again, patient numbers were low (n=5), with one being excluded, and the impact of radiographer decision making was not considered.

Another potential benefit of using EBH imaging with improved visualisation is that it may increase the possibilities for linac-based ART. More sophisticated methods have been addressed in the literature to improve image quality for the purposes of ART. Examples of this are the use of synthetic CTs to improve auto-segmentation (Dai et al., 2021). These methods are promising for adaptive RT, but don’t address the poorly defined structures used for verification of routine

linac-based non-adaptive treatments, where delivery that is consistent with planning is pertinent to achieving safe and accurate treatment.

6.5.1 Strengths/limitations

As described, pancreatic lesions and surrounding soft tissue remain challenging and should be addressed given that the use of SABR for this disease site is expanding. A strength of this study was the acquisition of pairs of imaging datasets i.e. EBH and FB from the same treatment session, in the same position, minimising any confounding factors due to positional changes. Small number of patients were included, however multiple imaging datasets were analysed to provide reliable results which clearly demonstrated a significant improvement in image quality with this sample size. This study did not include inter- or intra-observer variation in matching or the ability to delineate these structures fully on CBCT or provide an assessment of correlation of soft tissue structures to target volume. However, the potential for improved decision making during the registration process is demonstrable in these results. Use of EBH imaging in the SABR setting does improve visualisation of structures and increases radiographer confidence in decision making. Future work will investigate other the suitability of surrogate structures and the feasibility of adaptive RT with EBH imaging.

6.6 Conclusion

EBH imaging significantly improved the image quality, visualisation of structures and confidence in decision making for pancreatic RT using CBCT_EBH compared to CBCT_FB. This is the first study to quantify the improvement of using CBCT_EBH in pancreatic cancer. Improved safety and efficacy of treatment delivery offers potential to investigate dose escalation in future studies. Improvements were found across experts and clinical observer groups, showing the potential to improve the safety and accuracy of dose escalated RT in future studies.

Chapter 7 Deliverability end exhale breath hold (EBH) radiotherapy using an external surrogate for motion

7.1 Aims and objectives

The aim of the work reported in this chapter was to assess the feasibility of planning and delivering SABR to pancreatic ductal adenocarcinoma (PDAC) patients using two methodologies. These were i) a motion encompassing technique i.e. an ITV approach in free-breathing; and ii) an individualised EBH technique using a 3D-CECT_EBH data set and the exhale phase of the 4DCT acquired in FB (4DCT_EXHALE).

Objectives

1. Calculate the volumetric difference between individualised PTV_BH and PTV_FB volumes created from GTV_BH and ITV_FB and using a breath hold and free-breathing approach.
2. Compare the dosimetric outcomes of plans generated using PTV_BH and PTV_FB.
3. Quantify image quality, structure visualisation and confidence in decision making for FB and EBH CBCT acquisitions.
4. Verify that volumes created for PTV_BH and PTV_FB approaches can be delivered using CBCT imaging at each fraction

7.2 Introduction

For tumour sites that are affected by respiratory motion, recommendations on breath-hold (BH) techniques have been reported for many years, with key guidance being published in 2006 (Keall et al., 2006). There are 2 main methods of BH, which include deep inspiration BH (DIBH) and end-exhale BH (EBH), with both being used for pancreatic stereotactic ablative radiotherapy (SABR). Both methods require volumes to be created using different phases of the breathing cycle, and treatment to be delivered in that phase (Aznar et al., 2022). Chosen methodologies depend on availability of departmental equipment e.g. planning and delivery systems and motion management devices. A local understanding on

how well these perform are crucial to delivering high quality radiotherapy (RT), and appropriate quality assurance measures are required for implementation (Jiang et al., 2008).

The Varian Real-time Position Management™ (RPM) system employs an external motion surrogate i.e. to detect motion using an infrared marker block that is positioned on the chest or abdomen. The marker box moves with the patient's body contour on respiration and allows a CT scan to be acquired at either a phase of the breathing cycle; or at multiple couch positions throughout the breathing cycle. External surrogates do have their limitations, with concerns reported over the correlation with internal motion. These have been well documented in breast and lung RT (Fassi 2018; Hoisak et al., 2004; Rong et al., 2014), with more limited data describing their use in PDAC (Feng et al., 2009; Huguet et al., 2015). In the UK, there has been reluctance to implement the use of external surrogates alone for treatment delivery, with these generally being disallowed in UK led trials.

Studies of PDAC SABR planned and treated using the RPM system routinely use implanted fiducial markers that act as a tumour surrogate, due to concerns of differential motion (Petterson et al., 2020; Zeng et al., 2019). Such internal surrogates are necessary due to the target volume and gastro-intestinal (GI) tract being difficult to visualise and verify using CBCT alone. This becomes especially important in SABR treatments where a small margin of 3-5mm is applied, with the intention of delivering ablative doses.

BH techniques can facilitate the acquisition of high-quality planning images, which are key to accurate delineation of target volumes (Yang et al., 2014). In the UK there has been a trend towards the use of EBH planning scans e.g. 3DCECT_EBH where the patient has CT planning images acquired during a verified BH phase (UK SABR Consortium, 2019; UK SABR Consortium, 2022). BH scans acquired with intra venous (IV) and oral contrast provide excellent image

quality with improved identification of disease, arteries and vessels enabling target volume and organ at risk (OAR) delineations. PDAC can be difficult to define on imaging, especially at tumour boundaries where it is infiltrative, with poor soft tissue contrast. Even in surgical cases exploration is required to truly determine vascular and neural spread, which highlights the importance of optimal contrast enhanced multiphasic imaging to aid RT planning (Buchs et al., 2010). RT planning CT and MR scans for delineation are mostly performed in exhale due to abdominal organs spending the greatest time in the exhale position (Heerkens et al., 2014).

One concern of an EBH technique is the tolerability for patients where exhale may be more challenging, such as patients who have co-morbidities that affect compliance (Dawson et al., 2005). Work by Lens et al., (2016) also studied organ velocity in both DIBH and EBH, and found organ motion to be greatest in the inhale position. There are data to describe the use of both exhale and inhale methods, with comparisons not strongly favouring either. However, EBH remains the preferred option at least within the UK for intra-abdominal tumours. Most importantly is that an individualised approach is used to ensure that patient specific motion is incorporated. Data for DIBH reproducibility is mainly published for liver (Eccles et al., 2006) and lung (Josipovic et al., 2016; Peng et al., 2011) that showed acceptable levels of reproducibility. For pancreas, inter BH i.e. where multiple BH are required in a session, reports have found larger variation than other sites, and may require anisotropic margins to compensate (Han-Oh at al., 2021).

When treating in FB, a 4DCT is used to determine motion at planning and facilitates creation of an internal target volume (ITV). This captures the full extent of target motion throughout the breathing cycle. In the UK, there has been wide adoption of an ITV approach when treating PDAC (UK SABR Consortium, 2022). However, this method results in a large PTV (Wolthaus et al., 2008) which may not be reproducible throughout a full course of RT (Lens et al., 2014); and poorer CBCT image quality for localisation and verification at treatment. BH images have been shown to improve image quality in lung cancer

patients, although assumed, comparable data is not available for pancreas patients (Boda-Heggeman et al., 2016; Jospovic et al., 2016). CBCT images acquired using a Varian Truebeam™ use an external surrogate to verify EBH i.e. the RPM system. This system allows CBCT acquisition and treatment delivery to be executed in the same way as the CT planning acquisition, by verifying planned against treatment breathing trace. Here we hypothesise that CBCT image quality improves when using a EBH approach, which allows localisation and verification of target volumes and relevant structures, thus improving confidence in image registration for pancreatic SABR. The aim of the work reported in this chapter was to assess the feasibility of planning and delivering SABR to PDAC patients using two methodologies that included a EBH and FB approach.

7.3 Methodology

7.3.1 Patient cohort

All patients included were diagnosed with PDAC and had been staged as either borderline resectable (BRPC) or locally advanced (LAPC) and had been treated with neoadjuvant chemotherapy and hypo-fractionated RT. Patients who had MR imaging, were suitable for SABR, and had both FB and EBH imaging available were selected. This study was carried out retrospectively, with standard of care imaging data used for replanning and image assessment.

7.3.2 Patient preparation

Patients were in a fasted state for 2 hours prior to pre-treatment scanning to ensure an empty stomach at each appointment. Dilute oral contrast (Gastrografin ®, 5-10ml in 125-250ml H_2O) was administered 15 minutes before scanning, with volume/concentration recorded to ensure reproducibility at treatment appointments. Patients were prepared for the acquisition of CT images in EBH. This included a telephone appointment prior to the scan, which consisted of an in-depth explanation of the procedure and a run-through of the proposed protocol. This was then repeated immediately before the CT appointment to ensure the exhale BH was reproducible and feasible. Information

on the effects of IV contrast was also given to the patient in preparation for a successful EBH acquisition e.g. flushing. In some cases, abdominal compression was applied for motion management using a ZiFix™ Abdominal/thoracic Motion Control System (QFix, Avondale, PA).

7.3.3 Imaging for planning CT Scan

3D-CECT_EBH was acquired in a supine position on a Philips Big Bore™ RT CT simulator (Philips Healthcare) with a slice thickness of 2mm. EBH acquisition was performed using the patient's natural exhale, verified using the Varian RPM™ system (Varian Medical Systems, Palo Alto, CA). Immobilisation was used to support patients' arms above their head i.e. an indexed wingboard, customised vacuum bag with headrest and indexed knee rest to improve comfort. Reference points were marked externally on the patients' skin to aid set-up at MRI. Immediately following 3D-CECT_EBH acquisition, a 4DCT was acquired in free-breathing (4DCT_FB) with additional IV contrast being administered.

7.3.4 MRI scan

An MRI scan was acquired with the same immobilisation as CT and in treatment position (as above). This was acquired immediately following CT, so that preparation was consistent for all scans. MR sequences were all acquired in EBH. Sequences were acquired on a GE Signa HDxt1.5T™ (HD23.0_VOL_1210a) (GE Medical Systems) and included an Axial FIESTA 4mm and Axial FIESTA 4mm FS sequence.

7.3.5 Definition of target volumes

All volumes were created by a clinical oncologist (CO) with experience in treating PDAC, with input from a consultant radiologist specialising in abdominal imaging. Delineations were performed using all available information including DICOM registered 3DCT and 4DCT, which were co-registered to MR planning

images. Radiology reports and visualisation of diagnostic CT and MR were used, where available. On the 3D-CECT_EBH dataset the gross tumour volume (GTV_3DCECT_BH) was delineated by including macroscopic pancreatic tumour and peritumoral nodes as visualised on all available imaging, including any area of uncertainty e.g. adjacent vessels. Registered CT and MR images were used to aid this delineation. From the GTV_3DCECT volume, 2 methodologies were applied to create different target volumes and resultant PTV volumes:

- **Internal target volume** free breathing (ITV_FB) was created using a Boolean of the GTV_3DCECT_EBH and GTV in the inhalation (GTV_inhale), and GTV in the expiration (GTV_exhale) phase of the 4DCT. The full 4D movie was then played to ensure the full GTV was captured throughout the breathing cycle. An isotropic 5mm margin was applied to create planning target volume free breathing (PTV_FB)

- **Gross target volume breath hold** (GTV_BH) was then created using an individualised approach using a Boolean of the GTV_3DCECT_EBH and the GTV-exhale phase of the 4DCT. An isotropic 5mm margin was applied to create planning target volume breath hold (PTV_BH)

7.3.6 Planning criteria for target volumes and Organs at risk

Optimal and acceptable PTV constraints are shown in table 7.1. Relevant OAR were delineated using the guidance set out in UK guidance (UK SABR Consortium, 2022), informed by evidence (Benedict et al., 2010; Gerhard et al., 2021; ICRU 91, 2017). These included duodenum, stomach, small bowel, large bowel, kidneys, liver, and spinal cord (Table 7.2). Constraints for OAR dose are included in table 7.3.

PTV Dose Criteria:			
	Constraint	Optimal	Acceptable
PTV	D95%	-	≥95%
	D98%	≥95%	-
	D50%		≥100% (±1%)
	D2%	≤105%	≤107%

Table 7.1. Optimal and acceptable dose criteria for PTV

OAR	Consensus Contouring Guidance
Bowel_Large	The large bowel encompasses the caecum, ascending colon, transverse colon, descending colon, and sigmoid colon in one contour. Bowel loops do not need to be joined up. Contour from the ileocaceal junction to the recto-sigmoid junction. The large bowel can be discriminated from the small bowel by the appearance of bowel contents, presence of haustra, sacculations, and appendices epiploicae. The contour adheres closely to the outer boundary of the external wall and includes large bowel contents.
Bowel_Small	The small bowel encompasses the jejunum, and ileum in one contour (duodenum is contoured separately). Bowel loops do not need to be joined up. Contour from the duodenojejunal junction to the ileocaecal junction. Ensure small bowel in the lower pelvis caudal to the recto-sigmoid junction is included. The small bowel can be discriminated from the large bowel by the appearance of bowel contents and the presence of valvulae conniventes. The contour adheres closely to the outer boundary of the external wall and includes small bowel contents.
Duodenum	The duodenum should be defined separately from the bowel whenever possible and, in particular, when in close proximity to the tumour. The duodenum should be contoured from the pylorus to the duodenojejunal junction/ligament of Treitz. The majority of the structure is fixed to the retroperitoneum and follows a C-shaped course around the head of the pancreas. The contour follows four anatomical sections: 1) 5cm in length and anterolateral to the body of the L1 vertebra 2) 7-10cm descending adjacent to the L1-3 vertebral bodies 3) 6-8cm in length, turning medially and crossing the L3 vertebral body. The aorta and inferior vena cava are posterior; the superior mesenteric artery and vein lie anteriorly 4) 5cm in length and ascending from the L3 vertebral body to approximately the cranial border of the L2 vertebral body The contour adheres closely to the outer boundary of the external wall and includes duodenal contents. Take care to distinguish the duodenum from the head of the pancreas as the structures are in close proximity.
Kidney_Cortex_L Kidney_Cortex_R Kidney_Cortex	Each kidney cortex should be contoured separately from the upper to the lower pole. The kidney cortex structure is the kidney parenchyma and includes the fibrous capsule surrounding the kidney, the kidney cortex, and the kidney medulla. The structure excludes cysts, the kidney pelvis, pararenal fat, and the adrenal gland. *Kidney_Cortex* is a summation of the right and left kidney cortex and may be used for dose reporting purposes.
Liver	The liver should be contoured in its entirety from the cranial diaphragmatic aspect to the caudal tip of the right lobe, using soft tissue windowing. The inferior vena cava should be excluded from the liver contour when it is clearly separate from the liver. The gall bladder should be excluded. Intravenous contrast may be helpful in distinguishing the left border of the liver from adjacent structures.
Skin	The skin is the 5mm inner rind of the external body contour. Please note actual skin thickness will vary dependent on region of interest.
SpinalCanal	The spinal canal is contoured according to the inner limits of the spinal canal using bone windows. The cranial border is at the level of the tip of the dens of the C2 vertebra. The caudal border is the most caudal slice where the spinal canal is visualized, usually at the level of the L5-S1 vertebral bodies. This structure is used to assess either spinal cord or cauda equina dose constraints. No PRV is required.
Stomach	The stomach should be contoured from the gastro-oesophageal junction to the pylorus. Contour to the outer extent of the external wall, including stomach contents.

Table 7.2. Standardised nomenclature and guidance on delineating normal tissue structures, as defined by the UK national consensus (UK SABR Consortium, 2022)

OAR	Constraint	Optimal
Duodenum	Dmax 0.5cc	<30Gy
	D5cc	<25Gy
	D9cc	<15Gy
	D10cc	<25Gy
Stomach	Dmax 0.5cc	<33Gy
	D5cc	<25Gy
	D10cc	<25Gy
Small bowel	Dmax 0.5cc	<30Gy
	D5cc	<25Gy
Large bowel	Dmax 0.5cc	<32Gy
Liver	Mean	<13Gy
Kidneys	Mean combined	<10Gy
	If one kidney or one kidney mean dose >10Gy then dose to single kidney or kidney receiving lower dose:	V10Gy<10%
Low dose Kidney	V5Gy	0%
Spinal cord	Dmax 0.5cc PRV	<25Gy

Table 7.3. OAR dose constraints

7.3.7 Planning aims and optimisation

Each patient had 2 plans created based on each of the PTV volumes i.e. PTV_FB and PTV_BH. These were planned using a prescribed median dose to PTV of 35Gy in 5 fractions, with duodenum dose constraints being prioritised over PTV where overlap was present. Clinician discretion was used to evaluate the risks versus the benefit of dose to PTV and OAR structures. MDT peer review was undertaken for all volumes, with representation from clinical oncology trainees, clinical oncologists, physicist, and expert radiographer.

7.3.8 Treatment planning and calculation

The Varian Eclipse Treatment Planning System™ (TPS) v16.1 (Varian Medical Systems, Palo Alto, CA, USA) was used to create 2 volumetric arc therapy (VMAT) plans i.e. a FB plan using PTV_ITV; and a EBH plan using PTV_BH. To allow comparison, a prescription median dose of 35Gy in 5 fractions was used for all patients, and all plans. Where close proximity of OAR required dose reduction to the PTV, this was allowed using an inhomogeneous approach. This ensured that GTV or ITV received the prescription dose, whilst reducing dose to PTV at the area of overlap. This study followed guidance set out in the RATINGS publication (Hansen et al., 2020).

An interactive dose-volume optimiser was used to define and fine-tune the desired doses to the PTV and OAR. The photon optimiser uses the Acuros XB advanced dose calculation algorithm v16.1 to compute an optimal plan. The dose calculation was performed for a grid size of 1.25mm.

Plans were created for a Varian TrueBeam™ with HD-Multi-Leaf Collimator. All plans were generated using 10FFF photons at a dose-rate of 2400MU/min. Two full coplanar arcs, with the collimator rotated to 30° in the clockwise direction and 330° in the anti-clockwise direction. Collimator jaw tracking was utilised for each plan.

All plans were created and checked by experienced planners with competencies in abdominal SABR planning. To reduce inter-operator variability, these were carried out or checked by 1 consistent planner. Planners aimed to achieve PTV optimal D98% ≥ 95% or mandatory D95% ≥95% PTV coverage, whilst meeting mandatory OAR constraints (Table 7.3).

7.3.9 Deliverabilty

To assess the plan deliverability, RadCalc™ v6.3 was used to extract and quantify several complexity parameters: the average leaf pair opening (ALPO), the modulation factor (MF) and the total number of monitor units (MU).
CBCT acquisition

Images were acquired on a Varian Truebeam™ linear accelerator using CBCT exposure settings of 45mA, 125 kV, 805mAs. End exhale CBCT_EBH was acquired using the Varian RPM System to verify EBH. An EBH threshold was defined using the parameters from acquisition of the planning CT. This was set to include a +/- 2mm threshold. Any deviation from this exhale resulted in the CBCT being interrupted, resuming once planned EBH was achieved again. Immediately following this, a CBCT_FB was acquired using a single continuous rotation of the gantry. This included the full breathing cycle, with no interruptions. Dilute oral contrast (Gastrographin®) 5-10ml in 125/250ml water was administered before imaging, consistent with planning.

7.3.10 On treatment image registration

CBCT images had previously been registered to the planning CT with online corrections for set-up error having been applied at time of treatment. Registration was performed using a rigid registration with 6 degrees of freedom (6-DOF) couch to correct for patient positioning using a pre-defined region of interest (ROI), which included bony anatomy around the PTV. Radiographers used the position of nearby vessels and arteries; celiac artery (CA), superior

mesenteric artery (SMA) and superior mesenteric vein (SMV) to aid the registration check. Manual adjustments were made based on soft tissue taking into consideration all information. This was followed by a visual check of all transversal slices to verify full coverage of ITV, and position of OAR. A visual check on the sagittal, coronal, and transversal plane were performed by treatment radiographers to ensure agreement of the final match.

7.3.11 Expert observer assessment (retrospective)

CBCT image datasets were viewed in Varian Offline Review ® (Varian Medical Systems, PA, CA). The dataset was designed to evaluate image pairs i.e. FB and EBH images from the same patient and same session. The images were split over multiple sessions to reduce any familiarity with volumes and confounding factors. At each assessment, conditions were kept the same i.e. automatic window level settings were used throughout the study, with the same viewing terminal and lighting conditions. This was scheduled at times where each observer had no clinical commitments, to prevent interruptions and distractions.

7.3.12 CBCT assessment of image quality

Image quality assessment is described in chapter 6, with the same expert observer assessment methodology applied here. In summary, images were assessed by 2 radiographers with expert knowledge on abdominal RT (>10 years). Assessments were made on the CBCT_EBH and CBCT_FB for each treatment session, using scoring criteria developed in chapter 6 (Table 7.4). This consisted of an overall image quality assessment of each dataset, assessment of artefacts and a visual assessment of relevant structures. An assessment of how confident observers were of volumes coverage for each acquisition technique i.e. GTV_BH, ITV_FB, PTV_BH and PTV_FB were made for each dataset.

Overall image quality assessed according to streaks and artefacts around the PTV	Structures
1. No artefacts 2. Minor 3. Moderate 4. Major	Assessment of streaks and artefacts in the PTV region. Defined as PTV+1cm.
Assessment of surrogate structures	
1. I can clearly identify this structure and could confidently use it to manually adjust the match 2. I can identify this structure and could use it as a guide but would not be confident to manually adjust the match 3. I can vaguely see this structure and would not be confident to use as a guide or for manually adjusting the match 4. I cannot see this structure at all	Assessment of below structures Coeliac artery Superior mesenteric artery Superior mesenteric vein Duodenum
Assessment of gross tumour volume (GTV) How confident are you that GTV is encompassed by PTV?	
1. Extremely confident that target volume can be verified in relation to the PTV 2. Fairly confident 3. Not very confident 4. Not at all confident	Assessment of GTV coverage with PTV

Table 7.4. Scoring criteria to quantify image quality, visualisation of structures and confidence in decision making. This scoring criteria was developed for pancreas image quality evaluation for chapter 6 and is adapted from previous methods described for lung (Sweeney et al., 2012; Josipovic et al., 2016)

7.3.13 Plan and image analysis

The FB and EBH plans were quantitatively compared by dose volume histogram (DVH) analysis. Comparisons were made for the PTV and OAR between the FB and EBH plans. For each plan, the total number of MUs, the volume and dose achieved for PTV structures and dose constraint parameters were recorded and compared between PTV_FB and PTV_BH. Cumulative DVH's were produced by extracting dose metrics in 0.05Gy increments for all targets and OAR i.e.. PTV_BH, PTV_FB, duodenum, stomach, and small bowel to represent the mean, median Q1, Q3, min and max of the population. Data is presented throughout as means and standard deviation (SD), or median with interquartile range (IQR). All statistical analysis was performed using IBM SPSS Statistics (Version 28.0.0.0). Wilcoxon signed rank test was used for both the planning aspects (small sample size not normally distributed, and for the image quality aspects (ordinal data) to test for statistical significance, all were set at $p=\leq 0.01$ due to the small sample size and to detect a reliable difference.

7.4 Results

7.4.1 Patients

Seven patients were planned using PTV_BH and PTV_FB as per described methodology. This resulted in a total of 14 planning PTV and respective plans being created and analysed. Three patients were planned and treated with abdominal compression. Five fraction pairs of CBCT_FB and CBCT_EBH i.e. acquired on same fraction and in the same position were quantitatively analysed. One dataset was excluded due to one image not being in the same position. A total of 70 CBCT were reviewed, with 68 CBCT datasets included in the final analysis.

7.4.2 Volumes

The mean difference in volume between PTVs showed that PTV_BH was 37.8% smaller than the PTV_FB (PTV_FB=115.5±59.6; PTV_BH=84.9±40.2) (Table 7.5). A decrease was observed for all volumes, with a lower range of % difference observed in patients with abdominal compression, 3.7%-18.2% compared to 13.4-47.5% (Figure 7.1).

Patient	AC	PTV_FB (cm3)	PTV_BH (cm3)	Difference
1	No	79.4	42.4	-46.6%
2	No	183.5	142.0	-22.6%
3	No	198.8	104.3	-47.5%
4	No	134.8	116.8	-13.4%
5	Yes	35.2	28.8	-18.2%
6	Yes	79.1	76.2	-3.7%
7	Yes	97.5	83.9	-13.9%
Mean	-	115.5	84.9	-23.7%
SD	-	59.6	37.2	17.0%

Table 7.5. PTV_FB and PTV_BH volumes for each patient (cm^3) and calculated difference (%). AC = abdominal compression used.

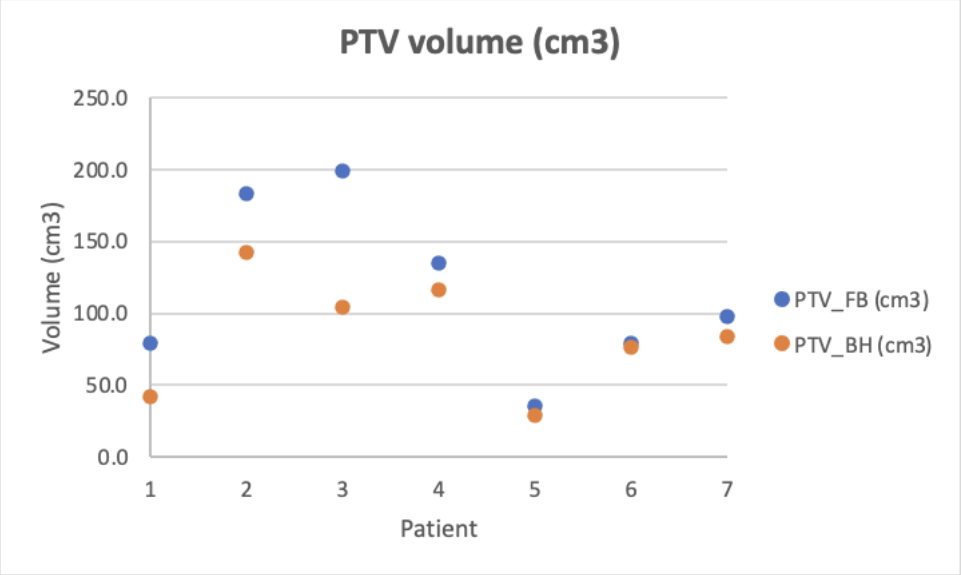


Figure 7.1. Scatter plot showing paired PTV_BH and PTV_FB volumes (cm^3) for each individual patient. Patient 5,6 and 7 had AC used throughout planning and treatment.

7.4.3 Dosimetric -PTV dose

For the PTV's, similar dosimetric outcomes were achieved for each of the planning criteria, with a mean percentage difference of <1%, with little variation (SD<1%) between PTV_FB and PTV_BH (Table 7.6). No repeated measurements between PTV_FB and PTV_BH were statistically significant, with difference in volume being p =0.018, D98% p= 0.462, D95% p = 0.34, D50% p = 0.715, D2% p=

0.68 and MU p= 0.091. All plans were deemed clinically acceptable by the CO. On average, the total MU for EBH plans were 3.3% lower; there was an increase in MF; and a decrease in ALPO compared to FB plans.

Patient	D98% Optimal > 95%			D95% Acceptable > 95%			D50% Acceptable >100%(±1%)			D2% Optimal < 105% Acceptable < 107%		
	PTV_FB	PTV_BH	% Diff D98%	PTV_FB	PTV_BH	% Diff D95%	PTV_FB D50%	PTV_BH D50%	% Diff D50%	PTV_FB D2%	PTV_BH D2%	% Diff D2%
1	94.7	94.4	-0.3	96.7	96.6	-0.1	100	100	0	101.4	101.4	0
2	84.1	84.3	0.2	85.1	85.1	0	100.7	100.8	0.1	105.8	105.6	-0.2
3	90	91.3	1.4	91	92.4	1.5	99.6	100.3	0.7	103.8	103.4	-0.4
4	85.3	86.3	1.2	86.4	87.5	1.3	100.3	100.2	0	105.2	104.9	-0.3
5	97	97	0	98.6	98.7	0.1	101.8	101.6	-0.2	104	104	0
6	95.7	95.2	-0.5	98.1	97.7	-0.4	101.9	101.9	0	104.5	104.4	-0.1
7	97.2	97.4	0.2	98.3	98.4	0.1	100	100	0	101.3	101.3	0
Mean	92	92.3	0.3	93.5	93.8	0.4	100.6	100.7	0.1	103.7	103.6	-0.1
SD	5.5	5.2	0.01	5.9	5.6	0.01	0.9	0.8	0	1.8	1.7	0.2

Table 7.6. Percentage of PTV_FB and PTV_BH structure receiving specified dose (%) for each patient and % difference (% Diff) between FB and EBH plans.

7.4.4 Dosimetric OAR dose

The Dmean values for all OAR decreased between the FB and EBH plans, with mean (SD) Dmean % decreases of -17.4% (10.0) for duodenum, -7.6% (14.5) for stomach, -21.0% (17.2) for small bowel, -15% (12.0) for liver, and -14.3% (12.4) for combined kidneys. No statistically significant difference was found between PTV_FB and PTV_BH, with all being p>0.01. Duodenum came close to significance, with p= 0.018 (Table 7.7). Figures 7.2-7.5 illustrate the OAR percentage (%) differences across all patients and includes the spread of the data. Absolute dose (Gy) for EBH and FB plans are shown in figures A4.7.6-7.9 (appendix 4), with all mean absolute doses for each constraint showing a small reduction (Gy).

Structure and criteria	PTV_FB Mean (Gy)	SD	PTV_BH Mean (Gy)	SD	p value
Duodenum Dmax 0.5cc	30.8	2.7	30.6	3.4	0.671
Duodenum D5cc	25.8	5.5	25.5	6.3	0.127
Duodenum 9cc	23.7	6.8	22.7	8.0	0.042
Duodenum D10cc	23.2	7.2	22.1	8.5	0.043
Duodenum mean	10.6	4.4	8.7	4.2	0.018
Stomach Dmax 0.5cc	14.2	15.4	13.7	16.5	0.273
Stomach D5cc	10.5	11.2	10.1	12.0	0.061
Stomach D10cc	8.8	9.4	8.5	10.0	0.027
Stomach mean	2.1	2.1	2.0	2.2	0.046
Small Bowel Dmax 0.5cc	30.0	6.2	25.4	8.7	0.046
Small Bowel D5cc	23.9	5.7	18.4	5.9	0.061
Small Bowel mean	5.7	1.6	4.5	1.7	0.028
Liver mean	1.2	0.8	1.0	0.8	0.026
Kidney (combined) mean	3.1	1.1	2.6	1.2	0.027
Kidney low dose V5Gy (percentage volume %)	5.1	12.1	2.0	4.9	0.18

Table 7.7. Achieved dose criteria mean and standard deviation in Gy (except for low dose kidney expressed as percentage of volume (%)) for PTV_FB and PTV_BH plans.

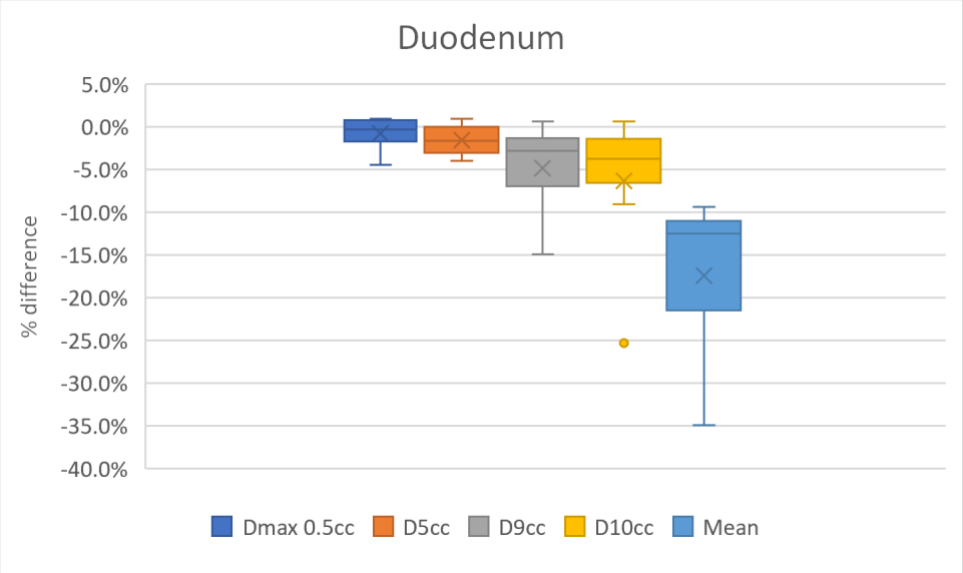


Figure 7.2 Box and whisker plots showing OAR dose difference (%) for duodenum constraints. Box and whisker plots showing median (line), mean (cross), interquartile range (Q1-Q3), whiskers represent range of values and outliers represented by dots.

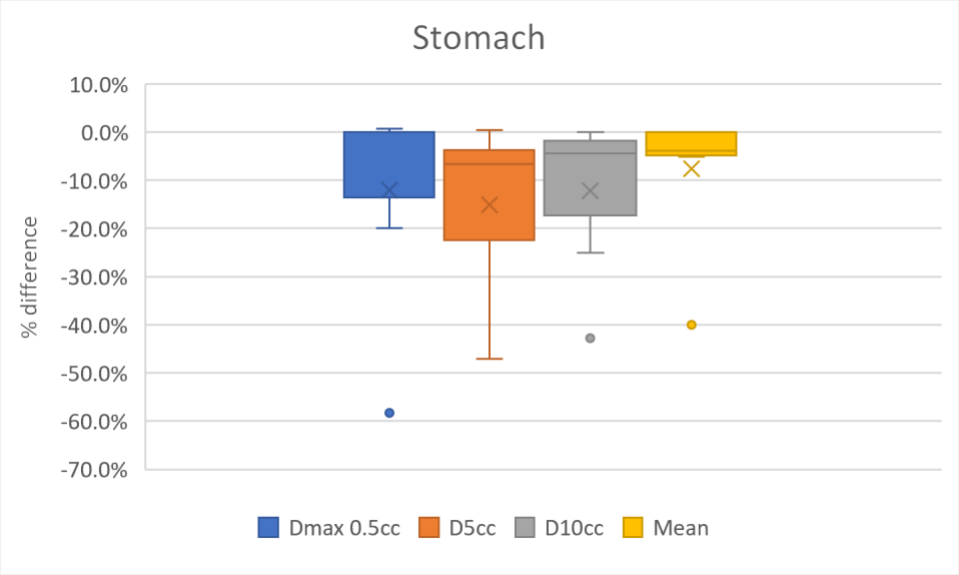


Figure 7.3 Box and whisker plots showing OAR dose difference (%) for stomach constraints. Box and whisker plots showing median (line), mean (cross), interquartile range (Q1-Q3), whiskers represent range of values and outliers represented by dots.

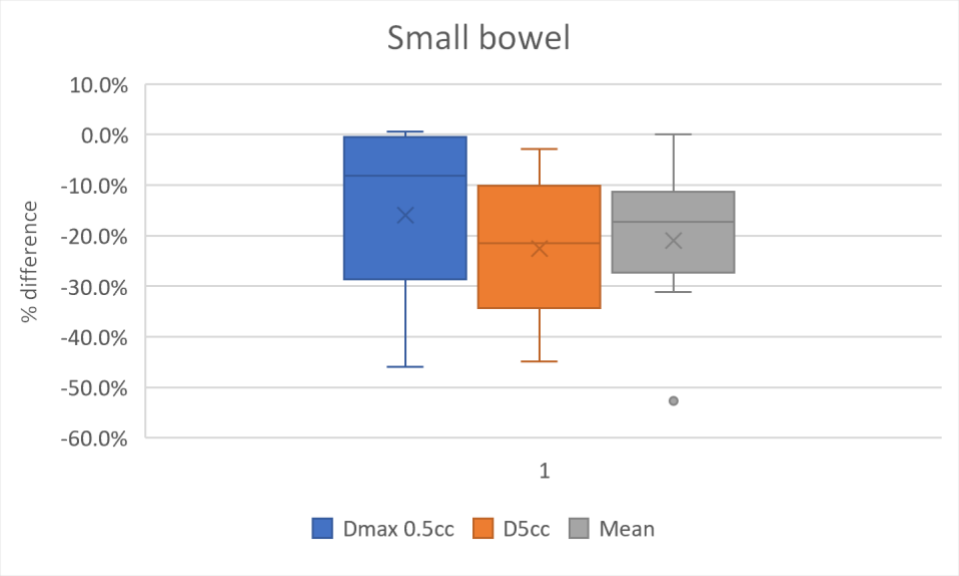


Figure 7.4 Box and whisker plots showing OAR dose difference (%) for small bowel constraints. Box and whisker plots showing median (line), mean (cross), interquartile range (Q1-Q3), whiskers represent range of values and outliers represented by dots.

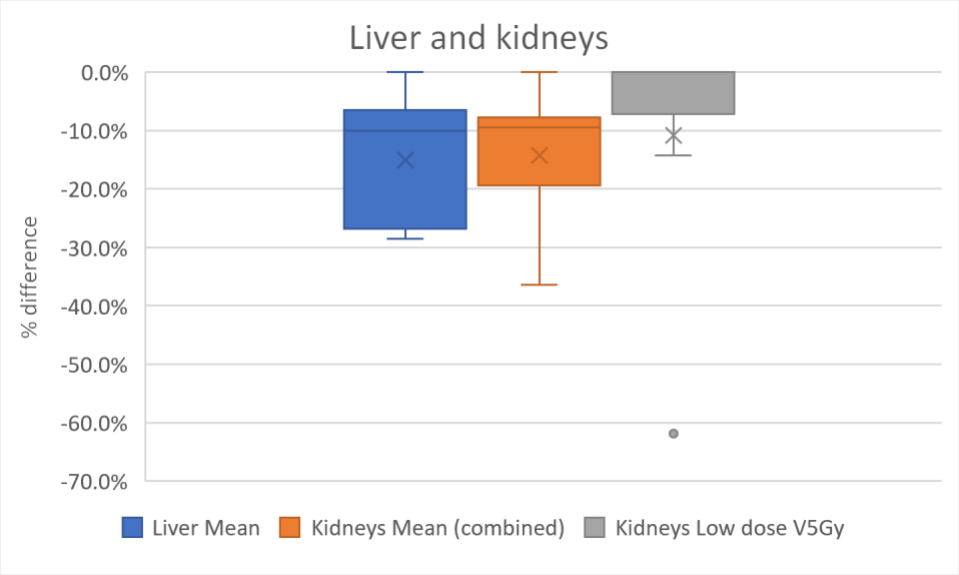


Figure 7.5 Box and whisker plots showing OAR dose difference (%) for liver and kidneys. Box and whisker plots showing median (line), mean (cross), interquartile range (Q1-Q3), whiskers represent range of values and outliers represented by dots.

7.4.5 Cumulative DVH profiles

Cumulative FB and EBH DVH are shown for PTV, duodenum, stomach, small bowel, liver, and kidneys (Figures A4.7.10-A4.7.15, appendix 4). The main difference between PTV_FB and PTV_BH shown on the cumulative DVH is less variation where dose falls off. For duodenum, the median was reduced, with less variation.

7.4.6 Image quality analysis

Image quality was assessed for all patients and showed the majority of scores to be a 2 (minor artefacts) in BH images, and a 4 (major artefacts) in FB (Figure 7.16). The difference between BH and FB image quality was statistically significant (p=<0.001). On 31/34 (91%) fractions, the EBH images were improved quality compared to the FB images. For 1/34 (3%) of fractions, the EBH image was scored worse quality than the EBH image, which was for an AC patient.

That same patient (paired fractions 24-29, figure 7.16) had the same score for their EBH and FB images on another 2 fractions.

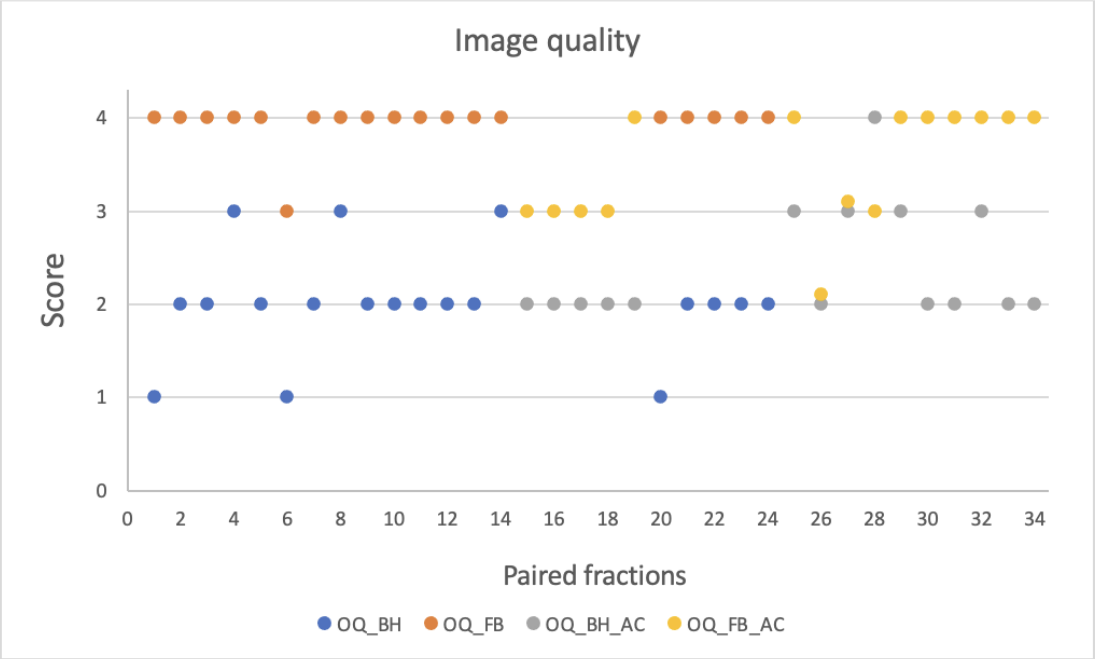


Figure 7.16. Overall image quality (OQ) scored for paired EBH and FB CBCT images, for all fractions evaluated (n=34). OQ_BH and OQ_FB (Non-AC); and OQ_BH_AC and OQ_FB_AC (with AC).

7.4.7 Structures

Data is shown for all structures in figure 7.17. Mean (SD) EBH and FB scores were CA 1.4 (0.7) and 3 (0.8) respectively; SMA 1.5 (0.7) and 3.0 (0.8); SMV 2.4 (1.1) and 3.7 (0.6). A statistically significant difference was observed for all structures ($p=<0.001$). Difference in duodenum scores between EBH and FB were also statistically significant ($p<0.001$), mean (SD) being 1.8 (0.9) and 3.1 (0.8) respectively (Figure 7.18). The majority of fractions showed an improvement in scores, with 6/34 (18%) of fractions having the same score on FB and EBH images.

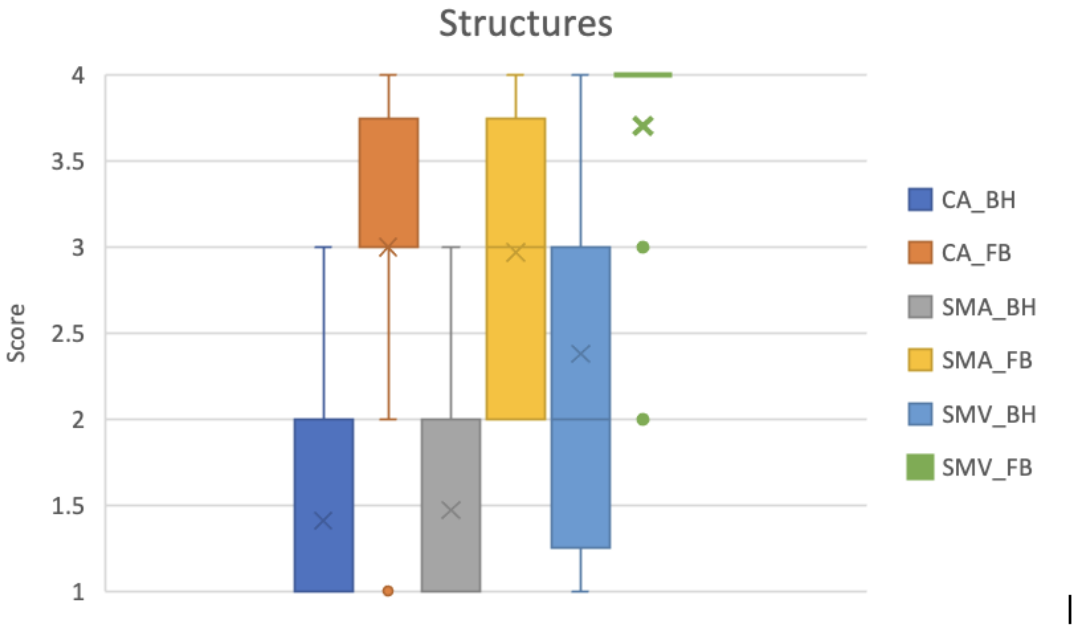


Figure 7.17. Visibility of celiac artery (CA), superior mesenteric artery (SMA) and superior mesenteric vein (SMV) and confidence in using them in decision making process.

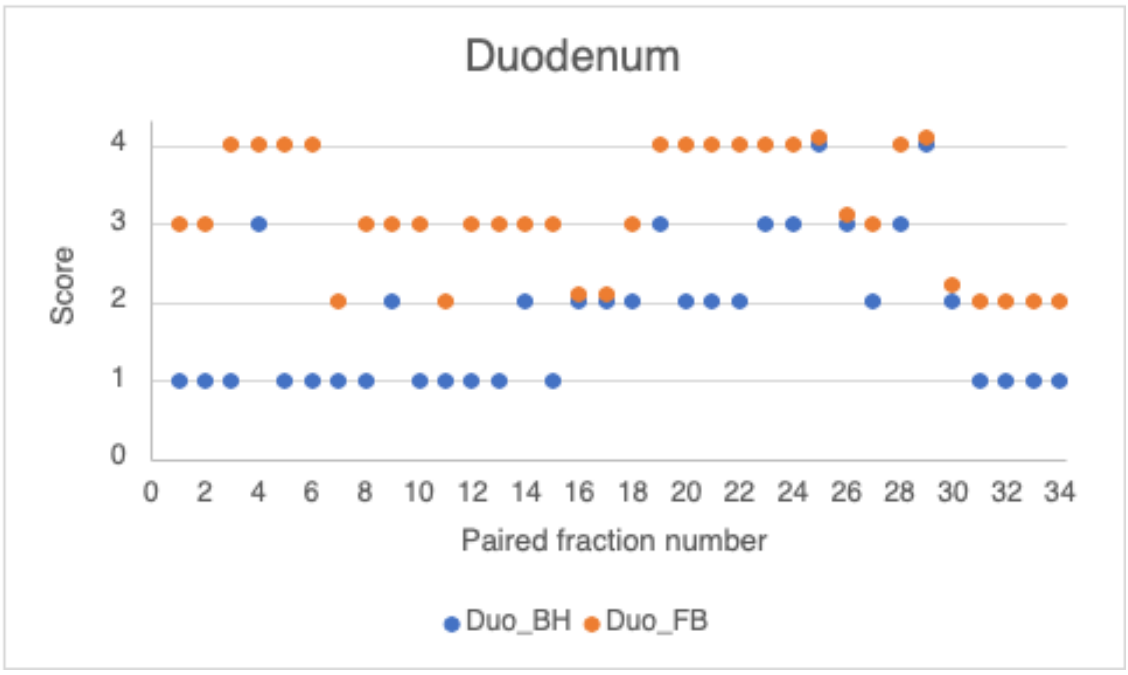


Figure 7.18. Visibility of duodenum and confidence in using them in decision making process, plotted for paired EBH and FB images.

7.4.8 Target volumes

Mean (SD) target volumes were GTV_BH 1.4 (0.6) and ITV_FB 3.0 (0.8); PTV_BH 1.4 (0.6) and PTV_FB 3.0 (0.8) (Figure 7.19). There was a statistically significant difference between BH and FB for all target volumes ($p<0.001$). Using CBCT_EBH 33/34 (97%) of images were scored a 1-2 i.e. as 'extremely confident' or 'fairly confident' in the assessment of GTV_BH (Table 7.8). For CBCT_FB, scores of 1-2 were observed in 9/34 (26%) of patients, with 25/34 (74%) being scored 3-4, i.e. 'not very confident' or 'not at all confident'. For PTV_BH and PTV_FB, 1-2 scores were observed in 33/34 (97%) and 15/34 (44%) respectively, and scores of 3-4 were observed in 1/34 (3%) and 25/34 (74%). The score of 1-2 for 97% of BH volumes showed all except 1 could be verified with confidence, compared to 26% of PTV_FB, the difference in means were statistically significant $p\leq0.001$.

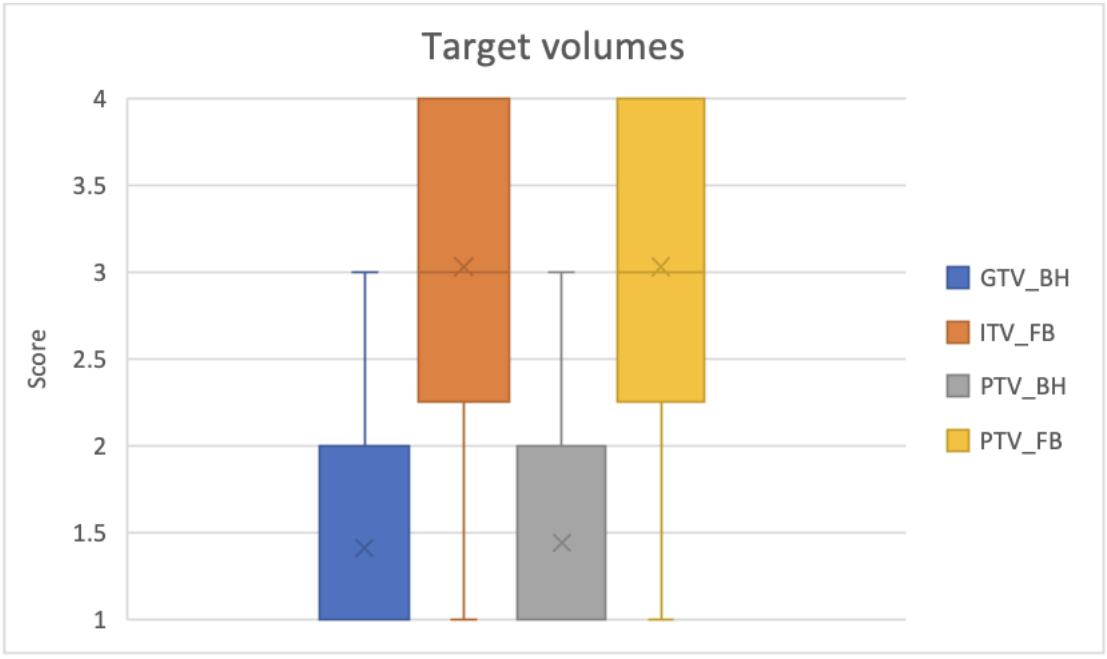


Figure 7.19 Box plot of all CBCT_FB and CBCT_EBH scores evaluated for GTV_BH, ITV_FB, PTV_BH and PTV_FB. Scores are described in table 7.4.

Score	GTV_BH	% of scores	ITV_FB	% of scores	PTV_BH	% of scores	PTV_FB	% of scores
1	21	61.8	1	2.9	20	58.8	1	2.9
2	12	35.3	8	23.5	13	38.2	8	23.5
3	1	2.9	14	41.2	1	2.9	14	41.2
4	0	0	11	32.4	0	0	11	32.4
Total	**34**	**100**	**34**	**100**	**34**	**100**	**34**	**100**

Table 7.8 Frequency and % of each score for GTV_BH, ITV_FB, PTV_BH and PTV_FB. Scoring criteria is described in detail in table 7.4, with scores of 1 showing highest confidence in verifying target volumes for treatment; and 4 being indicative of no confidence. A total of 34 CBCT_EBH datasets were used to assess GTV_BH and PTV_BH scores; and 34 CBCT_FB datasets were assessed to score ITV_FB and PTV_FB.

7.5 Discussion

The aim of this work was to assess the feasibility of planning and delivering pancreas SABR using an exhale BH technique. Both FB and BH planning methods resulted in clinically acceptable plans, but the on-treatment deliverability i.e. verification and confidence in delivering treatment, was only determined as feasible using CBCT_EBH imaging. The rationale for conducting this work was that the RPM is widely available and could improve treatment delivery, where other motion management solutions are not available. However, concerns over quality and reproducibility have hindered its use for treatment delivery for PDAC. The pancreas moves with respiration, so the RPM role in this work was to quantify improvements in imaging and determine if feasible to verify tumour and OAR position with CBCT_EBH.

This study found BH significantly improved image quality, visualisation of structures and confidence in decision making, with all paired measurements being statistically significant. Overall, CBCT_EBH imaging allowed significantly greater confidence in delivering pancreatic SABR treatment using the Varian™ RPM system without fiducials than with CBCT_FB. The assessment of PTV_BH resulted in 97% demonstrating confidence in verifying coverage, which was significantly more than in CBCT_FB at 26%. Duodenum visualisation improved

although in some cases it was still challenging. Visualisation and confidence in using duodenum for matching purposes increased from 27% to 76%; with 18% of scores being scored the same between the 2 methods. The study used a two-part assessment to answer the research question, which included a volumetric, dosimetric and deliverability assessment of the planning and delivery of pancreatic SABR patients using an ITV approach in FB (motion-encompassing); or an individualised BH technique (4DCT_EXHALE and 3D-CECT_BH).

This work showed that whilst volumes were almost 24% on average smaller with BH plans, clinically acceptable plans were achieved for both methods. This was consistent with other reports where PTV volumes were larger than BH by 20.2% (Lens et al., 2014). Although not directly comparable to this work, as these volumes were based on a volume with CTV and a larger PTV margin. Other authors found the difference between a GTV and ITV approach showed a difference of 25- 34%, with ITV being subject to larger inter-observer variability (Cattaneo 2010; Goldstein et al., 2010; Versteijne et al., 2017). For EBH, volume reduction was observed in all patients, although as expected this reduction was less in the group who had AC. No differences were shown to be statistically significant, although had this had been a homogeneous group of patients then significance might have been reached, especially volume difference which was 0.018.

7.5.1 Dosimetric

The planning criteria for the individualised PTV_BH plans were either improved, or at least equivalent to FB plans. An evaluation of the dosimetric outcomes for both methods i.e. PTV_BH and PTV_FB, showed OAR dose reductions were achieved with BH plans. When reporting relative change between FB and EBH constraints in this small group there were noticeable improvements in OAR dose i.e. % change. However to ensure these were not being overstated, the absolute change in dose was also presented here. This showed these were modest across the population, so further study of a larger group without AC will assess this benefit in more detail. The results showed an increase in MF and decrease in ALPO, suggesting that for the EBH plans the delivery of the beam is more complex than for the FB plans.

7.5.2 Image quality/visualisation

A free-breathing ITV is challenging to verify on treatment, as CBCT_FB results in motion artefacts in an area where poor soft tissue contrast already exists. As discussed previously, one way to overcome this problem in FB imaging is to use implanted fiducial markers, which act as a surrogate for target volume, but these don't provide information on OAR positioning. The study presented here did not use fiducials as tumour surrogate, with the intention of using actual target volumes for verification.

Quantification of CBCT image quality using CBCT_EBH acquisition allowed GTV_BH and PTV assessment to be carried out with confidence in 97% of fractions. This was a statistically significant improvement compared to the paired CBCT_FB dataset where only 26% of PTV could be assessed with confidence. BH imaging increased matching confidence by improving image quality, therefore allowing target volume to be assessed for any positional uncertainties; and on treatment IGRT registration to correct for target volume rather than a sub-optimal surrogates. CBCT_EBH datasets for all patients showed an improvement in overall image quality; visualisation of structures; confidence in registration and decision making; and improved confidence in PTV coverage assessment. In all, except for 1 patient, the GTV_BH and PTV_BH could be verified with confidence, this was considerably different from the ITV_FB and PTV_FB volume assessment, where 73.6% of these volumes did not allow confidence in image registration. This demonstrates the positive impact that CBCT_EBH imaging in PDAC has in aiding decision making.

Improved visualisation of all structures were actualised using RPM BH plans when assessed using visible target volumes rather than fiducial markers or surrogates. Nearby structures were also assessed, however their correlation to target volume were not. By assessing radiographer confidence in online registration using target volume, the ability to treat without fiducials can be considered. Fiducials used in SABR also have limitations, they cause artefacts that may

obscure priority structures (Habermehl et al., 2013) e.g. targets and OAR. Where only one marker is used, there is a chance that undetected migration can occur.

Fiducials used as a surrogate to a 3D PTV structure has limitations, as they don't allow identification of GI tract and PTV interface. The proximity of target volumes to OAR in conjunction with steep dose gradients require particular accuracy around the gastro-intestinal (GI) and PTV interface, where high dose regions can cause significant tissue injury (Benedict et al., 2010). Improved planning images, delineation on these and optimised volumetric imaging for linac-based treatments are necessary to achieve this, all aspects where the addition of fiducials do not provide this information. Optimised image quality is of high priority in treating PDAC, where it increases the opportunity to use novel and emerging techniques to treat patients who otherwise have limited options e.g. LAPC where local control is of utmost importance.

7.5.3 Margins

The investigation carried out in this chapter was designed to include patient specific motion, where data from more than one dataset was included in the delineation process. For ITV, this included the 3DCECT_BH and 4DCT_FB datasets, and for EBH, this included a patient specific approach which included a Boolean of two delineations that captured GTV position at BH and at the exhale phase of the FB scan. This composite volume was named GTV_BH and had a 5mm isotropic PTV margin added. Technically this EBH approach could be described as already applying an internal margin as it adds additional information on positional uncertainties between exhale position (4DCT) and EBH (3DCECT_EBH). This allowed uncertainties for each patient to be captured, although reality it is still a snapshot.

A patient specific approach has been previously recommended for lung (Lu et al., 2018) and for pancreas (Han-Oh et al., 2021), who both specifically stated that an additional margin of 2mm was required left-right and anterior-posterior to the ITV margin, resulting in 4, 4 and 6mm respectively. Han-Oh et al. (2021) recommended multiple BH's should be acquired for CT planning to ensure coverage of PTV in 95% of cases, which is method that will be considered in

future work. Nakamura et al., (2011) recommended a 5mm margin to account for uncertainty, based on multiple planning CT images acquired in succession.

7.5.4 On treatment intrafraction

On-treatment methods have been described to deal with intrafraction changes during a session. Zeng et al. (2019) reported intrafraction motion under DIBH conditions and found residual motion to be large, in some cases >5mm. However, the motion was random resulting in a recommendation of an additional 2mm PTV margin to account for this source of error when treating in DIBH. The problem with adding a population margin for all patients is that this may not be adequate for some patients whilst causing unnecessary dose to normal tissue for others. Their work was an assessment made in DIBH which may not be indicative of the EBH procedure, as reported by Lens et al. (2016). This warrants a similar study to be carried out in EBH, due to the nuanced differences. Han-Oh et al. (2018) recommended an anisotropic margin with DIBH techniques to be quite different in that deep inspiration can vary, with possible confusion over what is a reproducible deep inspiration, and the possibility of drift. Where patients are asked to end exhale, this position is not forced, but may be more difficult to achieve. A reproducible exhale should be more consistent i.e. when patient finishes exhaling. At the point where they hold their breath, further exhale should not be a natural reaction.

The work presented here did not include any assessment of Intra-fraction motion or inter-breath hold variability on treatment, although patient specific volumes. To some degree, CBCT_FB does include some information on this, as it is acquired over a full gantry rotation and will show blurring. In CBCT_FB the constant acquisition over 1 minute is similar to an average intensity projection (Ave-IP) of the 4DCT_FB. The CBCT_EBH images acquired here were done in multiple BH's, again providing an image that includes uncertainties in EBH reproducibility. In the assessment of image quality in this work, blurring could be assumed as displaying some of the target volume uncertainty, helpful in ensuring target coverage was achieved within the PTV. Although target volumes

are visualised with more confidence in the BH images, it is not as straightforward as assessing a lung tumour in the middle of lung with good contrast. Overall, decision making is multi-factorial and assessment requires optimal conditions.

7.5.5 External surrogates limitations

External surrogates do have their limitations e.g. motion is most prominent in the superior-inferior direction and the marker block only measures AP motion which may not correlate with GTV position, with modelling being required for other directions (Huguet et al., 2015). This indicates the importance of optimisation of CBCT_EBH imaging to compliment the RPM system to improve image quality i.e. increasing confidence in the assessment of target position. Another limitation is the options for monitoring intrafraction motion. Reports of poor correlation of the RPM marker block, abdominal wall or target volume surrogates to actual target volumes have demanded caution in using these methods for pancreas SABR (Feng et al., 2009; Huguet et al., 2015).

Jayachandran et al. (2010) discussed the limitation of using bony anatomy in the set-up and delivery of RT by comparing shifts to fiducial markers. They reported that in only 20% of fractions bony anatomy provided a good registration, which is more of a problem of the bony registration technique than the RPM system. Current data that aims to use fiducial free approaches are limited and fail to take into consideration the improvements in CBCT image quality and acquisition techniques that have enabled better visualisation of soft tissue.

Zeng et al. (2022) studied the accuracy of surface guided RT (SGRT) which is also an external surrogate. They reported that additional image verification of internal targets is necessary to ensure reliability of these. They used a variety of markers to measure residual motion throughout arcs, although they measured stents and surgical clips which may not be reliable surrogates of tumour motion e.g. stent may overestimate target volume motion (Goldstein et al., 2010; van der Horst et al., 2014). Their results highlight the uncertainties of delivering abdominal RT, however the study methodology applying potentially unsuitable

surrogates adds uncertainty to these results (Zeng et al., 2022). Previous work by this same group identified less residual motion using the RPM system, although the same intrafraction assessment was used (Zeng et al., 2019). Like the methodology applied here, they also applied a small threshold to the RPM gating window, which may have ensured more reproducibility between multiple EBH.

7.5.6 Strengths and limitations of study

This study cohort included small patient numbers with some cases who had AC applied. The heterogeneous group does mean that data should be interpreted with caution and may not be generalisable. However, the strength of this methodology was that it used an end-to-end FB and BH approach to assess the feasibility of delivering SABR with each method. This was done using FB and EBH images acquired in exactly the same conditions, in the same session. In previous studies, image quality has not been quantified as a benefit to a EBH technique although it is extremely important in actual dose planned being delivered.

Even with limitations of an external surrogate method, there are multiple benefits of the EBH technique as a whole. These include reduced volumes, reduced OAR dose and improved confidence in image registration. Visualisation of structures and confidence in decision making is extremely important in delivering RT accurately and precisely, although being an area that is not well described. The benefit of using advanced planning methods can only be realised if advanced IGRT techniques are applied at the treatment stage. If implementing BH techniques with an external surrogate, adequate investigation of all other sources of uncertainty must be used to inform the necessary margins and ensure effective doses can be delivered, whilst minimising dose to OAR.

7.6 Conclusion

Complex volumes on 3D and 4D CT planning scans require volumetric IGRT to localise and verify target position and assess OAR at each fraction. To deliver safe and accurate RT to a dose that is clinically meaningful, assessment of target

volume coverage on treatment is required. Poor image quality CBCT_FB affects decision making in the registration process which is significantly improved using CBCT_EBH. Improvements in image quality and confidence when delivering SABR treatments with BH are reported here, providing an opportunity to improve safety and feasibility of delivering high dose per fraction treatments for this challenging site. Further work will study a larger homogeneous group, with other sources of uncertainty applied to the RT protocol.

Chapter 8 Final discussion and conclusion

8.1 Future directions

8.1.1 Challenges in effectively treating PDAC

Pancreatic cancer is a worldwide problem and remains a cancer of unmet need, predicted to be an even bigger problem in the future as it is forecast to be 1 of the top 3 of cancers responsible for death by 2025 (Sung et al., 2021). The controversy surrounding the role of RT for pancreatic ductal adenocarcinoma (PDAC) has long since been acknowledged and discussed, with contradictory study results validating opinions on whether RT is effective or not; or, more crucial to that is whether it has a negative impact on outcomes. Although PDAC is very much a systemic disease, surgery and systemic treatments have not provided the improved outcome data that patients need (CRUK, 2023).

Varying opinions on the role that RT plays in the pathway has affected clinical decisions, and possibly the progression of RT protocols. Consistently poor outcomes demonstrate this cancer is still one of unmet need, requiring collective ambition to improve patient outcomes across wider multi-disciplinary teams (MDT). The rapidly changing field of RT has seen the development and implementation of advanced planning and delivery systems, which have facilitated more safe, accurate, and precise treatments which warrant further optimisation and investigation within clinical trials. A national drive in the UK towards implementing high quality SABR for pancreatic cancer has promoted the use of this for locally advanced pancreatic cancer (LAPC) and by providing national guidance with complementary education days for the MDT demonstrates the motivation to develop services nationwide. This thesis was conducted at a time where there were few departments delivering SABR in the UK, and a national programme was being developed.

The paradigm around the most effective treatment modalities and how they are used in combination have seen progressive changes. Neo-adjuvant treatment has allowed improved patient selection, which can help stratify patients for

individualised RT. Delivering effective multi-modality treatments with improved outcomes is the priority going forward. At times, it may seem that challenges in treating PDAC are insurmountable, with recognition that the complex tumour microenvironment (TME) provides an obstacle in delivering either systemic treatment or RT with efficacy. However, with optimisation of all areas of uncertainty, it is time for RT to demonstrate how it can help overcome these hurdles.

8.1.2 Challenges of running high quality studies

As addressed earlier in this thesis, there are huge challenges in running high quality studies in PDAC, which are not insignificant. The diversity of patient characteristics and disease management alone make high powered study difficult. Some of the issues encountered throughout this thesis are consistent with these issues, albeit on a small scale. Patients who are diagnosed with metastatic disease are already excluded from RT. Those who are non-metastatic will follow the neo-adjuvant approach, where they may not tolerate treatment, or may not respond well leading to a diagnosis of metastatic disease. The number who go on to have RT are small, and the inhomogeneous patient characteristics make it challenging to study groups.

8.1.3 Optimising RT for PDAC

The aim of this thesis was to identify uncertainties and optimise different components of the RT pathway. Throughout this pathway significant issues exist which amplify the uncertainties. These uncertainties are multi-faceted, for example, motion is not only affecting positional changes in pancreas but also affecting planning image quality which has an impact on delineation; blurring affect dose calculation; and motion artefacts on CBCT affects image quality which impacts decision making. The diagram from Chapter 2 showed the interlinking of these factors, demonstrating the importance of refining components of the pathway, whilst keeping awareness of the bigger picture.

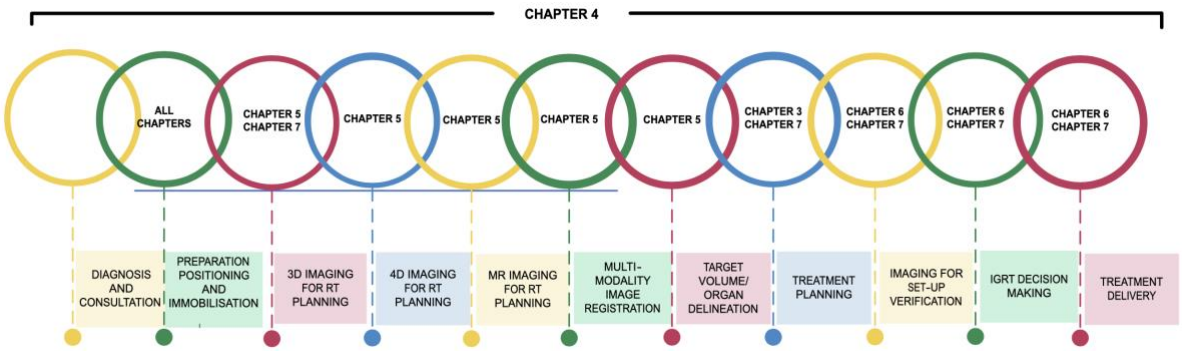


Figure 2.1 Components of the RT pathway that demonstrate the interaction of all components in the chain and where there are opportunities to introduce systematic and random errors. This figure is adapted from Njeh (2008).

8.1.4 The central role of the RTT

The RTT led work conducted throughout this thesis highlights the essential role they play in contributing to RT for PDAC. Historical controversies in RT trials have contributed to differing views on the optimal treatment strategies and sequencing of treatment, for this patient cohort. This emphasises the necessity of working with the MDT to identify avenues where incremental improvements would optimise treatment; and could improve the opportunity of conducting prospective trials for future patients.

The thesis aimed to enhance the safety, accuracy, and precision of RT for PDAC patients, with importance to delivering effective doses to the disease while minimising dose to normal tissue. The thesis considered uncertainties associated with each component, acknowledging the impact they can have on safety and accuracy. RTT are integral MDT members who contribute to treatment planning, delivery, quality assurance (QA), patient support, and research. Through this involvement in the MDT, this radiographer led work considered a comprehensive approach to improving treatment for patients, which included discussions with patient representatives.

While RTTs have significant responsibility for on-treatment IGRT, their comprehensive understanding of errors and uncertainties across the treatment pathway allows opportunities to highlight suboptimal processes. Multiple factors influence treatment quality at every stage of the patient pathway. Through this understanding, this thesis was designed to encompass investigations into the

optimisation of delineation, planning, and on-treatment aspects. Under the guidance of experts from various disciplines in the MDT, has resulted in enhanced research collaborations. The promotion of teamwork has led to an inter-disciplinary team approach (IDT) to address this critically important area of unmet need.

8.1.5 Outcomes from this thesis

The work in this thesis has allowed the implementation of dose-escalation within clinical trials, where the full pathway has been optimised and carefully executed. There are still sources of uncertainties in the components of the process, however these incremental steps to optimise has changed clinical practice and allowed RT protocols to be optimised within clinical trial protocols.

Evidence over the past decade has supported the use of dose-escalated SABR, with an aim to improve local control of disease. In particular, some groups have investigated SABR in eradicating disease that has spread to the nearby tissues (Chuong et al., 2013; Holyoake et al., 2021; Passoni et al., 2013). Differential motion between surrounding vasculature structures and primary disease in the pancreas is of concern in borderline resectable pancreatic cancer (BRPC), where RT is being used to kill remaining tumour cells in the “unresectable” or “borderline” region (Tempero et al., 2017). The usefulness of soft tissue structures in the image registration process, has been inhibited by the poor soft tissue visualisation at the treatment stage of RT. Topics investigated in this thesis have included the optimisation of target delineation which has been deemed the weakest link for many years (Njeh, 2008); and the visualisation of soft tissue using IGRT. The latter improving treatment delivery and providing an opportunity to explore adaptive RT and dose escalation to areas at risk of positive resections.

8.1.6 Retrospective review of outcomes

The first results chapter (chapter 3) reported the clinical outcomes of conventionally fractionated VMAT for PDAC, reporting dosimetric and clinical

outcomes of the standard of care at the beginning of this thesis. Although this aspect was not particularly novel, it was important in defining a local baseline. These outcomes documented a baseline of outcomes from VMAT treatment, ensuring that standard of care practice was of sufficient quality before optimising. These patients had no additional MRI imaging, had standard free-breathing IGRT and treatment delivery.

8.1.7 Motivation to optimise specific components

Consensus is important in RT, helping groups to move forward in a collective manner. The survey in chapter 4 was carried out to ensure there was a clear direction of travel across CO and COtrain that would prioritise optimisation in the most important areas. There was a clear message that optimisation for this disease site was of interest, and confirmation that experts agreed on how challenging these patients are to treat. The results from this survey were used to define the project aims and objectives for subsequent chapters, although not all areas of importance could be addressed within this work.
Multi-modality imaging for RT planning

The work in chapter 5 demonstrated that even with multi-modality planning CT and RT MRI images, inter-observer variation (IOV) was high and dice similarity coefficient (DSC) was low for CO and COtrain when delineating PDAC volumes. One important thing to note was that this methodology provided limited clinical information and no access to previous diagnostic imaging. This was to measure the true differences with MR and CT alone. Delineation is a major source of uncertainty, and recognising the limitations of using MR and CT imaging is an important factor in improving the quality of RT. Not only is this problematic at that part of the pathway, but it results in systematic error which affects subsequent treatments thereafter.

Although there have been a number of reports on IOV in this disease site, there is not sufficient evidence of multi-modality acquisition on the same day, or MR images being co-registered with planning CTs. As the use of MRI in RT planning

for PDAC has gained interest, there are still fundamental issues that exist when implementing protocols into the pathway. The high variability identified has brought into question a number of short term and long-term solutions. The first issue raised was the accurate registration of the CT and MR images. Although automatic registrations are applied, the anatomical site in question requires human interaction in the registration process to prioritise the registration around disease burden. Adequate guidance in training is necessary to ensure the best registration possible is achieved, and that the addition of MR imaging does not increase uncertainty through poor registration. Any lack in knowledge and training could result in a poor registration and be a source of systematic error that affects all treatments.

8.1.8 Optimising IGRT image quality for decision making

Chapter 6 demonstrated how breath hold (BH) imaging improved the visualisation of target volumes, duodenum, arteries, and veins. This can potentially impact LAPC and BRPC patients. For the latter, where simultaneous integrated boost (SIB) to such regions is used to improve resectability this can provide improved IGRT. Irradiation can result in tissue damage to pancreas and surrounding structures, with this being described following SABR using single fraction RT (Cupp 2008). Also of concern is the possibility that tissue damage could result in technically challenging surgical procedures, which again brings into question the suitability of this SIB technique.

The results clearly illustrate the improvement CBCT_EBH image acquisition can have on identifying the intended target volume, and the location of duodenum. These developments are key to improving on-treatment verification protocols, which have an impact on not only patient safety, but may improve treatment outcomes. With fiducials, it is essential to acknowledge that providing a surrogate for target volume does not completely address the safe and effective delivery of high dose RT, as duodenum cannot be assumed to be in a reliable position.

8.1.9 Improving visualisation of dose-limiting structures

The identification of dose relative to duodenum, and other luminal GI structures is imperative in decision making. With a growing interest in the community to increase dose, optimised volumetric information is needed to improve confidence in localising and verifying treatment delivery. The aim to minimise dose to OAR structures such as duodenum is essential in minimising the risk of severe toxicity e.g. perforation.

Although visualisation of duodenum was not improved to the same magnitude as some other soft tissue structures, there was a clear increase in the confidence of decision making. Given the large and complex shape of the duodenum, where descending, transversal and ascending portions need to be considered, challenges do still exist in identifying the structure, especially where abutting soft tissue structures with similar soft tissue resolution. It would be interesting to investigate their visualisation on images acquired on MR-linac.

The duodenum is a difficult structure to avoid when matching high dose regions, although this ultimately will be the barrier to delivering tumoricidal doses. This is due to inter-fractional changes e.g. shape and position. Where the structure descends (second part) it sits next to pancreas where it is often next to the PTV (head of pancreas tumours). It also sits horizontally, (third part) which transverse across the inferior aspects, meaning that observers need to be mindful of applying corrections to any one point, and need to consider the implications these shifts have through all planes and sections of the duodenum. Contrast was used to improve visualisation of the duodenum, however transit times are affected by inter and intra-patient variability, success not always guaranteed. Other structures of relevance in high-dose RT for PDAC include stomach and small bowel. It is understood that between fractions there can be considerable changes in GI tract volume that may lead to delivery of toxic doses (Chen et al., 2016). Superior soft tissue visualisation on the MR-linac provides more opportunity to visualise the duodenum and other GI structures and adapt position (Bohoudi et al., 2017; Chuong et al., 2021; Parikh et al., 2022).

8.1.10 Delivering SABR with an external surrogate

There has been concern over the suitability of external surrogates in respiratory motion management in pancreas. This has been a limitation for departments that do not have other motion mitigation techniques. The work presented in chapter 7 showed that FB and BH planning volumes can allow clinically acceptable plans to be created. Using the scoring criteria developed in Chapter 6, the CBCT_EBH and FB images were evaluated to determine how confident radiographers were in delivering SABR to these volumes, assessed on each dataset. Confidence in delivering treatment was only found using CBCT_EBH imaging. More importantly, this showed that delivering SABR with a FB method and CBCT verification could not be done with confidence.
A potential limitation of this data and desirable future addition to this study will be an assessment of intra-fraction motion throughout a BH treatment. When this is quantified, confidence in delivering BH with an external surrogate can be achieved. There are data that suggest a margin should be applied to planning volumes, but these should be patients specific and would require investigation alongside local set-up protocols (Han-Oh et al., 2021; Zeng et al., 2019). Real time tracking on the MR-linac uses real-time imaging that can identify target volume. Assessment of which can result in treatment interruption, with no need for an ITV using this technique and requiring a GTV to PTV margin of 3mm (Chuong et al., 2021).

Advanced technologies can offer patient empowerment throughout their simulation and treatment delivery, where real-time visualisation of their tumour position can allow them to adapt their breath-holds (van Sornsen de Koste et al., 2018) The problem is that MR-linac treatments are not accessible to most and optimized linac-based RT is still advantageous.

8.1.11 Patient choice

One of the under-reported benefits of RT in this complex patient group is the importance of patient choice. Often PDAC patients have suffered a long period on multiple cycles of toxic systemic treatments, which have impacted their quality of life (QoL). There may be a desire to have a period of respite from such treatments, whilst still feeling their disease is being actively managed. With patients being aware of the ominous prognosis of their disease, QoL is of high importance, and patient involvement in decision making made even more important, ensuring patients are well informed about what their treatment options are.

Patient decision making on their disease management is of course important for all cancer patients. However, it could be argued that for such a poor prognosis cancer, there are different justifications for treatment and overall survival may not be at the top of patient's priority. A study which included healthcare professionals, researchers and patient advocates recently published that top priority was quality of life, not OS (Allen et al., 2023). This is important to consider when designing studies around specific endpoints.

RT is localised, and can be used for local control, preventing further spread and alleviating symptoms. As discussed earlier, the majority of patients die with local progression, so delivering effective locally targeted therapy is key at this stage.

SABR treatments also offer the patient the opportunity to receive a course of RT over a shorter period of time in much fewer fractions than that of conventionally fractionated dose. This reduces the burden on their time spent travelling to and waiting in hospitals.

8.1.12 Impact on margins

When delivering RT, a key consideration is the probability of delivering a sufficient dose to target volume i.e. 95% of the dose. As recommended by Van Herk et al., (2000) a systematic error requires a larger PTV margin to be applied than that of a random error. Their calculation states that a systematic error requires a multiplication factor of 2.5, whereas the random component would be multiplied by 0.7.

When using the ITV approach to compensate for motion, a large volume is created which implicitly treats motion as systematic error. This has always divided opinion on the optimal method of creating target volumes for RT, with the ITV effectively geometrically creating a larger PTV than may be unnecessary. Conversely, BH and Mid-ventilation techniques may allow smaller planning volumes, but these require extra considerations of other sources of uncertainty. One major source of uncertainty is illustrated in the MR-CT delineation study in chapter 5 where the variation in volumes across observers was reported. This chapter showed that larger volumes had greater agreement, which also indicates that the more information used would result in higher agreement. The findings of chapter 5 re-enforce how important it is to improve accuracy and precision before implementing BH techniques, making sure that uncertainties are minimised and accounted for. The improved consistency of ITV volumes and their large volumes show how caution should be applied to BH volumes, where they are smaller and have less consistency between observers, increasing the risk of not geographical miss.

A calculation of all uncertainties may exceed these values, however the premise of high dose hypofractionated RT is that accuracy and precision are essential components, so high uncertainty should call into question whether it is feasible or not to deliver. This is an attraction of online ART, where high dose regions can be altered and recalculated based on the anatomical position of that session, resulting in better dosimetric outcomes including improved target coverage (Bohoudi et al., 2017; Nierer et al., 2022).

8.1.13 MR-Linac

MR-Linacs have demonstrated many benefits in delivering RT to PDAC. These include the ability to visualise targets and OAR, as well as adapt treatment based on daily changes. These are becoming more common, with a lot of energy going into addressing research questions through large consortiums (Kerkmeijer et al., 2016; de Mol van Otterloo et al., 2020).

These have by no means replaced linac treatments, so the importance of continuing to optimise RT with linac-based treatment platforms are crucial for the majority of patients, which formed the aims of this thesis. One of the main problems with delivering RT in the abdominal region is using the appropriate motion mitigation strategies and ability to localise and verify treatments effectively. The latter has prevented departments from delivering high ablative doses, due to the concern of not being able to confirm avoidance of dose limiting structures that are in close proximity.

In chapter 6 the image quality from FB and BH scans were scored in a blinded manner to quantify the difference in image quality and confidence in matching. As IGRT has developed over the years, there has been a shift in responsibilities. Radiographers who specialise in site specific clinical activities are taking on responsibilities of delivering highly complex treatments, with the appropriate entitlements. To do this, it is essential that confidence in online decision making is achievable. The assessment of image quality is subjective; however, this work created a method of quantifying the difference in acquisition techniques. It is also a subject that is under-reported, even though Njeh (2008) conveyed that importance when the highlighted the quote by the famous physicist Harold Jones, “If you can’t see it, you can’t hit it and if you can’t hit it you can’t cure it”. They then went on to argue the case in 2017 that the value of IGRT was constrained by planning images being of insufficient quality, resulting in poor delineation even though localisation had improved (Njeh and Dong, 2017). The evidence from this thesis strongly supports the necessity of optimising all stages of the pathway to reduce uncertainty. Figure 2.1 demonstrates the interconnectivity of processes.

When discussing uncertainty in RT there are key sources that feature, including delineation and set-up. Image registration and IGRT decision making is at times not considered, although these both could introduce systematic errors. Radiographer decision making in pancreas RT is not well discussed in the evidence, although a decision aid was published by Daly et al. (2021). Using CBCT for this challenging site requires education, training, and competence for those undertaking image review.

Online adaptive RT has been investigated by MR-Linac groups, with the ability to adapt plans that respond to changes in volume and position of abdominal structures. The duodenal changes that occur between RT fractions can be accounted for, and adaptive plans can be implemented to suit these changes. The quantified benefit of BH images identified in chapter 6 and 7 will be further investigated in feasibility studies of linac-based ART protocols. The delineation of key structures will be used to determine the feasibility of ART methodologies using this platform. Image quality has caused limitations to online ART in this setting, but there remain opportunities to explore this further.

8.1.14 Adaptive RT on a LINAC

The value of CBCT can be further explored in the context of ART for PDAC (Dai et al., 2021). There is high utilisation of CBCT for IGRT in this tumour site, although image quality has made it challenging to redefine target and OAR volumes due to image quality. Variations in soft tissue size, location and shape make decision making even more important at each fraction. An obvious impact of improving CBCT image quality is not only that better decision making can be applied to online corrections before treatment delivery, but also provides opportunity to utilise these images for adaptive purposes. The relatively new Varian Ethos™ (Varian Medical Systems, Palo Alto, CA) platform allows ART through artificial intelligence (AI) planning software, where fast automated online adaption can be performed. At this time, there have not been reports on how BH imaging and adaption has been implemented, although offering promise in future directions.

8.1.15 Proton radiotherapy

The utilisation of protons in pancreatic RT is attractive due to the ability to deliver focussed dose to the depth of target volume using the Bragg peak, quickly decreasing allowing normal tissue dose to be minimised. The dosimetric benefit of proton therapy was reported in a comparison of IMRT, VMAT and PT plans to be lower dose to the kidney and stomach (Ding et al., 2014); and in regions receiving low dose only in another study (Thompson et al., 2014). The benefit of PT dose reducing so quickly outside target could be compromised by the impact of uncertainty and error, where changes in position and anatomy could result in dose not being deposited where intended. Solutions for dealing with such uncertainties are required to ensure proton therapy is safe and effective.

8.1.16 Radiosensitivity

The radiosensitivity of pancreatic cancer tumours and how they respond to high dose per fraction treatments is still under investigation with many ongoing trials investigating ablative doses (Burkon et al., 2021). This in combination with the unknown response of dose-limiting GI structures adjacent to the pancreas, leaves many challenges in delivering safe linac-based RT that reaches tumoricidal dose.

It is known that the linear quadratic model does not provide a reliable estimate of dose, but with high dose per fraction protocols being investigated within studies, outcomes can be used to understand more about the radiosensitivity of disease and normal tissue. Given that dose escalation has shown favourable results in controlling local disease although reported as significant (Zarosky et al., 2019), there is more to be done in terms of delivering the biologically effective doses (BED) required. This can only be achieved where collective efforts are focussed towards delivering the highest quality of RT across delivery platforms i.e. recognising and dealing with all sources of uncertainty. Dose-limiting structures remain the biggest concern in dose-escalation, so with increased confidence in image quality and decision making this can be realised.

This thesis doesn't explore the radiobiology of pancreatic cancer, or molecular characteristics, however, the work conducted has improved the quality of RT and can be implemented in studies translational studies. The dense and fibrous stroma around disease is made up of multiple components. Stroma is thought to be a contributing factor that leads to poor response through resistance to treatment and tumour progression. Working in collaboration with lab-based groups are required to ensure that understanding this can help to improve future treatment strategies. This can then be translated into the clinic, for testing with the optimal treatment plans. Even where previous investigations have tested radiosensitisers, these may benefit from being revisited with SABR.

8.1.17 Future work in advanced imaging

There is one aspect that cannot be ignored going forward and has the opportunity to improve all modalities of treatment. When delivering multi-modality treatment, clinicians rely on radiological information when selecting patients for further treatment. The use of CT, MRI and PET are utilised following treatment, to restage patients and determine response. However, their ability to characterise tissue has been shown to have limitations in determining what remains visible on imaging as disease or fibrotic tissue. This has led to poor standards of patient selection (Ferrone et al., 2015). This leaves concern of how reliable this process is, with a patient's disease management plan being heavily reliant on decisions made from a sub-optimal process. How clinicians reach their decisions is not well understood but has the ability to majorly affect a patient's treatment plan.

The next efforts should focus on imaging response, where novel applications of imaging techniques can be investigated and validated, to provide sensitive and specific data that can stratify patients; and/or adapt their treatment. The study by Ferrone et al., (2015) showed striking results when assessing response in a group of patients who had undergone treatment prior to surgery. Assessment of radiological investigations showed that patients who were deemed as

inoperable, were in fact operable when surgical exploration was carried out. Promise has been shown in the application of diffusion MRI to characterise tissue (Messina et al., 2020); correlate response using apparent diffusion coefficient (ADC). By investigating novel imaging techniques e.g. intra-voxel incoherent motion studies, this may be further improved (Gurney-Champion et al., 2018).

With the complex TME which has proven challenging in effectively treating PDAC, there will be lots to gain from detecting tissue characteristics between and during treatment modalities. Advanced imaging techniques could be used to assess the impact radiosensitisers and cytotoxic drugs have on disease and normal tissue when combined with RT. This will complete investigation of the pathway described in figure 2.1, where diagnosis and consultation can be improved.

Appendices

Appendix 1. Sample questionnaire

1. **How many years of experience do you have as a consultant GI Clinical Oncologist? If you are a Clinical Oncology trainee, please state zero.**

Using contrast enhanced 3DCT/4DCT alone i.e. no additional imaging modality, how would you describe the level of difficulty when delineating pancreatic tumour volumes for

2.

   a. **Borderline resectable pancreatic cancer?**

   1 – Very difficult

   2 – Difficult

   3 – Neutral

   4 – Easy

   5 – Very easy

   b. **Locally advanced pancreatic cancer?**

   1 – Very difficult

   2 – Difficult

   3 – Neutral

   4 – Easy

   5 – Very easy

Add any additional comments here

3. **How much inter-observer variation do you think there is between consultant GI Clinical Oncologist observers**

   A. **With 3D/4DCT alone?**

      a. Volumes will be similar between observers

b. Minor variation

c. Moderate variation

d. Major variation

Add any additional comments here

4. **With MR/CT fusion?**

a. Volumes will be similar between observers

b. Minor variation

c. Moderate variation

d. Major variation

Add any additional comments here

4. How much impact do you think the addition of MRI for planning i.e. MR/CT fusion opposed to CT alone for delineation, will have on gross tumour volumes (GTV)?

1. No impact

2. Minor impact

3. Moderate impact

4. Major impact

Add any additional comments here

5. How much impact do you think the addition of MRI for planning i.e. MR/CT fusion opposed to CT alone for delineation, will have on the dosimetric outcomes of the treatment plan?

1. No impact

2. Minor impact

3. Moderate impact

4. Major impact

Add any additional comments here

6. **Using your current experience of the radiotherapy planning and delivery process for pancreatic cancers, how important do you think it is to**

    a. **Improve tumour delineation by reducing any current variation in tumour outlining between consultant Clinical Oncologists**

        1 – Not at all important

        2 – Slightly important

        3 – Moderately important

        4 – Very important

        5 – Extremely important

    Add any additional comments here

    b. **Optimise the quality of planning images to give better visualisation of tumour volume and organs at risk**

        1 – Not at all important, images are as good as we need

        2 – Slightly important

        3 – Moderately important

        4 – Very important

        5 – Extremely important

    Add any additional comments here

    c. **Optimise on-treatment images to improve soft tissue visualisation for IGRT matching protocols**

        1 – Not at all important

        2 – Slightly important

3 – Moderately important

4 – Very important

5 – Extremely important

Add any additional comments here

d. Improve motion management techniques and strategies

1 – Not at all important

2 – Slightly important

3 – Moderately important

4 – Very important

5 – Extremely important

Add any additional comments here

e. Deliver a standardised education package to junior clinicians on delineation

1 – Not at all important

2 – Slightly important

3 – Moderately important

4 – Very important

5 – Extremely important

Add any additional comments here

f. Peer review volumes and plans with representation from a multi-disciplinary team

1 – Not at all important

2 – Slightly important

3 – Moderately important

4 – Very important

5 – Extremely important

Add any additional comments here

7 **Please rank topics according to how you would prioritise them i.e. number 1 is the improvement you see as most important and 6 is least important:**

a. Improve tumour delineation by reducing variation between consultant clinical oncologists

b. Optimise the quality of planning images to give better visualisation of tumour volume and organs at risk

c. Optimise on-treatment images to improve soft tissue visualisation for IGRT matching protocols

d. Improve motion management techniques and strategies.

e. Deliver a standardised education package to junior clinicians on delineation

f. Peer review volumes and plans with representation from a multi-disciplinary team

Add any additional comments here

8. Please indicate your level of agreement with the following statements

A. Standard of care radiotherapy dose and fractionation schedules in the UK are adequate in treating locally advanced pancreatic cancer

1 – Strongly agree

2 – Agree

3 – Neither agree or disagree

4 – Disagree

5 – Strongly disagree

Add any additional comments here

4. Standard of care radiotherapy dose and fractionation schedules in the UK are adequate in treating borderline resectable pancreatic cancer

1 – Strongly agree

2 – Agree

3 – Neither agree or disagree

4 – Disagree

5 – Strongly disagree

Add any additional comments here

9. How important do you think it is to improve standard of care imaging to assess treatment response before/after radiotherapy?

1 – Not at all important

2 – Slightly important

3 – Moderately important

4 – Very important

5 – Extremely important

If you answer 2-6 i.e. slightly- extremely important, please comment on which imaging modality and how this could improve response assessment

Comments

Appendix 2. Multi-modality imaging for target delineation

Dear Participant,

Thank you for agreeing to participate in MRI delineation study for pancreatic cancer.

Before you begin, please could you complete a pre-study questionnaire. This is to capture your views on optimising pancreatic RT. The survey can be accessed by following the below link.

https://link.webropolsurveys.com/S/C58F8E832E7E4AA2

Each observer will be given a unique number which will be used as a suffix to the anonymised patients, listed at the end of this document e.g. observer 49 would enter ***ZZ_PanP1Ob49*** to open patient 1, ***ZZ_PanP2Ob49*** to open patient 2 etc. In the list below, each anonymised patient has some clinical information attached.

Delineation instructions

Stage 1 requires delineation to be performed on the CT_1 (3DCT breath hold) dataset and the relevant 4DCT images i.e. CT_RP_00 and CT_RP_60.

N.B. MRI should not be viewed until stage 2 and should not be completed within the same session to ensure reliability and validity of results.

Volume definitions are included below:

On the 3D CECT and 4DCT delineate the following structures:

GTV_3D – This should include pancreatic tumour visible on image

GTV_inhale – On the maximum inhale bin of the 4DCT delineate GTV

GTV_exhale-- On the maximum exhale bin of the 4DCT delineate GTV

ITV_CT -On the 3D CECT create the ITV using Boolean operators to produce a union of GTV_3D, GTV_ inhale and GTV_ exhale

Once ITV_CT is created, verify that involved disease is adequately covered on all phases of 4DCT

Now using registered 3DCT, 4DCT and MR images

GTV_MR-- delineate disease visualised on MR only

GTV_MR_CT – This will be your GTV_3D amended using registered MR and CT scan

ITV_MR – This is your GTV_MR_CT and any motion from GTV_inhale* and GTV_exhale*

*** may need amended, based on information from MR, please create copy of these structures if necessary and name MR_CT_inhale and MR_CT_exhale**)
i.e. using MR and all 3D/4D information.
Thank you for your participation in the study, your time is much appreciated.

Patient identification and clinical information

ZZ_PanP1ObXX

eus-- large mass in uncinate

CT-- mass lesion in the uncinate process of pancreas now measuring 26 mm. Reduced narrowing of the SMV, but persistent SMA encasement

ZZ_PanP2ObXX

CT-- head of pancreas mass around 1.6 cm . Persistent circumferential encasement of the common hepatic artery and unchanged tight focal narrowing of the portal vein. Accessory right hepatic artery arising from the SMA has apparent soft tissue contact anteriorly, but no encasement.

ZZ_PanP3ObXX

eus-- 25mm mass in head of pancreas -Mass clear of SMV/PV

ct-- head of pancreas mass measuring 30 mm . Contact with the SMV but no narrowing

ZZ_PanP4ObXX

head lesion measures 2.5 cm approximately, contacts the superior mesenteric vein, . There is partial resection of the pancreatic head with a Roux-en-Y small bowel resection and hepatico-enterostomy

ZZ_PanP5ObXX

eus-- Body of pancreas lesion

Close to coeliac, involving splenic A

ct-- large body of pancreas mass encasing the common hepatic artery, and in contact with the coeliac axis and SMA. DJ flexure also involved.

ZZ_PanP6ObXX

eus-- 3cm mass in uncinate process obstructing CBD and PD

ct-- HOP lesion which measure around 25 mm . Persistent involvement of SMV tributaries. Also involvement of adjacent SMA and progressive soft tissue adjacent to more proximal SMA.

ZZ_PanP7ObXX

eus-- Infiltrative mass arising in medial uncinate process extending inferiorly and involving wall of SMV and 50% of SMA

ct-- soft tissue bulk arising from the uncinate process encasing the SMA, measuring 30 x 22 mm

ZZ_PanP8ObXX

ct HOP mass measures 32 x 20mm

-Atrophy of pancreatic body and tail

-<180 degree encasement of SMA

-SMVl occluded with large collaterals

ZZ_PanP9ObXX

ct-- Head of pancreas mass measures 34 x 35 mm

the mass involves the superior mesenteric artery and splenic vein to SMV confluence.

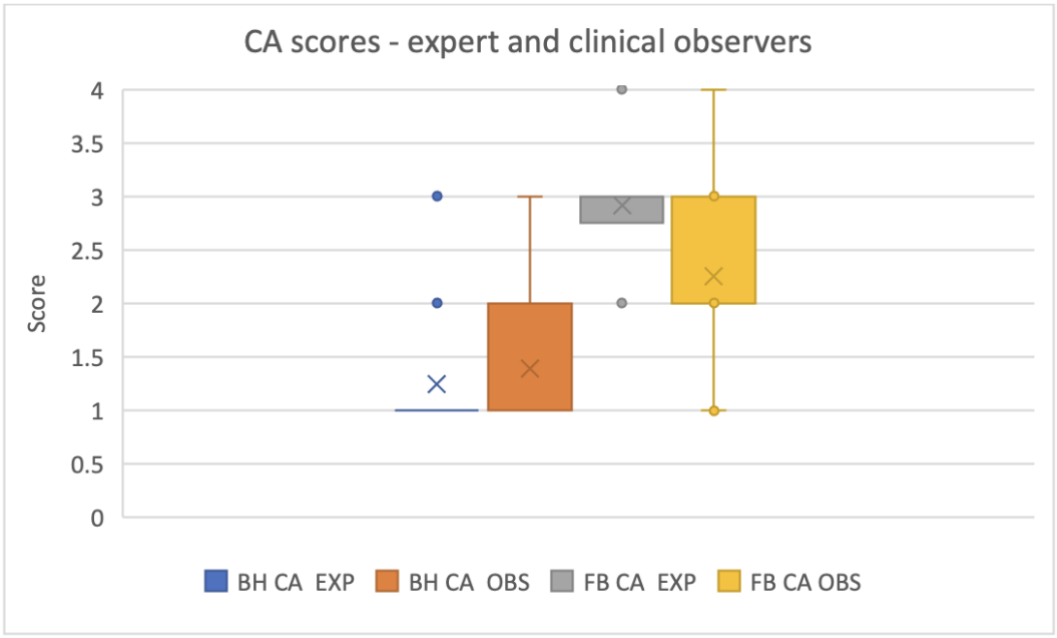


Figure A3.6.13. Boxplot showing mean (cross), median (line), IQR and minimum/maximum (whiskers) for celiac artery scores for expert and clinical observers, for all BH and FB datasets.

Figure A3.6.14. Boxplot showing mean (cross), median (line), IQR and minimum/maximum (whiskers) for superior mesenteric artery scores for expert and clinical observers, for all BH and FB datasets.

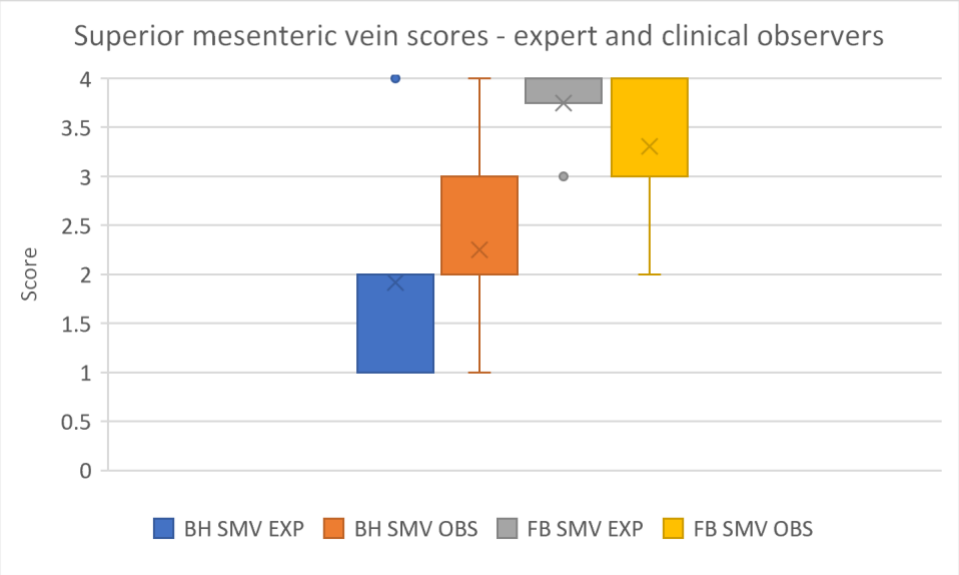


Figure A3.6.15. Boxplot showing mean (cross), median (line), IQR and minimum/maximum (whiskers) for superior mesenteric vein scores for expert and clinical observers, for all BH and FB datasets.

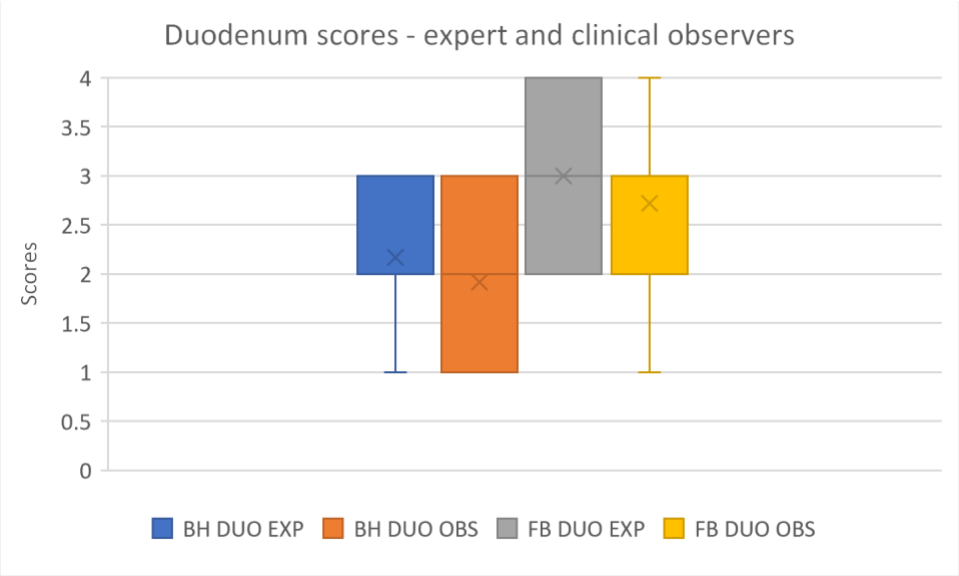


Figure A3.6.16. Boxplot showing mean (cross), median (line), IQR and minimum/maximum (whiskers) for duodenum scores for expert and clinical observers, for all BH and FB datasets.

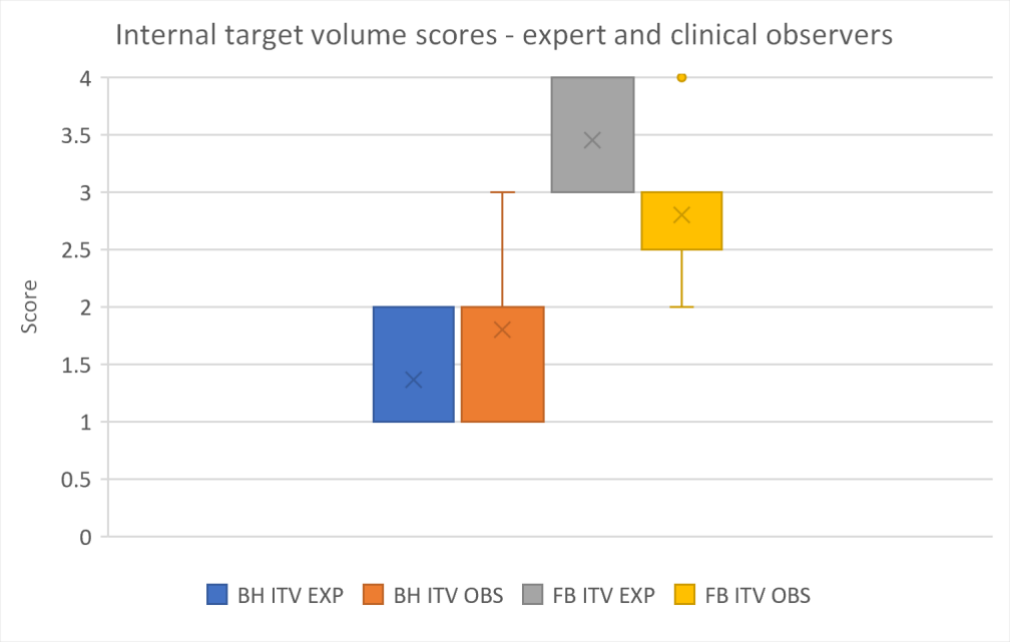


Figure A3.6.17. Boxplot showing mean (cross), median (line), IQR and minimum/maximum (whiskers) for gross tumour volume and internal target volume (GTV/ITV) scores for expert and clinical observers, for all BH and FB datasets.

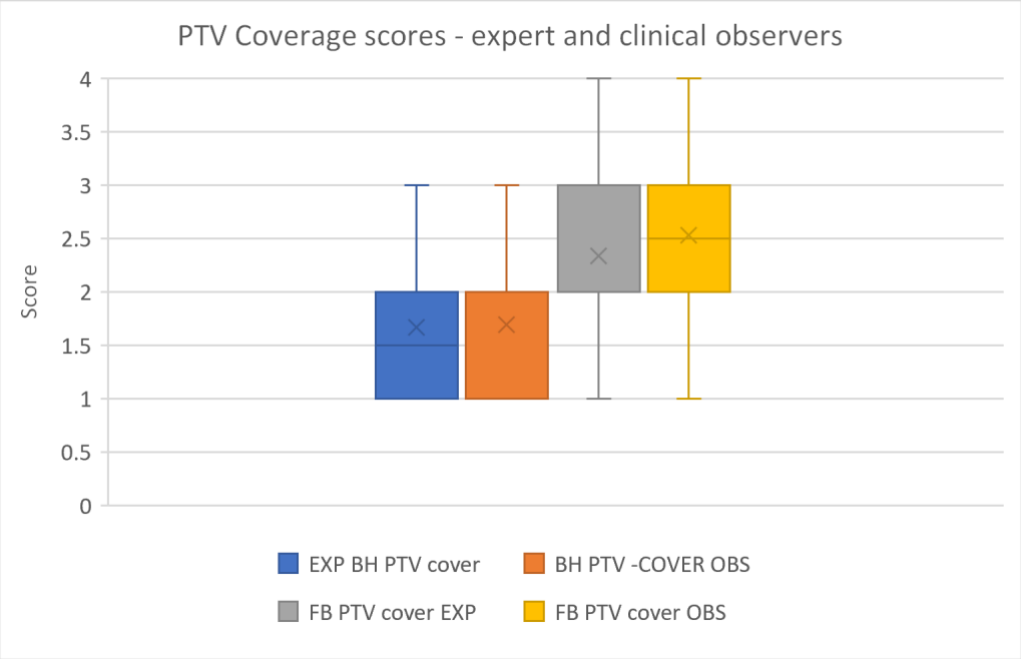


Figure A3.6.18. Boxplot showing mean (cross), median (line), IQR and minimum/maximum (whiskers) for PTV scores for expert and clinical observers, for all BH and FB datasets.

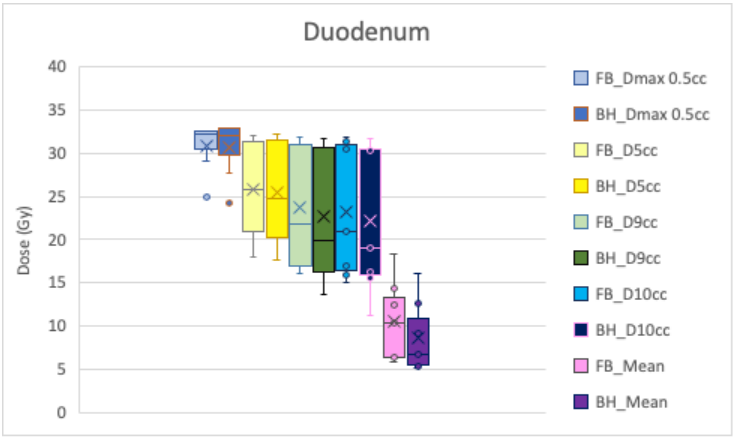


Figure A4.7.6. Box and whisker plots showing achieved duodenum dose (Gy) for each constraint, calculated for EBH and FB plans. Box and whisker plots showing median (line), mean (cross), interquartile range (Q1-Q3), whiskers represent range of values and outliers represented by dots.

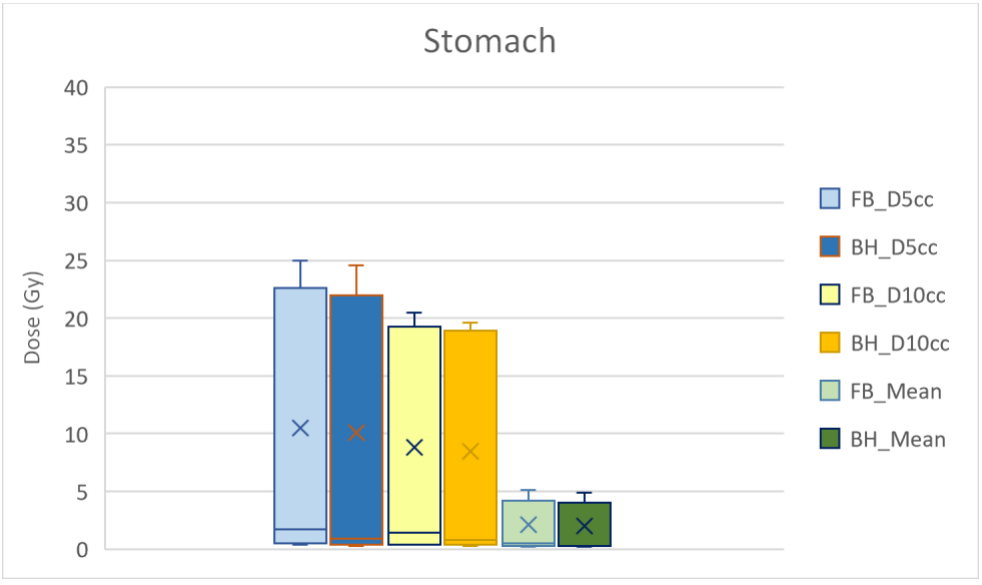


Figure A4.7.7. Box and whisker plots showing achieved stomach dose (Gy) for each constraint, calculated for BH and FB plans. Box and whisker plots showing median (line), mean (cross), interquartile range (Q1-Q3), whiskers represent range of values and outliers represented by dots.

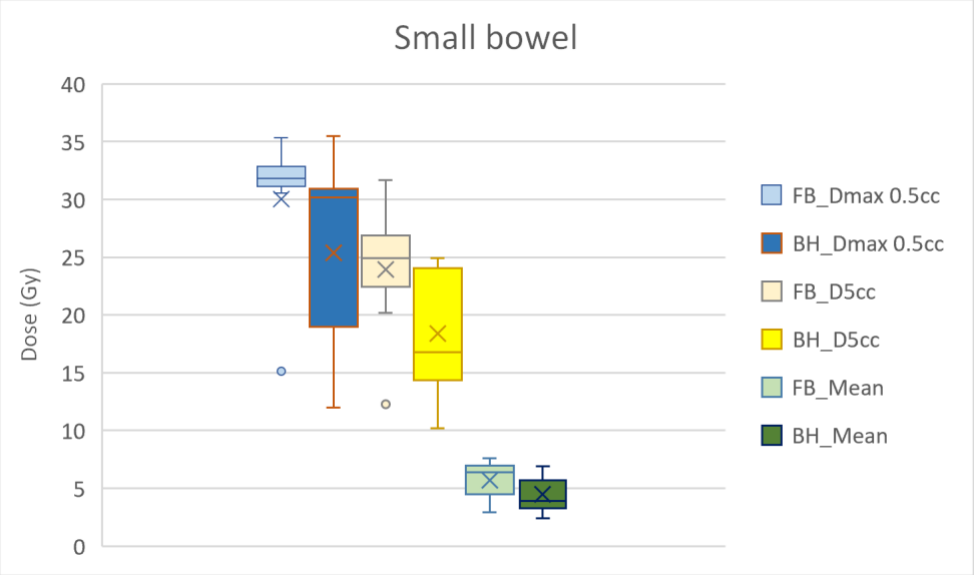


Figure A4.7.8. Box and whisker plots showing achieved small bowel dose (Gy) for each constraint, calculated for EBH and FB plans. Box and whisker plots showing median (line), mean (cross), interquartile range (Q1-Q3), whiskers represent range of values and outliers represented by dots.

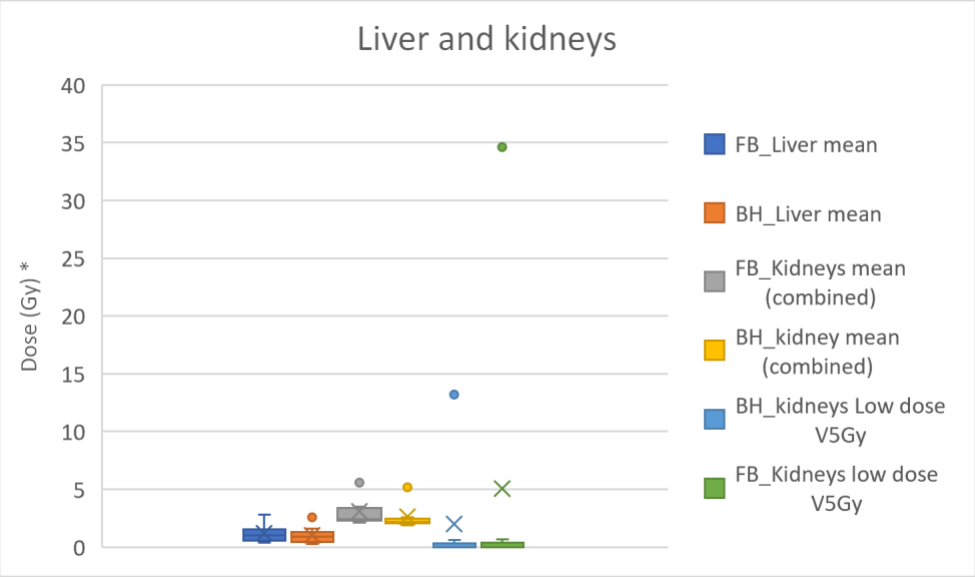


Figure A4.7.9. Box and whisker plots showing achieved for liver and kidneys dose (Gy) for each constraint, calculated for EBH and FB plans. Box and whisker plots showing median (line), mean (cross), interquartile range (Q1-Q3), whiskers represent range of values and outliers represented by dots. * Kidney low dose V5Gy is expressed as percentage volume (%).

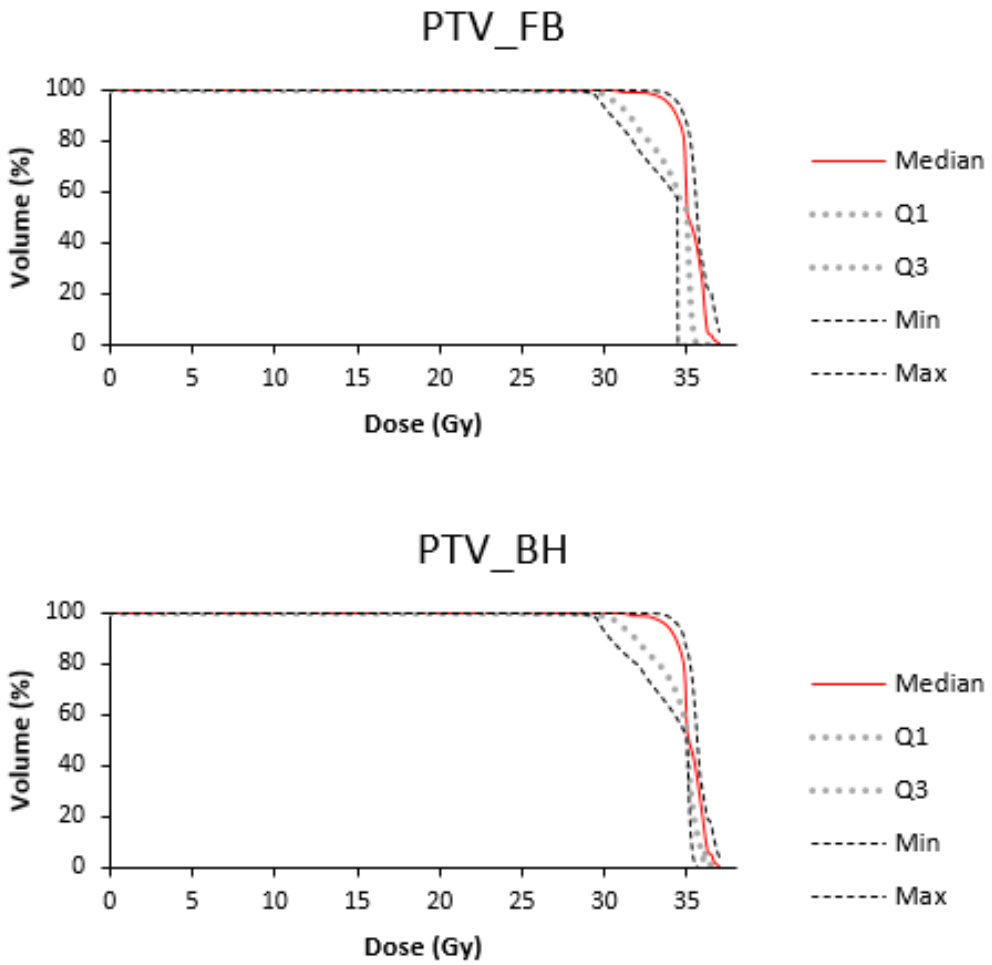


Figure A4.7.10 Cumulative DVH representing all patients, for PTV_FB and PTV_BH, showing median, IQR, minimum and maximum.

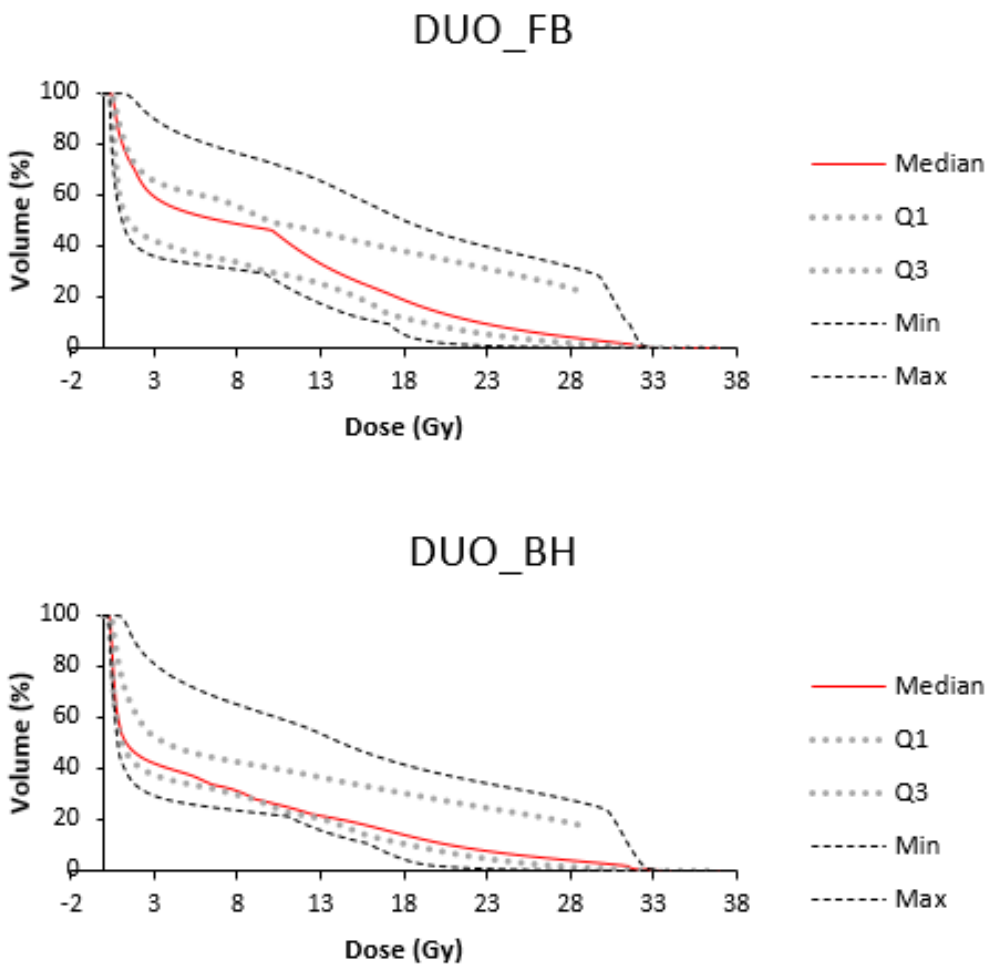


Figure A4.7.11 Cumulative DVH representing all patients, for duodenum_FB and duodenum_BH, showing median, IQR, minimum and maximum.

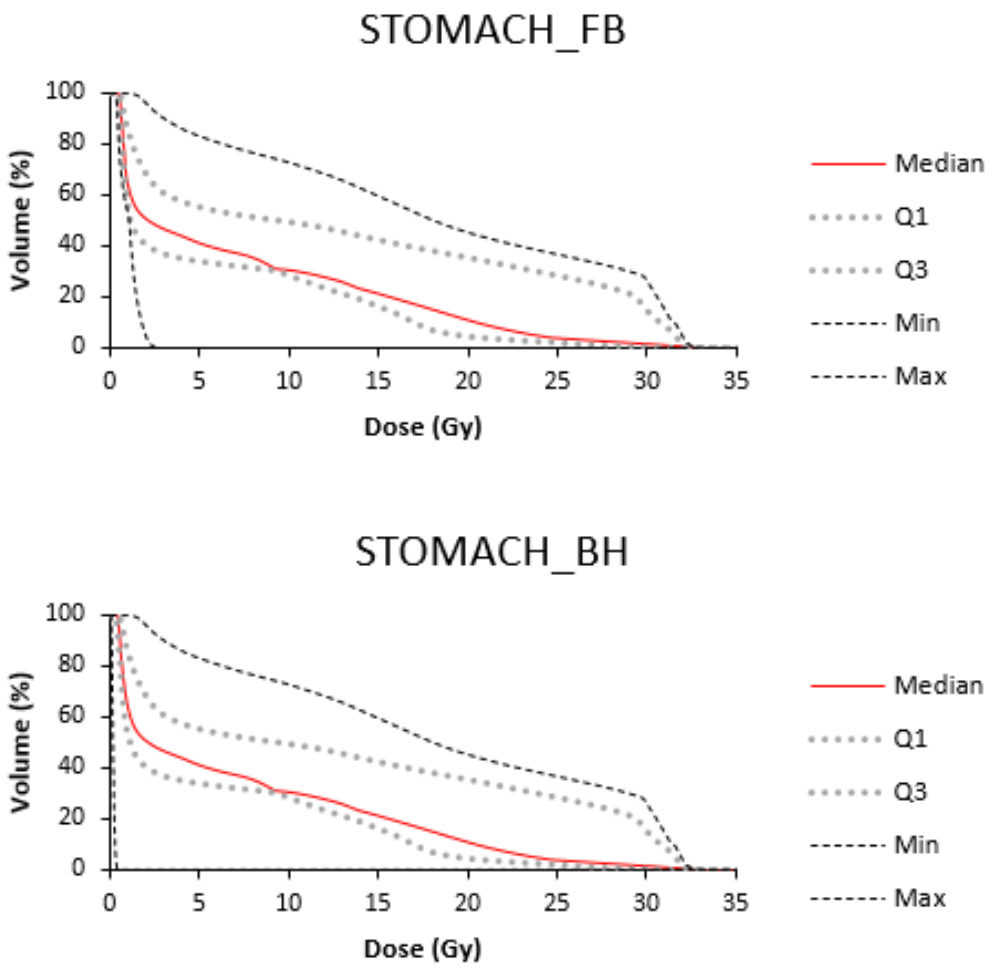


Figure A4.7.12 Cumulative DVH representing all patients, for stomach_FB and stomach_BH, showing median, IQR, minimum and maximum.

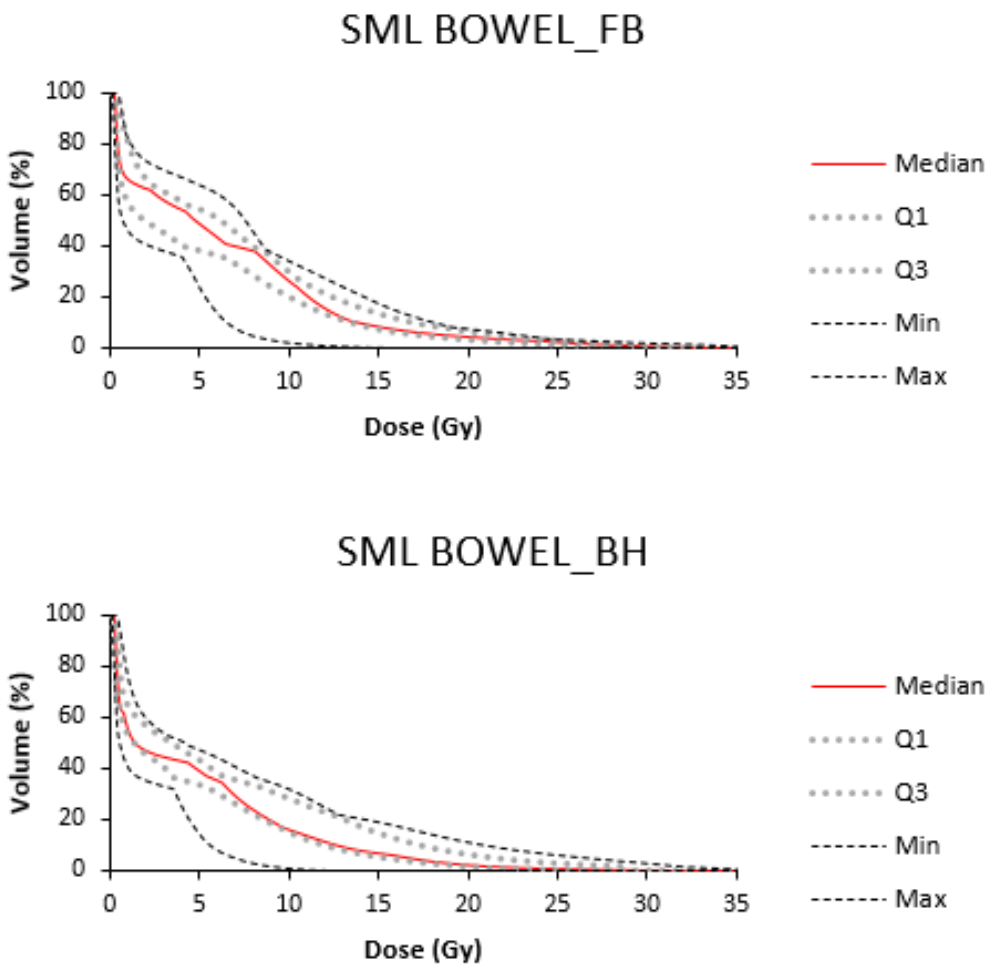


Figure A4.7.13 Cumulative DVH representing all patients, for small bowel_FB and small bowel_BH, showing median, IQR, minimum and maximum.

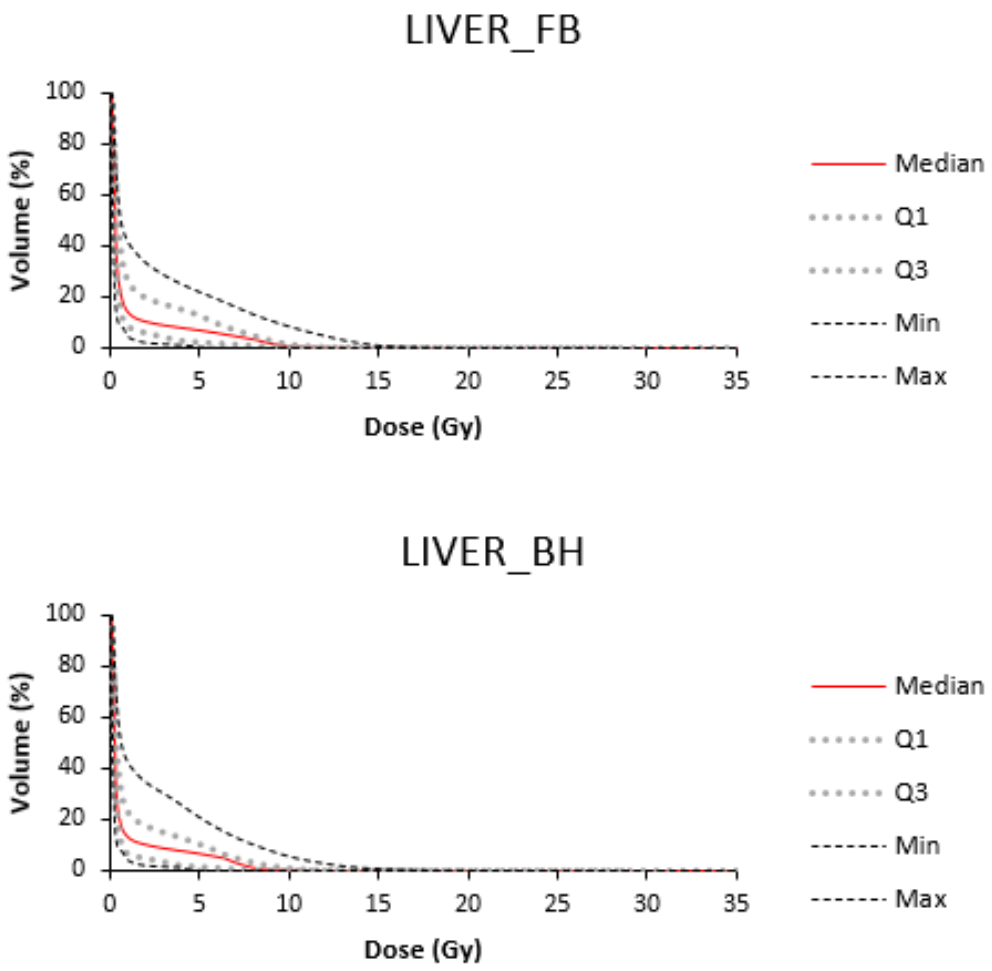


Figure A4.7.14 Cumulative DVH representing all patients, for liver_FB and liver_BH, showing median, IQR, minimum and maximum.

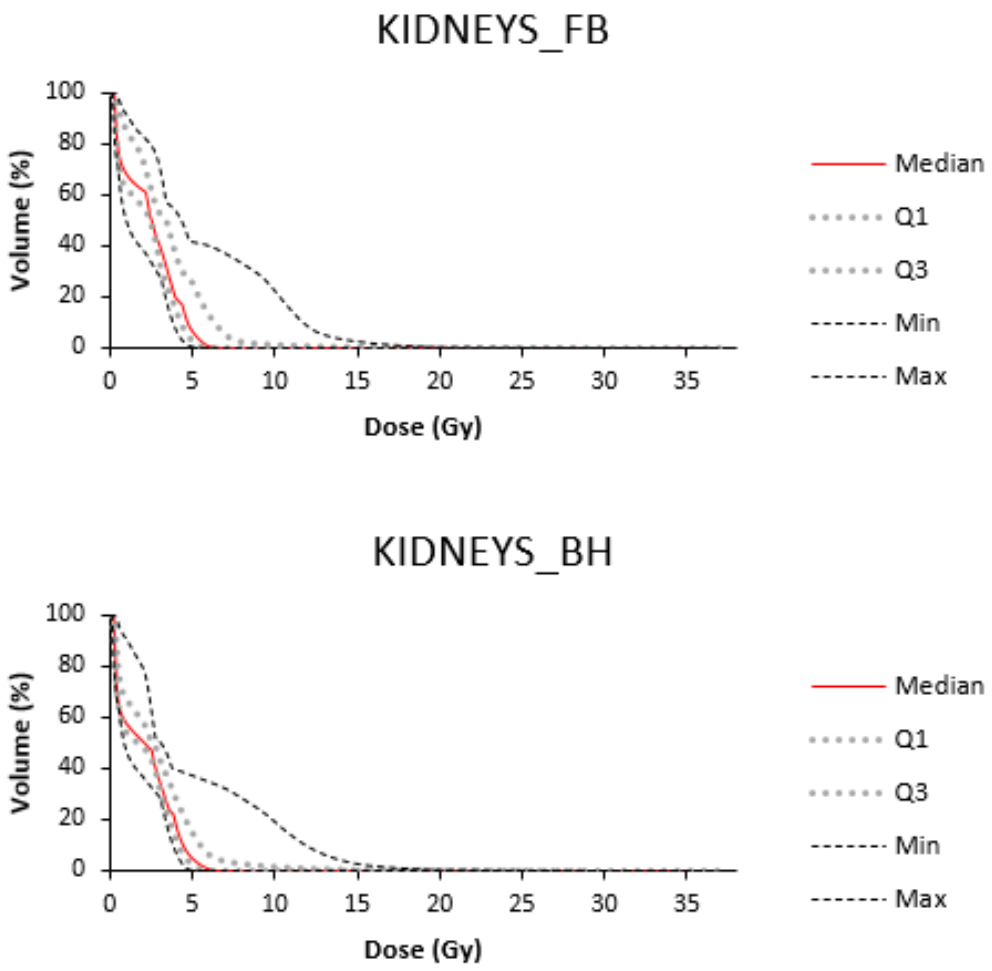


Figure A4.7.15. Cumulative DVH representing all patients, for kidneys using PTV_FB and PTV_BH, showing median, IQR, minimum and maximum.

Invited presentations related to thesis

ESTRO Meets Asia (2019) Education session on SBRT for Pancreatic Cancer. Singapore. (Faculty)

UK SABR Consortium (2019) Motion management workshop. Harrogate.
The Royal College of Radiologists (2020) RT for Pancreatic Cancer. Online. (Faculty)

CRUK RadNet symposium: AHP launch (2020) Optimising RT for Pancreatic Cancer. Online

The Royal College of Radiologists (2022) National Implementation of SABR for non-metastatic Pancreatic Cancer. London (Faculty)

UK SABR Consortium (2022) Motion management workshop. (Chair) Sheffield
Scottish Radiographers Research Forum (2022) Online.

The Royal College of Radiologists (2023) National Implementation of SABR for non-metastatic Pancreatic Cancer. London (Faculty)

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