Developing the Role of Proton Beam Therapy in Oesophageal Cancer

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Summary

Oesophageal cancer continues to be associated with a poor prognosis. Proton beam therapy's distinct physical characteristics widen the therapeutic ratio in oesophageal cancer and has the potential to improve outcomes. This thesis aims to examine how proton beam therapy may improve outcomes in oesophageal cancer and documents efforts to expand its role. In Chapter 2, a comprehensive systematic literature review demonstrates the paucity of high-quality evidence in this field. Following this, a series of radiotherapy planning studies investigates potential dosimetric advantages of proton beam therapy for distal oesophageal cases. In chapter 3, proton beam therapy is shown to reduce lung and heart dose compared to photon radiotherapy. Normal tissue complication probability modelling establishes that this may reduce the risk of treatment related pulmonary and cardiac toxicity. Chapter 4 demonstrates that spleen dose constraints may successfully be introduced in oesophageal cancer for proton and photon plans, potentially resulting in lower lymphopenia rates and greater immune sparing. Chapter 5 highlights the impact of different beam arrangements on dose to organs at risk and individual cardiac substructures. The latter half of the thesis highlights work underpinning the development of novel clinical trials of proton beam therapy in oesophageal cancer. Chapter 6 details the work of creating a radiotherapy delineation protocol by comparing two established protocols in a delineation comparison study, showing that geometric expansion of volumes results in more consistent target volumes compared to 'free-hand' delineation. In chapter 7, public and patient involvement work is shown to inform and refine the design of a two new trials of proton beam therapy in oesophageal cancer. A final chapter discusses and summarises the current areas of interest in this field, expanding on current trial development work and future directions.

Declarations and Statements

This work has not previously been accepted in substance for any degree and is not being concurrently submitted in candidature for any degree.

Signed: [redacted](Owen Jerom Anak Nicholas)

Date: 26th June 2021

This thesis is the result of my own investigations, except where otherwise stated. Where correction services have been used, the extent and nature of the correction is clearly marked in a footnote(s).

Other sources are acknowledged by footnotes giving explicit references. A bibliography is appended.

Signed: [redacted](Owen Jerom Anak Nicholas)

Date: 26th June 2021

I hereby give consent for my thesis, if accepted, to be available for photocopying and for inter-library loan, and for the title and summary to be made available to outside organisations

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Date: 14th February 2022

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Note: Appendices are submitted as a separate volume.

Acknowledgements

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List of Abbreviations

Abbreviation	Definition
3D-CT	Three-Dimensional Computed Tomography (planning scan)
4D-CT	Four-dimensional Computed Tomography (planning scan)
5D-CT	Five-dimensional Computed Tomography (planning scan)
3DCRT	Three-Dimensional Conformal Radiotherapy
5-Fu	5-Flurouracil
AA	Ahmed Abbas, PhD Candidate, Swansea University
AJCC	American Joint Committee on Cancer
ALARA	As Low As Reasonably Achievable
AP	Anterior-Posterior
AS	Agelos Saplaouros, Research Physicist at the Rutherford Cancer Centre, Newport
ASb	Adam Selby, Physicist at South West Wales Cancer Centre, Swansea
AUC	Area Under the Curve
AV	Atrio-Ventricular
BCSH	British Committee for Standards in Haematology
BED	Biological Equivalent Dose
CALGB	Cancer and Leukemia Group B
CBCT	Cone Beam Computed Tomography
CCTG	Canadian Cancer Trials Group
CERR	Computational Environment for Radiotherapy Research
CF	Cisplatin and 5-fluorouracil
CI	Confidence Interval
CM	Centimetre
CP	Carboplatin
CR	Complete Response
CRM	Circumferential Resection Margin
CRT	Chemo-radiotherapy
CRUK	Cancer Research United Kingdom
CSG	Clinical Studies Group (NCRI)
CSS	Cancer Specific Survival
CT	Computed Tomography
CTCAE	Common Terminology of Common Adverse Events
CTE	Commissioning Through Evaluation

CTRAD	Clinical and Translational Radiotherapy Research Working Group
CTV	Clinical Target Volume
DCRT	Definitive Chermo-radiotherapy
DFS	Disease Free Survival
DICOM	Digital Imaging and Communications in Medicine
DMFS	Distant Metastasis Free Survival
DVH	Dose Volume Histogram
EAR	Excess Absolute Risk
EBRT	External Beam Radiotherapy
ECF	Epirubin/Cisplatin/5-Fluorouracil
ECX	Epirubin/Cisplatin/Xeloda(Capecitabine)
EDIC	Effective Dose to Circulating Immune Cells
EM	External Margin
EMR	Endoscopic Mucosal Resection
EORTC	European Organisation for Research and Treatment of Cancer
EQD2	Equivalent Dose in 2 Gray per fraction
ESMO	European Society for Medical Oncology
ESTRO	European Society fir Therapeutic Radiology and Oncology
EU	European Union
EUD	Equivalent Uniform Dose
EUS	Endoscopic Ultrasound
FAQ	Frequently Asked Questions
FDG	Fluoro-deoxyglucose
FFCD	French Federation for Digestive Cancer
FLOT	5-Fluorouracil/Leucovorin(folinic acid)/Oxaliplatin/Docetaxel
FOLFOX	5-Fluorouracil/Leucovorin(folinic acid)/Oxaliplatin
FRCR	Fellow of the Royal College of Radiologists
FU	5-Fluorouracil
GEJ/GOJ	Gastro-oesophageal junction
GHG	Radiotherapy Quality Assurance Global Harmonisation Group
GI	Gastro-Intestinal
GORD	Gastro-oesophageal Reflux Disease
GORTEC	Head and Neck Oncology and Radiotherapy Group (France)
GTV	Gross Tumour Volume

Gy	Gray
HI	Homogeneity Index
HR	Hazard Ratio
HU	Hounsfield Unit
IBA	Ion Beam Applications S.A.
IBM	International Business Machines Corporation
ICORG	All-Ireland Co-operative Oncology Research Group
ICRU	International Commission on Radiation Units and Measurements
IGRT	Image Guided Radiotherapy
IM	Internal Margin
IMI	Innovative Medicines Initiative Fund (EU)
IMPT	Intensity Modulated Proton Therapy
IMRT	Intensity Modulated Radiotherapy
IO	Immunotherapy
IORT	Intra-operative Radiotherapy
IQR	Interquartile Range
ITV	Interval Target Volume
IV	Intravenous
JL	Jamil Lambert, Principal Proton Physicist, Rutherford Cancer Centres
LA	Left Atrium
LAD	Left Anterior Descending Artery
LC	Local Control
LCX	Left Circumflex Artery
LET	Linear Energy Transfer
LKB	Lyman-Kutcher-Burman (NTCP Model)
LL	Left Lateral
LLUMC	Linda Loma University Medical Centre, Linda Loma, USA
LMC	Left Main Coronary Artery
LN	Lymph Node
LPO	Left Posterior Oblique
LRC	Loco-Regional Control
LRCR	Loco-Regional Control Rate
LRRFS	Loco-Regional Relapse Free Rate
LV	Left Ventricle

LX	Location Unknown
MC	Monte-Carlo
MDACC	MD Anderson Cancer Centre
MFO	Multi-Field Optimisation
MLC	Multi-Leaf Collimator
MLD	Mean Lung Dose
MRI	Magnetic Resonance Imaging
MS-CT	Multi-Slice Computed Tomography
MV	Megavoltage
NA	Neoadjuvant
NACRT	Neoadjuvant Chemoradiotherapy
NACT	Neoadjuvant Chemotherapy
NCCE	National Cancer Centre East, Kashiwa, Japan
NCCJ	National Cancer Center Japan, Chiba, Japan
NCI	National Cancer Institute, USA
NCRI	National Cancer Research Institute
NG	Naso-gastric
NHS	National Health Service
NICE	National Institute of Clinical Excellence
NIHR	National Institute of Health Research
NIHR-CED	NIHR Centre for Engagement and Dissemination (previously called Involve)
NOGCA	National Oesophago-Gastric Cancer Audit
NSCLC	Non-small Cell Lung Cancer
NTCP	Normal Tissue Complication Probability
OAR	Organs At Risk
OEC	Oesophageal Cancer
OGD	Oesophago-gastro-duodenoscopy
OR	Odds Ratio
OS	Overall Survival
OT	Occupational Therapy
PA	Posterior Anterior
PBS	Pencil Beam Scanning (also known as spot scanning)
PBT	Proton Beam Therapy
PD-1	Programmed Death 1 Receptor

PDL-1	Programmed Death Ligand 1
PET	Positron Emission Tomography
PFS	Progression Free Survival
PICO	Population/Intervention/Comparison/Outcome
PIS	Patient Information Sheet
PMRC/UoT	Proton Medical Research Centre, University of Tsukuba, Tsukuba, Japan
PO	Posterior Oblique
POC	Post-Operative Complications
PPI	Patient and Public Involvement
PR	Partial Response
PREMs	Patient Reported Experience Measures
PROMs	Patient Reported Outcome Measures
PROTECT	Proton versus Photon Therapy for Esophageal Cancer Clinical Trial
PRV	Planning at Risk Volume
PS	Performance Status
PSPT	Passive Scattering Proton Beam Therapy
PTCOG	Particle Therapy Co-operative Group
PTV	Planning Target Volume
QA	Quality Assurance
QUANTEC	Quantitative Analyses of Normal Tissue Effects in the Clinic
RA	Right Atrium
RBE	Relative Biological Effectiveness
RCA	Right Coronary Artery
RCC	Rutherford Cancer Centre
RCR	Royal College of Radiologists
RCT	Randomised Controlled Trial
RFS	Relapse Free Survival
RL	Right Lateral
ROI	Region of Interest
RPO	Right Posterior Oblique
RR	Response Rate
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group (USA)
RTQA	Radiotherapy Quality Assurance

RTTQA	Radiotherapy Trials Quality Assurance Group (UK)
RV	Right Ventricle
SA	Sino-Atrial
SABR	Stereotactic Ablative Radiotherapy
SBRT	Stereotactic Body Radiotherapy
SCC	Squamous Cell Carcinoma
SCCA	Seattle Cancer Care Alliance
SFO	Single Field Optimisation
SG	Sarah Gwynne, Consultant Clinical Oncologist
SIB	Simultaneous Integrated Boost
SM	Set-up Margin
SOBP	Spread Out Bragg Peak
SPR	Stopping Power Ratio
SWWCC	South West Wales Cancer Centre, Swansea, United Kingdom
TAP	Thorax-Abdomen-Pelvis
TCP	Tumour Control Probability
TD	Tolerance Dose
TMG	Trials Management Group
TNM	Tumour Node Metastatic Staging System
TPS	Treatment Planning System
TTB	Total Toxicity Burden
TV	Target Volume
TVD	Target Volume Delineation
TYA	Teenage and Young Adults
UCLH	University College London Hospitals
UI	Uniformity Index
UICC	Union of International Cancer Control
UK	United Kingdom
UMMC	United Memorial Medical Centre
UP	University of Pennsylvania
USA	United States of America
UZ	Universitair Ziekenhuis Leuven, Belgium
VCC	Velindre Cancer Centre
VMAT	Volumetric Arc Therapy

WBC	White Bloods Count
WCRC	Wales Cancer Research Centre

Chapter 1: Introduction

1.1 Introduction to thesis

Following this introductory chapter, this thesis is divided into two broad parts based on their overarching themes. Taken together, they form a narrative of the work that aims to examine and define a role for proton beam therapy (PBT) in oesophageal cancer (OEC).

Part 1 considers the dosimetric advantages of PBT in OEC that may translate into clinical benefit. It runs from chapter 2 until chapter 5. In chapter 2, there is a comprehensive systematic literature review on the dosimetric and clinical outcomes of PBT in oesophageal cancer. Chapters 3, 4 and 5 considers potential dosimetric advantages and novel planning developments of PBT in OEC through a series of planning studies, focussing on findings that may improve clinical outcomes.

Part 2 considers the work underpinning the development of clinical trials of PBT in OEC. Chapter 6 considers aspects of radiotherapy (RT) protocol development detailing work that aims to refine a target volume delineation (TVD) protocol for oesophageal cancer. Chapter 7 reports patient and public involvement (PPI) work undertaken in the development of two original trials of PBT in OEC.

The thesis closes with a chapter of discussion and future directions.

1.2 List of outputs

The following are the outputs related to work in this thesis. Also included is a summary of my contribution for each output. Publications which are included in the main body of the thesis have a full authorship declaration included in the beginning of the chapter. Full versions of all outputs are included in the appendix (submitted in a separate volume).

Publications (first author):

OJ Nicholas, S Prosser, HR Mortensen, G Radhakrishna, MA Hawkins, SH Gwynne Proton Beam Therapy in Oesophageal Cancer: A Systematic Literature Review of Dosimetric and Clinical Outcomes. Clin Oncol (R Coll Radiol). 2021 Apr 28:S0936-6555(21)00152-7. doi: 10.1016/j.clon.2021.04.003. Epub ahead of print. PMID: 33931290.

Contribution: Study conception, data collection and analysis, manuscript preparation and editing. Full authorship declaration included in Chapter 2.

OJ Nicholas, C Bowden, A Selby, O Bodger, P Lewis, R Webster, G Radhakrishna, G Jones, M Hawkins, S Mukherjee, T Crosby , S Gwynne. Comparative Dosimetric Analysis and Normal Tissue Complication Probability Modelling of Four-Dimensional Computed Tomography Planning Scans Within the UK NeoSCOPE Trial. Clin Oncol (R Coll Radiol). 2020 Dec;32(12):828-834. doi: 10.1016/j.clon.2020.06.022. Epub 2020 Jul 19. PMID: 32698962.

Contribution: Data collection and analysis, manuscript preparation and editing.

OJ Nicholas, O Joseph, A Keane, K Cleary, SH Campbell, SH Gwynne, T Crosby, G Radhakrishna, MA Hawkins. Patient and Public Involvement (PPI) refine the design of ProtOeus: A Proposed Phase II Trial of Proton Beam Therapy (PBT) in Oesophageal Cancer. The Patient - Patient-Centered Outcomes Research. doi : 10.1007/s40271-020-00487-8 (accepted November 2020)

Contribution: Study conception, data collection and analysis, manuscript preparation and editing. Full authorship declaration included in the Chapter 7.

Publications (co-author)

M Lowe, A Gosling, **OJ Nicholas**, T Underwood, E Miles, YC Chang, RA Amos, NG Burnet, CH Clark, I Patel, Y Tsang, N Sisson, S Gulliford. Comparing Proton to Photon Radiotherapy Plans: UK Consensus Guidance for Reporting Under Uncertainty for Clinical Trials. Clin Oncol (R Coll Radiol). 2020 Jul;32(7):459-466. doi: 10.1016/j.clon.2020.03.014.

Contribution: Part of the CTRAD/RTTQA working group. Manuscript preparation and editing of whole manuscript, especially the section on the overview of uncertainty. As a clinician involved in this project, I ensured a clinical perspective throughout the whole manuscript.

M Thomas, HR Mortensen, L Hoffmann, DS Møller, EGC Troost, CT Muijs, M Berbee, R Bütof, **OJ Nicholas,** G Radhakrishna, G Defraene, P Nafteux, M Nordsmark, K Haustermans, Proposal for the delineation of neoadjuvant target volumes in oesophageal cancer, *Radiotherapy and Oncology* (2020), doi: https://doi.org/10.1016/j.radonc.2020.11.032

Contribution: Participation as an international collaborator to helped assess and validate the proposed delineation protocol for the PROTECT Study. I also contributed to manuscript editing.

S Gwynne, S Wright, F Apostolopoulos, **OJ Nicholas**, R Jennings, R Banner, A Poon King, A Selby. Spleen – The Forgotten Organ at Risk? Clin Oncol (R Coll Radiol)– Accepted November 2020. DOI : https://doi.org/10.1016/j.clon.2020.11.011

Contribution: Part of a local splenic dose working group. Involved in data collection and pathway development.

Abstracts/Presentations

Evaluating inter-observer variation in oesophageal target volume delineation: a comparison of two trial delineation protocols. **OJ Nicholas**, G Lewis, B Thomas, E Spezi, M Smyth, SH Gwynne. Presented as a Poster Discussion at ESTRO 2020 Vienna.

Contribution: Study conception, data collection and analysis. Abstract preparation and editing.

Dosimetric comparison of neoadjuvant proton beam therapy vs VMAT in distal oesophageal cancer. **OJ Nicholas**, A Selby, J Lambert, R Hugtenburg, SH Gwynne. Poster at ESTRO 2020 Vienna

Contribution: Study conception, data collection and analysis. Abstract preparation and editing.

A new nodal delineation protocol for upper third oesophageal cancers in the SCOPE 2 trial. **OJ Nicholas**, G Radhakrishna, R Banner, S Mukherjee, M Hawkins, T Crosby, SH Gwynne. Poster at ESTRO 2020 Vienna

Contribution: Data collection and analysis. Abstract preparation and editing.

Optimising Splenic Dose with PBT and VMAT for Distal Oesophageal Cancer. **OJ Nicholas**, A Saplaouras, J Lambert, GW Fegan, R Hugtenburg, SH Gwynne. Abstract accepted ESTRO 2021 Madrid.

Contribution: Study conception, data collection and analysis. Abstract preparation and editing.

1.3 Incidence and epidemiology of oesophageal cancer

OEC is the 13th most common cancer and 7th most common cause of cancer mortality in the United Kingdom (UK) accounting for approximately 9,200 cases and over 7,900 deaths in 2017. Although significant improvements have been made in recent decades, survival rates remain poor with one-year survival rates at around 46.3% and 10-year survival rates of only around 12% [1]. Globally, OEC is the 6th most common cause of cancer mortality, accounting for over 508,000 deaths in 2018 [2].

OEC has a male predilection with an approximately 2:1 ratio of male to female incidence. Incidence is strongly related to age with 4 in 10 cases occurring in patients aged 75 years or older [1].

1.4 Anatomy of the oesophagus

The oesophagus is muscular tube that usually measures 18cm-25cm long. It commences at the upper sphincter below the pharynx, ending in the stomach at the gastro-oesophageal junction (GOJ) where there is a lower sphincter that prevents reflux of stomach contents. The oesophageal wall consists of 4 layers: mucosa, submucosa, muscularis propria, and adventitia. Unlike other parts of the GI tract, the oesophagus does not have a distinct serosa which allows oesophageal tumours to spread beyond the wall, invading local tissue.

Over most of its length, the oesophagus is lined by squamous epithelium. In the lower third of the oesophagus/GOJ, the oesophagus is lined by a columnar epithelium from which adenocarcinomas arise [3].

1.5 Histology

Squamous cell carcinomas (SCC) or adenocarcinomas (AC) account for over 90% of oesophageal tumours. Historically, SCCs accounted for most cancers, however, in recent decades, the incidence of ACs has increased dramatically in Western populations and is now the most common histology in the UK [4]. In many parts of the world such as Northern Iran and North Eastern China, SCC remains the predominant histology [5, 6]. ACs typically occur the lower third/GOJ of the oesophagus whereas SCCs may occur anywhere in the oesophagus.

1.6 Aetiology

OECs occur as a result of chronic inflammation and inflammatory reactions that lead to increased cell turnover. Major risk factors for AC include gastro-oesophageal reflux disease (GORD) leading to Barrett's oesophagus with intestinal metaplasia, obesity and smoking. For SCCs, smoking, alcohol intake and dietary factors are common risk factors.

1.7 Staging

1.7.1 AJCC/UICC TNM 8th edition

The latest edition of the 8th edition TNM staging manual for OEC was published in 2017. Staging criteria that were previously defined as tumour classifications are now defined as categories and subcategories. In this edition, OECs are clearly categorised according to their histological subtype, reflecting the increased understanding of variation in clinical course and management strategies. The 8th edition defines cancer location according to the epicentre of the tumour (the central point between the top and bottom of the tumours as measured by endoscopy) rather than the upper border of the tumour. In addition to pre-treatment clinical staging (cTNM), this latest version of the staging manual also includes pathological TNM staging (pTNM) and post-neoadjuvant TNM staging (ypTNM). Table 1 provides an overview of categories/subcategories and corresponding criteria. Table 2 describes cTNM stage groupings. Figure 1 provides a description of T categories.

Category	**Criteria**
T category	
TX	Tumour cannot be assessed
T0	No evidence of primary tumour
Tis	High-grade dysplasia, defined as malignant cells confined by the basement membrane
T1	Tumour invades the lamina propria, muscularis mucosae, or submucosa
T1a[a]	Tumour invades the lamina propria or muscularis mucosae
T1b[a]	Tumour invades the submucosa
T2	Tumour invades the muscularis propria
T3	Tumour invades the adventitia
T4	Tumour invades adjacent structures
T4a[a]	Tumour invades the pleura, pericardium, azygos vein, diaphragm, or peritoneum
T4b[a]	Tumour invades other adjacent structures, such as the aorta, vertebral body, or trachea
N category	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1–2 regional lymph nodes
N2	Metastasis in 3–6 regional lymph nodes
N3	Metastasis in ≥7 regional lymph nodes
M category	
M0	No distant metastasis
M1	Distant metastasis
Adenocarcinoma G category	
GX	Differentiation cannot be assessed
G1	Well differentiated, with >95% of the tumour composed of well-formed glands
G2	Moderately differentiated, with 50%–95% of the tumour showing gland formation

G3[b]	Poorly differentiated, with tumours composed of nest and sheets of cells with <50% of the tumour demonstrating glandular formation
Squamous cell carcinoma G category	
GX	Differentiation cannot be assessed
G1	Well-differentiated, with prominent keratinization with pearl formation and a minor component of nonkeratinizing basal-like cells, tumour cells arranged in sheets, and mitotic counts low
G2	Moderately differentiated, with variable histologic features ranging from parakeratotic to poorly keratinizing lesions and pearl formation generally absent
G3[c]	Poorly differentiated, consisting predominantly of basal-like cells forming large and small nests with frequent central necrosis and with the nests consisting of sheets or pavement-like arrangements of tumour cells that are occasionally punctuated by small numbers of parakeratotic or keratinizing cells
Squamous cell carcinoma L category[d]	
LX	Location unknown
Upper	Cervical oesophagus to lower border of the azygos vein
Middle	Lower border of the azygos vein to lower border of the inferior pulmonary vein
Lower	Lower border of the inferior pulmonary vein to the stomach, including the oesophagogastric junction

[a]*Subcategories.*
[b]*If further testing of "undifferentiated" cancers reveals a glandular component, categorize as adenocarcinoma G3.*
[c]*If further testing of "undifferentiated" cancers reveals a squamous cell component or if after further testing they remain undifferentiated, categorize as squamous cell carcinoma G3.*
[d]*Location is defined by epicentre of oesophageal tumor.*

Table 1: Cancer staging categories for cancer of the oesophagus and oesophagogastric junction (Adapted from AJCC/UICC TNM 8th Edition, Rice et al.) [7].

Squamous cell carcinoma (SCC)			
cStage group	cT	cN	cM
0	Tis	N0	M0
I	T1	N0–1	M0
II	T2	N0–1	M0
	T3	N0	M0
III	T3	N1	M0
	T1–3	N2	M0
IVA	T4	N0–2	M0
	T1–4	N3	M0
IVB	T1–4	N0–3	M1

Adenocarcinoma (AC)			
cStage group	cT	cN	cM
0	Tis	N0	M0
I	T1	N0	M0
IIA	T1	N1	M0
IIB	T2	N0	M0
III	T2	N1	M0
	T3–4a	N0–1	M0
IVA	T1–4a	N2	M0
	T4b	N0–2	M0
	T1–4	N3	M0
IVB	T1–4	N0–3	M1

Table 2 Clinical (cTNM) stage Groups (Adapted from AJCC/UICC TNM 8th Edition, Rice et al.) [7].

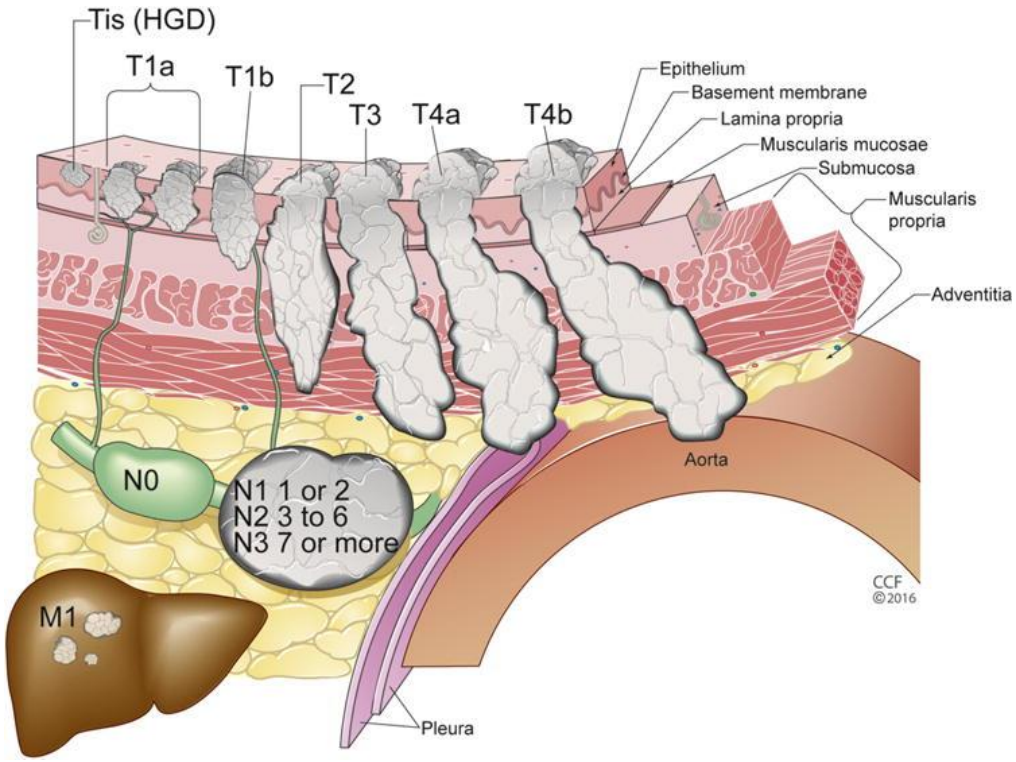

Figure 1: TNM (8th Edition) categories for OEC (Rice et al.) [8].

1.7.2 Classification by location

While this edition only mandates that SCCs are staged according to tumour location, it is still useful to classify all oesophageal tumours according to location; cervical, upper, middle and lower; in order to determine the appropriate management course and to aid radiotherapy planning. Location is typically determined during oesophageal-gastro duodenoscopy (OGD) and endoscopic ultrasound (EUS) where the upper and lower boundaries are measured in relation to the distance from incisors. Location of the tumour as measured on OGD and EUS is particularly useful in aiding the delineation of the tumour for radiotherapy planning. Cervical oesophageal tumours are defined as tumours from the upper oesophageal sphincter to the sternal notch (typically 15 cm-20 cm from incisors). Upper tumours are located from the level of the sternal notch to the azygous vein (typically 20 cm-25 cm from incisors). Middle tumours are located from the level of the lower border azygos vein to the inferior pulmonary vein (typically 25 cm-30 cm from incisors). Lower oesophageal tumours are located from the lower border of the pulmonary vein to the stomach, encompassing the GOJ (typically 30-42 cm from incisors). In TNM 8th Edition, tumours that traverse the GOJ and whose epicentre are located no more than 2 cm into the gastric cardia (Sievert Type I/II) are staged as OECs, while tumours extending further (Sievert Type III) are considered stomach cancers [7].

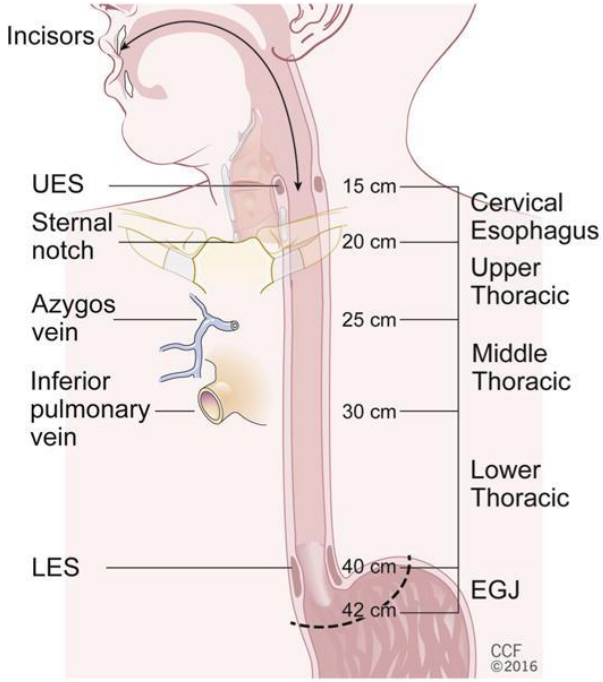

Figure 2 Classification of oesophageal cancers according to location (Rice et al.[8])

1.7.3 Investigations

In order to comprehensively stage OEC, multiple modalities of investigations are required. The initial investigation that establishes diagnosis is usually an OGD, which may assess the length of disease (assuming scope is passable) and obtain a tissue biopsy. Pathological examination of the biopsy specimen is required to confirm the diagnosis. Further staging includes a full clinical examination and a computed tomography of the chest, abdomen and pelvis (CT TAP) to ascertain for any metastatic spread. In patients who may be suitable for curative treatment, further imaging with an 18F-fluorodeoxyglucose-positron emission tomography (FDG-PET) is helpful in identifying previously undetected distant metastases, having superior accuracy and sensitivity compared CT alone [9]. Additionally, an EUS is usually undertaken, as this remains the gold standard for assessing T/N stage and submucosal spread of locally advanced tumours [10].

1.8 Management of Oesophageal Cancer

1.8.1 Overview

The management of OEC is determined by histological subtype and cTNM staging, patient fitness/performance status and comorbidities. Figure 3 provides an overview of management strategies for the treatment of non-metastatic oesophageal cancer as per ESMO consensus guidelines (published 2016) [11].

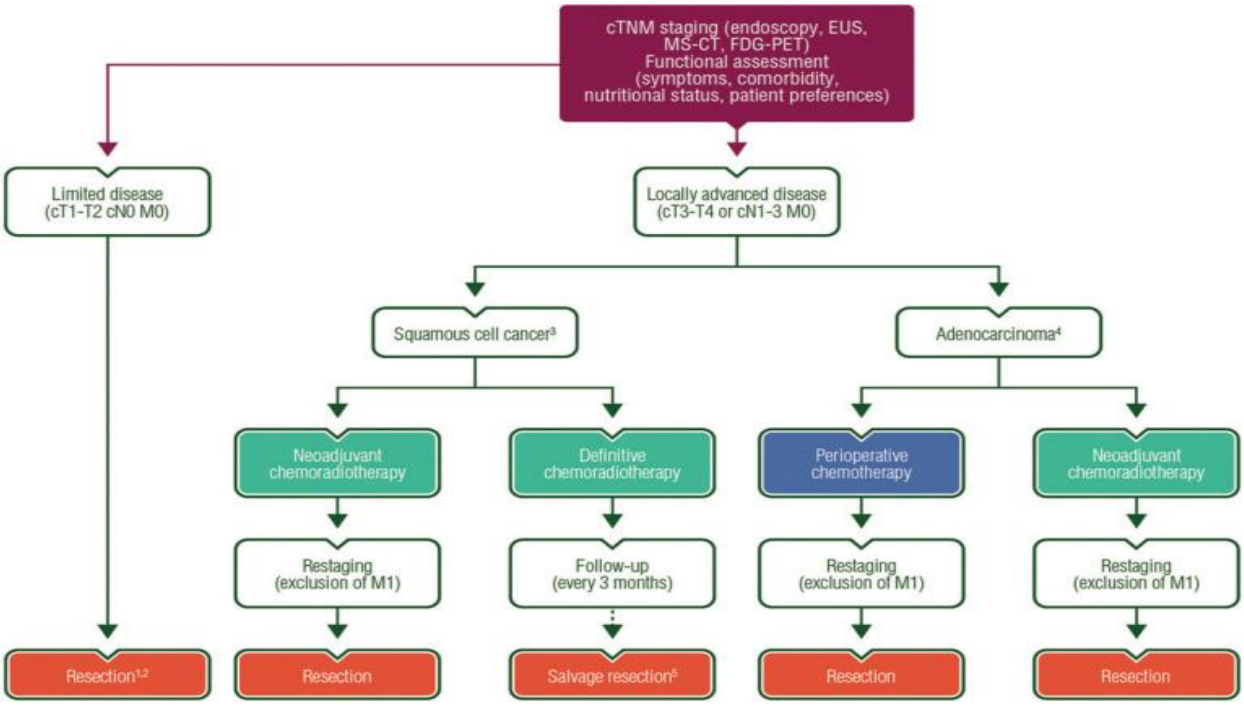

Figure 3: ESMO Treatment algorithm for the treatment of local/locoregional resectable thoracic oesophageal cancer. EUS, endoscopic ultrasound; FDG-PET, fluorodeoxyglucose-positron emission tomography; MS-CT, multislice-computed tomography; cTNM, clinical tumour, node, metastases classification according to AJCC/UICC (Adapted from 'Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up')[11].

1.8.2 Early stage disease (cT1-T2, cN0, cM0)

For patients with Stage I/II disease of either histological subtype, surgical resection is the management option of choice. For very early tumours (Tis-T1aN0M0) endoscopic resection by endomucosal resection (EMR) or endoscopic submucosal dissection is effective and well-tolerated [12]. For other early stage tumours (>T1a-T2), radical and transthoracic oesophagectomy (Ivor-Lewis procedure) is the surgical technique of choice. The benefit of neoadjuvant (NA) treatment in this group of patients is uncertain as numbers included in studies are limited but appears to not influence survival outcomes [13, 14].

1.8.3 Locally advanced disease (cT3-T4, cN1-N3, cM0)

Disease greater than T2 or node positive disease (any T stage) are considered locally advanced and warrant a different treatment approach to patients with early stage disease. In patients with good performance status and limited comorbidities, NA or peri-operative treatment strategies are advocated prior to surgical resection. In patients with SCC, definitive chemoradiotherapy (dCRT) may be considered an equivalent alternative to surgery [15, 16]. In patients with AC who are unfit or refuse surgical resection, dCRT may be considered an acceptable alternative treatment strategy, although this is considered marginally inferior to surgical resection based on retrospective data [17, 18].

Notably, no head to head randomised controlled trials (RCTs) comparing surgery to dCRT in AC have been successfully carried out.

1.8.4 Neoadjuvant/perioperative chemotherapy (NACT)

Several RCTs and meta-analyses have shown the benefit of neoadjuvant chemotherapy (NACT) and perioperative chemotherapy compared to surgery alone [13, 19-21] establishing it as a standard of care. The OEO2 study showed that 2 cycles of NA cisplatin and infused 5-flurouracil improved 5-year overall survival (OS) vs surgery alone (23% vs 17.1%) [19]. The MAGIC trial reported that 6 cycles (3 pre-operative, 3 post-operative) of a 3-drug regiment [epirubicin, cisplatin, and infused 5-fluorouracil (ECF)] improved 5 year OS by 13% (36% vs 23%) [20]. More recently, the FlOT4 trial showed that 8 cycles (4 pre-operative, 4 post-operative) of a 4-drug FlOT regiment (5-fluorouracil, leucovorin, oxaliplatin, docetaxel) improved median OS (50 months vs 36 months) compared to the 3-drug regiment used in MAGIC making it a new standard of care [21]. It is important to note that all three trials recruited predominantly lower third/GOJ ACs, with the MAGIC and FlOT4 trials also including a significant proportion of patients with stomach cancer.

As both the OEO2 and MAGIC trials were UK-based studies, clinicians in the UK have traditionally favoured using NACT as opposed to neoadjuvant chemoradiotherapy (NACRT) strategies, particularly for patients with AC. Recent survey data suggests that UK oncologists perceive NACT to be less toxic, causing less post-operative morbidity and mortality, compared to NACRT [22].

1.8.5 Neoadjuvant chemoradiotherapy (NACRT)

NACRT prior to surgical resection has become an international standard of care following the publication of several phase III RCTs and meta-analyses that showed superior survival outcomes to surgery alone [13, 23-25]. Of these, arguably the most influential is the CROSS trial, a randomised phase III Dutch study that compared NACRT to surgery alone. This study delivered a dose of 41.4Gy/23# over 4.5 weeks with weekly carboplatin/paclitaxel and recruited patients with both AC and SCC. This trial reported a doubling of the median OS of 48.6 months vs 24 months for NACRT followed by surgery vs surgery alone respectively. In the subgroup analyses of SCCs only, the improvement was even more marked with a median OS of 81.6 months vs 21.6 months for NACRT group and surgery alone group respectively. Clear resection margin (R0) rates were also significantly improved with NACRT (92% vs 69%) [23].

Radiotherapy dose levels used vary in different regions internationally, with North America commonly favouring a dose of 50.4Gy/28# as used in the CALBG 9781 and INT 0123 trials [24, 26]. In mainland Europe, the lower dose CROSS-type fractionation schedule of 41.4Gy/23# is more commonly used. In the UK there a preference for using NACT rather than NACRT, but where used, a dose fractionation of

45Gy/25# is often used. This is largely due to the influence of the UK NeoSCOPE trial; a phase II NACRT trial that compared two different chemotherapy schedules, and is widely credited with re-introducing NACRT to UK practice [27, 28].

1.8.6 Surgery

The most common surgical approach for lower and GOJ oesophageal tumours is a radical transthoracic oesophagectomy (Ivor-Lewis method). This procedure combines a laparotomy, a right thoracotomy and an intrathoracic oesophagogastric anastomosis formation. The procedure includes thoracic and abdominal lymphadenectomies and may be performed as an open or minimally invasive procedure (hybrid or total minimally invasive). Other surgical approaches include a transhiatal oesophagectomy although this may lead to inferior oncological outcomes particularly in node positive patients [29, 30].

Despite advances in peri-operative care and the use of minimally invasive techniques, oesophagectomy remains associated with very significant rates of morbidity, particularly affecting the lung and heart, and mortality. A recent prospective international database of 2704 oesophagectomy patients from 24 high-volume centres reported an overall incidence of complications of 59% with the most common being pneumonia (14.6%) and atrial dysrhythmia (14.5%). 90-day mortality was 4.5%. Most received NA treatment with 46.1% receiving NACRT and 29.5% having NACT alone [29]. A study by Reichert et al. showed that oesophagectomy (Ivor-Lewis) affected respiratory function post-operatively to a greater extent than major lung resection with up to 50% of oesophagectomy patients developing pneumonia post-operatively in their series, highlighting the pulmonary toxicity caused by oesophagectomies [31].

1.8.6.1 Circumferential resection margin (CRM)

Complete surgical removal of the tumour is the primary goal of surgery. Complete macroscopic and microscopic resection (R0 resection) of the tumour is a strong independent prognosticator of outcomes in oesophageal cancer. Improved R0 rates correlate with an improvement in 5 year survival. [32] An ‘involved’ margin is defined as the presence of cancer cells <1mm of resection specimen [33].

1.8.7 Toxicity of neoadjuvant treatment: comparing NACRT to NACT

There is an inevitable trade-off between improved cancer specific survival and increased toxicity, particularly in the immediate post-operative period, when NA treatments are used. Common toxicities include chemotherapy related side-effects such as myelosuppression, nausea, vomiting, diarrhoea, fatigue and mucositis. RT related toxicities include fatigue and oesophagitis. In the post-operative period, an increased intensity of NA treatment results in increased rates of complications including pulmonary, cardiac and post-operative mortality. A recent network meta-analysis of 31 trials that included over 5000 patients, showed that NACRT improved overall survival (OS) when compared to all

other treatments including surgery alone (HR 0.75, 95% CR 0.67-0.85) and NACT (HR 0.83. 95% CR 0.70-0.96). However, the risk of postoperative mortality increased when comparing NACRT to either surgery alone (RR 1.46, 95% CR 1.00-2.14) or to NACT (RR 1.58, 95% CR 1.00-2.49) [25]. The cause of higher rates of post-operative morbidity and mortality with NACRT is not clearly defined but has been attributed, in part, to the irradiation of the lungs and heart in the pre-operative period. Retrospective data have independently shown that both mean lung dose and lung V5 (%, volume of lung receiving 5Gy or more) during NACRT is strongly correlated with increased rates of post-oesophagectomy pulmonary complications [34, 35]. Notably, both are low-dose dosimetric endpoints that are often associated with the low-dose 'bath' that seen with modern conformal photon therapy techniques such as intensity modulated RT (IMRT) and volumetric arc therapy (VMAT). Although a direct link between post-operative cardiac toxicity and pre-operative cardiac irradiation is less clear, emerging evidence in multiple tumours sites adds weight to this hypothesis. For example, Speirs et al. showed that heart dose during radiotherapy is a predictor of OS in non-small cell lung cancer irrespective of cancer related outcomes [36]. A recent single-institution analysis of cardiac surgery outcomes showed that prior mediastinal radiation, even at low doses, resulted in higher rates of post-operative mortality [37]. The seminal work by Darby et al. shows the link between cardiac radiation dose and an increased risk of cardiovascular disease in patients with breast cancer, with a mean heart dose increase of 1Gy correlating with a 7% increase in the rate of cardiovascular disease [38]. It is important to note that all data supporting the link between pre-operative radiation dose to organs at risk (OARs) and post-operative toxicity is retrospective.

Table 3 summarises the rates of R0, pathological complete response (pCR) and rates of severe cardiac/pulmonary toxicities, any severe toxicities and post-operative mortality rates for selected reported clinical trials of NA treatments in OEC.

	Trial	Treatment	R0 rate (%)	pCR (%)	G3/4 Pulmon-ary (%)	G3/4 Cardiac (%)	Any G3/4 toxicity (%)	90-day surgical mortality (%)
Neoadjuvant/Perioperative Chemo (NACT) Trials	OEO2 [21]	CF x 2	60	4	16	4	41	7*
		Surgery alone	54	2	15	4	42	7*
	MAGIC [20]	ECF x 6	-	8.5	-	-	45.7	5.6 (30d)
		Surgery alone	-	8.3 (ypT1)	-	-	45.3	5.9(30d)
	FlOT4 (AC only) [21]	FlOT x 8	85	-	-	-	50	5
		ECF/ECX x 6	78	-	-	-	51	8
	Oe05 [39]	ECF x 4	66	11	33	12	62	6 (30d)
		CF x 2	60	3	27	11	56	5 (30d)
Neoadjuvant Chemoradiotherapy Trials (NACRT)	NeoSCOPE (AC only) [40]	Ox/Cap induction + CRT 45 Gy/25# (Carbo/Taxol)	80.5	29.3	36.6	9.8	54.3	2.8 (30d)
		Ox/Cap induction + CRT 45 Gy/25# (Ox/Cap)	72.2	13.9	40.0	25.7	51.2	2.4 (30d)
	CROSS [23]	CRT 41.4 Gy/23# (Carbo/Taxol)	92	29	46	21	-	6.9
		Surgery only	69	-	44	17	-	5.9
	Walsh et al. (AC only) [41]	CRT 40 Gy/15# (Cis/5-FU)	n/a	25	48	24.1	-	3
		Surgery alone	n/a	-	58.1	23.6	-	2
	Burmeis-ter et al. [42]	CRT 35 Gy/15# (Cis/5-FU)	80	16	20	12	-	4.8
		Surgery alone	59	-	28	14	-	5.5
	NeoRES [43]	Cis/5-FU x 3 + CRT 40 Gy/20#	87	28	22	9	55	8
		Cis/5-FU x 3	74	9	13	5	45	3

*Table 3 Summary of Pathological results and Post-Operative Toxicities in selected trials of Neoadjuvant Treatments. *deaths attributable to surgery, timeframe not specified. R0 = clear resection margin; pCR = pathological complete response; Cis/5-FU = cisplatin and 5-fluorouracil; OxCap = oxaliplatin and capecitabine; carbo/taxol = carboplatin and paclitaxel; ECF/X = epirubicin, cisplatin, 5-fluorouracil/capecitabine; FlOT = 5-flurouracil, leucovorin, oxaliplatin and docetaxel; CRT = chemoradiotherapy; # = fractions; AC = adenocarcinoma*

1.8.8 Summary of neoadjuvant treatments

There remains significant debate over the optimal NA approach for OEC, including the optimal approaches for AC and SCC. There are significant variations between regions with the UK favouring the use of NACT whilst many other parts of the Europe and North America favour the use of NACRT [28, 29]. There are several trials and meta-analyses that have attempted to directly compare NACRT to NACT with inconclusive results. There appears to be at least a trend to increased R0 resection and improved OS with NACRT at the expense of increased toxicity [25, 43-45]. Studies directly comparing NACRT to NACT in OEC are currently underway; the international TOPGEAR study (GOJ OEC only, completed accrual, survival data not reported) [46] and the NeoAEGIS study (NCT01726452)(currently accruing) [47] aim to further elucidate this debate.

1.8.9 Definitive chemoradiotherapy (dCRT)

DCRT is a comparable, and in many cases, preferable treatment option to surgical resection for the patients with SCC. The RTOG 85-01, which recruited predominantly SCC patients, defined the dose level of 50 Gy/25# and established the survival benefit adding concurrent cisplatin/5-FU (median OS 12.5 months vs 8.9 months) to radiotherapy [48]. RCTs by Stahl (2005) and Bedenne et al. (2007), further established that the role of dCRT in SCC in the era of modern radiotherapy [49, 50]. A Cochrane review published in 2017 that included predominantly patients with SCC showed that the addition of surgery to chemoradiotherapy for patients improved local control but not OS at the expense of increased toxicities. Radiotherapy doses used ranged from 40 Gy-65 Gy [51].

For patients with AC, dCRT is used as an alternative treatment in patients who are unfit or unwilling to undergo surgery. There remains a paucity of randomised data comparing surgery and dCRT in this group of patients. The UK SCOPE 1 trial, a trial of dCRT with or without the addition of Cetuximab for patients who were deemed unsuitable for surgery, included 26% of AC patients. Many were not suitable for surgery due to the extent of disease (e.g. T4b) or comorbidities. Although the addition of Cetuximab resulted in a worse OS, the control arm of dCRT alone reported an impressive median OS of 25.8 months for AC patients with a 3-year survival rate of 43.8%. In the UK, many departments have adopted the radiotherapy protocol as described in the control arm of the SCOPE 1 trial of induction cisplatin/capecitabine followed by CRT with 50 Gy/25# as a standard approach for dCRT [27].

1.8.9.1 Dose escalation in oesophageal cancer

Local control rates from dCRT remain inferior to surgical resection. Dose escalation to the tumour theoretically improves the tumour control probability (TCP) and has been extensively investigated as a potential solution. However, evidence supporting its routine use remains elusive. The phase III INT 0123 trial, which reported in 2002, compared a higher dose of 64.8 Gy vs a standard dose of 50.4 Gy.

The trial was ended early due to futility, with long term outcomes reporting no difference in local control rates or OS with the higher dose. There were an increased number of deaths in the higher dose arm although most occurred before a dose of 50.4 Gy was delivered. As this was an older trial, commentators have suggested that the use of older RT techniques such as 3D-CRT may be partly be to blame for the trial's negative result [26]. However, the newer the ART-DECO study, which utilised modern radiotherapy techniques (VMAT/IMRT), compared a higher dose of 61.6 Gy/28# [delivered via a simultaneous integrated boost (SIB)] to a standard dose of 50.4 Gy/28#, reported (in abstract format) that local control rates and OS were not improved with the higher dose. There was a non-significant trend to improved locoregional control at the expense of increased toxicities. Full results are awaited [52]. In the UK, the currently recruiting phase II/III SCOPE 2 study (NCT02741856) is a four-arm study that compares Carboplatin/Paclitaxel vs Cisplatin/5-FU induction chemotherapy escalated with a second randomisation that compares a 60Gy dose escalated regime [delivered via SIB to the Gross Tumour Volume (GTV)] vs a 50 Gy standard dose arm. It also has an embedded phase II study of systemic therapy adaptation based on interim PET response [27].

1.8.9.2 Brachytherapy

Although the use of brachytherapy in OEC has declined in recent years, it remains a treatment modality with an excellent therapeutic ratio; by delivering dose to the tumour without traversing surrounding normal tissues. The main of role of brachytherapy in the curative setting is in combination with external beam radiotherapy (EBRT) where it may be utilised to deliver a boost intraluminally to the primary tumour. The phase I/II RTOG 9207 study delivered 50 Gy via EBRT with concurrent chemotherapy followed by two brachytherapy boost schedules (either high-dose-rate 5 Gy during Weeks 8, 9, and 10, for a total of 15 Gy, or low-dose-rate 20 Gy during Week 8). Although one-year survival was acceptable at 49% there was an unacceptable rate of treatment toxicity and death, including a 12% rate of fistula formation [53].

In the palliative setting, the use of brachytherapy is more established. Two RCTS have compared intraluminal brachytherapy to stent insertion showing that brachytherapy resulted in higher health-related quality of life (QoL) scores and patients remaining dysphagia-free for longer [54, 55].

1.8.10 Adjuvant treatments

Selected patients with locally advanced disease who did not receive NA or perioperative treatments may benefit from adjuvant treatment post-surgery. The Intergroup 0116 trial compared adjuvant CRT with surgery alone for patients with GOJ and gastric tumours. The trial used one cycle of infusional 5-FU/Leucovorin chemotherapy followed one month later by concurrent CRT(45Gy) with the same chemotherapy. Following CRT, a further 2 cycles of infusional 5-FU/leucovorin were administered. The

trial showed significant 3-year OS improvements (50% vs 41%), however, only 64% of patients were able to complete the full treatment cycle [56]. The low rates of treatment completion post-operatively were also seen in the UK MAGIC trial, where only 50% of patients were able to complete the full three courses of post-operative chemotherapy. In the UK, neoadjuvant or peri-operative strategies are preferred over adjuvant treatments. The rationale behind this approach is partially attributed to the toxicity from oesophagectomy resulting in patients frequently being unable to complete adjuvant treatments [20, 21].

Following NACRT and surgery, early clinical data suggests that there may be an emerging role for adjuvant immunotherapy (IO). An uncontrolled phase II trial of 24 patients who underwent NACRT and surgery but did not achieve pCR and R0 resection were administered 4-weekly Durvalumab (anti-PDL-1) for up to a year, showed a favourable relapse-free survival (RFS) of 78.6% [57]. The PACIFIC trial showed that adjuvant Durvalumab following dCRT in stage III non-small cell lung cancer resulted in a significantly improved OS, highlighting the promise of this approach for OEC [58]. More recently, results were presented at ESMO 2020 of the CHECKMATE 0577 trial, which randomised patients who underwent NACRT followed by oesophagectomy but did not achieve pCR to one year of adjuvant nivolumab (anti PD-1) vs placebo, reported significantly improved disease free survival (DFS) at one year. These encouraging results represents the first randomised clinical data showing benefit of IO for oesophageal cancer in the adjuvant setting, potentially establishing its use as a future standard of care [59].

1.8.11 Salvage treatment options

Salvage surgery following dCRT is a highly toxic procedure that results in peri-operative mortality rates of up to 25% [60]. However, there is some, albeit limited, prospective data supporting this approach for carefully selected patients who have not responded to dCRT. The French FFCD 9102 trial, which included predominantly SCC oesophagus patients, compared two different radiotherapy schedules (protracted vs split-course) following induction chemotherapy. There was a second randomisation in the at least partial responders to surgery or further CRT. For these partial responders, surgery resulted in improved local control rates but there was no difference in OS or QoL scores [50]. In the same trial, for patients who were non-responders (n=111) and therefore not included in the second randomisation, surgery resulted in improved OS (17.7 month vs 5.5 months) [61]. For patients with AC, the role of surgery following dCRT is less clear and unsupported by clinical trial data. In these cases, the risks and benefits of surgery will need to be weighed up on an individual patient basis.

Reirradiation is an emerging treatment option for multiple tumours sites such as head and neck cancer with trial data reporting 2 year OS rates of up to 25% [62]. In OEC the role is less defined but may be

considered for carefully selected patients with in-field recurrent or residual disease. Several small retrospective case series that included predominantly SCCs report reasonable rates of local control and OS using a conventional fractionation schedule, although the optimum dose-level is yet to be determined [63]. Crucially, toxicity from this treatment can be severe, including significant risks of oesophageal perforation, fistula formation and high rates of radiation pneumonitis [63, 64].

Stereotactic body radiation therapy (SBRT) plays a role for isolated recurrences in many tumour sites such as head and neck [65] but again has limited evidence of its use in oesophageal cancer. Further advances in radiation therapy, including the use of PBT, will undoubtedly increase the safety of delivering additional radiation dose to patients, thus increasing its utility in OEC.

Reirradiation is a complex and emerging field but is outside the scope of this thesis.

1.8.12 Metastatic oesophageal cancer

Around 70% of OECs present at an advanced stage where curative treatment is not possible. Prognosis in this group of patients is poor, typically not exceeding 12 months [1]. In addition, many patients who have undergone curative treatment will have their disease recur, necessitating palliative treatments. The treatment options for this group of patients will need to be taken on an individual basis, taking into account patient symptoms, fitness and preferences. Treatment should be directed towards palliating symptoms, improving quality of life and improving OS [11].

Dysphagia is a common symptom for patients with advanced OEC. Insertion of a metal stent provides prompt and comparatively durable alleviation of symptoms. Other treatment options include brachytherapy and EBRT [66]. A recent phase III RCT by Byrne et al, the ROCS study, compared the addition of radiotherapy following stenting to stenting alone found that the addition of radiotherapy did not prevent the recurrence of dysphagia or improve OS [67].

For patients with an adequate performance status, palliative systemic treatment with cytotoxic or targeted agents may be considered. It is important to note that most randomised data that assess the use of palliative systemic agents in AC of the oesophagus include or are extrapolated from patient cohorts that include stomach cancer. For AC, chemotherapy regimens that include platinum-based agent (Oxaliplatin, Cisplatin) with infusional 5-FU or Capecitabine are commonly used with clinical data showing good response rates and improvement of OS [11]. Epirubicin is traditionally added as part of triplet regime (e.g. ECF/ECX) and remains commonly used. However, recent retrospective data has questioned its efficacy. [68] Approximately 15% of patients with AC of OEC/GOJ/stomach will over-express the HER2 receptor. In these patients, the addition of Trastuzumab (Herceptin) offers additional survival advantage when used in combination with chemotherapy [69]. Second-line

systemic options includes taxane-based or irinotecan-based chemotherapy used in combination or as a single agent. Recent data suggests anti-PDL-1/PD-1 agents (e.g. Pembrolizumab) in tumours with PDL-1 overexpression may confer a significant survival benefit [70].

1.9 Summary of the management of oesophageal cancer

OEC can be broadly divided into two broad entities based on histology and location: thoracic SCCs and thoracic/lower/GOJ ACs. SCCs are more radiation-sensitive and benefit to a greater extent from the use of RT within the treatment paradigm, in the definitive or NA setting. Surgery may be omitted for many cases of SCC without affecting OS rates. For ACs, both a tri-modality approach with NACRT, or bi-modality approach with NACT, followed by surgical resection are standards of care for locally advanced tumours. Both NA strategies are associated with better OS at the expense of increased toxicity including high rates of post-operative pneumonia and cardiac arrhythmias.

1.10 External beam radiotherapy (EBRT) techniques – current and future technologies

Since radiation was first used to treat cancer over a century ago, the technology used to deliver it has been in a constant state of evolution and refinement. Any improvements in radiation technology aim to achieve one or both, of two things: firstly, to improve target conformality, i.e. moulding radiation dose to the shape of the target and secondly, reducing dose to normal tissues surrounding the target. Theoretically, any tumour may be eradicated if given a high enough radiation dose. However, the dose that may be safely delivered is limited by the dose to and consequent toxicity in normal tissues that are adjacent to the tumour. The dose range that may effectively treat the tumour with an acceptable level of toxicity to normal tissue is referred to as the 'therapeutic window' or 'therapeutic ratio'. Successive radiation technologies have sought to widen the therapeutic window, by increasing conformality to the target volume, and/or decreasing the dose to surrounding normal tissue, thus broadening the clinical applications and utility of radiotherapy in the treatment of cancer.

The work in this thesis specifically covers forms of external beam radiotherapy (EBRT). Other forms of RT include brachytherapy, which is briefly covered in section 1.8.9.2., and intra-operative radiotherapy (IORT), a novel form of RT that delivers radiation during surgery using specialised equipment. IORT currently has limited clinical application in OEC and is outside the scope of this thesis.

1.10.1 Three-dimensional conformal radiotherapy (3DCRT)

First introduced in the 1980s, three-dimensional conformal radiotherapy (3DCRT) was the first RT technology to use cross sectional imaging e.g. computed tomography (CT) to aid planning of RT. Prior to using CT scans, RT was planned according to the height and width of the tumour as seen on a two-

dimensional x-ray simulator. The advent of CT imaging technology allowed the tumour to be visualised in 3D, and dose to be conformed according to the shape of the tumour. 3DCRT is typically 'forward-planned', meaning a treatment planner (i.e. dosimetrist/physicist) will arrange several beams (typically 2-7 beams), with or without wedges/collimators to modulate dose, before a treatment planning algorithm calculates the dose distribution. Creating a treatment plan can potentially be very time-consuming as different permutations of beams arrangements, beam weighting and wedging/collimators need to be trialled and resultant plan assessed by the treatment planner. As plans are manually created, the degree of complexity to the final plan is limited by the skill and experience of the treatment planner.

In OEC, 3DCRT plans typically consist of a four beam arrangement (e.g. anterior, posterior, right lateral, left lateral) allowing for coverage of the centrally located oesophageal tumour and its adjacent lymph node areas whilst adequately sparing dose to OARs such the lung, heart and spinal cord. Figure 4 shows typical beam arrangement and dose distribution of an oesophageal plan.

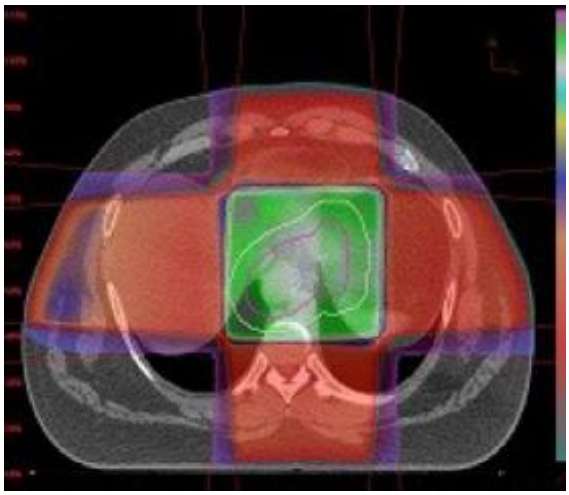

Figure 4 Typical 4 beam arrangement for oesophageal cancer using a 4-beam arrangement with 3DCRT. GREEN – High dose; RED – Low dose.

1.10.2 Intensity-modulated radiotherapy (IMRT)/volumetric modulated arc therapy (VMAT)

IMRT is an advanced form of conformal RT that has increased in use over the past 2 decades to become to the most common method of delivering radical radiotherapy in the UK [71]. IMRT is an umbrella term that is covers conventional IMRT (e.g. 'step and shoot', 'sliding window'), tomotherapy (e.g. helical) and VMAT. IMRT is particularly useful for irregular, concave and complex shapes that are in close proximity to critical organs at risk (OARs) [72].

In addition to CT planning as used in 3DCRT, increased computing power allows IMRT plans to deliver radiation beams of non-uniform intensity. Increased computing power also allows IMRT to be 'inverse-planned', a method of planning where the treatment planning system (TPS) is set specific planning

objectives or goals that need to be achieved in order to create a clinically appropriate plan. Specific objectives are set for the minimum dose that needs to be received by the planned target volume (PTV) and separate objectives are set for the maximum dose that can be received by an OAR e.g. a 95% of PTV to receive 95% of 50 Gy, and lung volume receiving >20 Gy (V20 Gy) to be <20%. TPSs will use an algorithm that will run through permutations of beams with varying intensity in order to create a plan that achieves these objectives in a process known as plan optimisation. The intensity of each beam may be modulated, effectively using hundreds of beamlets to create a final plan that is both conformal to the target volume and sparing of normal tissue. This additional layer of automated dose modulation allows for a plan where the complexity far exceeds one that is possible from a 'forward-planning' method [73].

Originally, IMRT was developed to be delivered using conventional linear accelerators (as used in 3D-CRT) where IMRT may be delivered using either a 'step and shoot' or 'sliding window' method. 'Step and shoot' refers to a technique that delivers multiple static dose segments within each field (beamlets of dose) that together produce an intensity-modulated field. In the sliding window technique, dynamic multi-leaf collimators (MLCs) move constantly across the field at varying rates to deliver the intensity modulated dose for that beam. VMAT is a form of IMRT in which a specialised linear accelerator delivers hundreds of mini beams in a 360-degree arc around the patient [72]. A major advantage of VMAT is the reduced fraction delivery time compared to 3D-CRT and IMRT. This has huge implications for departmental workflows, allowing for more patients to be treated with fewer resources, resulting in a positive cost/benefit ratio leading to the rapid adoption of this technology across the world [74].

An important feature of IMRT plans is that there is often a significant area of low dose 'bath' due to the multiple beams and entry points used. The use of the optimiser in the planning process may also result in increased dose to organs that have not been delineated or given an objective. Therefore, it is crucial that careful assessment of the plan is undertaken as an additional safety precaution.

As with many other tumours sites, IMRT/VMAT is now the most common RT technique used for radical RT in OEC in the UK [27]. Compared to CDCRT, retrospective data suggests IMRT results in lower dose to OARs and may contribute to improved OS. Notably, however, there are no prospective trials that directly compare IMRT/VMAT to 3DCRT in OEC [75].

Figure 5 shows a typical plan and dose distribution of VMAT in oesophageal cancer demonstrating a typically conformal high dose region (red) and low-dose bath (light purple).

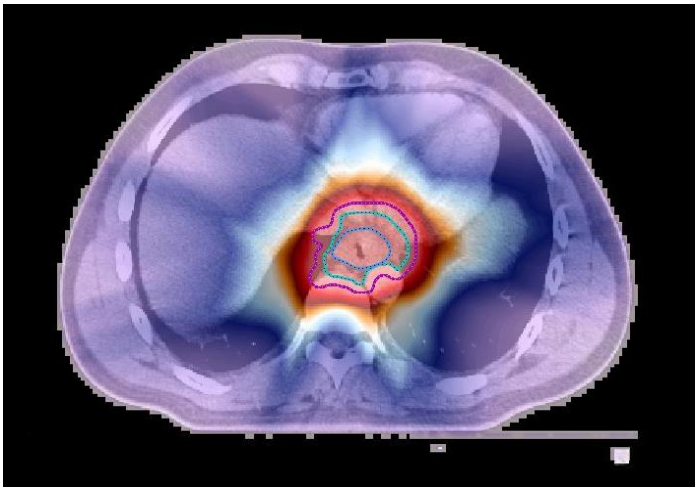

Figure 5 Typical dose distribution in a lower oesophageal tumour IMRT plan. RED – high dose; Purple = low dose.

1.10.3 Particle beam therapy

The rationale for using charged particles as opposed to standard photon (x-ray) techniques is its favourable intrinsic physical properties, in particular, the Bragg peak. Charged particles that are currently used for clinical applications include proton beam therapy (PBT), which is by far the most widely available technology, and carbon ions, which are limited to a small number of centres in Japan and Germany. Helium ions are another heavy particle which has been used in the clinic. Its use remains experimental [76].

For the purposes of this thesis, I will focus on PBT, giving an overview of its physical properties, current technologies and special considerations required for treatment planning and delivery. I will also summarise the current knowledge and clinical applications of PBT in OEC in a systematic review of its dosimetric and clinical outcomes in chapter 2.

1.11 Proton beam therapy – the current UK landscape

PBT is a form of radiation therapy that utilises protons to deliver dose to the tumour as opposed to high energy x-rays (photons) used in conventional RT. The use of protons in medical treatment is not new, having first been used on patients as early as 1946 [77]. Recent technological advances such as increased computational power and the development of image guided RT (IGRT) have refined how PBT is delivered, thus expanding its utility. Coupled with a relative reduction in start-up costs, this has instigated a sharp proliferation in the number of PBT centres in recent years, widening access to PBT for patients worldwide. As of September 2020, there are currently over 100 PBT centres in operation worldwide, with over 20 new facilities established in Europe in the last 5 years alone [76]. Since 2008, NHS patients have had access to PBT through the NHS England Highly Specialised Commissioning Proton Overseas Programme. The programme limits eligibility for PBT to specific indications where PBT is deemed sufficiently advantageous, including paediatric and teenage/young adult (TYA)

tumours, skull base tumours, paraspinal sarcomas and other selected tumours close to the spine. It has been considered a success with approximately 1200 patients treated to date in accredited overseas centres including the University of Florida Proton Therapy Institute, Procure Oklahoma (USA), Paul Scherer Institute (Switzerland) and Westdeutsches Protonentherapiezentrum Essen (Germany). In March 2015, NHS England announced a £250 million investment to set-up two NHS PBT centres, to be based in the Christie in Manchester and University College London Hospitals (UCLH) in London. In late 2018, the Christie PBT centre opened and treated its first patient with the UCLH centre due to open in 2021. Once fully operational, the combined treatment capacity for both centres will be approximately 1500 patients per year, far exceeding demand based on the current NHS eligibility criteria. A central strategic aim of the NHS England programme is to utilise the additional capacity to develop a robust evidence base for PBT use in novel indications. As a result, nearly 50% (700 of 1500 patients) of the treatment capacity has been ring-fenced for research, including treatment of patients within the context of randomised controlled trials (RCTs) [78, 79]. In addition to the NHS centres, the private sector has separately developed a network of PBT centres in the UK, with the largest provider, Rutherford Cancer Centres, opening its first PBT centre in Newport, Wales in early 2018. Of note, NHS Wales, which is administered by the devolved Welsh government, has commissioned non-paediatric/TYA PBT services for Welsh NHS patients at the Rutherford Newport Centre [80].

1.11.1 Protons vs photon radiotherapy – A comparison of physical characteristics

Protons and photons have fundamentally different physical characteristics. These differences determine the way they interact with matter and how their physical characteristics are exploited for use in the clinical setting. Protons are positively charged particles with a relatively rest-mass (relative atomic mass = 1) that penetrate tissue to a finite depth which is dependent on proton energy, while photons (or x-rays) are electromagnetic waves with no charge or mass that completely penetrate tissues, gradually losing intensity along the radiation track. Protons are encompassed by a Coulomb field (electrostatic field) and interact with both the electrons and nuclei of matter. Each individual proton undergoes multiple Coulomb interactions throughout the beam path, with each Coulomb interaction causing tiny amounts of lateral scatter and small amounts of kinetic energy loss, slowing the proton down until it stops completely. The rate of kinetic energy loss is dependent on the individual properties of the material and is referred to as the ‘stopping power’. The stopping power ratio (SPR) is typically determined by a stoichometric calibration of a patient’s individual planning CT from a pre-determined Hounsfield unit (HU) to SPR calibration curve. The rate of kinetic energy loss increases as the proton slows down, resulting in a peak of dose deposition at the end of the proton range. The depth in which protons deposit the maximum dose is commonly referred to as the Bragg Peak (see figure 6). The depth to which protons penetrate tissue is determined by the energy of the

proton; the greater the energy, the deeper the Bragg peak. This finite range is advantageous as it results in the absence or a very low 'exit dose' at the distal edge of the radiation beam, allowing for significant sparing of tissues distal to the target volume. As a monoenergetic proton's Bragg Peak is narrow, usually measuring several millimetres, this necessitates the use of multiple energy levels to create a radiation plan that covers the whole of target volume. This 'spreading out' of the peak is referred to as the spread-out Bragg Peak (SOBP) [81-83]. The PBT techniques used to create SOBP and deliver PBT clinically is covered in section 1.12.

In contrast to protons, photons using energies that are typically used in clinical practice (e.g. 6MV - 15MV) deposit s maximum dose (Dmax) at a depth of approximately 0.5cm-3cm. Beyond the Dmax, photons continue to penetrate tissues with a gradual decrease in the dose deposited as photons are scattered or lost. As photons carry zero charge, unlike protons, they do not undergo Coulomb interactions. The most dominant interaction in tissue is the Compton effect, where the incident photon interacts with electrons in the absorbing material resulting in scattering of the photon and a transfer of energy to a 'recoil' electron. As most tumours sit deeper than the Dmax, producing a clinically useful photon plan often requires multiple beam angles to create a composite plan where the sum of doses from individual beams results in an adequately high dose at the target volume. An intrinsic flaw in photon radiotherapy is that all photon plans (with the exception of very superficial tumours) utilises a region of the photon beam where the dose is falling off. This results in plans that that will inevitably deliver excess dose to regions proximal and distal to the target volume [81, 83].

Figure 6 highlights the different relative doses in depth for photons and protons and illustrates the proton Bragg peak and SOBP.

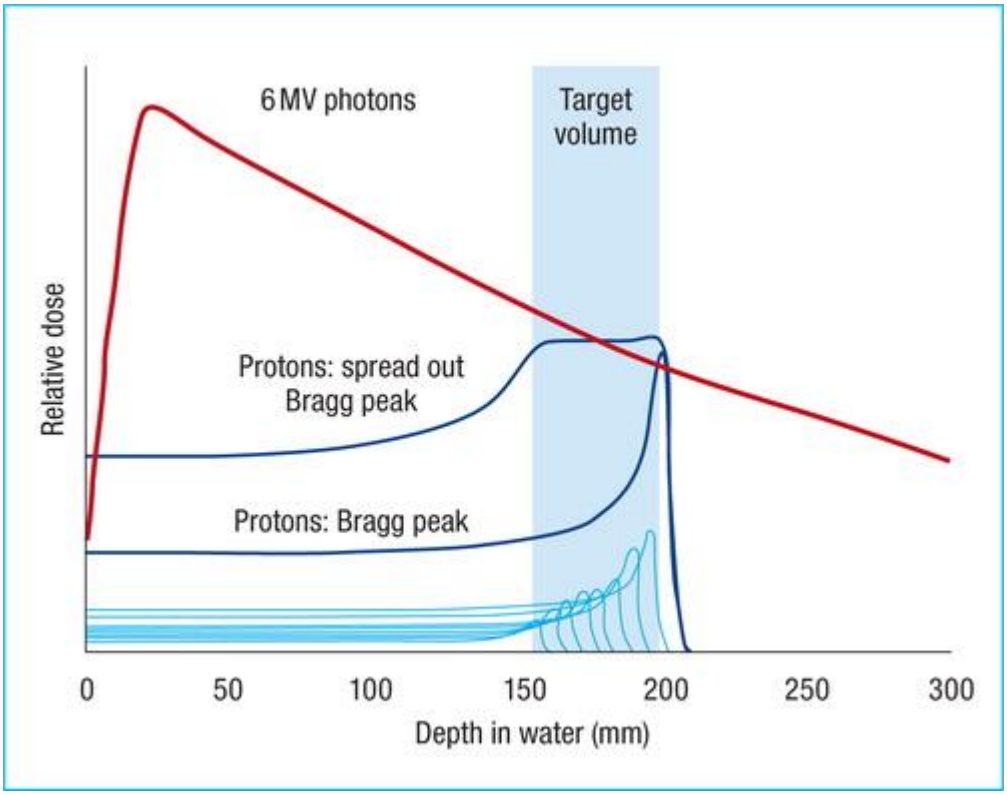

Figure 6 Examples of different relative doses with respect to depth for 6MV photons, mono-energetic protons and a proton SOBP [84].

1.12 PBT equipment and current technologies

Highly specialised infrastructure and technical expertise are required to produce proton beams that are suitable for clinical use, contributing to the high start-up cost of PBT technology. Protons are typically generated using hydrogen gas as a source, with electrons removed by an electrical field in order to create protons. Protons then need to be accelerated in order to achieve an energy level that is sufficiently high for clinical use. Modern PBT centres use a cyclotron to accelerate the particles. Once inserted, the cyclotron accelerates the protons outward from the centre in a spiral using a magnetic field until it reaches a sufficiently high energy. The monoenergetic proton beam line is then degraded using an energy selection system in order to create a series of beam energies that are useful clinically. These beams are then directed to individual gantries using a series of magnets. There are two common PBT technologies that are used to deliver radiation to the patient; the older passive scattering proton therapy (PSPT; also known as uniform scanning) and more modern pencil beam scanning (PBS; also known as spot-scanning) [85, 86]. A brief overview of these are given in the following sections.

1.12.1 Passive scattering proton therapy (PSPT)

With passive scattering, the beam goes through a range modulation wheel, and then through usually two scattering foils; the first to widen the lateral width of the beam, and the second, to 'flatten' the beam creating a uniform beam with a series of Bragg Peaks or SOBP. The beam is shaped further in

the snout of the nozzle, which contains an aperture and range compensator. The aperture (collimator) shapes the lateral boundaries of the beam while the range compensator conforms the distal edge of the beam. Both the aperture and range compensator are custom-made for each individual radiotherapy plan.

There are several drawbacks of PSPT. The use of custom-made equipment is resource-intensive and limits flexibility for quick plan alterations. Using a range compensator distributes dose proximally to the target volume often resulting in areas of unwanted dose. Additionally, the use of multiple foils and an aperture(s) results in greater neutron contamination, which increases the risk of serious long-term effects such as second malignancies [86].

1.12.2 Pencil beam scanning (PBS) PBT

As most European centres are relatively new, PBS is the predominant PBT technique available in Europe. All high energy PBT centres in the UK, NHS or in the private sector, use PBS technology.[76] As with PSPT, protons are accelerated in a cyclotron before going through an energy degrader or 'range shifter' to create a range of energies. In PBS, a narrow beam of protons (pencil beam) is precisely shaped and directed using a set of magnets in order to 'paint' the dose on the target volume in a series of 'spots'. Once an area at a particular depth is treated, the proton energy is altered, and the next 'layer' of dose can be painted. This is repeated until the whole target volume is covered.

There are several advantages to PBS. Firstly, it is significantly less time consuming to plan, with no custom parts needed, and requires less time to deliver PBT treatment, allowing for a greater number of patients to be treated. It also allows the use of intensity modulated PBT (IMPT) where multiple beams with varying intensity are used to create a composite plan. IMPT allows for the treatment of complex shapes and is therefore useful in more tumour sites compared to PSPT. Additionally, PBS also results in less dose proximally due to a lack of a range compensator while the lack of a scattering foils and apertures results in less neutron contamination. The disadvantages of PBS include greater lateral scatter due to the absence of an aperture and greater susceptibility to dose distortion due to organ motion compared to PSPT [85, 86].

1.13 Uncertainties in PBT and mitigation strategies

(note: Some text from the following sections are taken and adapted from 'Comparing Proton to Photon Radiotherapy Plans: UK Consensus Guidance for Reporting Under Uncertainty for Clinical Trials' Lowe et al 2020 [87]. I am a co-author on this paper and made a significant contribution to this section of the paper. Additional details of this work is covered in Chapter 8 of this thesis. A full manuscript is attached in the appendix.)

1.13.1 Overview of uncertainties in PBT

As previously discussed, the inherent advantage of protons is that they stop. However, there is uncertainty as to where they stop, termed range uncertainty. This is due, in part, to uncertainties in the calibration of the patient's CT scan to relative proton stopping powers, uncertainties in the mean excitation energies of tissues, and the handling of different tissue densities by analytical dose algorithms [82].

Uncertainties in proton therapy can result in not only a displacement but also a distortion of the delivered dose. As proton Bragg peaks may be positioned throughout the target volume, these uncertainties can result in regions of under-dose of the clinical target volume (CTV), overdose of critical OARs and unplanned cold or hot spots. For photon radiotherapy, setup uncertainties are typically accounted for using geometric expansion margins in the form of planning target volumes (PTVs) and planning organ at risk (OARs) volumes (PRVs) (ICRU 1999 [88]; 2010[89]). However, due to inherent range uncertainties in protons, conventional margins may not appropriately account for the effect of setup errors on the treatment plan [90].

1.13.2 Robust optimisation/robust evaluation

Instead of using PTVs and PRVs, it may be more appropriate to incorporate range uncertainties and setup uncertainties into the plan creation and evaluation process. This is termed robust optimisation and robust evaluation respectively. Robust optimisation adds a bespoke 'margin' based on range and setup uncertainties inherent to individual plans. Typically, a range uncertainty of approximately +/- 3.5% is considered during robust optimisation. Robust evaluation assesses the quality of proton plan uncertainty using 'error scenarios'. These 'error scenarios' are evaluated by calculating what a given plan would look like if the patient was shifted (in the case of setup uncertainties, e.g. 5mm in all directions) or if the stopping power of each tissue was systematically higher or lower (in the case of range uncertainties). The procedure results in several dose distributions that can be evaluated to ensure that the plan is safe and effective when inevitable variations in patient setup and image calibration are considered [91].

To help distil this increased amount of information into something that is practically useful to those reviewing plans, the 'worst-case' or 'second worst-case' from these error scenarios may be reported. For the CTV this may be the minimum value of a given coverage metric and for OARs this may be the maximum value of an upper dose constraint. This may be visually represented as a dose volume histogram (DVH) with error margins to aide clinician review during plan approval.

1.13.3 Anatomical changes including breathing motion

Though it can be relatively straightforward to evaluate setup and range uncertainties, anatomical changes present an arguably larger source of uncertainty. The impact of changes such as weight loss, sinus filling, tumour progression, respiratory motion etc. are not comparable between photons and protons and this should be considered for individual clinical scenarios.

Strategies to mitigate for inter-fraction anatomical change includes increased use of image guidance during treatment such as daily cone-beam CTs (CBCT) and scheduled repeat planning CTs. For example, the TORPEdO trial (a phase III trial of proton therapy vs intensity modulated radiotherapy for multi-toxicity reduction in oropharyngeal cancer) mandates a repeat planning CT mid-treatment with an evaluation of the dose to relevant structures with replanning required to maintain some minimum standards.

Accounting for intra-fraction motion such as breathing is potentially more challenging. This is particularly important for PBS which is susceptible to interplay effects; where the relative motion of the target and scanning proton beam results in a significant degradation of dose distribution [92]. Several strategies exist to mitigate the impact on distribution. Firstly, during treatment simulation, the magnitude of tumour motion can be quantified by the use of 4DCT, where a planning CT is taken for the full respiratory cycle, in order to generate an Internal Target Volume (ITV) which is generated using gross target volumes (GTV) in all respiratory phases. Recent work by Dolde et al. suggested that using time-resolved magnetic resonance imaging (4D MRI) in treatment simulation allows more detailed assessment of intrafraction tumour motion [93]. During treatment planning, strategies such as robust optimisation are essential in order to incorporate uncertainty into the final plan [94]. Selecting beam angles also plays a role in minimising uncertainty due to intrafraction motion. Beams angles should be as parallel as possible to the organ motion, with a beam path avoiding tissue density inhomogeneity where possible [91]. Additionally, optimising individual fields to achieve target constraints independently [single field optimisation (SFO)], is shown to be more robust to intra-fraction changes compared to multi-field optimisation (MFO)/intensity modulated proton therapy (IMPT) where all fields are simultaneously optimised to the target volume [90]. During treatment delivery, motion management techniques such as abdominal compression, gating and beam tracking will further reduce the effect of breathing motion [95, 96]. An additional strategy includes employing a method called re-scanning or dose re-painting where the dose is delivered in n scans with $1/n$ of the original spot weight. It mitigates the interplay effect through statistical averaging, is shown to reduce interplay effects sufficiently for lung and abdominal tumours [97-99]. Other methods include beam tracking, where the CTV is monitored throughout the treatment, and compensation made in order to reduce the impact of intra-fraction motion [96].

It is important to note that there is currently no defined guidance when considering PBT uncertainty and mitigation strategies in research and clinical studies. For any clinical trial, clearly defined RT quality assurance (RTQA) protocols are crucial to ensure the safety and accuracy of any RT treatment. As PBT's physical properties are fundamentally different to photon RT, a different approach to RTQA is required to ensure consistency and reproducibility in PBT treatments. Chapter 8 discusses PBT Trial RTQA in additional detail.

1.13.4 Variable relative biological effectiveness (RBE)

An additional uncertainty from proton treatment is the assumption that the biological effect of the physical dose is a constant, i.e. the relative biological effectiveness (RBE) is fixed at 1.1 times relative to the physical dose of photons. This value is derived from historical in-vivo experiments and remains a standard in clinical practice. However, there is now clear evidence that proton RBE is variable and dependant on linear energy transfer (LET), physiological and biological factors and the clinical endpoint under investigation. As LET increases, so does proton RBE with Paganetti et al. estimating, in cell lines, that RBE across a SOBP to varies from 1.1 at the entrance to 1.7 at the distal end of the beam. Furthermore, there is data that suggests RBE increases as the tissue α/β decreases adding further uncertainty to treatment [100]. A method of mitigating this uncertainty is to incorporate biological parameters such as LET in the optimisation process. As RBE increases with LET, LET may be used as a surrogate for RBE changes. LET-based optimisation is shown to be feasible, and is now increasingly available, including in commercially available treatment planning systems (TPS) [91].

In most clinical settings, an RBE of 1.1 is still typically used and while inaccurate, there is no strong evidence suggesting its use results in clinically significant differences. As biological optimisation technology becomes more widely available, it is likely to become mainstream in the robust planning of PBT. Although variable RBE in PBT is a complex and important field on which substantial research is being undertaken, it falls outside the scope of this thesis. Further work in this thesis uses an RBE factor of 1.1 for all dosimetric studies.

1.14 Conclusions

With poor long-term survival rates and high rates of treatment related toxicity, OEC remains an area of vast unmet clinical need. RT, in combination with chemotherapy, plays an integral role in the management of OEC in the curative and palliative setting. There is clear evidence that tri-modality treatment strategies results in superior oncological outcomes compared to surgery alone at the expense of higher rates of toxicity. Modern photon RT techniques such as IMRT have resulted in improved dosimetric distribution and have been widely adopted, potentially resulting in improved toxicity rates and contributing to improved OS. PBT's superior physical characteristics may improve

this therapeutic ratio further by allowing sparing of OARs without compromising target volume coverage; further reducing toxicity rates, including post-operative complications rates, and contribute to improved survival.

Part 1: Exploring the Potential of PBT in Oesophageal Cancer – from Dosimetric Superiority to Clinical Benefit

Chapter 2: The Promise of PBT in Oesophageal Cancer: A Systematic Review of Dosimetric and Clinical Outcomes

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Candidate contributed to study conception, data collection and analysis, manuscript preparation and editing.

Author 1 contributed to conducting literature search and methodology section.

Authors 2, 3, 4 contributed to manuscript review and editing.

Author 5 contributed to study conception, data analysis, manuscript editing.

2.1 Introduction

OEC may benefit from PBT due its location in the central mediastinum and proximity to critical OARs. Most OECs occur in the mid or distal third oesophagus, within close proximity to the heart, lung, liver and spleen. PBT allows maintenance or escalation of dose to the target volume while simultaneously reducing dose to these OARs. Dosimetric superiority potentially translates into improved toxicity and survival outcomes. These associations are seen in other tumours near the mediastinum, such as in lung cancer where dose to lung is shown to correlate with pneumonitis rates and heart dose has been found to be a prognostic factor for long-term survival [36, 101]. For breast cancer, an increase of 1Gy in mean heart dose results in a 7.4% increase in rate of major coronary events [38]. In OEC, the links are less established, but emerging data suggests a similar relationship between dosimetric and clinical outcomes. For example, Wang et al. showed that mean lung dose correlated with post-oesophagectomy complication rates [34] while Takeuchi et al. showed that mean heart dose correlated with rates of symptomatic pericardial effusions following RT for oesophageal cancer [102]. It is clear that PBT, with its physical advantages, may meaningfully contribute to improving outcomes in OEC. This review aims to assess if the current evidence base supports or refutes this hypothesis.

2.2 Aims and objectives

This review of current literature aims to assess and summarise potential advantages of PBT over standard RT techniques for patients with non-metastatic OEC. To ensure a clinical focus, this analysis assesses relevant dosimetric parameters that may result in improved clinical outcomes, like dose to critical OARs such as the heart and lung and target volume coverage. In addition, it summarises any reported clinical endpoints such as toxicity rates, progression free survival (PFS) and OS. The overall objective of this study is to give an up-to-date and comprehensive overview of the use of PBT in OEC, its potential benefits and highlight current issues surrounding its use. More importantly, this review assesses if further evaluation of PBT in OEC, preferably in the context of robust RCTs, is warranted.

PICO (Population, Intervention, Comparison, Outcome) Questions

1. In patients with non-metastatic OEC, does PBT offer dosimetric advantages over photon radiotherapy?
2. In patients with non-metastatic OEC, does PBT confer any improvements in measurable clinical outcomes compared to photon radiotherapy?

Outcomes and Measures

Co-primary outcomes

- PBT gives a statistically significant ($p<0.05$) and clinically meaningful reduction in dose parameters to OARs (e.g. lung and heart) while maintaining an equal or comparable dose to target volume.
- PBT has evidence of clinical benefit measured by endpoints such as OS, PFS and toxicity endpoints.

Secondary outcomes

- Descriptions of treatment protocols of PBT in OEC including intent/dose/fractionation/chemotherapy type.
- Current techniques used to deliver PBT to oesophagus (e.g. pencil beam scanning, passive-scattering)
- Key volumetric descriptors used to assess proton beam therapy for oesophageal cancer

Eligibility Criteria

Inclusion criteria

- Full text articles only
- Non-metastatic oesophageal cancer
- All patients 18 or over
- Published after 2010

Exclusion criteria

- Articles focussing on the technical aspects of PBT planning and delivery
- Articles focussing on quality of life questionnaire data
- Articles focussing on health economics aspects of PBT
- Review articles
- Non-full text articles
- Non-English
- Studies with non-OEC patients
- Studies with non-localised OEC patients
- Studies with fewer than 10 patients
- Studies with multiple publications on the same cohort (unless reporting different endpoints)
- Studies using PBT for reirradiation

Study types for sub-analysis

Dosimetric studies

Dosimetric studies; experimental (planning study), prospective or retrospective clinical data

Clinical studies

Prospective and retrospective studies reporting clinical outcomes with PBT in OEC

Table 4 PICO Question and Full Eligibility Criteria

2.3 Methods

2.3.1 Search strategy

A systematic review was performed using structured search terms following the Preferred Report Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A systematic literature search was performed using Medline, Embase, Cochrane Library and Web of Science. The initial search was performed on 17th March 2020 and last performed on 17th December 2020. All databases were searched from 2010 to present to reflect current available technology. Thesaurus and natural language terms around the concepts of 'cancer of the oesophagus', 'proton beam therapy', and 'proton planning' were identified for each database. Searches were performed on text wording rather than title or abstract alone. Full reference lists of studies selected for inclusion from the initial searches were reviewed for additional manuscripts of interest (backward chaining). Citation checks of the final selected studies were also performed on Web of Science and Google Scholar on 17th December 2020.

Full search methodology including search terms for each database and a PRISMA checklist are included in the appendix.

2.3.2 Eligibility criteria

Eligible studies were English language studies for non-metastatic OEC, involving patients over the age of 18. Studies that reported outcomes for re-irradiation or metastases including oligo-metastases were excluded. Studies relating to the technical aspects of proton beam therapy planning and delivery e.g. motion management, planning optimisation, were deliberately excluded in order to maintain a clinical focus, as were studies assessing the health economic implications of this technology. Full objectives including PICOs question, outcomes and eligibility criteria are detailed in table 4.

2.3.2.1 Study selection

Duplicates and conference abstracts were removed, and remaining articles were assessed for eligibility by two independent reviewers (ON, SG). A total of 256 full-text articles were assessed for eligibility, with 32 articles selected for inclusion in final analysis. See PRISMA flow diagram (figure 1) for full details. The analysis is divided into two sections: dosimetric studies and clinical studies. The first section considers all relevant dosimetric studies, including studies which included comparison to standard photon techniques such as IMRT/VMAT and 3D-CRT. The second section considers reported clinical outcomes including survival and toxicity endpoints. Five studies included both dosimetric data and clinical outcome data. For these studies, dosimetric outcomes are detailed in the dosimetric studies section (see table 2) and clinical outcomes are detailed in the clinical studies section (see table 3).

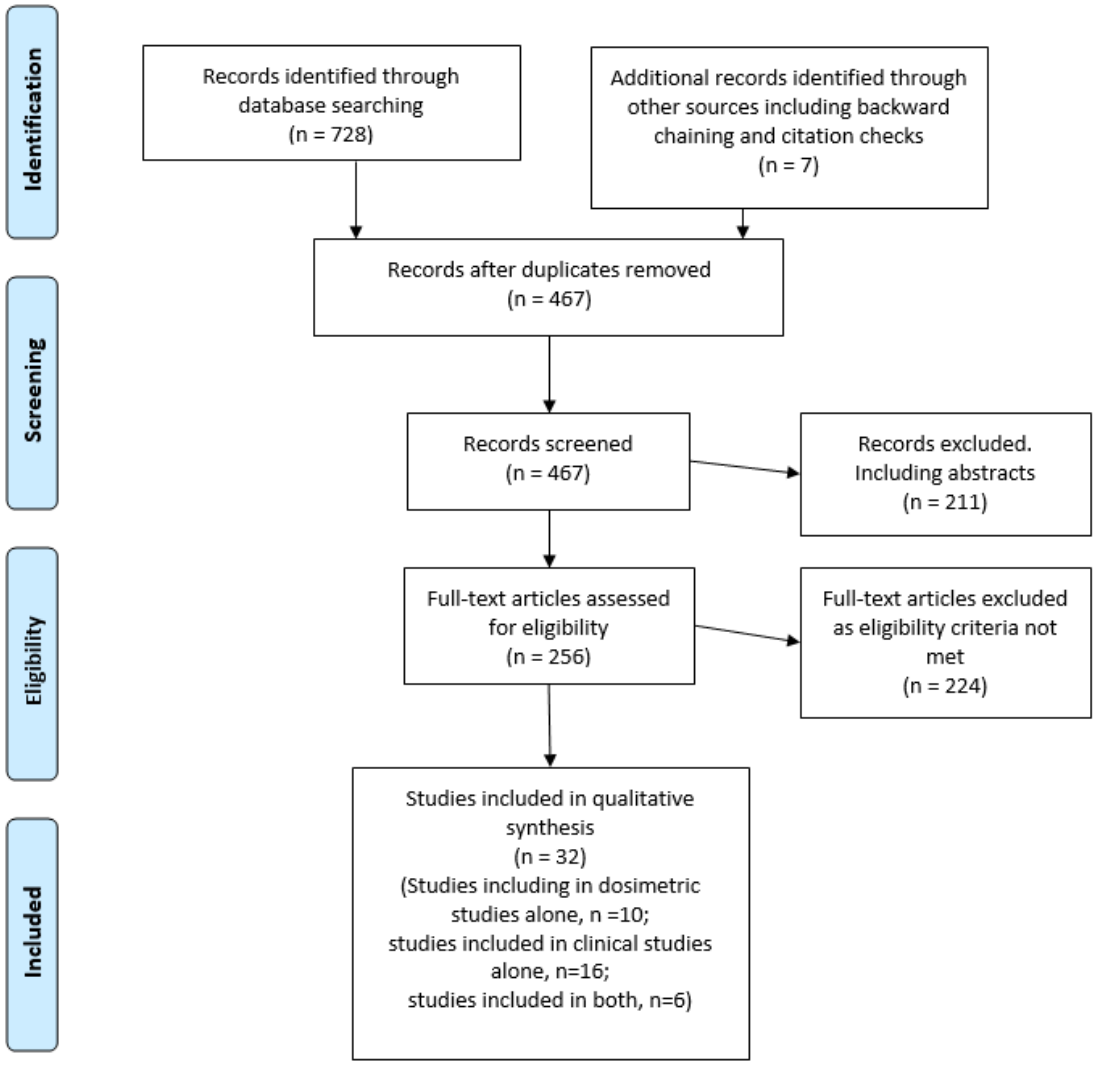


Figure 7: PRISMA Flow Diagram

2.4 Results

Table 5: Dosimetric Studies

Ref.	Study Design	No. of patients (n) and tumour type	RT intent/protocol	PBT technique	Comparison	Results	Notes
Xi et al., 2017[103]	Retrospective, Single centre (MDACC)	n = 343 (PBT, n=132; IMRT n=211) Mostly distal AC	Definitive 50.4Gy/28# with chemotherapy	PS/PBS	IMRT	PBT superior: Lung – Mean, V5, V10, V20; Heart – Mean, V30. No difference: PTV coverage; Heart V40	Clinical outcome data in Table 3
Shiraishi et al., 2017[104]	Retrospective, Single centre (MDACC)	n = 727 (PBT, n=250; IMRT, n=477) Mostly distal AC	Definitive/NA 50.4Gy/28# mostly with chemotherapy	Mostly PS (PBS, n = 13)	IMRT PS vs PBS	*PBT vs IMRT* PBT superior for all cardiac substructures except RCA -V30, V40; LCX -V30, V40 *PBS vs PS* PBS superior: Whole heart - V20, V30, V40; RA – mean, V5, V10, V20, V30, V40; LA – V30, V40; LMC- mean, V20, V30, V40; LCX – V10, V20, V30, V40; No difference: RV/LV/LAD/RCA.	
Welsh et al., 2011[105]	Retrospective, Single centre (MDACC)	n=10 Distal tumours	Definitive 50.4Gy/28 # (PTV) 65.8Gy/28 # (GTV) with chemotherapy	PBS	IMRT vs 3 PBT beam arrangements	*IMRT vs AP/PA* PBT superior: Lung – Mean, V5, V10, V20; Spinal cord. No difference: Heart; Liver.	

						IMRT vs LPO/RPO PBT superior: Lung – mean, V5, V10; Heart – mean, V10, V20, V20, V30; Liver – mean. No difference: lung V20; Spinal Cord. *IMRT vs AP/LPO/RPO* PBT superior: Lung – mean, V5, V10, V20; Heart – Mean, V10, V20, V30; Liver; spinal cord. Comparable coverage of GTV/PTV for all beam arrangements	
Jingya Wang et al., 2015[106]	Retrospective, Single centre (MDACC)	n = 55 Mostly distal tumours	Definitive/ NA 50.4/28# with chemotherapy	PS	IMRT	PBT superior: Lung – Mean, V5, V10, V20; Heart –V10, V20, V30, V40; Cord (Dmax); Liver - mean. IMRT superior: Lung - V40, V45, V50. No difference: Mean heart dose.	Distance of PTV to carina and percentage of uninvolved heart inversely correlated to mean lung and heart dose respectively
Wang et al. 2020 [107]	Retrospective analysis of G3+ Cardiac events, Single centre (MDACC)	n=479 (PBT=159; IMRT, n=320)	Definitive/NA 41.4Gy/23# - 50.4Gy/28# With chemo	PS/PBS	IMRT	PBT superior: Heart - V5, V30, Mean Cardiac dose parameters associated to G3+ Cardiac events	Clinical outcomes in Table 3

Prayongrat, et al., 2017[108]	Retrospective, Single centre (MDACC)	n = 19 Mostly distal/GOJ AC	Definitive/NA 41.4-50.4Gy/23-28# With chemotherapy	PBS	-	Selected results: Mean Lung dose – 4.94Gy (±2.31); Lung V20 - 9.45% (± 4.94); Mean Heart dose - 7.86Gy (±5.04); Acceptable PTV coverage.	Clinical outcome data in Table 3
Hirano et al., 2018[109]	Retrospective, Single Centre (NCCJ)	n=27 SCC only	Definitive 60Gy/30# with chemotherapy	PBS	3DCRT IMRT	*PBT vs 3DCRT* PBT superior: Lung – Mean, V5, V20; Heart - V10, V20, V30, V40; Spinal cord (max dose); Conformity index (CI)*. No difference: Lung V10, V15. *PBT vs IMRT* PBT superior: Lung - Mean, V5, V10, V20; Heart - Mean, V20, V30, V40; CI. No difference: Spinal cord (max dose). No correlation between toxicities and dosimetric parameters	CI determined as the volume of the 90% prescription isodose surface divided by PTV
Ling et al.,2014 [110]	Retrospective, Single Centre (LLUMC)	n = 10 AC only	NA 50.4Gy/28#, no chemotherapy information	PS	3DCRT IMRT	*PBT vs IMRT* PBT superior: Lung – Mean, V5, V10, V15; Heart – mean, V25, V30, V40, V50, LAD, LV, pericardium; Other – Liver, Spinal cord, stomach V50. No difference: Lung V20, V30, V40; stomach V20; CI; Uniformity index (UI); homogeneity index (HI)	

						PBT vs 3DCRT PBT superior: Lung – V5, V50; Heart – Mean, V25, V30, V40, V50, LAD LV, Pericardium; Other – liver, spinal cord; UI, HI. No difference: CI	
Liu et al., 2019[111]	Retrospective, Single centre (Mayo)	n=35 (PBT, n=19; IMRT, n=16)	Definitive/NA 50.4Gy/28# No chemotherapy information	PBS	VMAT	PBT superior: Lung – Mean, V5; Heart – mean, V30; Liver – Mean, V20. No difference: Lung V20; Heart- V30, V40; liver -V30; spinal cord; kidney; stomach.	Utilised small-spot IMPT VMAT resulted in more robust coverage of CTV
Makishima et al., 2015[112]	Retrospective, Single Centre (PMRC/UoT)	n=44 SCC only	Definitive 60Gy (median) with chemotherapy	PS	3DCRT	PBT superior: Lung – Mean, V5, V10, V20; Heart -V30, 40, 50.	Unmatched baseline characteristics with comparison group Clinical outcome data in Table 3
Macomber et al., 2018[113]	Retrospective, Single centre (SCCA/UoW)	n=55 (PBT, n= 18; IMRT, n=21; 3DCRT, n=16) Mostly distal AC	NA 50.4Gy/28# with chemotherapy	PBS	IMRT 3DCRT	PBT superior: Heart – Mean, V5, V40. No difference: Heart V50. No correlation between dose and clinical outcomes (see table 3).	Clinical outcome data in Table 3
Zeng et al., 2016[114]	Retrospective, Single centre (SCCA/UoW)	n = 13 Mid and distal	NA 50.4Gy/28# with chemotherapy	PS/PBS	PBT beam arrangements:	PA vs AP/PA: PA has lower heart dose (except V40), comparable lung dose	Mid-oesophageal tumours excluded

		tumours, SCC/AC			PA vs AP/PA PA vs PA/LPO AP/PA vs PA/LPO	PA vs PA/LPO: PA has lower lung dose, other parameters comparable. AP/PA vs PA/LPO: AP/PA has lower lung dose, higher heart dose. PA - highest cord doses but all within tolerance	from dosimetric comparison Clinical outcome data in table 3
Feng et al. 2020 [115]	Planning Study	n=20 Distal tumours only	50Gy/25#	PBS	2 Superior-Inferior (S-I) direction posterior oblique beams (couch 270°) 2 Right-Left (R-L) direction posterior oblique beams (couch 180°)	*S-I vs R-L beam arrangements:* S-I superior: Lung – V5, V30 Liver -Dmean, NTCP endpoints R-L superior: Cord Dmax CTV hot-spot control Comparable plan robustness for S-I and R-L When interplay considered, S-I superior for heart Dmean and V30, lung Dmean and V5Gy, Liver Dmean. Higher Cord Dmax	Matched tumour volume characteristics
Celik et al. 2020 [116]	Planning Study	n=20 GOJ tumours (Sievert I and II)	NA 41.4Gy/23#	PBS	PBT 2 Field(2F) PBT 3 Field(3F) VMAT	Selected results (*VMAT vs 2F vs 3F):* Mean lung dose - 8.6±2.9Gy vs 3.2±1.5 Gy vs 2.9 ± 1.2Gy Mean heart dose - 9.9±1.9Gy vs 3.7 ± 1.3Gy vs 4.0 ± 1.4Gy Left ventricle - 6.5 ± 1.6Gy vs 1.9±1.5Gy vs 1.9±1.6Gy No difference for liver/kidney/stomach/spleen/bowels	Secondary cancer risk – estimates for lung cancer only

						Estimated risk per 10,000 patient years (VMAT vs PBT): Secondary cancer (EAR) - 19.2 ± 5.7 vs 6.1 ± 2.7 Cardiac failure (RR) - 1.5 ± 0.1 (VMAT) and 1.1 ± 0.1 (PBT) Coronary artery disease (RR) - 1.6 ± 0.4 (VMAT) and 1.2 ± 0.3 (PBT)	
Warren et al., 2017[117]	Planning study	n = 21 Mid-tumours only	Definitive 50Gy/25# (PTV) 62.5Gy/25# (GTV+5mm)	PBS	VMAT 3DCRT	PBT superior: Bone – mean, V10; Thoracic vertebrae (TV) – mean dose. No difference: Other bone/TV parameters.	More significant bone sparing with PBT for patients with larger PTV
Warren et al., 2016[118]	Planning Study	n = 21 Mid-tumours only	Definitive 50Gy/25# (PTV) 62.5Gy/25# (GTV+5mm)	PBS	VMAT	PBT superior: Lung – Mean, V20; Heart – Mean, V5, V30. No difference: Cord (Dmax) CTV coverage (for nominal plans)	For dose escalation: VMAT – constraints met for 16/21 cases PBT – constraints met for 20/21 cases PBT - CTV coverage less robust to setup errors

Abbreviations: MDACC = MD Anderson Cancer Centre, Houston, USA ; PMRC/UoT = Proton Medical Research Centre, University of Tsukuba, Tsukuba, Japan; NCCJ = National Cancer Center Japan, Chiba, Japan; LLUMC = Linda Loma University Medical Centre, Linda Loma, USA; Mayo = Mayo Clinic, Phoenix, USA; SCCA/UoW = SCCA Proton Therapy Centre/University of Washington, Seattle, USA; Gy = Gray; NA = neoadjuvant; PBT = proton beam therapy; PS = passive scattering; PBS = pencil beam scanning(also referred to as spot-scanning and IMPT); IMPT = intensity modulated proton therapy; IMRT = intensity modulated radiotherapy; VMAT = volumetric arc therapy; 3DCRT = 3D conformal radiotherapy; GTV = gross tumour volume; CTV = clinical target volume; PTV = planning target volume; AC = adenocarcinoma; SCC = squamous cell carcinoma; RCA = right coronary artery; LCX = left circumflex; RA = right atrium; LA = left atrium; LV = left ventricle; RV = right ventricle; LMC = left main coronary artery; LAD = left anterior descending;

LPO = left posterior oblique; RPO = right posterior oblique; AP = anterior-posterior; PA = posterior-anterior; CI = conformity index; UI = uniformity index; HI = homogeneity index; TV = thoracic vertebrae; EAR = Excess absolute risk; RR = relative risk; 2F = 2-field; 3F = 3-field

Table 6: Clinical Studies

Reference	Summary of study design	No. of Patients (n) and tumour description	Radiotherapy description	PBT type	Comparison	Results	Additional notes
Lin et al., 2020[119]	Prospective (Phase II RCT), Single centre (MDACC)	n=107 (IMRT, n=61; PBT, n=46) Mixed histology/ location, mostly distal AC tumours	Definitive/NA (47.4% had surgery) Mostly 50.4Gy/28# with chemotherapy	PS (80%) /PBS	IMRT	Total Toxicity Burden (TTB)* -posterior mean TTB was 2.3 times higher for IMRT vs PBT. Post-operative complications (POC) score was 7.6 times higher for IMRT vs PBT. Survival - Comparable 3yr PFS rate (50.8% v 51.2%) and 3-year OS rates (44.5% v 44.5%).	145 patients randomised Co-primary endpoints were TTB and PFS. *TTB is a composite score of 11 distinct adverse events including post-operative complications.
Shiraishi et al., 2018[120]	Retrospective , Single centre (MDACC)	n=480 (n= 272 in propensity matched analysis) Mostly distal AC	NA 50.4Gy/28# With chemotherapy	PS/PBS	IMRT	PBT - 71% risk reduction of G4 lymphopenia. IMRT/older age/larger PTV results in higher rate of G4 lymphopenia. OS/PFS/DMFS better in absence of G4 lymphopenia.	Multivariate/univariate logistic regression models used to identify factors associated with G4 lymphopenia

Lin et al., 2017[121]	Retrospective, Single centre (MDACC)	n=580 Mostly distal AC tumours	NA 50.4Gy/28# with chemotherapy	PS/ PBS	3DCRT IMRT	*PBT vs 3DCRT/IMRT* PBT superior (post-op): Pulmonary complications (OR 0.447); cardiac complications (OR 0.518); wound complications (OR 0.266); reduced length of hospital stay. No difference: 90 day post-op mortality rates - 4.2%, 4.3%, and 0.9%, respectively, for 3D, IMRT and PBT (p=0.264) *PBT vs IMRT alone*: Trend to reduction in pulmonary complications (p=0.077); No difference in cardiac complications (p=0.695).	
Wang et al., 2020 [107]	Retrospective analysis of G3+ Cardiac events, Single centre (MDACC)	n=479 (PBT=159; IMRT, n=320)	Definitive/NA 41.4Gy/23# - 50.4Gy/28# With chemo	PS/PBS	IMRT	G3+ Cardiac events in 18% of total cohort. Median 7m post-RT, 81% within 2 years. Fewer G3+ cardiac events in PBT group vs IMRT, at 2yrs - 18% vs 11%, p=0.053. Mean heart dose correlated with rate of G3+ Cardiac Events (HR 1.034, 95% CI 1.006-1.062, p=0.015)	Dosimetric outcomes reported in Table 2

Chen et al. (2019) [122]	Prospective Phase I/II trial of dose escalation, Single centre (MDACC)	n=46 (PBT, n=7; IMRT, n=39) Mixed histology/location	Definitive/NA 50.4Gy/28# + SIB to GTV (3mm) to 63Gy/28#	n/a	Dose escalation study, single arm	PBT vs IMRT: No difference in local control No difference in overall survival Whole trial cohort vs contemporaneous cohort: SIB had superior local control (hazard ratio, 0.49; 95% CI, 0.26-0.92; P = .03) and overall survival (hazard ratio, 0.66; 95% CI, 0.47-0.94; P = .02)	Trial primarily assessing safety and feasibility of SIB. No randomisation or endpoints related to PBT.
Zeng et al., 2016[114]	Retrospective, Single centre (UoW/SCCA)	n = 13 Mid and distal tumours, SCC/AC	NA 50.4Gy/28# with chemotherapy	PS/ PBS	PBT beam arrangements PS vs PBS	pCR rate - 25% G3 oesophagitis – 7.7% G3 neutropenia – 7.7% G3 nausea – 7.7% Post op pulmonary toxicity – 33.3% Post op cardiac toxicity – 16.7% No difference in toxicities or outcomes with PS vs PBS	Dosimetric outcomes reported in Table 2
DeCesaris et al., 2020 [123]	Retrospective, Single centre (UMMC)	n=54 (PBT, n=18; Photons, n=36) Distal/GOJ, AC	NA 50.4Gy/28# with chemotherapy	PBS	IMRT	pCR rate – No difference, 7% *vs.* 22% (PBT vs IMRT), (p=0.63) 18m OS – No difference, 83% (95% CI, 71% to 95%) vs. 59% (95% CI, 50% to 68%) (PBT vs IMRT) (p=0.31) Major peri-operative events – no difference 19% vs 22% (PBT vs IMRT) 5 perioperative deaths with IMRT, 0 in PBT arm	Unmatched tumour characteristics with PBT patients having higher tumour and nodal stages

Macomber et al., 2018[113]	Retrospective, Single centre (LLUMC)	n =55 (PBT, n= 18; IMRT, n=21; 3DCRT, n=16) Mostly distal AC	NA 50.4Gy/28# with chemotherapy	PBS	IMRT 3DCRT	Median OS - 73 months, 1yr OS - 92% 2yr OS - 77%. pCR rate -20% No correlation between heart dose/radiation modality and clinical outcomes	Dosimetric outcomes reported in Table 2
Prayongrat et al., 2017[108]	Retrospective, Single centre (MDACC)	n=19 Mostly distal/GOJ AC	Definitive/NA 50.4Gy/28# with chemotherapy	PBS	-	G3-4 oesophagitis – 15.8% G3-4 haematological tox – 10.5% G1-2 cardiac – 15.8% G1 Pleural effusion – 15.8% No cases of pneumonitis 1yr OS - 100% 2yr OS - 87.5% 2yr PFS - 50.6%	Dosimetric outcomes reported in Table 2
Bhangoo et al. (2020)[124]	Retrospective, Single Centre (Mayo)	n=62 (PBT=32, IMRT=32) Mixed histology/location, mostly distal AC	Definitive/NA (53.2% had surgery) 45Gy/25# with boost to 50Gy (median)	PBS	IMRT	pCR rates – 33% vs 39% (p=0.14) G3 Tox – no difference (p=0.71) *1yr outcomes* Local control – 92% vs 84% (p=0.87) 1 yr LRCR = 92% vs 80% (p=0.76) PFS - 71% vs 45% (p=0.15) OS - 74% vs 71% (p=0.61)	Imbalanced patient characteristics in both arms
Routman et al., 2019[125]	Retrospective, Single centre (Mayo)	n = 144 (PBT, n=65; photon, n=79) Mostly AC, lower With chemotherapy	Definitive/NA 41.4-50.4Gy/23-28#	PBS	3DCRT IMRT	Whole cohort uni/multivariate models: CTV per 100 cm3, stage III/ IV and photon RT associated with higher rates of G4 Lymphopenia Propensity matched cohort (n=100):	PBT used RPO/LPO beam arrangement

						G4 lymphopenia rate – PBT 24% vs Photon 60%. [OR 4.75 (2.01-11.24), P < .001]	
Lin et al., 2012[126]	Retrospective, Single centre (MDACC)	N = 62 Mix histology Mostly AC and lower third	Definitive/ NA 50.4Gy/28# With chemotherapy	PS	-	Selected Toxicity: G3-5 Lung -1.6% G3-5 Oesophagitis-9.7% 3yr outcomes(estimated) OS – 51.7% RFS - 40.5% DMFS – 66.7% LRCR – 56.5%	Likely overlap of patients in Lin et al. (2017)[121] paper. 46.8% underwent surgical resection
Fang et al., 2018[127]	Retrospective, Single centre (MDACC)	n=448 (n=220 in propensity matched analysis) Mostly AC, lower third tumours	Definitive 45-50.4Gy/25-28# With chemotherapy	-	IMRT	IMRT associated with more G4 lymphopenia (OR 2.13 (1.19-3.81), P < .01) Reduction lymphocyte count/higher stage/greater PTV associated with worse OS. PBT benefitted lower third tumours more in reducing rate of G4 lymphopenia Radiation modality not associated with OS	Patients who developed distant metastases within 1 month of RT (21%) excluded from analysis
Xi et al., 2017[103]	Retrospective, Single centre (MDACC)	N = 343 (PBT, n=132, IMRT n=211) Mostly AC and lower tumours	Definitive 50.4/28# With chemotherapy	PS/PBS	IMRT	No difference in toxicities between both groups 5yr outcomes vs IMRT: OS – 41.6% vs 31.6% (p=.011)	Unmatched patient baseline characteristics

						PFS – 34.9% vs 20.4% (p=0.01) DMFS – 64.9% vs 49.6% (p=0.31) LRRFS – 59.9% vs 49.9% (p=0.75) Patients with stage III disease in subgroup analysis: 5yr OS (34.6% vs 25.0%, p = 0.038) 5yr PFS (33.5% vs 13.2%, p=0.005) No difference for Stage I/II patients	Additional analysis with some matched characteristics show PBT still superior for OS, PFS, LRFFS and DMFS Dosimetric outcomes reported in Table 2
Takada et al., 2016[128]	Retrospective, Multi-centre (Japanese centres)	N = 47 Mostly SCC, mix location	Definitive Two phase RT First phase -3DCRT 36Gy/20# 2nd phase PBT, 33-39.6Gy/15-18# with chemotherapy	n/a	-	Selected results: Early toxicity– 10.6% oesophagitis G3 late toxicity – 1 oesophageal fistula, 2 oesophageal stenosis, 1 pneumonitis 3yr OS, PFS, LC – 59.2%, 56.3%, 67.7% respectively	
Ishikawa et al., 2015[129]	Retrospective, Single centre (PMRC/UoT)	N = 40 Mostly upper and middle third tumours Histology n/a	Definitive 50-60Gy/30# With chemotherapy	PS	-	G3 oesophagus acute tox -22% G3 oesophagus late tox -5% No grade 3-5 acute or late cardiac/pulmonary toxicity 2yr LRC - 66.4%, CSS – 77.4% 3yr OS – 70.4%	Patients endoscopically assessed at 50Gy with 40% given 4-10Gy boost if residual tumour
Mizumoto et al., 2010[130]	Retrospective ,mostly single	n = 51 Mostly SCC	Definitive Photon RT with PBT boost (n=33)	PS	-	G3 oesophagitis 12% Post RT ulceration - 49%	Patients treated from 1985-2005

	centre (PMRC/UoT)		Median dose -80Gy over 59 days PBT alone (n=18) Median dose - 79Gy over 57 days (33-64 days) No chemotherapy			1yr: OS-62.2%,PFS – 45.5%, LRCR-64.5% 3yr: OS – 34.3%, PFS – 24.6%, LRCR – 42.8% 5yr: OS - 21.1%, PFS – 24.6%, LRCR – 38.0%	
Mizumoto et al., 2011[131]	Retrospective, Single centre (PMRC/UoT)	n = 19 Mostly SCC	Definitive 78gy (median) No chemotherapy	PS	-	One G3 oesophagitis 1 yr OS 79.0% 5 yr OS 42.8%	Patients from 1990 – 2007 Potential overlap in patient cohort with Mizumoto et al. 2010[130]
Ono, Wada, Ishikawa, Tamamura, & Tokumaru, 2019[132]	Retrospective, Multi centre (4 Japanese centres)	n = 202 Mostly thoracic SCC	Definitive 87.2 Gy (Median dose, Mix Photon and PBT RT) With/without chemotherapy (59.7% received chemotherapy)	PS/PBS	-	G2 oesophageal fistulas – 4% (n=8) G3 oesophageal ulcer – 4% G3 Pneumonitis – 0.5% 3 yr OS - 66.7%, LC- 70.2% 5 yr OS - 56.3%, LC – 64.4%	
Ono et al., 2020 [133]	Retrospective, Multi centre (4 Japanese centres)	n=38, Thoracic SCC, All aged ≥75 years	Definitive 82.7Gy (Median dose, Mix Photon and PBT RT) With/without chemotherapy (42.6% received chemotherapy)	PS/PBT	-	G3 ulcers – 5.3% No lung/heart G3 toxicities Median survival – 64m 2 yr OS: 74.9% 3yr OS: 66.2% 5yr OS: 56.2%	59.3% had Stage I/II disease Ono et al. 2015 [134] excluded – likely overlap in patient cohort.

Sato et. al., 2020 [135]	Retrospective, Single centre (NCCE)	n=44 SCC only All T1 with mostly N0/N1 disease	Definitive 60Gy with chemotherapy	n/a	-	G3 oesophagitis – 2.3% No G4 toxicity CR rates – 98% 3yr OS – 95.2% Local recurrence – 11%, all underwent salvage treatment	All patients underwent close endoscopic follow-up
Makishima et al., 2015[112]	Retrospective, Single centre (PMRC/UoT)	n= 44 (PBT, n=25 photon, n=19) SCC only	Definitive Median dose 60Gy (40Gy to CTV1, 6-Gy to CTV2) with chemotherapy	PS	3DCRT	PBT toxicity: Mostly G1 lung and heart except one G2 cardiac 3DCRT toxicity: Mostly G1, 16 episodes G2/3 lung and cardiac, one G5 lung.	Dosimetric outcomes reported in Table 2 Unmatched patient characteristics Higher rate of adverse events in PBT compared to NTCP models

Abbreviations: MDACC = MD Anderson Cancer Centre, Houston, USA ; PMRC/UoT = Proton Medical Research Centre, University of Tsukuba, Tsukuba, Japan; NCCE = National Cancer Centre East, Kashiwa, Japan; LLUMC = Linda Loma University Medical Centre, Linda Loma, USA; Mayo = Mayo Clinic, Rochester, USA; SCCA/UoW = SCCA Proton Therapy Centre/ University of Washington, Seattle, USA; UMMC = University of Maryland Medical Centre, Baltimore, USA; RCT = randomised controlled trial; NA = neoadjuvant; Gy = Gray; PBT = proton beam therapy; PS = passive scattering; PBS = pencil beam scanning [also known as spot-scanning, intensity modulated proton therapy(IMPT)]; IMRT = intensity modulated radiotherapy; VMAT = volumetric arc therapy; 3DCRT = 3D conformal radiotherapy; SIB = Simultaneous Integrated Boost; GTV = gross tumour volume; CTV = clinical target volume; PTV = planning target volume; AC = adenocarcinoma; SCC = squamous cell carcinoma; RPO = right posterior oblique; LPO = left posterior oblique; TTB = total toxicity burden; POC = post-operative complication; G1-5 = Grade 1-5; mOS = median overall survival; OS = overall survival; PFS = progression free survival; DMFS = distant metastases free survival; RFS = relapse free survival; LCRC = locoregional control rate; LRRFS = locoregional relapse free rate; LRC = locoregional control; CSS = cancer specific survival; LC = local control; pCR = pathological complete response; NTCP = normal tissue complication probability; EAR = excess absolute risk.

2.5 Discussion

2.5.1 Dosimetric Studies

All studies are either retrospective or planning studies, with most using data from a single institution. There is substantial variation in radiotherapy intent, dose, chemotherapy protocol, tumour histology, tumour location and PBT technique (PS/PBS). The studies generally reported multiple dosimetric parameters for lung, heart and spinal cord. They consistently show an overall reduction in dose to the heart and lung although not in all reported parameters. Notably, target volume (GTV/CTV/PTV) coverage are not reported in all studies. The studies which include target volume statistics report comparable coverage to photon techniques [103, 105, 108, 118]. Clinical outcomes were reported in some of these studies and are detailed in the following section.

2.5.1.1 Heart and Lung doses

For cardiac doses, there is a general reduction in most parameters, with the exception of a few studies which showed no significant difference in mean heart dose [103, 106] and another which reported no difference in volumes receiving high dose V50 heart [113]. For patients with lower third tumours in which CTV/PTV is often incident with the heart, there is still significant reduction in dose for most reported parameters. Shiraishi et al. reported that dose to all cardiac substructures other than to the left circumflex (LCX) and right coronary artery (RCA) are significantly reduced compared to IMRT [104]. Wang et al. (2020) reported that mean heart dose of <15Gy correlated with fewer Grade 3 and above (G3+) cardiac events in their retrospective cohort [107].

For the lung, there is a consistent reduction in most parameters. Predictably, in the absence of a 'low-dose bath' associated with IMRT, lower dose parameters such as mean dose, V5 and V10 showed very significant dose reduction in comparison with IMRT/VMAT with some studies reporting an approximately 50% reduction [103, 112, 120]. Dose bath to large lung volumes are likely to cause pneumonitis and therefore this is likely to be clinical meaningful. For higher dose parameters such as lung V40, Wang et al. (2015) reports that PBT is inferior to IMRT although these volumes are small [106]. In another study, Celik et al. [116] estimated a lower dose to lung resulted in a reduction of excess absolute risk (EAR) of secondary lung cancers per 10,000 patient years of nearly 70% with PBT(19.2 ± 5.7) compared to VMAT (6.1 ± 2.7).

2.5.1.2 Other OARs

For the spinal cord, there appears to be minimal sparing with a comparable or lower dose compared to photon techniques [105, 106, 109, 111, 118]. This is expected as a posterior-anterior(PA) and posterior oblique (PO) beams that traverse the spinal cord are often used in PBT. Warren et al. reports

that mean dose to thoracic vertebrae and bone can be significant reduced with PBT. This is postulated to reduce the risk of haematological toxicity including lymphopenia [117]. Dose to liver and stomach is reported in several studies, with all meeting standard dose constraints. For reported parameters, the dose to liver is consistently reduced, the clinical impact of which is uncertain.

2.5.1.3 Beam arrangements

Three studies compared the dosimetric outcomes of different combinations of PBT beam arrangements for oesophageal tumours [105, 114, 115]. Zeng et al. showed multiple combinations of beams could comfortably achieve dose and target constraints with the authors concluding that even a single PA beam is a feasible option. This paper demonstrated that different beam arrangements preferentially spared different OARs. For example, AP (anterior-posterior)/PA beams resulted in a higher heart dose, but lower lung dose compared to a PA/LPO (left posterior oblique) arrangement [114]. A recent paper by Feng et al. showed that a novel superior-inferior PO beam arrangement was a feasible option and compared to right-left PO beams, may result in lower lung doses and greater robustness to respiratory motion when interplay effects are considered [115].

Multiple different beam arrangements appear clinically acceptable with different arrangements preferentially sparing different OARs with adequate target volume coverage. This suggests PBT may allow, to a greater degree than photons, a personalised approach to the radiotherapy planning that may be tailored to take into account the comorbidities of individual patients, for example by preferentially sparing the heart or lung.

2.5.2 Clinical studies

There is only one prospective randomised study of PBT in OEC. We identified a further prospective trial which included PBT data, but this primarily assessed dose escalation in OEC. All other published clinical outcome data for PBT in OEC is retrospective, with most patients treated in a single US centre (MDACC). Despite sizable patient numbers in some of these studies, it is likely that several articles report findings based on overlapping patient cohorts. There is significant variation in type and location of tumours treated, tumour stage at presentation, treatment intent, dose, fractionation, PBT technology used, follow-up schedule and reported outcomes.

2.5.2.1 Prospective data

This study by Lin et. al [119] is a Phase IIB single centre (MDACC) RCT that compared patients who received PBT in the NA and definitive setting to those receiving IMRT. While most patients received a dose of 50.4Gy/28# (91.6% of patients), there is significant variation in type of chemotherapy. Chemotherapy regiments used included: fluorouracil (5-FU) and capecitabine (X) plus taxane (T)(55.1% of patients), Carboplatin (CP) plus T(21.5% of patients) and 5-FU plus Oxaliplatin (OX)(18.7% of patients). The primary endpoint of this trial was total toxicity burden (TTB) and PFS. TTB is a novel composite score of 11 adverse events that relies on a multivariate Bayesian model that accounts for the incidence and severity of each type of toxicity including post-operative complications [136]. The POCs were assessed at 30-days post op and included 6 potentially recurrent toxicities at 12 months. The study reported that mean TTB was 2.3 times higher for IMRT and mean post-operative complications score was 7.6 times higher for IMRT implying a significant reduction of toxicity burden for patients receiving PBT. Three-year PFS and OS for both arms showed no significant difference. This trial was approved for early closure and analysis by the data safety monitoring board in early 2019, before the activation of the multi-centre Phase 3 NRG-GI006 study of proton versus photons in OEC (NCT03801876).

The trial included patients that did not have surgery and suffered significant dropout rates post-randomisation to the PBT arm mainly due to insurance denial. Of the 145 patients randomised, only 21 patients proceeded to surgery following PBT. The RT dose and chemotherapy used in the trial were heterogenous although balanced between both arms. In addition, while TTB is a rational metric that encompasses the complex multi-organ effects of tri-modality treatment, it is yet to be widely validated outside the trial. Despite these limitations, these results are undoubtedly promising. It confirms the safety of PBT treatment and provides the first prospective data showing that dosimetric advantage translates to significantly improved toxicity outcomes. The findings of the currently recruiting phase 3 NRG-GI006 study are eagerly anticipated.

Of note, there is a further prospective study by Chen et al. included in this review. However, this was a Phase I/II study that primarily assessed safety and feasibility of SIB with no randomisation or pre-specified endpoints related to PBT. In this study, there was no difference in OS or PFS for patients who received either PBT or IMRT [122].

2.5.2.2 Neoadjuvant (NA)

There are several retrospective studies which reported on the use of NA PBT. In this setting a dose of 50.4Gy/28# is predominantly used; significantly higher than dose used in the CROSS trial of 41.4Gy/23#. Lin et al. (2017) gives a comprehensive report of post-operative complications, with PBT resulting in lower pulmonary, cardiac, wound complications and reduced length of hospital stay compared to photon techniques (3DCRT/IMRT) [121]. However, compared to IMRT alone, the current standard of care for many centres, there is only a trend to lower pulmonary complications and no difference in cardiac complications. Another study by Shiraishi et al., [120] showed there was a lower rate of G4 lymphopenia in the PBT group which in turn, correlates with improved survival outcomes and local control rates. In a separate study that included 46.8% of patients who underwent surgery, Lin et al. (2012) [126] reported favourable 3yr survival outcomes and local control rates which are at least comparable to reported RCT data [23].

While these data are promising, it is unclear if these potential benefits are maintained when using a lower dose fractionation, as is common in European practice. Additionally, as surgery is often not mandatory in many American centres, as seen in Lin et al.'s prospective study, these data are prone to inadvertent reporting bias, particularly when considering post-operative complications. Further prospective trials with robust radiotherapy and surgical protocols are required to accurately quantify the benefits of PBT in this setting.

2.5.2.3 Definitive

Most studies reported the use of PBT in the definitive setting for OEC. There is a substantial variation in RT dose/protocol and use of chemotherapy. Most studies used a dose of 50-60Gy, comparable to current practice [137]. Several studies from Japan report outcomes using a dose-escalated schedule with PBT in combination with photon RT. Ono et al. (2019) [132] delivered a median dose of 87.2Gy; significantly higher than doses commonly used in European centres [11]. While most toxicities appear acceptable, 8 patients developed oesophageal fistulas (G2+) post-RT.

Some studies looked predominantly at patients with SCC of the oesophagus. Here, 3yr OS rates range from 34.3% to 70.4% which is comparable or superior to most published data [138] with acceptable toxicities. The largest cohort (Ono et al (2019), n =202) [132] reported impressive 3yr and 5yr OS of 66.7% and 56.3% respectively. However, there was significant variation in treatment delivered e.g.

72.7% received elective nodal irradiation (58.9% with photons) and only 59.7% received concurrent chemotherapy. The study also included 55.4% of patients with operable disease, including 35.6% with Stage 1 disease, making survival outcomes difficult to interpret. The same group also published data on smaller cohort of patients aged above 75 years with mostly with early stage tumours using a median dose of 82.7Gy. This showed a promising median survival of 64 months for an elderly patient group with acceptable toxicity rates albeit with G3 ulcer rate of around 5% [133].

Studies that treated predominantly AC of the oesophagus generally did not exceed 50.4Gy in combination with chemotherapy. Here toxicity rates appear comparable or lower than photon techniques except for Grade 4 (G4) lymphopenia, which is lower in PBT in all reported studies. Survival outcomes appear at least comparable or superior to photon RT. In a single centre retrospective cohort, Xi et al. found superior OS and PFS with a 5yr OS of 41.6% (PBT) vs 31.6% (IMRT) (p = 0.011), and 5yr PFS rates of 34.9%(PBT) vs 20.4%(IMRT) (p=0.01) [103]. Fang et al., however, in a propensity-matched analysis of PBT vs IMRT, found that OS was not associated with radiation modality [127].

2.5.2.4 Cardiac Toxicity

In a retrospective cohort (treated both definitively and NA), Wang et al.[107] found PBT resulted in fewer serious cardiac events(G3+) vs IMRT [IMRT vs PBT: 2yr rate 18% vs 11%; 5yr rates 21% vs 13%; p= 0.053] . In a sub-analysis, they showed PBT contributed to a greater reduction in cardiac events for patients with underlying cardiovascular disease [IMRT vs PBT: 2yr 30% vs 11%; 5yr rates 32% vs 14%; p= 0.018)]. The median time to a serious cardiac event was seven months, with 81% of events occurring within two years. A separate study by Lin et al. [121] that reviewed post-operative complications showed no difference in cardiac complication rates with PBT. These studies suggest that PBT may not have an impact on cardiac complications in the immediate post-operative period but may significantly reduce cardiac toxicities in the medium term (from 3 months - 2 years post-RT), especially for high risk patients with underlying cardiac disease.

2.5.2.5 Grade 4(G4) lymphopenia

The rate of G4 lymphopenia is an emerging predictive bio-marker, correlating negatively with survival and local control rates post-RT for a number of tumour sites [139, 140]. This clinical endpoint has been reported by several studies included in this analysis. Three studies [120, 125, 127] used in both the NA setting and definitive settings showed PBT reduced the incidence of G4 lymphopenia, with the rate appearing to correlate with an increased size of PTV and a lower tumour location. The reasons for a reduction of G4 lymphopenia with PBT is not completely established but is likely to be related to a reduced integral and OAR dose compared to photon RT techniques. A planning study by Warren et al. reported a lower dose to bone which may provide a dosimetric rationale for this outcome [117]. A

more recent study suggests dose to circulating immune cells may be a contributing factor [141]. In their entire surgical cohort, Shiraishi et al. showed that absence of G4 lymphopenia was associated with better OS and PFS. However, in their matched analysis, there remained a PFS advantage but only a trend towards improved OS [120].

2.5.3 Passive scattering (PS) vs pencil beam scanning (PBS)

Historically, PBT to the oesophagus was delivered using passive scattering (PS) technique which is less conformal, particularly to tissues proximal to target volume, compared to newer pencil beam scanning [PBS or spot-scanning/intensity-modulated PBT (IMPT)] technique [85]. Most clinical data included in this review used PS. Outside the US and Japan, most centres are newer and therefore equipped with only PBS technology [76]. Two studies compared outcomes between the two delivery techniques. Shiraishi et al. found that most cardiac substructures received lower doses with PBS compared to PS, [104] while Zeng et al. found no difference in toxicities between the two delivery techniques [114]. Most other studies grouped the results of PBS and PS together, making analysis difficult.

2.5.4 Other technical considerations of delivering PBT to oesophagus

Uncertainties in PBT may result in a dose displacement and a distortion of delivered dose resulting in potential under-dosing of targets volumes and overdose of OARs. The range uncertainty in protons is due, in part, to uncertainties in calibration of the patient's CT to relative proton stopping powers and the handling of tissue heterogeneities by analytical dose algorithms [82]. This is especially pronounced for regions with large density heterogeneities such as the oesophagus. Factors such as intra-fraction motion [e.g. due to breathing (causing interplay effects), peristalsis] and inter-fraction changes (e.g. weight loss, tumour progression) further compound these uncertainties [96]. Multiple strategies have been developed to mitigate these uncertainties including robust optimisation/analysis [142, 143], rescanning [144], advanced on-treatment imaging/verification(image-guided RT, IGRT) [145], use of more accurate dose algorithms (e.g. Monte-Carlo) [82], and motion management techniques (e.g. breath-hold, gating) [99]. Many studies included in this analysis were carried out without the benefit of many of these recent technological advances. For example, Lin et al.'s (2020) [119] prospective study, which commenced recruitment in 2012, used daily kV imaging rather than cone beam CTs for treatment verification of PBT patients. The rapid development and adoption of new technologies such as advanced treatment planning systems, on-board volumetric imaging and motion analysis are likely to improve the certainty of delivered dose for future patients.

Another emerging area of interest is the impact of variable proton RBE on control rates and toxicity outcomes [100]. While this is a complex and emerging topic that is outside the scope of this review, it is important to note that all studies included in this review used RBE factor of 1.1 for PBT indicating

that this remains a standard approach for most centres. All published clinical outcomes of PBT are at least comparable or superior to photons, with no unexpected toxicity signals, providing reassurance of the safety of PBT to the oesophagus despite these uncertainties.

2.6 Conclusion

There is a growing body of evidence supporting the use for PBT in OEC in both the NA and definitive setting. However, most evidence is of low quality, being based mainly on retrospective cohorts with only one prospective study. The substantial variation in intent, techniques, dose, fractionation and use of chemotherapy means the role and 'gold-standard' protocol for PBT in oesophageal cancer is yet to be defined.

Based on current evidence, dosimetric advantages over photon techniques are substantial and difficult to refute. In particular, low dose parameters of the lung are significantly reduced with PBT potentially reducing toxicities such as radiation pneumonitis. Clear but less substantial reductions are seen with cardiac (whole heart/substructures), spinal cord and liver doses. Target volume (GTV/CTV/PTV) coverage appears comparable but is not consistently reported in all studies. Whilst these dosimetric advantages are theoretical it is important to recognise that some health systems, such as in the Netherlands, utilise dosimetric parameters to model normal tissue complications probability (NTCP) with an arbitrary but deemed to be clinical significant threshold of 10% NTCP-value reduction to select patients that are suitable for PBT [146].

For the clinical outcomes there appears to be a significant pattern of reduction in toxicity burden as reported in the published prospective study and other large retrospective cohorts. Importantly, there is a significant decrease in rate of post-operative lung and heart toxicities, wound healing and length of hospital stay. Beyond the immediate post-operative period, emerging data suggests that PBT reduces the incidence of severe cardiac events and reduces the risk of secondary lung cancers. The impact of PBT on survival outcomes are less obvious. Prospective data suggests it is at least equivalent to photon RT techniques and demonstrates the safety of PBT in OEC. Some studies showed an improvement in PFS and at least a trend to improved OS in comparison to photon techniques but again, the quality of evidence is low and based on mainly single-centre, retrospective cohorts.

Adjuvant IO is likely to play increasing role post NA CRT and surgery for OEC following the promising results from the Checkmate-577 trial [147]. Reducing post-operative toxicities with PBT may maximise the number of patients who are able to receive and complete this treatment. There is also some data suggesting that PBT is less immunosuppressive than photons, possibly due to a lower integral dose and greater sparing of tumour-infiltrating T-lymphocytes, potentially enhancing the efficacy of IO in this setting [148].

There is currently no evidence suggesting that variable proton RBE results in either superior control rates or unexpected toxicities. Importantly, most published studies have a limited follow-up period of several years, meaning long-term effects on survival of OAR sparing may yet be seen. G4 lymphopenia,

an emerging biomarker for poor survival in OEC, may be a potential influence on improving survival outcomes with PBT.

An area that is not explored in detail in this review is the high cost of PBT treatment and additional resources required to deliver these treatments. This is outside the scope of this review. However, it is essential that resource implications are systematically assessed in any future PBT trials by including robust and transparent health economic analyses as suggested by a recent review by Jones et al.[149]. This includes appropriate use of patient reported outcomes measures (PROMs) with longer term follow-up to assess late toxicities. Studies included in this review show that PBT has the potential to reduce late toxicities of treatment including cardiac events and secondary cancer risks suggesting the greater upfront costs of PBT may be justified with longer-term savings.

Overall, there remains a paucity of randomised, prospective data advocating the use of PBT with only a single prospective trial published to date despite the significant numbers of patients treated with PBT. The groups of patients that will benefit most from PBT are yet to be defined. Future efforts should focus on establishing a robust evidence base for the use of PBT in OEC with, prospective clinical trials such as the NRG-GI006 study. These studies should have quality-assured standardised protocols to ensure real-world reproducibility of results, robust health economic analyses to ascertain accurate cost/benefit ratios from PBT and include patient-focussed endpoints such as toxicity reduction and OS. Future work should also include the development of predictive biomarkers to determine patients who will benefit most from PBT, the incorporation of advanced planning techniques (e.g. LET-based planning) and image guidance.

While there is currently insufficient evidence to recommend PBT as a standard of care in the treatment of OEC, it undoubtedly holds substantial promise; potentially improving outcomes for a cancer that continues to have a dismal prognosis. For this, PBT clearly warrants urgent further evaluation.

Chapter 3: Dosimetric Parameters and Normal Tissue Complication Probability (NTCP) comparison for PBT vs VMAT in Lower Third Oesophagus Cancers

3.1 Introduction

As summarised in the first two chapters, the hypothesis that PBT may contribute to improving outcomes in OEC clearly warrants further examination. This chapter investigates and quantifies potential dosimetric benefits of PBT over photon RT in OEC in greater detail. The systematic review in chapter 2 highlights the significant heterogeneity of patients treated with PBT in the currently published literature. This work looks specifically at a patient cohort with lower third/GOJ AC of the oesophagus undergoing NACRT. This work investigates the potential improvements that may be derived from PBT in the pre-operative setting thus providing a novel addition to published knowledge.

3.1.1 Aims and objectives

In patients with lower third/GOJ OEC undergoing NACRT, the aims and objectives of this work are:

1) Develop the skills and practical methods of creating clinically acceptable PBT plans.
2) To assess if target volume (TV) coverage for PBT is adequate and comparable to VMAT in order to ascertain the efficacy (non-inferiority) of PBT treatments.
3) To quantify dose reductions to OARs, focussing on heart and lung endpoints.
4) Quantify the potential clinical impact of any dose reductions to the lung and heart using established NTCP models.
5) Comparative analysis of 3DCRT, VMAT and PBT technologies, with regards to OAR sparing and TV coverage, highlighting the potential impact of technological advances in RT for OEC.
6) Explore novel dosimetric aspects of PBT in OEC:
    a) Splenic dose in comparison to VMAT and novel splenic dose constraints (Chapter 4)
    b) The influence of beam arrangements of OAR dose (Chapter 5)
    c) Dose to cardiac substructures with PBT (Chapter 5)

3.1.2 Overview of dosimetric comparison studies

Dosimetric comparison studies, or treatment planning studies, are often used in literature to compare plans produced using different treatment modalities on the same clinical datasets. Clinical cases and planning parameters are kept constant where possible, with the only variable being the RT technique used. There should be an adequate number of cases (usually >=5) to ensure a variety of clinical scenarios such as tumour location and size of TV, reflecting real-life practice. Reported dosimetric parameters should be pre-specified prior to planning work being undertaken and are commonly based on endpoints of interest. Results are commonly presented and compared using dose volume histogram (DVH) results for specific endpoints such as planning treatment volume (PTV) coverage and dose to OARs of interest (e.g. spinal cord, lung, heart) [150].

Dosimetric comparison studies are useful for several reasons. Firstly, they facilitate the introduction of a new technology in RT prior to treating patients, analogous to pre-clinical laboratory work for drug interventions. It allows researchers to assess potential benefits of a new radiation technique and overall feasibility of a treatment approach by giving 'hands-on' experience to physicists and clinicians creating plans for these techniques. Secondly, it informs clinicians making treatment decisions on the best technique to use in specific clinical scenarios by quantifying potential advantages and disadvantages of a technique in a given clinical setting. This can be especially useful for situations where RCTs are not possible such as in paediatric tumours, where it may be unethical to carry out RCTs, or rare cancers, where low incidence rates make recruitment unfeasible. These studies provide researchers with valuable pre-clinical data that inform clinical trial design, which remains the 'gold standard' of assessing any new technology. Finally, by publishing detailed methodology in creating these plans, these planning studies may provide a blueprint for treatment planners on how to reliably recreate plans in the clinical setting [150].

3.1.3 Limitations of dosimetric comparison studies

Like other pre-clinical work, planning studies are only hypothesis generating. Data derived from these studies on its own are inadequate to change practice. The non-clinical setting of these studies means that many of the real-life intricacies of clinical cases are often lost. For example, as many treatment planning studies are based on a single pre-treatment planning CT scan, it would be challenging to reproduce the anatomical changes throughout a treatment course, potentially diminishing any supposed dosimetric advantages of a new RT technique. Additionally, due to small patient numbers, planning studies are unlikely to cover all permutations of a clinical presentation. Crucially, there is no guarantee that dosimetric advantages translates into clinical benefit. Prospective RCT data remains the 'gold-standard' method of assessment. Results from any dosimetric comparison studies need to

be interpreted in the light of these uncertainties. Despite these limitations, treatment planning studies remain a vital step in the introduction of a new RT technique into the clinical setting. Specific limitations of this study are discussed later in this chapter.

3.2 Materials and methods

3.2.1 The NeoSCOPE trial

NeoSCOPE was a non-blinded, randomised (1:1 via a centralised computer system), 'pick a winner' phase II trial for patients with resectable oesophageal AC investigating the benefit of two different NACRT regimens for OEC. Both arms were given two 3-weekly cycles of oxaliplatin (130 mg/m^2 intravenously on day 1) and capecitabine 625 mg/m^2 orally twice daily from day 1 to day 21) as induction chemotherapy. For the CRT phase, patients were randomised to 45 Gy/25# with either oxaliplatin (85 mg/m2 intravenously on day 1, 15, 29) and capecitabine (625 mg/m2 bd orally on days of RT or carboplatin AUC2 and paclitaxel 50 mg/m2) administered intravenously on days 1, 8 15, 22, 29 of RT. RT was delivered using 3D conformal (3DCRT) plans. Surgery was performed 6 to 8 weeks after NACRT. Primary endpoint was pCR. Secondary endpoints included toxicity, surgical morbidity/mortality, resection rate and OS. Full results of the study are published elsewhere [40].

The trial included a detailed RT Trials Quality Assurance (RTTQA) programme including a detailed RT protocol and guidance document, pre-accrual RT workshop, outlining exercise, and central evaluation of contouring and planning [151]. It was the first multi-centre trial in the UK to incorporate four-dimensional computed tomography (4D-CT) scans into the RT planning process with all patients with lower oesophageal/GOJ tumours encouraged to use 4D-CT planning [40]. Of the 85 patients that were recruited to the trial, 28 patients utilised 4D-CT planning [27]. Twenty of these cases, along with their robustly quality-assured treatment volumes and OAR structures, form the datasets used in this dosimetric comparison study.

3.2.2 Target volumes in 4D-CT cases in the NeoSCOPE trial

The target volumes as used in the NeoSCOPE trial are as per standard International Committee on Radiation Units and Measurements (ICRU) nomenclature. TV is an umbrella term that is used to cover the planning target volume (PTV) or the internal target volume (ITV). ITV refers to a CTV that incorporates physiological movement that are unable to be accounted for during treatment e.g. respiratory motion. Table 7 and Figure 8 describes nomenclature used to describe the target volumes as per ICRU 29, ICRU 50 and ICRU 62 guidelines [152, 153].

Target Volume	Definition

Gross Target Volume (GTV)	The GTV is the volume that contains the visible or clinically detectable tumour. This may be on clinical examination or on imaging. This is the smallest of all volumes and is not present in every plan (e.g. adjuvant RT following excision of the main tumour mass).
Clinical Target Volume (CTV)	The CTV is the volume which has been determined to require radiation treatment. This includes the GTV as well as areas of clinical risk – such as lymph node groups or the region about the GTV that may have microscopic involvement. The CTV should be included in every plan.
Internal Target Volume (ITV)(also referred to as iCTV)	The ITV includes a margin to account for physiological patient movements that are unable to be accounted for during treatment. This may include movement of the gut, beating of the heart or respiration. The margin required is known as the internal margin (IM) and may vary in height, breadth and depth based on the location within the body. The ITV is a newer concept that attempts to divide treatment inaccuracies into internal patient factors and external factors. If a method to reduce the effect of internal movements is used (e.g. respiratory gating) then the ITV can be substantially reduced.
Planning Target Volume (PTV)	The PTV is an expansion from the ITV to account for external treatment inaccuracies. These may vary based on the department and the treatment site – for instance a treatment inaccuracy of 7 mm for body treatments and 3 mm for head and neck treatments. This distance is the external margin (EM). Improving the external factors which lead to treatment inaccuracies may reduce the external margin and allow for smaller PTV expansions.
Organs at Risk (OARs)	Organs at risk are volumes placed on organs which are susceptible to radiation. They place constraints on the beam arrangement and dose that may be delivered. OARs may have different radiation tolerances based on the tissue involved
ICRU Reference Point	The ICRU recommends reporting the dose at a single point within the PTV. The point should be clinically relevant, easily defined, and placed in a region of uniform dose (away from steep dose gradients or inhomogeneities if possible). The point should be at the centre of the PTV and at the intersection of the beam axes if possible

Table 7shows definitions of volumes and concepts used in radiotherapy planning based on ICRU 50 and ICRU 62 guidelines

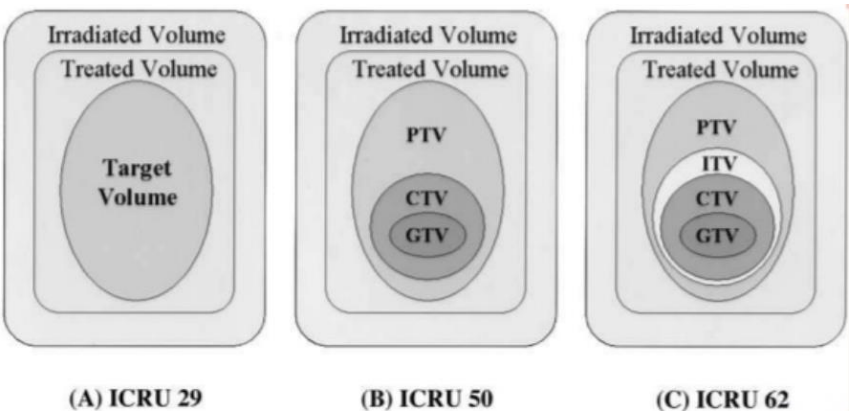


Figure 8 shows target volumes as described by ICRU 29, ICRU 50 and ICRU 69. PTV: planning target volume; CTV: Clinical target volume; ITV: internal target volume; GTV: gross target volume [154].

3.2.3 Approval for data use and transfer to Rutherford Cancer Centres

A formal application to use these anonymised datasets for a proton dosimetric comparison study was submitted to the trial sponsor, Velindre University NHS trust, in May 2018. The application included a specific request to transfer of the datasets to my collaborators, Rutherford Cancer Centres, Newport (Rutherford Health plc). In September 2018 the sponsor approved the use and transfer of the 20 NeoSCOPE datasets for this study.

3.2.4 Rutherford Cancer Centres

Rutherford Cancer Centres are a network of private PBT centres in the UK which opened its first centre in Newport, South Wales in 2017, treating its first patient with PBT in April 2018. In Wales, Rutherford Cancer Centres are commissioned to deliver PBT for NHS patients that are eligible through NHS criteria. My collaborators at the Rutherford are Dr Jamil Lambert PhD (JL), principal proton physicist, and Agelos Saplaouras (AS), research physicist. JL has over a decade of experience in clinical PBT planning and provided expert guidance in the proton component of this dosimetric comparison study.

The Rutherford Cancer Centre in Newport is equipped with an IBA Proteus One machine, which utilises pencil-beam scanning PBT (PBS) technology with capability to deliver intensity modulated proton therapy (IMPT). The IBA Proteus One machine is a compact, single-room proton therapy system that features an isochronous cyclotron, 220^{o} partial-rotation compact gantry, scanning-beam delivery nozzle, image-guidance system with cone-beam CT and stereoscopic imaging capabilities and a 6D robotic couch [155].

3.2.5 Data transfer and preparation

The 20 datasets from NeoSCOPE were transferred in DICOM format to our institutional database [South West Wales Cancer Centre, (SWWCC)] from an RTTQA database in Velindre University NHS

Trust, Cardiff. Cardiff was the RTTQA site for NeoSCOPE. The same 20 cases were transferred to our collaborators, Rutherford Cancer Centre in Newport, Wales. These datasets contained the contrasted single-phase CT planning scans with patients immobilised in treatment position along with the target volumes and OARs as treated in the NeoSCOPE trial. As these were 4D-CT cases, ITVs that were generated using the NeoSCOPE outlining protocol from all respiratory sequences in the planning CT were included. The PTV was generated by applying a 5 mm margin in all directions to the ITV and included in with datasets. All structures from these cases underwent a meticulous QA programme by the trial RTTQA team and approved for clinical use in the trial. The RTTQA protocol for the NeoSCOPE study is published elsewhere [151, 156]. Table 8 outlines the structures that are included with the datasets. The NeoSCOPE delineation protocol is included in the appendix.

Type of volume	Outlined structures
Target Volumes	Gross Tumour Volume (GTV) – GTV_ref, GTV_MaxInsp, GTV_MaxExp Clinical Target Volumes (CTV) – CTVA_ref/ CTVA_MaxInsp/CTVA_MaxExp; CTVB_ref, CTVB_MaxInsp/CTVB_MaxExp Internal Target Volume (ITV) Planning Target Volume (PTV)
Spinal Cord	Spinal cord canal Spinal cord planning organ at risk volume (PRV)
Lungs	Combined lungs Right lung Left lung
Heart	Whole heart
Liver	Whole liver
Stomach	Whole stomach
Kidneys	Combined kidneys Right kidney Left kidney

Table 8: Quality-assured structures included with the 20 NeoSCOPE datasets

3.2.6 Planning goals and dose constraints

Reported dose and planning constraints used in this study were taken from the NeoSCOPE trial protocol. The dose used in the trial was 45 Gy in 25#. Dose constraints used are outlined in table 9.

Dose reported	Constraint

Total PTV volume (ccm)	-
PTV (type B algorithm)	V95% >99%
ICRU maximum dose	D1.8cc <107%
Combined lung V20 Gy	<25%
Heart V25 Gy	<50%
Heart V40 Gy	<30%
Liver V30 Gy	<60%
Spinal cord PRV	D0.1 cc < 40 Gy
Left Kidney V20 Gy	<25%
Right Kidney V20 Gy	<25%
Stomach V50	<16(optimal)/25 ccm(mandatory)

Table 9: Planning goals and dose constraints as taken from NeoSCOPE trial

These are the mandatory constraints as used in the NeoSCOPE trial. In addition to the NeoSCOPE constraints, V5 lung and mean lung dose was also reported although plans were not optimised to these constraints. These were selected as additional endpoints as there is evidence of correlation between volume of lung receiving >5 Gy and mean lung dose with increased post-oesophagectomy lung toxicity [34, 35]. If constraints were comfortably met without compromising TV coverage, the optimiser was pushed further to reduce doses to OARs. A reduction in dose to lung and heart were prioritised over other OARs as dose to these structures were most likely to influence toxicities which most commonly affects the lung and heart in OEC. This process is covered in more detail in the following sections.

3.2.7 VMAT planning

VMAT plans were created in collaboration with a SWWCC physicist, Adam Selby (ASb). Plans were created on an in-house TPS, Pinnacle (Phillips, v16.2). Each plan was inversely planned according to the NeoSCOPE trial constraints (see table 9) and utilised a Type B algorithm. Each case was planned to ensure the PTV volume receiving 95% of the prescribed dose was >99%. In addition, V5 lung and mean lung dose were reported. Dose to OARs were kept as low as possible, as per the ALARA ('as low as reasonably achievable') principle. Spinal cord PRV and PTV coverage were first and second priority constraints respectively, followed by dose to other OARs. If dose constraints for spinal cord PRV and PTV were met, the optimiser was pushed to reduce dose to lung and heart further. All plans used one full 360^{o} arc. The first four cases were inversely planned with the optimiser manually tweaked to improve dose distribution to OARs. The resulting plans were reviewed by myself and ASb and were found to be meet or exceed mandatory constraints. The following 16 plans utilised the Pinnacle^{3} AutoPlanning Engine which uses template-based automation to create VMAT plans. This engine has

been shown to produce high-quality and consistent plans, and is used in clinical practice to improve departmental radiotherapy workflow [157]. Dose constraints and a standardised prioritisation protocol, based on the first four manually created plans, were inputted into the AutoPlanning engine. ASb and I then reviewed the resulting 16 plans with manual tweaks on the optimiser if it was felt plans could be improved.

A good target conformality was achieved for all cases. Dose received by OARs as set out in the NeoSCOPE protocol were assessed and presented in a DVH table. In an attempt to 'quality-assure' the plans, each plan was reviewed. All plans were deemed to be clinically acceptable, passing all mandatory constraints.

3.2.8 Three dimensional conformal RT (3DCRT) planning

The 3DCRT plans used in this comparison were created for a separate but related study. This study compared plans created using single-phase planning scans (3D-CT) and 4D-CT planning scans concluding that treatment plans derived from 4D-CT planning scans were superior, resulting in lower dose to OARs and significantly reduced relative risk in calculated heart and lung NTCP endpoints. The results of this study have been published in full and included in the appendix [158]. As the same 20 cases from NeoSCOPE were used, it was possible to reuse these data as an additional comparison arm to the VMAT vs PBT study, providing an additional perspective on available RT technology. The plan statistics from the 4D-CT arm were used in this study. Only selected dosimetric endpoints of interest (lung, heart, liver, spinal cord) and NTCP endpoints from 4D-CT plans were used for comparison to minimise data duplication.

3DCRT plans were created by ASb using an in-house treatment planning system (TPS), Oncentra MasterPlan (version 4.3). The parameters as used in the NeoSCOPE trial were used (see table 4) and utilised a Type B algorithm. Each case was planned to ensure the PTV volume receiving 95% of the prescribed dose was >99%. Dose to OARs were kept as low as possible, as per the ALARA principle. All plans used a 4-beam arrangement as per the local clinical protocol.

Good target conformality was achieved for all cases. Dose received by OARs as set out in the NeoSCOPE protocol were assessed and presented in a DVH table. To 'quality-assure' the plans, each plan was reviewed by Dr Sarah Gwynne (SG), who was the RTTQA lead for the NeoSCOPE trial. All plans were deemed to be clinically acceptable, passing all mandatory constraints.

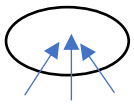
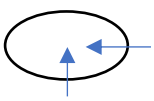
3.2.9 PBT Planning

3.2.9.1 Overview of PBT planning

PBT plans in this study were created in collaboration with JL and AS, physicists at the Rutherford Cancer Centre, Newport. All plans were created on their in-house TPS, Pinnacle (Phillips, V14) and utilised a pencil-beam (Type A) algorithm. Plans were robustly optimised using treatment parameters from the NeoSCOPE trial. In addition, V5 lung and mean lung dose were reported. Details on beam arrangements, robust optimisation and robust evaluation are covered in the following sections.

3.2.9.2 Selection of beam arrangements

As discussed in Chapter 1, beam arrangements often have a greater influence on dose distribution of PBT plans compared to photon techniques. Careful selection of beam angles is a crucial step in achieving the intended dosimetric outcome of a proton plan. As elaborated in the systematic review in Chapter 2, several beam arrangements have been proposed for OEC cases. Table 10 outlines several different proposed arrangements with pros and cons.

Beam arrangements	**Pros**	**Cons**
3 Beam: Posterior-Anterior (PA) /Right Posterior Oblique (RPO)/ Left posterior oblique (LPO) 	• More robust to anatomical change including breathing motion • Distal end of beam in three locations, reducing probability of a high-LET 'hotspot' in a cardiac substructure e.g. right atrium • Likely to meet all dose constraints	• Likely higher lung/heart dose
2 Beam – PA/Left lateral(LL) or right lateral (RL) 	• Likely lower lung/heart dose compared to a 3-beam arrangement • Likely to meet all dose constraints	• Less robust to anatomical change compared to 3 beam arrangement

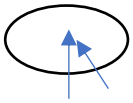
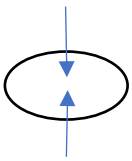
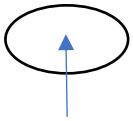
2 Beam – PA/RPO or LPO 	• Likely lower lung/heart dose compared to a 3-beam arrangement • Likely to meet all dose constraints	• Less robust to anatomical change compared to 3 beam arrangement
2 Beam – PA/AP 	• Lower dose to lung compared to PA/LPO or RPO • Likely to meet all dose constraints	• Higher whole heart dose vs other beam arrangements • Risk of 'hot-spot' in spinal cord or in a cardiac substructure • Less robust to anatomical change compared to 3 beam arrangement
1 Beam - PA 	• Lowest lung dose of all arrangements • Lower whole heart dose • Likely to meet all dose constraints	• Not robust to anatomical change and breathing motion • Risk of 'hot-spot' at distal end of beam, likely in a cardiac substructure • Higher spinal cord dose

Table 10: Proposed beam arrangements for oesophageal cases including pros and cons.

The beam arrangements were trialled and discussed with JL. All beams arrangements were found to meet planning goals and dose constraints. In an attempt to increase robustness to anatomical change and breathing motion, we decided on a three posterior beam arrangement (PA/RPO/LPO) with gantry angles of 135°, 180° and 135° with the couch rotated 180° (equivalent to 225°). Three beams are more robust than two as it blurs out the breathing motion and reduces the effect of anatomical changes along any one beam path. Posterior beams generally traversed the vertebrae and surrounding soft tissue, thus avoiding the lung and minimising the impact of diaphragmatic motion.

Beam arrangements and impact on TV coverage and OAR dose are further explored in Chapter 5.

3.2.9.3 Robust optimisation

As discussed in Chapter 1, robust optimisation refers to the process of creating plans that are robust to intrinsic range uncertainties in PBT. Robust optimisation aims to include these uncertainties

explicitly in the optimisation process. Plans are optimised with the aim of meeting plan objectives even when the defined errors (such as patient setup errors) occur [87].

For this study, PBT plans were robustly optimised to the ITV rather than the PTV. Dose coverage to PTV were also reported in order to maintain uniformity for comparison. A 5 mm setup uncertainty in all directions (X, Y, Z axis) and a 3.5% range uncertainty were used in the optimisation processed. A combination of setup and range uncertainties, creating 15 permutations of uncertainty scenarios, were used. Table 11 illustrates this further.

	Independent				Combination			
	X (mm)	Y (mm)	Z (mm)	Range (%)	X (mm)	Y (mm)	Z (mm)	Range (%)
1	0	0	0	0	0	0	0	0
2	0	0	0	+3.5	0	0	0	+3.5
3	0	0	0	-3.5	0	0	0	-3.5
4	+5	0	0	0	+5	0	0	+3.5
5	-5	0	0	0	+5	0	0	-3.5
6	0	+5	0	0	-5	0	0	+3.5
7	0	-5	0	0	-5	0	0	-3.5
8	0	0	+5	0	0	+5	0	+3.5
9	0	0	-5	0	0	+5	0	-3.5
10					0	-5	0	+3.5
11					0	-5	0	-3.5
12					0	0	+5	+3.5
13					0	0	+5	-3.5
14					0	0	-5	+3.5
15					0	0	-5	-3.5

Table 11: This table demonstrates different permutations of uncertainty scenarios when setup and range uncertainty are assessed independently or as a combination. When setup and range uncertainty are assessed independently of each other, this results in fewer permutations and may not be reflective of real-life scenarios as both setup and range uncertainty may occur simultaneously. Combining both setup and range uncertainties result in a greater number of permutations and incorporates uncertainties that are more likely to occur in real-life patients. (Table adapted from Lowe et al. 2020)[87].

For all dose outcomes including ITV/PTV coverage, worst case and second-to-worst case scenarios were reported. Although some centres advocate the reporting worst case scenarios, including the UK RTTQA group [87], clinical practice in Rutherford Cancer Centre is to report the second to worst case. Assuming a Gaussian distribution, the second worst case scenario is felt to more closely reflect 'real-life' doses. It is also the strategy employed by Penn Medicine Radiation Oncology, University of

Pennsylvania (UPenn), an experienced US-based PBT centre, who peer-review plans for the Rutherford Cancer Centre (personal communication with JL).

An additional consideration in the optimisation process is the decision to use either single field optimisation (SFO) or a multi-field optimisation (MFO) [also referred to as intensity modulated proton therapy (IMPT)] techniques. As discussed in Chapter 1, SFO refers to an optimisation technique in which all field are optimised independently, with each aiming to satisfy the optimisation objectives. MFO refers a technique in which all fields are optimised simultaneously. SFO results in fields with fewer in-field dose gradients but a less conformal target coverage compared to MFO [87]. In order to increase robustness to anatomical changes and breathing motion, it was decided to use an SFO approach for all PBT plans in this study.

3.2.10 Normal Tissue Complication Probability (NTCP) modelling

3.2.10.1 Overview of NTCP modelling

In an attempt to quantify the clinical significance of the calculated dose volume differences between treatment plans derived by each planning technique, NTCP were calculated for the heart and the lung volumes within each case. NTCP models describe the probability of complications in normal tissues during a radiation course in terms of dose-response curves. They are based on the assumption that a certain percentage of normal tissue will have unfavourable reaction from a particular dose during a radiation course. The Lyman-Kutcher-Burman (LKB) model was selected to predict the NTCP, as used often within the literature. As the LKB model assumes that normal tissue is uniformly irradiated which does not reflect clinical practice, the model includes a histogram-reduction algorithm which transforms a multi-step dose volume histogram obtained for a specific treatment plan into a biologically iso-effective uniform dose, equivalent uniform dose (EUD) [159-161].

The LKB model calculates NTCP values for different tissues using the following equations and parameters :

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{-t^2/2}\, dt$$

where

$$t = \frac{D - TD_{50}(v)}{mTD_{50}(v)}$$

$$TD_{50}(v) = TD_{50}(l)v^{-n}$$

D represents the Equivalent Uniform Dose (EUD) delivered to the organ (that results in the same NTCP as the planned non-uniform dose distribution). TD_{50} is the tolerance dose for a homogenous dose distribution to a whole organ =at which 50% of patients are likely to experience a defined toxicity within 5 years.. $TD_{50}(v)$ is the tolerance dose for a partial volume *v*. *m* represents the slope of the NTCP dose-response curve. The parameter m multiplied by TD_{50}(v) approximates the standard deviation of volume V. *n* represents the volume effect of the organ being assessed which can range from 0-1, where n=0 indicates a completely serial structure where the maximum dose dominates outcomes and n=1 indicates a completely parrallel structure where the mean dose is related to outcome. D is maximum dose of the DVH to ensure V < 1. .

Equation 1 Lyman-Kutcher-Burman Equations for NTCP

The LKB model describes the sigmoidal dose response observed by OARs as an error function. This function is used to calculate the probability of a specific toxicity endpoint occurring and is dependent upon the magnitude of the dose incident on the OAR, as well as the proportion of the OARs volume which is irradiated to that dose level.

3.2.10.2 Selection of endpoints and LKB model parameters

As NACRT is commonly linked to lung and heart complications post-operatively, I selected NTCP modelling endpoints for these organs. There are currently no well-validated LKB models for post-operative lung and heart complications, therefore I selected comparable parameters as surrogates for these endpoints. A review of the literature led to two sets of LKB parameters being chosen for the heart and the lungs respectively in an attempt to minimise any impact of a single LKB model parameter. The lung models selected assess the probability of inducing grade 2 or grade 3 (or higher) radiation pneumonitis, and the heart endpoints under investigation are pericardial effusion and radiation induced valvular dysfunction. Table 12 details selected lung/heart NTCP endpoints and their respective LKB model parameters.

Along with the DVH data for the heart and lung exported from the TPS, the model parameters ***n, a, m*** and ***TD50*** were used within the LKB model to generate NTCP data for each patient. ***m*** represents the slope of the NTCP dose-response curve. **n** represents the volume effect of the organ being assessed which can range from 0 to 1. ***a*** is the inverse of ***n*** i.e. a=1/n.

Organ	LKB Model Parameters	Endpoint	Reference
Heart	n= 0.35, a=2.857,m=0.1,TD50=48Gy	Pericarditis/pericardial effusion	Burman et al[159]
Heart	n=0.16, a=6.25,m=0.67,TD50=32.8Gy	Radiation induced heart valvular dysfunction	Cella et al[162]
Lung	n=0.8703, a=1.149,m=0.18,TD50=24.5Gy	Lung pneumonitis (>grade 3)	Yorke et al. [101]
Lung	n=1, a=1,m=0.45,TD50=29.2Gy	Lung radiation pneumonitis: grade 2, (symptoms requiring steroids) or higher	De Jaeger et al [163]

Table 12 Lung/heart NTCP endpoints and their respective LKB model parameters

CERR was used to generate NTCP values using the DVH data and LKB parameters. CERR is an open source software environment that is based on MATLAB and can be used to evaluate treatment plans using various parameters [164]. All RT plans (DICOM format) were imported into CERR. For each clinical case, I compared three radiotherapy plans: 3DCRT, VMAT and PBT. Using an inbuilt LKB NTCP modelling tool in CERR, probabilities of each investigated endpoint were derived and compared. Both relative risk and absolute risk reductions with 95% confidence intervals are reported for each endpoint.

3.2.11 Statistical analysis

All key metrics for the VMAT and PBT plans were included for all 20 patients. The mean of each reported dosimetric outcome and percentage difference were reported. More specifically, since each patient provided matching observations for the two plans (VMAT and PBT), each constraint was tested separately using paired t-test (two-tail) to assess statistical significance.

In the comparison of the 3DCRT, VMAT and PBT plans, selected metrics of important OARs such as the lung and heart for the three plans were included. Summary measures such as minimums, maximums, medians and interquartile range were included.

In addition, the findings from NTCP analysis were reported in terms of absolute and relative risk reduction with confidence intervals to assess statistical significance.

3.3 Results

3.3.1 PBT vs VMAT plans

ROI	DVH Parameter	Objective	VMAT	PBT	% Diff.	P value
PTV	V95%	>99%	99.5	95.6	-3.9	<0.001
ITV	Robust second-to-worst scenario	-	-	98.9	-0.6	0.01
	Robust worst-case scenario	-	-	98.4	-1.1	-
External	D1.8 ccm	<107%	46.3	47.6	2.7	<0.001
Cord_PRV	D1 ccm	<40Gy	21.8	24.3	11.3	0.92
Lungs	V20 Gy (%)	<20%	7.3	5.3	-27.4	0.002
	V5 Gy (%)	-	45.6	17.9	-60.8	<0.001
	Mean dose (Gy)	-	7.0	3.2	-54.6	<0.001
Heart	V40 Gy	<30%	7.0	4.5	-36.4	<0.001
	V25 Gy	<50%	20.8	9.9	-52.4	<0.001
Liver	V30 Gy	<60%	7.6	5.6	-25.6	<0.001
Lt Kidney	V20 Gy	<25%	0.4	3.4	661.8	<0.004
Rt Kidney	V20 Gy	<25%	0.1	0.2	132.9	0.63

Table 13 Results directly comparing mean statistics of each reported outcome for VMAT and PBT plans with p-value (paired t-test).

Table 13 shows a direct comparison of mean values for each reported dosimetric endpoint for VMAT and PBT plans.

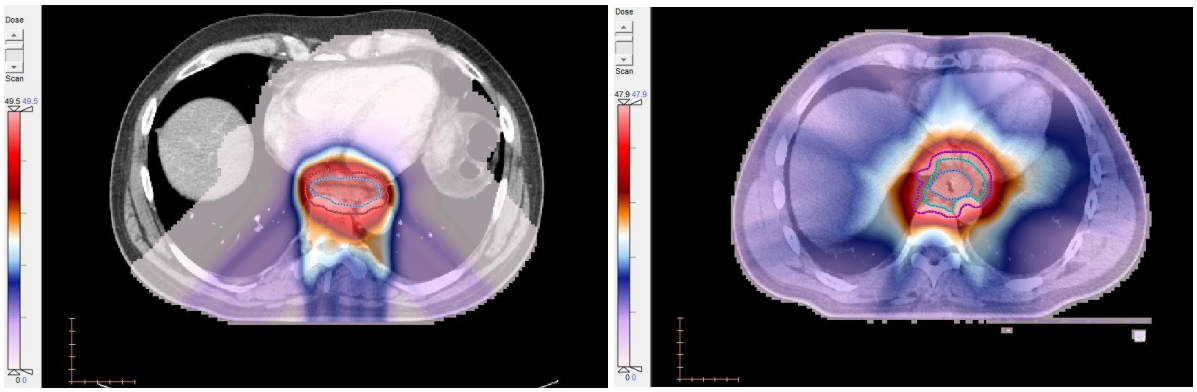


Figure 9 An illustrative axial slice from the same case comparing dose distributions for PBT(L) and VMAT (R). Note beam arrangement used in PBT plan. High dose is region is in RED, low dose in PURPLE.

3.3.1.1 Target volume coverage

In terms of PTV coverage, PBT plans were significantly inferior to VMAT plans with a mean V95% of 95.6% and 99.5% respectively. This is partly because PBT plans were robustly optimised to ITV rather than PTV. Looking at the second-to-worst scenario of ITV coverage, TV coverage improves to 98.9%.

3.3.1.2 Spinal Cord Dose

There is no significant difference to spinal cord dose for VMAT and PBT with maximum doses to D0.1 ccm cord PRV of 21.8 Gy vs 24.3 Gy respectively (p=0.92). As the beam arrangements consisted of three beams (PA, LPO, RPO), only the PA beam directly traversed the spinal cord allowing adequate sparing. Different beam arrangements that were trialled (see table 10), such as single PA beam and two beams (PA and LPO or RPO), resulted in a higher dose to the spinal cord but still met the mandatory dose constraint of <40 Gy. This is not formally reported here but the effect of beam arrangements is investigated in more detail in Chapter 5.

3.3.1.3 Dose to Lungs and Heart

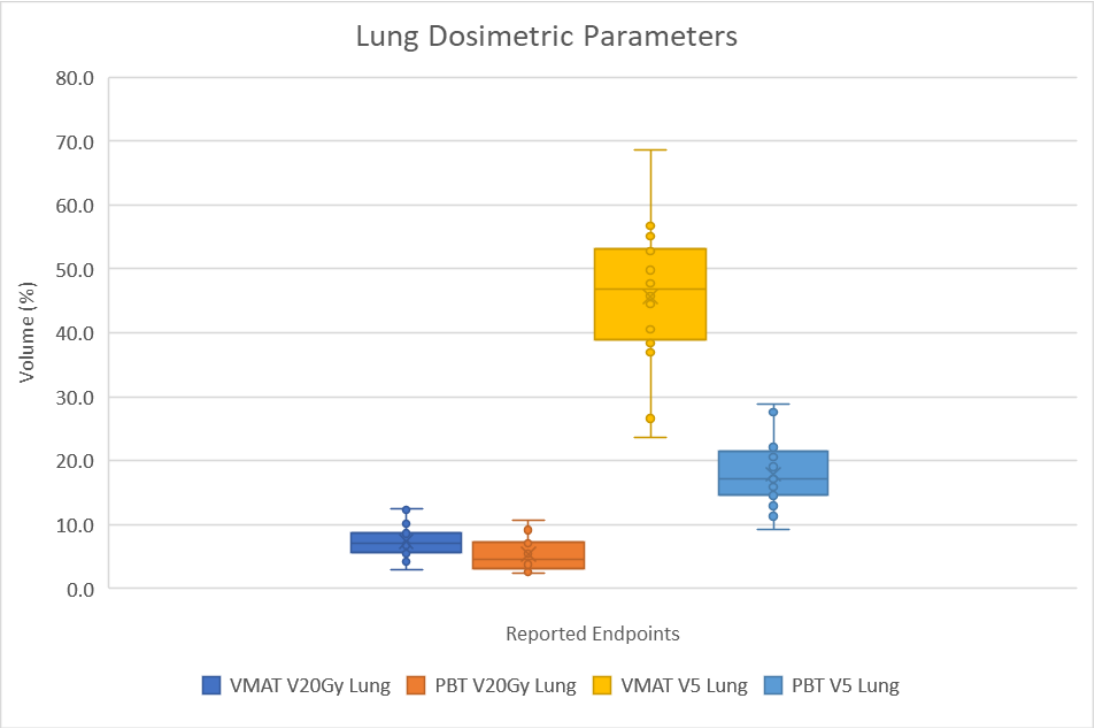


Table 14 Box plot of Lung Dosimetric Endpoints for VMAT and PBT for all 20 cases.

There is significant improvement in all reported lung dosimetric parameters for PBT plans compared to VMAT. For lung V20, there was an average reduction of 27.4% with PBT in comparison to VMAT with lung V20 of 7.3% vs 5.3% (p<0.05) for PBT plans and VMAT plans respectively. While this is a significant reduction, it is it important to note both absolute values are low, with VMAT also delivering low V20 doses. Table 14 shows that most plans, V20Gy was marginally lower with PBT. For the lower dose lung parameters of V5 and mean dose, an even greater reduction was seen for PBT compared to VMAT. For Lung V5, PBT resulted in 17.9% vs 45.6% for VMAT (p <0.05), representing a 60.8% reduction. Table 14 highlights how in most cases PBT resulted in a significant reduction of lung V5. For mean lung dose, PBT resulted in 3.2 Gy vs 7.0 Gy for VMAT (p <0.05), which represents a 54.6%

reduction. As VMAT utilises a full 360-degree arc to deliver the dose to the target volume, a substantial proportion of total lung volume will be inadvertently irradiated albeit at a low dose.

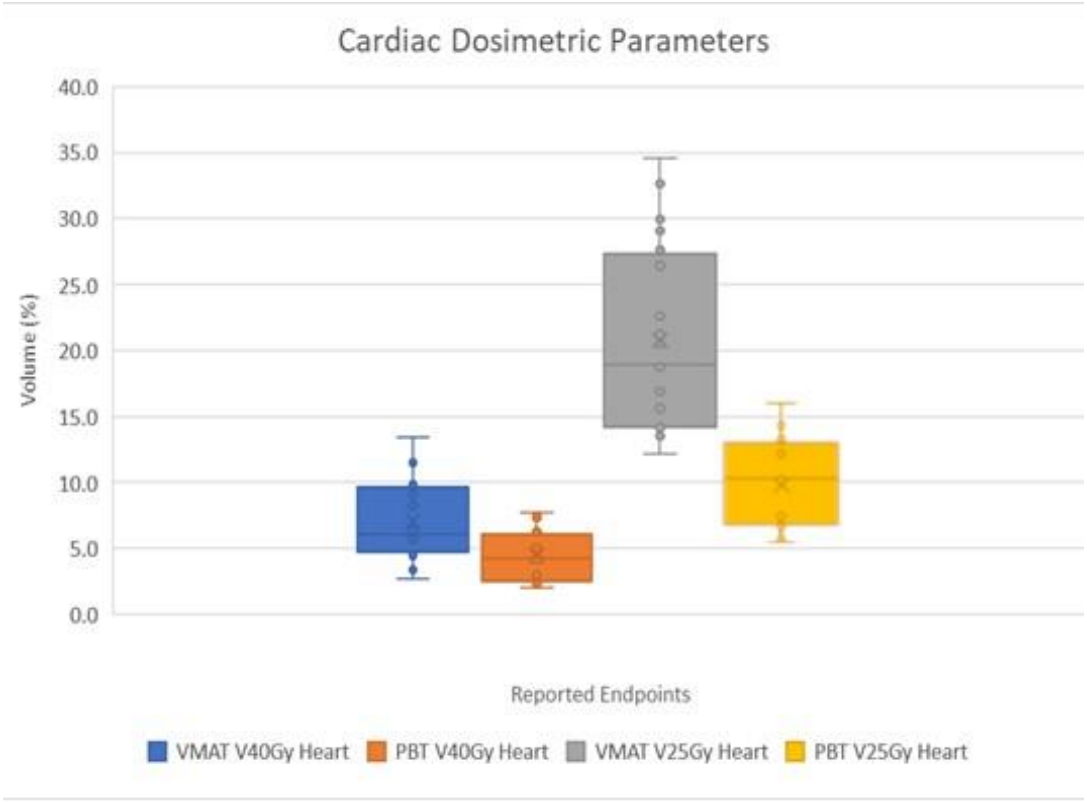


Table 15 Box plot showing cardiac dosimetric parameters for VMAT and PBT for all 20 cases

For heart doses, again PBT showed a reduction in dose in both reported dosimetric parameters compared to VMAT; for heart V40, 4.5% and 7.0% ($p<0.05$) respectively, a reduction of 36.4%; and for heart V25, 9.9% and 20.8% ($p<0.05$) respectively, a reduction of 52.4%. Table 15 highlights how there were reductions in most cases for heart dosimetric parameters with PBT. There is a comparatively lower degree of sparing of high dose heart regions (i.e. heart V40) compared to the low dose regions (i.e. heart V25). It is also important to note that the distal edge of all three PBT beams are at a similar region of the heart and may result in a much higher dose to a specific cardiac substructure whilst VMAT will likely irradiate the whole heart in a more uniform manner. The impact of dose to specific cardiac substructures is investigated in more detail in chapter 5.

3.3.1.4 Dose to other OARs

Dose to the kidneys and liver are also reported in this study. For liver V30, PBT reported a mean reduction of 25.6% compared to VMAT with 5.6% vs 7.6% ($p<0.05$), respectively. While this is a significant dosimetric improvement, absolute doses are small and is of questionable clinical significance except in patients with severe hepatic impairment. For right and left kidneys, VMAT

delivered in significantly lower doses to the left kidney and no difference in the right kidney. Notably, both organs received minimal dose using either plan and will likely result in negligible clinical impact.

3.3.2 PBT vs VMAT vs 3D-CRT

Organ/dose constraint	Units	Dose				
		Mean	Minimum	Maximum	Median	Interquartile Range (IQR)
Combined Lung V20 (3DCRT)	%	12.3	3.8	24	10.9	8.7-15.9
Combined Lung V20 (VMAT)	%	7.3	3.0	12.5	7.1	6.2-8.6
Combined Lung V20 (PBT)	%	5.3	2.4	10.6	4.5	3.3-7.0
Heart V25 (3DCRT)	%	48.9	18	79.8	50.4	33.6-60.2
Heart V25 (VMAT)	%	20.8	12.2	34.6	18.9	14.3-26.7
Heart V25 (PBT)	%	9.9	5.7	15.8	10.4	7.2-12.4
Heart V40 (3DCRT)	%	10.3	4.7	18.6	8.5	7.1-13.9
Heart V40 (VMAT)	%	7.0	2.8	13.4	6.1	4.7-9.4
Heart V40 (PBT)	%	4.5	2.0	7.7	4.3	2.5-5.7
Liver V30 (3DCRT)	%	12.9	2.49	19.8	12.8	10.8-16.3
Liver V30 (VMAT)	%	7.6	1.8	14.0	7.5	5.2-8.6
Liver V30 (PBT)	%	5.6	1.0	10.1	5.6	3.9-6.8
Spinal cord PRV (3DCRT)	cm^3	3167	2635	4351	3160	2847-3363
Spinal cord PRV (VMAT)	cm^3	2180	1800	3750	2335	1990-2644
Spinal cord PRV (PBT)	cm^3	2430	2520	3120	2555	2293-2823

Table 16 Comparison of key dosimetric outcomes including mean, maximum, minimum, median and IQR for 3DCRT, VMAT and PBT plans

Table 16 compares the metrics of three different plans that were created for the same 20 cases, highlighting the potential sparing of OARs that may be achieved when different RT techniques are used. 3DCRT results in the highest dose to all OARs, followed by VMAT, with PBT showing the best dosimetric outcomes in most OARs. The clearest improvements are seen in the lung V20 and heart V25. For lung V20, there is significant improvement with 12.3%, 7.3% and 5.3% for 3DCRT, VMAT and PBT respectively. Comparing 3D-CRT to VMAT, there is a reduction of lung V20 by 40.6% ($p < 0.05$). Comparing 3D-CRT to PBT, this represents a 56.9% reduction of lung V20 ($p<0.05$). The IQR for all three plans indicates that the majority of cases benefit from the use of PBT in reducing lung V20. Similarly, for heart V25, the mean value is 48.9%, 20.8% and 9.9% for 3DCRT, VMAT and PBT respectively. Comparing 3DCRT to VMAT, this represents a reduction of 57.5%. Comparing 3DCRT to PBT, there is a reduction of 79.8%. There is also a significant but less substantial reduction in heart V40 and liver V30. Once again, the IQR shows that most cases would benefit use of VMAT and PBT compared to 3DCRT for these dosimetric endpoint. 3DCRT results in a higher dose to spinal cord compared to the other two technologies, with no difference seen in spinal cord dose for VMAT and PBT.

3.3.3 NTCP comparison

OAR	Radiobiological model	Endpoint	Absolute NTCP Values, % (95% CI)		
			3DCRT	**VMAT**	**PBT**
Heart	Kutcher et al. [159]	Pericarditis/pericardial effusion	0.03 +/- 0.004	0.0001 +/- 0.00007	4.8e-7 +/- 5.2e-7
Heart	Cella et al. [162]	Radiation induced heart valvular dysfunction	50.3 +/- 1.9	44.5 +/- 1.6	40.7 +/- 1.5
Lung	Yorke et al. [101]	Lung pneumonitis (grade 3 or higher)	0.02 +/- 0.01	0.01+/- 0.005	0.0003 +/- 0.0001
Lung	De Jaeger et al. [163]	Lung radiation pneumonitis: grade 2, (symptoms requiring steroids) or higher	4.8 +/- 0.5	4.6 +/- 0.4	2.4 +/- 0.2

Table 17 Absolute NTCP values for 3DCRT, VMAT and PBT

OAR	Radiobiological model	Endpoint	Absolute risk reduction, % (95% CI)			Relative risk reduction, % (95% CI)		
			VMAT vs 3D-CRT	PBT vs 3D-CRT	PBT vs VMAT	VMAT vs 3D-CRT	PBT vs 3D-CRT	PBT vs VMAT
Heart	Kutcher et al. [159]	Pericarditis/pericar -dial effusion	0.03 +/- 0.04	0.03 +/- 0.04	1.1e-4 +/- 0.76e-4	97.7+/- 2.0	99.8+/- 0.6	95.4 +/- 7.6
Heart	Cella et al. [162]	Radiation induced heart valvular dysfunction	5.8 +/-1.0	9.7 +/- 1.2	3.8 +/- 0.67	11.5 +/- 1.8	19.1+/- 1.9	8.6 +/- 1.4
Lung	Yorke et al. [101]	Lung pneumonitis (grade 3 or higher)	0.01+/- 0.009	0.02+/- 0.01	0.01+/- 0.004	7.57+/- 34.8	97.2+/- 0.9	95.4+/- 2.2
Lung	De Jaeger et al. [163]	Lung radiation pneumonitis: grade 2, (symptoms requiring steroids) or higher	0.2+/- 0.2	2.4+/- 0.4	2.2+/- 0.3	3.1 +/- 5.1	48.4 +/- 3.5	46.3 +/- 3.8

Table 18 Absolute risk reduction and relative risk reduction of NTCP endpoints for all three technologies

Table 17 shows the mean absolute NTCP values for all 20 plans. Table 18 compares the absolute and relative risk reductions from all three RT techniques. PBT results in the lowest probability of all four tested endpoints. For the pericardial effusion/pericarditis endpoint, the absolute NTCP values of these were very small for all techniques, indicating a small likelihood of this occurring in the clinical setting. Notably, PBT and VMAT both resulted in significant risk reduction compared to 3DCRT. For the other cardiac endpoint of valvular dysfunction, absolute NTCP values are much higher indicating a higher likelihood of clinical relevance, with 3DCRT resulting in the highest probability of this endpoint occurring. Improvements were achieved with VMAT and PBT compared to 3DCRT, with PBT resulting in the lowest probability of all three techniques. In the lungs, G3 (or higher) and G2 (or higher) radiation pneumonitis endpoints were both assessed. For G3 toxicity, absolute values are small. This again indicates that this endpoint is unlikely to be clinically significant irrespective of RT technique used. Notably, there is a minimal improvement when comparing VMAT and 3DCRT. PBT results in significant relative risk reduction of G3 pneumonitis compared to 3DCRT and VMAT. For G2 pneumonitis (or higher), absolute values are larger indicating the real possibility of this endpoint occurring in the clinical setting. Again, no significant improvements are seen when comparing VMAT and 3DCRT. However, PBT resulted in significant improvements with relative risk reductions of nearly 50% compared to 3DCRT and VMAT.

3.4 Discussion

This work demonstrates a reduction in dose to OARs such as the lungs and heart when using PBT compared to VMAT and 3DCRT for lower third/GOJ tumours of the oesophagus. Some reduction is also seen in liver doses with no significant difference in dose to spinal cord and kidneys. ITV coverage for PBT is marginally inferior but comparable to VMAT PTV coverage.

3.4.1 Acute pulmonary toxicity

Substantial reductions of over 50% are seen in mean lung dose and lung V5 suggesting that the use of PBT may translate into clinically relevant reductions in acute lung toxicity (i.e. toxicity within 3 months of treatment). In the context of NA treatment, a likely improvement is a reduction in pulmonary complications following oesophagectomy. Multi-institutional data have established this is as the most common acute toxicity following oesophagectomy affecting approximately one third to half of all patients. Many of these complications are severe with some leading to post-operative mortality [29]. While the causative mechanisms are not fully established, there are some clinical and dosimetric data that points to a distinct correlation between dose to lung in the pre-operative period and rates of post-operative lung complications. In their retrospective study of 444 patients, Wang et al. showed post-operative lung toxicity was strongly associated with pre-operative mean lung dose. In their study, use of PBT resulted in significantly lower rates of post-operative lung toxicity compared to VMAT and

3DCRT; 13.9% vs 23.8% vs 30.3% for PBT, VMAT, 3DCRT respectively; with multivariate analysis showing mean lung dose fully accounted for differences in toxicity seen when using different radiation modalities [34]. Retrospective data published by Lin et al., showed that PBT nearly halved the rate of pulmonary complications compared to photon radiotherapy (IMRT/3DCRT) implying again that dose to lung is a main factor in this reduction, although when comparing PBT to IMRT alone, there was only a non-significant trend to reduced pulmonary complications [121]. It is important to point out that in both these studies there was heterogeneity in the patient/tumour characteristics and radiotherapy dose. Additionally, PBT delivered was often the older PS technique which may result in a less conformal plan. In this study, NTCP modelling using the LKB model also indicates a likely clinical improvement in lung endpoints. The strongest signal in my data is the reduction seen in the probability of G2 (or higher) radiation pneumonitis endpoint where PBT approximately halves the relative risk. While values of absolute risks are low, they are not insubstantial; with this endpoint predicted to occur in 4.6% and 2.4% for VMAT and PBT respectively; signifying that this is likely to be a clinically relevant reduction. Furthermore, these values are almost certainly underestimates as the limitations of the NTCP model used means that the effects of concurrent chemotherapy use and lung tissue injury due to surgery are not accounted for. It is important to recognise that this NTCP endpoint is an imperfect surrogate for post-operative lung toxicity therefore this data should be interpreted with caution. However, the data implies that the seemingly marginal reductions in lung radiation dose may indeed correlate with significant reductions in lung pathology in real-world patients.

This study reaffirms the dosimetric advantages of PBT to lung in OEC as seen in some other planning studies of PBT in OEC (outlined in Table 5, Chapter 2). A strength of this study is the homogenous patient cohort (i.e. all lower third/GOJ tumours) and standardised RT protocol including dose and beam arrangements. Additionally, the NeoSCOPE cases used in this study had robustly quality-assured structures that followed a stringent trial delineation protocol. These factors infer that these results will be reproducible, with comparable levels of dosimetric improvements, in the context of a robustly quality-assured prospective clinical trial. The results from my study and previous work suggests that post-operative lung toxicity is likely to be reduced with PBT thus providing a promising endpoint for investigation in any future prospective clinical trials.

3.4.2 Late pulmonary toxicity

The pulmonary NTCP endpoints investigated in my study are likely to more meaningfully translate to the real-world setting for late toxicities compared to acute toxicity predictions as radiation pneumonitis is not usually seen until several months after RT. This analysis demonstrates that risk of grade 2 (or higher) radiation pneumonitis is nearly halved while for grade 3 or higher pneumonitis, the relative risk is reduced by over 90% with PBT compared to either 3DCRT or VMAT. The absolute risks

are small but are still clinically relevant. These findings translate into approximately 1 in 45 people avoiding symptoms of radiation pneumonitis (grade 2 or higher) if PBT is used. Again, this is likely a significant underestimate for this group of patients as the NTCP models do not consider the added toxicity when used RT is used concurrently with chemotherapy and additional insults to normal lung due to oesophagectomy and subsequent post-operative complications (e.g. pneumonia). In the context of clinical trials, it is crucial that these late effects are systematically assessed through objective measures such as pulmonary functions tests and, arguably more importantly, subjective measures such as patient reported outcomes measures (PROMs) tools.

3.4.3 Cardiac toxicity

This work shows that PBT results in a substantial reduction in cardiac dose with an approximately one third reduction in the higher dose constraint (heart V40) and over 50% reduction in the lower dose constraint (heart V25). The NTCP modelling suggests that there is a significant relative risk reduction of pericarditis/pericardial effusion by over 90% and of valvular dysfunction by just under 10%. For pericarditis/pericardial effusion endpoint, the absolute values are miniscule, indicating that this will be a rare outcome and is of unlikely clinical relevance for this level of dose reduction. However, for the valvular dysfunction endpoint, the absolute values are much greater indicating that there may be a clinically important benefit to patients. Additionally, the heart is considered as a whole structure in this study. Delineating individual cardiac substructures and interrogating dose distributions with PBT may reveal further benefits of PBT. This is explored in Chapter 5.

The impact of PBT in reducing acute cardiac toxicities such as post-operative cardiac complications is less clear. In multi-institutional retrospective data, cardiac toxicities are found to be the second most common complication post-oesophagectomy. Most common of these are atrial dysrhythmias. It is unclear if a reduction in pre-operative cardiac dose decreases the risk of this occurring. Data from Chen et al. that suggests that a dose to specific substructures such as the sino-atrial node and right atrium results in higher rates of cardiac arrhythmia, although sample size was small and was in a cohort of lung cancer patients [165]. This is a logical correlation as the sino-atrial node is located within the right atrium with both substructures critical to the electrical conduction system of the heart. Other work by Mukherjee et al. suggests that cardiac dose in patients with lower third/GOJ oesophageal tumours negatively impacts ventricular ejection fraction, [166] which may conceivably increase the risk of post-operative cardiac and late toxicities such as heart failure. Additionally, reducing rates of pulmonary complications may in turn reduce the rates of cardiac complications as both organs are inextricably linked, with established knowledge that a respiratory insult (e.g. pneumonia) may lead to cardiac toxicities such as atrial dysrhythmias [167].

An important consideration for cardiac doses is the impact of PBT's range uncertainty. This study considers the whole heart as an OAR rather than considering the impact of dose in various cardiac substructures. Range uncertainty for PBT is greatest at the distal end of the beam. With the beam arrangements used in this study, the distal edge of all three beams lie directly in or close to cardiac tissue potentially resulting in an inadvertently higher dose to some cardiac substructures e.g. right atrium. The distal end of the beam is also where there is the greatest variation in LET and therefore the potentially the highest RBE, [100, 168] potentially resulting in unexpected biological effects in one or more of the cardiac substructures, raising a concern for unanticipated cardiac toxicity. Strategies exist to mitigate these potential effects including the incorporation of variable RBE/LET in proton plan optimisation [168] and utilising a Monte-Carlo based algorithm to more accurately predict the dose distribution [169]. Most of these approaches are currently experimental but are rapidly entering the clinical sphere.

3.4.4 Target volume coverage

For PBT plans, there is inferior PTV coverage compared to VMAT plans raising the possibility of poorer local control with PBT. However, PBT plans were robustly optimised using ITV coverage as a planning constraint rather than PTV. In this study, robustly optimised ITV coverage was acceptable. On robust evaluation, the mean second-to-worse ITV coverage for all 20 cases was marginally lower than the PTV coverage in VMAT plans. Comparing robust coverage of ITV for PBT plans to PTV coverage for photon plans is thought to be a more appropriate metric for comparison and has recently been recommended by joint RTTQA/CTRAD consensus guidance in the UK [87]. The marginally lower ITV coverage in this study is unlikely to have a significant clinical effect, however, it does emphasise that PBT is much more susceptible to uncertainty and special care needs to be taken to ensure TVs are appropriately covered during plan delivery. Most clinical data of PBT in OEC, including from Lin et al.'s prospective study, is reassuring and shows that PBT is at least equal to photon techniques in terms of local control rates [119]. In any future clinical trials, it is essential that disease specific outcomes such as pCR/R0 rates and PFS are rigorously evaluated in order to ameliorate these concerns further.

3.4.5 Limitations

Specific limitations have already been alluded to earlier in the discussions including the use of specific NTCP models as imperfect surrogates for lung and heart toxicity, and the impact of PBT range uncertainty on dose to cardiac substructures. Another important limitation to point out is the use of a single mid-ventilation phase of the 4D-CT to optimise PBT plans implying that the impact of motion on PBT dose distribution may not be completely mitigated. Of note, the Lin et al.'s prospective study used a similar approach, although 4D-CT was not mandated in this trial [119]. To account for some of this uncertainty in this study, I have used ITV coverage as a planning constraint, planning using robust

optimisation and deliberately using SFO rather than MFO in all the PBT plans. In addition, beam arrangements that are less susceptible to motion and changes in tissue densities along the beam path were selected. The optimal approach to planning PBT in OEC is yet to be established. Potential approaches include planning methods that have been commonly used in lung cancers such as using average intensity projection (AveIP) [170] scan rather than using a single mid-ventilation phase or a resource intensive approach of creating individual plans for each respiratory phase (e.g. creating 10 individual plans) then combining to create a composite final plan [171]. The value of either approach have not been widely validated in OEC but clearly warrant further investigation. Additional motion management strategies may also be utilised to mitigate the impact of respiratory motion further, such as abdominal compression, respiratory gating, and the use of rescanning in treatment delivery to reduce the effect of interplay. Another limitation of this work is that it does not account for inter-fractional changes. A potential solution is assessing target volume coverage and OAR dose on weekly cone beam CTs or weekly repeat planning scans (including weekly 4D-CT). By using deformable registration and robust evaluation of plans, replanning can be instigated should the original plan be inadequate. Further work into this area will need to be carried out to ascertain the optimal approaches. In any future clinical trials, it is crucial that the RT protocol proactively considers these uncertainties in PBT, employing mitigation strategies where possible.

3.5 Conclusions

This work adds to the growing body of evidence that PBT reduces dose to the lungs and heart; critical organs when considering the common toxicities following oesophageal surgery; in lower third/GOJ OEC cases. The dosimetric study and the NTCP modelling data suggest that PBT may result in tangible reductions in post-operative lung complications, late lung complications and some long-term cardiac toxicities. This study utilised a robust and reproducible approach to planning, incorporating strategies that reduce the impact of respiratory motion where possible. Further work is required to ascertain the impact of range uncertainty on specific cardiac substructures and will be considered in the following chapters. I will also investigate if PBT may be used to further reduce dose to spleen, a novel OAR in OEC, in chapter 4.

Dosimetric studies alone are inadequate to influence clinical practice. The ‘gold standard’ of assessing any new technology remains assessment within prospective RCTs where possible. This study demonstrates the dosimetric benefits of PBT over photon techniques which may translate to potential clinical benefits during NACRT for lower/GOJ OEC cases.

Chapter 4: Optimising Splenic Dose in PBT and VMAT for Lower Oesophageal Cancers

4.1 Introduction

Chapter 3 established that PBT is likely to result in lower doses to typically recorded OARs such as the lungs and heart. Based on NTCP modelling performed, this may translate to lower rates of pulmonary and cardiac toxicity. This chapter investigates additional potential advantages of PBT in OEC by assessing if it is feasible to reduce dose to the spleen, a novel OAR, with PBT.

4.1.1 The spleen as an OAR

The spleen is in the left upper abdomen, above the left kidney and adjacent to the gastric fundus and GOJ. It is the largest organ of the lymphatic system and has several functions including the filtering of blood, removing microbes and inadequate red blood cells, producing white blood cells (WBCs) including lymphocytes, and antibody synthesis. Although an important organ, it is a non-vital organ as the body can adapt in its absence, with some of its functions taken up by other organs such as the liver, in the event splenic dysfunction or a splenectomy [172]. It is well established that patients with an absent or dysfunctional spleen are subject to a greater risk of fulminant infection. Therefore, the British Committee for Standards in Haematology (BCSH) recommends a pre-specified schedule of vaccinations for common pathogens such as *streptococcus pneumoniae* and lifelong antibiotic prophylaxis for these patients [173].

The impact of splenic irradiation is not completely defined but is likely to result in some degree of functional hyposplenism. Studies that followed childhood cancer survivors indicate prior splenic irradiation results in splenic atrophy and is associated with an increased life-time risk of overwhelming fatal sepsis [174, 175]. A recent retrospective study by Trip et al. on a cohort of gastric cancer patients has shown that doses as low as 10 Gy mean splenic dose convey an increased risk of overwhelming and potentially fatal sepsis, with doses over >40 Gy associated with a substantially increased risk [176]. Splenic irradiation has also been linked to an increased rate of G4 lymphopenia, an emerging prognostic biomarker in many cancers including OEC and pancreatic cancers. Lymphocytes are exquisitely sensitive to radiation, with *in vitro* data showing that the lethal dose required to reduce surviving fraction of lymphocytes to 50% is only 1.5 Gy, and to reduce it to 10% is approximately 3 Gy [177]. Saito el al. showed that 1 Gy increase in mean splenic dose predicted a 2.9% decrease in nadir absolute lymphocyte count in OEC patients [178]. In a study of pancreatic cancer patients, Chadha et al. showed that doses as low as 9.8 Gy mean splenic dose correlates with a higher rate of G4 lymphopenia, which in turn correlates with poorer OS [179]. For OEC, with its location in the central

mediastinum, additional factors such as irradiation of organs such as the heart and lungs which have significant blood pools containing circulating immune cells including lymphocytes are also likely to be contribute to lymphopenia rates [141].

The spleen is increasingly regarded as an OAR that requires a dose constraint and dose reporting. The Royal College of Radiologists (RCR) have recently released draft guidance for splenic irradiation (for all tumour types) suggesting optimal constraints of mean splenic dose <10 Gy and a mandatory constraint of <40 Gy [180]. In a retrospective study at SWWCC, we analysed the splenic dose for all patients who received radical and neoadjuvant CRT for oesophageal cancer (all IMRT/VMAT, median dose 50 Gy) from 2016-2019. The study found that over 50% patients with OEC received >10 Gy mean dose to the spleen, (publication included in appendix) [181] implying that without delineating the spleen as an OAR and placing a constraint, the TPS is likely to push dose to the spleen, potentially resulting in adverse effects on patients.

4.1.2 Aims and objectives:

The aims and objectives of this study are:

1) Ascertain feasibility of reducing dose to the spleen in lower third/GOJ oesophageal tumours with PBT and VMAT, while meeting dose constraints to other OARs.
2) Test spleen constraints used during optimisation of PBT and VMAT plans, that may be used in future trial protocols and clinical practice.
3) Quantify any dosimetric advantages to the spleen, if present, of PBT over VMAT.

4.2 Methods

All PBT and VMAT plans were created in collaboration with AS and JL, physicists at the Rutherford Cancer Centre, Newport. The same 20 lower third oesophagus/GOJ clinical cases from the NeoSCOPE trial were used in this study (see section 3.2 for full details). In addition to the already delineated structures, the whole spleen was contoured as an organ of interest on the reference planning CT in each of the 20 cases as per RTOG normal organ contouring guidance [182]. The dose to whole spleen without optimisation to spleen were reported for the existing PBT plans (see section 3.3 for full details) to act as a baseline, and to inform if the addition of spleen dose constraints were feasible.

4.2.1 Replanning with spleen constraints

4.2.1.1 PBT plans

All PBT plans were replanned using dose constraints from the NeoSCOPE trial as outlined in Chapter 3 (see table 9, section 3.2.6 for full details) with the addition of new planning constraints for the spleen. Plans were created on Pinnacle (Phillips, v14) treatment planning system and utilised a pencil-beam

(Type A) algorithm. Beam arrangements used were identical to the ones used in non-spleen optimised PBT plans i.e. three-beam arrangement (PA/RPO/LPO) with gantry angles of 135°, 180° and 135° with the couch rotated 180° (equivalent to 225°). If spleen constraints were unable to be met with those beam arrangements, different PBT beam arrangements were trialled. While these results are not fully reported, they are explored in the discussion section.

Dose reported	Constraint
Mean	<4.5 Gy (optimal)
V10 Gy	<12% (optimal)
Mean	<10 Gy (mandatory)
V15	<20% (mandatory)

Table 19 Spleen Dose Constraints

The dose constraints for the spleen are shown in table 19. The mandatory spleen dose constraints are informed by work from Trip et al. who reported an increased risk of functional hyposplenism with a mean splenic dose of >10Gy for patients with gastric cancer [176]. The optimal dose constraints are taken from work by Blais et al. who proposed spleen constraints to avoid severe lymphopenia in pancreatic cancer patients [183]. Optimal dose constraints were primarily chosen to assess how much splenic dose reduction was possible while achieving adequate TV coverage and constraints for other OARs. ITV and PTV coverage were the most strongly weighted constraints during optimisation, followed by lung, heart and spleen constraints (mandatory constraints– primary dose goals; optimal constraints– secondary dose goals) that were all equally weighted.

4.2.1.2 VMAT plans:

In order to compare PBT spleen dose to standard photons techniques, new VMAT plans were created for the 20 NeoSCOPE cases. All plans were created in collaboration with AS on the Pinnacle (Phillips v16.2). All plans used NeoSCOPE dose constraints (table 9, section 3.2.6) and spleen constraints as detailed in table 17. Similar optimisation methodology to PBT planning was used where PTV coverage was the mostly highly weighted constraint, followed by equally weighted constraints on heart, lung, spinal cord and spleen. In order to streamline the planning process, AS created a script to create plans using the Pinnacle^3 AutoPlanning Engine.

4.2.2 Statistical analyses

The mean of key plan metrics for all 20 cases are reported and compared [Table 20 - PBT (non-spleen) vs PBT (spleen); Table 21 - PBT (spleen) vs VMAT (spleen)]. For each key plan metric, a proportional difference (%) is reported. As each patient provided matching observations for the two plans (spleen and non-spleen), each constraint was tested separately using paired t-test (two-tail) to assess

statistical significance. For reference, the key plan metrics for VMAT (non-spleen) plans as reported in Chapter 3 (see table 11, Section 3.3.1) are included. Data analyses were performed on Microsoft Excel and SPSS (IBM, v26).

4.3 Results:

ROI	DVH Parameter	Objective	PBT (Non-Spleen)	PBT (Spleen)	% Diff.	P-value
PTV	V95%	>99%	95.6	96.5	0.9	0.09
ITV	Robust second-to-worst scenario	-	98.9	98.8	-0.1	0.17
	Robust worst-case scenario	-	98.4	98.2	-0.2	0.21
External	D1.8ccm	<107%	47.6	48.9	2.7	<0.001
Cord_PRV	D1ccm	<40 Gy	24.3	32.3	32.9	<0.001
Lungs	V20 Gy (%)	<20%	5.3	5.2	-1.9	0.8
	V5 Gy (%)	-	17.9	17.4	-2.8	0.4
	Mean dose (Gy)	-	3.2	4.0	25.0	0.3
Heart	V40 Gy	<30%	4.5	5.4	20.0	0.008
	V25 Gy	<50%	9.9	10.6	7.1	0.003
Liver	V30 Gy	<60%	5.6	6.8	21.4	0.03
Lt Kidney	V20 Gy	<25%	3.4	6.8	100.0	0.4
Rt Kidney	V20 Gy	<25%	0.2	*		-
Spleen	V15 Gy	<20%	13.7	10.7	-21.9	0.05
Spleen	V10 Gy	<12%	23.6	18.1	-23.3	0.009
Spleen	Mean dose (Gy)	<4.5 Gy, <10 Gy	8.3	6.3	-24.1	0.01

*Table 20 Comparison of key metrics (mean) of PBT (Non-Spleen = NOT optimised to spleen constraints) plans vs. PBT (Spleen = optimised to spleen constraints) plans for the 20 cases. *Right kidney dose not consistently reported. Where reported, dose is minimal and unlikely to be of clinical significance.*

Table 20outlines the key metrics from PBT plans without the addition of spleen constraints compared to PBT plans that were optimised with spleen constraints. For all three reported spleen parameters, optimising to spleen successfully reduced dose to the spleen. Most plans achieved mandatory constraints while optimal constraints were regularly not met. This is examined in more detail later in this section. PTV coverage and robust coverage of ITV are comparable in both plans. Although cord dose is significantly higher for plans optimised to spleen constraints, all plans comfortably met spinal cord dose constraints. There were no significant differences seen in any of lung parameters, implying dose to spleen may be reduced without compromising lung dose. However, heart dose was higher in both recorded parameters. While statistically significant, the absolute increase in heart dose is

marginal (non-spleen vs spleen; V40 - 4.5% vs 5.4%; V25 - 9.9% vs 10.6%). Liver doses are significantly higher in spleen optimised plans but this is unlikely to be clinically significant because the absolute values are low. Not all kidney doses were reported, but where reported, no significant difference were seen and of low absolute value.

ROI	DVH Parameter	Objective	VMAT (Non-spleen)	PBT (Spleen)	VMAT (Spleen)	% Diff. (Between spleen optimised plans)	P-value
PTV	V95%	>99%	99.5	96.5	99.5	3.1	<0.001
ITV	Robust second-to-worst scenario	-	-	98.8	-	-	-
	Robust worst-case scenario	-	-	98.2	-	-	-
External	D1.8ccm	<107%	46.3	48.9	47.7	-2.5	<0.001
Cord_PRV	D1ccm	<40Gy	21.8	32.3	22.9	-29.1	<0.001
Lungs	V20Gy (%)	<20%	7.3	5.2	8.1	55.8	<0.001
	V5Gy (%)	-	45.6	17.4	45.5	161.5	<0.001
	Mean dose (Gy)	-	7.0	4.0	7.4	85.0	<0.001
Heart	V40Gy	<30%	7.0	5.4	6.9	27.8	0.01
	V25Gy	<50%	20.8	10.6	15.9	50.0	<0.001
	Mean	-	7.6	6.1	13.8	126.2	<0.001
Liver	V30Gy	<60%	7.6	6.8	6.1	-10.3	0.2
Kidneys	V20Gy	<25%	-	3.6	1.8	-50.0	0.1
Spleen	**V15Gy**	**<20%**	-	**10.7**	**7.5**	**-29.9**	**0.05**
Spleen	**V10Gy**	**<12%**	-	**18.1**	**17.2**	**-5.0**	**0.7**
Spleen	**Mean dose (Gy)**	**<4.5Gy, <10Gy**	-	**6.3**	**6.3**	**0.0**	**0.9**

Table 21 Comparison of key metrics (mean) for PBT (spleen) and VMAT (spleen) plans for the 20 cases. Non-spleen optimised VMAT plans results are included for reference.

Table 21 compares the key metrics for PBT (spleen) and VMAT (spleen) plans. The results from VMAT (non-spleen) plans are also included for reference. It is important to note that the VMAT (non-spleen) plans were created in SWWCC and VMAT (spleen) plans were created in the RCC and therefore plans may not be directly comparable due to differences such as TPS calibration.

4.3.1 PBT (spleen) vs VMAT (spleen)

Splenic doses for PBT and VMAT plans that are optimised to spleen appear comparable apart from V15 Gy spleen where VMAT results in a lower splenic dose with an approximately 30% reduction. Mean dose to spleen is very similar for both sets of plans. However, as seen in results detailed in Chapter 3, VMAT results in significantly higher dose to lung, particularly in lower dose parameters such as V5 lung and mean lung dose. There is also greater heart V25 and V40 with VMAT compared to PBT. In order to characterise the dose distribution, mean heart dose was also reported showing VMAT resulted in over double the mean heart dose. Cord doses were lower with VMAT compared to PBT plans, although all plans comfortably met dose constraints. Liver and kidneys doses were both lower with VMAT but absolute values are small indicating it is likely to be clinically insignificant.

4.3.2 VMAT (Spleen) vs VMAT (non-spleen)

Including spleen constraints during optimisation for VMAT plans appeared to result in little difference in most reported parameters including lung, PTV coverage and cord dose. The only is exception is mean heart dose where spleen optimised VMAT plans results in a greater dose compared to non-spleen optimised dose. Importantly, this was only a reported endpoint and not a dose constraint used during optimisation.

4.3.3 Spleen DVH parameters

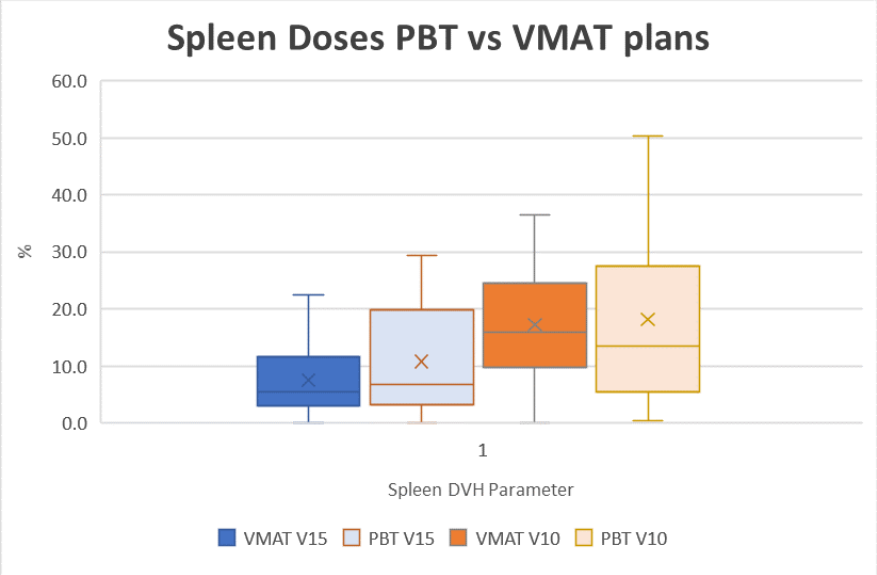


Figure 10 Box and whisker plot for V15 and V10 Spleen from PBT (spleen) and VMAT (Spleen) plans

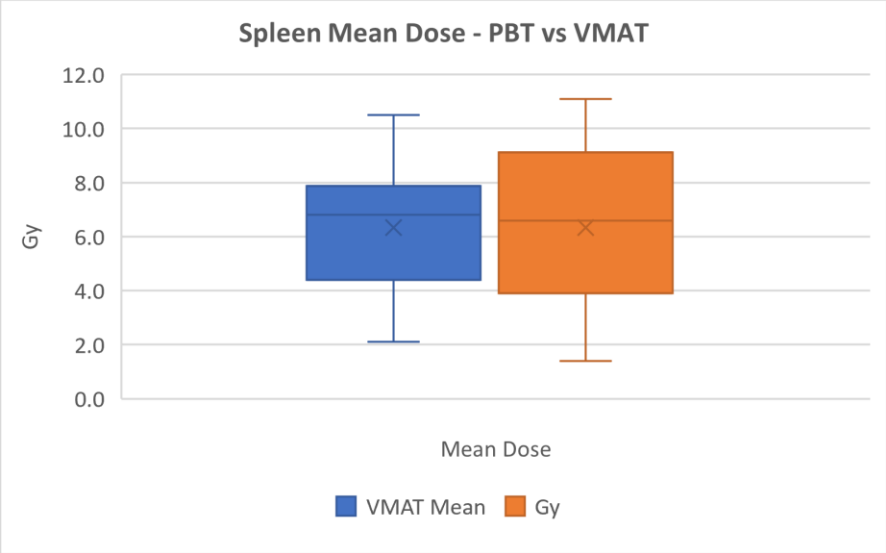


Figure 11 Box and whisker plot for Spleen Mean Dose from PBT (spleen) and VMAT (Spleen) plans

Figure 10 and 11 show the summary reporting measures including mean, median and interquartile ranges for the reported spleen DVH parameters for PBT (spleen) and VMAT (spleen) plans. While mean and median values are comparable, PBT plans had greater interquartile range and more distant outliers compared to VMAT in all three reported parameters suggesting splenic dose is more consistent and less dependent on individual anatomy with VMAT.

Dose constraint	Proportion of cases where constraint NOT Met	
	PBT	VMAT
V15 <20% (mandatory)	25%	5%
V10 <12% (optimal)	50%	70%
Mean <10 Gy (mandatory)	10%	5%
Mean <4.5 Gy (optimal)	65%	30%

Table 22 Proportion of cases that did not meet spleen constraints for PBT (spleen) and VMAT (spleen) plans

Table 22 details the proportion of plans that did not meet splenic dose constraints. A greater proportion of PBT plans exceeded the mandatory and optimal dose contraints compared to VMAT with the exception of V10 <12%. 65% of PBT plans did not meet mean dose <4.5 Gy constraint compared to VMAT where the dose contraint was not met in 30% of cases. Most plans met the mean spleen dose <10Gy constraint.

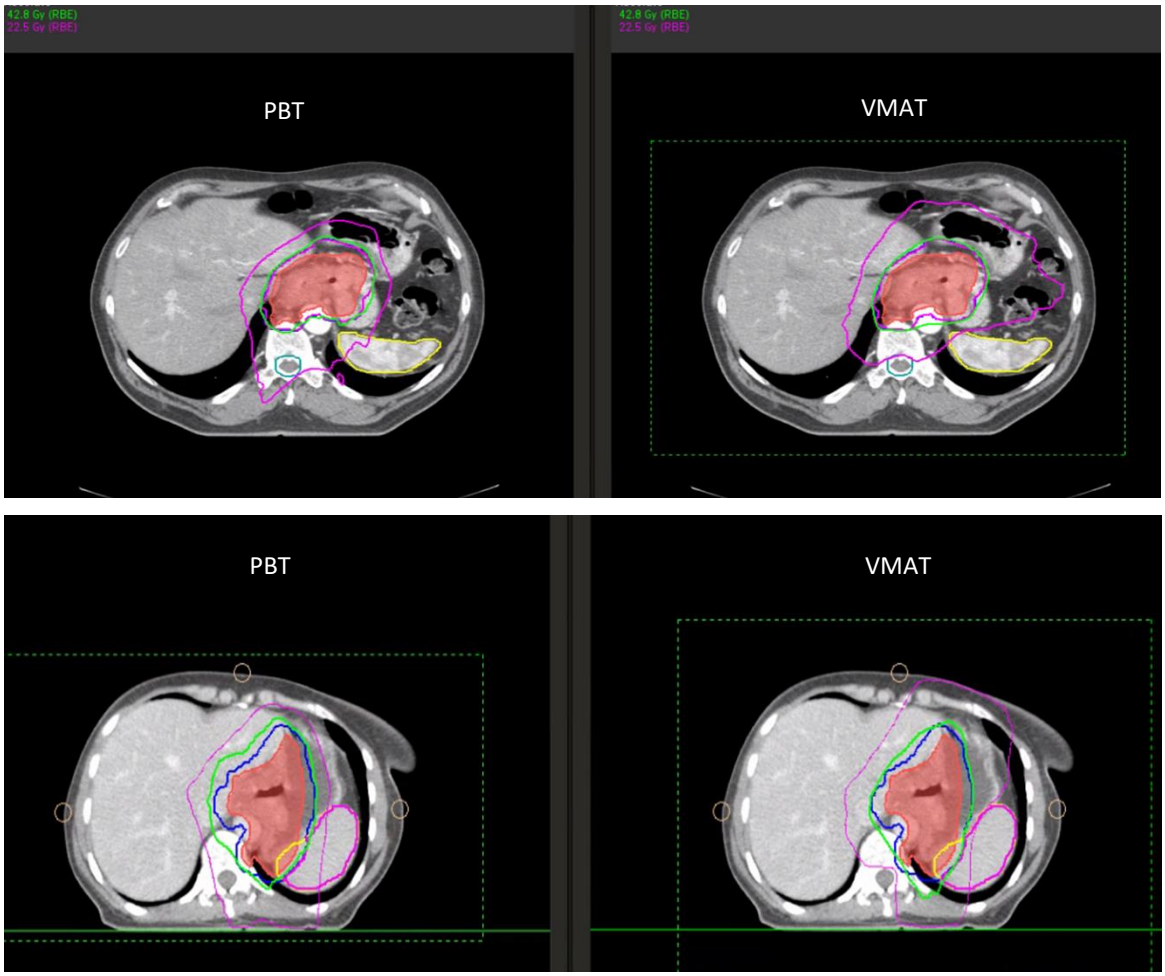


Figure 12 Axial CT slices around the level of the gastro-oesophageal junction for two separate cases. Spleen is outlined in both cases. PBT plan is on the LEFT, VMAT plan is on the RIGHT. GREEN - 95% isodose; PURPLE - 50% isodose.

Figure 12 shows examples of two cases where the spleen was located in close proximity to the PTV volume. In the case in the bottom image of Figure 12, there was overlap between the PTV and the spleen resulting in spleen doses were relatively high using either PBT or VMAT. In both cases PBT plans did not meet all constraints including the mandatory constraints, while VMAT plans exceeded the optimal constraints but met mandatory constraints of mean dose <10 Gy and V15 <20%.

4.4 Discussion:

This planning study demonstrates that the spleen can successfully be incorporated as an OAR for a majority of lower third/GOJ OEC cases at a dose level of 45 Gy/25# without exceeding dose constraints for other OARs. These results are expected to be reproducible for other typical NA fractionations including 41.4 Gy/23# (CROSS fractionation) and 40.05 Gy/15# (moderate hypofractionation). For PBT, optimising to additional spleen constraints resulted in an approximately 20-25% dose reduction to the spleen at the expense of higher cord and cardiac doses. While increase in cardiac dose is statistically significant, the absolute increase is marginal e.g. a proportional increase of 7% for V25; and therefore, unlikely to be clinically significant. PBT cardiac doses remained substantially lower than for VMAT plans. For the spinal cord PRV dose, there is a significant increase in point maximum dose (D1 ccm) when PBT plans are optimised to spleen. However, all plans comfortably meet the mandatory spinal cord PRV dose constraint. As a serial organ, the clinical impact of this increased dose to the cord is likely to be negligible other than in exceptional situations such as prior irradiation. It is important to note that dose for reported lung parameters are comparable for both sets of PBT plans, suggesting that one of the main dosimetric advantages of using PBT over VMAT in OEC i.e. improved lung sparing, is maintained when spleen constraints are added.

The results from the PBT plans that were optimised to spleen could perhaps have been predicted as beam arrangements [i.e. three-beam arrangement (PA/RPO/LPO) with gantry angles of 135°, 180° and 135° with the couch rotated 180° (equivalent to 225°)] were not changed in order to avoid the spleen. Additionally, plans were created using an SFO approach rather than MFO /intensity modulated PBT (IMPT) that would have likely achieved more conformal dose distributions. As discussed in Chapter 3, this approach is taken to maximise robustness to intrafraction motion e.g. due to respiratory motion, as much as is possible. In most cases, the optimiser achieved spleen dose constraints by increasing the beam weighting of the posterior 180° beam and in some cases, the RPO 225° beam, resulting in a higher cord dose and heart dose. However, despite PBT's physical characteristics, in some cases splenic dose constraints were not achieved. This is particularly apparent for cases where PTV/ITV lies in close proximity to the spleen highlighting a potential weakness of PBT in this setting. For this study, although not fully reported, several other beam arrangements were explored, such as using a right lateral beam and posterior beam (270°, 180°). This resulted in lower doses to the spleen at the expense

of increase liver doses and reduced robustness to due to liver motion. Further work is required to ascertain the safety of this approach. Figure 13 gives an example of this approach, showing the dose distribution in the case where there was PTV and spleen overlap.

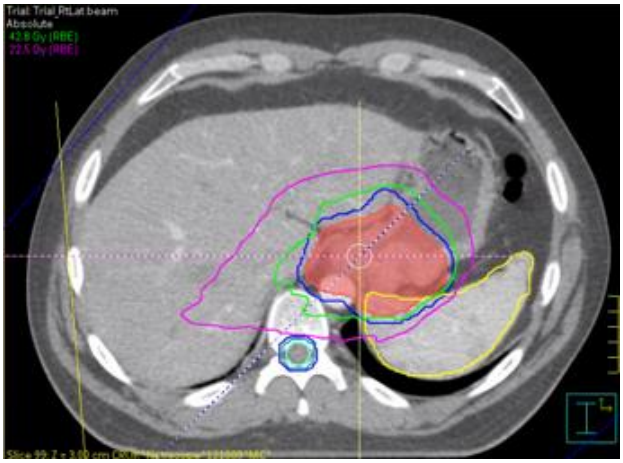


Figure 13 Dose distribution when a right lateral and posterior beam arrangement is used in an attempt to reduce spleen dose. Acase where there was PTV/Spleen overlap was used. GREEN - 95% isodose; PURPLE - 50% isodose.

VMAT performed well in reducing the dose to spleen, and in many cases, performed better than PBT. Although both VMAT plans included in this study were created in different centres and therefore may not be directly comparable, there appears to be very comparable PTV coverage and dose to other OARs when spleen constraints are introduced. VMAT performed better than PBT when the PTV was in close proximity or overlapped the spleen, highlighting the superior high dose conformality of VMAT compared to PBT. At the dose fractionation of 45 Gy/25# used in this study, 95% (19/20) of VMAT plans achieved the mean spleen dose <10 Gy constraint without appearing to compromise dose to other OARs. Conversely, VMAT was regularly unable to achieve the tighter optimal spleen constraint of V10 <12% (proportion of cases not achieved: 70% - VMAT vs 50% - PBT), including in cases where the PTV was not in close proximity to the spleen, reflecting the significant low-dose bath region associated with VMAT.

Dose constraints for the spleen are yet to be fully established for OEC. This study took dose constraints from current literature based on work in pancreatic cancer and gastric cancer [176, 179, 183]. Of note, the RCR in the UK are currently preparing a guidance document for splenic radiotherapy (for all tumour types), suggesting an optimal spleen constraint of mean dose <10Gy and a mandatory constraint of mean dose <40Gy [180]. These constraints are largely informed by the same gastric cancer study from Trip et al. who recorded increased rates of severe infections if the spleen received a dose greater than those constraints. This study shows that a mean splenic dose of <10Gy is likely to be achievable for most cases in lower/GOJ OEC using either VMAT or PBT and certainly, all plans comfortably meet the mandatory constraint of mean <40 Gy. Neither PBT nor VMAT consistently met the optimal constraints

tested although VMAT arguably performed better than PBT. A dose constraint of mean spleen dose <10 Gy appears to be feasible for most cases and is therefore an appropriate optimal constraint to be considered for implementation in clinical practice or in a trial protocol. For all cases, the highest recorded mean spleen dose was 11.1 Gy, suggesting that an additional mandatory constraint of <40 Gy will be easily achievable, and therefore could be much lower e.g. mean splenic dose <20 Gy, although further work is required to fully assess this.

4.4.1 Future work

The exact impact of splenic irradiation on clinical outcomes in lower/GOJ OEC is yet to be ascertained. While work from Saito el al. has recognised the correlation between splenic dose and lymphopenia in OEC, [178] much of the published data on its clinical impact has been derived from pancreatic and gastric cancers. It is important to recognise that unlike the pancreas and stomach, the distal oesophagus lies more proximally, in the mediastinum, adjacent to the heart, lungs and thoracic vertebrae. So et al. calculated dose the received by lungs, heart and total body dose in oesophageal CRT; weighted according to a verified mathematical formula; as a surrogate for effective dose to circulating immune cells (EDIC) and found a correlation between EDIC, G4 lymphopenia rates and survival outcomes [141]. Future work should assess the feasibility and accuracy of this approach, ideally, by prospectively collecting data on EDIC, splenic dose and G4 lymphopenia rates, and assessing for any correlation with clinical outcomes such as infection rates, PFS and OS. Due to a lower integral dose, it is possible that PBT will still confer significant advantage in terms of lower G4 lymphopenia rates over photon techniques despite the results from this study.

The positive early results from the Checkmate-577 study of adjuvant Nivolumab (anti-PD1) has seen IO enter the treatment paradigm in OEC following NACRT and surgery [147]. It may become especially important to maintain a functioning immune system throughout the course of NACRT in order maximise the efficacy of IOs. Reducing splenic dose and total integral dose by introducing splenic dose constraints and by using technologies such as PBT may be useful 'immune-sparing' strategies. Future prospective studies should explore how these strategies affect the efficacy of IO in these patients.

4.5 Conclusion:

It is feasible to reduce splenic dose and achieve a mean dose <10 Gy constraint for most cases using PBT with a three-beam arrangement (LPO/PA/RPO) while meeting all other dose constraints. In spleen optimised cases, cardiac dose and spinal cord dose is likely to be higher although the clinical impact of this increase is likely to be insubstantial. VMAT also achieved splenic dose reduction meeting the mean dose <10 Gy constraint in most cases. In many cases, VMAT outperformed PBT. PBT may still

result in lower rates of G4 lymphopenia in oesophageal cancer cases due to a lower integral dose compared to VMAT.

Spleen doses, EDIC and rates of G4 lymphopenia with correlations to clinical outcomes should ideally be assessed the setting of a prospective study. An optimal dose constraint of mean splenic dose of <10 Gy is a feasible optimal constraint to be included in future trial radiotherapy planning protocols.

Chapter 5: Exploring the Effects of PBT Beam Arrangements on dose to Organs-at-Risk and Cardiac Substructures

5.1 Introduction:

In Chapters 3 and 4, the PBT's potential to reduce doses to OARs such as the lungs, heart and spleen compared to photon radiotherapy techniques were explored. As discussed in chapter 3 (see section 3.2.9.2) PBT plan dose distributions are very dependent on beam arrangements selected. This chapter begins to explores the potential effects of PBT beam arrangements on TV coverage, OAR doses and on doses to individual cardiac substructures.

Complications following cardiac irradiation are well established and may clinically manifest in a variety of ways. Immediately following RT, inflammatory effects may occur, leading to pericarditis and myocarditis. In the months and years following RT, cardiac irradiation is linked to increased rates of ischaemic heart disease (including myocardial infarctions), pericardial effusions, heart failure, valvular dysfunction and conduction defects [184]. In RT planning, whole heart metrics are typically used to assess cardiac dose. The Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) report on cardiac radiation evaluates dose to the heart as a whole organ and recommends a V25 Gy of <10% to minimise the endpoint of long-term cardiac mortality [185]. However, emerging evidence suggests dose to individual substructures may be better predictors of specific endpoints compared to mean heart dose [186]. For example, in breast cancer, irradiation of the left anterior descending artery (LAD) is shown to be a better predictor of coronary artery calcification and LAD stenosis compared to mean heart dose [187]. Also in breast cancer patients, van den Bogaard et al. demonstrated that left ventricle (LV) V5 was a better predictor of acute coronary events (ACE) compared to mean heart dose [188]. In lung cancer patients, dose to structures at the base of the heart i.e. superior vena cava, ascending aorta and pulmonary artery, was shown to be associated with poorer OS [189]. Recent sub analyses of the RTOG 0617 trial of dose escalation in lung cancer showed an association between atrial and pericardial dose with OS [190]. In OEC, while the link between dose to cardiac substructures and clinical outcomes are not yet fully established, possibly due to the relatively poor prognosis and limited follow up period, it is likely that many of these findings would be replicated. As survival outcomes improve, it will become increasingly important to assess how dose to individual cardiac substructures may affect long-term toxicity and survival outcomes.

Improved imaging, image-guidance RT (IGRT) and the increasing availability of conformal techniques, including PBT, means it is now possible to assess and optimise dose to individual substructures [191]. As shown in Chapter 3, PBT results in a lower whole heart dose in lower OEC compared to photon RT

techniques. However, the dose to individual substructures is not clear. A three posterior beam arrangement, as utilised in chapter 3 and 4, results in the distal edge of the beams coinciding with cardiac tissue potentially resulting in an unexpected hotspot in one or more cardiac substructure. Additionally, the distal edge of the beam has the greatest range uncertainty, variation in LET and RBE, this potentially leads to unexpected toxicity outcomes. The danger of this is highlighted in a prospective study of breast cancer patients treated with PBT which showed an unexpectedly high incidence of rib fractures post-RT, possibly due to end-of-range radiobiological effects [192].

This study is to assess the effect of different PBT beam arrangements on standard OARs and cardiac substructures in lower OEC cases. It is predominantly hypothesis-generating, aiming to inform the direction of future work in this area.

5.2 Methods:

This work was carried out in collaboration with Ahmed Abbas (AA), Medical Physics PhD Candidate, Swansea University.

Two cases (referred to as Case X and Case Y for clarity) from the NeoSCOPE trial were randomly selected. For both cases, PBT plans were created on Eclipse TPS (Varian Medical Systems, Palo Alto, CA) in SWWCC in collaboration with AA. A dose of 45 Gy/25# were used. Planning dose constraints used were as per the NeoSCOPE trial. (See section 3.2.6, table 9). Seven beam arrangements were trialled and are detailed in table 23.

Number of beams	Beam angles (°, gantry angle)
2	180°, 145°
2	180°, 90°
2	180°, 45°
2	180°, 160°
3	180°, 145°, 225°
3	180°, 145°, 240°
3	180°,145°,90°

Table 23 PBT beam arrangements used in this study

Beam arrangements were selected based on previously published work on this area [114] and work previously reported in this thesis. An additional beam combination that included a 45° beam was trialled to assess the effect of a more anterior beam on dose to OARs. Multiple beams (2 or 3) rather than single beam arrangement were favoured in order to maintain a degree of robustness to intra-fraction motion. As per previous work, PBT plans for this study were robustly optimised to the ITV rather than the PTV. A 5 mm setup uncertainty in all directions (X, Y, Z axis) and a 3.5% range uncertainty were used in the optimisation process. For each beam arrangement, dose to OARs were reported. The mean ITV coverage and dose to OARs as per NeoSCOPE dose constraints were reported for each beam arrangement. For one case (Case Y), cardiac substructures were delineated as per a validated contouring atlas by Feng et al. [115]. Dose to each of these cardiac substructures were reported using the different beam arrangements. No additional constraints were places on the optimiser for the cardiac substructures.

5.3 Results:

ROI	DVH parameter	Obj.	Beam arrangements						
			180°, 145°	**180°, 90°**	**180°, 45°**	**180°, 160°**	**180°, 145°, 225°**	**180°, 145°, 240°**	**180°, 145°, 90°**
ITV	V95% (mean)	>99%	102.3	102.3	102.3	102.2	102.3	102.3	102.2
Cord PRV (+5mm)	D1 ccm	<40 Gy	21.2	18	23.4	31.6	24.8	23.6	14.1
Lungs	V20 Gy	<20%	4.7	2.4	2.1	4.2	3.6	3.7	4.0
	V5 Gy	-	8.7	11.2	7.0	6.8	11.7	14.7	13.6
	Mean dose (Gy)	-	2.1	2.1	1.4	1.8	2.1	2.5	2.4
Heart	V40 Gy	<30%	2.4	2.5	2.7	2.4	2.3	2.4	2.4
	V25 Gy	<50%	4.0	5.3	6.4	4.8	4.9	4.9	5.0
Liver	V30 Gy	<60%	1.9	2.0	1.9	1.9	2.0	2.1	2.0
L kidney	V20 Gy	<25%	1.7	0	0	1.4	0	0.3	0.2
R Kidney	V20 Gy	<25%	0	0	0	0	0	0	0
Stomach	V50 Gy	<16/25 ccm	0	0	0	0	0	0	0

*Table 24 Plan statistics including dose to OARs for 7 PBT Beam Arrangements for **Case X.***

ROI	DVH parameter	Obj.	Beam arrangement						
			180°, 145°	**180°, 90°**	**180°, 45°**	**180°, 160°**	**180°, 145°, 225°**	**180°, 145°, 240°**	**180°, 145°, 90°**
ITV	V95% (mean)	>99%	102.4	102.5	102.3	102.4	102.7	102.3	102.4
Cord PRV (+5mm)	D1 ccm	<40 Gy	25.3	18	17.9	33.5	18.8	16.9	16.9
Lungs	V20 Gy	<20%	2.9	1.6	1.4	2.8	2.3	2.3	2.3
	V5 Gy	-	5.7	12.4	5.7	6.3	14.0	15.6	15.0
	Mean dose (Gy)	-	1.7	2.1	1.1	1.4	2.1	2.3	2.2
Heart	V40 Gy	<30%	2.4	2.8	3.0	2.6	2.5	2.5	2.5
	V25 Gy	<50%	6.3	7.7	9.1	6.4	6.6	6.6	6.9
Liver	V30 Gy	<60%	3.1	3.1	3.2	3.2	3.4	3.5	3.1
L kidney	V20 Gy	<25%	0	0	0	0	0	0	0
R Kidney	V20 Gy	<25%	0	0	0	0	0	0	0
Stomach	V50 Gy	<16/ 25ccm	0	0	0	0	0	0	0

*Table 25 Plan statistics including dose to OARs utilising 7 PBT beam arrangements using **Case Y**.*

Dose to Cardiac substructures (Gy)							
ROI	**Beam Arrangement**						
	180°, 145°	**180°, 90°**	**180°, 45°**	**180°, 160°**	**180°, 145°, 225°**	**180°, 145°, 240°**	**180°, 145°, 90°**
Whole Heart (mean)	3.6	5.4	10.3	3.6	3.8	3.8	4.7
R Atrium	4.5	4.3	5.6	4.8	4.6	4.3	4.2
Ascending Aorta	0.0	0.0	4.0	0.0	0.0	0.0	0.0
L Atrium	11.2	16.4	19.4	11.5	12.0	11.8	14.6
L Ventricle	0.2	2.6	11.3	0.2	0.3	0.5	1.8
R Ventricle	0.5	0.4	7.5	0.5	0.8	0.6	0.4
LMC	0.0	0.0	4.7	0.0	0.0	0.0	0.0
LAD	0.0	0.0	12.4	0.0	0.0	0.0	0.0
RCA	0.0	0.3	10.5	0.0	0.0	0.0	0.2
AV Node	2.9	2.5	15.6	3.1	3.0	3.1	2.5
Aortic Valve	0.0	0.0	8.8	0.0	0.0	0.0	0.0
Mitral Valve	4.3	6.5	20.2	5.5	5.0	4.2	5.0
Tricuspid Valve	0.3	0.2	4.8	0.2	0.2	0.3	0.2
Pulmonary Valve	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Pulmonary Artery	0.1	0.1	0.1	0.1	0.0	0.0	0.0

*Table 26 Plan statistics including dose to cardiac substructures utilising 7 PBT beam arrangements using **Case Y**. LMC - Left main coronary artery; LAD - left anterior descending artery; RCA - right coronary artery; AV - atrio-ventricular.*

5.4 Discussion:

5.4.1 Effect PBT Beam Arrangements on OAR dose

For both cases, all beam arrangements comfortably met the planning dose constraints. Differences were seen in doses to OARs depending on beam arrangements used. For the lungs, results for the higher dose parameter (V20) were generally low, with all plans measuring a V20 of <5%. However, for the lower dose parameter (lung V5) there was substantial variation between different beam arrangements suggesting clinical significance as greater 'low dose bath' may increase post-operative lung toxicity rates and rates of symptomatic pneumonitis in OEC [193]. Due to an additional beam traversing lung tissue, predictably, beams arrangements that utilised three beams as opposed to two generally resulted in a greater lung V5. In the prior chapters, a three-beam arrangement was used in the interest of maintaining robustness to respiratory and other intra-fraction motion. This work shows that lung V5 is substantially reduced by using fewer beams while meeting all other constraints, suggesting that a two-beam arrangement may be a feasible and preferable option in distal OEC. However, the consequent loss of robustness from using fewer beams needs to be mitigated. Motion management and IGRT strategies may mitigate uncertainty sufficiently in distal OEC to facilitate the safe use of a two-beam arrangement. Further studies are required to confirm this.

For spinal cord doses, all plans met constraints. Again, the beam arrangements used had a significant impact. Beam arrangements that used predominantly posterior beams such the 180°/160° arrangement had a higher dose compared to arrangements with lateral or anterior beams. For most cases, the higher spinal cord doses are unlikely to be clinically significant as dose is comfortably within normal tissue constraints. However, in specific situations such as re-irradiation, using beam arrangements that include a lateral (e.g. 90°) or anterior (e.g. 45°) beam may allow cord tolerance doses to be met. This may provide a treatment option for patients with localised recurrence who otherwise have limited curative options in OEC. The use of PBT in re-irradiation in OEC is a growing field and is currently under further examination [194].

5.4.2 Effect of PBT Beam Arrangements on Cardiac Substructures

All beam arrangements comfortably met cardiac dose constraints. DVH parameters for the whole heart were comparable for all beam arrangements with the exception of beam arrangements which used an anterior (45°) or lateral beam (90°) which resulted in higher cardiac doses. Notably, doses to the right and left atrium were comparatively high in relation to whole heart mean dose for all beam arrangements. This is likely to be due to the proximity of the atria to the ITV in this case. Dose to the atria were marginally lower when predominantly posterior beams were used. Dose to the right atrium, in particular, may be clinically relevant as the sino-atrial (SA) and part of the atrio-ventricular (AV)

node is located within it [195]. Irradiation of the SA node at doses seen in this study (i.e. 3-5Gy) have been previously reported to be associated with development of new atrial arrhythmias[165]. As atrial arrhythmias are common following oesophagectomy [29] this suggests that limiting dose to the right atrium in NA setting may potentially reduce incidence rates. For patients who are particularly at high risk of this, such as an underlying history of cardiac arrhythmias, may benefit from utilising PBT beam arrangements that minimise dose to natural pacemakers such as the SA node.

Doses to the right and left ventricles and to the coronary arteries are very low for all beam arrangements, except for arrangements that used the 45° or 90° beam. Dose to the ventricles and coronary arteries is likely to be clinically relevant, as dose to these substructures have been shown to be a predictor of adverse cardiac outcomes such as ischaemic events, heart failure and all-cause mortality [188, 196]Again, patients who are at high risk, such as with underlying ischaemic heart disease or heart failure, beam arrangements should be selected to reduce the dose to these specific substructures.

Another notable finding is the relatively high dose received by the mitral valve is seen all beam arrangements. As discussed in Chapter 3 (see section 3.3.3), NTCP modelling data suggests both PBT and VMAT results in significant absolute risks on radiation induced valvular dysfunction in oesophageal cancer, with PBT resulting in substantial relative risk reductions. Crucially, NTCP modelling carried out in the chapter 3 was based on mean whole heart dose. The high mitral valve dose relative to mean whole heart dose suggests that the NTCP value of valvular dysfunction calculated in chapter 3 may be a significant under-estimate. Currently, there are no NTCP models that assess outcomes based on specific substructure dose. Further work is required to ascertain dose constraints of specific substructures, and to develop NTCP models for specific outcomes based on dose to individual substructures.

5.4.3 Limitations and Future work

As this study used only two cases, and only one for the assessment of cardiac substructures dose, further work on additional cases is required to assess a variety of patient and tumour anatomy. Additionally, this study does not compare cardiac substructure doses for PBT plans to VMAT plans. Whilst work in Chapter 3 shows an overall reduction in whole heart dose metrics with PBT compared to VMAT, the differences in dose to individual substructures is unclear. It is important to note VMAT commonly utilises a 360° arc in OEC, it is more likely to distribute dose more homogenously across the whole heart (see section 3.2.7). Therefore, dose is likely to be distributed differently across the substructures compared to PBT. Further work is required to ascertain if PBT has any dosimetric advantage over VMAT in this setting.

While some PBT uncertainty is mitigated with the use of robust optimisation, this does not account for all aspects of uncertainty in this study. Some of the uncertainty in PBT for distal OEC is derived from the intrinsic range uncertainty of PBT and the impact of intra-fraction changes such as diaphragmatic motion. Most beam combinations used in this study utilised posterior or posterior oblique beams, with the distal edges converging within cardiac substructures. PBT range uncertainty means that cardiac substructures near the end-of-beam such as the coronary arteries or atria may be receiving a higher dose than expected, potentially leading to unexpected toxicities. The end of range is also where the PBT RBE is greatest and may also contribute to higher toxicity. Future work should consider trialling Monte-Carlo (MC) based planning to assess the effect of different beam arrangements on range uncertainty, and subsequent dose to cardiac substructures. Additionally, LET-based planning should be trialled to assess the impact of end of range RBE changes [82] on dose to these structures.

Another limitation of this study is the poor visualisation of some cardiac substructures such as the coronary arteries on CT, which may lead to inaccurate delineation, and therefore inaccurate dose estimation. Additionally, my work does not consider cardiac motion. Studies using different imaging modalities such as cardiac MRI, either independently or as a hybrid with CT, have showed improved visualisation of these structures [191]. Although it is unclear if this will result in tangible clinical improvements, improved accuracy of cardiac substructure delineation may allow for more accurate and effective sparing. Future studies should examine the utility of improved cardiac imaging modalities in this setting.

As seen by the high relative doses received by the mitral valve and atria compared to mean heart dose, this work makes a case for routine interrogation of cardiac substructures dose in PBT for OEC. However, it is important to recognise that dose-volume constraints for cardiac substructures that are linked to clinical outcomes are yet to fully be established. Data linking cardiac substructure dose to outcomes is already being undertaken prospectively in some cancer sites, such as in the BACCARAT study in breast cancer patients [186]. Similar studies may be carried out in oesophageal cancer, potentially as a pre-planned exploratory endpoint for a subsection of patients in a clinical trial. An original RCT of PBT in OEC is currently being developed in the UK, ProtIeus (further details included in Chapter 7 and Chapter 8), where this may potentially be included as an exploratory endpoint.

5.4.4 A potential for 'personalised RT'

Having the option of multiple beam arrangements that are clinically acceptable in PBT allows clinicians and planners to tailor bespoke RT treatment plans that take into account individual patient co-morbidities. This level of flexibility is simply not achievable with photon RT due to the inherent physical

characteristics of x-rays. PBT may allow patients who have specific medical contraindications to OEC CRT to receive treatment. As an example, for patients with significant left-sided heart failure (e.g. ejection fraction <40%, where OEC CRT is a relative contraindication), beam arrangements that delivers nearly zero dose to the left ventricle may be selected. Similarly, for patients with underlying lung disease, such as fibrotic lung disease, which is generally seen as a relative contraindication to RT, an PA/AP or single PA beam arrangement that delivers zero or close to zero dose to the lungs may instead be utilised. For clinical scenarios such as re-irradiation where previous spinal cord doses are often a limiting factor, the ability to spare individual OARs such as the spinal cord may allow radical RT to be delivered where previously not possible. As with many new RT techniques, assessing bespoke PBT approaches for a heterogenous patient cohort in a randomised and prospective manner is challenging. Instead, observational data collection of clinical cases and outcomes, akin to NHS England's Commissioning through Evaluation (CTE) programme for SABR, [197] may facilitate appropriate evaluation of this approach, assessing safety and helping develop an evidence base. While this idea requires a substantial amount of further work for validation, it is clear that PBT permits a level of flexibility that was not previously possible with photon RT.

5.6 Conclusion

This work shows that multiple beam arrangements are likely to result in clinically acceptable plans for OEC. Generally, anterior beams including beams at 90° should be avoided in order to reduce whole heart and cardiac substructure dose. Consideration should continue to be given on how beam arrangements affect robustness to inter and intra-fraction motion. There is significant potential for further planning studies including a comparison study with VMAT and work exploring the impact MC based algorithms and LET-based planning.

PBT allows the selective sparing of individual OARs including cardiac substructures to a degree that is simply not possible with photon RT. This opens up the potential of personalised RT in OEC, offering the possibility of treating patients who may not have curative options and reducing toxicities of patients with specific underlying comorbidities. While more work in required in this field, this study signals the substantial further potential of PBT in OEC beyond dose reduction to the lung and whole heart.

Part 2: Developing Randomised Controlled Trials of PBT in Oesophageal Cancer

Introduction to Part 2:

In Part 1 of this thesis, some of the main dosimetric advantages of PBT in OEC were explored and quantified. In Chapter 3, the significant dose reduction to the lungs and heart were highlighted, with NTCP modelling data suggesting these reductions are likely to be clinically relevant. Chapter 4 showed how splenic dose may be reduced in PBT and VMAT for patients with lower OEC, suggesting achievable dose constraints that may be used in clinical practice or in a clinical trial protocol. Chapter 5 explored the way different beam arrangements affect OAR and cardiac substructure dose and detailed further work that may be done in this area. Despite these dosimetric benefits, as summarised in the systematic review in Chapter 2, there remains a paucity of prospective data of PBT in OEC with only a single RCT published to date. To the best of my knowledge, as of March 2021, there is only a single currently recruiting RCT of PBT for OEC globally; the Phase 3 NRG-GI006 study in the USA (NCT03801876) [198]. With rapidly expanding PBT capabilities in the UK and Europe, coupled with strong support from funding bodies and governmental organisations, researchers have a been given an exciting and unique opportunity to develop new trials of PBT for OEC.

This part of the thesis aims to address the lack of prospective data by detailing some work undertaken to develop new trials of PBT in OEC. Throughout my research fellowship, I have actively contributed to the development of Protieus (Chief Investigator (CI): Professor Maria Hawkins, University College London Hospital), a proposed randomised, Phase II trial of NA PBT in OEC. In addition, I have made some contribution to the development of a multi-centre, randomised Phase III European trial of NA PBT in OEC, the PROTECT study.

This part of the thesis details some of this trial development work. It is divided into 3 chapters. Chapter 6 focusses on RT delineation protocol development by means of a delineation comparison study. Chapter 7 concentrates on trial development, elaborating on patient and public involvement (PPI) work for two trials of PBT in OEC. The conclusion chapter will present concluding remarks and future directions of PBT in OEC.

Chapter 6: Evaluating Variation in Target Volume Delineation for OEC using the NeoSCOPE and Neo-AEGIS Trial Protocols

6.1 Introduction

Target volume delineation (TVD) remains the single biggest source of uncertainty within the radiotherapy treatment pathway. Unlike many steps in the radiotherapy treatment pathway, TVD is carried out manually by the treating clinician with minimal automation and often without peer review. As a result, this step of the pathway remains prone to human error irrespective of the skill and experience of the clinician. Dosimetric advantages that may be derived from the use of a new technology such as PBT or VMAT may be easily lost and in some circumstances, patient outcomes compromised, due to inconsistencies in TVD. Evidence from clinical trials suggests deviation from delineation protocols in clinical trials result in inferior local control and survival outcomes [199, 200].

RCTs are designed to compare a 'standard of care' against one or more novel interventions with consistency vital to maintaining confidence in conclusions drawn from a trial result. To ensure this, it is mandatory for all current RT trials to incorporate RT quality assurance (RTQA) protocols [200]. The aim of any RTQA programme in a clinical trial is to ensure adherence to trial protocol in all aspects in the radiotherapy treatment pathway such as TVD but also patient simulation, treatment planning and treatment delivery. In the UK, RTQA in NIHR-portfolio radiotherapy trials is administered by the UK Radiotherapy Trials Quality Assurance group (RTTQA) [201]. In the context of a trial of PBT, consistency in target volume delineation is especially important. Minor errors in TVD may be amplified due to PBT's intrinsic end-of-range uncertainties of range and RBE, potentially resulting in significant unintended dose distortions and unexpected clinical outcomes. Additionally, due to the sharp dose fall off with PBT, as with all precision RT techniques, areas not included in the TV are likely to receive minimal dose, leaving a minimal safety margin for TVD errors.

All TVD protocols should aim to generate consistent volumes that adequately cover the tumour and areas at risk, and a standardised approach OARs delineation. An effective delineation protocol should avoid ambiguity and be laid-out in a way that encourages consistency. In the past decade in the UK, there have been two RCTs of NACRT in OEC; the currently recruiting Neo-AEGIS study and the NeoSCOPE study (reported 2017) [40, 47]. Both trial protocols take a different approach to creating a TV despite recruiting similar patient groups. By means of a delineation comparison study this work aims to:

1) Critically assess and compare delineation protocols from the NeoSCOPE and Neo-AEGIS trials focussing on how the delineation instructions are presented.

2) Systematically comparing outlines from study participants, specifically assessing for areas of ambiguity in the protocol that may introduce inconsistency
3) Incorporate any conclusions into the development of a TVD protocol for an original trial of PBT in OEC.

6.2 Methods

6.2.1 Delineation comparison study design and participants

Two anonymised datasets with quality-assured structures; a middle-third case and a lower-third oesophagus case; were selected from the Cardiff RTTQA database. Cases with different tumour locations were selected in order to assess the separate sections of the trial TVD protocols. As this study aims to evaluate only the TVD protocol, not the clinician's ability to interpret staging investigations, the quality-assured GTVp were included in datasets that were sent to each clinician. Both cases had no involved nodes (N zero). Only 3D-CT scans (single-phase) were used in order to simplify the study. The anonymised datasets were sent to 10 clinicians across the UK with experience in treating OEC patients. Each clinician was asked to generate CTVA, CTVB and PTV volumes based on the GTVp for both cases, using the NeoSCOPE trial delineation protocol and the Neo-AEGIS trial delineation protocol, thus producing 2 sets of target volumes for each case. Table 27 shows the clinicians involved in the study.

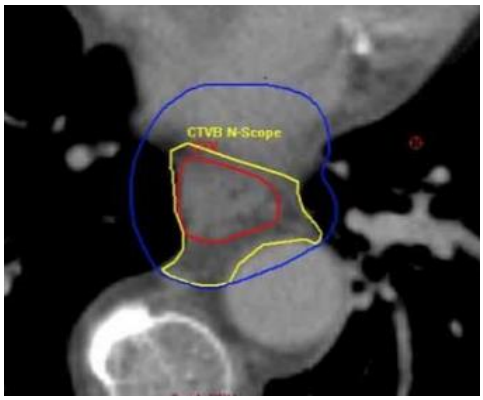
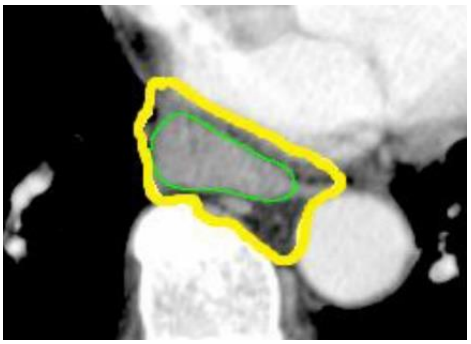
Centre name	**Number and role of participants involved**
Velindre Cancer Centre (VCC), Cardiff	1 consultant clinical oncologist
Leeds Cancer Centre, Leeds	2 consultant clinical oncologist
South West Wales Cancer Centre (SWWCC), Swansea	2 consultant clinical oncologists
Cancer Centre, Belfast	1 consultant clinical oncologist
Cancer Centre, Coventry	1 consultant clinical oncologist
Castle Hill Hospital, Hull	1 consultant clinical oncologist
South Wales Oncology Training Scheme (with experience in VCC and SWWCC)	2 post-FRCR trainees
Total participants	**n = 10**

Table 27 Centres and clinicians involved in the delineation study

6.2.2 Comparison of delineation protocols

Both delineation protocols give instruction on generating volumes that adequately cover areas at risk of local infiltration of the primary tumour and areas at risk of local spread (e.g. elective irradiation of nodal areas at risk). In the NeoSCOPE protocol, the CTVA refers to volume which incorporates the superior and inferior margins of the volume, while in the Neo-AEGIS protocol, the CTVA incorporates a 5mm minimum margin around the tumour. For CTVB, the NeoSCOPE protocol aims to cover areas at risk of local spread including circumferential/lateral areas of the primary tumour and inferior extension below the GOJ (for lower third tumours). In the Neo-AEGIS protocol, the CTVB incorporates both the superior/inferior margin as well as circumferential/lateral areas and areas below the GOJ (for lower third tumours), before combing CTVA to CTVB to form CTV_Comb from which the PTV is derived. A notable difference is that the Neo-AEGIS protocol uses a 'free-hand' approach for delineating the CTVB above the diaphragm whereas the NeoSCOPE protocol uses a geometric expansion margin followed by editing for normal tissues. For areas below the GOJ, both protocols use a 'free-hand' approach to cover nodal areas at risk of spread. The PTV refers to a planning target volume that incorporates a setup margin (SM) and an internal margin (IM). Table 28 includes excerpts from both protocols, outlining the instructions on how CTVA, CTVB (above the diaphragm), CTVB below the GOJ and PTV are to be generated. Full delineation protocols are included in the appendix.

	NeoSCOPE	**Neo-AEGIS**
CTVA	The GTV is copied and labelled 'CTVA'. This is grown manually along the axis of the oesophagus and should be both 20 mm superior to the proximal GTV margin and 20 mm inferior to the distal GTV margin if defined by primary tumour. The whole circumference of the oesophageal wall should be included throughout the length of CTVA.	CTVA is defined by an isotropic margin of 0.5 cm around GTVpn using the TPS. CTVA may be edited to exclude vertebrae where CTVA is directly abutting anterior vertebra but must NOT be edited elsewhere, i.e. lung, pericardium, great vessels, trachea, main bronchi.

CTVB	Circumferential CTVA is then copied and labelled 'CTVB'. It is grown by adding 10 mm in right-left and anterior-posterior directions using the Treatment Planning System (TPS). CTVB is then edited to exclude lung, pericardium, large vessels, trachea and right/left main bronchi and the vertebrae. Editing the CTVB (yellow) avoids unnecessary inclusion of the lung and heart. (the image below is taken from the NeoSCOPE protocol, GTVp – red, CTVB - yellow) 	CTVB will comprise of the 'fat pad' around the oesophagus. The 'fat pad' is contoured at the same levels as the GTVpn and for 3 cm superior and inferior (S/I) to GTVp. It is bordered posteriorly in places by the anterior aspect of the vertebral body. The CTVB should not include bone, lung, pericardium, trachea, bronchus or great vessels (it should include the Azygous/Hemiazygous veins). (the image below is taken from NeoAEGIS the protocol, GTVp- green, CTVB yellow) CTVB should fully encompass: - the entire 'fat pad' along the length of the GTVpn and for 3 cm cranially and caudally to GTVp - the entire oesophagus along the length of the GTVpn and for 3 cm cranially and caudally to GTVp - malignant peri-oesophageal nodes - benign nodes along its course without a margin (but CTVB should not be extended cranially or caudally to include benign nodes the Azygos and/or Hemiazygos vein(s) where in close proximity to CTVB. 

CTVB below the GOJ (for lower third tumours)	Below the GOJ CTVB is grown manually to 20 mm below GTV. This volume includes CTVN5 mm, and the elective nodal regions at high risk of microscopic spread along the lesser curve of stomach, the left gastric artery and coeliac region where these lie within 20 mm of the GTV. Superiorly, this volume includes the fat space below the diaphragm around the cardia and gastrohepatic fat between the lesser curve and the medial liver edge. Inferiorly, it includes the fat space around the coeliac artery, bounded by the pancreas anteriorly, small bowel and liver laterally, and aorta posteriorly An assessment of the potential for mucosal spread into the stomach laterally and posteriorly must be made on a case by case basis. The extent of this volume is hard to define anatomically but is usually no greater than 2cm in lateral extent. In order to include LNs along the lesser curve, it is anticipated that some of the lesser curve will be included (protocol appendix includes examples) especially in tumours of the GOJ and/or with gastric extension. The elective nodal regions of the splenic hilum, greater curvature, and short gastric vessels are not included, even for patients with Type II GOJ tumours.	Where GTVn includes nodes in the abdomen, CTVB is extended to include that entire nodal station. No other abdominal nodal stations will be electively included. For example, if GTVn includes a coeliac node, the entire coeliac axis is included in CTVB. Patients with malignant nodal disease outside paracardial, lesser curvature/gastro-hepatic ligament and/or coeliac stations are ineligible for this study. There is no 'fat pad' around the cardia/fundus stomach. Therefore, to describe the appropriate caudal expansion for junctional tumours a small 'cuff' of cardia/fundus is contoured, encompassing the entire circumference of the cardia/fundus for 2 cm caudal to GTVp. An assessment of the potential for mucosal spread into the stomach laterally and posteriorly must be made on a case by case basis. The extent of this volume is difficult to define anatomically but is usually no greater than 2cm in lateral extent. In order to encompass involved nodal stations along the lesser curve, it is anticipated that some of the lesser curve will be included, especially in tumours of the OGJ and/or with gastric extension. Below the OGJ, CTVB should fully encompass: - malignant upper abdominal nodes - benign peri-oesophageal nodes along its course - entire nodal station(s) containing malignant nodes - [Nodal stations that do NOT contain malignant nodes will NOT be electively included]
PTV	CTVB is copied and automatically grown using the TPS by 10mm superiorly (5mm IM and 5mm SM), 10 mm inferiorly (5mm IM + 5mm SM) and 10mm (5mm IM and 5mm SM) circumferentially. This new volume is labelled PTV.	The Planning Target Volume (PTV) is created using the TPS via the expansion of CTV_Comb (sum of CTVA and CTVB) by an isotropic margin of 1 cm (0.5 cm Internal Margin (IM) and 0.5 cm Set-up Margin (SM), in all dimensions.
Number of illustrative CT slices included*	52	51
Number of worked examples	3	3

*Table 28 Excerpts for delineation instructions adapted from both protocols for CTVA, CTVB, CTVB below the GOJ and PTV. *Number of illustrative CT slices include images from middle third and lower third delineation instructions, explanations of nodal areas-at-risk and images included in worked examples. It does not include images included for OAR delineation.*

6.2.3 Data analysis

6.2.3.1 Qualitative Analysis

For each case, two sets of target volumes were delineated by the clinicians and returned to our database. The completed CTVA/CTVB/PTV volumes were reviewed by a RTTQA reviewer (ON) with experience in in reviewing cases for OEC trials. Each of the submitted volumes underwent an individual case review and were categorized as 'acceptable as per protocol', 'acceptable variation' and 'unacceptable variation' from protocol, as per European Organisation for Research and Treatment of Cancer (EORTC)/Global Harmonization Group (GHG) RTQA naming conventions [202]. The definitions of individual categories are outlined in table 29.

Acceptable as per protocol	The radiation therapy treatment was delivered to the patient according to the protocol.
Acceptable Variation	The radiation therapy treatment was delivered to the patient not according to all of the protocol specifications, but no clinical impact affecting the trial outcome is expected due to the deviation(s). The observed protocol deviations do not exceed the defined protocol criteria for an acceptable variation.
Unacceptable Variations	The patient has been planned/treated not according to the protocol and the deviation(s) could have a clinical impact on him/her that would affect the trial outcome. The variation(s) exceed the defined protocol's criteria for an unacceptable variation. The consequence of the deviation(s) is deemed significant enough by the trial Principal Investigator/RTQA reviewer to increase the trial's uncertainty and thus may increase the probability that the true trial outcome is obscured if the patient's data was to be included in the trial's final analysis.

Table 29 EORTC/GHG standardised nomenclature for individual case reviews[202].

In this study, unacceptable variations were defined as protocols deviation that may to lead to an adverse clinical outcome i.e. reduced local control or increased toxicity. Each individual volume was divided into separate steps which were assessed independently using the same nomenclature in order to ascertain which steps in the protocol were not being adhered to appropriately. For example, CTVB in NeoAEGIS was divided into CTVB length, CTVB below the GOJ and CTVB 'fat pad' delineation. It is therefore possible to have more than one protocol deviation for each submitted case.

6.2.3.2 Quantitative Analysis

Quantitative assessment of variation in outlining was made using the Kouwenhoven index (generalised conformity index, CIgen) and analysis of the geometric volume of each structure. The Kouwenhoven index is a measure of similarity of TVDs independent of the number of observers. The greater the CIgen, the greater the level of agreement between observers [203]. The Kouwenhowen index calculations were done by importing the structure sets into Matlab (Mathworks, version 2018b) and using a scripting tool. Geometric volume was calculated using a volumetric assessment tool in the treatment planning system (TPS). (Prosoma, v4.1)

All data was collated and processed in Microsoft Excel and SPSS (v26, IBM).

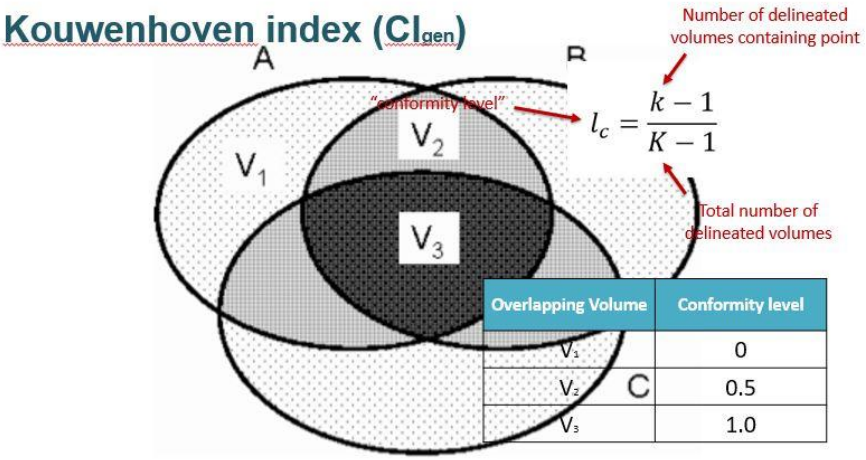


Figure 14 Kouwenhoven index (CIgen)

6.3 Results

Each participant submitted two sets of structures for lower-third and middle-third cases respectively. A total of 40 sets of structures were submitted by the study's 10 participants.

6.3.1 Qualitative analysis

For both cases, a qualitative assessment of the volumes submitted were carried out. There were a greater number of protocol deviations seen in CTVB volume compared to CTVA for both cases using either protocol. Structures generated using the Neo-AEGIS resulted in a proportionally greater number of variations from protocol. There were no protocol deviations seen in the generation of PTV in any of the submitted volumes. There were proportionally fewer protocol deviations seen in the middle-third case submissions compared to the lower third case for either delineation protocol. For the middle-third case, 4/10 (40%) of Neo-AEGIS structures had at least one unacceptable variation from protocol, compared to 1/10 (10%) for the NeoSCOPE structures. For the lower third Neo-AEGIS case, 6/10 (60%)

of structures had at least one unacceptable variation from protocol, compared to 0/10 (0%) for the NeoSCOPE structures. Table 30 and 31 highlights the number of acceptable or unacceptable variations from protocol for individual structures for both cases.

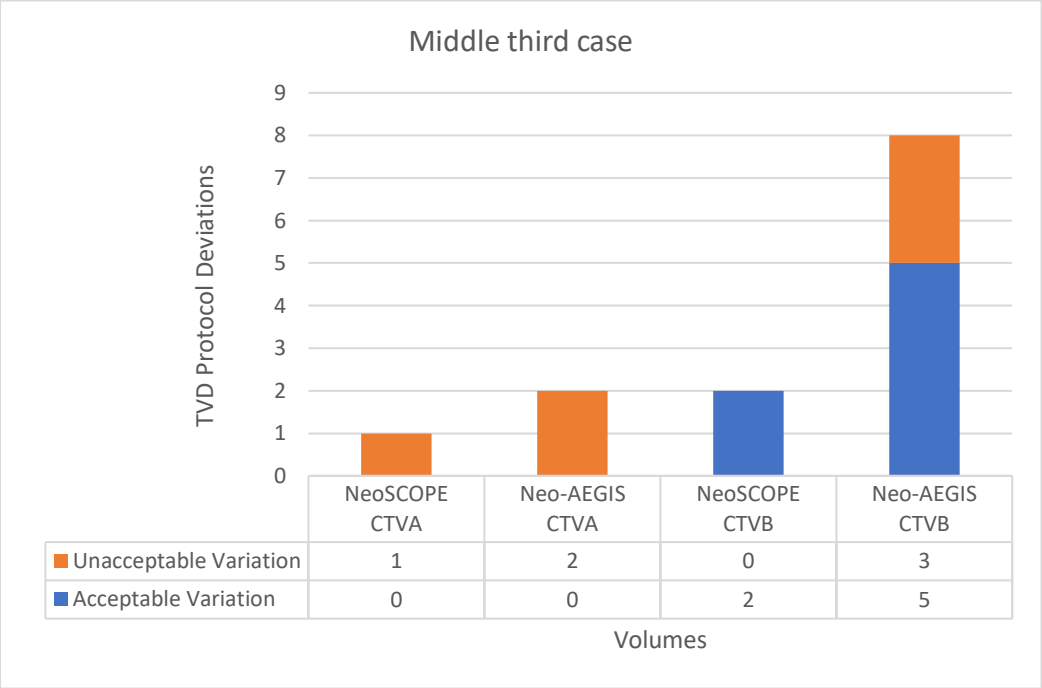


Table 30 Number of acceptable and unacceptable protocol deviations for individual structures for the middle third case

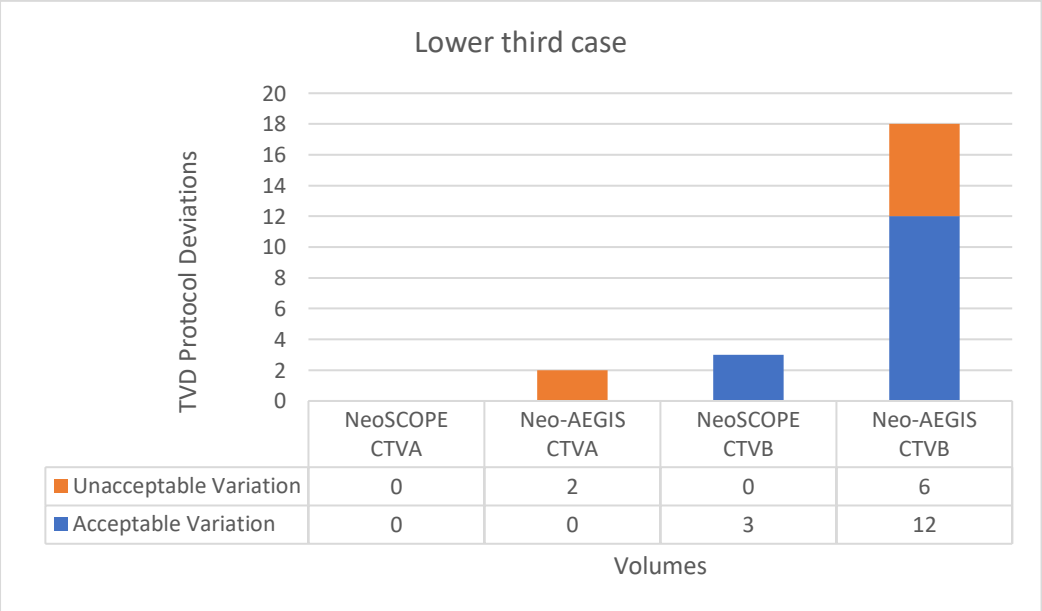


Table 31 Number of acceptable and unacceptable protocol deviations for individual structures for the lower third case.

Figures 15 (a and b) and 16 (a and b) show a breakdown of the variations from protocol seen in the cases delineated using the Neo-AEGIS protocol by individual steps.

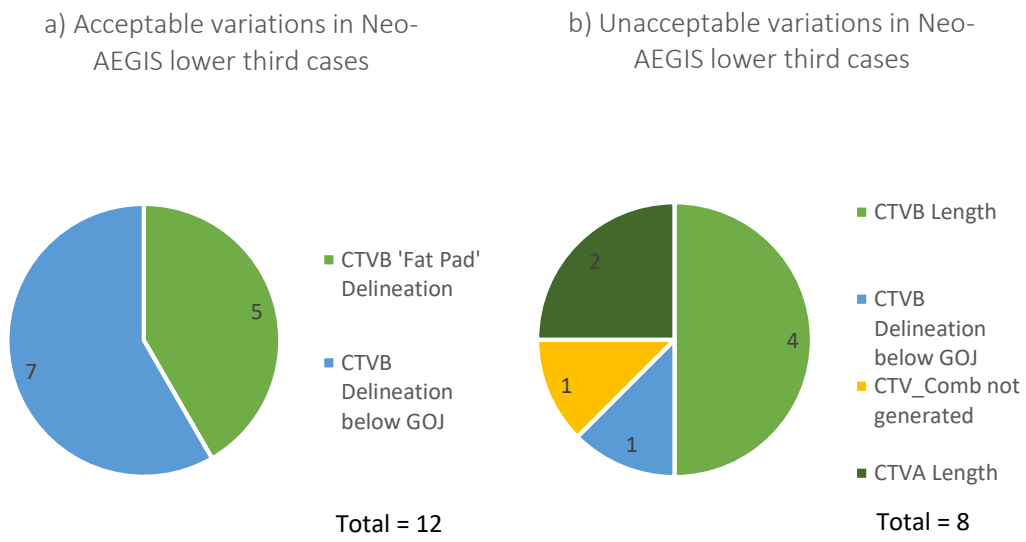


Figure 15a and 15b shows individual protocol variations from lower-third cases using the Neo-AEGIS protocol, broken down by individual steps. Acceptable variations(R), Unacceptable variations (L).

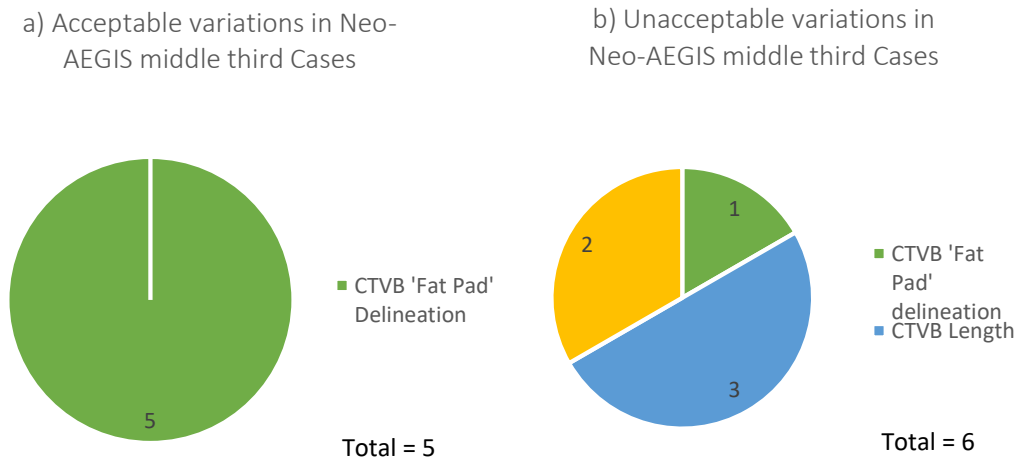


Figure 16a and 16b shows individual protocol variations from middle thirds cases using the Neo-AEGIS protocol, broken down by individual steps. Acceptable variations(R), Unacceptable variations (L).

For both the lower-third and middle-third cases, CTVB 'fat pad' delineation or CTVB delineation below the GOJ accounted for all the acceptable variations from protocol. For unacceptable variations from protocol, inappropriate CTVB length accounted for half of all variations seen, with inappropriate CTVA length, CTVB 'fat pad' delineation, CTVB delineation below GOJ and no CTV_Comb also resulting in unacceptable variations. Figure 17 and figure 18 illustrates the inter-observer variation seen in CTVB around the level of heart and the GOJ for cases outlined using the Neo-AEGIS protocol compared to CTVBs from the NeoSCOPE protocol at the same level.

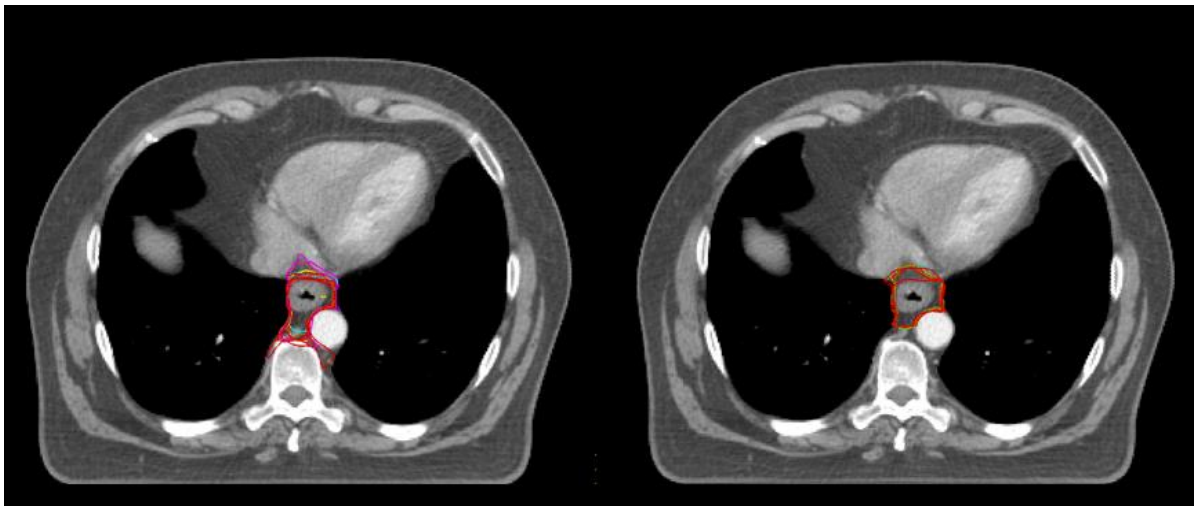


Figure 17 Lower-third case CTVB volumes around the level of the heart delineated by study participants following the Neo-AEGIS (L) and NeoSCOPE (R) protocols

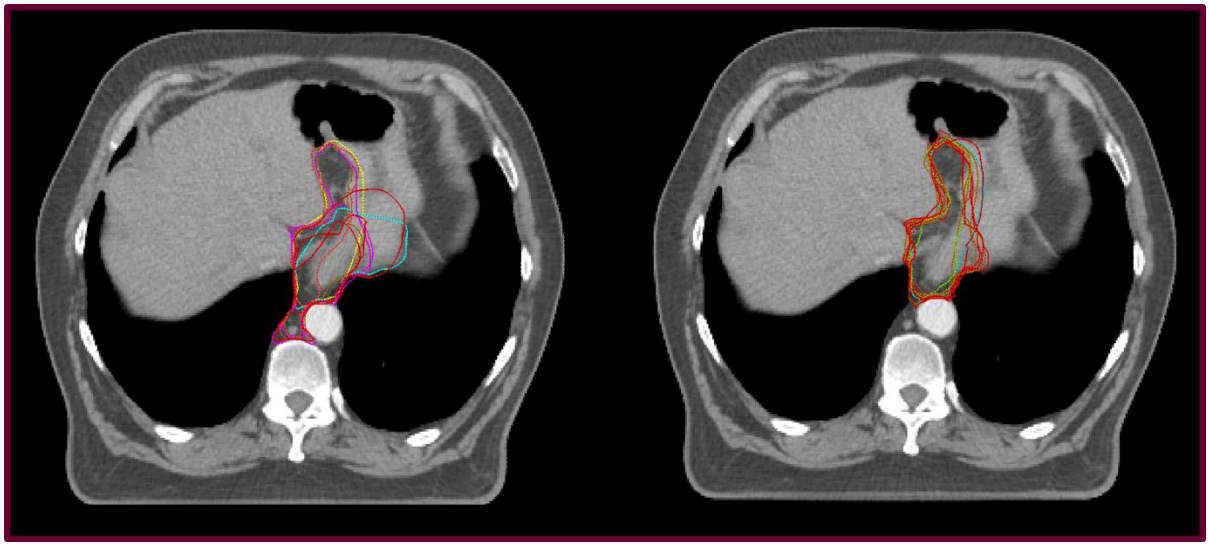


Figure 18 Lower-third case CTVB volumes around the level of the GOJ delineated by study participants following the NeoAEGIS (L) and NeoSCOPE (R) protocols

6.3.2 Quantitative analysis

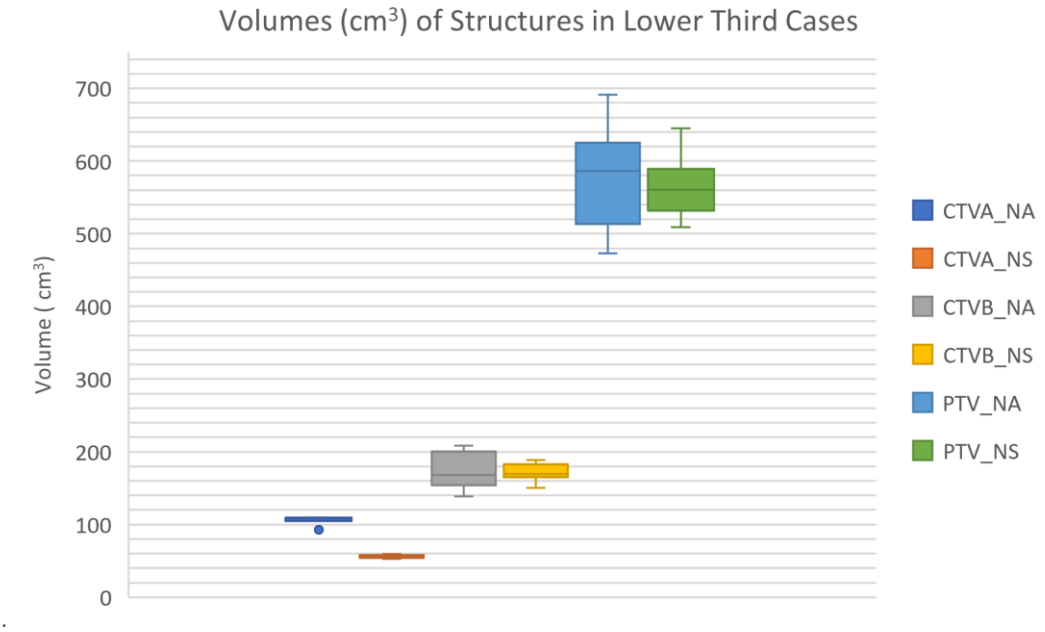


Figure 19 Comparison of absolute volumes (in cm3) for CTVA, CTVB and PTV structures for the Lower Third Case generated using the Neo-AEGIS (NA) and NeoSCOPE (NS) protocols

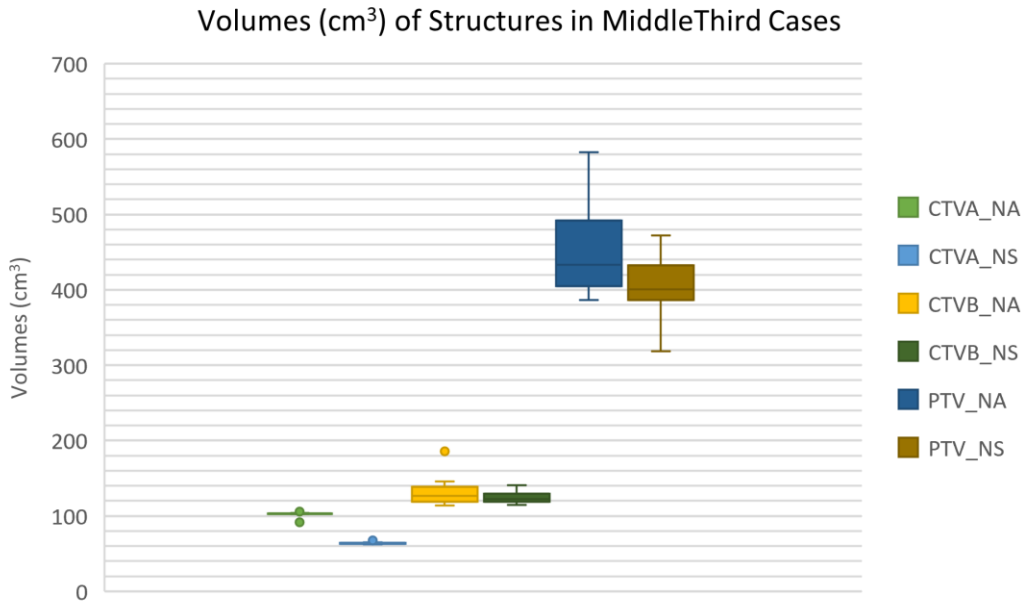


Figure 20 Comparison of absolute volumes (in cm3) for CTVA, CTVB and PTV structures for the middle third case generated using the Neo-AEGIS (NA) and NeoSCOPE (NS) protocols

Figures 19 and 20 show the absolute geometric volume of the submitted structures. In both figures, the box plot of the left represents the NeoAEGIS volumes and the right, NeoSCOPE. The NeoSCOPE TVD protocol generally resulted in smaller volumes for both cases which is in keeping with the protocol instructions. CTVAs are very different structures in both protocols, so little can be inferred from its comparison. For both the cases, there is a smaller interquartile range for the CTVB and PTV

structures with the NeoSCOPE structures, indicating greater consistency in outlined structures.

Volume	Middle third		Lower third	
	Neo-AEGIS	**NeoSCOPE**	**Neo-AEGIS**	**NeoSCOPE**
CTVA	0.95	0.93	-*	0.92
CTVB	0.70	0.84	0.60	0.76
PTV	0.77	0.84	0.67	0.81

*Table 32: Calculated values of Kouwenhoven index (CIgen) for CTVA, CTVB and PTV structures delineated by participants. Lower values indicate poorer agreement. * Value for Neo-AEGIS Lower-Third CTVA unavailable due to processing error. Visual check showed very good agreement.*

Table 32 shows the CIgen for the various structures. For both protocols, the CTVB has a lower generalised conformity compared to the CTVA, indicating greater variation in submitted volumes. There was some improvement seen in with addition of a geometric margin for the PTV, increasing overlap of the volumes. In both cases, greater inconsistency was seen in the cases outlined with the Neo-AEGIS protocol. This particularly marked for the CTVB volume in the lower third case, where CIgen of 0.60 indicates poor consistency of outlining between observers.

6.4 Discussion

This study shows that the Neo-AEGIS protocol resulted in a greater number of protocol deviations and greater inter-observer variation of TVD compared to the NeoSCOPE protocol in all structures. The greatest number of acceptable and unacceptable variations were seen in CTVB structures, with the CTVB below the GOJ having the lowest CIgen of all assessed structures.

6.4.1 CTVB above the GOJ

For volumes above the GOJ, the main source of acceptable variations from protocol for the NeoAEGIS cases is the delineation of the mediastinal ‘fat pad’. The Neo-AEGIS protocol takes an arguably more pragmatic approach to describing what areas are to be included in the CTVB, with clinicians using a ‘free-hand’ approach to delineate the ‘fat-pad’. The protocol describes structures that should be included in the mediastinal ‘fat-pad’ and includes several illustrative images but does not provide a slice-by-slice atlas of what should be included at each level. As there is ambiguity in the Neo-AEGIS protocol about what constitutes the ‘gold-standard’ for ‘fat-pad’ delineation, in a more subjective assessment of these volumes (individual case review), the reviewer often deemed these volumes as having an acceptable variation from protocol. In the quantitative assessment of the structures, the CIgen for middle-third case CTVB for the Neo-AEGIS is lower than for the NeoSCOPE case (0.70 vs 0.84) indicating lower agreement in the outlining of CTVB above the GOJ when using the Neo-AEGIS

protocol. It may be inferred that a cause of these inconsistencies may lie in the recognition and definition of what is the 'fat-pad' and the 'free-hand' approach that is used to delineate this volume. For the CTVB above the diaphragm, the NeoSCOPE protocol is more didactic in its approach, using a geometric margin that is grown using the TPS, before editing back away from normal tissue. This appears to be more unambiguous, with our data suggesting that this approach results in a more consistently delineated structure, with fewer variations from protocol, a smaller inter-quartile range of geometric volume and a higher CIgen, indicating greater overlap in between observers.

6.4.2 CTVB at the level of/below GOJ

For volumes below the GOJ, the variations from protocol were commonly seen in CTVB length and general delineation of CTVB below the GOJ. The Neo-AEGIS protocol resulted in more inconsistencies of volumes outlined, with a CIgen for CTVB in the lower-third case of 0.60, indicating low general agreement of volumes. As the lower-third case used was a node negative case, the NeoAEGIS protocol does not recommend that any elective nodal areas are irradiated but gives instruction to include a small cuff of cardia/fundus for junctional tumours, assessing risk of mucosal spread on a case-by-case basis for areas 2cm distal to the GTVp. It also gives instruction on including upper abdominal nodes in CTVB irrespective of nodal involvement. These instructions are pragmatic and therefore more ambiguous, likely resulting in clinicians outlining very different areas as highlighted in figure 16. For CTVB length, above the GOJ, the Neo-AEGIS protocol states that volumes should be extended 2 to 3cm caudal to the GTVp. Below the diaphragm, observers are instructed to extend CTVB 2cm below the GTVp. It is likely that the discrepancy in instructed length was misinterpreted by several of the observers, many of which resulted in unacceptable variations from protocol by extending the volume 3cm distal to GTVp below the GOJ. In comparison, the NeoSCOPE protocol recommends that for junctional tumours/lower third tumours, the CTVB volume should encompass the elective nodal regions at high risk of microscopic spread along the lesser curve of stomach, the left gastric artery and coeliac region within 2cm of the GTV irrespective of nodal involvement. The protocol also allows for assessment of submucosal spread on a case by case basis but crucially includes atlas-based anatomical boundaries of what should be included. While this 'free-hand' approach is likely to have caused inconsistency in the outlines; resulting in a CIgen of 0.76, the lowest of the NeoSCOPE volumes; an atlas-based approach to the nodal areas to be included potentially resulted in more consistent outlines. There is no discrepancy in instructions for length of volume which again may have minimised the risk of error by individual observers.

6.4.3 Inconsistency in outlining for PBT trials

As technological advances in radiotherapy such as VMAT and PBT improves plan conformality and precision, it becomes increasingly important that TVD consistency improves accordingly. The quality

of a treatment plan is only as good as its weakest link. Poor quality of outlining not only mitigates any potential gains from a new technology but is possibly detrimental to patient outcomes. There may be benefits to a more pragmatic protocol as this allows incorporation of local practice and clinical experience, allowing a flexibility in approach that may be desirable in a multi-centre trial. However, one may argue that inconsistency of volumes should be minimised as clinical trial data has shown that inconsistencies in TVD may result in inferior outcomes for patients. Older techniques such as 2DRT or 3DCRT used large fields, resulting in larger high dose regions, inadvertently providing a safety margin when target volumes were inaccurately delineated. Increasing conformality results in smaller high dose regions. While this allows for better sparing of normal tissues, this increases the risk of missing the target volume if these are not adequately delineated and quality-assured. For PBT, the risk may be even more pronounced. The well-documented distal dose fall-off means that areas of risk that are not delineated are likely to receive little to no dose. The range uncertainty and variable RBE at the end of beam, means that an inappropriately large volume may result in unexpected radiobiological effects in structures that are commonly at the end of a beam as the heart, stomach or liver. Failure to address inconsistencies in TVD delineation may result in a negative trial, or worse, a trial that inaccurately shows detriment when using PBT.

6.4.4 Limitations

There are several limitations to this study. Importantly, it is not defined if the study participants are more familiar with one of the two protocols. For example, some participating clinicians may have only had experience in the NeoSCOPE protocol with little exposure to the Neo-AEGIS trial protocol resulting in simple errors such as CTVA and CTVB length. Of note, many of the clinicians invited to participate in this study work in recruiting centres for both trials. It may be argued that any study protocol should be easily interpretable irrespective of experience or exposure and any potential for misinterpretation should be minimised where possible. Another limitation is that the qualitative assessment (individual case review) of the structures was done by a single reviewer, possibly introducing the risk of random error and systematic bias. However, the quantitative analysis is more objective, with results appearing to agree with the more subjective qualitative assessment of the submitted volumes. A further limitation of this work is that not all parts of the protocol were assessed. As the cases chosen were 3D-CT (single-phase planning CT) cases and node negative, parts of the protocol were not systematically compared. Notably, cases used in this study were relatively straightforward cases, with any added complexity such as 4D-CT and ITV generation likely to add further inconsistencies in the outlines. Finally, a further limitation is this study does not assess whether expansion margins to form CTV structures used to derive the final target volumes adequately covers the areas at risk. This is outside the scope of this study. However, this study shows that Neo-AEGIS results in a larger final

treatment volume due to greater coverage of the mediastinal ‘fat-pad’ and a greater length of CTVB compared to NeoSCOPE for an identical case. Future work should include an analysis of local failure rates in both trial cohorts, which may further elucidate the ‘at risk’ areas. However, it is important to note that both trial protocols are from major, multicentre trials, led by experts in the field, with protocols that have undergone a peer-review process.

6.5 Conclusions

This work demonstrates how specific steps in a TVD protocol are presented impacts the level of consistency in the final volumes. Conclusions that may be drawn from this work to incorporate into future iterations of a delineation protocol for OEC include:

- Use of geometric margins where possible, minimising ‘free-hand’ drawing of volumes. Geometric expansion margins followed by editing for normal structures is likely to result in more consistent volumes as it avoids ambiguity on which areas to include.
- Where there is necessity to use a ‘free-hand’ approach, it is useful to take an atlas-based approach including slice-by-slice picture atlas. ‘Free-hand’ volumes with clearly defined anatomical boundaries appear more likely to result in more consistent volumes.
- When instructing on TV length (superior/inferior margins), it is essential to be clear and concise, avoiding what may be perceived as discrepancy in the required margins. Future iterations should consider including a summary section that include superior/inferior margins so observers may double-check their delineated volumes.

The conclusions drawn from this study will directly feed into the development of the protocol for Protieus, an original trial of NA PBT in OEC. The details of this trial are covered in additional detail in Chapter 7, Chapter 8 and the appendix.

Chapter 7: Patient and Public Involvement (PPI) in PBT Trials of OEC

Sections 7.1-7.4 has been accepted for publication in The Patient: Patient Related Outcomes Journal in November 2020.

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Author Details and their Roles:

Olivia Joseph, PPI officer; Annie Keane, PPI officer; Kate Cleary, PPI officer; Sue H Campbell, patient representative; Sarah Gwynne, Consultant Clinical Oncologist; Tom Crosby, Consultant Clinical Oncologist; Ganesh Radhakrisha, Consultant Clinical Oncologist; Maria Hawkins, Professor of Radiation Oncology.

Paper 1 Patient and Public Involvement Refines the Design of ProtOeus: A Proposed Phase II trial sof Proton Beam Therapy in Oesophageal Cancer

Candidate contributed to study conception, data collection and analysis, manuscript preparation and editing

Author 1 contributed to conducting data collection and methodology, manuscript writing and methodology

Author 2,3,4 contributed to data collection and manuscript editing

Author 5, 7 contributed to study conception, data collection, manuscript editing

Author 6 contributed to manuscript editing

Author 8 contributed to study conception and manuscript editing

7.1 Introduction to patient and public involvement (PPI) in PBT research

Involving patients in research is shown to improve the overall quality and relevance of research with these trials more likely to recruit and retain participants [204-206]. Emerging evidence suggests research which has meaningful input from patients with lived experience of the condition under study is likely to have a greater impact [206]. The UK National Institute of Health Research's (NIHR) recognises the value of PPI in research, founding INVOLVE [now renamed NIHR Centre for Engagement and Dissemination (NIHR-CED)], a national advisory group that promotes PPI in health research. INVOLVE recommends a model of co-production of research that involves patient contributions at every stage of the research cycle including in the development phase [207].

Clinical trials in PBT present a distinct set of challenges for researchers and patients. Firstly, trial feasibility may depend on patients being willing to travel for treatment; away from home and their support networks for several weeks; to one of the limited number of PBT centres which are often located in academic institutions in major cities [76]. For those unable or unwilling to travel, this raises the issue of inequity of access to PBT which is especially important in a publicly funded health system like the NHS. Moreover, for neoadjuvant (pre-surgery) trials, patient pathways involving PBT are likely to be more complex, necessitating a more demanding level of coordination between PBT and tertiary surgical centres. Trial design in PBT also presents fresh challenges. PBT is often utilised to reduce the late effects of radiotherapy, such as in paediatric cancers, where benefits are not seen for several decades. New trials of PBT have a difficult task of selecting primary endpoints that are patient-focussed and scientifically robust yet deliverable within the timeframe of a funded research cycle.

Here we describe how our early partnership with patients in the development of this trial has helped us refine trial design and co-develop solutions to these challenges with the target population.

7.2 Methods:

The ProtOeus study (Neoadjuvant Proton Beam Therapy in Cancer of the Oesophagus, now renamed Protieus) is a proposed (pre-funding) randomised phase 2 trial comparing NA CRT with PBT to photons (IMRT/VMAT) for patients with resectable OEC. We sought out patient views at an early stage in trial development to ensure that patient views were embedded in all aspects of the trial. Figure 21 shows the proposed trial design prior to PPI work with several proposed radiotherapy dose schedules. At this point, this trial had been discussed in CTRAD trial development workshops where the trial was originally conceived and developed. These workshops are generally attended by researchers with minimal input from patient contributors into individual trials. Trial endpoints, trial design and proposed patient pathway are included in the Table 33, Figure 21 and Figure 22 respectively.

Co-Primary Endpoint	Toxicity reduction by 1/3 - 90 days morbidity (cardiac and lung) Non-inferiority to standard nCRT - pCR rate, R0 rate
Secondary Endpoints	Progression Free Survival Overall Survival Rate of Grade 4 Lymphopenia Patient reported outcome measures (PROMs) Health Economic Analyses 6 month toxicity endpoints – incl. leak rates Translational work

Table 33 Proposed primary and secondary endpoints for the ProtOeus trial prior to PPI work.

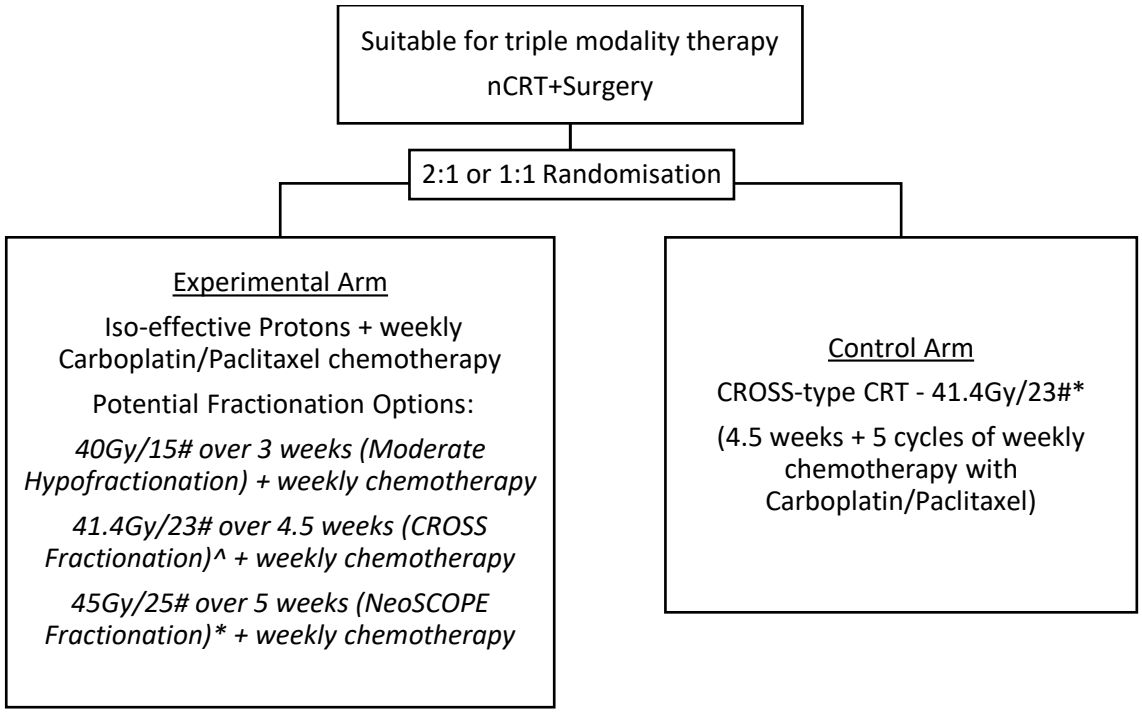

*Figure 21: Proposed Trial Design pre-patient involvement work for the ProtOeus trial. Gy = Gray); # = number of radiotherapy fractions; ^Shapiro et al. [23]; *Mukherjee et al.[40].*

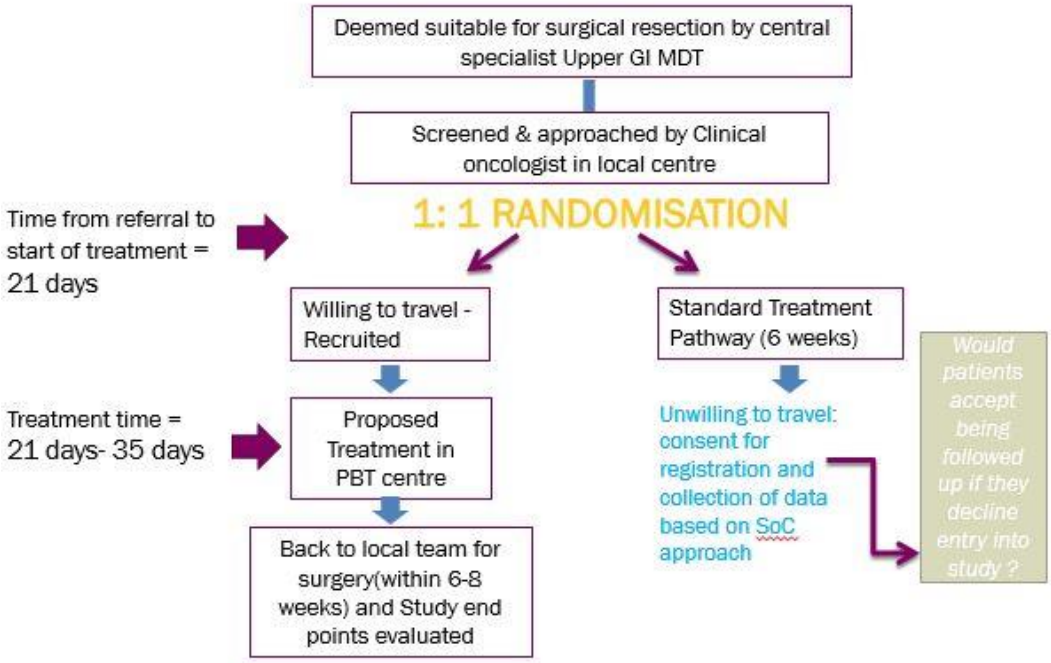

Figure 22 Proposed Patient pathway for the ProtOeus trial.

Three focus groups were held in separate UK locations; Central Manchester, Wigan and Cardiff; over a period of 7 months from November 2018 to June 2019. We included locations that were varying distances from PBT centres in order to get broad representation from the whole country rather than just in cities where the PBT centres were located.

7.2.1 Recruitment:

Participants were invited via three main routes. Firstly, patient engagement teams from Manchester University NHS Trust and Wales Cancer Research Centre (WCRC) sent out adverts via social media networks and to regular patient contributors. Additionally, personal invitations were sent out to individual patients who had been identified by their treating clinicians as potentially interested in participating. Finally, we utilised existing patient networks such as OEC support groups and other cancer support centres (e.g. Maggie's Centres) to advertise the meetings. For example, the focus group meeting in Wigan was incorporated into a regular meeting of an established OEC support group. Invitations were extended to carers/spouses as it was felt to be important to include their perspective, recognising the crucial role they play in a patient's journey. Information on the trial and the focus groups were given to the patient prior to the meeting. No specific written consent was obtained, but all patients gave implied consent for responses to be used. All participant data and responses were

anonymised. Patients were reimbursed for their time in line with NIHR guidance and provided with refreshments.

7.2.2 Focus groups:

The sessions were held as a facilitated focus group with presentations (from investigators) followed by semi-structured open ended questions (from investigators and facilitators) [208] organised around pre-determined topics. This method is commonly used in PPI work [209]. The topics of discussion were based on previously published PPI work carried out by the TORPEdO trial (a trial of PBT in head and neck cancer) [210, 211] and from feedback received in CTRAD trial development workshops. The meetings were facilitated by members of the patient involvement team (non-clinicians); in Manchester and Wigan, by patient involvement managers from Manchester University NHS Trust, and in Cardiff, by a patient involvement officer from WCRC. Patient responses and comments were recorded using written notes by facilitators during the session.

7.2.3 Selection of Topics:

Specific questions were asked on perception of PBT as this was a topic much publicised in UK media and with at a cost of £250 million to the NHS, remained a debated political issue in the UK. Another important aspect was acceptability of travel to a PBT centre prior to surgery and feasibility of the patient pathway. As many patients in the UK do not live near an NHS PBT centre, travel was felt to be a potential barrier to entry which may disproportionately impact patients from a lower socio-economic group. Further questions were asked on trial design where different potential radiotherapy fractionation schedules and trial endpoints were presented in order to ascertain patient preference. Other topics include patient information sheets and possible clinical scenarios, including the need for admission to an acute hospital local to the PBT centre, in the event of an emergency. Table 34 details specific questions asked during focus group meetings.

1) Perceptions of Proton Beam Therapy
2) Patient acceptability on travelling for PBT a) Would travelling to Manchester or London for PBT be acceptable? b) What additional support would be required at the PBT Centre?
3) Patient pathway and trial Design a) Thoughts on trial name b) What are your views on the patient pathway? c) What are your views on randomisation? d) What are your views on different fractionation schedules? e) Which trial endpoint is most important?
4) Patient information

a) What type of patient information is would be most useful? Would any other form of media (e.g. videos, apps) be useful? b) How would you like the patient information presented?
5) Clinical Scenarios a) What are your thoughts about being treated at a local hospital for any emergencies? b) What are your views on being under the care of a different oncologist whilst at the PBT centres?

Table 34: Pre-determined areas of discussion and specific questions asked to all PPI contributors

7.2.4 Data analysis:

Written notes were transcribed onto Microsoft Excel/Microsoft Word in preparation for data analyses. In each of the pre-specified areas of discussion, key issues and themes raised by the participants across the different groups were identified and then summarised to determine a representative overall response from the whole group [212]. Data from each focus group were analysed by at least two independent researchers (usually the facilitator and an investigator). These responses were then collated and discussed among all investigators and facilitators, following which a summative analysis was performed [213]. Individual quotes that helped illustrate the summarised feedback were identified and also included in this report.

7.3 Results:

The focus groups were attended by 21 patients in total (Wigan – 10; Cardiff – 7; Central Manchester - 4). The participants included patients who had undergone treatment for OEC including with radiotherapy and surgery, patients who had undergone treatment for other cancers including with chemotherapy or radiotherapy, spouses/carers of OEC patients and experienced PPI contributors. Many of the participants had not previously been involved in PPI activities. There was a wide geographical representation with patients from as far afield as Pembrokeshire, West Wales. Figure 23 illustrates the geographical locations of patients in relation to the PBT centres. As an example of travel times, a train journey from Pembrokeshire (West Wales) to Manchester takes approximately 7 hours, while a train journey from Wigan to Manchester takes just under one hour [214].

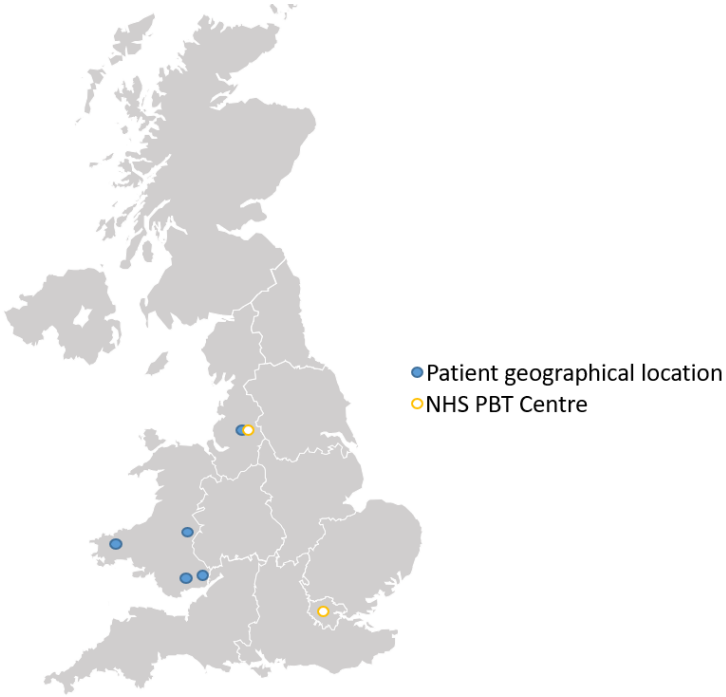

Figure 23 UK map showing patient home location and NHS PBT centres

7.3.1 Perception of proton beam therapy

Participants reported PBT was generally perceived to be a superior treatment to standard radiotherapy techniques and felt it would contribute to reduced toxicity and better cure rates making the trial very attractive to patients.

7.3.2 Patient acceptability on travelling for PBT

All participants reported that they would be willing to travel for PBT if offered participation in this trial. This included a patient in the Cardiff focus group, who would have travel for approximately 7 hours to get to the Manchester PBT centre. However, participants felt that there would be some patients would not travel due to the additional burden this would place on family as well as a potential loss of earnings due to time off work. The following is a quote from a participant in the Cardiff meeting: '*It is unacceptable that some people may miss out on treatment just because they can't afford travel. For example, train travel from Fishguard (West Wales) to Manchester is £150 per person and £300 per couple.'* Participants felt very strongly that travel and accommodation expenses should be covered to ensure all UK patients had equal access to PBT and so no one would be unjustly penalised for living a long distance away from a PBT centre.

Patients agreed that dietician and physiotherapy support would be essential. Some patients suggested additional 'pre-habilitation' facilities be made available with others suggesting additional 'hospitality packs' considering the amount of free time when not undergoing treatment.

7.3.3 Patient pathway and trial Design

7.3.3.1 Trial name and pathway

Most contributors felt that the ProtOeus trial name was acceptable and explained the trial. The treatment pathway was acceptable to all participants but emphasised that delays had to be avoided so that time to surgery would not be jeopardised.

7.3.3.2 Randomisation

Participants accepted that randomisation was an essential component of good clinical trials. Some participants reported that the 1:1 randomisation was preferable to the 2:1 randomisation as this reflected clinical equipoise.

7.3.3.3 Fractionation schedules

Several fractionation schedules were proposed (see figure 21). Participants generally favoured the shorter, moderately hypofractionated treatment schedule (40Gy in 15 fractions over 3 weeks) as this meant patients would spend less time away from home at the PBT centre, lessening the impact on family life and income. A patient quote summarises this: '*Less time off work, including for spouse, is important as patients and families may have financial pressures.*' Participants were very positive about receiving fewer cycles of chemotherapy as this was perceived to be a main cause of toxicity.

7.3.3.4 Trial endpoints

Proposed trial endpoints were presented to patients (see Table 33). Participants all felt that toxicity reduction was a more important endpoint compared to clinical equivalence. Several participants had had previous nCRT followed by surgery for oesophageal cancer and recognised that it was treatment with severe side-effects. One quoted '*chemoradiotherapy is strong and many people drop out.*' Some patients mentioned that despite being cancer-free and several years from surgery the treatment still had a debilitating impact on their quality of life. One patient commented that they '*still had weakness and tiredness from the treatment*.'

7.3.3.5 Patient information

It was highlighted that patient information must be written simply and concisely, avoiding any complex medical terminology. Several PPI representatives volunteered to contribute to the writing of patient information sheets. Although most participants felt that written information with a section for FAQs was adequate with no need for additional media content, some felt additional video content would be beneficial.

7.3.4 Clinical scenarios

Participants did not raise any concerns regarding clinical scenarios including transfer to an acute hospital local to the PBT centre should the clinical need arise. The participants highlighted the importance of good lines of communication between referring hospital and the PBT centre, suggesting weekly email updates and teleconferences with their usual oncologist if required.

Table 35 summarises refinements to trial design following input from PPI contributors.

Aspect of trial Design	Initial Proposed Design	Refinements following PPI
Provision of support	Specialist supportive care (dieticians, physiotherapy etc.) Cover accommodation for patients plus one (e.g. spouse, carer) Travel expenses not covered	Consider provision of pre-habilitation services in addition to specialist supportive care and a 'hospitality pack'. Cover travel expenses for all patients plus one (e.g. spouse, carer)
Randomisation	2:1 randomisation or 1:1 randomisation	1:1 randomisation
Fractionation Schedule	41.4Gy/23# with 5 cycles of Carboplatin/Paclitaxel Or 40Gy/15# with 3 cycles of Carboplatin/Paclitaxel or 45Gy/25# with 5 cycles of Carboplatin/Paclitaxel	40Gy/15# with 3 cycles of Carboplatin/Paclitaxel
Trial Endpoints	Toxicity Reduction and pathological complete response(pCR) and clear resection margin rate(R0) are co-primary endpoints	Toxicity Reduction is the sole primary endpoint pCR and R0 rate become secondary endpoints
Patient information	Written information only Consideration of other media (videos, apps etc.)	Written information will be provided Additional video content favourable but not necessary Patient-facing materials will be reviewed by PPI contributors

Clinical Scenarios and Communication	Referral to acute hospital in cases of emergencies (e.g. heart attack, Stroke)	No concerns raised regarding referral to local acute hospitals Regular communication with referring centre with weekly email updates or teleconferencing to be incorporated into trial protocol

Table 35 Changes introduced to Trial Design s following focus group meetings with patient contributors

7.4 Discussion

This work is a good example of how public and patient involvement can change, refine and improve a trial. As the focus groups were carried out at the start of the trial development process, this allowed patient's views to be embedded into every aspect of trial design including decisions such as radiotherapy and chemotherapy schedules. We believe this is particularly noteworthy as clinical decisions such as this are often purely the domain of the investigators who are deemed to be the experts. To the best of our knowledge we are the first radiotherapy trial to incorporate patient's views into selection of the intervention arm. We recognise this approach may not be clinically appropriate for many other trials. However, in OEC, there remains a wide variation in 'standard of care' NA fractionation schedules used across the world, with each of our proposed dose schedules having some evidence base supporting its use [23, 40, 41]. In this situation where there is a degree of clinical equipoise, it is especially useful to get patient views, and should be encouraged in the design of future trials if clinically appropriate.

To our knowledge, two other PBT trials in the UK have undertaken PPI focus groups during their trial development; the currently recruiting TORPEdO trial [215] and a proposed low-grade glioma PBT trial [216]. Both projects are extremely valuable with some of their findings echoing ours. However, as both those focus groups were based in locations that were close to the PBT centres, we believe our work has comparatively better geographical representation from across the UK and is therefore more reflective of the general population who will be offered participation in PBT trials. As with work that was carried out by the TORPEdO trial, our work suggests that some UK patients are willing to travel for PBT treatment, [211] perhaps due in part to the positive media coverage that has been received by this treatment. Of note, NHS England currently do not routinely fund travel costs to UK PBT centres, although accommodation costs are covered for the patient plus one carer/spouse for patients that live over one hour away [217]. Our work has shown that without adequate support in terms of travel reimbursement and accommodation, it is likely that a segment of the population will actively choose to forego this treatment. For some patients (e.g. self-employed), an additional consideration is the financial impact due to loss of earnings. We feel strongly that inequity of access to PBT should be avoided as much as possible with a clear consensus from our patient feedback that travel costs should

be reimbursed to facilitate trial participation. It is becoming increasingly clear that investigators in any future PBT trials will need to take deliberate steps to ensure equity of access to trial participation for all patients and in the particular, seek appropriate funding to cover travel costs. Issues around equity of access to PBT will need to be taken into consideration by any future PBT trial proposals and their funders.

Participants placed a strong emphasis on toxicity reduction and minimising the impact of treatment. Patients were also very clear in their support for a moderately shortened (hypofractionated) treatment schedule to minimise disruption to patient's lives. Most participants chose toxicity reduction over efficacy endpoints as the preferred primary endpoint of the study. This echoes findings in several other studies such as recent work by Lorgelly et al. that shows cancer patients value toxicity reduction just as much as survival outcomes [218]. Despite this, many clinicians remain wedded to 'hard' endpoints such as pathological complete response and survival when designing trials. Our trial design had originally included pathological response rates (pCR) and clear resection margin (R0) as a co-primary endpoint with toxicity reduction, as the investigators had concerns that toxicity reduction alone would be inadequate. However, patient feedback has suggested otherwise and validates our approach of making toxicity reduction the sole primary endpoint of the study. Further patient input will be required to refine patient- facing materials including patient reported outcome measures (PROMs) questionnaires to ensure that they appropriately address all aspects of daily wellbeing.

A criticism of PPI work is that it inherently attracts very motivated patients, often with higher income and education levels, as well as experienced patient contributors who may have a vested interest in the research; resulting in an over-representation of these views. In an attempt to acquire a broader view, we deliberately invited and successfully recruited patients from non-urban areas of the UK and patients with no prior experience in PPI work, giving a voice to an often under-represented group of patients.

We believe that the challenges in this trial will be mirrored in many research groups across the world who are in the process of developing similar trials. Each country and health system will have unique challenges that will require bespoke solutions which will undoubtedly benefit from patient input. It is important to note that this method of holding focus groups for PPI uses targeted questioning with a clear aim of incorporating patients views into a specific research project and therefore, according to published literature, is not defined as qualitative research but rather as a method of patient engagement [219]. Other than the requirement of a skilled facilitator, it required minimal experience, cost and technological infrastructure to set up and is therefore easily reproducible for researchers who want to incorporate patient perspectives into clinical research. In the current pandemic, widely

available video-conferencing tools may be the preferred method of carrying out similar work. We would encourage any potential researchers to include patients early in trial development to ensure genuine co-production of research and to include a wide range of patients in order to attain true 'lay' representation.

This work resulted in direct and tangible impact into the final trial design. We believe the incorporation of patient's views into trial design are invaluable and will ultimately improve patient enrolment, trial feasibility and overall impact; augmenting the likelihood of a successful trial.

7.5 Additional PPI work for the Protieus study

The details of the bulk of PPI work for this study has been covered in the section 7.1 to 7.4 of this chapter. PPI work was carried out at an early point of trial development and therefore directly influenced the final trial design. The earlier iteration of the trial has been modified to include 12 months of adjuvant IO following the positive results of the CM577 trial [147]. The name of the trial has been changed to Protieus (Pre-operative Proton Beam Therapy and Adjuvant Immunotherapy in Oesophageal Adenocarcinoma) to reflect this change.

In addition to the PPI work already reported, a further meeting was held on 26th January 2021 with two patient representatives, to obtain patient's views on the addition of one year of adjuvant IO following chemo-PBT and surgery. Questions and responses from this meeting are outlined in table 30.

Questions	Summary of Responses
Does the addition of IO make the trial more or less attractive to patients?	PPI contributors felt that IO would make the trial more attractive to patients.
Do you have any specific concerns about the trial design as it is?	Felt the risk of increased side-effects would raise concerns for some, but most patients would accept this if it increased cure rates.
Will the additional one year of treatment (6 weekly) with IO be acceptable to patients?	Yes, this would be acceptable for most patients but some will inevitably drop out, particularly if they experience significant side-effects.
What information will patients require prior to agreeing to participation?	Patient information sheets (PIS) written in plain English regarding potential benefits and side effects of IO to facilitate informed decision making by the patient.
Do patients require any additional support?	No additional support needed. Reiterated the need for good key worker support throughout the whole process so patients are able to access help when needed.

Table 36 Questions and summary of responses from an additional PPI meeting held to discuss the addition of IO (26th January 2021).

This work highlights that IO is likely to make the trial more attractive to patients. While there are some concerns over toxicity, the PPI contributors felt that if patients were adequately informed and counselled, most patients would accept the potential trade-off of improved survival rates. The two patient contributors have also formally joined the trials management group (TMG) and will provide

ongoing PPI input into governance, management and delivery of the study. PPI contributors will also review any patient-fronted materials priors to finalisation.

7.6 PPI work for the EU PROTECT Study

PROTECT (Proton versus Photon Therapy for Esophageal Cancer–a Trimodality Strategy) is a multi-centre European Phase III RCT of neoadjuvant PBT vs. standard RT. (CI – Professor Marianne Nordsmark, Aarhus University Hospital, Denmark, Co-CI – Professor Karin Haustermans, Universitair Ziekenhuis KU Leuven, Belgium). The study is led by researchers at the Danish Particle Therapy Centre, Aarhus University Hospital, Denmark and KU Leuven, Belgium with collaborators from across Europe including centres in Germany, United Kingdom, Switzerland, Netherlands, Italy, Czech Republic and France. This study aims to recruit approximately 400 patients over four years with a primary endpoint of reducing post-operative pulmonary complications post-oesophagectomy. This study has taken a consortium-based approach to trial development. Different aspects of trial development and management are divided into pre-defined work packages and led by separate members of the consortium.

Clinicians in the UK and Denmark [(Work package co-leads: Dr Hannah Rahbek Mortensen (Aarhus), Professor Maria Hawkins (UCLH)] were tasked with leading the work package for PPI. As this is a multi-centre, pan-European trial, different centres had varying levels of experience and interest in PPI for research. Therefore, as an initial step, a scoping survey was designed and distributed to ascertain the level of interest and experience in PPI work. Additional questions were added by collaborators from the Health Economics work package. A seven-question survey was sent (via survey monkey) to 66 email contacts of the PROTECT Consortium, representing 19 institutions and 11 countries. Five questions were surrounding PPI work and a further two questions surveying experience in the use of patient reported outcomes (PROMs) and patient reported experiences measures (PREMs) tools.

Number of responses – 15/66 (23.1%). Number of centres represented – 12/19 (63.2%).

	Survey Questions	**Responses**
Q1	Do you or your centre have experience in engaging in PPI programmes in research?	Yes – 12 (80%) No – 3 (20%)
Q2	Would your centre be willing to participate in PPI activities for PROTECT?	Yes – 12 (80%) No – 3 (20%)
Q3	Please tick activities that your centre is interested in participating in:	(*Ticked Yes*) 11/15 (73.3%)

	a) Identifying suitable patient representatives to be involved in patient focus groups b) Carrying out patient focus groups c) Distributing patient fronted materials (e.g. PROMs questionnaires) to patient representatives d) Distributing e-questionnaires to patient representatives e) No, we do not want to participate in any PPI activities for PROTECT	7/15 (46.7%) 10/15 (66.7) 9/15 (60.0%) 1/15(6.7%)
Q4	Does your centre have a representative that is willing to participate and help coordinate PPI programmes for the PROTECT study?	Yes – 10 (66.6%) No – 5 (33.3%)
Q5	If your centre cannot commit to carrying out PPI activities, is there a suitable person(s) or organisation(s) that can represent patient views during these activities (e.g. national oesophageal cancer patient groups, regular PPI contributors) that are willing to be contacted?	Yes: 9 (75%) No: 3 (25%) Skipped: 3
Q6	In your hospital or healthcare system, do you regularly collect data using PROMS (e.g. EORTC surveys or EQ-5D, or self-reports of health and wellbeing)?	Yes: 13 (87%) No: 2 (13%)
Q7	In your hospital or healthcare system, do you regularly collect data using PREMS (e.g. questions on patient satisfaction with their care)?	Yes: 5 (35.7%) No: 9 (64.3%) Skipped: 1

Table 37 Summary of results from PROTECT PPI Scoping Survey

While there was a low percentage of overall responses (23.1%), the scoping survey had reasonably good representation (63.2%) in terms of number of centres contacted. Importantly, unlike the PPI work undertaken for the Protieus study, the study design of PROTECT has been finalised at the point of seeking PPI input, and therefore PPI is likely to lead to some general refinements to the study, including refining patient facing materials such as PROMs/PREMs questionnaires, rather than major changes to study design. The survey shows that a majority of responders would be willing to undertake some form of PPI work for the study. However, approximately 20% of those that responded refused any participation. The survey also shows that unlike many UK institutions, many European institutions appear to not have any PPI officers/managers that may help coordinate PPI work. Whilst not the focus of this work, the scoping survey also highlights low use of PREMs tools in many European centres.

7.6.1 PROTECT Trial TVD protocol

TVD protocol and atlas development for PROTECT is led by researchers in UZ Leuven, Belgium. I participated in a TVD protocol validation study. The results of this study have been published in full and is included in the appendix for reference.

7.7 Discussion - UK vs. European approaches to PPI in research

In the UK, engaging patients, carers and the public in research, is regarded as a core element of trial development and management. The NIHR Centre for Engagement and Dissemination (NIHR-CED, previously called INVOLVE) helps coordinates and provides guidance for research undertaken in UK, recommending that PPI is carried out in all stages of research including trial design since its inception over two decades ago [207]. As discussed in earlier in this chapter, the UK-based Protieus trial incorporated PPI feedback directly into all aspects of trial design, making it truly patient-led research. For PBT research, PPI work is especially vital as research questions in PBT often investigate toxicity reduction, which are partly assessed by PROMs tools. Patient input is essential in ensuring trial design is patient-focussed and selected PROMs tools adequately assesses outcomes that are important to patients. Moreover, PBT centres are often funded at great expense by the taxpayer, and due to being in major academic institutions in major cities, often necessitates patient travel to these centres for treatment. PPI gives an opportunity to taxpayers, who are potential patients themselves, to influence how this funding is used and ensure equity of access to PBT services. In contrast to the UK approach to PPI, the survey of European PBT centres showed varying levels of experience and interest in undertaking PPI in research with 20% of centres reporting no experience in PPI and being unwilling to participate. This may be due to the absence of a central leadership through bodies such as the NIHR-CED in the UK and appropriate levels of funding. It is encouraging to see that most centres who responded in the survey showed a willingness to undertake some form of PPI work, therefore showing that most centres recognise the value of PPI. This provides a good opportunity for UK researchers to influence PPI practices to the wider European RT research community and to develop a collaborative PPI network among the European PBT centres. Ongoing work is being carried out to develop a full PPI plan for the PROTECT study including an inbuilt study assessing how this work may influence future PPI practice in some of the collaborating European centres.

7.8 Conclusion

At time of writing, the PROTECT trial has been successfully granted funding through the Innovative Medicines Initiative (IMI), a private-public partnership that aims to fund cutting edge research through a partnership between the European Union and industry partners, while Protieus has been invited to

a full submission to CRUK. Data from these studies will be eagerly anticipated, with these two proposed RCTs potentially marking an exciting starting point for PBT in OEC in Europe.

Chapter 8: Final Remarks and Future Directions

8.1 Introduction

This thesis has attempted to present an informative, multi-faceted and nuanced examination on how PBT may meaningfully contribute to improving toxicity and survival outcomes for patients with OEC, highlighting ongoing efforts to develop the evidence base to support its use. This final chapter presents a summary of the preceding chapters, expanding on key discussion points, and elaborates on trial development activities. It aims to synthesise findings from both parts of the thesis; linking the pre-clinical data from Part 1 and the trial development work highlighted in Part 2; to present a coherent discussion on the current state-of-the-art, including a summary of ongoing trials, and possible future directions of PBT in OEC.

8.2 Summary of findings and their implications

In chapter 2, a systematic review summarises a growing body of evidence supporting its use but highlights a paucity of prospective evidence. The exception is a single phase II RCT which showed that PBT is likely to contribute to reduction in treatment toxicity including post-operative complications. In chapter 3, it is shown the PBT is likely to significantly reduce cardiac and pulmonary doses in a majority of lower third/GOJ oesophageal cases tested with comparable coverage of the TV. NTCP modelling shows that these dose reductions are likely to result in a reduction in pulmonary and cardiac toxicity endpoints including pneumonitis and valvular damage. Significant relative risk reduction of these endpoints implies that dose reductions are likely to be clinically meaningful. Chapter 4 looked specifically at including the spleen as an OAR. This study showed that a dose constraint can be successfully placed on the spleen using PBT and VMAT without significantly affecting overall the plan quality. VMAT appeared to be superior to PBT in sparing the spleen, particularly in cases where the PTV lies in proximity to the spleen, highlighting the superior high dose conformality of VMAT. The clinical impact of splenic dose sparing is uncertain but may result in improved immune sparing and lower rates of G4 lymphopenia, potentially resulting in improved efficacy of adjuvant IO and improving survival outcomes. Chapter 5 explored the effects of different PBT beam arrangements on OAR dose and individual cardiac substructures. Different combinations of beams were found to result in dose being deposited in different OARs, but most combinations resulted in acceptable coverage of the TV, with OAR doses within planning tolerances. This implies that different beam arrangements may be used to preferentially spare OARs, raising the potential of a personalised approach to RT planning based on individual patient characteristics and comorbidities.

In chapter 6, two oesophageal RT trial TVD protocols were compared. A delineation comparison study showed that the NeoSCOPE TVD protocol resulted in greater consistency in final volumes generated,

suggesting that the method of geometrical expansion with editing is favourable compared to a 'free-hand' approach. A TVD protocol for a new PBT oesophageal RT will therefore adopt this approach in order to improve consistency of outlines and limit uncertainty in PBT treatment. Chapter 7 discusses PPI work undertaken during the development phase of an oesophageal cancer PBT trial, giving an exemplar on how PPI may enhance trial design, thereby improving trial feasibility, retention and relevance to patients. Chapter 7 also describes the initial PPI scoping work carried out for a European oesophageal PBT trial, PROTECT. Scoping data shows that for many European centres, there is limited experience in carrying out PPI, giving an opportunity for UK researchers to introduce good PPI practices in PBT centres across Europe.

8.3 Oesophageal PBT Treatment Planning and Delivery – Discussion and Future Directions

8.3.1 Management of PBT uncertainty

Part 1 of this thesis clearly demonstrates that PBT likely results in dosimetric improvements, in particular, to the heart and lungs while maintaining dose to the TV. At first glance this clearly demonstrates PBT's superiority to photons, however, it is important to recognise that there remains much uncertainty in treatment planning and delivery of PBT that may limit any theoretical advantages. In my studies, range uncertainty was accounted for as much as was possible, but this was limited to the TPS capabilities that were available. The management of uncertainty and the technology available to address it is rapidly evolving. New commercial TPSs such as Raystation (*RaySearch Laboratories*) and Acuros XB in Eclipse (*Varian Medical Systems*) have incorporated Monte-Carlo (MC) based algorithms, making this technology accessible to PBT centres around the world [220, 221]. Of note, at time of writing, the NHS PBT centres (both of which are Varian Centres) are yet to install any MC based TPSs although this is likely in the near future (personal communication with Dr Ganesh Radhakrishna, The Christie PBT Centre). The incorporation of a more accurate planning algorithm will certainly account for some uncertainty in PBT treatments. As these TPSs become more widely available, future clinical and pre-clinical studies will need to utilise MC algorithms in planning. Similarly, PBT trial protocols will need to consider making MC based planning mandatory for tumour sites with significant tissue heterogeneity such as the oesophagus. Interestingly, the trial RT protocol of the EU oesophageal PBT trial, PROTECT, has mandated the use of MC based planning for all oesophageal plans (personal communication with Dr Hannah Rahbek Mortensen, Danish Centre for Particle Therapy, Aarhus). For the UK Protieus trial, due in part to the lack of MC based systems in the NHS PBT centres, this has not been included this in the draft RT protocol, although it will be considered in future iterations once there is access to these systems. Further work is still required in order to define a 'gold-standard' for planning PBT for oesophageal cancer. Ideally, both the UK and EU PBT oesophagus trials should have

comparable if not identical approaches to planning. This would enable high-quality data pooling for analysis and accurately assess the differences, such as moderate hypofractionation in the Protieus trial. Perhaps more importantly, having similar planning protocols for both trials will help establish a current standard, allowing future work to build on and refine these protocols.

8.3.2 Motion management and IGRT

The use of MC based algorithms reduces some range uncertainty on a nominal plan, but in OEC, significant additional uncertainty is derived from the intra-fraction and inter-fraction motion that cannot be accounted for by a TPS. For distal/GOJ oesophageal tumours in particular, the impact of diaphragmatic motion during treatment is likely to result in far greater levels of uncertainty than that attributed to range straddling of protons. Here, it is crucial that due diligence is given to appropriate image guidance and motion management. As with most aspects of PBT, a clear 'gold standard' for IGRT in oesophageal cancer is yet to be defined. Several strategies for offline and online verification have been proposed, such as daily cone-beam CT (CBCT) including 4D-CBCT, and weekly planning CT scans. Additionally, appropriate immobilisation techniques will need to be considered. This may include abdominal compression belts, gating techniques and surface guided tracking. Moreover, in order to account for interplay effects, techniques such as rescanning may be adopted. All of these options are likely to improve the quality of delivered treatment and should be considered for clinical use. However, adoption of these technologies is likely to be dependent on their availability in a PBT centre, TPS capabilities, treatment capacity and other resource constraints. Further work is required to assess the impact of these individual strategies in reducing uncertainty and motion. As with PBT treatment planning, an IGRT protocol in a clinical trial would provide a useful starting point towards developing a 'gold standard', allowing prospective evaluation of these strategies and future refinement.

8.3.3 Variable RBE and LET-based planning

Another area of uncertainty is the variable RBE in PBT. In my work, I have used a fixed proton RBE conversion ratio of 1.1 to photon RBE. Although this has now been shown to be inaccurate with RBE now expected to be variable (ranging from 1.1-1.35)[222], as demonstrated in the systematic review in chapter 2, this value remains widely used in clinical practice and therefore used here. There is yet to be definitive evidence demonstrating that this discrepancy leads to any clinically adverse outcomes. Akin to MC based TPS systems for range uncertainty, LET-based planning systems may further reduce RBE uncertainty. They are now entering the clinical sphere, potentially becoming commonplace in the next 3 to 5 years. At present, there is no LET-based planning capability in any of the UK PBT centres (personal communication with Dr Ganesh Radhakrishna, The Christie PBT Centre). Further studies should assess how LET-based planning affects the dose distribution in OEC, focussing on OARs located

at the end of beam such as the cardiac substructures. Prospective assessment of toxicity rates in the context of a clinical trial will help clinically validate the use of LET-based planning studies. The incorporation of LET-based optimisation may enable safer dose delivery with PBT, allowing proton's intrinsic physical advantages to be exploited to improve patient outcomes.

8.3.4 Conclusions for PBT treatment planning in OEC

In summary, there remains much that is unknown about PBT uncertainty and the appropriate mitigation strategies in OEC. While it is imperative that future clinical trials employ strategies that mitigate for PBT uncertainty, in practice, much of what is possible will be limited by available technology and skills of a treating centre. It is important to be reminded that PBT is not a brand-new technology. There is already a significant body of published data on multiple clinical cohorts for OEC. Whilst almost all historical clinical data has poorly described RT planning techniques with no MC or LET-based planning and patchy detail on IGRT, published clinical data shows no unexpected toxicity signals nor does it reveal poor local control rates with PBT. This should provide reassurance for clinicians aiming to treat OEC with PBT. Clinical trials should incorporate as many uncertainty mitigation strategies as is practical but be aware that, with adequate due diligence, patient safety is unlikely to be compromised due to PBT uncertainty. In addition to testing clinical endpoints, trials present an excellent opportunity to introduce standardised practices in PBT planning and IGRT and provide a current 'gold standard' that may be continually revised and improved on in future work.

8.4 PBT trial RTQA

There are additional considerations needed to ensure PBT trials are appropriately standardised and quality-assured. In chapter 6, a delineation comparison study highlighted significant interobserver variation based on the way delineation guidance is presented in a TVD protocol. For PBT trials, robust RTQA of volumes are vital. Minor TVD protocol variation arguably impacts PBT to a greater degree than photon RT as minor variations may significantly alter dose distributions. Additionally, PBT's Bragg peak and the lack of a PTV expansion means that areas not accurately delineated in the TV are likely to receive close to zero or zero dose i.e. a total geographical miss. However, in terms of RTQA protocols for TV review, PBT trials do not present significant challenges. Irrespective of treatment modality used, TVs will need submission by recruiting centres to a central RTQA site, where robust peer-review and timely feedback may be given. In practical terms, the delivery of RTQA protocols for TV review are to be likely to be similar to photon trials and therefore relatively straight-forward.

For PBT treatment plan review, however, PBT trials pose significant additional challenges to RTQA protocols. Firstly, as a new technology in a novel tumour site, there is limited experience in creating PBT plans for OEC. For example, in the UK, there are only a handful of physicists based in the UK PBT

centres who have experience of creating these plans. These physicists are likely to be simultaneously responsible for creating PBT plans for trial patients and performing plan RTQA. New processes are required to ensure that robust RTQA checks and balances are in place for PBT trials. Having external peer-reviewers from abroad (e.g. US, European PBT centres) may be necessary. Additionally, as discussed earlier, there is no set 'gold-standard' for PBT plans, including uncertainty analysis, in many tumour sites including OEC, making plan RTQA challenging. The absence of a rudimentary standard in PBT plan reporting has been recognised by CTRAD and the National RTTQA group in the UK. As part of the work undertaken in this thesis, I was involved in a CTRAD/RTTQA working group to develop national guidance on reporting PBT plans under uncertainty and comparing these to photon plans. In summary, this guidance sets out basic principles that should be adhered to for all PBT trials that are comparing PBT to photon RT plans. It recommends that all assessing CTV/ITV coverage under uncertainty for PBT is the best equivalent to PTV coverage for photon RT. Additionally, it recommends that all robust optimisation and evaluation methodology are clearly laid out to ensure transparency and reproducibility in non-trial patients. Full guidance is included in the appendix. (Lowe et al. 2020[87]).

To the best of my knowledge, this guidance represents the first set of published guidelines for the reporting of PBT plan uncertainty in clinical trials anywhere in the world. As protons are inherently different to photons, it requires specific considerations in order to facilitate consistent comparisons in clinical trials. There is recognition that across the world, PBT plan reporting and comparison processes are often not robust nor transparent, and when present there is wide variation in practice. This is highlighted in the literature review produced for this paper (see appendix for full manuscript). Of the 35 papers reviewed by the working group, only 13 studies considered uncertainty in the treatment planning process. Of those 13 studies that considered uncertainty, there was a wide variation in methods and uncertainty scenarios used. This guidance aims to provide some consistency, especially in the context of clinical trials. Importantly, multiple caveats are included, recognising the breadth and complexity of clinical scenarios in different tumour sites. This guidance therefore provides only a 'minimum standard' of what should be reported, rather than an absolute 'gold-standard.' Where necessary, additional considerations to the stipulated guidance are required.

The UK has an excellent track-record of delivering well designed, quality-assured RT trials that have helped change practice and introduce new technologies such as IMRT [27, 223]. Currently, there is a strong drive to develop new trials of PBT with several UK-based PBT trials that are presently either funded or in late stages of development for multiple tumour sites including for head and neck cancer, low-grade gliomas, breast cancer, and OEC [210, 216]. This makes the publication of these guidelines very timely. As PBT is often criticised as unproven and lacking an evidence base, it is crucial that any

trials of PBT are robustly quality-assured and transparent to ensure that trial results are trustworthy and reproducible. These guidelines will help trial development groups to develop robust RTQA protocols and improve the overall quality of RT in their trial. It also encourages transparency by the stipulating the inclusion of uncertainty analysis in the trial RT protocols. For groups working outside the UK, these guidelines may provide a blueprint for RTQA standards in PBT trials.

In summary, these guidelines will improve consistency in uncertainty reporting for PBT trials in the UK. Future updates of these guidelines will be required, to ensure guidance is in keeping with rapidly changing technology and knowledge in this field.

8.5 Developing an original trial of PBT in OEC

8.5.1 Overview

As argued throughout this thesis, PBT in OEC holds significant promise but still requires evaluation in prospective RCTs. To my knowledge, there is only one currently recruiting RCT of PBT in oesophageal cancer, the NRG-G1006 study in the USA. In Europe, with support from the organisations like CTRAD and the EORTC, there are substantial efforts underway to develop original trials of PBT in OEC. There are currently two proposed RCTs of PBT in OEC in Europe, both of which are, at time of writing, are at yet to open to recruitment but in advanced staging of planning. Throughout my research fellowship, I have been a core member of the trial development group of the UK Protieus trial. PPI work for this study has been detailed in Chapter 7.

8.5.2 Trial development meetings

Wider support from the broader radiotherapy community is a vital cog in the development of original RT trials in the UK. Since its inception in 2010, CTRAD has been organising trial proposal guidance meetings to provide peer-review input to trial ideas before submission to funding. These proposal meetings aim to refine and add value to trials in development, in order to facilitate successful funding in what is an increasingly challenging funding environment. In addition to trial development, CTRAD has been influential in coordinating a UK wide approach to developing trials of PBT across a range of tumour sites [198]. Several PBT trials workshops have been held over the past few years, refining design and accelerating the funding of these trials. In order to refine a trial of PBT for OEC, the original trial idea was presented and refined through many of these trial development meetings.

The Protieus (Pre-operative chemo-Proton Beam Therapy and adjuvant Immunotherapy in cancer of the oEsophagUS, previously referred to as ProtOeus) study (CI: Professor Maria Hawkins, University College London) is a proposed Phase II RCT that aims to investigate if moderately hypofractionated (40.05 Gy/15#) chemo-PBT in the preoperative setting for adenocarcinoma of the oesophagus

significantly reduces severe post-operative toxicity. It also assesses if PBT permits timely initiation of adjuvant IO when compared with standard chemoradiotherapy delivered as part of triple modality therapy using IMRT. I was involved in the discussions for this trial in the following trial development meetings:

Meeting	Location and Date
CTRAD Proton Trials Proposal Meeting	Leeds, 17.5.18. Manchester, 1.3.19 London, 8.1.19 Virtual meeting, 2.9.20 (presented with the addition of IO)
National Cancer Research Institute (NCRI) Upper GI Clinical Studies Group (CSG)	London 24.5.19 Virtual meeting, 23.11.20 (presented with the addition of IO).
National Oesophagus RT development meeting	Manchester 11.6.19

Table 38 Trial development meetings where Protieus was discussed

8.5.3 Protieus Trial Documents

A draft radiotherapy protocol, including an overview of delineation, RTQA strategy and planning guidance, were created for this study. In addition, patient information sheets developed with input from patient involvement collaborators were drafted. The draft versions of these documents have been included in the appendix. As of April 2021, the Protieus trial, in its current iteration with the addition of one year of adjuvant IO, has been invited for full submission to CRUK.

8.6 Comparison on ongoing oesophageal cancer PBT trials

A central thrust of this work has been to explore and expand the evidence base for PBT in oesophageal cancer with the thesis culminating in reports of the development work for two proposed RCTs; Protieus and PROTECT. Both trials are 'traditional' head-to-head randomised comparisons of one technology versus the other. A further trial of PBT in oesophageal cancer is the currently recruiting NRG-G1006 study in the US. Key descriptions from all three studies are summarised in table 39.

	Protieus (UK)	PROTECT (EU)	NRG-GI006 (US)
Status	Submitted for Funding	Success EU IMI2	Currently Recruiting
Trial Stage	Phase II	Phase III	Phase III
Adjuvant Immunotherapy?	Yes (for 12 months)	No	No
Recruitment Target (patients)	130	~400	300
Histology	ACs only	AC/SCC	AC/SCC
IMRT Arm (control)	41.4G y/23#	41.4 Gy/23# or 50.4 Gy/28#	50.4 Gy/28#
Proton Arm (experimental)	40.05 Gy/15#	41.4Gy/23# or 50.4Gy/28#	50.4 Gy/28#
Chemotherapy	Weekly Carboplatin/Paclitaxel	Weekly Carboplatin/Paclitaxel	Weekly Carboplatin/Paclitaxel or FOLFOX
Centres	~15 UK, with 2 PBT centres	Proton Centres in 9 European Countries	>50 US centres
Primary Aim and Endpoint for PBT	Improvement in 90-day grade 3-5 toxicity	Improvement in 90-day post-surgery pulmonary complications	Non-inferior (or superior) OS with less cardiopulmonary toxicity

Table 39 Comparison of Protieus, PROTECT and NRG-G1006. AC – Adenocarcinoma; SCC- Squamous cell carcinoma; FOLFOX – 5-FU/Leucovorin/Oxaliplatin.

8.6.1 Clinical Endpoints

Through this process of trial development, it has become clear that selecting appropriate primary outcome measures for PBT trials is challenging. Clinical trials need to test clinically relevant endpoints to ensure it has sufficient clinical impact and is attractive to clinicians and patients, but one that is feasible and deliverable within the fixed timeframe of a funded clinical trial. Interestingly, both the UK and EU trials independently derived the primary outcome measure of toxicity reduction in their trial design, reflecting the strong pre-clinical signals, including NTCP modelling data, and early clinical data purporting this as a likely benefit of PBT in oesophageal cancer. While toxicity is an important and clinically meaningful endpoint, it implies that both trials feel toxicity reduction is PBT's strongest asset in this context and most likely endpoint to result in a positive trial. Survival outcomes have been relegated to secondary endpoints. In contrast to the European studies, the currently recruiting NRG-GI006 study (NCT03801876), led by MD Anderson Cancer Centre in the US, has joint primary outcome

measures of overall survival and CTCAE grade 3 and above toxicity. It aims to enrol 300 patients over approximately four years from over 50 centres with a plan for an initial report by 2027 [198]. This is well powered study with ambitious primary outcome measures which should be commended. However, having survival as a primary endpoint potentially lengthens the interval to trial reporting allowing the possibility of other technologies to enter the treatment paradigm of oesophageal cancer, such as carbon ion therapy and IO, potentially superseding PBT and making the trial findings less relevant. In contrast, both the European and UK trial has selected an endpoint of toxicity at 90 days post surgery, meaning that both trials, if funded, are likely to report their primary findings earlier than the US trial, despite not yet being open to recruitment. However, as both trials have included survival as only secondary endpoints, there is a risk that the findings may be insufficient to convince gatekeepers of healthcare funding (e.g. NICE) of the value of PBT in this setting. Both protocols are strict in mandating surgery making them true assessments of NA PBT.

8.6.2 Trial protocols

Unlike the UK and EU studies, the NRG-GI006 study does not mandate oesophagectomy following CRT and is therefore a trial that assesses PBT in both the NA and definitive settings. The discrepancy with standard UK and European practice may limit its potential impact. These protocol inconsistencies may make data interpretation challenging and its influence on UK practice where there is clear separation in RT dose levels depending on intent. In contrast, the UK and European trial both assess PBT only in the NA setting.

The PROTECT study uses standard fractionations schedules of 41.4 Gy/23# and 50.4 Gy/28# that are commonly used worldwide. As it is a multi-centre international study, it has taken a pragmatic approach offering the option of these two fractionations for both the control and experimental arm for individual participating centres to choose. This may be viewed as both a strength and a flaw of the study. The pragmatic approach facilitates a large number of centres to recruit patients, thereby helping achieve its ambitious goal of recruiting nearly 400 patients in 4 years. However, as the fractionation schedules are not radiobiologically equivalent, statistical analysis of the results including toxicity outcomes and control rates may be challenging.

The fractionation used in the Protieus study of 40.05 Gy/15# is somewhat more controversial and has been the subject of much debate in CTRAD PBT trial proposal meetings. It is, however, not a novel fractionation with a historical RCT of NACRT showing the efficacy and safety of this fractionation [41]. Justification of the fewer chemotherapy cycles comes from the estimation that NACRT in oesophageal primarily affects local control of disease rather than controlling distant metastatic disease. In terms of local tumour control, the BED 40.05 Gy in 15# is roughly equivalent to 50 Gy in 25#, and due to the

moderate hypofractionation, may result in fewer late effects. Importantly, a shortened treatment schedule is preferred by most patients in our PPI focus groups. Fewer fractions will also result in lower overall healthcare costs. As Protieus is a Phase II study which aims to recruit only around 130 patients, this fractionation may be assessed for safety and efficacy in more detail before further testing in a phase III study.

All three trials have their individual strengths and potential weaknesses. Ultimately, data from all three trials are likely to be very important steps in the evolution of PBT from an experimental treatment to a potential standard of care in OEC and are eagerly anticipated.

8.7 Non-RCT evidence

Throughout this thesis, I have strongly advocated the need for RCT data before PBT can be considered a standard of care in OEC. While RCT data remains the highest level of evidence [224], it is important to recognise that not all aspects of PBT may be easily evaluated in an RCT. The clearest argument for the use of PBT in clinical practice is its lower integral dose, leading to a reduction of long term sequalae of radiation exposure such as secondary cancers and growth inhibition. As such, in most advanced healthcare systems, PBT is recommended in international guidelines, including NHS clinical commissioning policy, to be used in the treatment of paediatric cancers [198]. Notably, there is no RCT data to support the use of this treatment in this population [225]. Similarities may be drawn to IMRT, whose advent in the early 2000s was met with some scepticism. There remains a paucity of high quality evidence that demonstrates the benefit of IMRT over 3DCRT in many tumour sites including OEC [75, 226]. Despite this, IMRT is now widely accepted as a standard of care for most tumour sites including OEC [27]. As with IMRT over a decade ago, SABR is currently undergoing similar levels of scrutiny with multiple trials underway and the recently completed NHS England Commissioning Through Evaluation (CTE) Programme. The success of the CTE programme has resulted in SABR being routinely commissioned by NHS England for some indications such as oligometastatic disease [227]. All these RT technologies have a common predicament of trying to prove that dosimetric superiority translates to cost-effective clinical benefit. Carrying out RCTs certainly remains central part of the bigger picture of an evidence base for PBT, however, other methods of evaluating PBT should also be given due consideration where an RCT is not feasible. For example, a CTE programme such as used for SABR may be an appropriate way of collecting medium and long-term outcome data for PBT in multiple tumour sites including for re-irradiation. Another method includes the model-based approach used in the Netherlands, where an arbitrary threshold of 10% reduction in NTCP needs to be demonstrated before PBT treatment is funded [146]. It is vital that PBT is objectively and

systematically assessed with robust health economic assessment but approached with an open mind with its use not confined to only indications with RCT evidence.

8.8 Conclusion

This work has shown that PBT is likely to be dosimetrically superior to photon RT for distal OECs, particularly in reducing dose to the lungs and heart. This may lead to a reduction in treatment related toxicity, including post-operative toxicities, potentially improving outcomes. Other aspects of PBT such as a lower integral dose and the ability to create more personalised RT plans may result in further clinical benefit. Clinical trial evidence supporting the use of PBT is still lacking, however, substantial progress has been made in developing new RCTs of PBT in OEC. Data from ongoing and future trials are eagerly anticipated and may see PBT become a standard of care in the treatment of OEC in the coming decade.

Glossary of terms

Biological effective dose (BED)	A measure of true biological dose delivered by a particular combination of dose per fraction and total dose to a particular tissue, characterised by a specific α/β ratio.
Four-dimensional CT planning scan (4D-CT)	
Generalised conformity index (CIgen)/Kouwenhowen index	A measure of similarity of target volume delineations independent of the number of observers (range 0-1). The greater the CIgen, the greater the level of agreement between observers.
Intensity modulated radiotherapy (IMRT)	Treatment delivery techniques that modulates the intensities of beams, as well as geometrically shaping them. IMRT can enable high dose volume to be shaped to avoid critical structures.
Linear energy transfer (LET)	Rate of energy dissipation along the path of charged particles. In radiobiology and medical physics, exposure is measured in kiloelectron volts per micrometer of tissue (keV/micrometer T).
Multi-field optimisation (MFO)/Intensity modulated proton therapy (IMPT)	Multi-field optimisation or intensity-modulated proton therapy is an optimisation technique with which all fields are optimised simultaneously resulting in inhomogeneous but complementary fields which combine to provide highly conformal target coverage. However, this can be more sensitive to uncertainty than single-field optimisation (SFO).
Radiotherapy quality assurance (RTQA)	Quality management system aimed at ensuring safe delivery of radiotherapy
Range uncertainty	Uncertainty in the range of proton beams, typically evaluated as a systematic 3.5-5% error on the relative proton stopping power of all tissues.
Relative biological effectiveness (RBE)	Relative biological effectiveness. The ratio of biological effectiveness of different modalities. Protons are known to be more effective than photons and an RBE of 1.1 is typically used but this is uncertain and may vary along the proton path and especially in the Bragg peak.

Robust optimisation	The inclusion of uncertainties explicitly in the optimisation process. Plans are optimised with the aim of meeting objectives even when defined errors (such as patient setup errors) occur.
Robust evaluation	The evaluation of a plan under uncertainty by assessing the plan recalculated in different uncertainty scenarios to ensure that it is still safe and effective when defined errors (such as patient setup errors) occur.
Robustness	The extent to which an aspect of a treatment plan is insensitive to defined conditions. e.g. clinical target volume coverage may be considered robust to setup and range uncertainties of defined magnitudes if the minimum dose to the clinical target volume in each of these scenarios meets the treatment aims.
Setup uncertainty	Uncertainty in patient setup assuming rigid shifts of the patient position, typically of the order of a few millimetres
Single field Optimisation (SFO)	Single-field optimisation. Optimisation technique with which all fields are optimised independently, each aiming to satisfy the optimisation objectives. This results in fields with fewer in-field dose gradients compared with multi-field optimisation (MFO)/intensity-modulated proton therapy (IMPT)
Stopping power	A measure of how much a material slows down the proton beam. It is calculated from the loss of energy per unit path length and often expressed relative to water. Lung tissue has a low relative stopping power and bone has a high relative stopping power.
Target volume (TV)	An umbrella that covers both Internal Target Volume (ITV) in PBT planning and Planning Target Volume(PTV) for photon planning. See table 6 in Chapter 3 for full list of ICRU target volume definitions
Target volume delineation (TVD)	The process of deriving a target volume (e.g. PTV) based on clinical information including diagnostic imaging and RT delineation protocols.
Three-dimensional Conformal Chemoradiotherapy (3DCRT)	Treatment delivery techniques that uses imaging techniques (usually CT) to simulate patient's anatomy to develop a treatment plan. Typically 'forward planned' and less conformal than IMRT.

Uncertainty scenarios	Potential or anticipated errors for which the dose distribution is recalculated. These may be used during robust optimisation or during plan evaluation. They are sometimes referred to as error scenarios.
Volumetric Arc Therapy (VMAT)	A specific form of IMRT that utilises a specialised linear accelerator that delivers radiation dose continuously as the treatment head rotates around the patient. It allows the simultaneous variation of three parameters during treatment delivery, *i.e.* gantry rotation speed, treatment aperture shape via movement of MLC leaves and dose rate.
Worst case scenario	Often applied in different contexts, the worst-case dose may be the worst reported dose for a given metric over all uncertainty scenarios (e.g. the highest reported maximum dose over all scenarios for an organ at risk). The 'worst-case scenario' is typically a physically realisable scenario (either a setup shift or a systematic change in relative stopping power) in contrast to the 'worst-case dose distribution', which can sometimes be used to describe a composite distribution taking, e.g. the highest voxel value over all scenarios for each point outside the target volume and the lowest voxel value within the target volume. Also used as second to worse case scenario.

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