Appendix E: Radiotherapy Treatment Planning and Quality Assurance Protocol

Introduction

This document describes the process for radiotherapy treatment planning of rectal cancer and has been developed for the purpose of the TREC trial. It uses a similar approach to that described in the NCRI ARISTOTLE trial with appropriate modifications made for the earlier stage of disease studies within the TREC trial (see acknowledgements at the end of this section).

The aim is to facilitate the delivery of a protocol defined radiotherapy technique and to allow quality assurance (QA) procedures to be applied to demonstrate that this is achieved.

There is considerable debate about target volume definition in rectal cancer. Reasons for this include the limited number of studies of patterns of failure, the lack of QA in the delivery of radiation therapy and a paucity of data from surgical lymphadenectomy series. An additional factor is widespread differences in views amongst radiation oncologists regarding their preferred volume of elective nodal irradiation. To our knowledge, a direct comparison of differing target volumes within the context of clinical trials has never been performed.

In developing the ARISTOTLE Trial, the TMG spent considerable time discussing this issue and this has helped define the radiotherapy target volume definition guidelines for use in this study. We have considered the target volume definition guidelines used in our own phase II studies (1-5), the recommendations of a Belgian group (6) and the recent RTOG contouring guidelines (7). Important recent publications include data from the Dutch TME trial (8), a Swedish group (9), a review of lateral pelvic lymph node dissection (10) and studies from the Netherlands in alteration in target volume shape (11-12).

It is recognised that during the conduct of TREC, it may be necessary to modify the defined protocol either because of the publication of convincing new data regarding target volume definition or development consensus views. A formal protocol amendment will be made should the TMG decide that a significant change in the described protocol is required.
Radiotherapy Treatment Planning

CT planning and delineation of defined target volumes on individual planning CT scans is mandatory. This approach is superior to the determination of the CTV according to bony landmarks approach (Corner et al).

**Patient setup:**

It is recommended that appropriate immobilisation is used and that a scan/treatment position is used which the centre is familiar with. It is recognised that the supine position may be used by some centres. A belly board may be used but it is not a requirement.

A radio-opaque marker must be placed at the anal verge prior to the CT planning scan by the supervising clinical oncologist or an appropriately trained radiotherapy radiographer. The GTV of early rectal tumours is often poorly defined on planning CT. In this situation, the GTV outlined is derived from measurements of the inferior border of the tumour by palpation or on rigid sigmoidoscopy by the surgeon. The anal marker serves as a vital reference point.

**Patient data acquisition:**

The scan limits are the superior aspect of L5 superiorly to 4cm below a radio-opaque marker indicating the anal verge. The recommended slice thickness is 3mm (a maximum of 5mm is acceptable).

**Use of contrast**

Oral - small bowel contrast is recommended but not mandated. Gastrografin 20mls in 1 litres of water is taken 45-60 minutes prior to the planning scan is in routine use. Alternatively, dilute contrast agents in routine diagnostic use are allowed.

Intravenous (iv) – the use of iv contrast is recommended and encouraged but not mandated. The major advantage of using intravenous contrast is the ability to identify the internal iliac arteries in the planning scan in the superior aspect of the pelvis (and to distinguish them from nodal structures) and assist in the delineation of the anterior CTV. The alternative approach of using the diagnostic imaging to identify the arteries and then identify them on a non-contrast planning scan is more time consuming and less accurate.

An outline template for iv contrast is described at the end of this document to assist departments who currently do not have such a protocol. All participating centres are encouraged to develop their own local protocol in keeping with Royal College of Radiologists (RCR) guidelines.

Where contrast-enhanced CT planning scans are to be used, for the dose calculation there may be an effect on the monitor unit calculation which will not be representative of the treatment situation. The magnitude of this effect will vary between individual patients, scanning protocols and centres. There are two acceptable approaches to planning:

1. Use of both contrasted-enhanced and non-contrast CT scans. The contrast-enhanced scan is used for target volume definition and fused with the non-contrast scan which is used for dose calculation.
2. Use of single contrast-enhanced scan and assignment of unit density to heavily contrasted areas.
Definition of Treatment Volumes

The target volume definition process requires the delineation of gross, clinical and planning target volumes. It is recommended that a colour scheme is used for each contour:

These are defined as follows. It is recommended that this nomenclature is adhered to in order to aid plan assessment form completion and dose reporting:

**Gross tumour volume (GTV) (Contour = red)** all gross sites of disease (primary, nodal and extramural vascular invasion). For the purpose of the TREC Trial only primary tumour will be contoured, as presence of nodal disease or extramural vascular invasion are exclusion criteria. It is important to realise that the GTV may not be visible on the planning CT scan. Therefore the information used to localise the primary tumour on the planning CT have to be obtained from a combination of imaging techniques including MRI, CT, endorectal ultrasound as well as appropriate clinical findings from digital rectal examination and rigid sigmoidoscopy.

**Clinical target volume (CTV)** will encompass areas of microscopic spread beyond the defined GTV. The system used describes two distinct volumes - CTVA and CTVB which are then combined to form the Final CTV (CTVF).

**CTVA** (contour = light blue) includes GTV + 1cm. This defines the surrounding safety margin of potential subclinical involvement (superior, inferior, lateral, anterior and posterior).

**CTVB** (contour = dark/royal blue) includes the mesorectum and the loco-regional nodes considered at risk of involvement
- This include the nodes within the mesorectum, presacral space and the internal iliac nodes
- External iliac nodes are not included in CTVB

**Final CTV (CTVF)** (contour = purple) is produce by combining CTVA and CTVB. Discuss with treatment planning the best way of combining these two volumes.

**Planning Target Volume (PTV) (contour = green)** is defined as CTVF+ 1cm (superiorly, inferiorly, anteriorly, posteriorly and laterally). This volume ensures coverage of the CTV taking into account the systematic and random set up errors, changes over time in the patient geometry and internal organ movement that may occur when delivering a radical course of radiation. The most important factor is inter-fraction organ motion. (ICRU Report 50, ICR 1993 (14)).

Further detail is now provided to assist as the guide of the creation of the various volumes:

**GTV delineation (contour = red)** – The primary tumour should be outlined. It is recognised that the interface between gross tumour and the normal rectum may be difficult to define and that the rectal lumen may change in shape and size. It is recommended that on each slice all normal rectal wall between areas of macroscopic disease should be included as part of the GTV (see below)

The macroscopic tumour as shown is highlighted in pink. It is not always possible to identify the gross tumour as the bulk of malignant tumour may have been removed by EMR or excision biopsy. However, at the site of the residual tumour or scar the remainder of the rectal wall may be
thickened. If no tumour is visible on the planning CT scan, this information should be obtained from the endoscopy findings, clinical examination or initial staging MRI /CT scans.

**Recommended delineation of the GTV:**

The outlined GTV is shown in red – this encompasses all macroscopic extent of tumour or the scar and also the uninvolved rectal wall at the site of the tumour.
CTV A (contour = light blue) is derived by applying a 1cm margin to the GTV in all directions (anterior, posterior, superior, inferior and lateral). This is shown schematically below:

The GTV is shown in red and the CTVA is shown in light blue
CTV B (contour=dark/royal blue contour) – includes the mesorectum, presacral and internal iliac nodes. The external iliac nodes are NOT electively included. An example of CTVB contouring is shown below:-

In this example the internal iliac arteries are outlined by a yellow contour and the 7mm margin by a dotted yellow contour. This patient has a generous mesorectum. The anterior border is 1cm anterior to the anterior mesorectal fascia. The internal iliac arteries are shown in yellow with a 7mm margin shown with a yellow dotted line. In the most inferior slice the contour are shown (the is used in the absence of levator/sphincter complex involvement (see below)

Examples are used below to illustrate further detail for each of the borders of the CTVB
**Superior limit** is at the level of the S2/3 interspace (determined on the sagittal or scout view on the planning system) providing there is a 2cm margin above the most superior limit of GTV. The CTVB superior border should only be extended above the S2/3 interspace if necessary to achieve a minimum 2cm margin above the most superior aspect of GTV.
**Inferior limit** - is at the superior limit of puborectalis or 1cm inferior to CTVA whichever is the more inferior. The superior limit of puborectalis is best identified on the CT planning scan as the slice where the mesorectal fat is no longer seen (tapers to nothing).

In this example the inferior border of the CTVB is at the point where the mesorectum stops inferiorly.

Above diagrams redrawn from Shihab et al (15)

**Lateral limit** – is defined at different levels in the pelvis:

- **Upper pelvis** – is determined by the 7mm margin lateral to the internal iliac arteries

In this example the inferior border of the CTVB is 1cm inferior to CTVA.
In this diagram contrast is seen in the internal iliac vessels and the yellow contour is a 7mm margin around each vessel (the anterior and posterior borders are discussed below). The lateral contour is placed on the lateral aspect of the 7mm margin and extends “vertically” back to the sacrum as shown above.

**Mid pelvis** - is the medial aspect of obturator internus.

**Low pelvis** - is determined by the extent of the GTV. The malignant polyp is unlikely to involve the levators or sphincter and the CTVB is the outer border of the anorectal sphincter complex.
Anterior limit – is determined at different levels described below:-

Upper pelvis – is determined by the position of the internal iliac arteries. The internal iliac arteries (or the most anterior branch if more than one artery is seen) should be identified. The anterior limit is 7mm anterior to these vessels. It is common for the artery to be more anterior on one side compared with the other. The CTVB is defined by the more anterior of the two and the border is drawn parallel to the couch (see diagram below).

A 7mm contour is shown around the internal iliac arteries and the contour is defined by the more anterior of the two with a contour parallel with the couch.

Mid pelvis – the anterior border is 1cm anterior to the anterior mesorectal fascia or the anterior limit of the lateral (internal iliac) pelvic lymph node “compartment” whichever is the more anterior. (The shape and volume of the mesorectum varies considerably between patients).
In this example there is a small mesorectum and the anterior border is determined by the lateral pelvic node “compartment”

In this case the anterior border is 1cm anterior to the anterior mesorectal fascia

It is recognised that the anterior border is more difficult to define between the two regions described above (ie moving from superior to inferior, where the internal iliac arteries are no longer seen and before the anterior mesorectal fascia is well seen). This difficult area varies in length between patients. The following may be helpful:
- define CTVB starting at the cranial end using the internal iliac arteries as far as they are visible
- define the CTVB from the mid pelvis level upwards as far as the anterior mesorectum and lateral pelvic nodal compartment are easily seen
- aim for a smooth transition between these two (viewed on the saggital CT planning view)

**Low pelvis**
The anterior border is determined by the absence or presence of gross tumour involvement of levator or the sphincter complex

Levator or sphincter involvement absent
Posterior margin - sacrum - throughout most of the pelvis the posterior border is the anterior surface of the sacrum. At the level of the coccyx, only the sphincter complex is included in the CTVB
The **CTVF (purple contour)** – is created by combining the CTVA and CTVB.
**PTV** (green contour) – this is defined as the addition of a 1cm margin (anteriorly, posteriorly, laterally, superiorly and inferiorly) to the CTVF.
Trial Management Group assessment of CTV definition
The TMG recognise the challenge to deliver a consistent approach to delineation of the CTV in rectal cancer and the relative lack of training for clinical oncologists in normal radiological pelvic anatomy. The TMG have used the ARISTOTLE protocol to contour test cases and the results from this experience have lead to modifications to this planning Appendix.

Radiotherapy treatment planning workshops
Centres have been invited to participate in radiotherapy planning workshops led by members of the ARISTOTLE TMG. These were held on a regional basis prior and will facilitate an interactive environment to enhance skills in target volume definition, allow sharing of outlining techniques and identify areas of uncertainty that can then be addressed. Advice can also be provided from Clatterbridge (0151 3344000), Birmingham (0121 3713567) and Leeds (0113 2068570).

Organs at Risk -
The femoral neck, bladder and small intestine are considered organs at risk and it is recommended these are outlined.
When outlining the small bowel (optional), the superior limit is 2cm above the upper limit of PTV. It is not usually possible to influence the dose to the posterior bladder that is delivered. It is accepted that limiting the dose delivered to the femoral neck is an important aim but there is a lack of data to define a dose volume constraint in the context of rectal cancer planning.

Dose and dose volume guidelines
All doses are prescribed as target absorbed doses according to International Commission on Radiation Units (ICRU) guidelines. A total dose of 25Gy in 5 daily fractions over one week should be delivered treating 1 fraction per day, using 5 Gy per fraction. All fields must be treated during one treatment session. Radiotherapy should start on a Monday and finish on a Friday. If an interruption of radiotherapy is unavoidable or radiotherapy cannot start on a Monday (eg Bank Holiday), additional days of irradiation should be added after the weekend in order to deliver the prescribed dose. No more that one fraction is to be given per day. It is conventional to report the dose to the ICRU reference point, the maximum dose to the PTV and the minimum dose to the PTV. The isocentric treatment plan is usually specified to receive 100% with the 95% isodose line encompassing the PTV and no more than +7% and -5% inhomogeneity within the target volume.

It is also advised to examine the dose distribution in both coronal and sagittal views to ensure the optimal anatomical arrangement of isodoses around the target volume.

The following dose volume requirements are provided for the PTV and external patient outline.

<table>
<thead>
<tr>
<th>ROI objective</th>
<th>Defined as</th>
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<tbody>
<tr>
<td>PTV min</td>
<td>D99% ≥ 95% (23.75Gy)</td>
</tr>
<tr>
<td>PTV max</td>
<td>D5% &lt; 105% (26.25Gy)</td>
</tr>
<tr>
<td></td>
<td>D2% &lt; 110% (27.5Gy)</td>
</tr>
<tr>
<td>Patient Outline absolute max</td>
<td>D1.8cc &lt; 110% (27.5Gy)</td>
</tr>
<tr>
<td></td>
<td>Lateral patient dose distant from PTV &lt;80% to 85%</td>
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Treatment Planning
Dose calculation should be performed on a 3D scan using either Type A or Type B algorithm and pixel-based in homogeneity correction is considered standard practice and is a mandatory requirement. A minimum dose calculation matrix of 3mm is mandated.

In instances where the PTV, due to margin creation, extends up to or beyond the patient external outline it is recommended that the original, unaltered PTV is used for planning but that a further modified PTV (labelled appropriately as 'PTV_mod') may be generated which avoids encroaching
outside but approaches the external patient outline to within at least 5mm, and is used for dose reporting purposes only – i.e. shielding is defined in beams-eye-view based on original PTV but min dose might be low as <99% of PTV lies within patient volume, so in this instance minimum dose may be considered to ‘PTV_mod’ which has been modified to no more than 5mm within the patient external outline.

Radiation therapy should be delivered with photon energies ≥6 MV using a linear accelerator. Equipment of 10 MV or higher is recommended, as is the use of 3D conformal radiotherapy. Typically a three field arrangement will be used, though it is recognised that an additional anterior field may be required in exceptional circumstances where the lateral patient dose distant from the target volumes exceeds 80-85% of the reference dose. Mixed energy beams are allowed with higher photon energy for the lateral beams compared to the posterior beam (which may be of lower energy to improve superficial coverage where the target approaches the patient surface). The use of multileaf collimators is strongly recommended.

More complex treatment methods such as IMRT are not considered necessary to achieve the required dose objectives for this trial. The reproducibility of treatment delivery is an important consideration. At present an IMRT approach is not recommended for patients in TREC. In the instance where a significantly different approach to treatment from that used, the centre must discuss this with the TMG.

**Verification and correction procedures**

The rectum does move during a course of radiotherapy (16) (17). Recent data suggests that this is most marked in the upper rectum in patients with resectable disease (11). However the patient group included in the TREC trial will mainly consist of low and mid rectal cancer.

**On treatment verification**

It is recommended that the best available positional verification methods should be used to ensure correct delivery – which may include electronic portal imaging compared to treatment planning DRRs, or cone beam CT imaging matched to planning CT scan. Consideration should be given to imaging the initial three fractions so that a correction for systematic error can be applied. Electronic portal imaging (EPI) can monitor setup displacement on a daily basis in the phase of treatment (18). Isocentre should be moved if disagreement is seen in excess of agreed tolerance levels based on local study – usually 5mm. This process also allows radiographers to evaluate the whole set-up and thus to assess and correct systematic errors. These images should be audited on a weekly basis. Using EPI the MLC configuration can also be verified for consistency and reproducibility.

**Quality assurance**

The quality assurance programme for the TREC trial will be co-ordinated the NCRI Radiotherapy Trials Quality Assurance (RTTQA) group. Further details of the QA programme can be found at [www.rtrialsga.org.uk](http://www.rtrialsga.org.uk)

**Pre-trial QA requirements:**

1. Questionnaires:
   - National radiotherapy trials baseline questionnaire
   - National radiotherapy trials QA staff questionnaire

2. It is recommended that the PI at every investigator site attend one of the ARISTOTLE QA workshops prior to patient recruitment.

**On-going Trial QA**

**Trial Data Collection:**

Data will be collected by the RTTQA group for all patients treated in the TREC trial.
Recruiting sites will export, anonymised CT images, plan (RP), dose cubes (RD) and structure sets (RS) for all patients in the trial.

Acknowledgements
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References
8 Fuller ref

Intravenous contrast template

This policy should be in broad agreement with RCR Recommendations: -

Where contrast-enhanced CT planning scans are to be used for the dose calculation there may be an effect on the monitor unit calculation, which will not be representative of the treatment situation. The magnitude of this effect will vary between individual patients, scanning protocols and centres. There are three acceptable solutions:

- use of single contrast-enhanced scan only. If the centre is satisfied that there are no dosimetric implications of using contrast.
- use of single contrast-enhanced scan and assignation of unit density to heavily contrasted areas.
- use of both contrasted-enhanced and non-contrast CT scans. The contrast-enhanced scan is used for target volume definition and fused with the non-contrast scan which is used for dose calculation.

It is anticipated that the first or second option will be used in most if not all centres

Additional issues to consider with the use of iv contrast enhanced radiotherapy planning scans

Safety:
- It is strongly recommended that each centre develop its own working instructions for the delivery of iv contrast for radiotherapy planning scans.
- It is also recommended that the RCR document ‘Standards for Iodinated Intravascular Contrast Agent Administration to Adult Patients’ is read and followed.
- The following should be considered:
  - Patient identification:
    o Ensure the correct patient is scanned following the correct protocol.
    o Ensure consent form is completed
  - Awareness of features associated with increased risk of reaction:
    o History of allergy or asthma.
    o Ask if patient has had previous contrast-enhanced imaging
  - Awareness of medical support:
    o A member of the radiotherapy team should be contactable through-out the duration of the scan and the emergency drugs trolley should be brought round to the scanner or be easily accessible.

Effects of intravenous contrast in renal insufficiency:
- ensure recent creatinine is available and that patient is not clinically dehydrated. Risks are increased in elderly patients, patients with cardiac failure, and diabetics (especially if taking oral metformin).
- the trial protocol require patients to have a calculated GFR>50 mls/min – iv contrast should not be administered to patients whose serum creatinine is greater than 150ummol/l
- if there is doubt concerning the patients suitability for iv contrast it should not be administered as this is not a protocol requirement

Practical issues:
- insert cannula
- position patient in radiotherapy position
- select correct imaging protocol; consider requirement for pre and post-contrast image acquisition
- optimise image quality with iv contrast: These are recommendations based on experience from three centres, who have kindly allowed us to review their clinical protocols: Mount Vernon Hospital, Royal Marsden NHS Trust, and Velindre NHS Trust. Centres need to be
aware that these recommendations are from clinical experience with their own hardware and software, and that some degree of local development may be required.

- Type: Omnipaque or Visipaque
- Temperature: ensure contrast is brought to room temperature
- Volume: 100ml
- Infusion rate: 2.5-3mls per sec.
- Time between injection and CT: 35-40s
- Remove cannula at completion of scan