Working in partnership with West Midlands cancer alliance

WEST MIDLANDS RADIOTHERAPY NETWORK

West Midlands Radiotherapy Clinical Protocol

Upper Gastrointestinal Radiotherapy Protocol

Revision History

Version	Date	Summary of changes
1.0	07.05.2021	Approval by EAG
2.0	08.12.2023	EAG Approved
3.0	12.6.2026	Various changes agreed by review group and with lead input from Dr Scott-Brown Ratified by EAG
Review Date	June 2028	

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1. Purpose

To provide a standardised departmental protocol for planning and delivery of external beam radiotherapy for patients with gastro-oesophageal, pancreatic and hepatic cancers within the West Midlands.

Please refer to the Royal College of Radiologists (RCR) Dose Fractionation Guidance Version 4, January 2024.

Additional resources are found in the reference section and appendices.

Radiotherapy for upper GI cancers is delivered across the West Midlands as part of collaborative partnership working.

2. Information & Consent

- Each Patient should be consented with individualised information of planned treatment, individualised risk / benefits and toxicities
- Booking form and consent completed by IR(ME)R practitioner
- Patients should also receive a Local patient information sheet or MacMillan information booklets

3. Responsibility

- To comply with the Ionising Radiation (Medical Exposure) Regulations 2017 the following roles are defined:
- Referrer & Practitioner: The consultant clinical oncologist is responsible for the care of the patient including correct referral for treatment consent, justification prescription and treatment authorization as defined in departmental protocol but in accordance with this regional protocol.
- Operators: Radiographers, physicists and technologists, Consultant Clinical Oncologists and other medical staff are responsible for individual tasks associated with the plan production, verification and treatment delivery as per departmental protocols but in accordance with this regional protocol and are undertaken on the auspices of the practitioner.
- It is the responsibility of department management teams to ensure departmental protocols are consistent with this regional protocol and that any disagreement with the content of this protocol is raised through the West Midlands Expert Advisory Group.

4. Clinical Trials

- All patients that are eligible should be offered the opportunity to join a clinical trial
- A full list of available clinical trials can be found at Clinical trials - West Midlands Radiotherapy Network

5. Peer review

Peer review should be undertaken in line with the West Midlands regional guidance agreed in December 2025 which identifies which cases should be subject (as a minimum) to peer review.

6. Oesophagogastric Cancers

6.1 Indications for Adenocarcinomas

Neo-adjuvant

- Neo-adjuvant chemo-radiotherapy prior to surgery for operable oesophageal and gastro-oesophageal junction adenocarcinomas (although in the UK peri-operative chemotherapy usually favoured over neo-adjuvant chemoradiotherapy)

Definitive

- No clear role for definitive radiotherapy or chemoradiotherapy in gastro-oesophageal adenocarcinomas, may be considered in patients not suitable for resection.

Adjuvant

- Patients with resected adenocarcinomas that are R1, at low risk of distant recurrence, may be considered for post-operative chemoradiotherapy.

Non-curable

- Palliative radiotherapy as indicated

6.2 Indications for Squamous Cell Carcinomas (SCC)

Neo-adjuvant

- Neo-adjuvant chemo-radiotherapy prior to surgery for operable oesophageal and gastro-oesophageal junction squamous cell carcinomas

Definitive

- Definitive chemoradiotherapy for oesophageal and gastro-oesophageal junction squamous cell carcinomas

Adjuvant

- No clear role for post-operative radiotherapy as patients undergoing surgery for SCC are likely to have had neo-adjuvant chemoradiotherapy

Non-curable

- Palliative radiotherapy as indicated

6.3 Pre-referral Investigations

- Bloods (FBC, U&E, LFT, Bone profile)
- Endoscopy
- Biopsy for histological confirmation
- CT chest, abdomen and pelvis with contrast
- Endoscopic ultrasound (EUS) if potentially resectable – decision regarding need for EUS is made at the MDT on a case-by-case basis
- 18-FDG PET scan if radically treatable
- Staging laparoscopy if gastric adenocarcinoma or adenocarcinoma involving gastro-oesophageal junction
- Full lung function

6.4 Dose and Fractionation

Neo-adjuvant

- 41.4Gy in 23# with weekly concurrent Carboplatin and Paclitaxel

Definitive

- 50Gy in 25# with induction and concurrent chemotherapy (Cisplatin and Capecitabine; or Carboplatin and Paclitaxel; or Carboplatin and Capecitabine)
- 50-55Gy in 20# with no chemotherapy
- Consider 60-65Gy in 30# dose escalation with chemotherapy for cervical oesophageal carcinoma

Adjuvant

- 40-50 Gy in conventional fractionation schedules with consideration of concurrent chemotherapy

Non-curable

- 40Gy in 15#
- 30Gy in 10#
- 20Gy in 5#
- 8Gy in 1#

6.5 Scanning Technique

- CT slice thickness of 2.5mm is recommended, but any thickness ≤3mm is adequate.
- Patients should be scanned in the treatment position:

i) For cervical and upper 1/3 oesophageal tumours: patients will be scanned supine with arms down by their side with knee support and immobilisation using a 5 point shell or equivalent.

ii) For middle 1/3, lower 1/3 and GOJ tumours: patients will be scanned supine with arms above head with knee support and immobilisation with thermoplastic device or vacuum cushion as per local protocols.

- 3DCT should be acquired with patient free-breathing rather (as opposed to breath-hold).
- Use of 4DCT:

i) For proximal (cervical, upper and middle 1/3 tumours): 4DCT planning scans should not be used.

ii) For distal (lower 1/3 and GOJ tumours): 4DCT planning scans should be considered (see SCOPE 2 Protocol – in appendix 1)

- Intravenous contrast should be used (providing there is no contraindication) but no oral contrast
- The use of oral contrast is not recommended, but maybe used for selected patients at the discretion of the prescribing clinician.
- Patients should be asked to fast for 2 hours and then drink 200mls of liquid 30 minutes prior to CT planning *and* treatment in an attempt to reproduce the same anatomical position of the stomach due to filling throughout treatment. Variations to this procedure are permitted, particularly for patients with tumours of cervical, upper and middle 1/3 oesophagus where stomach preparation may have negligible benefit, but it is crucial the same stomach preparation procedure is followed before planning and treatment. Patients who have a nasogastric tube inserted and are unable to drink due to dysphagia should use their tube for this purpose.

1. Superior scan limits should be 1cm superior to the apices of the lungs or 6cm superior to the proximal disease, whichever is highest
2. Inferior scan limits should be L4 for mid and lower third patients to ensure adequate OAR coverage, but can be to bottom of lungs for upper third patients

Diagnostic information should be taken from the diagnostic CT scan, EUS if undertaken (referenced to CT identifiable structure) and PET-CT

6.6 Target Delineation

Neo-Adjuvant

- As per NeoAEGIS clinical trial protocol (see appendix 2)

Definitive

- As per SCOPE2 clinical trial protocol (see appendix 1)
- If escalating dose for cervical oesophagus SCC use Leeds Upper 1/3rd Oesophageal protocol (see Appendix 3 – note this is currently under review as at March 2026)

Adjuvant

- Use pre-operative staging investigations as well as operative notes to delineate tumour bed and likely area of margin positivity.

Palliative

- As per Oncologist's preference

6.7 Organs at Risk

	41.4Gy in 23# (Neo-Aegis)	**50Gy in 25#** (SCOPE2) and **50Gy in 20#**		
Structure name		**Constraint**	**Optimal**	**Mandatory**
External	D1.8cc <107% of highest prescribed dose	D1.8cc	<107% of highest prescribed dose	
Spinal Cord	D0.1cc < 45Gy			
SpinalCord_PRV	D1cc <40Gy clinician may allow a discretionally point maximum dose up to 45Gy	D0.035cc *	< 40Gy	< 42Gy
Heart	V40 < 30% V25 < 50%	Dmean V30Gy	< 25Gy < 45%	<30Gy -
Lungs (Combined lungs)	V20 < 25%	Dmean V20Gy	< 17Gy < 20%	<19Gy ≤25%
Stomach_excl_PTV (Stomach excluding PTV_5000)	Not defined	V50Gy	< 16cc	< 25cc
Liver	V30 < 30%	Dmean V30Gy	≤28Gy < 30%	≤30Gy -
Kidney_L and Kidney_R (Individual kidneys)	V20 < 70% with contralateral kidney V20 <30% Combined V20 < 50%	V20Gy	< 25%	≤30%

*An alternative suitably small volume may also be used if it is not possible to report the dose to 0.035cc within the TPS used.

6.8 Pre-Treatment/Treatment Verification

- Daily online imaging performed using 3D cone beam CT or Tomotherapy MVCT as available
- Local protocols must be available describing action levels and concomitant patient imaging doses.

7. Stomach cancers

7.1 Palliative

- 6-8 Gy in 1#
- 20 Gy in 5# over 1 week

As per RCR Guideline 2024 - outside of palliative setting, role of radiotherapy in gastric cancer is unclear, and lack contemporaneous evidence of clinical benefit.

8. Pancreatic cancers

8.1 Indications

- Borderline resectable or locally advanced pancreatic cancers meeting the following criteria:
    - Biopsy proven adenocarcinoma of the pancreas / ampulla
    - PS ≤ 2
    - No evidence of distant metastases (normally before and after 3-6 months of neo-adjuvant chemotherapy)
    - No prior abdominal radiotherapy
    - Agreement of Hepatobiliary MDT
    - This protocol could be used for specific and selected patients where the target organs are closely associated (duodenal/small bowel). These patients will remain off protocol and require counter-signature by a member of the pancreas site team and MPE.
- Palliative Radiotherapy as indicated

8.2 Pre-Referral Investigations

- Blood tests (FBC, U&E, LFT, Bone profile, Ca19.9)
- Biopsy with confirmatory histology
- CT scan of chest, abdomen and pelvis with contrast
- Consider 18-FDG PET scan

8.3 Dose and Fractionation

- 50.4Gy in 28# with concurrent Capecitabine
- 36-45Gy in 15# with concurrent Capecitabine
- See section below for SABR option

- Palliative
  - 30-36 Gy in 10-12#
  - 20-25 Gy in 5
  - 8-10 Gy in 1#

8.4 Scanning Technique

- The RCR Covid guidelines (2020) for Pancreas (scanning technique, contouring guidelines and target delineation) are still applicable
- For those wishing to use 28#, refer to SCALOP-2 clinical trial protocol (see appendix 5)

8.5 Target Delineation

- Consider SCALOP-2 clinical trial protocol (see appendix 5

8.6 Organs at Risk

Structure	Tolerance	
	50.4Gy in 28#	36-45Gy in 15#
Kidney	V20 < 40% (individual) V20 < 30% (combined)	Mean combined <12Gy If single kidney or one kidney receives >12Gy mean dose then single kidney or kidney receiving lower dose V12 < 10%
Liver	V30 < 30% Mean dose 28Gy	Mean dose <24Gy
Stomach	Dmax 0.1cc < 58Gy V50 < 5cc V45 < 75cc	Dmax 0.5cc < 40Gy D5cc < 36Gy
Small Bowel	Dmax 0.1cc < 58Gy V50 < 10cc V15 < 120cc	Dmax 0.5cc < 45Gy D5cc < 36Gy
Duodenum	Dmax 0.1cc < 58Gy V50 < 10cc V15 < 60cc	Dmax 0.5cc < 45Gy D5cc < 36Gy
Large Bowel	-	Dmax 0.5cc < 48Gy
Spinal Cord PRV	Dmax 0.1cc < 45Gy	Dmax 0.1cc < 35Gy

8.7 Pre-Treatment/Treatment Verification

- Daily online imaging performed using 3D cone beam CT or Tomotherapy MVCT as available

- Local protocols must be available describing action levels and concomitant patient imaging doses.

8.8 SABR for Primary Pancreas and biliary tract

Patients who may be suitable for SABR should be referred to your local pancreatic SABR provider Locally advanced non-metastatic pancreatic cancer meeting the eligibility criteria for SABR.

Patients should meet all the following **inclusion criteria**:

• Over 18 years old

• Have a diagnosis of LANPC following a specialist pancreatic or hepatopancreaticobiliary (HPB) MDT and are unsuitable for surgery

• Histology or cytology confirming adenocarcinoma, OR; if no tissue diagnosis, only where this has been agreed by the HPB MDT as appropriate i.e. radiology and clinical presentation strongly support a diagnosis of malignancy and repeated attempts at obtaining tissue have been unsuccessful

• Have received at least 3 months of systemic chemotherapy and the disease has remained localised, OR; patients where systemic therapy has had to be terminated early due to chemotherapy toxicity but where performance status remains ≤ 2 following HPB MDT discussion

• Locoregional disease where the primary tumour +/- involved nodes can be encompassed in a radiation volume

• Adequate pancreatobiliary drainage (patent stent, where present, and bilirubin less than 1.5 times the upper limit of normal)

• Patients are suitable for pancreas SABR as determined by SABR and/or specialist HPB MDT. *Technical suitability should be assessed by the MDT and should include motion management or mitigation. A strict upper limit on tumour size is not specified as tumour location and proximity to organs at risk will dictate suitability for SABR but, generally it would be expected that target size should be ≤7 cm*.

• WHO performance status ≤ 2

Treatment with SABR is unsuitable for people who:

• Are not considered candidates for chemotherapy, in whom palliative radiotherapy may be offered primarily for symptom management

• Have received prior upper abdominal radiotherapy

• Have a tumour directly invading the gastro-intestinal (GI) tract - defined as gross invasion into GI tract lumen as evidenced on endoscopy and/or on cross sectional imaging

• Have evidence of metastatic disease

9. Hepatic Cancers

Patients who may be suitable for SABR should be referred to local approved Hepatic SABR centre.

To be eligible for SABR, patients must meet the following criteria:

- Confirmed diagnosis of localised HCC (primary, recurrent or progressive disease) by at least one criterion listed below:
  - Pathologically (histologically or cytologically) proven diagnosis of HCC
  - Radiological imaging consistent with classical HCC appearances
- No evidence of extrahepatic metastases or malignant nodes > 3.0 cm in sum of maximal diameters.
- Unsuitable for surgical resection or transplant
- Unsuitable or refractory to TACE
- ECOG performance status 0-1
- Adequate haematological and liver function
- Childs-Pugh Class A
- Maximum dimension of any lesion 5 cm
- Life expectancy greater than 6 months

10. Clinical Monitoring

10.1 On Treatment Review

- Clinical review and monitoring of blood tests to be conducted as indicated
- After completion of treatment arrangements should be made for patients to be seen in the outpatient clinic for clinical review

10.2 End of Treatment Letter

- On completion of treatment a summary of the radiotherapy dose administered and toxicities experienced are documented
- In addition, the expected acute and late side effects are detailed with recommended treatments

11. References

SCOPE-2: Study of Chemoradiotherapy in Oesophageal cancer including PET response and dose Escalation V3 31.01.2020

SCALOP-2 Trial protocol: Systemic therapy and Chemoradiation in Advanced Localised Pancreatic Cancer - 2. V5

The Royal College of Radiologists. "Radiotherapy dose fractionation" *4th edition*. 2024

Leeds Cancer Centre. Upper Third Oesophageal Cancer Single Phase Clinical Protocol. V3 22.04.2015

NHS England. Clinical Commissioning Policy for Stereotactic Ablative Radiotherapy (SABR) for Hepatocellular Carcinoma (Adults) (URN: 1913) [200206P]

Royal College of Radiologists, Radiotherapy dose fractionation Fourth edition, 2024

Review of upper GI protocol

This protocol was reviewed and agreed by the WM Radiotherapy Upper GI review group in March 2025
Expert input: Dr Scott-Brown, UHCW
Clinical reviewers: Dr Mano Joseph, UHNM and Dr Rajanee Bhana, RT Network clinical lead, Dr Dev Srinivasan, RWT
MPE lead: Helen Howard, UHB, Gareth Webster, WAH
Other reviewers: Dr Thilina Ruwanpura, UHNM; Simon Jassel, UHNM; Puja Hillman, RWT; Melissa Cowell, RWT; Georgina Glennon, SaTH

Appendix 1 Scope 2 trial

SCOPE 2

Radiotherapy Planning Guidance Document

SCOPE2: **S**tudy of **C**hemoradiotherapy in **O**esophageal cancer including **P**ET response and dose **E**scalation

A randomised Phase II/III trial to study radiotherapy dose escalation in patients with oesophageal cancer treated with definitive chemo-radiation with an embedded Phase II trial for patients with a poor early response using positron emission tomography (PET)

Version:	**3.0**
Date:	**31/01/2020**
EudraCT No.:	**2015-001740-11**
Funder:	**Cancer Research UK**
Name of Sponsor:	**Velindre NHS Trust**

Appendix 1 Scope 2 trial protocol

3 Target volume delineation

General principles of target volumes defined in this protocol

3.1 Target volume definition (TVD)

Patients will be divided into two separate groups according to the location of the *centre of the primary tumour*:

a) Proximal tumours (tumours of cervical, upper and middle 1/3 oesophagus) defined here as primary tumours whose midpoint is above 32cm ab oral (NB proximal extent of primary being no more proximal than 15cm ab oral is an eligibility criteria).

b) Distal tumours (tumours of lower 1/3 of oesophagus and gastro-oesophageal junction (GOJ)), defined here as primary tumours whose midpoint is below 32cm ab oral (NB distal extent of primary tumour being less than 2cm from the GOJ is an eligibility criteria).

This distinction accounts for the need to manually outline the CTV below the GOJ for lower tumours. There is also significant movement in this region, particularly due to respiration, which requires a larger PTV margin. Where possible, centres will be encouraged to use 4DCT for planning of lower tumours so margins for Internal Target Volume (ITV) are patient specific.

The target volume definitions used in SCOPE2 for the most part follows the principles previously established in SCOPE1 and NeoSCOPE studies and are detailed in the next sections, but there are differences and investigators are encouraged to read this protocol carefully.

Please conform to the suggested nomenclature used in this protocol (including upper/lowercase characters & spaces or additional characters).

GTV

Two GTVs are to be defined, both taking into account all of the available diagnostic information. GTVp is defined as the primary tumour and involved peri-oesophageal nodes (within 30mm of primary tumour) and GTVn is defined as lymph nodes which are >30mm from the primary tumour. Creation of both of these volumes is necessary as only GTVp will form the boost volume for the high dose arm. (For cases without separate GTVn volumes above the diaphragm, GTVpn should still be created but will be the same volume as GTVp)

It is acknowledged that the disease delineated may be longer than was initially expected at the time the patient was recruited into the trial (e.g., due to combining diagnostic information from multiple modalities at the time of target volume delineation). If after delineation, the tumour fails any of the trial inclusion criteria (e.g., length of disease, extension beyond GOJ) please note this on the Plan Assessment Form and inform the RTTQA contact as soon as possible. The SCOPE2 TMG reviewers will review the target volumes delineated and whether OAR dose objectives are within tolerance to determine whether a protocol deviation is recorded or whether to recommend that the patient's radiotherapy treatment should be modified, or in certain circumstances treated outside of the trial. The presence of a hiatus hernia can also cause challenges in defining the GTV; if unsure how to proceed in this situation, please inform the RTTQA contact as soon as possible.

Appendix 1 Scope 2 trial protocol

CTV

Clinical target volume encompasses the areas at risk of microscopic spread and involves the fatty peri-oesophageal tissue extending cranially and caudally along the oesophagus and is limited by surrounding normal structures such as large vessels, vertebra, pericardium, pleura and liver. CTV is edited for normal structures, recognising that these are natural barriers to spread. Most of this editing will apply above the diaphragm but should be continued below the diaphragm where appropriate. However, we have defined an absolute minimum GTV-to-CTV margin of 5mm; this ensures that the editing of CTV for normal structures is not taken completely back to GTV. CTV should also not be edited for a normal structure affected by T4 disease at any point along the CTV's length, e.g., in the context of T4 right pleural disease, do not edit the CTV extending into right lung at all (for an example see Appendix 2).

Above the diaphragm the nodal areas at risk are within the CTV, but below the diaphragm manual editing of CTV is needed to include the nodal areas at risk (see atlas in Appendix 1 and worked examples in Appendix 3-4). This includes any involved nodes plus margin (CTVn), and the elective nodal regions at high risk of microscopic spread along the lesser curve of stomach, the left gastric artery and coeliac region where these lie within 20mm inferior of the GTV. Superiorly, this volume includes the fat space below the diaphragm around the cardia and gastrohepatic fat between the lesser curve and the medial liver edge. Inferiorly, it includes the fat space around the coeliac artery, bounded by the pancreas anteriorly, small bowel and liver laterally, and aorta posteriorly, where this is within 20mm of the GTV (see Appendix 4 for example). This is not full elective lymph node irradiation, rather this is growth of the CTV in the direction of known lymphatic spread (see lymph node stations below). An assessment of the potential for mucosal spread into the stomach must be made on a case by case basis. To account for mucosal spread, CTV is extended along the mucosa of the lesser curve of the stomach. This volume should also be extended anteriorly to include the gastrohepatic ligament. Please see Section 0 and worked examples in Appendix 4. The elective nodal regions of the splenic hilum, greater curvature, and short gastric vessels are **not** included, even for patients with Type II GOJ tumours.

There is no elective lymph node radiotherapy for proximal (cervical, upper or middle 1/3) tumours.

Appendix 1 Scope 2 trial protocol

3.2 Proximal tumour target volume delineation without SCF involvement

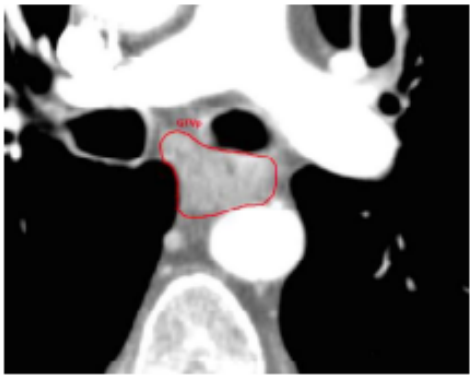
Gross tumour volumes

GTVp consists of the primary tumour, any involved nodes (within 30mm of the primary tumour) and the circumference of the oesophagus at the level of disease. In situations where nodal involvement is found within 30mm superior or inferior of the primary tumour, the whole circumference of the oesophagus between these structures is included in the GTVp. At the level of the involved nodes, the circumference of the oesophagus is also included.

GTVn consists of lymph nodes (LNs) > 30mm away from the edge of the primary tumour. Where more than one GTVn is required these should be named differently i.e., GTVn1, GTVn2 etc. Only the node should be outlined at this stage – it is not required to include the full circumference of the oesophagus. Where it is known that there is LN involvement at a certain level (e.g., on EUS) but not possible with the available imaging to delineate an individual LN for GTVn, the circumference of the oesophagus at the same level may be used as a surrogate.

Note that lymph nodes coincident with the primary tumour (and within 30mm sup-inf of the primary tumour) should be included in GTVp and do not require a separate GTVn structure.

Above the diaphragm, GTVpn is created by combining GTVp, any GTVn volumes above the diaphragm and the circumference of the intervening oesophagus. For cases without separate GTVn volumes above the diaphragm, GTVpn should still be created but will be the same volume as GTVp. (Note: GTVp should also be kept as a separate structure as this will be used to generate PTV_6000 for patients randomised to the high dose arm). For nodes below the diaphragm, although GTVn will be created, it will not be merged with GTVp to create GTVpn.



GTVp (red contour) – the involved coincident subcarinal node is included in GTVp and does not require a separate GTVn volume

Summary of GTVs for proximal tumour target volume delineation

- ***GTVp = primary tumour + any involved nodes within 30mm***
- ***GTVn = any involved nodes >30mm from primary tumour***
- ***GTVpn = GTVp + any GTVn occurring above diaphragm[1]***

Appendix 1: Scope 2 trial protocol

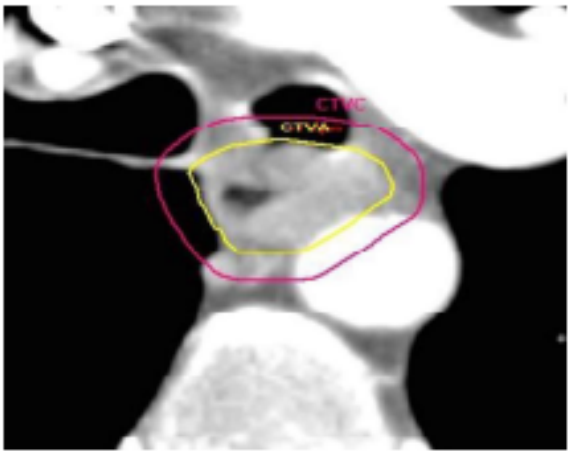
[1] For cases without separate GTVn volumes above the diaphragm, GTVpn = GTVp (but GTVpn should still be created)

Clinical target volumes

Creating CTVs

CTVA is derived by copying GTVpn, renaming this CTVA and growing it manually in both the superior and inferior direction along the axis of the oesophagus to include the entire circumference of the oesophagus. The superior and inferior margin of CTVA will either be 20mm from the superior and inferior extent of GTVp **or** 10mm from the highest/lowest involved lymph node (GTVn), whichever is the more proximal/distal.

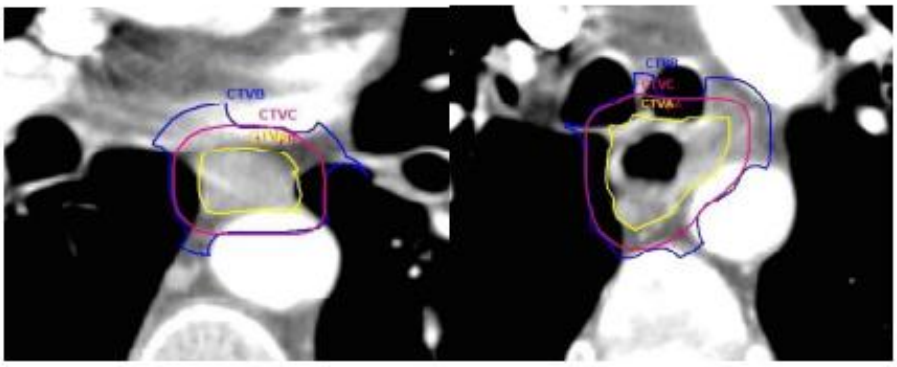
Next CTVC is derived by copying CTVA, renaming it CTVC and growing it 5mm in right-left and anterior-posterior directions using the Treatment Planning System (TPS).



CTVA (yellow contour) and CTVC (pink contour)

Next CTVB is derived by copying CTVA, renaming it CTVB and growing it by 10mm in right-left and anterior-posterior directions using the TPS. CTVB is then edited for barriers to spread to exclude lung, pericardium, large vessels, trachea and right/left main bronchi, liver and the vertebrae, both above and below the diaphragm. Do **not** edit beyond CTVC (see figure below). Note for T4 tumours, CTVB should **not** be edited for a normal structure that is affected by T4 disease **at any point** along the CTV length, e.g. in the context of T4 right pleural disease, do not edit CTVB for the right lung (and see Appendix 2).

Appendix 1: Scope 2 trial protocol



CTVB (blue contour) edited back to CTVC (pink contour) to avoid normal structures

Summary of CTVs for proximal tumour target volume delineation

- ***CTVA = GTVp + 20mm sup-inf (manually grown along direction of oesophagus) OR GTVn + 10mm sup-inf margin[1]***
- ***CTVC = CTVA + 5mm circumferentially (but not sup-inf) – this is the minimum expansion around CTVA and is respected when CTVB is edited***
- ***CTVB = CTVA + 10mm circumferentially (but not sup-inf), edited for normal structures[2] but NOT beyond CTVC***

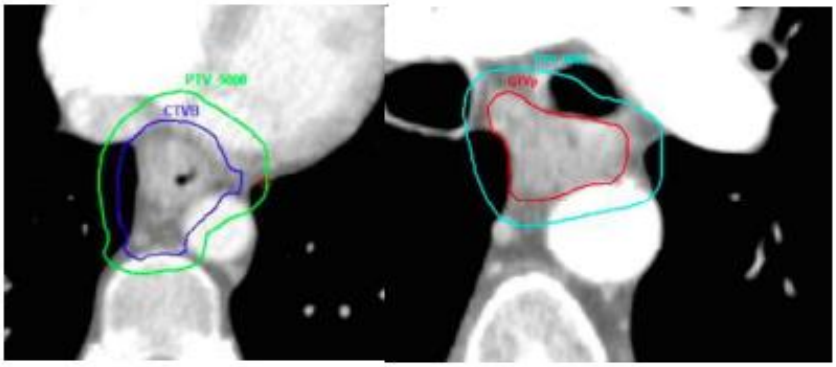
[1] If GTVn is more proximal/distal than GTVp

[2] Normal structures include lung, pericardium, large vessels, trachea, right and left main bronchi, liver and the vertebrae, both above and below the diaphragm.

Planning target volumes

In both the standard and high dose arms, PTV_5000 is derived by growing CTVB by 10mm in the sup-inf direction and 5mm circumferentially using the TPS.

In the high dose arm, PTV_6000 is derived by growing GTVp by 5mm in all directions using the TPS.



PTV_5000 (green contour) and PTV_6000 (turquoise contour)

Appendix 1: Scope 2 trial protocol

Summary of PTVs for proximal tumour target volume delineation

- ***Standard arm: PTV_5000 = CTVB + 10mm sup-inf + 5mm circumferentially***
- ***High dose arm: PTV_5000 = CTVB + 10mm sup-inf + 5mm circumferentially***
  PTV_6000 = GTVp + 5mm sup-inf + 5mm circumferentially

Section 3.66 provides a quick reference tabular summary of target volume delineation

Appendix 1: Scope 2 trial protocol

3.3 Proximal tumour target volume delineation with SCF involvement

Patients with tumours of the upper third that are more than 15cm ab oral are eligible for participation in SCOPE2. Involvement of supraclavicular (SCF) lymph nodes (LNs) are considered N+ rather than M1 disease by TNM criteria and therefore eligible for participation providing total contiguous disease length is <13cm. Please note, this guidance applicable for eligible patients according to updated eligibility criteria which states "tumours staged as T1-4 and N+/-, as described in section 6.1. M1 nodes which are encompassable within the radical radiotherapy volume are eligible".

For cervical and upper 1/3 oesophageal tumours: patients will be scanned supine with arms down by their side with knee support and immobilisation using a 5 point shell or equivalent.

Gross tumour volumes

Delineation of GTVp and GTVn follows the protocol as outlined in section 3.2. For patient with involved LNs in the SCF that are > 30mm from GTVp, the involved LNs should be outlined separately as GTVn. Where more than one GTVn is required these may be helpfully named separately, e.g. GTVn1, GTVn2 etc, depending on the TPS available.

Clinical Target Volumes

For patient with N0 disease, DO NOT include any areas of elective nodal irradiation. CTV volumes follow that of section 3.2.

GTVn are grown by a 5mm margin (6mm sup-inf if using 3mm slices) in all directions and labelled CTVn (for multiple nodes, label as CTVn1, CTVn2 etc.). This defines a minimum margin around positive nodes to assist in the delineation of CTVscf.

Delineate the whole of the supraclavicular (SCF) nodal region on both the ipsilateral and contralateral side ensuring the minimum margin of 5mm around positive nodes. We have used the RTOG Breast Outlining Guidance for definition of the SCF. The whole ipsilateral and contralateral SCF should then delineated and labelled CTVscf.

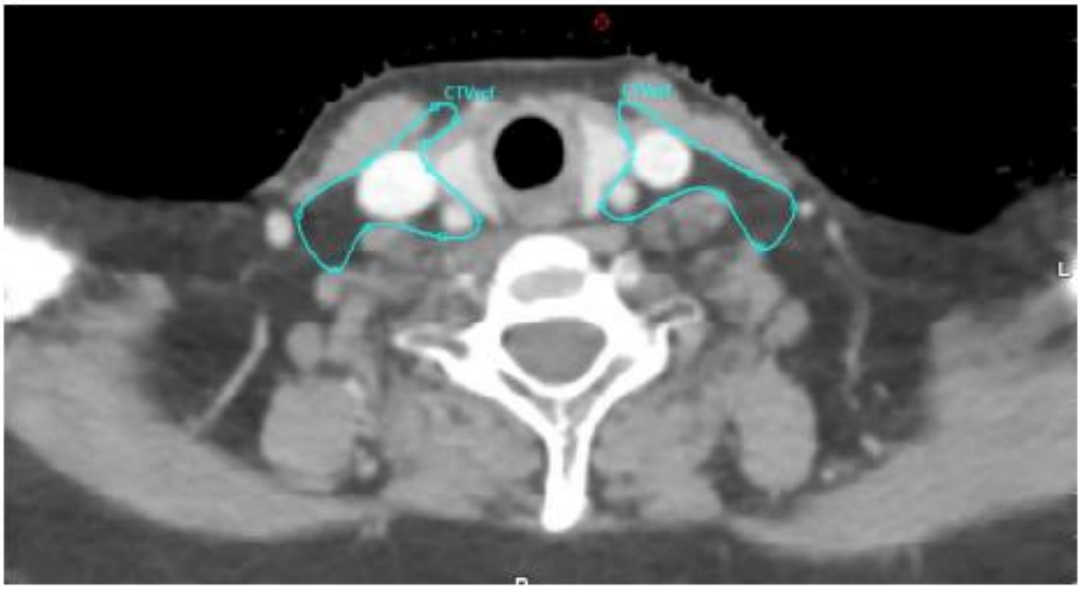
<u>Anatomical Boundaries for the Supraclavicular Fossa</u>

(Adapted from the RTOG Breast Cancer Contouring Atlas)

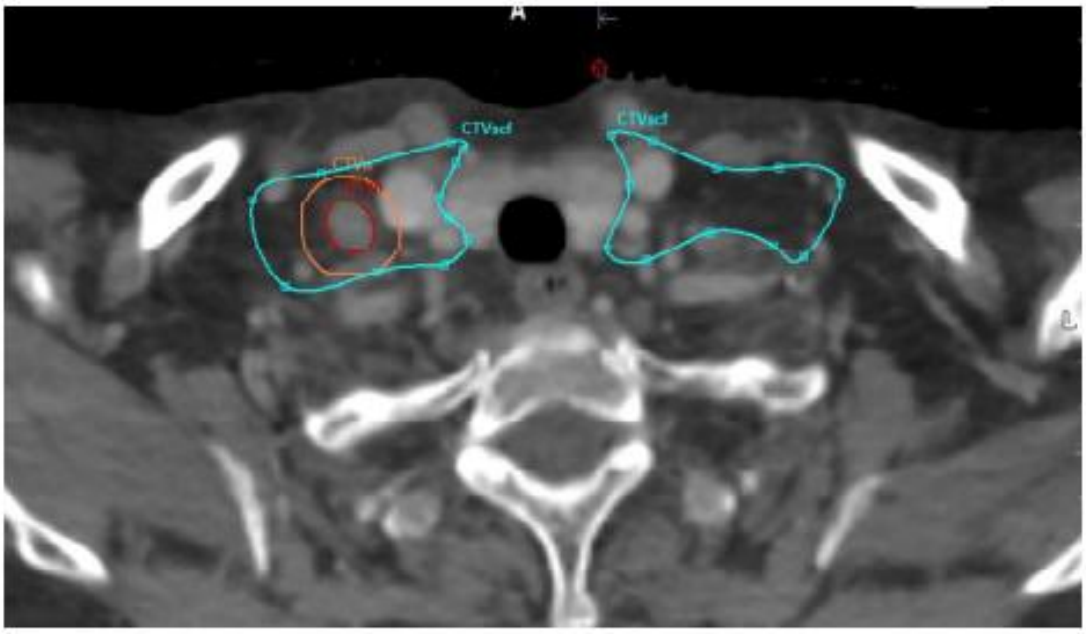
Cranial	Caudal	Anterior	Posterior	Lateral	Medial
Caudal to the cricoid cartilage	**Cranial aspect of the Sternoclavicular Joint*	Sternocleido mastoid (SCM) muscle	Anterior aspect of the scalene muscles	Cranial: lateral edge of SCM m. Caudal: Junction 1strib / clavicle	Excludes thyroid and trachea

*Caudal boundary adapted from RTOG Head and Neck and RTOG Breast Guidelines

Appendix 1: Scope 2 trial protocol

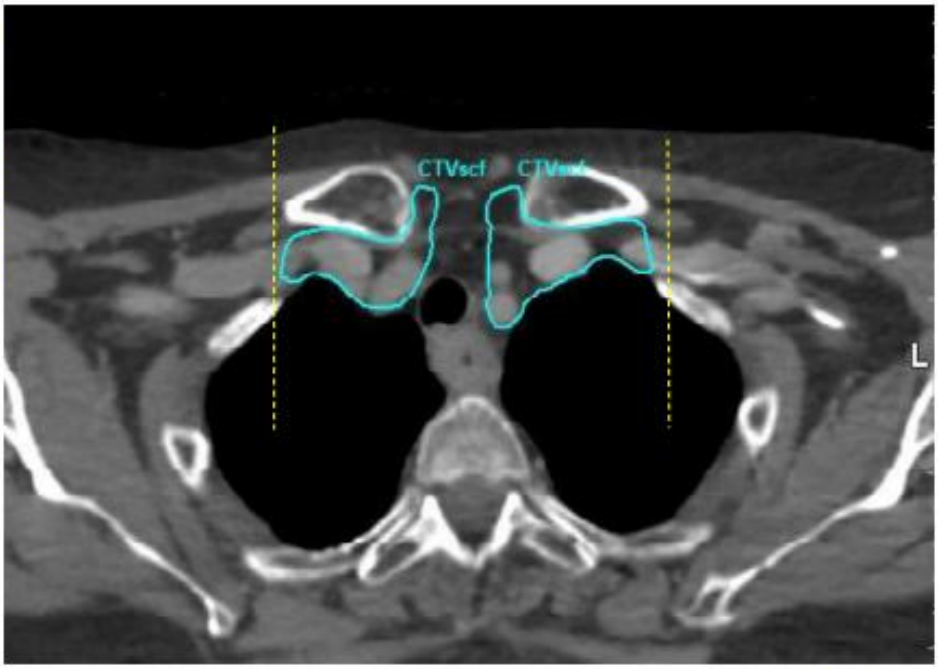


Top Slice – Start below the Cricoid Cartilage, exclude thyroid and thyroid cartilage. Use SCM as anterior and lateral boundary

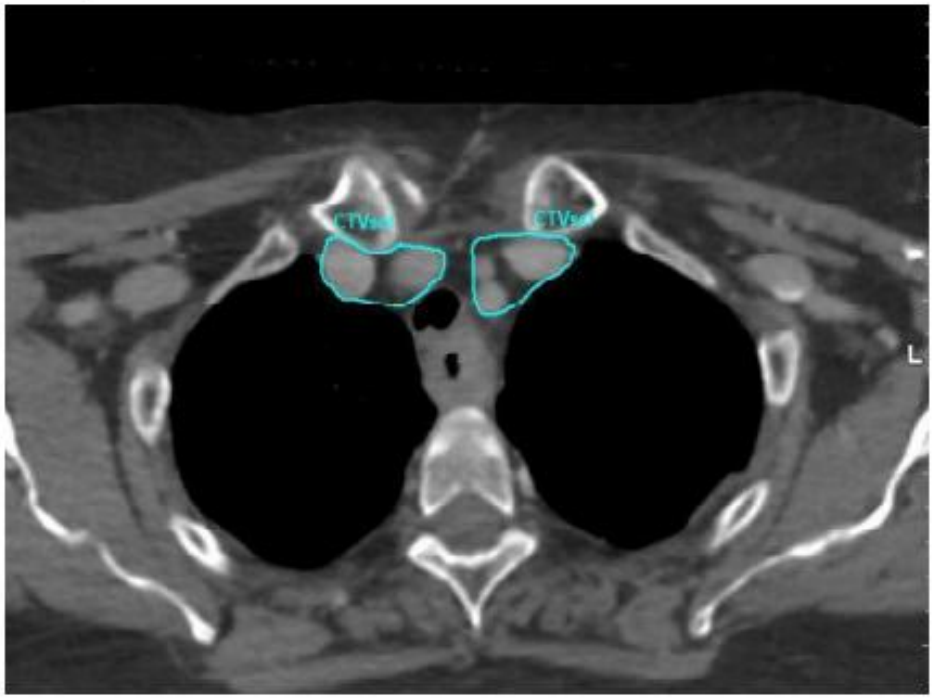


Ensure that there is a minimum margin of 5mm (CTVn) around involved node.

Appendix 1: Scope 2 trial protocol

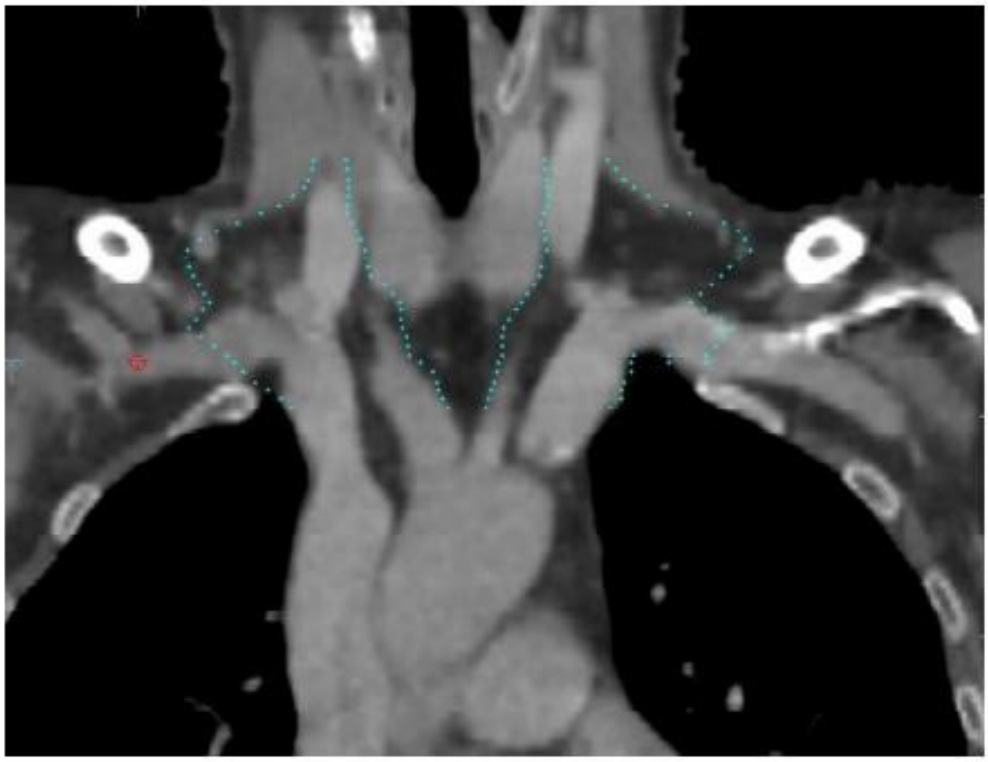


Use SCM as anterior boundary. Lateral boundary (caudal) is Junction between 1st rib and Clavicle (see dotted line)



Inferior Slice – Stop at the Cranial Aspect of Sternoclavicular Joint

Appendix 1: Scope 2 trial protocol



Planning Treatment Volume

Add 5mm margin (6mm sup-inf if using 3mm slices) in all directions to the CTVscf to form PTVscf. Combine PTVscf to the rest of the standard dose PTV to form final PTV_5000.

N.B. neck nodes will not be boosted in SCOPE 2, hence no high dose PTV_6000.

Summary of volumes

GTVn = whole involved node, >30mm from GTVp

CTVn = Involved node + 5mm in all directions

CTVscf = CTVn + whole bilateral SCF

PTVscf = CTVscf + 5mm margin in all directions (6mm sup-inf if using 3mm slices)

PTV_5000 = PTVscf + standard dose PTV

Appendix 1: Scope 2 trial protocol

3.4 Distal tumour 3DCT target volume delineation

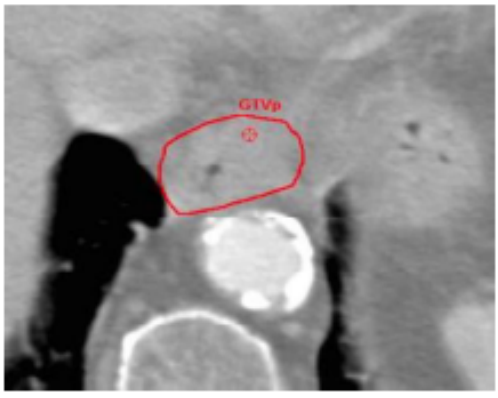
It is clear that with respect to distal (lower 1/3 and GOJ) tumours that there is significant movement, particularly due to respiration. Where possible, centres are encouraged to follow the 4DCT target definition protocol described in Section 3.4. When this is not possible, the 3D protocol should be followed. The SCOPE2 CI and 4DCT planning leads would be happy to discuss with PIs in these centres regarding the barriers to implementation, and any ways of overcoming them.

Gross tumour volumes

GTVp consists of the primary tumour (above or below GOJ), any involved nodes above the diaphragm which are within 30mm of the primary tumour volume, and the circumference of the oesophagus at the level of disease.

Above the diaphragm, GTVn consists of lymph nodes (LN) > 30mm away from the edge of the primary tumour. Only the involved nodes should be included in GTVn – it is not required to include the full circumference of the oesophagus at this stage. Where it is known that there is LN involvement at a certain level (e.g. on EUS) but not possible with the available imaging to delineate an individual LN for GTVn, the circumference of the oesophagus at the same level may be used as a surrogate. Below the diaphragm, involved nodes are no longer in continuity with the oesophagus, and so are outlined separately and labelled GTVn. Where more than one GTVn is required these may be helpfully named separately, e.g. GTVn1, GTVn2 etc, depending on the TPS available.

Above the diaphragm GTVpn is created by combining GTVp, any GTVn volumes above the diaphragm and the circumference of the intervening oesophagus. For cases without separate GTVn volumes above the diaphragm, GTVpn should still be created but will be the same volume as GTVp. (Note: GTVp should also be kept as a separate structure as this will be used to generate PTV_6000 for patients randomised to the high dose arm). For nodes below the diaphragm, although GTVn will be created, it will **not** be merged with GTVp to create GTVpn.



GTVp (red contour)

Appendix 1: Scope 2 trial protocol

Summary of GTVs for distal tumour volume delineation

- ***GTVp = primary tumour (above or below GOJ) + any involved nodes within 30mm***
- ***GTVn = any involved nodes >30mm from primary tumour occurring above the diaphram AND/OR any involved nodes below diaphragm***
  GTVpn = GTVp + any GTVn occurring above diaphragm[1]

[1] For cases without separate GTVn volumes above diaphragm, GTVpn = GTVp (but GTVpn should still be created)

Clinical target volumes

Creating CTVs

CTVA is derived by copying GTVpn, renaming this CTVA and growing it, manually along the axis of the oesophagus, to include the entire circumference of the oesophagus. The superior margin of CTVA will either be 20mm from the superior extent of GTVp **or** 10mm from the highest involved lymph node (GTVn), whichever is the more proximal. Inferiorly, CTVA is grown manually in the inferior direction along the axis of the oesophagus for 20mm **or** until the GOJ is reached.

CTVC is derived by copying CTVA, renaming it CTVC and growing it 5mm in right-left and anterior-posterior directions using the Treatment Planning System (TPS).

Below the diaphragm, any GTVn are grown by a 5mm margin in all directions and labelled 'CTVn' (for multiple nodes, label as CTVn1, CTVn2 etc). This defines a minimum margin around positive nodes to assist in the delineation of CTVB.

CTVB is derived by copying CTVA, renaming it CTVB and growing it by 10mm in right-left and anterior-posterior directions using the TPS.

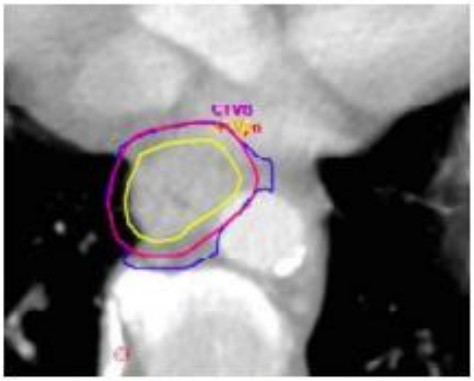
Both above and below the diaphragm, CTVB is then edited for barriers to spread to exclude lung, pericardium, large vessels, trachea, right/left main bronchi, liver and the vertebrae. Do **not** edit beyond CTVC (see figure below). Note for T4 tumours, CTVB should **not** be edited for a normal structure that is affected by T4 disease **at any point** along the CTV length, e.g. in the context of T4 right pleural disease, do not edit CTVB for the right lung (and see Appendix 2).

Below the diaphragm, CTVB is extended manually to include the volume at risk. This volume includes CTVn and the elective nodal regions at high risk of microscopic spread. Note CTVB should be manually edited to include the gastrohepatic fat space when it is first seen, even if this is above the diaphragm on some CT slices. An assessment of the potential for mucosal spread into the stomach must be made on a case by case basis, however CTVB should be manually contoured beyond the external surface of the lesser curvature of the stomach and into the gastric wall/mucosa. It is recommended that at least 5mm (+/-2mm) of the gastric wall is included but it is not expected that this is formally measured out on each CT slice. Instead the outlining clinician uses their clinical acumen to ensure that an adequate amount is included in the manual extension of CTVB (see Appendix 1, nodal region at risk: left gastric artery and lesser curvature).

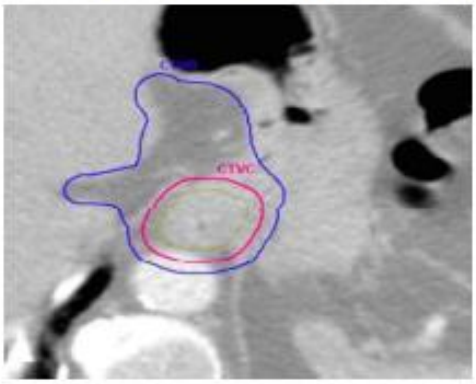
In terms of CT slices, the lowest level of CTVB will be 20mm below the lowest slice on which GTVp is outlined **or** 10mm below the lowest slice on which GTVn is outlined (whichever is the more distal).

Appendix 1: Scope 2 trial protocol

This volume should also be extended anteriorly to include the gastrohepatic fat encompassed by the stomach anteriorly, lesser curve of the stomach on the left lateral side, the liver edge or porta hepatis on the right lateral side and the aorta posteriorly (see Section 3.1 above and atlas/worked examples in Appendix 4). Margins for CTVC will be respected when modifying CTVB.



CTVB (blue contour) edited back to CTVC (pink contour) to avoid normal structures



CTVB (blue contour) manually edited to include the gastrohepatic fat space as soon as it is visible

Summary of CTVs for distal tumour target volume delineation

- ***CTVn = any GTVn below the diaphragm + 5mm[1]***
- ***CTVA superior extent (extension along oesophageal axis) = 20mm beyond GTVp OR 10mm beyond GTVn (if GTVn is more proximal than GTVp); inferior extent = 20mm beyond GTVp OR 10mm beyond GTVn (if GTVn is more distal than GTVp) but do NOT extend beyond GOJ***
- ***CTVC = CTVA + 5mm circumferentially (but not sup-inf) – this is the minimum expansion around CTVA and this margin is respected when CTVB is edited***
- ***CTVB (above diaphragm) = CTVA + 10mm circumferentially (but not sup-inf), edited for normal structures[2], but respecting margin of CTVC***

Appendix 1: Scope 2 trial protocol

- ***CTVB (once below diaphragm) = GTVp + 20mm inferiorly OR GTVn + 10mm inferiorly (whichever is more distal), edited for normal structures[2] and also extended manually to include CTVn and elective nodal regions at high risk of microscopic spread[3]***

[1] Assists manual outlining of CTVB below the diaphragm, see below

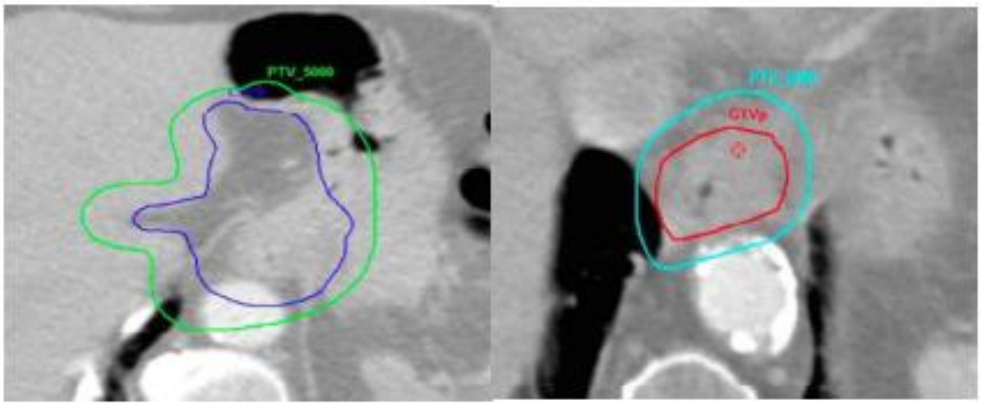
[2] Normal structures include lung, pericardium, large vessels, trachea, right and left main bronchi, liver and the vertebrae, both above and below the diaphragm

[3] Includes: the lesser curve of stomach, the left gastric artery and coeliac region where these lie within 20mm of the GTV. Superiorly, this volume includes the fat space below the diaphragm around the cardia and gastrohepatic fat between the lesser curve of the stomach and the medial liver edge, and the aorta posteriorly. Inferiorly, it includes the fat space around the coeliac artery, bounded by the pancreas anteriorly, small bowel and liver laterally, and aorta posteriorly.

Planning target volumes

In both the standard and high dose arms, PTV_5000 is derived by growing CTVB by 10mm in the superior direction, 15mm in the inferior direction and 5mm circumferentially using the TPS.

In the high dose arm, PTV_6000 is derived by growing GTVp by 5mm in all directions using the TPS.



PTV_5000 (green contour) and PTV_6000 (turquoise contour)

Summary of PTVs for distal tumour target volume delineation

- ***Standard arm: PTV_5000 = CTVB + 10mm superiorly + 15mm inferiorly + 5mm circumferentially***
- ***High dose arm:***
  PTV_5000 = CTVB + 10mm superiorly +15mm inferiorly + 5mm circumferentially
  PTV_6000 = GTVp + 5mm sup-inf margin + 5mm circumferentially

Section 3.6 provides a quick reference tabular summary of target volume delineation

Appendix 1: Scope 2 trial protocol

3.5 Distal tumour 4DCT target volume delineation

4DCT Outlining Principles

4DCT allows the tumour motion to be imaged over a patient's respiratory cycle, thereby allowing patient specific volumes to be generated which account for physiological organ motion. This guidance document provides detail on the process of generating an Internal Target Volume (ITV) utilising 4DCT data sets generated from the corresponding phases of respiration. In order to encompass all the effects of motion on the target volume on, the ITV can only be made bigger following the review of all the datasets from the corresponding phases of respiration.

A webinar presented by Dr Radhakrishna on delineation using 4DCT is available to RCR Fellows and Members at https://www.rcr.ac.uk/clinical-oncology/events/webinars/previous-webinars. The webinar can also be viewed at https://attendee.gototraining.com/77621/recording/2634586369351112193 and we encourage PIs to watch this before submitting the 4DCT pre-accrual outlining exercise.

The process of scan acquisition, the choice of reference dataset and motion management should be detailed in the centre's Process Document for the SCOPE2 Trial (see Section 8.1).

4DCT Acquisition

It is recommended that patients receive both a 3DCT and 4DCT scan in a single scanning session. The inclusion of the 3DCT scan ensures that data is available for planning should the 4DCT data be deemed wholly or partially unusable (due to machine limitations, e.g. scan length limitations, or patient suitability, e.g. imaging artefacts due to the patient's breathing pattern). It has been shown in literature that anywhere from 30% (Rietzel, et al., 2006) to 90% (Yamamoto, et al., 2008) of 4DCT volumes generated by commercially available methods will contain some form of imaging artefact. The severity of the artefacts is correlated with abdominal displacement and irregular breathing. It has been shown that GTVs contoured on 4DCT are larger than GTV contoured at end-expiration (Persson, et al., 2010) or breath-hold scans (Persson, et al., 2011).

If there is any concern about the quality of the 4D scan, it is recommended that target volume delineation is solely done using 3DCT following the 3D target volume delineation protocol as detailed in section 3.3. The RTTQA team would be happy to review the 4DCT datasets to assist in the identification of any problems with the local 4D image acquisition process, as well as offering potential solutions to such issues.

The use of Average or Maximum Intensity Projections (AveIP, MIPs) for target volume delineation have not been proven suitable for oesophageal tumours and this is **not** permitted in SCOPE2 (Chen et al., 2014). The Average Intensity Projection may be used for planning and dose calculations.

Either of the two methods of acquiring 4DCT datasets described below is accepted in SCOPE2:

1. Contrast-enhanced 4DCT that includes all the organs at risk. A 3DCT scan is not required in this instance. For patients with inhale and exhale phases of equal duration, the time-weighted average tumour position corresponds to mid-inhale/exhale. However, as most patients are exhale-biased, the corresponding time-weighted average phase occurs later in the exhale phase. An in-house study found that for the majority of patients, 40% Ex best represented

Appendix 1: Scope 2 trial protocol

the time-weighted average position. It is acceptable to use the time-weighted average data set for planning and dose calculations. Examples of IV contrast timings for 4DCT are presented in Appendix 7.

2. Contrast enhanced 3DCT (CECT) scan (as per 3D protocol) followed by 4DCT scan. The 3DCT scan will be used the planning reference data set and the 4DCT data set used solely to derive the ITV. Both CT datasets should be co-registered.

A minimum of 10 4DCT reconstructed phases distributed throughout the patient's respiratory cycle are recommended.

4DCT Outlining Method

Based on experiences in NEOSCOPE the following 4DCT outlining method is mandated for SCOPE2.

From the 4DCT data sets, identify the extreme phases of motion (MaxIn and MaxEx). It is recommended that the dataset that best represents the time weighted average is used as the reference (Ref) dataset of the 4DCT phases (if contrast-enhanced). Planning is undertaken either on the reference 3D dataset or the reference dataset of the 4D scan (ensuring that all OARs are included). In cases where one of the extreme phases of motion (MaxIn or MaxEx) will be used for treatment delivery (e.g., Exhale Breath-Hold) then this must be labelled as the reference dataset. Otherwise it is recommended that the reference dataset is also outlined. The choice of reference, MaxIn and Max dataset must be explicitly stated in the Plan Assessment Form.

Gross tumour volume (GTV), Clinical target volume (CTV) and Internal target volume (ITV)

GTV, CTVA, CTVC and CTVB contours are generated (as per the distal tumour 3DCT target volume delineation protocol described in Section 0) using the MaxIn, MaxEx and Ref datasets defined above, giving multiple GTV (GTVpn_MaxIn, GTVpn_Ref, GTVpn_MaxEx), CTVA (CTVA_MaxIn, CTVA_Ref, CTVA_MaxEx), CTVB (CTVB_MaxIn, CTVB_Ref and CTVB_MaxEx) and CTVC (CTVC_MaxIn, CTVC_Ref, CTVC_MaxEx) volumes.

The ITV is defined as the composite CTVB volumes (i.e., ITV is the union or sum of CTVB_MaxIn, CTVB_Ref and CTVB_MaxEx) and must be edited to account for any additional motion seen **from all other 4DCT phases** (i.e. the editing will result in the ITV only being made bigger, to account for the maximum extent of these motion effects). Note it is recommended that the ITV is reviewed on each CT slice for the duration of the respiratory cycle; **please do not assume that the ITV initially created will sufficiently cover areas of additional motion from the remaining respiratory phases**. The above contours must be associated with the reference dataset.

Planning target volume

The setup margin (SM) is applied for treatment inaccuracies and PTV_5000 derived by growing ITV by 5mm in all directions using the TPS.

For the high dose arm, PTV_6000 is derived by growing GTVp_Ref by 5mm in all directions using the TPS. It is necessary to use the more conservative GTVp_Ref to derive PTV_6000 rather than a larger GTVMotion delineated across many respiratory phases, as the latter could result in a significant portion of the proximal stomach being included in the high dose volume; this could be associated with a very high risk of complications.

Appendix 1: Scope 2 trial protocol

Following the generation of the PTV, the organs at risk structures and planning should be carried out on the reference data set only.

Summary of PTVs for distal tumour target volume delineation using 4DCT

- ***Standard arm: PTV_5000 = ITV + SM = ITV + 5mm isotropically***
- ***High dose arm: PTV_5000 = ITV + 5mm isotropically***
  PTV_6000 = GTVp_Ref + 5mm isotropically

Appendix 1: Scope 2 trial protocol

3.6 Target volume delineation summary

The following target volumes should be labelled using the nomenclature specified below (Santanam et al., 2012).

A CT slice thickness of 2.5mm is recommended, but any thickness ≤3mm is adequate. When the chosen CT slice thickness does not allow the exact sup-inf margin specified in the protocol below to be used, please round these margins to the nearest millimetre. **When using 2 or 3mm slices, 5mm sup-inf margins should be rounded upwards to 6mm**. E.g., when using a 3mm CT slice thickness, a 5mm isotropic margin should be applied as a 6mm sup-inf margin and a 5mm circumferential margin. A 10mm sup-inf margin can be rounded down to 9mm.

Structure name	Description
GTVp	Includes: • Primary tumour (above or below GOJ) • Any involved nodes above the diaphragm and ≤30mm of the primary tumour volume • The circumference of the oesophagus at the level of disease
GTVn	Includes: • any involved nodes >30mm from primary tumour (GTVp) occurring above the diaphragm • any involved nodes below the diaphragm It is not required to include the full circumference of the oesophagus at the level of these involved nodes.
GTVpn	Includes: • Union of GTVp and any GTVn occurring above the diaphragm • The circumference of the intervening oesophagus/proximal stomach Do not include any nodes below the diaphragm in this volume. Note in the absence of GTVn above the diaphragm, GTVpn = GTVp
CTVA	GTVpn extended along the axis of the oesophagus: • With a sup-inf margin of 20mm from the edges of GTVp **or** 10mm from the

Appendix 1: Scope 2 trial protocols

	highest/lowest involved lymph node (GTVn) (whichever is the more proximal/distal) • The whole circumference of the oesophageal wall should be included • Inferiorly CTVA should not extend below the GOJ	
CTVn	Any GTVn below the diaphragm + 5mm isotropically	
CTVC	CTVA+ 5mm circumferential margin	
CTVB	CTVA + 10mm circumferentially: • CTVB is edited to exclude lung, pericardium, large vessels, right and left main bronchi, liver and the vertebrae, both above and below the diaphragm. DO NOT edit beyond CTVC. For T4 tumours, DO NOT edit the respective structure (e.g. if T4 right pleura, do not edit the CTVB extending into right lung at any point). • Manual extension of CTVB for elective nodal regions should commence immediately below the diaphragm i.e. when the gastrohepatic fat space is first seen • *Below the diaphragm* CTVB is grown manually to include the volume at risk to a total of 20mm below GTVp **or** at least 10mm below the lowest GTVn (whichever is more distal). This volume includes CTVn and the elective nodal regions at high risk of microscopic spread.	
ITV (For distal tumours where 4DCT used)	CTVB_MaxIn + CTVB_Ref + CTVB_MaxEx ITV then manually grown to account for any additional motion seen from all other 4DCT phases of the respiratory cycle.	
PTV_5000 (Standard and high dose arm)	Proximal Tumours (4DCT not permitted)	CTVB + 10mm sup, 10mm inf, 5mm circumferentially
	Distal tumours (4DCT not used)	CTVB + 10mm sup, 15mm inf, 5mm circumferentially

Appendix 1: Scope 2 trial protocol

		Distal tumours (4DCT used)	ITV + 5mm isotropically
PTV_6000 (High dose arm only)	Proximal and distal tumours (where 4DCT not used)	GTVp + 5mm isotropically	
	Distal tumours (4DCT used)	GTVp_Ref + 5mm isotropically	

Appendix 2: NeoAEGIS trial protocol

NeoAEGIS

Radiotherapy Planning Guidance Document

Neo-AEGIS (NEOadjuvant trial in Adenocarcinoma of the oEsophagus and oesophagoGastric junction International Study): Randomised Clinical Trial of neoadjuvant and adjuvant chemotherapy (Modified MAGIC regimen) vs. neoadjuvant chemoradiation (CROSS protocol) in adenocarcinoma of the oesophagus and oesophago-gastric junction

Protocol Number: ICORG 10-14
Version Number/Date: Version 1.0 dated 18 May 2015

3 Middle 1/3rd tumour Target Definition Protocol

Gross tumour volume (GTV)

The GTV consists of the gross tumour (**GTVp**) and malignant lymph nodes (**GTVn**). **GTVp and GTVn** include the entire circumference of the oesophagus at the level of tumour and/or nodal disease.

GTVp and **GTVn** are combined without a margin to form **GTVpn** using the Treatment Planning System (TPS).

GTVpn should encompass disease considered positive which may be in conjunction with Upper GI Radiologist on consideration of all the diagnostic modalities i.e. should not be reduced in case of negative PET/CT if considered positive on other modalities. It is not possible to state in this protocol the interpretation which might be made of CT, EUS and CT/PET in any particular situation, which as well as the sensitivity and specificity of these investigations will depend on the certainty of the specialist Radiologist and those carrying out the EUS. For example a slightly enlarged lymph node on CT may appear benign on EUS and be non-avid with respect to a strongly avid primary tumour on CT/PET and may not be considered malignant. Notwithstanding the above however, a node considered malignant on EUS should always be included.

Clinical target volume (CTV)

The CTV is made up of the GTV including a margin for occult disease. There are three CTVs in this protocol, **CTVA**, **CTVB** and **CTV_Comb**.

CTVA is defined by an isotropic margin of 0.5cm around **GTVpn** using the TPS. Thus **CTVA** defines a minimum margin around tumour and malignant nodes that must be respected when **CTV_Comb** is created.

CTVA may be 'trimmed' to exclude vertebra where **CTVA** is directly abutting anterior vertebra but must NOT be trimmed elsewhere, i.e. lung, pericardium, great vessels, trachea, main bronchi. See Figure 1a, b and c.

Appendix 2: NeoAEGIS trial protocol

Figure 1a - CTVA (orange) may be trimmed above diaphragm to exclude vertebra (GTVpn is shown in green)

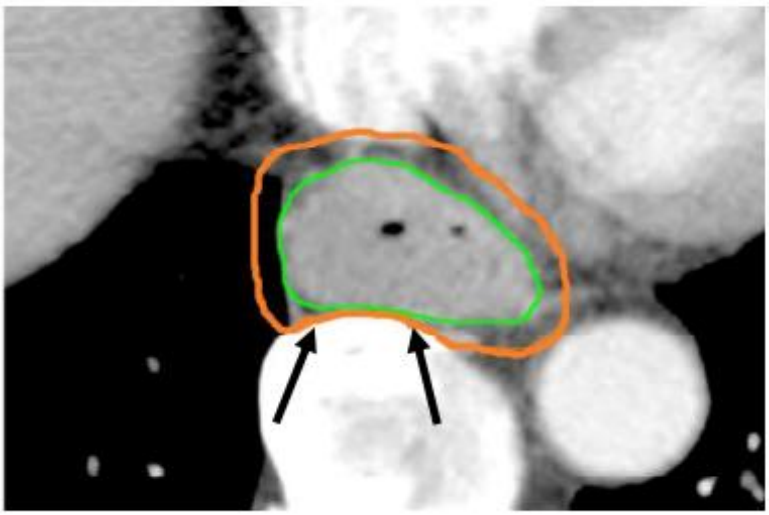
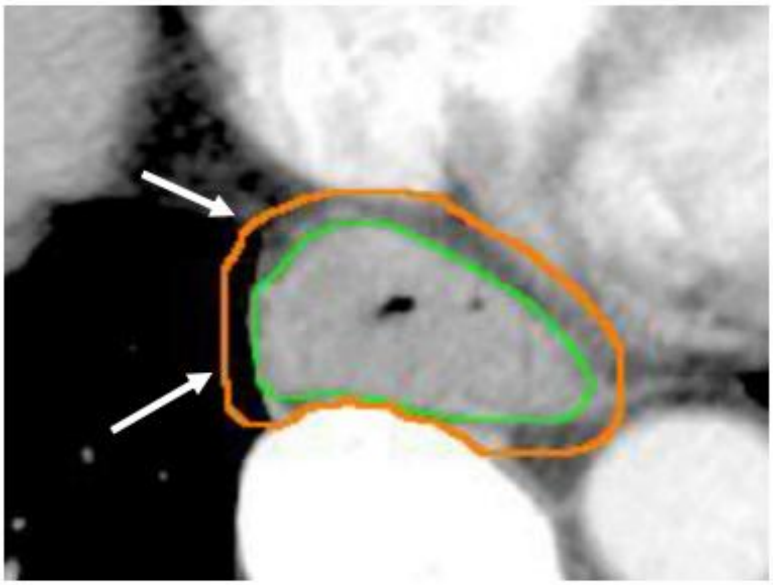
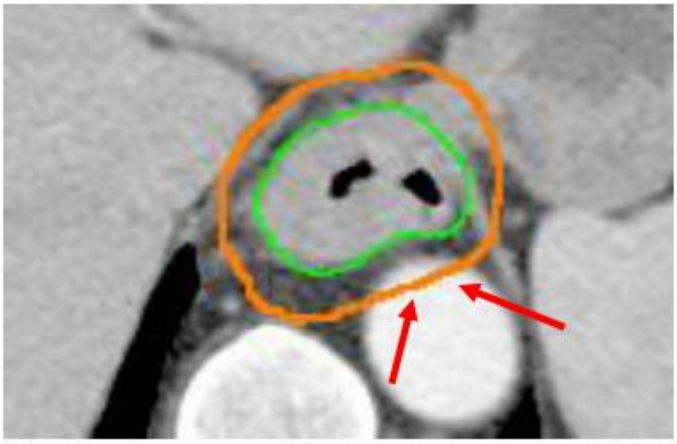


Figure 1b and 1c – CTVA (orange) is not trimmed off lung, pericardium, great vessels, trachea or bronchi



Appendix 2: NeoAEGIS trial protocol

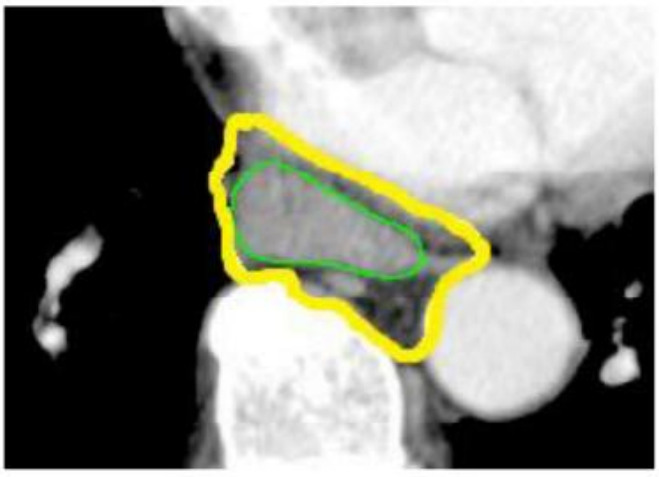


CTVB will comprise of the 'fat pad' around the oesophagus. This 'fat pad' is visible on CT and is the site of peri-oesophageal nodes. It is of varying thickness, and may be extremely thin or almost non-existent in places.

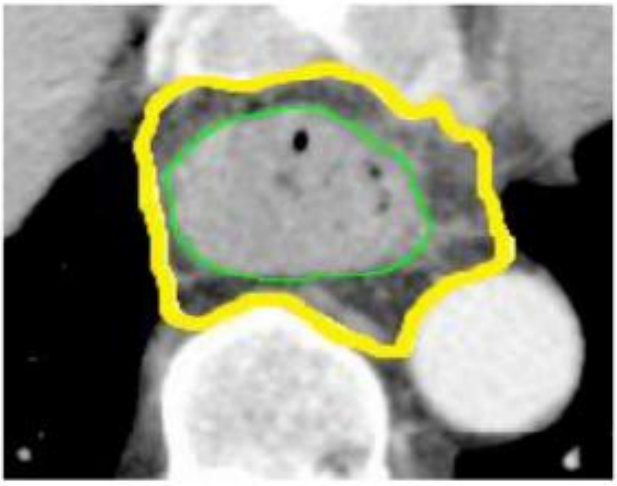
The 'fat pad' is contoured at the same levels as the **GTVpn** and for 3cm superior and inferior (S/I) to **GTVp.** It is bordered posteriorly *in places* by the anterior aspect of the vertebral body. The **CTVB** should NOT include bone, lung, pericardium, trachea, bronchus or great vessels (it SHOULD include the Azygous/Hemiazygous veins). (Figure 2a, b and c). Note that in places the fat pad extends very lateral in a thin strip anterior to the aorta; here discretion may be applied and not all of the visible fat need be included (Lateral extension to half the level of the midpoint of the aorta is reasonable, See Figure 2a, left lateral aspect of **CTVB**).

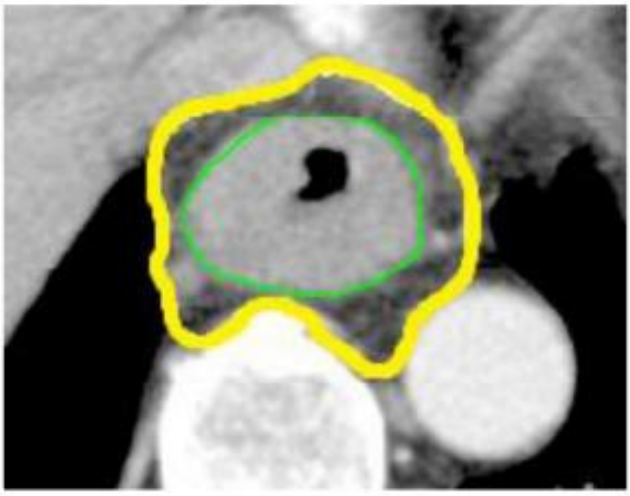
NB: Where the superior or inferior extent of **GTVpn** is defined by nodal disease which is more than 2cm from **GTVp** then **CTVB** should only extend 1cm from **GTVn.**

Figure 2a, b and c - CTVB (yellow) comprises the fat pad around the oesophagus



Appendix 2: NeoAEGIS trial protocol





CTVB should fully encompass:

- the entire 'fat pad' along the length of the **GTVpn** and for 3cm S/I to **GTVp**
- the entire oesophagus along the length of the **GTVpn** and for 3cm S/I to **GTVp**
- Malignant peri-oesophageal nodes
- Benign nodes along its course without a margin (but **CTVB** should not be extended to include benign nodes)
- the Azygos and/or Hemiazygos vein(s).

Thus **CTVB** encompasses the entire GTV with a cranio-caudal margin to account for occult submucosal spread of tumour. The 'fat-pad' is encompassed to cover subclinical nodal disease.

Some discretion is required in interpreting the extent of the 'fat pad' eg around the vertebra, the infra-bronchial tissues and aorto-pulmonary window.

Appendix 2: NeoAEGIS trial protocol

CTVA and **CTVB** are combined without a margin using the TPS to form a combined CTV (**CTV_Comb**).

Planning target volume (PTV)

The Planning Target Volume (**PTV_4140**) is created using the TPS via the expansion of **CTV_Comb** by an isotropic margin of 10mm (5mm IM and 5mm SM), in all dimensions.

The posterior margin may be reduced where **CTV_Comb** is directly abutting vertebrae (internal margin not required as tumour cannot move into vertebrae, only setup margin is required), to a minimum distance of 5mm. This does NOT apply to any other structures (such as lung, pericardium, great vessels, trachea, main bronchi).

Summary of Volumes

GTVpn = GTVp + GTVn

CTVA = GTVpn + 0.5cm (isotropic margin)

CTVB = GTVpn + 3cm S-I + 'fat pad'

CTV_Comb = CTVA + CTVB

PTV_4140 = CTV_Comb + 1cm isotropic margin

Appendix 2: NeoAEGIS trial protocol

4 Lower 1/3rd and GOJ tumour 3D CT Target Definition Protocol

The use of 4DCT for planning is not currently approved within NeoAEGIS.

Gross tumour volume (GTV)

The GTV consists of the gross tumour (**GTVp**) and malignant lymph nodes (**GTVn**). Malignant nodes (**GTVn**) may be above or below the OGJ. Above and at the junction, **GTVp** includes the entire circumference of the oesophagus/junction at the level of disease. Below the OGJ **GTVp** does NOT include the entire circumference of the stomach at the level of disease, but just the gross tumour.

The GTV should encompass disease considered positive which may be in conjunction with Upper GI Radiologist on consideration of all the diagnostic modalities i.e. should not be reduced in case of negative PET/CT if considered positive on other modalities. It is not possible to state in this protocol the interpretation which might be made of CT, EUS and CT/PET in any particular situation, which as well as the sensitivity and specificity of these investigations will depend on the certainty of the specialist Radiologist and those carrying out the EUS. For example a slightly enlarged lymph node on CT may appear benign on EUS and be non-avid with respect to a strongly avid primary tumour on CT/PET and may not be considered malignant. Notwithstanding the above however, a node considered malignant on EUS should always be included.

GTVp and **GTVn** are combined without a margin to form **GTVpn** using the TPS.

Clinical target volume (CTV)

The CTV is made up of the GTV_{TN} including a margin for occult disease. There are three CTVs in this protocol, **CTVA**, **CTVB** and **CTV_Comb**.

CTVA is defined by an isotropic margin of 0.5cm around **GTVpn** using the TPS. Thus **CTVA** defines a minimum margin around tumour and malignant nodes that must be respected when **CTV_Comb** is created.

Above the diaphragm, **CTVA** may be 'trimmed' to exclude vertebra where **CTVA** is directly abutting anterior vertebra but NOT trimmed elsewhere, i.e., lung, pericardium, great vessels, trachea, main bronchi. See Figure 1 a,b,c.

Below the diaphragm, **CTVA** may not be 'trimmed'.

Appendix 2: NeoAEGIS trial protocol

CTVB above the OGJ

Above the OGJ, **CTVB** will comprise of the 'fat pad' around the oesophagus. This 'fat pad' is visible on CT and is the site of peri-oesophageal nodes. It is of varying thickness, and may be extremely thin or almost non-existent in places (see figure 2 a,b,c).

The 'fat pad' is contoured at the same levels as the GTVpn, for 3cm S/I to the GTVp. Where this inferior expansion extends beyond the OGJ, a 2cm margin only is required. It is bordered posteriorly *in places* by the anterior aspect of the vertebral body. The **CTVB** should NOT include bone, lung, pericardium, trachea, bronchus or great vessels (it SHOULD include the Azygous/Hemiazygous veins). (Figure 2a, b and c). Note that in places the fat pad extends very lateral in a thin strip anterior to the aorta; here discretion may be applied and not all of the visible fat need be included (Lateral extension to half the level of the midpoint of the aorta is reasonable, See Figure 2a, left lateral aspect of **CTVB**).

NB: Where the superior extent of **GTVpn** is defined by nodal disease which is more than 2cm from **GTVp** then **CTVB** should only extend 1cm from **GTVn**.

CTVB should fully encompass:

- the entire 'fat pad' along the length of the **GTVpn** and for 3cm superior and 2-3cm inferior to **GTVp**
- the entire oesophagus along the length of the **GTVpn** and for 3cm superior and 2-3cm inferior to **GTVp**
- Malignant peri-oesophageal nodes
- Benign nodes along its course without a margin (but **CTVB** should not be extended to include benign nodes)
- the Azygos and/or Hemiazygos vein(s).

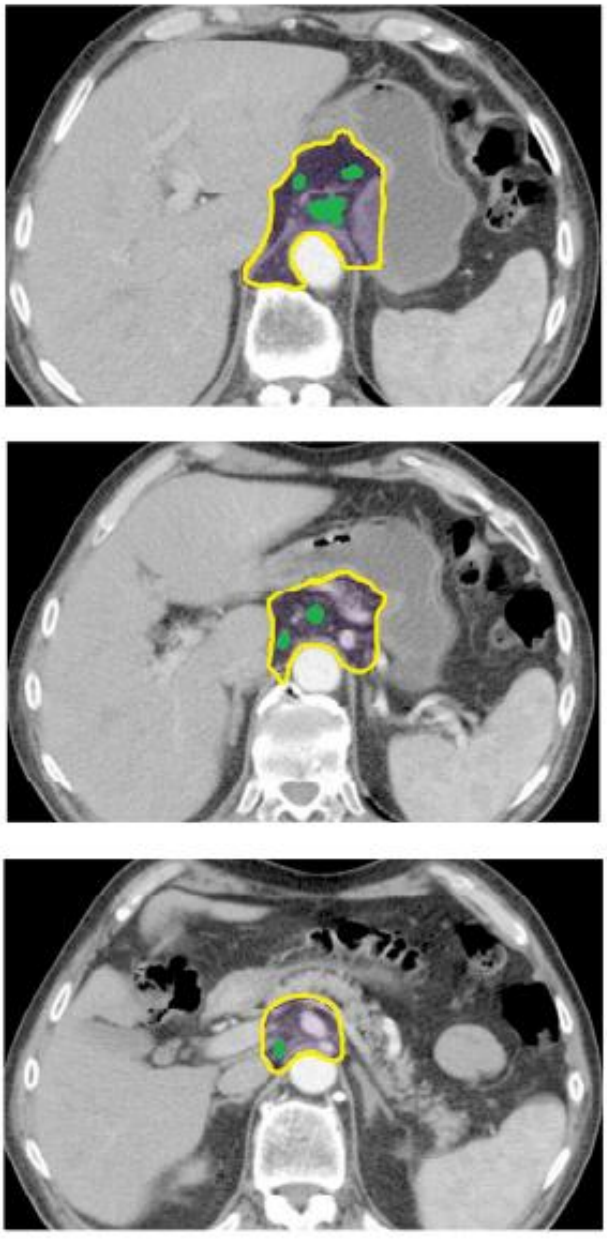
Some discretion is required in interpreting the extent of the 'fat pad' eg around the vertebra, the infra-bronchial tissues and aorto-pulmonary window.

CTVB below the OGJ

Where **GTVn** includes nodes in the abdomen, **CTVB** is extended to include that entire nodal station. No other abdominal nodal stations will be electively included. For example if **GTVn** include a Coeliac node, the entire Coeliac axis is included in **CTVB**. (Figure 3a, b and c). Patients with malignant nodal disease outside paracardial, lesser curvature/gastro-hepatic ligament and/or coeliac stations are ineligible for this study.

Appendix 2: NeoAEGIS trial protocol

Figure 3a, b and c: CTVB below the diaphragm. In this example the patient has malignant gastrohepatic ligament/ lesser curve and coeliac axis nodes. CTVB (yellow) is extended to include that entire nodal station. No other abdominal nodal stations will be electively included.



Appendix 2: NeoAEGIS trial protocol

There is no 'fat pad' around the cardia/fundus stomach. Therefore to describe the appropriate caudal expansion for junctional tumours a small 'cuff' of cardia/fundus is contoured, encompassing the entire circumference of the cardia/fundus for 2cm caudal to **GTVp**.

An assessment of the potential for mucosal spread into the stomach laterally and posteriorly must be made on a case by case basis. The extent of this volume is difficult to define anatomically but is usually no greater than 2cm in lateral extent. In order to encompass involved nodal stations *along* the lesser curve, it is anticipated that some of the lesser curve will be included, especially in tumours of the OGJ and/or with gastric extension.

Below the OGJ, CTVB should fully encompass:

- malignant upper abdominal nodes
- Benign peri-oesophageal nodes along its course
- Entire nodal station(s) containing malignant nodes
- [Nodal stations that do NOT contain malignant nodes will NOT be electively included]

Thus **CTVB** encompasses the entire GTV with a cranio-caudal margin to account for occult submucosal spread of tumour. Above the OGJ, the 'fat-pad' is encompassed to cover subclinical nodal disease. Below the OGJ, where a malignant node or nodes is/are found in a nodal station, the entire nodal station is included to cover subclinical nodal disease.

CTVA and **CTVB** are combined without a margin using the TPS to form a combined CTV (**CTV_Comb**).

Planning target volume (PTV)

The Planning Target Volume (**PTV_4140**) is created using the TPS via the expansion of **CTV_Comb** by an isotropic margin of 1cm in all dimensions.

PTV_4140 above the diaphragm

The posterior margin may be reduced where **CTV_Comb** is directly abutting vertebrae (IM not required as tumour cannot move into vertebrae, only SM is required), to a minimum distance of 0.5cm. This does NOT apply to any other structures (such as lung, pericardium, great vessels, trachea, main bronchi).

PTV_4140 below the diaphragm

The 1cm margin may not be reduced.

Appendix 2: NeoAEGIS trial protocol

Summary of Volumes

GTVpn = GTVp + GTVn

CTVA = GTVpn + 0.5cm (isotropic margin)

Above the OGJ
CTVB = GTVpn + 3cm S-I + 'fat pad'

Below the OGJ
CTVB = [**GTVp** (+ 3cm superior extension+ 'fat pad') + 2cm inferior extension] + [**GTVn** + nodal station (of involved node[s])]

CTV_Comb = CTVA + CTVB

PTV = CTV_Comb + 1cm isotropic margin

Appendix 3 Leeds Upper 1/3rd Oesophageal protocol

CLINICAL ONCOLOGY SERVICE

Upper - Third - Oesophageal - Cancer -Single -Phase Clinical Protocol

Treatment selection

Intent Radical for patients with locally advanced upper third oesophageal squamous cell carcinoma with no evidence of direct invasion into airways by tumour.

Primary outcome - year Local Control of 70%; Expected median survival of 12 months.

Patient information - Coming for radiotherapy.

Scheduling

Most patients will have at least 2 cycles of induction chemotherapy (Cis/Carbo and 5FU/capecitabine) completed 3 - 4 weeks prior to starting chemoradiation. Concurrent chemotherapy with Cisplatin 60-100 mgm^{-2} or carboplatin AUC 3 - 3.3.Category 1.

Pre-treatment process

Essential pre-treatment documentation

Biopsy proven squamous cell carcinoma or adenocarcinoma.
Maximum disease length (including involved nodes superiorly and inferiorly to the tumour) = 10 cm.
CT Thorax, Abdo and Pelvis.
CT PET scan.
Bronchoscopy if direct invasion of airways suspected on imaging.
Consider EDTA GFR; Consider infusional 5FU if GFR< 30 $mlmin^{1}$.
WCC > 3; Neuts> 1.2; plats > 100; Hb >10.
Patients with dysphagia scores of 3 or worse must have alternative feeding support (RIG/PEG/surgical placed feeding jejunostomy) prior to starting treatment.

Patient positioning	Supine and 5 point thermoplastic immobilisation shell.
Imaging	3D contrast enhanced CT planning scan with IV contrast (if not contraindicated), as per radiographer work instruction.
Scan Limits	As per radiographer protocol from base of skull and includes both lungs (2mm slice thickness).

Appendix 3 Leeds Upper 1/3rd Oesophageal protocol

Target definition

GTV $_{primary}$	The GTV $_{primary}$ is localised on axial slices of the planning CT scan using the relevant imaging to define a reference point (tracheal carina or the arch of the aorta) as well as the superior and inferior extent of the GTV. In principle, the GTV $_{primary}$ should encompass disease (including para oesophageal nodal disease in proximity with primary tumour) defined on any of the imaging modalities used (i.e. CT, PET and/or EUS if undertaken), even if only apparent on a single modality.
CTV A $_{primary}$	The GTV $_{primary}$ is copied and labelled 'CTV A $_{primary}$' (so that the GTV is preserved as a separate structure) and extended manually by 20mm superior to the proximal GTV $_{primary}$ margin and 20mm inferior to the distal GTV $_{primary}$ margin by drawing along the line of the oesophagus. The whole circumference of the oesophageal wall should be included throughout the length of the CTV A $_{primary}$.
CTV 60 $_{primary}$	CTV A primary is grown by 10mm anteriorly and laterally. The posterior margin is generated with a 5mm growth and should be sculpted to the bone of anterior vertebral body. The peri oesophageal nodal regions in the superior mediastinum should be covered. CTV 60 is edited to exclude lung, pericardium and large vessels.
CTV 66 $_{primary}$	CTV A $_{primary}$ + 2mm safety margin = CTV 66 $_{primary}$
PTV 60 $_{primary}$	CTV 60 $_{primary}$ + 6mm in all directions.
PTV 66 $_{primary}$	CTV 66 $_{primary}$ is copied and labelled PTV 66 $_{primary}$.
GTV 66 $_{node}$	Any pathologically involved node (by imaging criteria) involved in nodal levels III, IV, V or the superior mediastinal region (if encompassable within RT portal). Lymph node levels are illustrated in figure 1 below.
CTV 54 $_{node}$	CTV 54 includes all of the intermediate risk nodal regions[14,19]: Level III, IVa, IVb and Vc (lower region) bilaterally (Unless macroscopic nodal involvement when it should be included in CTV 66 $_{node}$).
CTV 66 $_{node}$	GTV 66 $_{node}$ is grown by 5 mm in all directions and edited to exclude bone, airways, lung, pericardium and large vessels.
PTV 54 node	CTV 54 node + 6mm in all directions.
PTV 66 $_{node}$	CTV 66 $_{node}$ is grown by 6mm in all directions.

In cases of any macroscopic level III, IV and V node positive disease:

1. No skin involvement, the PTV node should be sculpted to 5mm* below the skin surface or
2. If there is skin involvement, then no editing of margins should be carried out and bolus placed over affected region.

**NB- This may result in the CTV being larger than the PTV if growing algorithm extends lume beyond skin surface. Plan to PTV.*

Appendix 3 Leeds Upper 1/3rd Oesophageal protocol

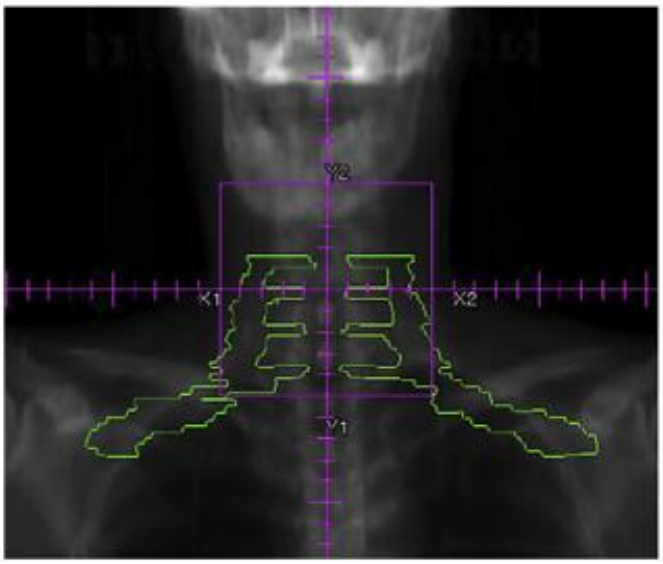
Figure 1:

Organs at risk

Brachial Plexus	Outlined by clinician. Should extend from exit of nerve roots from neural foramina of C5 down to T1, and be contoured along its track. (Figures 2 and 3).
Dose constraints	**Node negative** patients, Brachial Plexus D 60Gy < 1 cc. **Node positive** with nodal involvement in close proximity to the brachial plexus D65Gy < 1cc All patients should be consented for the risk of brachial plexopathy. A recent publication (ref 16) has suggested that $V70_{Gy}$ <10% and $V74_{Gy}$ <4% are acceptable dose constraints for the brachial plexus in patients undergoing treatment for a head and neck malignancy. Our constraints are therefore likely to be conservative.
Ref:	[9,12,13,16].

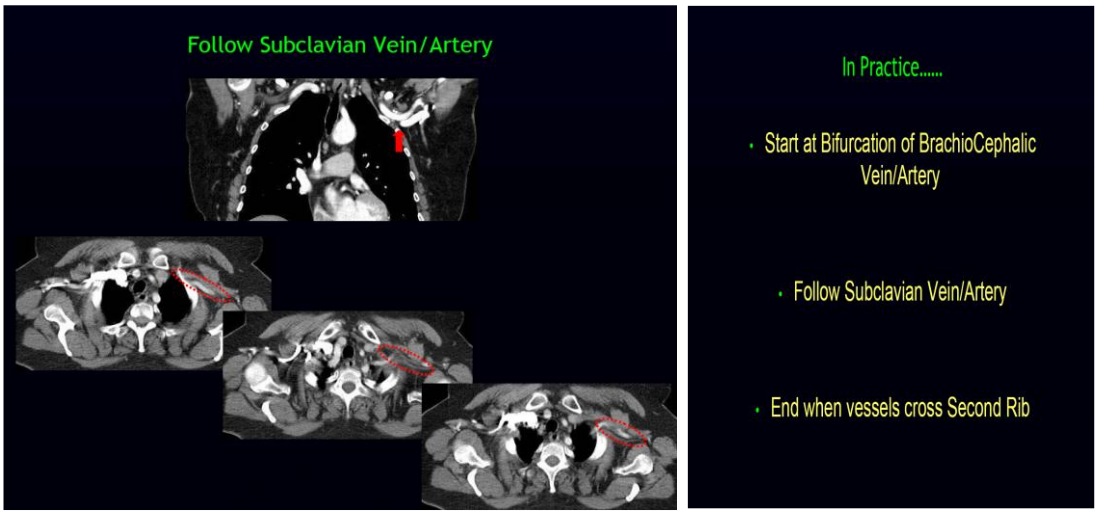
Figure 1:

1. Identify and contour C5, T1, and T2.
2. Identify and contour the subclavian and axillary neurovascular bundle.
3. Identify and contour anterior and middle scalene muscles from C5 to insertion onto the first rib.
4. To contour the brachial plexus OAR use a 5-mm diameter paint tool.
5. Start at the neural foramina from C5 to T1; this should extend from the lateral aspect of the spinal canal to the small space between the anterior and middle scalene muscles.
6. For CT slices, where no neural foramen is present, contour only the space between the anterior and middle scalene muscles.
7. Continue to contour the space between the anterior and middle scalene muscles; eventually the middle scalene will end in the region of the subclavian neurovascular bundle.
8. Contour the brachial plexus as the posterior aspect of the neurovascular bundle inferiorly and laterally to one to two CT slices below the clavicular head.
9. The first and second ribs serve as the medial limit of the OAR contour.



Appendix 3 Leeds Upper 1/3rd Oesophageal protocol

Figure 2: contouring of the lower brachial plexus



Spinal Canal PRV	The spinal canal should be outlined on slices that include or are within 2cm of the PTV in the superior and inferior directions. A Planning Risk Volume (PRV $_{spinal\ canal}$) = Spinal canal + 3mm circumferential margin to account for positional error.
Dose constraints	Max dose 48Gy to canal.
Lung	Both lungs should be outlined for assessment of dose to this organ.
Dose constraints	Lung V_{20Gy}<25%; mean lung dose < 15Gy.
Ref	[1,15].
Responsibility	It is the responsibility of the treating clinician to outline the brachial plexus. It is the responsibility of medical physics staff to outline the lungs and spinal canal PRV. It is the responsibility of the clinician to outline any other OAR.
Prescribed Dose	66Gy in 33 fractions as single phase over 6.5 weeks to PTV 66 $_{primary}$ and PTV 66 $_{node}$ The PTV 60 will therefore receive 60 Gy in 33 fractions. The PTV 54 will therefore receive 54 Gy in 33 fractions. With an estimated alpha/beta ratio for oesophageal cancer of 4.9Gy (ref 17) this equates to 58.4 Gy to PTV 60, and 51.2 Gy to PTV 54, in 2Gy fractions.

PTV dosimetric coverage

PTV	Isodose	Target volume (%)

	>90%	99
	>95%	95
	<105%	5
	<107%	2

If IMRT / Rotational Arc (VMAT) is not feasible, these constraints will not be met.

Treatment

Review Clinical review: Clinician or GI Chemo -radiotherapy CNS once a week via GI review clinic and 1 review via H & N Nurse led procedures appointment in review clinic. Therefore review twice a week. Dietetic review as per dietician protocol.
Weekly with FBC and biochemistry. As per Proforma.

Responsibility : Clinician Team.

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Associated documents:	None

Appendix 4 RCR Covid guidelines

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RADIOTHERAPY PROTOCOL: Radical Pancreas 15 fraction

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Background

This document describes suggested 15# regimes for borderline resectable and locally advanced pancreatic adenocarcinoma (PDAC) for use in the current COVID-19 pandemic. These reflect pragmatic protocols adapted from the available literature but it is recognised that there is a paucity of prospective published clinical trial

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evidence. These are adapted from draft research protocols where IMRT and utilisation of motion management is mandated. The reviewers are not responsible for the use of these protocols which have not been prospectively tested within a UK setting and centres employ them at their own risk. Where 3D conformal planning or population based set up margins are used, although pragmatic alternatives are suggested based on consensus opinion, these are not based on published evidence. In all centres, prospective recording of toxicity data is strongly encouraged to facilitate a timely retrospective analysis of outcomes in this cohort.

Within the UK, 15 fraction regimens (36Gy/15#) will be evaluated in the resectable/borderline resectable setting in the PRIMUS 002 trial (CRT component likely to open end 2020). This dose fractionation was used in the PREOPANC trial (1) with concurrent gemcitabine based chemotherapy. Although this recently reported trial failed to show an overall survival benefit for the addition of gemcitabine based CRT compared to patients going to immediate surgery, a predefined subgroup analysis did show a survival benefit in the borderline resectable setting with an improved R0 resection rate (71% vs. 40%) (2). In this protocol it is given with concurrent capecitabine in accordance with current UK practise.

In the locally advanced setting, the potential benefits of 15# compared to long course chemoradiation include reducing total treatment time and hospital visits. Published retrospective data and protocols using a 15# regimen come predominantly from US experience where 15# protocols have been used in the setting of dose escalation. These utilise a Simultaneous Integrated Boost (SIB) dose painting technique with a central stereotactic tumour boost up to a dose of 67.5Gy/15# using advanced motion management for treatment delivery (3-8). This approach has been given with a variety of concomitant chemotherapy regimens, most commonly capecitabine.

In this non-dose escalated protocol, 45Gy/15# has been chosen as it has a similar BED (α/β 10) to 50.4Gy/28# which is the current UK standard from the SCALOP trial (Table 1). A two level IMRT SIB technique is recommended, treating a larger volume to a lower dose within GI tolerance (40Gy/15#) to account for microscopic disease. The central boost region will receive 45Gy/15#. The volumes are similar to those used in the SCALOP-2 trial interventional arm. These doses have been chosen pragmatically acknowledging that 45Gy/15# is hotter to normal tissues than conventionally fractionated regimens (BED_3 90 compared with 80.6 for 50.4Gy and 86 for 54Gy, see Table 1).

Table 1: Table of dose equivalence (not taking into account time factor)

Fractionation	BED α/β 10	BED α/β 3
50.4Gy/28#	59.5	80.6
54Gy/30#	63.7	86.4
36Gy/15#	44.6	64.8
40Gy/15#	50.5	75.3

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45Gy/15#	58.5	90

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7	Treatment planning
8	Treatment delivery
9	Follow-up after treatment
10	References

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1. Objective and scope

To summarise the planning and treatment of patients receiving 15# hypofractionated radiotherapy for pancreatic malignancies.

2. Indications

- Patients with borderline resectable adenocarcinoma of the pancreas (as defined by local MDT).
- Patients with locally advanced adenocarcinoma of the pancreas (as defined by local MDT).

Pre-radiotherapy investigations

- Patients may require an MRI to aid tumour definition, if not well defined on CECT (at discretion of clinician)
- PET to rule out metastatic disease (if part of departmental policy)
- DMSA scan may be required if renal dose likely to be significant

3. Therapeutic schemata

Dose prescription

- Borderline resectable PDAC
  The dose to PTV_{3600} will be 36Gy in 15 fractions (2.4 Gy per fraction) delivered over 3 weeks (Mon-Fri)

- Locally advanced PDAC
  The dose to PTV_{4500} will be 45Gy in 15 fractions (3 Gy per fraction) delivered over 3 weeks (Mon-Fri). The dose to PTV_{4000} will be 40Gy in 15 fractions (2.67 Gy per fraction). This is delivered as a SIB.

  If using either 3D conformal planning and/or 3D CT for simulation, 40Gy/15# with no SIB is suggested.

Chemotherapy

- In both regimes radiotherapy will be given with concurrent oral capecitabine 830mg/m2 BD on days receiving radiotherapy.

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4. Pre-treatment

Patient simulation and immobilisation:

- Preferred: patient positioned supine with arms immobilised above the head supported by appropriate immobilisation (eg. lung board or vacbag) with knee immobilisation.
- Motion management varies in each institution. The use of abdominal compression, assisted breath hold techniques e.g. ABC, gating or tracking as per institutional policy should be used where available.
- 4D CT based ITV approach as a minimum is strongly recommended.
- The use of advanced planning techniques (IMRT/VMAT) are strongly recommended.
- Two hours nil by mouth prior to scan and treatment
- ~150mL of dilute oral contrast or water 10-15 minutes prior to scanning to aid visualisation of upper GI tract. Record volume given in setup note.
- Exhale breath hold contrast enhanced CT delay for pancreatic phase (3D CECT) followed by 4DCT

5. Volume definitions

4D-CT planning (contrast exhale CT followed by non-contrast 4DCT)

On the 3D CECT, outline GTV_T and GTV_N :-

- GTV_T = includes the macroscopic pancreatic tumour visible on imaging
- GTV_N = peritumoural lymph nodes (> 1cm in short axis diameter and considered suggestive of involvement on diagnostic imaging).
- On the maximum inhale and maximum exhale bins of the 4D-CT outline each GTV again to create GTV_T_inhale, GTV_N_inhale, GTV_T_exhale and GTV_N_exhale.
- On the 3D CECT create the ITV using a Boolean operator. Produce a union of GTV_T, GTV_N, GTV_T_inhale, GTV_N_inhale, GTV_T_exhale and GTV_N_exhale
- Once ITV is created, verify that the involved tumour/nodes are adequately covered on all phases of 4DCT

3D-CT planning

On the 3D CT, outline GTV_T and GTV_N as above.

GTV_3D = GTV_T + GTV_N

CTV

Borderline resectable

CTV_4D= ITV + 0.5cm in all directions

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Locally advanced

CTV_4D= ITV + 0.5cm in all directions, then edit back to exclude areas of overlap with uninvolved GI tract (but do not edit beyond ITV).

PTV

Borderline resectable

- PTV_{3600} = CTV_4D + 0.5cm in all directions

Locally advanced

- PTV_{4500} (2 level SIB IMRT/VMAT technique using 4DCT)

  1. PTV_{4500} = ITV + 0.5cm in all directions
  2. PTV_{4000} = CTV_4D + 0.5cm in all directions

- PTV_{4000} (3D-conformal planning)

  PTV_{4000} = CTV_4D + 0.5cm in all directions

- PTV_{4000} (3D CT planning)

  PTV_{4000} = GTV_3D + 1.5 cm sup and inf and 1cm ant/post/left/right

Organs at risk

Duodenum: The whole of the duodenum from below the pylorus to the fourth part of duodenum (up to the ligament of Treitz) should be outlined.

Stomach: The whole stomach should be outlined

Small bowel: Individual loops of small bowel should be outlined on all slices from 2cm above to 2cm below the PTV not including colon and duodenum. Consider further additional contouring if non-coplanar beams are used.

Large Bowel: Outline all large bowel from 2cm above to 2cm below the PTV

Liver: Outline the whole liver

Kidneys: Both kidneys outlined separately

Spinal cord: The spinal cord from 2cm above to 2cm below PTV. If non-coplanar beams are used, a greater length should be outlined.

Spinal cord PRV: Spinal cord + 5mm

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7. Treatment planning

IMRT planning as per ICRU 83 guidance

Table 2: Suggested PTV constraints for 36Gy/15#

Structure	Constraint	Optimal	Mandatory
PTV_{3600}	D95%		≥95% (34.20Gy)
	D98%	≥95% (34.20Gy)	
	D50%		≥100% (36Gy)±1%
	D2%	≤105% (37.8Gy)	≤107% (38.52Gy)

Table 3: Suggested PTV constraints for 45Gy/15# SIB (VMAT/IMRT)

OAR constraints take priority over PTV/ITV coverage. Achievable coverage of PTV_{4500} by D95% will be dictated by proximity/overlap of PTV with GI tract*.

Structure	Constraint	Optimal	Mandatory
PTV_{4500}	D95%		≥95% (42.75Gy)*
	D98%	≥95% (42.75Gy)	
	D2%	≤105% (47.25)	≤107% (48.15)
	D50%		≥100% (45Gy) ±1%
PTV_{4000}	D95%		≥95% (38Gy)
	D98%	≥95% (38Gy)	
	D50%		≥100%(40Gy)

Table 4: Suggested PTV constraints for 40Gy/15# SIB (3DC/3D CT planning)

Structure	Constraint	Optimal	Mandatory
PTV_{4000}	D95%		≥95% (38Gy)
	D2%		≤107% (42.8Gy)

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Table 5: OAR constraints

Organ		Optimal	Mandatory
Duodenum	Dmax 0.5cc		≤45Gy
	D5cc	≤36Gy	-
Stomach	Dmax 0.5cc	≤40Gy	≤45Gy
	D5cc	≤36Gy	-
Small bowel	Dmax 0.5cc		≤45Gy
	D5cc	≤36Gy	-
Large bowel	Dmax 0.5cc	≤48Gy	≤51Gy
Liver			Mean ≤ 24Gy
Kidneys	Mean combined	≤12Gy	≤15Gy
	If one kidney or one kidney mean dose >12Gy then dose to single kidney or kidney receiving lower dose:		V12Gy ≤10%
Spinal cord	Dmax 0.5cc PRV	≤35Gy	≤37.5Gy

* *Taken from ABC-07 trial protocol (adapted duodenum and small bowel -optimal constraints used as mandatory)*

8. Treatment delivery

Patients should follow the same fasting and drinking instructions as performed prior to their radiotherapy planning CT. They should remain nil by mouth for 2 hours and to drink 150mls of water prior to treatment.

Daily Online position verification is mandated (CBCT or MR-guided). Imaging and corrections should be carried out as daily with on line match and reposition. A bone

match followed by soft tissue CBCT match is recommended with priority given to OAR position.

Consider prophylactic anti-emetic and PPI

9. Follow up after treatment

CTCAE v5.0 should be used for prospective evaluation of toxicity with recommended time points of data collection at 4 weeks, 3 months and then 3 monthly until 2 years of follow up is reached (intervals for follow up beyond this point at discretion of local investigator).

For borderline resectable - repeat of baseline imaging at 2 weeks post RT. Aim for surgery at 4-6 weeks.

For locally advanced patients, CT imaging (+/- other imaging modalities as per local policy) is recommended at 3 months and then as per local policy thereafter.

Table 4: Suggested follow up schedule for locally advanced pancreatic cancer

	Time Point			
	4 weeks	3 months	3 monthly until 2 years	Post 2 years
Toxicity assessment	√	√	√	As per local policy
CT*		√	As per local policy	As per local policy
Ca 19-9	As per local policy	As per local policy	As per local policy	As per local policy

* +/- additional imaging as per local policy

9. References

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Appendix 5: SCALOP 2 trial protocol

Full title: A multi-centre randomised study of induction chemotherapy followed by capecitabine (+/-nelfinavir) with high or standard dose radiotherapy for locally advanced non-metastatic pancreatic cancer

Short title: Systemic therapy and Chemoradiation in Advanced LOcalised Pancreatic cancer – 2

Acronym: SCALOP-2

Protocol Version & date:	SCALOP-2_Protocol_V6.0_10Oct2017
Sponsor Protocol Number:	OCTO_063
EudraCT Number:	2013-004968-56
Ethics Number:	15/SC/0103
ISRCTN Number:	50083238
UKCRN ID:	18700
ClinicalTrials.gov number:	NCT02024009
IRAS Project ID:	154496

Appendix 5: SCALOP 2 trial protocol

8.1 Optional Pre-Radiotherapy Investigations

PET/CT scan abdomen is optional. PET/CT may be of assistance in identifying disease not visible on CT and distinguishing pancreatic tumour from duodenum. GTV defined by diagnostic CT scan must not be reduced based on PET scan, unless clearly identified as being normal structure on PET/CT.

8.2 Radiotherapy Planning, Delivery and Quality Assurance Guidelines

Please refer to the Radiotherapy Planning, Delivery and Quality Assurance Guidelines document which will be available on the RTTQA website http://www.rttrialsqa.org.uk/rttqa/?q=scalop-2 for:

- Radiotherapy localisation, simulation and immobilisation
- Target volume delineation including Organs at Risk (OARs)
- Dose constraints to planning target volume and OARs
- Treatment verification
- Radiotherapy quality assurance

Tumour Volume definition (TVD) should be discussed with a pancreatic/upper GI radiologist and joint contouring with the radiologist is recommended. Outlining of the volumes of interest should take account of all available imaging (e.g., CT, MRI, ^{18}FDG-PET-CT). In particular GTV should NOT be reduced if negative on PET-CT, if it has been identified as abnormal on other imaging modalities. Where tumour abuts/involves vessels, include the entire circumference in the GTV. Target volumes are defined according the principles outlined in ICRU 83. **Prophylactic regional nodal irradiation will not be used.**

8.3 Gross Tumour Volume (GTV) and Composite GTV (GTV_C)

For 3D conformal planning:
On contrast enhanced 3D CT scan:
GTV_T= includes the macroscopic pancreatic tumour visible on imaging.
GTV_N= loco regional lymph nodes >1cm in short axis diameter. If peri-tumoural node is <1cm, confirm with radiology that lymph node is non-malignant and do not include in GTV.
GTV_3D= GTV_T +GTV_N

For 4D Planning:
On contrast enhanced 3D CT (or equivalent), acquire GTV_3D as above
On 4DCT:
GTV_T_inhale; GTV_N_inhale
GTV_T_exhale; GTV_N_exhale
Create the composite GTV (GTV_C) using a Boolean union of operator adding GTV_T; GTV_N; GTV_T_inhale; GTV_N_inhale GTV_T_exhale; GTV_N_exhale
Once GTV_C is created verify that involved tumour/nodes are adequately covered on all phases of 4DCT.

Clinical Target Volume (CTV):
CTV for 3D planning:
CTV_3D= GTV_3D + 0.5 cm expansion in all directions
Edit CTV when overlapping with GI tract.

CTV for 4D planning:
CTV_4D=GTV_C+0.5 cm expansion in all directions.
Edit CTV when overlapping with GI tract.

Planning Target Volume (PTV):
Conventional dose RT Arms:
PTV for 3D planning
PTV5040=CTV_3D with following margins:
Cranial: 0.5 cm (exhale breath-hold*) or 1.5cm (free breathing);
Caudal: 1.5 cm
Ant-Post and lateral: 1.0 cm

PTV for 4Dplanning
PTV5040= CTV_4D+0.5cm in all directions

Appendix 5: SCALP 2 trial protocol

High dose RT Arms:
The use of 4D CT or motion management is recommended.
PTV for 3D planning
PTV5400 = CTV_3D with following margins:
Cranial: 0.5 cm (exhale breath-hold*) or 1.5 cm (free breathing);
Caudal: 1.5 cm
Ant-Post and lateral: 1.0 cm

PTV6000= GTV_3D + 0.5cm in all directions

PTV for 4D planning
PTV5400= CTV_4D+0.5cm in all directions.
PTV6000=GTV_C

Table 14. 3D and 4D volumes

Volumes	3D	4D
GTV	GTV_T GTV_N GTV_3D=GTV_T +GTV_N	GTV_T GTV_N GTV_T_inhale; GTV_N_inhale GTV_T_exhale; GTV_N_exhale
GTV_C	n/a	GTV_C = Boolean addition of all GTV
CTV	CTV_3D= GTV_3D+ 0.5cm in all directions (edit for GI overlap)	CTV_4D= GTV_C+ 0.5cm in all directions (edit for GI overlap)
PTV5040	CTV_3D with 0.5 cm cranial (exhale breath-hold*) or 1.5cm (free breathing); 1.5 cm caudal and 1.0 cm (ant-post; left-right)	CTV_4D+0.5cm in all directions
PTV5400	CTV_3D with 0.5 cm cranial (exhale breath-hold*) or 1.5cm (free breathing); 1.5 cm caudal and 1.0 cm (ant-post; left-right)	CTV_4D+0.5cm in all directions
PTV6000	GTV_3D+ 0.5 cm3D in all directions	GTV_C

***Exhale breath-hold should only be used with 3DCT where exhale breath-hold can be confirmed**

8.4 Radiotherapy Dose prescription

Conventional dose RT arms: The dose to the PTV will be 50.4Gy in 28 fractions (1.8Gy per fraction) treating once daily, 5 days per week, using photon beams of 6MV or higher. Dose to 95% of the PTV (PTV D95%) should be at least 93%. The maximum dose allowed within the PTV to a point that is 0.1 cc is 107% of the prescribed dose.

High dose RT arms: The dose to the larger PTV (PTV5400) will be 54Gy in 30 fractions (1.8Gy per fraction) treating once daily, 5 days per week, using photon beams of 6MV or higher. Simultaneous integrated boost (SIB) will be delivered to PTV6000 so that this volume receives a total dose of 60Gy in 30 fractions (2Gy per fraction). 95% of PTV should ideally receive ≥90% of the prescribed dose, maximum dose to a point that is 0.1cc should be ≤ 115% of prescribed dose. Where there is PTV and GI tract overlap, accept a dose of ≥83% of prescribed dose at the region of the overlap (see Planning, Delivery and Quality Assurance Guidelines document for details).

RT should ideally start on a Monday but a Tuesday is acceptable if for example it has not been possible to collect blood samples on a Sunday.

8.5 Radiotherapy technique

Patients are treated in free breathing. Intensity Modulated RT (IMRT) is mandated for high dose arms and preferred over 3D conformal RT for standard dose arm. Prior IMRT accreditation is necessary through the NCRI RTTQA group or equivalent.

8.6 Radiotherapy Dose constraints

The radiotherapy target and OAR dose constraints are outlined below (see the Planning, Delivery and Quality Assurance Guidelines document for additional details).

Appendix 5: SCALOP 2 trial protocol

Description	Naming Convention	Variable	Optimal	Mandatory
PTV High dose RT arms	PTV6000	D99%	≥ 95%	≥ 90% (≥ 83%)*
	PTV6000	D95%	≥ 97%	≥ 93% (≥ 90%)*
	PTV5400	D99%	≥ 95%	≥ 90%
	PTV5400	D95%	≥ 97%	≥ 93%
	PTV6000 & PTV5400	DMax (0.1cc)	≤ 110%	≤ 115%
PTV Conventional dose RT arms	PTV5040	D99%	≥ 95%	≥ 90%
		D95%	≥ 97%	≥ 93%
		Dmax (0.1cc)	≤ 105%.	≤ 107%
Kidney receiving higher dose	Kidney_R or Kidney_L	V20Gy	≤ 40%	≤ 45%
Combined Kidneys		V20Gy	≤ 30%	≤ 35%
Liver	Liver	V30Gy	-	≤ 30%
		Mean	≤ 28Gy	≤ 30Gy
Stomach	Stomach	Dmax (0.1cc)	≤ 58Gy	≤ 60Gy
		V50Gy	< 5cc	-
		V45Gy	< 75cc	-
Small Bowel	SmallBowel	Dmax (0.1cc)	≤ 58Gy	≤ 60Gy
		V50Gy	< 10cc	-
		V15Gy	< 120cc	-
Duodenum	Duodenum	Dmax (0.1cc)	≤ 58Gy	≤ 60Gy
		V50Gy	< 10cc	-
		V15Gy	< 60cc	-
Spinal Cord PRV	SpinalCord_05	Dmax (0.1cc)	-	≤ 45Gy

* When the GI tract overlaps with a PTV, there is scope to reduce the dose in this region in order to prioritize GI tract sparing.

Appendix 5: SCALOP 2 trial protocol

All attempts must be made to meet optimal constraints (but failure to meet will not be regarded as protocol violation). If any mandatory constraints cannot be met, please contact the QA Physicist.

While optimizing plan in the high dose arm, prioritize GI tract over PTV (see Planning, Delivery and Quality Assurance Guidelines document for details).

8.7 Management of unscheduled gaps in radiotherapy treatment

This will be managed in lines with the latest RCR guidance.
https://www.rcr.ac.uk/docs/oncology/pdf/BFCO(08)6_Interruptions.pdf

Radiotherapy interruption – compliance criteria:
Per- protocol: Total delay of 0-7 days (5 working days)
Variation acceptable: 8-14 days (10 working days)
Variation unacceptable: > 14 days (> 10 working days)
NB Capecitabine and nelfinavir should not be administered if RT is stopped for toxicity.

8.8 Expected Adverse Events of Radiotherapy

Nausea, vomiting, diarrhoea, fatigue, weight loss, oesophagitis, gastritis, duodenitis, gastro-intestinal ulceration, gastro-intestinal haemorrhage, gastro-intestinal perforation, gastro-intestinal fistula, intestinal obstruction, radiation dermatitis, diabetes, second malignancy (rare).

It may be difficult to separate out the adverse effects of RT from concurrent chemotherapy and as such management of key toxicity related to chemoradiotherapy is discussed in **Section 7.4**.

9 Trial assessments

If indicated, clinical assessments should be performed within 7 working days (ideally within 3 working days) before Day 1 of the scheduled cycle. Though if clinic day is a Friday and chemotherapy starts on Tuesday, the research nurse or member of medical team must confirm with the participant that there has been no deterioration since the review, before starting chemotherapy. In such an event, this must be recorded in the CRF.

If participants show symptoms suggesting disease progression before any of the scheduled visits and scans, then CT scans should be performed according to normal institutional practice. Details of these scans should be captured at the next follow up visit. If these scans show disease progression, subsequent scheduled scans will not be required, and treatment will be at local investigator's discretion.

Quality of life and translational sample collection will be conducted in Stage 2 participants only. For details about processing translational samples, see Section 13.

9.1 Assessments during induction chemotherapy

Unless specified, assessments apply to Stage 1 and Stage 2.

9.1.1 Pre-induction therapy

After informed consent but before the start of the first cycle of chemotherapy (Stage 2 participants only):

- Quality of Life (QoL) questionnaire QLQ-C30 and PAN26 and EQ5D
- Translational blood sample (if consented)
- Translational biopsy (if consented): Request paraffin diagnostic block from pathology where available – see Section 13 for more details

9.1.2 Induction chemotherapy treatment assessments

Up to 7 working days before the start of each cycle of GEMABX chemotherapy (bloods within **2 working** days of cycle 1 i.e. bloods on a Monday to start chemotherapy on a Wednesday). Exceptions: Bloods should be taken on a Friday for Day 1 chemotherapy starting the next Monday):

- Clinical examination (including vital signs and weight)
- WHO PS