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Developing the Role of Radiotherapy for Inoperable Gastric Cancer

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Summary (Abstract)

Gastric cancer (GC) is a leading cause of mortality worldwide, resulting in 4,000 deaths per year in the UK. Surgical resection is the only cure, but 60-70% of patients are unsuitable for surgery, for whom palliative treatment is limited to systemic anti-cancer therapy and/or low-dose radiotherapy on occurrence of local symptoms. Poor outcomes highlight the urgent need for novel treatment strategies. Therefore, this thesis explores whether radiotherapy could have a role in the management of non-metastatic, inoperable GC.

Firstly, a retrospective service evaluation explores treatment patterns and outcomes in South West Wales, to inform potential sample size for future trials. A systematic review of definitive, pre-operative and high-dose palliative radiotherapy evaluates efficacy, safety, dose/fractionation schedules and techniques in use. A survey of UK oesophago-gastric clinical oncologists explores current opinion, practice, and appetite for future trials. During a study of interobserver variability (IOV) in gastric tumour volume delineation (TVD) using computed tomography and magnetic resonance imaging (MRI), conformity indices are analysed, and qualitative and quantitative effect of MRI evaluated. Finally, comparison of two pre-operative radiotherapy protocols evaluates user-experience and analyses the volumetric and dosimetric advantages of each.

The results demonstrate a largely non-randomised evidence base supporting the efficacy and safety of gastric radiotherapy, but optimal dose/fractionation remains unknown and technique varies. The survey demonstrates infrequent use of gastric radiotherapy in the UK, due to limited evidence and toxicity concerns, but support for a future UK trial is high. Clinician confidence in TVD is low, further demonstrated by considerable IOV in delineation of gastric tumour volumes. The addition of MRI improves subjective TVD experience, though impact on IOV is conflicting. Dosimetric analysis of pre-operative protocols demonstrates substantial dose to organs-at-risk following elective nodal irradiation.

The findings of this thesis have informed the development of the first UK trial of gastric radiotherapy, GastroSCOPE.

Declarations and Statements

DECLARATION

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

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Date .....28/03/2025.....

STATEMENTS

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.

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I would like to dedicate this MD thesis to my husband, Jason, and our children – my reason for being. Without their unconditional love, endless patience, and support, none of this would be possible. I am who I am today because of you.

Personal Bibliography

The following citations refer to poster presentations, oral presentations and full-length articles relating to this thesis (in reverse chronological order):

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List of Abbreviations

3D-CRT	3-dimensional conformal radiotherapy
AC	Dr Amy Case
APPA	Anterior Posterior – Posterior Anterior
ASCO	American Society of Clinical Oncology
ASTRO	American Society of Radiation Oncology
BED	Biologically effective dose
BS	Becky Slinger, Radiotherapy Physics Clinical Scientist (SBUHB)
BT	Blood transfusion
CBCT	Cone beam CT
cCR	Clinical complete response
CIN	Chromosomal instability
CRT	Chemoradiotherapy
CT	Computed tomography
CTV	Clinical Target Volume
CTCAE	Common Terminology Criteria for Adverse Events
DFS	Disease Free Survival
DIBH	Deep inspiration breath-hold
EBRT	External beam radiotherapy
EBV	Epstein Barr Virus
EORTC	European Organisation for Research and Treatment of Cancer
EQD2	Equivalent dose in 2Gy fractions
ESMO	European Society of Medical Oncologists
ESTRO	European Society for Radiotherapy and Oncology
EUS	Endoscopic Ultrasound
FDG-PET/CT	^{18}F-Fluorodeoxyglucose [FDG] Positron Emission Tomography [PET] with CT
FGFR2	Fibroblast Growth Factor Receptor 2
GC	Gastric Cancer
GJ	Dr George Joseph, Consultant Radiologist
GOJ	Gastro-Oesophageal Junction
GS	Genomically stable
GTV	Gross Tumour Volume
GTVn	Gross Tumour Volume – nodes

GTVp	Gross Tumour Volumes – primary tumour
Hb	Haemoglobin
HDHB	Hywel Dda Health Board
HER 2	Human Epidermal Growth Factor Receptor 2
HIPEC	Hyperthermic Intraperitoneal Chemotherapy
ICRU	International Commission on Radiation Units and Measurements
ICTRP	International Clinical Trials Registry Platform
IGC	Inoperable gastric cancer
IGRT	Image-guided radiotherapy
IHC	Immunohistochemistry
IMRT	Intensity modulated radiotherapy
ISH	In Situ Hybridisation
ISRCTN	International Standard Randomised Controlled Trial Number
ITV	Internal Target Volume
JBI	Joanna Briggs Institute
KF	Dr Kieran Foley, Consultant Radiologist
LN	Lymph Node
LND	Lymph Node Dissection
mAb	Monoclonal Antibodies
MDT	Multi-disciplinary team
MLC	multi-leaf collimator
MMR	Mismatch Repair Deficiency
mOS	Median Overall Survival
MRI	Magnetic resonance imaging
MSI	Microsatellite instability
MSI-H	Microsatellite instability - High
MV	Megavolatage
NA	Not applicable
NCCN	National Comprehensive Cancer Network
NCBD	American National Cancer Database
NICE	National Institute for Health and Care Excellence
NOGCA	National Oesophagogastric Cancer Audit
NS	Not stated
OAR	Organ at risk

OG	Oesophago-Gastric
OS	Overall survival
PBT	Proton beam therapy
pCR	Pathological complete response
PDL1	Programme Death-Ligand 1
PDL1-CPS	Programme Death-Ligand 1 Combined Positive Score
PIPAC	Pressurised Intraperitoneal Aerosolised Chemotherapy
pPR	Pathological partial response
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PRV	Planning Organ-at-risk-Volume
PTV	Planning Target Volume
QOL	Quality of Life
RCR	Royal College of Radiologists
RCT	Randomised controlled trials
RPLN	Retroperitoneal lymph node
RR	Response rate
RT	Radiotherapy
SABR	Stereotactic ablative body radiotherapy
SACT	Systemic Anti-Cancer Treatment
SBUHB	Swansea Bay University Health Board
SEER	Surveillance, Epidemiology and End Results Program
SG	Dr Sarah Gwynne, Consultant Clinical Oncologist
SOC	Standard Of Care
SR	Systematic Review
SUMS	Swansea University Medical School
SWW	South West Wales
TCGA	The Cancer Genome Atlas
TPS	Treatment planning system
TNM	Tumour Node Metastases
TVD	Tumour volume delineation
UGI	Upper gastrointestinal
VEGFR-2	Vascular Endothelial Growth Factor Receptor-2
VMAT	Volumetric Modulated Arc Therapy
WHO	World Health Organisation

List of abbreviated chemotherapy regimens

5-FU	5-fluorouracil
ECF	Epirubicin, cisplatin, 5-FU
ECX	Epirubicin, cisplatin, capecitabine
EOX	Epirubicin, oxaliplatin and capecitabine
FLOT	5-FU, leucovorin, oxaliplatin and docetaxel
FOLFIRI	5-FU, leucovorin and irinotecan
mDCF	Docetaxel, cisplatin and 5-FU
S-1	Oral fluoropyrimdine compound containing tegafur, gimeracil and oteracil
SOX	S-1, oxaliplatin
XELOX	Capecitabine and oxaliplatin

Chapter 1

Introduction to Gastric Cancer, Radiotherapy and Thesis Aims

1. Introduction to Gastric Cancer, Radiotherapy and Thesis Aims

1.1 Introduction to Gastric Cancer

1.1.1 Epidemiology

Gastric (stomach) cancer (GC) is the fifth most common cancer globally, representing over 1 million new diagnoses each year, and is a significant cause of mortality, responsible for over 750,000 deaths annually.[1] In contrast, in the UK, GC is the 17th most common cancer. Although incidence has decreased by 31% in the last decade, absolute numbers are likely to remain stable in coming years, largely due to the aging population. Despite this, GC remains a significant cause of cancer mortality in the UK, causing approximately 4,000 deaths every year.[2]

1.1.2 Aetiology

GC is more common in men than women (2:1), and is a disease of aging, with peak incidence between the age of 85-89 years in the UK.[2]

Chronic gastritis resulting from *Helicobacter Pylori* infection is a major risk factor for distal (non-cardia) GC, with 93.2% of patients with gastric adenocarcinoma testing positive for *H. Pylori* in the Eurogast-EPIC study.[3] Additionally, approximately 10% of malignancies are associated with Epstein Barr Virus (EBV).[4] Lifestyle factors resulting in increased risk of gastric malignancy include high salt, low fruit/vegetable diet, poorly preserved or smoked foods, pernicious anaemia and smoking.[5]

Conversely, proximal stomach (cardia) or gastro-oesophageal junctional tumours are related to obesity and chronic gastro-oesophageal reflux, possibly explaining the increased proportion of cardia vs non-cardia tumours seen in the Western countries (see Figure 1.1 and section 1.1.10).[6,7]

Approximately 10% of GCs are familial, and 1-3% have germline mutations. The three major familial syndromes include Hereditary Diffuse GC, Gastric Adenocarcinoma and Proximal Polyposis of the Stomach, and Familial Intestinal GC, but only Hereditary Diffuse GC has been genetically explained (CDH1 or CTNNA1 mutation). Several other syndromes such as Lynch, Li-Fraumeni and Familial Adenomatous Polyposis are also associated with GC.[8]

1.1.3 Anatomy

The stomach is divided into cardia, fundus, lesser and greater curves, antrum and pylorus. Incidence by anatomical site within the stomach is shown in Figure 1.1. In the UK, tumours of the cardia are the most common, comprising 32% of all cases, followed by body of the stomach 12.2% and pyloric antrum 8.8% (though nearly a third are unspecified/ overlap regions).

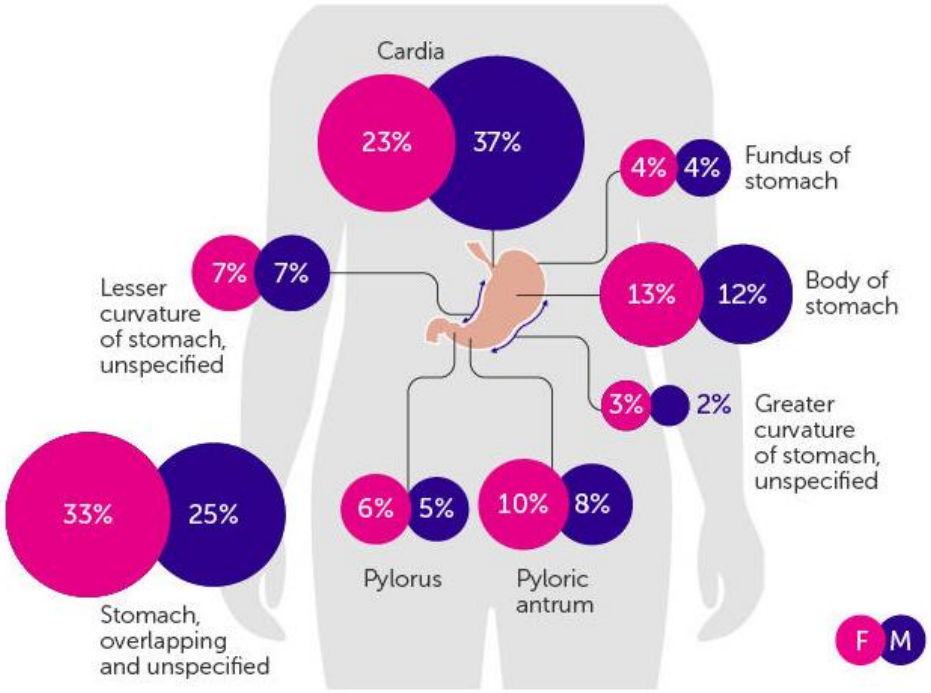


Figure 1.1 *- Distribution of gastric cancer by anatomical site. (Cancer Research UK statistics 2016-2018, Credit: Cancer Research UK[1]) Pink circles represent female incidence, blue circles male incidence.*

The gastro-oesophageal junction (GOJ) is considered a distinct anatomical entity, separate from both the oesophagus and stomach. Histologically, the true GOJ is defined as the Z-line, but clinically the GOJ is referred to as the 3cm that spans the end of the distal oesophagus and the beginning of the stomach. The Siewert-Stein classification is most commonly used to define tumour location within the GOJ, shown in Figure 1.2.[5,9] Siewert type I GOJ tumours are located in the distal oesophagus 1-5cm above the anatomical GOJ. Type II tumours are considered true junctional, or cardia tumours, arising between 1cm above and 2cm below the GOJ, and type III tumours are located 2-5cm below the GOJ. In contrast to type I and II tumours, which are managed as oesophageal tumours, type III tumours are staged and managed as gastric adenocarcinomas, and will be considered as such for this thesis.

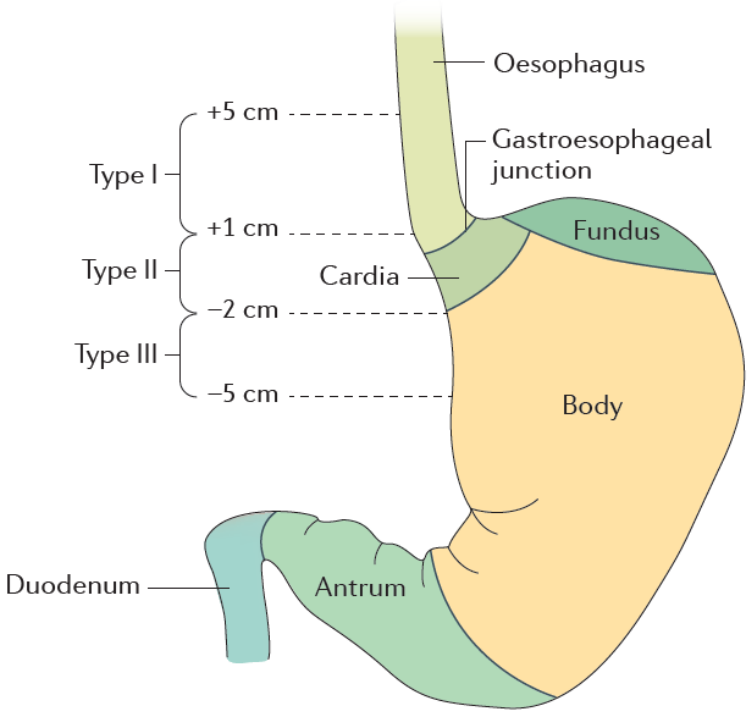


Figure 1.2. *The Siewert Stein classification of gastro-oesophageal junctional (GOJ) tumours, reproduced from Ajani et al.*[5]

1.1.4 Histological and molecular classification

Adenocarcinoma is the most common histological subtype, comprising 95% of gastric malignancies (and as such, exclusively discussed henceforth by this thesis). There are a number of different histological sub-classifications of adenocarcinoma worldwide, though the Lauren classification is most widely used, classifying tumours as intestinal (53% of gastric adenocarcinoma), diffuse (33%) or unclassified (14%), and much simpler than the 2019 World Health Organisation (WHO) histological classification, which lists many complex subtypes.[10] Lauren subtype is relevant prognostically, with diffuse type cancer associated with poorer prognosis (Appendix 1, Table A1.1) [11]

Linitis Plastica is a subtype of diffuse GC, accounting for approximately 10%, which displays an infiltrative process that usually involves the whole organ, causing abnormal sub-mucosal thickening and a so called “leather-bottle stomach” appearance. Unfortunately, 91.1% are poorly differentiated, and 77.7% have signet ring morphology, explaining its aggressive phenotype and dismal 5 year overall survival (OS) of 5%.[12]

Molecular understanding of GC has improved significantly over recent years, with the description of 4 distinct molecular subtypes by The Cancer Genome Atlas (TCGA) summarised in Figure 1.3, including; EBV associated tumours, microsateillie instability high (MSI-H), genomically stable (GS) and tumours with chromosmal instability (CIN).[13]

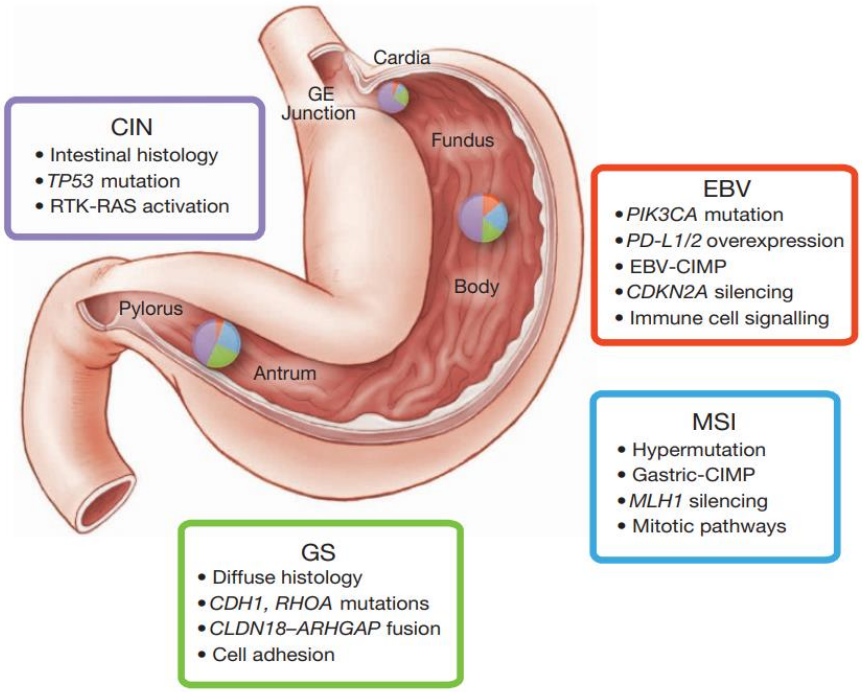


Figure 1.3. *Key features of the four molecular subtypes of gastric cancer, with anatomical distribution of each subtype shown by the inset charts. CIN = Chromosomal instability, EBV = Epstein Barr Virus, MSI = Microsatellite instability, GS = Genomically stable. Reproduced under the Creative Commons license.*[13]

Molecular phenotype does not yet guide the management of resectable GC, with the same surgical approach +/- cytotoxic chemotherapy regardless of histological subtype or molecular biology at present. However, in the advanced setting, biologically-driven treatment strategies have been used for some years, with individual biomarkers such as HER2 (Human epidermal growth factor receptor 2), PD-L1 (programme death-ligand 1) and MSI (microsatellite instability) tested at diagnosis to guide inclusion of therapies such as anti-HER2 monoclonal antibodies (mAb) or immunotherapy (see Table 1.1 and section 1.1.8). However, at present, molecular subtyping into the four TCGA subgroups (Figure 1.3) or whole genome next generation sequencing does not take place routinely in the advanced setting. The inherent radiosensitivity of each molecular subtype is also not yet understood.

Biomarker	Description	Frequency in gastric adenocarcin-oma	Method of detection	Currently tested as SOC in UK?	Drug, (mechanism of action)	NICE approved for UK use, *indication*
HER2	Human epidermal growth factor receptor 2	~17-20%[14]	IHC for HER2 protein expression or ISH for HER2 gene amplification	Yes	Trastuzumab (mAb to HER2)	Yes, for HER2 positive cancers
PD-L1	Programme death-ligand 1	~60% have PD-L1 CPS ≥5%[15]	CPS score	Yes	Nivolumab, Pembrolizumab (PD-1 inhibitors)	Yes, for PDL1 CPS ≥1%
MSI	Microsatellite instability is the result of high numbers of mismatch errors in DNA, as a result of mismatch repair (MMR) deficiency	~8% are MSI-High (MSI-H)[16]	Either via IHC to detect loss of MMR proteins, or via molecular tests to show microsatellite alterations	Yes	Nivolumab, Pembrolizumab (PD-1 inhibitors)	Yes (Pembrolizumab), second line for MSI-H tumours.
Claudin 18-2	Tight junction protein found exclusively in gastric mucosa cells	~40% show moderate to strong expression[17]	IHC using a CLDN18 assay.	No	Zolbetuximab, (mAb to CLDN18.2)	No
FGFR2	Fibroblast Growth Factor Receptor 2	Overexpression or amplification in 30% [18]	IHC for FGFR2 overexpression	No	Bemarituzumab (mAb to FGFR2)	No

Table 1.1. *Summary of the molecular biomarker or genetic alterations of clinical relevance in the UK.*

1.1.5 Diagnosis

Symptoms may be non-specific such as poor appetite, fatigue, or weight loss. Gastro-intestinal symptoms such as dyspepsia, early satiety, nausea or abdominal pain may also occur, but owing to the deformable character of a luminal organ such as the stomach, tumours are often advanced before specific symptoms occur. Anaemia, caused by acute or chronic bleeding from the tumour, is also usually a late clinical sequlae.

Upper GI endoscopy is the cornerstone of both clinical and histological diagnosis, allowing both identification of the tumour, and biopsy. Accurate staging with computed tomography (CT) of the thorax, abdomen and pelvis is mandatory, with staging laparoscopy and peritoneal washings recommended for potentially resectable disease to comprehensively assess the peritoneum for occult metastases.[19] Some centres also conduct endoscopic ultrasound (EUS) to aid T (tumour) and N (nodal) staging due to its improved sensitivity.[20] However, EUS is highly operator dependent and access is limited, accounting for its infreqent use in GC staging in the UK.

FDG-PET/CT (^{18}F-fluorodeoxyglucose [FDG] positron emission tomography [PET] with CT), a form of radioisotope imaging, is of limited use in GC due to 22-56% of diffuse gastric adenocarcinomas being non-avid on PET-CT. Despite this, a recent systematic review showed that addition of PET-CT changed management (usually from radical to palliatve) in 3 – 29% of cases, thus is funded as an adjunct for distant staging in Wales (though is not routinely recommended in the most recent European Society Medical Oncologists [ESMO] guidance).[21]

The potential role of magnetic resonance imaging (MRI) for GC will be discussed in Chapter 5, but is not currently a standard staging investigation.

1.1.6 Staging

GC and Siewert type III GOJ tumours are staged according to the American Joint Committee on Cancer/ Union for International Cancer Control, Tumour Node Metastases (AJCC/ UICC TNM) 8th edition (see Table 1.2 and 1.3).[22]

T - Primary Tumour Stage	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ: intraepithelial tumour without invasion of the lamina propria, high grade dysplasia
T1	T1a Tumour invades lamina propria or muscularlis mucosae T1b Tumour invades submucosa
T2	Tumour invades muscularis propria
T3	Tumour invades subserosa
T4	T4a Tumour perforates serosa T4b Tumour invades adjacent structures
N – Regional Lymph Nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph nodes
N1	Metastases in 1-2 regional lymph nodes
N2	Metastases in 3-6 regional lymph nodes
N3	N3a Metastases in 7-15 regional lymph nodes N3b Metastases in 16 or more regional lymph nodes
M- Distant Metastases	
M0	No distant metastases
M1	Distant metastases Includes peritoneal seeding, positive peritoneal cytology and omental tumour not part of continuous extension.

***Table 1.2**. TNM8 Gastric Cancer Staging. Table adapted from AJCC/UICC TNM 8th edition Gastric Cancer.*[22]

Stage Group	T	N	M
I	T1, T2	N0	M0
IIA	T1, T2	N1, N2, N3	M0
IIB	T3, T4a	N0	M0
III	T3, T4a	N1, N2, N3	M0
IVA	T4b	Any N	M0
IVB	Any T	Any N	M1

***Table 1.3.** Clinical Stage grouping, AJCC/UICC TNM 8th edition Gastric Cancer*[22]

The lymph node (LN) areas classified as 'regional' in TNM8 are peri-gastric, and those along the left gastric, common heptaic, splenic and coeliac arteries. TNM8 classifies retropancreatic, mesenteric and para-aortic nodes as M1, or distant metastatic disease.

1.1.7 Current UK management of resectable disease

Surgery remains the only curative treatment for GC. Very early, T1a lesions can be managed with endoscopic resection, or surgical resection alone, though unfortunately, this only represents a minority of disease in the UK.[19]

Resectable, ≥stage IB disease requires multi-modal therapy. In the UK, this consists of peri-operative chemotherapy (i.e. before and after surgery) with either platinum doublet chemotherapy (e.g. oxaliplatin + capecitabine, or 5-fluorouracil [5-FU]) based on the MAGIC[23] trial and Ychou study [24] among others), or, if the patient is sufficiently fit, triplet chemotherapy in the form of FLOT (5-FU, leucovorin, oxaliplatin and docetaxel). The latter is based on the FLOT4 study, which reported a median OS of 50 months, compared to 35 months with MAGIC style chemotherapy.[25]

Extent of surgical resection depends on tumour location, stage and tumour biology, but radical gastrectomy with at least a D2 lymphadenectomy (see Appendix 1, Table A1.2 for definition) and excision of at least 15 nodes, performed at a high volume specialised centre, is recommended following the Dutch D1/D2 study.[26]

For patients who are not able to undergo pre-operative chemotherapy, 6 months of adjuvant chemotherapy (i.e. post-operative), in the form of 5-FU plus either oxaliplatin or docetaxel, should be considered, based on a meta-analysis which showed a 6% absolute survival benefit at 5 years.[27]

Post-operative radiotherapy (RT) may be considered for selected high risk patients, and is discussed in detail in Chapter 1.2.

1.1.8 Treatment of locally advanced (inoperable) or metastatic disease

Unfortunatley the majority of patients have locally advanced, inoperable, or metastatic disease from the outset, and for these patients, all available treatment options are palliative intent, and prognosis is poor (section 1.1.9). Figure 1.4 is a schema of the current UK and EU standard of care (SOC) systemic anti-cancer treatment (SACT) options in the advanced setting. In all lines of therapy, excellent multdisciplinary palliative care is essential.

First-line cytotoxic chemotherapy of choice is platinum (e.g oxaliplatin, cisplatin or carboplatin) with 5-FU (either infusional 5-FU or oral capecitabine). In 2008, REAL2 demonstarted mOS (median overal survival) of 11.2 months with a EOX (epirubicin, oxaliplatin and capecitabine), but subsequent studies revealed little additional benefit to epirubicin, and no benefit to addition of taxane in this setting, leaving doublet chemotherapy the current regimen choice.[19,24,28]

As discussed in section 1.1.4, molecular biology is increasingly driving treatment decisions, with HER2, PDL1, and MSI being tested at the outset to inform optimal therapy (Table 1.2, Figure 1.3.). For the approximately 20% of patients with HER2 positive disease , monocolonal antibody trastuzumab is added to chemotherapy with mOS of up to 16 months (vs 11.8 months with chemotherapy alone) shown in the TOGA study.[29]

Two landmark studies have evaluated the addition of immunotherapy (with PD-L1 [programme death ligand 1] inhibitors) to chemotherapy in the first line for patients with unresectable gastro-oesphageal cancer. Checkmate 649 and Keynote-859 demontsrated a mOS benefit of 3.3 and 2.4 months respecitively, compared to chemotherapy alone, leading to NICE (National Institute for Health and Care Excellence) approval of Nivolumab (for PD-L1 CPS [PD-L1 Combined positive score] ≥5) and Pembrolizumab (PD-L1 CPS≥1).[15,30]

MSI is used as a surrogate to measure for mismatch repair deficiency (MMR), representing approximately 4-8% of GC. These tumours typically exhibit high mutational burdens and high levels of PD-L1, and are generally less chemosensitive, but are extremely sensitive to checkpoint inhibition, with excellent response rates to PD-L1 inhibitor monotherapy, which is now approved in the 2nd line for this group (if checkpoint inhibitor naïve). [31,32]

However, for the majority of patients in the second line (who remain fit enough for SACT), options are limited to chemotherapy (either taxane or irinotecan). However, benefits are small, with average OS benefit of 6 weeks.[33,34] In Europe, VEGFR-2 (vascular endothelial growth factor receptor-2) inhbitor, ramicurimab, with or without paclitaxel is approved based on results from the RAINBOW and REGARDS studies respectively, with the former showing a mOS of 9.6 months for ramicurimab plus paclitaxel vs 7.4 months with paclitaxel plus placebo .[35] However, this is not currently NICE approved for use in the UK.

Transtuzumab deruxtecan is an anti-HER2 monoclonal antibody-drug conjugate which demonstrated promising activity in the 2nd line for patients who remained HER2 positive following prior trastuzumab therapy in the phase II Destiny-Gastric02 study[36]. As such, the agent is now under evaluation in the phase III, DESTINY-Gastric04 trial, though is available outside of clinical trials elsewhere in Europe.

In the third line and beyond, for the few fit enough, chemotherapy is the only option, with trifluridine-tipiracil (Lonsurf) demonstrating a mOS of 5.7 months vs 3.6 months placebo in the phase 3 TAGS study.[37]

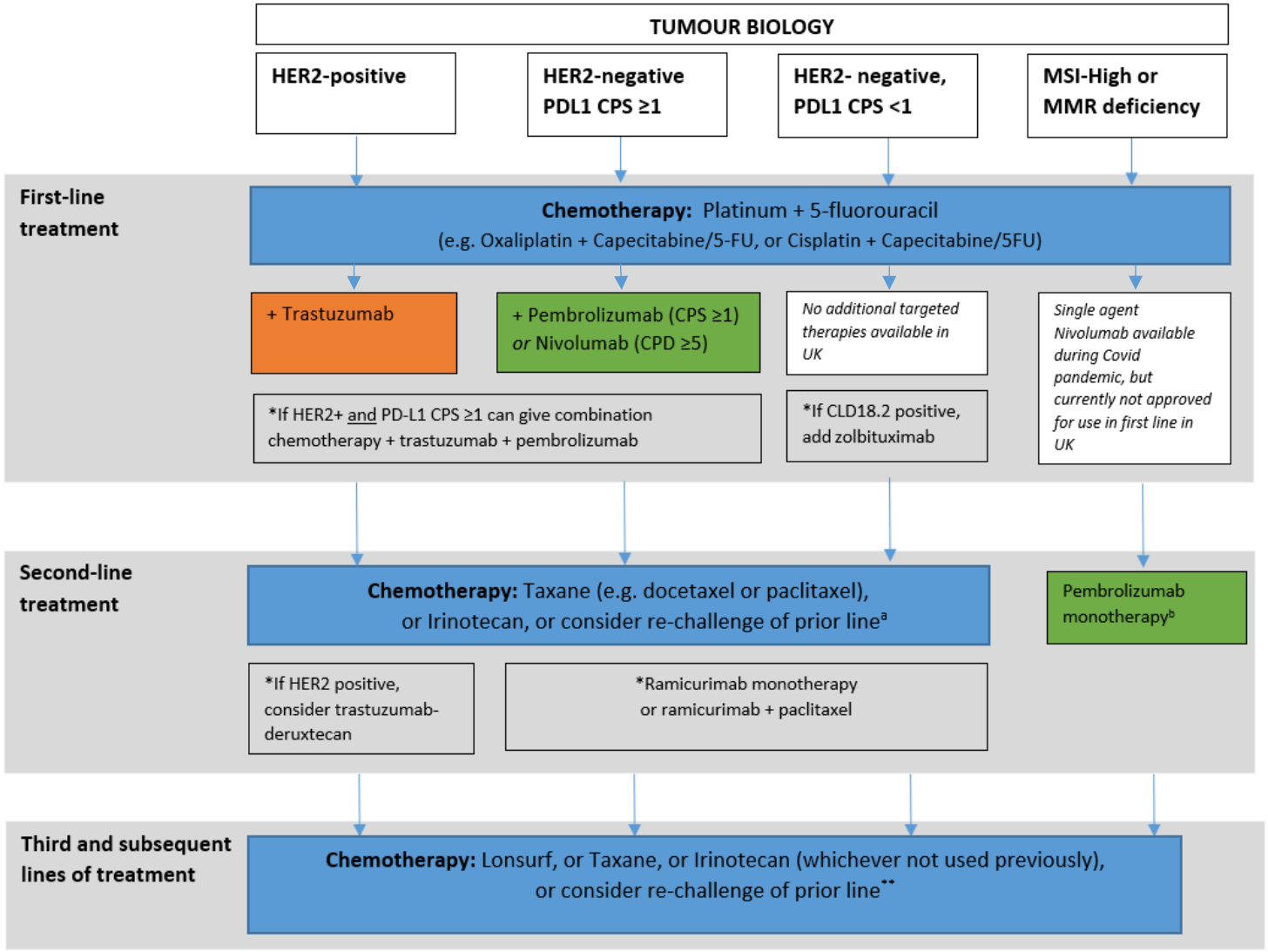


Figure 1.4. *Palliative SACT options for advanced gastric cancer, in the first, second and subsequent lines in the UK. Based on ESMO 2024 guidance.*[19]
*Blue = chemotherapy options, green = immunotherapy checkpoint inhibitors, orange = anti-HER2 therapy, grey = treatment listed in ESMO guidance but not currently NICE approved for UK use. * Options in grey are licenced, and listed in current ESMO guidelines, but not currently NICE approved for routine use in UK.*
[a] If well tolerated and progression-free interval >6 months. [b] Pembrolizumab is NICE approved following progression during or after one prior therapy.

Palliative RT is useful for bleeding primary tumours, discussed in more detail in Chapter 3. Endoscopic stent placement can be helpful for dysphagia or obstruction, depending on anatomical position of the tumour.

1.1.9 Prognosis

In the UK, the National Oesophago-Gastric Cancer Audit (NOGCA) data 2022 shows that 45.8% of patients present with stage IV disease, with lower proportions presenting in earlier stages (11% stage 0/1, 18% stage II, 26% stage III).[38] Overall survival reflects the overwhelming late presentation of disease, with 1 and 5-year median overall survival of 47.4% and 21.6% respectively in the UK. For patients with metastatic disease, prognosis is very poor, and even with SACT is measured in the region 9-11 months, highlighting the urgent need for novel treatments. [15,28]

1.1.10 Global variation in practice – East vs West

There is international variation in both incidence and outcome of GC, with over 70% of cases occurring in Asia, where prognosis is typically better than in the West. The reasons for this are multiple; different aetiology and biology, earlier stage of detection, and more aggressive surgical management strategies, to name a few (see Appendix A, Table A1.3).[39] The high prevalence in the East justifies the requirement for national screening programmes, with evidence suggesting that endoscopic screening in Japan and South Korea result in earlier diagnosis and reduce GC mortality. [40-42] A series comparing GC incidence between the Netherlands and Japan showed that in Japan, 58.9% of patients presented with local, node negative, disease and only 11.6% with distant metastases, compared to 19.9% local and 45.2% metastatic in the Netherlands, with the increase in late presentation in the West partly explaining the inferior prognosis.[43]

There are two main differences in oncological management; the chemotherapeutic agents in use, and a preference for post-operative rather than peri-operative chemotherapy. Regarding chemotherapy, S-1 (which contains tegafur - an oral fluoropyrimidine, and two enzyme inhibitors aimed to reduce its toxicity), is prescribed widely in East Asia, and is the backbone chemotherapy of choice in most Asian GC studies. However, it is not used in the West due to increased toxicity seen in a Western compared to Asian population.[39] However, recommendations regarding molecularly targeted agents such as HER2, PD-L1 and VEGFR2 inhibitors for advanced disease in the East largely mirror the West, with some minor variation in sequencing.[19,44]

Post-operative chemotherapy is the standard approach in the East, with only selected patients considered for peri-operative therapy. This is following the ACTS-GC, CLASSIC and JACCRO GC-07 studies, all of which demonstrated significant survival benefits.[45-47] In contrast to European practice, peri-operative chemotherapy is only weakly recommended in Japanese and Korean guidance. [48]

In summary, it is important to consider the global heterogeneity of this disease, and fundamental differences in practice across the east and west when considering the context of the literature subsequently presented in this thesis.

1.1.11 Future directions

In the peri-operative setting, the role of immunotherapy in addition to chemotherapy is being evaluated in a number of studies. One such study, MATTERHORN, is evaluating the role of anti PD-L1 antibody, Durvalumab in combination with FLOT for resectable patients. Interim results suggest improved rates of pathlogical complete response, but survival outcomes are awaited.[49]

A number of biomarker driven approaches are being investigated in the advanced setting. Claudin-18.2 is a tight junction protein found only in gastric mucosa, and is expressed moderately to strongly in >40% of gastric adenocarcinomas. Zolbetuximab is a monoclonal antibody directed to Claudin-18.2 and was evaluated in the phase III GLOW and SPOTLIGHT studies, the latter reporting a mOS of 18.2 months (Zolbetuximab + chemotherapy) vs 15.5 months (chemotherapy alone), though at present this remains unfunded in the UK.[17]

Fibroblast Growth Factor Receptor 2 (FGFR2) overexpression is also being investigated as a potential therapeutic target for GC, with the phase III FORTITUDE examining mAB, Bemarituzumab study eagerly awaited. [50]

Hyperthermic intraperitoneal chemotherapy (HIPEC) and Pressurised IntraPeritoneal Aerosilised Chemotherapy (PIPAC) are methods of administrating cytotoxic chemotherapy directly into the peritoneal cavity in an effort to control peritoneal dissemination. Neither are currently NICE approved for GC in the UK, but the currently recruiting PICCOS (Pressurised IntraPeritoneal Aerosolised Chemotherapy in the management of Cancers of the Colon, Ovary and Stomach) trial will evaluate PIPAC as a first line treatment for GC in the phase II setting.

Radiotherapy, particularly in the pre-operative setting, and in combination with checkpoint inhibition, is being extensively investigated, and will be discussed in detail in Chapter 3.

1.2 Principles of Radiotherapy for Gastric Cancer

Radiotherapy (RT) is the use of geographically targeted radiation with x-rays (most commonly megavoltage [MV] photons) to cause cell damage and death. The standard international unit of absorbed radiation dose is Gray (1 Gy = 1 joule/kg^{-1}). A RT prescription specifies 'dose/fractionation,' where the 'dose' is the total dose delivered in Gy, and 'fractionation' is the division of dose into discrete treatments, abbreviated by #. For example, 20Gy/5# refers to a total absorbed dose of 20Gy being delivered over five separate treatments.

Biological effect of irradiation is determined not just by total dose, but by fraction size, overall treatment time and the biology of the tumour. Biologically Effective Dose (BED), allows comparison of fractionation regimens and is used to consider the effect of fractionation on changes in acute and late reactions, and effect on the tumour. An alternative way to compare regimens is the 'Equivalent Dose in 2Gy fractions' (EQD_2) – a method of converting different dose/fractionation regimens to an equivalent schedule in 2Gy fractions which would give the same biological effect, and allow easy comparison of different treatment schedules. However, neither BED nor EQD_2 allow evaluation of difference in overall treatment time. These models will be referred to when comparing fractionation regimens used for GC in Chapter 3.

1.2.1 Radiotherapy treatment modalities for gastric cancer

In the delivery of gastric RT, the most common treatment modality (i.e. type of RT) is external beam RT (EBRT) with megavoltage photons (6-10MV), generated via a linear accelerator, which can deliver 2-dimensional (2D), 3D-conformal (3D-CRT), and intensity modulated RT (IMRT). Other modalities such as electrons and brachytherapy have no role in gastric RT due to their inappropriate dose distribution to achieve optimal coverage for gastric volumes.

Stereotactic ablative RT (SABR) is a form of precise, ultra-hypofractionated RT which delivers ablative doses to achieve maximal cell death via a single, or small number, of high dose fractions (for example, for nodal SABR, a dose of 30-45Gy/3# over 1 week). The role of SABR in the upper gastro-intestinal (UGI) tract has been proven for pancreatic, hepatocellular and biliary tract malignancies, and oligometastatic (defined as 1-5 metastatic sites, typically more than 6 months after successful treatment of primary disease) lymph node disease for selected cases, but its role in GC is unknown. However, an increasing number of trials are exploring the role SABR for oligometastatic GC (which will be outlined in chapter 3).[51]

Heavy ion RT using carbon ions is not used in the UK and will not be discussed further. Proton Beam Therapy (PBT) is being researched in several tumour sites, including the oesophagus, but at present, there is no established role for PBT in GC, with evidence limited to three case reports from the 1990s totalling 8 patients, with no clinical trials underway. [52-54]

Therefore, this thesis will hence forth focus on EBRT delivered with megavoltage photons.

1.2.2 Tumour volume delineation

Tumour volume delineation (TVD) is part of the RT planning process during which a Clinical Oncologist (or other appropriately trained professional, such as a clinical scientist) uses computer software, called Treatment Planning System (TPS) to manually outline the anatomical targets that should be i) included in the RT field and, ii) avoided by the RT field. Additionally, volumes may be created to account for any changes in tumour position, or setup errors to ensure adequate coverage during treatment. The nomenclature used for each volume is internationally standardised in the ICRU 83 (International Commission on Radiation Units and Measurements, Report 83), as summarised in Table 1.4 and illustrated in Figure 1.5.[55] Volumes are constructed on CT scans that are acquired specifically for treatment planning (termed 'planning CT'), with the patient carefully immobilised in the same position as subsequent treatment, to maximise the reproducibility of the resulting RT plan. A 3D-CT scan is acquired as a minimum standard, though in recent years, the introduction of 4D-CT, which takes time and motion into account, has become standard of care in tumour sites where significant motion can occur, for instance, lung and oesophagus, due to respiratory motion.

For radical dose RT, most clinicians will refer to a RT planning guidance document, termed a 'RT protocol,' which describes the anatomical structures that should be included in each volume. For older, 2D approaches, the protocol would comprise of a description of 2D field size, including upper, lower and lateral limits, and which organs should be shielded. In the era of 3D-CRT and IMRT, target volumes are delineated to create gross tumour volume (GTV), clinical target volume (CTV) and planning target volume (PTV) (Table 1.4) with the protocol describing specific structures to manually delineate, and how to 'grow' these volumes (by applying geometric margins) to create a final RT plan. Tumour biology such as pattern of spread dictates the extent of margins, and which lymph node stations are included in CTV volumes.

Target	Definition
Gross Tumour volume (GTV)	• The gross demonstrable extent of tumour. May consist of primary tumour (e.g. GTVp), involved regional lymph nodes (e.g. GTVn), or distant metastatic disease. • In some cases, e.g. post-operatively, there is no GTV. • Various imaging modalities may be used to define GTV (e.g. diagnostic CT, FDG-PET-CT, EUS, and MRI).
Clinical Target Volume (CTV)	• Volume to account for subclinical/ microscopic disease. • May contain GTV (i.e. with a margin around the tumour to account for microscopic disease), or in the case-of post-operative treatment (where there is no GTV), represent an area high risk for subclinical disease. • May also encompass high-risk lymph node areas. • CTV is tumour dependent based on predicted biological behaviour and pattern of spread

Planning Target Volume (PTV)	• Margin to account for geographical uncertainty due to variation in patient position and organ motion (i.e. systematic and random error)
	• Ensures the prescribed absorbed dose will be delivered to all parts to the CTV
	• PTV consists of:
	  ○ **IM (internal margin)** = Accounts for change in size/shape or movement of the target (e.g. due to adjacent organ motion, filling or emptying)
	  ○ **SM (set-up margin)** = External factors that influence target, such as patient position for treatment
	• PTV = CTV + IM + SM

Internal target volume (ITV)	• Margin to account for target motion, or change in shape, for example due to organ motion secondary to respiration or filling/emptying • ITV= CTV+IM
Organ at Risk (OAR)	Normal tissues that if irradiated could suffer significant morbidity, thus should be considered during treatment planning (e.g. avoided, or dose to structure limited)
Planning organ at risk (PRV)	Margin added to OAR to account for uncertainty and variation in position (analogous with adding a PTV to the OAR volume)

Table 1.4. *Nomenclature used for tumour volume delineation based on ICRU 83.*[55]

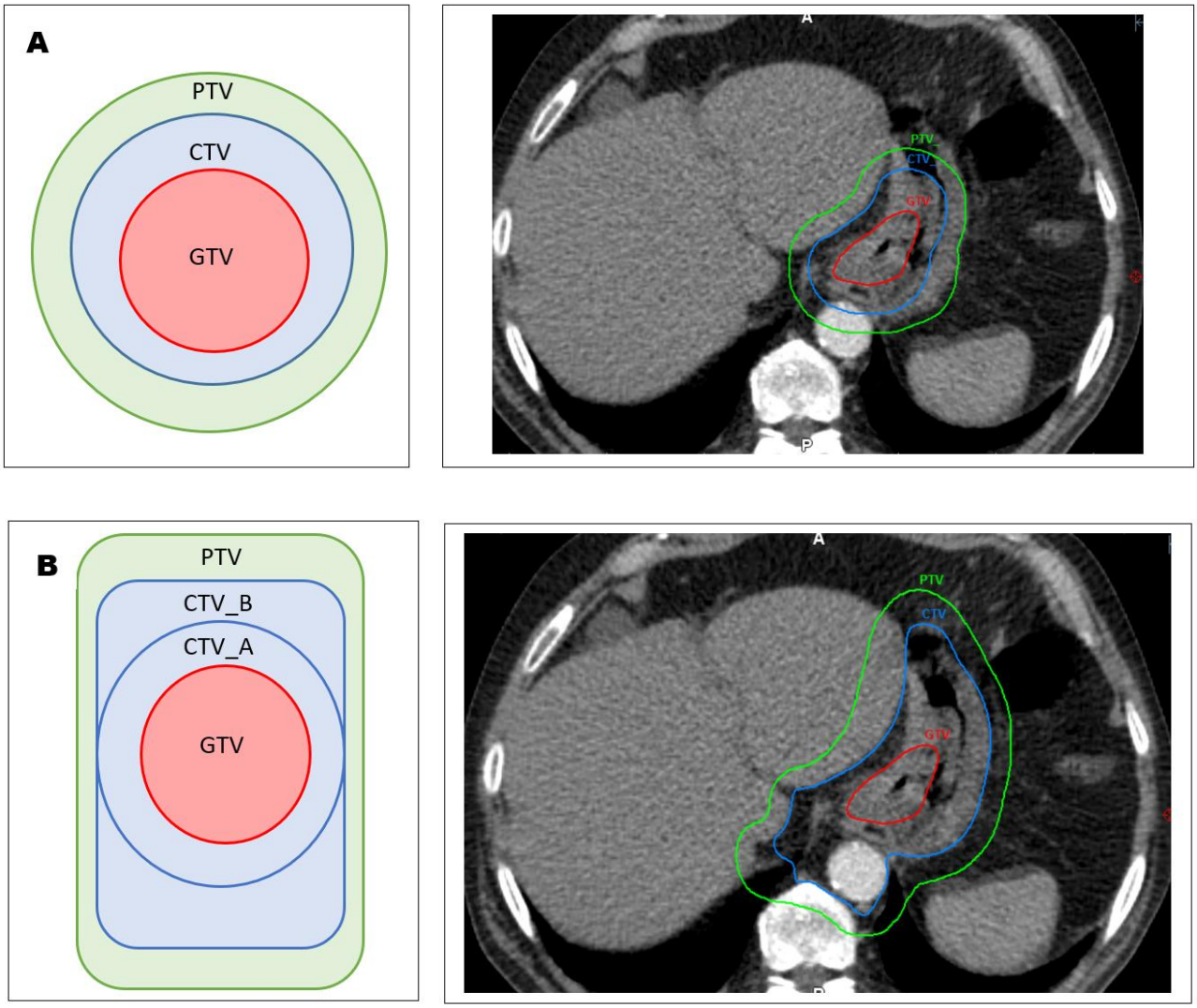


Figure 1.5. *Schematic representation of RT volumes*

Figure 5A ***(top)*** *Left is a schematic representation of GTV (red), CTV (blue) and PTV (green), where each volume has been expanded in a circumferential fashion. Right is an example of circumferential volumes expanded around a gastric tumour as seen on CT.*

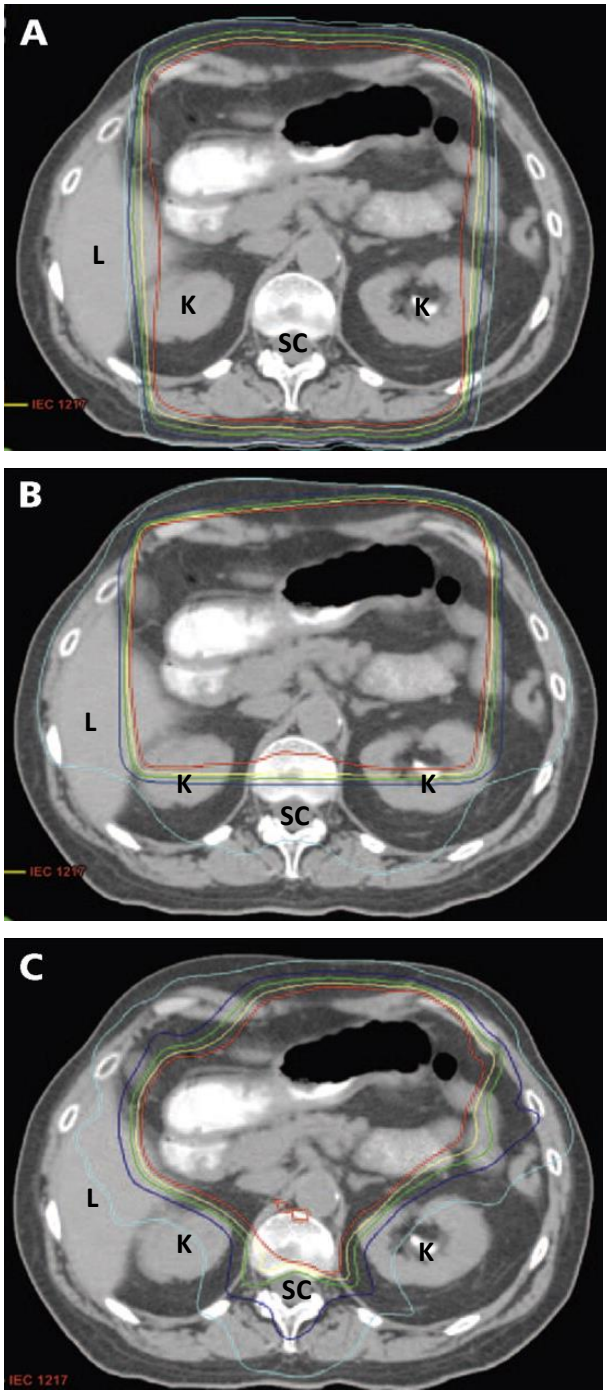
Figure 5A ***(bottom)*** *Left is a schematic representation of GTV (red), CTV (blue) and PTV (green), illustrating anisotropic expansion of CTV – it has been expanded more in the superior/inferior plain than laterally. Right is a CT based example of the same GTV as above, with a CTV grown around it that encompasses the whole stomach and lymph node areas.*

1.2.3 RT planning techniques

The simplest way to deliver MV photon RT is 2-dimensionally by applying a single beam directly to the tumour, or a pair of beams in a parallel-opposed plane (termed anterior-posterior parallel opposed pair, APPA), with basic shielding using lead cut-outs to spare nearby organs at risk.

In the 1980s, 3D-CRT was introduced, which allowed multiple, non-coplanar beams. CT-simulation allowed better visualisation of the tumour and more refined target volume delineation, resulting in smaller, more conformal fields.

The 1990s saw the introduction of IMRT, which via a “step and shoot” approach, delivers a number of small beams from different angles with small, lead leaves moving in and out of the field at each step (called multi-leaf collimators, MLCs). This provides the ability to shield dose with increased accuracy, effectively curving isodoses to conform to the target volume and improve sparing of organs at risk (OAR). Volumetric Modulated Arc Therapy (VMAT) is a way of delivering IMRT via a continuous arc, with variable dose rate and constant MLC motion resulting in excellent conformity and reduced treatment time. Figure 1.6 shows each of these techniques, as applied to GC.



Key: Coloured isodose lines:

Red =45Gy

Yellow = 43Gy

Green = 40Gy

Figure 1.6. *Dosimetric comparison of 2D, 3D-CRT and IMRT RT planning techniques for GC, showing the variation in dose distribution and increased sparing of OARs, such as spinal cord (SC), liver (L) and kidneys (K) with IMRT compared to 2D planning. Figure from Callister et al, reproduced with permission from Harborside Press*[56].

Figure 1.6A. *2D AP-PA approach, where 1 photon beam is directed anteriorly, and a posterior beam directly opposite in a parallel manner, with the area demarcated by a red isodose line treated to 45Gy, and little sparing of OARs.*

Figure 1.6B. *3D planning, where lateral/oblique beams are added to spare dose posteriorly, with limited sparing to OARs.*

Figure 1.6C. *IMRT planning with much better conformity of the red isodose line, and sparing of kidneys, spinal cord and liver.*

1.3 The Current Role of Radiotherapy for Gastric Cancer

The concept of gastric RT is far from novel. The first recorded application of RT for GC dates back to 1895, when Victor Despeignes, a French hygienist, believing cancer to be of parasitological origin, treated a 52-year-old patient with stomach cancer, with radiation. Though the patient only survived 16 days following therapy, which was supported by a fascinating regimen of milk, Condurango wine and injected artificial serum, both excellent tumour control and symptom alleviation was gained, with 50% reduction in size reported, leading to his conclusion that,

"…we ask ourselves if, dealing with a less advanced and less rapid cancerous affliction, we might not have the hope, if not of a cure, at least, of a prolonged survival by using the treatment that we have inaugurated."[57]

It was not until 1969 that the first randomised controlled trial of gastric chemoradiotherapy (CRT) was published, reporting survival advantage with the addition of 5-FU chemotherapy to RT for GC (13 vs 6 months), and reported 2 cases of complete clinical response.[58] Subsequent studies in the 1980s and 1990s reported mixed results, but offered potential improved local control and survival benefits to RT. [59]

However, most would consider the US Intergroup 0116 trial as the seminal gastric RT study.[60] Published in 2001, this randomised controlled trial reported a 9% absolute overall survival benefit at 3 years with the addition of post-operative CRT to surgery alone. Though quickly adopted as SOC in many countries, this approach was not universally adopted due to several concerns regarding this study's findings:

- 54% had less than a D1 lymphadenectomy, raising the concern that RT was compensating for suboptimal lymph node dissection (LND)
- Significant rates of toxicity, with ≥grade 3 gastrointestinal toxicity of 33%, and 17% failing to complete treatment due to toxicity
- Relevance of the study findings in the context of peri-operative chemotherapy (which was to become SOC shortly after publication of this study)

Many large international randomised controlled trials have followed INT-0116, to clarify the role of RT in the post-operative setting, summarised in Table 1.5. The Korean ARTIST trial was the first, which compared post-operative chemotherapy to CRT in the context of D2 LND, and reported no overall disease-free survival (DFS) benefit, but unplanned sub-group analysis showed superior

DFS in those with lymph node positive disease in the RT arm (77.5% vs 72.3% p=0.037), prompting the design of ARTIST 2.[61,62] ARTIST 2 included only stage II and III, node positive patients who underwent D2 LND, and showed no benefit to the addition of RT to doublet chemotherapy.[63] Further validation came from CRITICS, this time comparing optimal peri-operative chemotherapy to pre-operative chemotherapy plus post-operative CRT, demonstrating no PFS or OS benefit with the addition of post-operative RT.[64] Thus the overarching conclusion of this body of evidence is that in the context of adequate LND and optimal peri-operative chemotherapy, there is no additional survival benefit of post-operative CRT. This had led to the current UK position of post-operative CRT being reserved for selected high-risk patients, i.e. those who have had less than the recommended D2 LND, positive resection margin, or did not receive peri-operative chemotherapy, following Multidisciplinary Team (MDT) discussion. [51]

Study name	Year	No. of patients	Study design	Dose/#	LND	Event free survival	OS	≥G3 toxicity
INT 0116[60]	2001	556	S *vs* S + CRT	45Gy/25#	D2: 10% D1: 36% D0: 54%	RFS = 19 months S vs 30 months CRT (p=<0.001)	3 yr OS = 41% S vs 50% CRT (p=0.005)	CRT arm: GI toxicity 33%
ARTIST 1[61]	2012	458	S + C vs S + C + CRT	45Gy/25#	>D2: 100%	3 yr DFS = 74.2% C vs 78.2% CRT (p=0.08)	5 yr OS 73% C+ 75% CRT (p=0.484)[62]	CRT arm: G3 nausea 12.3% G3 vomiting 3.1% G3 diarrhoea 0.9% G4 GI 0%
CALGB 80101 (Alliance)[65]	2017	546	S + C + CRT + C (5FU + LV) *vs* S + C + CRT + C (ECF)	45Gy/25#	≥15 LN removed: 62% ECF, 50% 5FU+LV	DFS = 39% 5FU+LV vs 37% ECF (p=0.94)	5 yr OS =44% 5FU+LV vs 44% ECF (p=0.69)	Both arms: G3 Nausea, 16-17%, G3 Vomiting 9-11% G3 Diarrhoea 7-14%
CRITICS[64]	2018	788	C + S + C *vs* C + S + CRT	45Gy/25#	D1+: 86%	5-year EFS = 39% C vs 38% months CRT (p=0.92)	mOS = 43 months C vs 37 months CRT (p=0.9)	CRT arm: G3 anorexia 14% G3 nausea 9% G3 vomiting 5% G3 diarrhoea 3% G4 GI perforation 1%
ARTIST 2[63]	2020	546	S + C (S-1) *vs* S + C (SOX) *vs* S + C+ SOXRT	45Gy/25#	>D2: 100%	3-year PFS = 74% SOX vs 73% SOXRT vs 65% S-1	NS	SOXRT arm: G3/4 anorexia 2% G3/4 nausea 0% G3/4 vomiting 0% G3/4 diarrhoea 2%

***Table 1.5**. Large randomised controlled trials of post-operative CRT for GC.*
≥G3 toxicity defined as CTCAE grade 3 or higher toxicity due to RT. S= Surgery. CRT = chemoradiotherapy. RT = radiotherapy alone. C= chemotherapy alone. 5FU + LV = 5-fluorouracil + leucovorin. ECF = Epirubicin, cisplatin + 5FU. EFS = Event free survival. RFS = Relapse free survival. PFS = Progression free survival. DFS = disease free survival. 3DCRT = 3D conformal RT. S-1 = tegafur/gimeracil/oteracil. SOX = S1 + Oxaliplatin. SOX = SOX + RT.
See Appendix 1, Table A1.2 for definition of D0, D1, D2 LND.

More recently, attention has shifted to the potential value of pre-operative CRT, with a series of early studies from the MD Anderson, reporting clinical complete response rates of up to 30%.[66,67] Promising efficacy in the pre-operative setting, paired with prior poor completion rates of any post-operative treatment (49.5% completed post-operative chemotherapy in MAGIC[23], and 46% and 50% for post-operative chemotherapy and CRT respectively in CRITICS[64]) has driven the shift in focus to the preoperative setting. TOPGEAR, the first multi-centre phase III randomised controlled trial (RCT) randomised patients with Siewert type II/III and gastric adenocarcinoma to either peri-operative chemotherapy (initially ECF/ECX, but FLOT was subsequently added to the protocol following the FLOT4 study[25]) compared to 2 cycles of peri-operative chemotherapy plus CRT; 45Gy/25# with 5FU or capecitabine. [68] The recently published results reported no additional survival benefit of pre-operative CRT compared to peri-operative chemotherapy alone (mOS 46 vs 49 months respectively, 95%CI 35 to 61). However, CRT doubled pathological complete response (8% vs 17%) and increased major pathological response (i.e. <10% residual tumour) from 29% to 50%. Additionally, CRT was no more toxic than chemotherapy alone, with G3 gastrointestinal toxicity of 28% and 25%, with RT being completed as planned by 92% of patients. The results of further randomised trials in this setting, CRITICSII and PREACT are eagerly awaited.[69,70] However, in the absence of randomised data demonstrating survival benefit, pre-operative RT is not currently considered standard of care, and as such is not routinely recommended in UK Royal College of Radiologists (RCR) guidance.[51]

Palliative RT is most commonly used for bleeding tumours, with two meta-analyses showing bleeding response rates of approximately 75%.[71,72] The review by Tey *et al.,* also suggested a role for alleviation of obstruction and pain, with response rates of 68% and 67% respectively.[72] The current UK RCR dose fractionation recommendation is 6-8Gy/1# OR 20Gy/5#.[51] At present, only approximately 20% of “non-curative” patients with gastric or type III GOJ tumours in the UK will undergo palliative RT.[38]

1.4 Thesis outline and aims

As outlined in this introductory chapter, complete surgical resection is the only curative option for patients with GC, and for those with inoperable disease, even in the absence of distant metastases, the only oncological treatment options are palliative intent SACT, with the option of low-dose (8Gy/1# or 20Gy/5#) palliative RT or stenting for local symptoms. Regrettably, this is the case for majority of patients, with national UK audit data from 2022 showing average resection rate of 32%, meaning over two thirds do no undergo curative treatment.[38] Though for many of these patients surgery is not appropriate due to metastatic disease from the outset, there remains a significant number of patients with inoperable, non-metastatic disease with very limited treatment options - approximately 1200 patients with stage 1-3 disease did *not* undergo curative surgery between 2019-2021 in the UK.[73] Unfortunately, despite improvements in SACT, and even in the absence of metastatic disease at diagnosis, inoperable GC (IGC) still heralds a very poor prognosis, with a mOS of approximately 11 months with chemotherapy.[74] ***This highlights the urgent need for more research and novel treatment paradigms for this devastating disease.***

As discussed in section 1.3, gastric RT is not a new concept, with a wealth of research exploring its role post-operatively, and growing interest in the pre-operative setting. Despite this, gastric RT is still not widely practiced in the UK, where it is generally reserved for palliation. In contrast, for patients with adenocarcinoma of the anatomically neighboring oesophagus or GOJ, RT has become an established definitive treatment option for patients unsuitable for surgery, with encouraging survival data[75-79]. However, as there is currently no phase III evidence to support this approach for GC, radical RT is *not* currently considered SOC for patients with IGC in Europe or Asian countries, though of note, definitive dose CRT *is* recommended for consideration in the US NCCN (United States National Comprehensive Cancer Network) guidelines for patients with upfront inoperable disease.[80]

Both the proven benefit of RT in the oesophagus/ GOJ, and the growing body of evidence demonstrating the efficacy and safety of pre-operative gastric RT, with a pathological complete response rate of up to 30%, ***supports the further evaluation of RT as a potential treatment modality for patients with inoperable disease***.[67,81]

Therefore, the research question asked by this thesis is, **"Could radiotherapy have a role in the management of inoperable, non-metastatic GC?"** The objectives were as follows:

1. To conduct a service evaluation of GC treatment, outcomes, and current use of RT across South West Wales (Chapter 2)
2. To conduct a comprehensive systematic review (SR) to evaluate the evidence-base for definitive, pre-operative and palliative gastric RT, specifically; efficacy, safety and RT technique. (Chapter 3)
3. To engage with the Oesophago-Gastric (OG) Oncology community to ascertain current practice across the UK, clinician opinion, and technique relating to gastric RT, and gather information about clinician interest in a definitive trial (Chapter 4)
4. To identify areas of RT technique that require further evaluation and develop RT planning studies to address these:
    a. An interobserver variability study of TVD of gastric RT volumes to evaluate accuracy and variation between clinician volumes when compared to a 'gold standard' volume, and evaluate whether this is improved with the addition of MRI to CT (Chapter 5)
    b. A volumetric and dosimetric comparison of gastric RT protocols (TOPGEAR, CRITICS II) to compare nodal volumes, dose to organs at risk, and general ease/ usability of protocol and accompanying supporting materials to inform development of future UK gastric RT protocol (Chapter 6)
5. To develop a set of recommendations for a future clinical trial protocol and accompanying gastric RT protocol based on the former studies and systematic review (Chapter 7).

Chapter 2

Evaluation of Treatment and Outcomes of Gastric and Siewert III Gastro-oesophageal Junctional Tumours in South West Wales 2019-2021

2. Evaluation of Treatment and Outcomes of Gastric and Siewert III Gastro-oesophageal Junctional Tumours in South West Wales 2019-2021

2.1 Introduction

National cancer registry data from across England and Wales is collected and published annually by the National Oesophagogastric Cancer Audit (NOGCA), providing an excellent overview of treatment patterns and outcomes for patients with GC.[38] However, there are limitations to current national datasets, particularly when attempting to understand outcomes for a particular subgroup of patients, for example non-metastatic inoperable gastric cancer (IGC), as outcomes are generally reported by TNM stage group. Additionally, whilst NOGCA data reports that 20% of patients undergoing non-curative treatment in the UK will receive palliative RT, detailed information regarding RT delivery (e.g. dose/fractionation), is lacking.

It is essential to properly understand the presentation, treatment patterns, and size of a potential sample population when considering the impact and recruitment to future clinical trials investigating the role of RT for IGC, underlying the need for a South West Wales (SWW) service evaluation of GC treatment and outcomes as part of this wider research.

2.2 Aims

The main aims of this service evaluation were to:

- establish incidence of gastric or Siewert type III GOJ cancer, stage at presentation, and performance status at presentation
- establish treatment patterns, specifically use of RT
- calculate local overall survival
- provide a local database from which potential recruitment numbers to future clinical trials can be estimated, in turn informing number of centres/duration of future studies.

2.3 Methods

2.3.1 Identification of patients

A list of all patients presenting to the respective UGI MDT with gastric or GOJ cancers between 1.8.2019 and 30.7.21 was obtained from Swansea Bay University Health Board (SBUHB) and Hywel Dda Health Board (HDHB) cancer services. Identified cases were screened, and only those with a first confirmed MDT diagnosis of gastric or type III GOJ carcinoma during the dates stated went on to full data collection, see Figure 7. As this study was a service evaluation of treatment and outcomes, ethical approval was not deemed necessary. However, permission was sought from SBUHB Information Governance prior to publication of anonymised results in this thesis.

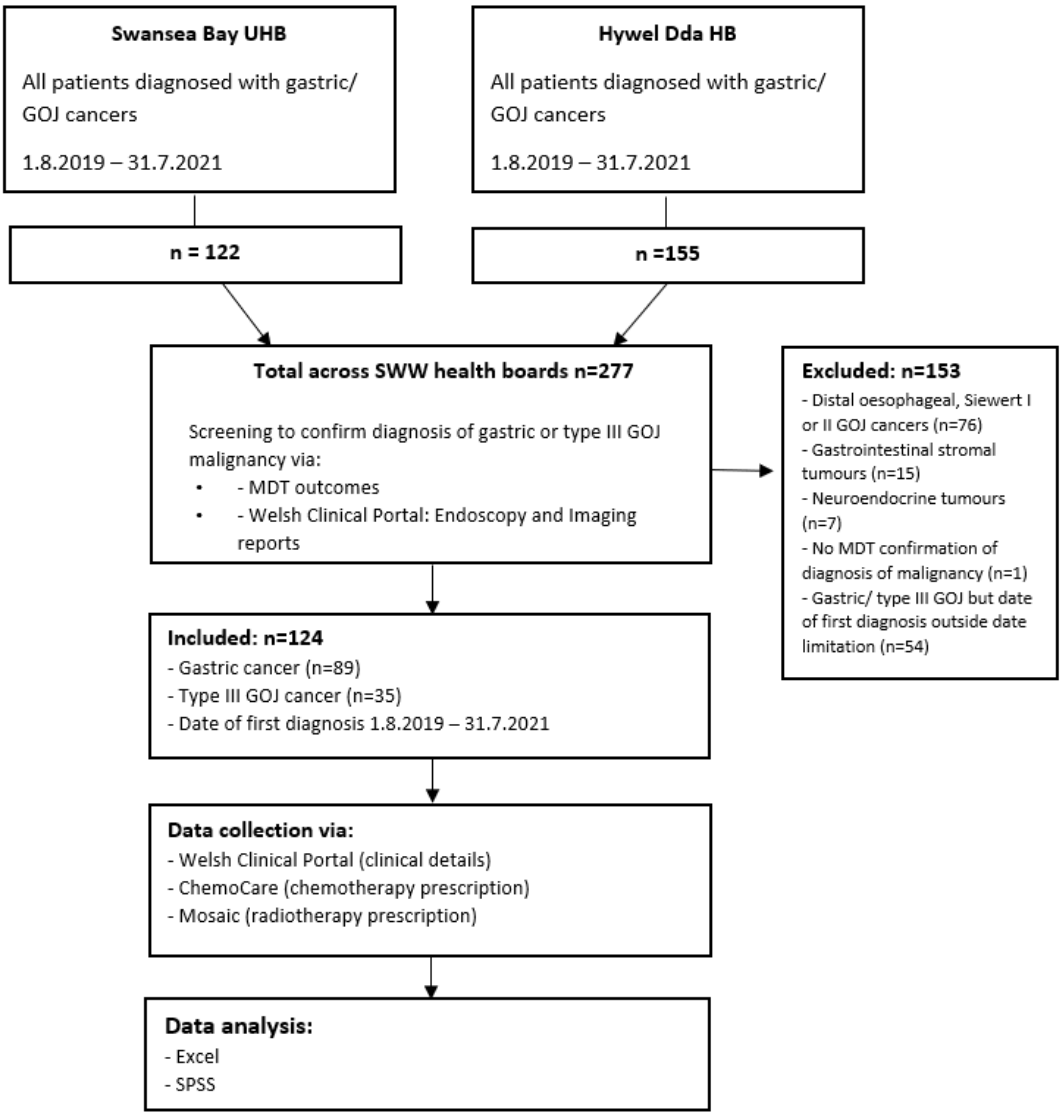


***Figure 2.1**. Methods for identification of patient population, data collection and analysis.*

2.3.2 Data collection and management

Data was extracted from electronic databases; Welsh Clinical Portal (MDT outcomes, clinical letters, UGI endoscopy and radiology reports) ChemoCare (chemotherapy prescription and administration data) and Mosaic (RT data). A list of data points extracted for each patient is listed in Appendix 2. Data was recorded in a password protected Excel spreadsheet, on an NHS encrypted laptop. Prior to exporting into IBM SPSS (v29.0.2.0) for analysis, data was completely anonymised, and only necessary outcome data exported.

2.3.3 Data analysis

Basic data analysis was performed in Excel. Overall Survival (OS) was calculated via Kaplan Meier curves using SPSS.

2.4 Results

2.4.1 Incidence by primary site, histological subtype, and stage

Between 1.8.2019 and 1.8.2021, n=124 patients with gastric or Siewert type III GOJ (see 1.1.3, Figure 1.2 for anatomical description) were included (n=58 in SBUHB, n=66 in HDHB). The majority (72%) had a diagnosis of gastric cancer, compared to type III GOJ (28%). Adenocarcinoma was the commonest histological subtype (87%, n=108), of which 56% were poorly differentiated or signet cell morphology, 30% moderately differentiated and only 3% well differentiated. Of the remaining patients, 4.8% had either high-grade dysplasia or atypical cells suspicious for malignancy, 0.8% had squamous cell carcinoma, with the remaining samples being non-diagnostic. Table 2.1 shows proportion of patients presenting by TNM clinical stage group compared to NOGCA data.[38]

	Number/% presenting by TNM stage group			Number/% undergoing surgery, or 'curative intent treatment' by TNM stage group		
TNM stage group	No. presenting at diagnosis (SWW data)	% presenting at diagnosis (SWW data)	% presenting at diagnosis (UK NOGCA data)	No. undergoing surgery (SWW data)	% undergoing surgery (SWW data)	% undergoing curative intent treatment (UK NOGCA data)
0/I	10	8%	11%	5	50%	65.8%
II	9	8%	18%	5	55%	56.6%
III	34	29%	26%	6	17.65%	52.1%
IV	66	55%	45%	3	4.5%	4.9%

***Table 2.1**. Proportion of patients presenting by TNM clinical stage, and proportion of patients who underwent surgery/ curative intent treatment by stage in South West Wales (SWW) compared to UK NOCGA data.[38]*

2.4.2 Treatment – Surgery

Overall, 15.3% of patients underwent surgery (n=19). Proportion undergoing surgery by stage is shown in Table 2.1. Of those undergoing surgery, n=14 (73.6%) had curative intent surgery, n=3 had open and close laparotomy, n=1 emergency resection for obstruction and n=1 palliative resection. Of the 39 patients with stage I-IVa disease who did not undergo surgery, reasons were; medically unfit for surgery/ significant co-morbidity n= 21 (53%), locally advanced/ surgically inoperable disease n= 6 (15%), frailty/ poor PS n=5 (13%), rapid disease progression n=2 (5%), died by MDT discussion date n=1 (3%), having radical CRT n=1 (3%), not stated n =3 (8%).

Of the three patients with stage IV disease who underwent surgery, two had stage IVa disease (i.e. locally advanced but non-metastatic) and underwent palliative surgery (n=1 due to perforation, n=1 due to gastric outlet obstruction), and one patient with stage IVb disease (i.e. metastatic) presented as an emergency with gastric perforation and underwent a palliative partial gastrectomy.

2.4.3 Treatment – Palliative SACT

31 patients underwent ≥1 cycle of palliative SACT, of which n=26 (84%) had first line chemotherapy only, n=3 (9%) had two lines, and n=2 (6%) had three lines of therapy. All 10 HER2 positive patients also received at least 1 cycle of trastuzumab. In the first line, mean number of cycles was 4 (range 1-7) and 11 different chemotherapy regimens were administered. Proportion of

patients undergoing palliative SACT by stage of presentation were; stage I 10%, stage II 33%, stage III 24% and stage IV 31%

2.4.4 Treatment – Radiotherapy

Thirteen (10%) of the total cohort underwent RT, of which over half had type III GOJ tumours (61%). Indications for RT were as follows; bleeding/ melaena n=7, local control n=4, radical intent n=1 (in a patient with a T2N0M0 type III GOJ tumour and synchronous T4N0M0 oesophageal primary being treated with CRT), and adjuvant n=1. One patient was retreated 10 months after initial RT (receiving a total of 2 x 6Gy/1#). Dose and fractionation schedules prescribed are shown in Figure 2.2

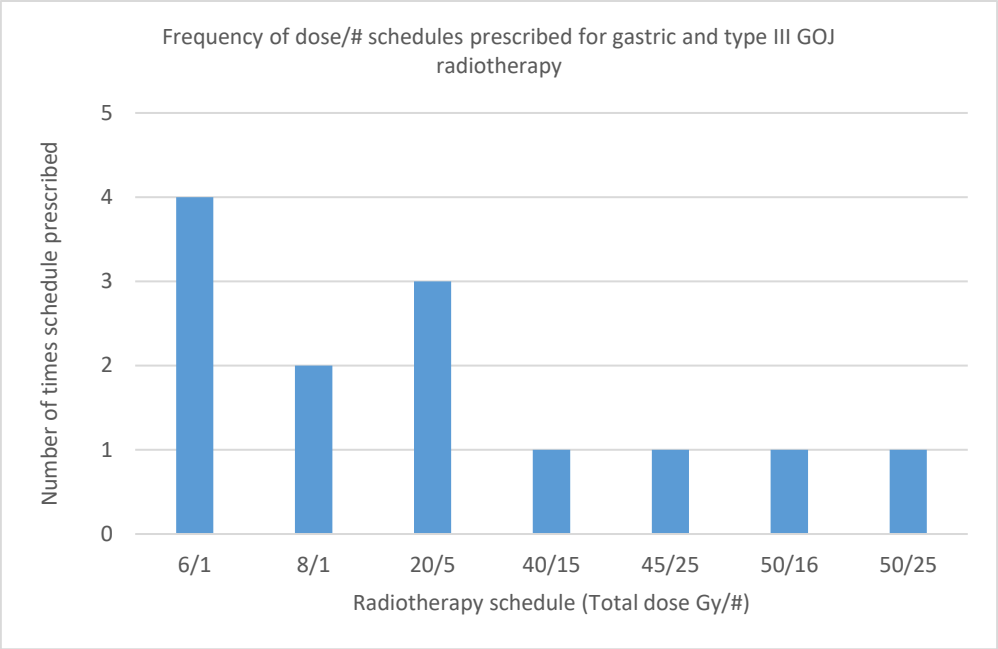


***Figure 2.2**. Bar chart showing frequency of dose/# schedules prescribed for gastric and type III GOJ tumours*

2.4.5 Outcomes

After at least 9 months follow up, the median overall survival (OS) for the whole study population was 4.8 months (95%CI 3.5-6.3, range 2 days – 32.7 months). Median OS by TNM clinical stage group was 17.8, 12.4, 9.4 and 2.9 months for stages I, II, III and IV respectively (log rank $p<0.001$), with Kaplan Meier curves shown in Figure 2.3. The overall one- year OS by stage is shown in Table 2.2.

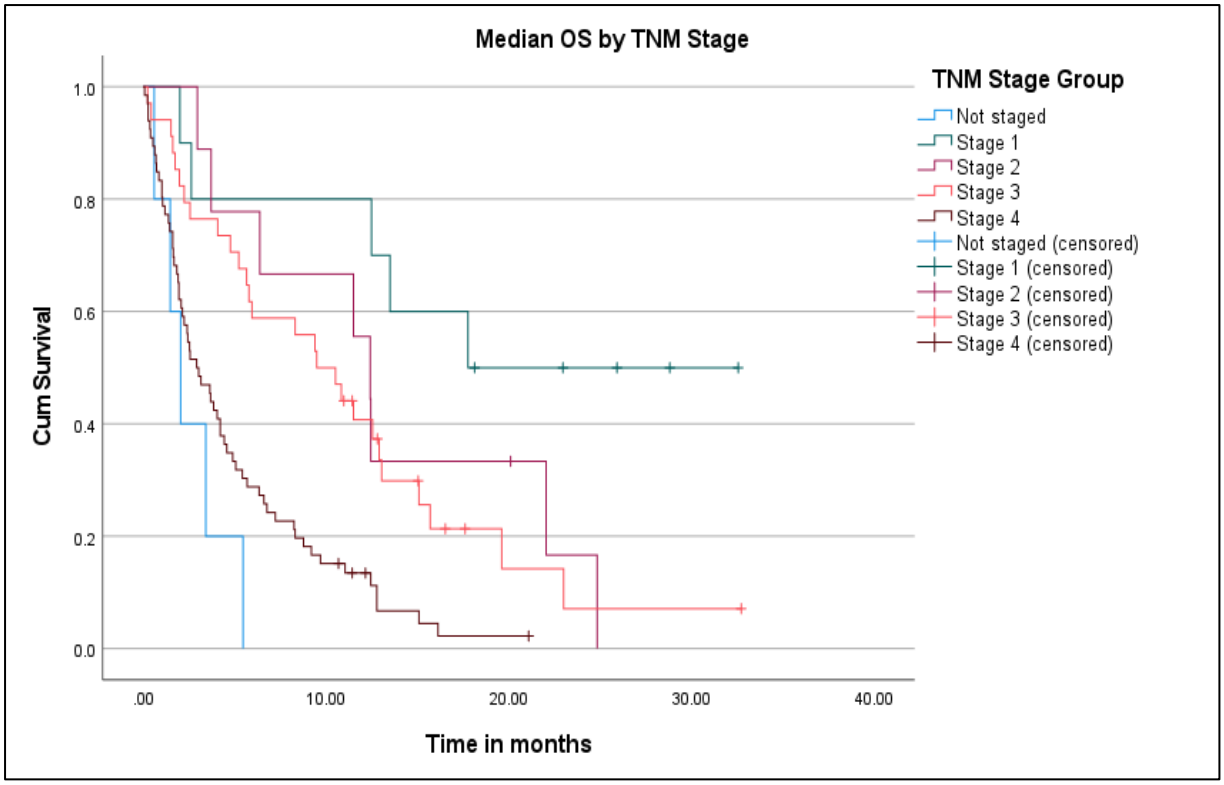


Figure 2.3. *Kaplan Meier curves showing median OS by TNM stage group*

Stage	One year OS (SWW data)	One year OS (ONS data)
I	80%	88.5%
II	55%	71.4%
III	40%	63.2%
IV	13%	21.4%

Table 2.2*. One-year overall survival by TNM clinical stage group for SWW compared to Office for National Statistics one-year age standardised net cancer survival 2013-2017 (NB. This relates to data for England only)*

For those with stage I-III disease (i.e. non-metastatic), the median OS for those who underwent surgery (n=13) *vs.* those who did not undergo surgery (n=40) was 26.3 months vs 8.8 months (log rank p<0.001), and is shown by Kaplan Meier curves in Figure 2.4.

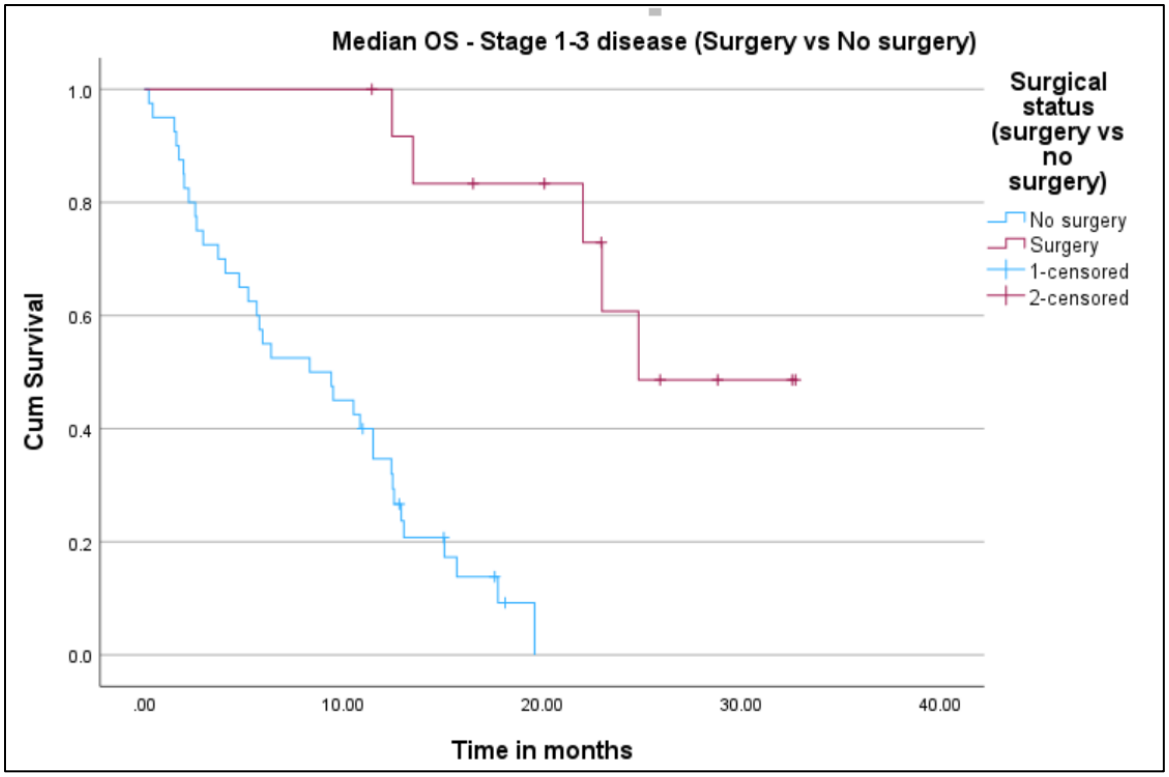


Figure 2.4. *Median OS for stage I-III disease - surgery vs no surgery*

Median OS for those with stage IV disease for those who did not receive palliative SACT was 1.9 months (95% CI 1.5-2.3) compared to 8.8 months (95% CI 4.6-12.9 months) for those who did receive ≥1 cycle of SACT (p<0.001).

2.4.6 Potential population for future trials

Of the 39 patients with stage I-IVa disease who did not undergo surgery, the mean age was 76 years. Eight patients were of good performance status (0-1), three had PS=2 and one PS=3. However, 22 were not seen by oncology as not deemed suitable candidates for oncological therapies by the MDT, or did not have their PS recorded. Overall n=9 underwent palliative SACT.

Six had RT, of which four had RT as their only treatment (i.e. no SACT). Of these four patients, n=2 had 6Gy/1# palliative RT for bleeding, but n=2 had radical doses (50Gy/16#, 50Gy/25#).

Using the ability to receive ≥1 cycle of palliative SACT (n=9), or radical dose RT (n=2) as a surrogate measure for suitability to undergo SACT or RT treatment within a future clinical trial, the potential population of patients with inoperable, non-metastatic disease for future clinical trials is n=11 over a two-year period.

2.5 Discussion

2.5.1 Comparison of SWW to UK NOGCA audit data

In SWW more patients present with later stage (i.e. III and IV) compared to UK NOGCA data, with 55% of patients presenting with stage IV disease, compared to 45% nationally (Table 2.1). Potential reasons for this include socio-economic status of this population. Rates of surgical resection are also lower than national data (overall rates of curative intent surgery 32% NOGCA vs 15% SWW). Low rates of patients presenting with earlier stage (I/II) disease undoubtedly accounts for some of the difference, though difference in MDT opinion regarding resectability between high volume tertiary centres versus lower-volume district general hospitals is also likely to contribute.

Overall survival is poorer in SWW compared to ONS (Office for National Statistics) England data – this is likely multifactorial due to aforementioned later stage at presentation, lower surgical resection rates, and socio-economic status of the population.

This service evaluation was performed prior to the centralisation of oesophagogastric surgery in South Wales, with all radical surgery now being performed at a high-volume centre in Cardiff. This, along with the development of a regional MDT, incorporating all centres across South east and west Wales has likely impacted surgical decision making, potentially increasing in numbers considered suitable for a radical approach, thus should be re-evaluated by an updated analysis of surgical resection rates.

2.5.2 Impact of surgery on OS for those with non-metastatic disease

This retrospective service evaluation has shown a significant difference in OS for patients with stage I-III disease who underwent surgery compared to those who did not (26.3 vs 8.8 months respectively, $p<0.001$). However, there are a number of confounders not measured by this study which are may have caused selection bias, including number/type of co-morbidities, degree of frailty, performance status, stage of disease and subsequent oncological treatments. The most common reason for not undergoing surgery in this study was medical co-morbidity – however, how frequently said co-morbidity also precluded oncological therapy, and subsequent impact on outcome was not evaluated.

2.5.3 Use of radiotherapy for gastric and type III GOJ cancer in SWW

NOGCA data between 2019-2021 shows that 21% of patients with 'non-curatively' treated gastric or type III GOJ cancer underwent RT.[38] In this study, excluding the two patients who underwent radical intent RT (n=1 definitive, n=1 adjuvant), 10% (n=11 of 105 patients 'non-curatively' managed) had RT in SWW, which is half the national rate. Reasons for this are not clear, but may be related to burden of metastatic disease precluding benefit of local RT treatment, which was not evaluated.

In this cohort, it is noted that 61% of patients who underwent RT had type III GOJ tumours, which is relatively high given that only 28% of the study population had junctional tumours. RT is a well-established, frequently used treatment for distal oesophageal and type I/II junctional tumours, which may account for the increased rates of RT for type III tumours GOJ compared to gastric. Similarly, of the three patients who received doses higher than currently recommended for gastric/ type III GOJ tumours in the RCR dose fractionation 4th edition (i.e. 40Gy/15# or 50Gy/16#, or 50/25#), all had type III GOJ tumours. These doses are established for treatment of oesophageal and type I/II GOJ tumours, and extrapolation of this evidence to type III tumours may explain dose selection in these cases.[51] All patients being treated for bleeding received RCR recommended doses; 6Gy/1# (n=4), 8Gy/1# (n=2) or 20Gy/5# (n=1).

2.5.4 Limitations

Limitations of this service evaluation include its retrospective nature, reliance on accurate data collection at MDT and accuracy of subsequent entries into electronic databases. The population size is relatively small, though a strength of this 'real-world' series is the ability to provide a true reflection of stage of presentation and outcome, as often patients of advancing age or poorer performance status are excluded from prospective clinical trials.

The period of data collection for this study spanned over the Covid-19 pandemic which may have resulted in later stage at presentation, and fewer patients undergoing SACT, compared to non-pandemic times, though this is hypothesised rather than evidence-based in this setting.

The method of estimation for numbers of inoperable, non-metastatic patients who may be suitable for future RT trials applied here is crude, and based on an assumed fair performance status and absence of co-morbidities, which is necessary to undergo SACT. This has been applied as a surrogate for suitability for subsequent clinical trials, rather than specific inclusion/exclusion criteria. It is also based on current treatment paradigms, and may underestimate the numbers of patients

suitable or accepting of non-SACT based therapies, for example, definitive RT or upfront palliative RT alone, which is not currently standard of care. It will be necessary to re-evaluate potential numbers with specific trial design in mind.

2.5.5 Impact on clinical trial design

Based on the estimation of five non-metastatic, inoperable patients being suitable for oncological therapy or clinical trials each year in the SWW region (extrapolated from n=11 in a two-year period [section 2.4.6]), a multi-centre approach will be necessary for any future clinical trials evaluating this group. However, the estimated population served by SBUHB and HDHB combined is approximately 760,000, so numbers will likely be higher in other more populous regions. Nevertheless, efficient study design is vital, and a feasibility run-in period should be considered.

Subsequent trials should also bear in mind that medical co-morbidity is the most common reason to not undergo curative surgery, and consider this when designing cohorts, inclusion and exclusion criteria, as well as considering the intensity of trial treatment.

Rates of RT are generally low, with only 4 patients having radical intent RT (and 3 of these having GOJ tumours). Reasons for low RT use should be further explored, and the resulting lack of experience in gastric RT planning and delivery should also be considered when developing any UK gastric RT protocol.

2.6 Conclusion

In conclusion:

- Outcomes of patients with gastric and type III GOJ tumours are poor, and are worse in SWW than England.
- This retrospective data confirms that a small proportion of patients with stage I-III disease undergo surgery, and that this figure is lower in SWW than nationally, confirming that a substantial proportion of non-metastatic patients having palliative intent treatment from the outset, with significantly worse outcomes.
- RT rates are low, and reasons for this should be explored further.
- Due to relatively small numbers of patients with non-metastatic, inoperable disease who may be suitable for subsequent oncological therapies, any future clinical trials will need to be multi-centre to maximise recruitment.

Chapter 3

A Systematic Review of Gastric Radiotherapy in the Pre-operative, Definitive and Palliative Setting.

3. A Systematic Review of Gastric Radiotherapy in the Pre-operative, Definitive and Palliative Setting

3.1 Introduction

To inform and refine a specific hypothesis regarding the role of RT for IGC, it is imperative to understand the current literature regarding the efficacy of RT for gastric adenocarcinoma, safety of delivering RT to the in-situ stomach, RT doses and planning techniques in use internationally, and explore potential survival benefit in this context. Therefore, a comprehensive systematic review was performed to establish what evidence already exists, and the research questions that remain unanswered, to inform a future gastric RT trial.

3.2 Aims

The aims of this systematic review were to evaluate the current evidence for gastric RT in relation to:

- efficacy
- tolerability
- impact on quality of life
- RT technique, including dose fractionation schedules in use
- evidence of dose/response relationship of radiation for gastric adenocarcinoma
- explore the currently active international gastric RT clinical trials

3.3 Methods

3.3.1 Scoping Search

In order to minimise duplication of research effort and inform and refine the main search strategy, a scoping search was performed to establish the systematic reviews already published evaluating gastric RT. A PubMed (Medline, Embase, Epistemonikos) search was performed on

4.1.2022 using the search terms 'stomach,' 'gastric,' 'cancer,' and 'radiotherapy.' Of 61 results, 35 records were excluded, and 27 systematic reviews +/- meta-analysis (describing the Preferred Reporting Items for Systematic reviews and Meta-Analyses [PRISMA] systematic methodology) were included for full assessment (Figure 3.1). The included reviews were then categorised by clinical context (Table 3.1).

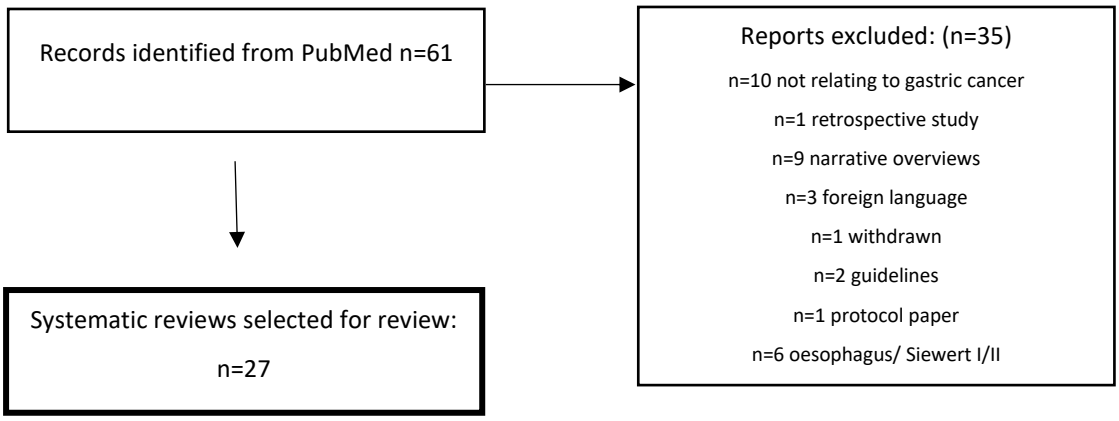


***Figure 3.1**. Scoping Search inclusion/exclusion*

Setting	**Number of published systematic reviews (all)**	**Number of reviews including formal meta-analysis**	**Publication date range**
Pre-operative[82]	1	1	2015-2019
Post-operative[83-90]	8	7	2013-2020
Pre- and Post-operative[91-97]	7	3	2002-2021
Pre-, Post- and Intra-operative[98-100]	3	3	2009-2014
Intra-operative[101,102]	2	1	2015-2017
Definitive	0	0	NA
Palliative[71,72]	2	2	2017-2020
Radiotherapy technique[103-106]	4	1	2016-2021
Total	**27**	**18**	NA

***Table 3.1**. Number of systematic reviews by clinical setting, number of published reviews and publication date*

Of the 27 systematic reviews identified by the scoping search, eight had been completed in the post-operative setting, including seven meta-analyses.[83-88,90] In the post-operative setting, RT is delivered following gastrectomy, thus the stomach and tumour are no-longer in situ, with treatment aimed at the surgical bed and elective lymph nodes. Therefore, the post-operative evidence base is of limited relevance in the pre-operative, definitive, and palliative setting, where RT is directed at the in-situ tumour and stomach. Given this, and the extensive evaluation of existing literature that has already been performed in the post-operative setting, it was decided to exclude post-operative RT from the future search strategy for this review.

There were no reviews of definitive intent gastric RT (i.e. non-surgical, oncological treatment with curative intent) – signifying a gap in the literature and important question for the main review.

Only two systematic reviews of palliative RT have been published, the most recent in 2020.[71,72] Both explored a range of doses, including low-dose fractionation schedules (defined in this section [3.3.1] below) but detailed description of RT technique was not provided. As several palliative RT studies have subsequently been published since the last systematic review, and the potential importance of higher-dose fractionation regimens for inoperable disease, high-dose palliative records were included in the subsequent main search (see definition of 'high-dose palliative' in this section [3.3.1] below).

Pre-operative studies offer the significant benefit of reporting pathological response rates, more accurate than clinical response rates which are usually based on imaging alone. Additionally, as pre-operative RT is given to the in-situ stomach, it is possible to evaluate feasibility of treating whole stomach volumes, relevant when considering treatment of inoperable disease. Only one systematic review and meta-analysis solely evaluating pre-operative gastric RT has been published to date (the others include pre- with peri- and post-operative treatment), which did not include any description or evaluation of the RT techniques used.[82] Given this, and that prior reviews are 3 years outdated, pre-operative studies were also subsequently included in the main search, though with specific questions around efficacy, safety, and RT technique in this context.

The range of dose/fractionation schedules described in the literature informed the definition of doses as follows for the subsequent review:

- Definitive studies were defined as those delivering ≥45Gy BED10 (BED10 = biologically effective dose, $\alpha/\beta=10$) to non-metastatic disease

- High-dose palliative studies were defined as having the primary aim of local/symptom control, including only ≥30Gy BED10 (as predominately mixed/ low-dose regimens have been analysed by previous systematic review).
- Pre-operative studies including any dose/fractionation (Gy/#).

3.3.2 Main Search Strategy

The main review was registered with PROSPERO (CRD42022297080, date of registration 15.2.2022) and performed in accordance with PRISMA standards.[107]

Electronic databases MEDLINE (OVID), EMBASE (OVID) and The Cochrane Library were searched using a combination of text terms and relevant controlled vocabulary described in Supplementary materials (Appendix 3.1). Duplicate results were identified using EndNote and manually excluded. Following the initial search (10.3.2022) and data extraction, an updated search was performed on 27.3.2023. Web of Science (Clarivate) was used to conduct forward citation tracking for a sample of included studies. Meeting proceedings from the American Society of Clinical Oncology (ASCO), American Society of Radiation Oncology (ASTRO) and European Society for Radiotherapy and Oncology (ESTRO) for the 2 years preceding the search date were manually searched.

3.3.3 Eligibility Criteria

Following pilot screening of 3000 titles, additional inclusion/exclusion criteria were applied to further refine the selected titles (original and final eligibility criteria are listed in Appendix 3.2). Clinical studies published in English, after 1.1.1998, of any design, reporting external beam RT (EBRT) to the primary tumour in patients with gastric or Siewert III GOJ adenocarcinoma in the definitive (≥45Gy BED10), high-dose palliative (≥30Gy BED10), or pre-operative setting (any dose/#) were included. Papers that also included Siewert I/II or oesophageal tumours were permitted, providing outcome data for the gastric/type III GOJ cohort were specifically reported. Only abstracts published in previous 2 years, reporting novel data, not subsequently published in full text format were included.

Exclusion criteria included non-carcinoma (e.g. lymphoma), studies only reporting the post-operative setting, RT techniques other than EBRT (e.g. intraoperative RT brachytherapy), case series of <5 patients, book chapters, letters, editorials and in-vitro studies.

To fully appraise the current status of published literature relating to gastric RT, and for cross-reference of citations, systematic reviews (reporting recognised methodology) were retained for separate evaluation, though their results were not collated with that of the selected original studies presented in this review.

3.3.4 Selection process

Citations were uploaded to Covidence systematic review online software, where all titles and abstracts were screened by the principal reviewer (Dr Amy Case, AC). Any records with potential to meet the eligibility criteria were retained for full text review, prior to final inclusion or exclusion. A second reviewer (Dr Sarah Gwynne, SG) independently reviewed all full text titles for which eligibility was deemed uncertain by principal reviewer, plus a random sample of 10% of included and excluded titles. Any discrepancy was discussed between both reviewers to reach a conclusion. Risk of bias assessment was performed (AC) using the most appropriate JBI (Joanna Briggs Institute) checklist for the study type (section 3.4 and Appendix 3.3).[108]

3.3.5 Data collection

Basic data extracted from eligible papers included demographics, study design and patient characteristics. RT data collected included dose/fractionation, RT technique such as modality (e.g. 3D-CRT, IMRT), definition of GTV, CTV or PTV and description of image guidance used. Survival, toxicity and quality of life (QOL) data was also collected. A comprehensive list of data points is available in Appendix 3.4. Data was collated in an Excel spreadsheet by study type (i.e. definitive/palliative/ pre-operative).

3.3.6 Clinical trial registry search

In order to explore the future direction of gastric RT research, and to evaluate the scope of clinical trials currently active, but that may have not yet reported, a search of the following clinical trials registries was performed; clinicaltrials.gov, the World Health Organisation (WHO) International Clinical Trials Registry Platform (ICTRP) and the International Standard Randomised Controlled Trial Number (ISRCTN) registry. Initial date of searches was 21.06.2023, with searches updated on 1.8.2024.

Using the search terms “gastric cancer” and “RT,” 199 titles were retrieved from clinicaltrials.gov and 81 from ICTRP. No relevant trials were identified on the ISRCTN registry. The

following types of study were excluded from further evaluation; post-operative RT trials, current status defined as “completed,” “unknown” (for >10 years), “terminated” or “suspended”, duplicate records, studies not primarily recruiting gastric cancer patients, and studies deemed irrelevant (for example, not investigating external beam RT, or only including oesophagus and GOJ). Additionally, the respective registries must have provided some study updates in at least the last 10 years to suggest they remained active for the study to be included.

3.4 Results

The PRISMA flow diagram (Figure 1) summarises the screening process.[109] A total of 12,436 records were screened and 2509 assessed for eligibility. Following full text review, 11 definitive, 21 high-dose palliative and 20 pre-operative studies were selected for final analysis. To appraise the current status of published literature relating to gastric RT, systematic reviews (reporting recognised methodology) were retained for separate evaluation, though their results were not collated with that of the selected original studies presented in this review. Reports describing RT technique retained by the overarching search to inform technique for future trials will not be discussed further in this chapter, but are shown on the PRISMA diagram for completeness given their inclusion in the search criteria.

A high number of studies met the initial inclusion criteria in the pre-operative setting (n=56). The primary aim of the review of the pre-operative evidence base was to evaluate efficacy via pathological complete response (pCR) rate, safety, and RT technique. This data is most accurately described in prospective clinical studies, with lack of detailed patient level RT data (for example, detail regarding dose/fractionation) presented by retrospective institutional studies and national database reviews (e.g. analysis of the Surveillance, Epidemiology and End Results Program [SEER], or American National Cancer Database [NCDB]). Given this, and the high number of prospective pre-operative studies identified by the search (compared to a relative paucity of prospective evidence in the palliative and definitive setting), only the 20 prospective pre-operative clinical trials providing detailed efficacy, safety and RT technique data were selected here for full evaluation.

No previously published systematic reviews of definitive CRT for inoperable GC were identified during our search. In the palliative setting, this review encompasses an additional 10 papers to those evaluated by the most recent review by Viani *et al.* in their 2020 meta-analysis. [71]

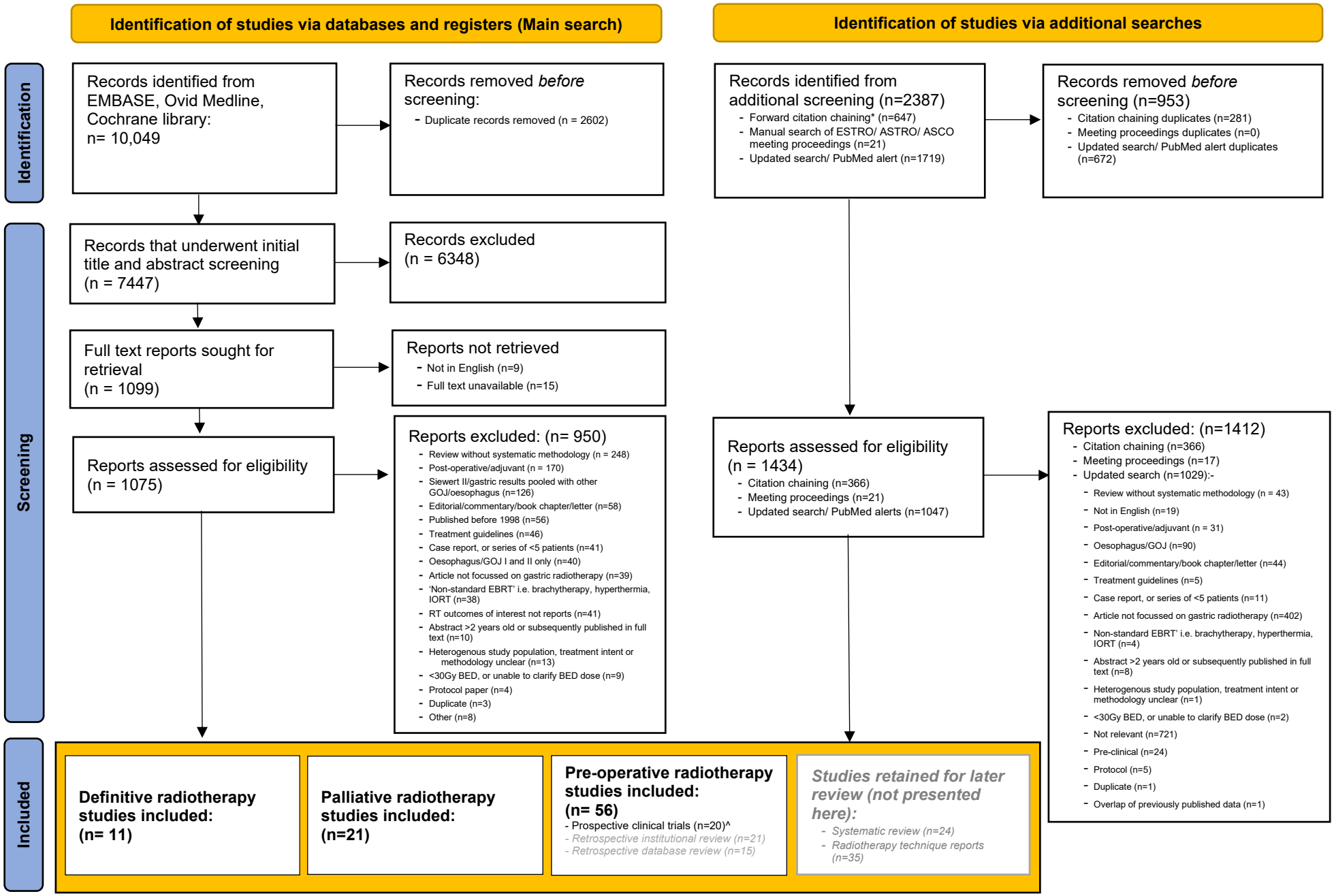


Figure 3.2. *PRISMA 2020 flow diagram showing screening process for initial and additional searches, the latter including citation chaining, manual searches of meeting proceedings and updated search results. *Forward citation chaining was conducted on all selected definitive and neoadjuvant titles. ^20 prospective clinical studies underwent full text review.*

Risk of bias assessment was carried out on all selected papers. At present, there is no consensus regarding the optimal, validated tool for critical appraisal of non-randomised studies. Therefore, each selected study was critically appraised by AC using the most appropriate JBI tool for the study design.[108] Studies scoring ≥7 points were deemed low risk of bias, 4-6 moderate risk, and <4 high risk of bias, (in line with scoring thresholds used by other authors).[110] Most studies were deemed low risk of bias (n=48/52), four moderate risk, and none high risk – thus all were included in the final analysis. Detailed risk assessment tables are available in Appendix 3.3.

3.4.1 Definitive setting (i.e. ≥45Gy BED10, non-metastatic disease)

Of the 11 selected definitive studies, 10 studies representing 549 patients, of whom 354 underwent RT (the remainder randomised to no RT), were included for analysis, summarised in Table 3.2.[111-120] Nine are non-randomised. The eleventh selected study, a retrospective review of RT for non-metastatic, inoperable stage I-III of the NCDB database was included for separate analysis and discussion given its significant population size, but has not been analysed with the 10 selected definitive studies due to inclusion and pooling of palliative doses in the results.[74]

3.4.1.1. Treatment regimens

Dose/fractionation is similar across studies, with 9 of 10 delivering between 45Gy-50.4Gy in 25-28# (BED10 = 52.1-59.4Gy), with treatment completion rates of 81-100%. Two studies report a boost of 5.4Gy/3# to a GTV boost volume (after 45Gy/25# to PTV).[111,113] However, definition of RT volumes were inconsistent with no two studies reporting the same target volumes (Appendix 3.5). Of seven studies that provided detail, five included an elective regional LN volume. 3D-CRT was the most common treatment planning modality (n=6) followed by IMRT (n=4). Only 1 study reported image-guided RT (IGRT) technique, stipulating deep inspiration breath-hold (DIBH), stomach filling protocol and twice weekly cone-beam CT (CBCT).[111] All studies permitted concurrent chemotherapy with RT; four also allowed induction, and two post-operative chemotherapy. SACT varied across studies, but all included either 5FU, taxane or platinum (either single agent or in combination).

Study details		Patient population				Treatment details			
First Author (Year of publication)	**Study type**	**Total no. of patients (no. planned for RT)**	**% Gastric /GOJ**	**Patient Characteristics**	**M Stage**	**Radiotherapy**	**% completing planned RT**	**Chemotherapy**	**% completing chemotherapy**
Liu *et al.* [111] (2017)	Phase 2, multicentre, single arm	36	100% gastric	n= 21 co-morbid unsuitable for surgery n =8 unresectable disease n = 7 refused surgery	M0	45Gy/25# + 5.4Gy/3# boost	86%	Induction mDCF x2 cycles Concurrent weekly docetaxel 20mg/m^2 x6 Adjuvant mDCF x 2cycles	97% induction (n=35/36) 86% concurrent (n=30/35) 75% adjuvant (n=27/30 who underwent CRT)
Wydmanski *et al.* [112] (2014)	Phase 2, single centre, single arm	13	100% gastric	n= 6 (46.2%) refused surgery n= 7 (53.8%) CI to anaesthesia	M0	45Gy/25# over 5 weeks	92.3%	Concurrent 5FU (bolus infusions 325mg/m^2 D1-5, 29-33)	38% (of n=5 having chemotherapy 100% completed)
Safran *et al.*[113] (2000)[a]	Phase 2, multicentre, single arm	27	100% gastric	Unresectable or borderline resectable n=6 tumours >10cm length n= 6 medical CI to surgery n=1 T4 disease n = 6 coeliac LNs n= 7 retroperitoneal LNs	M1 (n=7) RPLN, portal or mesenteric LN permitted	45Gy/25# + /- 5.4Gy/3# boost (if inoperable, n=12)	99%	Concurrent Paclitaxel (50mg/m^2, weekly for up to 6 weeks)	89%
Chen *et al.* [114] (2022)	Prospective, randomised trial (Phase NS), single centre	74	100% gastric	Stage II-IIIC, must have refused or have contra-indications to surgery	M0	45Gy/25# over 5 weeks	NS	All patients: concurrent oxaliplatin (130mg/m^2 q21) and tegafur (40mg/m^2 BD 14 days, q21) + For Group B (n=34): Propranolol 10-60mg BD	NS
Xing *et al.*[115] (2012)	Phase 1 (investigating MTD docetaxel), multicentre	21	100% gastric	Unsuitable for resection due to advanced T/N stage or medically CI. n=10 T4 severe adjacent invasion n = 6 Bulky nodal metastases n= 5 Both T4 and bulky N	NS	50.4Gy/28#	NS	Concurrent Cisplatin (20mg/m^2 weekly) Docetaxel (5mg/m^2 – 15mg/m^2 in increments of 2.5mg/m^2 per dose level)	NS
Leong *et al.*[116] (2003)[a]	Prospective data collection as part of a pilot toxicity/feasibility study, single centre	26 (n=8 CRT)	62% Gastric[b], 38% GOJ/cardia[b]	2 cohorts: Group 1 (n=18) = Post-operative RT following R0 resection. Group 2 (n=8) = Locally advanced, not suitable for surgical resection due to tumour size/invasion of adjacent structures/ advanced locoregional LN involvement/ medically unsuitable for surgery	M0	45Gy/25# over 5 weeks	81%[b]	Induction ECF x1 cycle Concurrent 5FU continuous infusion (225mg/m2/day 7 days per week throughout entire period of RT) Adjuvant ECF x2 cycles[c]	n=1 failed to completed concurrent 5FU/adjuvant ECF n=2 failed to complete adjuvant chemotherapy
Dong *et al.*[117] (2018)	Prospective case series, non-randomised, single centre	194 (n=31 CRT)	91.2% gastric[b] 8.8% gastric cardia and GOJ[b]	n=59 locally advanced, MO, could not undergo radical resection, or residual disease/local recurrence after radical resection, of which 31 had CRT n= 94 organ mets n= 41= distant LN mets	M0 = 30%[b] M1 = 70%[b]	45-50.4Gy/25-28# over 5-6 weeks	NS	For CRT both sequential chemo or concurrent CRT were permitted (regimens NS)	NS
Mizrak Kaya *et al.*[118] *(*2018)[d]	Retrospective case series, single centre	71 (n=57 CRT)	60.6% gastric, 39.4% GOJ III	Technically operable patients who did not have surgery due to: n=34 (47.9%), medical co-morbidity[b] n= 14 (19.7%) poor performance status[b] n=23 (32.4%) patient choice.[b]	M0	Median dose 45Gy (range 36-50.4)	NS	Induction (46.5%) or concurrent (33.8%) FU +/- platinum. 19.7% had chemo alone[b]	NS

Taki *et al.*[119] (2017)	Retrospective case series, single centre	21	100% gastric	n=14 unresectable local recurrence n=2 unresectable primary locally advanced n=5 inoperable primary due to poor general condition	M0	50Gy/25# over 5 weeks	100%	Concurrent TS-1 (80mg/m2) daily 4 weeks, q42, n=15 OR 5FU 250mg/m2 + cisplatin 5mg/m2 d1-5, 8-12, 15-19, 22-26 n=5	n=1 radiotherapy alone Chemotherapy discontinued due to leucopenia n=9
Suzuki *et al.*[120] (2012)[d]	Retrospective case series, single centre	66	45.5% gastric, 54.4% GOJ III	Reasons for no surgery: n=20 (30.3%) Stage IV before CRT, 8 positive peritoneal cytology, 6 with T4 disease, 6 local RPLN) n=17 (25.8%) co-morbidities, n= 5 (7.6%) patient choice, n= 22 (33%) too frail and or tumours too bulky for surgery, who developed predominantly peritoneal mets **after** CRT (and n=2 died during CRT)	M0= 77.3% (n=51) M1 = 22.7% (n=15)[e]	45Gy/25# over 5 weeks or 50.4Gy/28#	NS	Induction (62.1%, regimen NS) Concurrent (100%) FU +/- taxane or platinum	NS
Studies combining definitive and palliative doses[a]									
Li *et al.* [74] (2018)[f]	Retrospective NCDB review	4795 (n=1479 CRT)	100% gastric	Non-metastatic, inoperable stage I-III disease	M0	Median dose 45Gy (IQR 43.2-50.4Gy)	NS	n= 947 concurrent n= 524 sequential (regimens not stated)	NS

Table 3.2. *Study characteristics of selected definitive radiotherapy studies*

CI = Contra-indication, LN = lymph nodes, NS= not stated, NA = not applicable, RPLN = retroperitoneal lymph node. mDCF = Docetaxel 37.5mg/m2 d1 and 8, cisplatin 25mg/m2 d1-3, and 5FU 750mg/m2/24h d1-d5 q3 weeks. ECF = epirubicin 50mg/m^2 d1, cisplatin 60mg/m2 d1, 5FU 200mg/m2/day infusion continuously.

[a] Permitted patients to proceed to surgical exploration.

[b] Data quoted relates to whole study population (not just CRT cohort)

[c] A small number of patients had 5FU 425mg/m2/day and leucovorin 20mg/m2/day for 5 days in place of ECF pre and post radiation n=2/8.

[d] Potential overlap between case-series. Suzuki et al. have previously reported on a subset of the patients reported by Mizrak Kaya et al. (both studies from MD Anderson)

[e] Patients with positive peritoneal washings but no gross peritoneal disease permitted.

[f] Displayed with 'definitive' studies as reports on patients with non-metastatic, inoperable disease, treating up to 50.4Gy. However, palliative intent dose regimens also included in study, and results pooled. Therefore, considered separately from other "definitive" studies in this review.

3.4.1.2 Outcomes

Median overall survival (mOS) ranged from 11-26.4 months, shown in Table 3.3. Clinical complete response (cCR) rate ranged between 12-45%, with 6 studies reporting cCR>20%, and overall response rate (RR, i.e. complete + partial response) between 37.5 – 83%.

A significant relationship between clinical response and OS was reported by four studies. *Liu et al.* reported a longer OS for patients achieving cCR than those who did not (median not reached vs 17.7 months p=0.004).[111] Similarly, Suzuki *et al*. reported mOS of 30.7 months following cCR vs 10.6 months if <cCR, with cCR only statistically significant variable on multivariate analysis.[120] Two further studies report cCR a statistically significant prognostic factor on uni/multivariate analysis. [112,118]

Two studies compared chemotherapy alone to CRT. Dong *et al.* reported 1 yr OS of 21.4% and median survival time of 7.5 months following chemotherapy alone vs 32.3% and 11 months for CRT (p=0.038).[117] Of note, they also showed a statistically significant benefit with the addition of RT in the metastatic cohort; 1 yr OS 23.4% chemo alone vs 40.8% CRT, and MST 6.6 months vs 10 months respectively (p=0.04). Mizrak Kaya *et al.* also compared chemo alone to CRT – mOS was 2.2 years for patients treated with combined CRT and 1.6 years for those who did not receive RT (HR 0.62), with multivariate analysis confirming that RT as part of treatment was related to longer OS (p=0.05).[118]

Study details			Response			Survival			Toxicity (CTCAE criteria)		
First Author (Year of publication)	**No. of patients**	**BED10Gy range**	**cCR (%)**	**cPR (%)**	**SD (%)**	**mOS**	**1 year OS**	**3-year OS**	**G3/4 Gastrointestinal**	**G3/4 Haematological**	**Mortality/ cause**
Liu *et al.*[111] (2017)	36	53.1 – 59.5	n=13/36 (36%)	n=17/36 (47%)	n=4/36 (11%)	25.8 months	NS	42%	G3/4 nausea = 31% (n= 11)[a] G3/4 vomiting =26 % (n=9)[a] G3/4 anorexia = 17% (n=6)[a] G3/4 diarrhoea = 3% (n=1)[a]	G3/4 neutropenia = 14% (n=5)[a] G3/4 lymphopenia = 40% (n=14)[a] G3/4 thrombocytopenia = 6% (n=2)[a] G3/4 febrile neutropenia = 6% (n=2)[a]	Nil
Wydmanski *et al.*[112] (2014)	13	53.1	n=5/12 (41.7%)	n=1/12 (8.3%)	n=2 (16.7%)	17.1 months	59%	48%	G3 nausea/vomiting = 7.7% (n=1) G4 GI toxicity = 0	G3/4 lymphocytopenia = 92.3% (n=12)	n=1 (7.7%) cause uncertain
Safran *et al.*[113] (2000)	27	53.1 – 59.5	n=3 (12%)[b]	n=12 (44%)[b]	n=7 (26%)[b]	11 months[#]	52%	NS	G3 esophagitis/gastritis = 15% (n=4)[c] G4 = 11% (n=3)[c] G3 nausea/vomiting 19% (n=5)[c] G4 = 0[c] G4 anorexia = 4% (n=1)[c] G3 diarrhoea 4% (n=1)[c]	G3 neutropenia = 4% (n=1)[c] G3 thrombocytopenia = 8% (n=2)[c] G4 haematological = 0[c]	Nil
Chen *et al.*[114] (2022)	74	53.1	n=12 (16%)[b]	n=29 (39%)[b]	n=24 (32%)[b]	NS	NS	NS	G3/G4 gastrointestinal = 2.7%[b]	G3/G4 bone marrow suppression =0[b]	NS
Xing *et al.*[115] (2012)	21	59.5	n=6 (28.6%)	n=8 (38.1%)	n=4 (19%)	NS	NS	NS	G3 nausea/vomiting = 4.8% (n=1) G4 GI toxicity = 0	G3 neutropenia =14.3% (n=3) G4 neutropenia= 4.8% (n=1)	Nil
Leong *et al.*[116] (2003)	26 (n=8 CRT)	53.1	n=1 (12.5%)	n=2 (25%)	NS	NS	NS	NS	G3 GI toxicity = 25% (n=2)	G3/4 haematological = 25% (n=2)	Nil
Dong *et al.*[117] (2018)	194 (n=31 CRT)	53.1 – 59.5	NS	NS	NS	11.1 months[d]	32.3%[d]	NS	G3/4 gastrointestinal = 20.6%[b]	G3/4 leukopenia = 24.5%[b] G3/4 granulocytopenia = 31.4%[b] G3/4 thrombocytopenia = 2.9%[b]	Nil[#]
Mizrak Kaya *et al.*[118](2018)	71 (n=57 CRT)	NS (Median dose 45Gy)	n= 32 (45%)	NS	NS	26.4 months[d]	NS	NS	NS	NS	NS
Taki *et al.*[119] (2017)	21	60	n=5 (23.8%)	n=9 (42.8%)	n=3 (14.2%)	19.8 months	NS	NS	NS	NS	NS
Suzuki *et al.*[120] (2012)	66	53.1 – 59.5	n=23 (34.8%)	NS	NS	14.5 months *(MO)* 16.8 months *(M1)*	NS	22.6%[b]	NS	NS	n=1 myocardial infarction n=1 septic shock
Studies combining definitive and palliative intent/doses[¤]											
Li *et al.* [74] (2018)	4795 (n=1479 CRT)	NS (Median dose 45Gy)	NS	NS	NS	12.3 months *(CRT)* 11.3 months *(chemo)*	NS	NS	NS	NS	NS

***Table 3.3**. Outcome data for the selected definitive papers. Toxicity reported according to CTCAE grading (Common Terminology Criteria for Adverse Events).*

cCR= Clinical complete response (includes pathological response when stated), cPR= clinical partial response, SD = stable disease, mOS= median overall survival, G3/NS= not stated. LAGC CRT = locally advanced gastric cancer, chemoradiotherapy. [a] toxicity to concurrent CRT section of treatment stated. [b]result refers to all patients in study across all groups (For Safran et al. also includes those who underwent subsequent surgery.) [c] CALGB criteria used to grade toxicity. [d]results refers to the cohort with local advanced GC who underwent CRT.

3.4.1.3 Toxicity

Most common grade 3-4 (i.e. G3 severe, G4 life-threatening) toxicities as reported according to Common Terminology Criteria for Adverse Events (CTCAE) criteria were nausea/vomiting, with the proportion of patients experiencing G3-4 nausea/vomiting across studies ranging from 2.7-31%, neutropenia (0-14.3%), and lymphopenia (24.5% - 92.3%). Late toxicity was reported by two papers; Liu *et al*. n=2 (n=1 duodenal ulcer, n=1 gastric ulcer) and Leong *et al.* n=1 (G3 enteritis which occurred 4 months after completion of CRT).[111,116] A total of 3 deaths during CRT were recorded across all studies (0.5% of 549 patients) though none were directly attributed to treatment by the study authors.[112,120] Dong *et al.* reported G3/4 gastrointestinal toxicity in 20.6% of patients following CRT compared to 17.4% after chemotherapy alone, finding no statistically significant difference (p=0.571).[117]

3.4.1.4 Quality of life (definitive setting)

Quality of life (QOL) was reported in only 1 study, within which QOL data was presented for 16 patients, with high global scores post treatment (median 91.7) measuring using the validated European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire.[111]

3.4.1.5 Mixed definitive/palliative intent review

The NCDB retrospective review of 4,795 patients with stage I-III un-resected, non-metastatic GC patients who did not undergo surgery, compared chemotherapy alone (n=3,316, 69.2%) vs CRT (n=1,479 30.8%), with a median dose of 45Gy.[74] They reported mOS of 11.3 months and 2yr OS with chemotherapy alone vs 12.3 months and 28.3% for CRT (p<0.001). Median survival for those who received <45Gy was 9 months vs 14.3 months for those who received >45Gy (p<0.001). Of note, on multivariate analysis, receipt of CRT was a significant predictor for improved OS.

3.4.2 High-dose Palliative Setting (i.e. primary aim of local/symptom control, ≥30Gy BED10)

Twenty-one studies were selected, representing a total of 955 patients who underwent palliative intent RT (summarised in Table 3.4).[121-141] All are non-randomised, and only two are prospective (1 phase II, 1 phase I). Of 19 observational studies, 18 are retrospective reviews, 17 of which are single centre series. The vast majority of studies originate from East Asia, >50% from Japan, with only 2 studies evaluating RT in a Western population.

Study populations represent a high proportion of patients with metastatic disease (18 studies report >50% with M1 disease), with nearly all reporting a highly symptomatic population at baseline. Bleeding was an index symptom for 100% of patients in over 70% of selected studies, and median baseline haemoglobin (Hb) ranged from 5.1-9.0.

Haemostasis was the primary outcome measure in 16 of the 21 studies, though definition of bleeding control varies widely, with some studies defining response as reduction in blood transfusion (BT) requirement (generally over a 4-week period), some using improvement in Hb as a surrogate measure, and others reporting subjective symptom improvement (Appendix 3.6). Survival outcomes and toxicity were frequently reported secondary outcomes, though local control rates were not commonly measured in this population.

Study details			Patient population					Primary outcome measure	Treatment delivered		
First Author (Year of publication)	**Study type**	**Site**	**Total no. of patients**	**% Gastric /GOJ**	**M Stage**	**Performance status (PS)**	**Patient characteristics**		**Radiotherapy dose/fractionation (or median dose if not stated)**	**Median dose $BEDGy_{10}$ (range)**	**Concurrent Chemotherapy % (regimen)**
Prospective clinical trials											
Tey *et al.* [121] (2019)	Phase II, single arm	Singapore	50	Gastric 100%	74% M1	PS 1-2 = 90%, PS 3-4 = 10%	100% had bleeding as index symptom, n=2 pain, n=1 obstruction	Haemostasis	36Gy/12#	48.6Gy	Not permitted
Yoshikawa *et al.* [122] (2009)	Phase I	Japan	9	Gastric 100%	22% M1	PS 0-1 = 100%	100% had symptoms of pain or obstruction	Tolerability of concurrent chemotherapy	Up to 45Gy/25#	NS	100% (paclitaxel and cisplatin)
Observational studies											
Saito *et al.*[123] (2022)	Multicentre prospective observational study	Japan (15 centres)	55	Gastric 100%	76% M1	PS 0-2 = 75% PS 3 = 25% (PS 4 excluded)	100% bleeding, with Hb <8. Median baseline Hb 6.2	Haemostasis	8Gy/1# (21%) 20Gy/5# (32%) 30Gy/10# (38%)	28Gy	NS
Takeda *et al.*[124] (2022)	Retrospective review, multicentre	Japan (4 centres)	117	Gastric 97.5%	75.8% M1	NS	Evaluated patients who had RT for bleeding Median baseline Hb 8.2	Haemostasis	30Gy/10# (64.2%) 20Gy/5# (19.2%)	39Gy (7.8-60Gy)	11.7% (NS)
Yagi *et al.* [125] (2023)	Retrospective cohort study, single centre	Japan	48 (n=25 RT cohort)[a]	Gastric 100%	NS	PS 0-1= 56%, PS 2-3 = 44%	100% had either endoscopically confirmed bleeding, symptoms of bleeding or need for BT. Median baseline Hb 9.4	Haemostasis	39Gy/13# (52%) 30Gy/10# (24%) 36Gy/10# (8%) 50Gy/25% (4%) 24Gy/8# (4%) 15Gy/5# (4%)	NS	NS
Katano *et al.*[126] (2022)	Retrospective cohort study, single centre	Japan	23	Gastric 100%	87% stage IV	PS 0-2 = 100%	100% had symptoms such as bleeding or obstruction. Median baseline Hb 9	Haemostasis	30Gy/10# (52%) 20Gy/5# (43%) 8Gy/1# (4%)	39Gy[b]	13% (SOX or FOLFOX)
Sugita *et al.* [127] (2022)	Retrospective review, single centre	Japan	33	Gastric 100%	85% stage IVB	PS 0-2 = 85% PS 3-4 = 15%	100% endoscopically confirmed bleeding. Median baseline Hb 6.3	Haemostasis	30Gy/10# (76%) 20Gy/5# (12%) 20Gy/10# (3%) 18Gy/6# (3%) 8Gy/1# (3%) 6Gy/2# (3%)	39Gy[b]	NS
Kawabata *et al.*[128] (2022)	Retrospective review, single centre	Japan	20	Gastric 100%	45% M1	PS 2 = 30% PS 3-4 = 70%	100% endoscopically confirmed bleeding. Median baseline Hb 6.2	Haemostasis	30/10# (80%) 10.5Gy/3# (5%) 15Gy/5# (5%) 20Gy/5# (5%)	39.9Gy (14.1-39.9Gy)	0
Yu *et al.* [129] (2021)	Retrospective review, single centre	Korea	61	Gastric 100%	67.2% M1	PS 0-2 =31.1% PS 3-4 =68.9%	100% endoscopically confirmed bleeding. Median baseline Hb 7.1	Haemostasis	Median dose = 30Gy (range 12.5-50Gy)	39Gy (16-60Gy)	0
Lee, J *et al.* [130] (2021)	Retrospective review, single centre	Korea	57	Gastric 100%	87.7% M1	PS 1-2 =82.4% PS 3-4 =17.5%	100% endoscopically confirmed bleeding. Median baseline Hb 6.6	Haemostasis	25Gy/5# (29.8%) 20Gy/5# (24.6%) 30Gy/10 # (22.8%) 45Gy/25# (5%)[d]	37.5Gy (23.6-58.5Gy)	17.5% (NS)
Mitsuhashi *et al.* [131] (2021)	Retrospective review, single centre	Japan	28	Gastric 100%	53% stage IV	PS 0-2 = 57%, PS 3-4 = 43%	Evaluated patients who had RT for bleeding.	Haemostasis	30Gy/10# (60%) 40Gy/20# (21%) 20Gy/5# (4%)[e]	NS	10.7% (S-1 and CPT-11)

Sasaki *et al.* [132] (2020)	Retrospective cohort study, single centre	Japan	36	Gastric 100%	100% M1	Ps 0-2 = 100%	100% had bleeding, pain or obstruction. N=18 had received prior anti-PDL1 therapy before RT	Response of primary tumour to RT, after prior anti-PD1 therapy	30Gy/10#	39Gy [b]	NS
Hiramoto *et al.* [133] (2018)	Retrospective review, single centre	Japan	23	Gastric 100%	91.3% M1	PS 0-2 =95.7% PS 3-4 =4.3%	All exhibited bleeding (n=18) and/or obstruction (n=10)	Haemostasis, Response of RT for obstruction	Median 42Gy/20# (range 30-60Gy/ 10-30#)	50.8Gy [b]	43.5% (cisplatin + 5FU n=8, 5FU+ methotrexate n=1, S-1 n=1)
Lee, Y *et al.* [134] (2017)	Retrospective review, single centre	Korea	42	Gastric 100%	83.3% M1	PS 1-2= 81%, PS 3-4 = 19%	All had evidence of bleeding	Haemostasis	Median = 39.6Gy (range 14-50.4Gy) Median # = 20 (7-28)	46.9Gy (16.8-60Gy)	16.7% (5FU+ leucovorin)
Mizrak Kaya *et al.*[135] (2017)[c]	Retrospective cohort study, single centre	USA	101	Gastric/ GOJ III = 29.7%	100% M1	NS	All had metastatic disease. 25.7% subsequently underwent surgery after CRT	OS	Median = 50.4Gy (range 45-65Gy)	NS	100% (5FU + platinum OR taxane)
Tey *et al.* [136] (2014)	Retrospective review, single centre	Singapore	115	Gastric 100%	67.8% M1	PS 0-2 =90.4% PS 3-4 = 9.6%	All required at least 1 symptom such as bleeding (n=103), pain (n=11) or obstruction (n=17)	Symptom response (bleeding, pain, obstruction)	30Gy/10# (40%) 36Gy/12# (33%) 20Gy/5# (16.5%) 40Gy/16# (4%) 8Gy/1# (2.6%)[f]	39Gy	0
Choi *et al.* [137] (2012)	Retrospective review, single centre	Hong Kong	28	Gastric 100%	64.3% M1	PS 1-2=75%, PS 3-4= 25%	All had evidence of low-grade GI bleeding, and all except n=2 required BT prior to RT. Median baseline Hb 6.9	Haemostasis	30Gy/10# (82.6%) 22.5Gy/5# (28.6%) 32.5Gy/13# (4.3%) 40Gy/20# (4.3%)	39Gy [b]	0
Asakura *et al.* [138] (2011)	Retrospective review, single centre	Japan	30	Gastric 100%	96% M1	PS 0-2 = 60%, PS 3-4 = 40%	All required BT, 87% symptomatic of melaena or haematemesis. Median baseline Hb 5.1	Haemostasis	30Gy/10# (90%) 27Gy/9# (7%)[g] 21Gy/7# (3%)[g]	NS	40% (S1+cisplatin n=6, S-1 n= 1, methotrexate + 5FU n= 2, 5FU n= 2, paclitaxel n=1)
Lee, J *et al.* [139] (2009)	Retrospective review, single centre	Korea	23	Gastric 100%	87% M1	PS 1-2= 74%, PS 3-4= 26%	100% endoscopically confirmed bleeding	Haemostasis	Median 30Gy/10# (range 30-44Gy/ 10-22#)	39Gy [b]	NS
Hashimoto *et al.*[140] (2009)	Retrospective review, single centre	Japan	19	Gastric 100%	100% Stage IV	PS 1-2 = 79%, PS 3-4 = 21%	Median baseline Hb 5.4	Haemostasis	40Gy/16# (53%) 20Gy/10# (10%) 50Gy/25# (5%) 40Gy/20# (5%) 35Gy/14# (5%)[h]	50Gy	21% (5FU+cisplatin n=1), S-1 n=1, paclitaxel n=1, 5FU + methotrexate n=1)
Kim *et al.* [141] (2008)[c]	Retrospective review, single centre	USA	37	Gastric 100%	73% M1	NS	54% bleeding, 43% dysphagia, 19% pain	Symptom control	Median 35Gy/14# (range 20-36Gy)	41Gy (25-41Gy)	65% (most commonly fluoropyrimidine)

Table 3.4. *Study characteristics of selected palliative studies.*

BT = Blood transfusion, OS = overall survival, QOL = quality of life, NS= not stated. CPT-11 = camptothecin-11. Hb stated in g/dL.

[a] Cohort comparing surgery to RT, n=25 of 48 patients underwent RT, n=23 had palliative surgery. [b] Not directly stated but median BED10 calculated from stated median total dose/#.

[c] Potential overlap between patient populations recruited from same centre with cross over of dates of inclusion/recruitment to study. [d] 10 other dose/# regimens listed in publication, each n=1, not listed here. [e] 4 other dose/# regimens not listed in table, of patients whom could not complete the schedules 24 Gy/12# (4%), 34/17 (4%), 36/18 (7%). [f] 3 other dose regimens not listed in table 37.5Gy/15# (1.7%), 30 Gy/12# (0.8%), 35Gy/14# (0.8%). [g] Represent patients who could not complete planned 30Gy/10#. [h] 4 other dose/# not listed in table: 27Gy/9# (5%), 18Gy/9# (5%), 7.2Gy/4# (5%), 2Gy/1# (5%).

3.4.2.1 Treatment regimens

A total of 38 different dose/fractionations were reported across studies, most commonly 30Gy/10# (n=12), 20Gy/5# (n=8), or 8Gy/1# (n=4), with >80% describing at least 3 different dose/fractionation regimens within their study. Most studies reported median dose BED10 ≥39Gy (87.5%, n=14 of 16 studies providing this data).

There is significant variation in target volumes, with two studies treating whole stomach, five partial stomach (i.e. gross tumour plus CTV/PTV margin) and eight allowing either approach (Appendix 3.7). Only two included regional lymph nodes in the treatment field. Of studies describing RT technique, APPA (n=8) or 3DCRT (n=8) were most commonly used, with only one study allowing IMRT. Assessment of motion during RT planning is becoming increasingly common, with some form described by 50% of studies published since 2020 (n=5/10), but only 27% prior (n=3/11). Methods for assessment of respiratory motion include 4DCT (n=3) and 3-phase planning CT taken in varying phases of respiration (n=1), with stomach motion evaluated via simulation with barium contrast (n=1) or direct fluoroscopy (n=1).

RT completion rates are high, ranging from 68-100%, though 9 of the 10 studies report completion rates in excess of 80%.

3.4.2.2 Outcomes

Symptom response rates are summarised in Table 3.5. Overall bleeding response rates ranged from 59.6 – 95%, with 11 of 16 studies reporting response rates of >70%. Re-bleeding rates ranged from 11-60%. Several studies (n=8) report statistically significant reductions in BT requirement post RT, including some striking differences, for example Asakura *et al.,* who reported mean BT volume of 2236ml pre- to 273ml post-RT.[124,126-129,131,138,139] Five papers reported increase in Hb post-RT (range 1.8 – 3.4 g/dl).[127-130,139]

Median OS from date of RT ranged from 2.7 – 5.2 months (excluding the Mizrak Kaya *et al.,* study, which quoted mOS from diagnosis of 41.5 months[135]). Median re-bleeding free survival ranged from 1.5 -11.9 months. Improvement in other symptoms, such as pain or obstruction ranged from 45.5-100% and 52.9-100% respectively.[121,122,133,136,141]

Five studies reported a significant association between bleeding control and survival.[121,127,130,134,136] The largest of these, by Tey *et al.,* (n=115 patients) reported the mOS of RT responders was significantly longer than for non-responders (47 vs 113.5 days, $p<0.001$).[136] This was

echoed by Lee *et al.,* who demonstrated median OS for responders of 16.6 weeks vs 5.1 weeks for non-responders.

Several studies reported improved outcomes when RT was combined with chemotherapy. Asakura *et al*. reported a 3-month cumulative incidence of re-bleeding of 60% with RT alone vs 17.5% with CRT [138]. Three studies found the addition of chemotherapy to RT a statistically significant prognostic factor on multivariate analysis, of which Yagi *et al*. report mOS of 6.5 months for RT + CT vs 1.6 months for RT alone [125,127,129]. Kim *et al.* reported a trend in improvement in mOS with addition of SACT to RT, 6.7 months CRT vs 2.4 months RT alone, with CT not increasing toxicity significantly (G3 = 15% RT alone vs 21% CRT)[141].

Study details			Symptom response rates (as defined by each paper, see supplementary materials, appendix 6)				Radiological/ pathological response	Survival (months)		Toxicity		
First Author/ Year of publication	**No. of patients**	**Median BED10Gy (range)**	**Bleeding**	**Re-bleeding**	**Other bleeding endpoints**	**Other symptom endpoints**		**mOS**	**Median bleeding free survival***	**G3-4 Gastrointestinal**	**G3-4 Haematological**	**Mortality (cause)**
Prospective clinical trials												
Tey *et al.* [121] (2019)	50	48.6	80%	NS	Median duration of response = 3.4 months (in responders)	100% pain response. 100% obstruction response	NS	2.7	NS	Overall G3 toxicity =5% (n=1 gastritis, n=1 anorexia)	0	0
Yoshikawa *et al.* [122] (2009)	9	NS	NS	NS	NS	100% pain response 89% obstruction response	NS	NS	NS	G3 anorexia n=1, G3 nausea n=1, G3 vomiting n=1, G3 esophagitis n=1,	G3 neutropenia n=1, G3 anaemia n=1, G4 thrombocytopenia n=1	n=1 (Pneum-onia and DIC)
Observational studies												
Saito *et al.* [123] (2022)	55	28	69% (PP = 90% at 8 weeks)	32%	Mean duration of response = 2.3 months.	NS	NS	3.8	NS	G3 anorexia = 2%[a]	0	0
Takeda *et al.* [124] (2022)	117	39 (7.8-60)	59.6% (77.8% in those followed up >4wks)	NS	Mean volume of BT before RT= 716ml, after RT = 230ml (p0.0001)	NS	NS	3.7	NS	Overall ≥G3 = 5%. G3 anorexia n=5. G4 GI perforation n=1	NS	0
Yagi *et al.* [125] (2023)	48 (n=25 RT cohort)[b]	NS	88%	40%	NS	NS	NS	4.9[b]	NS	0[b]	0[b]	0[b]
Katano *et al.* [126] (2022)	23	39[c]	NS	NS	83% had reduced BT requirement after RT. Mean units transfused decreased from 4.2 to 1.7. No difference in mean Hb before vs after RT.	70% pain and obstruction symptom response	NS	3.9	NS	0	0	0
Sugita *et al.*[127] (2022)	33	39[c]	73%	21%	Mean Hb 6.3 pre-RT vs 9.7 post-RT (p=0.0001). 91% required BT pre-RT vs 24% post-RT.	NS	NS	3.7	4.9	0	0	0
Kawabata *et al.* [128] (2022)	20	39.9 (14.1-39.9)	95%	11%	Mean Hb 8.0 pre-RT vs 9.8 post-RT. Mean units transfused decreased from 6.8 pre-RT to 0.6 post-RT	NS	NS	NS	11.9	G3 anorexia n=1	NS	n=1 (GI perforat-ion)
Yu *et al.* [129] (2021)	61	39 (16-60)	88.5%	35.2%	Hb at 1, 2, 3 months post-RT higher than pre-RT (p<0.001). Average daily BT requirement decreased post-RT from 217ml pre-RT to 4ml post-RT (p<0.001)	NS	NS	4.8	6	G3 Nausea = 1.6%	0	0
Lee, J *et al.* [130] (2021)	57	37.5 (23.6-58.5)	75.4%	60% (at 3 months)	Mean Hb 6.6 pre-RT vs 9.7, 10.3 and 9.7 immediately, 1- and 2-months post-RT (p<0.001)	75.4% subjective symptom improvement in melaena/ haematemesis.	PR = 24.3% SD = 64.9%	NS	1.5	0	0	0

Mitsuhashi *et al.* [131] (2021)	28	NS	NS	NS	No significant decrease in Hb 4 weeks post-RT. No patients required BT within 4 weeks of RT. One year BT free survival = 69%	NS	NS	NS	NS	0	0	n= 1 (Haemor-rage)
Sasaki *et al.* [132] (2020)	36	39[c]	NS	NS	NS	"Palliation of symptoms" =77.8% anti-PDL1 exposed, 66.7% anti-PDL1 naïve (p=0.71)	PR = 28% anti-PDL1 exposed vs 0% anti-PDL1 naïve (on CT)	NS	NS	0	0	0
Hiramoto *et al.* [133] (2018)	23	50.8[c]	88.8%	NS	NS	80% obstruction response	NS	3.9	3.4	0	0	0
Lee, Y *et al.* [134] (2017)	42	46.9 (16.8-60)	69%	37%	Median time to palliation of bleeding = 15 days	NS	NS	2.9	3.4	0	0	0
Mizrak Kaya *et al.*[135] (2017)[d]	101	NS	NS	NS	NS	NS	NS	41.5 (gastric cohort)	NS	NS	NS	NS
Tey *et al.* [136] (2014)	115	39	80.6%	NS	Mean net % relief of bleeding = 92%[e]	52.9% partial response of obstruction (net % relief 85.6%[e]) 45.5% partial response of pain (net % relief 91.3[e])	NS	2.8	3.2	Overall = 3% (G3 N+V n=1, G3 gastritis n=1, G3 anorexia n=1)	0	0
Choi *et al.* [137] (2012)	28	39[c]	65.2%	NS	NS	NS	NS	2.2	2.0	0	0	0
Asakura *et al.* [138] (2011)	30	NS	73%	50%	77% had improvement in melaena/ haematemesis. Mean BT volume 1 month pre-RT 2236ml vs 273ml post-RT (p<0.0001)	NS	NS	3.6	2.6	G3 bleeding (late) n=1	G3 leucopenia n=3 G4 leucopenia n=1 G4 thrombocytopenia n=1	0
Lee, J *et al.* [139] (2009)	23	39[+]	91%	NS	Mean Hb 9.1 before RT vs 10.6 after RT (p<0.001). Mean BT units 1 month pre-RT 9.5 vs 2.8 post-RT (p<0.001)	NS	NS	4.0	NS	0	0	0
Hashimoto *et al.* [140] (2009)	19	50	68%	NS	NS	50% response rate in improving dysphagia and oral intake	NS	3.4	1.5	G3 nausea n=1 G3 anorexia n=3	G3 anaemia n=9[f] G3 leucopenia N=2 G4 anaemia n=6	0
Kim *et al.*[141] (2008) [d]	37	41	70%	NS	70% had bleeding controlled without need for additional intervention	81% dysphagia response 86% pain response Median duration of control of pain/dysphagia 6.2 months	NS	5.2	11.4	*RT alone:* G3 nausea n=2 *CRT:* G3 nausea n=2 G3 dehydration n=1	*CRT:* G3 neutropenia n=2	0

Table 3.5. *Outcomes of palliative papers.*

N+V = nausea and vomiting, NR = not recorded, PP = per protocol, BT = Blood transfusion

[a] Radiation related adverse events quoted. [b] Cohort comparing surgery to radiotherapy, n=25 of 48 patients underwent RT, n=23 had palliative surgery. The results stated in the table relate to the radiotherapy cohort only. [c] Not directly stated but median BED10 extrapolated from stated median total dose/#. ¤ Phase I, therefore primarily focussed on toxicity data rather than efficacy.

[d] Bleed free survival relates to those who had initial haemostatic response to RT. Therefore, this figure can be longer than the mOS, the latter also including those who did not have a response to RT.

[e] 'Percent net symptom relief' was defined as the ratio between duration of symptom relief and duration of survival multiplied by 100'. [f] 10 patients had G3 anaemia at start of RT

3.4.2.3 Dose/response rate

There was variation across studies regarding a RT dose-response relationship, summarised in Appendix 3.8. Six studies [123,126,127,130,131,133] found no association between RT dose and symptom response/haemostatic effect, compared to five that did [124,129,134,140,141]. The latter all delivered a higher median BED of ≥39Gy. The largest, Takeda *et al.*, (n=117), reported haemostatic control rate of 71.1% for those who received BED10 ≥39Gy vs 32.4% <39Gy [124]. Similarly, *Yu et al.* report statistically significant improvement in time to re-bleeding for doses >39Gy BED10 (19.3 vs 2.6 months). Lee *et al*. report BED10 ≥36Gy was significantly associated with bleeding control [129,134]. A higher dose of BED10 ≥ 50Gy was found to be correlated with treatment success by Hashimoto et al [140]. Though Tey *et al*. found no evidence of symptom response using a cut off median BED of 39Gy, they reported a trend for poorer LC with BED ≤39Gy [136]. Kim *et al*. reported inferior LC in patients treated with BED <41Gy, they did not find an association with OS. Conversely, Mizrak Kaya *et al*. reported longer OS for patients receiving <50.4Gy [135,141].

3.4.2.4 Toxicity

Overall, toxicity rates were very low, with nine studies reporting no ≥G3 toxicity, and G3 gastro-intestinal toxicity 5% or less in the others. Across all studies there were three deaths (0.3% of 955 patients); n=1 GI perforation, n=1 pneumonia, n=1 haemorrhage)[122,128,131].

3.4.2.5 Quality of life

Only one study reported QOL data in the palliative setting. Tey *et al.* demonstrated improvement in global health status at the end of RT in 44% of 36 patients who completed EORTC QLQ C30 assessment following treatment.[121] One month after RT, 63%, 31% and 50% of patients experienced improvement in fatigue, nausea/vomiting and pain subscales, though there was notable drop off in completion rates with only 16 of 38 patients completing the subsequent QOL assessment.

3.4.3 Pre-operative

The 20 selected pre-operative prospective studies represent 617 patients, of which 537 underwent pre-operative RT for resectable gastric cancer, including three small, randomised studies,[142-144] and nine phase II single arm studies (Table 3.6)[67,145-152]. Though all relatively small studies (range 9-43 patients), they represent the broadest population of all settings, with 50% including Western patients (from Europe/North America).

Study Details			Treatment details		Outcome			CTCAE radiotherapy / chemoradiotherapy gastrointestinal toxicity		
First author (Year)	**Study type**	**No. of patients**	**Radiotherapy Total dose/#, duration (Median BED10)**	**Systemic therapy details**	**pCR**	**pPR**	**mOS**	**Grade 3 GI**	**Grade 4 GI**	**Mortality**
Randomised studies										
Wang *et al.*[142] (2021)	Randomised controlled trial (pre-operative CRT vs post-operative CT)	60 (n=30 pre-op CRT arm)	45Gy/25#, 5 weeks (BED10 = 53.10 Gy)	-Concurrent (XELOX) x2 cycles -Adjuvant (XELOX) x4 cycles	16.7%	60%	NS	G3 nausea n=5 G3vomiting n=2 G3 diarrhoea n=2	Nil	Nil
Saeidi *et al.* [143] (2014)	Randomised controlled trial (pre- vs post-operative CRT)	25 (n=12 pre-op CRT arm)[a]	45Gy/25#, 5 weeks (BED10 = 53.10 Gy)	-Concurrent (cisplatin + 5FU) x 2 cycles -Adjuvant (ECX) x3-4 cycles	NS	NS	13.4 months	G3/4 non-haematological GI n=4	n=2	n=2
Wang *et al.*[144] (2022)	Phase II, randomised, single centre (pre-op CRT vs CT)	75 (n=38 pre-op CRT arm)[a]	45.1Gy/22# [40Gy + 5.1Gy SIB to PGTV] (BED10=54.20Gy)	- Concurrent S-1 daily - Adjuvant (oxaliplatin + S-1) 4-6 cycles	13.8%	24.1%	NR	G3 nausea n=2 (5.3%) G3 anorexia n=2 (5.3%) G3 gastritis n=2 (5.3%) G3 oesophagitis n=3 (7.9%)	Nil	Nil
Single arm, phase II trials										
Tang *et al.*[145] (2022)	Phase II, single arm, single centre	36	45Gy/25#, 5 weeks (BED10 = 53.10 Gy)	- Induction (XELOX + camrelizumab) x1 cycle - Concurrent (Capecitabine + camrelizumab), daily) - Post RT (XELOX+ camrelizumab)) x1 cycle - Adjuvant (XELOX) x4 cycles	35.3%[b]	35.3[b]	NR	G3 nausea n=1	Nil	Nil
Liu *et al.*[146] (2017)	Phase II, single arm	36	45Gy/25#, 5 weeks (BED10 = 53.10 Gy)	-Induction (S-1 + oxaliplatin) x 1 cycle -Concurrent (S-1) X 1 cycle -Post-RT (S-1 + oxaliplatin) x 1 cycle -Adjuvant (S-1 + oxaliplatin) x 4 cycles, then S-1 for 1 year	13.9%	36.1%	30.3 months	Nil	Nil	Nil
Michel *et al.*[147] (2014)	Phase II, parallel single arm studies, multi-centre	42	50Gy/25#, 5 weeks (BED10 = 60.00 Gy)	- Induction (FOLFIRI) x4 cycles - Concurrent 5FU infusion	8.6%	NS	26.4 months	G3/4 digestive toxicities = 4.8%		Nil
Trip *et al.*[148] (2014)	Phase I/II, single arm, multi-centre	25	45Gy/25#, 5 weeks (BED10 = 53.10 Gy)	-Concurrent (carboplatin + paclitaxel) weekly x5	16%[c]	52%[c]	15 months	G3 oesophagitis n=1 (4%) G3 anorexia n=1 (4%) G3 nausea n=1 (4%)	Nil	Nil
Rivera *et al.*[149] (2011)[d]	Phase II, single arm, multi-centre	17	45Gy/25#, 5 weeks (BED10 = 53.10 Gy)	-Induction (cisplatin + irinotecan) x 2 cycles -Concurrent (cisplatin + irinotecan) x4 weekly	0%	NS	12.8 months[b]	G3/4 asthenia 44%	N=2[b] (18%)	n=2 (18%)
Rivera *et al.*[150] (2009)[d]	Phase II, single arm, multi-centre	23	45Gy/25#, 5 weeks (BED10 = 53.10 Gy)	-Induction (cisplatin + irinotecan) x 2 cycles -Concurrent (cisplatin + irinotecan) x4 weekly	8%[b]	NS	12.8 months[b]	NS	NS	n=1 (9%)
Wydmanski *et al.*[151] (2007)	Phase II, single arm	40	45Gy/25#, 5 weeks (BED10 = 53.10 Gy)	-Concurrent (5-FU +/- leucovorin) x2 cycles -Adjuvant (5-FU + leucovorin) x4 cycles	17.5%	20%	NR	G3 vomiting n=1	Nil	Nil
Ajani *et al.*[67] (2006)	Phase II, single arm multi-centre,	43	45Gy/25#, 5 weeks (BED10 = 53.10 Gy)	- Induction x2 cycles (5FU infusion, cisplatin) - Concurrent (5FU infusion 5 days/week, paclitaxel weekly)	26%	NS	23.2 months	G3 anorexia n=3 G3 diarrhoea n=5 G3 oesophagitis/ gastritis n=3 G3 dehydration n=8 G3 N+V n=13	G4 anorexia n=3 G4 diarrhoea n=1 G4 vomiting n=1	Nil

Klautke *et al.*[152] (2004)	Phase II, single arm, single centre	21	50.4Gy/28# (45Gy/+ 5.4Gy boost to primary tumour) (BED10 = 59.47 Gy)	- Concurrent (5FU + cisplatin OR paclitaxel + cisplatin) x2 cycles	14%	62%	13 months (18 months R0, vs 10 months R1/not operated)	Nil	Nil	Nil
Phase I trials										
Matsuda *et al.*[153] (2014)	Phase I, single centre	9	40Gy/20#, 4 weeks (BED10 = 48.00Gy)	-Concurrent (S-1 + cisplatin, escalating dose levels) x 1 cycle -Post RT (S-1 + cisplatin) x 1 cycle	11.1%[e]	44.4%[e]	NS	G3 nausea n=1 G3 diarrhoea n=1	Nil	Nil
Takahashi et al. [154] (2011)	Phase I, single centre	10	40Gy/20#, 4 weeks (BED10 = 48.00Gy)	-Concurrent (S-1 + cisplatin, escalating dose levels) x 1 cycle -Post RT (S-1 + cisplatin) x 1 cycle	10%[e]	20%[e]	NS	Nil	Nil	Nil
Allal *et al.*[155] (2005)	Phase I, single centre	19	Level 1: 31.2Gy/26#, 2# per day, 5 days/week (BED10=34.94Gy) Level 2: 38.4Gy/32# (BED10=43.01Gy) Level 3: 45.6Gy/38# (BED10=51.07Gy)	-Induction x1 cycle -Concurrent x 1 (cisplatin, 5FU infusion, leucovorin)	5%	42%	NS	G3/4 N+V n=1 (5%) G3/4 mucositis n=7 (37%)	Nil	Nil
Prospective, single arm studies, phase not specified										
Chung *et al.*[156] (2013)	Prospective feasibility study, single arm	9	45Gy/25#, 5 weeks (BED10 = 53.10 Gy)	-Concurrent x2 (cisplatin, S-1) -Adjuvant (S-1 or 5FU derivative)	14.3%[e]	28.6%[e]	NS	NS	NS	Nil
Rostom *et al.*[157] (2013)	Prospective feasibility study, single arm.	41	45Gy/25#, 5 weeks (BED10 = 53.10 Gy)	-Induction (5-FU infusion, cisplatin, docetaxel) x2 cycles -Concurrent (5-FU infusion + docetaxel)	21.4%[b]	46%	27.8 months	G3 anorexia n=4 G3 dehydration n=9 G3 oesophagitis n=3 G3 gastritis n=1 G3 nausea n=7 G3 vomiting n=4	G4 anorexia n=2 G4 vomiting n=2	Nil
Inoue *et al.*[158] (2012)	Prospective feasibility study, single arm	12	50Gy/25#, 5 weeks (BED10 = 60.00 Gy) Dose reduction to 40Gy permitted if adverse events.	-Concurrent S-1 x2 cycles	8.3%[e]	66.7%[e]	NS	G3 anorexia n=2 G3 nausea n=2	Nil	Nil
Ajani *et al.*[159] (2005)	Prospective, single arm	41	45Gy/25#, 5 weeks (BED10 = 53.10 Gy)	- Induction x2 cycles (5FU infusion, cisplatin, paclitaxel) - Concurrent (5FU infusion 5 days/week, paclitaxel weekly)	20%	15%	NR	G3 anorexia n=1 G3 mucositis n=1 G3 N+V n=11 G3 dehydration n=1 G3 pain on eating n=2	G4 N+V n=1 G4 dehydration n=2 G4 pain on eating n=3	n=1
Ajani *et al.*[66] (2004)	Prospective, single arm, multi-centre	33	45Gy/25#, 5 weeks (BED10 = 53.10 Gy)	- Induction x2 cycles (5FU infusion, leucovorin, cisplatin) - Concurrent (5FU infusion 5 days/week)	30%	24%	33.7 months	G3 dehydration n=2 G3 anorexia n=1 G3 N+V n=3	Nil	n=2

Table 3.6. *Selected prospective pre-operative studies – study characteristics, treatment regimen and key outcomes.*

NS= not stated. NR= not reached. N=V = nausea + vomiting, FOLFIRI = 5-FU, leucovorin, irinotecan. ECX = epirubicin, cisplatin, capecitabine. CRT = chemoradiotherapy. CT = chemotherapy. XELOX = Oxaliplatin, capecitabine. [a] Results for pre-operative cohort stated [b] Where study included GOJ, gastric only outcomes are denoted with [b]. [c] Becker classification, grade 1a, no residual tumour deemed pCR, grade 1b <10% residual tumour and grade 2 10-50% residual tumour pooled for pPR. [d] Rivera at all have presented two cohorts of patients – but no cross over was identified between cohorts, thus both are presented here (2009 cohort were deemed resectable upfront, whereas 2011 cohort unresectable upfront). [e] Where JGCA pathological response criteria were used, grade 3 (no residual tumour) was classed as pCR, and grade 2 (between 2/3rds and entire tumour affected by degeneration or necrosis) was classed a pPR. [f] study follow-up duration 36 months.

3.4.3.1 Treatment regimens

All studies prescribed between 40 - 50.4Gy (with the exception of one dose escalation phase I study which prescribed 31.2-45.6Gy), with 45Gy/25# the most prescribed RT regimen in the pre-operative setting (n=13, 65%). All gave concurrent chemotherapy, with 5-FU or derivatives being administered in 85% of studies, and doublet regimens (66%) more common than single agent regimens (33%). One study evaluated the addition of immunotherapy to concurrent CRT.[145] There is a divide in approach regarding RT target volumes, with 50% describing a whole stomach-based volume, and 45% a GTV-based geometric expansion (Appendix 3.9). However, elective lymph node volumes are frequently included, described in 70% of studies. Three studies base inclusion of nodal stations on location of primary tumour.[144,146,155] Two describe boosting the GTV (45.1-50.4Gy).[144,152] Motion management is poorly described, but in seven studies describing RT technique, fasting is the most common method of managing variation in stomach filling/position (n=4). RT treatment completion rate ranged from 53-100%, though 9 of 11 studies report completion rates >85%.

3.4.3.2 Outcomes

In the 19 studies reporting pathological response rates, pCR rate ranges from 0-35.3%, with 73.6% of studies reporting pCR>10%, and 21% reporting pCR> 20% . The highest pCR rate (35.3%) was seen in the study that combines immune checkpoint inhibition with CRT.[145] Partial response (pPR) ranged between 15-66.7%, though variation exists in grading systems used. mOS ranged from 12.8 months – not reached.

3.4.3.3 Toxicity

Rates of gastro-intestinal toxicity are very low, with nil G4 GI toxicity reported by 60% of studies, including the two studies delivering >50Gy. A total of eight deaths were reported across all 20 studies (1.3% of 617 patients), four of which were post-operative, two neutropenic sepsis and two cardiac causes. [66,143,149,150,159]

3.4.4 Currently active clinical trials

30 active clinical trials investigating RT for gastric cancer were identified – 25 from clinicaltrials.gov (Appendix 3.10) and five from ICTRP (Appendix 3.11), summarised by intent in table 3.7. There are no active clinical trials specifically investigating the role of definitive CRT for IGC. The vast majority of research is being undertaken in the pre-operative setting (n=21/30 studies, 70%), including three phase III RCTs enrolling a total of 1752 patients, with an additional three randomised phase II studies aiming to recruit an additional 499 patients.

Clinical setting/ treatment intent of trial intervention	Number of trials registered with clinicaltrials.gov	Number of trials registered with ICTRP
Definitive (i.e. radical) chemoradiotherapy	0	0
Pre-operative chemoradiotherapy	20	1
Radiotherapy for oligometastatic disease	4	0
Palliative radiotherapy (excluding SABR oligometastatic disease)	1	0
Intent not specified/ unclear	0	4
Total number of active, relevant clinical trials identified	**25**	**5**

Table 3.7. *Currently active clinical trials of radiotherapy for gastric cancer by clinical intent*

A dose of 45Gy in 25# is by far the most common dose under investigation, being delivered by all three phase III studies, further establishing this as the internationally accepted dose for pre-operative CRT. Approach to motion management and image guidance is sparsely described, though three studies do stipulate 4DCT, and one is investigating MR image guidance and a daily adaptive approach, suggesting a move towards more refined motion management for this group. Additionally, a study from the Netherlands aims to investigate the feasibility of fiducial markers for IGRT for pre-operative gastric RT.

There has been an explosion in the number of studies combining checkpoint inhibition with RT, which is being explored by 19 studies, the majority in the pre-operative setting. Four studies are evaluating the role of stereotactic RT for oligometastatic disease. Interest is growing regarding the role of hypofractionation, the subject of six studies, of which three are evaluating 25Gy/5#.

3.5 Discussion

3.5.1 Efficacy - *Is RT an effective local treatment for GC?*

This review has demonstrated the clear role of RT in managing the symptoms of advanced inoperable GC, with high rates of haemostatic response rates demonstrated here. However, most data relate to a largely metastatic, heavily pre-treated, symptomatic population for which RT was used reactively in response to symptoms, rather than pre-emptively, with focus on symptomatic relief rather than local control/survival benefit. Though it is currently unknown whether there is a role for pre-emptive RT in GC (i.e. with intention to reduce or delay the onset of symptoms), the phase III ROCS study, demonstrated that upfront palliative oesophageal RT almost halved upper GI bleeding events from 28% to 16% across the time period of the trial, and increased median time to GI bleeding from 49 to 65.9 weeks, raising the possibility that pre-emptive RT may also prove beneficial for local control in IGC. [160]

In the definitive setting, encouraging clinical complete response rates of up to 45% clearly signal the potential efficacy of CRT regimens (BED10>53Gy) for IGC in the non-metastatic population.

Impressive pCR rates of up to 35.3% in the pre-operative setting further support the efficacy of RT in providing effective local control. Whilst the recently published phase III TOPGEAR study (not included by this review due to the pooling of Siewert II tumours with gastric tumours), which compared pre-operative CRT (45Gy/25#) to peri-operative chemotherapy alone, did not report an overall survival benefit with the former, the pCR rate was doubled (17% CRT vs 8% chemotherapy alone), and major pathological response increased from 29% to 50% following CRT, further emphasising its efficacy as a local treatment.[68] The outcomes of further multicentre randomised controlled studies including CRITICS II are eagerly awaited.[70]

3.5.2 Efficacy - *Does addition of RT improve survival for inoperable GC?*

It is evident that though effective in managing symptoms, survival is short when low-dose RT (defined here as <30Gy BED10) is used reactively on occurrence of symptoms such as bleeding, in patients with advanced disease (2.7 – 5.2 months). However, haemostatic control is associated with improved survival – thus it is possible that RT given pre-emptively, as well as managing distressing symptoms, may confer a survival benefit.

In the definitive setting, there is data to suggest that upfront RT, particularly for those with non-metastatic disease, may improve OS compared to SACT alone (11-26.4 months) which may be further extended for those achieving cCR (up to 30.7 months). Induction chemotherapy followed by RT resulted in an impressive 41.5 month mOS in the gastric cohort presented by Mizrak Kaya *et al.,* superior to the 22.8 months achieved in the oesophageal group.[135] Nevertheless, this data is largely non-randomised, further highlighting the need for a randomised controlled trial of pre-emptive RT for inoperable disease.

3.5.3 Tolerability - *Is gastric RT well tolerated?*

The data presented here reveals very low rates of toxicity, with ≥G3 gastrointestinal toxicity of <5% following high-dose palliative regimens (BED10 28-50.8Gy), despite most studies using old-fashioned APPA techniques. In the post-operative setting, the adoption of modern RT techniques has seen reduction in ≥G3 toxicity (from 33% in INT0116 to 0-17%) in later phase 3 studies.[63,64,161]

Though gastrointestinal toxicity was slightly higher in the definitive studies (≥G3 up to 31%), this is likely in part due to combination with multiple chemotherapeutic agents - the highest rates were in studies delivering triplet regimens in addition to RT. Data regarding late toxicity of gastric radiation in the inoperable setting is lacking, likely due to the short overall survival of the patient population. Across all studies, only four reported late radiation toxicity, affecting a total of six patients; n=1 gastritis, n= oesophagitis, n= 1 G3 enteritis, n=1 G3 gastric bleeding, n=1 duodenal ulcer, n=1 gastric ulcer.[116,138,157]

Treatment completion rates are high, even in the definitive and pre-operative setting where high doses (BED10 up to 59.47Gy) are delivered to large volumes including elective regional nodes. This is echoed by TOPGEAR which reported 92% of patients completed the planned 45Gy/25# (BED10 = 53Gy).[81] Together this demonstrates the feasibility of delivering high BED10 regimens to volumes that include the entire stomach with acceptable rates of ≥G3 toxicity.

3.5.4 Does gastric RT affect quality of life?

Though prospective QOL data is sparse, high QOL scores reported by Liu *et al.,* suggest that QOL is not impaired, and may be improved by irradiation to the primary tumour, further fuelling the hypothesis that a proactive rather than reactive approach to RT in the inoperable setting would lead to prolonged maintenance of QOL for these patients. [111] Robust, prospective randomised QOL data is needed to address this question.

3.5.5. What is the optimal dose of RT for inoperable GC?

An important factor to consider when contemplating the optimal RT dose for IGC is that of dose-response relationship (Appendix 3.8). Six studies found no association between radiation dose and symptom response/haemostatic effect.[123,126,127,130,131,133] However, these studies are small (range 23-57 patients), and mostly deliver median BED10 of 39Gy or less. In contrast, five studies report a statistically significant relationship.[124,129,134,140,141] These studies all have higher median BED of ≥39Gy. The largest, Takeda *et al.,* which included 177 patients, reported haemostasis rate of 71.1% for those who received BED10 ≥39Gy vs 32.4% <39Gy.[124] A similar cut off was reported by Yu *et al.,* reporting statistically significant improvement in time to re-bleeding for doses >39Gy BED10 (19.3 vs 2.6 months), and by *Lee et al.,* who report BED10 ≥36Gy was significantly associated with bleeding control.[129,134] A higher dose of BED10 ≥ 50Gy was found to be correlated with treatment success by Hashimoto *et al.*[140]

It should be emphasised that the primary outcome of nearly all of these studies was haemostasis, with dose-response conclusions largely limited to bleeding control, rather than local control or survival. Data for the latter is sparse and conflicting. Though a study of 115 patients by Tey *et al.,* found no evidence of symptom response using a cut off median BED of 39Gy, they did find a trend for poorer local control with BED ≤39Gy.[136] This finding is supported by the NCDB review of >1400 patients which reported shorter mOS for patients who received<45Gy vs >45Gy (9 vs 14.3 months respectively, p<0.001). Conversely, whilst Kim *et al.,* report inferior local control in patients treated with BED <41Gy, they did not find an association with OS (6 months OS <41Gy 33 months vs 47 months ≥41Gy, p=0.43), and Mizrak Kaya *et al.,* reported longer OS for patients receiving <50.4Gy.[135,141]

Two previous meta-analyses of palliative gastric RT have reached conflicting conclusions regarding dose-response. In their review of 7 studies (n=291 patients), Tey *at al.,* report no difference in response rate of bleeding between high BED (≥39Gy) vs low BED (<39Gy) regimens.[72] In contrast, the later Viani *et al.,* review (11 studies, n=409 patients) report a significant relationship between BED10 and bleeding response (p=0.001), with a significantly worse response in the subgroup of studies with BED10 <30Gy.[71] However, again, these findings relate only to bleeding response in a co-morbid population.

Dose escalation above BED10=60Gy has not been investigated in the pre-operative setting by any randomised trials to explore either safety or any additional benefit to local control.

The high haemostasis rates achieved by low BED regimens, short, and lower-dose fractionation schedules remain appropriate for those with high disease burden, poor condition and

limited life expectancy. However, the large body of retrospective data demonstrating the safety and efficacy of high BED regimens in both the palliative and definitive setting, with many studies exceeding 50Gy BED10, has led many study authors to conclude that high BED schedules should be considered for those with lower disease burden/ better performance status. Nonetheless, the conflicting evidence regarding dose-response, and lack of randomised data means that the optimal RT schedule remains unclear for this group, and UK practice remains unchanged.

3.5.6 What is the optimal combination of RT with SACT?

Though RT offers excellent local control for inoperable disease, with local relapse rates as low as 9.5%, rates of distant recurrence are high (up to 70%), demonstrating the importance of optimal systemic therapy in combination with local treatment.[111,135] This is echoed in the curative setting, where local relapse following post-operative RT is in the region of 11%, but distant relapse rates are significant (27%).[64]

In the palliative setting, a number of studies reported improved outcomes when RT was combined with chemotherapy. Three studies found the addition of chemotherapy to RT a statistically significant prognostic factor on multivariate analysis, with Yagi *et al.,* reporting mOS for those having RT followed by chemotherapy of 6.5 months vs 1.6 months for RT alone.[125,127,129] Kim *et al.,* report a trend in improvement in mOS with the addition of chemotherapy to RT, 6.7 months CRT vs 2.4 months RT alone.[141] Additionally, they found that addition of chemotherapy did not increase toxicity significantly (G3 = 15% RT alone vs 21% CRT).

The role of consolidation RT following induction SACT has been explored in the metastatic setting. Hingorani *et al.,* reported on 97 patients (n=30 gastric); 53 underwent consolidation RT following 3 months of induction chemotherapy, 44 underwent chemotherapy alone, and showed a stark mOS benefit with addition of RT, 23.3months (RT group) vs 14 months (chemo alone), and increase in time to local progression of 17.4 vs 8.3 months respectively.[162] Mizrak Kaya *et al.,* also reported significantly longer OS (32.5 months vs 21.8 months) for those who had >3 month induction chemotherapy followed by RT, with shorter survival to those who did not receive any chemotherapy (12 months).[135] In summary, this data would support the addition of SACT to RT for patients suitable for systemic therapy.

For patients with advanced, HER2-negative GC, whose tumours express PD-L1 (CPD ≥1%), the addition of PD-L1 inhibition, is now SOC in the UK [30]. Two studies discussed here have reported impressive synergy between checkpoint inhibition and RT in GC; i) Neo-Planet, which reported pCR rate of 35.3% in the preoperative setting,[145] and ii) Sasaki *et al.* which measured RT response in 18

metastatic GC patients who had previously been exposed to anti-PDL1 compared to 18 who had not, reporting 70% reduction in tumour volume on CT scan in 28% of the anti-PDL1 group vs 0% in the anti-PDL1 naïve group, and 63% vs 0% endoscopic response.[132] Further evidence supporting the immunotherapy-RT combination pre-operatively is building – SHARED recently reported an even more impressive pCR of 42.1% after CRT + sintilimab, and the results of a significant number of other pre-operative IO-RT studies are eagerly awaited.[163]

Further data is needed to establish the optimal timing of RT in conjunction with chemotherapy, immunotherapy and other targeted therapies such as anti-HER2 therapy. Whether any molecular subtype of GC responds more favourably to RT than others remains unknown and should be investigated by future studies.

3.5.7 Limitations

The lack of randomised data is the biggest limitation of this body of evidence. The retrospective nature of most of this data, and high risk of selection bias (i.e. clinician selection of fitter patients with lower disease burden for higher BED regimens/ multimodality therapy, and lower BED regimens/ omission of SACT for those in poorer condition a possible confounding factor) renders it difficult to draw conclusions regarding dose-response relationship or optimal SACT regimen. Additionally, variation of the definition of primary outcome (e.g. haemostasis) limits comparison of RT response in the palliative setting, as does the heterogeneity in patient population across studies.

3.6 Conclusion

This systematic review of definitive, palliative and pre-operative gastric RT has demonstrated a significant body of largely non-randomised, observational evidence to support that RT is an effective treatment for primary gastric adenocarcinoma, which can achieve pathological complete response rates of up to 35.3% when combined with optimal SACT – highlighting high-dose RT as a potential treatment option for those with inoperable disease, who presently have no other curative treatment options.

This review has also shown that treating the whole in-situ stomach and elective lymph node volumes with RT doses of up to BED10=60Gy is safe and well tolerated using modern RT techniques, though international consensus regarding optimal RT technique, motion management and TVD is

lacking. In the absence of randomised data, the optimal RT dose in each setting remains unknown, and alternative dose fractionation schedules, particularly hypofractionation should be explored further.

Given the high propensity of gastric adenocarcinoma to metastasise, it is vital that RT is paired with personalised, optimal SACT to optimise outcomes. Future trials should explore possible synergy and timing of gastric RT in relation systemic treatment (such as immunotherapy and targeted therapies), as well as investigate RT response by molecular subtype, allowing treatment stratification in future studies, and identification of patients who may derive the most benefit from RT.

Though there are a growing number of clinical trials contributing to the evidence in the pre-operative setting, prospective studies exploring the role of high-dose RT for IGC remain non-existent – making this an important research question to explore in future randomised controlled trials.

Chapter 4

A Survey to Evaluate Clinical Oncologist Opinion and Practice of Gastric Radiotherapy in the UK

4. A Survey to Evaluate Clinical Oncologist Opinion and Practice of Gastric Radiotherapy in the UK

4.1 Introduction

Current UK Royal College of Radiologists (RCR) guidance recommends the consideration of gastric RT in either the post-operative setting, for selected high-risk patients who have not undergone optimal peri-operative SACT or surgical resection (i.e. less than D2 LND, or R1 resection), or in the palliative setting, where low-doses (such as 6-8Gy/1# or 20Gy/5#) are prescribed in response to symptoms, such as bleeding.[19,164] This is in line with the current body of evidence laid out in the preceding chapters, where the most randomised research to date has been conducted in the post-operative setting (section 1.3, Table 1.5). As current evidence supporting pre-operative, definitive or high-dose palliative RT largely consists of non-randomised, observational data (Chapter 3), the latter are not currently recommended for routine use in current UK guidance. This is in contrast to the US, where NCCN and American Radium Society (ARS) guidance lists pre-operative RT with 45- 50.4Gy/25-28# as an option for patients with inoperable, non-metastatic disease.[80,165]

Despite its inclusion in guidance, post-operative RT is anecdotally infrequently prescribed in the UK. This is thought largely due to clinician concerns relating to treatment toxicity and poor tolerance of gastric RT, dating back to the INT-0116 trial, which reported 33% G3 gastrointestinal toxicity following post-operative CRT, with 17% of patients failing to complete treatment.[161] However, this study was conducted in the era of 2D APPA RT planning techniques, with limited shielding of OARs (see section 1.2.3), likely contributing to toxicity rates. Despite subsequent RCTs, conducted in the era of more conformal IMRT techniques, reporting much lower rates of G3/4 toxicity, for example as low as 9% G3 nausea, 5% G3 vomiting and 14% G3 anorexia reported by CRITICS (section 1.3, Table 1.5), the legacy of the former INT-0116 study seemingly remains a significant concern for treating clinicians.[166] However, UK data to verify oncologist opinion and practice in this field is lacking.

Additionally, local SWW and national audit data described in Chapter 2 demonstrates that palliative RT is only prescribed in 10-20% of patients with GC (section 2.5.3). SWW data also demonstrated that RT was more commonly used in the context of Siewert III GOJ than gastric tumours. This is possibly owing to the inclusion of anatomically neighbouring Siewert I-II tumours in

oesophageal RT trials, thus increasing the evidence base as well as clinician familiarity and experience treating junctional tumours compared to their gastric counterparts.

However, despite seemingly low rates of gastric RT use in the UK at present, a UK case-series reporting three patients with IGC who experienced good local control and limited toxicity following RT with 45Gy/25#, raises the question as to how many other UK clinicians may occasionally prescribe high dose RT in the inoperable setting – a figure currently unknown. [167] Indeed, at present, there is a lack of evidence describing current patterns of gastric RT among UK clinicians, particularly relating to IGC. Though reasons for perceived low-uptake may include the limited evidence base, clinician apprehension regarding treatment toxicity, and lack of experience in gastric RT planning, evidence to support these hypotheses is currently lacking. However, understanding the current opinion of the oesophagogastric (OG) clinical oncology community is essential for the development of future trials, to ensure the clinical relevance and acceptability of research questions posed, enable concerns regarding treatment tolerability to be addressed, and develop necessary educational tools to support establishment of a novel gastric RT protocol.

4.2 Aims

The aim of this study was to establish current UK practice, clinician opinion and gastric RT technique, to help shape future clinical trial design and gastric RT protocol development.

There were 5 main areas of focus:

i. Oncologist opinion and current practice relating to pre-operative, definitive and palliative RT
ii. RT technique including gastric TVD, RT planning and dose/ fractionation.
iii. Oncologist experience in gastric TVD
iv. Educational resources and protocols currently being used in the UK or deemed essential for future development.
v. Opinion regarding the future of clinical trials of gastric RT for IGC in the UK.

4.3 Methods

An electronic questionnaire was developed for distribution to currently practicing UK OG clinical oncologists. Figure 4.1 provides an overview of study methodology. Swansea University Medical School (SUMS) ethics approval was granted (SUMS RESC 2022-0102) on 5.12.2022 prior to survey distribution.

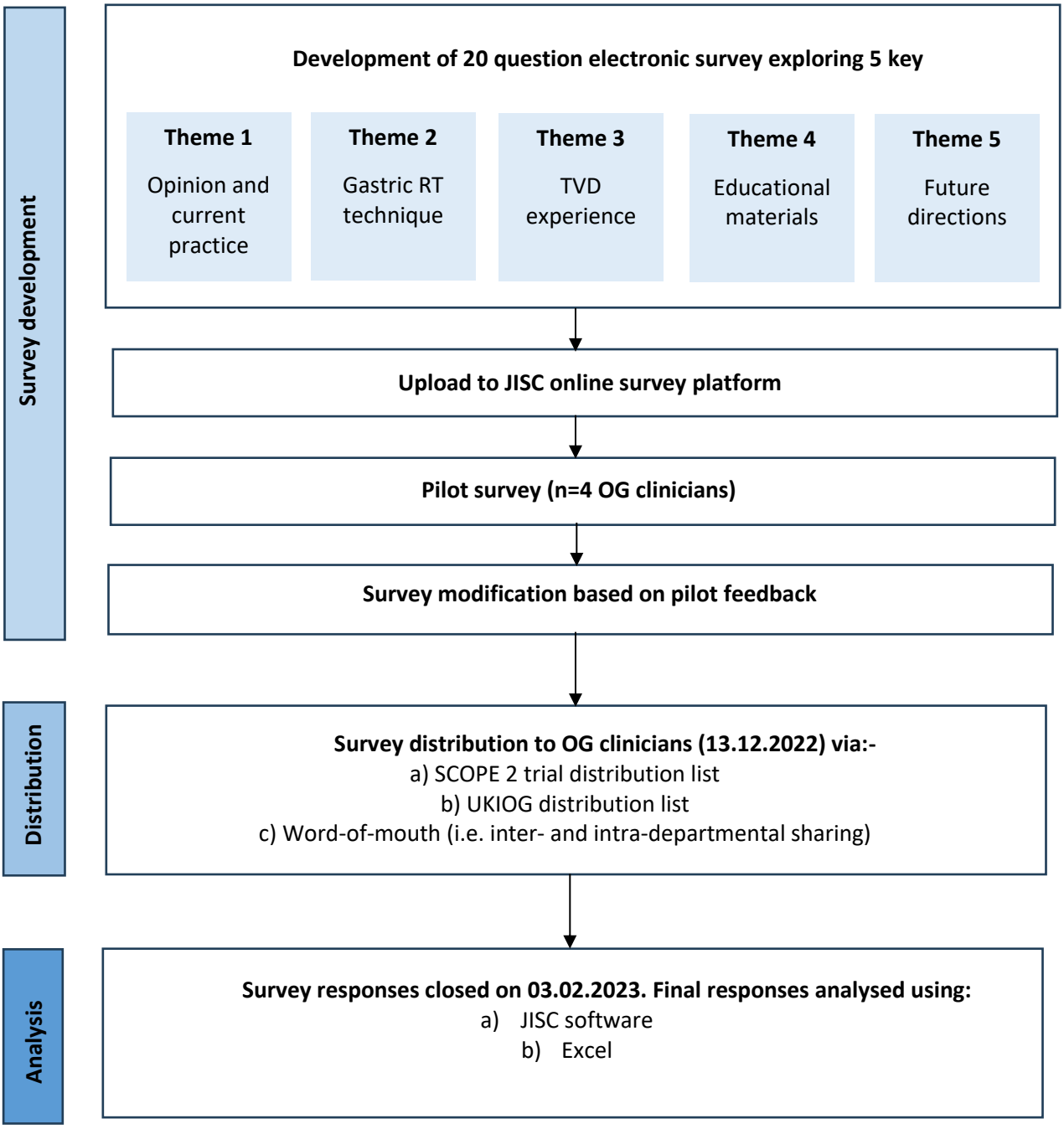


Figure 4.1. *Flow diagram summarising survey development, distribution and analysis. UKIOG = UK and Ireland Oesophagogastric Cancer Group*

4.3.1 Questionnaire design

A 20-question electronic survey was developed exploring five over-arching themes. Survey structure, number of questions and key areas explored by theme are summarised in Table 4.1. Questions were predominately closed-style with pre-defined options to minimise time-taken for completion, enhance response rates and allow descriptive analysis of the data. A small number of free text responses, particularly where 'other' was selected in response to closed questions, were included to further enhance feedback. A full copy of the survey is available in Appendix 4.1

Theme	**Number of questions**	**Key areas explored**
Consent	1	• Confirmation of consent (see PIS Appendix 4.2)
Demographics	1	• Number of years prior experience treating OG cancer
Theme 1 - Current practice and clinician opinion	3	• Respondents asked to rate their agreement of RT as a treatment option in post-operative, pre-operative, definitive and palliative setting (1= strongly disagree, 5= strongly agree) • Frequency of gastric RT use in last 3 years • Reasons for infrequent use
Theme 2 - RT technique	10	• Dose/# schedules in use • Use of concurrent SACT • Gastric RT TVD protocols in current use • Prior experience delineating duodenum as OAR • RT planning technique in use (2D,3D-CRT, IMRT/VMAT) • Simulation and image-guidance technology in use, or desired for future trials
Theme 3 - Oncologist experience in gastric TVD	1	• Confidence in accurate TVD of a post-operative, or pre-operative/definitive gastric RT plan (rated 1= not at all confident, 10= extremely confident)
Theme 4 - Supportive educational materials	1	• Most useful educational tools to support gastric TVD
Theme 5- Future directions	2	• Clinician support of a future clinical trial of definitive CRT (Y/N) • Approximate number of patients meeting potential trial inclusion criteria each year
Consent to further contact	1	• Option to indicate interest in taking part in development of future gastric RT protocol (e.g. TVD of a test case)

Table 4.1. *Summary of key areas and number of questions by theme. For full survey see Appendix 4.1*

Prior to answering the specific survey questions, participants were required to give their consent (question 1). A URL link to the Participant Information Sheet (PIS) was attached to the consent statement (see Appendix 4.2).

Theme 1 aimed to ascertain the clinical settings in which there was currently the most agreement for the use of RT, with opinion relating to gastric and Siewert III GOJ tumours indicated separately to allow comparison of RT use between anatomical sub-sites. Reasons relating to infrequent use of RT were explored, to identify main barriers or concerns that may be relevant to future trial design.

Theme 2 aimed to define range of dose/fractionation schedules in use across the UK, including concurrent SACT. Treatment modality, planning techniques and image-guidance currently available across centres was also explored, to understand technology currently in use, and what may need to be developed/mandated to ensure optimal technique within a clinical trial. Information regarding current gastric RT protocols in use to aid TVD was also collected, largely to inform whether particular protocols are consistently favoured by UK clinicians and inform protocol development for a subsequent trial. In this section clinicians were also asked their prior experience of duodenal delineation (e.g. from other tumour sites). As an OAR which will likely be relevant to future gastric RT TVD protocols, which can be challenging to contour if inexperienced, the aim of this question was to highlight what proportion of clinicians may require further training to optimise RT quality assurance of any future trial.

Theme 3 asked clinicians to rate their confidence in accurately delineating gastric RT volumes in the post-operative, pre-operative or definitive setting in order to explore whether infrequent use of gastric RT would result in low clinician confidence levels in technical aspects of gastric RT planning.

In a similar vein, theme 4 explored which educational materials clinicians would find most useful for gastric TVD – with responses vital to enable development of the most beneficial tools for subsequent trials.

Finally, theme 5 explored clinician support for a potential future trial of definitive CRT for IGC. As well as gauging clinical acceptability of such a study, a follow up question to estimate the approximate number of patients who may meet hypothetical inclusion criteria was posed – the latter necessary to estimate number of recruiting sites that may be required for any subsequent trial.

Upon completion of the questionnaire, participants were invited to leave their contact details to allow invitation to take part in later studies, though this was entirely optional.

4.3.2 Pilot

Prior to wider distribution, four local clinical oncologists specialising in OG cancer were asked to complete the first version of the questionnaire, and provide feedback, which is summarised in Table 4.2

Feedback area	Clinician 1	Clinician 2	Clinician 3	Clinician 4
Time to complete	11 minutes	15 minutes	12 minutes	5-10 minutes
Ease to complete	Quite easy	No comment	Very easy to complete	No comment
How easy questions were to understand	"A little wordy. And a busy oncologist may give up on this"	"I found the nodal outlining section a little confusing and difficult to complete as not currently doing gastric RT so difficult to comment on nodal outlining, but there was no N/A option, just yes or no"	"…make sure there is a 'I don't ever use gastric RT' tick box in each question as I think very variable- some centres will. We hardly ever do here anymore…"	"Should only be able to tick one option (can currently tick more than one)."
Questions deemed important that were not explored	"Ask about concerns about toxicity more specifically. I think for most clinicians this would their biggest concern"	No comment	No comment	"Need to separate when asks about experience in last few years GOJ III from distal "
Any software glitches encountered.	No problems.	No comment	No comment	No comment

Table 4.2. *Summary of clinician feedback gathered during questionnaire pilot.*

Time taken for completion ranged from 5-15 minutes and was deemed acceptable by pilot observers. The survey was modified to reflect the feedback provided as follows:

- Question wording was streamlined where possible, without losing important detail in the question stem/instructions
- A further question exploring specific toxicity concerns, including a free text box, was added (Question 6, see Appendix 4.1)
- "Not applicable" or "Not applicable – I would not use gastric RT in this setting" was added to all relevant questions
- Survey software was checked +/- modified to limit the number of answers respondents could give, where possible.
- Separation of gastric and type III GOJ tumours for questions relating to current opinion and practice (questions 3 and 5 – see Appendix 4.1)

4.3.3 Distribution

A Swansea University approved, secure, online survey technology, JISC v2 (https://www.jisc.ac.uk/online-surveys) was used to enable electronic distribution and completion.

The target audience was UK-based consultant clinical oncologists who specialise in the treatment of OG cancer. To maximise exposure and response rates, organisations were approached which; a) comprise high numbers of consultant clinical oncologists specialising in OG cancer, b) are well respected, national organisations supporting high quality research in the OG community, and c) are enriched in clinicians who are currently engaged in RT research, thus more likely to respond. The following two organisations meeting this brief were identified: the SCOPE2 trial mailing list (a UK clinical trial of RT for oesophageal cancer), and the 'UK and Ireland OG Cancer Group (UKIOG)" mailing list (a multidisciplinary forum for OG specialists from across the UK). Following the approval of the organisation leads, administrators distributed the survey invitation, which included a brief explanation of the aims, survey link and the participant information sheet (See Appendix 4.2). Consultant oncologists were also asked to share the survey link with relevant colleagues within their centres.

The survey was opened on 13.12.2022 and closed on 03.02.2023, following reminder emails sent via the same distribution channels.

4.3.4 Data analysis

Basic descriptive analysis (e.g. frequency, percentage) was performed within JISC online software, and data exported to Excel for further analysis. To protect participant anonymity, the email addresses provided were uncoupled from responses for analysis. Open-ended responses were categorised into themes and grouped accordingly for analysis.

4.4 Results

43 consultant clinical oncologists with expertise in OG cancer completed the survey. Prior clinician experience is shown in Figure 4.2. 29 of 43 respondents (67.5%) had been practicing >6 years.

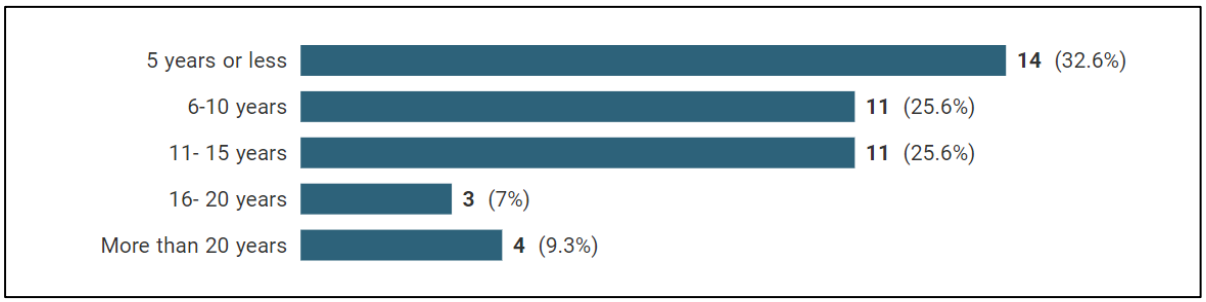


***Figure 4.2**. Bar chart showing length of time spent practicing as a consultant clinical oncologist specialising in OG cancer of the n=43 respondents*

4.4.1 Results of Theme 1 - Opinion regarding the current role of gastric RT

Table 4.2 shows clinician agreement with RT as a treatment option for each indication (post-operative, pre-operative, definitive, palliative). Responses 1 ('strongly disagree') and 2 ('disagree') were combined to represent general disagreement, and 4 ('agree') and 5 ('strongly agree') for general agreement with each indication for RT.

For gastric tumours, 28.6% of respondents agreed with post-operative RT compared to 52.4% who disagreed with RT for this intent. For type III GOJ, a similar proportion agreed, 26.2%, but fewer were in disagreement, 40.5%.

In the pre-operative setting, only 7.1% were in general agreement with RT as an indication for gastric tumours, in stark contrast to 45.2% for type III GOJ tumours. Similarly, 80.9 % were in general disagreement of pre-operative RT for GC, compared to only 38.1% for type III GOJ. This was echoed in the definitive setting, where 9.5% were in agreement with RT for GC compared to 46.6% for type III GOJ.

For palliative RT, agreement with RT as a treatment option was high at 83.7% for both gastric and type III GOJ tumours, with disagreement also 11.7% for both.

Of note, no clinicians strongly agreed with RT in the post-operative, pre-operative or definitive setting for gastric tumours.

Clinical indication	Post-operative		Pre-operative		Definitive		Palliative	
Rank	**Gastric**	**Type III GOJ**	**Gastric**	**Type III GOJ**	**Gastric**	**Type III GOJ**	**Gastric**	**Type III GOJ**
1 Strongly disagree (%)	9.5	2.4	21.4	4.8	16.7	4.7	4.7	4.7
2 Disagree (%)	42.9	38.1	59.5	33.3	59.5	32.6	7	7
3 Neither agree nor disagree (%)	19	33.3	11.9	16.7	14.3	16.3	4.7	4.7
4 Agree (%)	28.6	21.4	7.1	38.1	9.5	32.6	48.8	39.5
5 Strongly agree (%)	0	4.8	0	7.1	0	14	34.9	44.2

***Table 4.3**. Respondents (%) were asked to rank from 1 = strongly disagree, to 5 = strongly agree with regards to whether they would consider RT (+/- chemotherapy) as a treatment option in the circumstances shown.*

Figure 4.3 shows the mean clinician rank (1-5) by each indication for RT. For gastric cancer (Figure 4.3a), the mean rank only favoured the palliative setting as an indication for RT (mean 4.02), compared to type III GOJ tumours (Figure 4.3b) where mean rank favoured the palliative (mean rank 4.12), definitive (3.19) and pre-operative setting (3.1).

There was no statistically significant association between prior clinician experience and opinion relating to gastric RT for any indication (Appendix 4.3), though limited by small sample size.

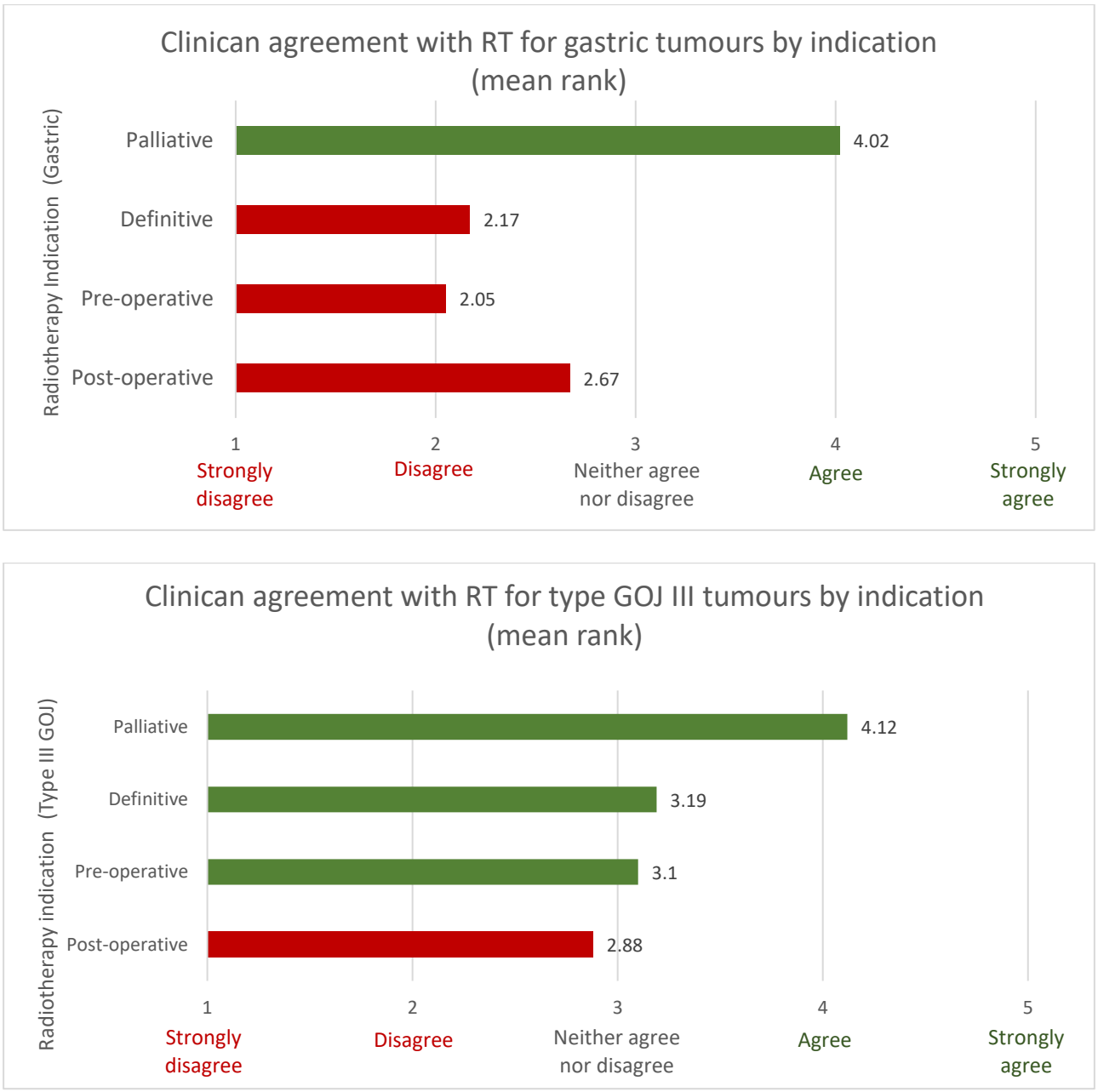


Figure 4.3. *Respondents were asked to rank from 1 = strongly disagree, to 5 = strongly agree with regards to whether they would consider RT (+/- chemotherapy) for each clinical indication*
Figure 4.3a *(top) shows mean rank for gastric cancer.* ***Figure 4.3b (bottom)*** *shows mean rank for Siewert type III GOJ. Green bars represent circumstances where mean rank was >3, indicating agreement. Red bars represent mean rank < 3, indicating disagreement.*

When asked the reasons for selecting 'disagree' or 'strongly' disagree to any indications above, n=30 respondents provided a total of 43 free text comments. These have been grouped by theme and displayed in figure 4.4. The most common reasons were inadequate evidence (n=15, 50% of respondents), toxicity concerns (n=11, 36.7%) and its absence in UK treatment guidelines (n=20%). Other themes include a preference for systemic anti-cancer therapy (SACT) for disease not amenable

to surgery due to risk of metastatic dissemination, and the difficulty defining target volumes for gastric cancer.

A selection of direct quotes reflecting these concerns include:

- *"never used, always taught too toxic…"*
- *"very limited meaningful evidence to support its usage"*
- *"…As part of my training I have been led to believe that high doses of radiotherapy to the stomach are poorly tolerated"*
- *"lack of evidence to show a benefit and increased risk of adverse events"*
- *"I very rarely use RT for gastric ca as this is largely a systemic disease and believe the best modality is combo chemo and surgery"*
- *"We have never treated gastric cancers or GOJ cancers with cardia extension over 2cm (i.e. outside SCOPE-2 guidelines) with radical treatment. This is due to difficulty in delineation of these cancers"*

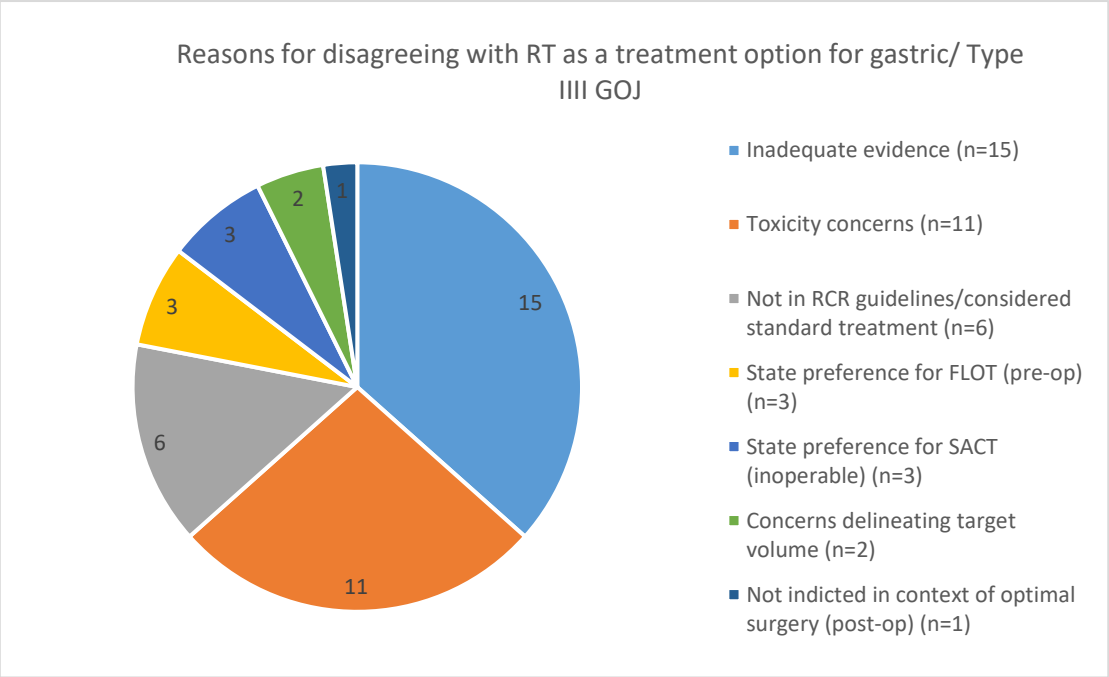


Figure 4.4. *Clinician reasons for selecting 'disagree' or 'strongly disagree' when asked if they would consider gastric RT as a treatment option for any clinical indication. Responses shown grouped by theme.*

Question 5 asked clinicians to quantify the number of times they have prescribed gastric RT. by indication over the last 3 years. Responses are shown in Figure 4.5.

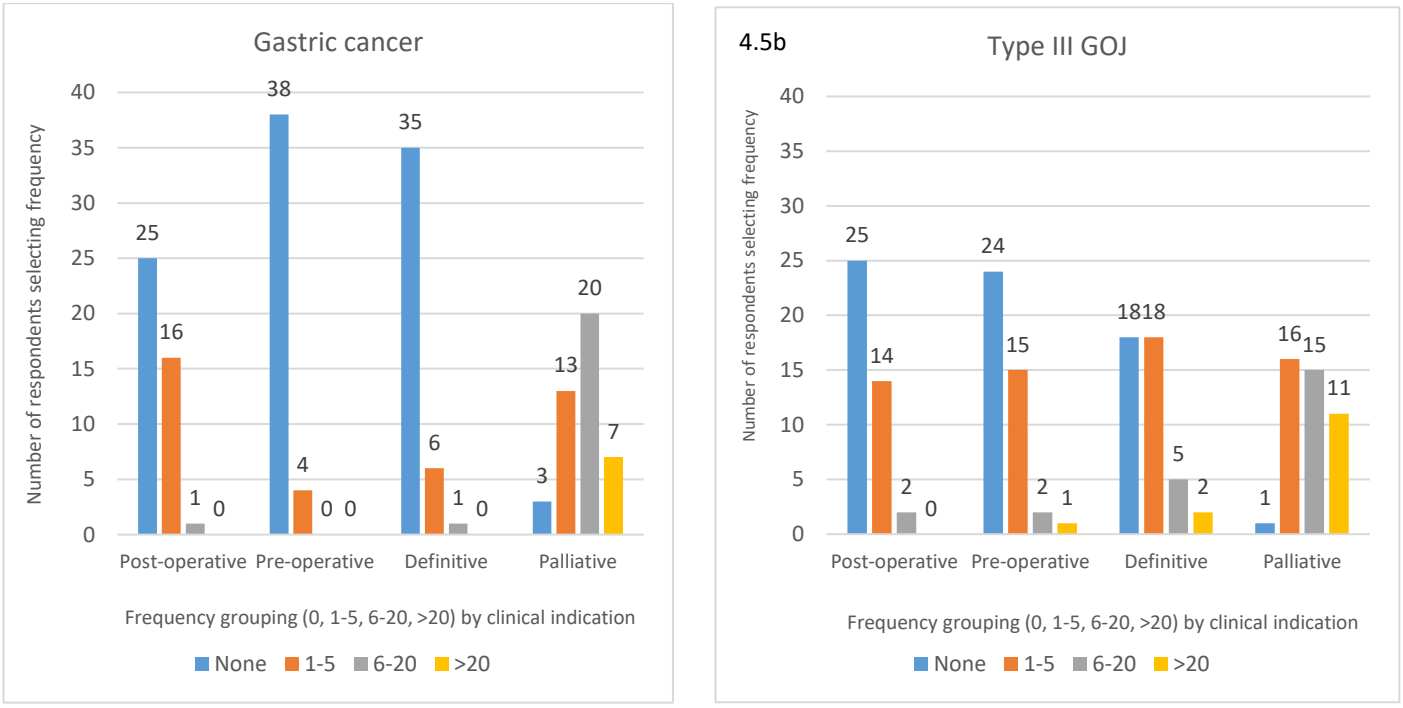


***Figure 4.5**. Number of times RT was prescribed in the preceding 3 years for gastric (Figure 4.5a, left) and type III GOJ cancers (Figure 4.5b, right)*

For gastric cancer, most clinicians have not prescribed any RT in the preceding three years, with 59.5%, 90.5% and 83.3% of clinicians selecting 'none' in the post-operative, pre-operative and definitive setting respectively. In the definitive setting, a higher proportion, 16.7%, of clinicians have prescribed RT than the 9.5% who agreed with its indication in the definitive setting in the prior question. Pre-operative RT prescription rates were low, and consistent with opinion, with only 8.5% having prescribed at least once in last 3 years.

Though post-operative prescription rates are similar for type III GOJ cancer (39% prescribed at least once in last 3 years) as gastric (40.5%), there are much higher rates of prescription pre-operatively (42.9%), and definitively (58.1) for type III GOJ tumours – consistent with much higher rates of agreement seen in the previous question.

Palliative is the most frequently used intent of RT, with 93% of clinicians having prescribed it for gastric and 97.7% for type III GOJ, and the majority reporting at least 6 times in the last 3 years (62.8% gastric, 60.5% type III GOJ).

Question 6 explored reasons for infrequent 'radical' RT prescription. Responses are shown in Figure 4.6. In keeping with question 4, the most common reasons were that RT is rarely indicated in line with current standard UK practice (88.4%), lack of UK gastric RT protocol (53.5%) and toxicity concerns (44.2%).

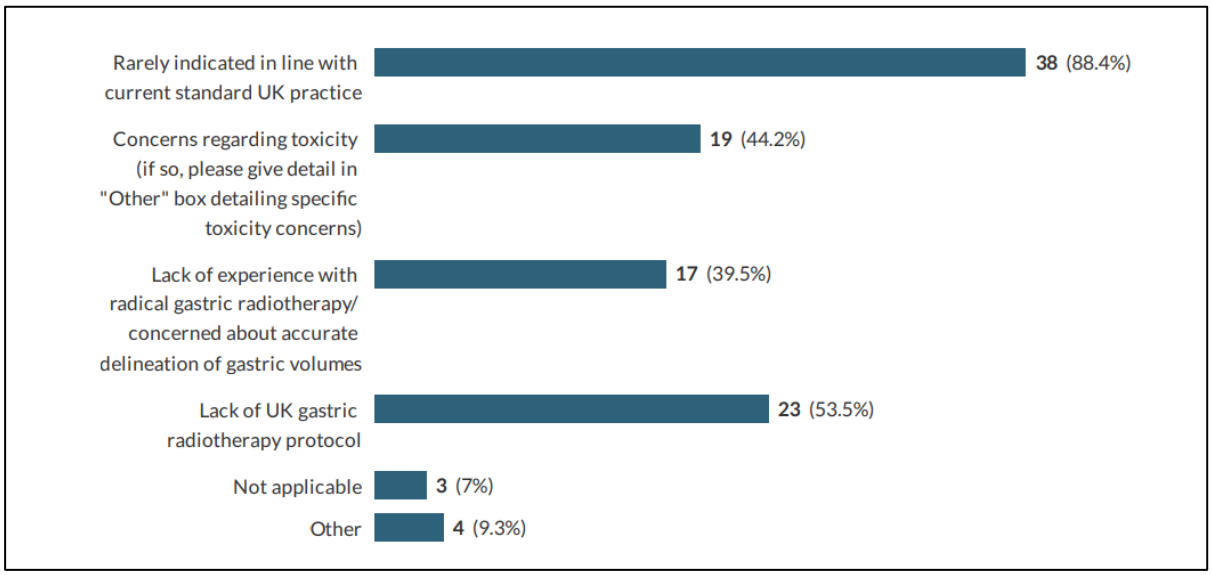


***Figure 4.6**. Reasons for infrequent radical radiotherapy use (<3 cases/year), where respondents could select any that applied.*

Those who selected 'toxicity concerns' or 'other' were asked to expand in free text. Themes not already covered previously included concerns regarding patient nutrition, hyposplenism, late RT toxicity such as fibrosis or ulceration, and technical difficulties with tumour motion/ deformation. Considering toxicity concerns specifically, these consisted of general GI toxicity n=8, nausea and vomiting, n=7, anorexia/requirement for nutritional support n=5, late toxicity n=1, hyposplenism n=1 and fatigue n=1.

4.4.2 Results of Theme 2 - Radiotherapy Technique

Different dose/fractionation regimens currently in use in the UK by indication are shown in Figure 4.7. Though the majority selected that they would not prescribe RT in these circumstances, when a dose was prescribed;

- Post-operative 25/29 (86%) who gave a dose would give 45Gy/25#
- Pre-operative 8/12 (66%) would give 45/25#

- Definitive 10/17 (58%) would give 50Gy/25#

Three respondents entered answers in the free text box; 41.4Gy/23#, SIB (simultaneous integrated boost) to 50Gy with 45Gy to elective nodal volume, and a non-specific “radical dose”.

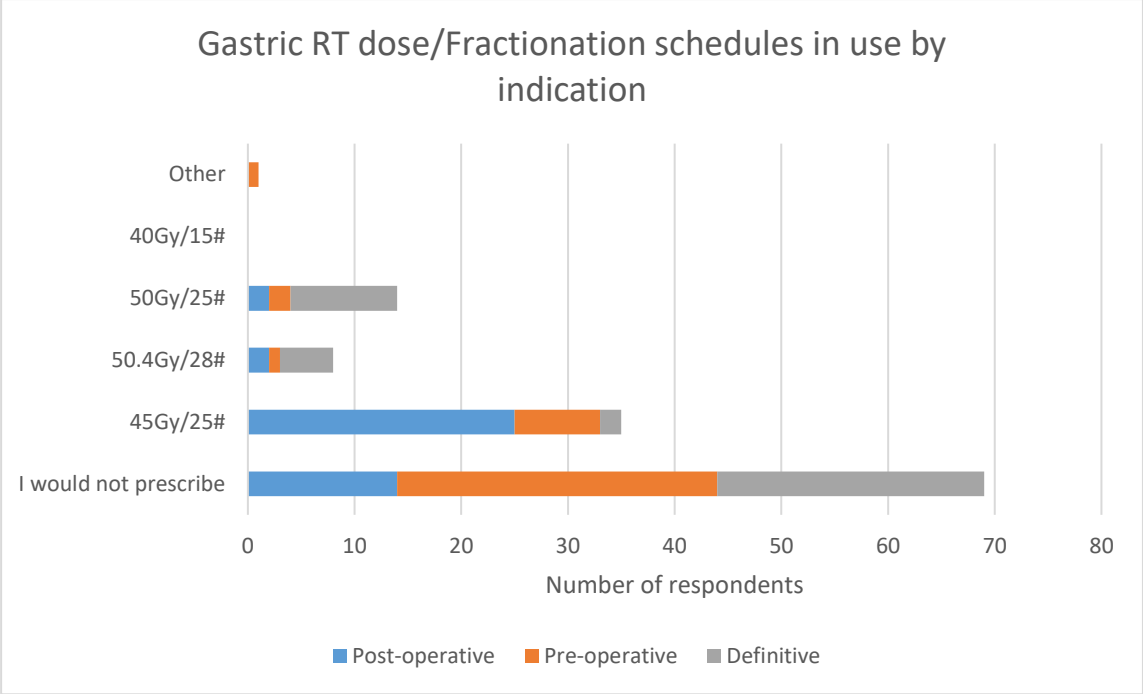


***Figure 4.7**. Dose/fractionation regimen favoured by clinicians in the post-operative, pre-operative and definitive setting for gastric RT.*

With regards to concurrent chemotherapy, of those who responded n=22 (95.7%) would recommend concurrent SACT. The remaining n=20 selected ‘not applicable – I would not prescribe radical gastric radiotherapy’ for this question. When asked which concurrent chemotherapy regimen they would prescribe; 44% (n=10) selected single agent fluoropyrimidine (5FU), 30% (n=7) selected platinum + 5FU, and 26% carboplatin + paclitaxel (n=6).

The RT protocols used for delineation guidance are shown in Figure 4.8a (post-operative) and 4.8b (pre-operative/definitive). Where protocols were selected (i.e. excluding those who selected ‘not applicable’), local departmental policy was most common for both (post-operative 37.5% of selected protocols, pre-operative/definitive 34.7%). In keeping with more clinicians prescribing post-operative RT, n=40 selected a protocol in the post-operative setting, where, after local policy, INT0116 MacDonald protocol was most popular (32.5% of selected regimens). Only n= 23 selected a

pre-operative protocol, with TOPGEAR (21.8%), followed by CRITICS I/II (17.4%) being most frequently used. Of interest, n=3 selected a post-operative regimen to aid delineation of pre-operative or definitive volumes.

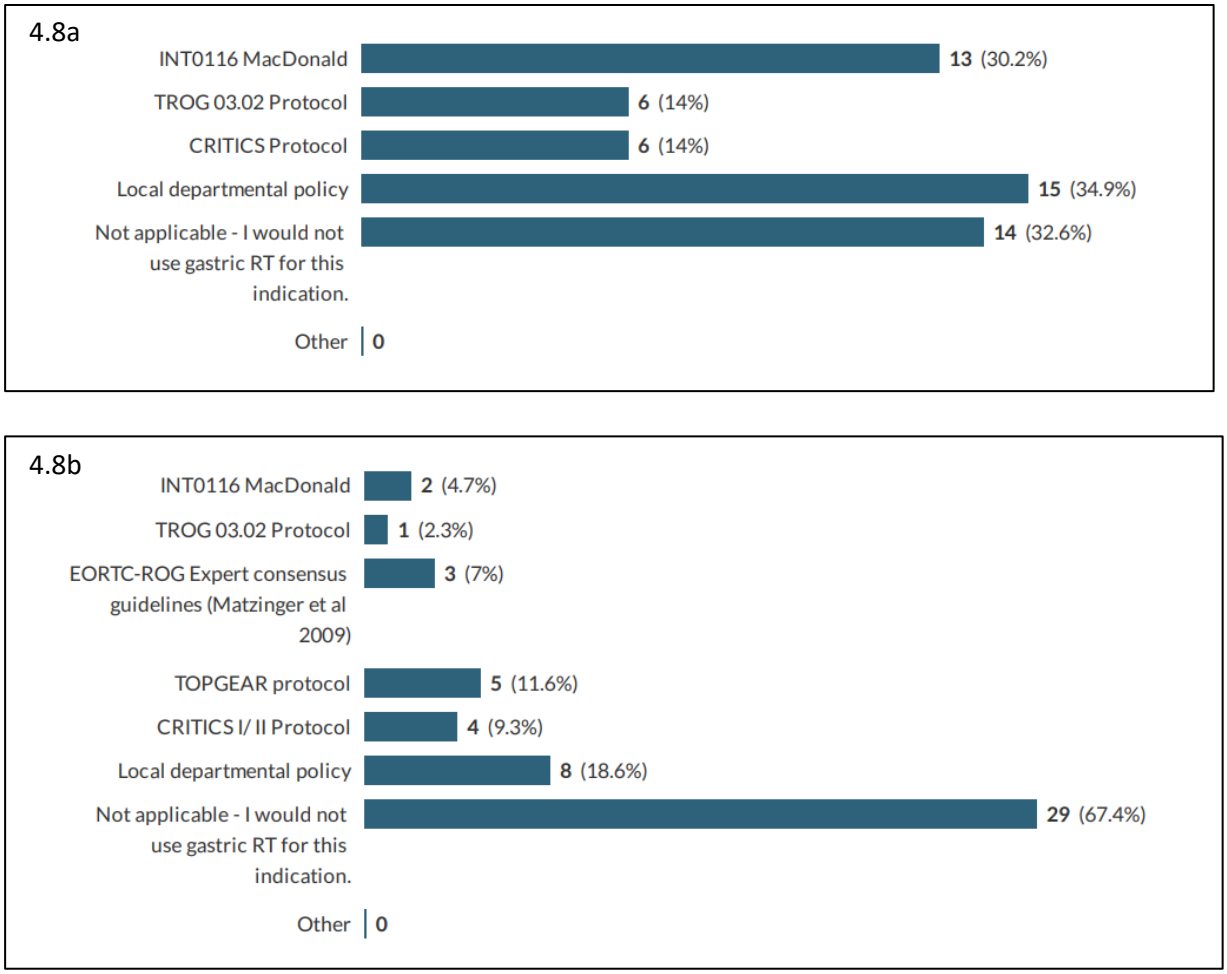


***Figure 4.8**. Preferred RT protocol to guide delineation in the post-operative (4.8a, top) and pre-operative or definitive settings (4.8b, bottom)*

Oncologists were then asked how they would approach nodal delineation respective to the RT protocol followed. N=37 provided a valid response (n=2 did not provide any answers, n=2 provided a 'no' response to 'not applicable', with no other valid answer, and n=2 provided 'yes' to not-applicable, but also chose another response to contradict this). Of the valid responses, n=23 chose 'not applicable/ not able to comment' (62%), n=9 would follow nodal delineation without modification (24.3%), n=7 (18.9%) would omit nodal levels and n=4 (10.8%) would add nodal levels. Four clinicians indicated they would both include additional nodes or omit nodes based on the volume.

With respect to other tumour sites of expertise, 48.8% report experience outlining upper abdominal lymph nodes areas, and 62% have experience delineating duodenum. Of those with familiarity delineating upper abdominal lymph nodes, experience in abdominal (n=9) or lymph node SABR (n=7) was most common. Expertise treating pancreatic cancer with RT was the most common reason for duodenal delineation experience (n=20)

When considering current RT techniques used, excluding those who selected 'not applicable' (n=17), 96.6% would use IMRT or VMAT for radical gastric RT, with only 1 respondent choosing a 2D approach. Techniques for patient simulation and treatment verification are summarised in Table 4.4.

	No. (/26)	%
Standard CT planning scan with IV and oral contrast	22	85
On treatment verification CBCT	20	77
Gastric filling protocol	18	69
4D CT	14	54
Surface guidance	4	15
Abdominal compression	3	12
Other	1	4
DIBH	0	0

Table 4.4. *Patient simulation and treatment verification techniques currently in use for radical gastric RT. Responses for n=26 who answered this question shown, with n=17 who selected 'not applicable – would not use gastric RT for this indication' excluded.*

Where CBCT was selected, frequency of imaging was asked in free text box, with responses shown in figure 4.9. Other responses given were that abdominal compression could be explored, but was not currently standard in this group, and exhale breath hold rather than DIBH.

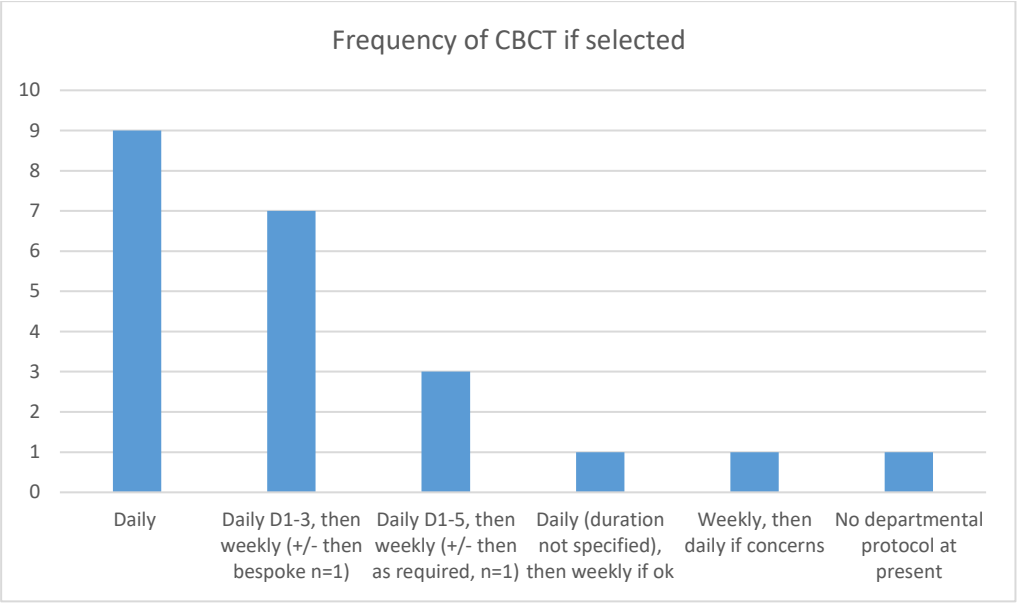


Figure 4.9. *Frequency of CBCT imaging.*

When asked which aspects of planning, set up or delivery were desirable if setting up a new definitive technique, a gastric filling protocol, abdominal compression, and 4DCT were the most popular techniques, as shown in Figure 4.10. Similarly, when asked desired frequency of CBCT, daily was most popular (n=10) followed by day 1-3 (then weekly CBCT) n=3.

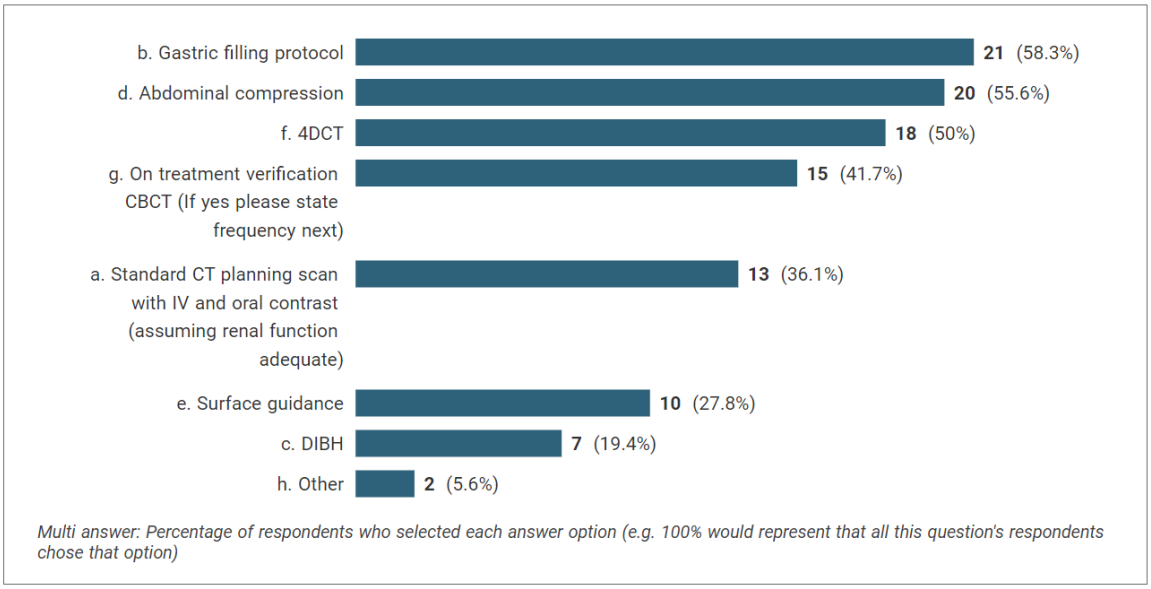


Figure 4.10. *Additional aspects to RT planning/ set up/ delivery that would be considered desirable which are not currently used as standard for radical gastric RT.*

4.4.3 Results of Theme 3 - Oncologist experience in TVD

Oncologists were asked to rate their confidence in accurately delineating a post-operative, and a pre-operative or definitive gastric RT plan, where 1 = not at all confident, and 10 = extremely confident. Mean rank was 4.33/10 for post-operative and 4.52 for pre-operative/definitive.

When responses were grouped into low (1-3), moderate (4-7) or high (8-10) confidence, only 9% and 17% would rate their delineation confidence as high for post-operative or pre-operative/ definitive respectively, as shown in Figure 4.11. The majority, 56% would rate confidence as moderate in the post-operative setting, compared to low (45%) for pre-operative/definitive – reflective of the lower prescription rates seen. Very few (9-17%) were highly confident with gastric TVD.

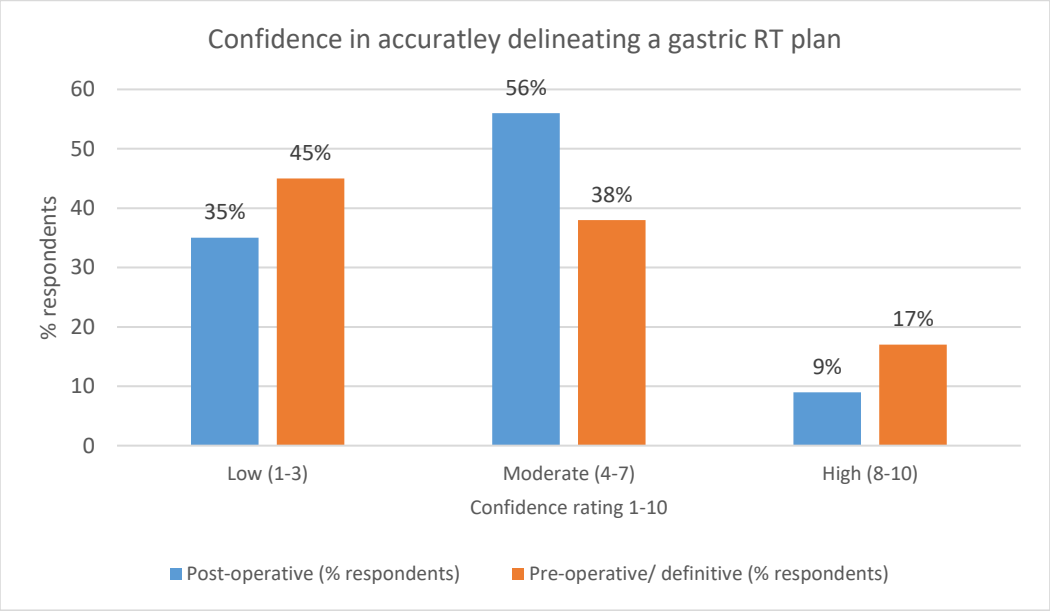


Figure 4.11. *Oncologist confidence rating grouped into low (1-3), moderate (4-7) or high (8-10) for the post-operative (blue) compared to pre-operative/definitive setting (orange).*

4.4.4 Results of Theme 4 -Supporting educational materials

When asked which educational materials or interventions would be useful to aid pre-operative or definitive gastric RT delineation, clinicians selected the following (could select >1):

- 93% clear tumour volume delineation protocol
- 81.4% peer review

- 76.7% nodal atlas
- 74.4% worked example
- 74.4% outlining workshop with an expert
- 65.1% radiology educational materials to guide identification of key structures
- 62.8% webinars.

Only 1 (2.3%) selected that they felt the existing available materials were sufficient.

4.5.5 Results of Theme 5 - Future directions

When asked if they would supportive of a clinical trial further investigating the role of definitive CRT for inoperable, non-metastatic gastric cancer, 76.6% selected 'Yes,' with the remaining 23.3% selecting that they would need to see supporting evidence presented before they would feel able to answer, and no respondents answered 'No.'

With regards to numbers of patients seen each year with inoperable, non-metastatic gastric cancer, this was ≤10 in all centres, with 53.5% seeing 3-5 patients per year who meet these criteria, followed by 30.2% seeing 6-10, and 16.3% 0-2.

Thirty-three oncologists (76.7%) agreed to being contacted in future regarding testing gastric RT protocols or test cases.

4.5 Discussion

As hypothesised, this survey has shown that, at present, most UK OG clinical oncologists do not feel there is a routine role for gastric RT in the post-operative, pre-operative or definitive setting, and as such RT is infrequently prescribed for these indications. However, clinicians are more likely to consider irradiation as a treatment modality for Siewert type III GOJ tumours, likely due to extrapolation of the oesophageal and GOJ RT evidence base, higher levels of clinician confidence treating junctional tumours, and smaller volumes of stomach requiring irradiation, thus lowering toxicity concerns.

The reasons for low rates of RT prescription were lack of evidence (and as such, it not being considered standard of care in the UK), toxicity concerns, and lack of a UK gastric RT protocol. A future randomised clinical trial, which incorporates a detailed RT protocol, will address two of these

concerns. However, significant apprehension around side-effects of gastric RT remains, highlighted by 44.2% of clinicians, with toxicity concerns also shaping nodal volumes, with n=7 omitting nodal areas to minimise treatment volume, thus toxicity. As discussed in section 4.1, many of these anxieties relate to the era of INT 0116. However, when considering these concerns, one must also consider that **all** adjuvant therapy following gastrectomy is poorly tolerated, not just radiation. Similar to the post-operative RT trials, post-operative chemotherapy alone also demonstrates low completion rates, with only 42% completing post-operative chemotherapy in MAGIC, and 46% in the more recent FLOT 4 study.[23,25] In the era of IMRT, both post-operative (CRITICS, ARTIST), and pre-operative studies (TOPGEAR) have demonstrated much lower rates of toxicity.[61,81,166] Additionally, this survey has demonstrated almost universal of IMRT or VMAT across UK centres, minimising volume to organs at risk compared to older 2D techniques. This, combined with proactive use of modern anti-emetics such as 5-HT_3 antagonists, should go some way to minimising toxicity in future trials. Therefore, a future trial using IMRT/VMAT, motion management techniques and optimal prophylactic anti-emetics, should result in a more positive toxicity profile than the historical post-operative studies. In addition, future gastric RT protocols should aim to rationalise treatment volume, for example, by including only very high-risk nodal levels, in order to further allay clinical oncologist toxicity concerns.

As anticipated, this survey has confirmed that IMRT or VMAT has become standard RT technique in the UK. However, variation exists around motion management techniques currently in practice, which include gastric filling protocol (69%), 4DCT (54%), surface guidance (15%) and abdominal compression (12%). In contrast, a much higher, 58.3% would want to see abdominal compression evaluated in a future clinical trial (alongside 4DCT [50%] and gastric filling protocol [58.3%]) – this should be considered for inclusion in subsequent trials.

The lack of experience in delineating and prescribing gastric RT, and the absence of a UK consensus gastric RT protocol, resulted in low confidence rates in gastric TVD. This survey has revealed above all, a clear delineation protocol would be the most useful tool to improve clinician confidence, in addition to peer review, a nodal atlas, worked examples and expert workshops – these should all be incorporated into subsequent trials. Less than half have experience in identifying upper abdominal lymph node areas (48.4%), further demonstrating the necessity of a nodal atlas, and 38% do not have experience in delineating duodenum. This is mandated in pre-operative gastric RT protocols, such as TOPGEAR, which demonstrated the duodenum as the most common site of major deviation from protocol.[168] Without training and experience the duodenum can be challenging to delineate correctly, thus additional radiology education will be required. In light of this, robust RT quality assurance (RTQA) of any subsequent trials will be vital to ensure accuracy and to minimise

interobserver variation in tumour volume delineation – especially given the novelty of gastric TVD to the UK clinical oncology community.

With regards to the future of gastric RT research, the high proportion (76.6%) who would support a clinical trial in this setting is extremely encouraging, with the suggestion that the remainder could be converted from an 'unsure' to a positive view following presentation of more supporting information. This supports further development of a UK gastric RT trial.

Most clinical oncologists see approximately 3-10 patients per year with inoperable, non-metastatic gastric cancer. This suggests that in order to recruit to a future trial investigating this population, multiple centres will need to open in order to recruit in a timely manner. These estimates will contribute to later sample size calculations and trial planning.

Limitations of this survey include the small sample size. Questions regarding dose/fractionation were limited to the radical setting, and with hindsight, it would have been useful to understand the range of palliative dose schedules also being prescribed across the UK.

4.6 Conclusion

Gastric RT is not often practised in the UK at present, due to lacking evidence and toxicity concerns. However, there is support for further research into the role of RT for inoperable gastric cancer from the clinical oncology OG community. Future trials must include detailed RT protocols, atlases, and educational materials to improve clinician confidence, and ensure good RT quality assurance.

Chapter 5

Interobserver variability in target volume delineation for gastric radiotherapy using CT and MRI

5. Interobserver variation in target volume delineation for gastric radiotherapy using CT and MRI

5.1 Introduction

Randomised evidence evaluating the role of RT for IGC, particularly in the definitive and high-dose palliative setting is currently lacking, exhibited by the systematic review presented in Chapter 3. In the absence of phase III evidence and consensus gastric RT guidelines, there is currently marked variation in gastric RT technique seen across currently published studies. It is also evident that in the UK, 'radical' doses of RT are used infrequently, if at all, with one of the main reasons for this being the lack of a consensus UK gastric RT protocol to inform and guide clinicians, and various protocols currently used for reference in the pre- and post-operative setting (Chapter 4).

Whilst most definitive studies included in the SR consistently described delineation of GTV, detail around how to most accurately define this volume is lacking, and disparity exists in the CTV, with some studies including the whole stomach, and others describing a variety of isotropic margins around the GTV to create a CTV. Therefore, in order to ensure consistent delivery of high-quality RT in any future clinical trial and enable safe use of high-dose gastric RT in clinical practice, it is essential to develop a robust gastric RT protocol, with clear description of GTV, CTV and PTV volumes (see section 1.2.2, Table 1.4 for definition).

When developing a RT protocol, as well as considering which tissues are most at risk of malignant involvement for inclusion within the treatment field, it is vital to optimise accuracy and consistency in the identification and delineation of these tissues to maximise chance of treatment success. Inaccurate delineation of gross primary tumour volume (GTVp) will lead to systematic geographical miss at the time of RT treatment, which over consecutive treatments could lead to significant under-dose to the tumour (thus reducing chances of disease control), or potential overdose to surrounding tissues, increasing toxicity of therapy. Accurate TVD is also vital in the era of modern RT techniques, such as IMRT and VMAT, which can deliver RT with millimetric precision, magnifying the importance of any delineation errors.

Therefore, this chapter aims to identify optimal imaging techniques to maximise accuracy of delineation of GTVp and whole stomach volumes, and minimise variation in TVD between clinicians, to inform a robust gastric RT protocol for future clinical trials.

5.1.1 What is interobserver variability (IOV) in radiotherapy planning?

TVD is usually based on a CT scan acquired for RT planning purposes (described in Chapter 1.2.3). Interpretation of the CT images depends on prior experience and training of the clinician (i.e. the 'observer'). CT images of the GI tract are susceptible to variation and artefact (i.e. image interference) caused by stomach filling, type of contrast administered and respiratory motion during acquisition of the scan, all of which can result in varied interpretation. Stage and biology of disease may also influence the volumes generated by individual clinicians. Collectively all of these factors result in differences in TVD between clinicians – termed 'interobserver variability' (IOV), and is relevant across all tumour sites.

Deviations in RT protocol (of which inaccurate TVD and significant IOV are important components) have been associated with poor outcomes in several clinical trials.[169-171] Clinician volumes are often compared to a "gold standard" or "reference" volume to assess accuracy – though even robust, expert, consensus volumes are subjective, based on imaging appearances rather than true histological assessment of tumour extent. Though consistently attaining 100% match to a "gold standard" volume is practically impossible due to the variables listed above, minimising variability with the gold standard is considered one way to optimise RT quality, improve adherence to RT protocol, and thus improve outcomes.

5.1.2 IOV in gastric radiotherapy – the existing evidence

A literature review has revealed 5 studies evaluating interobserver variability (IOV) in gastric RT, all of which assess post-operative CTV volumes, summarised in Table 5.1.[172-176] Given the post-operative nature of these studies, primary tumour was not present for evaluation of GTV volumes.

Author (year)	Clinical setting	No. of observers	No. of cases evaluated	Comparative process	Metrics
Jansen *et al.* (2010)	Post-operative	10	1 (CTV and PTV delineated)	Median 3D- PTV was constructed for comparison of the individual observer volumes	• CTV/ PTV volume (cm^3) • Distance from median PTV • Calculated median V95 and median V107 for each treatment plan.
Moretones *et al.* (2012)	Post-operative	4	9 (Observers outlined 4 slices on each case)	One clinician appointed main observer "A," to which all others "B" were compared.	• CTV volume (cm^3) • For position and shape evaluation, observer A was compared to the other observers using Conformity index = $(A \cup B)/(A \cap B)$
Li *et al.* (2016)	Post-operative	4	10 (CTV and OAR delineated[a])	Compared the interobserver and inter-CT difference of maximal dimensions and volume	• Maximum dimensions of antero-posterior and left-lateral field • CTV/OAR volume (cm^3) • Distance between centre of mass (CM) • Conformity Index = $(A \cup B)/(A \cap B)$ • Variation in dose distribution to PTV and OARs (D_{99}, D_{95}, D_1)
Socha *et al.* (2016)	Post-operative	20	1 (Observers outlined CTV on 4 slices before and after a training workshop)	An "expert" volume was used as reference for comparison	• Maximum dimensions of cranio-caudal axis • CTV volume (cm^3) • Distance between centre of mass (CM) • Concordance index = AI/RA x100%, or VI/RV x100% • Discordance index = (1-AI/DA) x 100%, or (1- VI/DV) x100% • Questionnaire exploring areas of main difficulty
Onal *et al.* (2017)	Post-operative	29	1 (CTV and PTV delineated)	An "expert" volume was used as reference for comparison	• CTV/PTV volume (cm^3) • Distance from reference PTV to individual PTV at 4 sites; cranial border, porta hepatis, splenic hilum and caudal border. • Conformity Index = $(A \cup B)/(A \cap B)$ • Kappa index to analyse difference in pre-and post-course volumes[b]

Table 5.1. *Summary of the existing IOV studies for gastric cancer.*

[a] Each patient had 3 CTs on consecutive days using active breath hold, with CT's rigidly co-registered.

[b] Observers delineated two set of volumes, one before, and one after a training workshop, with these volumes compared using the kappa index. V95= volume receiving 95% of the treatment dose. V107 = volume receiving 107% of the treatment dose. AI = area of intersection. RA = reference area. VI = volume of intersection. RV= reference volume. DA = delineated area. DV = delineated volume.

Significant IOV exists across all 5 studies. Moretones *et al.* compared CTV volumes for 9 post-operative patients delineated by 4 clinicians and reported a statistically significant difference in the standard deviation of CTV volume of 198.10cm^3, which was ascribed to interobserver variability.[172] Jansen *et al.* also reported substantial variation in CTV volume ranging from 240cm^3 to 821cm^3, with the greatest area of variation being the caudal extent.[173] In their work evaluating interobserver and inter-CT variation using active breath hold technology in post-operative gastric RT, Li *et al*. reported significant variation in CTV volume among observers (average CTV volume 674cm^3+/- 138cm^3 1SD, range 332- 969cm^3), but none between CTs, and no variation in OAR delineation. They too reported the most variation in the cranio-caudal extent of the volumes, and identified other areas of variation including lower verge of splenic hilum and porta hepatis, para-oesophageal nodes, and abdominal aorta/inferior vena cava.[174]

Two groups have assessed the impact of educational gastric contouring workshops on IOV. Onal *et al.* reported that pre-course volumes were larger and demonstrated more variation than post course volumes, with difference between delineated volume and reference volume of 19.8% pre-course (-42.4%- 70.6%) and 12.3% post-course (- 12.0 – 27.3%). Here too, most variation was seen at the caudal part of the target volume, though this improved after the educational course.[175] Similarly, Socha *et al.* reported poorer conformity pre-training than post-training (49% vs 59%,p=0.39), with the dome of the diaphragm the site of most variation. Elective nodal volumes were identified as the main area of difficulty on a questionnaire completed by observers.[176]

In the pre-operative setting, the TOPGEAR study has analysed the CTV volumes of 196 patients whose RT plans were evaluated as part of their RTQA programme[177], revealing a pass rate of 72%. At least one aspect of CTV required adjustment in 89% of cases (inadequate coverage of duodenum was the most common error), suggesting a degree of IOV within this study. However, to my knowledge, there are currently no published studies specifically assessing IOV of the GTVp of gastric tumours in either the pre-operative or definitive setting.

In summary, each of these studies demonstrate marked IOV in post-operative gastric CTV. Though volumes in the definitive or pre-operative setting will vary to those reported above (due to the tumour and stomach remaining in situ), there are important lessons to be learned with regards to common areas of CTV variation that resonate across settings, that should be considered for future gastric RT studies to optimise IOV.

5.1.3 Role of MRI in gastric cancer

Following initial diagnostic endoscopy, CT is currently considered the standard imaging modality for gastric cancer staging (+/- diagnostic laparoscopy, PET-CT or EUS for selected cases). The overall diagnostic accuracy of CT for T-staging gastric carcinoma ranges between 77.1-88.9%.[178] However, MRI offers superior soft tissue contrast to CT, additional functional imaging sequences, spares ionising radiation, and may have a role in gastric cancer, where it is shown to have high sensitivity and specificity for T-stage evaluation.[179-181] A systematic review and meta-analysis of 11 studies (n=439 patients) evaluating the utility of MRI for pre-operative staging for gastric carcinoma reported the overall pooled diagnostic accuracy of MRI for T stage was 81%, with pooled sensitivity and specificity of 91% and 93% respectively for T3-T4 disease.[182]

Compared to CT, MRI showed superior accuracy for T-staging in a meta-analysis published by Seevaratnum *et al.* who reported overall accuracy of 82.9 +/- 3.7% for MRI compared to 71.5% +/- 2.7% for CT ($p < 0.014$), though only 3 studies were included in this analysis.[183] The trend for higher T-stage accuracy of MRI has been reported by others, though a statistically significant difference has only been shown by one study (diagnostic accuracy of 81% for MRI vs 73% for spiral CT).[184-186]

The addition of functional MR sequences, such as diffusion-weighted imaging (DWI) has also proven useful in improving accuracy of T-stage evaluation. DWI measures the movement of water molecules in tissue, providing information regarding tissue cellularity, and is helpful in distinguishing benign from malignant tissue. Figure 5.1 exemplifies some of the differences in tumour appearance on CT, T2 weighted MR, and DWI.

Liu *at al.* showed that addition of DWI to contrasted-enhanced T2-weighted MRI improved T-staging to 88.2% (compared to 76.5% for contrasted enhanced T2 MRI alone, p=0.031), with similar improvements also reported by Caivano *et al*. who demonstrated the addition of DWI to conventional MR sequences could increase diagnostic accuracy of T-stage by 7%. [187,188]

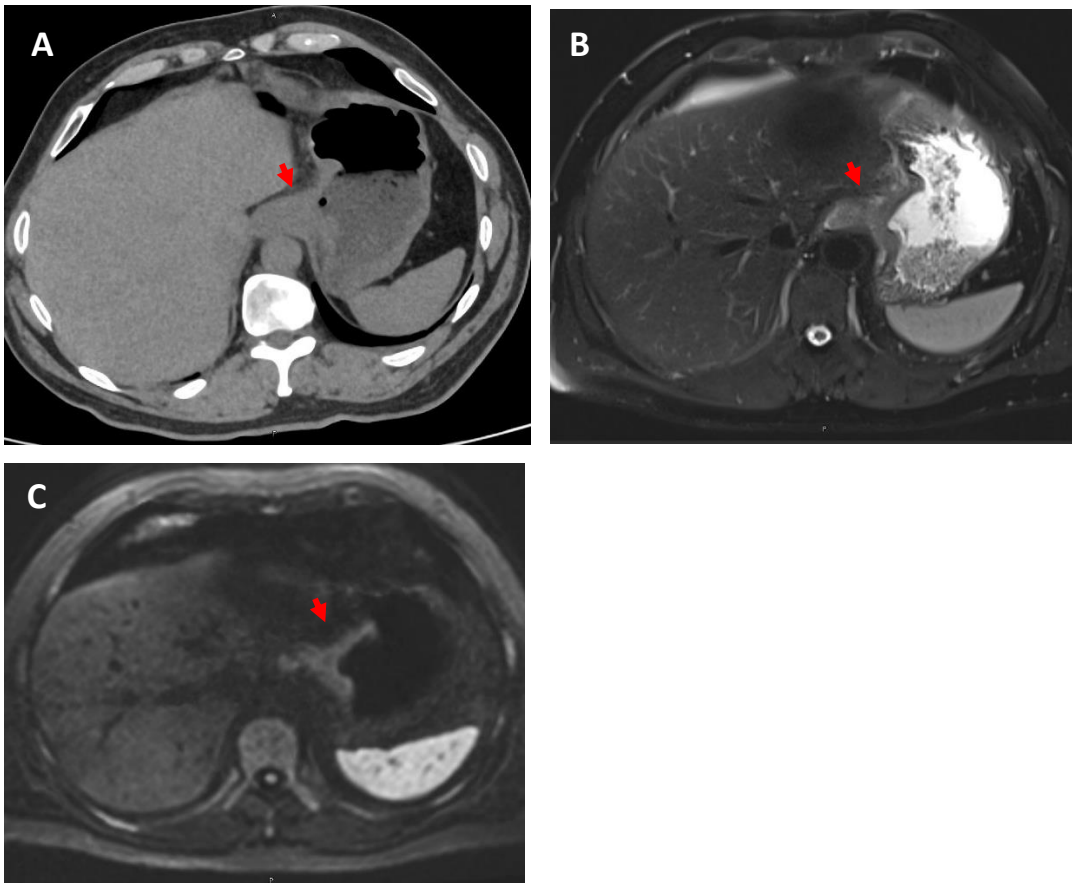


Figure 5.1. *A type III GOJ tumour (arrowed) extending into stomach on CT (image A), T2 fat saturated MRI (image B) and diffusion weighted MRI (DWI - image C). Though difficult to differentiate tumour from normal stomach wall on CT, T2 imaging shows the tumour mor clearly contrasted by fluid content, and on DWI tumour restriction results in the tumour appearing brighter than normal gastric wall.*

5.1.4 Role of MRI in gastric radiotherapy

Delineation of gastric RT treatment volumes usually takes place on dedicated CT images, acquired with a patient in the treatment position, but the true extent of gastric tumours can be challenging to identify on CT alone. Whilst endoscopy, and where applicable, EUS or PET-CT, can inform clinician contours, they are not used directly for planning purposes, and MRI is not currently used to aid TVD in gastric cancer.

However, the superior soft tissue contrast provided by MRI has been shown to improve TVD in rectal cancer where White *et al*. reported that delineation on MRI resulted in smaller volumes and better interobserver agreement than on CT, which in some cases would affect dose received.[189] MRI has also been shown to improve inter-observer agreement in other tumour sites such as bone, lung and head and neck tumours. [190-192] As such, MRI is listed as an essential pre-treatment investigation to aid optimal TVD in a number of national RCR consensus RT protocols. [193-195]

Literature regarding the role of MRI for gastric RT planning is limited to case reports. Chun *et al.,* describe the use of MR-adaptive RT to deliver a radical dose to a recurrent gastric carcinoma. An IMRT plan was generated based on both a conventional CT-based Linac and an MR-guided system. The MR plan demonstrated smaller GTV volumes, lower whole stomach dose, as well as "better visualisation of the target" (Figure 5.2).[196] A second case report by Song *et al.,* describes the value of daily MR imaging generated by an MR-LINAC, particularly for identifying intra-fraction motion of both tumour and stomach over a 5 week course of radical gastric RT.[197]

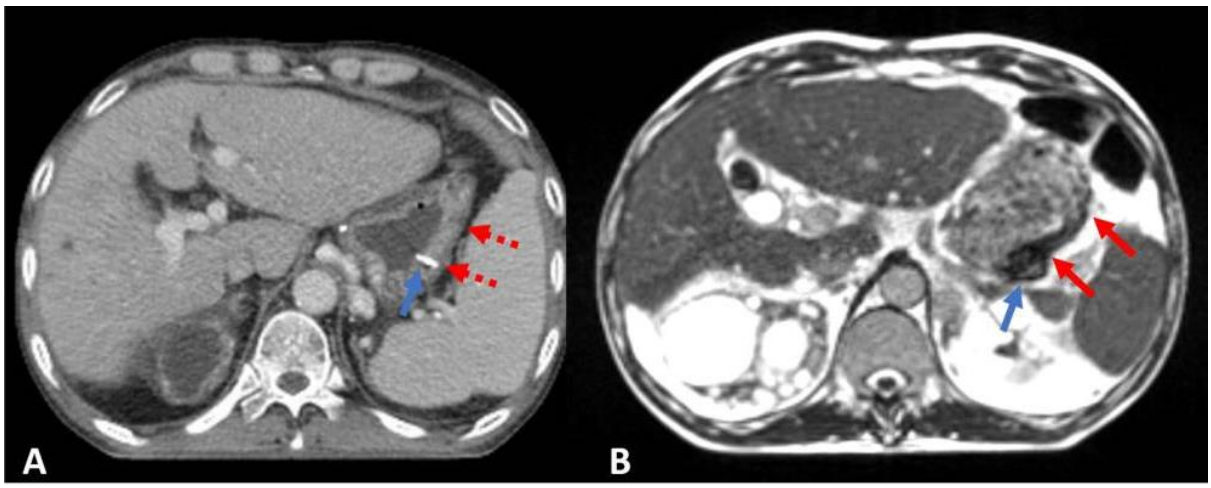


Figure 5.2. *Image taken from Chun et al.,196 (reproduced under the Creative Commons Attributions License) depicting a clip (blue arrow) and tumour (red arrow) on simulation CT (A) and on MRI (B). Note the improvement in tumour definition on MRI compared to CT.*

In summary, although MRI remains a non-standard investigation for gastric cancer staging (potentially due to limited availability and costs), there is growing evidence to support its value in T-staging, particularly with the addition of functional imaging sequences such as DWI. MRI has already proven a useful tool to optimise TVD and IOV in other tumour sites, and there are case reports highlighting its value in gastric cancer RT. This forms the basis of the hypothesis that MRI with DWI may improve TVD and reduce IOV for gastric cancer compared to CT alone.

5.2 Aims

The aims of this study were to:

- To conduct a quantitative assessment of IOV in tumour volume delineation (TVD) of GTVp and whole stomach volume using CT alone, versus CT plus MRI.
- To gather qualitative data from observers to establish whether the addition of MRI improves ease and reduces time for TVD in gastric cancer.
- To evaluate which MR sequences are subjectively most useful for TVD in gastric cancer.
- To identify maximal areas of IOV/ inaccuracy in TVD in order to inform development of a future gastric RT protocol to ensure areas of most variation are optimally described in manuals and training programmes.

5.3 Methods

This study was approved by the SUMS Ethics Review Committee (SUMS RESC 2022-0128A) and Swansea Bay University Health Board Information Governance Committee.

5.3.1 Test case development

Initially, four hypothetical, anonymous clinical test cases were developed, each including a clinical description, CT and MRI images with corresponding radiology reports (anonymised and re-reported by study radiologist, Dr Kieran Foley to maintain patient confidentiality) and planning CT images, on which study participants (i.e. clinician 'observers') were subsequently asked to conduct TVD. Cases were selected that would allow comparison of TVD in a variety of anatomical locations within the stomach and tumour stage, as described in Table 5.2.

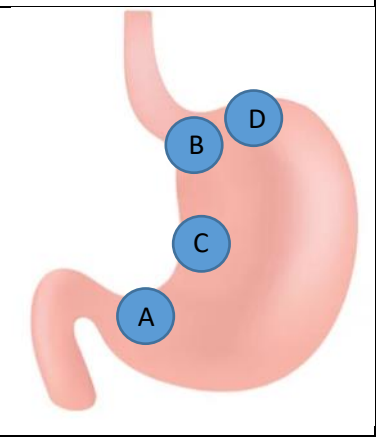
Case	Anatomical location/ description	Stage	Diagram showing anatomical distribution of cases
A	Large pyloric tumour with extra-gastric extension and peri-tumoural lymph node metastases	T4b N2 M1 (liver)*	
B	Siewert type III, GOJ tumour with extension into peri-gastric fat, peri-tumoural lymph node metastases	T4a N1 M0	
C	Large lesser curve tumour, with extra-gastric extension. Suspicious peri-gastric lymph nodes	T4b N1 M0	
D	Siewert type III tumour, extending into fundus and lesser curve. Large, numerous locoregional nodes.	T3 N3a M1 (liver)*	

Table 5.2. *Summary of test cases developed for the study.*
**observers asked to disregard liver metastases for purpose of this study*.

Diagnostic CT scans for each case were anonymised and imported into local Treatment Planning System (TPS, Prosoma®) in lieu of a CT planning scan. As dedicated gastric MRI is not currently routinely performed for staging, retrospective MRI liver sequences (undertaken for the evaluation of liver lesions) were used, due to the similarity in the sequences acquired (i.e. T2, DWI, delayed contrast). These were subsequently utilised by observers for reference, but not co-registered due to differences in patient preparation and positioning between CT and MRI scans.

Though four test cases were developed, two (case A and C) were selected for the first phase of TVD in the study. This was due to the limited number of observers, thus it was felt preferable to concentrate observers over 2 cases to maximise number of volumes for each case whilst still allowing comparison of TVD across different anatomical locations in the first instance.

Along with the clinical description to accompany each case, an "Instruction Manual for Observers" was developed which described phases of the study, defined the GTV and CTV volumes to be outlined and provided a CT Atlas demonstrating a worked example and identifying key structures (Appendix 5.1). A short guide to interpretation of MRI images for gastric RT and MRI atlas was also developed to aid clinicians unfamiliar with this imaging modality (Appendix 5.2).

5.3.2 Identification of Observers

Consultant OG clinical oncologists or post FRCR fellows were invited to participate by email by via the following:

- Database of clinicians who participated in National Gastric Radiotherapy Survey (Chapter 4), who indicated they would like to take part in future studies
- Distribution of invitational email via the following national networks:
    - SCOPE 2 clinician database (national phase III oesophageal RT trial)
    - UKIOG (UK and Ireland Oesophagogastric Cancer Group) database

5.3.3 Data collection

Following receipt of the participant information sheet (Appendix 5.3), observers were allocated to Case A or C in an alternating fashion in the order of receipt of their email confirming participation. Whilst it was initially planned to invite observers to complete a second case following completion of their first (i.e. Case B or D), it quickly became apparent during the study that due to time constraints and clinical work-load, most observers would be able to complete only one case, thus data was collected for Case A and C only.

Participating observers were provided with the relevant clinical description and imaging for each case (Appendix 5.4), the instruction manual (Appendix 5.1), imaging atlases (Appendix 5.2) and asked to delineate in 2 stages, summarised in Figure 5.3. TVD was performed individually and observers were blinded to each other's volumes. After each phase, observers returned their volumes to the SBU Radiotherapy Physics department via secure drop box, as per study SOP (Appendix 5.5). Volumes were anonymised and uploaded into Prosoma by the study clinical scientist, Becky Slinger. Observers were provided MRI imaging for phase 2 only after their phase 1 CT-based volumes were returned to the drop box.

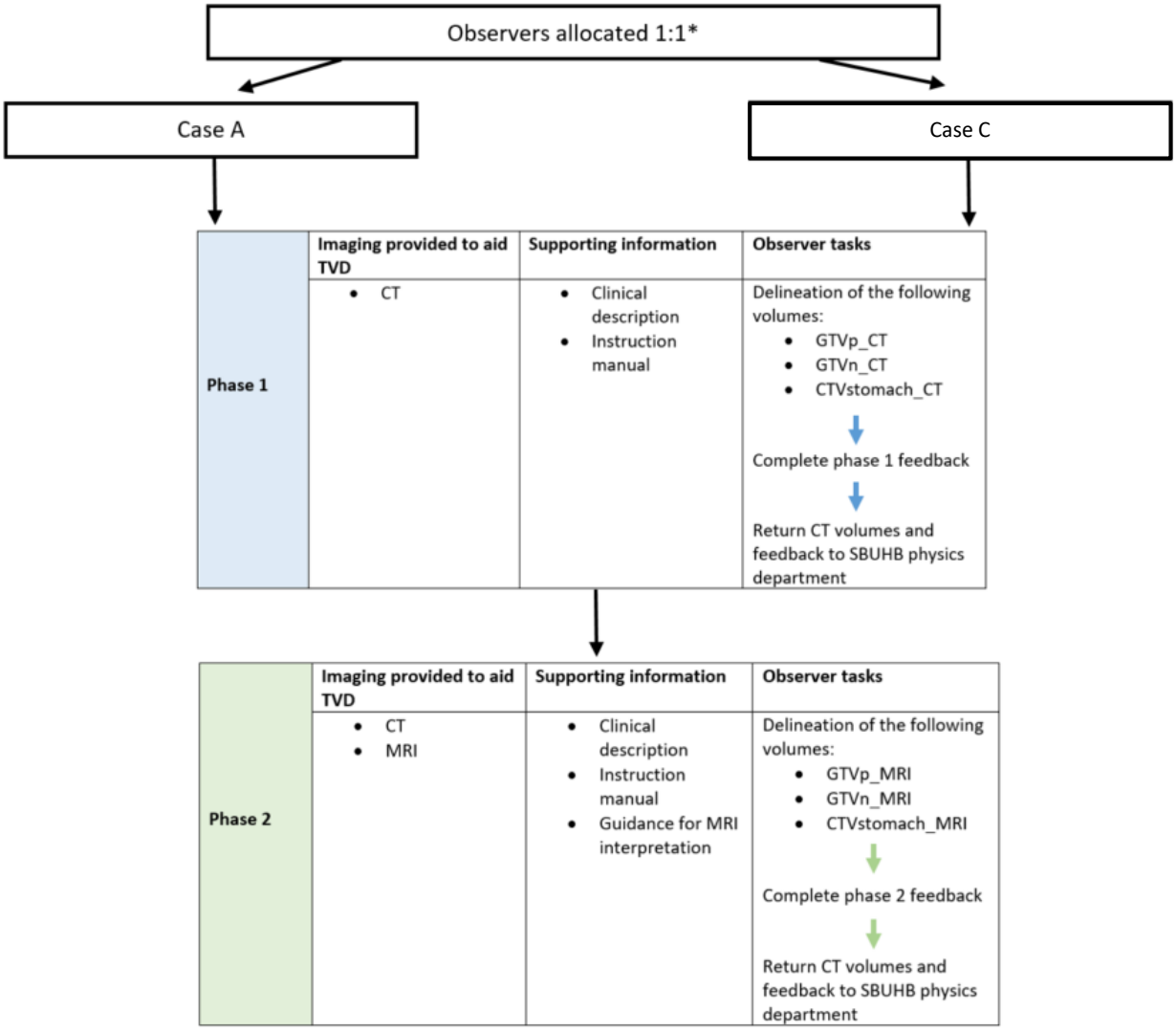


Figure 5.3. *Flow chart summarising the two phases of the IOV study, documents shared with observers for each phase, and tasks they were asked to complete.*
** 2 observers completed both cases. GTVp = Gross tumour volume of primary tumour. GTVn = gross tumour volume of involved lymph nodes. CTVstomach = Clinical tumour volume of whole stomach. Detailed instructions described exactly what should be included in each volume were suppled in the 'Instruction manual' (Appendix 5.1)*

5.3.4 Qualitative Feedback

Prior to taking part, observers were asked to complete a short survey about their gastric RT experience to date in the post-operative, pre-operative and definitive setting, as well experience in delineating the stomach as an organ at risk.

After each phase of TVD, observers were then asked to complete the table below (Table 5.3), to explore ease of delineation, time taken for TVD and perceived areas of difficulty. This was purposefully kept short to maximise response rates.

Test Case	**Approximate time to delineate CTVstomach**	**Approximate time to delineate GTVp**	**Ease identifying CTVstomach** (please rate 1-10, 1= difficult, 10= easy)	**Ease identifying GTVp** (please rate 1-10, 1= difficult, 10= easy)	**Comments** (please comment on areas you found straight forward or difficult to delineate)
Gastric_IOVstudy_case_A (CT alone)					

Table 5.3. *Qualitative feedback table for completion after TVD at each phase of study. The example given here is the table distributed after phase 1. An identical table was sent after phase 2 (with the exception of test case name indicating MRI was used)*

5.3.5 Generation of reference volume

A single 'gold standard' reference volume was created for GTVp, GTVn and CTVstomach at a consensus meeting of 2 OG oncologists (AC, SG) and 2 specialist OG radiologists (KF, GJ). The radiologists had independently delineated the two cases using both CT and MRI (as it was felt that all available imaging should be used to create the most accurate volume that best reflected the true extent of GTVp and CTVstomach), with final reference volume (GTVp_reference and CTVstomach_reference) agreed following discussion at the consensus meeting.

5.3.6 Generation of conformity indices

All data was anonymised and exported to CERR (Computational Environment for Radiotherapy Research) for analysis, which was performed by Professor Emiliano Spezi (Cardiff University). All GTVp and CTVstomach observer volumes were compared against the respective reference volume. GTVn was not analysed due to high number of missing observer data. A description of the conformity indices generated is outlined in Table 5.4.

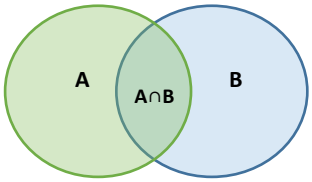
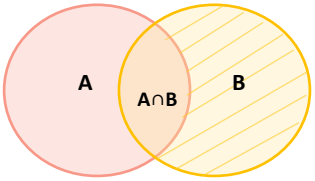
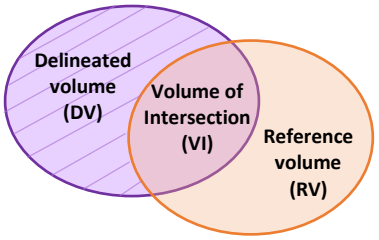
Conformity Metric	Description of metric/ values	Diagram
Jaccard Conformity Index (JCI)	Measures observer agreement (ratio of overlap of two volumes over union of the two volumes under comparison). 0 = no agreement 1 = perfect agreement	JCI = (A ∪ B)/(A ∩ B) 
Geographical Miss Index (GMI)	Calculates proportion of reference volume (B) not included in observer volumes (A) (i.e. measures the degree of **under outlining)** 0 = no reference volume missed 1 = 100% reference volume missed	GMI = B – (A ∩ B) /B 
Discordance Index (DI)	Calculates the proportion of observer volume (DV) not included not the reference volume (RV) (i.e. measures degree of **over-outlining**) 0 = complete concordance 1 = complete discordance	DI = (1-VI/DV) 

Table 5.4. *Description of conformity indices generated.*

5.3.7 Statistical analysis

Data was exported to SPSS for analysis and tested for normality via using Shapiro-Wilks. As most data was not normally distributed, and due to small sample number, median and interquartile range are presented here.

5.4 Results

Nineteen observers undertook the TVD exercise, two of whom took part in both cases, resulting in a total of 21 sets of volumes (Case A n=11, Case C n=10).

5.4.1 Conformity analysis

Eighty-four RT structures were analysed for conformity against the reference volume. Table 5.5 summarises the median conformity indices generated based on whole volume data for both Case A and Case C. Individual observer data is presented in Appendix 5.6.

Conformity index (median)	Case A					Case C				
	Gold Standard	GTVp_ CT	GTVp_ MRI	CTV stomach_ CT	CTV stomach_ MRI	Gold Standard	GTVp_ CT	GTVp_ MRI	CTV stomach_ CT	CTV stomach_ MRI
JCI (median)	1	0.66	0.71	0.84	0.85	1	0.88	0.83	0.91	0.91
GMI (median)	0	0.26	0.25	0.15	0.13	0	0.05	0.05	0.05	0.06
DI (median)	0	0.03	0.04	0.02	0.02	0	0.07	0.10	0.03	0.03

Table 5.5. *Median conformity indices for each structure analysed, for both Case A and C*

For phase 1 (CT alone), IOV was worse for Case A than Case C, both for GTVp (JCI 0.66 vs 0.88), and for CTVstomach (JCI 0.84 vs 0.94). Similarly, GMI of GTVp was also worse for Case A than C (0.26 vs 0.05), suggesting a higher degree of under-outlining for Case A. Conversely, DI (a measure of over-outlining) was low across both cases, though slightly higher for Case C.

For Case A, GTVp conformity improved with addition of MRI (JCI 0.66 vs 0.71) with improvement in JCI between phase 1 and 2 (CT+MRI) for 72.7% of observers (Table 5.6), and improvement in GMI and DI for 63.6% respectively.

In contrast, for Case C GTVp conformity worsened following MRI (JCI 0.88 vs 0.83), with a reduction in both JCI and DI for 80% of observers. However, there was improvement in GMI (i.e. a reduction in under-outlining) in 60% of observers, albeit small (median improvement in GMI = 0.02)

Conformity of CTVstomach was high for CT for both cases, with MRI adding very little.

Conformity index	Gross description	Change in median value following addition of MRI	Case A GTVp (n=11)	Case C GTVp (n=10)	Case A CTV stomach (n=11)	Case C CTV stomach (n=10)
JCI	Observer agreement 0= no agreement 1=perfect agreement	Improved	72.7%	20%	54.5%	20%
		No difference or worse	27.3%	80%	35.4%	80%
GMI	Under-outlining 0 = no ref volume missed 1 = 100% ref volume missed	Improved	63.6%	60%	54.5%	40%
		No difference or worse	36.4%	40%	45.5%	60%
DI	Over-outlining 0 = complete concordance 1= complete discordance	Improved	63.6%	20%	45.5%	20%
		No difference or worse	36.4%	80%	54.5%	80%

Table 5.6. *Change in conformity index for JCI, GMI and DI based on percentage of individual observer median values that were closer to the reference value following addition of MRI. For JCI, an increase in median value following MRI (i.e. closer to 1) was considered improved agreement with reference volume. For GMI and DI a decrease in median value following MRI (i.e. closer to 0) was deemed an improvement in conformity to reference value.*

5.4.2 Volume analysis

Median volume for GTVp and CTVstomach, compared to the reference volume are shown in Table 5.7, and individual observer volume data is displayed in Figure 5.4.

Volume	Case A		Case C	
	GTVp	CTVstomach	GTVp	CTVstomach
Median (cc)	255.98	626.23	502.51	1021.31
Interquartile range (cc)	52.89	57.01	165.36	77.51
Mean (cc)	255.93	599.53	536.45	1008.21
Range (cc)	163.8 - 297.43	333.40 – 678.03	455.35 - 687.52	896.47-1124.25
SD (cc)	38.11	94.03	87.10	66.16
Reference volume (cc)	340.38	704.91	482.13	1047.26

Table 5.7. *Median volume for each structure for both cases, compared to reference volume. Volumes were generated for phase 2 only, as both CT+ MRI was used to generate the reference volume (i.e. no reference volume based on CT alone exists for comparison)*

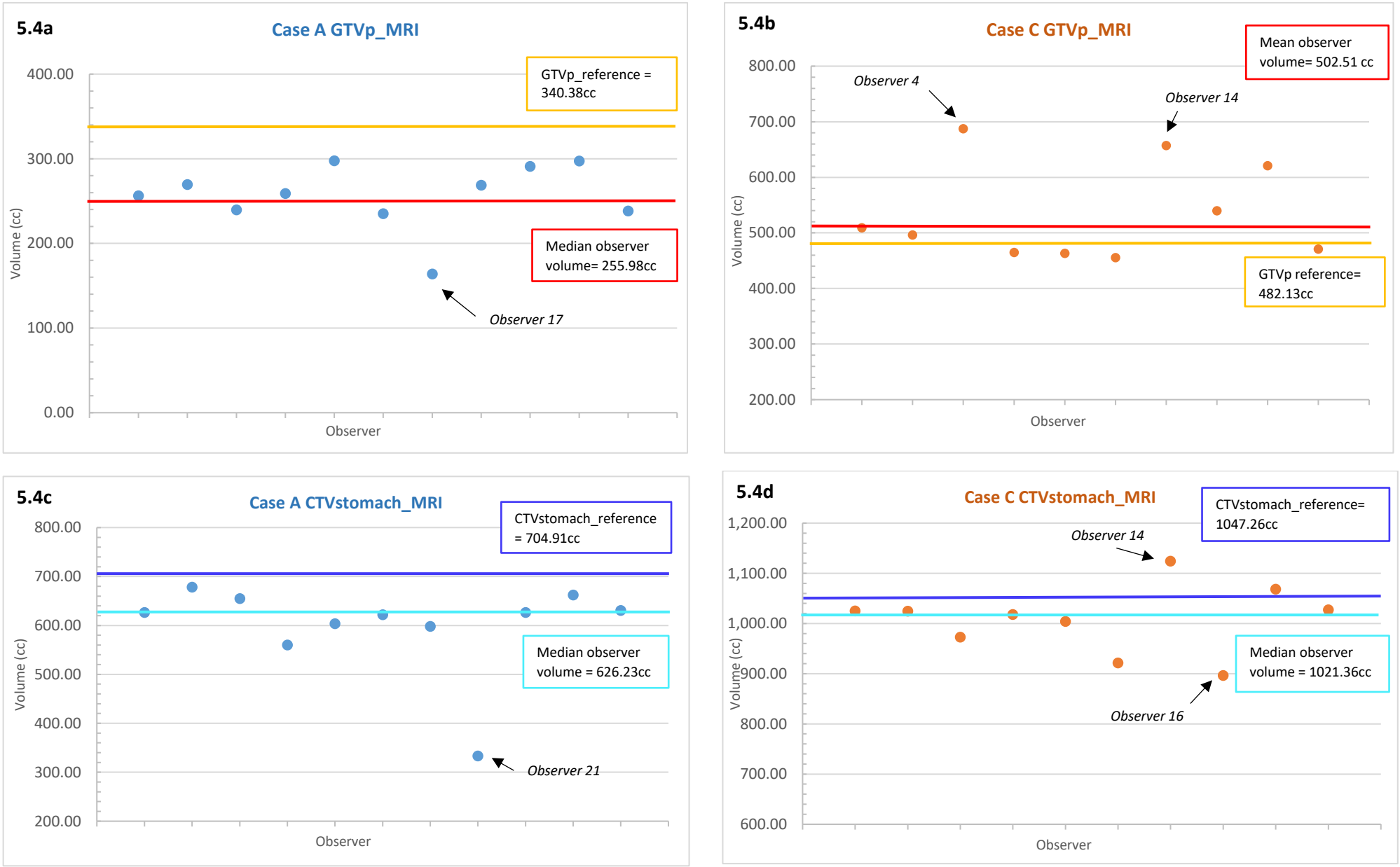


***Figure 5.4**. Volume for each individual observer (Case A =blue dots, Case C = orange dots). For GTVp, reference volume shown by the yellow line, and median observer volume the red line. For CTV stomach, reference volume is shown in dark blue, and median observer volumes is shown in light blue. Outliers are indicated by arrows.*

For **Case A** GTVp, all observer volumes were smaller than the GTVp_reference volume. Figure 5.5 shows the observer and reference volumes on a selection of axial slices. The GTVp_reference encompasses much more extra-gastric extension than the observer GTVp structures, accounting both for the overall difference in volume and high GMI, though three observers did include an additional lymph node, not included in the reference structure, which may have diluted the difference in median volume between reference and observer volumes.

The GTVp for observer 17, identified as an outlier (observer 17 = 163.80 vs reference = 340.38cc) is shown in Figure 5.6, which demonstrates both incorrect inclusion of only the stomach wall and exclusion of extra-gastric extension, accounting for the large difference.

Figure 5.7 demonstrates areas of most variation in CTVstomach volume, again largely due to omission of extra-gastric extension (observers were instructed that CTVstomach should include the whole GTVp). There was also some variation seen cranially around the gastro-oesophageal junction (GOJ), with some observers extending volumes more superiorly than the CTVstomach_reference (discussed in more detail in slice-by-slice analysis below).

Observer 21 was identified as an outlier for CTVstomach (observer21 = 333.80 vs reference= 626.23cc), which on review of the planning CT (Figure 5.8), appears to be due to an erroneous structure, reason for which is unclear, potentially failure of TPS system to interpolate volumes on these slices.

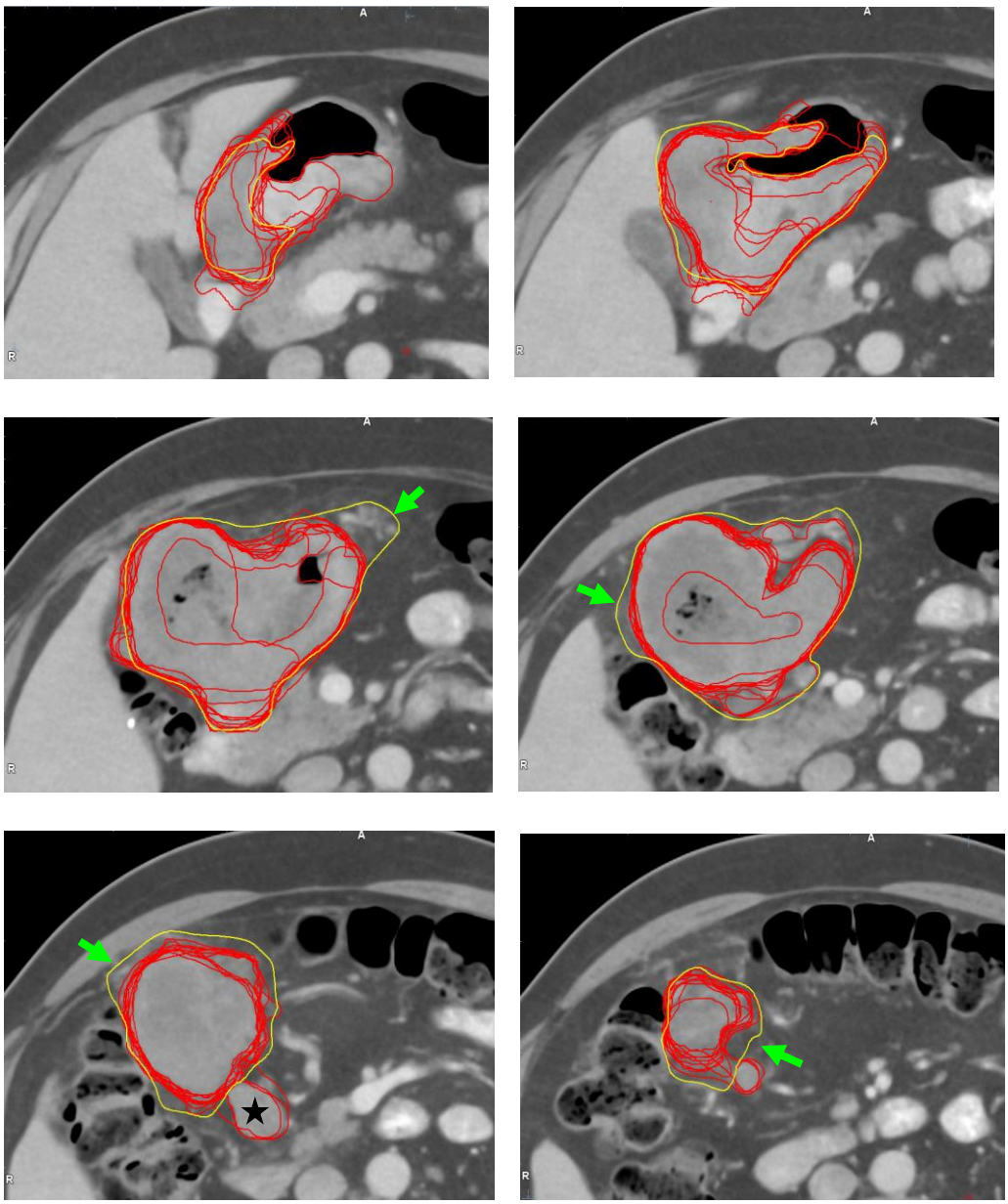


Figure 5.5. *Axial slices of planning CT (selected slices moving L-R from superior top left, to inferior bottom right) demonstrating GTVp_reference (yellow) and observer GTVp volumes (red) based on phase 2 (CT+MRI) for Case A. The green arrows indicate areas of extra-gastric extension, not encompassed by most observers. The black star shows the lymph node included by 4 observers.*

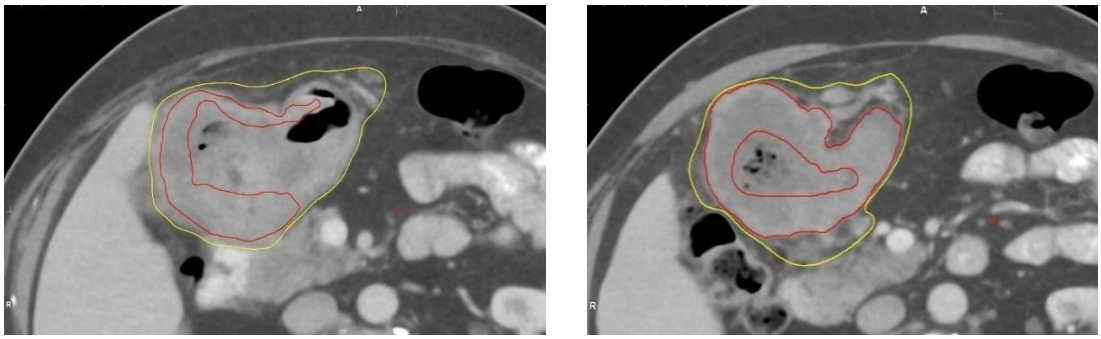


Figure 5.6. *Case A, phase 2. GTVp Observer 17 (red) compared to GTVp_reference (yellow) at two different levels showing the incorrect inclusion gastric wall only, with the volume excluding the centre of the stomach on slice 154.2, explaining the marked difference in volume (observer 17 = 163.80 cc vs reference volume = 340.38cc)*

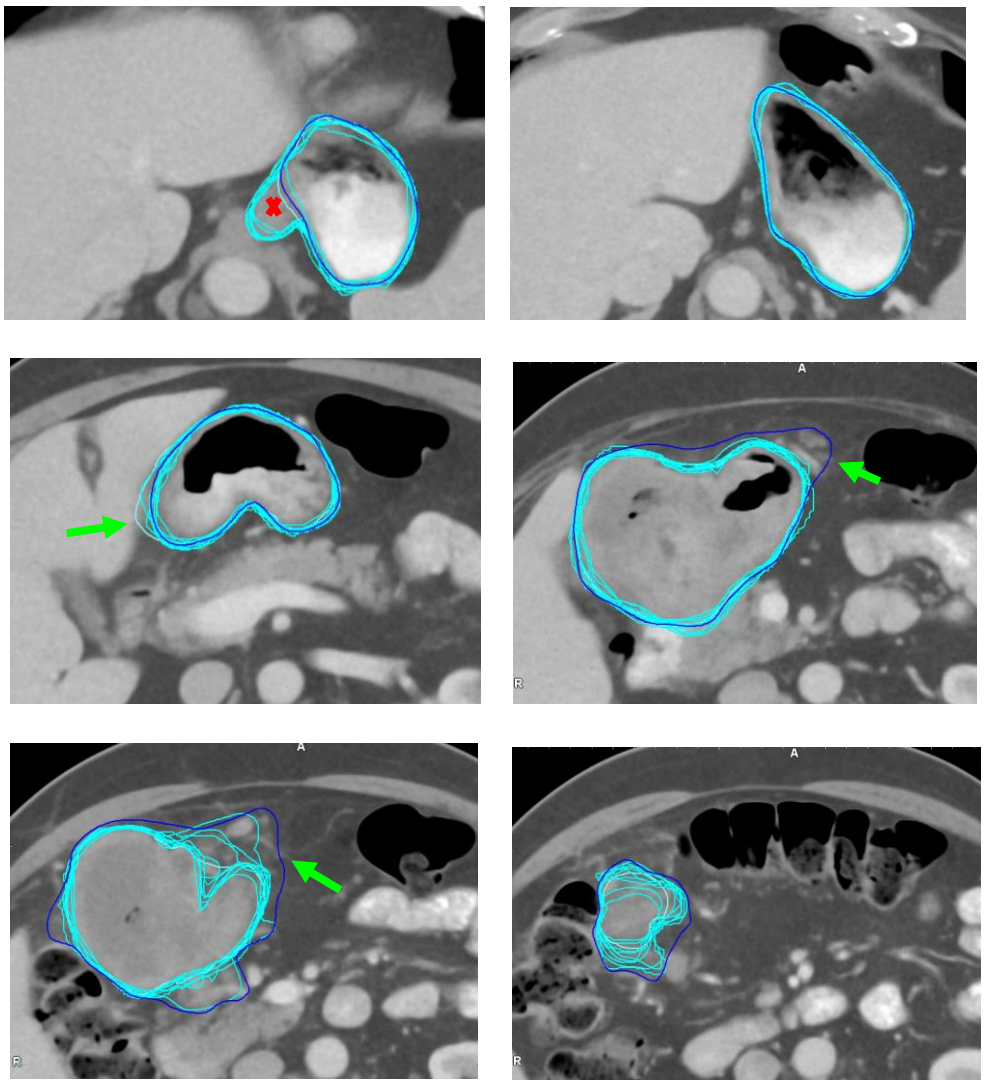


Figure 5.7. *Case A. Axial slices of planning CT (selected slices moving L-R from superior top left, to inferior bottom right). CTVstomach_MRI volumes for each observer (light blue) and CTVstomach_reference shown (dark blue line). The green arrows indicate areas of extra-gastric extension, not encompassed by most observers. The red X indicates the GOJ – another area of variation.*

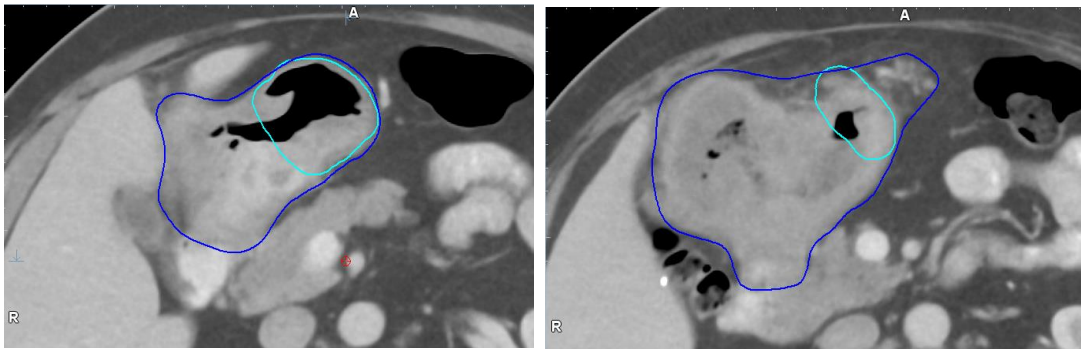


Figure 5.8. *CTVstomach volume shown for Observer 21 (light blue) and CTVstomach_reference (dark blue) showing an erroneous whole stomach volume accounting for significant difference in volume between the two.*

For **Case C,** median observer GTVp volume (502.51cc) is larger than GTVp_reference (482.13cc). On review of planning CT images (Figure 5.9), this appears due to variation at the GOJ and incorrect inclusion of whole stomach/ stomach contents at the level of the GTVp. Omission of the extra-gastric extension in the gastro-hepatic space is also evident. This is best exemplified by two largest volumes, observer 4 and 14 shown in Figure 5.10 (GTVp_observer4 = 687.52cc, GTVp_observer 14 = 657.25cc cc *vs* GTVp_reference = 502.51cc).

Median observer CTVstomach volume (1021.31cc) was smaller than CTVstomach_reference (1047.26cc). Imaging reveals consistency in observer and CTVstomach_reference at the middle of the volume (body of stomach) with most variation cranially at the GOJ, and caudally at the pylorus and duodenum, demonstrated in Figure 5.11. Observer 16 has contoured the smallest CTVstomach volume, with Figure 5.12 demonstrating this is likely due to omission of distal stomach at the inferior extent of the volume (CTVstomach_ observer16 = 896.47cc vs CTVstomach_reference=1047.26cc). Observer 14 has contoured the largest volume (Figure 5.14) – likely due to incorrect inclusion of duodenum in the whole stomach volume (CTVstomach_ observer14 =1124.24cc).

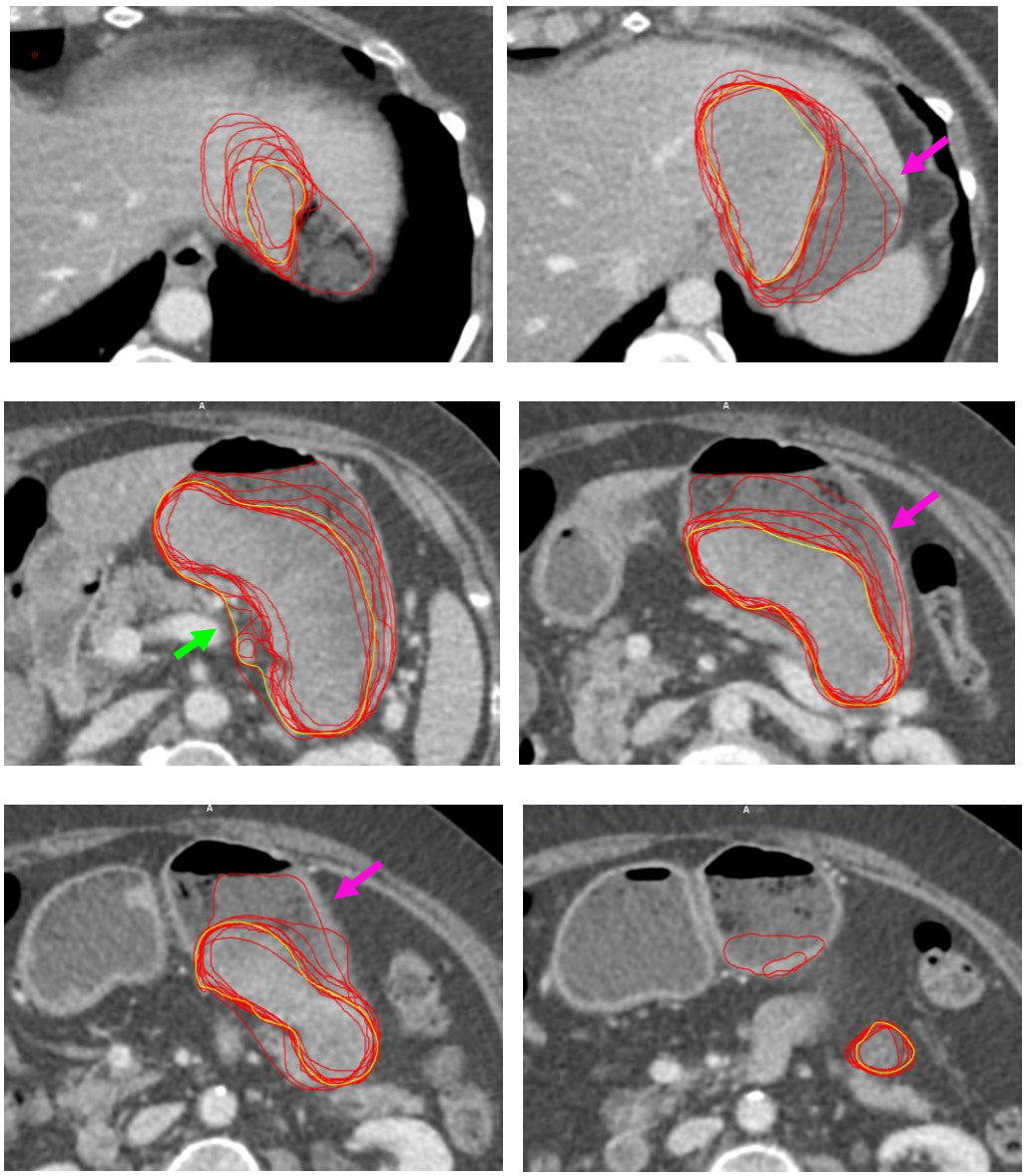


Figure 5.9. *Case C, GTVp_MRI. Axial slices of planning CT (selected slices moving L-R from superior top left, to inferior bottom right) demonstrating GTVp_reference (yellow) and observer GTVp volumes (red) based on CT+ MRI. The pink arrows indicate stomach contents which have been included in the GTVp volume by several observers. The green arrow shows extra-gastric extension in the gastro-hepatic space which has been included in the GTVp_reference but to varying degrees by observers.*

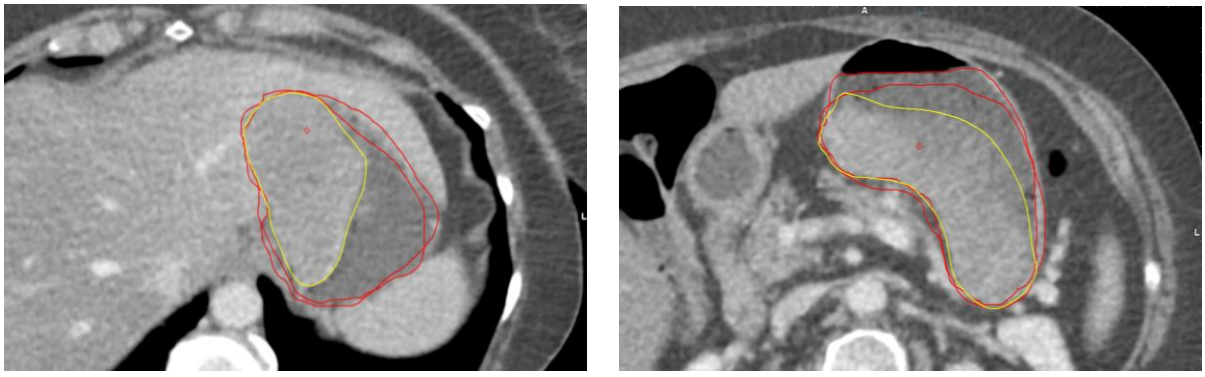


Figure 5.10. *Case C GTVp_MRI for Observers 4 and 14 (red) compared to GTVp_reference (yellow) at two different levels showing the large volume of non-involved stomach/ stomach contents included at these levels, explaining the marked difference in volume (observer 4= 687.52, observer 14 = 657.25cc cc vs reference = 502.51cc)*

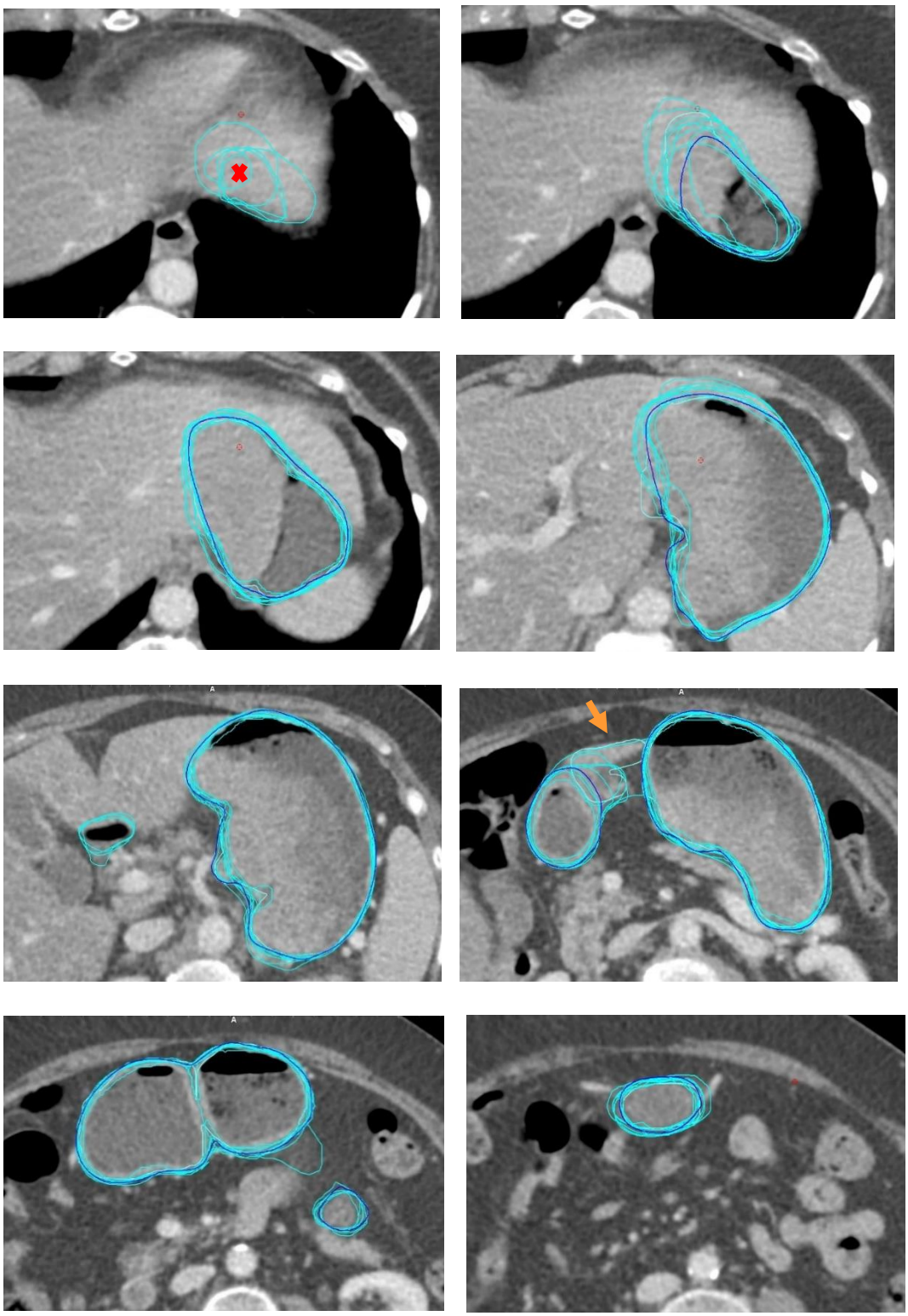


Figure 5.11. *Case C. CTVstomach_MRI volume for each observer (light blue) and CTVstomach_reference shown (dark blue line) Axial slices of planning CT (selected slices moving L-R from superior top left, to inferior bottom right). Superiorly the most variation is seen at the GOJ, indicated by red X. The orange arrow indicates some variation between body of stomach and pylorus/ duodenum.*

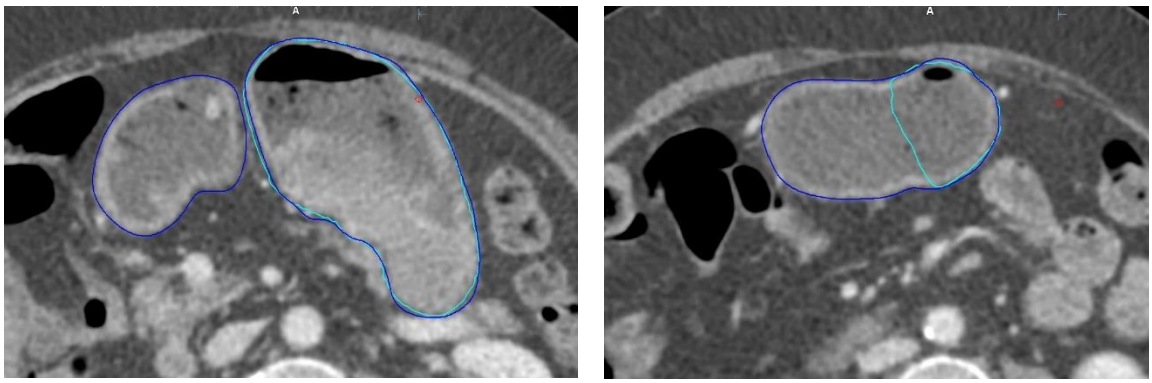


Figure 5.12. *CTVstomach volume shown for Observer 16 (light blue) and CTVstomach_reference (dark blue) demonstrating the omission of the distal loop of stomach by the observer accounting for a significantly smaller volume i.e. under outlining (observer 16= 896.47cc vs reference =1047.26)*

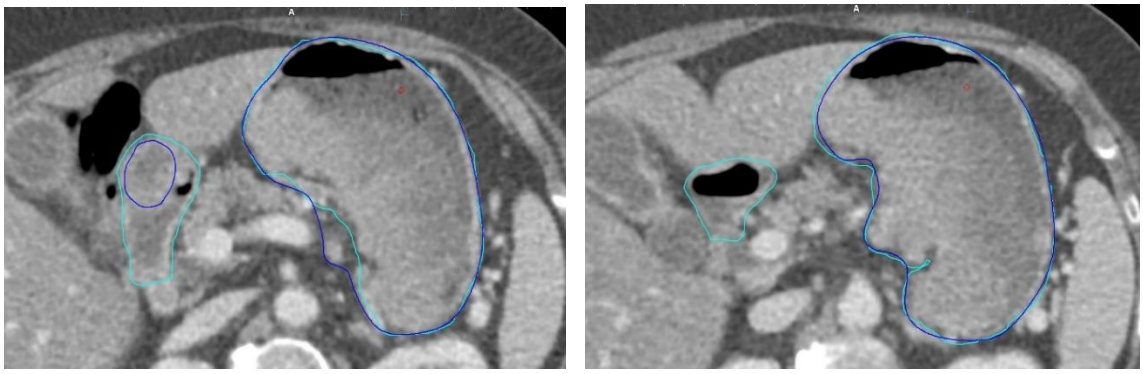


Figure 5.13 *CTVstomach volume shown for Observer 14 (light blue) and CTVstomach_reference (dark blue) demonstrating the incorrect inclusion of duodenum in stomach volume, resulting in larger volume, i.e. over-outlining (observer 14= 1124.24 vs reference =1047.26)*

5.4.3 Slice-by-slice analysis of JCI

To further evaluate where the most IOV exists anatomically, median JCI for GTVp was calculated for each CT slice following phase 1 and 2, for both cases. Only GTVp was chosen for slice-by-slice evaluation following the whole volume data analysis above, which showed most variation for GTVp, with CTVstomach demonstrating generally high conformity. For this analysis, a JCI of ≥0.7 was considered good agreement with the reference volume, a value which is reported as demonstrating good conformity, and used by other authors.[198,199]

5.4.3.1 Case A JCI slice by-slice analysis

Table 5.8 shows the median JCI for each axial CT slice for phase 1 (GTVp_CT) and 2 (GTVp_MRI) of Case A. For individual observer slice-by-slice data see Appendix 5.6.

Based on CT alone, the most IOV is seen cranio-caudally. Six observers started outlining GTVp too superiorly, increasing the cranial length of the volume by 5mm-50mm (median increase 22.5mm) above GTV_reference. Further variation is observed inferiorly with JCI <0.7 for most observers following CT alone (Figure 5.15). The most agreement is seen in the proximal to mid GTVp with a median JCI of ≥0.7 for 85.7% observers at the 7 most proximal slices of GTVp_reference (slice numbers -157.7 to -154.7).

CT Slice no.	Median JCI by slice			No. of observers with JCI >0.7		
	GTVp_CT	GTVp_MRI	Change between CT and MRI	GTVp_CT	GTVp_MRI	Change between CT and MRI
-162.7	0	N/A	N/A	0	N/A	N/A
-162.2	0	N/A	N/A	0	N/A	N/A
-161.7	0	N/A	N/A	0	N/A	N/A
-161.2	0	N/A	N/A	0	N/A	N/A
-160.7	0	N/A	N/A	0	N/A	N/A
-160.2	0	N/A	N/A	0	N/A	N/A
-159.7	0	N/A	N/A	0	N/A	N/A
-159.2	0	N/A	N/A	0	N/A	N/A
-158.7	0	0	0	0	0	0
-158.2	0	0	0	0	0	0
-157.7*	0.69	0.77	0.07	5	6	1
-157.2	0.72	0.78	0.06	6	6	0
-156.7	0.75	0.75	0.00	7	8	1
-156.2	0.77	0.77	0.00	8	7	-1
-155.7	0.74	0.77	0.02	7	9	2
-155.2	0.79	0.82	0.02	7	9	2
-154.7	0.78	0.80	0.01	8	9	1
-154.2	0.73	0.72	-0.01	8	8	0
-153.7	0.67	0.69	0.02	4	4	0
-153.2	0.66	0.61	-0.05	2	1	-1
-152.7	0.74	0.67	-0.07	6	3	-3
-152.2	0.64	0.61	-0.03	3	1	-2
-151.7	0.50	0.55	0.05	2	1	-1
-151.2	0	0	0	2	0	-2

Table 5.8. *Median JCI by axial CT slice for phase 1 (GTVp_CT) and phase 2 (GTVp_MRI) for* ***Case A,*** *and number of observers with JCI >0.7 (deemed good agreement) for each slice. Slice -162.7 is most superior (i.e. cranial extent) and -151.2 inferior (i.e. caudal extent). Improvement in JCI following MRI is indicated by green values, worsening by red values.*

** GTVp_reference begins at slice 157.7, with any observer GTVp volumes beginning more superiorly than this having a JCI =0 due to no agreement/no conformity. Greyed out rows marked N/A signify slices where there are no GTVp_reference or observer GTVp structure delineated, thus JCI cannot be calculated.*

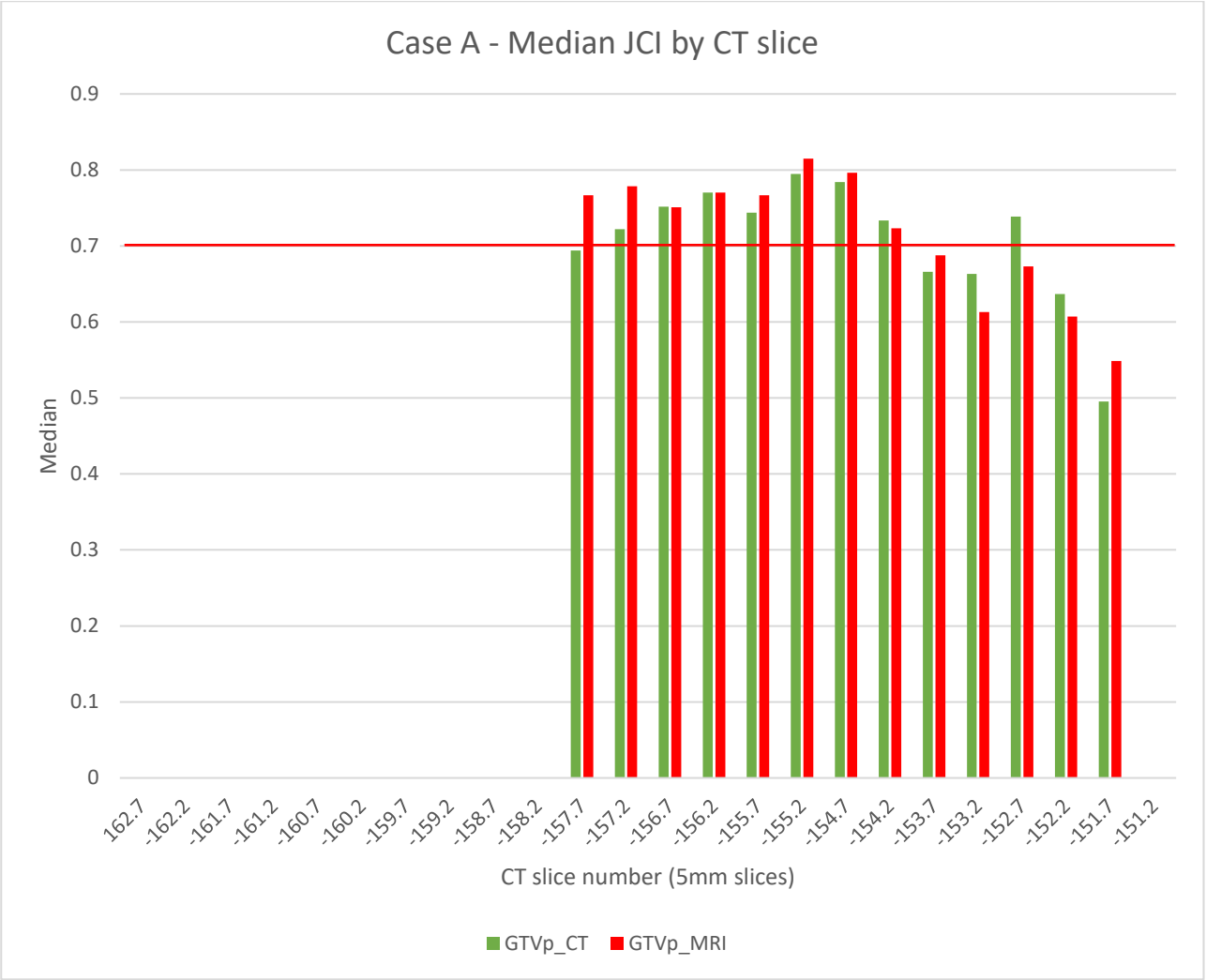


***Figure 5.14**. Median JCI by CT slice for GTVp_CT (green) and GTVp_MRI (red) for Case A. No bars are shown where JCI= 0. Red line at median JCI at 0.7 indicates threshold for 'good agreement.'*

Following MRI, JCI improved the most in the proximal half of GTVp. Correct identification of the superior edge of the tumour improved following MRI, with no observer GTVp structures extending >10mm beyond the GTVp_reference (n=5, median increase 10mm). JCI improved in 5 of the 7 most proximal slices of GTVp_reference, following MRI, where there was also an increase in the number of observers achieving a JCI >0.7.

However, JCI worsened in 5 of the 7 most distal slices. On review of individual observer GTVp structures, this corresponds with the previously discussed inclusion of a separate prominent lymph node in the GTVp by 3 observers (23,27,28), that had not been included after CT alone (Figure 5.16). Figure 5.17 compares the appearance of this node on diagnostic CT compared to DWI MRI sequences, showing the marked enhancement and possible contiguous appearance on MRI, which likely contributed to observers including this node in the GTVp rather than a separate GTVn. This corresponds to an increased DI for these 3 observers (see Appendix 5.6, table A5.5)

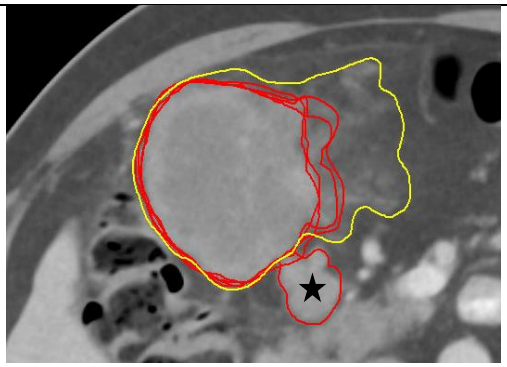
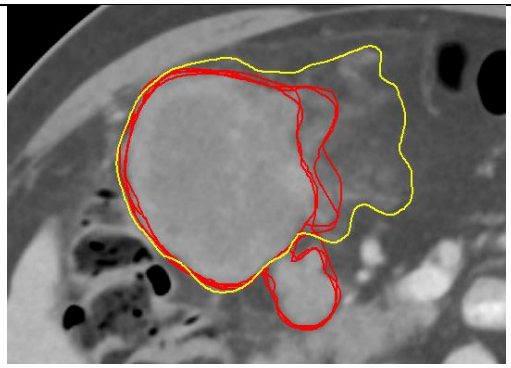
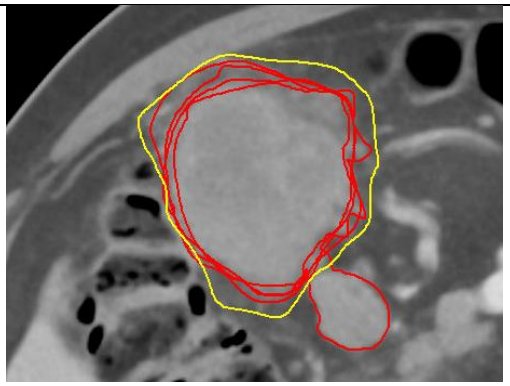
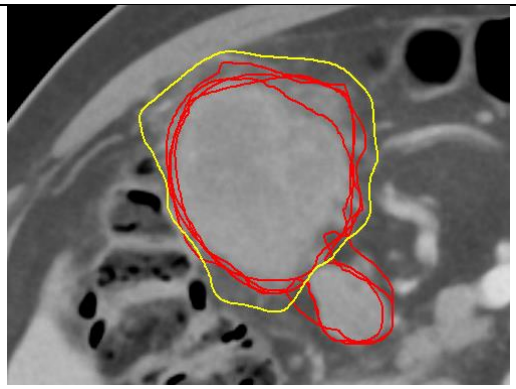
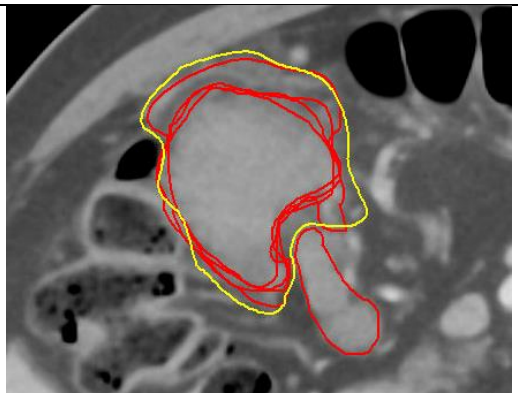
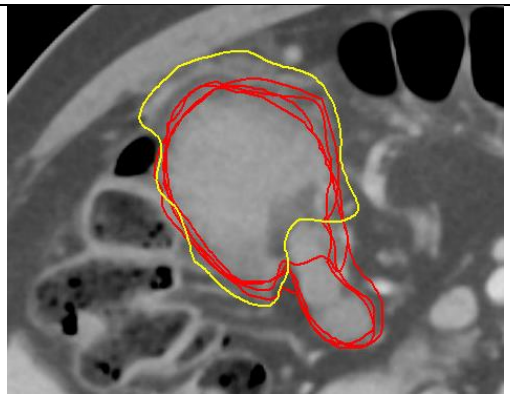
CT Slice	GTVp_CT (Case A)	GTVp_MRI (Case A)
-153.2		
-152.7		
-152.2		

Figure 5.15. *Distal slices of planning CT showing GTVp_CT (left) and GTVp_MRI (right) for observers 11, 23, 27, 28, demonstrating inclusion of additional lymph node (denoted with black star on first image) after MRI that was only included by 1 observer on the planning CT, but was included by 4 observers after MRI, contributing to reduction in JCI distally following MRI.*

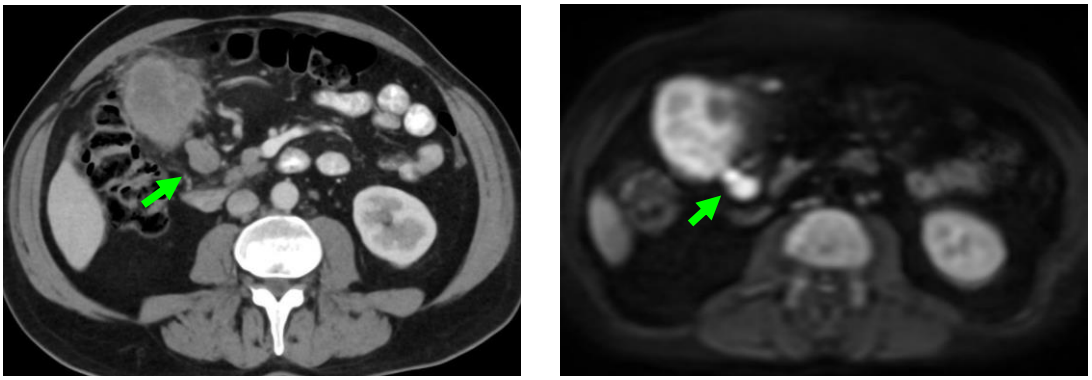


Figure 5.16. *Corresponding axial slice of diagnostic CT (left) and DWI MRI (right) at the level of node (green arrow) included by observers 11, 21, 27 and 28, showing its marked enhancement on DWI, increasing visibility, and likely contributing to its inclusion in GTVp volume.*

5.4.3.2 Case C JCI slice by-slice analysis

Table 5.9 shows the median JCI for each axial CT slice for phase 1 and 2 of Case C. For individual observer slice-by-slice data see Appendix 5.6.

As with Case A, most variation is seen at the cranio-caudal extent of the volume, though difference less marked for Case C, where only 2 observers began contouring GTVp too superiorly, and to a lesser extent than Case A (n=1 one outlined 1 additional slice [5mm], n=1 outlined 2 additional slices [10mm]). JCI was lowest at the top and bottom slice of GTV_reference (i.e. slice -200.3 and -187.8), but JCI was high for the majority of slices, with 100% observers achieving JCI >0.7 for 89.3% of slices (25 of 28 slices), as demonstrated in Figure 5.18.

CT Slice no.	Median JCI by slice			No. of observers with JCI >0.7		
	GTVp_CT	GTVp_MRI	Change between CT and MRI	GTVp_CT	GTVp_MRI	Change between CT and MRI
-201.3	0	0	0	0	0	0
-200.8	0	0	0	0	0	0
-200.3*	0.56	0.53	-0.03	3	1	-2
-199.8	0.89	0.85	-0.04	10	7	-3
-199.3	0.89	0.87	-0.03	10	8	-2
-198.8	0.88	0.75	-0.13	10	6	-4
-198.3	0.88	0.81	-0.07	10	7	-3
-197.8	0.87	0.84	-0.03	10	7	-3
-197.3	0.88	0.83	-0.05	10	8	-2
-196.8	0.92	0.87	-0.05	10	9	-1
-196.3	0.88	0.86	-0.02	10	9	-1
-195.8	0.90	0.86	-0.04	10	9	-1
-195.3	0.90	0.85	-0.06	10	10	0
-194.8	0.90	0.88	-0.03	10	10	0
-194.3	0.89	0.84	-0.05	10	10	0
-193.8	0.89	0.85	-0.05	10	10	0
-193.3	0.88	0.82	-0.07	10	10	0
-192.8	0.90	0.82	-0.07	10	10	0
-192.3	0.85	0.80	-0.05	10	9	-1
-191.8	0.92	0.85	-0.06	10	10	0
-191.3	0.90	0.83	-0.07	10	10	0
-190.8	0.87	0.78	-0.10	10	8	-2
-190.3	0.86	0.80	-0.05	10	9	-1
-189.8	0.90	0.85	-0.05	10	9	-1
-189.3	0.92	0.84	-0.08	10	9	-1
-188.8	0.85	0.82	-0.03	10	8	-2
-188.3	0.76	0.72	-0.04	8	6	-2
-187.8	0.67	0.68	0.01	3	4	1

***Table 5.9**. Median JCI by axial CT slice for phase 1 (GTVp_CT) and phase 2 (GTVp_MRI) for **Case C,** and number of observers with JCI >0.7 (deemed good agreement) for each slice. Slice -201.3 is most superior (i.e. cranial extent) and –187.8 inferior (i.e. caudal extent). Improvement in JCI following MRI is indicated by green values, worsening by red values.*

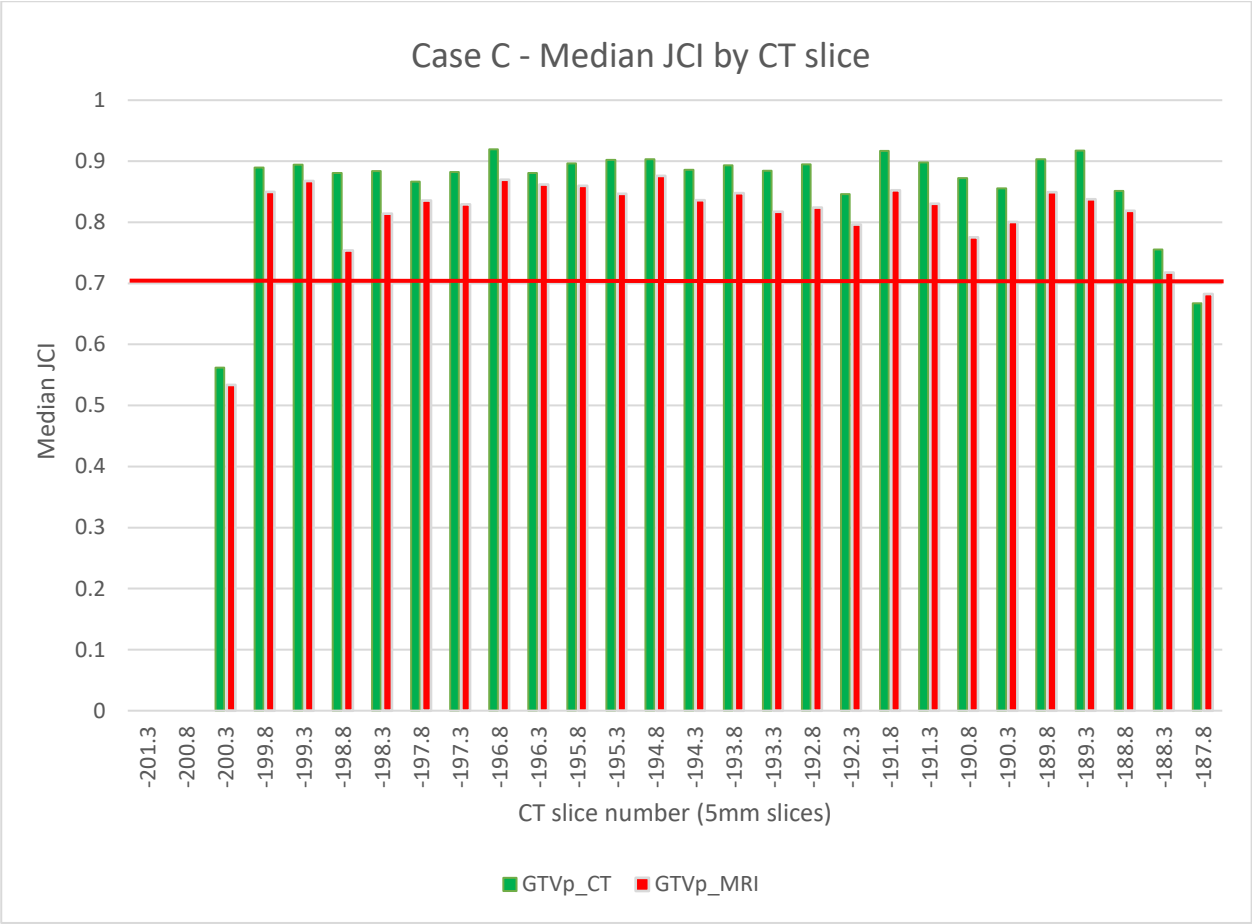


Figure 5.17. *Median JCI by CT slice for GTVp_CT (green) and GTVp_MRI (red) for Case C. No bars are shown where JCI= 0. Red line at median JCI at 0.7 indicates threshold for "good agreement.*

Following MRI, JCI worsened on 89.3% of slices. The most difference is seen in the proximal volume, with the biggest reduction number of observers achieving JCI >0.7 between slices -199.8 to 197.8, with the worst slice being -198.8 (reduction from 10 to 6 observers). GTVp_CT and GTVp_MRI structures for these slices are shown in Figure 5.19, which demonstrates an increase in number of observers over outlining the lateral edge of the tumour compared to GTV_reference, following MRI. This over-outlining is consistent with worsening DI across most observers, shown in Appendix 5.6, Table A5.6.

JCI only improved for one slice following MRI, the most caudal slice, though median JCI improved by only 0.01.

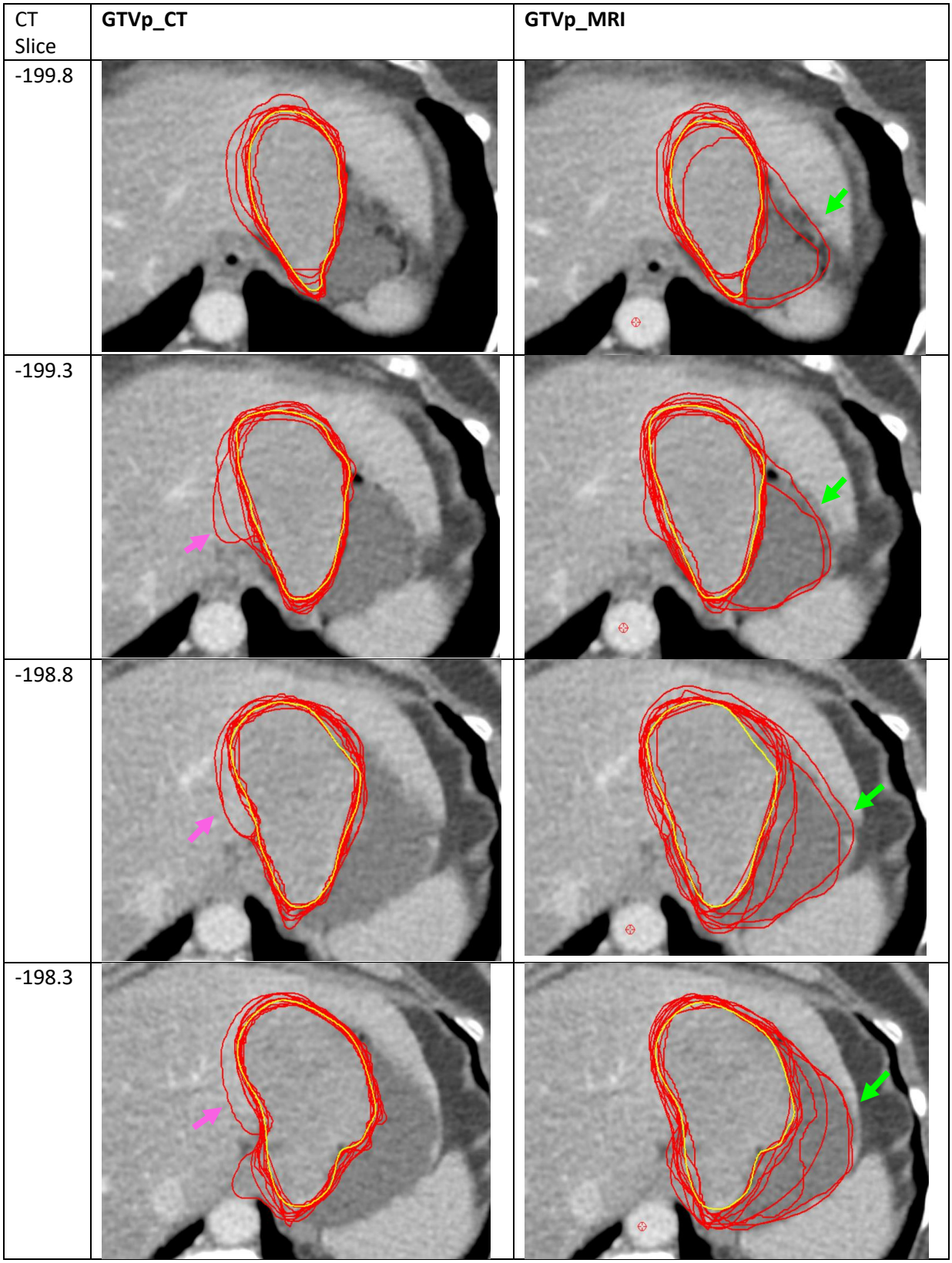


Figure 5.18. *Slices -199.9 to -198.3 planning CT showing GTVp_CT (left) and GTVp_MRI (right) for all observers. Reduction in over-outlining is seen at the medial edge of the GTVp (pink arrow), but there is increased over-outlining at the lateral edge by a number of observers (green arrow).*

5.4.4 Qualitative Feedback

All 19 observers completed the qualitative feedback.

5.4.4.1 Prior experience

Prior experience relating to prior gastric RT experience is summarised in Figure 5.20 and Table 5.10. 52.6%, 5.2% and 26.3% report prior experience in gastric TVD in the post-operative, pre-operative and definitive setting respectively. In the post-operative setting, 70% of observers had prior experience in ≤5 cases. Of the five observers with definitive experience, two had experience in 6 cases, but the remaining three observers had delineated ≤2 cases. 84.2% of observers had prior experience delineating the stomach as an organ at risk (in the context of planning other tumour sites, for example oesophagus), with 43.7% reporting experience in ≥20 cases.

For Case A, 8 of 11 observers (72.7%) had prior gastric RT experience, compared to 3 of 10 observers (30%) for Case C. With regards to stomach delineation experience, mean number of cases previously delineated per observer was 24.7 for Case A, compared to 6.9 for Case C.

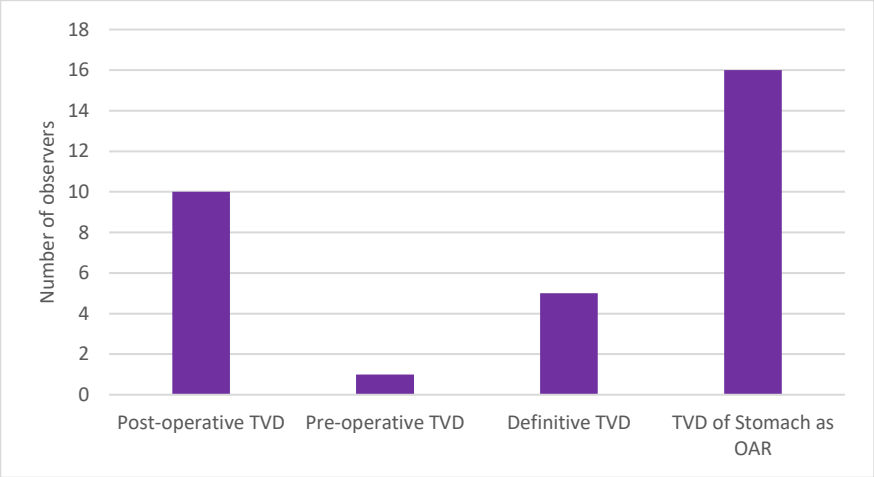


Figure 5.19. *Number of observers reporting prior TVD experience by clinical setting, or delineation of whole stomach as OAR*

	Number of observers (%)	Mean no. of cases delineated	Standard deviation	Range
Post-operative TVD	10 (52.6%)	5.3	3.4	1-10
Pre-operative TVD	1 (5.2%)	6	N/A	N/A
Definitive TVD	5 (26.3%)	3.4	2.1	1-6
TVD of Stomach as OAR*	16 (84.2%)	21	25.5	1-100

Table 5.10. *Prior gastric RT TVD experience of observers, including number of cases delineated in each setting.*
**where a range/estimation was provided, the upper value was used to calculate mean*

5.4.4.2 Time for TVD

Approximate time spent undertaking TVD for each volume is summarised in Table 5.11 and Figure 5.21. Regarding Case A, there was no difference in median time between phase 1 (CT) vs phase 2 (CT+MRI) for CTVstomach delineation, median time of 10 minutes for both phases. 36.3% of observers reported shorter time for delineation of CTVstomach for phase 2, 45.4% longer delineation time, and 18.2% no difference. Median time for TVD of GTVp was reduced from 25 minutes for phase 1 to 15 minutes for phase 2, with 45.4% reporting shorter time for phase 2, 36.3%, longer and 18,2% no difference.

For Case C, delineation time of CTVstomach was reduced by 5 minutes for phase 2 (median time 20 minutes for phase 1 vs 15 minutes phase 2), with 50% of observers reporting reduced TVD time for phase 1 and 20% reporting increased time. Median time for delineation of GTVp was increased with the addition of MRI, from 20 minutes for phase 1, to 22.5 minutes for phase 2, with 60% of observers reporting longer delineation time, compared to 30% shorter.

Time (minutes)	**CASE A (n=11)**				**CASE C (n=10)**			
	Phase 1 (CT alone)		**Phase 2 (CT+MRI)**		**Phase 1 (CT alone)**		**Phase 2 (CT+MRI)**	
	CTV stomach	GTVp	CTV stomach	GTVp	CTV stomach	GTVp	CTV stomach	GTVp
Median	10	25	10	15	20	20	15	22.5
Interquartile range	12	25	4	25	29	8	11	16

Table 5.11. *Approximate time spent for TVD for each volume.*

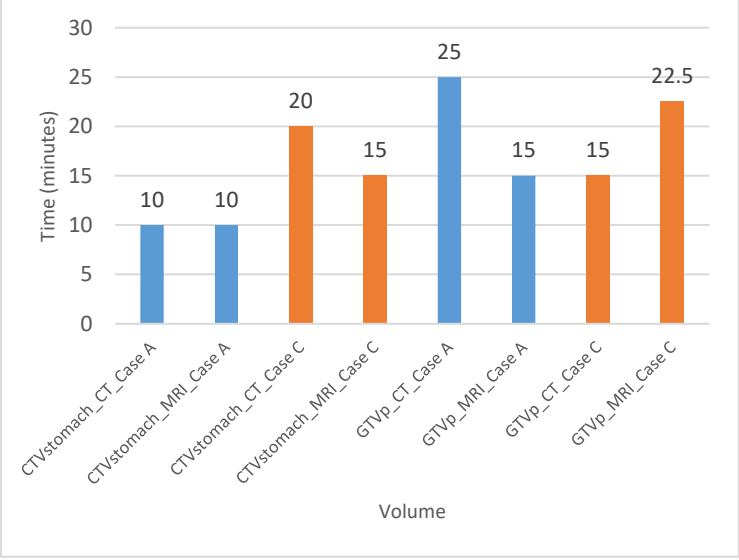


Figure 5.20. *Change in median time for TVD by volume, with structures displayed side-by side. Case A (blue), Case C (orange)*

Observers were retrospectively asked to disclose their approach to TVD for phase 2; whether they had copied phase 1 volumes and subsequently modified these with the additional MRI information (i.e. 'copy+modify'), or if they had created brand new volumes for phase 2. This information was only returned for 18 of 21 sets of volumes. N=11 (61.1%) reported creating new volumes, and n=7 (38.9%), using a copy+modify approach. There was no statistically significant difference between approach to TVD and time taken for GTVp delineation (chi-square asymptotic significance [2-sided] p=0.387), though findings should be interpreted with caution due to small sample size (see Appendix 5.6 Table A5.14)

5.4.4.3 Ease rating

Table 5.12 summarises the 'ease of delineation' scores for each volume for both case A and C

Ease of delineation score (1-10)	**CASE A (n=11)**				**CASE C (n=10)**			
	Phase 1 (CT alone)		**Phase 2 (CT+MRI)**		**Phase 1 (CT alone)**		**Phase 2 (CT+MRI)**	
	CTV stomach	GTVp	CTV stomach	GTVp	CTV stomach	GTVp	CTV stomach	GTVp
Median score	8.00	5.00	8.00	7.00	5.5	6.0	6.0	8.0
Interquartile range	1.00	4.00	1.00	2.00	4.9	3.0	3.0	2.0

Table 5.12. *Ease of TVD rating for each volume (1 = difficult, 10 = easy)*

For **Case A**, median score for CTVstomach was 8.0 for both phase 1 and 2. For GTVp, median ease rating was 5.0 for phase 1 vs 7.0 for phase 2. The addition of MRI improved ease of TVD of CTVstomach for 63.6% (n=7) of observers, with a median improvement of 1 point. 27.3% (n=3) of observers reported no change in ease rating, and 9.1% (n=1) reported a lower score following MRI. For GTVp, the addition of MRI improved ease rating for 72.7% (n=8) of observers, with a median improvement of 2 points. 27.3% (n=3) reported no changed in ease rating with addition of MRI, but none rated MRI as inferior to CT alone. (Figure 5.X).

For **Case C**, the median ease rating for CTVstomach was 5.5 and 6.0 based on phase 1 and 2 respectively. For GTVp, median was 6.0 for phase 1, increasing to 8.0 following MRI. 60% (n=6) of observers reported an improvement in ease rating for CTVstomach with the addition of MRI for Case C, with median improvement of 1 point. 30% (n=3) reported no change and 10% (n=1) reported a worse score. For GTV, 90% (n=9) reported an improved ease rating with the addition of MRI, with median improvement of 2 points. 30% (n=3) reported no change and, as for Case A, none rated MRI as inferior to CT.

When considering both cases together, the addition of MRI to CT improved ease of delineation score for GTVp for 81% of observers (n=17/21), with no observers reporting worse scores following MRI. A larger degree of improvement in ease rating was seen for GTVp delineation (median improvement in score of 2 points) than for CTVstomach (1 point).

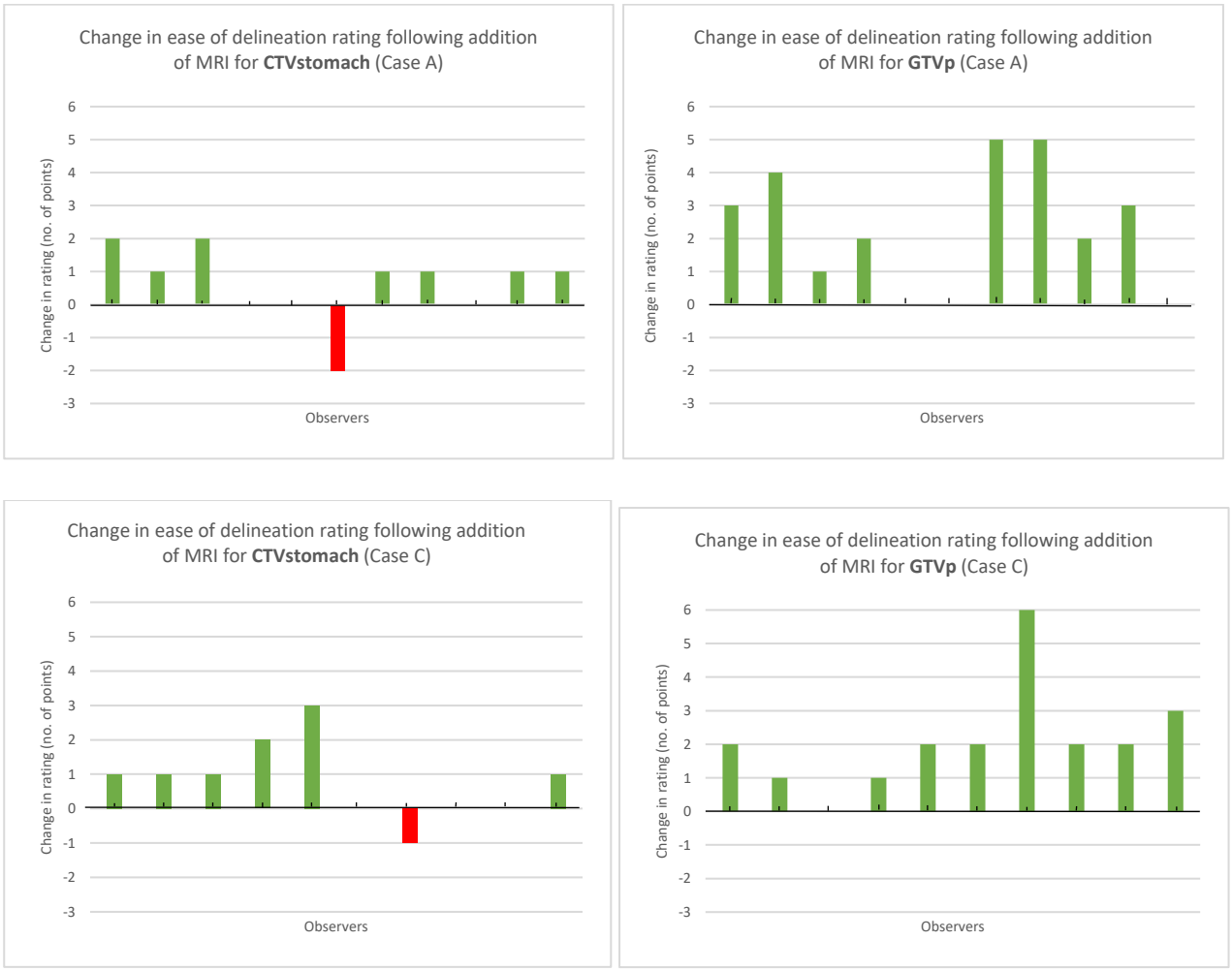


Figure 5.21. *Change in ease of delineation score (i.e. difference in score between phase 1 [CT alone] vs phase 2 [CT+MRI]) for Case A (top row): CTVstomach (left) and GTVp (right), and Case C (bottom row). CTVstomach (left) and GTVp (right). Each bar represents an individual observer, with positive change in ease rating shown in green, negative in red, and no bar is shown where there was no change.*

When considering prior radical gastric RT experience, there was no statistically significant association between prior experience and change in ease rating between phase 1 and phase 2 (chi-square asymptotic significance [2-sided] p=0.953) though findings should be interpreted with caution due to small sample size (see Appendix 5.6 Table A5.15)

5.4.4.4 Feedback themes

95% (n=20/21) of observers reported difficulties in TVD following phase 1 (CT alone). Common perceived areas of difficulty were differentiation of tumour from normal stomach wall or contents (n=9), identification of pylorus and duodenum (n=8), involved lymph nodes (n=7) and boundary/involvement with adjacent organs (n=4). (Figure 5.23). All feedback is recorded in Appendix 5.7. Some examples of representative observer comments include:

- *"Difficult to differentiate normal stomach from tumour. Difficult to identify the exact proximal extent of tumour"(Case A)*
- *"Appreciating the superior and inferior extent of tumour was difficult, as was extragastric extension. Top end of GTV was particularly tricky, where it merged with stomach contents…" (Case A)*
- *"Very difficult to identify the intra-luminal margin of the GTV even with good gastric filling" (Case C)*
- *"…Also determining the boundary between liver and tumour is challenging. As always, the pyloric region leading to the duodenum is challenging" (Case C)*

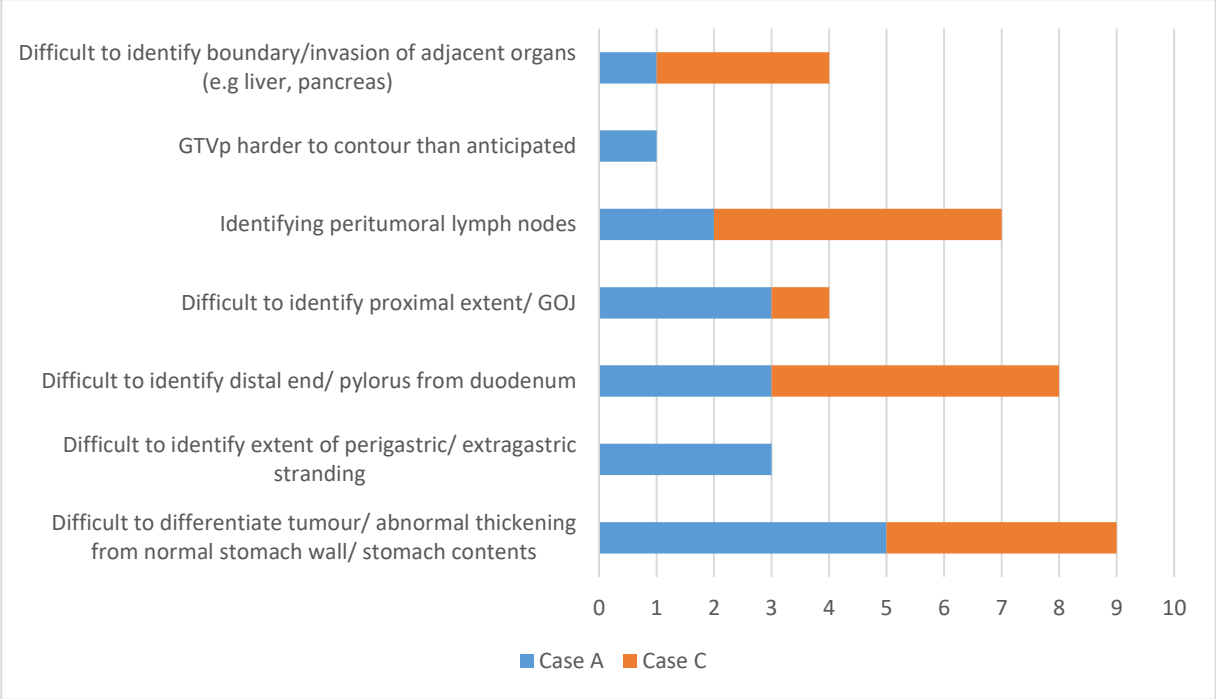


Figure 5.22. *Qualitative feedback themes identified following phase 1 (CT alone). Case A (blue) and Case C (orange) Bars represent number of comments in each category.*

Following phase 2, n=15 (71.4%) reported that MRI improved visualisation for TVD, with themes summarised in Table 5.13. Positive feedback included improved visibility of GTVp (n=5), GTVn (n=6) and extra-gastric extension (n=2). Five observers identified DWI as particularly useful, compared to only one for T2 sequences.

The differences in stomach filling/position between CT and MRI and inability to co-register the MRI with CT were highlighted as most common difficultly faced in phase 2, with n=3 observers also highlighting the lack of experience and education in MRI interpretation.

MRI based feedback	**Number of comments**		
	Case A	**Case C**	**TOTAL**
Positive themes			
Easier to identify GTVp with MRI	3	2	5
Easier to identify GTVn with MRI	4	2	6
MRI made contouring generally easier	2	3	5
DWI helpful to visualise tumour	3	2	5
T2 sequences helpful to visualise tumour/nodes	0	1	1
MRI generally increased size of volumes due to increased visibility/ appreciated of extra gastric extension	1	1	2
MRI helped with definition of invasion into nearby organs (liver)	0	2	2
Negative themes			
Difficult to correlate MRI with CT (due to filling/ position/ lack of co-registration)	3	3	6
Harder to appreciate fat stranding on MRI	1	0	1
Lack of experience interpreting MRI/ more education required	2	1	3
MRI didn't add to CT/ contours didn't change	1	2	3

Table 5.13. *Themes identified from qualitative feedback following phase 2 (CT+MRI), grouped by positive and negative comments.*

Some representative observer comments following phase 2 include:

- *"Much easier with MRI, especially GTVp and GTVn." (Case A)*
- *"Whole stomach volume didn't really change. However, I did extend GTV further sup and inf, and also included more extra-gastric stranding. I found DWI and contrast enhanced imaging most useful… MRI generally made me extend rather than decrease the size of my volumes." (Case A)*

- *"Whilst MRI does make tumour more visible and MRI atlas very good, I often wanted to ask questions. Lack of confidence in interpreting MRI, especially at the edge of tumour... A webinar/ question and answer session would be helpful." (Case A)*
- *"GTVp clearly seen on MRI. Easier to outline, especially where there is liver invasion. Would help if the images were fused." (Case C)*
- *"Subjectively it felt that MRI made it easier to identify the GTVp but the final GTVp volume was very similar to what was drawn on the CT alone. MRI did not contribute much in outlining CTVstomach. Difference in gastric filling between the CT and MRI added some confusion." (Case C)*
- *"I'm not sure MRI added a huge amount compared to diagnostic CT in terms of voluming, particularly the CTVstomach" (Case C)*

5.5 Discussion

5.5.1 What are the areas of most variation and inaccuracy in gastric TVD?

This study has identified several areas of variation in TVD of GTVp for gastric RT including:

- ***Cranio-caudal extent of the GTVp*** – with proximal slices of both cases displaying the lowest JCI, and extension of volumes more superiorly than GTVp_reference in both cases, up to 50mm in Case A.
- ***Differentiation between tumour and normal stomach wall, or stomach contents*** - resulting in over-outlining errors. This is particularly evident in Case C, where median DI was 0.07 (phase 1) – 0.10 (phase 2), though individual observer DI values reached up to 0.33 (Appendix 5.6, Table A5.6) – equating to 33% of additional 'normal' tissue included in RT treatment volumes, which is clinically relevant due to potential increase in treatment toxicity.
- ***Extra-gastric extension***– evidenced best by Case A, with omission of areas of extra-gastric extension resulting in high GMI of 0.26 – equating to 26% of the tumour volume being missed by observers. This is clinically extremely significant as would result in under-treatment of the tumour and likely compromise disease control.

These areas are consistent with key aspects of IOV reported by the current literature, particularly variability in the cranio-caudal extent of volumes, highlighting the importance of clear definition relating to the upper and lower extent of volumes in any future gastric RT protocol.[173,174] They also align with the areas of most difficulty highlighted by qualitative feedback - also consistent with the existing literature. Socha *et al*. conducted a questionnaire of 12 participants following a gastric RT contouring course to explore difficulties in TVD. Though the main area of difficulty identified by their participants was delineation of the elective nodal area (which is not relevant here), there were several areas of difficulty that were consistent

with the findings of this study, namely unfamiliarity with radiological anatomy of the upper abdomen and lack of experience in gastric RT. Conflicting recommendations in guidelines were highlighted as a reason for difficulty in elective nodal TVD, further emphasising the importance of clear descriptions within consensus RT protocols.

JCI values for GTVp were lower for Case A than Case C. Whilst this may be due to differences in visibility of tumour on cross-sectional imaging between cases, or prior experience of observers between groups, it is possible some variation exists due to limitations of the conformity indices used. Metrics measuring overlap, such as JCI and GMI are known to be sensitive to structure size, especially to smaller volumes, where small variation in TVD can have a large impact on metric. [199,200] Therefore, it is possible that the higher conformity values seen in Case C, which evaluated larger volumes than Case A, are partly due to reduced sensitivity of the metric rather than solely due to better delineation accuracy in Case C than Case A. Future work investigating whether larger differences in IOV exist for earlier stage, smaller volume tumours is necessary to further evaluate the significance of these conformity metrics in gastric cancer.

It also worth noting that while a JCI value of >0.7 has been used by a number of prior studies in other tumour sites to demonstrate good conformity, there is no specific evidence to validate this threshold – and it has been suggested that acceptability of variation depends on the clinical context and consequences of IOV. More work is required to further evaluate the optimal, clinically relevant JCI threshold in the context of gastric RT.

CTVstomach volumes for both cases demonstrated high JCI values, indicating lower IOV. However, when considering ease of delineation rating, this was much lower for Case C (median ease rating 5.5/10 after phase 1, 6/10 phase 2) than Case A (8/10 both phases). This may be due to differences in the prior experience, with mean number of prior whole stomach delineations being 6.9 for Case C observers, compared to 24.7 for Case A. Additionally, four Case C observers (40%) specifically commented on difficulty identifying the stomach – duodenal border, compared to only one comment for Case A, suggesting anatomical differences between cases may have also contributed.

5.5.2 Does MRI quantitively improve accuracy and reduce IOV?

Data is conflicting with regards to the effect of MRI on conformity of gastric RT volumes. For Case A, addition of MRI resulted in improvement in JCI for 72% of observers, with particular improvement at the proximal GTVp, where JCI values were most improved, and significant reduction in extent of over-outlining observed. In contrast, for Case C, JCI worsened following MRI for 80% of observers, largely due to increase in DI (i.e. over outlining) following MRI.

However, a number of potential confounders exist, which may account for this conflicting data. Lack of observer experience and training in gastric MRI interpretation, particularly DWI, was identified as an

important confounder in qualitative feedback, with inexperience possibly resulting in increased observer uncertainty and contributing to larger IOV seen in Case C. Educational workshops have been shown as valuable tools to reduce IOV in post-operative RT, therefore it is reasonable to assume that training sessions that incorporate gastric MR interpretation would result in improved conformity in this setting, and should be incorporated by future IOV studies.[175,176]

5.5.3 Does MRI improve ease of gastric TVD?

Subjective ease of TVD markedly and consistently improved following the addition of MRI for both cases, with overall improvement in ease rating in 81% of observers, and 71.4% specifically reporting that MRI improved visualisation for TVD. Notably, for GTVp, no observers reported worsening ease ratings, suggesting additional imaging only helped, rather than hindered TVD. Themes highlighted by observers as areas of difficulty were consistent with areas of greatest IOV in TVD e.g. differentiation between tumour and normal stomach/contents, extent of extra-gastric extension and cranio-caudal extent of GTVp volumes.

Whilst MRI did not consistently quantitively improve IOV in these areas, given the marked subjective improvement in ease of TVD, it is possible that further education and experience in interpreting MRI would result in reduced IOV in future.

5.5.4 Which MR sequences are subjectively most useful for gastric TVD?

Qualitative feedback identified DWI as a useful MR sequence to aid TVD – commented on specifically by n=5 observers. This is consistent with the literature, which has also identified DWI as a useful imaging sequence for T-staging.[187,188] However, a confounding factor in this study is the limited number of MRI sequences available to observers (T2 and DWI) for evaluation. This was intentional, to minimise overwhelm for oncologists not familiar with interpreting multiple MR sequences and allow focus on the two sequences specialist OG radiologists deemed likely to be most informative for TVD. For Case A, DWI imaging resulted in inclusion of an involved node in GTVp volume by 3 observers. Whilst this in the context of this study, this increased IOV, in the clinical setting addition of all involved disease in treatment volumes is vital for optimal disease control or cure – thus DWI could prove a useful tool for identification of involved nodal disease following appropriate training.

5.5.5 Limitations of the study

There are several limitations and confounding factors including:

- Small number of observers.
- Inclusion of only 2 test cases.

  Though design of this study set out to evaluate 4 cases of varying stage and anatomical location, it was not possible to do so due to lack of clinician time to conduct numerous TVD cases. Though the 2 cases selected allowed comparison of TVD at different anatomical sites, both cases were locally advanced (T4b), so IOV of smaller tumours, which may have been more subtle on cross-sectional imaging, could not be evaluated.
- Experience bias.

  The design of the study meant that all clinicians saw and delineated using CT first, introducing experience bias when viewing the MR images. Though this does not bias conformity data (as in true clinical practice, clinicians would only use MRI in addition to, and not in place of CT), it does bias ease rating and time taken for TVD, so should be taken into consideration when interpreting results.
- Use of retrospective, non-dedicated MRI images.

  The retrospective nature of the study, particularly relating to use of MRI liver as a surrogate for gastric MRI, resulting in differing patient preparation (i.e. differences in stomach filling) and position between modalities, resulted in increased complexity in image interpretation and inability to co-register images for TVD, adding further confounding factors to both conformality and qualitative assessments.
- Lack training/ education relating to MRI interpretation.

5.5.6 Further work

Time constraints of this research limited the extent of slice-by-slice data analysis performed. Future work evaluating the slice-by-slice variation in GMI and DI is required to fully understand the areas of most IOV, and potential advantages and pit-falls of using gastric MRI for TVD.

Further IOV studies should be performed utilising prospective planning CT, ideally with 4DCT to also evaluate the impact of motion, along with prospective, dedicated MRI stomach with appropriate patient preparation and positioning. In addition, future work should evaluate TVD of earlier gastric tumours, which may be less readily visible on CT, where MRI may have added benefit.

5.6 Conclusion

This first, hypothesis generating study assessing IOV of gastric primary tumour volume delineation has shown significant variation exists using CT alone. The addition of MRI subjectively improved ease of TVD, but impact on IOV was variable, possibly related to confounding factors such as prior gastric TVD experience of observers and/or interpretation of MRI. In addition to addressing these issues, further IOV studies should utilise prospective planning CT with co-registered MRI in treatment position, with appropriate patient preparation, to optimally evaluate the impact of MRI in this setting.

The study also highlights the main areas of variation in gastric TVD, particularly around the cranio-caudal extent of the volume, extra-gastric tumour extension and differentiation of stomach from normal stomach wall or stomach contents. Any future gastric RT planning protocol should include precise delineation instructions (particularly relating to these areas of difficulty) and be implemented following adequate education and training, to maximise accuracy, minimise IOV and optimise patient outcomes.

Chapter 6

A Qualitative, Volumetric and Dosimetric Comparison of Gastric Radiotherapy Protocols

6. A Qualitative and Quantitative Comparison of Gastric Radiotherapy Protocols

6.1 Introduction

Previous chapters have demonstrated the low confidence of UK clinicians in TVD for gastric RT and highlight the lack of a consensus gastric RT protocol in the UK (Chapter 4). In addition, Chapter 5 has demonstrated substantial IOV in gastric TVD, with both under- and over-outlining of gastric tumours, which could theoretically impact efficacy and toxicity. Therefore, it is vital that any future trial of high-dose RT for IGC (i.e. >30Gy BED), be that definitive or palliative intent, incorporates both a detailed, user-friendly RT protocol to optimize accuracy of TVD, and a robust education programme, to both improve clinician confidence and reduce IOV.

In the development of a novel RT protocol for future trials, it is necessary to consider several factors including:

1. Volumes generated (i.e. GTV, CTV, PTV) incapsulate both macroscopic and microscopic disease as well as and at-risk nodal sites (where appropriate).
2. Volumes are plainly described, well-defined and TVD method clearly explained, to optimize accuracy and reduce IOV.
3. Consideration of the TVD approach taken by other evidenced-based protocols, particularly those that the audience may already be familiar with, to optimize consistency and subsequently improve IOV.
4. The protocol is user-friendly, easy to follow, and not too onerous for busy clinicians.

Whilst Chapter 5 has identified multiple areas of variation in TVD of GTVp that should be clearly defined in future RT planning guidance documents, this chapter aims to analyse and compare the strengths and weakness of existing gastric RT protocols, particularly relating to CTV and elective nodal volumes, and qualitatively assess the general usability of guidance documents, to inform and optimize a future RT protocol.

6.1.1 Comparison of existing pre-operative protocols

Chapter 3 has demonstrated the current variation in gastric RT technique internationally, particularly in the definitive and palliative settings where randomised trials are few, and as such, published gastric RT protocols are absent.

To date, the largest evidence base, and the most used gastric RT protocols, exist in the post-operative setting (e.g. CRITICS, TROG 03.02). However, these protocols are difficult to apply IGC due to lack of in-situ tumour, or stomach, in the RT volume.[166,201,202] Nevertheless, such guidance is still informative, particularly when considering at-risk nodal levels that may need inclusion in the definitive setting.

In contrast, pre-operative gastric RT volumes encompass the in-situ tumour and whole stomach, more applicable in the inoperable setting. Here, it is possible to draw from the only European consensus gastric RT guidance - the 2009 EORTC-ROG (European Organisation for Research and Treatment of Cancer – Radiation Oncology Group) expert opinion guidelines for pre-operative RT, as well as from the growing number of active randomised trials, including 2 international, multi-centre trials: the recently published TOPGEAR, and the in-progress CRITICS-II trial. Both trials feature RT protocols, written in the era of IMRT, describing both RT technique, and TVD in varying detail.[68,70,203]

Pertinent aspects of gastric RT technique described by the EORTC-ROG, TOPGEAR and CRITICS-II protocols are summarised in Table 6.1. Despite all using the same RT dose (45Gy/25#), and gross similarities in terms of anatomical structures included in treatment volumes, there is some variation in RT technique, with the biggest differences seen in relation to TVD of the CTV volume (Appendix 6, Table A6.2).

	TOPGEAR (v8 2017)	CRITICS-II (v6.0 2020)	EORTC-ROG Guidelines (2009)
Technique	IMRT or 3D conformal Split field	IMRT/IGRT/ VMAT	3D CRT or IMRT
Motion management	- Consistent stomach filling (early morning following light breakfast) recommended - No recommendation for 4D scanning.	- No gastric filling recommendations - 4DCT mandated	- No gastric filling recommendations - "Individualised identification of the target volume has to be performed if possible" (though no specific recommendation re: motion management)
GTV	Primary tumour and involved regional LN (including perigastric tumour extension and any sites of adherence for T4 tumours)	Not delineated	GTVtumour to include perigastric tumour extension. GTVnodes to include involved nodes
CTV (overview)	Stomach, tumour bed and regional lymphatics	Encompasses tumour, stomach and first draining lymph node stations.	Tumour, partial or whole stomach based on tumour position, and elective lymph node stations corresponding to specific tumour location.
CTV expansion	1cm oesophagus + 1cm duodenum for all, plus **GOJ tumours**: +4cm oesophagus **Pylorus/duodenal invasion**: + 4cm duodenum	**GOJ tumours**: +4cm oesophagus **Tumours <5cm GDJ**: +5cm duodenum	**Pylorus/duodenal invasion**: +3cm duodenum
CTV (elective nodal stations)	LN stations 1-13 included in all patients regardless of tumour location. - Plus LN station 16 for length of CTV. - Plus LN station 20 for GOJ tumours	All LN stations included in all patients (recommended). If tumour extension is very well demarcated, individualise LN stations based on tumour location: - **GOJ/ proximal third:** 1-4, 9-13 - **Middle third:** 3-13 - **Antrum/ distal third**: 3-9, 11-13 + all combinations when tumour invaded more than one part of the stomach before start of treatment.	Selective LN stations corresponding to tumour location: - **Type 3 GOJ**: 1,2,3,4sa,7,9,10,11p, 11d,19,20,110,111 - **Proximal third**: 1,2,3,4sa, 4sb,7,9,10,11p, 11d,19 - **Middle third:** 1,2,3,4sa,4sb,4d,5,7,8a, 8b,9,10,11p,11d,18,19 - **Distal third:** 3,4d,5,6,7,8a,8b,9,11p,12a, 12b, 12p,13,17,18
PTV	PTV= CTV +1cm uniform expansion Margin increased in cases of significant superior-inferior respiratory motions/ significant variation in gastric filling	4D setup should be used CTV +10mm in all directions (reduced to 5mm posteriorly with respect to bony structures like vertebrae and both kidneys)	An ITV should be created to account for target motion. If no facilities for evaluation of target motion are present, minimum margins are: ITV = CTV + 1.5cm all directions. PTV = ITV + 0.5cm

Table 6.1. *Summary of RT technique recommended in CRITICS-II, TOPGEAR and EORTC-ROC Guidelines. LN = lymph node – see Table 6.2 and Figure 6.1 below for description of JCGA LN stations. GOJ = Gastro-oesophageal junction. GDJ: Gastro-duodenal junction*

6.1.2 Classification of lymph node stations for RT planning

Extent of elective nodal volume encompassed by CTV is one of the main areas of variation between the TOPGEAR, CRITICS-II and EORTC-ROG protocols. The Japanese Gastric Cancer Association (JGCA) classifies the upper abdominal nodes into 33 lymphatic stations, commonly referred to when describing both extent of lymphadenectomy performed during gastrectomy, and the nodal levels included in gastric RT volumes, and are summarised in Table 6.2 and Figure 6.1 (for full JCGA description, see Appendix 6, Table A6.2).[204] LN stations 1-12 and 14v are defined as regional, others non-regional, thus metastatic. Where there is direct oesophageal invasion, stations 19, 20, 110 and 111 are also considered regional. LN stations 1-12a are excised during a modified D2 dissection, whilst only stations 1-7 are removed during the now considered sub-optimal D1 dissection.

JCGA Station number	Gross Anatomical location (as per JRSGC)
1	Right cardiac
2	Left cardiac
3	Nodes along the lesser curve
4	Nodes along the greater curve
5	Suprapyloric nodes
6	Infrapyloric nodes
7	Nodes along the left gastric artery
8	Nodes along the common hepatic artery
9	Nodes around the coeliac axis
10	Nodes at the splenic hilum
11	Nodes along the splenic artery
12	Nodes at the hepatoduodenal ligament
13	Nodes at the posterior aspect of the pancreas head
14	Nodes at the root of the mesentery
15	Nodes in the mesocolon of the transverse colon
16	Para-aortic LNs
17	LNs on the anterior surface of the pancreatic head beneath the pancreatic sheath
18	LNs along the inferior border of the pancreatic body
19	Infradiaphragmatic LNs predominantly along the subphrenic artery
20	Paraoesophageal LNs in the diaphragmatic oesophageal hiatus
110	Paraoesophageal LNs in the lower thorax
111	Supradiaphragmatic LNs separate from the oesophagus
112	Posterior mediastinal LNs separate from the oesophagus and the oesophageal hiatus

Table 6.2. *JCGA lymph node station classification, modified from Rosa et al.,[205] showing the original Japanese Research Society for Gastric Cancer gross anatomical description. The more detailed JCGA classification is available in Appendix 6, Table A6.2*

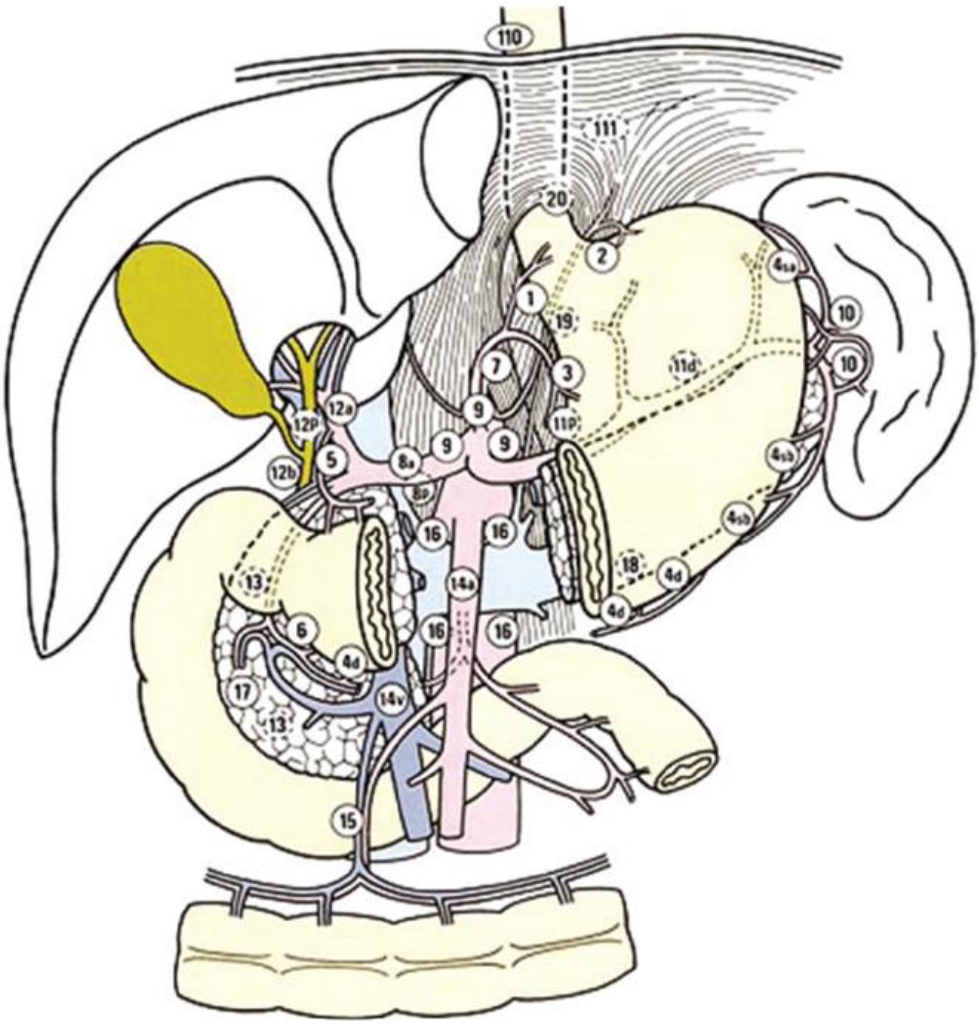


Figure 6.1. *Numbering and location of JCGA LN stations (see Appendix 6, Table A6.2 for full anatomical description of each nodal level). Reproduced with permission from Translational gastroenterology and hepatology.*[205]

6.1.3 Patterns of lymphatic spread in GC

A surgical series by Yi *et al.,* retrospectively examined surgical specimens of 875 patients who had undergone radical gastrectomy to analyse patterns of LN spread to inform CTV delineation.[206] They reported incidence of LN involvement of up to 61.8% in the perigastric stations (1-6), and up to 26.6% for stations 7-12, with an orderly spread through stations 1-16 related to the position of the tumour. For distal tumours, they demonstrated relatively lower involvement of peri-gastric nodes, while involvement of distal nodal groups 15 (25%) and 16 (20%) was more common. However, when considering all tumour locations, the latter stations are much less frequently involved (LN station 14 involvement in <0.1% of proximal tumours, 7% mid-tumours; Stations 15 + 16 <0.1% proximal and mid-gastric tumours) supporting a selective approach to elective nodal delineation based on tumour location.

Retrospective recurrence data in the post-operative setting (summarized in Table 6.3) demonstrates that overall rates of loco-regional relapse are much lower than that of distant recurrence, but where LN are the only site of recurrence, para-aortic LNs (station 16) are most commonly involved, followed by stations 12-14. Though post-operative data is only representative of recurrences outside of a surgical field (i.e. after dissection of stations 1-11/12a), it remains relevant as high rates of recurrence may warrant consideration of inclusion of certain LN stations in elective nodal volumes of high-risk patients.

First author (year)	No. of patients	Type of LND (LN stations)	Adjuvant treatment	Regional recurrence rate	Incidence of LN recurrence
Chang (2012)[207]	382	D2 (1-12a)	93.5% SACT 0% RT	23.8%	Station 16b =61.5% Station 16a = 58.2% Station 12 = 28.6% Station 14 = 19.8% Station 13 = 15.4% Station 9 = 15.4%
Yang (2018)[208]*	129	D2 (1-11)	66% pre-op SACT 26% pre-op CRT	NA~	Station 16b =51.2% Station 16a = 39.5% Station 13 = 36.4% Station 12 = 33.3% Station 9 = 28.7% Station 14 = 27.9%
Yang (2018)[209]*	324	D2 (1-11)	100% post-op CRT	7.1%	Station 16a = 38.9% Station 16b= 33.3% Station 13 = 33.3% Station 12 = 27.8%
Yu (2015)[210]	458	D2 or D2+ (ns)	50% post-op SACT 50% post-op CRT	6.1%	89.3% regional recurrence in "Group 3 LN" i.e. stations 13,14,16a)

Table 6.3. *Patterns of lymph node recurrence following radical surgery +/- SACT/RT.*
**Same group, though slightly different inclusion criteria, but maybe some overlap between patient population reported. ~Only included patients with regional recurrence*

6.1.4 Comparison of elective nodal stations included in current protocols

How to optimally apply this data to elective nodal irradiation for gastric RT, particularly in the definitive setting, remains unknown. In the pre-operative RT protocols considered above (Table 6.1), the main differences in elective nodal CTV relate to whether the LN stations recommended for inclusion are tailored to anatomical location of the tumour (e.g. approach recommended by EORTC-ROG guidelines), or a more standardized approach is taken, recommending inclusion of all nodal levels regardless of tumour location (e.g. as in TOPGEAR). The latter argue that due to limitations in current staging modalities, and in the absence of pathological staging, it is prudent to include all levels for all patients in the pre-operative setting. In contrast, individualization of LN stations included in the CTV as recommended by the EORTC-

ROG guidance allows smaller treatment volumes. Table 6.4 compares JCGA LN stations included by the 3 pre-operative protocols described here, along with 3 post-operative protocols for comparison, demonstrating the largest area of variation in the distal nodal groups.

Further differences are seen in approach taken to create the elective nodal CTV, which are likely to result in further variation in treatment volume – CRITICS-II signposts to ESTRO-ACROP guidance to inform extent of nodal volume (which includes detailed description of every JCGA LN station and an interactive atlas), TOPGEAR signposts to earlier adjuvant guidance from the TROG 03.02 study, and EORTC-ROG recommends a vessel-based approach (relevant vessels are outlined and expanded by 5mm to encompass LN stations). [201,211]

However, increasing the number of nodal stations included in the RT field will also inevitably increase field size and dose to OARs, thus possibly increase treatment toxicity – the latter already shown to be a significant concern of UK OG oncologists. These risks need to be balanced with the risk of sub-optimally treating at-risk nodal stations in any subsequent protocol, particularly in the definitive setting. This chapter aims to compare different approaches to pre-operative gastric RT to further inform the optimal approach for novel studies.

LN classification		Pre-operative protocols			Post-operative protocols		
JCGA LN station	**TNM 8**	**TOPGEAR**	**CRITICS-II**	**EORTC-ROG**	**Smalley *et al.*[212]**	**TROG 03.02[201]**	**French guidelines[213]**
1	Regional	X	#	#	X	X	#
2	Regional	X	#	#	X	X	#
3	Regional	X	X	X	X	X	X
4	Regional	X	X	#	X	X	#
5	Regional	X	#	#	X	X	#
6	Regional	X	#	#	X		#
7	Regional	X	X	X	X	X	X
8	Regional	X	#	#		X	#
9	Regional	X	X	X	X	X	#
10	Regional	X	#		#	#	#
11	Regional	X	X	X	#	X	X
12	Regional	X	X	#	X	#	#
13	Distant	X	X	#	X	#	#
14	Regional	X			#		
15	Distant						
16	Distant	X					
17	Distant			#	#		#
18	Distant			#	#		#
19	Regional*			#			#
20	Regional*	X	#	#	#	#	#
110	Regional*		#	#	#	#	#
111	Regional*			#			#
112	Regional*			#			#

Table 6.4. *Comparison of the JCGA LN stations recommended for inclusion in elective nodal volumes based on 3 pre-operative and 3-post-operative protocols. For anatomical description of JCGA LN stations, refer to Table 6.2/ Figure 6.1. For simplicity, all LN levels recommended regardless of tumour location are indicated.*
*X = inclusion of LN station in CTV regardless/across all locations. # = included based on tumour location only. Empty, shaded cells are not recommended for inclusion. *LN considered regional if oesophageal involvement.*

6.2 Aims

This RT planning study aimed to compare two contemporary, internationally relevant pre-operative RT protocols, deemed most likely to be applied to future clinical practice in the UK (TOPGEAR, CRITICS-II), with particular focus on:

a) A qualitative comparison of general ease/ usability of the protocol and accompanying supportive materials.
b) A volumetric comparison of the structures delineated according to each protocol.
c) A dosimetric comparison of the resulting RT treatment plans to evaluate dose to organs at risk, and PTV coverage for each method.

6.3 Method

This study was approved by the SUMS Ethics Review Committee (SUMS RESC 2022-0128A) and Swansea Bay University Health Board Information Governance Committee. A flow diagram summarising the over-arching method for this study is shown in Figure 6.2.

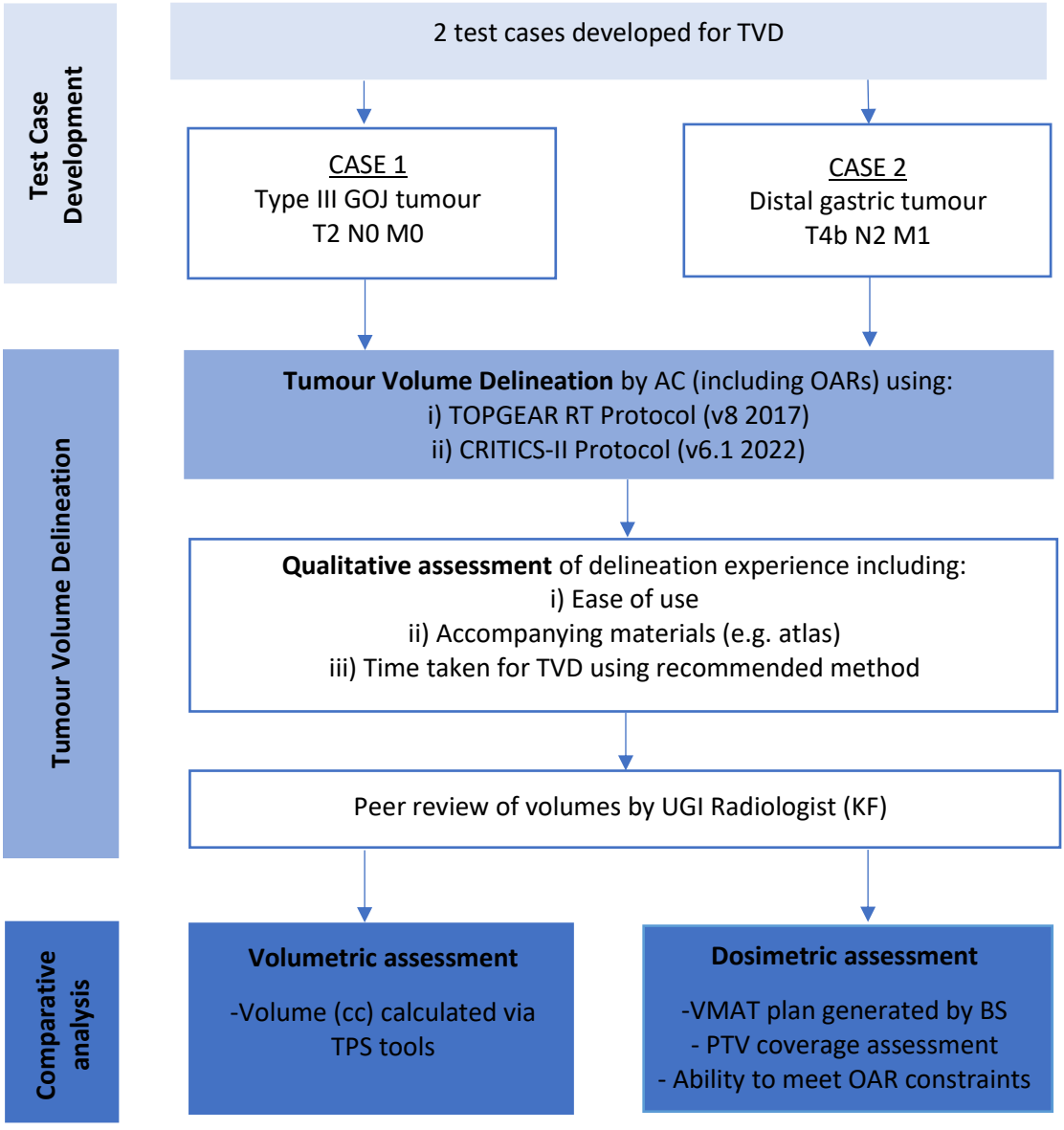


***Figure 6.2**. Flow diagram summarising generation of test cases, TVD and comparative analysis.*

6.3.1 Test case development

Two test cases were developed for TVD. Clinical cases were selected from the retrospective service evaluation data (Chapter 2) that would represent different anatomical locations and stages for comparison. Table 6.5 summarises the pertinent clinical details of each case.

Case 1, a type III GOJ tumour, was selected as this patient was treated with radical intent RT (due to a second mid-oesophageal SCC – which will not be discussed further in this context), thus a CT planning scan with an in-situ tumour was already in existence on local treatment planning software (TPS, Prosoma). Imaging within the TPS was re-saved with an anonymized title ('Gastric Case 1') so that all subsequent exported data was anonymous.

Case 2, a distal gastric tumour, was previously used for the MRI IOV study in Chapter 5 (Case A). This case was selected due its opposing anatomical location to Case 1, because imaging was already anonymized and uploaded into TPS (diagnostic CT used in lieu of a CT planning scan), and the case already had a radiologist reviewed GTV, to minimize additional peer-review time. It should be noted this case would not have been considered operable (due to both being very locally advanced, and due to presence of metastatic disease), thus in clinical practice would not have been suitable for either pre-operative trial, but was selected to test the protocols in the context of a large volume, locally advanced, heavily node positive, inoperable tumour.

Clinical Features	**Case 1**	**Case 2**
Tumour location	Type III GOJ	Distal stomach (pylorus)
Endoscopic findings	Malignant tumour at the GOJ extending to gastric fundus.	Large tumour occupying most of the pylorus, not causing an obstruction.
Staging CT findings	Enhancing wall thickening in the gastric cardia with adjacent prominent LN in the GOJ	Bulky, partially necrotic mass centered on the pylorus. Large extra-gastric component with direct contact of the liver and gall bladder, and posteriorly extending towards pancreatic head. Several peri-tumoral lymph nodes metastases, largest located between the tumour and the pancreatic head.
PET-CT findings	Moderate uptake in the proximal stomach over a distance of 3cm relating to the malignancy. Suspicious 1cm left gastric nodes adjacent to the stomach has minimal uptake but remains suspicious on CT.	N/A
MDT TNM Stage	T2 N0 M0	T4b N2 M1*
Simulation scan details	CT planning scan: - • 3mm slices • Included lung apices to lower border of L3 • IV contrast • Supine, arms above head	Diagnostic CT used in lieu of CT planning scan: - • 5mm slices • Included lung apices to lower border of L3 • IV contrast • Supine, arms above head

Table 6.5. *Clinical information for the two test cases developed for TVD. *Liver metastases were disregarded for this study*

6.3.2 Tumour volume delineation

TVD was undertaken by AC using the relevant RT protocol, guidance documents and atlases:

i. TOPGEAR RT protocol (v8, 2017)[68]
ii. CRITICS-II RT protocol (v6.1, 2022)
    The CRITICS-II trial website also contains the protocol, atlas, and sign-posts to the ESTRO-ACROP nodal delineation guidance.[214]

OARs specified by each protocol were also delineated. For CRITICS-II, the relevant LN stations were individually delineated as per ESTRO-ACROP definition to guide CTV. Volumes were then peer-reviewed by an expert UGI radiologist (KF) to check accuracy of GTV delineation, inclusion of correct lymph node stations as described in each protocol, as well as OARs, particularly duodenum.

6.3.3 Qualitative assessment of RT protocols

During TVD of Case 1, observations relating to the following qualitative aspects of the delineation experience were undertaken, and documented contemporaneously by AC:

i. General ease of use (i.e. clarity of descriptions, explanation of structures to be included in each volume).
ii. Accompanying materials (e.g. atlases).
iii. Approximate time taken for TVD using recommended method.

6.3.4 Quantitative assessment: Volumetric and Dosimetric analysis

Volume of each structure calculated within OSL ProSoma (v4.2) using the 'VOI statistics' tool to allow simple comparison.

For dosimetric analysis, final delineated volumes for each case (TOPGEAR and CRITICS-II) were exported into the Philips Pinnacle3 (v16.2) treatment planning software. Using the lowest relevant dose constraints described by each protocol (Table 6.6), a VMAT plan was constructed by Becky Slinger (BS), a Radiotherapy Physics Clinical Scientist at South West Wales Cancer Centre. Dose constraint achievement and Dose Volume Histograms (DVH) were reported for both protocols for each case for comparison. In addition, mean and maximum dose to duodenum, small bowel, and kidneys were reported. Optimisation was achieved using the Pinnacle3 Auto-planning module, with the same objectives applied to each planning case. No further, volume-specific, optimisation was applied, so there are likely further improvements that could be made with each plan in terms of OAR sparing and conformity. However, applying a standard treatment technique to each case and using the planning system's automatic

planning engine has allowed comparison based on the volume differences alone and has removed any variations due to planner optimisation expertise.

Volume	Dose constraint by protocol	
	CRITICS-II	**TOPGEAR**
PTV	V95% >98% D2% <107%	V95>95% DMax <107% Median 44-5-45.9Gy
Liver	Mean <30Gy	Mean <30Gy 1/3 liver ≤50Gy 2/3 liver ≤35Gy
Kidney_R	V18Gy <33%	Mean <23Gy 1/3 kidney ≤35Gy 2/3 kidney ≤20Gy
Kidney_L	V18Gy <33%	Mean <23Gy 1/3 kidney ≤35Gy 2/3 kidney ≤20Gy
Cord_PRV	DMax <45Gy	DMax <45Gy
Heart	V40Gy <30%	V40Gy <30%
Lung	V20Gy ≤30%	V20Gy ≤30% Mean <18Gy

Table 6.6. *Dose constraints provided for TOPGEAR and CRITICS-II. Those shaded yellow were selected for optimisation of plans for this study. NS= Not stated, so local constraint used.* ***DMax*** *is the near-point maximum dose to the structure of interest.* ***VxGy*** *is the percentage of the volume of the organ receiving xGy or higher (e.g. V18Gy <33% denotes volume of organ receiving 18Gy or higher should be <33%).* ***V95%>98%*** *is the % volume receiving at least 95% of the prescription dose, which should be >98%.* ***PRV*** *= Planning organ-at-risk volume (margin added to an AOR volume to which dose constraints are applied).*

6.4 Results

6.4.1 Qualitative results – User experience

Observations regarding general user experience, ease of application and usefulness of accompanying materials were made via contemporaneous notes taken during TVD of Case 1 for each protocol and are summarised in Table 6.7.

In general, TOPGEAR was felt to be more descriptive and easier to follow than the CRTIICS-II protocol. The former included an excellent introductory section, advising which anatomical structures clinicians should familiarise themselves with to aid TVD, which was very helpful for a first-time user. GTV and CTVstomach were clearly described with easy-to-follow instructions, and clear description of how much oesophagus and duodenum should be included. However, the CTV nodal volume is described in a long section of prose, which, though descriptive, was difficult to follow and lacked detail regarding medial, lateral, and inferior extent of volume, leaving some uncertainty. Also, it was difficult to visualise how the CTV should transition on axial slices between LN stations.

In contrast, the CRITICS-II protocol is intentionally simple, and advocates a single CTV volume, generated by delineating every 1cm and interpolating between slices. It is derived from the post-operative CRITCIS trial, so some of the detail is not relevant in the pre-operative setting, which is confusing at times. There are conflicting statements regarding extent of LN stations to be included, with both inclusion of all stations (1-13), and a tailored approach to levels included based on tumour location recommended. How to practically include chosen LN levels inside the CTV volume during delineation is left to the clinician. A LN atlas is included, but description of extent of each level is not included. Users are sign-posted to ESTRO-ACROP nodal delineation guidance. To ensure the relevant LN stations were covered, I opted to delineate each level as per ESTRO-ACROP guidance. This was extremely time consuming, required identification of several small vessels to generate individual volumes, which was very challenging and required radiology support. Like TOPGEAR, it was difficult to visualise how to transition the CTV volume between LN stations.

Neither protocol described how to include involved lymph node in the CTV volume (i.e. what margin should be applied to GTV). To clarify this, the Chief Investigator of TOPGEAR was contacted, who confirmed a 5mm margin should be applied to GTVnodes to create CTVnodes, and included in the final CTV volume. There was no response from the CRITICS-II team, so the same principle was applied for the CRITICS-II volume.

Volume	TOPGEAR	CRITICS-II
GTV	• Clear definition of GTV volume.	• No GTV required
CTV(stomach)	• GTV to CTV expansion well defined by T-stage. • Clear definition of CTV(stomach) (i.e. whole stomach) • Proximal (oesophagus 1-5cm) and distal (duodenum 1-5cm) extent clearly described based on tumour location	• Advises one CTV volume to encompass tumour, stomach and LNs • Extent of stomach included (whole or partial) left to clinician discretion • Clear definition of how much oesophagus to include for GOJ tumours (4cm), but not for distal tumours. • Clear definition of extent of duodenal inclusion for distal tumours (5cm), but inferior margin unclear for GOJ tumours
CTV(nodal)	General description provided, but lacks detail for inexperienced outliners, specifically regarding: • Extent of volume around the hepatogastric ligament (sup/inf) • How to practically include coeliac axis, splenic hilum and SMA within the CTV • Inferior margin of CTV not well described • 'Medial half of duodenum' not well defined in text, though can be deduced from atlas • Unclear how much pancreas to include to ensure retropancreaticoduodenal nodes are included.	• Conflicting statements regarding whether all, or selected LN stations should be included. • No descriptive methodology for how to create a volume that encompasses the relevant levels. • Therefore ESTRO-ACROP atlas used to delineate each level, then single CTV created that encompassed all.
PTV	• Clear definition (1cm circumferentially) • 4D not required	• Clear definition • 4D recommended but not applicable for this case
CT Image Atlas	• 1 case (10 images), well-labelled	• 3 cases from different tumour sites (13-16 images per case), non-labelled • LN atlas provided, not labelled, does not define extent of each LN station
Other accompanying materials	• Signposts user to TROG 03.02 (post-operative trial by same group, so of limited applicability • Good educational introductory paragraph advising which key anatomical landmarks should be delineated to aid TVD.	• Signposts to ESTRO-ACROP nodal delineation guidance • Easy to access supporting materials online.
Time taken for TVD	• Basic anatomy/ OARs = 5 hours • TVD = 4 hours	• ESTRO-ACROP nodal levels =8 hours • TVD = 2 hours

Table 6.7. *Observations regarding ease of use for TVD for each protocol and accompanying materials*

6.4.2 Evaluation of accompanying materials

Both protocols include an atlas with a 'worked example.' TOPGEAR contains a single case of 10 images demonstrating CTV with anatomical landmarks and is well labelled. Users are sign-posted to TROG 03.02 protocol (post-operative) which is not easily accessible online (document was sought from TOPGEAR CI), and is post-operative, so of limited applicability.

CRITICS-II provides three cases within their atlas featuring proximal, mid and distal tumours, with 13-16 images for each case. However, the images are not labelled, and example CTV volumes are somewhat erratic, for example, in some axial slices the aorta is excluded from the volume, but partially included on neighbouring slides. The CRITICS-II trial website includes links to the ESTRO-ACROP guidance and atlas, which is very descriptive, as well as planning guidance documents.

6.4.3 Time taken for TVD of Case 1

For TOPGEAR, total TVD time was 9 hours, 5 hours for initial delineation of landmarks as recommended in the protocol, followed by approximately 4 hours for TVD of GTV, CTV and PTV.

For CRITICS-II, total TVD was 12 hours. Delineation of ESTRO-ACROP nodal levels was very time consuming (approximately 8 hours, plus 2 hours peer review). CTV delineation then took approximately 2 hours (though GTV and CTV stomach was copied from TOPGEAR volume).

Time was not recorded for Case 2 given that the GTV and CTV were pre-delineated following previous study.

6.4.4 Quantitative results: Volumetric analysis

The volume of GTV, CTV and PTV generated for each protocol for both Case 1 and 2 is shown in Table 6.8.

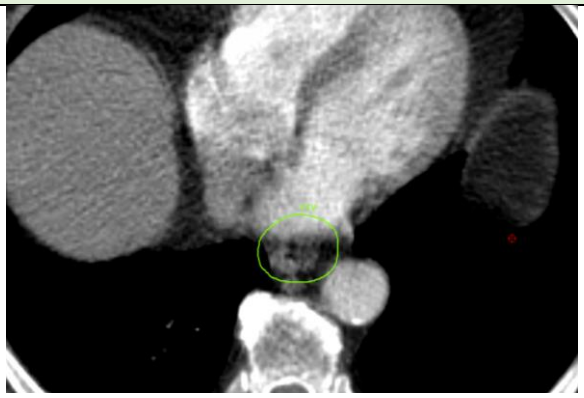
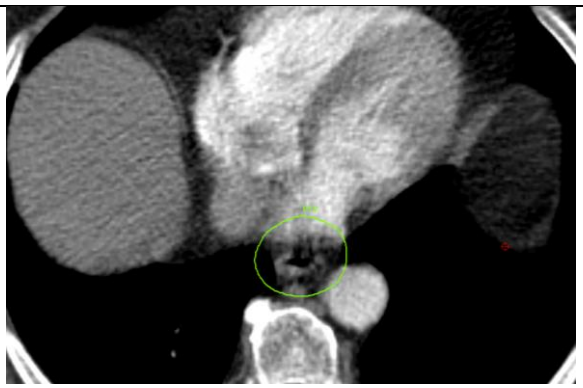
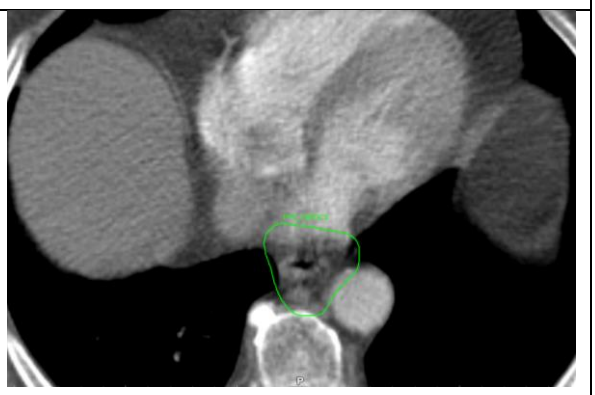
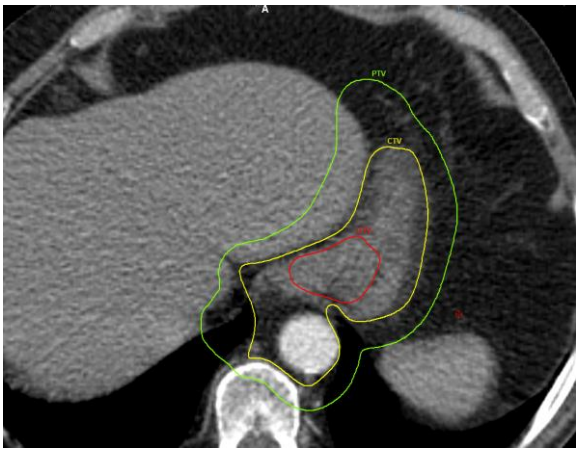
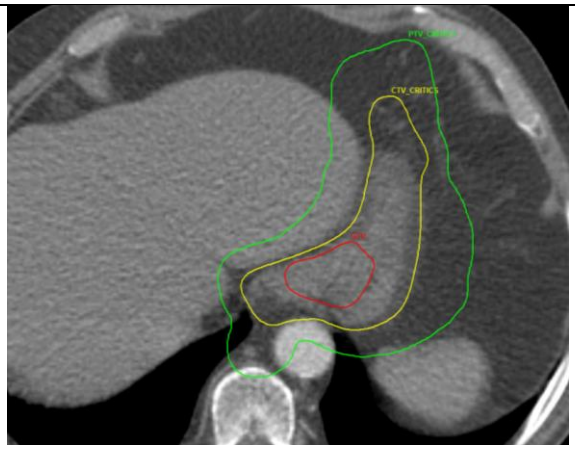
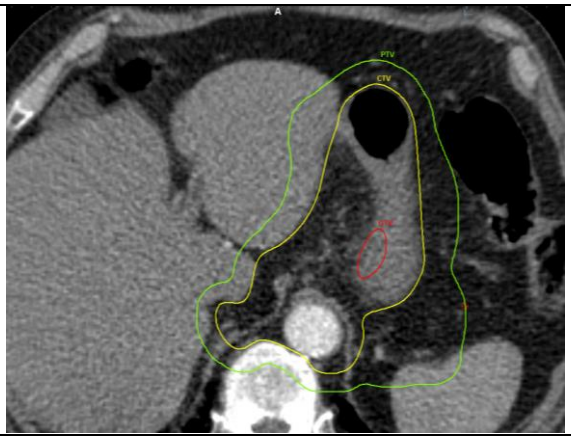
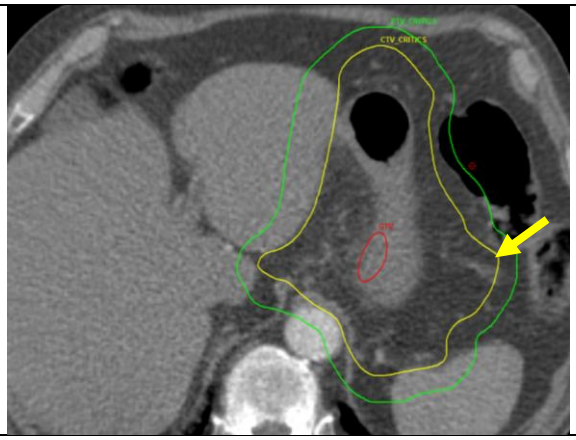
	Case 1		**Case 2**	
	TOPGEAR	CRITICS-II	TOPGEAR	CRITICS-II
GTVp volume(cc)	18.9	NA	335.7	NA
CTV volume (cc)	835.8	522.9	1790	1170
PTV volume (cc)	1670	1250	3040	2220
PTV length (cm)	19.5	13.2	19.5	17.5

Table 6.8. *Volume (cc) for each structure (GTV, CTV, PTV) for each protocol for cases 1 and 2, and length of PTV. Reference GTV was used for both cases. NA = not applicable*

For Case 1, CTV volume was 37.4% smaller for CRITICS-II (522.9cc) than TOPGEAR (835.8). As such, both PTV volume and length were smaller for CRITICS-II than TOPGEAR, measuring 25% smaller in volume (CRITICS-II= 1250cc vs TOPGEAR 1670cc) and 32.3% smaller in length (CRITICS-II= 13.2cm vs TOPGEAR 19.5cm).

Figure 6.3 shows CTV and PTV volumes for Case 1 on a selection of axial CT slices, demonstrating areas of most variation between protocols. Superiorly, there is little difference in volume extent, with TOPGEAR commencing only 1 slice (3mm) more superiorly than CRITICS-II (with both mandating inclusion of 4cm distal oesophagus for GOJ tumours.) At the proximal stomach, the main area of variation is at the greater curve, where there are differences in how far the volume extends anterolaterally. In its description of CTV, TOPGEAR does not dictate how far the left lateral volume should extend past the greater curve of the stomach to include station 4 nodes. However, deliberate inclusion of station 4 during delineation of CRITICS-II volumes (see Figure 6.3, slice -36, yellow arrow) led to the CTV volume extending to include more peri-gastric tissue around the greater curve.

However, the most variation is seen distally. Firstly, this is due to inclusion of para-aortic nodes by TOPGEAR, which increases the extent of the volume circumferentially around the aorta for the entire length of CTV. Secondly, TOPGEAR also describes that the whole pancreas is usually included when attempting to cover the splenic hilum, stomach and para-aortic nodes, thus the entire pancreas is included here, which along with the para-aortic volume, pushes the left lateral extent of the TOPGEAR wider than CRITICS-II CTV at the same level (Figure 6.3, slice -45,-69, turquoise arrows).

	CASE 1	
Slice no.	**TOPGEAR**	**CRITICS II**
33 (superior most slice TOPGEAR)		N/A
30 (superior most slice CRITICS-II)		
-21 Proximal stomach		
-36 Mid-stomach		

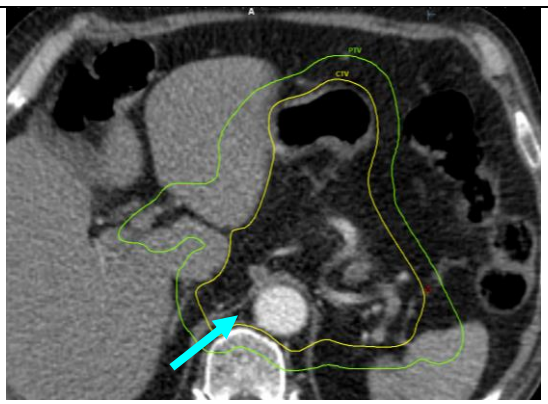
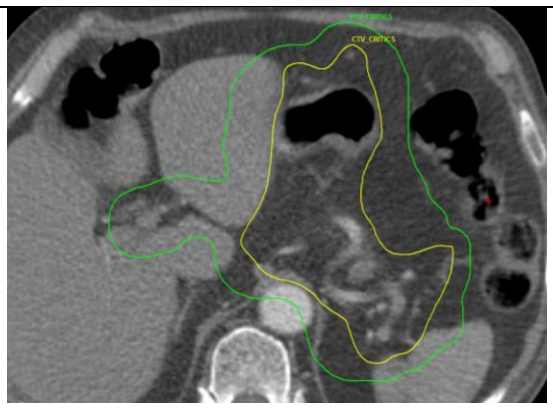
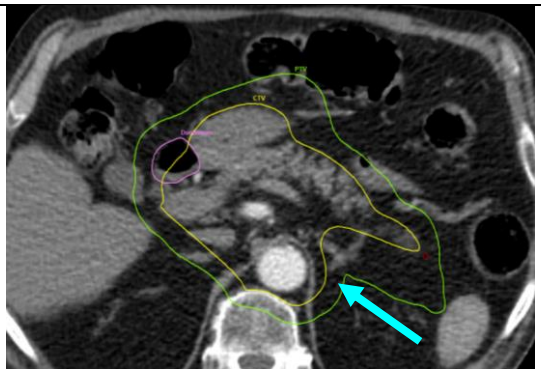
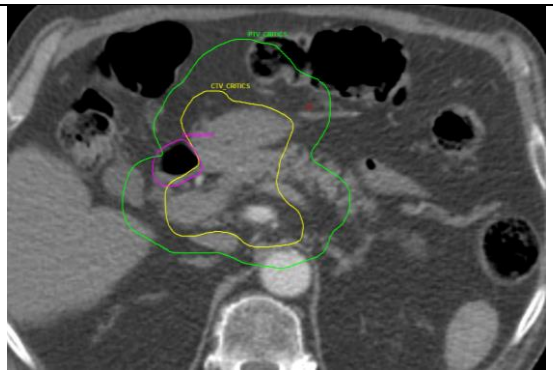
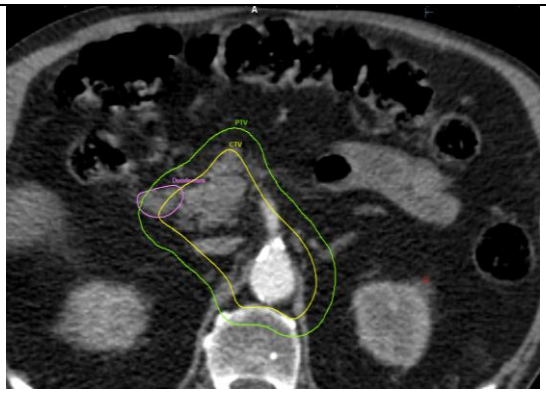
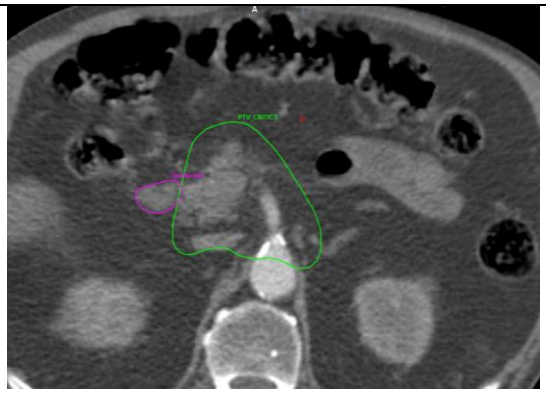
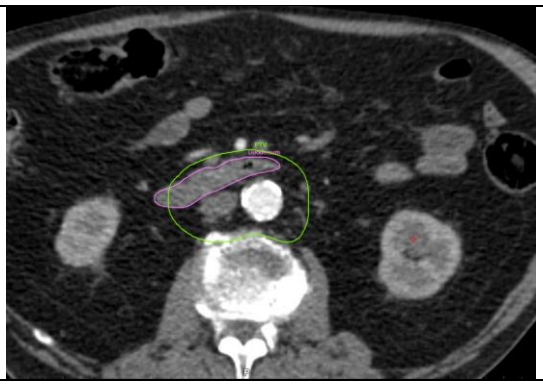
-45 Antrum/ splenic hilum		
-69 Pancreas		
-99 (inferior most slice CRITICS-II)		
-159.0 (inferior most slice TOPGEAR)		N/A

***Figure 6.3**. CTV and PTV volumes for **Case 1** for TOPGEAR (left) and CRITICS-II (right) on corresponding axial CT slices. GTV= red, CTV = yellow, PTV = green, Duodenum = pink. Yellow arrows depict the extension of volume further along the greater curve of the stomach in the CRITICS-II CTV and PTV volume. The turquoise arrow shows the inclusion of para-aortic nodes in TOPGEAR.*

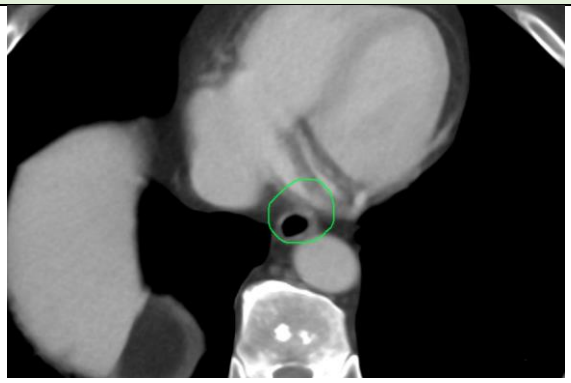
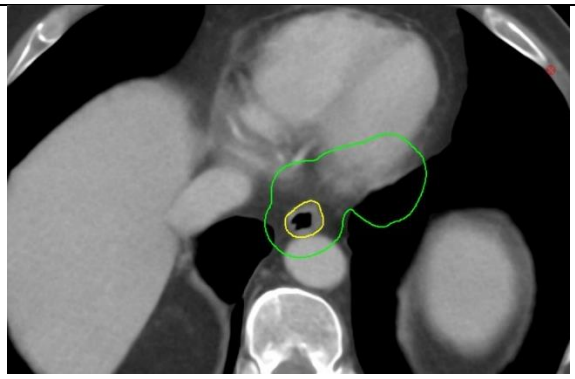
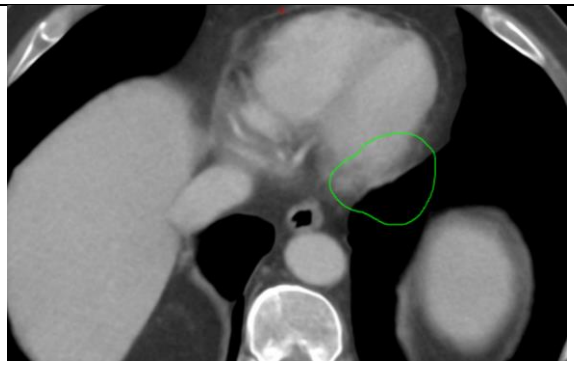
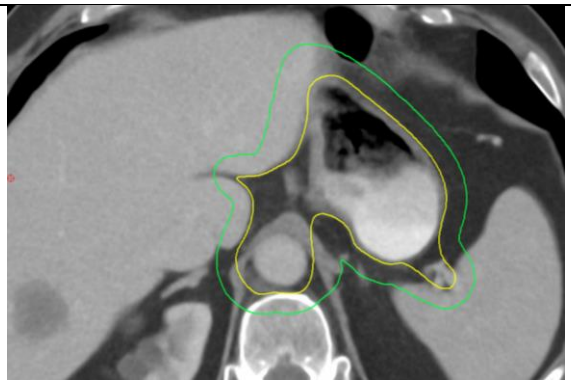
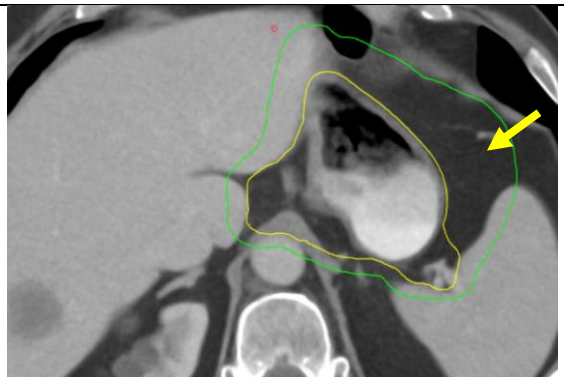
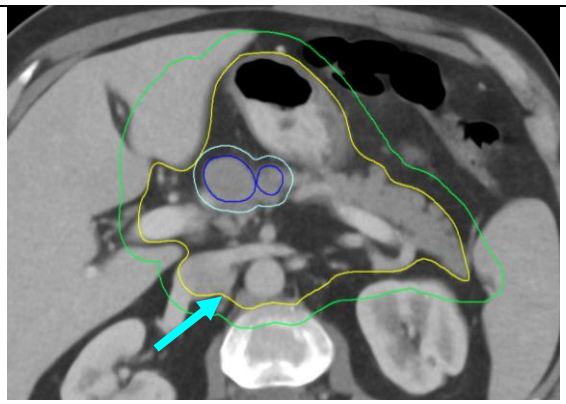
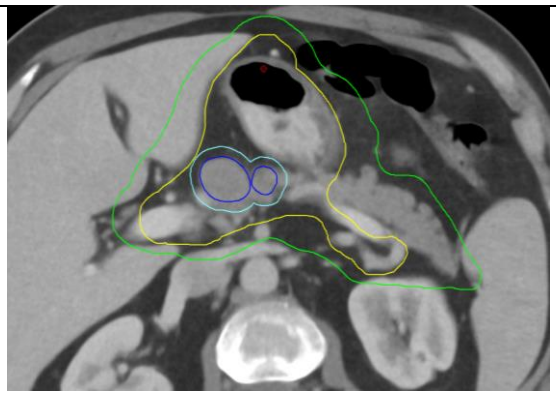
Finally, the CTV volume extends far lower for TOPGEAR than CRITICS-II, explaining much of the difference in both volume and length of PTV. It is difficult to exactly determine the lowest slice of CTV for either protocol. TOPGEAR describes delineation of the second part of the duodenum to the point at which it joins the third part (though only the medial half of the duodenum needs to be included in the absence of direct duodenal involvement), thus this was interpreted as the most inferior extent of the CTV. On the other hand, CRTIICS-II does not define the inferior extent of the volume for a GOJ tumour, thus CTV has been extended to include the lowest slice at which LN stations 1-13 are covered by the volume, according to ESTRO-ACROP definition (see Appendix 6.3 for delineation of LN stations for Case 1). Following this guidance, the TOPGEAR PTV ends 20 slices (6cm) more inferiorly than that of CRITICS-II.

Case 2 volumes were much larger than Case 1, reflecting the more locally advanced tumour (T4b) and nodal disease. Case 2 demonstrated a similar difference in volume between protocols, with a 34.6 % difference in CTV, (CRITICS-II= 1170cc vs TOPGEAR 1790cc), and 27% difference in PTV volume (CRITICS-II= 2220cc vs TOPGEAR 3040cc). There was less difference in PTV length (CRITICS-II = 17.5cm vs TOPGEAR= 19.5cm), suggesting that unlike for case 1, where much of the difference was attributable to difference in superior-inferior extent of the volume, for this case, most of the difference in volume was circumferential. These are demonstrated in the axial CT slices shown in Figure 6.4.

TOPGEAR gives a clear description of the superior extent of the CTV volume, mandating inclusion of 1cm oesophagus in all cases, thereby indicating the upper most extent of the volume for distal gastric tumours (Figure 6.3, slice 168.2). However, CRITICS-II does not provide information regarding inclusion of any distal oesophagus for distal gastric cases, thus the CTV begins at the proximal stomach.

Similar differences in elective nodal volume are seen for Case 2 as for Case 1, particularly the inclusion of LN station 4 around the greater curve extending the PTV volume in CRITICS-II, and the inclusion of para-aortic nodes and entire pancreas resulting in a wider volume inferiorly for TOPGEAR. However, in this case, further differences are seen at the GTV, at the level of the pylorus (Figure 6.4, slice 155.7, red arrow). This is accounted for by the TOPGEAR protocol recommendation of a 1cm isotropic CTV margin around GTV for T4 tumours, thereby extending the TOPGEAR volume more anterolaterally.

The inferior extent of the CTV volume is more readily described by both protocols in the case of a distal tumour, with TOPGEAR recommending a 4cm extension into duodenum, 5cm for CRITICS-II. In addition, due to the distal location of the tumour and vicinity to the duodenum, the entire duodenal circumference has been included in the TOPGEAR volume. Once combined with nodal volume, there is only 3mm difference in lower extent of PTV volume between both protocols.

	CASE 2	
Slice no.	**TOPGEAR**	**CRITICS II**
168.2 (Superior PTV TOPGEAR_		N/A
167.2 (Superior PTV CRITICS-II)		
164.2 Proximal stomach		
159.7 Antrum/ Pancreas		

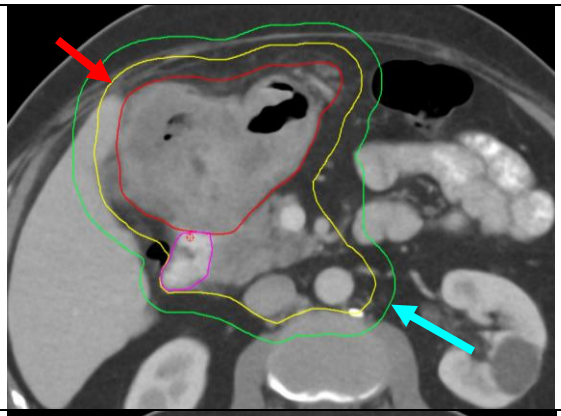
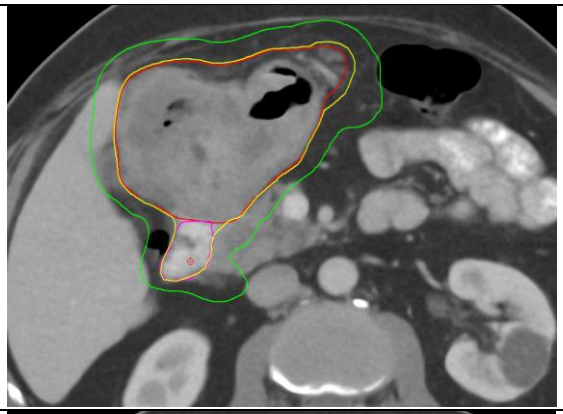
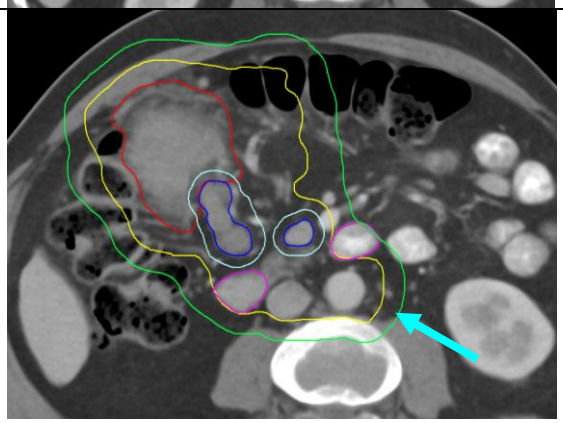
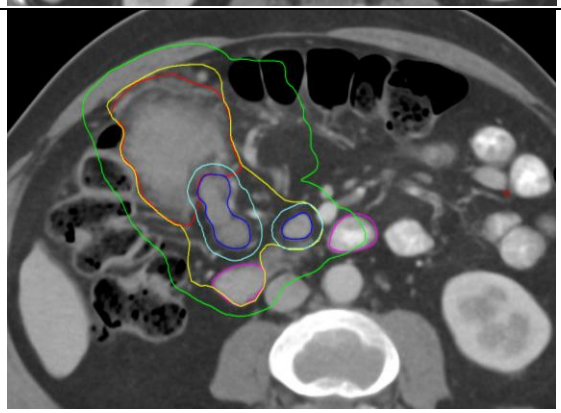
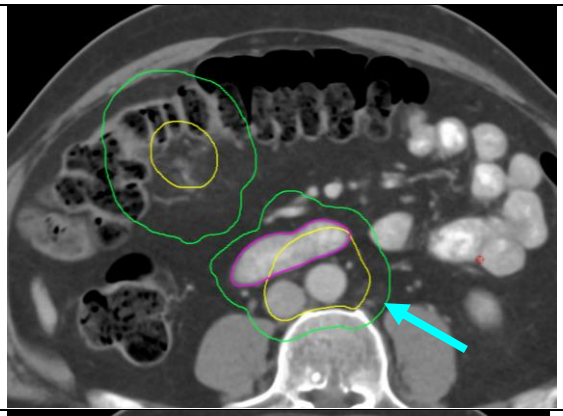
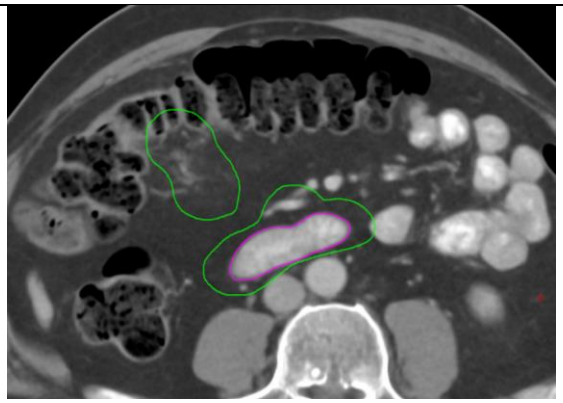
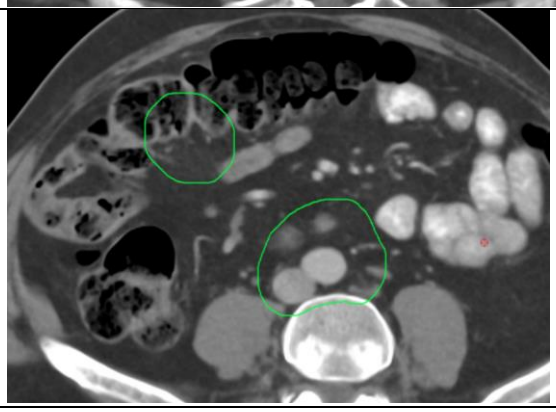
155.7 GTV/ pylorus		
152.2 Pylorus		
150.2 (inferior PTV slice CRITICS-II)		
149.2 Lowest PTV TOPGEAR		N/A

Figure 6.4. *CTV and PTV volumes for **Case 2** for TOPGEAR (left) and CRITICS-II (right) on corresponding axial CT slices. GTV= red, CTV = yellow, PTV = green, GTVnode = dark blue, CTVnode= light blue, duodenum = pink. Yellow arrows depict the extension of volume further along the greater curve of the stomach in the CRITICS-II CTV and PTV volume. The turquoise arrow shows the inclusion of para-aortic nodes in TOPGEAR. The red arrow shows the 1cm expansion around the GTV to form CTV in TOPGEAR.*

6.4.5 Quantitative results: Dosimetric analysis

Table 6.9 shows the dose volume optimisation results for both protocols for Case 1 and 2.

		Case 1		Case 2	
Volume	**Constraint**	**TOPGEAR**	**CRITICS-II**	**TOPGEAR**	**CRITICS-II**
PTV	**V95 >98%**	99.38%	99.34%	96.53%*	97.07%*
PTV	**D2% <107%**	0%	0%	0.01%	0.02%
PTV	**Median (D50%)**	45.27Gy	45.15Gy	44.84Gy	44.92Gy
Liver	**Mean <30Gy**	22.23Gy	22.98Gy	22.89Gy	22.91Gy
Kidney_R	**V18Gy <33%**	3.62%	0.34%	2.18%	6.44%
Kidney_L	**V18Gy <33%**	5.73%	0.95%	28.03%	9.84%
Kidneys	**Mean <23Gy**	8.07Gy	3.51Gy	13.44Gy	9.01Gy
Cord_PRV	**DMax <45Gy**	34.76Gy	30.98Gy	39.13Gy	23.79Gy
Heart	**V40Gy <30%**	0.88%	1.14%	2.44%	1.97%
Lungs	**V20Gy ≤30%**	4.40%	5.88%	1.66%	1.87%
Duodenum^	**Mean <45Gy** **DMax**	41.85Gy 47.43Gy	11.17Gy 46.22Gy	44.82Gy 47.17Gy	43.16Gy 46.78Gy
Small bowel ^	**Mean <45Gy** **DMax**	24.18Gy 46.23Gy	14.15Gy 42.45Gy	21.07Gy 46.89Gy	16.53Gy 45.69
Spleen^	**Mean <10Gy**	33.23Gy	34.27Gy	32.84Gy	29.78Gy

Table 6.9*. Dose volume optimisation (DVO) results. *Not meeting target constraint, but deemed acceptable coverage. ^Constraints not used for optimisation (as not mandated in either protocol), but values reported for comparison.*
DMax *is the near-point maximum dose to the structure of interest.* ***VxGy*** *is the percentage of the volume of the organ receiving xGy or higher (e.g. V18Gy <33% denotes volume of organ receiving 18Gy or higher should be <33%).* ***V95%>98%*** *is the % volume receiving at least 95% is the prescription dose, which should be >98%, ^The spleen was not optimised on, only reported.* ***D50%*** *is the median dose to the volume.*

PTV coverage is excellent for Case 1 meeting mandatory constraint of V95>98% (i.e. volume receiving 95% of the dose [45Gy] is >98%, for both protocols). For Case 2, though the 98% mandatory constraint was not met by either, it was >95% thus deemed acceptable given the size of the PTV volume for this case. Median dose to the PTV to the volume was within 1% of the prescription dose for all volumes. There were no hot spots receiving >107% of the dose for Case 1, but there were some hot spots for Case 2 (though minimal), due to the optimisation process struggling with the large size of the volume.

When considering constraints applied for optimisation (i.e. liver, kidneys, heart, lungs, spinal cord), all constraints were met for both protocols for each case. Figure 6.5 shows the cumulative dose volume histograms (DVH) for liver, lungs and heart, demonstrating little difference between protocols. An example of the isodose distributions for Case 1 are shown in Figure 6.6, illustrating the 'low dose bath' encompassing liver and spleen.

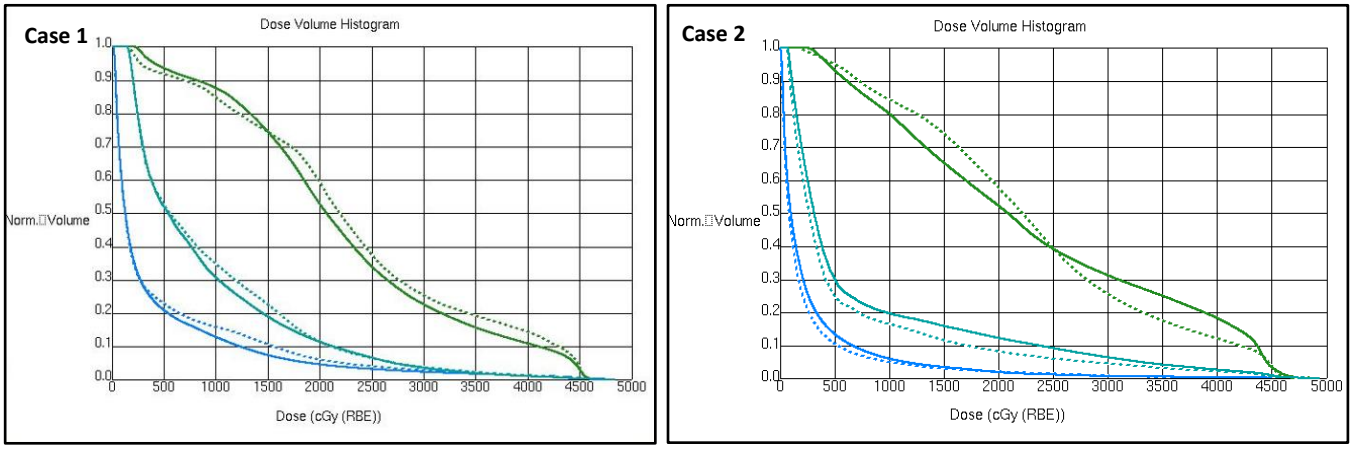


Figure 6.5. *Cumulative DVH for liver, lungs and heart for Case 1 (left) and Case 2 (right), where the TOPGEAR volumes are represented by a solid line, and CRITICS-II by a dashed line. Key: Liver = green, Lungs = blue, Heart = teal.*

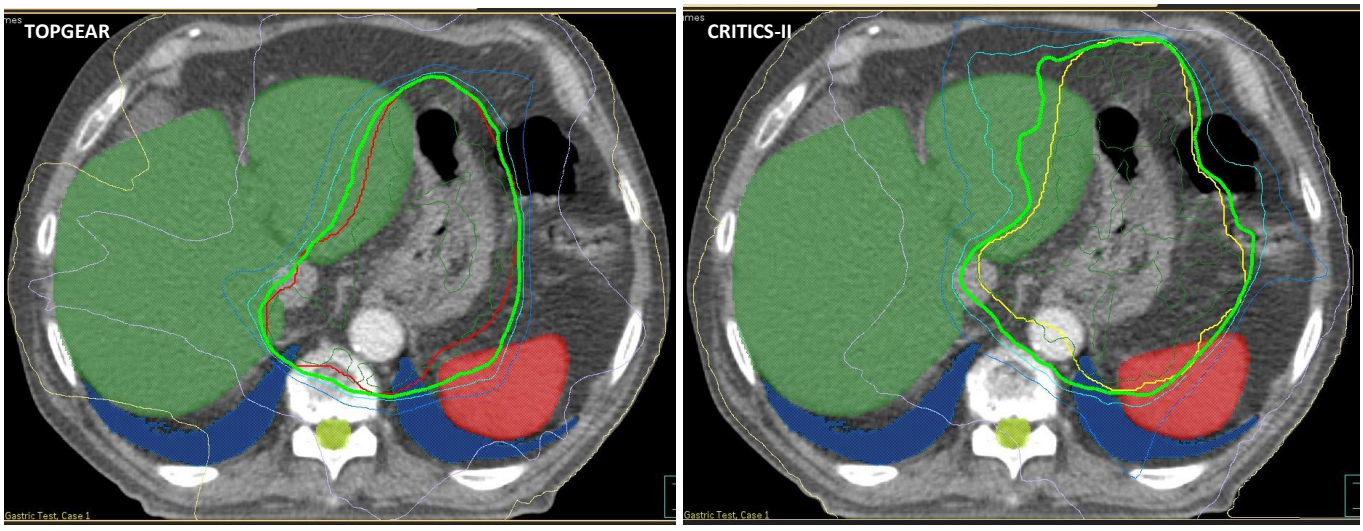
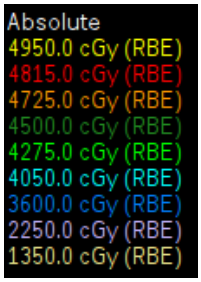


Figure 6.6*. Isodose distribution for TOPGEAR (left) and CRITICS II (right), for a single axial slice of Case 1.*



Solid green line = 95% isodose (42.75Gy)
Solid red line = TOPGEAR PTV. Solid yellow line = CRITICS-II PTV
Liver = solid green shading. Spleen = solid red shading. Lungs = solid blue shading.
Key to the left illustrates the colours of the other corresponding isodose lines (shown as fine lines)

Cord PRV is within tolerance for all volumes, though dose is lower for the CRITICS-II volumes for both cases, likely due to the inclusion of para-aortic lymph nodes in TOPGEAR pushing the volume posteriorly towards the spinal canal (see Figure 6.3, turquoise arrows).

Similarly, dose to both right and left kidney was well within dose constraints for both cases. However, some differences were noted, demonstrated in the cumulative DVHs in Figure 6.7. For Case 1, both right and left kidney dose was lower for CRITICS-II (V18Gy = 0.34% right, 0.95% left, mean dose = 3.51Gy) than TOPGEAR (V18Gy = 3.62% right, 5.73% left, mean dose 8.07Gy). Figure 6.8 demonstrates the isodose distribution for both cases, illustrating the smaller CRITICS-II PTV, which does not extend as far posteriorly as the corresponding TOPGEAR volume, resulting in reduced low dose bath coverage of the kidneys in the CRITICS-II plan, particularly on the left of the slice shown. For Case 2, right kidney dose was slightly higher for CRITICS-II, due to slightly more low dose coverage. However, the dose to left kidney was much higher for TOPGEAR (V18Gy = 28.03%) than CRITICS-II (V18Gy = 9.84%). This is accounted for by the extension of the TOPGEAR volume much more laterally to the left to cover the splenic hilum, pancreas and para-aortic nodal areas, resulting in the PTV skimming the left kidney. In addition, due to the constraints provided to the optimiser (i.e. absence of spleen), it is possible that more dose has been pushed through the left in an effort to keep liver and right kidney within tolerance.

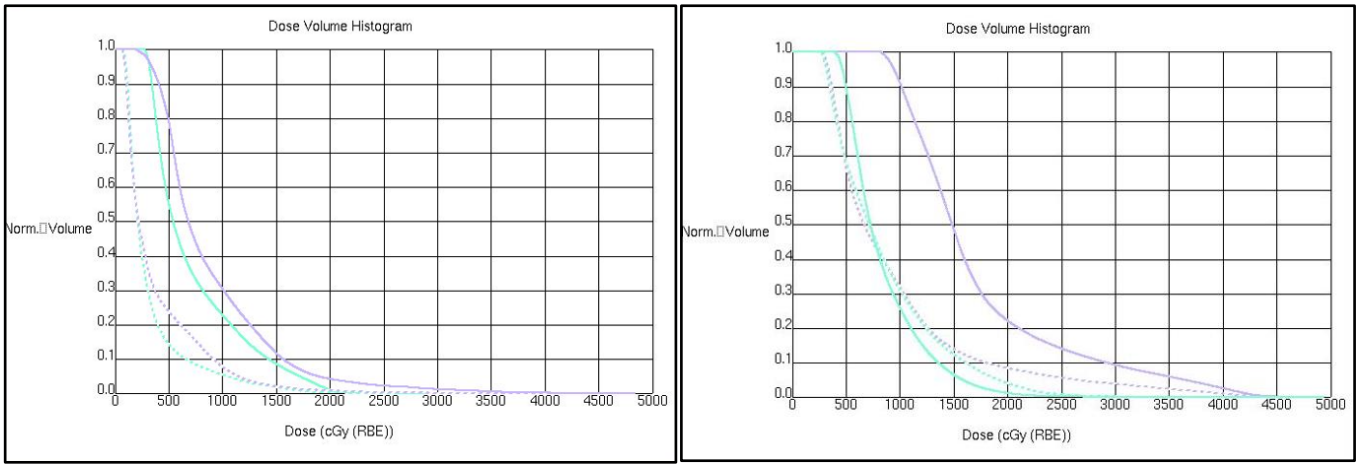


Figure 6.7*. Cumulative DVH for right and left kidney for Case 1 (left) and Case 2 (right), where the TOPGEAR volumes are represented by a solid line, and CRITICS-II by a dashed line. Key: Right kidney = mint green, Left kidney = lilac.*

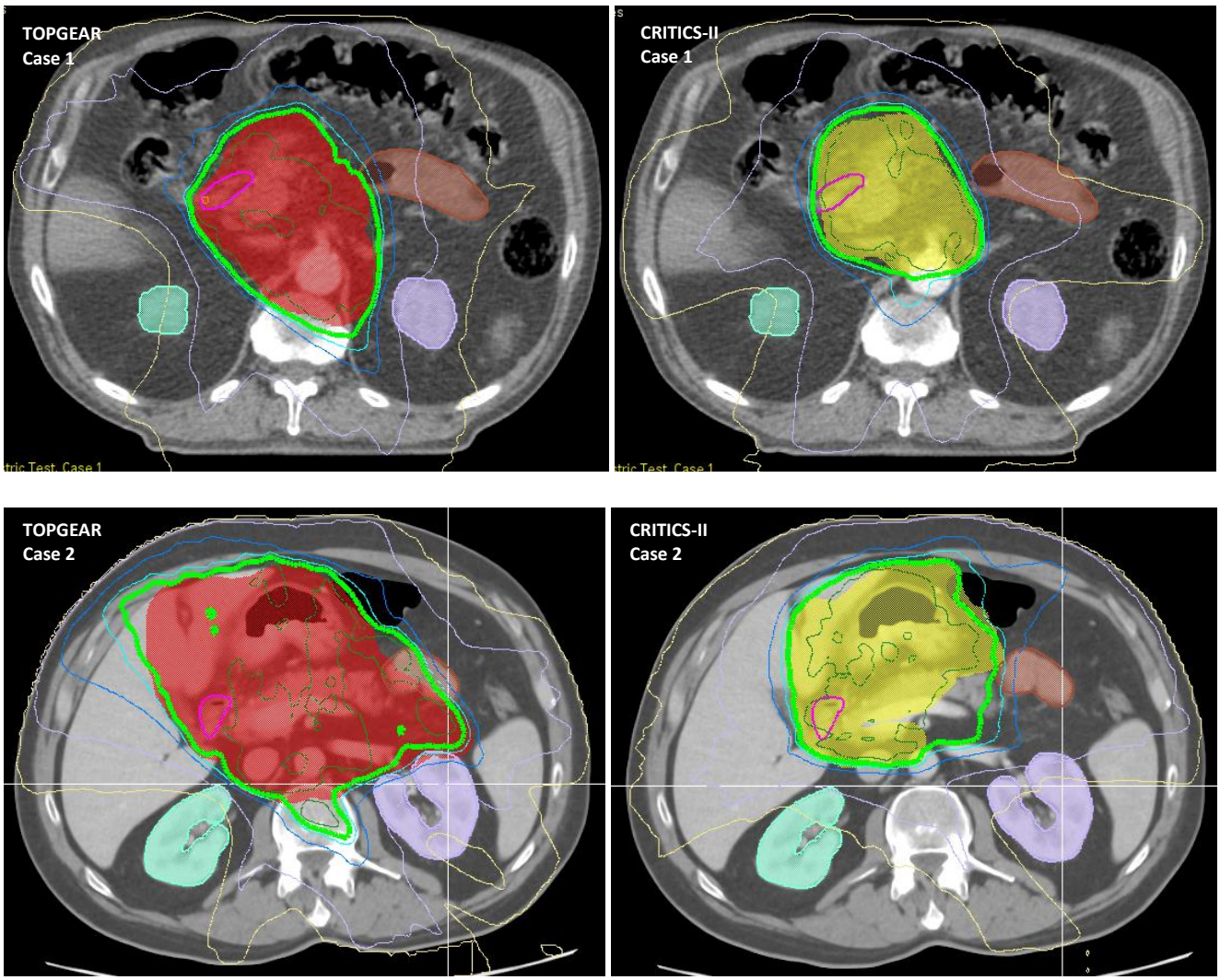
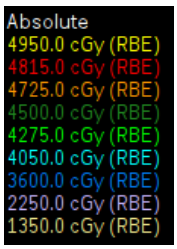


Figure 6.8. *Isodose distribution for TOPGEAR (left) and CRITICS II (right), for a single axial slice of Case 1 (top row) and Case 2 (bottom row).*



Solid green line = 95% isodose (42.75Gy)
Solid red shading= TOPGEAR PTV. Solid yellow shading= CRITICS-II PTV
Right kidney = mint green shading. Left kidney = lilac shading
Key to the left illustrates the colours of the other corresponding isodose lines (shown as fine lines)

Dose to duodenum, small bowel and spleen have been reported here for comparison and information, but were not optimised using the planning process, given that they were not named constraints in either protocol. Cumulative DVH for duodenum and small bowel is shown in Figure 6.9.

For Case 1, mean dose to duodenum is significantly higher for TOPGEAR (Mean = 41.85Gy) than CRITICS-II (11.17Gy). This is due to the inferior extension of the TOPGEAR volume to include the 2nd part of the duodenum, resulting in significantly more duodenum being included within the PTV, even with only the medial half being included within the CTV (Figure 6.2). Resulting isodoses are shown in Figure 6.10.

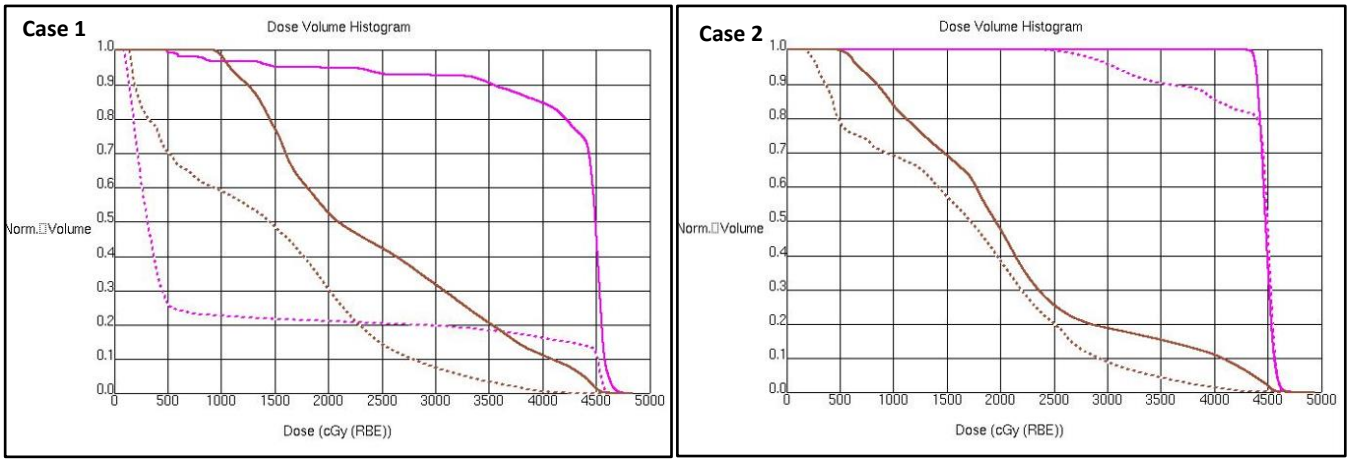


Figure 6.9. *Cumulative DVH for duodenum and small bowel for Case 1 (left) and Case 2 (right), where the TOPGEAR volumes are represented by a solid line, and CRITICS-II by a dashed line. Key: Duodenum = pink and Small Bowel = orange.*

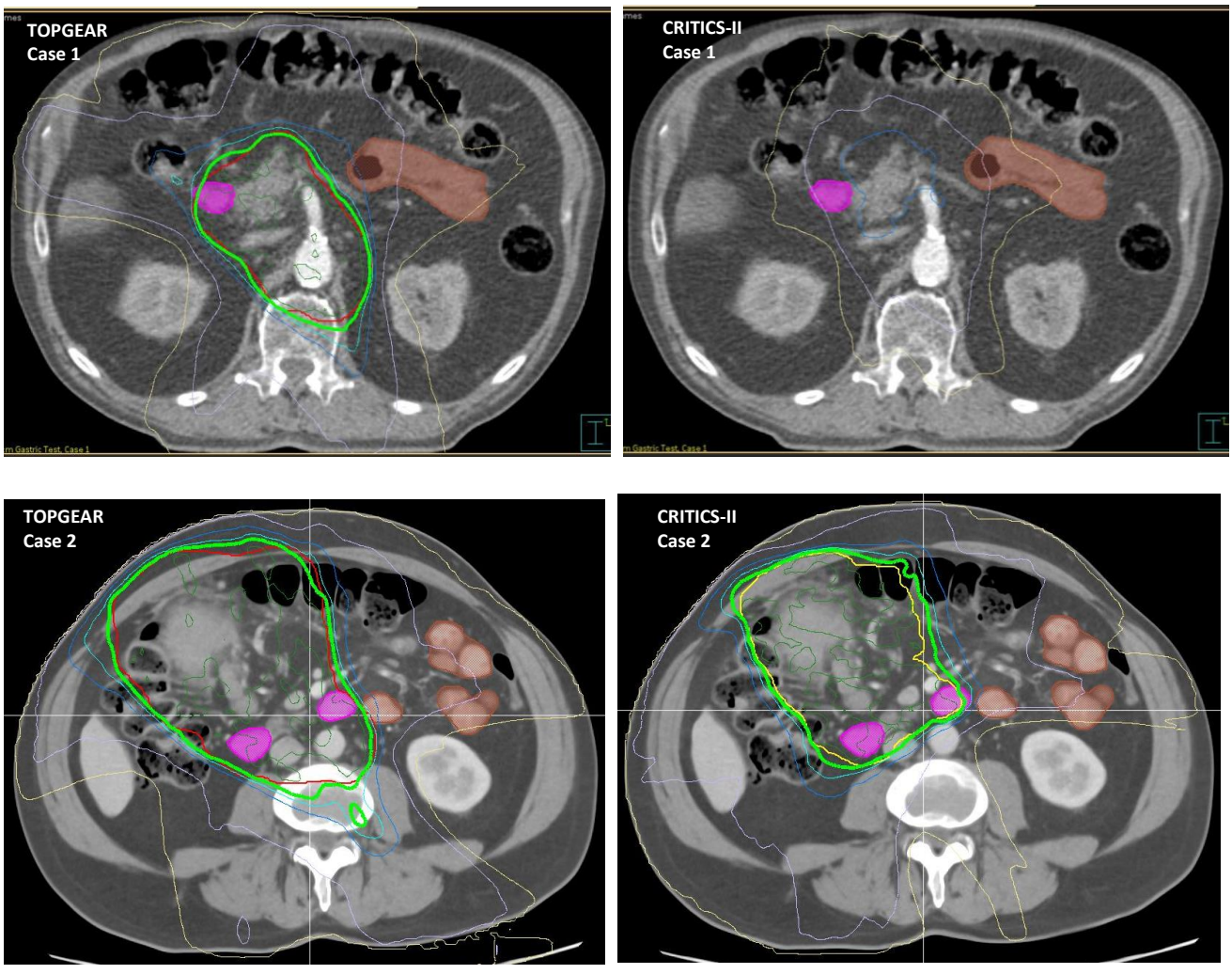


Figure 6.10*. Isodose distribution for TOPGEAR (left) and CRITICS II (right), for a single axial slice of Case 1 (top row) and Case 2 (bottom row).*
Solid green line = 95% isodose (42.75Gy)
Solid red line= TOPGEAR PTV. Solid yellow line= CRITICS-II PTV
Solid pink shading = duodenum. Solid orange shading = small bowel.
Key to the left illustrates the colours of the other corresponding isodose lines (shown as fine lines)

Less difference is seen for the duodenal doses received for Case 2. This is likely due to the distal tumour location, and similar recommendations by both protocols relating to inferior extension of volume and duodenal inclusion. Figure 6.9 again demonstrates the inclusion of para-aortic nodes by TOPGEAR resulting in the volume extending further to the left than CRITICS-II, thus pushing more low dose to spinal cord and left kidney. Mean small bowel dose was lower for CRITICS-II than TOPGEAR for both cases.

Mean spleen dose was significantly higher than the local target of mean<10Gy for both protocols and cases. This is likely due to not being optimised for during the planning process (as not a named constraint in either protocol) using Pinnacle Autoplan, so not to compromise coverage of the named constraints.

6.5 Discussion

6.5.1 Usability of protocols and supportive materials

As a UK clinician, familiar with using detailed, prescriptive guidance documents to aid TVD, such as the SCOPE2 RT protocol,[215] I found the higher level of description afforded by TOPGEAR preferrable to the simplified approach of CRITICS-II. In fact, the sweeping single-volume CTV and lack of detail offered to guide construction of said volume by the latter had the effect of making TVD more, rather than less, time consuming, due to the consequential reliance on delineation of each nodal station as per ESTRO-ACROP guidance to ensure adequate coverage within CTV. Though the authors argue this was intentional due to the belief that 'overly detailed protocols are not of great help and may lead to marginal misses in RT,' one would argue that less prescriptive CTV guidance may result in increased IOV and weaker quality assurance.

Detailed prose is difficult to follow when undertaking TVD, requiring frequent re-reading of passages of text. Neither protocol included useful summary tools, for example, TVD summary tables, diagrams or definitions of nomenclature, which are commonly used in the oesophageal RT protocols (SCOPE 1,2) with which UK clinicians are familiar, and would be useful to incorporate in any novel guidance.[215,216]

Chapter 4 shown that 76.7% and 74.4% of UK OG clinicians would find a nodal atlas and worked example useful supportive materials in future gastric RT protocols. Whilst these were included in both protocols assessed by this study, they were limited due to inclusion of only one case (TOPGEAR), or inadequate labelling and inconsistency (CRITICS-II), thus were of limited benefit during this exercise. This further emphasises the vital importance of a detailed atlases and a variety of worked examples, exemplifying both normal anatomical and application of protocol to different tumour positions, in any future RT protocol.

Delineation of both protocols was extremely time consuming due to my relative inexperience in gastric TVD. Time taken for identification of landmarks, and speed of delineation of nodal stations, which were particularly time consuming at the outset, would improve significantly with experience. TOPGEAR highlights the importance of correct identification of anatomical structures to aid TVD, though did not provide any additional materials to support this process. Whilst I was able to identify useful papers to aid duodenal delineation, tools such as interactive atlases would have been helpful.[217] Chapter 4 demonstrated that 48.8% of survey respondents had prior experience in delineation of upper abdominal LN areas, and 62% had experience delineating duodenum – thus for many oncologists this process would have been more straightforward, though nevertheless highlights that approximately 40% may benefit from additional education and training to enable accurate delineation of key structures. I also spent significant time re-referring to protocols due to somewhat ambiguous definition of volumes, which would improve with increased familiarity of each protocol following more experience.

The statements made regarding usability of these protocols is limited to that of a single observer, and requires validation by larger qualitative studies to fully evaluate pros and cons of protocol format.

6.5.2 Optimising elective nodal CTV based on quantitative analysis

It follows that the more elective nodal stations included, the larger the CTV volume will be. Given the high rates of lymphatic involvement of the peri-gastric nodes, the rationale for including stations 1-12 pre-operatively is clear. The approach taken by TOPGEAR, while more user-friendly, resulted in station 4 (i.e. greater curve nodes) being under-covered by CTV, compared to CRITICS-II, where station 4 nodes were included by virtue of the specific delineation and inclusion of each nodal station. This may be possible to overcome in future protocols by the addition of a lateral margin to the silhouette of the greater curve (edited for OARs), which may improve station 4 coverage whilst avoiding specific delineation of LN stations according to ESTRO-ACROP guidance, which was very time-consuming and is not feasible in day- to day clinical practice.

Inclusion of the more distal nodal stations 13-16 is conflicting, and we have demonstrated that their inclusion, particularly para-aortic nodes (station 16) increases PTV and in turn, dose to OARs. Given the increased dose to duodenum, small bowel, spleen, and kidneys demonstrated here when extending CTV inferiorly to include more distal nodal stations, one must be mindful of the risk: benefit ratio of irradiating the latter. Whilst TOPGEAR results suggest that CRT using these extensive nodal volumes to 45Gy was safe, with G3 gastrointestinal toxicity rates following CRT comparable to SACT alone (28% vs 25%), all G3 toxicity was 66% and is not insubstantial.[68]

Rates of metastatic spread to the distal nodal groups are very low for junctional, or proximal gastric tumours, as explored in section 6.1.3. (LN station 14-16 involvement in <0.1% for proximal tumours).[206] This

supports selective inclusion of most at-risk nodal stations based on tumour location, and omission of distal nodal groups for proximal/ junctional tumours, potentially sparing toxicity. For distal tumours, involvement of distal nodal groups is more common, thus their inclusion warranted. However, Yang *et al.,* demonstrated that 72% of recurrent station 16 LNs were located in the upper half of station 16b1 (demonstrated by Figure 6.11), and that those with node positive disease were statistically most at risk.[208] Therefore, with further research, it may be possible to risk stratify patients, and further refine and reduce extent of distal nodal volume.

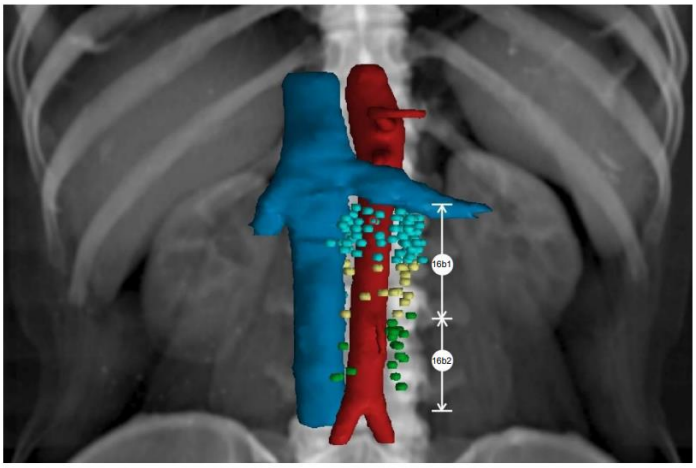


Figure 6.11*. Three-dimensional analysis of station 16b lymph node recurrence. The blue dots represent upper half of 16b1 nodes, yellow dose lower half and the green dots 16b2 nodes. Reproduced from Yang et al., under the Creative Commons Attribution License.*[208]

Extent of elective LN inclusion should also take into account concurrent systemic therapy, including immunotherapy or novel targeted agents. GC is largely considered a systemic disease due to its high rates of distant metastatic recurrence, even following radical treatment. Thus, optimal radical RT should be in addition to, and not in place of optimal SACT. Given this, one must consider whether in the context of systemic therapy it is necessary to treat all at-risk nodal stations, and whether low risk stations could be omitted to reduce treatment toxicity? The answer is unknown, but should be considered by clinical trialists of any future definitive studies. Further, one could argue that elective lymph node volumes could be completely omitted in palliative studies, where intent is not curative, and large treatment volumes risk impairing quality of life.

6.5.3 Optimising CTV stomach based on quantitative analysis

Inclusion of the whole stomach, plus an oesophageal and/or duodenal margin also significantly adds to PTV size. Both protocols advocate extension of the whole stomach volume to include 4cm distal oesophagus for proximal, and 4-5cm of duodenum for distal tumours. Whilst the 4cm oesophageal

inclusion for case 1 had little impact on OAR dose (lung and heart), additional inclusion of duodenum (even in the context of a proximal tumour) significantly added to the PTV of TOPGEAR. Exact definition of the inferior limit of CTV was unclear in both protocols, and so it is possible there is some over-outlining in these cases. Nevertheless, it is still worthwhile considering the impact of recommendations made regarding inclusion of entire stomach in all cases, and the generous margins of ≥4cm oesophagus or duodenum.

The EORTC-ROG authors point out that whilst delineating the whole stomach had previously been deemed necessary due to difficulty assessing exact tumour position within the stomach, the definition of this large volume should be reconsidered to avoid toxicity.[203] They quote <5% of patients have tumour cells >3cm from the macroscopic edge of the tumour, thus recommend a 5cm GTV margin to have a comfortable security margin, with the exception of mid stomach tumours for which the whole stomach excluding cardia and pylorus is delineated. However, one would postulate that in the era of advanced IGRT and motion management techniques, it may be possible to reduce the 5cm margin down 3cm to cover microscopic disease whilst minimizing toxicity. Taking such an approach would make accurate assessment of inter-and intra-fractional (i.e. between or during each treatment) stomach motion imperative, to avoid geographical miss.

Whilst CRITICS-II mandates the use of 4D-CT, which will account for respiratory motion, few other gastric RT trials to date have made any specific recommendations or adjustment to account for gastric motion, as seen in Chapter 3. However, gastric motion of patients treated within CRITICS-II has been evaluated by Bleeker *et al.,* who in their evaluation of 14 patients, measured the motion gastric tumours implanted with 2-6 fiducial markers on daily 4D CBCT over 20-25 fractions.[218] They reported considerable interfractional displacement (i.e. movement between fractions, day-to-day) of the tumour of 1.6-8.8mm, with the least motion seen in the cardia, and most in distal greater curve. Median respiratory motion was 10.8mm (range 5.2 – 20mm). Interfractional and respiratory motion were both considerably more prominent than intrafractional motion (i.e. movement pre- and post- fraction, median 3.6mm). Whilst respiratory motion can be partially accounted for by TVD on all respiratory phases of a 4DCT, interfractional stomach motion is more difficult to counteract, and would require large generic margins of up to 20mm to account for all possible motion. One method to reduce and personalize this margin could be by adopting an adaptive strategy via a 'library of plans.' [219] This approach involves creation of multiple RT treatment plans which account for variation in organ position and size, with the 'best match' selected each day of treatment based on CBCT evaluation. Whilst evidence exists to support a 'library of plans' approach for pelvic organs, due to the considerable increase in time and expertise required in planning and delivery, this is not currently common place in the UK.[220-222] Nonetheless, any future trials incorporating smaller treatment volumes should mandate motion management, for example via 4D-CT or gastric filling strategies, and motion should be evaluated by daily CBCT, with pre- and post- treatment CBCT also considered to evaluate

intra-fractional motion. This will be vital for any subsequent definitive trials, particularly if boosting dose to primary tumour.

6.5.4 Limitations of the study

There are a number of limitations of this small, exploratory study including:

- Only two cases were compared. Whilst this allows basic comparison of opposing tumour locations, evaluation of more cases, including early and late-stage tumours of different anatomical locations should be undertaken to allow more detailed volumetric and dosimetric comparison. Additionally, case 2 was more advanced than either protocol was designed to treat, with large volumes pushing constraints hard.
- TVD was performed by a single observer (AC), and whilst peer reviewed by an expert UGI radiologist (KF), volumes were not peer reviewed by clinical oncologists with experience in delineating according to either protocol (due to infrequency of use of pre-operative RT in the UK and neither trial being open to UK centres).
- Experience bias exists due to the observer delineating using TOPGEAR first, thus has reviewed anatomy in great detail already prior to attempting CRITICS-II TVD, which may have biased time for TVD and qualitative observations. Experience bias could be reduced by delineation of more cases, alternating which protocol was used first, or ideally by including more observers.
- Only auto-optimisation was performed, and duodenal/splenic constraints were not included. It may be possible to further optimise both conformality and improve dose constraints by conducting further optimisations runs.
- Neither protocol here, or the work conducted in the former chapter, has addressed the issue of gastric motion, with cases planned only in 3D.

6.5.5 Future work

Prior to adoption in any clinical trials, any future gastric RT protocols should undergo planning studies to evaluate the dosimetric consequences of volume size, extent of nodal irradiation and effect of motion. Such studies should include several observers, evaluate several cases demonstrating both variation in tumour stage and anatomical location, and should include 4D-CT. Plans should then be optimised over several phases to explore whether tighter constraints could be applied in the context of modern image-

guidance and VMAT planning techniques. Also, additional constraints could be added to the optimisation process, for example duodenum, small bowel and spleen, to further reduce potential toxicity.

6.6 Conclusion

This small, exploratory study has highlighted some important considerations for the development of future gastric RT protocols. Given the infrequent use of gastric RT in the UK and low clinician confidence in gastric TVD, descriptive protocols, with clear definition of volumes, summary tables and diagrams will be subjectively easier for clinicians to utilise. Well-labelled imaging atlases are vital, and should include several cases to demonstrate variation in anatomy and tumour location. Where elective nodal radiation is required, an approach that encompasses the relevant LN stations via easily identifiable surrogate landmarks would be preferred to delineation of individual lymph node stations, which is time consuming and not feasible in every day clinical practice. However, elective nodal radiation should be personalised based on tumour position and risk of nodal spread to minimise dose to OAR and possible subsequent toxicity, and take into account concurrent SACT and intent of therapy, with rationalisation to only the most high-risk nodal groups, or even complete omission considered where risk outweighs benefit. As well as further work to investigate gastric tumour motion, more research to qualitatively and quantitatively evaluate any subsequent protocols will be required to optimise usability, reduce dose to OARs, and improve IOV.

Chapter 7

Conclusions and Recommendations for Future Clinical Trials

7. Conclusions and Recommendations for Future Clinical Trials

In this final chapter I will make recommendations, based on the results presented in this thesis, that should be considered in the design of any future gastric RT clinical trials, and discuss the development of GastroSCOPE, a proposed UK clinical trial of RT for IGC.

7.1. Do current GC outcomes justify the need for future RT clinical trials?

The work in Chapter 2 has demonstrated the poor survival outcomes for patients with GC across SWW between 2019-2021, with mOS of 17.8, 12.4, 9.4 and 2.9 months for stages I, II, III and IV respectively. Additionally, outcomes for patients with stage I-III disease who do not undergo surgery is considerably worse than those who have a curative resection, due to limitations in palliative treatment options (mOS 26.3 months vs 8.8 months), underlying the urgent need for improved treatment strategies. Only 10% of SWW patients underwent RT, with most having low-dose reactive treatment for bleeding, highlighting the low use of RT, and potential under-utilisation, for this group of patients. Extrapolating the data from this service evaluation has revealed a potential population of 11 patients over a 2-year period who may be considered suitable for a future clinical trial, with co-morbidity being a common justification for patients being deemed unfit for oncological therapy.

Resulting recommendations for future trials:

- *Novel treatment strategies are urgently required to improve outcomes for patients who are unable to undergo curative surgery*
- *Numbers of patients with non-metastatic, inoperable GC suitable for oncological treatment is modest, necessitating a multi-centre approach of any future clinical trials.*
- *The co-morbid, frail population should be considered in design and patient selection of future trials.*

7.2 What evidence currently exists to support the potential role RT for IGC? Where are the gaps?

The comprehensive systematic review presented in Chapter 3 has demonstrated that a substantial body of largely non-randomised evidence exists supporting the efficacy and safety of RT in the definitive, pre-operative and palliative setting. This review is, to my knowledge, the first evaluating definitive RT, and offers the most up-to-date review of gastric RT in the palliative setting.

Efficacy is best demonstrated in the pre-operative setting, where this review identified pCR rates of up to 35.3% reported by Tang *et al.,* with 13 other studies reporting rates in the region of 10-30% (see section 3.4.3, Table 3.6), consistent with the 17% pCR reported by the recently published RCT, TOPGEAR.[68] These figures are not insubstantial when applied to inoperable, non-metastatic disease, where treatment is currently exclusively palliative, and a treatment strategy resulting in complete response for 10%, let alone 30% of patients would be significant. Though it is known that pCR does not always translate to cure, it may result in survival benefit, further supporting the evaluation of high-dose RT in addition to SACT in the inoperable setting in an effort to improve outcomes.[223] The efficacy of RT for IGC is further supported by cCR rates of up to 45% seen in the definitive studies included in this review (section 3.4.1, Table 3.3), and excellent rates of haemostatic control in the palliative setting, where the latter was associated with improved survival (section 3.4.2.2). However, the nearly all palliative data relates to a metastatic, co-morbid, heavily pre-treated population, and the potential benefit of higher-dose, pre-emptive treatment to prevent, or delay symptoms (and potentially reduce hospital admission, and improve QOL), rather than reactive treatment upon symptom occurrence, is largely untested, representing a gap in the current evidence base.

Safety across a variety of dose/fractionation schedules has also been demonstrated by the review (including doses of up to 60GyBED10 to the whole-in situ stomach, and boosted doses to GTVp), with acceptable levels of G3 gastrointestinal toxicity, and high rates of treatment completion. Palliatively, regimens of 28-50.8Gy BED10 (doses generally higher than currently used in this setting in the UK) have demonstrated reassuringly low rates of G3 gastrointestinal toxicity of <5%, making it an attractive option for frailer patients in need of local symptom control. Though this data may allay clinician concerns, prospective randomised data is required to verify this, especially in the context of the survey findings in Chapter 4. Prospective QOL data, though encouraging, is lacking and should be addressed by future trials.

The systematic review has demonstrated the current lack of consensus with regards to optimal RT technique, with a heterogenous approach to TVD seen across published studies to date, and few describing modern motion-management techniques. With regards to dose/fractionation, in

the definitive setting, dose/fractionation of 45-50.4Gy/25-28 (BED10 53.1-59.5) has been demonstrated as safe, and potentially efficacious in non-randomised studies, but this dose should be explored in phase III trials. Boost to GTVp, whilst incorporated by some studies, has not been tested prospectively in large numbers of patients, though could prove to be a useful technique to increase dose to primary tumour, whilst rationalisation of elective nodal volume and optimal motion management may minimise dose to OARs. The effect of hypofractionation has not been explored in this setting, (where most studies deliver 1.8Gy/#), an attractive option for future trials due to both reduced treatment time for patients, and improved cost-efficiency for stretched healthcare services. In the palliative setting, a wide-range of schedules have been reported in the literature, including some hypofractionated schedules, with conflicting evidence regarding dose/response relationship (section 3.4.2.3, Appendix 3.8), indicating the urgent need for randomised data to define the optimal schedule.

Due to the high propensity of gastric adenocarcinoma to metastasise, RT should complement, and not replace optimal SACT – a concept supported by this review, which has identified several studies demonstrating benefit when the two modalities are combined (section 3.5.6), though optimal timing of RT in relation to SACT remains unknown. That said, there is evidence to support a 'consolidative' approach to RT following a course of upfront SACT, which should be explored further in randomised trials.[135,162] The fairly recent addition of immunotherapy to the GC armamentarium gives rise to the possibility of a synergistic response between checkpoint inhibition and RT – demonstrated by two studies in this review, one reporting the highest pCR of all included studies of 35.3%.[145] Given the recent NICE approval of check-point inhibitors in the first line metastatic setting for eligible patients (with approximately 40-60% of patients receiving immunotherapy in practice), a trial investigating RT alongside standard of care chemo- or chemo-immunotherapy would allow the unique opportunity to compare the effects of RT with and without immunotherapy.

Perhaps one of the most significant limitations of the current evidence base is its composition of mainly non-randomised, observational studies in the definitive and high-dose palliative setting, where published RCTs are lacking. The gap in the literature is not being addressed by any currently active trials – with only one palliative and no definitive studies identified by my registry searches. Additionally, most data relate to an East Asian population, thus are not truly representative of the Western population. Studies identified have not explored the interplay between the molecular subtypes of GC and radiation, and as such there are currently no known biomarkers to predict RT response.

Resulting recommendations for future trials:

- *The largest gap in the evidence is the definitive and high-dose palliative settings – future trials should be focus on these areas.*
- *Any future trial should be randomised, phase II or III, to adequately contribute to the current evidence base, and to be deemed practice changing in the UK.*
- *RT should be an adjunct to optimal SACT (for those fit enough for the latter).*
- *In the definitive setting, minimum dose/fractionation equivalent to 53.1–59.5Gy BED10, with boost to primary GTV considered. Hypofractionation should also be explored.*
- *In the palliative setting, research should focus on the role of earlier, higher-dose (i.e. >30Gy BED10), pre-emptive RT rather than reactive, low-dose RT on occurrence of symptoms (the latter having a considerable evidence base already)*
- *Exploration of the radiosensitivity of the different molecular subtypes of GC, and potential predictive biomarkers is required.*
- *Potential synergy between immunotherapy, the immune microenvironment and RT should be explored.*
- *Any future trials must include prospective QOL data, particularly in the palliative setting, where survival benefit may be limited, thus QOL of utmost importance.*

7.3 What is current UK practice, and what support exists for future gastric RT trials?

The survey of UK OG clinical oncologists presented in Chapter 4 demonstrates current low rates of agreement with RT as a treatment modality in the post-operative (28.6% of respondents in agreement), pre-operative (7.1%) and definitive setting (9.5%) for GC, compared to the palliative setting (80.9%), with main reasons for infrequent use being lack of evidence (88.4%), toxicity concerns (44.2%) and a lack of UK gastric RT protocol (53.5%).

In keeping with its infrequent use, and absence of a consensus RT protocol, most clinicians would rate their confidence in pre-operative or definitive gastric TVD as moderate (38%) or low (45%). A clear TVD protocol (93%), nodal atlas (76.7%), worked example (74.4%) and outlining workshops (74.4%) were identified as educational materials that would be deemed useful in any future protocol.

Encouragingly, 76.6% of respondents were supportive of a future clinical trial investigating the role of definitive CRT for non-metastatic, inoperable gastric cancer. The majority estimated treating 3-5 patients each year with non-metastatic, inoperable disease, consistent with the estimation from SWW calculated in Chapter 2, and further highlighting the multi-centre approach that will be required for any subsequent clinical trials.

Resulting recommendations for future trials:

- *High quality, randomised evidence will be required to bring about a change in practice in the UK in the context of current clinician opinion.*
- *RT volumes must be rationalised to reduce possible toxicity, a major concern for treating clinicians.*
- *Clear toxicity and QOL end-point data should be incorporated to further address these concerns.*
- *A detailed RT protocol with accompanying educational materials, including nodal atlases and worked examples, and TVD workshops are vital to address low confidence levels and lack of experience in gastric RT.*
- *A multi-centre design will be required to enrol sufficient numbers of patients into any future randomised trial, though positive support from UK clinicians will aid recruitment.*

7.4 What RT techniques should be incorporated into future gastric RT trial protocols?

The need for a consensus, detailed, UK gastric RT protocol has resonated throughout this thesis. The work presented in Chapters 5 and 6 has explored technical aspects of gastric RT TVD that should be noted in the development of any subsequent trial protocol.

Chapter 5 is the first study of its kind to evaluate IOV for GTVp for gastric adenocarcinoma, and to explore the role of MRI in addition of CT for TVD in this context. The study revealed considerable IOV in TVD of GTVp, attributable to both under- and over-outlining (section 5.4.1, Table 5.5). Areas of most variation were cranio-caudal extent and extra-gastric extension - these areas must be clearly defined in subsequent protocols, with supportive educational materials and workshops to improve identification of the latter on cross-sectional imaging. In relation to the hypothesis that addition of MRI to CT may improve TVD, and reduce IOV for gastric TVD, impact on

conformity was conflicted between the cases evaluated in this study, likely due to a number of confounding factors. However, subjectively, MRI improved ease of TVD for 81% of observers (section 5.4.4.3), with DWI proving a particularly useful sequence. Indeed, any subsequent definitive gastric RT trials that incorporate a boost to GTVp will need to include optimal imaging techniques to aid accurate delineation. With adequate training and radiologist support, MRI may be a useful tool that could be further explored in subsequent, prospective trials.

Chapter 6 has evaluated two international, pre-operative trial protocols, TOPGEAR, and CRITICS-II, comparing user-experience, and assessing the volumetric and dosimetric advantages and disadvantages of each. The experience of a single observer has suggested that more detailed, prescriptive RT protocols are preferred, and that additional material in the form of labelled atlases and examples are required in the context of users who are relatively inexperienced in gastric irradiation. Dosimetrically, inclusion of distal nodal groups in the PTV increases dose to OARs, particularly duodenum and small bowel, which could result in increased treatment toxicity, giving support to further refinement of elective nodal levels. A personalised approach to elective nodal irradiation should be considered by future trials, taking into account tumour location, risk factors such as T-stage and nodal burden, and treatment factors such as concurrent SACT. Distal nodal groups could potentially be omitted in the case of proximal gastric or junctional tumours, and oesophageal volume reduced in the case of distal gastric tumours. However, recurrence patterns would need to be evaluated following such an approach in the definitive setting. In the palliative setting, total omission of nodal volumes should be considered, and circumferential tumour margins rationalised to reduce toxicity whilst optimising tumour control. However, respiratory and interfractional stomach motion has not been addressed by this study and should be evaluated in further work.

Resulting recommendations for future trials:

- *RT protocols must clearly define areas of most variation, particularly the cranio-caudal and extra-gastric extent of GTVp*
- *An education programme and training in gastric cross-sectional imaging interpretation will need to accompany any RT protocol to reduce IOV*
- *MRI, particularly DWI sequences, acquired with patient in the treatment position, could be incorporated into trial RT protocols to allow further evaluation of potential benefit, but will require adequate clinician training to avoid increasing uncertainty*

- *RT volumes must be rationalised to minimise toxicity:*
    - *Elective lymph nodes volumes for definitive treatment should be rationalised based on tumour location.*
    - *In the palliative setting, volumes should treat only the most high-risk peri-gastric nodes (e.g. 1-7), or omit nodal volume altogether.*
- *Lymph node volumes, whilst informed by ESTRO-ACROP definitions, should be constructed in a manner that uses surrogate landmarks for ease and time efficient TVD.*
- *Both respiratory and inter-fraction gastric motion must be evaluated in any subsequent trial.*

7.5 GastroSCOPE

GastroSCOPE aims to be the first UK clinical trial of RT for IGC. Informed by the work presented in this thesis, the trial has been further developed by an expert trial development group, led by Dr Sarah Gwynne, to which I have contributed significantly, and will be named co-lead applicant on the imminent funding application. GastroSCOPE will investigate the role of high-dose palliative RT for patients with inoperable gastric, or type III GOJ tumours. The trial schema is presented in Figure 7.1.

7.5.1 Contribution of this work to GastroSCOPE trial design

The high-dose palliative, rather than definitive setting, has been chosen, due the relatively small, non-randomised evidence base supporting definitive RT for IGC at present, the infrequent use of 'radical dose' gastric RT in the UK, and concerns raised by the OG oncology community around the toxicity of gastric RT, which need to be addressed. Additionally, in the UK, RT has recently fallen out of favour in the pre-operative setting for oesophageal cancer, due the perceived lack of benefit shown by recently published ESOPEC and TOPGEAR.[68,224] Although Chapter 4 has demonstrated strong clinician support for future gastric RT trials, whether it is the right time to attempt a trial of definitive RT in the current landscape is uncertain, further contributing to the decision to instead focus on the high-dose palliative setting. However, if positive, the evidence generated by GastroSCOPE will support the development of a future definitive trial. Additional clinician surveys have demonstrated support for this approach (work not presented in this thesis), with 29 centres across the UK expressing an interest in opening GastroSCOPE based on current design (if funded).[225]

The trial design addresses several the recommendations made by this thesis, namely:

- Randomised, phase II, UK multi-centre trial
- Basket design, which following clinician feedback, incorporates a wide-presentation of inoperable disease, and includes patients of various fitness for treatment including:
    - Cohort A: Non-metastatic disease, inoperable disease, fit enough for SACT
    - Cohort B: Non-metastatic, inoperable disease, but not well enough for upfront SACT
    - Cohort C: Low-volume metastatic disease, fit enough for SACT (Cohort C)

This approach acknowledges the co-morbid population, who are not always suitable for SACT. Given potentially low numbers that could be recruited per cohort (Chapter 2,4) the basket design aims to optimise accessibility, recruitment and efficiency for Research and Development/ Clinical Trial Units (effectively '3 trials in 1').

- Combines optimal standard of care SACT (including anti-HER2 and anti-PDL1 therapy) with consolidation RT for Cohorts A and C – to optimise both local and systematic control. This also presents a rare opportunity to evaluate the interplay between SACT and RT in gastric adenocarcinoma via novel translational studies.
- Explores novel, hypofractionated regimens, of considerably higher dose than is conventionally currently used in the UK .

Endpoints of the trial are demonstrated in Table 7.1. Progression free survival (PFS) has been selected as the endpoint for Cohorts A and C due to its importance to patients, and to add high quality survival outcome data to the current palliative evidence base, where data is currently focused on haemostatic control, and randomised survival data is lacking. However, for Cohort B, where patients are not suitable for SACT, the primary outcome will instead focus on incidence of stomach-related bleeding events (i.e. can pre-emptive, higher-dose RT reduce bleeding, or increase the time it takes until a patient experiences a bleeding event?). Given the lack of prospective cohort data demonstrated by Chapter 3, QOL data will be collected in all 3 arms and is a secondary outcome measure.

Figure 7.1 GastroSCOPE trial schema (March 2025)

GASTROSCOPE

Patients with gastric, or Siewert type III gastro-oesophageal junction (GOJ) adenocarcinoma. PS 0-2. Age ≥16 years

Locally advanced, inoperable*, non-metastatic **

* Inoperable due to local extent of disease, patient choice or co-morbidities precluding surgery
** T_{any} N_{any} M0 (non-regional nodes, i.e. M1, are not permitted)

Suitable for SACT

Not for upfront SACT+

+Uncertain benefit, contra-indication, or patient declines SACT. PS 0-2, Life expectancy >3 months.
SACT may be given at a later date, as long the patient completes radiotherapy first (if randomised to intervention arm). Cross over from GastroSCOPE A permitted if poor tolerance after 1 cycle of SACT

Low volume metastatic disease#

Defined as metastatic disease limited to 2 organs and 1 extra regional LN station, with a total of ≤5 metastatic lesions (or 1 organ with 2 extra-regional stations). No single metastasis may measure >3cm Excluded: Peritoneal disease detectable on CT, or staging laparoscopy (but staging lap is not mandatory for entry to study). Known brain metastases (dedicated neuroimaging not required for asymptomatic individuals). Bone metastases when there are more than 2 discrete lesions or MSCC (as per standard staging investigations, dedicated bone imaging of asymptomatic individuals is not a required).

GastroSCOPE: A
SACT alone *vs* SACT + RT 40Gy/15#

Consent, eligibility assessment and registration to study

9 weeks of SOC SACT[a]

Restaging CT: RECIST stable or responding disease

Randomised 1:1

Control arm

SOC SACT alone

Further 2 – 9 weeks SOC SACT[b]

Can include Palliative radiotherapy for symptoms[c]

Intervention arm

Further 2-9 weeks SOC SACT[b]

RADIOTHERAPY

40Gy/15# over 3 weeks to primary tumour

Maintenance anti-HER2 / anti-PDL1 (if eligible)

Follow up: CT scan at 9-week intervals until progression

GastroSCOPE: B
Best Supportive Care vs RT alone 25Gy/5#

Consent, eligibility assessment and registration to study

Randomised 1:1

Control arm

Best Supportive care

Can include Palliative radiotherapy for symptoms[c]

Intervention arm

RADIOTHERAPY ALONE

25Gy/5# over 1-2 weeks to primary tumour

Follow up: Stomach bleeding events recorded, FBC, QOL

GastroSCOPE: C
SACT alone *vs* SACT + RT 25Gy/5#

Consent, eligibility assessment and registration to study

9 weeks of SOC SACT[a]

Restaging CT: RECIST stable or responding disease

Randomised 1:1

Control arm

SOC SACT alone

Further 2 – 9 weeks SOC SACT[b]

Can include Palliative radiotherapy for symptoms[c]

Intervention arm

Further 2-9 weeks SOC SACT[b]

RADIOTHERAPY

25Gy/5# over 1-2 weeks to primary tumour

Maintenance anti-HER2 / anti-PDL1 (if eligible)

Follow up: CT scan at 9-week intervals until progression

[a]SOC SACT can consist of 2 or 3 weekly regimens of clinician's choice i.e.:
If 2 weekly regimen – 4 x 2 weekly cycles, then restage
If 3 weekly regimen – 3 x 3 weekly cycles, then restage
[b]After randomisation – further 2 – 9 weeks SACT permitted i.e.:
If 2 weekly regimen - 1-5 cycles permitted at clinician discretion, up to max 9 cycles permitted.
If 3 weekly regimen – 1-3 cycles permitted at clinician discretion, up to max 6 cycles permitted
[c]Palliative radiotherapy may be given for symptoms as per RCR dose/fractionation 4th edition i.e.:
6-8Gy/1# or 20Gy/5# (BED10 <30Gy) only AFTER randomisation in control arm, or AFTER RT intervention following suitable RT-free interval if clinically appropriate

	Cohort A	Cohort B	Cohort C
Primary Outcome	PFS*	Incidence of stomach-related bleeding events up to 6 months from randomisation	PFS*
Secondary Outcome	QOL	QOL	QOL
	Time to treatment failure	Incidence of stomach-related bleeding events up to 6 months from randomisation, and other stomach related events	Time to treatment failure
	OS	OS	OS
	Safety	Safety	Safety
	RT completion rate	RT completion rate	RT completion rate
	Conversion to resectability	Conversion to resectability	Conversion to resectability

Table 7.1. *Proposed endpoints for each Cohort of GastroSCOPE.*
**Based on RECIST criteria of a centrally reviewed CT scan.*
*** As defined in the ROCS trial as blood transfusion, haematemesis, other descriptions of upper gastrointestinal haemorrhage or bleeds, or interventions related to bleeding (such as argon plasma coagulation or additional RT).*

Working with a Cardiff University Clinical Trials Unit statistician, Angela Casbard, a statistical analysis plan has been developed. For Cohorts A and C, based on 90% power, 20% one sided α, 45 months accrual and 6 months follow-up, to show a PFS benefit of ~5 months with the addition of RT (HR 0.65), the sample size requires 98 events in 127 patients. In order to allow for 30% drop out following first 9 weeks of SACT due to disease progression (rendering them ineligible for randomisation), **196 patients will need to be registered in cohorts A and C.** Expression of interest (EOI) data gathered by survey data (not published in this thesis) supports potential recruitment of ~400 patients in cohort A and C, suggesting feasibility of the sample size. For Cohort B, applying a 20% two-sided significance level and 90% power to detect the difference between a proportion of 0.65 in the control group, and 0.35 in the intervention group (odds ratio 0.29), the sample size in each group is 35, which allowing for 10% attrition, requires **80 patients to be recruited to cohort B.** Feasibility of recruitment to cohort B is supported by EOI data of ~100 patients per year.

Patient and Public Involvement (PPI) representatives have been involved throughout the development of the study, with formation of a Patient Advisory Group, and a number of events including focus groups and a PPI event with a local OG cancer support group, has revealed very high levels of support for the trial.

7.5.2 Radiotherapy Protocol development for GastroSCOPE

The RT protocol, whilst still in development, will incorporate several findings of this thesis. Firstly, dose/fractionation schedule is based on the results of the systematic review. Two different dose/fractionation schedules will be investigated within GastroSCOPE, 40Gy/15# over 3 weeks for patients in Cohort A, with non-metastatic disease and who are fit enough for upfront SACT. With a BED10 = 50.57Gy, this is almost equivalent to the radical doses reported in the definitive and pre-operative setting, and much higher than conventional UK doses for palliative gastric RT (Table 7.2). Moreover, it allows randomised investigation of a novel hypofractionated regimen for gastric RT, which reduces overall treatment time, and fits in with SACT scheduling. For Cohorts B and C, given the increased frailty of this group due to their comorbidity, or more advanced disease, a slightly lower dose/fractionation schedule was selected, 25Gy/5# over 1-2 weeks, in an effort to minimise toxicity whilst still providing some local control benefit for this group. Whilst lower dose than Cohort A, with a BED10 of 37.50Gy, this still represents a significantly higher dose than is currently used in the UK (Table 7.2), is well within the range of doses shown to be safe in the analysis of palliative evidence base (section 3.4.2.4), with the additional novelty of being used upfront, pre-emptively.

Though relatively novel to GC, both dose/fractionation schedules have been previously investigated in other UGI tumour sites, where they have demonstrated safety and efficacy.[51]

	GastroSCOPE Cohort A	**GastroSCOPE Cohort B and C**	**TOPGEAR/ CRITICS-II**	**UK RCR palliative dose recommendations**	
Dose/#	40Gy/15#	25Gy/5#	45Gy/25#	20Gy/5#	6-8Gy/1#
BED10	50.57Gy	37.50Gy	53.10Gy	28.00Gy	9.60 – 14.40Gy

***Table 7.2**. Equivalent BED10 doses for the proposed dose/fractionation schedules for GastroSCOPE compared to the pre-operative setting and currently recommended UK regimens.*

In keeping with the findings of Chapters 4, 5 and 6, a detailed RT protocol, along with atlases and worked examples will be developed, with sections providing additional detail to the areas of most variation. RTQA workshops will be held to improve clinician confidence in TVD and reduce IOV. RT volumes will focus on GTV, with a 3cm mucosal CTV margin to account for submucosal spread. Given the additional dose to OARs demonstrated in Chapter 6 when extensive nodal volumes are treated, the latter will be omitted in GastroSCOPE to rationalise volumes in an attempt to reduce toxicity. This is felt appropriate due to the palliative intent of treatment, with priority being optimising local

control rather than trying to sterilise all sites of disease (particularly in Cohort B), and due to the inclusion of SACT to contribute to systemic control in Cohorts A and C.

GastroSCOPE will mandate 4D-CT to allow for adequate assessment of respiratory motion during the treatment planning process, and allow future research into stomach motion. A 2-hour fast will be recommended – this has been modified from the results of Chapter 3, which demonstrated most studies recommended a 4-hour fast. The latter was felt by the trial development group to be too long a period of regular starvation for a potentially malnourished group of patients – though its impact on interfractional stomach motion should be analysed via collection of daily CBCT images.

In light of the exploratory findings of Chapter 5, optional gastric MRI RT planning scans have been included within GastroSCOPE to further evaluate the value of MRI for gastric TVD. Images will be acquired using novel tailored gastric imaging protocols, including DWI sequences. The evaluation of prospective, dedicated imaging, with the patient appropriately prepared and positioned, and with adequate clinician training in MRI interpretation will allow comprehensive assessment of its role in gastric TVD. It is known from the SCOPE trials, that mandating optimal RT planning techniques within a trial, with the support of an RTQA programme, drives the implantation into standard clinical practice.[226] Therefore, it is anticipated that the inclusion of optimal motion management and imaging techniques within GastroSCOPE will contribute to improving treatment accuracy and reducing the variation in practice demonstrated in Chapters 3 and 4, both within, and outside of the clinical trial setting.

7.7 Final words - Could RT have a role in the management of inoperable, non-metastatic GC?

It is my view that the work presented here undoubtedly supports the hypothesis that high-dose RT could have a role in the management of IGC, where it could improve symptoms and QOL, whilst potentially improving survival outcomes for an understudied, under-represented group of patients. GC is a global problem, particularly affecting developing countries. RT, if proven to be beneficial, may prove to be a useful adjunct, or alternative to SACT, where access to the latter, particularly to novel targeted therapies, may be challenging. Hypofractionated schedules, may be of relevance, not just in the NHS where resources are limited, but also other health economies and developing nations.

Ultimately, this question can only be answered by a well-designed, multi-centre, randomised controlled trial. If funded, GastroSCOPE could provide some of these answers, and provide evidence that could bring about a change in practice in the UK.

Appendices

Appendix 1

Table A1.1. The Lauren Classification of gastric adenocarcinoma.
Histopathological and clinical features. The % frequency is that stated in the original Lauren publication, but may vary between populations.[10,11]

Lauren Classification (% frequency of gastric adenocarcinoma)	**Differentiation**	**Histopathological features**	**Clinical features**
Intestinal (53%)	Well - moderate	Cells exhibit adhesion. Arranged in tubular or glandular formation. Associated with intestinal metaplasia.	Most commonly affects the gastric antrum. Male> female. Associated with better prognosis.
Diffuse (33%)	Poor	Tumour cells lack adhesion, infiltrate the stroma as single, scattered tumour cells. May form signet rings.	Associated with younger age, females. Predilection for peritoneal metastases. Worse prognosis.
Unclassified (14%)	NA	Atypical structure that belongs to neither intestinal nor diffuse group. In modern practice, this group are commonly further sub-classified according to WHO criteria, and includes rare acinar carcinomas	NA

Table A1.2. – Definition of D levels for lymph node dissection.
Lymph node stations removed during D1,D2, and D3 lymph node dissections during total gastrectomy.[204,227] For further definition of JCGA LN stations, see Appendix 6.2.

D-level	**Definition (JCGA LN stations resected)**
D0	Any lymphadenectomy less than D1
D1	1-7
D1+	D1 + 8a, 9, 11p
D2	D1 + 8a, 9, 11p, 11d, 12a For tumours invading oesophagus, 19,20 and 100 should be added to D2
D2+	D2 + 10 +/- splenectomy (splenectomy only if proximal stomach tumour invading greater curve) D2 + 14v (if distal stomach tumour with station 6 involvement) D2 + 13 (if invading duodenum)

Table A1.3. Comparison of the epidemiology, aetiology, treatment strategies and prognosis of GC in the Eastern (i.e. Asia) vs Western (i.e. Western Europe, North America) world.
LND = lymph node dissection. [1,227,228]

	West	**East**
Prevalence (5-year, both sexes)	Europe = 213,013 (11.8%) North America = 50,387 (2.8%) Latin America = 96507 (5.3%)	Asia = 1,397,478 (77.4%)
Anatomical site of disease	Higher proportion of cardia tumours in West compared to East	Approximately 90% are non-cardia.
Aetiology	Higher rates of obesity, GORD, alcohol and smoking more prevalent – associated with cardia tumours	*H. Pylori*, high salt and nitrite diet more prevalent risk factors - associated with non-cardia cancers
Stage at presentation	45-50% present with advanced/ metastatic disease	>50% diagnosed with early stage / node negative disease
5-year overall survival	~20%	~65% Japan, 71.5% S. Korea
Treatment preferences - surgery	Historically less extensive D1 LND performed, though in modern practice, D2 LND recommended	D2 LND standard for all T1N+ or >T2N0/1
Treatment preferences – resectable disease	Peri-operative chemotherapy favoured as SOC	Post-operative chemotherapy favoured as SOC
Treatment preferences – chemotherapy regimen	Infusional 5-FU or capecitabine standardly used in regimens	S-1 in use as fluorouracil-based agent in regimens
Treatment preferences – post-operative chemoradiotherapy	Selected high risk cases only	Selected high risk cases only

Appendix 2

Table A2.1. Data collected from each patient record

Demographics	MDT (SBU/HD)
	NHS No
	DOB, Age at diagnosis
Diagnostic Information	Site: Gastric/ Type III GOJ
	Morphology: Adenocarcinoma/other
	Histology/ differentiation
	HER2 status: Positive/ negative/ not done
	MSI status: Stable/ unstable/ not done
	Basis of diagnosis
	Date of diagnosis
Staging	T, N and M stage
	Clinical stage at presentation to MDT (TNM 8)
	Sites of metastatic disease at presentation
Treatment intent	Treatment intent at diagnosis: Curative/ palliative
Surgery	Staging laparoscopy performed: Y or N If Y, Occult peritoneal disease: Y or N
	Operation performed
	Post-operative TNM stage, pT, pN, pM, Nodal status
	Mandard score
	If not for surgery, why
Oncological treatment	Performance status (oncology assessed)
	Co-morbidities as listed in WCP letters
SACT	Peri-operative chemotherapy: Y/N, Regimen, No. of cycles administered, Reason if no peri-operative chemotherapy
	Any other adjuvant therapy?
	Palliative SACT: Y/N, No. of lines, Regimen, No. of cycles, Maintenance therapy, reason if no palliative SACT
Radiotherapy	Stomach RT: Y/N
	Date completed
	Dose/#
	Indication
Outcome data	Date of recurrence (if radically treated)
	Date of death
	Survival from diagnosis to death
	Survival from recurrence to death
	Survival to censor date (1/2/2022)

Appendix 3

Appendix 3.1. - Systematic Review Search Strategy

Searches conducted 10th March 2022 Susan Prosser in
Ovid MEDLINE(R) ALL <1946 to March 09, 2022> and separately in
Ovid Embase <1974 to 2022 March 09>
Combined into Endnote file (Total of 10049 references).
Deduplicated and manually scanned – resulting in 7447 references

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Ovid MEDLINE(R) ALL <1946 to March 09, 2022>

1 exp Stomach Neoplasms/ 104457
2 ((stomach or gastric) adj4 (cancer* or carcin* or malig* or tumour* or tumor* or neoplas* or adenocarcinoma)).ti,ab,kf. 117630
3 exp Radiotherapy/ 199985
4 exp Chemoradiotherapy/ 18265
5 Radiotherapy.ti,ab,kf. 201773
6 Radiation therapy.ti,ab,kf. 85925
7 Chemoradiotherapy.ti,ab,kf. 20933
8 Chemo-radiotherapy.ti,ab,kf. 3315
9 Radiochemotherapy.ti,ab,kf. 4076
10 Radio-chemotherapy.ti,ab,kf. 1467
11 Chemoradiation.ti,ab,kf. 13558
12 Proton therap*.ti,ab. 3760
13 proton beam*.ti,ab. 4425
14 proton plan*.ti,ab. 255
15 ((gastrooesophageal junction or gastroesophageal junction or oesophagogastric junction or esophagogastric junction or GE junction or GEJ or GOJ or OJG or EGJ) adj4 (cancer* or carcin* or malig* or tumour* or tumor* or neoplas* or adenocarcinoma)).ti,ab. 2775
16 exp Chemotherapy, Adjuvant/ 44594
17 exp Radiotherapy, Adjuvant/ 23788
18 16 and 17 8838
19 1 or 2 or 15 142461
20 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 18 372303
21 19 and 20 4393
22 limit 21 to english language 3416

Embase <1974 to 2022 March 09>

1 exp stomach cancer/ 135217
2 ((stomach or gastric) adj4 (cancer* or carcin* or malig* or tumour* or tumor* or neoplas* or adenocarcinoma)).ti,ab,kf. 151385
3 exp Radiotherapy/ 590933
4 exp Chemoradiotherapy/ 65730
5 Radiotherapy.ti,ab,kf. 296171
6 Radiation therapy.ti,ab,kf. 136545
7 Chemoradiotherapy.ti,ab,kf. 34923
8 Chemo-radiotherapy.ti,ab,kf. 7005
9 Radiochemotherapy.ti,ab,kf. 6941
10 Radio-chemotherapy.ti,ab,kf. 2687
11 Chemoradiation.ti,ab,kf. 26740
12 Proton therap*.ti,ab. 6917
13 proton beam*.ti,ab. 6708
14 proton plan*.ti,ab. 626
15 ((gastrooesophageal junction or gastroesophageal junction or oesophagogastric junction or esophagogastric junction or GE junction or GEJ or GOJ or OJG or EGJ) adj4 (cancer* or carcin* or malig* or tumour* or tumor* or neoplas* or adenocarcinoma)).ti,ab. 5109
16 1 or 2 or 15 185992
17 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 699525
18 16 and 17 10201
19 limit 18 to english language 9018
20 limit 19 to (article-in-press status or embase status or in-process status) 6633

Appendix 3.2. – Inclusion and Exclusion Criteria

- Inclusion Criteria:
    - Clinical studies in the neoadjuvant, definitive and palliative setting (in palliative setting minimum radiotherapy dose of ≥30Gy BED)
    - Studies evaluating external beam radiotherapy for gastric carcinoma (+/- chemotherapy)*
    - Studies including Siewert type 3 GOJ tumours (as long as they are reported separately from Siewert type 1 or 2 tumours)
    - Radiotherapy targeted to primary gastric tumour, not to sites of metastases
    - Clinical studies of ≥5 patients undergoing gastric radiotherapy
    - Radiotherapy modelling studies / dosimetric studies (any number of patients),
    - English language
    - Abstracts published in the 2 years preceding search date
    - Abstracts must include original data that includes at least 1 variable being collected
- Exclusion Criteria:
    - Studies of non-carcinoma (e.g. gastrointestinal stromal tumours, lymphoma, neuroendocrine tumours)
    - Studies solely reporting the adjuvant* (i.e. post-operative) setting
    - Studies reporting radiotherapy techniques other than external beam radiotherapy (e.g. brachytherapy)*, intraoperative radiotherapy*, or outdated techniques that are no longer widely used in clinical practice*
    - Case series <5 patients
    - Studies published before 1.1.1998*
    - Book chapters, letters/ editorials
    - Animal studies, in-vitro
    - Narrative overviews (with no discussion relating to review methodology)
    - Overlapping data that is updated by subsequent publication
- Updated criteria:

    Criteria with an * represent refined criteria, modified following pilot screening of 3000 records. The date restriction was added given concern about the high number screening records during pilot screening, and papers published since 1.1.1998 included, as it was felt such studies would be more representative of modern radiotherapy techniques, and would result in a more clinically relevant review, and also a date that encompassed most relevant neoadjuvant, definitive and palliative studies identified by the scoping search (PROSPERO record was updated accordingly).

- Systematic reviews (SR):

SR conducted with formal SR methodology will be retained to inform status of research for each clinical setting and to enable comprehensive citation tracking, but will be evaluated separately to papers reporting original data

Appendix 3.3 – Risk of Bias Assessment

Table A3.1 .Risk of Bias assessment – Definitive studies

* Q4/5 (regarding consecutive/complete inclusion) less applicable in prospective phase I/II setting due to prospective patient recruitment for clinical trials (e.g. requirement for patient consent)
# Q11 relevant only to cohort and RCT checklist only. Q12+13 relevant for RCT checklist only. Y = Yes, N = No, U= Unclear NA = not applicable.

Author/Year	Study type	JBI tool used	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11#	Q12#	Q13#	Total	Overall risk (comment)
Liu *et al.* (2017)	Phase 2, single arm, multicentre	Case Series	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y				10	
Wydmanski *et al.* (2014)	Phase 2, single arm, single centre	Case Series	Y	Y	Y	NA*	NA*	Y	Y	Y	Y	Y				8	
Safran *et al.* (2000)	Phase 2, single arm, multicentre	Case Series	Y	Y	Y	NA*	NA*	N	Y	Y	Y	Y				7	Only very basic demographic data present (e.g. no histological subtypes)
Chen *et al.* (2022)	Randomised controlled study	RCT tool	Y	U	Y	N	N	U	Y	U	Y	Y	Y	U	U	6	Moderate risk of bias, largely due to lack of concealment, blinding and detail surrounding treatment completion rates, follow-up duration, statistical analysis. However, included as deemed to contain enough overall detail to ascertain overall response to CRT and toxicity (across entire study population regardless of randomisation)
Xing *et al.* (2012)	Phase I, multicentre	Case Series	Y	Y	Y	NA*	NA*	Y	Y	Y	Y	Y				8	
Leong *et al.* (2003)	Prospective case series (feasibility study)	Case Series	Y	Y	Y	U	U	Y	Y	Y	Y	Y				8	
Dong *et al.* (2018)	Non-randomised controlled study	Case Series	U	U	U	Y	Y	Y	Y	Y	Y	Y				7	
Mizrak Kaya *et al* (2018)	Retrospective case series, single centre	Case Series	Y	Y	Y	U	U	Y	Y	Y	Y	Y				8	Potential overlap between populations due to cross over of dates of recruitment from the same centre
Taki *et al* (2017)	Retrospective case series	Case Series	Y	Y	Y	U	U	Y	Y	Y	U	Y				7	Unclear from which centre/ how many centres patients were recruited
Suzuki *et al.* (2012)	Retrospective case series, single centre	Case Series	Y	Y	Y	Y	U	Y	Y	Y	Y	Y				9	Potential overlap between populations due to cross over of dates of recruitment from the same centre
Li *et al.* (2018)	Retrospective review of cohort	Cohort Study	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y			10	Due to limitations of NCDB data, no detail regarding RT or chemotherapy regimens

Table A3.2. Risk of Bias assessment – Palliative studies

* Q4/5 (regarding consecutive/complete inclusion) less applicable in prospective phase I/II setting due to prospective patient recruitment for clinical trials (e.g. requirement for patient consent)
# Q11 relevant only to cohort and RCT checklist only. Q12+13 relevant for RCT checklist only. Y = Yes, N = No, U= Unclear NA = not applicable.

Author/Year	Study type	JBI tool used	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11#	Q12#	Q13#	Total	Overall risk (comment)
Tey *et al.* (2019)	Phase II, single arm	Case Series	Y	Y	Y	NA	NA	Y	Y	Y	Y	U				7	Risk of being underpowered - statistical analysis says 63 patients required for 95% significance and 95% power, but only 52 recruited.
Yoshikawa *et al.* (2009)	Phase I	Case Series	Y	Y	Y	NA	NA	Y	Y	Y	Y	Y				8	Phase I trial primarily assessing MTD of chemotherapy rather than investigating RT, but states efficacy and toxicity so included.
Saito *et al.* (2022)	Multicentre prospective observational study	Case Series	Y	Y	Y	NA	NA	Y	Y	Y	Y	Y				8	Possible selection bias due to clinician selection of for different RT regimens based on fitness
Takeda *et al.* (2022)	Retrospective review, multicentre	Case Series	U	U	Y	U	U	Y	Y	Y	Y	Y				6	Lack of detail regarding criteria on which cases were identified, how bleeding was defined, disease staged etc. Otherwise, clear descriptions. Possible selection bias due to clinician selection different RT regimens based on fitness, and modification of fields accordingly
Yagi *et al.* (2023)	Retrospective cohort study, single centre	Cohort study	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y			10	Risk of selection bias between two cohorts with regards to patients who underwent surgery compared to RT.
Katano *et al.* (2022	Retrospective cohort study, single centre	Case Series	Y	U	Y	Y	U	Y	Y	Y	Y	Y				8	
Sugita *et al.* (2022)	Retrospective review, single centre	Case Series	Y	Y	Y	U	U	Y	Y	Y	Y	Y				8	
Kawabata *et al.* (2022)	Retrospective review, single centre	Case Series	Y	Y	Y	U	U	Y	Y	Y	Y	Y				8	
Yu *et al.* (2021)	Retrospective review, single centre	Case Series	Y	Y	Y	U	Y	Y	Y	Y	Y	Y				9	
Lee, J *et al.* (2021)	Retrospective review, single centre	Case Series	Y	Y	Y	U	U	Y	Y	Y	Y	Y				8	
Mitsuhashi *et al.* (2021)	Retrospective review, single centre	Case Series	Y	Y	Y	U	U	Y	Y	Y	Y	Y				8	
Sasaki *et al.* (2020)	Retrospective cohort study, single centre	Cohort study	Y	Y	Y	Y	Y	Y	Y	U	Y	NA	Y			9	Primary outcome was to compare anti-PDL1 vs no-antiPDL1, but as states efficacy and toxicity of RT across both arms, so included.
Hiramoto *et al.* (2018)	Retrospective review, single centre	Case Series	Y	U	Y	U	U	Y	Y	Y	Y	Y				7	
Lee, Y *et al.* (2017)	Retrospective review, single centre	Case Series	Y	U	Y	U	U	Y	Y	Y	Y	Y				7	Baseline investigations to identify and define bleeding unclear ('clinical/lab findings')
Mizrak Kaya *et al.* (2017)	Retrospective cohort study, single centre	Case Series	Y	U	Y	U	U	Y	Y	Y	Y	Y				7	Only patients with an excellent response to chemotherapy underwent subsequent RT within this study. Within study, risk of selection bias due to clinician selection of RT dose and field. NB. Potential overlap between this population and that reported by Kim *et al.*

Tey *et al.* (2014)	Retrospective review, single centre	Case Series	Y	Y	Y	U	U	Y	Y	Y	Y	Y				8	Possible selection bias due to clinician selection of for different RT regimens based on fitness. Also treating field also at discretion of oncologist.
Choi *et al.* (2012)	Retrospective review, single centre	Case Series	Y	U	Y	U	U	Y	Y	Y	Y	Y				7	Definition of bleeding not specific "drop in Hb" or "evidence of low-grade GI bleeding"
Asakura *et al* (2011)	Retrospective review, single centre	Case Series	U	Y	Y	Y	Y	Y	Y	Y	Y	Y				9	Histological subtypes not stated
Lee, J *et al.* (2009)	Retrospective review, single centre	Case Series	U	Y	Y	U	Y	Y	Y	Y	Y	Y				8	
Hashimoto *et al* (2009)	Retrospective review, single centre	Case Series	Y	Y	Y	U	U	Y	Y	Y	Y	Y				8	
Kim *et al.* (2008)	Retrospective review, single centre	Case Series	Y	U	Y	Y	Y	Y	Y	Y	Y	Y				9	Definition of response to RT subjective "patient no longer complained of these symptoms…" Individual dose/# regimens not stated. NB. Potential overlap between this population and that reported by Mizrak Kaya *et al.*

Table A3.3. Risk of Bias assessment – pre-operative studies

* Q4/5 (regarding consecutive/complete inclusion) less applicable in prospective phase I/II setting due to prospective patient recruitment for clinical trials (e.g. requirement for patient consent.# Q11 relevant only to cohort and RCT checklist only. Q12+13 relevant for RCT checklist only. Y = Yes, N = No, U= Unclear NA = not applicable.

Author (Year)	Study type	JBI tool used	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11#	Q12#	Q13#	Total	Overall risk (comment)
Wang *et al. (2021)*	Randomised controlled study	RCT tool	Y	U	Y	N	N	U	Y	Y	Y	Y	Y	Y	Y	9	
Saeidi *et al.* (2014)	Randomised controlled study	RCT tool	U	U	Y	N	N	U	Y	Y	Y	Y	Y	Y	U	7	Very small RCT, no detail about randomisation, not scoring on major aspects that may introduce bias.
Wang *et al.* (2022)	Randomised phase II study, single centre	RCT tool	Y	N	Y	N	N	U	Y	Y	Y	Y	Y	Y	Y	9	
Tang *et al.* (2022)	Phase II, single arm, single centre	Case Series	Y	Y	Y	NA*	NA*	Y	Y	Y	Y	Y				8	
Liu *et al.* (2017)	Phase II, Single arm.	Case Series	Y	Y	Y	NA*	NA*	Y	Y	Y	Y	Y				8	
Michel *et al.* (2014)	Phase II, parallel studies, multi-centre,	Case Series	Y	Y	Y	NA*	NA*	Y	Y	Y	Y	Y				8	
Trip *et al.* (2014)	Phase I/II study, single arm, multi centre	Case Series	Y	Y	Y	NA*	NA*	Y	Y	Y	Y	Y				8	
Rivera *et al.* (2011)	Phase II, single arm, multi-centre	Case Series	Y	Y	Y	NA*	NA*	N	Y	Y	Y	Y				7	
Rivera *et al.* (2009)	Phase II, single arm, multi-centre	Case Series	Y	Y	Y	NA*	NA*	N	Y	Y	Y	Y				7	
Wydmanski *et al* (2007)	Phase II, single arm.	Case Series	Y	Y	Y	NA*	NA*	Y	Y	Y	Y	Y				8	
Ajani *et al.* (2006)	Phase II, single arm, multi-centre	Case Series	Y	Y	Y	NA*	NA*	Y	Y	Y	Y	Y				8	
Klautke *et al.* (2004)	Phase II, single arm, single centre	Case Series	N	Y	Y	NA*	NA*	Y	Y	Y	U	Y				6	
Matsuda *et al.* (2014)	Phase I, single centre	Case Series	Y	Y	Y	NA*	NA*	Y	Y	Y	U	Y				7	
Takahashi et al. (2011)	Phase I, single centre	Case Series	Y	U	U	NA*	NA*	Y	Y	Y	U	Y				5	
Allal *et al. (*2005)	Phase I, single centre	Case Series	Y	Y	Y	NA*	NA*	Y	Y	Y	Y	Y				8	
Chung *et al.* (2013)	Prospective feasibility study, single arm	Case Series	N	Y	Y	U	U	Y	Y	Y	Y	Y				7	
Rostom *et al.* (2013)	Prospective Feasibility study, single arm.	Case Series	Y	Y	Y	U	U	Y	Y	Y	N	Y				7	
Inoue *et al.* (2012)	Prospective feasibility study, single arm	Case Series	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y				10	
Ajani *et al.* (2005)	Prospective, single arm	Case Series	Y	Y	Y	U	U	Y	Y	Y	Y	Y				8	
Ajani *et al.* (2004)	Prospective, single arm, multi-centre	Case Series	Y	Y	Y	U	U	Y	Y	Y	Y	Y				8	

Appendix 3.4 – Data Extraction

Table A3.4. - Data extracted from each study (where applicable and data was available)

Study demographics	Year of publication Study type Dates of recruitment Site(s)
Patient characteristics *(definitive studies)*	Total number of patients/ numbers undergoing RT Performance status Age range/ median age % gastric/ type III GOJ tumours Histological subtypes Stages included Proportion of metastatic patients Baseline staging investigations performed
Patient characteristics *(palliative studies)*	Above plus: Median baseline Hb Proportion of symptomatic patients
Outcome measures *(palliative papers)*	Primary outcome measures Secondary outcome measures
Radiotherapy data	Total dose (Gy), number of #, duration Median total dose delivered (or mean if no median stated) BED10 (α/β) Treatment field including GTV, CTV (including elective lymph node levels if applicable) Modality (energy, technique) Motion management/ Image-guidance Dose constraints Proportion completing planned RT
Systemic anti-cancer therapy data (SACT)	Induction SACT (regimen(s), no. of cycles, proportion completing planned induction SACT) Concurrent SACT (regimen(s), no. of cycles, proportion completing planned induction SACT) Post-treatment SACT (regimen(s), no. of cycles, proportion completing planned induction SACT)
Response assessment	Imaging performed Toxicity grading system used QOL measures used Follow up (frequency, median follow-up time)
Survival data	Median overall survival (mOS) 1/2/3/5-year survival (where stated) Median relapse free survival (mRFS) Bleeding free survival *(palliative papers only, where stated)*
Response rate *(definitive papers)*	Overall response rate Clinical complete response Partial response rate Stable disease Progressive disease
Response rate *(palliative papers)*	Bleeding response, re-bleeding rate, median re-bleeding duration Other bleeding endpoints where stated: - Change in Hb - Change in blood transfusion volume Other symptom response rates (i.e. obstruction, pain) where applicable.
Toxicity	Gastrointestinal toxicity (Grade 3 and 4) Haematological toxicity (Grade 3 and 4) Mortality (i.e. grade 5 toxicity)
Quality of life	QOL measures
Patterns of relapse	Locoregional vs distant relapse rates
Dose/response relationship (palliative papers)	Conclusions stated with regards to dose-response.

Appendix 3.5 – Radiotherapy technique (definitive)

Table A3.5. Radiotherapy technique described by definitive papers.

***** Study also permitted RT to distant sites but technique for these patients not discussed here, only that of locally advanced GC subgroup. NS= not stated. IMRT = intensity modulated radiotherapy. DIBH = deep inspiration breath hold

First Author/ Year	Total dose Gy/ No. of fractions, duration	Treatment field	Included lymph nodes (LN)	Technique	Motion management/ IGRT
Liu *et al.* (2017)	50.4/28, 5.5 weeks (45/25 to PTV, 5.4/3 boost to BGTV)	GTV = pre-chemo tumour volume (GTV-p) and clinically positive LN (GTV-n). Boost GTV (BGTV-p) = GTVp +2-3cm. BGTV-n = GTVn +1cm. CTV = BGTVp+ BGTVn + 3cm craniocaudally, plus draining LN. CTV also included ITV with 1-2 cm margin. PTV = CTV + 0.5cm	Perigastric, celiac, portal hepatic, gastroduodenal, splenic-suprapancreatic, retro pancreaticoduodenal and para-aortic	IMRT	DIBH, 4 hours after a meal. Twice weekly CBCT
Wydmanski *et al.* *(*2014)	45/25, 5 weeks	Stomach, regional LN, 5cm oesophagus (if cardia) or 5cm duodenum (if gastroduodenal junction)	Gastric, coeliac, gastroduodenal, porta hepatis, splenic, suprapancreatic, retro pancreaticoduodenal, lower oesophageal	IMRT (n=8) 4 field isocentric (n=3) Tomotherapy (n=1)	NS
Safran *et al.* (2000)	45- 50.4/ 25-28, 5-5.5 weeks	Tumour + involved nodes + 2cm margin in all directions. A cone down was performed after 45Gy to encompass gross or microscopic disease + 1cm margin (for 5.4Gy boost)	Para-aortic LN and lymphatics above the common bile duct. For proximal tumours, paraoesophageal nodes also included plus 5cm oesophagus.	Multiple field techniques	NS
Chen *et al.* (2022)	45/25, 5 weeks	NS	NS	IMRT	NS
Xing *et al.* (2012)	50.4/ 28, 5.5 weeks	GTV included primary tumour and involved LN. CTV not described.	"Draining LN were not included in the CTV"	3D CRT (3-5 field)	NS
Leong *et al.* (2003)	45/25, 5 weeks	Tumour, anastomoses and stumps (dCRT fields were as for post-operative except there were no anastomoses that needed to be covered) and regional LN.	Peri-gastric, coeliac, splenic hilar, suprapancreatic, porta hepatis, pancreaticoduodenal, local para-aortic. If GOJ or proximal 1/3rd of stomach, pancreaticoduodenal could be omitted. If lower third stomach or antrum, splenic nodes omitted.	3D CRT (6 field, mono-isocentric)	NS
Dong *et al.* (2018)	45- 50.4/ 25-28, 5-6 weeks	To gastric tumour/regional LN*: GTV = GTV (tumour) + GTVn (regional LNs). CTV = (GTV tumour +2cm) + GTVn and lymph drainage areas. PTV = CTV + 1cm sup inf, 0.5cm all other directions.	NS	3D-CRT/ IMRT/IGRT	NS
Mizrak Kaya *et al.* (2018)	Median dose 45Gy (range 36-50.4). NS	NS	NS	NS	NS
Taki *et al.* (2017)	50/25, 5 weeks	GTV = primary lesion CTV = GTV +5mm. PTV = CTV +5-10mm + 5mm for penumbra	NS	3D CRT (4 field)	NS
Suzuki *et al.* (2012)	45- 50.4/ 25-28, 5-5.5 weeks	NS	NS	NS	NS
Li *et al.* *(*2018)	Median dose 45Gy (IQR 43.2-50.4Gy)	NS	NS	NS	NS

Appendix 3.6 – Outcome measures for palliative studies

Table A3.6. Summary of definition of primary and secondary outcome measures for each palliative study

BT = Blood Transfusion, RT = Radiotherapy, CTCAE = Common Terminology Criteria for Adverse Events, OS = overall survival, QOL = quality of life

First Author/ Year of publication	Primary outcome	Definition of primary outcome	Secondary outcomes	Definition of secondary outcomes
Tey *et al.* (2019)	Haemostasis	No further BT required on completion of RT and/or no further melena. Hypothesised response rate of 75%	i) Pain response ii) Obstruction response iii) Duration of symptom response iv) % net symptom relief v) OS vi) QOL vii) Toxicity	i) Partial response = decreased pain or same pain but decreased analgesia. Complete response = pain resolved ii) Categorised as a) requiring parenteral nutrition, b) liquids c) solids. Partial response = Improvement upward one category was partial response. Complete response = resolution of obstructive symptoms iii) Time from response until symptom recurrence or death iv) Ratio of duration of relief and survival time x 100 v) Time from completion of RT to death vi) EORTC QLQ-C30 + STO22 – change in score of ≥10 points clinically significant (particularly pain, nausea and fatigue scales at 1 month post RT) vii) CTCAE v3.0
Yoshikawa *et al.* (2009)	Tolerability of concurrent chemotherapy	Maximum tolerated dose of paclitaxel/cisplatin. Toxicity evaluated by NCI CTC v3.0 with DLT defined as ≥G3 toxicity.	Clinical response of pain or obstruction	Improvement of pain/obstruction defined by NCI-CTC v3
Saito *et al.* (2022)	Haemostasis	ITT bleeding response rate at 4 weeks defined as: - Hb ≥8 g/dL - 7 consecutive days without BT - Did not require salvage treatment for bleeding	i) Proportion completing RT ii) Adverse events iii) OS iv) Local salvage treatment	Adverse events graded with CTCAE v4.0 OS = time from enrolment to death
Takeda *et al.* (2022)	Haemostasis	- 50% or greater reduction in BT (4 weeks post RT) - Hb elevation of 1 g/dl or more (4 weeks post RT) - Improvement in objective clinical symptoms (4 weeks post RT)	Acute adverse events	CTCAE v5.0
Yagi *et al.* (2023)	Haemostasis	No further BT needed and/or no further melena episode (within 30 days from completion of RT). Re-bleeding defined as requiring BT within 30 days of RT.	Toxicity OS	CTCAE v5.0 OS = date of surgery or RT to date of death
Katano *et al.* (2022)	Haemostasis	Number of BTs (units of erythrocytes) before and for 1 month post RT	OS	OS = date of initiation of RT to death
Sugita *et al.* (2022)	Haemostasis	Successful haemostasis defined as no need for BT, no drop in Hb and no melaena/haematemesis for >1 month post RT. Requirement of other haemostatic treatments <1 month after RT classified as unsuccessful haemostasis.	OS Re-bleeding free survival	OS = date of initiation of RT to death Re-bleeding free survival estimated from end of RT
Kawabata *et al.* (2022)	Haemostasis	Treatment success was defined as the absence of a decrease in the serum Hb level, without a need for BT within 1 month after RT	i) Nutritional status ii) Re-bleeding free survival, iii) Toxicity	i) Nutritional status evaluated by mean serum albumin 1 month before and after. ii) Re-bleeding free survival = interval from last of day RT to the first day of an event including BT and re-irradiation. iii) CTCAE v5.0
Yu *et al.* (2021)	Haemostasis	Defined 'bleeding control' as: - Disappearance of melena or hematemesis, - No decline in Hb from baseline, - No need for further BT	i) Cumulative incidence of re-bleeding ii) OS iii) Toxicity	i) Re-bleeding defined as reappearance of clinical symptoms and/or additional BT due to decline in Hb ii) OS = date of initiation of Tt to death iii) CTCAE
Lee, J *et al.* (2021)	Haemostasis	Cumulative re-bleeding defined as time from RT completion to Hb dropping <7.0 g/dL or receiving a BT after RT (with or without Hb <7.0 g/dL)	i) OS ii) Presence of symptoms iii) Response on CT	i) OS = time from RT completion to death ii) Medical records checked for melaena or haematemesis 1 month post RT iii) RECIST 1.1 evaluation based on CT 1-2 months post RT

Mitsuhashi *et al.* (2021)	Haemostasis	RT defined as effective if no BT for >1 month after RT. Hb compared at start of RT to 4 weeks post RT.	i) Blood transfusion free survival ii) OS iii) Toxicity	i and ii) from start date of RT iii) CTCAE v5.0 within 60 days of RT
Sasaki *et al.* (2020)	Response of primary tumour to RT after prior anti-PD1 therapy	Volumetric CT assessment of % volume reduction, with response defined as >70% reduction in tumour volume.	i) Endoscopic response ii) Adverse events iii) Tumour infiltrating lymphocyte analysis	i) Endoscopic complete response = disappearance of all tumours. Endoscopic partial responses = tumour decrease by >2/3 of major axis, 1/2 of area or 1/3 of volume ii) CTCAE v5.0 iii) Flow-cytometry
Hiramoto *et al.* (2018)	i) Haemostasis ii) Obstruction response	i) No need for blood Tx for >1 month ii) Capable oral intake again and maintained for >1 month	i) Event free survival ii) OS, iii) Toxicity	i) Start date of RT to the first day of an event; BT, oral intake impossible or any cause of death ii) Diagnosis to death iii) CTCAE v3.0
Lee, Y *et al.* (2017)	Haemostasis	Re-bleeding defined as the bleeding symptoms such as hematemesis or melena developing a second time.	i) OS ii) Tumour bleeding free survival iii) Toxicity	i) Time from start of RT to death ii) Time from initial of RT to rebleeding or death., iii) CTCAE v3.0
Mizrak Kaya *et al.* (2017)	OS	Date of diagnosis to date of death	NS	NS
Tey *et al.* (2014)	Symptom response	i) Bleeding response = did not require further BT or gastroscopy. ii) Pain response =decreased pain or decreased analgesia, same pain but decreased analgesia or resolution of pain. iii) Obstruction response = upward improvement in category from requiring parenteral feeding, liquids or solids.	i) Duration of response ii) % net symptom response iii) Toxicity	i)The time from response in patients who achieved satisfactory palliation until symptom recurrence, progression or death ii) Duration of symptom relief and survival x100 iii) CTCAE v3.0
Choi *et al.* (2012)	Haemostasis	No further drop in Hb 4-6 weeks after RT without any BT.	i) Duration of haemostatic control ii) OS iii) Waiting time	i) Day of completion of RT to date of first BT or death ii) Date of RT planning day to death iii) Waiting time from RT planning day to starting RT
Asakura *et al.* (2011)	Haemostasis	Did not require BT for ≥1 month post RT	i) Toxicity ii) OS, iii) Re-bleeding free survival	i) CTCAE v3.0 ii) Beginning of RT to death iii) Time to re-bleeding from beginning of RT to death, with re-bleeding defined failure to achieve 1 month BT free survival, or required concomitant treatments for haemostasis
Lee, J *et al.* (2009)	Haemostasis	a) Subjective symptom relief of haematemesis or melaena. b) Objective - change in number of transfused packed red blood cells and mean Hb before and after RT	NS	NS
Hashimoto *et al.* (2009)	Haemostasis	A patient being alive with no need for BT ≥ 1 month post RT	i) Adverse events ii) Event-free survival iii) OS	i) CTCAE v3.0 ii) Last day of RT to the first day of event including BT or death iii) First day of RT to death
Kim *et al.* (2008)	Symptom control	Radiation was assumed to have relived symptoms if patient no longer complained of bleeding, dysphagia/obstruction and epigastric/abdominal pain, and did not require an intervention such as stenting or BT	i) Duration of symptom control ii) Toxicity iii) OS	i) Time until the patient was free of initial symptoms or the earliest time that the patient needed post-RT intervention to re-address symptom. ii) CTCAE V.30 III) From start of RT to death

Appendix 3.7 – Radiotherapy technique (palliative)

Table A3.7. Radiotherapy technique described by palliative papers.

***** Potential overlap between patient populations recruited from same centre with cross over of dates of inclusion/recruitment to study . **+** not directly stated but median BED10 calculated from stated median total dose/#
¥ 10 other dose/# regimens listed in publication, each n=1, not listed here. **§** 4 other dose/# regimens not listed in table, of patients whom could not complete the schedules 24 Gy/12# (4%), 34/17 (4%), 36/18 (7%).
^ 3 other dose regimens not listed in table 37.5Gy/15# (1.7%), 30 Gy/12# (0.8%), 35Gy/14# (0.8%). ****** represent patients who could not complete planned 30Gy/10#
¤ 4 other dose/# not listed in table: 27Gy/9# (5%), 18Gy/9# (5%), 7.2Gy/4# (5%), 2Gy/1# (5%).
~ Study identified n=30 patients, but only included= 23 who completed at least 30Gy/10#, with 7 patients excluded prior to data analysis. Thus 100% of the "per protocol" population completed RT, but completion of RT rate was 70% ITT.

Study author/year	Total Dose/fraction	Median BED10 (Range)	Volume	Technique	Motion management/ image guidance	Number completing planned RT dose
Tey *et al.* (2019)	36Gy/12#	48.6Gy	GTV = whole stomach, ***or*** GTV = partial stomach if able to localise tumour on CT. CTV = GTV + 0.5cm PTV = CTV + 1cm	APPA POP with MLC to spare OARs	NS	NS
Yoshikawa *et al.* (2009)	Up to 45Gy/25#	NS	GTV = tumour defined by CT/endoscopy or GI imaging. PTV = GTV + 5-20mm	NS	NS	NS
Saito *et al.* (2022)	8Gy/1# (21%) 20Gy/5# (32%) 30Gy/10# (38%)	28Gy	"Dose prescription and target volume were determined at the discretion of the treating radiation oncologist"	NS	NS	94%
Takeda *et al.* (2022)	30Gy/10# (64.2%) 20Gy/5# (19.2%)	39Gy (7.8-60)	CTV = GTV + 0-1cm, but CTV = whole stomach also allowed. ITV = CTV + 0-2cm based on tumour motion PTV= ITV +1cm. Modification of target volumes with consideration of the status of the patient was allowed	3CRT used with 2-4 fields. Multiple field irradiation permitted for OARs but no IMRT	4DCT to assess respiratory motion if available	NS
Yagi *et al.* (2023)	39Gy/13# (52%) 30Gy/10# (24%) 36Gy/10# (8%) 50Gy/25% (4%) 24Gy/8# (4%) 15Gy/5# (4%)	NS	CTV = primary lesion, with adequate margins	Most commonly APPA or oblique opposed beams	NS	100%
Katano *et al.* (2022)	30Gy/10# (52%) 20Gy/5# (43%) 8Gy/1# (4%)	NS	CTV = entire stomach. ITV = CTV expanded based on respiratory motion assessment. PTV= ITV +5mm	3DCRT with 4 field or conformal arc (No IMRT)	Respiratory motion assessed	NS
Sugita *et al.* (2022)	30Gy/10# (76%) 20Gy/5# (12%) 20Gy/10# (3%) 18Gy/6# (3%) 8Gy/1# (3%) 6Gy/2# (3%)	39Gy	NS	3DCRT	NS	NS
Kawabata *et al.* (2022)	30/10# (80%) 10.5Gy/3# (5%) 15Gy/5# (5%) 20Gy/5# (5%)	39.9Gy (14.1 – 39.9)	CTV = primary lesion only PTV = CTV + 1-1.5cm.	3D CRT	Early morning with fasting state, KV images acquired D1	95% n=1 discontinued at 10.5Gy/3# due to anorexia
Yu *et al.* (2021)	Median dose = 30Gy (range 12.5-50)	39Gy (16-60)	GTV= fungating mass or infiltrative gastric wall thickening CTV = GTV PTV = CTV + 1-2cm based on respiratory motion/uncertainty If 4DCT used, ITV = sum of GTV on 10 respiratory phases, then PTV = ITV +1cm	3DCRT using multiple coplanar or non-coplanar beams	4DCT since 2015. 4 hours fasting before treatment	83.6%

Lee, J *et al.* (2021)	25Gy/5# (29.8%) 20Gy/5# (24.6%) 30Gy/10 # (22.8%) 45Gy/25# (5%)[¥]	37.5Gy (23.6-58.5)	GTV = gross tumour lesion as seen on CT ITV = GTV considering respiratory motion CTV = ITV +0.3cm PTV = CTV +0.3cm	3DCRT (98.2%), IMRT (1.8%)	4DCT to assess respiratory motion	100%
Mitsuhashi *et al.* (2021)	30Gy/10# (60%) 40Gy/20# (21%) 20Gy/5# (4%) [§]	NS	*n=23 partial stomach:* GTV was determined using CT +/- metal markers at the caudal and cranial extent of tumour. CTV encompasses GTV at the time of simulation. *n=5 whole stomach:* If extent of tumour mass could not be examined, the entire tumour was determined as CTV. ITV determined with 6 phases of respiratory cycle over 2 days. PTV = 0.5 – 1cm margin	3DCRT, 3-5 portals	Four hour fast. CT in 3 phases of respiration: normal breathing, shallow hold inspiration and expiration. CT performed on two consecutive days to determine change in PTV. Daily CBCT.	86%
Sasaki *et al.* (2020)	30Gy/10#	39Gy[+]	NS	NS	NS	100%
Hiramoto *et al.* (2018)	30-60Gy/ 10-30#	NS	PTV = whole stomach +2cm	2-4 fields	NS	91%
Lee, Y *et al.* (2017)	Median dose =39.6Gy (range 14-50.4) Median # = 20 (7-28)	46.9Gy (16.8-60)	Whole stomach n=13, partial stomach n=29.	APPA POP with lateral field (71.4%), APPA only (28.6%)	Planned using CT for 64.3%. Stomach motion observed on fluoroscopy and margins modified if necessary	NS
Mizrak Kaya *et al.* (2017)	Median dose = 50.4Gy (range 45-65)	NS	"Dose and field design based on physician preference"	NS	NS	NS
Tey *et al.* (2014)	30Gy/10# (40%) 36Gy/12# (33%) 20Gy/5# (16.5%) 40Gy/16# (4%) 8Gy/1# (2.6%)^	39Gy	PTV = whole +1-2cm stomach (n=109)/partial stomach (n=6) PTV = partial stomach+1-2cm stomach (n=6)	3-field technique (83%) 2-field AP/PA (10%), Not CT planned AP/PA (7%)	Stomach motion during respiration considered in expansion of PTV	97.3%
Choi *et al.* (2012)	30Gy/10# (82.6%) 22.5Gy/5# (28.6%) 32.5Gy/13# (4.3%) 40Gy/20# (4.3%)	NS	Target volume = Primary tumour, whole stomach and the regional lymph nodes if the field size allowed. Partial stomach if huge gastric tumour. For patients who receive CT planning, the target volume was defined with 2cm margin.	Either APPA POP (56%) 3D conformal multiple field technique (43%)	NS	82%
Asakura *et al.* (2011)	30/10# (90%), 27/9# (7%)** 21Gy/7# (3%)**	NS	CTV (based on CT/endoscopy) + 'adequate margin' Regional lymph nodes were not included in CTV CTV = whole stomach n=6 (20%).	APPA POP or oblique opposed beams	NS	90%
Lee, J *et al.* (2009)	Median 30Gy/10# (range 30-44Gy in 10-22#)	NS	Target volume = partial or whole stomach according to tumour location with a generous margin	NS	2D simulation with 10-20ml barium contrast after 4-6 hour fast to assess diaphragmatic and gastric motion was carried out	100%~
Hashimoto *et al.* (2009)	40Gy/16# (53%) 20Gy/10# (10%) 50Gy/25# (5%) 40Gy/20# (5%) 35Gy/14# (5%)[¤]	50Gy	NS	APPA POP or oblique opposed beams	NS	68%
Kim *et al.* (2008)	Median 35Gy/14# (range 20-36Gy)	41Gy (25-41)	Primary tumour only. The entire stomach if linitis plastica. Regional nodes only if adjacent to primary and contributing to symptoms (n=3)	APPA 79%, 3-field 5%, 4-field 5%, Obliques 11%	NS	NS

Table A3.8. Dose/Response relationship

Studies which have evaluated relationship between dose and response rate and outcome, separated into those which do not report dose-response relationship, and those that do. Studies are listed in decreasing order of median BED10.
+ Not directly stated but median BED10 calculated from stated median total dose/#. **¥** 10 other dose/# regimens listed in publication, each n=1, not listed here.
§ 4 other dose/# regimens not listed in table, of patients whom could not complete the schedules 24 Gy/12# (4%), 34/17 (4%), 36/18 (7%). **^** 3 other dose regimens not listed in table 37.5Gy/15# (1.7%), 30 Gy/12# (0.8%), 35Gy/14# (0.8%).
¤ 4 other dose/# not listed in table: 27Gy/9# (5%), 18Gy/9# (5%), 7.2Gy/4# (5%), 2Gy/1# (5%)

Study author/year	No. of patients	Dose/fractionation	Median BED	Evidence of dose response relationship?	Association between BED and response/ outcome
No evidence of dose-response					
Hiramoto *et al.* (2018)	23	30-60Gy/ 10-30#	50.8[+]	**NO**	Univariate analysis showed no statistically significant difference between the total radiation dose and **symptom response**, with responders (n=19, 42.6Gy) and non-responders (n=4, 37.1Gy) p=0.31
Katano *et al.* (2022)	23	30Gy/10# (52%) 20Gy/5# (43%) 8Gy/1# (4%)	39Gy[+]	**NO**	Univariate analysis shows no statistically significant difference in **haemostatic effect**, or adverse events between the different radiation doses or fractions. (20Gy/8Gy vs 30Gy, HR 0.299, p=0.090)
Sugita *et al.* (2022)	33	30Gy/10# (76%) 20Gy/5# (12%) 20Gy/10# (3%) 18Gy/6# (3%) 8Gy/1# (3%) 6Gy/2# (3%)	39Gy	**NO**	No relationship between BED (39 vs <39Gy) and successful **haemostasis** (p=0.190) Multivariate analysis shows BED (39 vs <39Gy) not statistically significant factor for **OS** (p=0.170) or OS (p=0.311)
Lee *et al.* (2021)	57	25Gy/5# (29.8%) 20Gy/5# (24.6%) 30Gy/10 # (22.8%) 45Gy/25# n=3 (5%)[¥]	37.5Gy (23.6-58.5)	**NO**	On univariate/ multivariate analysis showed no difference in cumulative **re-bleeding** rate by total BED10 <37.5 Gy vs ≥37.5Gy (3-month CRR 46.4% vs 69%, p=0.134).
Saito *et al.* (2022)	55	8Gy/1# (21%) 20Gy/5# (32%) 30Gy/10# (38%)	28Gy	**NO**	Multivariable analysis showed that BED was not a significant predictor of **bleeding response.** Univariable Cox regression model showed that BED as not significantly associated with re-bleeding.
Mitsuhashi *et al.* (2021)	28	30Gy/10# (60%) 40Gy/20# (21%) 20Gy/5# (4%) [§]	NS	**NO**	No statistical significance for **BT free survival**; ≤39 Gy vs. >39 Gy (79.3% vs. 40.0%; p = 0.09), or **OS**; ≤39 Gy vs. >39 Gy (9.8% vs. 11.1%; p = 0.09). There was no statistically significant difference in the **one-year BTFS** rates according to BED10 of 39Gy or 48Gy (77.8% vs 25% p = 0.09).
Trend supporting dose-response					
Tey *et al.* (2014)	115	30Gy/10# (40%) 36Gy/12# (33%) 20Gy/5# (16.5%) 40Gy/16# (4%) 8Gy/1# (2.6%)^	39Gy	**NO** *(though trend present)*	No obvious dose response was evident for **symptom response** or recurrence using a cut off median BED of 39Gy. However, there was a trend for poorer **local control** with a BED for ≤39 Gy (p=0.12)
Mizrak Kaya *et al.* (2017)	101 (29.7% gastric/GOJ III)	Median dose = 50.4Gy (range 45-65)	NS	**NO** *(though trend present)*	Though not statistically significant, there was a trend towards **longer OS** for patients who receive <50.4Gy compared to those who received >50.4Gy (p=0.08)
Evidence of dose-response					
Hashimoto *et al.* (2009)	19	40Gy/16# (53%) 20Gy/10# (10%) 50Gy/25# (5%) 40Gy/20# (5%) 35Gy/14# (5%)[¤]	50Gy	**YES**	A BED10 of 50Gy or more was significantly correlated with treatment success (i.e. **haemostasis**) compared with a BED of <50Gy (p=0.040)

Lee, Y *et al.* (2017)	42	Median dose =39.6Gy. (range 14-50.4) Median # = 20	46.9Gy (16.8-60)	**YES**	Median RT dose was 40 Gy in responders vs. 21 Gy in non-responders, with the difference being significant (p < 0.001). BED10 for responders was significantly higher than the BED10 for non-responders (median 48 Gy vs. 26.4 Gy, p < 0.001) On multivariate analysis, BED10 ≥36Gy was significantly associated with **bleeding control** (p=0.001)
Kim *et al.* (2008)	37	Median 35Gy/14# (range 20-36Gy)	41Gy	**YES**	**Local control** was inferior in patients treated with BED < 41Gy (6-month local control 70% vs 100%, p=0.05). However, higher BED did not improve OS (6-month OS <41Gy 33 months vs 47 months ≥41Gy, p=0.43)
Takeda *et al.* (2022)	117	30Gy/10# (64.2%) 20Gy/5# (19.2%)	39Gy	**YES**	Multivariate analysis showed higher BED was associated with achievement of **haemostasis.** Rate of haemostasis 71.1% for those who received BED10 of ≥39Gy vs 32.4% for those who received <39Gy.
Yu *et al.* (2021)	61	Median dose 30Gy	39Gy	**YES**	Multivariate analysis showed high BED, >39Gy (p=0.007) was statistically significant for prolonging **time to re-bleeding** (19.3 months vs 2.6 months).

Appendix 3.9 – Radiotherapy technique (Pre-operative)

Table A3.9. Radiotherapy technique described by pre-operative papers

3D CRT – 3D conformal radiotherapy. APPA = Anterior-posterior/ posterior-anterior paired beams. Sib = Simultaneous integrated boost
~ Overlap between studies, Allal reported updated outcome data, Roth reporting acute toxicity data. *See Chapter 6 for description of JCGA nodal levels

Study author (year)	Total Dose/fraction (median BED10, range)	Tumour volume delineation / treatment fields	Elective lymph nodes	Technique	Motion management/ image guidance	Number completing planned RT dose
Wang *et al.* (2021)	45Gy/25#, 5 weeks (BED10 = 53.10 Gy)	GTV= tumour bed and regional metastatic lymph nodes	NS	3DCRT	Spontaneous breathing	100%

		CTV = GTV + 5-10mm margin PTV = CTV +5mm				
Saeidi *et al.* (2014)	45Gy/25#, 5 weeks (BED10 = 53.10 Gy)	NS	NS	APPA	NS	NS
Wang *et al.* (2022)	45.1Gy/22# [40Gy + 5.1Gy SIB to PGTV] (BED10=54.20Gy)	GTV and metastatic lymph nodes (GTVnd) PGTV (planning GTV) = GTV+ GTVnd +5mm CTV = GTV + GTVnd + elective lymph nodes PTV= CTV + 5-10mm radially, 10mm sup-inf SIB-RT planned:- PTV = 40.04Gy/22# PGTV boost = 45.1Gy/22#	Upper 1/3rd: Regions 110, 1-3, 4, 7-11, 16a* Middle 1/3rd: 1-3, 4, 5-9, 11p, 12, 16a* Lower 1/3rd: 3, 4, 5-9, 11p, 12, 16a*	IMRT	4-6 clips implanted around tumour + 1cm margin. 4 hour fast, followed by 300ml standard meal (ready to eat porridge) 15 mins pre-treatment	100%
Tang *et al.* (2022)	45Gy/25# (BED10=53.10 Gy)	GTV = primary tumour and metastatic lymph nodes CTV= GTV + elective nodes at high risk PTV= CTV + 5mm left and right (x), 10mm cranial and caudally (y), 5mm ant/post (z) Target area must include at least 3cm of distal oesophagus	Adjacent paraoesophageal and peri-gastric nodes, Suprapancreatic, coeliac trunk, splenic hilar (groups 1-7,9,10,12)	IMRT	3-4 hour fast	NS
Liu *et al.* (2017)	45Gy/25#, 5 weeks (BED10 = 53.10 Gy)	"Primary lesion and regional lymph node drainage"	"Regional nodes based on primary tumour location"	NS	NS	NS
Michel *et al.* (2014)	50Gy/25#, 5 weeks (BED10 = 60.00 Gy)	Entire stomach plus peri-gastric extension and draining lymph nodes. Lesions involving cardia/GOJ, a 3cm margin of oesophagus was included. Distal lesions/gastroduodenal junction, the duodenum was included.	Gastric, coeliac, portal hepatic, gastroduodenal, splenic-suprapancreatic and retropancreaticoduodenal.	APPA plus laterals	NS	85.7% completed >90% planned RT
Trip *et al.* (2014)	45Gy/25#, 5 weeks (BED10 = 53.10 Gy)	CTV = whole stomach and draining lymph nodes PTV= CTV+1cm	Japanese stations 1-13	3DCRT/IMRT	No dietary restrictions due to frequency of tube feeding	92%
Rivera *et al.* (2011)	As above Rivera 2009	Entire stomach, any perigastric extension, and lymph nodes. Lesions involving GOJ, a 5cm margin of oesophagus. Distal lesions near gastroduodenal junction, a 5cm margin of duodenum.	Gastric, coeliac, porta-hepatis, gastro-duodenal, splenic-suprapancreatic and retropancreatic-duodenal.	3DCRT	NS	76% received 100% RT dose
Rivera *et al.* (2009)	45Gy/25#, 5 weeks (BED10 = 53.10 Gy)	As above Rivera 2011	As above Rivera 2011	3DCRT	NS	53% received 100% RT dose
Wydmanski *et al.* (2007)	45Gy/25#, 5 weeks (BED10 = 53.10 Gy)	Stomach and regional lymph nodes	Gastric, coeliac, gastroduodenal, porta-hepatis, splenic, Suprapancreatic, retropancreaticoduodenal, lower oesophageal.	3DCRT	NS	100%
Ajani *et al.* (2006)	45Gy/25# (BED10=53.10 Gy)	Entire stomach, perigastric extension, draining LN. Lesions involving GOJ/cardia - 5cm margin of oesophagus. For lesions at GDJ - 5cm margin of duodenum included.	Gastric, celiac, porta hepatis, gastroduodenal, splenic-suprapancreatic and retropancreaticoduodenal.	3D CRT including oblique anterior and posterior fields	NS	NS
Klautke et al. (2004)	50.4Gy/28# [45Gy/+ 5.4Gy boost to primary tumour] (BED10=59.47Gy)	"Primary tumour + 4-5cm margin orally and aborally + 2cm circularly, plus lymph nodes"	Lymph nodes stations along oesophagus up to tracheal bifurcation, small curvature of the stomach, and para-aortally to the height of L2.	3D CRT (4 field isocentric technique)	Endoscopic clipping of tumour to aid TVD	100%
Matsuda *et al.*	40Gy/20#, 4 weeks (BED10 = 48.00Gy)	CTV = primary tumour + 3cm margin, plus metastatic nodes + 1cm margin, plus entire stomach and peri-	NS	3D CRT	Empty stomach	NS

(2014)		gastric and coeliac nodes. PTV = CTV +2cm margin				
Takahashi et al. (2011)	40Gy/20#, 4 weeks (BED10 = 48.00Gy)	"Primary tumour and surrounding lesions including lymph nodes"	NS	Anterior and left lateral fields with 45-degree wedges	NS	NS
Allal et al. (2005)	Level 1: 31.2Gy/26#, 2# per day, 5 days/week (BED10=34.94Gy) Level 2: 38.4Gy/32# (BED10=43.01Gy) Level 3: 45.6Gy/38# (BED10=51.07Gy)	Gross tumour and regional lymph nodes	Proximal tumours: juxta-cardiac, gastric, coeliac axis, splenic, left gastro-epiploic. Medial/distal: gastric, gastroepiploic, coeliac axis, porta-hepatis, splenic, subpyloric, and gastro-oesophageal junction was spared.	Two anteroposterior or multiple fields.	NS	94.7%
Chung et al. (2013)	45Gy/25#, 5 weeks (BED10 = 53.10 Gy)	"Primary tumour and adjacent metastatic nodes with a proper margin"	NS	Half beam, or multiple beam (>4 ports)	NS	100%
Rostom et al. (2013)	45Gy/25#, 5 weeks (BED10 = 53.10 Gy)	Entire stomach, any perigastric extension and lymph nodes. Lesions involving cardia/ GOJ, a 5cm margin of oesophagus was included. Distal lesions near the gastroduodenal junction, a 5cm margin of duodenum was included.	Gastric, coeliac, porta-hepatis, gastroduodenal, splenic-suprapancreatic and retropancreaticoduodenal.	3D CRT (with oblique anterior and posterior fields as required to shield kidney)	NS	NS
Inoue et al. (2012)	50Gy/25#, 5 weeks (BED10 = 60.00 Gy) Dose reduction to 40Gy permitted if adverse events.	GTV = Primary tumour plus metastatic lymph nodes. CTV = GTV + 5mm PTV= CTV +10-15mm to account for respiratory motion	NS	3D CRT	Empty stomach	100% (83.3% =50Gy, 16.6% = 40-45Gy)
Ajani *et al.* (2005)	45Gy/25# (BED10=53.10 Gy)	As above (Ajani et al., 2006)	As above (Ajani et al., 2006)	3D CRT. Anterior and posterior fields obliqued to avoid cord and right kidney	NS	NS
Ajani *et al.* (2004)	45Gy/25# (BED10=53.10 Gy)	As above (Ajani et al., 2006)	As above (Ajani et al., 2006)	APPA +/- lateral fields	NS	NS

Appendix 3.10 – Currently active clinical trials (1)

Table A3.10. Summary of the 25 currently active clinical trials investigating radiotherapy for gastric adenocarcinoma identified on the clinicaltrials.gov registry (01.08.2024)

HR = homologous recombination. NA = not applicable. CRT = Chemoradiotherapy. DFS = disease free survival. OS = overall survival. PFS = progression free survival. pCR = pathological complete response
*****Unknown status, registry last updated 2017 (expected completion date October 2021) ******Unknown status, registry last updated 2020 (expected completion date December 2021)

Clinical trials.gov identifier	Sponsor/ Lead centre	Title	Clinical setting	No. of patients	Phase	Randomisation	Treatment details		Primary end point	Expected Completion date
							Radiotherapy (concurrent SACT)	Systemic therapy		

Pre-operative studies										
NCT03013010	Shanghai Cancer Hospital, China	A Randomized, Controlled, Multicenter Study to Compare Preoperative Radiochemotherapy With Preoperative Chemotherapy in Patients With Locally Advanced Gastric or Esophagogastric Junction Adenocarcinoma (PREACT)	Pre-operative	682	Phase III, randomised	Pre-operative CRT + post-operative chemotherapy *vs* Peri--operative chemotherapy (1:1)	45Gy/25# (+S-1)	S-1 + oxaliplatin (pre- and post-operatively)	DFS	12.2023
NCT01815853	Sun Yat-sen University Cancer Center, China	Neoadjuvant Chemoradiotherapy vs. Chemotherapy With Radical Gastrectomy and Adjuvant Chemotherapy for Advanced Gastric Cancer (Neo-CRAG)	Pre-operative	620	Phase III, randomised	Pre-operative CRT post-operative chemotherapy *vs* Peri-operative chemotherapy (1:1)	45Gy/25# (+XELOX)	Oxaliplatin + capecitabine (pre- and post-operatively)	DFS	12.2025
NCT03223740	Sichuan Provincial People's Hospital, China	Preoperative Stomach Cancer Induction Chemotherapy and Radiation Therapy (President)	Pre-operative	450	Phase III, randomised	Pre-operative CRT + post-operative chemotherapy *vs* Post-operative CRT (1:1)	45Gy/25# (+capecitabine + weekly taxol)	Induction capecitabine + cisplatin. Post-operative capecitabine.	PFS	10.2021*
NCT02931890	The Netherlands Cancer Institute	A Multicentre Randomised Phase II Trial of Neo-adjuvant Chemotherapy Followed by Surgery vs. Neo-adjuvant Chemotherapy and Subsequent Chemoradiotherapy Followed by Surgery vs. Neo-adjuvant Chemoradiotherapy Followed by Surgery in Resectable Gastric Cancer (CRITICS II)	Pre-operative	207	Phase II, randomised	Pre-operative chemotherapy *vs* Pre-operative chemotherapy + CRT *vs* Pre-operative CRT (1:1:1)	45Gy/25# (+ weekly carboplatin + paclitaxel)	Docetaxel, Oxaliplatin, Cisplatin	Event free survival	07.2029
NCT05161572	Fudan University, China	A Randomized Phase II Trial of Perioperative Chemoimmunotherapy Verses Perioperative Chemoimmunotherapy Plus Preoperative Chemoradiation for Locally Advanced Gastric (G) or Gastroesophageal Junction (GEJ) Adenocarcinoma (Neo-RACING)	Pre-operative	152	Phase II, randomised	Pre-operative chemotherapy + IO + CRT + post-operative chemo IO *vs* Peri-operative chemotherapy + IO (1:1)	45Gy/25# (+ S-1)	Sintilimab PLUS S-1 + oxaliplatin (peri-operatively). Sinitilimab alone (post-operatively)	pCR	09.2026
NCT05687357	The Affiliated Nanjing Drum Tower Hospital of Nanjing University Medical School, China	Tislelizumab in Combination With Pre-operative Chemoradiotherapy Versus SOC for Patients With Locally Advanced Gastric/Gastroesophageal Junction Adenocarcinoma: a Multicenter, Randomized, Open-label, Phase IIB Trial	Pre-operative	140	Phase IIb, randomised	Pre-operative IO + CRT + post-operative chemoIO *vs* Pre-operative CRT + post-operative chemotherapy *vs* Peri-operative chemotherapy (1:1:1)	45Gy/30# (+ S-1)	Tislelizumab PLUS S1+ oxaliplatin, OR S-1+ nab-paclitaxel (pre-operatively). Tislelizumab alone post-operatively	pCR	08.2027
NCT06266871	West China Hospital, China	SOX Combined With Tislelizumab and Low-dose Radiation Therapy for Neoadjuvant Treatment of Locally Advanced Gastric/Gastroesophageal Junction Adenocarcinoma: a Prospective, Multi-center, Single-arm, Phase Ib/II Clinical Trial	Pre-operative	64	Phase Ib/II, Single arm	NA (single arm)	Low dose radiotherapy (dose/# not stated).	S-1 + Oxaliplatin + Tislelizumab (pre-operatively and post-operatively). S-1 + Oxaliplatin post-operatively.	Phase Ib: Optimal RT dose for phase II. Phase II: pCR	07.2026
NCT05002686	Ruijin Hospital, China	Safety and Efficacy of Sintilimab in Combination With Chemoradiotherapy Followed by D2 Surgical Resection in Patients With Advanced Gastric Cancer With Retroperitoneal Lymph Node Metastasis	Pre-operative	60	Phase II Single arm	NA (single arm)	45Gy/25#	Sintilimab, Albumin-Paclitaxel, Capecitabine, Oxaliplatin	1-year PFS	08.2024

NCT06121700	Fudan University Shanghai Cancer Centre, China	Radiotherapy, Chemotherapy and Anti-PD-1 Immunotherapy Followed by Surgical Resection in Patients With Limited Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma: A Prospective, Single Arm, Phase II Trial (Miracle-G)	Pre-operative, Hypofrac-tionation/ SABR	55	Phase II, Single arm	NA (single arm)	Hypofractionated RT to primary lesion (5-7#, dose/# not stated) PLUS Hypofractionated or SBRT to the metastatic lesions (4-8 #, dose/# not stated)	Clinician choice anti PD-L1 mAb + chemotherapy +/- anti-HER2 therapy if HER2+	OS	12.2027
NCT06426654	West China Hospital, China	Sintilimab Combined With Low-dose Radiation Therapy for Neoadjuvant Treatment of Locally Advanced Deficient Mismatch Repair/Microsatellite Instability-high Gastric Cancer: a Prospective, Multi-center, Single-arm, Phase Ib/II Clinical Trial	Pre-operative,	45	Phase Ib/II, Single arm	NA (single arm)	Low dose radiotherapy (dose/# not stated).	Sintilimab (pre- and post RT, then post-operatively)	pCR	08.2027
NCT06341595	The First Affiliated Hospital with Nanjing Medical University, China	Concurrent Chemoradiotherapy Combined With Sintilimab as Neoadjuvant Therapy for Advanced Gastric Cancer Patients With Para-aortic Lymph Node Metastasis: a Single-arm, Phase II, Exploratory Study.	Pre-operative,	40	Phase II, Single arm	NA (single arm)	'Extraperitoneal radiotherapy' 45-50.4Gy/ 25-28#, up to 60-66Gy for lymph node lesion	Sintilimab + S-1 + oxaliplatin. Post-operative treatment at clinician's discretion.	Recurrence free survival	12.2026
NCT04162665	Washington University School of Medicine, USA/ Seoul National University Hospital, Korea	Pre-operative Adaptive Short Course Radiation Therapy in Gastric Cancer	Pre-operative, Hypofrac-tionation	36	Phase II, Single arm	NA (single arm)	25Gy/5# with daily adaptive planning	CAPOX, FOLFOX, or FLOT	pCR	04.2027
NCT03776487	M.D. Anderson Cancer Center, USA	Pilot Study of Dual Checkpoint Inhibition Followed by Immuno-Chemoradiation in Patients With Resectable Gastric Adenocarcinoma (Concept ID 2016-NIV-0551)	Pre-operative	36	Phase I/II Single arm	NA (single arm)	25# (total dose not stated) (+ concurrent fluorouracil)	Oxaliplatin + fluorouracil + nivolumab + ipilumumab (pre-RT). Nivolumab (post-operatively if residual disease)	Incidence of adverse events	12.2026
NCT05387681	Wuhan Union Hospital, China	An Exploratory Clinical Study of Short-course Radiotherapy Combined With Envafolimab, Endostatin and SOX Regimen for Neoadjuvant Treatment of Resectable Locally Advanced Gastric/Gastroesophageal Junction Adenocarcinoma	Pre-operative, Hypofrac-tionation	35	Phase II, Single arm	NA (single arm)	25Gy/5#	Envafolimab, Endostatin and SOX (pre-operatively). Post-operative treatment at clinician's discretion.	pCR	12.2025
NCT04631757	Tianjin Medical University Cancer Institute and Hospital, China	A Prospective, Non-randomized, Phase II Study of Camrelizumab in Combination With Concurrent Chemoradiotherapy for Initial Unresectable Proximal Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma Conversion Therapy	Pre-operative	33	Phase II, Single arm.	NA (single arm)	45Gy/25# (+ camrelizumab + S-1)	Camrelizumab + S-1 + oxaliplatin	1 year PFS	12.2023 **
NCT05528367	Zhejiang Cancer Hospital, China	Tirelizumab in Combination With Chemoradiation in Patients With Unresectable Gastric Cancer or Gastroesophageal Junction Adenocarcinoma ：A Single Arm Phase II Clinical Study	Pre-operative	33	Phase II, single arm	NA (single arm)	45-50Gy/25# (+ Nab-paclitaxel + tirelizumab)	Tirelizumab + nab-paclitaxel + S-1	R0 resection rate	12.2024

NCT04523818	M.D. Anderson Cancer Center, USA	A Phase Ib Trial of Preoperative Short-Course Chemoradiotherapy Followed by Chemotherapy for Resectable Gastric Adenocarcinoma	Pre-operative, Hypofrac-tionation	30	Phase Ib, Single arm	NA (single arm)	10# (total dose not stated) (+ capecitabine or fluorouracil).	SOC chemotherapy at clinician's discretion peri-operatively.	Incidence of adverse events	12.2028
NCT06487429	Wuhan Union Hospital, China	Prospective, Phase II Clinical Study of Short Course Radiotherapy With Sequential Disitamab Vedotin Combined With S-1 and Sintilimab as Whole Course Neoadjuvant Therapy for HER2 Expressed Locally Progressive Gastric Cancer	Pre-operative, Hypofrac-tionation	28	Phase II, Single arm	NA (single arm)	25Gy/5#	Disitamab vedotin + sintilimab + S-1 (pre-operatively). Post-operative treatment at clinician's discretion.	pCR	05.2028
NCT05296005	Ohio State University Comprehensive Cancer Center, USA	Total Neoadjuvant Therapy for the Treatment of Gastroesophageal Junction (GEJ) and Gastric Cancers: A Pilot Trial	Pre-operative	20	Phase I, Single arm	NA (single arm)	25# (total dose not stated) (+ capecitabine or fluorouracil).	FLOT	1. No of patients able to complete treatment. 2. Incidence of adverse events.	12.2024
NCT05941481	Jiangsu Cancer Institute & Hospital, China	Neoadjuvant Chemo-hypofractionated Radiotherapy Plus PD-1 Antibody (Tislelizumab) in Locally Advanced Resectable Gastric or Gastroesophageal Junction Adenocarcinoma	Pre-operative, Hypofrac-tionation	21	Phase II, Single arm	NA (single arm)	30Gy/12#	Tislelizumab + XELOX	pCR	12.2025
Oligometastatic disease studies										
NCT05379972	University of Colorado, Denver, USA	Study of SBRT/Olaparib Followed by Pembrolizumab/Olaparib in Gastric Cancers	SABR	26	Phase II (with safety run in)	Non-randomised into two cohorts: HR deficient vs HR proficient	25Gy/5# (+ olaparib),	Pembrolizumab + olaparib	Objective response rate of unirradiated tumours.	12.2028
NCT04625894	Fudan University, China	Phase I Clinical Trial of Multisite Stereotactic Ablative Radiotherapy (SABR) Combined With Camrelizumab in Patients With Oligometastatic Gastrointestinal Cancer	SABR	7 (gastric subgroup)	Phase I, Single arm	NA (single arm)	Irradiation is to as many metastatic lesions as possible. Target dose will depend on site of the lesion and organs at risk (BED > 100Gy)	Camrelizumab	Dose limiting toxicities (≥G3 toxicity)	06.2023
NCT04248452	ECOG-ACRIN Cancer Research Group, USA	A Phase III Study of Consolidative Radiotherapy in Patients With Oligometastatic HER2 Negative Esophageal and Gastric Adenocarcinoma (EGA) (EA2183)	Oligometastatic disease	314	Phase III, randomised	Radiotherapy (up to 15 #) + SACT vs Continuation of SACT alone (randomised 2:1)	At discretion of treating oncologist up to 15# (recommended doses not stated) to all sites of disease	Oxaliplatin + 5-FU/ capecitabine +/- nivolumab (if CPD score ≥5)	OS	03.2028
NCT03161522	M.D. Anderson Cancer Center, USA	A Randomized Trial Comparing Early Local Chemoradiation Therapy +/- Surgery Versus Systemic Therapy for Patients With Esophageal or Gastric Cancer With Oligometastases	Palliative	100	Phase II, randomised	Maintenance chemotherapy alone (5FU/Capecitabine) vs Chemotherapy plus radiation +/- surgery to some or all of the remaining sites.	Total dose not stated (+5-FU/ capecitabine)	Induction chemotherapy (investigator choice) Maintenance: 5-FU/Capecitabine	OS	12.2026
Palliative intent studies										
NCT03061162	Yang, The Affiliated Nanjing Drum	Phase II Study of Pulsed Low Dose Rate Radiation Therapy for Gastric Cancer Patients With Peritoneal Metastasis	Palliative	40	Phase 2. Single arm	N/A single arm	Pulsed low dose rate 3-dimensional conformal	N/A	Side effects of pulsed low dose rate	03.2022

	Tower Hospital of Nanjing University Medical School, China						radiation therapy, 5 days a week for 25 days.		radiation therapy	

Appendix 3.11 – Currently active clinical trials (2)

Table A3.11. Summary of the 5 currently active clinical trials identified on the ICTRP registry that were not identified on the clinicaltrials.gov registry (Date of search 1.8.24).

Limited information is regarding by this registry relating to study intervention or expected completion date.

Main trial ID	Sponsor/ Lead centre	Official Title	Clinical setting	Phase	No. of patients	Study intervention	Primary end point	Current status
JPRN-jRCT1011200013 (Japan registry of clinical trials)	Hokkaido University Hospital, Hokkaido Gastrointestinal Cancer Study Group: HGCSG, Japan	Phase 1 trial of nivolumab and multisite radiotherapy for advanced gastric cancer (HGCSG2001)	Unclear	Phase I, Single arm	12	Combination of Nivolumab and radiotherapy (dose/ site not specified)	Safety	Last updated April 2024 – status "not recruiting"
ChiCTR2100048020 (Chinese registry)	The Affiliated Hospital of Youjiang Medical College, China	A single-arm, prospective clinical study of carrelizumab combined with apatinib and SOX in the treatment of advanced unresectable gastric cancer	Unclear	Phase II, Single arm	25	Carrelizumab, apatinib mesylate and SOX combined with radiotherapy – further details not specified	PFS, OS, Adverse events	Last updated Aug 2022 – status "recruiting"
ChiCTR2000034965 (Chinese registry)	Changzhou 2nd People's Hospital, China	Prospective single-center, randomized controlled phase II clinical study of low - dose, hypofractionated radiotherapy combined with PD-1 inhibitors for preoperative stage III gastric cancer	Pre-operative	Phase II	60 (20 each arm)	Radiotherapy combined with immunotherapy before surgery – further details not specified	DFS	Last updated 2020 – status "pending"
ChiCTR1900023370 (Chinese registry)	West China Hospital, Sichuan University, China	Phase I clinical study for albumin paclitaxel and capecitabine chemotherapy combined with local radiotherapy for initial unresectable locally advanced gastric cancer or para-aortic lymph node metastasis	Unclear	Phase I	24	Albumin-paclitaxel and capecitabine chemotherapy combined with local radiotherapy – further details not specified	MTD	Last updated 2019 - status "recruiting"
ChiCTR1900021580 (Chinese registry)	Sichuan Provincial Tumor Hospital, , China	Docetaxel and capecitabine chemotherapy combined with local radiotherapy for initial unresectable locally advanced gastric cancer or para-aortic lymph node metastatic gastric cancer stage I clinical study	Unclear	Phase I , Single arm	18	No intervention details stated	MTD, DLT	Last updated 2019 – status "pending"

Appendix 4

Appendix 4.1. National UK Gastric Radiotherapy Questionnaire

Introduction

Thank you for taking the time to read and complete this survey.

I am a Radiotherapy Research Fellow based at South West Wales Cancer Centre in Swansea, currently undertaking an MD exploring the role of radiotherapy for inoperable, non-metastatic gastric cancer.

My research is focussed on a small but important group of patients; those with locally advanced, non-metastatic disease, who are not suitable for surgery, and thus are left with no alternative radical treatment options, and only palliative systemic treatments at present. Similarly staged tumours of the gastro-oesophageal junction (GOJ) may be suitable for treatment with definitive chemoradiotherapy (dCRT), but there are currently no large-scale phase 3 data to support dCRT for locally advanced gastric cancer.

However, a systematic review of the literature has demonstrated:

- A number of small phase I/II studies of dCRT for locally advanced inoperable gastric cancer, with cCR rates ranging from 8 to 41.7%, 3 yr OS of 42-48%, and reassuring rates of G3 GI toxicity (no higher than 31%), accepting the acknowledged limitations of early phase studies and assessment of clinical response.
- Gastric CRT is efficacious in the neoadjuvant setting, with pCR rates of up to 30% in phase II studies.
- Gastric radiotherapy in the era of modern RT technique is well tolerated, with interim TOPGEAR data revealing 92% patients completed planned CRT, and G3 toxicity comparable to that of peri-operative chemotherapy.

Based on this, my research is exploring the potential role of dCRT, with a view to developing a UK gastric radiotherapy protocol, and future clinical trials in this setting.

Aims and Objectives

This questionnaire is aimed at UK based Consultant Clinical Oncologists, with expertise in treating oesophago-gastric cancers. The aims of this survey are to investigate:

1. The current clinical practice with regards to gastric radiotherapy in the UK
2. How you would approach gastric tumour volume delineation, radiotherapy planning and dose/fractionation.
3. What educational radiotherapy resources, protocols and guidelines you use to plan gastric radiotherapy, and what may be helpful in future.
4. Clinician familiarity with techniques, and confidence in accurately delineating gastric volumes.
5. Your opinion regarding the future of clinical trials in definitive gastric radiotherapy

This survey should take 10-15 minutes to complete.

The survey has been approved by the Swansea University Medical School Ethics Committee, and all responses will be anonymous.

Consent

I understand that taking part in this survey is entirely voluntary and I am under no obligation to do so.

I understand that my responses are anonymous and all results will be aggregated to prevent future identification of survey respondents (if you chose to provide your email address at the end of the survey, this will be uncoupled from your other responses).

I understand that anonymised results of this survey will be used in MD research, and results may form part of future publication, but results will not be directly fed back to participants.

I understand as data will be made anonymous it will not be possible to identify and remove your data at a later date, should you decide to withdraw from the study. Please also note that as data is being collected online, once the data has been submitted online, we will be unable to withdraw your information. We can however remove your email address from the database for later involvement at any time, should you wish.

Q1. I understand and consent to take part in this survey (please tick):

☐ Yes

☐ No

Demographics

Q2. How long have you been practicing as a Consultant Clinical Oncologist treating oesophago-gastric cancers?

5 years or less

6-10 years

11-15 years

16-20 years

More than 20 years

Theme 1– Opinion/Current practice

Q3. I would consider radiotherapy (with or without concurrent chemotherapy) as a treatment option in the following clinical circumstances (assume adenocarcinoma for all).

Please select one option for each row

	1 Strongly disagree	2 Disagree	3 Neither agree nor disagree	4 Agree	5 Strongly agree
GASTRIC - Post-operative	☐	☐	☐	☐	☐
GASTRIC - Pre-operative	☐	☐	☐	☐	☐
GASTRIC - Definitive (i.e radical dose ≥40Gy)	☐	☐	☐	☐	☐
GASTRIC - Palliative (i.e palliative dose <40 Gy)	☐	☐	☐	☐	☐
Type III GOJ - Post-operative	☐	☐	☐	☐	☐
Type III GOJ - Pre-operative	☐	☐	☐	☐	☐
Type III GOJ - Definitive (i.e radical dose ≥40Gy)	☐	☐	☐	☐	☐
Type III GOJ - Palliative (i.e palliative dose <40 Gy)	☐	☐	☐	☐	☐

If you have selected "disagree" or "strongly disagree" to any of these statements, please state why:

_____

_____

Q4. In the last 3 years, approximately how many times have you prescribed gastric radiotherapy for each clinical indication listed?

Please select one option for each row

	None	1-5	6-20	>20
GASTRIC - Post-operative	☐	☐	☐	☐
GASTRIC - Pre-operative	☐	☐	☐	☐
GASTRIC - Definitive (i.e radical dose ≥40Gy)	☐	☐	☐	☐
GASTRIC - Palliative (i.e palliative dose <40 Gy)	☐	☐	☐	☐
Type III GOJ - Post-operative	☐	☐	☐	☐
Type III GOJ - Pre-operative	☐	☐	☐	☐
Type III GOJ - Definitive (i.e radical dose ≥40Gy)	☐	☐	☐	☐
Type III GOJ - Palliative (i.e palliative dose <40 Gy)	☐	☐	☐	☐

Q5. If you do not routinely prescribe radical gastric radiotherapy, or do so very infrequently (e.g. <3 cases/year), what are the main reasons for this?

Please select any that apply

Rarely indicted in line with current standard UK practice

Concerns regarding toxicity *(*if so, please give detail below regarding specific toxicity concerns)*

Lack of experience with radical gastric radiotherapy/ concerned about accurate delineation of gastric volumes

Lack of UK gastric radiotherapy protocol

Not applicable

Other *(*if so, please give detail below)*

*If you selected "Toxicity Concerns" or "Other," please specify:

_____

_____

<u>Theme 2 – Radiotherapy Technique</u>

Q6. Regarding gastric radiotherapy, for those being treated with radical intent, what dose/fractionation would you most likely prescribe?

Please select one option for each row

	I would not prescribe RT in this circumstance	45Gy/25# (1.8Gy/# over 5 weeks)	50.4Gy/28# (1.8Gy/# over 5.5 weeks)	50Gy/25# (2Gy/# over 5 weeks)	40Gy/15 (2.67Gy/# over 3 weeks)	Other (state in free text box next)
Post-operative	☐	☐	☐	☐	☐	☐
Pre-operative	☐	☐	☐	☐	☐	☐
Definitive	☐	☐	☐	☐	☐	☐

If you would prescribe an alternative dose/# gastric radiotherapy that is not listed in the table, please state what dose/# you would use below:

_____

Q7. When prescribing radical intent gastric radiotherapy, would you recommend concurrent chemotherapy (assuming patient fitness)?

Please select one

Yes *(*If yes please state regimen below)*

No

Not applicable – I would not prescribe radical gastric radiotherapy

*If yes, please state what chemotherapy regimen you would use:

_____

Q8. If you were to outline a gastric cancer case for post-operative radiotherapy, which radiotherapy protocol would you refer to for delineation guidance?

Select all that apply

INT0116 MacDonald

TROG 03.02 Protocol

CRITICS Protocol

Local departmental policy

Not applicable – I would not use gastric RT for this indication

Other *(*please give detail below)*

*If you selected Other, please specify: _____

Q9. If you were to outline a gastric cancer case for pre-operative or definitive radiotherapy, which radiotherapy protocol would you refer to for delineation guidance?

Please tick all that apply

INT0116 MacDonald

TROG 03.02 Protocol

EORTC-ROG Expert Consensus (Matzinger et al 2009)

TOPGEAR Protocol

CRITICS I/II Protocol

Local departmental policy

Not applicable – I would not use gastric RT for this indication

Other *(*please give detail below)*

*If you selected Other, please specify: _____

Q10. With regards to nodal irradiation, please select any of the following statements which are applicable:

Please tick one option for each row

	Yes	No
a. I follow the nodal volumes as per protocol, without modification	☐	☐
b. I include additional nodal areas (for example due to concern about possible incomplete nodal coverage)	☐	☐
c. I omit certain nodal areas (for example due to concerns about toxicity/volume)	☐	☐
d. Not applicable/ unable to comment (e.g not currently using radical gastric RT)	☐	☐

If selecting "yes" to option b (including additional nodal areas) or option c (omitting nodal areas) to question 10, please give details here regarding your modification and reasons for doing so:

_____
_____

Q11. Do you have experience outlining upper abdominal lymph node areas due to expertise in another site? (for example, abdominal SABR)

Please tick one

Yes

No

If yes, please state your other site of expertise: _____

Q12. Do you have experience outlining the duodenum due to expertise in another tumour site (for example, pancreas)?

Please tick one

Yes

No

If yes, please state your other site of expertise: _____

Q13. What technique do you currently use for radical dose (i.e. post-operative, pre-operative or definitive, with dose >40Gy) gastric radiotherapy in your department?

Please tick all that apply

2D radiotherapy (AP-PA pair)

3D Conformal radiotherapy

IMRT/VMAT

Not applicable – would not use gastric radiotherapy for this indication

Other *(*please give detail below)*

*If you selected Other, please specify: _____

Q14. Which of the following is included as part of standard approach to radical (i.e. post-operative, pre-operative or definitive, with dose >40Gy) gastric radiotherapy planning/ patient set up at your centre?

Please tick all that apply

Standard CT planning scan with IV and oral contrast (assuming renal function adequate)

Gastric filling protocol

DIBH

Abdominal compression

Surface guidance

4DCT

On treatment verification CBCT *(*if yes please state frequency below)*

Other *(*please give detail below)*

Not applicable – would not use gastric radiotherapy for this indication

*If you selected "CBCT," please state frequency, or if you select "Other," please specify:
_____

Q15. If you were to roll out a new definitive radiotherapy technique at your centre, are there any additional aspects to radiotherapy planning/ set up/ delivery that you would consider desirable (that you do not currently use as standard for radical gastric radiotherapy in your centre)?

Please tick all that apply

Standard CT planning scan with IV and oral contrast (assuming renal function adequate)

Gastric filling protocol

DIBH

Abdominal compression

Surface guidance

4DCT

On treatment verification CBCT *(*if yes please state frequency below)*

Other *(*please give detail below)*

Not applicable – would not use gastric radiotherapy for this indication

*If you selected "CBCT," please state frequency, or if you select "Other," please specify:

_____

<u>Theme 3 – Oncologist experience in TVD</u>

Q16. Please rate your confidence in accurately delineating gastric radiotherapy volumes using currently available supportive materials/ protocols.

Please tick one option for each row

	1 Not at all confident	2	3	4	5	6	7	8	9	10 Extremely confident
Confidence in accurately delineating a post-operative gastric radiotherapy plan.	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Confidence in accurately delineating a pre-operative or definitive gastric radiotherapy plan.	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Theme 4 – Educational materials

Q17. What educational materials/ intervention would you find useful to aid in delineating pre-operative or definitive gastric radiotherapy volumes?

Please tick all that apply

Clear tumour volume delineation protocol

Nodal atlas

Worked example(s)

Radiology educational materials to guide identification of key structures

Webinars

Outlining workshop with an expert

Peer review

None of the above – I believe the currently available materials suffice

Other *(*please give detail below)*

*If you selected Other, please specify: _____

Theme 5 – Future Directions

Q18. Would you be supportive of a clinical trial further investigating the role of definitive chemoradiotherapy for inoperable, non-metastatic gastric cancer patients (for example, who are inoperable due to medical co-morbidity, technically inoperable, or patient wish?)

Please tick one

Yes

No

Unsure (I would need to see supporting evidence presented before I would feel able to answer)

Q19. Approximately how many patients do you see each year who would meet the following criteria: histologically proven gastric adenocarcinoma, no distant metastases on routine staging, deemed inoperable due to medical co-morbidity, patient declines surgery or technically locally inoperable?

Please tick one

0-2

3-5

6-10

11-20

>20

Q20. Would you be interested in helping us by testing a definitive gastric radiotherapy protocol/ any educational materials, for example by outlining a test case?

Yes

No

If you selected yes, please give your email address*:

_____

**Please note your email address will not be used for any other purposes or used outside the immediate MD project team, and will be stored on a secure, password protected database*

Thank you very much for participating in this survey

What if I have other questions?

If you have further questions about this study, please do not hesitate to contact us:

Dr Amy Case

Swansea University Medical School

[redacted]

[redacted]

Prof Hayley Hutchings

Swansea University Medical School

[redacted]

Appendix 4.2 – Participant Information Sheet

PARTICIPANT INFORMATION SHEET

Developing the role of radiotherapy for inoperable gastric cancer: A national questionnaire to establish current UK practice

What is the purpose of the research?

We are conducting research on the role of radiotherapy for inoperable, non-metastatic gastric cancer. As well as trying to establish the current evidence for gastric radiotherapy, part of this research includes developing optimal radiotherapy technique for gastric cancer and designing a gastric radiotherapy protocol.

In order to learn more about current gastric RT practice in the UK, a questionnaire has been developed, aimed UK-based Consultant Clinical Oncologists, with expertise in treating oesophago-gastric (OG) cancer.

The aims of this questionnaire to explore:

1. Current clinical practice with regards to gastric radiotherapy in the UK, specifically what settings it is used (post-operative, pre-operative, definitive, palliative) and how often it is prescribed
2. How oncologists would approach gastric tumour volume delineation, radiotherapy technique, and dose/fractionation.
3. The educational resources, radiotherapy protocols, and guidelines used by clinicians to aid gastric radiotherapy planning.
4. Clinician familiarity with techniques, and confidence in accurately delineating gastric volumes.
5. Gauge opinion regarding a future clinic trial exploring definitive chemoradiotherapy for inoperable, non-metastatic gastric cancer.

Your participation in this survey will take approximately 10-15 minutes.

At the end of the survey, you will be asked if you would like to share your email address for future communication regarding later studies as part of this MD. This is entirely voluntary.

Who is carrying out the research?

The data are being collected by Dr Amy Case, a clinical oncology trainee who is currently undertaking an MD in Healthcare studies at Swansea University Medical School. The research has been approved by Swansea University Medical School Research Ethics Committee.

What happens if I agree to take part?

If you agree to take part in the online survey, this should take no longer than 15 minutes to complete.

Your consent will be confirmed when you start the survey. Your responses will be anonymous and collected via and secure online survey platform. No personal information is required, though you have the option to leave an email address at the end of the survey. This will be uncoupled from your survey responses, which will remain anonymous. Email addresses will only be used for the purpose of this study, will not be shared with other parties, and will be stored on a secure database (which will be deleted on completion of this MD research).

Are there any risks associated with taking part?

The research has been approved by Swansea University Medical School Research Ethics Committee. There are no significant risks associated with participation.

Data Protection and Confidentiality

Your data will be processed in accordance with the Data Protection Act 2018 and the General Data Protection Regulation 2016 (GDPR). All information collected about you will be kept strictly confidential. Your data will only be viewed by the researcher/research team.

All electronic data will be stored on a password-protected computer file on a secure NHS Laptop. Your consent information will be kept separately from your responses to minimise risk in the event of a data breach.

Please note that the data we will collect for our study will be made anonymous, thus it will not be possible to identify and remove your data at a later date, should you decide to withdraw from the study. We can however remove your email address from the database for later involvement at any time, should you wish.

Please also note that as data is being collected online, once the data has been submitted online, we will be unable to withdraw your information.

What will happen to the information I provide?

An analysis of the information will form part of our report at the end of the study and may be presented to interested parties and published in scientific journals and related media. *Note that all information presented in any reports or publications will be anonymous and unidentifiable*.

Is participation voluntary and what if I wish to later withdraw?

Your participation is entirely voluntary – you do not have to participate if you do not want to. If you decide to participate, but later wish to withdraw from the study, then you are free to withdraw at any time, without giving a reason and without penalty.

Data Protection Privacy Notice

The data controller for this project will be Swansea University. The University Data Protection Officer provides oversight of university activities involving the processing of personal data and can be contacted at the Vice Chancellors Office.

Your personal data will be processed for the purposes outlined in this information sheet.

Standard ethical procedures will involve you providing your consent to participate in this study by completing the consent form that has been provided to you.

The legal basis that we will rely on to process your personal data will be processing is necessary for the performance of a task carried out in the public interest. This public interest justification is approved by Swansea University Medical School Research Ethics Committee,

The legal basis that we will rely on to process special categories of data will be processing is necessary for archiving purposes in the public interest, scientific or historical research purposes or statistical purposes.

How long will your information be held?

We will hold any personal data (i.e. any email addresses voluntarily provided) until the successful completion of the MD, at which time the database will be destroyed.

What are your rights?

You have a right to access your personal information, to object to the processing of your personal information, to rectify, to erase, to restrict and to port your personal information. Please visit the University Data Protection webpages for further information in relation to your rights.

Any requests or objections should be made in writing to the University Data Protection Officer:-

University Compliance Officer (FOI/DP)
Vice-Chancellor's Office
Swansea University
Singleton Park
Swansea
SA2 8PP
Email: dataprotection@swansea.ac.uk

How to make a complaint

If you are unhappy with the way in which your personal data has been processed, you may in the first instance contact the University Data Protection Officer using the contact details above.

If you remain dissatisfied, then you have the right to apply directly to the Information Commissioner for a decision. The Information Commissioner can be contacted at: -

Information Commissioner's Office,

Wycliffe House,

Water Lane,

Wilmslow,

Cheshire,

SK9 5AF

www.ico.org.uk

What if I have other questions?

If you have further questions about this study, please do not hesitate to contact us:

Dr Amy Case

Swansea University Medical School

[redacted]

[redacted]

Prof Hayley Hutchings

Swansea University Medical School

[redacted]

Appendix 4.3 – Statistical testing for association between prior clinican experience and opinion regarding gastric RT by indicaiton.

Post-operative gastric RT

Gastric Post-op	Disagree	Neither	Agree	Total
≤10 yrs experience	14	2	8	24
>10 yr experience	8	6	4	18
Total	22	8	12	42

Chi-Square Tests			
	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	4.198[a]	2	.123
Likelihood Ratio	4.249	2	.119
Linear-by-Linear Association	.010	1	.919
N of Valid Cases	42		
a. 2 cells (33.3%) have expected count less than 5. The minimum expected count is 3.43.			

Pre-operative gastric RT

Gastric Pre-op	Disagree	Neither	Agree	Total
≤10 yrs experience	22	1	1	24
>10 yr experience	12	4	2	18
Total	34	5	3	42

Chi-Square Tests			
	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	4.305[a]	2	.116
Likelihood Ratio	4.392	2	.111
Linear-by-Linear Association	3.048	1	.081
N of Valid Cases	42		
a. 4 cells (66.7%) have expected count less than 5. The minimum expected count is 1.29.			

Definitive gastric RT

Gastric definitive	Disagree	Neither	Agree	Total
≤10 yrs experience	19	3	2	24
>10 yr experience	13	3	2	18
Total	32	6	4	42

Chi-Square Tests			
	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	.273[a]	2	.872
Likelihood Ratio	.272	2	.873
Linear-by-Linear Association	.230	1	.632
N of Valid Cases	42		
a. 4 cells (66.7%) have expected count less than 5. The minimum expected count is 1.71.			

Palliative Gastric RT

Gastric palliative	Disagree	Neither	Agree	Total
≤10 yrs experience	4	1	20	25
>10 yr experience	1	1	16	18
Total	5	2	36	43

NB. One respondent did not answer first 3, but answered palliative question, hence total =43

Chi-Square Tests			
	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	1.135[a]	2	.567
Likelihood Ratio	1.228	2	.541
Linear-by-Linear Association	.881	1	.348
N of Valid Cases	43		
a. 4 cells (66.7%) have expected count less than 5. The minimum expected count is .84.			

Appendix 5

Appendix 5.1 – Delineation instructions

A STUDY TO EVALUATE THE EFFECT OF CT VERSUS MRI-BASED TUMOUR VOLUME DELINEATION ON INTEROBSERVER VARIABILITY IN GASTRIC CANCER

DELINEATION INSTRUCTIONS

Introduction

In order to potentially treat gastric tumours with radical dose radiotherapy it is imperative that tumour volume delineation is as accurate as possible. The aim of this study is to evaluate the accuracy and interobserver variability in tumour volume delineation of gastric tumours using CT alone, versus CT plus MRI.

To do this, we would like you to delineate the stomach and primary gastric tumour on CT alone, and then repeat the exercise with additional MRI images for reference.

Please see the Participant Information Sheet for more background information about the study, and how your data will be managed.

Study overview

There are 2 phases to delineation for each case:

- **Phase 1** – CT delineation
    - Delineation of GTVp (+/- GTVn) where appropriate and CTVstomach using CT alone
    - Complete feedback - 5 very short questions about your experience and time to complete the exercise using CT alone
    - Volumes and feedback returned to us at South West Wales Cancer Centre (SWWCC)

- **Phase 2** – CT+ MRI delineation
    - Delineation of GTVp (+/- GTVn) and CTVstomach using CT and a library of MRI images for reference
    - Complete feedback – Same 5 very short questions about your experience and time to complete the exercise repeated, this time regarding CT plus addition of MRI
    - Volumes and feedback returned to us at South West Wales Cancer Centre (SWWCC)

  If you are able to complete further cases, the process is repeated for each case.

Instructions

One of 4 cases below will be sent to your planning software:

Gastric_IOVstudy_case_A

Gastric_IOVstudy_case_B

Gastric_IOVstudy_case_C

Gastric_IOVstudy_case_D

Initially, we would like you to complete a minimum of 1 test case (outlining once on CT, and again on CT using MRI for guidance). However, if following completion of the first case, your time permits and you wish to contribute further to the study, further cases will be sent (up to a maximum of 4).

Documents

As well as the dicom file ready to delineate on your planning system, you will also need the following documents to complete the required TVD. These will be transferred with the dicom file to your radiotherapy planning department.

- This delineation instruction manual (also contains CT atlas)
- Clinical Information for the relevant case (word document)
- PowerPoint file of CT images for the relevant case*
- PowerPoint file of MRI images for the relevant case (sent following completion of phase 1, for use during phase 2)
- Guidance for gastric MRI interpretation (sent following completion of phase 1, for use during phase 2)

*For this study, diagnostic CT images have been used to create the RT planning test cases. As such, the PowerPoint of diagnostic CT images you have been provided are the same image set used as the planning CT, but have also been provided in PowerPoint format in case you find it helpful to refer to images in a different plane on a 2nd screen/monitor.

Phase 1 – CT Delineation

For each case, using the clinical information provided and diagnostic CT images, please delineate the following structures, and label using the following nomenclature (the '_CT' represents that these volumes have been delineated using CT alone):

Please note a CT atlas is provided on p6-10 of this document. We recommend adjusting window levels to optimise planning CT, for example using the mediastinal window level setting.

1. **GTVp_CT**
   Using the CT and endoscopy report provided, please delineate what you interpret as the gross tumour volume (GTV) of the primary tumour. Please include the entire extent of the tumour, including any extra-gastric extension. Any involved lymph nodes that are in continuity with the GTV should be included in the GTVp volume (i.e. if they form a contiguous mass).

2. **GTVn_CT** (if applicable)
   Any involved lymph nodes that are separate from GTVp should be contoured separately, and numbered (e.g. GTVn1, GTVn2, GTVn3).

3. **CTVstomach_CT**
   Please delineate the whole stomach. Do not include the gastro-oesophageal junction (GOJ) or duodenum in this volume (unless the GOJ is involved and therefore included in GTVp – see below). As a guide, in a patient with normal anatomy, the inferior end of the GOJ is where it crosses below the diaphragm, and where the stomach fans out to the fundus and lesser curve. Coronal images may aid this distinction (see atlas images).
   CTVstomach should include GTVp in its entirety. If the GTVp involves the GOJ, this should also be included in the CTVstomach_CT.

Observation

We would like to gather some qualitative data in order to evaluate time and ease of volume delineation using CT alone.

Therefore, for each case, please complete the relevant row for the case you have delineated, and return it to us via email. This table should be completed after phase 1 (i.e. using CT alone) as you will be asked to give feedback again after you repeat the exercise using MRI.

Test Case	**Approximate time to delineate CTVstomach**	**Approximate time to delineate GTVp** (alone, not including GTVn if applicable)	**Ease identifying CTVstomach** (please rate 1-10, 1= difficult, 10= easy)	**Ease identifying GTVp** (please rate 1-10, 1= difficult, 10= easy)	**Comments** (please comment on areas you found straight forward or difficult to delineate)
Gastric_IOVstudy_case_A (CT)					
Gastric_IOVstudy_case_B (CT)					
Gastric_IOVstudy_case_C (CT)					
Gastric_IOVstudy_case_D (CT)					

Returning your completed volumes and feedback

Once you have completed your phase 1 volumes, please email us at [redacted] and [redacted] and we will arrange the named radiotherapy in your department to transfer your volumes via secure file share.

Your qualitative feedback should be emailed to [redacted]k. On receipt, volumes and feedback responses above will be immediately anonymised before any further analysis.

Please note you cannot undertake phase 2 until we receive your phase 1 volumes.

Phase 2 – MRI delineation

On completion of phase 1, you will be sent a set of MR images that correspond to the test case(s).

We would then like you repeat the delineation exercise, creating the volumes as described below **using the MRI images** for reference, in addition to the CT and endoscopy findings available to you in phase 1.

A separate document detailing how to visualise gastric tumours on MR will be sent with the images.

Please note that due to changes in positioning and scan preparation, co-registration of these images with the planning CT is suboptimal, hence the PowerPoint images have been sent for reference and to aid delineation, rather than a Dicom file for fusion.

Using the relevant MR images in addition to the previous clinical information you were sent for the relevant case, please create the following volumes, labelled accordingly (ensuring you include "_MRI" to indicate these volumes were created using MRI)

1. **GTVp_MRI**
   Using the CT and endoscopy report provided, please delineate what you interpret as the gross tumour volume (GTV) of the primary tumour. Please include the entire extent of the tumour, including any extra-gastric extension. Any involved lymph nodes that are in continuity with the GTV should be included in the GTVp volume (i.e. if they form a contiguous mass).

2. **GTVn_MRI** (if applicable)
   Any involved lymph nodes that are separate from GTVp should be contoured separately, and numbered (e.g. GTVn1, GTVn2, GTVn3)

3. **CTVstomach_MRI**
   Please delineate the whole stomach. Do not include the gastro-oesophageal junction (GOJ) or duodenum in this volume (unless the GOJ is involved with GTVp – see below).
   As a guide, in a patient with normal anatomy, the inferior end of the GOJ is where it crosses below the diaphragm, and where the stomach fans out to the fundus and lesser curve. Coronal images may aid this distinction (see atlas images).
   CTVstomach should include GTVp. If the GTVp involves the GOJ, this should be included in the CTVstomach_CT (and will therefore constitute the uppermost slice of this volume).

Please also record the following observations about your experience, using MRI in addition to CT:

Test Case	**Approximate time to delineate CTVstomach**	**Approximate time to delineate GTVp**	**Ease identifying CTVstomach** (please rate 1-10, 1= difficult, 10= easy)	**Ease identifying GTVp** (please rate 1-10, 1= difficult, 10= easy)	**Comments** (please comment on areas you found straight forward or difficult to delineate)
Gastric_IOVstudy_case_A (CT + MRI)					
Gastric_IOVstudy_case_B (CT + MRI)					
Gastric_IOVstudy_case_C (CT + MRI)					
Gastric_IOVstudy_case_D (CT + MRI)					

Return your volumes and feedback responses to us as above.

Summary of nomenclature

Volume name	Phase of study	Definition
GTVp_CT	Phase 1 (using CT alone)	Gross tumour volume (GTV) of the primary tumour, including any extra-gastric extension. Involved lymph nodes that are in continuity with the GTV should be included in the GTVp volume (i.e. if they form a contiguous mass).
GTVn_CT	Phase 1 (using CT alone)	Any involved lymph nodes that are separate from GTVp should be contoured separately, and numbered (e.g. GTVn1, GTVn2, GTVn3)
CTVstomach_CT	Phase 1 (using CT alone)	Whole stomach. Do not include the gastro-oesophageal junction (GOJ) or duodenum in this volume (unless the GOJ is involved with GTVp – see explanation above). Should include GTVp
GTVp_MRI	Phase 2 (using CT + MRI)	Gross tumour volume (GTV) of the primary tumour, including any extra-gastric extension. Involved lymph nodes that are in continuity with the GTV should be included in the GTVp volume (i.e. if they form a contiguous mass).
GTVn_MRI	Phase 2 (using CT + MRI)	Any involved lymph nodes that are separate from GTVp should be contoured separately, and numbered (e.g. GTVn1, GTVn2, GTVn3)
CTVstomach_MRI	Phase 2 (using CT + MRI)	Whole stomach. Do not include the gastro-oesophageal junction (GOJ) or duodenum in this volume (unless the GOJ is involved with GTVp – see explanation above). Should include GTVp

What if I have other questions or need technical help?

If you have further questions or need assistance with file transfer, please do not hesitate to contact us:

Any general questions about study design/ contouring instructions/ qualitative data collection:

Dr Amy Case
Radiotherapy Research Fellow
South West Wales Cancer Centre

[redacted]

Questions about file upload to planning software/ transfer of files between RT departments:

Becky Slinger
Radiotherapy Physicist
South West Wales Cancer Centre

[redacted]

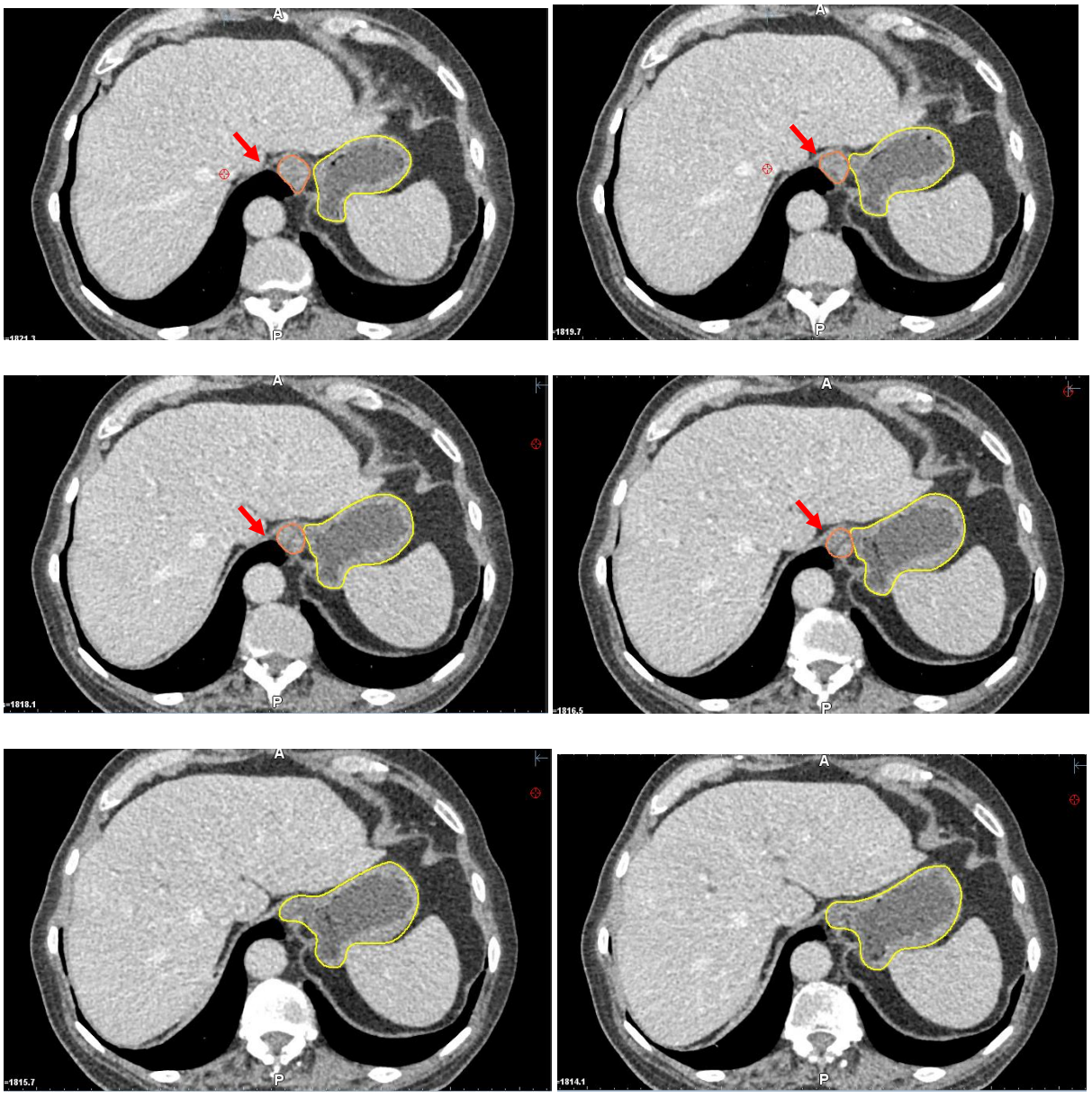
CT Atlas demonstrating whole stomach and GTVp volumes to aid delineation

Orange = Oesophagus. Yellow = CTVstomach. Red = GTVp. Green = Duodenum.

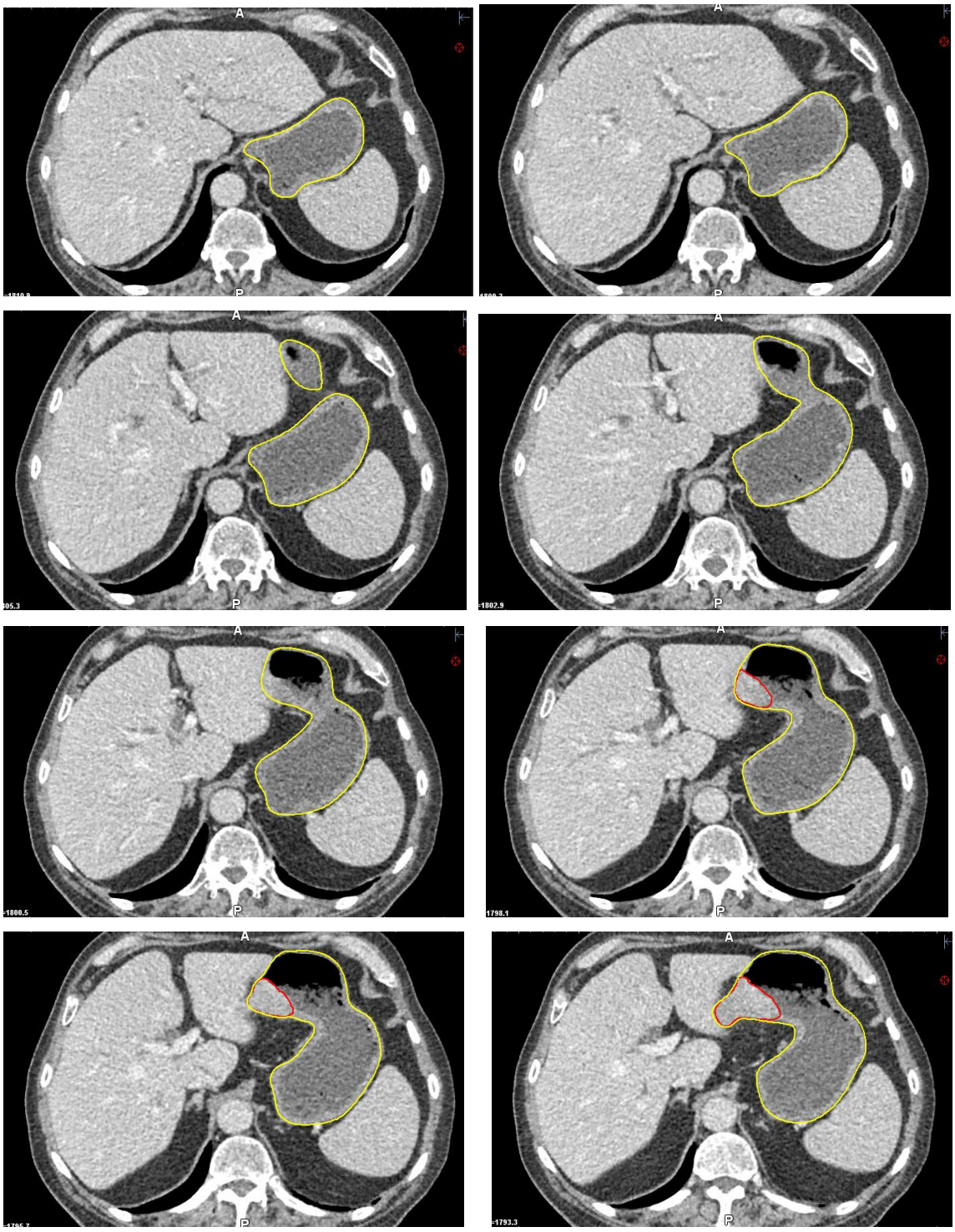
Please note oesophagus and duodenum do not need to contoured for this study, but are shown here to demonstrate anatomical boundaries.

The tumour shown here is a bulky pyloric tumour, delineated in red.

Images are presented cranially to caudally, horizontally across page L>R.



Red arrow indicates the thin linear muscle of the right diaphragmatic crus. At this level, the gastro-oesophageal junction traverses the diaphragmatic hiatus into the abdomen. In the absence of a hiatus hernia, the cardia is located here. Shortly after crossing the diaphragm, the gastro-oesophageal junction "fans" out becoming the fundus and lesser curve of the stomach. Where the gastro-oesophageal junction crosses behind the right diaphragmatic crus is considered the proximal boundary of the stomach volume. Refer also to the coronal images to aid this distinction (see p10).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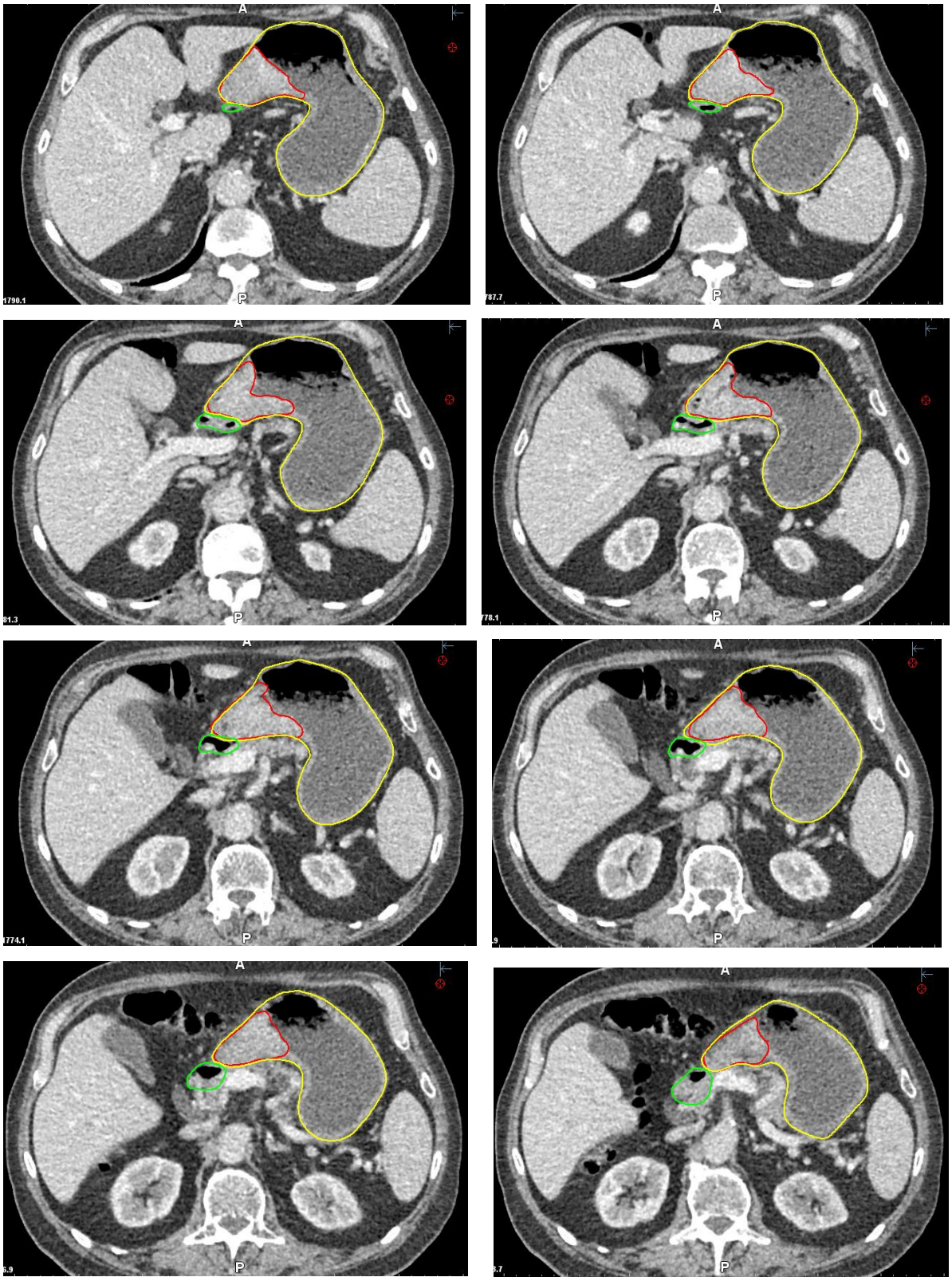
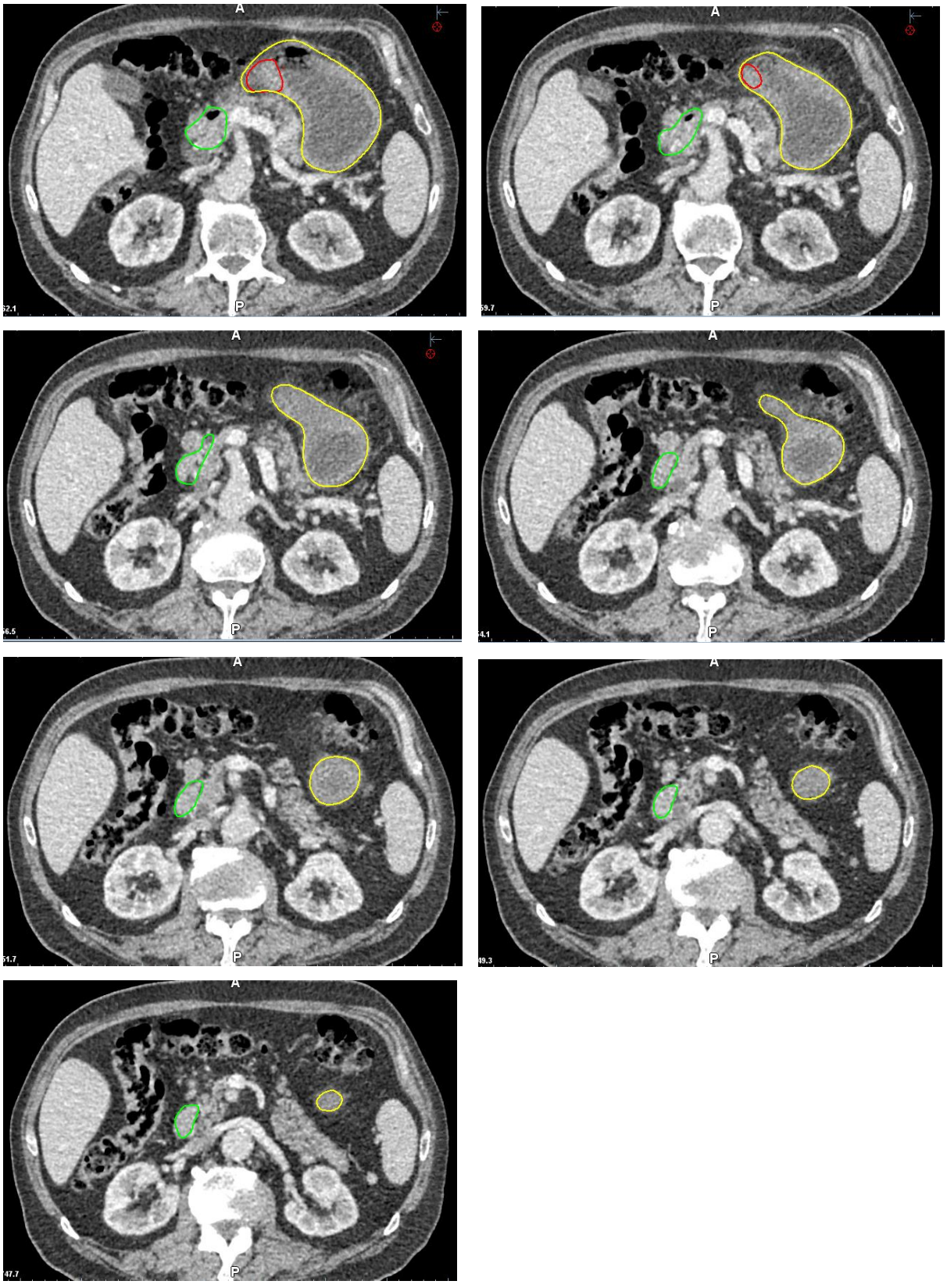


The inferior right lateral extent should include the pylorus, but not extend to include the duodenal cap (i.e. the first part of the duodenum) which is outlined here in green.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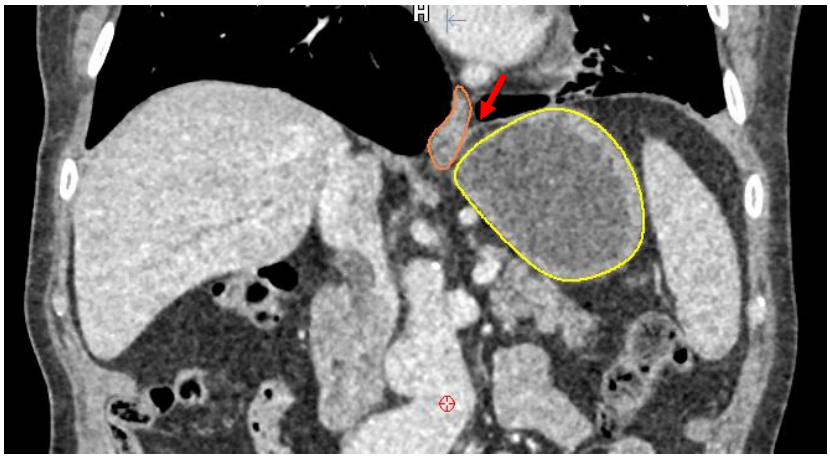
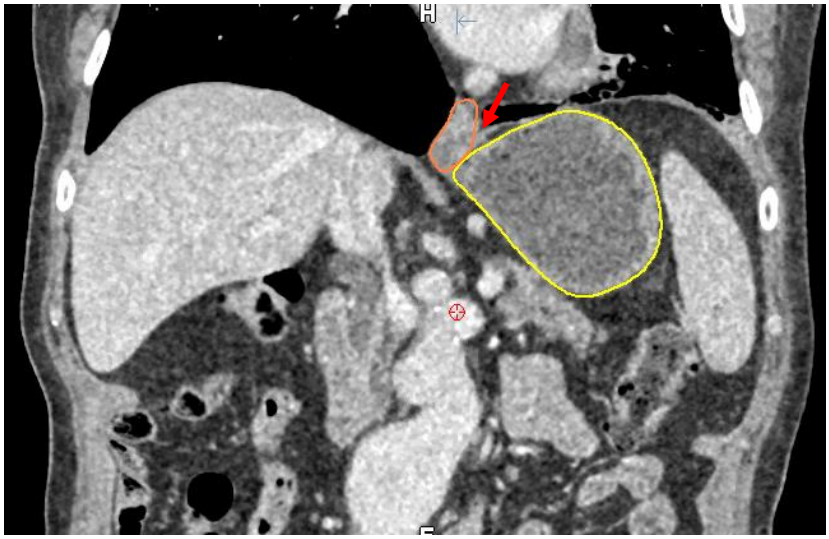
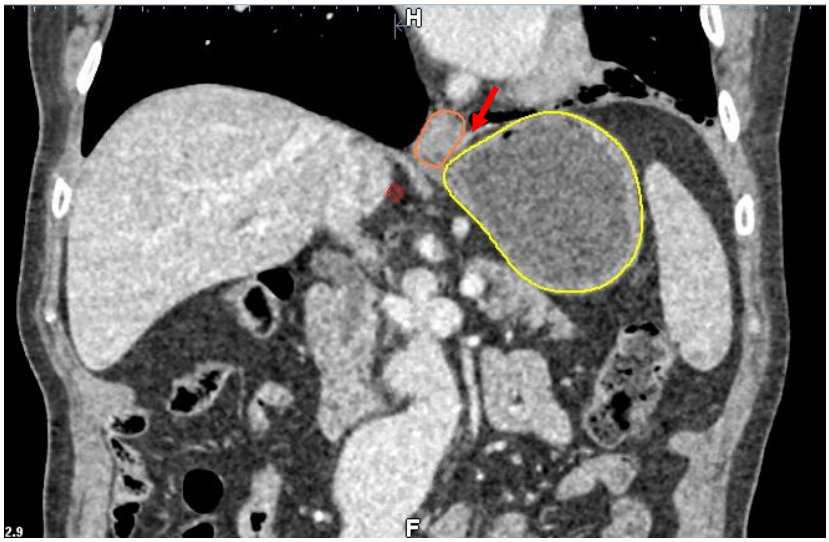
Coronal images depicting the GOJ

Red arrow showing diaphragm, which can act as a useful landmark to identify boundary of GOJ and stomach.







Appendix 5.2 – MRI Guidance document

A STUDY TO EVALUATE THE EFFECT OF CT VERSUS MRI-BASED TUMOUR VOLUME DELINEATION ON INTEROBSERVER VARIABILITY IN GASTRIC CANCER

Guidance for Interpreting MRI for Gastric Radiotherapy

MRI of the stomach is not currently used as an imaging modality for gastric cancer staging. Therefore, for the purpose of this study, gastric cancer patients who have had MRI liver have been selected to visualise the primary gastric tumour. The MRI protocols used to image the liver are very similar to those that would be applied to gastric cancer imaging, thus are being used as a surrogate examination.

Please find some helpful "hints and tips" below, that should aid MRI interpretation for tumour volume delineation (TVD).

You will also find a labelled atlas of specific MRI sequences that will be concentrated on during this study, namely T2-weighted sequences and diffusion weighted imaging (DWI) depicting gastric tumours (p.6-18).

Useful sequences

Interpretation of MRI can be challenging when first starting out, but the great advantage of MRI compared to CT is the superior contrast resolution, which allows better differentiation of soft tissue structures. This is particularly relevant in the abdomen, where organs of similar density are co-located.

At first, we recommend reviewing the CT, which you are probably more familiar with, then the MRI. Remember, the anatomy is the same for each patient, so consider the MRI and CT in parallel.

Which sequences are best for looking at the stomach and gastric tumours?

A standard sequence used in virtually all MRI protocols is a T2-weighted sequence. This sequence is usually performed in axial or coronal planes, or both, and is useful for delineating anatomy. You may have noticed that many MRI sequences have different names but are still T2-weighted sequences. These sequence names are specific to the manufacturer of the MRI scanner.

The following MR sequences may be useful to visualise the stomach and gastric tumours:

1. T2 weighted imaging (may also be called HASTE)

In this study, we provide T2-weighted images to delineate the anatomy of the stomach and surrounding organs. The images are "fat-saturated" meaning the intra- and extra- abdominal fat is dark leaving the viscera to demonstrate MRI signal. When reviewing these images, it is a good idea to review with the CT, which will help delineate the anatomy and is a modality that you are likely to be more familiar with.

The stomach wall will have higher signal than the peri-gastric fat but, admittedly, this is sometimes difficult to visualise. However, the gastric contents are bright (fluid signal), and any luminal gas is black. This will guide you to the outline of the stomach and duodenum.

2. Diffusion weighted imaging (DWI)

A DWI sequence allows radiologists to describe whether a tissue has "restricted diffusion." Certain parameters must be fulfilled to diagnose true restricted diffusion, but we provide a series of images that will guide you to the primary tumour and any involved lymph nodes. DWI is usually performed in a series of different settings therefore, you may see repeated DWI images. The important point to remember when participating in this study is that **the primary tumour is bright on DWI**. The characteristics, in combination with the CT and T2-weighted images, will allow you to outline the gastric tumour.

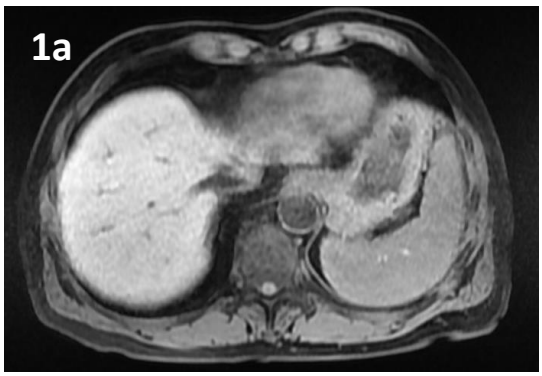
3. Post-contrast imaging

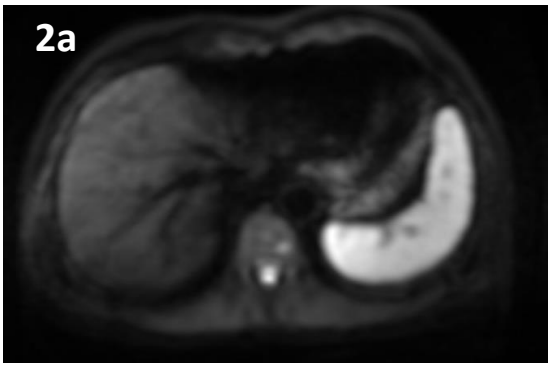
As with CT, gastric tumours enhance with contrast (gadolinium used in MRI), but the degree of enhancement can be variable depending on the tumour biology. The primary tumour will enhance more compared to background stomach, which appears as higher signal (brighter) on the images. In large tumours, with internal necrosis, enhancement is often poor centrally, but the periphery tends to show some enhancement. We have provided delayed contrast imaging which can help increase the conspicuity of the tumour. As before, we advise reviewing the post-contrast images with CT, T2 and DWI when considering the extent of disease.

Appearance of the normal stomach on MR

The normal gastric wall thickness is variable on imaging and affected by the degree of gastric distension. Ideally, the stomach should be distended when diagnosing and staging gastric tumours, but this is not always the case. When under-distended, the normal stomach wall can look quite thick. However, it is important to consider any asymmetry of the stomach (e.g., between greater and lesser curves), any areas of focal thickness (i.e., a mass), or any areas of focal enhancement that is different to the background stomach.

Image 1 (normal stomach)





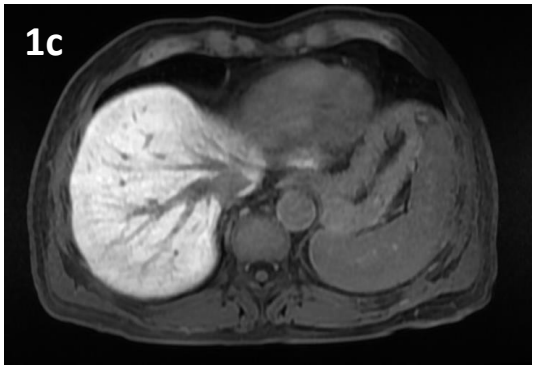


Image 1.
MR demonstrating normal stomach appearance on 3 different MR sequences:

a. T2 weighted
b. Diffusion weighted (DWI)
c. Delayed contrast (Ax LAVA 20 mins +C)

Image 2 (normal stomach)

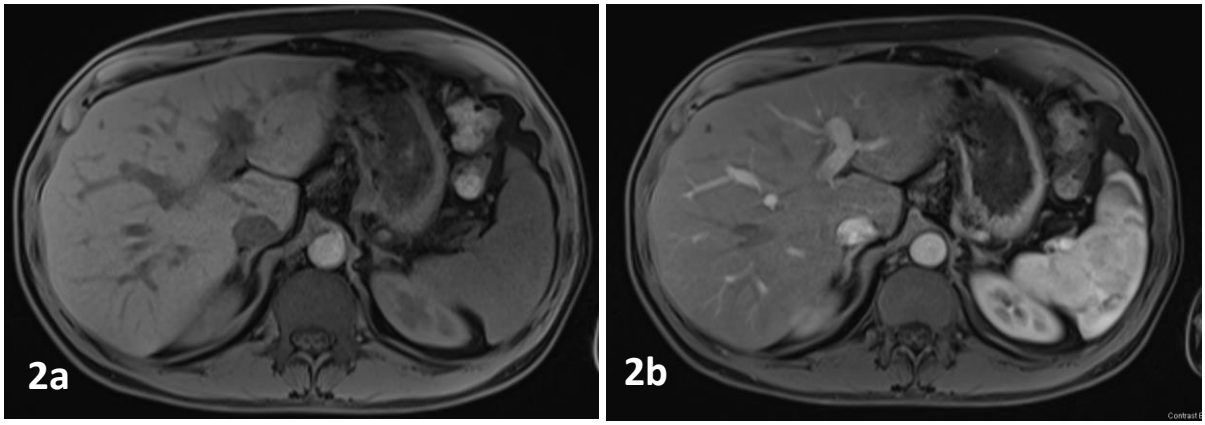


Image 2.
MR demonstrating normal stomach pre (a) and post contrast (b)

Image 3 (normal stomach)

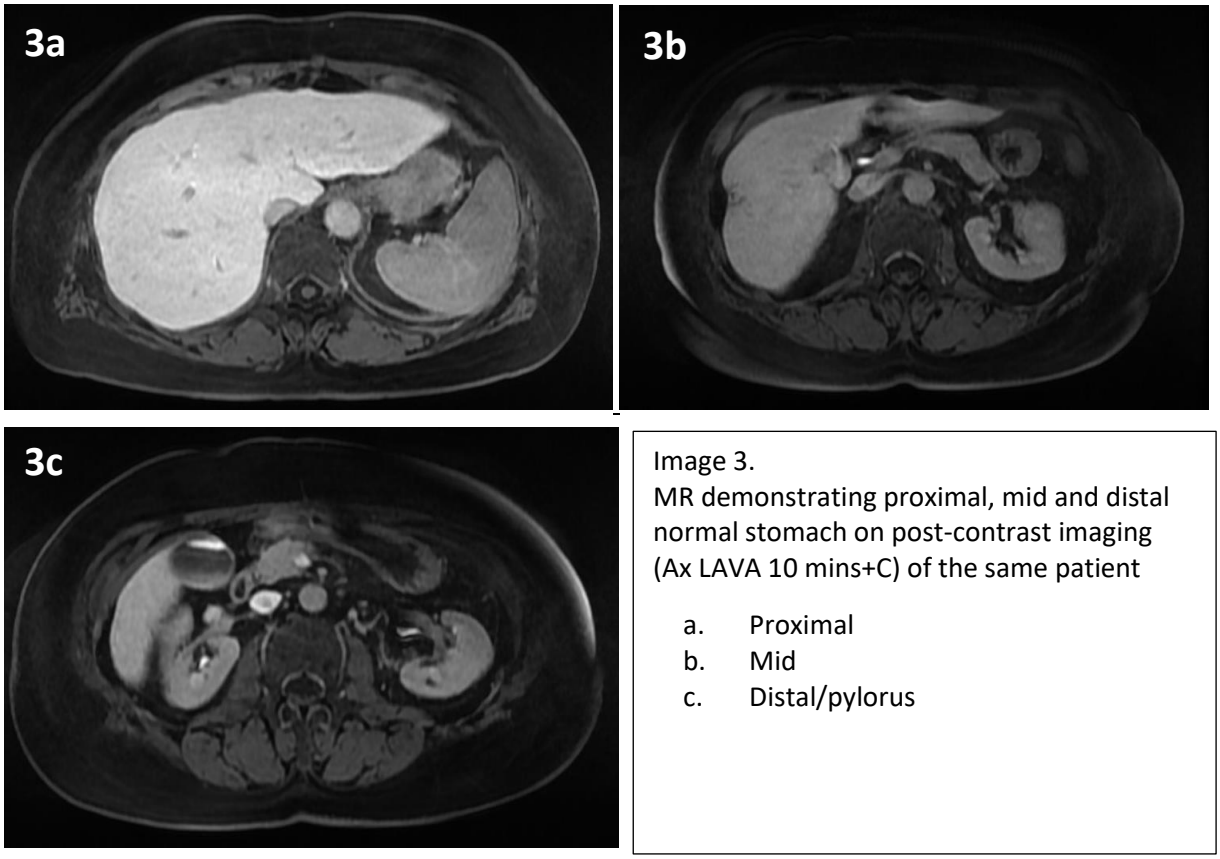


Image 3.
MR demonstrating proximal, mid and distal normal stomach on post-contrast imaging (Ax LAVA 10 mins+C) of the same patient

a. Proximal
b. Mid
c. Distal/pylorus

Appearance of gastric tumours on MR

Image 4

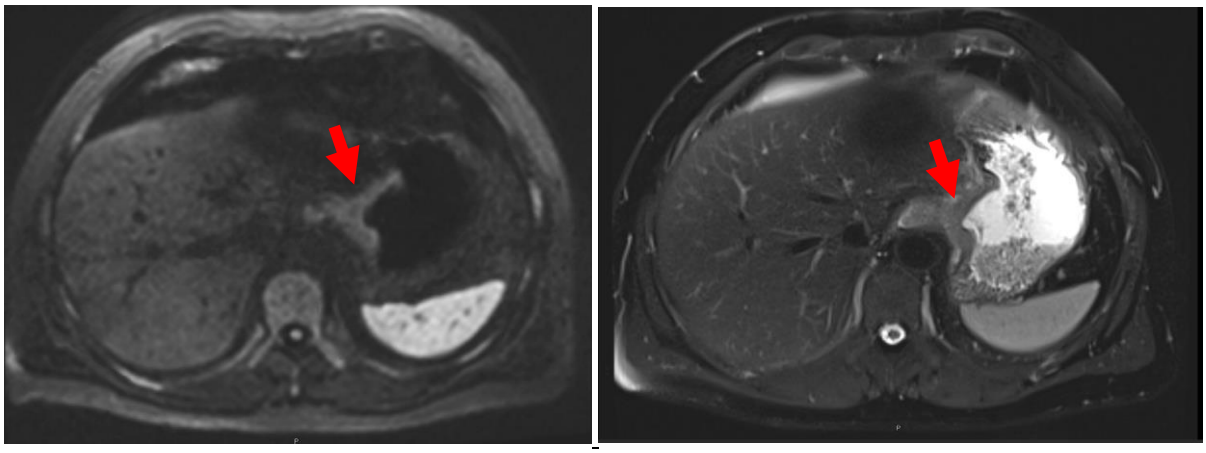


Image 4.
Shows tumour (arrowed) at the GOJ on a) DWI, the tumour restricts and appears brighter than the normal gastric wall, and b) T2 fat sat images demonstrating thickened gastric wall, contrasted by the fluid content of the stomach appearing white on T2 images.

Image 5

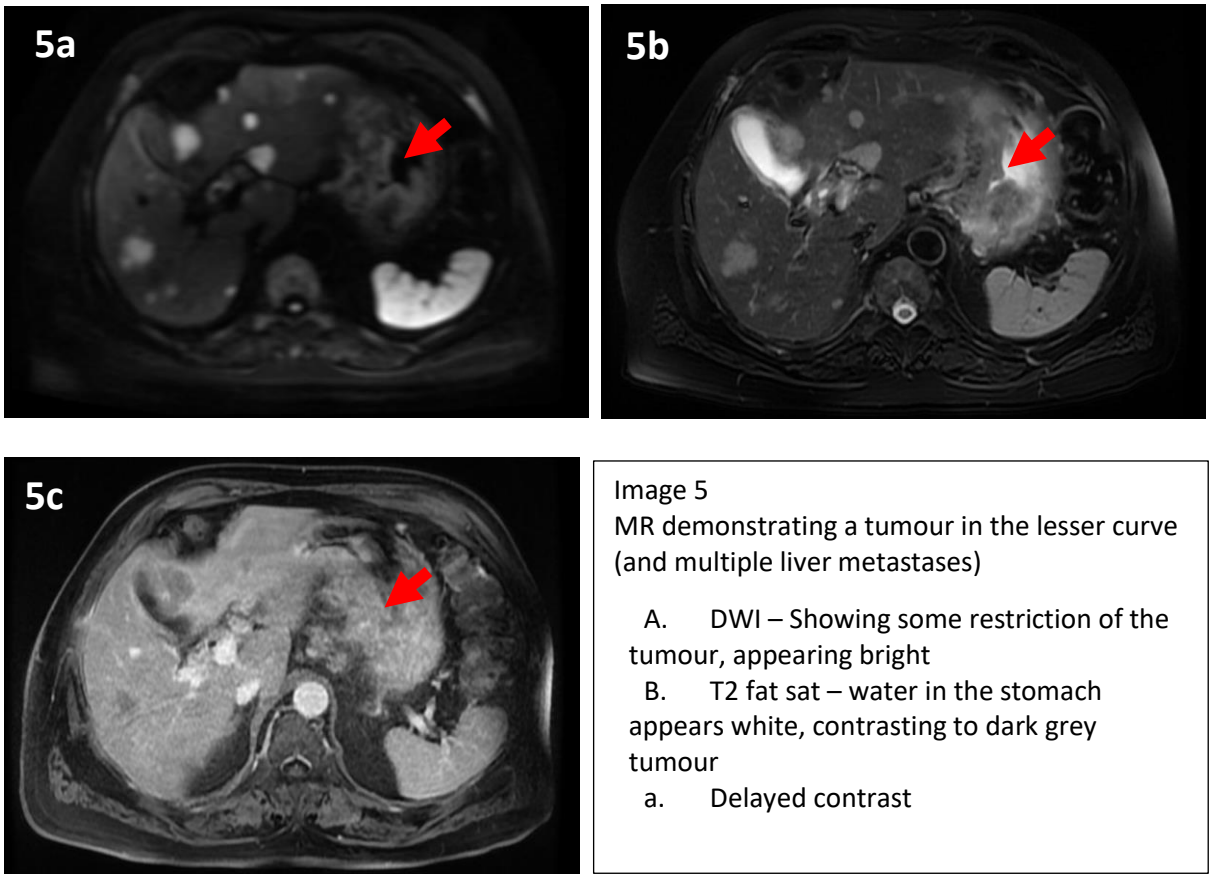
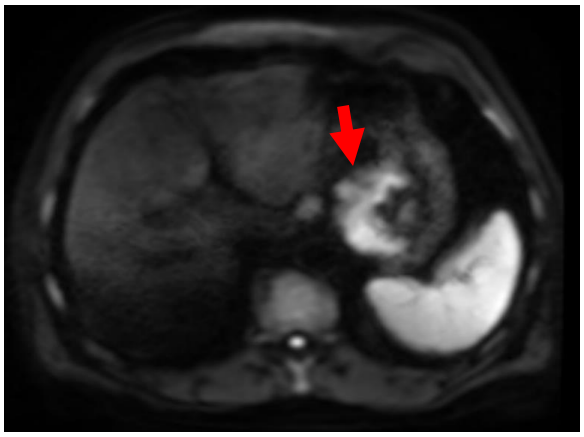
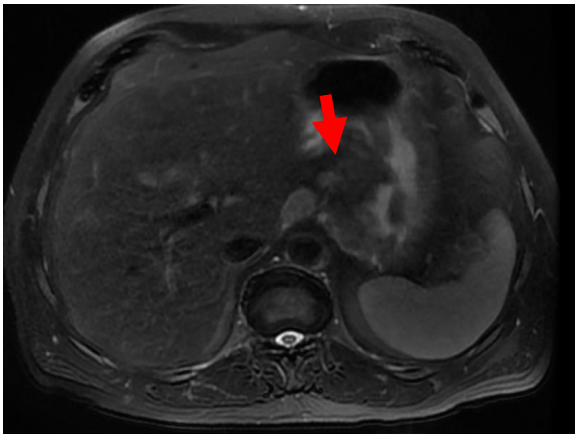


Image 5
MR demonstrating a tumour in the lesser curve (and multiple liver metastases)

A. DWI – Showing some restriction of the tumour, appearing bright
B. T2 fat sat – water in the stomach appears white, contrasting to dark grey tumour
a. Delayed contrast

Image 6





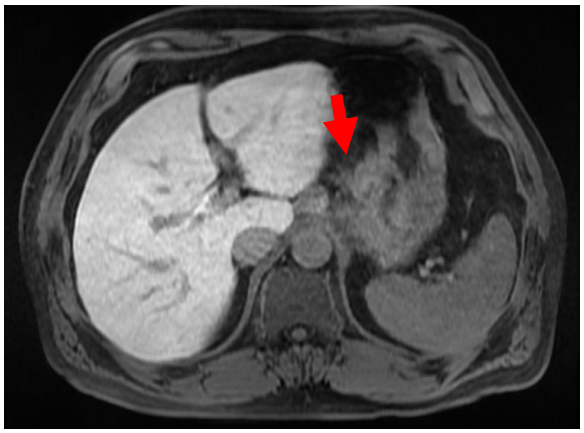


Image 6
MR demonstrating a tumour of the GOJ extending into stomach.

A. DWI – Showing some restriction of the tumour
B. T2 fat sat
C. Delayed contrast

MRI atlas depicting gastric tumour (with comparative CT images)

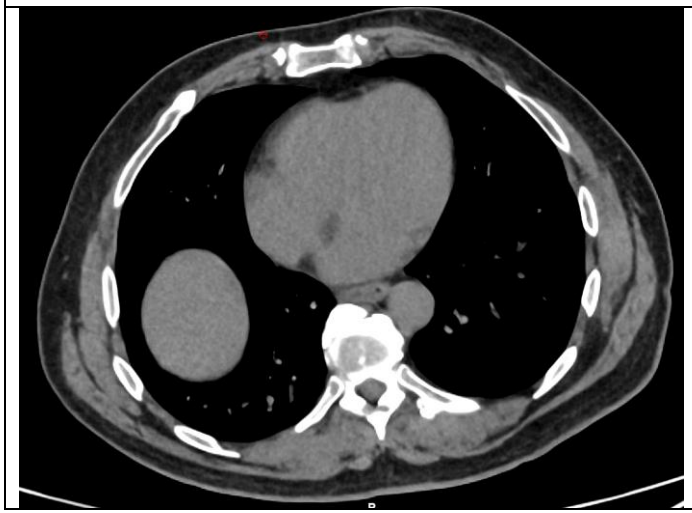
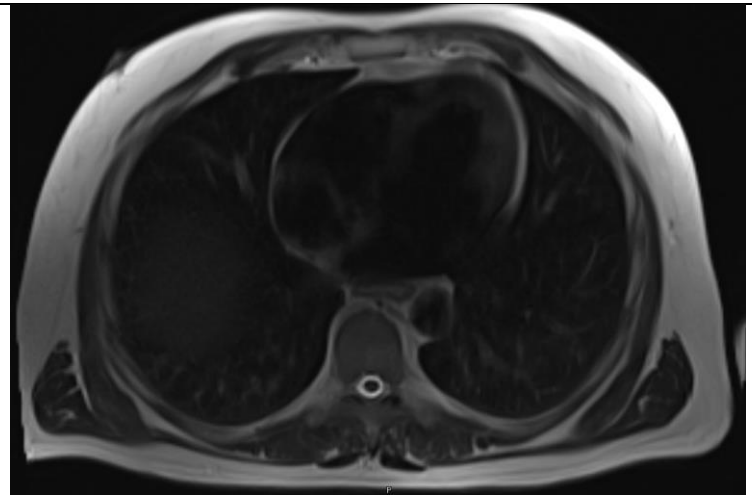
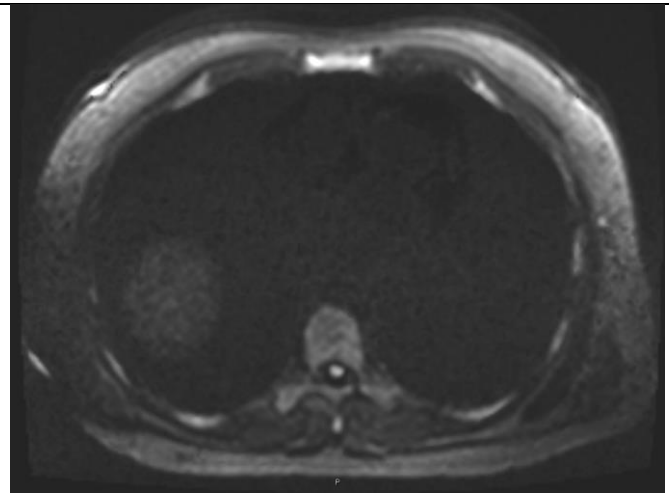
Atlas depicting a type III gastro-oesophageal tumour shown on CT (delineated), and MRI (T2) MRI (DWI – diffusion weighted) imaging. Images shown cranially to caudally.

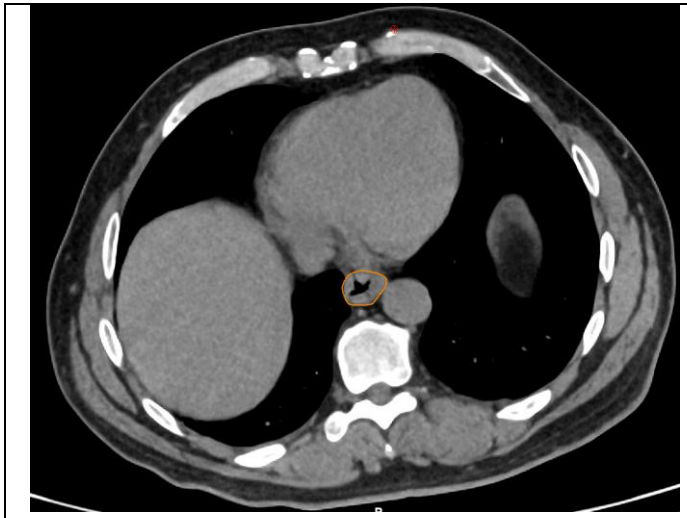
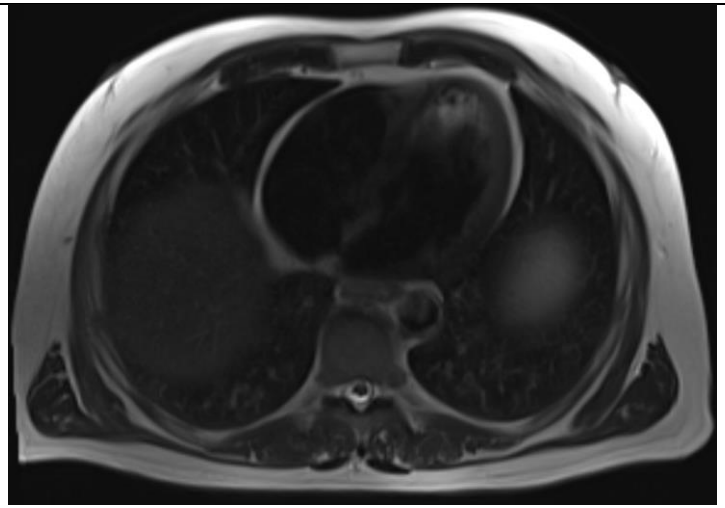
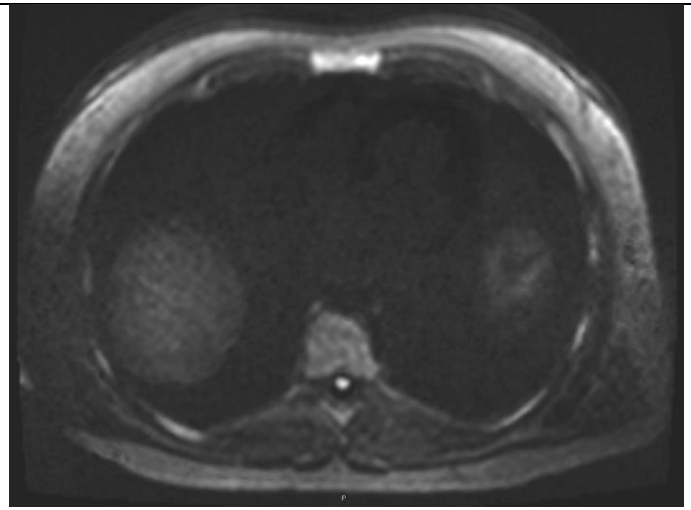
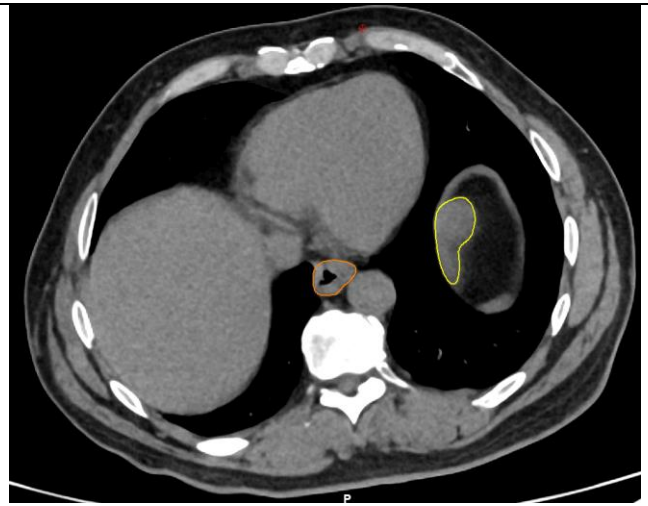
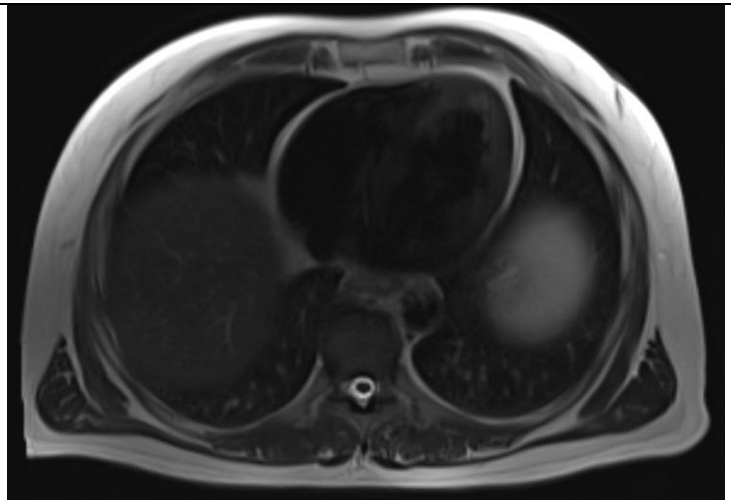
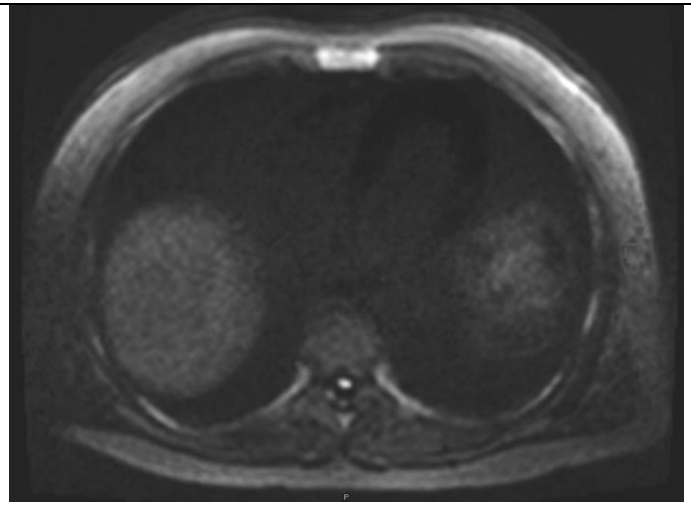
Tumour is staged as T4N1 and extends from distal oesophagus into the fundus, with the majority of the tumour centered on the gastric cardia, measuring approximately 6 x 4 cm. No overt infiltration through the gastric wall seen. There are suspicious small nodes in the left gastric position just beneath the tumour, just antero-superior to the aortic hiatus, but no confirmed coeliac lymphadenopathy.

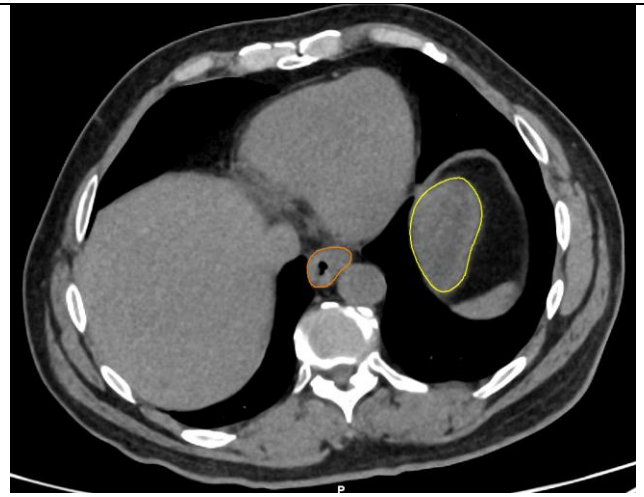
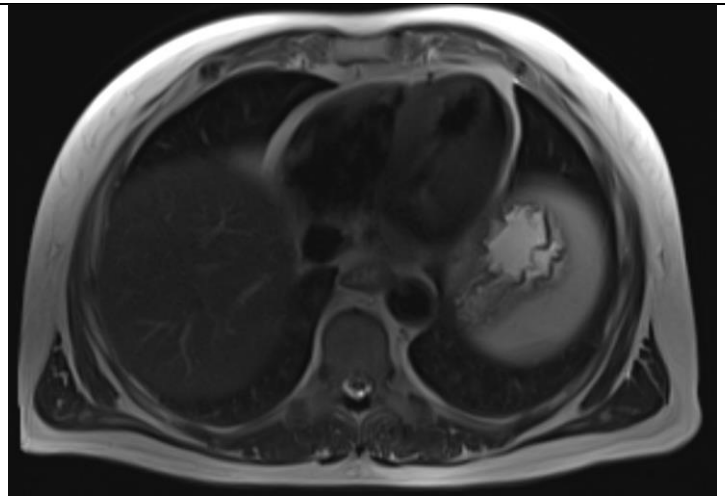
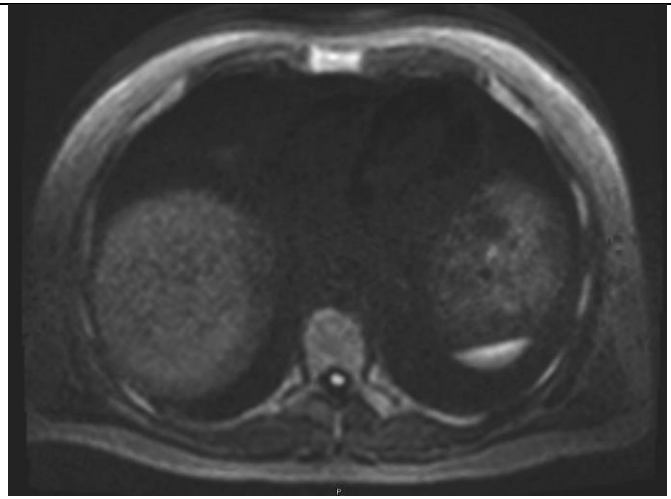
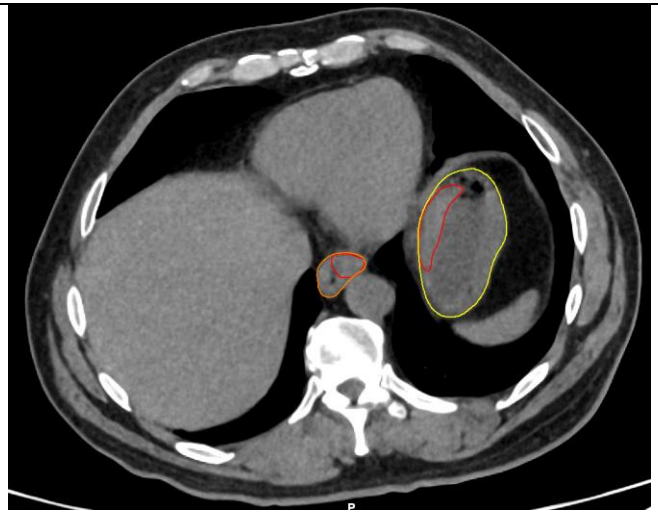
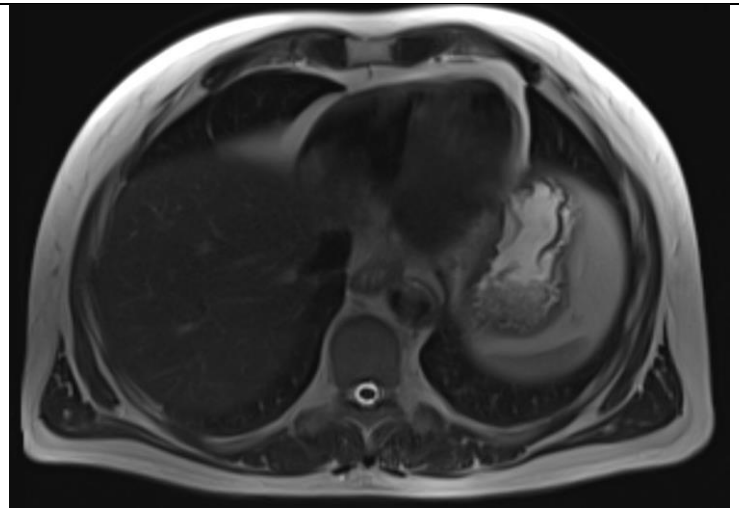
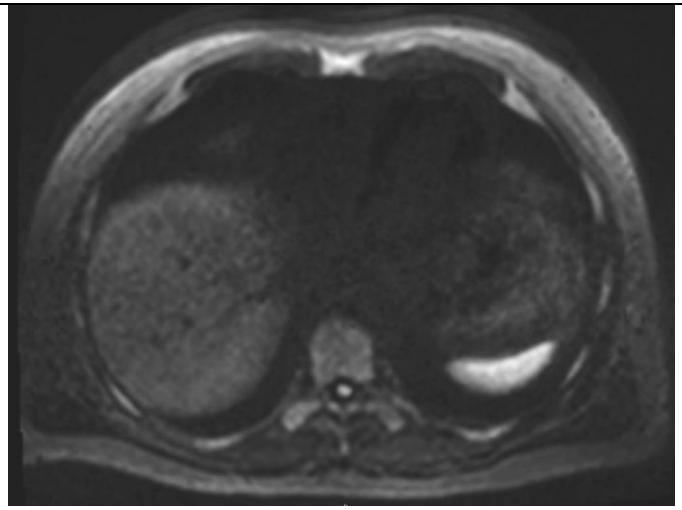
On the CT image set structures as delineated as follows: Orange = Oesophagus. Yellow = CTVstomach. Red = GTVp. Green = Duodenum.

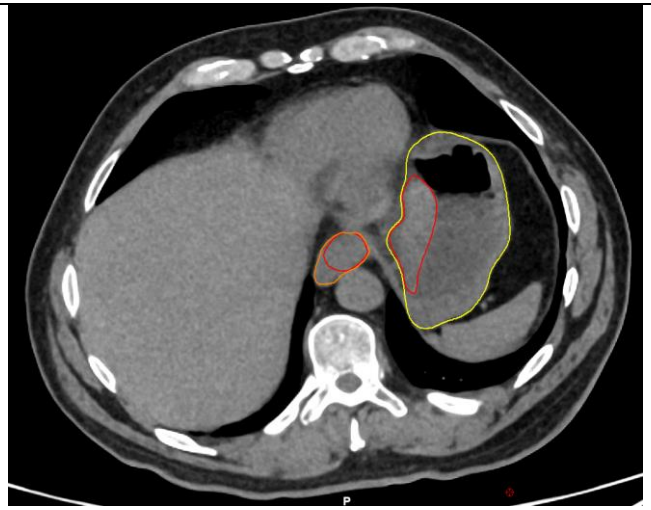
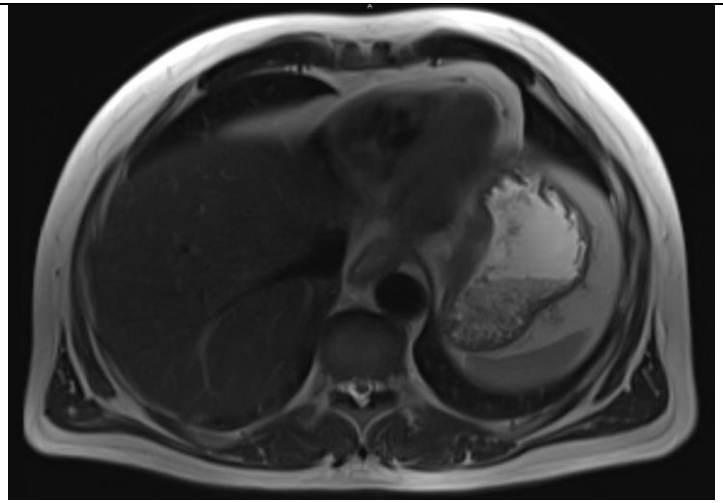
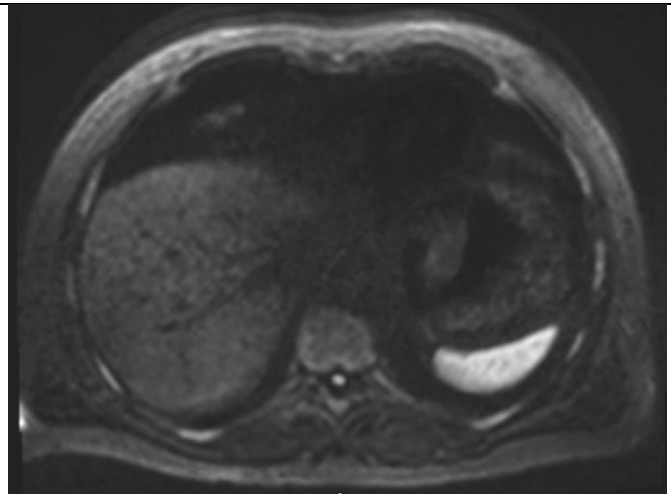
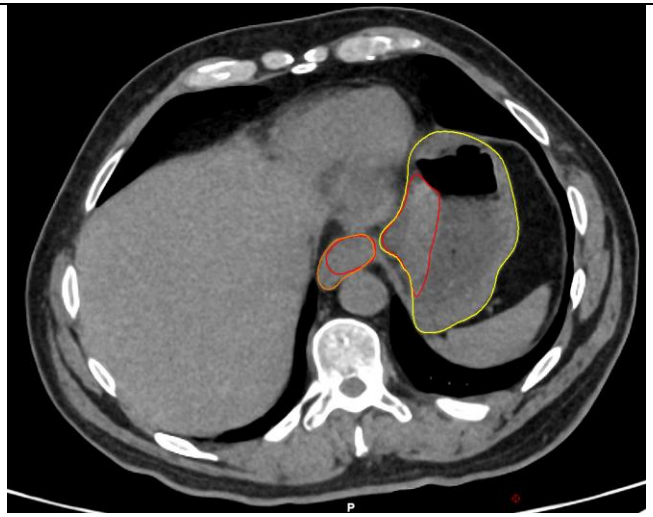
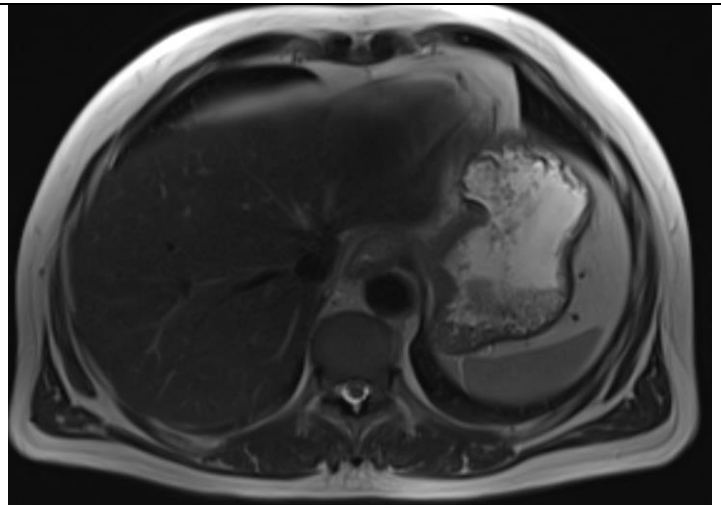
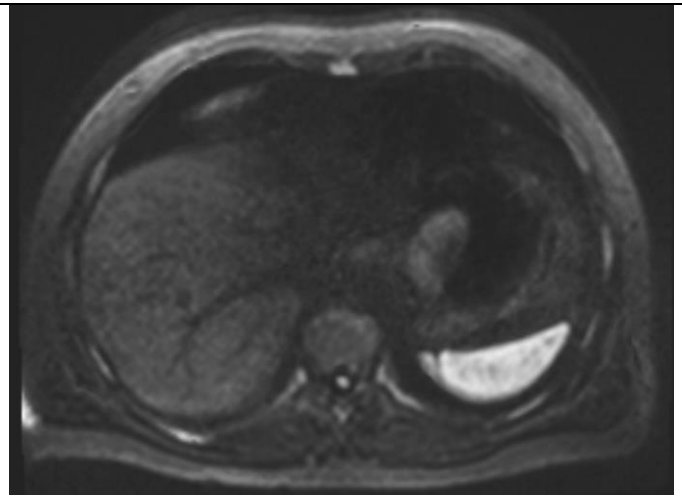
Please note:

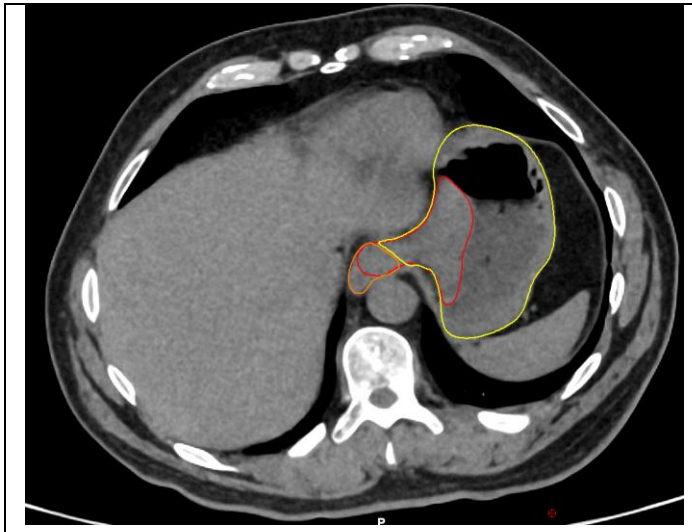
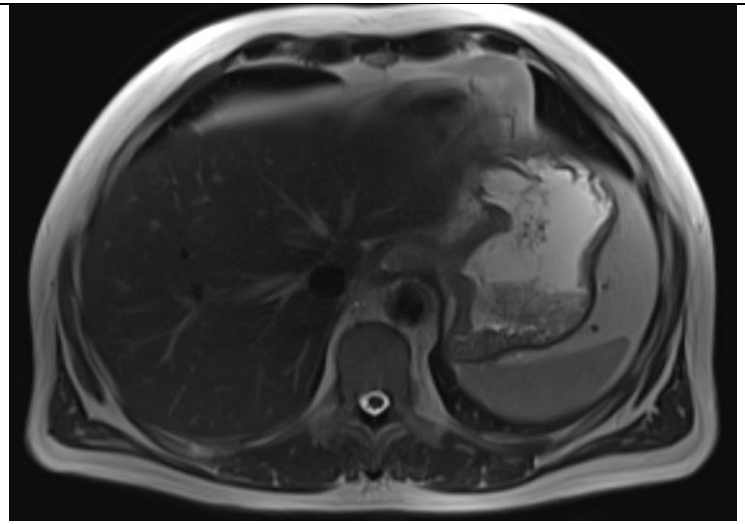
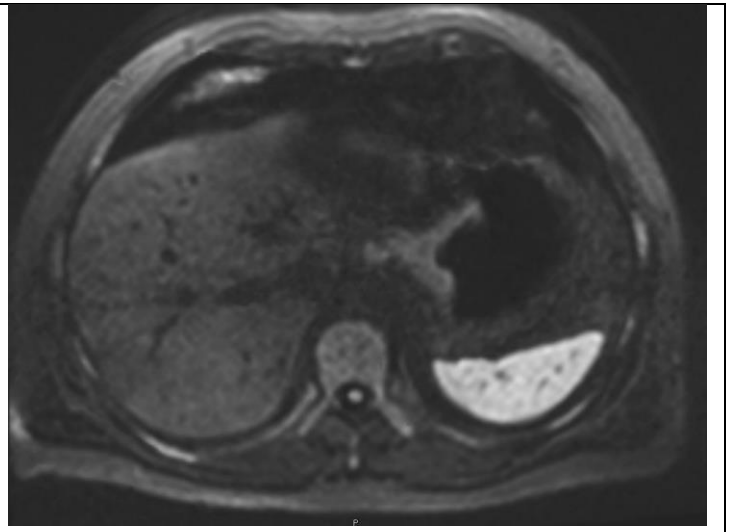
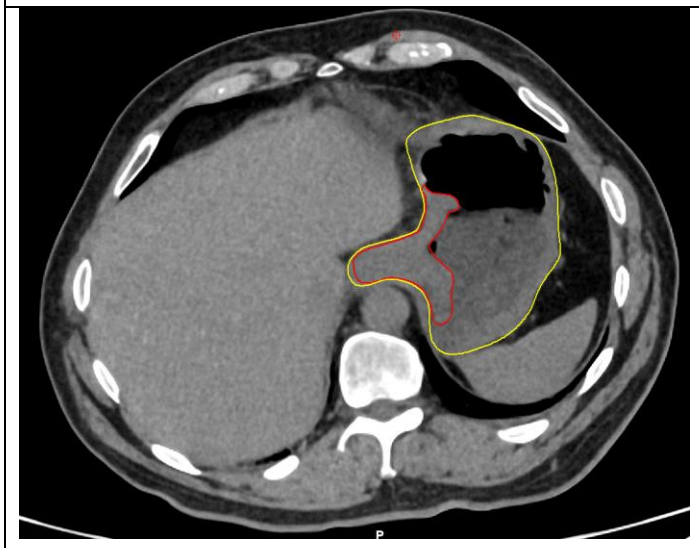
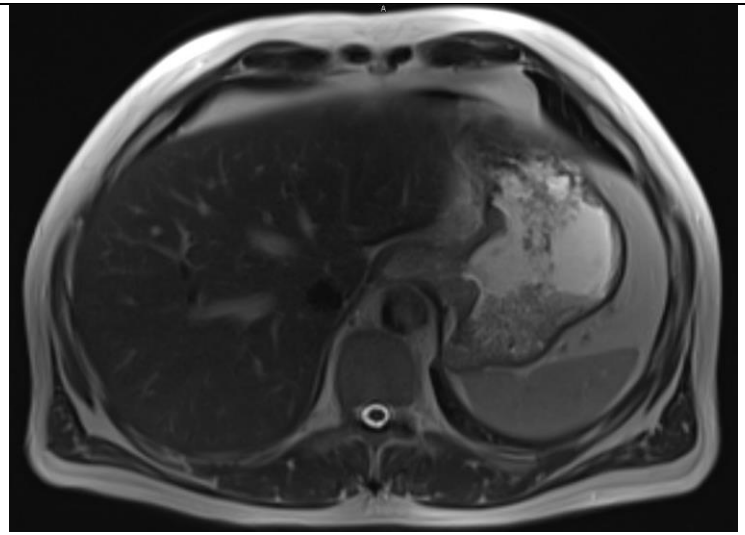
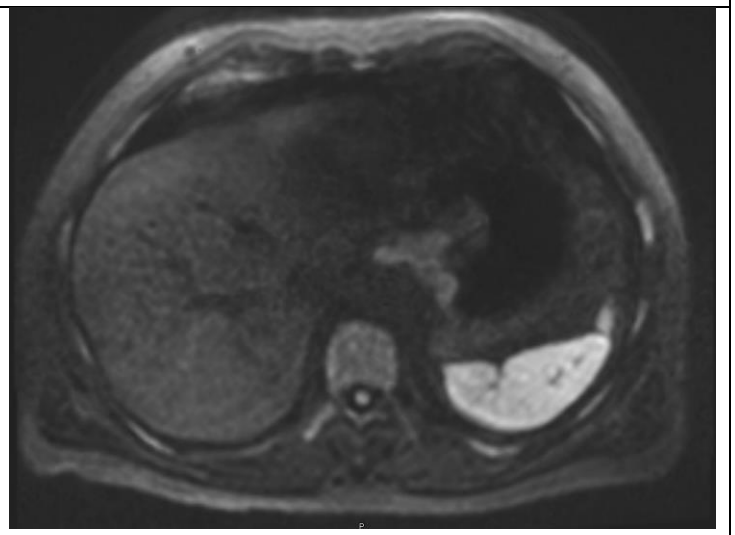
1. Oesophagus and duodenum do not need to contoured for this study, but are shown here to demonstrate anatomical boundaries.
2. The stomach is more distended in the CT images than MRI, explaining the difference in size and position of the stomach between the two sets of images.
3. In this example, left gastric lymphadenopathy is in contact with the gastric wall (i.e. continuous with tumour) and so has been included in GTVp.

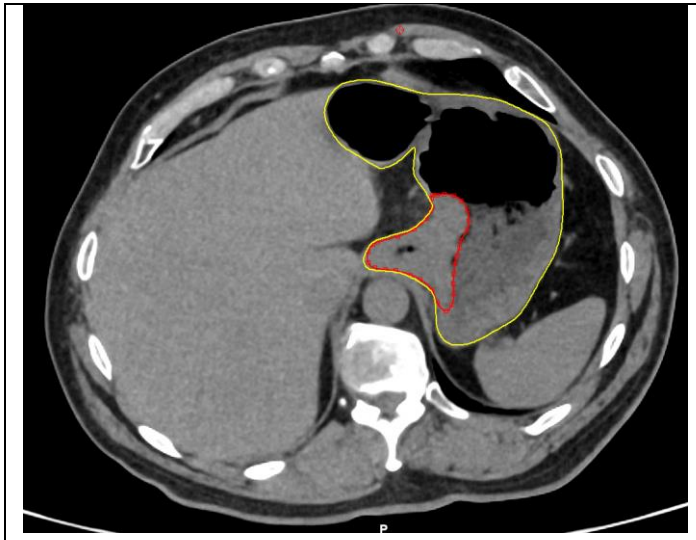
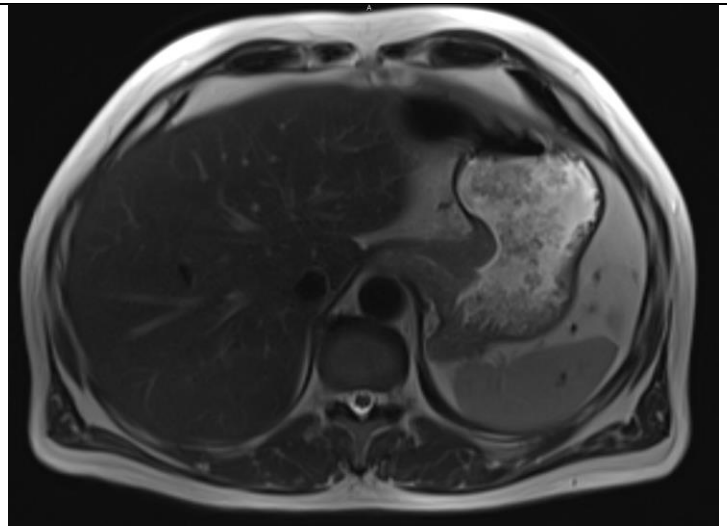
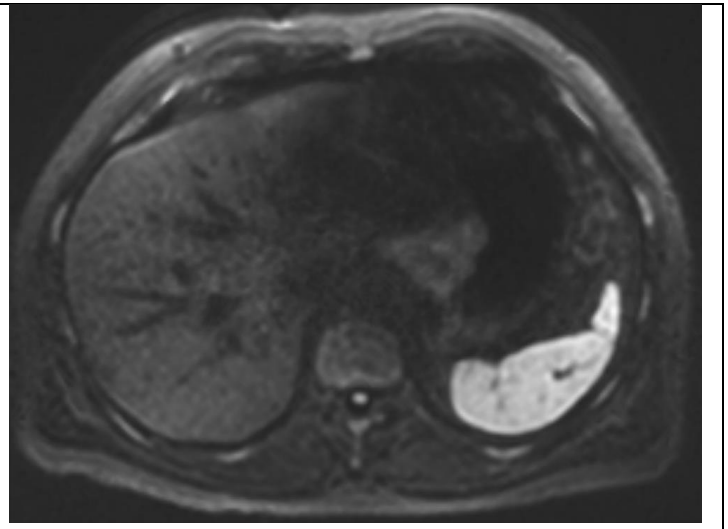
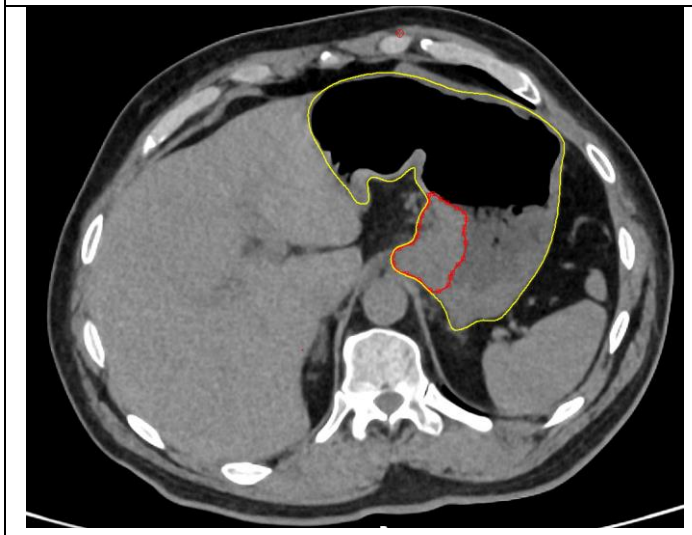
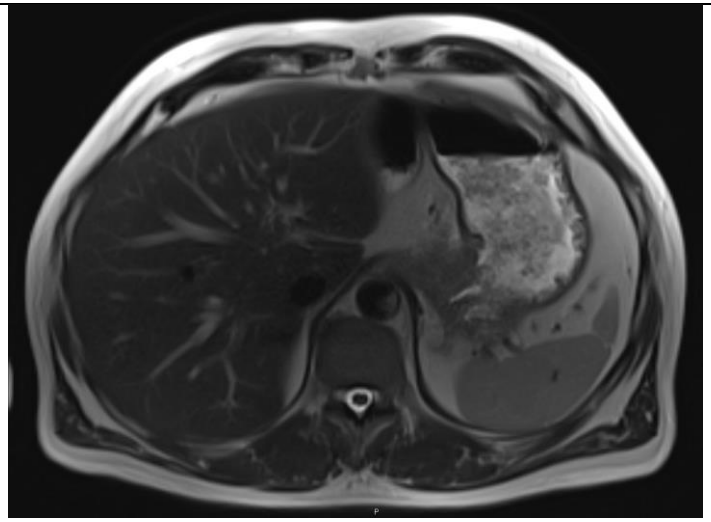
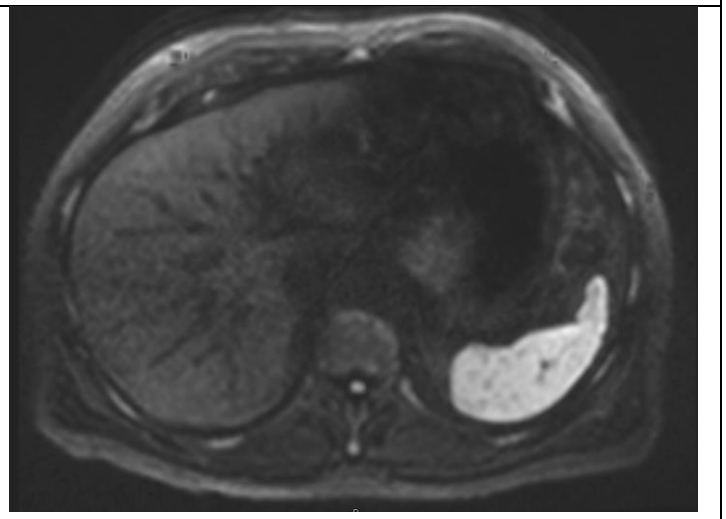
CT	MRI (T2)	MRI (DWI)
		

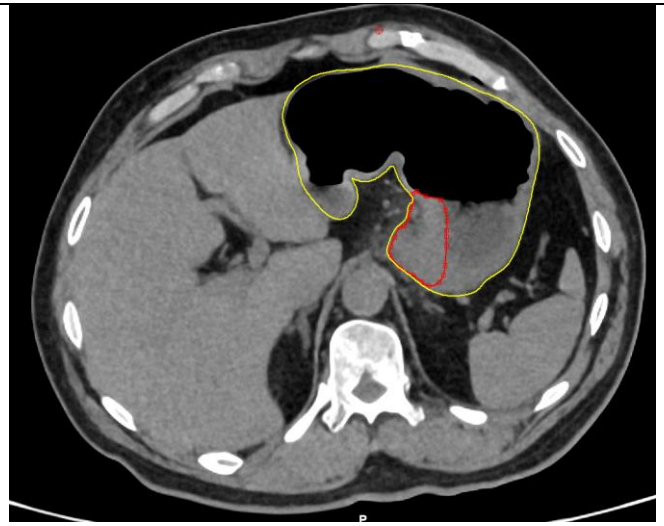
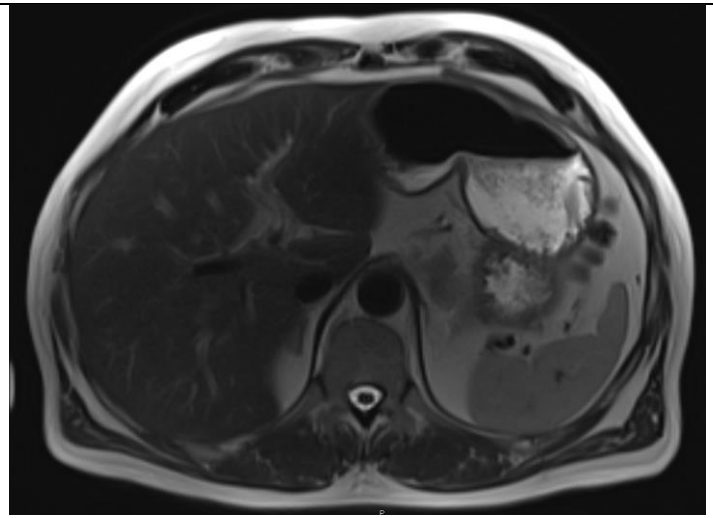
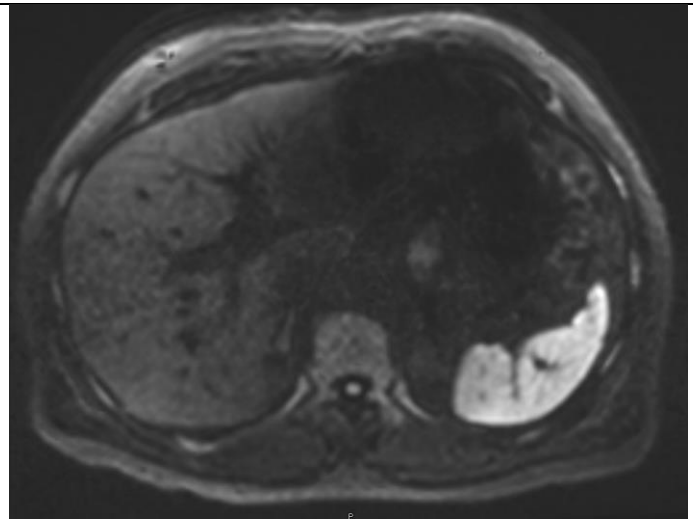
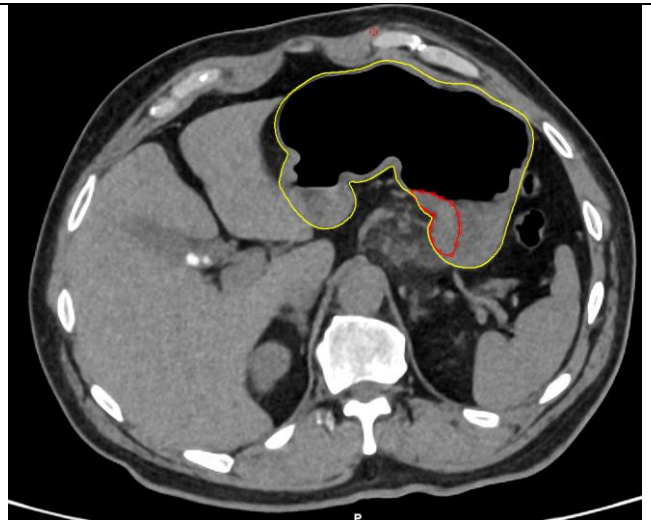
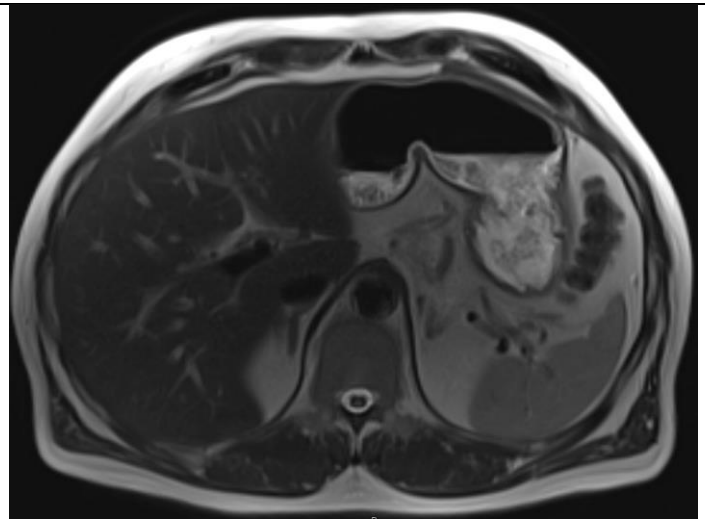
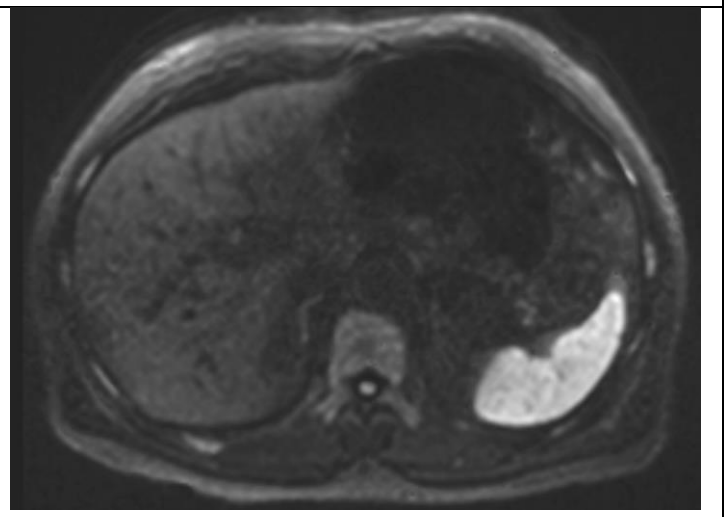







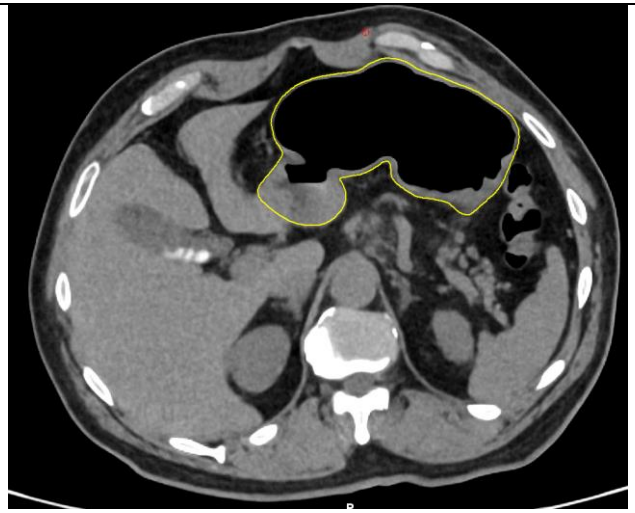
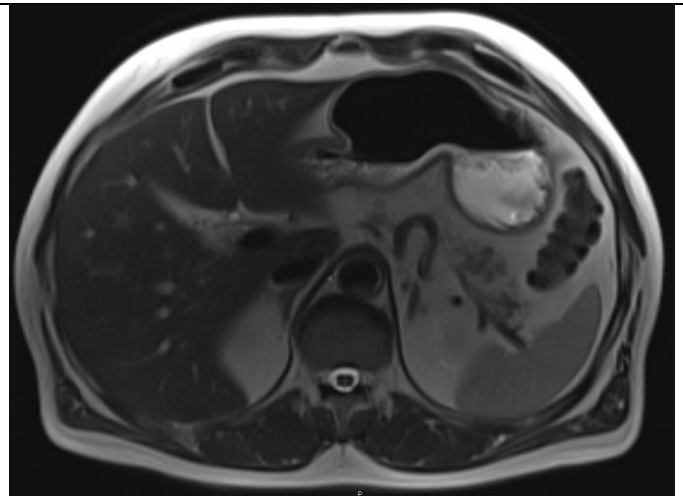
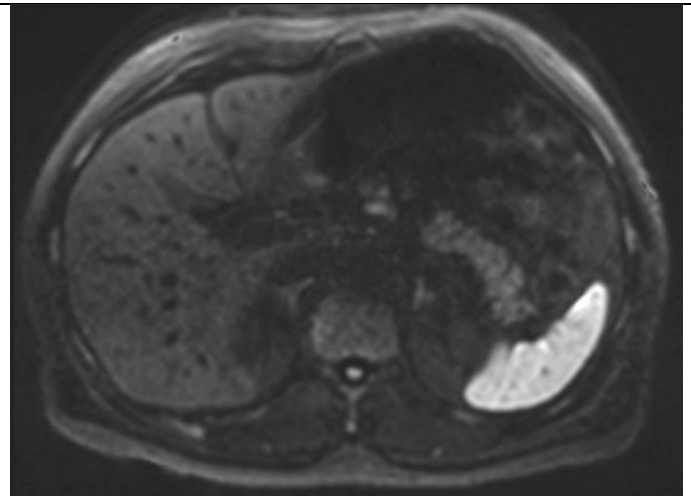
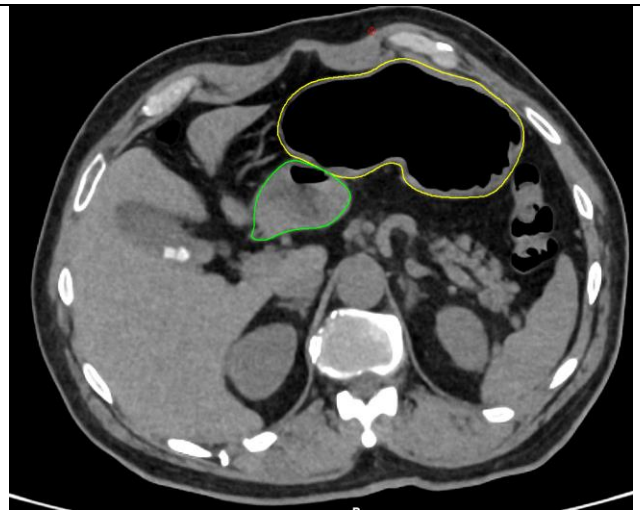
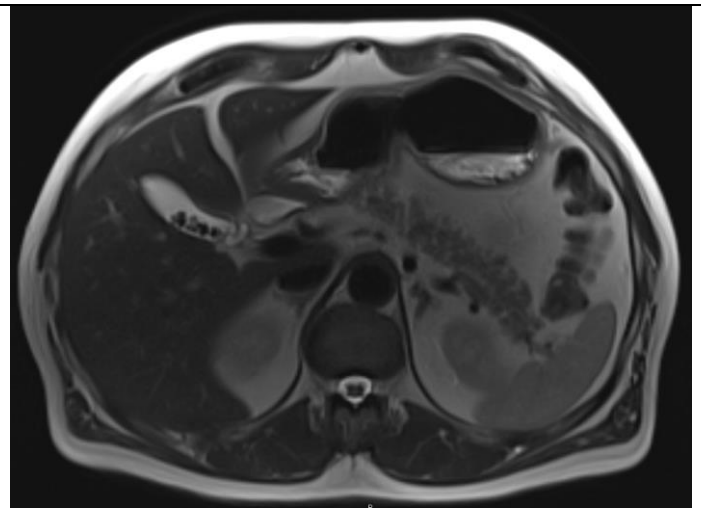
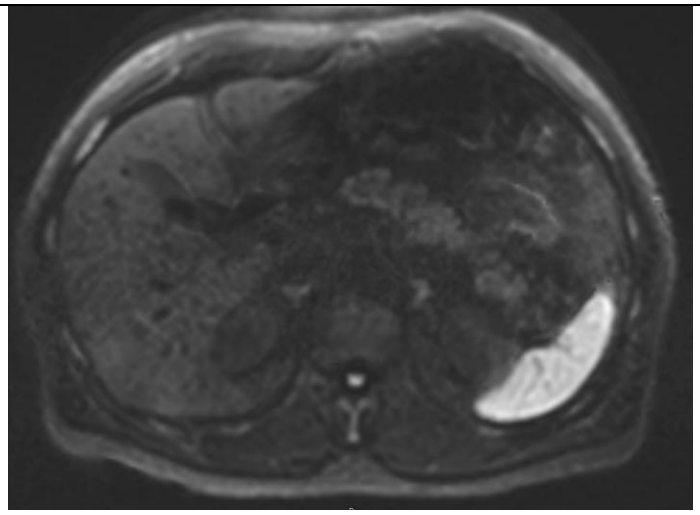







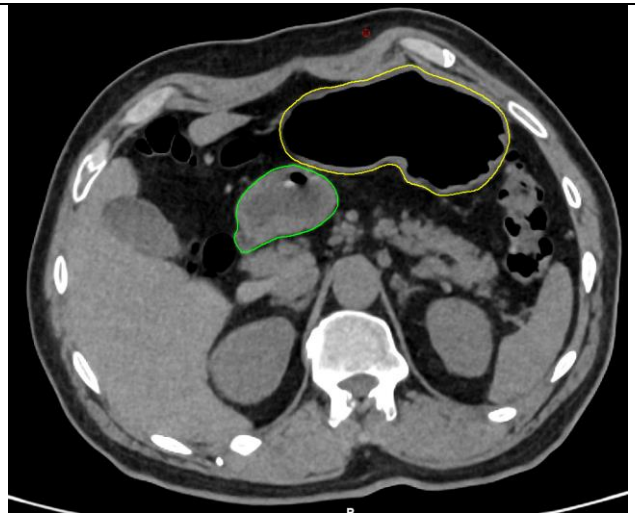
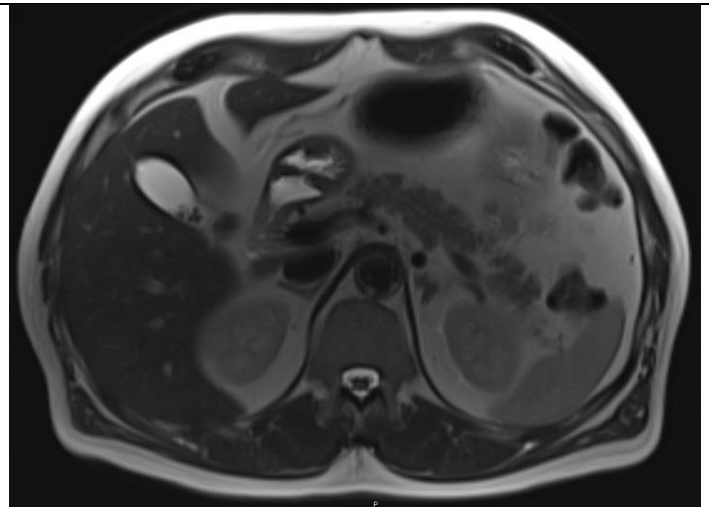
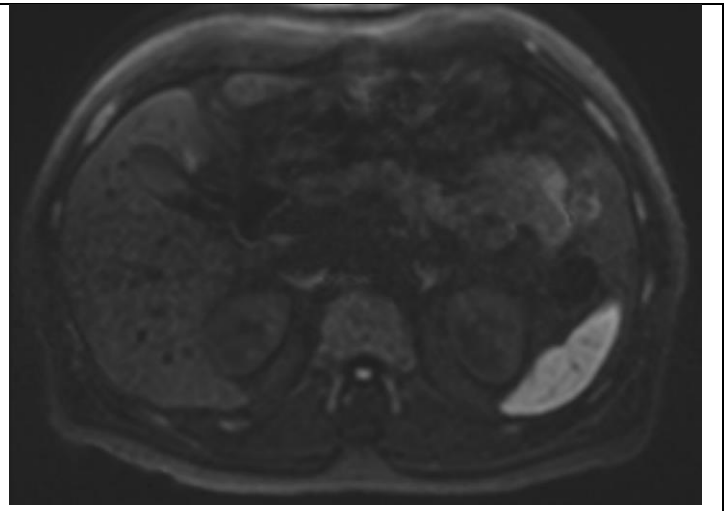
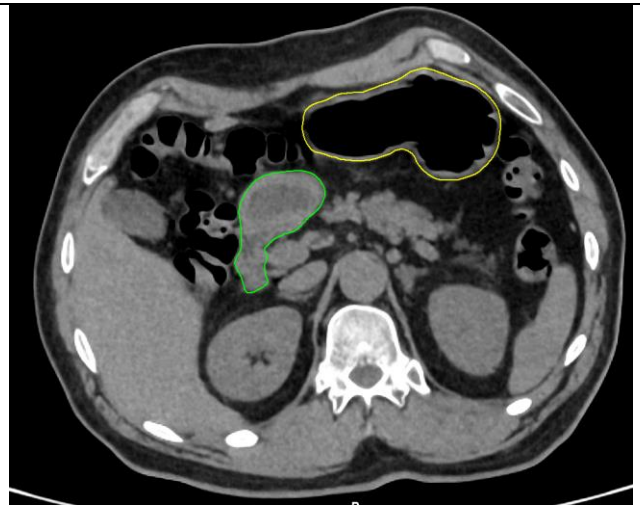
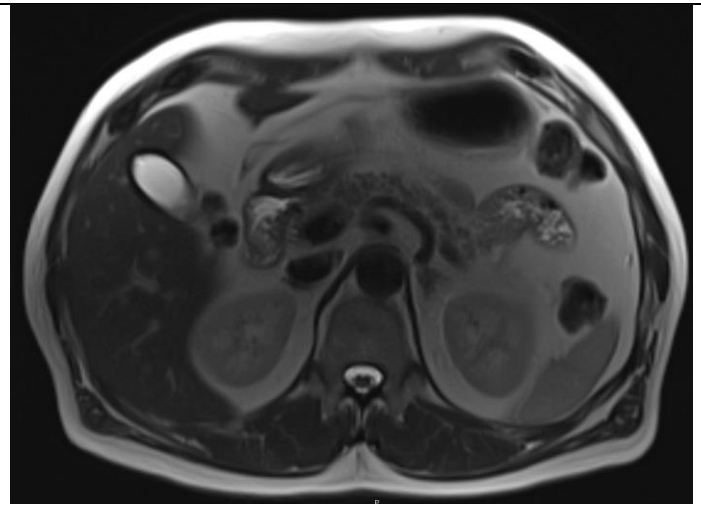
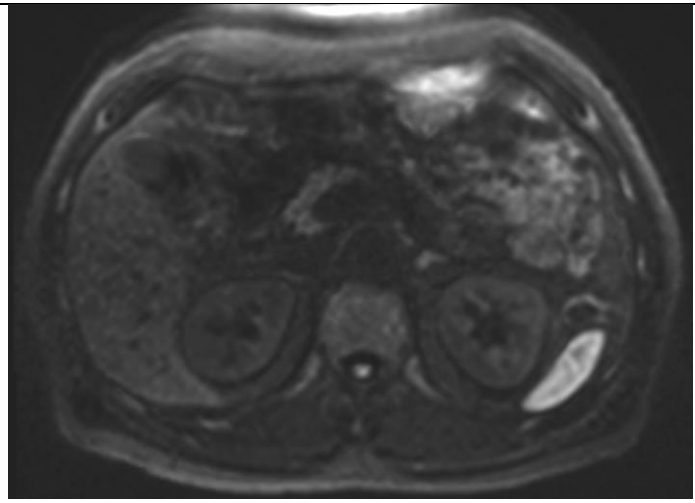







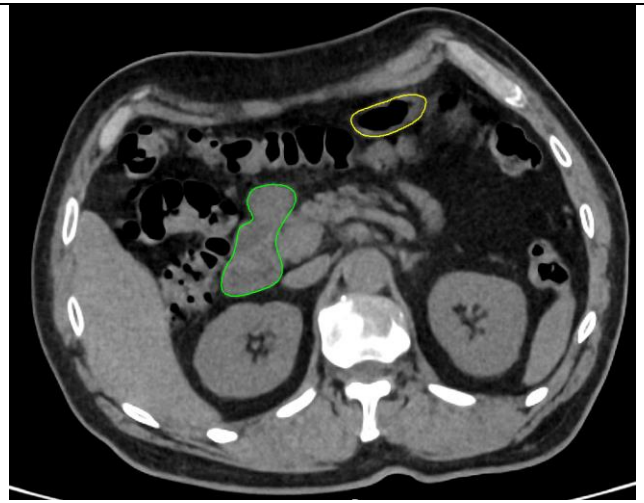
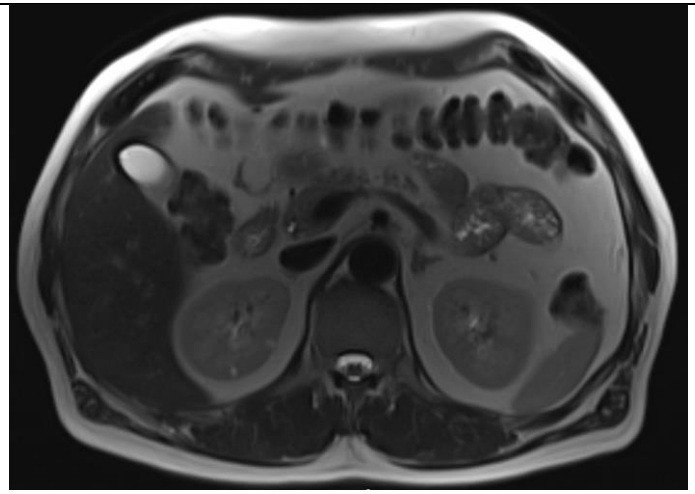
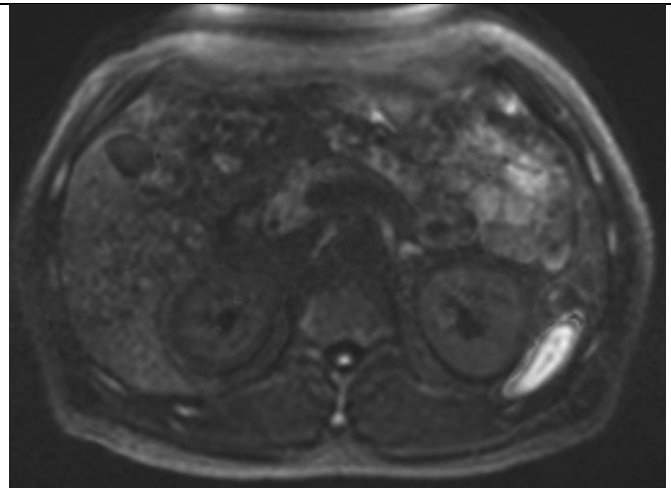
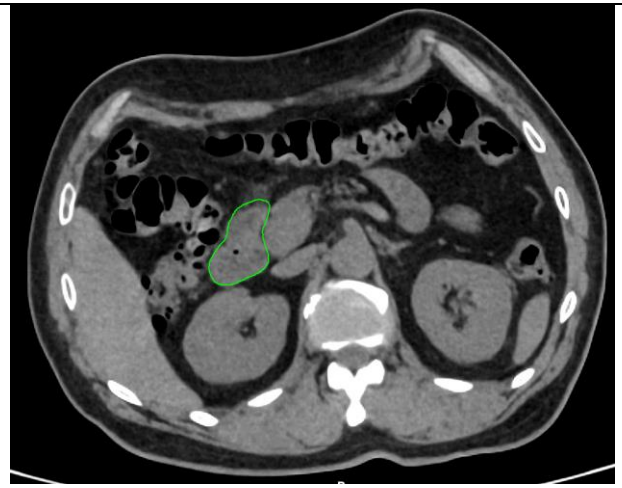
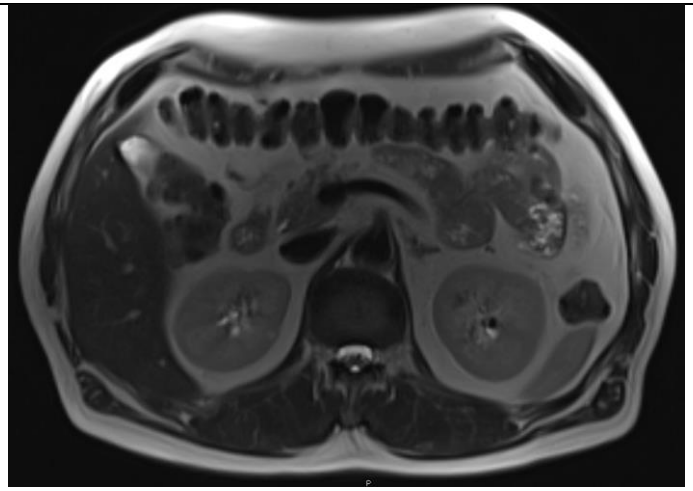
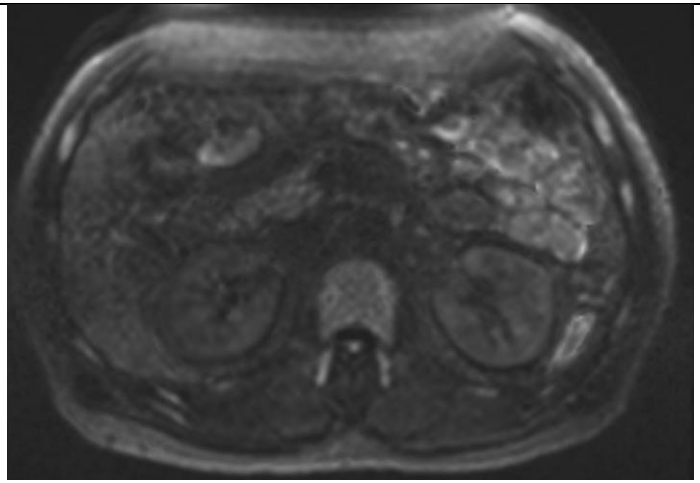







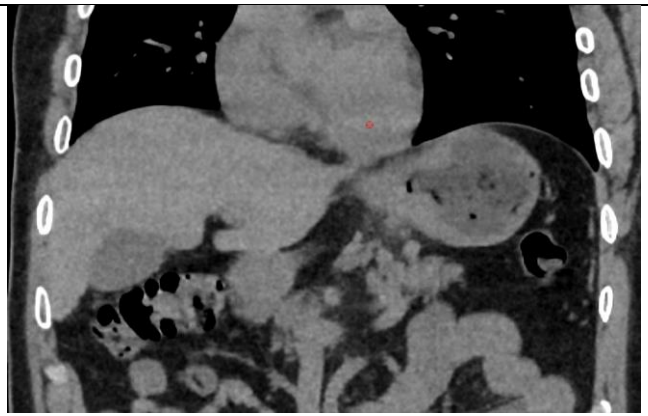
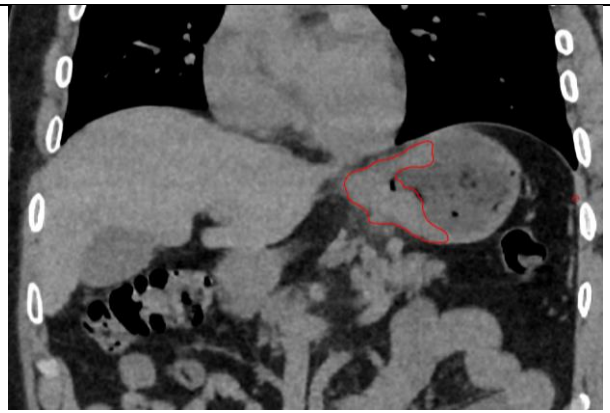
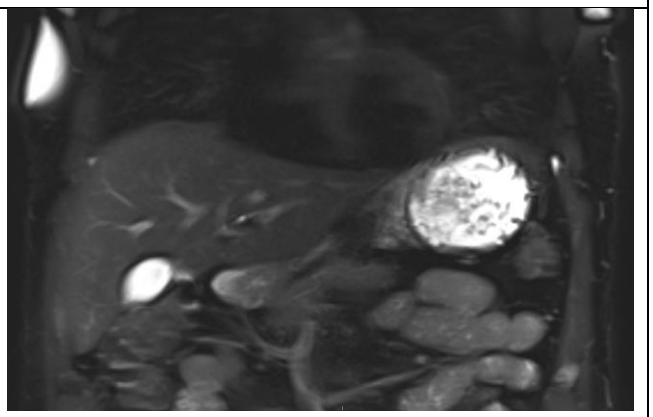
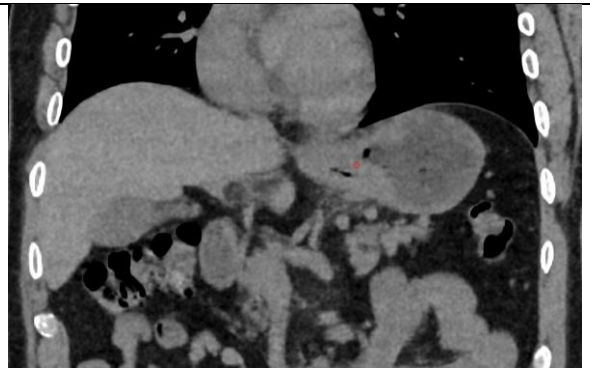
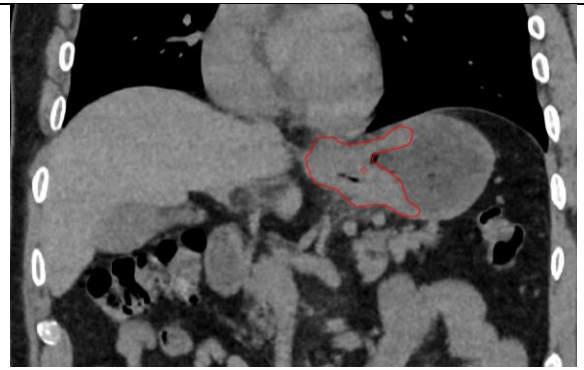
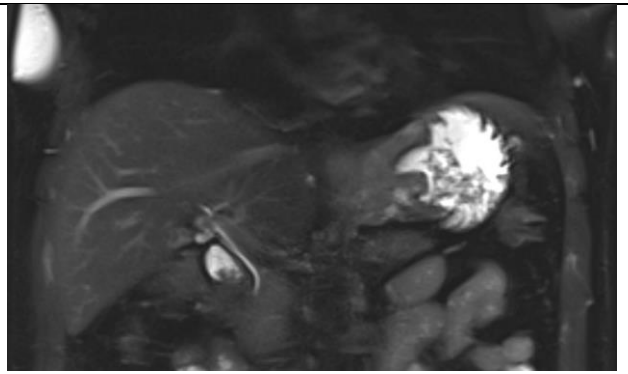







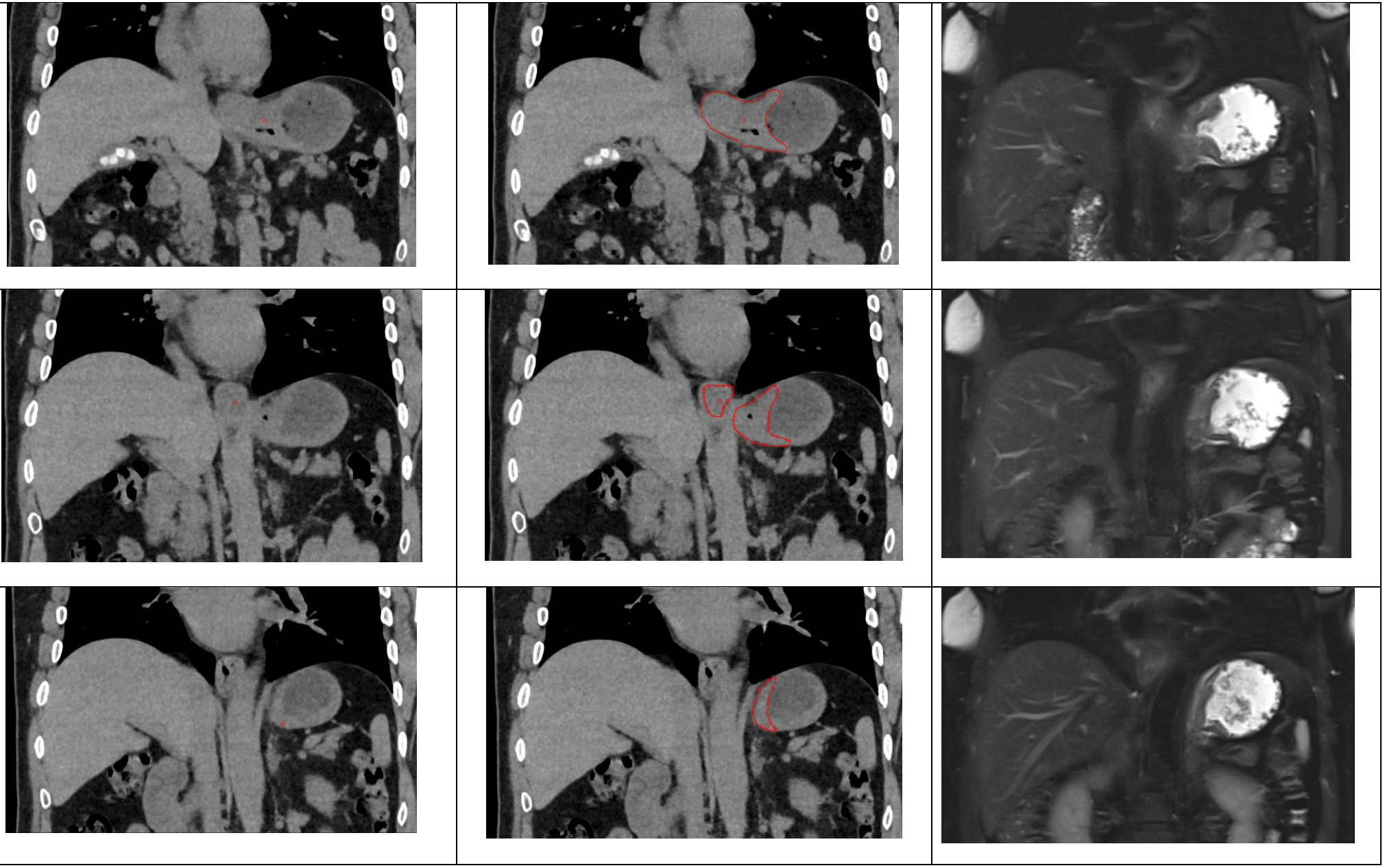







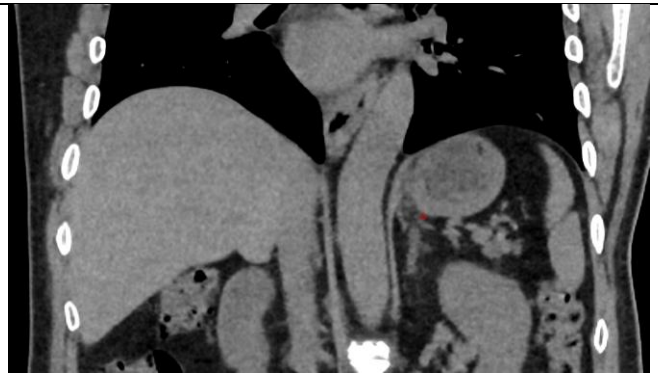
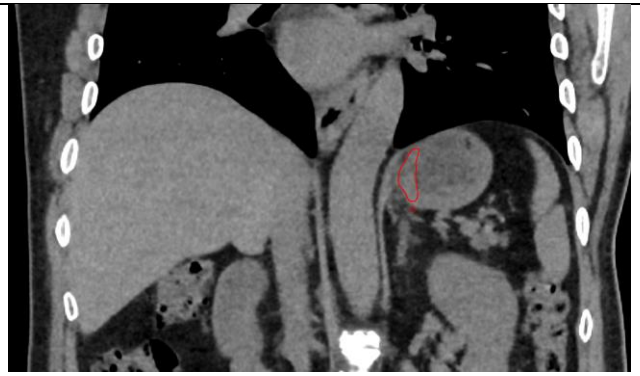
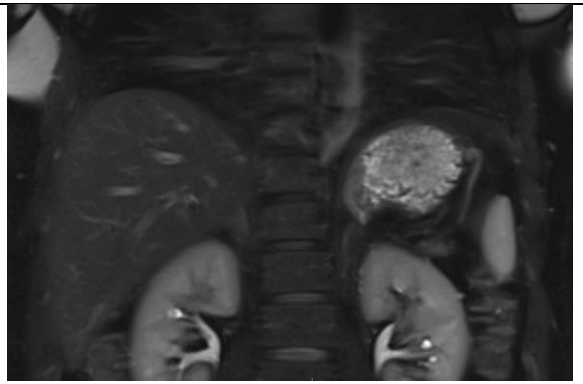
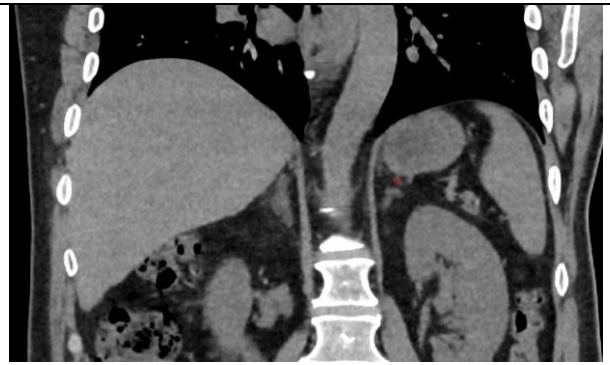
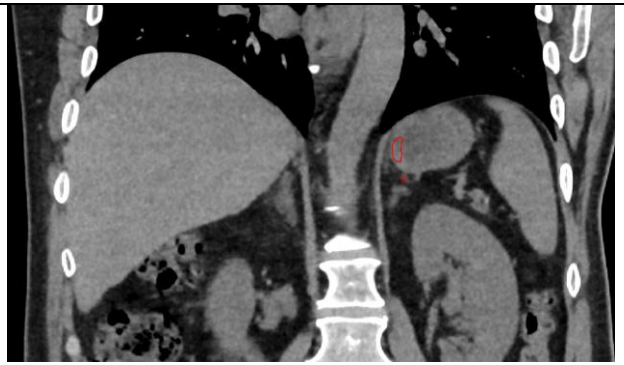
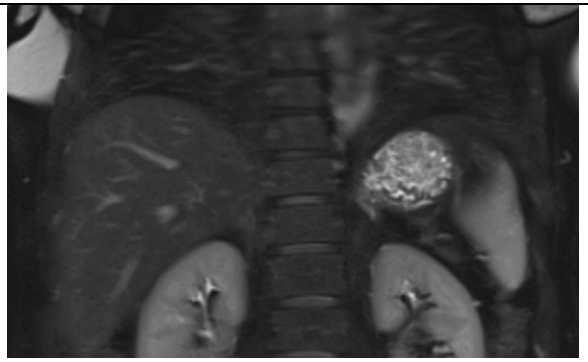







Coronal Images (CT, CT with GTVp shown, T2 weighted fat saturated MRI)

CT	CT (with GTVp delineated)	MRI (T2 fat sat)
		
		



Appendix 5.3 – Participant Information Sheet

PARTICIPANT INFORMATION SHEET

Developing the role of radiotherapy for inoperable gastric cancer: A Study to Evaluate the Effect of CT Versus MRI-Based Tumour Volume Delineation on Interobserver Variability in Gastric Cancer

What is the purpose of this study?

We are conducting research on the role of radiotherapy for inoperable, non-metastatic gastric cancer. As well as trying to establish the current evidence for definitive gastric radiotherapy, part of this research includes developing optimal radiotherapy technique for gastric cancer and designing a gastric radiotherapy protocol.

In order to develop a definitive gastric radiotherapy protocol, we are exploring the optimal approach to delineation of structures, particularly GTV (gross tumour volume) and CTV stomach (clinical target volume, in this case the whole stomach), including imaging modalities that will maximise accuracy of delineation.

The aims of this study are:

1. To explore interobserver variability in tumour volume delineation (TVD) of gross tumour volume of primary gastric tumours (GTVp) and whole stomach volume (CTVstomach) using CT alone, versus CT plus MRI.
2. To gather clinician feedback regarding ease of delineation and whether the addition of MRI improves ease/ time to delineate tumour volumes for gastric cancer.
3. To identify specific areas of variability/ error to inform further gastric radiotherapy protocol development.

You will initially be asked to complete one test case, for which you will delineate 2 volumes: GTVp (+/- GTVn if applicable) and CTVstomach, using CT alone. On completion, you will repeat the exercise, delineating the same volumes using MRI reports and imaging sequences.

You will be asked if you wish to complete further test cases, if your time permits. We ask you to complete a minimum of 1, and up to a maximum of 4 cases (all completely voluntary).

Who is carrying out the service evaluation?

The data are being collected by Dr Amy Case, a clinical oncology trainee who is currently undertaking an MD at Swansea University Medical School. The service evaluation has been approved by Swansea University Medical School Research Ethics Committee.

What happens if I agree to take part?

If you agree to take part, the radiotherapy test case(s) will be transferred to your radiotherapy planning software locally (via established transfer pathways used for radiotherapy trials quality assurance, RTQA).

You will be sent a set of delineation instructions including a list of structures that you are required to delineate, image atlas, and clinical information about the case. You will then save the case(s) and return them to our centre electronically (you will be informed how to do this).You will complete tumour volume delineation once using CT alone, and then once using both CT and MRI.

Your volumes will be saved on planning software held by Swansea Bay UHB. Before any data is analysed, your outlines will be anonymised.

We will also ask for your previous RT planning experience and for feedback on your experience outlining the case(s). This will also be anonymised prior to analysis.

With regards to your personal information, names and email addresses will be kept on a separate database (not linked to your responses to questions about prior experience or feedback regarding delineation experience), will not be shared with other parties, and will be stored on a password-protected computer file on a secure NHS Laptop which will be deleted on completion of this MD research.

Please note that once your submitted responses are anonymised, it may not be possible to identify and remove your data at a later date, should you decide to withdraw from the study. We can however remove your name and email address from the database at any time should you wish.

What will happen to the information I provide?

An analysis of the information will form part of our report at the end of the study and may be presented to interested parties and published in scientific journals and related media. Note that delineation and qualitative feedback data presented in any reports or publications will be anonymised and unidentifiable. However, your participation will be acknowledged in any subsequent publication, though you can opt out of being named should you wish.

Are there any risks associated with taking part?

The service evaluation has been approved by Swansea University Medical School Research Ethics Committee. There are no significant risks associated with participation.

Consent

By taking part in the study and submitting volumes/ qualitative responses, your consent is implied. As described below, participation is entirely voluntary – you do not have to take part.

Is participation voluntary and what if I wish to later withdraw?

Your participation is entirely voluntary – you do not have to participate if you do not want to. If you decide to participate, but later wish to withdraw from the study, then you are free to withdraw at any time, without giving a reason and without penalty. However, once your responses are anonymised, it may not be possible to remove them from the data analysis.

If you wish to withdraw from the study, then please contact Dr Amy Case (see contact details below).

How long will your information be held?

We will hold any personal data (i.e. any email addresses voluntarily provided) until the successful completion of the MD, at which time the database will be destroyed.

What if I have other questions?

If you have further questions about this study, please do not hesitate to contact us:

Dr Amy Case

Swansea University Medical School

[redacted]

[redacted]

Prof Hayley Hutchings

Swansea University Medical School

[redacted]

Appendix 5.4 – Clinical Information for Test Cases

A STUDY TO EVALUATE THE EFFECT OF CT VERSUS MRI-BASED TUMOUR VOLUME DELINEATION ON INTEROBSERVER VARIABILITY IN GASTRIC CANCER

CLINICAL INFORMATION FOR TEST CASE A

Test Case A (Gastric_IOVstudy_case_A)

65-year-old man

CT thorax, abdomen and pelvis report:

The stomach contains oral contrast, which passes through to the duodenum.

Bulky, partially necrotic mass centred on the pylorus. Large extra-gastric component extending anteriorly with direct contact of the liver and gallbladder and in close proximity of the anterior abdominal wall. The mass measures approximately 7 cm. There is also posterior extension toward the pancreatic head.

Several anterior and posterior peri-tumoural lymph node metastases are demonstrated. The largest is located between the tumour and the pancreatic head.

Solitary 3 cm deposit in the right hepatic lobe consistent with a metastasis.

Other solid abdominal organs appear unremarkable.
No para-aortic or iliac lymphadenopathy.
Bladder's diverticulum.
No bony lesion.

Conclusion: Large pyloric tumour with extra-gastric extension, lymph node and liver metastases.

NB – Please disregard the liver deposit for the purpose of this delineation exercise.

Endoscopy:

Large tumour occupying most of the pylorus, not causing an obstruction. Likely malignant. Biopsies were taken from the lesion.

MDT Staging:

TNM staging T4b N2 M1 (liver)

A STUDY TO EVALUATE THE EFFECT OF CT VERSUS MRI-BASED TUMOUR VOLUME DELINEATION ON INTEROBSERVER VARIABILITY IN GASTRIC CANCER

CLINICAL INFORMATION FOR TEST CASE

Test Case C (Gastric_IOVstudy_case_C)

75-year-old female

CT thorax, abdomen and pelvis report:

Large, solid, enhancing gastric tumour extending along lesser curve of the stomach to the antrum where it contacts the angularis incisura. The mass is predominately intra-luminal but extra-gastric extension is evident.

Tumour is in direct contact with the left lobe of the liver and is concerning for invasion. The mass is also in close proximity to the pancreatic parenchyma and left adrenal gland but fat planes are thought to be present between these structures.

Peri-tumoural lymph nodes are small but remain suspicious for involvement.

A low-density lesion in segment 7 of the liver is indeterminate and, given the volume of tumour, MRI liver is recommended.

No bone deposits.

Conclusion:

Large gastric tumour in direct contact with liver and suspicion of lymph node metastases. Indeterminate liver lesion – MRI recommended.

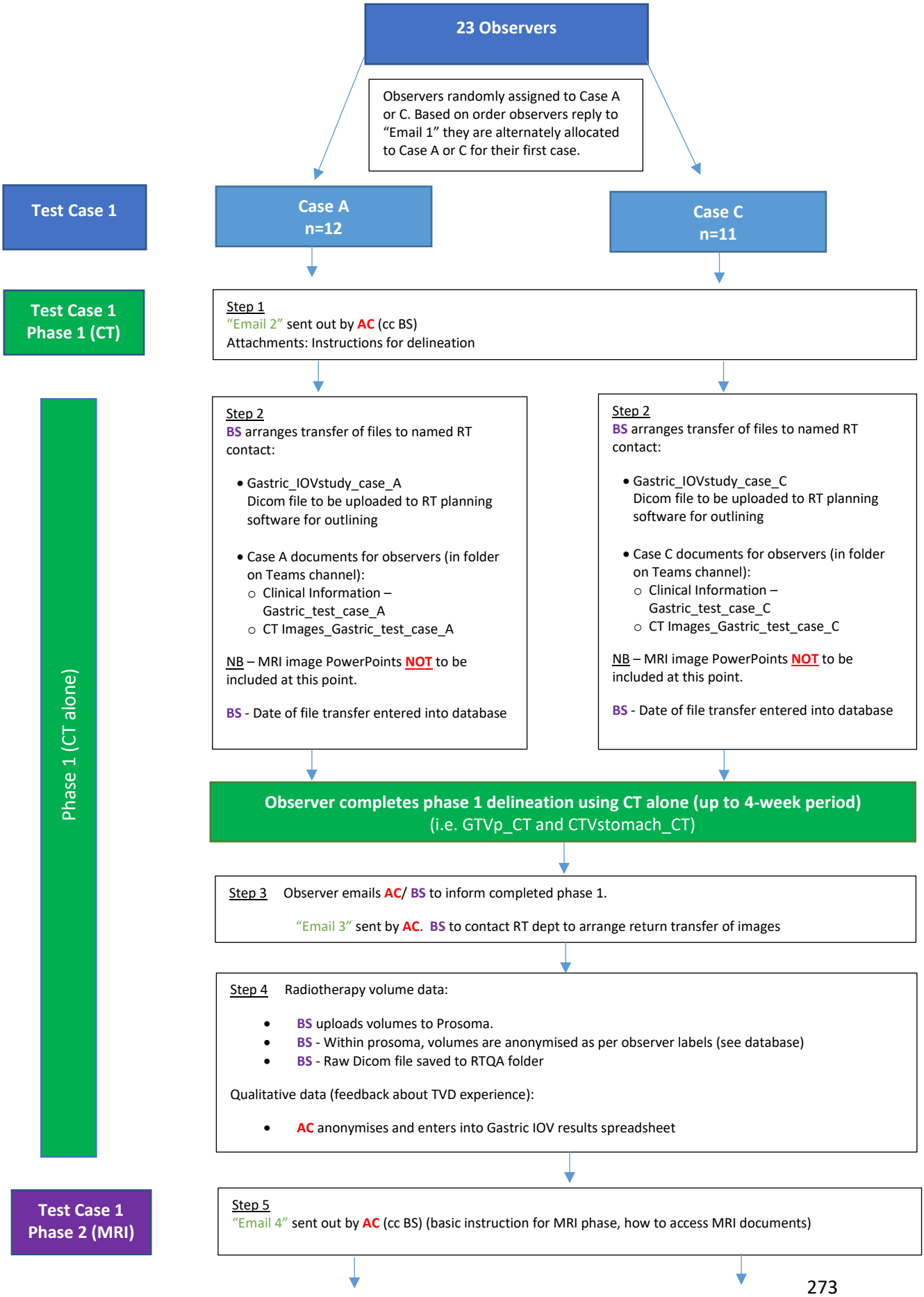
Endoscopy:

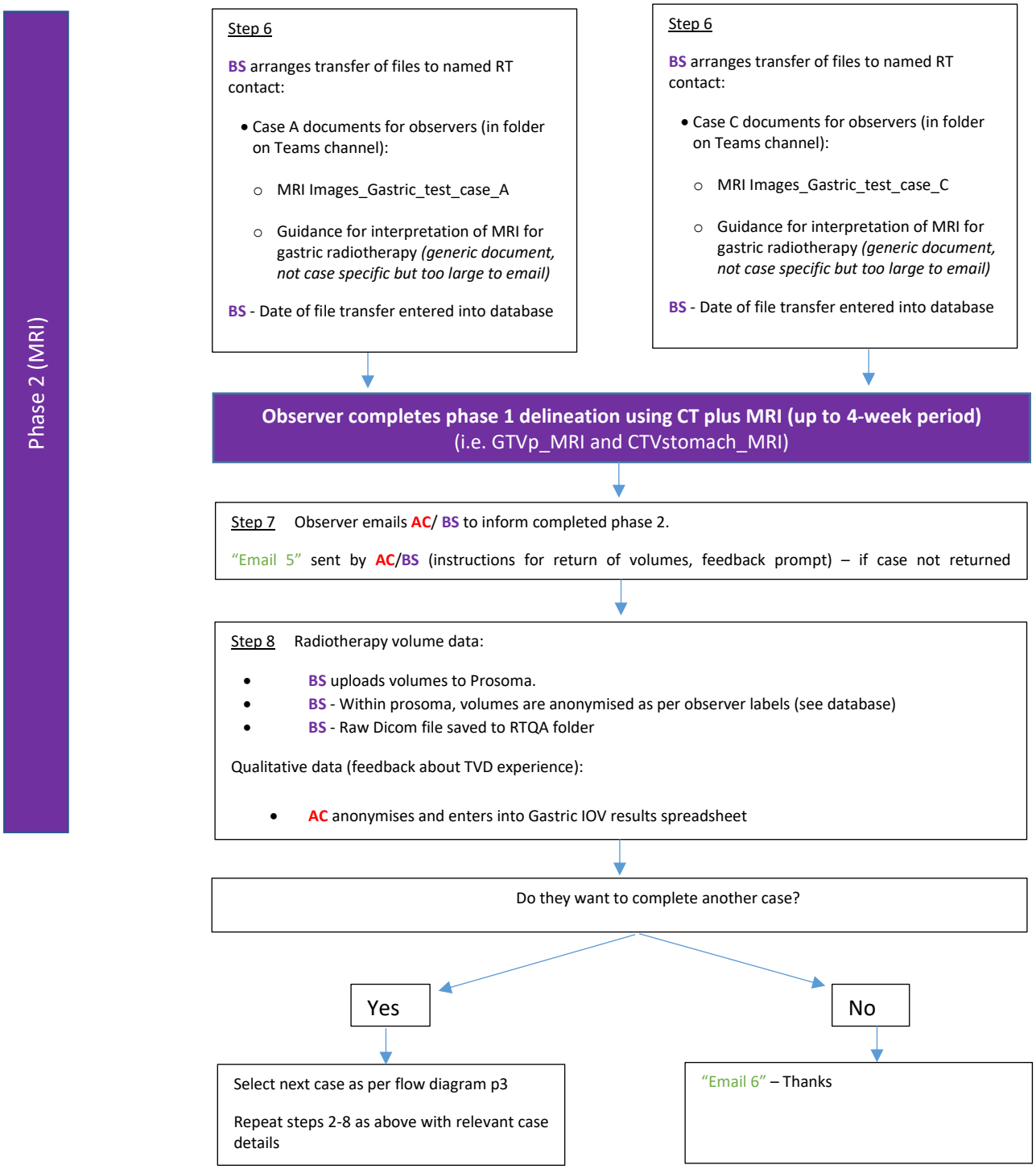
Malignant looking proximal gastric cancer, centred on the lesser curve

MDT Staging:

T4b N1 MX (liver)

Appendix 5.5 – Standard Operating Procedure for Data Handling




Phase 2 (MRI)
Step 6
BS arranges transfer of files to named RT contact:
Case A documents for observers (in folder on Teams channel):
MRI Images_Gastric_test_case_A
Guidance for interpretation of MRI for gastric radiotherapy (generic document, not case specific but too large to email)
BS - Date of file transfer entered into database
Step 6
BS arranges transfer of files to named RT contact:
Case C documents for observers (in folder on Teams channel):
MRI Images_Gastric_test_case_C
Guidance for interpretation of MRI for gastric radiotherapy (generic document, not case specific but too large to email)
BS - Date of file transfer entered into database
Observer completes phase 1 delineation using CT plus MRI (up to 4-week period)
(i.e. GTVp_MRI and CTVstomach_MRI)
Step 7 Observer emails AC/ BS to inform completed phase 2.
"Email 5" sent by AC/BS (instructions for return of volumes, feedback prompt) – if case not returned
Step 8 Radiotherapy volume data:
BS uploads volumes to Prosoma.
BS - Within prosoma, volumes are anonymised as per observer labels (see database)
BS - Raw Dicom file saved to RTQA folder
Qualitative data (feedback about TVD experience):
AC anonymises and enters into Gastric IOV results spreadsheet
Do they want to complete another case?
Yes
No
Select next case as per flow diagram p3
Repeat steps 2-8 as above with relevant case details
"Email 6" – Thanks

Appendix 5.6 – Conformity index/ volume results tables

WHOLE VOLUME DATA TABLES

Table A5.1. Case A - JCI

CASE A Jaccard Conformity Index (JCI) for each structure by observer (0= no agreement with reference volume, 1=perfect agreement , i.e. a change in values towards 1 shows improvement in conformity to reference value). Change in JCI between phase 1 (CT) and phase 2 (CT+MRI) is shown for each structure.

Observer number	GTVP_CT _JCI_A	GTVp_MRI _JCI_A	Change in JCI for GTVp	CTV stomach _CT_JCI_A	CTVstomach _MRI_JCI_A	Change in JCI for CTV Stomach
1	0.6754	0.7430	0.0676	0.8432	0.8455	0.0023
3	0.7741	0.7191	-0.0549	0.8651	0.8648	-0.0003
7	0.6534	0.6783	0.0249	0.8699	0.8614	-0.0084
9	0.6599	0.7369	0.0771	0.7943	0.7841	-0.0101
11	0.6939	0.7127	0.0188	0.8347	0.8417	0.0070
15	0.7543	0.6828	-0.0715	0.8182	0.8534	0.0352
17	0.5917	*0.4514**	-0.1404	0.8161	0.8261	0.0099
21	0.6279	0.7044	0.0765	0.7959	0.4668	-0.3290
23	0.6312	0.7614	0.1302	0.8388	0.8506	0.0117
27	0.8056	0.8111	0.0055	0.8945	0.8975	0.003
28	0.5122	0.6324	0.1201	0.8460	0.8460	0
MEDIAN	0.6598	0.7126	0.0249	0.8388	0.846	0.0023
MEAN	0.6798	0.6939	0.0231	0.8379	0.8125	-0.0253
IQR	0.1264	0.0646	NC	0.0490	0.3532	NC
ST DEV	0.0846	0.0930	NC	0.0309	0.1179	NC

Table A5.2. Case C - JCI

CASE C- Jaccard Conformity Index (JCI) for each structure by observer (0= no agreement with reference volume, 1=perfect agreement , i.e. a change in values towards 1 shows improvement in conformity to reference value). Change in JCI between phase 1 (CT) and phase 2 (CT+MRI) is shown for each structure.

Observer number	GTVP_CT _JCI_C	GTVp_MRI _JCI_C	Change in JCI GTVp	CTVstomach _CT_JCI_C	CTVstomach _MRI_JCI_C	Change in JCI CTV stomach
1	0.8503	0.8606	0.0102	0.8691	0.9190	0.0498
2	0.8382	0.8305	-0.0076	0.9068	0.8878	-0.0189
4	0.8818	0.6429	-0.2388	0.8946	0.8810	-0.0136
6	0.8789	0.8830	0.0041	0.9221	0.9142	-0.0079
8	0.8930	0.8735	-0.0195	0.9286	0.9198	-0.0088
10	0.7997	0.7803	-0.0194	0.8620	0.8648	0.0028
14	0.8919	0.7023	-0.1896	0.9136	0.9060	-0.0076
16	0.8714	0.8195	-0.0518	0.9272	0.7793	-0.1479
24	0.8766	0.7693	-0.1072	0.9151	0.9098	-0.0053
27	0.9217	0.9185	-0.0032	0.9522	0.9356	-0.0166
MEDIAN	0.8777	0.825	-0.0194	0.9144	0.9079	-0.0083
MEAN	0.8704	0.808	-0.0623	0.9091	0.8917	-0.0174
IQR	0.0448	0.1233	NC	0.0392	0.0422	NC
ST DEV	0.0337	0.0857	NC	0.0275	0.0447	NC

Table A5.3. Case A - GMI

CASE A –Geographical Miss Index (GMI) for each structure by observer (measures degree of under outlining, 0 = no reference volume missed, 1 = 100% reference volume missed, i.e. a change in values towards 0 shows improvement in conformity to reference value)

Observer number	GTVP_CT _GMI_A	GTVp_MRI _GMI_A	Change in GMI GTVP	CTV stomach _CT_GMI_A	CTVstomach _MRI_GMI_A	Change in GMI CTV stomach
1	0.3221	0.2529	-0.0691	0.1372	0.1348	-0.0024
3	0.1758	0.2506	0.0748	0.0781	0.0901	0.0120
7	0.3359	0.3115	-0.0244	0.1060	0.1072	0.0012
9	0.2581	0.2529	-0.0052	0.2000	0.2112	0.0111
11	0.2252	0.2202	-0.0049	0.1580	0.1516	-0.0064
15	0.2358	0.3140	0.0782	0.1760	0.1332	-0.0428
17	0.3011	0.5393	0.2382	0.1729	0.1639	-0.0090
21	0.2598	0.2603	0.0005	0.1945	0.5311	0.3365
23	0.3576	0.1981	-0.1594	0.1480	0.1319	-0.0161
27	0.1783	0.1611	-0.0172	0.0880	0.0828	-0.0051
28	0.4841	0.3416	-0.1425	0.1317	0.1317	0
MEDIAN	0.2598	0.2529	-0.0052	0.148	0.1332	-0.0024
MEAN	0.2849	0.2821	-0.0028	0.1445	0.1700	0.0253
IQR	0.1107	0.0938	NC	0.07	0.0566	NC
ST DEV	0.0893	0.1001	NC	0.0410	0.1248	NC

Table A5.4 **Case C - GMI**

CASE C –Geographical Miss Index (GMI) for each structure by observer (measures degree of under outlining, 0 = no reference volume missed, 1 = 100% reference volume missed, i.e. a change in values towards 0 shows improvement in conformity to reference value)

Observer number	GTVP_CT _GMI_C	GTVp_MRI _GMI_C	Change in GTV	CTV stomach _CT_GMI_C	CTVstomach _MRI_GMI_C	Change in CTV stomach
1	0.0938	0.0491	-0.0447	0.0461	0.0523	0.0062
2	0.0542	0.0795	0.0252	0.0533	0.0695	0.0163
4	0.0497	0.0506	0.0009	0.0892	0.0965	0.0073
6	0.1030	0.0789	-0.0241	0.0659	0.0581	-0.0077
8	0.0450	0.0860	0.0409	0.0535	0.0615	0.0080
10	0.1871	0.1477	-0.0394	0.1307	0.1283	-0.0024
14	0.0429	0.0250	-0.0179	0.0217	0.0143	-0.0074
16	0.0315	0.0452	0.0137	0.0376	0.1871	0.1495
24	0.0206	0.0054	-0.0152	0.0490	0.0377	-0.0113
27	0.0639	0.0535	-0.0103	0.0255	0.0425	0.0170
MEDIAN	0.0519	0.0520	-0.0127	0.0511	0.0598	0.0068
MEAN	0.0691	0.0621	-0.0071	0.0572	0.0747	0.0175
IQR	0.5602	0.0409	NC	0.0371	0.0631	NC
ST DEV	0.4867	0.0390	NC	0.0322	0.0505	NC

Table A5.5. Case A - DI

CASE A – Median Discordance Index (DI) for each structure by observer (measures degree of over outlining, 0 = complete concordance 1 = complete discordance, i.e. a change in values towards 0 shows improvement in conformity to reference value)

Observer number	GTVP_CT _DI_A	GTVp_MRI _DI_A	Change in DI GTVP	CTV stomach _CT_DI_A	CTVstomach _MRI_DI_A	Change in DI CTV stomach
1	0.0053	0.0072	0.0019	0.0261	0.0261	0
3	0.0728	0.0531	-0.0197	0.0664	0.0541	-0.0123
7	0.0238	0.0212	-0.0026	0.0299	0.0391	0.0091
9	0.1434	0.0181	-0.1252	0.0088	0.0073	-0.0015
11	0.1307	0.1076	-0.0230	0.0102	0.0091	-0.0011
15	0.0166	0.0065	-0.0101	0.0084	0.0177	0.0093
17	0.2057	0.0427	-0.1630	0.0159	0.0142	-0.0017
21	0.1945	0.0633	-0.1311	0.0146	0.0088	-0.0058
23	0.0268	0.0620	0.0352	0.0181	0.0231	0.0051
27	0.0236	0.0391	0.0155	0.0210	0.0233	0.0023
28	0.0134	0.0588	0.0454	0.0293	0.0293	0
MEDIAN	0.0268	0.0427	-0.0101	0.0180	0.0231	0.0000
MEAN	0.0779	0.0436	-0.0342	0.0226	0.0229	0.0003
IQR	0.1267	0.0439	NC	0.0191	0.0202	NC
ST DEV	0.0766	0.0300	NC	0.0164	0.1421	NC

Table A5.6. Case C - DI

CASE C – Discordance Index (measures degree of over outlining, 0 = complete concordance 1 = complete discordance, i.e. a change in values towards 0 shows improvement in conformity to reference value)

Observer number	GTVP_CT _DI_C	GTVp_MRI _DI_C	Change in GTV	CTV stomach _CT_DI_C	CTVstomach _MRI_DI_C	Change in CTV stomach
1	0.0675	0.0993	0.0318	0.0927	0.0318	-0.0609
1	0.1194	0.1052	-0.0142	0.0444	0.0490	0.0046
4	0.0755	0.3343	0.2587	0.0194	0.0274	0.0080
6	0.0225	0.0447	0.0223	0.0137	0.0311	0.0174
8	0.0677	0.0482	-0.0194	0.0199	0.0212	0.0013
10	0.0198	0.0976	0.0778	0.0096	0.0090	-0.0006
14	0.0709	0.2848	0.2139	0.0674	0.0818	0.0145
16	0.1031	0.1473	0.0442	0.0379	0.0504	0.0124
24	0.1069	0.2274	0.1205	0.0396	0.0565	0.0170
27	0.0163	0.0311	0.0147	0.0235	0.0239	0.0004
MEDIAN	0.0692	0.1022	0.0380	0.0306	0.0314	0.0063
MEAN	0.0669	0.1419	0.0750	0.0367	0.0382	0.0014
IQR	0.0822	0.1943	NC	0.0321	0.0287	NC
ST DEV	0.0372	0.1056	NC	0.0261	0.0212	NC

Table A5.7. Case A - Volume

CASE A – Volume (cc). Reference volume GTVp = 340.38cc, CTVstomach = 704.91

Observer number	GTVp_MRI _VOLUME_A (cc)	CTVstomach_MRI _VOLUME_A (cc)
1	256.14	626.23
3	269.36	678.02
7	239.41	654.88
9	258.98	560.08
11	297.42	603.49
15	235.00	621.95
17	*163.80**	597.87
21	268.78	*333.40**
23	290.99	626.43
27	297.15	661.91
28	238.10	630.53
Reference Volume	340.38	704.91
Median	255.98	626.23
Mean	255.92	599.53
IQR	52.89	57.00
Std Dev	38.10	94.02

Table A5.8. Case C – Volume

CASE C– Volume (cc). Reference volume GTVp = 482.13, CTVstomach = 1047.26

Observer number	GTVp_MRI _VOLUME_C (cc)	CTVstomach_MRI _VOLUME_C (cc)
1	509.01	1025.09
2	496.01	1024.64
4	687.52	972.93
6	464.91	1017.99
8	463.03	1004.18
10	455.35	921.13
14	657.25	1124.25
16	539.87	896.47
24	620.64	1068.12
27	470.94	1027.28
Reference Volume	482.13	1047.26
MEDIAN	502.51	1021.31
MEAN	536.45	1008.21
IQR	165.36	77.51
ST DEV	87.10	66.16

Table A5.9. Change in conformity between phase 1 (CT) and phase 2 (CT+MRI) for each structure.

For JCI, Jaccard Conformity Index (0= no agreement with reference volume, 1=perfect agreement , i.e. a change in values towards 1 shows improvement in conformity to reference value). For GMI, Geographical Miss Index (measures degree of under outlining, 0 = no reference volume missed, 1 = 100% reference volume missed, i.e. a change in values towards 0 shows improvement in conformity to reference value). For DI, Discordance Index (measures degree of over outlining, 0 = complete concordance 1 = complete discordance, i.e. a change in values towards 0 shows improvement in conformity to reference value).
% observers showing and improvement in CI for phase 2 has been calculated.

CI	JCI				GMI				DI			
Case	A	C	A	C	A	C	A	C	A	C	A	C
Volume	GTVp	GTVp	CTV stomach	CTV stomach	GTVp	GTVp	CTV stomach	CTV stomach	GTVp	GTVp	CTV stomach	CTV stomach
Change in CI for each observer	0.0676	0.0103	0.0023	0.0499	-0.0692	-0.0447	-0.0024	0.0062	0.0020	0.0318	0.0000	-0.0609
	-0.0549	-0.0077	-0.0003	-0.0189	0.0749	0.0252	0.0120	0.0163	-0.0197	-0.0142	-0.0123	0.0046
	0.0249	-0.2389	-0.0085	-0.0136	-0.0244	0.0009	0.0012	0.0073	-0.0026	0.2587	0.0091	0.0080
	0.0771	0.0041	-0.0101	-0.0079	-0.0053	-0.0241	0.0112	-0.0077	-0.1253	0.0223	-0.0015	0.0174
	0.0188	-0.0195	0.0071	-0.0088	-0.0049	0.0409	-0.0064	0.0080	-0.0231	-0.0194	-0.0011	0.0013
	-0.0715	-0.0194	0.0352	0.0028	0.0782	-0.0394	-0.0428	-0.0024	-0.0102	0.0778	0.0093	-0.0006
	-0.1404	-0.1896	0.0100	-0.0076	0.2382	-0.0179	-0.0090	-0.0074	-0.1630	0.2139	-0.0017	0.0145
	0.0765	-0.0519	-0.3290	-0.1479	0.0005	0.0137	0.3366	0.1495	-0.1312	0.0442	-0.0058	0.0124
	0.1302	-0.1073	0.0118	-0.0053	-0.1595	-0.0152	-0.0162	-0.0113	0.0353	0.1205	0.0051	0.0170
	0.0055	-0.0032	0.0030	-0.0166	-0.0172	-0.0103	-0.0052	0.0170	0.0155	0.0147	0.0023	0.0004
	0.1201		0.0000		-0.1426		0.0000		0.0454		0.0000	
Median change in CI	0.0249	-0.0195	0.0023	-0.0084	-0.0053	-0.0127	-0.0024	0.0068	-0.01016	0.0380	0.0000	0.0063
% observers with improved CI after MRI	72.7%	20.0%	54.5%	20.0%	63.6%	60.0%	54.5%	40.0%	63.6%	20.0%	45.5%	20.0%

Table A5.10 Slice-by-slice JCI: Case A, GTVp, Phase 1 (CT only)

Median JCI value for each observer by CT slice. CT slice 162.7 is the most superior slice on which any observers contoured GTVp. CT slice -157.7 is where the reference GTV begins. NaN = No GTVp contour on this slice for analysis.

CT Slice number	Observer												Median JCI for slice (GTVp_CT)
	Reference	1	3	7	9	11	15	17	21	23	27	28	
162.7	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	0	NaN	NaN	NaN	0
-162.2	NaN	NaN	NaN	NaN	NaN	NaN	NaN	0	0	NaN	NaN	NaN	0
-161.7	NaN	NaN	NaN	NaN	NaN	NaN	NaN	0	0	NaN	NaN	NaN	0
-161.2	NaN	NaN	NaN	NaN	0	NaN	NaN	0	0	NaN	NaN	NaN	0
-160.7	NaN	NaN	NaN	NaN	0	NaN	NaN	0	0	NaN	NaN	NaN	0
-160.2	NaN	NaN	NaN	NaN	0	NaN	NaN	0	0	NaN	NaN	NaN	0
-159.7	NaN	NaN	NaN	NaN	0	NaN	NaN	0	0	NaN	NaN	NaN	0
-159.2	NaN	NaN	NaN	NaN	0	NaN	NaN	0	0	NaN	NaN	NaN	0
-158.7	NaN	NaN	NaN	NaN	0	0	NaN	0	0	NaN	NaN	NaN	0
-158.2	NaN	NaN	NaN	NaN	0	0	NaN	0	0	0	0	NaN	0
-157.7	1	0.77	0.69	0.80	0.46	0.42	0.80	0.08	0.39	0.72	0.79	0.68	0.69
-157.2	1	0.61	0.58	0.62	0.85	0.80	0.74	0.72	0.75	0.46	0.93	0.41	0.72
-156.7	1	0.60	0.76	0.61	0.84	0.72	0.83	0.85	0.75	0.49	0.91	0.49	0.75
-156.2	1	0.66	0.79	0.61	0.87	0.76	0.83	0.83	0.77	0.71	0.92	0.46	0.77
-155.7	1	0.63	0.73	0.66	0.75	0.85	0.75	0.74	0.81	0.67	0.79	0.47	0.74
-155.2	1	0.67	0.82	0.64	0.83	0.83	0.84	0.79	0.78	0.61	0.88	0.49	0.79
-154.7	1	0.71	0.85	0.59	0.82	0.83	0.79	0.76	0.78	0.62	0.88	0.43	0.78
-154.2	1	0.76	0.85	0.63	0.78	0.72	0.74	0.72	0.73	0.57	0.88	0.45	0.73
-153.7	1	0.71	0.78	0.59	0.64	0.71	0.68	0.67	0.66	0.58	0.78	0.53	0.67
-153.2	1	0.66	0.74	0.68	0.59	0.56	0.68	0.59	0.63	0.67	0.71	0.62	0.66
-152.7	1	0.80	0.88	0.81	0.64	0.63	0.80	0.60	0.70	0.81	0.69	0.74	0.74
-152.2	1	0.65	0.86	0.78	0.52	0.53	0.67	0.49	0.60	0.82	0.64	0.64	0.64
-151.7	1	0.47	0.62	0.74	0.23	0.42	0.60	0.44	0.50	0.75	0.33	0.55	0.50
-151.2	1	0	0.34	0.81	0	0	0	0	0	0.81	0	0	0.00

Table A5.11 Slice-by-slice JCI: Case A, GTVp, Phase 2 (MRI only)

Median JCI value for each observer by CT slice for Case A. CT slice -162.7 is the most superior slice on which any observers contoured GTVp. CT slice -157.7 is where the reference GTV begins. NaN = No GTVp contour on this slice for analysis.

CT Slice number	Observer												Median JCI for slice (GTVp_MRI)
	Reference	1	3	7	9	11	15	17	21	23	27	28	
-162.7	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	N/A
-162.2	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	N/A
-161.7	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	N/A
-161.2	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	N/A
-160.7	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	N/A
-160.2	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	N/A
-159.7	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	N/A
-159.2	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	N/A
-158.7	NaN	NaN	NaN	NaN	NaN	0	NaN	0	NaN	NaN	0	NaN	0
-158.2	NaN	NaN	NaN	NaN	NaN	0	NaN	0	0	0	0	NaN	0
-157.7	1	0.87	0.64	0.80	0.77	0.49	0.82	0.22	0.52	0.77	0.77	0.68	0.77
-157.2	1	0.78	0.63	0.51	0.89	0.90	0.40	0.52	0.78	0.91	0.91	0.41	0.78
-156.7	1	0.72	0.78	0.53	0.83	0.87	0.52	0.50	0.71	0.86	0.91	0.75	0.75
-156.2	1	0.75	0.80	0.60	0.85	0.83	0.58	0.40	0.70	0.86	0.92	0.77	0.77
-155.7	1	0.74	0.77	0.73	0.75	0.87	0.77	0.30	0.81	0.78	0.79	0.65	0.77
-155.2	1	0.81	0.81	0.77	0.82	0.84	0.84	0.32	0.82	0.85	0.88	0.60	0.82
-154.7	1	0.79	0.80	0.73	0.81	0.81	0.84	0.36	0.78	0.84	0.88	0.61	0.80
-154.2	1	0.76	0.73	0.68	0.70	0.72	0.71	0.52	0.80	0.77	0.90	0.67	0.72
-153.7	1	0.73	0.71	0.69	0.66	0.71	0.69	0.63	0.67	0.68	0.82	0.68	0.69
-153.2	1	0.66	0.60	0.67	0.61	0.57	0.61	0.58	0.58	0.63	0.71	0.57	0.61
-152.7	1	0.80	0.66	0.73	0.70	0.59	0.67	0.60	0.68	0.67	0.69	0.66	0.67
-152.2	1	0.65	0.58	0.77	0.61	0.55	0.65	0.52	0.51	0.63	0.67	0.57	0.61
-151.7	1	0.55	0.61	0.63	0.34	0.45	0.59	0.55	0.40	0.76	0.59	0.54	0.55
-151.2	1	0	0	0	0	0	0	0	0	0.46	0	0	0

Table A5.12. Slice-by-slice JCI: Case C GTVp, Phase 1 (CT only)

Median JCI value for each observer by CT slice for Case C. CT slice -201.3 is the most superior slice on which any observers contoured GTVp. CT slice -203.3 is where the reference GTV begins. NaN = No GTVp contour on this slice for analysis.

CT Slice number	Observer											Median JCI for slice (GTVp_CT)
	GOLD	1	2	4	6	8	10	14	16	24	27	
-201.3	NaN	NaN	0	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	0
-200.8	NaN	NaN	0	NaN	NaN	NaN	NaN	0	NaN	NaN	NaN	0
-200.3	1	0.42	0.31	0.58	0.83	0.79	0.55	0.50	0.61	0.52	0.93	0.56
-199.8	1	0.80	0.76	0.92	0.88	0.90	0.81	0.92	0.91	0.87	0.95	0.89
-199.3	1	0.77	0.77	0.93	0.89	0.92	0.93	0.90	0.88	0.89	0.92	0.89
-198.8	1	0.82	0.77	0.90	0.91	0.87	0.91	0.88	0.88	0.81	0.95	0.88
-198.3	1	0.89	0.81	0.81	0.93	0.88	0.91	0.88	0.88	0.85	0.93	0.88
-197.8	1	0.87	0.82	0.83	0.92	0.87	0.89	0.86	0.85	0.84	0.96	0.87
-197.3	1	0.89	0.82	0.88	0.91	0.88	0.87	0.87	0.87	0.88	0.97	0.88
-196.8	1	0.91	0.88	0.88	0.92	0.93	0.78	0.93	0.92	0.94	0.93	0.92
-196.3	1	0.87	0.87	0.88	0.86	0.92	0.75	0.92	0.91	0.92	0.88	0.88
-195.8	1	0.87	0.89	0.89	0.88	0.90	0.83	0.91	0.91	0.90	0.91	0.90
-195.3	1	0.88	0.90	0.89	0.89	0.94	0.76	0.90	0.92	0.93	0.91	0.90
-194.8	1	0.90	0.91	0.91	0.91	0.90	0.86	0.94	0.89	0.91	0.89	0.90
-194.3	1	0.89	0.85	0.89	0.88	0.87	0.84	0.90	0.89	0.87	0.92	0.89
-193.8	1	0.73	0.91	0.91	0.89	0.86	0.84	0.92	0.88	0.90	0.97	0.89
-193.3	1	0.82	0.88	0.89	0.88	0.88	0.83	0.91	0.89	0.86	0.93	0.88
-192.8	1	0.78	0.91	0.90	0.77	0.88	0.68	0.91	0.89	0.93	0.91	0.90
-192.3	1	0.85	0.83	0.85	0.83	0.86	0.69	0.84	0.82	0.88	0.85	0.85
-191.8	1	0.92	0.92	0.92	0.87	0.94	0.79	0.94	0.91	0.90	0.94	0.92
-191.3	1	0.89	0.94	0.93	0.89	0.91	0.78	0.89	0.87	0.91	0.95	0.90
-190.8	1	0.89	0.87	0.85	0.87	0.90	0.81	0.91	0.78	0.85	0.93	0.87
-190.3	1	0.85	0.84	0.86	0.87	0.90	0.78	0.91	0.81	0.84	0.91	0.86
-189.8	1	0.85	0.90	0.93	0.91	0.90	0.79	0.92	0.89	0.90	0.97	0.90
-189.3	1	0.92	0.91	0.92	0.89	0.94	0.75	0.94	0.90	0.83	0.95	0.92
-188.8	1	0.90	0.75	0.90	0.86	0.84	0.77	0.92	0.80	0.76	0.94	0.85
-188.3	1	0.76	0.68	0.72	0.77	0.86	0.68	0.80	0.69	0.75	0.79	0.76
-187.8	1	0.67	0.67	0.78	0.79	0.73	0.00	0.43	0.51	0.66	0.70	0.67

Table A5.13. Slice-by-slice JCI: Case C GTVp, Phase 2 (CT + MRI)

Median JCI value for each observer by CT slice for Case C. CT slice -201.3 is the most superior slice on which any observers contoured GTVp. CT slice -203.3 is where the reference GTV begins. NaN = No GTVp contour on this slice for analysis.

CT Slice number	Observer											Median JCI for slice (GTVp_MRI)
	GOLD	1	2	4	6	8	10	14	16	24	27	
-201.3	NaN	NaN	0	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	0
-200.8	NaN	NaN	0	NaN	NaN	NaN	NaN	0	0	NaN	NaN	0
-200.3	1	0.35	0.35	0.28	0.50	0.61	0.64	0.57	0.59	0.49	0.93	0.53
-199.8	1	0.82	0.76	0.56	0.93	0.88	0.70	0.65	0.89	0.90	0.95	0.85
-199.3	1	0.85	0.81	0.61	0.94	0.88	0.86	0.62	0.88	0.90	0.92	0.87
-198.8	1	0.87	0.72	0.53	0.91	0.86	0.70	0.58	0.79	0.71	0.92	0.75
-198.3	1	0.85	0.83	0.60	0.90	0.87	0.71	0.58	0.80	0.65	0.91	0.81
-197.8	1	0.85	0.88	0.62	0.91	0.92	0.77	0.63	0.82	0.66	0.95	0.84
-197.3	1	0.86	0.84	0.63	0.90	0.88	0.81	0.68	0.81	0.71	0.91	0.83
-196.8	1	0.92	0.85	0.65	0.89	0.92	0.76	0.74	0.91	0.79	0.93	0.87
-196.3	1	0.87	0.86	0.67	0.88	0.86	0.79	0.75	0.88	0.77	0.90	0.86
-195.8	1	0.87	0.89	0.69	0.89	0.88	0.84	0.78	0.84	0.77	0.94	0.86
-195.3	1	0.90	0.91	0.71	0.88	0.82	0.80	0.76	0.87	0.81	0.95	0.85
-194.8	1	0.90	0.90	0.71	0.89	0.92	0.86	0.73	0.86	0.80	0.92	0.88
-194.3	1	0.88	0.91	0.70	0.85	0.87	0.81	0.71	0.78	0.82	0.90	0.84
-193.8	1	0.88	0.90	0.75	0.91	0.92	0.81	0.74	0.80	0.81	0.95	0.85
-193.3	1	0.84	0.89	0.72	0.92	0.90	0.79	0.73	0.79	0.74	0.91	0.82
-192.8	1	0.88	0.82	0.76	0.88	0.90	0.76	0.78	0.82	0.80	0.91	0.82
-192.3	1	0.84	0.80	0.68	0.82	0.88	0.72	0.74	0.78	0.79	0.85	0.80
-191.8	1	0.87	0.85	0.72	0.91	0.87	0.83	0.76	0.85	0.81	0.94	0.85
-191.3	1	0.89	0.83	0.69	0.89	0.86	0.83	0.73	0.83	0.81	0.94	0.83
-190.8	1	0.84	0.83	0.56	0.86	0.91	0.69	0.61	0.72	0.72	0.87	0.78
-190.3	1	0.83	0.85	0.54	0.89	0.90	0.75	0.60	0.74	0.77	0.91	0.80
-189.8	1	0.91	0.88	0.62	0.92	0.88	0.82	0.71	0.82	0.77	0.97	0.85
-189.3	1	0.91	0.80	0.58	0.87	0.86	0.81	0.81	0.85	0.82	0.95	0.84
-188.8	1	0.90	0.83	0.56	0.88	0.81	0.77	0.68	0.87	0.71	0.95	0.82
-188.3	1	0.72	0.79	0.45	0.78	0.52	0.72	0.70	0.68	0.77	0.79	0.72
-187.8	1	0.67	0.78	0.00	0.64	0.00	0.00	0.80	0.86	0.80	0.70	0.68

Table A5.14. Chi-Square for time and method

Chi-Square test to evaluate association between time taken for TVD and method used (i.e. copy+modify vs new volume)

Method for TVD vs Time				
		Method		Total
		Copy+modify	New volume	
Time taken	Faster	4	4	8
	Slower/No difference	3	7	10
Total		7	11	18

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.748[a]	1	.387		
Continuity Correction[b]	.143	1	.705		
Likelihood Ratio	.749	1	.387		
Fisher's Exact Test				.630	.352
Linear-by-Linear Association	.706	1	.401		
N of Valid Cases	18				
a. 3 cells (75.0%) have expected count less than 5. The minimum expected count is 3.11.					

Table A5.15. Chi-Square for ease rating and prior experience

Chi-Square test to evaluate association change in ease rating and prior gastric RT experience

Change in Ease Rating vs Prior Experience				
		Prior Experience		Total
		Yes	No	
Change in Ease Rating	0	2	2	4
	1-2	5	5	10
	>3	4	3	7
Total		11	10	21

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	.095[a]	2	.953
Likelihood Ratio	.096	2	.953
Linear-by-Linear Association	.066	1	.797
N of Valid Cases	21		
a. 5 cells (83.3%) have expected count less than 5. The minimum expected count is 1.90.			

Appendix 5.7 – Qualitative Feedback

Case A

A	**CTV based volumes**					**MRI based volumes**					**Change in "ease rating" between CT and MRI**	
Observer no.	**Approx time CTV stomach**	**Approx time GTVp**	**Ease identifying CTVstomach** (1= difficult, 10= easy)	**Ease identifying GTVp** (1= difficult, 10= easy)	**Comments**	**Approx time CTV stomach**	**Approx time GTVp**	**Ease identifying CTVstomach** (1= difficult, 10= easy)	**Ease identifying GTVp** (1= difficult, 10= easy)	**Comments**	**CTV stomach**	**GTVp**
1	45	30	3	3	Especially difficult identifying border of pylorus/pyloric mass from duodenum. Delineating tumour from normal stomach mucosa also tricky. Might also ask for help from radiologist re peritumoral lymph nodes.	5	15	5	6	Much easier with MRI, especially GTVp and GTVn.	+2	+3
3	10	5	7	5	Perigastric stranding was challenging	10	5	8	9	Fat stranding is missed on MRI	+1	+4
7	6	16	6	5	Contouring the GTVp was actually harder than I thought!	5	15	8	6	Interesting. I thought the DWI images were helpful to see the tumour, but the poorer definition of the images made it more difficult to corelate with CT. altogether the MRI made contouring a little easier.	+2	+1
9	10	15	8	7	More difficult to identify proximal GTVp extent. Included enhancing thickened gastric wall proximally but not entirely clear where the tumour edge is.	10	20	8	9	Easier to identify proximal extent of GTVp on MRI than CT and to identify involved nodes	0	+2
11	8	7	9	7	CTV stomach was straightforward as the GOJ was clearly identified. The disease posteriorly abutting the pancreas was more difficult to delineate.	6.5	7.5	9	7	I'm not sure the MRI added a huge amount compared to the diagnostic CT in terms of voluming, particularly the CTV stomach	0	0
15	18	25	9	7	Struggled with extragastric extension	40	40	7	7	Whilst MRI does make tumour more visible and MRI atlas very good, I often wanted to ask questions. Lack of confidence in interpreting MRI especially at edge of tumour etc when haziness seen ion CT. A webinar / question and answer session would be helpful	-2	0
17	10	40	7	2	Difficult to differentiate normal stomach from tumour. Difficult to identify exact proximal extent of tumour.	10	15	8	7	DWI very helpful	+1	+5
21	5	20	8	3	difficult to be fully precise and distinguish normal/pathologist stomach	10	15	9	8	No comment	+1	+5
23	20	40	8	5	Difficult to differentiate border of stomach/tumour. Also, I wasn't sure how many nodes to delineate. I didn't include the sub cm ones	10	50	8	7	I still found it hard to delineate border of stomach and GTVp due to what I felt was a change in anatomy e.g. stomach filling/positioning, but nodes were easier to see and I realise that some were clearly missed on CT delineation. Again, I didn't include very small nodes that were slightly brighter on DWI.	0	+2

27	45	40	7	4	Appreciating the superior and interior extent of tumour was difficult, as was extragastric extension. Top end of GTV was particularly tricky, where it merged with stomach contents. I found myself expanding CTV stomach quite generously to cover ill-defined stranding which I interpreted to be extragastric extension.	10	30	8	7	Whole stomach volume didn't really change. However, I did extend GTV further sup and inf, and also included more extragastric stranding. I found the DWI and contrast enhanced imaging most useful. On DWI some nodes I hadn't noticed on CT "lit up" and so I subsequently included them – added several nodes to CT volume as a result. MRI generally made me extend rather than decrease the size of my volumes.	+1	+3
28	10	60	8	1	The bulky distal end was easier, but middle and top was harder	10	60	9	1	The bulky distal end was easier, but middle and top was harder. The MRI showed an area I had missed but was harder than I thought to transfer to CT images, I imagine will get easier as get used to looking at MRI images. Slow computer made scrolling through a lot of MRI images quite hard but think we do need them all	+1	0

Themes in Case A free text feedback

CT based feedback	No. of comments
Difficult to differentiate tumour/ abnormal thickening from normal stomach wall	5
Difficult to identify extent of perigastric/ extragastric stranding	3
Difficult to identify distal end/ pylorus from duodenum	3
Difficult to identify proximal extent	3
Identifying peritumoral lymph nodes	2
GTVp harder to contour than anticipated	1
Difficult to identify extent of invasion into pancreas	1
MRI based feedback	No. of comments
Positive experiences:	
Easier to identify GTVp with MRI	3
Easier to identify GTVN with MRI	4
MRI generally made contouring easier	2
DWI helpful to visualise tumour	3
MRI generally increased size of volumes due to increased visibility/ appreciation of extragastric extension	1
Negative experiences:	
Difficult to correlate MRI with CT (due to filling/ position/ not co-registered)	3
Harder to appreciate fat stranding on MRI	1
Lack of experience interpreting MRI added uncertainty / more education required	2
MRI didn't add much to diagnostic CT	1

Case C

C	CTV based volumes					MRI based volumes					Change in "ease rating" between CT and MRI	
Observer no.	**Approx time CTV stomach**	**Approx time GTVp**	**Ease identifying CTVstomach** (1= difficult, 10= easy)	**Ease identifying GTVp** (1= difficult, 10= easy)	**Comments**	**Approx time CTV stomach**	**Approx time GTVp**	**Ease identifying CTVstomach** (1= difficult, 10= easy)	**Ease identifying GTVp** (1= difficult, 10= easy)	**Comments**	**CTV stomach**	**GTVp**
1	60	35	3	5	Difficult to differentiate between distended stomach and duodenum, and thickening in fundus also tricky to establish origin of. Also challenging to identify any peritumoural LN not confluent with GTVp	15	10	4	7	Again, much easier with MRI. Difficult when anatomy doesn't quite match up between imaging modalities	+1	+2
2	10	20	7	7	Difficulty knowing how much tumour is in lumen of stomach vs. fluid. Stomach-duodenal junction always difficult	15	25	8	8	Didn't actually find MRI changed my contours much.	+1	+1
4	20	30	4	8	Difficult to determine duodenal cap. Nodes were also difficult to delineate with thick slices on CT.	20	40	5	8	Nodes were easier to identify as was primary tumour on MRI DWI/T2 sequence imaging	+1	0
6	15	20	4	7	Not sure where to locate duodenal cap	15	15	6	8	Found looking at the different MRI sequences valuable	+2	+1
8	20	20	3	3	No comment	25	25	6	5	No comment	+3	+2
10	15	15	6	6	Difficulty identifying adrenal gland.	10	28	6	8	Easier using the MRI diffusion to identify the nodes I think!	0	+2
14	40	25	5	3	Some areas are more difficult to identify. E.g. I couldn't really tell which were the suspicious lymph nodes mentioned in the CT report. Also, the determining the boundary between the liver and tumour is challenging. As always, the pyloric region leading to the duodenum is challenging.							
16	30	20	8	7	Difficult to find nodes. Not much in history to suggest where the suspicious nodes are. GOJ difficult to find on CT scan.	15	20	8	9	GTVp seen clearly on the MRI. Easier to outline, especially where there is liver invasion. Would help if the images were fused.	0	+2
24	5	10	10	5	Very difficult to identify the intra luminal margin of the GTV even with good gastric filling.	5	20	10	7	Subjectively it was felt that MRI made it easier to identify the GTVp but the Final GTVp volume was very similar to what was drawn on the CT alone. MRI did not contribute much in outlining CTVstomach. Difference in gastric filling between the CT scan & MRI added some confusion.	0	+2
27	50	25	7	6	Difficult to tell what was node vs vessel vs extra gastric extension in the gastro-hepatic space. Also found it difficult to differentiate between stomach and liver superiorly – using coronals helped. Couldn't confidently define any GTVn but ?some in the gastrohepatic space/perigastric that I included. Difficult to tell the left lateral edge of the tumour (i.e. intragastric edge) on CT alone.	5	15	8	9	DWI helped with the gastrohepatic space – it was very restrictive so I expanded my medial GTVp more to fully cover these areas. The delayed contrast imaging helped with defining liver vs stomach as there was good contrast between the two. With the addition on MRI, I expanded my GTVp – therefore also CTVstomach.	+1	+3

Themes in Case C free text feedback

CT based feedback	No. of comments
Difficult identifying pylorus vs duodenal junction/cap	5
Difficult to identify LNs	5
Difficult identifying tumour vs fluid / intraluminal margin	3
Difficult identifying boundary between tumour and liver	2
Difficult identifying tumour vs stomach wall thickening vs normal stomach wall	1
Difficult to identify adrenal gland	1
Difficult to identify GOJ	1
MRI based feedback	No. of comments
Positive experiences:	
Easier to identify GTVp with MRI	2
Easier to identify GTVN with MRI	2
MRI generally made contouring easier (specific sequence not named)	3
DWI sequences helpful to visualise tumour/nodes	2
T2 sequences helped to visual tumour/nodes	1
MRI generally increased size of volumes due to increased visibility/ appreciation of extragastric extension/ nodes	1
Helped with definition of invasion into nearby organs (liver)	2
Negative experiences:	
Difficult to correlate MRI with CT (due to filling/ position/ not co-registered)	3
MRI didn’t change contours much	2

Appendix 6

Appendix 6.1 – Comparison of RT technique and TVD recommended by 3 pre-operative RT planning guidance documents (i.e. protocols)

	CRITICS II (v6.1 2022)	**TOPGEAR (v8, 2017)**	**EORTC Guidelines Matzinger 2009**
Dose/#	45Gy/25#	45Gy/25#	45Gy/25# No cone down or boost should be foreseen
CT Simulation/ Patient set up	• Supine, arms above head. Isocentre positioned a few cm left of T12 or L1. • Maximal CT slice thickness 5mm • CT from carina to the iliac crest (complete volume of heart, liver and kidneys to be encompassed) • IV contrast at discretion of oncologist	• Supine arms above head • Max CT slice 5mm • CT must include inferior extent of both kidneys, upper level depends on tumour location – if distal upper level should be above diaphragm to include whole stomach, if GOJ, need to include apices of lungs. • Use of IV contrast recommended (but is optional at discretion of treating oncologist) • Use of oral contrast also optional	• Planning CT before any induction chemotherapy. If induction chemo or >10% weight loss, second planning CT is required • IV contrast recommended • Oral positive or negative contrast media not recommended, but supported for diagnostic CT • Slice thickness no larger than 3mm • Supine arms above head • Immobilisation with thermoplastic shell/vac cushion, knees support
Motion management	• 4D scanning has to be performed to acquire information on movement of stomach/CTV • No diet is prescribed because due to the fact that tumour is in situ, it is not expected that a diet will result in stable filling status of the stomach	• Attempt to maintain consistent stomach filling during CT simulation (early morning following light breakfast) • No recommendation for 4D scanning.	• Individualised identification of the target volume has to be performed if possible • No standard procedure recommended – suggest min 1.5cm CTV to ITV margin if not respiratory gating performed.
GTV	NA	Primary tumour and involved regional LN (including perigastric tumour extension and any sites of adherence for T4 tumours)	GTV(tumour) to include perigastric tumour extension. GTV (nodes) involved nodes
CTV (overview)	Encompasses tumour, stomach and first draining lymph node stations. One CTV is contoured that encompasses all.	Stomach, tumour bed and regional lymphatics	Tumour, partial or whole stomach based on tumour position, and elective lymph node stations corresponding to specific tumour location.

CTV Stomach volume	• The stomach should always be part of the CTV – it is left to the discretion of the treating oncologist whether the whole stomach is included if the tumour is well demarcated on imaging and surgeon is doing a partial gastrectomy, but where a total gastrectomy is being performed, the whole stomach should be in the CTV • For proximal distal tumours with extension through the wall 2/3 – 3/4 of the left hemidiaphragm should be included in the CTV with a 1cm margin. • Hepatogastric ligament needs to be included in all cases • Anterior abdominal wall (parietal peritoneum) that is close to the gastric tumour should be included for T3/T4 tumours • CTV will extend left laterally as far as needed to include tumour extension or encompass lymph nodes that are to be treated.	• **<u>CTV stomach</u>** includes the GTV plus entire stomach from cardiac orifice to pyloric orifice. • T1/T2 – Gastric silhouette • T3– a margin of 0.5cm beyond GTV should be added (then modify the CTV to include uninvolved gastric silhouette) • T4- GTV +1cm (then modify the CTV to include uninvolved gastric silhouette) • A margin of 1cm of proximal oesophagus should be included in CTV stomach • A margin of 1cm of duodenum inferiorly until the first CT slice when it joins the third part of duodenum	**<u>CTV (gastric):</u>** • **Proximal third** CTV (gastric) = contour of stomach excluding pylorus and antrum (a min margin of 5cm from GTV has to be respected) • **Middle third** CTV(gastric)= contour of stomach from cardia to pylorus • **Distal third** CTV(gastric)= contour of stomach excluding cardia and fundus (a min margin of 5cm from GTV has to be respected)
GOJ tumours	For tumours of the GOJ – 4cm of proximal oesophagus is needed to encompass the first para-oesophageal nodes	The 1cm proximal oesophagus must be extended to 4cm for tumours of the cardia, GOJ or distal oesophagus.	NS
Gastro-duodenal junctions	For tumours <5cm from GDJ, a 5cm extra distal margin of the duodenum beyond the GDJ has to be taken	The 1cm margin of duodenum should be increased to 4cm for tumours involving pylorus/duodenum. If direct invasion of duodenum, the entire duodenal circumference needs to be treated	In case of infiltration of the pylorus or duodenum, CTV must be expanded along duodenum for 3cm from tumour
CTV Regional lymph nodes	<u>ALL lymph node stations included in all patients</u> (recommended) If tumour extension is very well demarcated, one could individualise for GOJ (proximal), Corpus (middle) and antrum (distal): • <u>GOJ/cardia/proximal 1/3</u> Para-oesophageal, subdiaphragmatic, perigastric, hepatogastric lig, perigastric celiac (left gastric artery, celiac axis), splenic hilum,	<u>ALL lymph node stations included in all patients</u> (JRSGC LN stations 1-13, 16): • Perigastric (1-5,7) • Celiac (7-9,11) • Splenic hilar (10) • Suprapancreatic • Porta hepatis (12) • Infrapyloric (6)	CTV(elective) corresponds to tumour location, defined by 5mm margin from corresponding vessels. JRSGC LN stations: • Type 3 GOJ: 1,2,3,4sa,7,9,10,11p, 11d,19,20,110,111 • Proximal third: 1,2,3,4sa, 4sb,7,9,10,11p, 11d,19 • Middle third: 1,2,3,4sa,4sb,4d,5,7,8a, 8b,9,10,11p,11d,18,19 • Distal third: 3,4d,5,6,7,8a,8b,9,11p,12a, 12b, 12p,13,17,18

	suprapancreatic, porta hepatis, pancreaticoduodenal (stations 1-4, 9-13) • Middle third – perigastric, suprapyloric, infrapyloric, celiac (left gastric artery, common hepatic artery and celiac axis), splenic hilum, suprapancreatic, porta hepatis, pancreaticoduodenal (stations 3-13) • Antrum/ distal 1/3: perigastric, hepatogastric lig, suprapyloric, infrapyloric, splenic artery, pancreaticoduodenal, porta hepatis, celiac (left gastric artery, common hepatic artery and celiac axis) suprapancreatic (stations 3-9, 11-13) + all combinations when tumour invaded more than one part of the stomach before start of treatment.	• Pancreaticoduodenal (13 - CTV only needs to cover the medial half of duodenal circumference rather than the entire circumference of the duodenum) • Para-aortic nodes (16) should be included for the entire length of the CTV, from its inferior extent cranially to the aortal hiatus. CTV should extend beyond the circumference of aorta for at least 1cm in all radial directions, except posteriorly where it should only extend to the anterior vertebral body.	
PTV	4D setup should be used CTV +10mm in all directions (an exception can be made on dorsal side with respect to bony structures like vertebrae and both kidneys, where a 5mm margin is sufficient)	PTV= CTV +1cm uniform expansion In some cases, the margin may have to be bigger, for example, when respiratory variation causes significant superior-inferior movement of the stomach, or when significant variation in gastric filling is expected.	If no facilities for evaluation of target motion are present, minimum margins recommended are: ITV = CTV + 1.5cm all directions. PTV = ITV + 0.5cM
OARs	On all slices, heart, spinal cord, liver and kidneys must be contoured		Lungs, liver, kidney and heart to be delineated. Spinal cord outlined for the whole volume of interest plus 2cm above and below
Technique	Only IMRT/IGART/ VMAT is allowed	IMRT or 3D conformal Split field	3D CRT or IMRT Volume should be treated by only one treatment plan (without superposition of different plans)
Additional info	Signposted to ESTRO-ACROP nodal volume guidelines	Signposted to TROG 03.02 trial guidelines	

Appendix 6.2 JCGA lymph node station classification

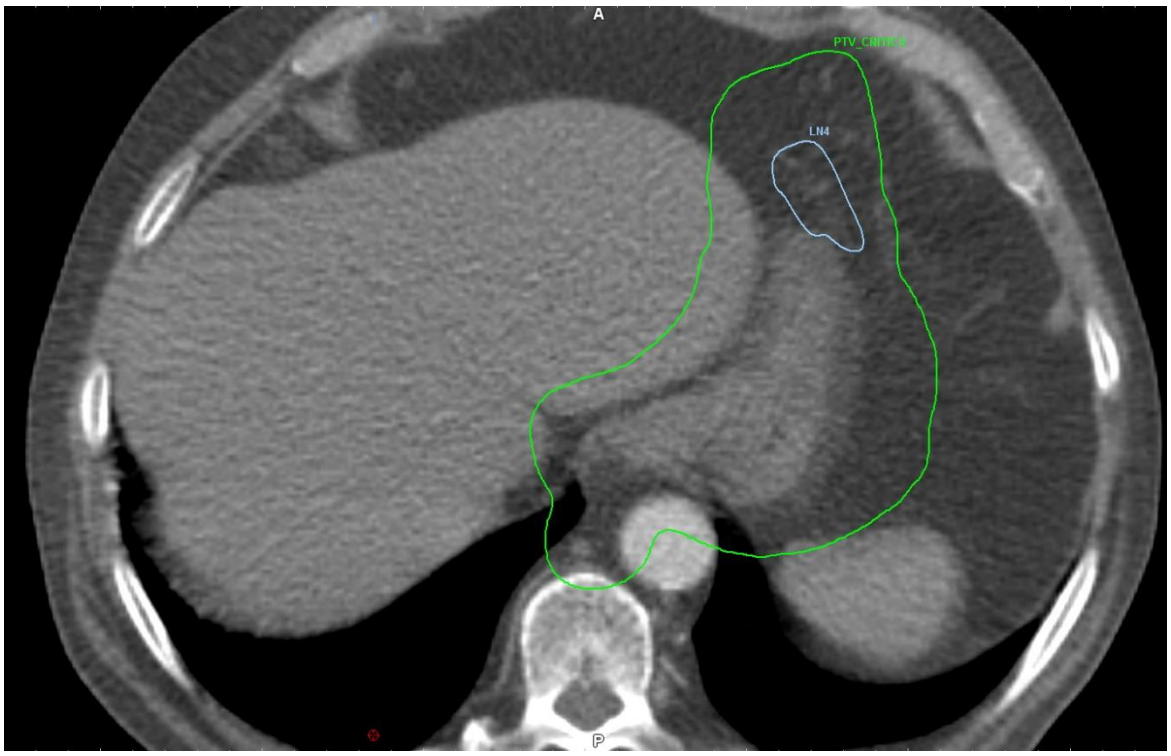
Modified from Rosa et al[205], showing the original Japanese Research Society for Gastric Cancer gross anatomical description, and the more detailed JCGA classification[204] NS=not stated

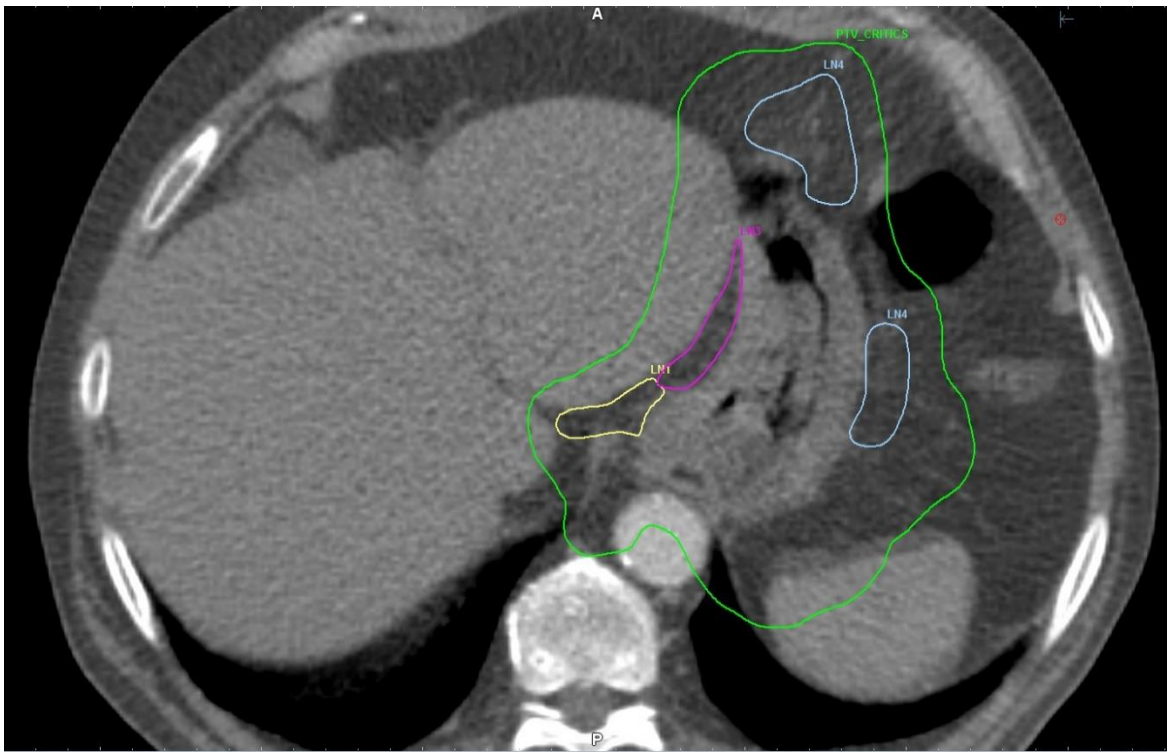
JCGA Station number	Gross Anatomical location (as per JRSGC)	Prescise anatomical definition as per JCGA
1	Right cardiac	Right paracardial LNs, including those along the first branch of the ascending limb of the left gastric artery.
2	Left cardiac	Left paracardial LNs including those along the oesophagocardiac branch of the left subphrenic artery
3	Nodes along the lesser curve	3a) Lesser curvature LNs along the branches of the left gastric artery 3b) Lesser curvature LNs along the 2nd branch and distal part of the right gastric artery
4	Nodes along the greater curve	4sa) Left greater curvature LNs along the short gastric arteries (perigastric area) 4sb) Left greater curvature LNs along the left gastroepiploic artery (perigastric area) 4d) Rt. greater curvature LNs along the 2nd ranch and distal part of the right gastroepiploic artery
5	Suprapyloric nodes	Suprapyloric LNs along the 1st branch and proximal part of the right gastric artery
6	Infrapyloric nodes	Infrapyloric LNs along the first branch and proximal part of the right gastroepiploic artery down to the confluence of the right gastroepiploic vein and the anterior superior pancreatoduodenal vein
7	Nodes along the left gastric artery	LNs along the trunk of left gastric artery between its root and the origin of its ascending branch
8	Nodes along the common heptaic artery	8a) Anterosuperior LN along the common hepatic artery 8p) Posterior LNs along the common hepatic artery
9	Nodes around the coeliac axis	Celiac artery LNs
10	Nodes at the splenic hilum	Splenic hilar LNs including those adjacent to the splenic artery distal to the pancreatic tail, and those on the roots of the short gastric arteries and those along the left gastroepiploic artery proximal to its 1st gastric branch
11	Nodes along the splenic artery	11p) Proximal splenic artery LNs from its origin to halfway between its origin and the pancreatic tail end 11d) Distal splenic artery LNs from halfway between its origin and the pancreatic tail end to the end of the pancreatic tail
12	Nodes at the hepatoduodenal ligament	12a) Hepatoduodenal ligament LNs along the proper hepatic artery, in the caudal half between the confluence of the right and left hepatic ducts and the upper border of the pancreas 12b) Hepatoduodenal ligament LNs along the bile duct, in the caudal half between the confluence of the right and left hepatic ducts and the upper border of the pancreas 12p) Hepatoduodenal ligament LNs along the portal vein in the caudal half between the confluence of the right and left hepatic ducts and the upper border of the pancreas

13	Nodes at the posterior aspect of the pancreas head	LNs on the posterior surface of the pancreatic head cranial to the duodenal papilla
14	Nodes at the root of the mesentry	LNs along the superior mesenteric vein
15	Nodes in the mesocolon of the transverse colon	LNs along the middle colic vessels
16	Para-aortic LNs	16a1 Para aortic LNs in the diaphragmatic aortic hiatus 16a2 Para aortic LNs between the upper margin of the origin of the celiac artery and the lower border of the left renal vein 16b1 Para aortic LNs between the lower border of the left renal vein and the upper border of the origin of the inferior mesenteric artery 16b2 Para aortic LNs between the upper border of the origin of the inferior mesenteric artery and the aortic bifurcation
17	NS	LNs on the anterior surface of the pancreatic head beneath the pancreatic sheath
18	NS	LNs along the inferior border of the pancreatic body
19	NS	Infradiaphragmatic LNs predominantly along the subphrenic Artery
20	NS	Paraoesophageal LNs in the diaphragmatic oesophageal hiatus
110	NS	Paraoesophageal LNs in the lower thorax
111	NS	Supradiaphragmatic LNs separate from the oesophagus
112	NS	Posterior mediastinal LNs separate from the oesophagus and the oesophageal hiatus

Appendix 6.3. JGCA LN stations delineated as per ESTRO-ACROP guidance.

Peer reviewed nodal volumes (KF) demonstrating inclusion of each level within PTV volume (bright green). Slices shown every 6mm (i.e. alternate slices)





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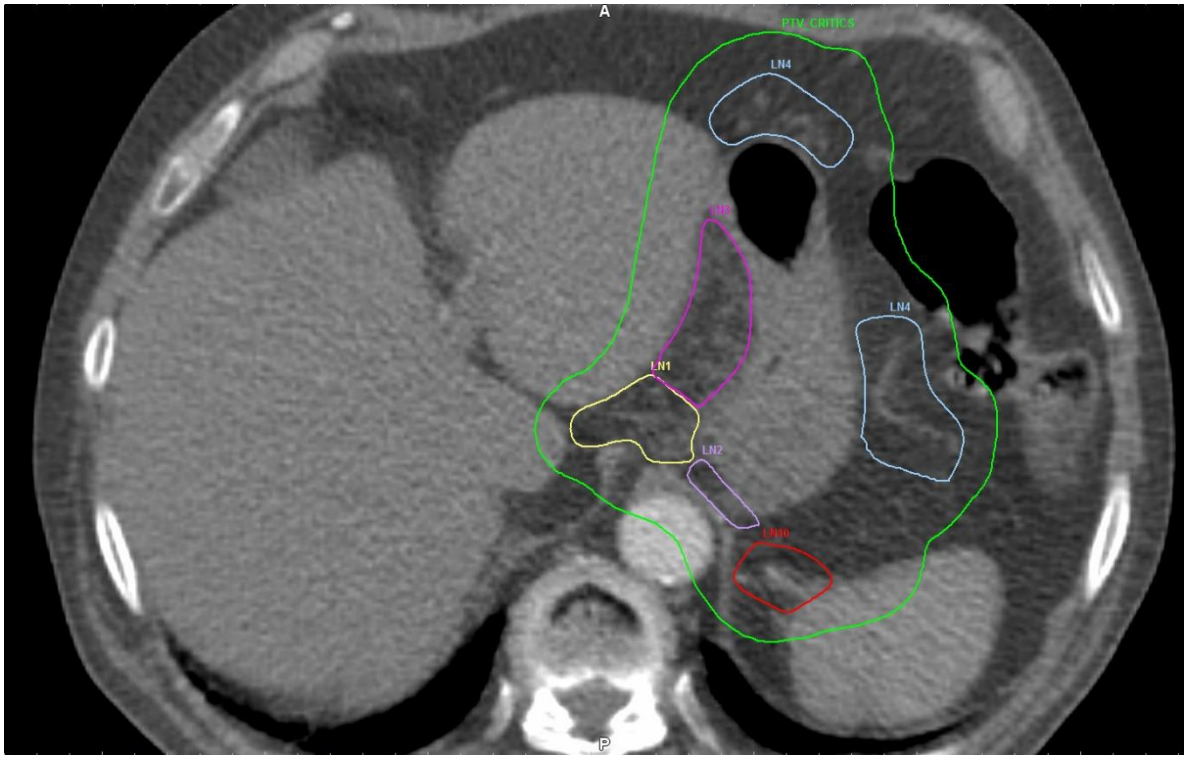

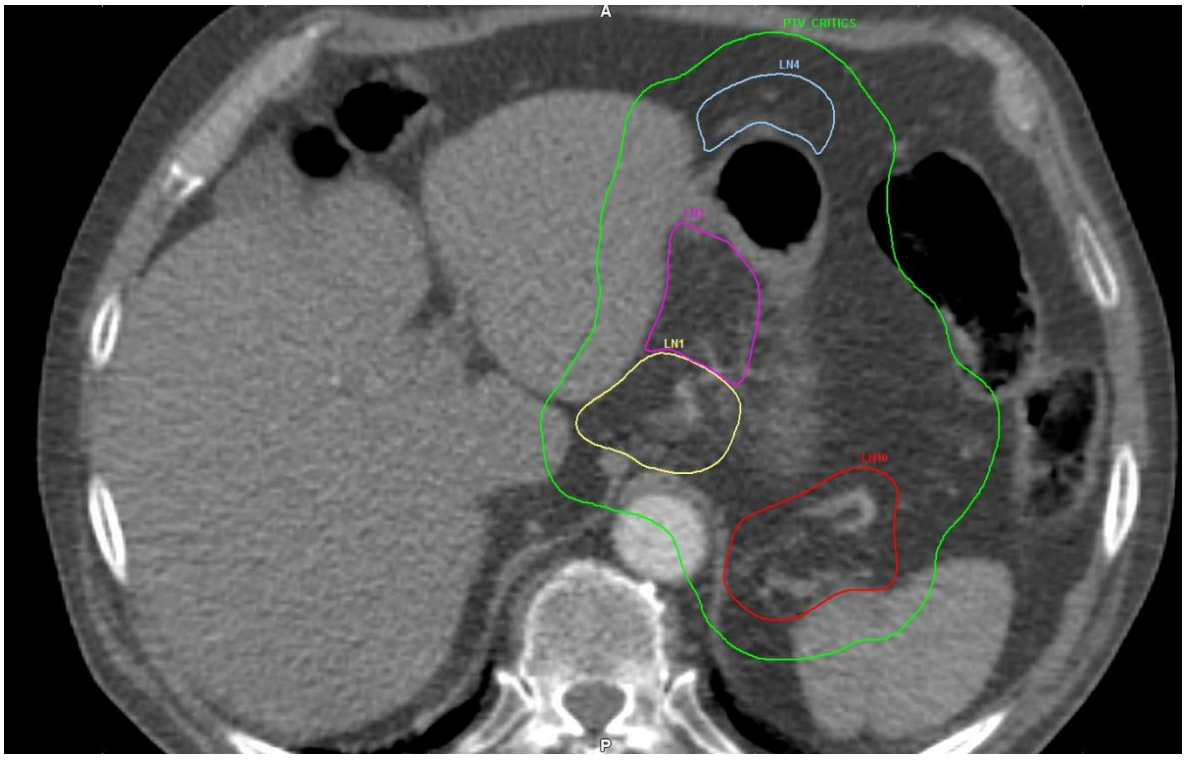

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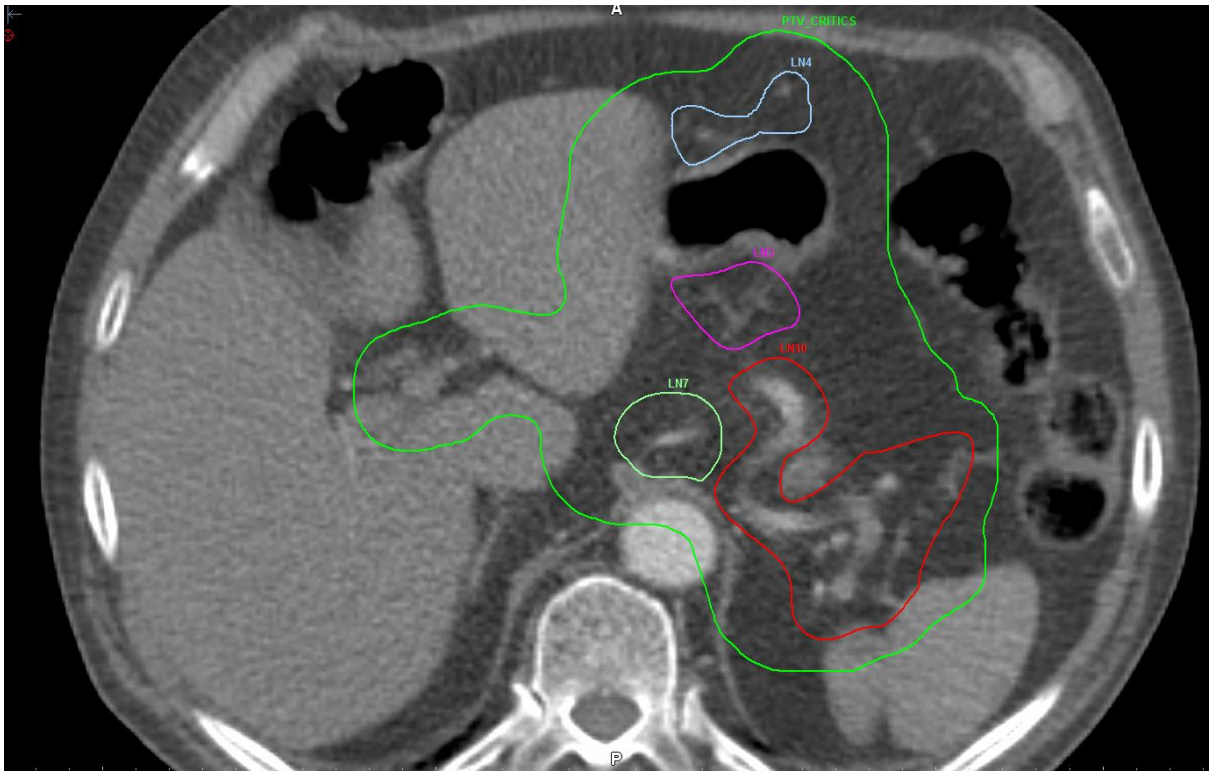

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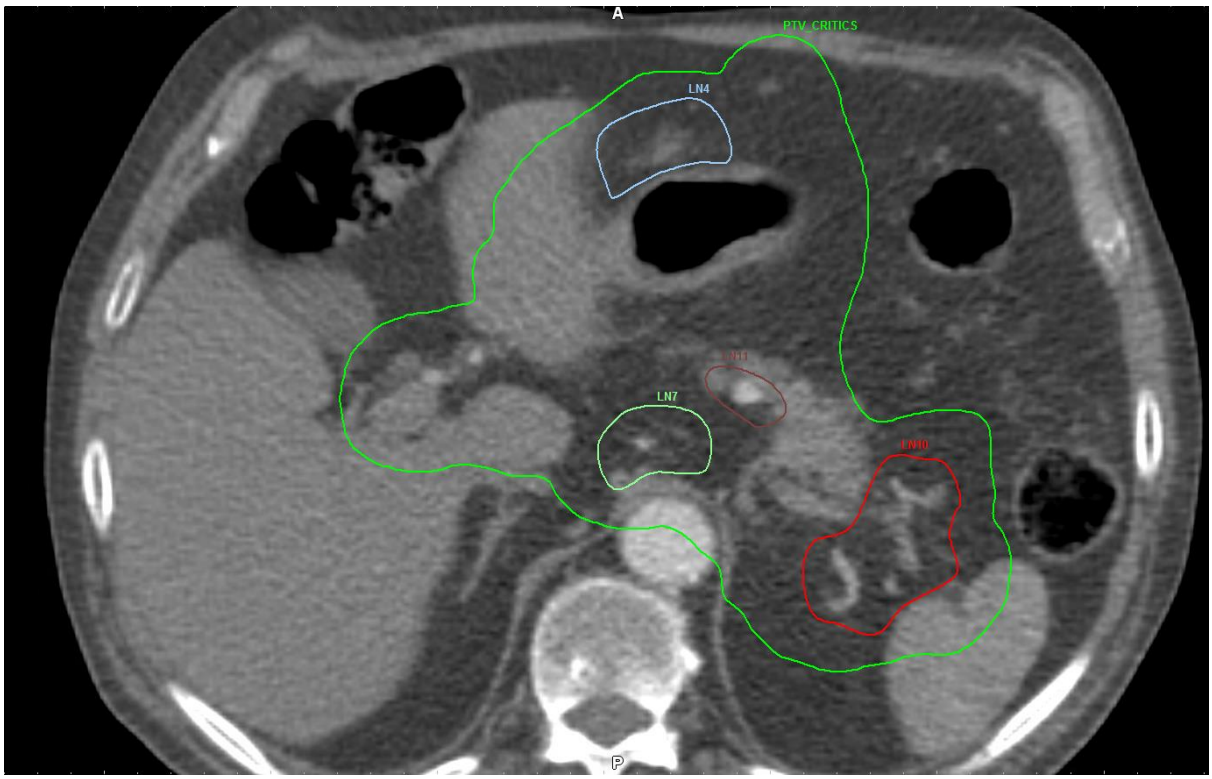

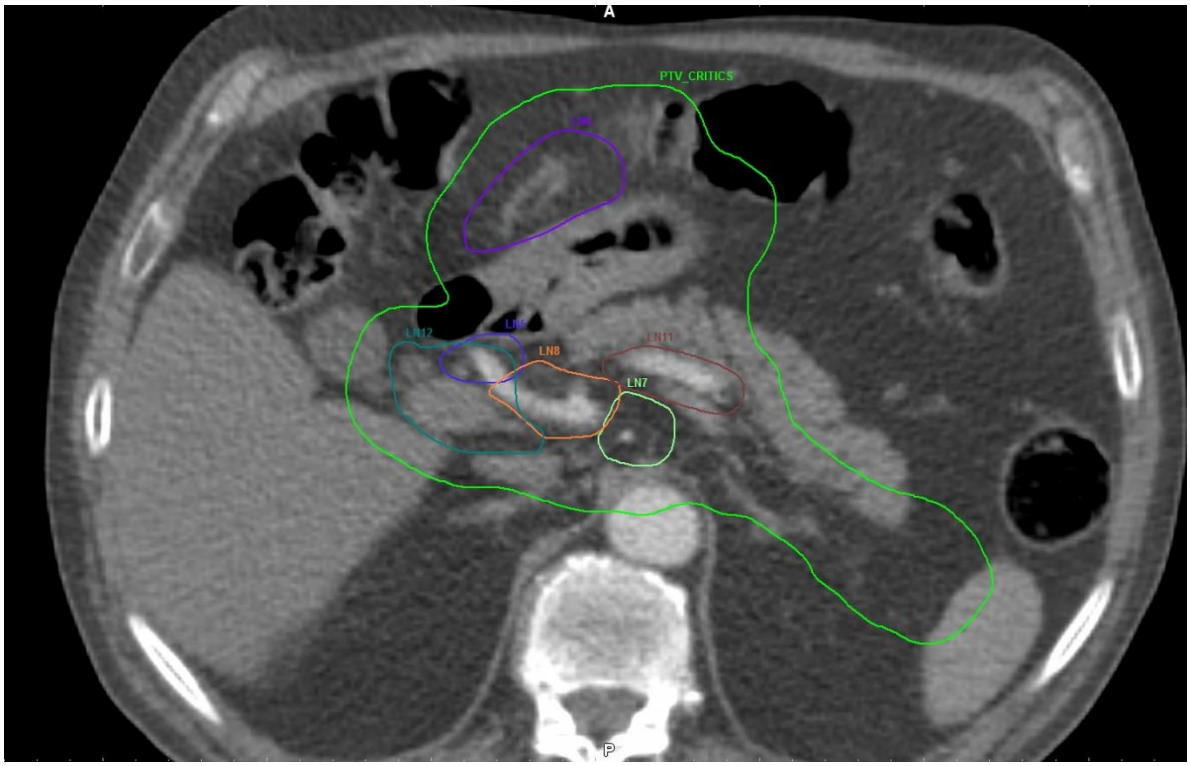
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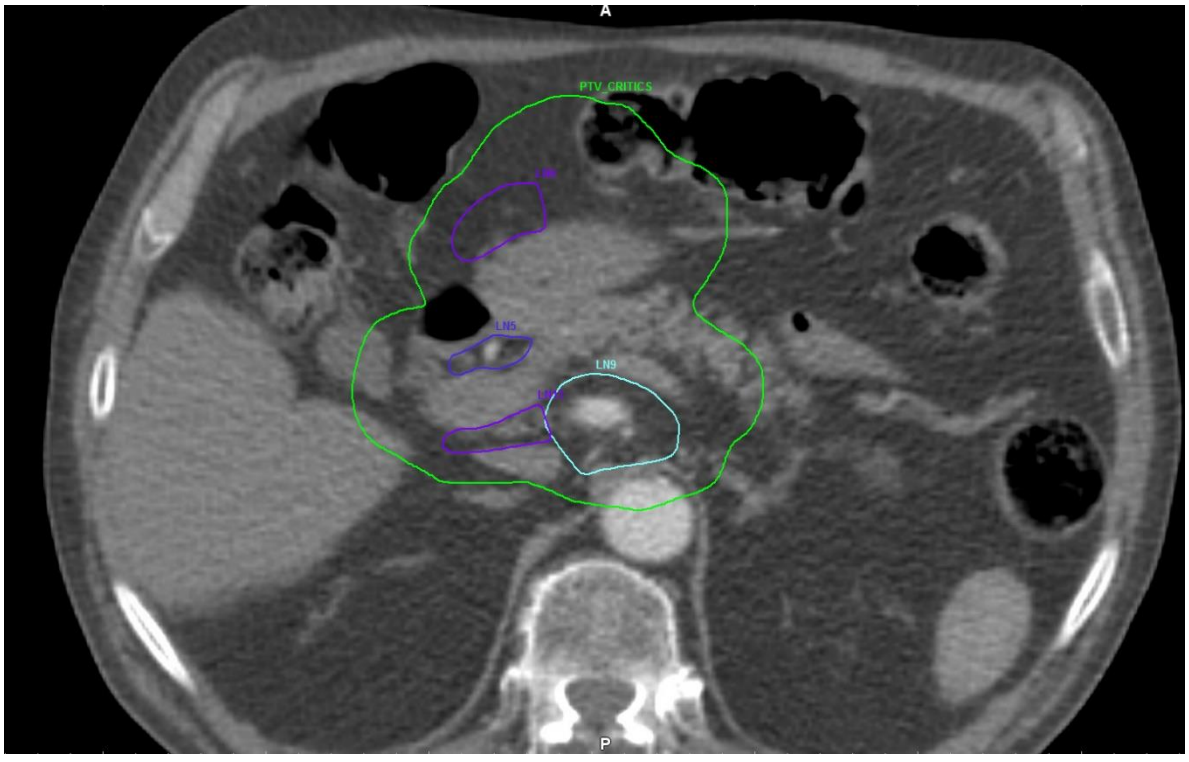
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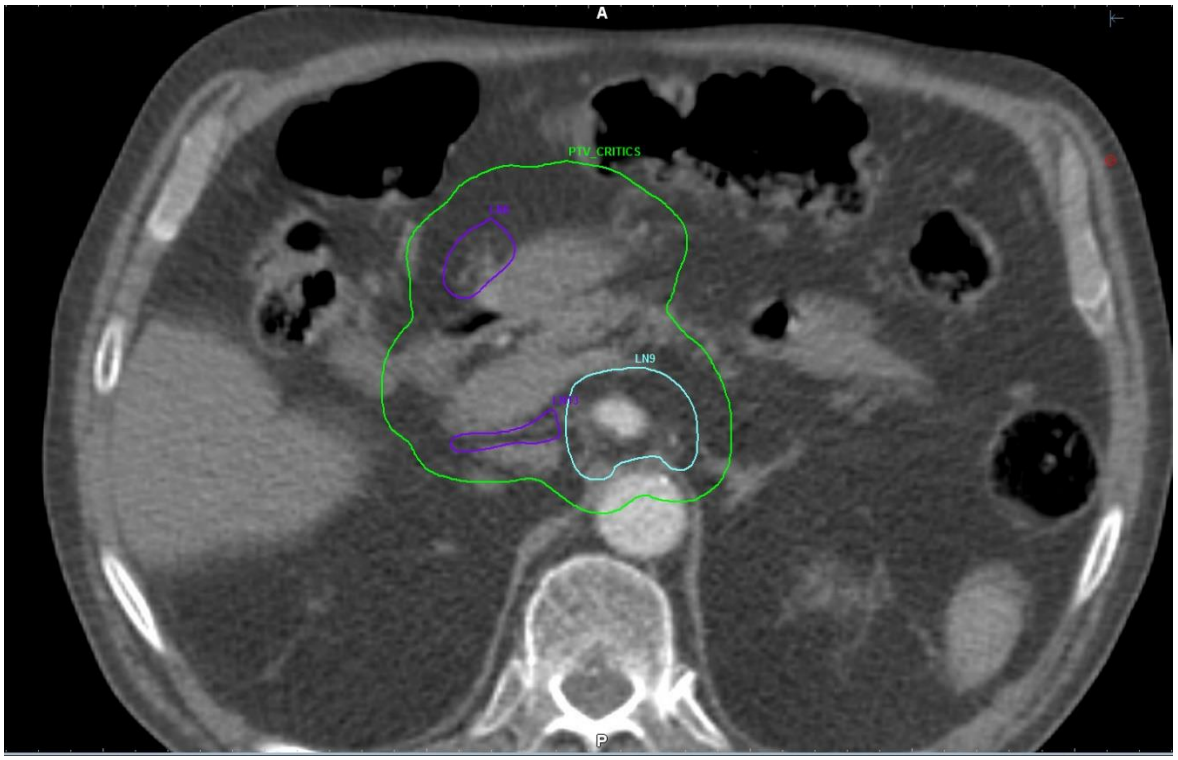

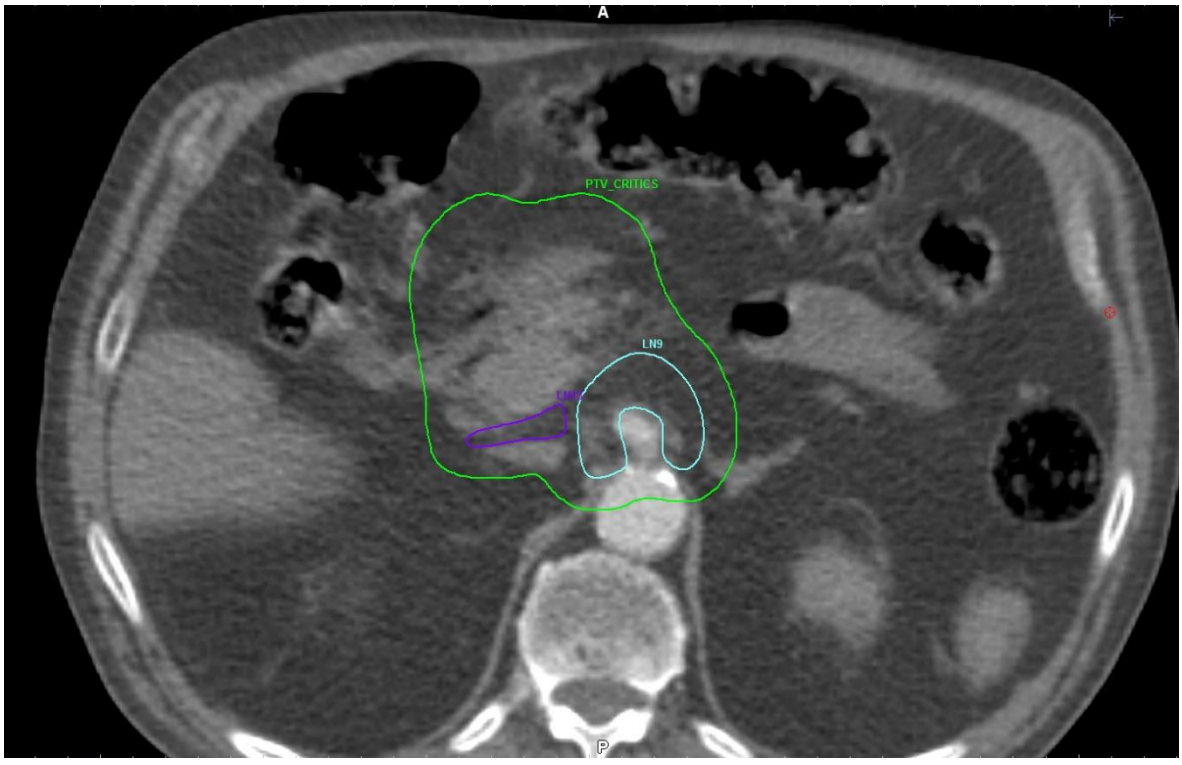

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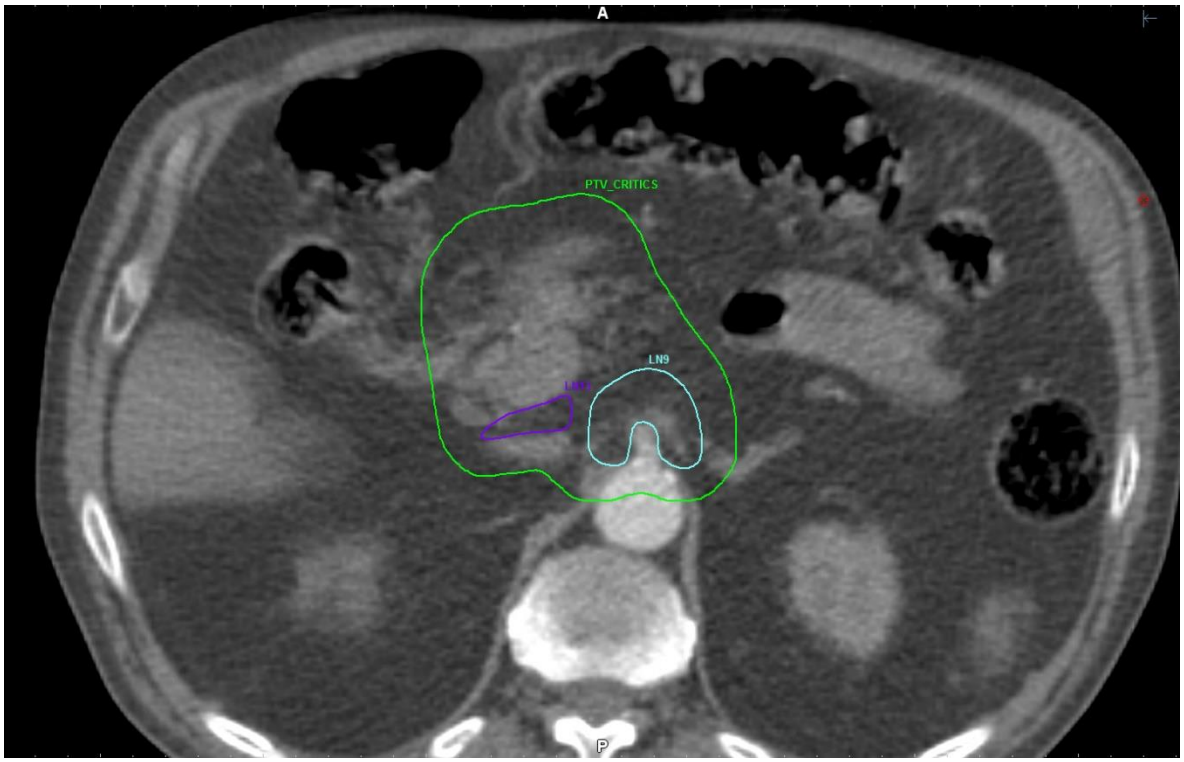

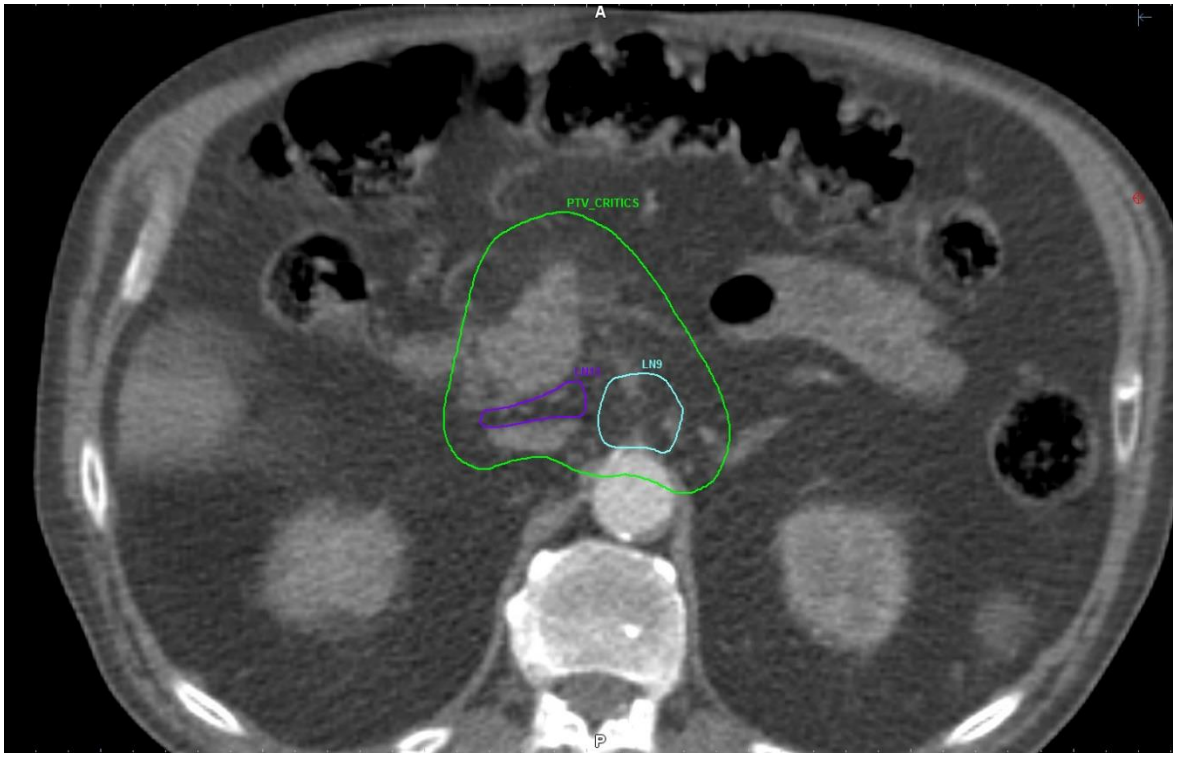

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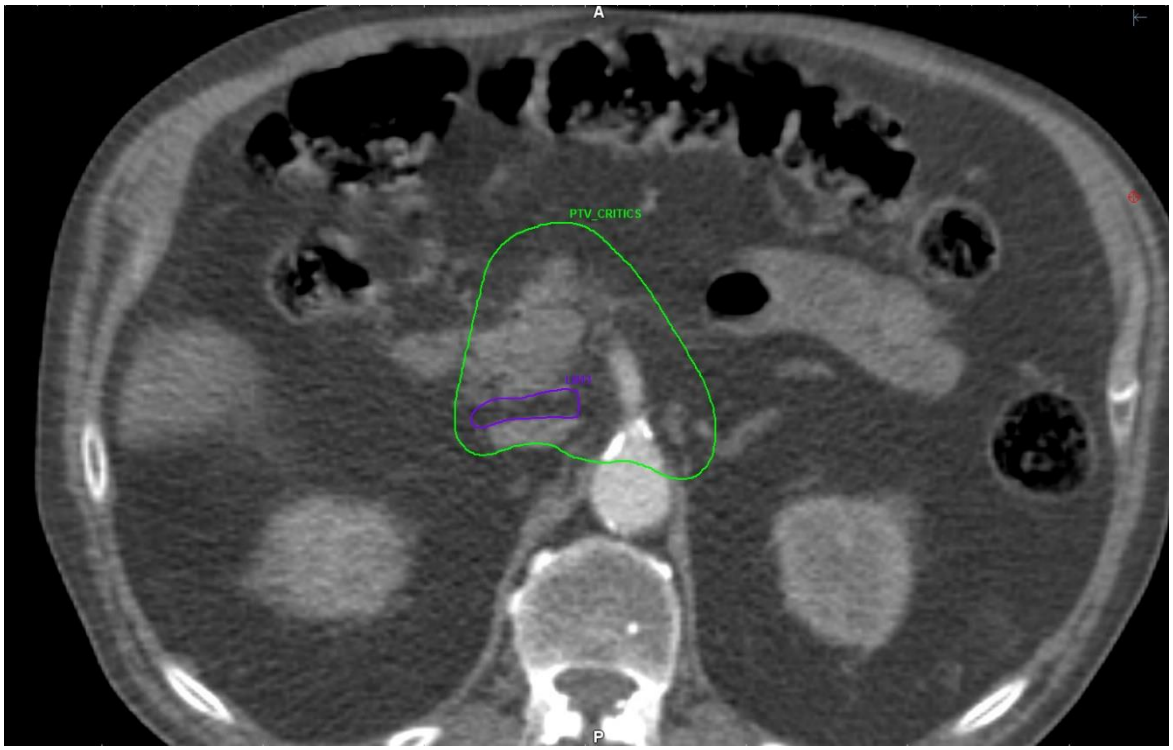

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Glossary

3D-CRT (3D conformal radiotherapy): uses a 3D planning scan and multi-beam arrangements to shape the radiotherapy volume and shield organs at risk.

Alpha/beta ratio (α/β): a measure of the radiosensitivity of specific tissues. A low α/β (1-3) indicates late response in normal tissues (late effects), and high α/β an early response (acute effects).

APPA (Anterior Posterior- Posterior Anterior): Simple technique used for 2D RT planning using two parallel opposed beams (one applied in the anterior – posterior direction, and the other posterior – anterior)

Biologically Effective Dose (BED): allows comparison of fractionation regimens and is used to consider the effect of fractionation on changes in acute and late reactions, and effect on the tumour.

Clinical Complete Response (cCR): total resolution of disease following treatment, as assessed by imaging or macroscopic visual assessment (i.e. not a pathological, microscopic evaluation)

Cone beam CT (CBCT): a low-resolution CT scan acquired during RT treatment to verify position of organs and volumes of interest, and check alignment prior to irradiation.

Conventional fractionation: a dose/fractionation of 1.8 – 2 Gy per fraction

Common Terminology Criteria for Adverse Events (CTCAE): Internationally accepted descriptive terminology which grades adverse events by severity. These are grossly categorised as grade 1 = mild, 2 = moderate, 3 = severe, 4 = life-threatening and 5 resulting in death due to the adverse event.

Deep inspiration breath hold (DIBH): a method of motion management for radiotherapy planning and treatment during which the patient holds a deep breath in order to reduce motion. Inflation of the lungs can also be used to displace organs out of the radiotherapy field.

Equivalent Dose in 2Gy fractions (EQD_2): a method of converting different dose/fractionation regimens to an equivalent schedule in 2Gy fractions

Fractionation: the division of dose into discrete treatments, abbreviated by #.

Gray (Gy): the standard international unit of absorbed radiation dose is Gray (1 Gy = 1 joule/kg^{-1})

Hypofractionation: Increase in number of fractions and reduction in dose per fraction below conventional level, i.e. <1.8Gy per fraction. Causes increased acute effects but decreased late effects

Hypofractionation: Reduction of number of fractions, and increased dose per fraction relative to conventional i.e. >2Gy per fraction (e.g. 20Gy/5#).Causes increased late effects but decreased acute effects.

Image guided radiotherapy (IGRT): uses imaging to guide precision radiotherapy by checking tumour location at the time of radiotherapy. There are various forms, for example using CBCT, MRI or fiducials (radio-opaque seeds planted near the tumour to guide treatment).

Intensity modulated radiotherapy (IMRT): a modern radiotherapy technique that uses advanced computer programs to plan multiple beams from various angles, and of varying intensity to create highly conformal treatment plans.

Pathological complete response (pCR): total resolution of all sites of cancer following treatment, with no cells visible on pathological microscopic assessment.

Volumetric modulated arc therapy (VMAT): delivers radiotherapy using a beam that continuously moves around the patient in an arc, whilst changing in shape and intensity, to allow rapid delivery of highly conformal treatment plans.

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