SYSTEMS-2

A Randomised Phase II trial of standard versus dose escalated radiotherapy in the treatment of pain in malignant pleural mesothelioma

Radiotherapy Planning and Delivery Guidelines

Version 1.0, 07 August 2017

This document sets out requirements for the radiotherapy planning and treatment of patients within the SYSTEMS-2 study and should be referred to in conjunction with the trial protocol.

The SYSTEMS-2 Trial Management Group (TMG) reserves the right to amend the Radiotherapy planning and delivery guidelines as appropriate. Such changes will not constitute an amendment and revised guidelines will be circulated to sites as needed.

Any questions relating to the detail within this document should be addressed in the first instance to the SYSTEMS-2 team.

For General Enquires:

Dr Miranda Ashton
SYSTEMS-2 Clinical Research Fellow
Miranda.Ashton@glasgow.ac.uk

Contents

1 PATIENT DATA ACQUISITION 4

2 TREATMENT PLANNING 4

3 DOSE SPECIFICATION AND TREATMENT 5

3.1 EXPECTED PTV COVERAGE 6

4 OAR DEFINITION 6

4.1 OAR GUIDANCE FOR RT PLANNING 7

4.2 SUMMARY TABLE FOR OAR DOSE CONSTRAINTS 8

5 TREATMENT VERIFICATION 9

6 RADIOTHERAPY QUALITY ASSURANCE 9

6.1 PRE-TRIAL QA 10

6.2 ON TRIAL QA 10

7 DATA EXPORT 10

1 PATIENT DATA ACQUISITION

A planning CT should be performed in the treatment position, while the patient is breathing normally. If the local team feel that a 4D CT is required for optimal planning purposes then this is acceptable, but not mandated.

Continuous 2.5-5mm slices should be acquired throughout the entire volume of both lungs, from the cricoids to iliac crest. Immobilisation techniques to be followed as per local practice.

In instances where the radiotherapy planning scan will also be used for the purpose of baseline imaging, (i.e. when the most recent contrast enhanced CT scan will be >8 weeks old at the start of the radiotherapy), then contrast should be used in the portal venous phase to ensure optimal pleural enhancement. The scan should be acquired using the narrowest slice width attainable without compromising clinical image quality.

2 TREATMENT PLANNING

Radiotherapy planning may be either 3D conformal or using IMRT as specified by clinician in advance of planning for each patient. There should be inhomogeneity correction. The use of radio-opaque markers to define painful sites is required at the time of image acquisition. In the pilot SYSTEMS trial, wire markings which outlined the upper and lower limits of the painful area were found to be extremely helpful to clinicians in defining the area to treat. Ultimately, the CTV should be outlined at the discretion of the treating Oncologist. For patients in whom CTV definition is difficult, the Beatson WoSCC can be contacted for advice. If there is felt to be a neuropathic component to the pain due to nerve root involvement, the nerve root may be included in the CTV.

The CTV will be outlined on each CT slice and grown by 1-2cm to form the PTV. The margin should be adapted at clinician's discretion according to disease site and adjacent organs at risk (OAR). Relevant OAR's should be outlined on each CT slice. These may include the contralateral lung, great vessels, oesophagus, spinal canal, trachea/proximal bronchus, brachial plexus, heart, liver, small and large bowel and both kidneys. DVHs for the PTV, contralateral lung, oesophagus, trachea, great vessels, spinal canal and heart will be

calculated in all cases. For target volumes in the lower chest, DVHs for the small and large bowel, ipsilateral and contralateral kidney will be calculated. For lower right sided tumours where more than 700cc of liver is likely to be scanned, a DVH can be calculated for the liver. Where target volumes lie in the left lower chest, a DVH will also be calculated for the stomach. If the PTV extends above T2, the ipsilateral brachial plexus can be assumed to be involved. Should there be any clinical concerns about toxicity this can be outlined as an OAR and a DVH calculated.

3 DOSE SPECIFICATION AND TREATMENT

All patients will be treated on a linear accelerator operating at 4-10MV. The dose will be prescribed using an isocentric technique. Plans generated using IMRT should be normalised with 100% prescription to the target volume median dose in accordance with ICRU83.
Centres unable to prescribe to the median dose due to their planning system capabilities can alternatively prescribe to the mean dose and should inform the QA team of this decision. The median and mean dose should both be reported on the Plan Assessment Form and are expected to be within 0.5 Gy (up to 1Gy) of each other.

Randomisation with allocation to treatment arm will take place after planning is complete. All patients will be planned for the 36 Gy in 6 fraction regimen initially and re-calculated to a 20 Gy in 5 fraction plan if necessary after randomisation. Dose prescribed to the median or mean will be 20 Gy in 5 daily fractions of 4 Gy or 36 Gy in 6 fractions of 6 Gy treating three times per week over a two week period. Although the 36 Gy in 6 fraction arm should be treated on alternate days (Monday, Wednesday, Friday), treatment may proceed on two days in a row up to a maximum of two occasions (e.g. Monday, Wednesday, Thursday, Monday, Thursday, Friday).

This is a hypo-fractionated radiotherapy regime with palliative intent and there are little data to support precise dose constraints to OARs around the PTV. The recommended constraints outlined below are therefore given as guidance for the inverse planning process but have largely been derived from modelling of tolerance limits for 5 fraction stereotactic radiotherapy intending radical doses to smaller volumes and are therefore not directly

comparable. While it is hoped that these values can be met in the majority of patients, the dose to the PTV should not be compromised to meet them unless the clinician feels that the dose to the OAR would likely result in a toxicity which would negate the palliative benefits of the radiotherapy.

In situations where dose constraints cannot be met and there is concern about acute toxicities to critical OARs, it is acceptable to reduce the total dose to 30Gy in 5 fractions, treating 3 times per week. This is anticipated to occur primarily with 3D conformal plans, but may occasionally be necessary with IMRT plans. The same approach can be taken for patients with a large volume of disease, in whom the full dose of 36 Gy is likely to cause significant toxicity. The clinician should record the reason for any dose reduction. The ultimate decision on whether or not to accept the plan is at the discretion of the treating Clinical Oncologist.

3.1 Expected PTV Coverage

	Constraint	Dose (%)
PTV minimum	D98%	>95%
PTV median	D50%	100%
PTV maximum	D2%	<107%

4 OAR DEFINITION

Contralateral lung: This should be contoured in every slice from the apex to the base.

Oesophagus: This should be contoured as a solid organ 4cm above and below the PTV. If a 4cm margin is not possible inferiorly, the gastro-oesophageal junction will determine the inferior limit.

Spinal canal: The spinal canal will be contoured for the length of the scan and this will be taken to represent the cord plus margin (Planning Organ at Risk Volume; PRV).

Trachea and proximal bronchus: The distal 2cm of the trachea should be contoured, along with the carina and the right and left main-stem bronchi.

Great vessels: The great vessels should be contoured starting at least 3cm above the superior extent of the PTV and continuing on every CT slice to at least 3cm below the inferior extent of the PTV. For right sided tumours, SVC will be contoured and for left sided tumours,

the aorta will be contoured. The ipsilateral pulmonary artery will be delineated for tumours of either side.

Brachial Plexus: The ipsilateral brachial plexus can be contoured from the spinal nerves exiting the neuro-foramen from the top of C5 to the top of T2.

Heart: This should be contoured on all slices; its cranial border will be the infundibulum of the right ventricle and the apex of both atria. The caudal border is defined as the lowest part of the left ventricle's inferior wall which is distinguishable from the liver.

Liver (only required for right sided tumours and where more than 700 cc of liver has been scanned): The whole liver should be outlined.

Kidneys (only required for inferior tumours): The whole of each kidney should be outlined separately.

Stomach: The whole stomach should be outlined (left sided tumours only).

Small bowel (only required for inferior tumours): The duodenum may be outlined from the pylorus to 3cm below the inferior extent of the PTV (low lying tumours only).

Large bowel (only required for inferior tumours): Loops of large bowel should be contoured to 3cm below the inferior extent of the PTV. This may include portions or all of the ascending, transverse and descending colon.

4.1 OAR Guidance for RT Planning

Contralateral lung dose should be kept as low as possible to reduce toxicity and to maximise dose delivery in the affected lung. Aim for the contralateral lung V20 to be <10% and ideally <5%. The V10 should be kept below 50% and the V5 below 70%.

Oesophagus: The length of oesophagus within the PTV should be minimised where possible and no more than 0.5 cc should receive 30 Gy.

Spinal Canal: The length of canal irradiated should be minimised. Spinal canal should be outlined as OAR and no more than 0.5 cc should receive more than 27 Gy.

Trachea and proximal bronchus: Dose should be minimised where possible.

Heart: Dose constraints to the heart are difficult to quantify as there are at least 4 targets: myocardium, pericardium, coronary arteries and the conduction system. Dose to the heart should be minimised where possible. Consideration should be given to shielding, especially for left sided tumours.

Liver: Liver dose should be minimised where possible as the side effects of radiation

hepatitis may negate any palliative benefit from the radiotherapy. Aim for a mean liver dose of less than 16 Gy.

Kidneys: The ipsilateral kidney should be shielded to reduce renal dose, but if this is not possible, efforts should be made to spare the contralateral kidney as much as possible. The mean kidney dose (individual and combined) should not exceed 10 Gy. If the mean dose of one kidney exceeds 10 Gy or there is a solitary kidney then the V10 should not exceed 45%. Where one kidney is to receive significant dose then a DMSA scan in advance of treatment can be considered to ensure the contralateral kidney has adequate function.

Stomach: Nausea and vomiting can be a problem when treating left sided tumours so stomach dose should be minimised where possible with no more than 0.5 cc receiving >30 Gy.

Small bowel: In cases where the PTV is low in the chest cavity and a significant proportion of the small bowel is likely to receive full dose this structure can be outlined as an OAR. In such circumstances, aim for no more than 0.5 cc of small bowel to receive >30 Gy.

Large bowel: If a significant proportion of the large bowel is likely to receive full dose due to a low lying PTV, this can be outlined as an OAR. No more than 0.5 cc of large bowel should receive >30 Gy.

Ipsilateral brachial plexus: If the PTV lies above the level of the T2 vertebrae, it can be assumed that the brachial plexus is within the radiation field. In such patients randomised to 36/6, the ipsilateral brachial plexus can be outlined and treated as an OAR if there is clinical concern about toxicity.

Great vessels: Dose should be minimised where possible.

Due to the palliative nature of this radiotherapy, creating PRVs by adding margins to any OARs other than the spinal cord is not felt to be warranted.

4.2 Summary Table for OAR Dose constraints

OAR	Constraint	Ideal Maximum dose
Contralateral lung	<5% <50% <70%	V20 Gy V10 Gy V5 Gy
Oesophagus	Dmax (0.5 cc)	30 Gy
Spinal canal	Dmax (0.5 cc)	27 Gy

OAR	Constraint	Ideal Maximum dose
Trachea and proximal bronchus	Dmax (0.5 cc)	36 Gy
Heart	Dmax (0.5 cc)	36 Gy
Liver	Mean Liver Dose	16 Gy
Kidneys (individual and combined)	Mean kidney dose	10 Gy
If solitary kidney or if one kidney mean dose >10Gy	<45%	V10 Gy
Stomach	Dmax (0.5 cc)	30 Gy
Great Vessels	Dmax (0.5 cc)	36 Gy
Small bowel	Dmax (0.5 cc)	30 Gy
Ipsilateral Brachial Plexus	Dmax (0.5 cc)	36 Gy
Large bowel	Dmax (0.5cc)	30 Gy

5 TREATMENT VERIFICATION

Verification by online imaging at first fraction to be signed off as per local practice. Subsequent kV/kV imaging to be used at centre's own discretion.

6 RADIOTHERAPY QUALITY ASSURANCE

The radiotherapy quality assurance (RT QA) programme for the study will be designed and implemented by the National Radiotherapy Trials QA (RTTQA) Group. The full details of the programme will be made available on the RTTQA group website www.rttrialsqa.org.uk. The RT QA programme for the SYSTEMS-2 trial will be streamlined, where appropriate, with previously completed QA for other clinical trials. All centres using IMRT delivery must have successfully completed the IMRT credentialing programme through the National RTTQA group or equivalent.

QA approval for outlining (TV and OARs) and planning associated with the SYSTEMS-2 trial will be given on the basis of streamlining with existing lung trials. For those centres

delivering treatment using IMRT appropriate independent dosimetry audit evidence will be required.

For those centres that are not QA approved for other lung trials a dummy run, planned to the SYSTEMS-2 protocol requirements, must be submitted and reviewed prior to being QA approved.

6.1 Pre-trial QA

- Facility questionnaire (FQ) - General and trial specific questions on equipment, software and techniques to be used for the trial
- Dummy run - QA of the outlining and planning technique for those centres where QA cannot be streamlined through a previous lung trial.
- Dosimetry audit – For IMRT delivery appropriate independent dosimetry audit evidence from centres will be required. Please contact the RTTQA group to discuss.

6.2 On trial QA

- Data collection for all patients - Anonymised data, in DICOM format, will be collected by the QA team for all patients treated in the trial. This may include a brief clinical history, diagnostic imaging, full planning data including; CT images, structure set, plan and dose cube

7 DATA EXPORT

For exporting the radiotherapy plan to the RTTQA the following is required:
DICOM format - the CT images, dose cubes (RD), plans (RP) and structure sets (RS).
There are three options for transferring data to the RTTQA group:

1. NHS Secure Server

This is the preferred option for centres within the UK.
To send a file please visit https://nww.sft.nhs.uk/sft/upload1
An nhs.net email account is needed for this.

2. FTP transfer

The ftp address is ftp://rttrialsqa.dnsalias.org/incoming

The username is anonymous

For password enter your email address

3. Encrypted CD

Diagnostic CT images (performed at baseline and week 9) will be reviewed centrally by a named consultant radiologist to allow consistent reporting to Modified RECIST criteria. This data can be transferred to the Beatson West of Scotland Cancer Centre by:

1. Encrypted CD

CDs will be provided by the Glasgow Clinical Trials Unit for secure transfer of images. Please send anonymised CT images to:

Laura Alexander
Project Manager
CRUK Clinical Trials Unit
Beatson West of Scotland Cancer Centre
1053 Great Western Road
Glasgow.
G12 0YN

2. NHS Secure Server

To send a file please visit https://nww.sft.nhs.uk/sft/upload1

An nhs.net email account is needed for this.