Appendix 4 – Radiotherapy procedures

THORACIC RADIOTHERAPY
Thoracic radiotherapy should start 21 days after day 1 of the first cycle of chemotherapy (day 22). A delay with the administration of the second cycle of chemotherapy should not delay the start of radiotherapy.

General radiotherapy details
Patients should be treated on a linear accelerator operating at 4-10 MV. The total dose of radiotherapy will be:
- BD arm: 45 Gy in 30 twice-daily fractions of 1.5 Gy
- OD arm: 66 Gy in 33 daily fractions of 2 Gy
The total dose is prescribed at the ICRU reference point and given according to the recommendations of the EORTC radiotherapy group (25) and ICRU 50 (26). Treatment will be planned with inhomogeneity corrections. IMRT will be permitted for the centres routinely using it for the treatment of lung cancer.

Radiation Quality Assurance:
The radiotherapy quality assurance program will be run by the Mount Vernon Hospital QA team. Planning information, copies of portal images (digital print-outs are acceptable) and dose distribution, including Dose Volume Histogram (DVH), with a copy of the treatment prescription should be available for central review. Details of radiotherapy practice will be established by completion of a questionnaire.
Treatment machine beam output data on the linear accelerators used to treat patients in the trial should have been audited by a recognised ASTRO/ESTRO or UK quality assurance programme within 12 months of the first patient in the centre entering the trial, and be rechecked at least once every 18 months.
We recommend that daily verifications should be done with open orthogonal images incorporating stable anatomical structures such as the spine for the first 3 days of treatment followed by weekly verifications. If available cone beam imaging can be used as an alternative to open orthogonal images. The orthogonal images will be checked by a senior radiographer and if possible reviewed by a qualified radiation oncologist, and compared with either the digitally reconstructed images or simulator images. The correction decision will be left to local policy. Differences of less than 0.5 cm from the initial images will be allowed. We suggest that if the difference is more than 0.5 cm the orthogonal images will be repeated prior to patient’s treatment. The Radiotherapy Quality Assurance Group will approve and monitor each centre’s procedures.

Patient treatment position:
Supine, with arms above head. Immobilisation using chest board and fixed arm position. The patient should be breathing normally.

Patient data acquisition:
A planning CT scan should be performed in the treatment position, whilst the patient undertakes a normal respiration, using 5 mm slices or less through the entire target volume. The whole thorax (cricoid to L2) should be covered using at least 1 cm slices to allow dose-volume histograms to be calculated for the lung, heart and the oesophagus.
Radiotherapy should be started within 3 weeks of planning.

Planning target volume (PTV)
The CT data will be transferred to the planning system.
The GTV (gross tumour volume) will be contoured by a qualified radiation oncologist specialised in thoracic malignancies. The contouring should be carried out using the mediastinal and the lung windows. The GTV is defined as identifiable tumour and involved lymph nodes (nodal involvement on CT scan is defined as nodes ≥ 1 cm in short axis). If PET scan is available for staging, the GTV should include PET positive lymph nodes.

The CTV (clinical target volume) comprises the GTV with a 0.5 cm margin of radiologically normal tissue in all directions. It will take into account microscopic spread. Manual adjustment of CTV is permitted to reduce dose to the spinal cord for example, when disease is adjacent to a structure such as a vertebra but is not thought to invade the structure

The PTV comprises the CTV with a 1 cm margin superiorly and inferiorly, and 0.8 cm margin laterally, at the 95% isodose. The CTV to PTV expansion should not be reduced as it is allowing for set up errors and organ motion. Prophylactic nodal irradiation should not be employed. Field reductions will not be allowed.

Treatment planning
Use of 3D conformal technique is required and beam’s eye views may be useful in the design of individual shielding. Dose volume histograms (DVH) for the PTV, normal lung, oesophagus, spinal cord and heart will be calculated in order to obtain full knowledge of the 3D dose distribution.

Dose specification and fractionation:
The dose will be specified at the ICRU reference point and fully corrected for heterogeneity. The dose distribution within the PTV should ideally be within ± 5% of the prescribed dose, and no more than ± 7% of the prescribed dose.

Definition of the organs at risk
The spinal cord, lungs, oesophagus and heart will be contoured for dose-volume histograms.

Both the right and left lungs should be contoured as one structure. Contouring should be carried out using pulmonary windows. All inflated lung should be contoured. The spinal cord will be contoured based on the bony limits of the spinal canal. The spinal cord should be contoured starting at least 10 cm above the superior extent of the PTV and continuing on every CT slice to at least 10 cm below the inferior extent of the PTV. The oesophagus will be contoured using mediastinal windowing on CT scan to correspond to the mucosal, submucosa, and all muscular layers out to the fatty adventitia. The oesophagus should be fully contoured (from cricoid cartilage to the gastro-oesophageal junction). The heart will be contoured along with the pericardial sac. The superior aspect (or base) for purposes of contouring will begin at the level of the superior aspect of the left atrium and extend inferiorly to the apex of the heart.

Beams
Isocentric treatment technique.
The number of beams will vary according to the position and the volume of the PTV in the thorax and to the maximum dose tolerated by the organs at risk. The treatment plan will be checked by a qualified radiation oncologist after discussion with the planning team. The dose-volume histogram will help to guide that choice.

Set-up verification
Cone beam or orthogonal images will be obtained on days 1 to 3 (or 2 to 4) and weekly thereafter.
TWICE-DAILY THORACIC RADIOTHERAPY

Schedule

45 Gy in 30 twice-daily fractions over a period of 19 days (radiotherapy to start on a Monday), 5 consecutive days a week

- The optimal overall treatment time should be 19 days, up to 21 days is a protocol deviation and should be recorded, above 21 days is a protocol violation.
- The interfraction interval will be 6 to 8 hours.
- Using conformal radiotherapy and 4 to 10 MV photons emitted from linear accelerators.
- Thoracic radiotherapy will start on cycle 1 day 22, if possible concurrently with the second cycle of chemotherapy (within 24 hours of day 1, cycle 2 of PE).
- Concurrent chemotherapy will be administered during the intervals between the 2 daily radiotherapy fractions.

Normal tissue constraints
To reduce late damages to the normal tissues the following rules will be applied

- Dose: 1.5 Gy per fraction
- Maximum spinal cord dose will not exceed 42 Gy. The spinal cord position must be identified throughout the PTV
- The percentage of lung minus PTV receiving more than 20 Gy will not exceed 35% (V20=35%, based on dose-volume histograms). The mean lung dose will be recorded
- The heart can receive the total dose (TD) to < 30% of its volume. For > 50% of cardiac volume, dose < 50% of TD is recommended

Treatment Delays
Every effort should be made to deliver the prescribed dose of radiotherapy in 19 days. If unavoidable delays occur, that could increase the overall treatment time beyond 19 days, e.g. due to machine breakdown, compensation should if possible be made by one of the following mechanisms:

- treating on a weekend day, or
- adjusting fraction size to deliver the total prescribed dose within 19 days;

However, fraction size should remain < 2.25 Gy

If the radiation schedule is interrupted for more than 1 week due to intercurrent illness consideration should be given to discontinuing treatment. Further treatment will depend upon the clinical situation and is at the discretion of the responsible clinician. Interruptions for < 1 week due to intercurrent illness or radiation toxicity will be recorded and treatment should be completed as planned.

HIGH DOSE ONCE-DAILY THORACIC RADIOTHERAPY

Schedule

66 Gy in 33 daily fractions over a period of 45 days (radiotherapy to start on a Monday), 5 consecutive days a week

- The optimal overall treatment time should be 45 days. Up to 47 days is a protocol deviation and should be recorded, above 47 days is a protocol violation.
- Using conformal radiotherapy and 4 to 10 MV photons emitted from linear accelerators.
- Thoracic radiotherapy will start on cycle 1 day 22, if possible concurrently with the second cycle of chemotherapy (within 24 hours of day 1, cycle 2 of PE).
Normal tissue constraints
To reduce late damages to the normal tissues the following rules will be applied
- Dose: 2 Gy per fraction
- Maximum spinal cord dose will not exceed 48 Gy. The spinal cord position must be identified throughout the PTV
- The percentage of lung minus PTV receiving more than 20 Gy will not exceed 35% (V20=35%, based on dose-volume histograms). The mean lung dose will be recorded.
- The heart can receive the total dose (TD) to < 30% of its volume. For > 50% of cardiac volume, dose < 50% of TD is recommended

Treatment Delays
Every effort should be made to deliver the prescribed dose of radiotherapy in 45 days. If unavoidable delays occur, that could increase the overall treatment time beyond 45 days, e.g. due to machine breakdown, compensation should if possible be made by one of the following mechanisms:
- giving two fractions on a subsequent day, with a minimum interval of six hours between fractions, or
- treating on a weekend day, or
- adjusting fraction size to deliver the total prescribed dose within 45 days;
However, fraction size should remain < 3 Gy.
If the radiation schedule is interrupted for more than 1 week due to intercurrent illness consideration should be given to discontinuing treatment. Further treatment will depend upon the clinical situation and is at the discretion of the responsible clinician. Interruptions for < 1 week due to intercurrent illness or radiation toxicity will be recorded and treatment should be completed as planned.

PROPHYLACTIC CRANIAL IRRADIATION
No later than 6 weeks after the last cycle of chemotherapy, patients without evidence of progressive disease on CXR or CT scan and with no clinical evidence of brain metastases will be given PCI. Simulation is mandatory for whole brain irradiation. Patients should be treated in supine position. Immobilisation by individual masks or other means is recommended. Treatment will be delivered with megavoltage machines of energies ranging from 4-10 MV photons. Treatment with a single beam is not acceptable. Doses are specified at the mid-plane of two opposed lateral whole brain fields, prescribed to the isocenter. The dose and fractionation of PCI will be left to the discretion of each principal investigator to allow for variation in local practice.