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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

List of amendments to date:
Not Applicable

A review of the protocol has been completed and is understood and approved by the following:

_____	_____	_____/_____/_____
Chief Investigator	Chief Investigator Signature	Date dd/mmm/yyyy
_____	_____	_____/_____/_____
Radiation Oncology Principal Investigator IRELAND	Radiation Oncology Principal Investigator Signature	Date dd/mmm/yyyy
_____	_____	_____/_____/_____
Radiation Oncology Principal Investigator UK	Radiation Oncology Principal Investigator Signature	Date dd/mmm/yyyy
_____	_____	_____/_____/_____
On behalf of ICORG, Title	ICORG Representative Signature	Date dd/mmm/yyyy

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1 Introduction

The protocol for NeoAEGIS has been developed through the Radiotherapy leads in ICORG. This has been developed in collaboration with the 'SCOPE' trials QA team.

The key points of reference for this work are the existing NeoAEGIS RT protocol, an Upper GI Radiotherapy Planning Workshop held October 27th 2011, Bristol, (Gwynne 2013), UK Patterns of Failure references (Button 2009, Dresner 2001) and the EORTC-ROG Guidelines for neo-adjuvant radiation of adenocarcinomas of the GE junction and stomach (Matzinger 2009).

This document outlines the key radiotherapy principles that will be used within the NeoAEGIS trial.

Changes and revisions to this document can only be made by the Radiation –Oncology Principal Investigators and will be review by the Chief Investigator and ICORG.

Any centre wishing to deviate from this radiotherapy planning and delivery document should seek agreement from the appropriate National Principal Investigator (listed in Sec. 8) before any patient is recruited.

1.1 Recommended Staging Investigation for Radiotherapy Planning

For staging purposes, it is recommended that all patients have a CT scan of the thorax, abdomen (+/- pelvis), PET-CT and an endoscopic ultrasound scan (EUS), noting the full extent of the disease with reference to anatomical landmarks (e.g., aortic arch or carina). It is highly recommended that diagnostic scans are reviewed, ideally along with the planning scans, with specialist Upper GI radiologists.

A EUS is attempted for all patients. In approximately 10% of cases, the EUS probe will not safely traverse the primary tumour. Whilst this varies according to user experience and the use of certain equipment (such as the use of the blind paediatric scope) valuable information can still be gained in respect to the proximal disease.

EUS staging should be performed within the context of a specialised Upper GI MDT. References to anatomical landmarks visible on the CT Planning Scans are vital (e.g. the superior extent of the aortic arch or the carina) together with clear recording of the extent of disease, including submucosal and nodal disease.

PET-CT has an established role in the UK in terms of staging oesophageal cancer and can be useful in determining the extent of disease, but the volume as defined by CT and EUS should not be reduced based on PET findings alone.

1.2 Dose prescription and fractionation

For NeoAEGIS the total dose of radiation will be 41.4Gy in 23 fractions, 1.8Gy per fraction, treating once daily, 5 days per week, over a total period of 4.5 weeks excluded Bank Holidays and weekends.

The dose will be prescribed and recorded as per ICRU 50/62.

2 Definition of treatment volumes

2.1 Target volume definition (TVD)

Eligibility for the NeoAEGIS trial includes patients with oesophageal and oesophago-gastric junction (OGJ) carcinomas who are to undergo an oesophagectomy.

As such, and for the benefits of this protocol, based on EUS patients oesophageal planning can be divided into:
middle 1/3rd - defined here as primary tumour epicentre between 24cm and 32cm ab oral.
lower 1/3rd and OGJ (Siewert types I-III) - defined here as primary tumour epicentre from 32cm ab oral to OGJ

Where the passage of the EUS scope across the tumour has not been possible, findings from diagnostic endoscopy and PET imaging must be used to define the disease centre.

Target volumes are defined following the principles of ICRU 50 and 62. Where there is overlap between the PTV and spinal cord PRV, or the two structures are in close proximity, it is up to the local Principal Investigator, where necessary on discussion with the Radiotherapy Principal Investigator, to weigh up the risk-benefits of compromising the target volume and risk of toxicity to the spinal cord. However, the risk of cord toxicity is low at the Radiotherapy dose in this protocol.

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

2.2 Radiotherapy localisation

In summary:

A planning CT scan should be performed as soon as possible following randomisation in order to keep to trial timelines, i.e. start CRT within 15 days of registration.

A CT slice thickness of 2.5mm is recommended, but any thickness ≤3mm is adequate.

Intravenous contrast should be used (providing adequate renal function), but oral contrast should not.

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 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.

Patients should be scanned in the treatment position, namely supine with arms above head with knee support and immobilisation with thermoplastic device or vacuum cushion as per local protocols.

The extent of the scan would be from 1cm superior to the apices of the lungs to the bottom of the L4 vertebra in order to ensure inclusion of all OARs (lungs, liver, kidneys and stomach). It is particularly important that the full lung volume is scanned as radiotherapy dose received by lung tissue and the volume of lung spared will be reported in both absolute and relative terms as part of this study. Diagnostic information should be taken from the diagnostic CT scan, EUS (referenced to CT identifiable structure) and PET-CT.

Fused CT/PET images should not be used within the NeoAEGIS study until further evaluation is undertaken and without discussion with the Chief investigator.

The use of 4DCT for planning is not currently approved within NeoAEGIS. The use of 4D planning will be encouraged within the NeoAEGIS trial but centres should only use this technique once there has been a protocol modification allowing this to be used and a 4D test case has been successfully undertaken.

Inverse planned IMRT should not be used for NeoAEGIS until further evaluation in this pre-operative setting is undertaken. If there is uncertainty regarding the planning and delivery technique used in a centre, this should be discussed with the Radiotherapy Principal Investigator.

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.

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

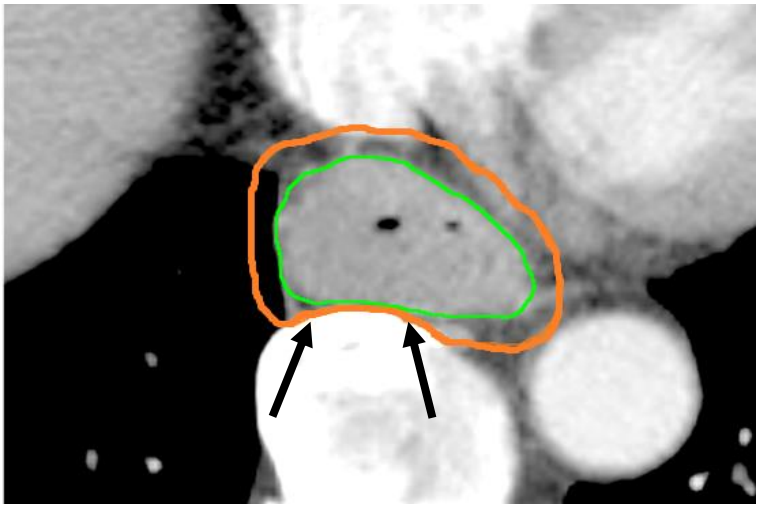
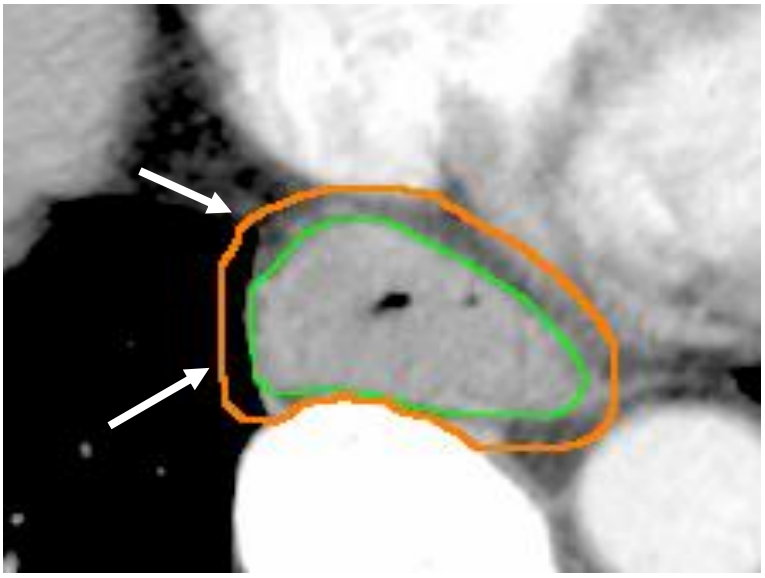
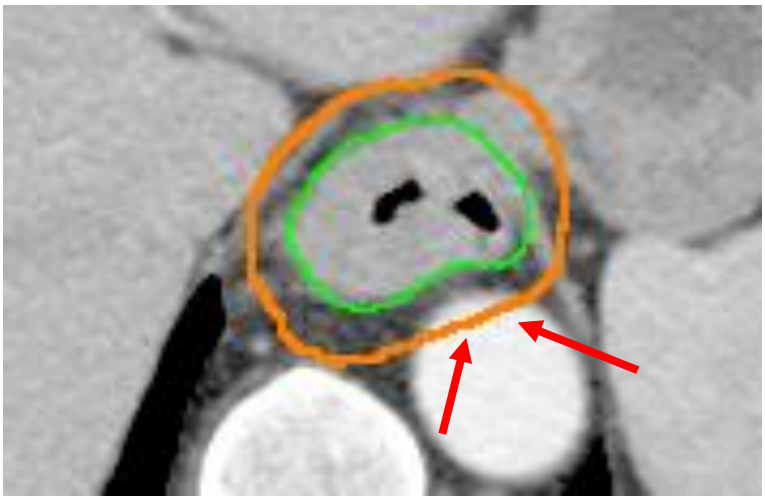


Figure 1b and 1c – CTVA (orange) is not trimmed off lung, pericardium, great vessels, trachea or bronchi



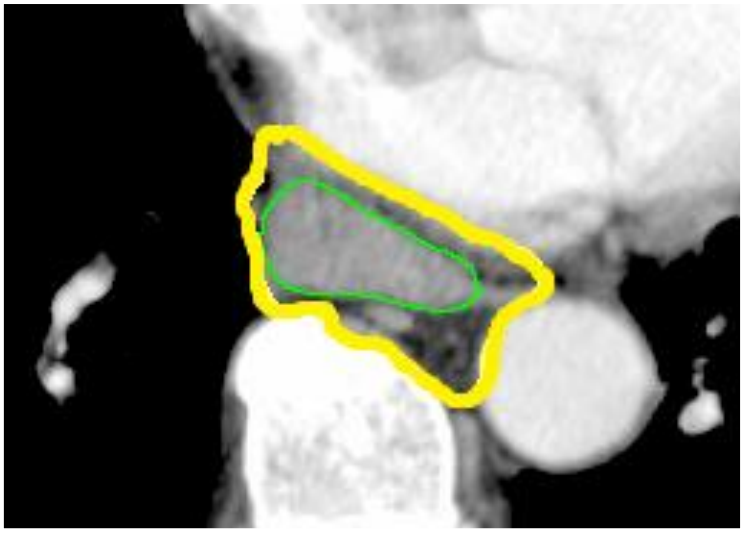


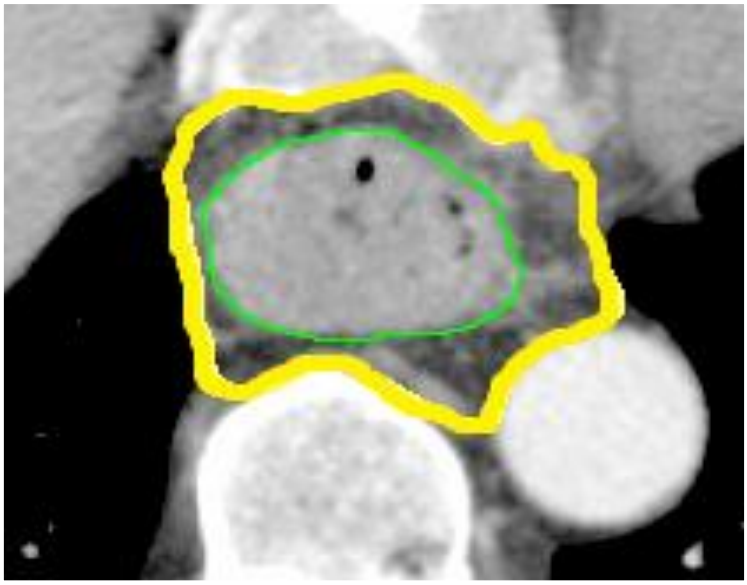
CTVB will comprise of the 'fat pad' around the oesophagus. This 'fat pad' is visible on CT and is the site of peri-oesophageal nodes. It is of varying thickness, and may be extremely thin or almost non-existent in places.

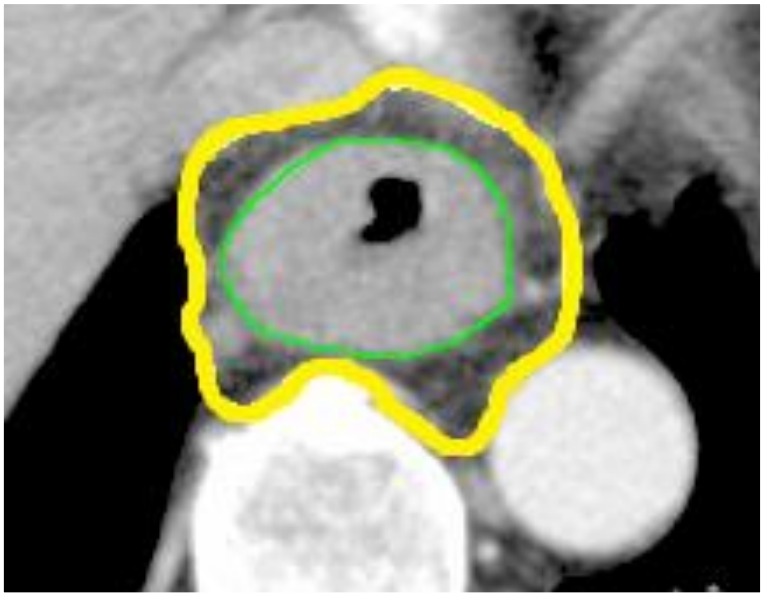
The 'fat pad' is contoured at the same levels as the **GTVpn** and for 3cm superior and inferior (S/I) to **GTVp**. It is bordered posteriorly *in places* by the anterior aspect of the vertebral body. The **CTVB** should NOT include bone, lung, pericardium, trachea, bronchus or great vessels (it SHOULD 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







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.

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

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'.

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:

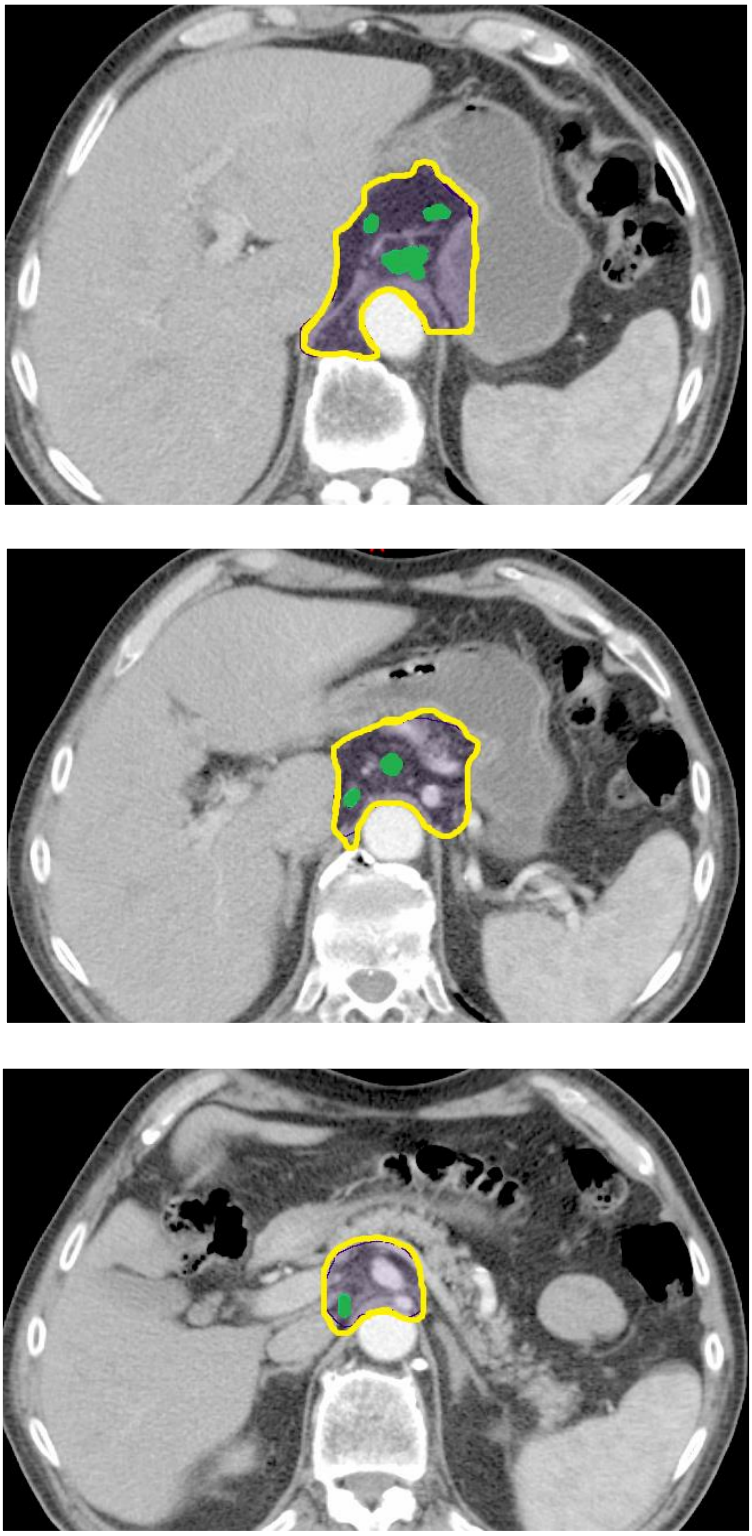
- the entire 'fat pad' along the length of the **GTVpn** and for 3cm superior and 2-3cm inferior to **GTVp**
- the entire oesophagus along the length of the **GTVpn** and for 3cm superior and 2-3cm inferior to **GTVp**
- Malignant peri-oesophageal nodes
- Benign nodes along its course without a margin (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.

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.



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.

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

5 Outlining of organs at risk

The following organs at risk (OAR) structures must be contoured and labelled using the nomenclature specified below [Santanam 2012].

Structure name	Description
SpinalCord	The spinal cord should be outlined on slices within 20mm above and below the PTV.
SpinalCord_PRV	A Planning Risk Volume (PRV) for the cord is created to account for positioning error; the size of the margin added to the cord being commensurate with the accuracy of treatment delivery expected and, as such, the tolerance level allowed in portal image verification on treatment. An acceptable protocol would be: an isotropic margin of 5mm generated around the spinal cord to create the Cord PRV necessitates no more than 5mm movement of the isocentre on treatment before corrective action is taken.
Lungs	The full extent of the right and left lungs are to be outlined, this should be done in such a way that the planning system will be able to calculate a combined lung Dose Volume Histogram (DVH).
Heart	The whole heart should be outlined to the extent of the pericardial sac (if visible). The major blood vessels (superior to the organ) and the inferior vena cava (towards the inferior extent of the heart) are excluded. The superior extent is often difficult to define and may be simplified by identification of the vessels superior to the heart. We use the point where the pulmonary trunk and the right pulmonary artery are seen as separate structures as an indication of the superior extent of the heart (see Appendix 4).
Liver	The whole liver should be outlined.
Kidneys	Both kidneys should be outlined separately.
Stomach	The whole stomach should be outlined in such a way that a stomach DVH can be produced. This will be for evaluation only as a Region of Interest (RoI) and will not be an OAR with dose constraints (see Appendix 5).

6 Treatment Plan Optimisation

A single phase 3D-conformal treatment plan should be produced and delivered from 4-5 gantry angles (though the number of gantry angles is not mandated). There should be no cone down or boost volumes but more than one beam may be delivered from the same gantry angle, e.g., filler fields to cool hotspots or opposed superior-inferior wedges to improve coverage at the extents of the PTV. Only coplanar beams should be used. If in doubt please contact the RTQA team via Radiotherapy Principal Investigator to discuss any queries.

A 'type B' calculation algorithm is strongly recommended to be used for dose calculation and optimisation.

Megavoltage photon energies ≥ 6MV is mandatory.

IMRT should not be used for NeoAEGIS until further evaluation in this clinical setting is undertaken. In individual circumstances, if recommended locally for dosimetric considerations, this should be discussed with the Radiotherapy Principal Investigator prior to treatment.

Dose limitations of Volumes of Interest (VOI) and of Organs at Risk (OAR)

Structure	**Naming convention***	**Dose Objective**	**Comments / acceptable ranges**
PTV if 'type B' algorithm used	PTV_4140	V95% ≥ 99% – (0.4*%lung/PTV overlap)	V95% objective is individually determined based on the percentage of PTV which overlaps with lung tissue according to the formula adopted from Wills 2009.
PTV if 'type A' algorithm used	PTV_4140	V95% > 99%	
PTV (general)		Dmedian = 100% (41.4Gy)	Underdosage of PTV is only allowed if requested due to the proximity of a serial OAR. In this situation a maximum of 5% of the PTV volume should receive less than 95% of the prescription dose. The median should be between 98-102% of the prescription dose (i.e., 41.4Gy).
ICRU Maximum dose	Please label patient outline as "External"	D1.8cc < 107%	Defined as the maximum dose to 1.8cc of any structure within the external contour of the patient.

Spinal cord	SpinalCord	D0.1cc < 45Gy	
Spinal Cord PRV	SpinalCord_PRV	D1cc < 40Gy	If the PTV lies close to or overlaps with the Spinal Cord PRV, the treating clinician may discretionally allow a point maximum dose up to 45Gy. Alternatively, they may report a PTV compromise (for type B algorithms this compromise must be noted regardless of the plan achieving the individualised PTV objective).
Combined Lungs	Lungs	V20Gy < 25%	The aim should be to minimise dose to the lung wherever possible to V20Gy < 25% Total lung volume and V5 lung, V5s lung and mean lung dose will be collected and reported on PAF but will not be a volume/dose constraint
Heart	Heart	V40Gy < 30% V25Gy < 50%	Optimal objective – to be achieved where possible but at lower priority than other objectives.
Liver	Liver	V30Gy < 30%	
Individual Kidneys	Kidney_L and Kidney_R	V20Gy < 70% with contralateral kidney V20Gy < 30%	The glomerular filtration rate of each kidney has to be taken into account in case of suspicion of a decreased renal function.
Combined Kidneys	Kidneys	V20Gy < 50%	
Stomach	Stomach		This will not be defined as an organ at risk but data collected to explore correlation with toxicity.

* Volumes of interest must use the nomenclature specified [Santanam 2012].

7 Treatment Verification

Use of imaging for setup and field verification is mandated within this study. **The use of cone beam CT matched to planning CT scans is mandatory within this study** (though exceptions will be permitted if discussed and approved with the National Radiotherapy Principal Investigator).

As a minimum requirement, institutions are required to obtain verification images three times in the first week of treatment (this must include the first day) and at least once each week thereafter.

More frequent imaging is allowed but is not required. On line or off line correction strategies are acceptable. The detailed description of the IGRT protocol at the participating centre must be included with the initial application for participation to the study. If modifications to the existing protocol are deemed necessary, this will be discussed with the Radiotherapy Principal Investigator.

The isocentre should be moved if disagreement is seen in excess of agreed tolerance levels based on local study – typically 5mm.

8 Communication with the surgical team.

In order to plan the patients operation, the surgeon will require a description of the PTV. In particular, the superior and inferior extent of this volume will need to be taken into account when considering the site of the surgical anastomosis.

To facilitate communication, the surgeons must be provided with a digital image, which indicates the position of the PTV in reference to anatomical landmarks, such as the carina. The simplest way to achieve this, is to take a print screen snapshot of the DRR, or the CT-reconstructed carinal image, from the TPS.

To take a print screen image of the PTV:

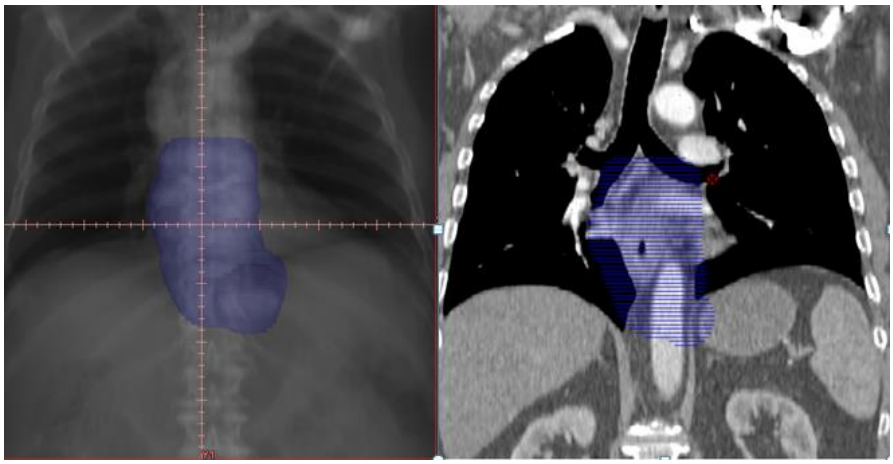
With the TPS as the active window – press alt + PrtScn.

Load Microsoft Paint (under ‘accessories’ on the Windows programs menu bar)

In Paint, press Ctrl + v. (This will copy the image into Microsoft paint)

The image can then be cropped / moved – and if necessary can be anonymised

Then save the image and forward to the surgeon.



In these examples, the left image shows the PTV on the DRR, and right image shows the PTV on the CT coronal reconstruction from the TPS.

9 The management of unscheduled gaps in radiotherapy treatment

In the event of unscheduled gaps to radiotherapy treatment, these should be managed in line with the latest RCR Guidance (The Timely Delivery of Radical Radiotherapy: Standards and Guidelines for the Management of Unscheduled Treatment Interruptions, Third Edition, 2008 - full document available at www.rcr.ac.uk). NeoAEGIS patients should be managed as Category 1 patients.

10 Radiotherapy quality assurance

We have taken the advice from the NeoSCOPE Investigators and the NCRI RTTQA Group. The necessary forms and details about how to upload plan data, questionnaires and planning documents can be obtained from the National PI or RTTQA contact for UK centres (listed below).

10.1 Pre-trial quality assurance

Completion of an outlining exercise:
All centres who wish to participate in NeoAEGIS must satisfactorily complete a pre-accrual outlining benchmark case of a mid and lower oesophageal cancer case using a 3DCT DICOM dataset provided by the RTTQA group.

Outlines will be compared against a consensus reference volume (gold standard) derived from the outlines of TMG members. Criteria for satisfactory completion will be at the discretion of the RTTQA members of the TMG. Attention will be paid to correct interpretation of imaging (GTV) and ability to follow the protocol to create CTV and PTV. Written feedback will be provided to all centres.

Completion of a planning exercise:
All centres who wish to participate must satisfactorily complete a planning exercise using a pre-outlined 3DCT DICOM dataset provided by the RTTQA group. A Plan Assessment form (PAF) should be completed and submitted at the same time.

Plans will be checked for consistency with this document's instructions. Criteria for satisfactory completion will be at the discretion of the RTQA members of the TMG. Written feedback will be provided to all centres.

Production of a Radiotherapy Process Document:
All centres who wish to participate in SCOPE2 should submit a Radiotherapy Process Document describing how trial patients will be scanned, planned and treated. These will be reviewed by RTTQA members of the TMG and clarifications may be required. A template for this document will be provided.

Completion of the NeoAEGIS Facilities questionnaire

Data submission:
All completed exercises and documents should be transferred to the RTTQA team via the National PI or RTTQA contact for UK centres.

10.2 On-trial quality assurance

The following radiotherapy planning data must be submitted for **each** NeoAEGIS patient before they start radiotherapy:

- Planning CT, Structures, Plan and Dose in DICOM format.
- Diagnostic reports (EUS, CT, PET-CT).
- Plan Assessment Form (PAF)

The local PI should approve the outlining and planning for each NeoAEGIS patient. The TMG encourage internal peer-review of trial patient treatment outlines and plans within individual participating centres and for centres to contact the NeoAEGIS RTTQA contact if there are concerns or queries regarding the trial protocol.

All data must be fully anonymised to include only the patient's trial number, date of birth and initials and submitted securely following instructions on the NeoAEGIS page of the RTTQA website. Non-anonymised or incomplete data will cause delays in the review.

Timely-retrospective review

Patients are required to commence radiotherapy within 15 days of signing consent meaning that prospective/real-time review is not practical. Instead, there will be *timely-retrospective* review of the outline and plan for the first patient case from each centre. A second case will also be reviewed should there have been an issue with the first case.

The radiotherapy planning data (listed above) should be submitted for review by the RTTQA team as soon as possible and the RTTQA team will give feedback to the centre within 2 weeks of the start of treatment. This outlining and planning assessment will be undertaken by the QA NeoAEGIS national subgroup and written reports will be returned to the centre.

A further 10% sample of NeoAEGIS radiotherapy patients will be selected for timely-retrospective review via centrally-administered block randomisation process. This will be the responsibility of each national Radiotherapy PI. At any point in the trial, extra patients from a centre may be selected for real time review if there are concerns regarding the previous case(s) a particular centre.

RTQA for each country will be maintained by a National PI:

Ireland

Dr Brian O'Neill, National PI and Radiotherapy CI	brian.oneill@slh.ie
Dr Moya Cunningham	moya.cunningham@slh.ie

UK

Dr Tom Crosby, National PI	tom.crosby@wales.nhs.uk
Dr Gareth Jones, UK RTTQA contact	gareth.Jones9@wales.nhs.uk

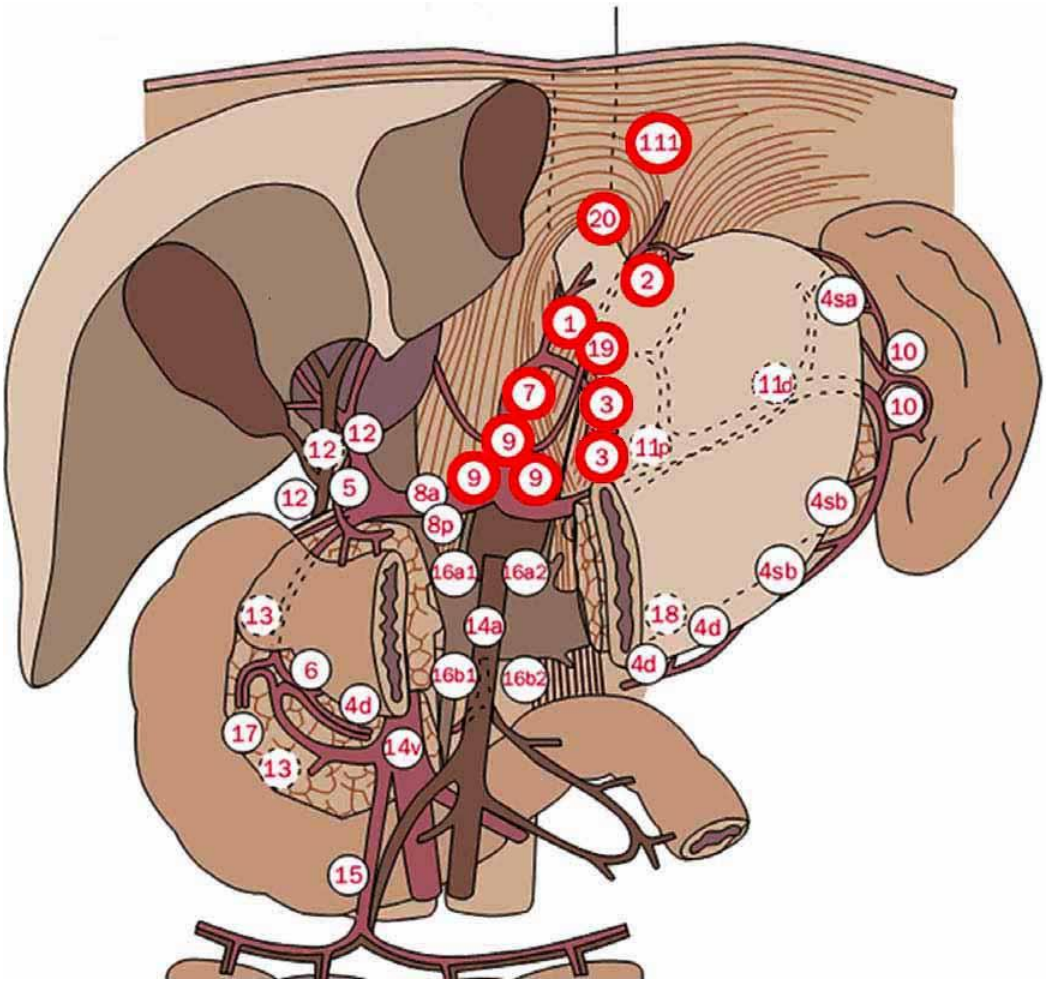
Denmark

Dr. Kenneth Hofland, National PI	kenneth.hofland@dadlnet.dk

France

TBD	TBD

Appendix 1 ***Nodal regions at risk for lower oesophageal, type I and type II tumours extending below the gastroesophageal junction***

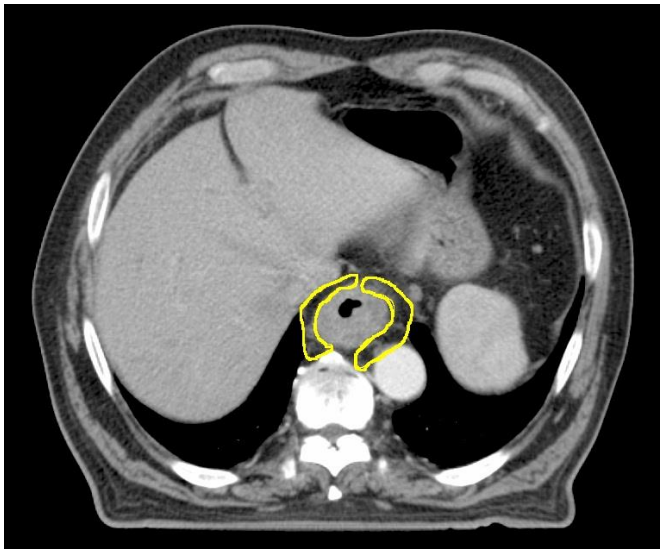


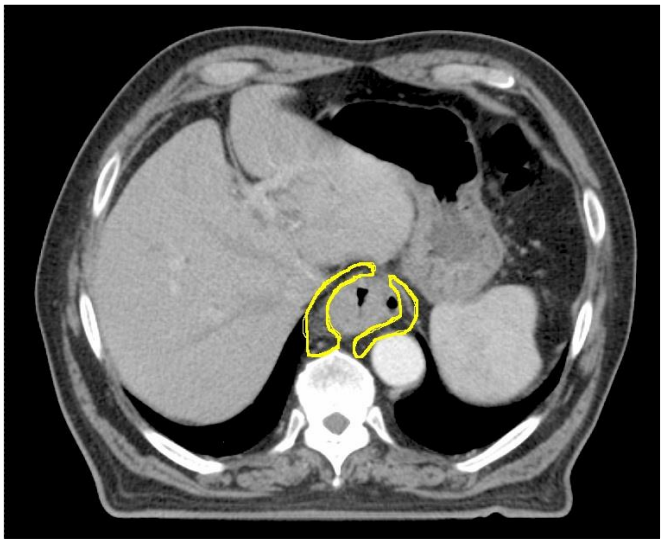
Elective nodal regions which are considered at risk for type I and type II tumours in NeoAEGIS are those that lie 2cm below the GTV in the regions identified in red above. Using the 2nd English edition of the Japanese classification of gastric carcinoma these are:

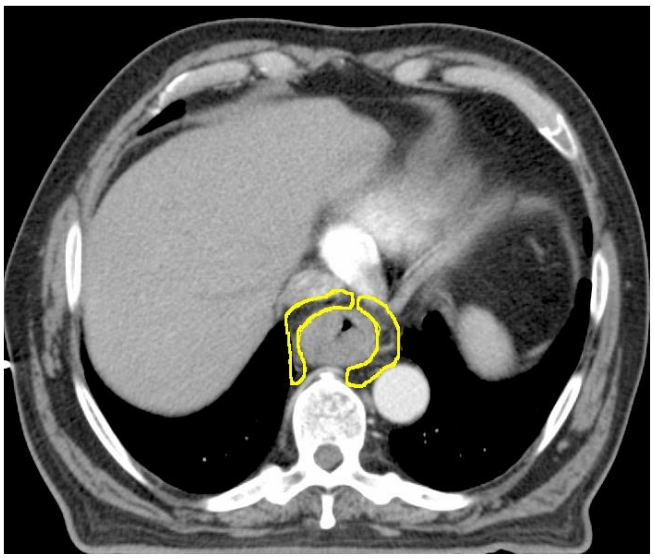
1+2	Left and right paracardial.
7	Lymph nodes along the left gastric artery.
3	Lymph nodes along the lesser curvature.
9	Lymph nodes around the celiac artery.

It does not include nodes along the short gastric vessels, distal splenic artery or around the splenic hilum.

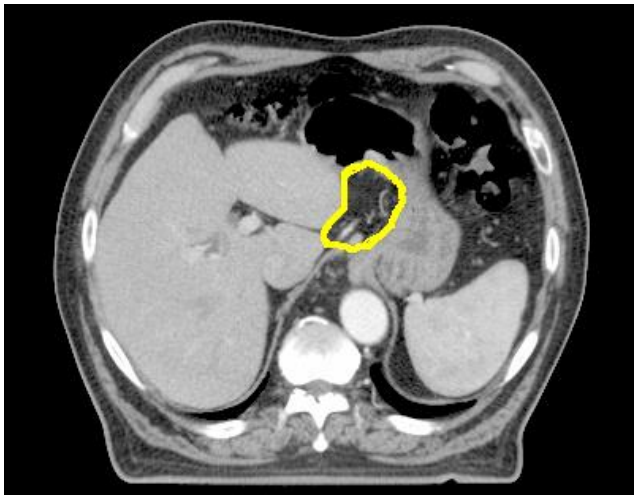
Nodal regions at risk: Right and left paracardial nodes.

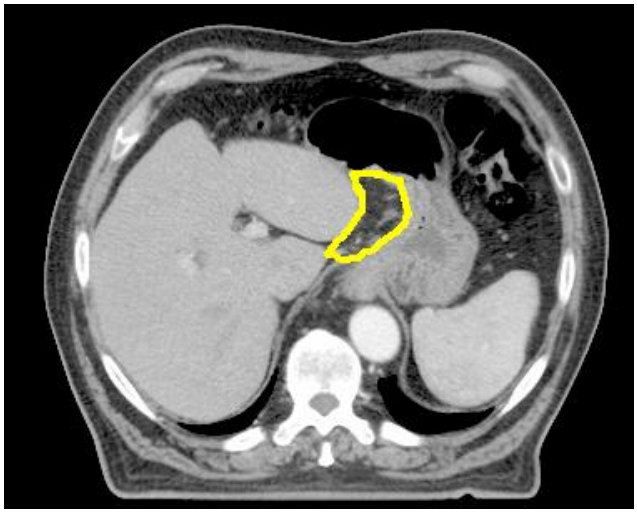




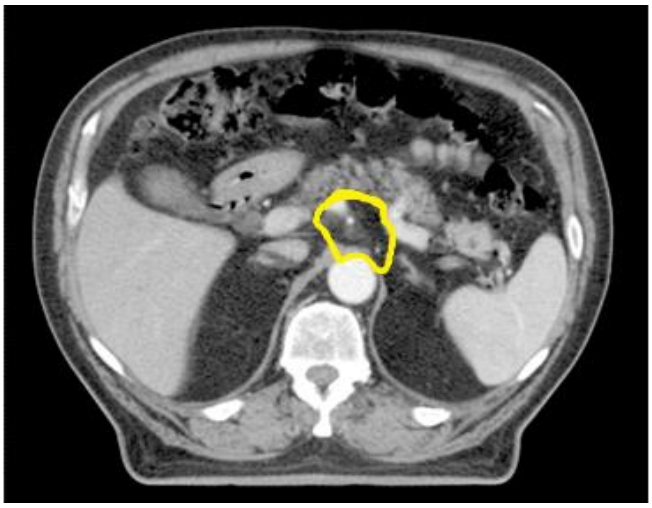


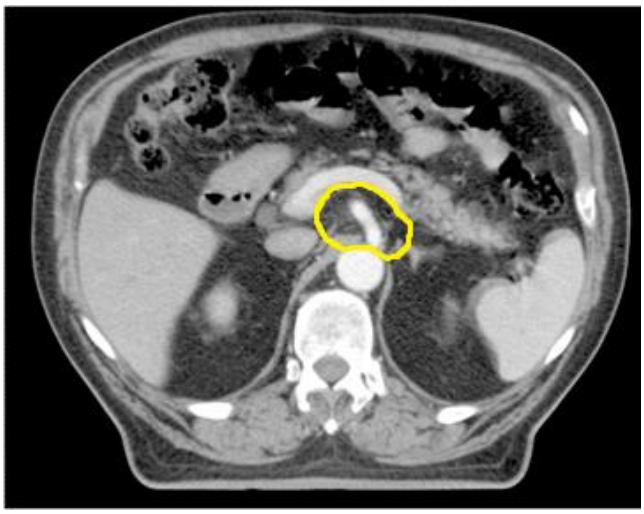
Nodal regions at risk: The left gastric artery and lesser curvature.

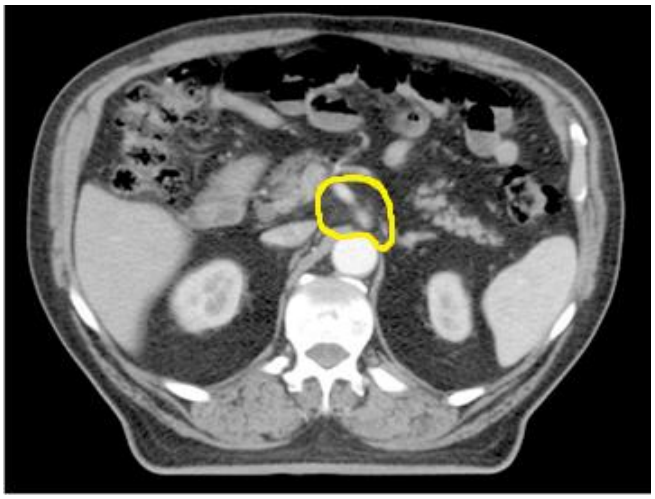




Nodal regions at risk: Coeliac Nodes.

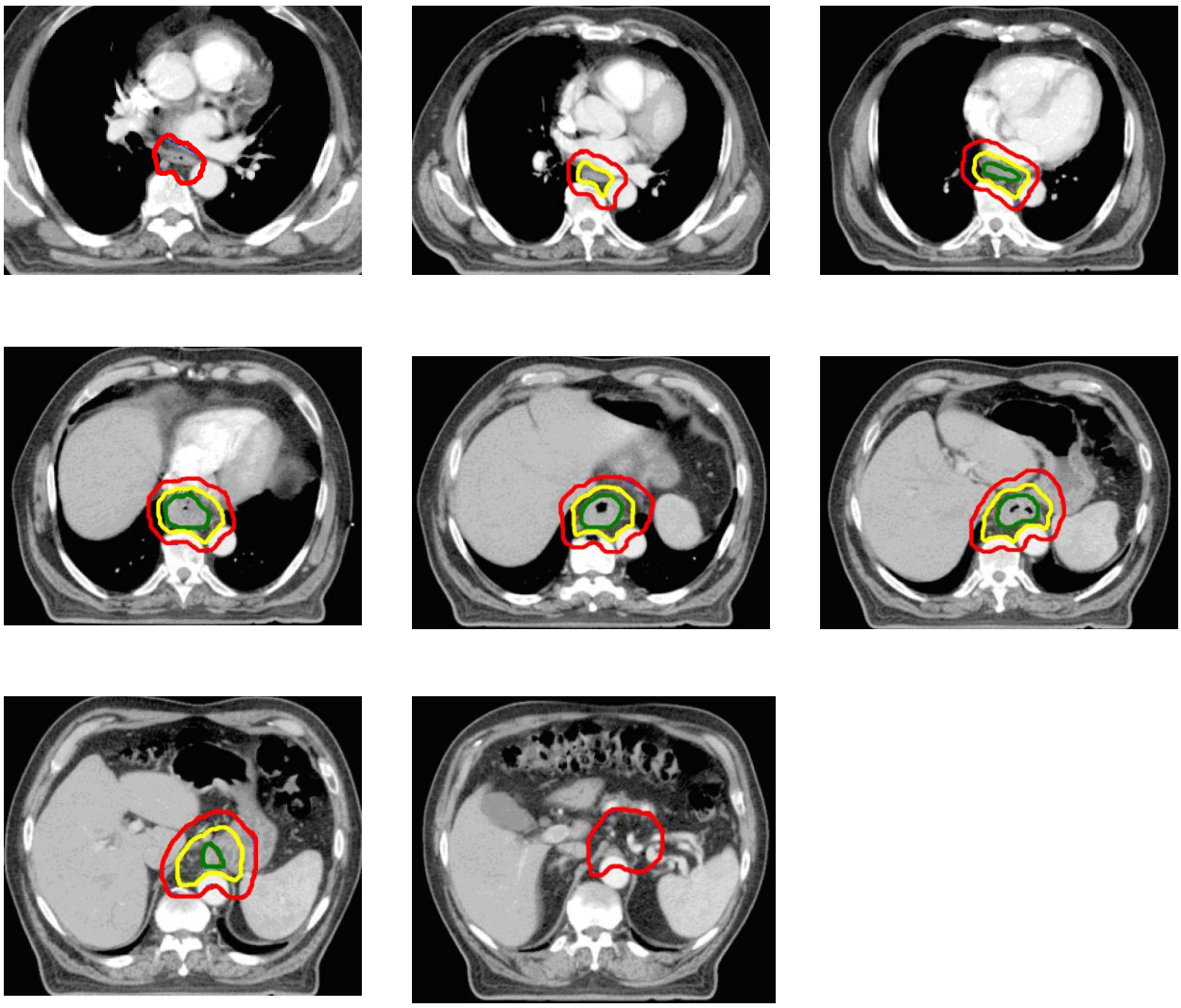






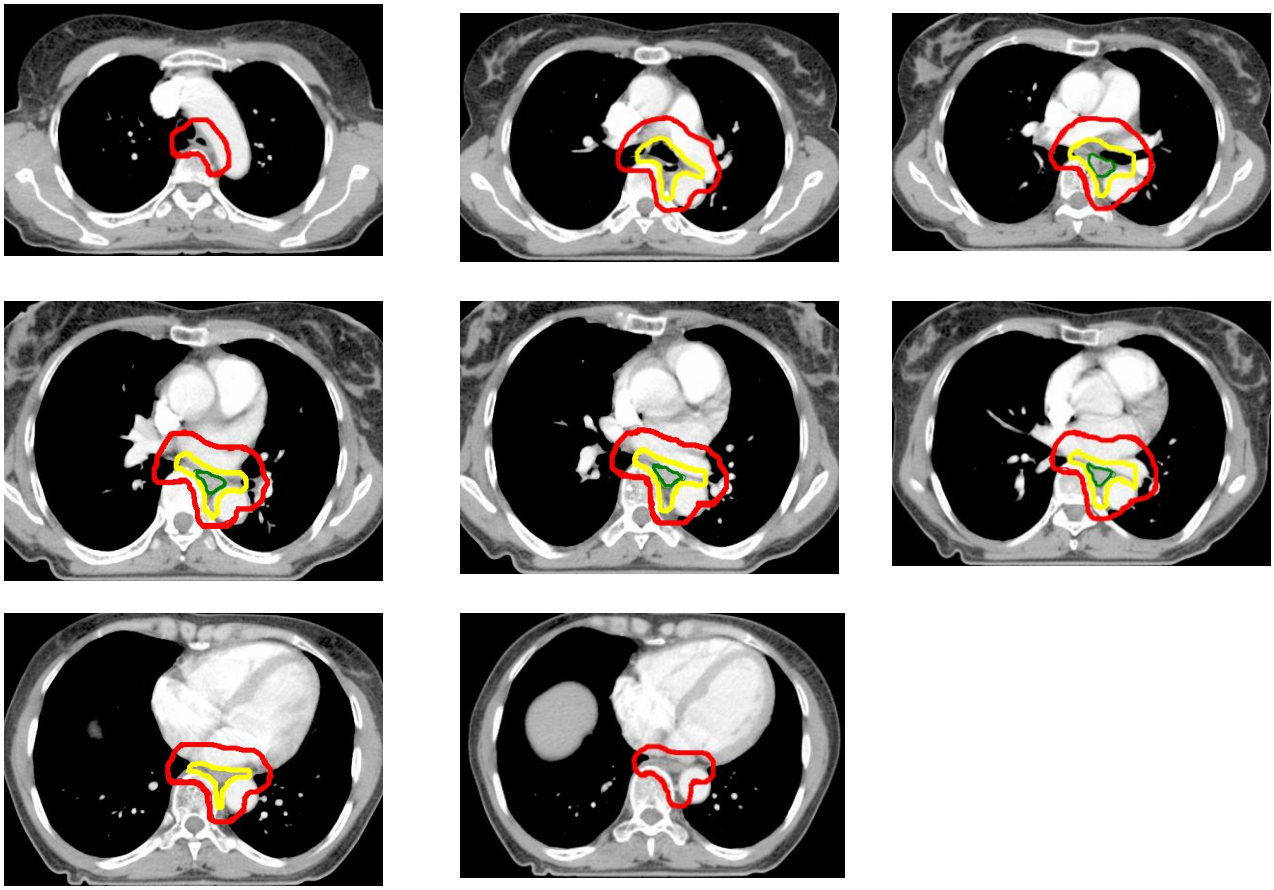
Appendix 2 *Lower oesophageal case example*

74 year old male with type I, poorly differentiated adenocarcinoma of OGJ which begins at 35cm from incisors and extends to junction 5cms in length. EUS stages the tumour as uT3N0. PET CT shows a tumour length of 6cm, no nodes were identified, or distant disease on PET CT scanning. Final clinical stage T3N0M0.
GTV (green), CTV combined (yellow), PTV (red)



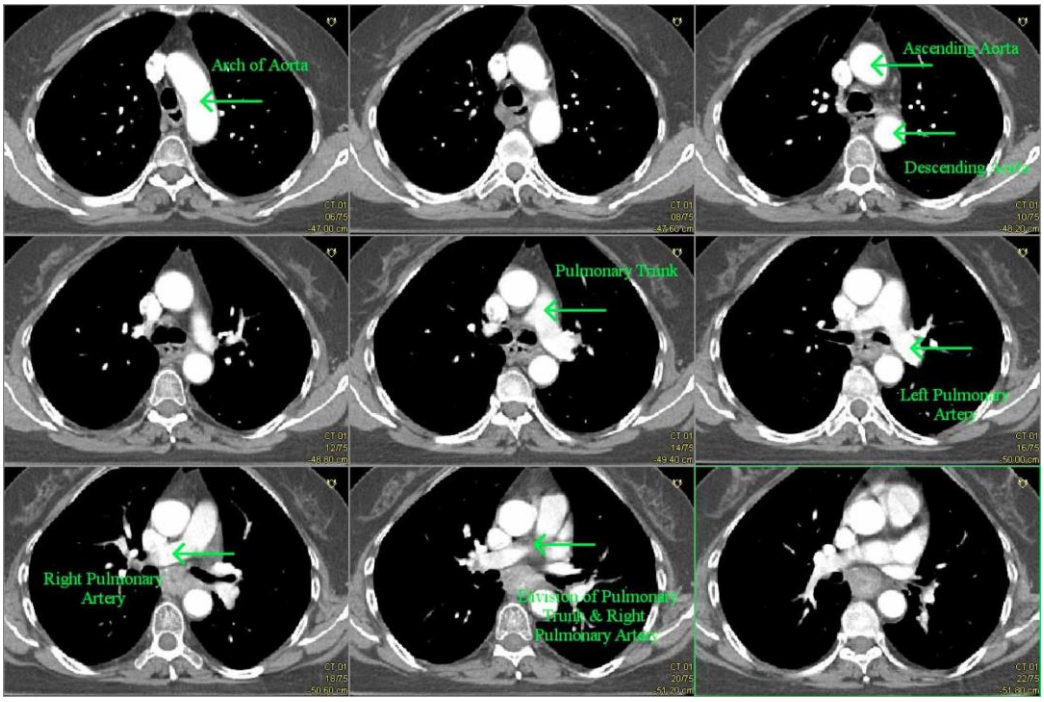
Appendix 3 *Middle 1/3 case example*

58 year old female, with a moderately differentiated adenocarcinoma in the mid oesophagus on EUS from 29 - 32cm. A 7mm peritumoural node is seen on EUS, uT2N1, the node is not visible on the diagnostic CT scan or PET scan. Clinical stage T2N1M0.
GTV (green), CTV combined (yellow), PTV (red)

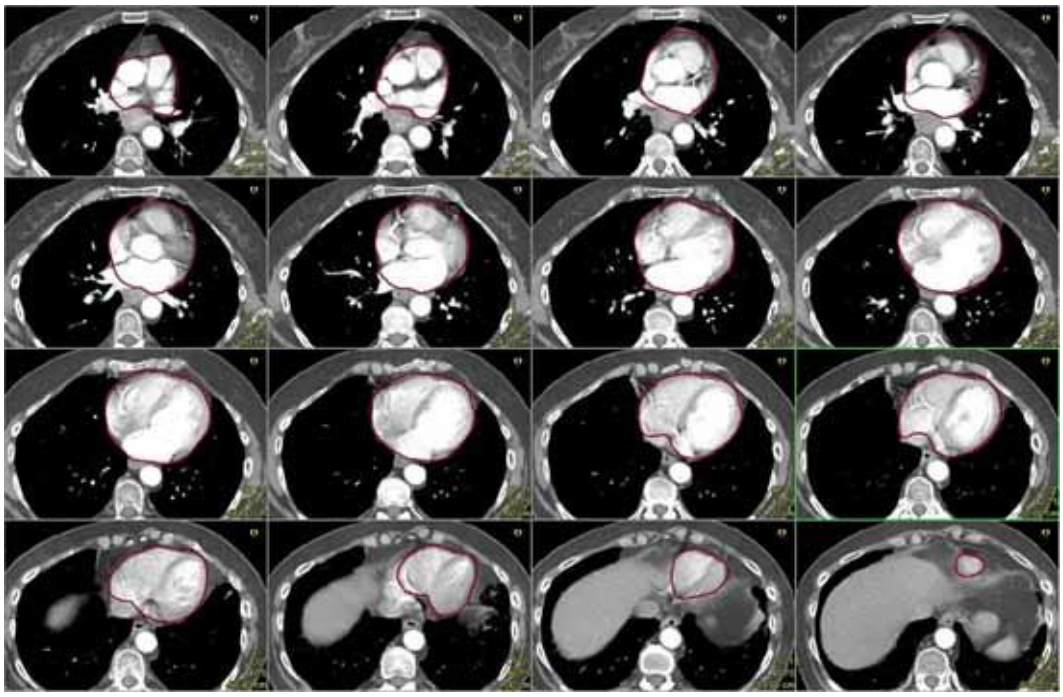


Appendix 4 *Delineation of Heart Volume*

The whole heart is outlined to the extent of the pericardial sac (if visible). The major blood vessels (superior to the organ) and the inferior vena cava (towards the inferior extent of the heart) are excluded. The superior extent is often difficult to define and may be simplified by identification of the vessels superior to the heart. We use the point where the pulmonary trunk and the right pulmonary artery are seen as separate structures as an indication of the superior extent of the heart.



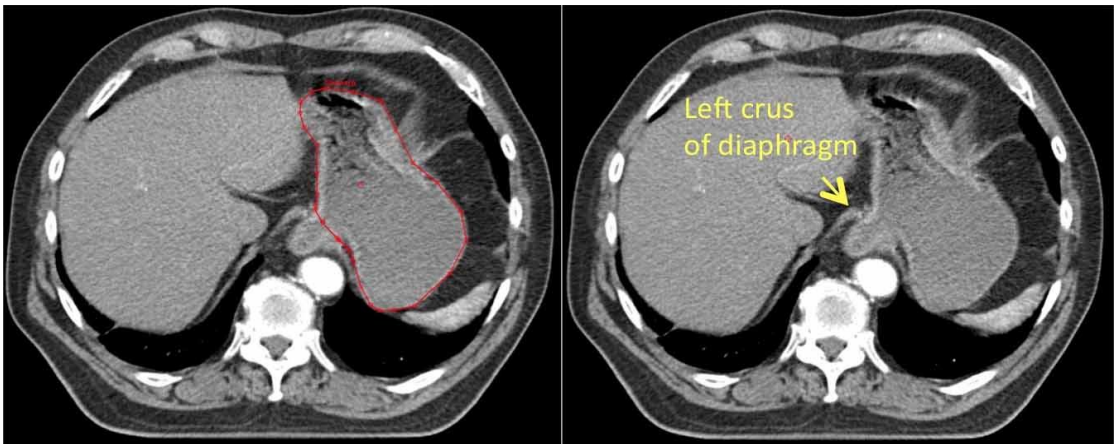
The definition of the heart is shown below on the same data set. Throughout, the heart is outlined to the extent of the pericardial sac. Inferiorly the organ is well defined compared to the surrounding tissues in the abdomen. However, if possible, the inferior vena cava should be excluded.



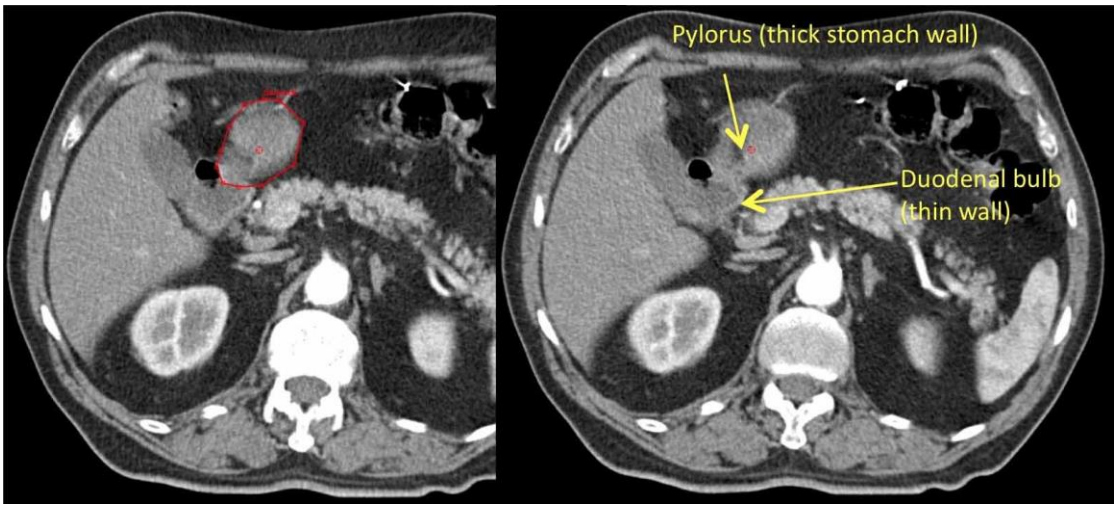
Appendix 5 *Delineation of stomach volume*

The stomach is outlined in its entirety from its proximal origin at the gastro-oesophageal junction to its distal extent at the pylorus–duodenal junction. Outlining is assisted by the use of digital image reconstruction, particularly in the coronal plane. At the gastro-oesophageal junction the stomach is identified on a contrast enhanced CT by a subtle increase in enhancement of the stomach mucosa. As the stomach descends it crosses the midline from left to right, and the wall thickness increases in the distal part (antrum and pylorus). The distal end is at the junction where the thick stomach wall changes to become the thinner duodenal wall.

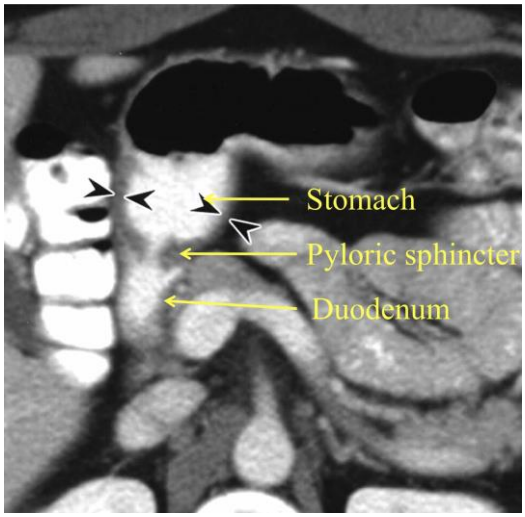
Begin by contouring the stomach at the point where the GOJ passes the left crus of the diaphragm, and work up and then down.



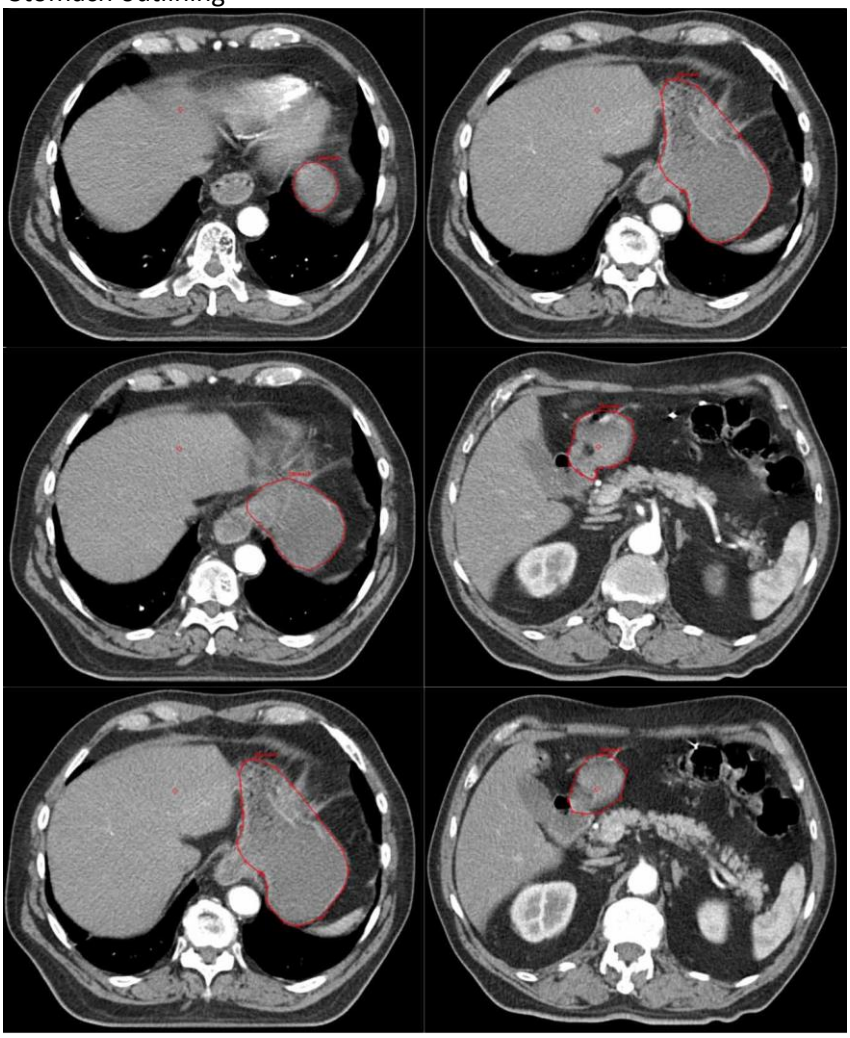
To identify the most distal extent, try to identify a change in wall thickness. The pylorus usually lies to the left of midline as shown:



The contrast enhanced CT below shows the distinction between the stomach proximal to the pyloric sphincter muscles and duodenal bulb distally.



Example of Stomach outlining



Appendix 6 Guidance on the use of contrast for 4D-CT

Depending on what scan functionality is available (in terms of 4DCT) it is recommended that a contrast enhanced 4D scan is acquired when the patient attends for their planning scan.Alternatively a contrast enhanced 3D helical scan (for planning) should be acquired. A 4D scan (to create the ITV) can be acquired before or after the 3d scan depending on the institutional protocol. In our experience the 4D scan should be acquired at the same scan session, ensuring minimal intra-scan patient movement for comparison of the 2 scan sets.Guidelines for how to acquire a contrast enhanced 4D scan are given here, using a protocol which is established in Leeds.

Exact scan delays for 4DCT scans have not been accurately calculated in radiotherapy. Due to the extended scan times (slow couch travel) with these scans, the timings will significantly differ to those suggested for 3D scanning (as recommended by RCR_1). The timings suggested below have been calculated using an equation by Kyongtae.T, 2010_2.

Visualisation of the heart and azygos vein are key so arterial and portal venous phase contrast enhancement is required.

Scan duration (SD) is **70s**, Injection duration (ID) is **34s** (3ml/s) or **50s** (2ml/s) for 100ml Niopam 300.

Peak enhancement of heart = $T_{(peak)} = T_{ID} + T_{CTT}$ (contrast transit time)

$T_{(peak)}$ = 34 + 15 so for 3ml/s: **49s**
$T_{(peak)}$ = 50 + 15 so for 2ml/s: **65s**

Peak enhancement of portal venous = 34 + 35 so for 3ml/s: **69s**
50 + 35 so for 2ml/s: **85s**

Scan delay = $T_{(delay)} = T_{(peak)} – ½ T_{SD}$

Scan delay arterial = 49 – ½ 70 so for 3ml/s: **14s**
65 - ½ 70 so for 2ml/s: **30s**

Scan delay PV = 69 – ½ 70 so for 3ml/s: **34s**
85 – ½ 70 so for 2ml/s: **50s**

So to encompass both arterial phase into PV phase through a single bolus injection, suggested delay for a normal breathing scan protocol is:

3ml/s 25s
2ml/s 40s

For a slow breathing scan protocol (4D followed by 3D) the scan duration increases and so the delay should be reduced further to the order:

3ml/s 15-20s *(safest minimum delay)*
2ml/s 25s

For further information and / or details for the scan acquisition processes described please contact Dr Ganesh Radhakrishna **(g.radhakrishna@nhs.net)** at the St. James' Institute of Oncology.

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1. Button MR, Morgan CA, Croydon ES, Roberts SA, Crosby TD (2009). Study to determine adequate margins in radiotherapy planning for oesophageal carcinoma by detailing patterns of recurrence after definitive chemoradiotherapy. Int J Radiat Oncol Biol Phys. 2009 Mar 1;73(3):818-23. Epub 2008 Aug 19.

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4. L. Wills, A. Millin, J. Paterson, T. Crosby and J. Staffurth. The effect of planning algorithms in oesophageal radiotherapy in the context of the SCOPE 1 trial. Radiotherapy and Oncology 2009:93(3);462-467.

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