Radiotherapy Protocol for the management of SABR to the adrenal gland for oligometastatic disease.

This is radiotherapy protocol for the East Midlands RT Operational Delivery Network (ODN). Tumour sites are: Oligometastatic disease to the adrenal gland of any histology.

Document revision History

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1. Treatments to include

- Radical radiotherapy only

2. Indications for treatment

Inclusion criteria (all of the following criteria must be met, unless within a clinical trial):

- Oligometastatic (defined as 1-3 extra-cranial metastatic lesion(s) in total within a maximum of 2 organs) histologically-proven malignancy with adrenal metastasis on imaging
- Minimal interval from the primary treatment of 6 months and primary disease controlled
- Tumour <5cm
- Surgery has been considered as an alternative to SABR, but thought less appropriate due to technical or patient factors
- Absent, or potentially treatable extra-adrenal disease
- WHO performance status 0-2
- Age ≥ 18 years
- Life-expectancy >6 months

Exclusion criteria:

- Tumours >5cm
- Single functioning kidney on the same side as the adrenal metastasis
- Systemic anti-cancer therapy administered within 28 days of SABR, or planned for <28 days following treatment
- Pregnant or lactating females
- Inability to comply with treatment requirements

Relative contraindications:

- Previous radiotherapy within the planned treatment volume
- If tumour has respiratory movement ≥1cm despite using techniques to reduce tumour motion, only proceed with treatment if target delineation is reliable and suggested normal tissue and tumour planning constraints can be achieved

All potential oligometastatic SABR patients should be discussed with a regional SABR MDT prior to treatment

3. Investigations required

Histological confirmation of malignancy.

Biopsy from metastasis not necessary if known primary cancer and MDT are in agreement that imaging is consistent with metastasis.

Diagnostic / staging imaging to include:

CT and PET-CT

Review of clinical history to include:

Current symptoms, performance status.

Previous radiotherapy

Assess whether patients have had previous radiotherapy, and if so whether there is likely to be any overlap which could affect ability to deliver treatment.

Chronic conditions or disease that affects radiosensitivity

Identifying conditions, which may confer increased radiosensitivity or risk (e.g. inflammatory bowel disease), affect delivery of radiotherapy or affect prognosis

Ongoing medication that may affect response to radiotherapy

Stop potentially radiosensitising agents for a duration prior to and following SABR where possible.

Others as required

Baseline FBC, U&E, LFT and cortisol.

A DMSA scan should be performed to check differential kidney function.

4. Information given to patients

- Patients will have the rationale, technique and potential acute and long-term toxicities of adrenal SABR discussed with them in new patient or radiotherapy clinic. They should be provided with the appropriate information leaflet.
- Surgical resection as an alternate treatment strategy should have been discussed if patients are thought to be potentially suitable.
- Pre-treatment considerations:
    - Patients should be on a prophylactic PPI (eg Lansoprazole 30mg OD or equivalent). This should be continued for a least 3 months post treatment.
    - Consider 8mg Ondansetron prior to each fraction.

5. Consent

Informed consent will be obtained by an IR(ME)R Practitioner (with a minimum of FRCR part 1) at new patient /planning clinic.

6. Trials Open

Consider current trials open in any of the Radiotherapy centres in the East Midlands:

- SARON – patients with oligometastatic non-small cell lung cancer at presentation may be suitable for treatment within the SARON trial. The trial randomises patients who have not progressed after chemotherapy to radical radiotherapy (SABR or conventional RT) to the primary lesion +/- nodes and SABR to the oligometastatic disease.

- HALT – patients with mutation positive NSCLC with oligoprogression on TKI therapy are randomised to SABR to sites of oligoprogression vs continuation of the TKI

7. Position and immobilisation

All patients will be CT scanned as per local protocol.

- Patients should be nil by mouth for 2 hours prior to their planning scan (and subsequently NBM 2 hours prior to each treatment).
- IV contrast should be given to aid delineation of the GTV if renal function is adequate and there are no contraindications. Oral contrast may be required if GTV is in close proximity to the stomach or duodenum; allow 10-15 minutes delay for optimal imaging.
- The extent of the scan should be cover the whole lungs (for volume-based constraint calculation) and at least 10cm inferior to the tumour, ensuring that the entirety of the liver and kidneys are included. CT slices should be ≤3mm thickness.
- If a patient is also receiving SABR to an extra-adrenal site (e.g. lung), they should be discussed with the treating clinician prior to CT planning. Where possible, inclusion of all sites on a single planning scan allows more accurate dose calculations.

<u>Motion Control:</u>

- If tolerated, all patients should be scanned with ABC in exhale breath hold, or abdominal compression alongside 4DCT imaging (if available within the treating centre).
- If the patient is unable to tolerate motion-control measures, or the equipment is not available within the treating centre, the primary CT (for the basis of dose calculation, GTV and OAR delineation) is a 3D-CT (free breathing) with contrast and a 4D-CT is performed to assess tumour motion (see GTV outlining below).

Immobilisation:

Patients should be scanned supine with arms above the head in a suitable immobilisation device such as a custom made vacuum bag. Knee and foot supports according to local protocol.

8. Planning

8.1. Volume Definition:

a. The GTV (to be outlined in *turquoise*) is the extent of the tumour, taking into account all diagnostic information on:
   - The contrast enhanced exhale ABC or
   - 4DCT with abdominal compression: GTV should be contoured on 3D contrast scan and also on the maximum inhale and maximum exhale phases from the 4D-CT or AIP (depending on local practice), these should then be amalgamated to create an ITV (to be outlined in violet)

b. GTV=ITV=CTV, unless significant uncertainty about the extent of the GTV in which case 5mm can be added to form CTV.

c. PTV (*use blue colour*) = CTV +5mm

d. Organs at risk (OAR) to be outlined.

Structure/Nomenclature	**Colour**	**Description**
SpinalCanal	Brown	• To be contoured on all slices using the inner limits of the spinal canal using bone windows.
Heart+A_Pulm	Pink	• The heart is contoured on mediastinal windows to include the pericardial sac. • The cranial border is at the cranial aspect of the pulmonary artery. • The caudal extent is at the apex of the heart where the left ventricle blends with the diaphragm. • Major vessels, including the inferior vena cava should be excluded. The pulmonary arteries are excluded below the main bronchi.
Lung_L Lung_R Lungs	Red Orange	• Each lung should be contoured separately on lung windows. • Contour the whole lung, from the apex to the diaphragm, including all inflated and collapsed lung. • Small vessels less than 10mm in diameter and vessels beyond the hilar region are included. • Exclude the proximal bronchial tree and the trachea. • '*Lungs'* is a summation of the right and left lung
Oesophagus	Maroon	• The oesophagus is contoured on mediastinal windows to include all muscle layers out to the fatty adventitia. • Contour from the lower edge of the cricoid cartilage to the gastroesophageal junction.
Liver	Navy	• The liver should be contoured in entirety from the cranial diaphragmatic aspect to the caudal tip of the right lobe, using soft tissue windows. • The inferior vena cava should be excluded from the liver contour when it is clearly separate from the liver. The gall bladder should be excluded.

Kidney_L Kidney_R Kidneys	Light green Bright green	• Each kidney should be contoured separately from the upper to the lower pole. • The kidney is easily distinguished from surrounding adipose tissue and is located at the level of the T12 and L3 vertebral bodies. • The structure excludes cysts, pararenal fat, and the adrenal gland. • *Kidneys* is a summation of the right and left kidney and may be used for dose reporting purposes.
Stomach	Violet	• The stomach should be contoured from the gastro-oesophageal junction to the pylorus. • Contour to the outer extent of the external wall, including stomach contents.
Duodenum	yellow	• The duodenum should be contoured from the pylorus to the duodenojejunal junction/ligament of Treitz. • The majority of the structure is fixed to the retroperitoneum and follows a C-shaped course around the head of the pancreas. • The contour follows four anatomical sections: 1) 5cm in length and anterolateral to the body of the L1 vertebra 2) 7-10cm descending adjacent to the L1-3 vertebral bodies 3) 6-8cm in length, turning medially and crossing the L3 vertebral body. The aorta and inferior vena cava are posterior; the superior mesenteric artery and vein lie anteriorly 4) 5cm in length and ascending from the L3 vertebral body to the cranial border of the L2 vertebral body • The contour adheres closely to the outer boundary of the external wall and includes duodenal contents. Take care to distinguish the duodenum from the head of the pancreas as the structures are in close proximity.
Bowel_Small	Dark green	• The small bowel encompasses the duodenum, jejunum, and ileum in one contour. • Contour from the pylorus to the ileocaecal junction. Ensure small bowel in the lower pelvis caudal to the recto-sigmoid junction is included. • The small bowel can be discriminated from the large bowel by the appearance of bowel contents and the presence valvulae conniventes. The contour adheres closely to the outer boundary of the external wall and includes small bowel contents.
Bowel_Large	Dark brown	• The large bowel encompasses the caecum, ascending colon, transverse colon, descending colon, and sigmoid colon in one contour. • Contour from the ileocaceal junction to the recto-sigmoid junction.

		• The large bowel can be discriminated from the small bowel by the appearance of bowel contents, presence of haustra, sacculations, and appendices epiploicae. • The contour adheres closely to the outer boundary of the external wall and includes large bowel contents.
Spleen	Light yellow	• The spleen varies in size and shape, but is usually 12 x 7 x 3cm and located at the left upper abdominal quadrant. • The stomach lies anterior to the spleen. Posteriorly, the spleen issurrounded by left 9th to 11th ribs and diaphragm. The left kidney is medial to the spleen and the caudal border is the left colic flexure. • The peritoneum surrounds the spleen and should be excluded from the structure. The shape of the spleen will be affected by the surrounding organs and adjustment of CT window and level may be necessary to better distinguish the border of the spleen against adjacent structures.
GreatVes	Purple	• The great vessels are contoured on mediastinal windows to include the vascular wall and muscle layers out to the fatty adventitia. • The structure abuts the Heart+A_Pulm contour. • Intravenous contrast may be helpful in distinguishing the great vessels from adjacent structures. • Contour the superior vena cava and the aorta. The branches of the aortic arch: the brachiocephalic artery, the left common carotid artery, and the left subclavian artery may be included. The inferior vena cava is included in the great vessels structure. The cranial aspect is where the inferior vena cava is clearly separate from the right atrium of the heart. • It may be appropriate to only contour the most proximal vessel depending on site of tumour
Chestwall_L Chestwall_R Chestwall	Peach Light Pink	• Each chest wall should be contoured separately. • The chest wall is a 2cm rind of the hemi-thorax outside of the thoracic cavity. The structure includes ribs, intercostal vessels, nerves and muscles, and excludes vertebral bodies, sternum, and skin. • The anterior-medial border is at the lateral edge of the sternum; the posterior-medial border is the lateral aspect of the vertebral body. • *Chestwall* is a summation of the right and left chestwall

† Above table from Guidelines for contouring: Mir R, Kelly SM, Xiao Y et al. Organ at risk delineation for radiation therapy clinical trials: Global Harmonization Group consensus guidelines **(1)**
https://doi.org/10.1016/j.radonc.020.05.038

8.2. Planning

a. Prescribed dose:

- 30-36Gy in 3# over one week
- 45Gy in 5# over 10 days
- Aim to treat on alternate days, minimum of 40 hours between treatments

b. Dose should be prescribed to 95% of PTV

c. Complex dose constraints need to be met. The maximum dose within the target volume should be between 110-140% of the prescription dose. Data from the CtE scheme indicated that there was benefit to dose conformity by planning with greater dose inhomogeneity (130-140%), particularly for the smaller volumes (<40cc).

d. Data from the CtE scheme found that R100% and R50% lose sensitivity to detect poor PTV dose conformity with decreasing PTV coverage, therefore modified metrics with Prescription Dose Spillage (PDS) and Modified Gradient Index (MGI) need also to be calculated as below.

$$\textbf{Prescription dose spillage} = \frac{\textbf{Vol (100\%)}}{\textbf{PTV V100\%}}$$

$$\textbf{Modified Gradient Index} = \frac{\textbf{Vol (50\%)}}{\textbf{PTV V100\%}}$$

Prescription Dose Spillage (PDS) requirements:

Vol(PTV) (cc)	Vol(100%)/PTV V100%		
	Target	Tolerance	Minor Deviation
<20	1.20	<1.25	1.25-1.40
20-40	1.10	<1.20	1.20-1.30
>40	1.10	<1.15	1.15-1.20

Modified Gradient Index (MGI) requirements:

Vol(PTV) (cc)	Vol(50%)/PTV V100%		
	Target	Tolerance	Minor Deviation
<20	5.5	7.5	7.5-9.5
20-40	4.5	6.0	6.0-7.5
>40	4.5	5.5	5.5-6.5

† above tables adapted from Stereotactic Ablative Body Radiotherapy: A Resource. UK SABR consortium. V6.1. 2019 **(2).** Target values are based on median data from the CtE scheme and should be achievable for around half of patients.

Definitions:

Vol(100%)/Vol(PTV) *= ratio of prescription isodose volume to PTV*

Vol(50%)/Vol(PTV) *= ratio of 50% prescription isodose volume to PTV*
Vol(100%) and Vol(50%) *= volumes of the patient receiving at least 100% and 50% of the prescription dose respectively*
PTV V100% *= the volume of the PTV receiving at least 100% of the prescription dose*

e. Dose constraints for organs at risk (OAR):

Structure	Metric	3 fractions		5 fractions		End point
		Optimal	Mandatory	Optimal	Mandatory	
Bowel_Large	$D_{0.1cc}$		28.2Gy		38Gy	G3+ colitis/ fistula
Oesophagus	$D_{0.1cc}$		25.2Gy		35Gy	G3+ stenosis/ fistula
Duodenum	$D_{0.1cc}$		22.2Gy	33Gy	35Gy	G3+

Structure	Metric	3 fractions		5 fractions		End point
		Optimal	Mandatory	Optimal	Mandatory	
	D_{10cc}		11.4Gy	25Gy		ulceration
Bowel_Small	$D_{0.1cc}$		25.2Gy	30Gy	35Gy	G3+ enteritis/ obstruction
	D_{5cc}		17.7Gy			
	D_{10cc}			25Gy		
Stomach	$D_{0.1cc}$		22.2Gy	33Gy	35Gy	G3+ ulceration/fistula
	D_{10cc}		16.5Gy	25Gy		
	D_{50cc}			12Gy		
BileDuct_Common	$D_{0.1cc}$	50Gy		50Gy		
Chestwall	$D_{0.1cc}$	36.9Gy		43Gy		G3+ fracture/ pain
	D_{30cc}	30Gy				
Lungs	V_{20Gy}	10%	15%	10%	15%	G3+ pneumonitis
	D_{mean}	8Gy		8Gy		
Heart+A_Pulm	$D_{0.1cc}$	26Gy	30Gy	29Gy	38Gy	G3+ pericarditis
Kidney_Cortex (individual/combined)	D_{mean}	8.5Gy		10Gy		G3+ renal function dysfunction
Kidney_Cortex (combined)	$D_{\geq 200cc}$		16Gy		17.5Gy	
If solitary kidney or one Kidney_Cortex individual D_{mean} constraint exceeded[††]	V_{10Gy}		33%	10%	45%	
Liver	$D_{\geq 700cc}$	15Gy	17Gy	15Gy		G3+ liver dysfunction, radiation-induced liver damage
	V_{10Gy}			70%		
	D_{mean}	13Gy	15Gy	13Gy	15.2Gy	

Structure	Metric	3 fractions		5 fractions		End point
		Optimal	Mandatory	Optimal	Mandatory	
Skin	$D_{0.1cc}$	33Gy		39.5Gy		G3+ ulceration
	D_{10cc}	30Gy		36.5Gy		
Spleen	D_{mean}		Report		Report	
GreatVes	$D_{0.1cc}$		45Gy		53Gy	G3+ aneurysm
SpinalCanal	$D_{0.035cc}$		20.3Gy		25.3Gy	Radiation myelopathy (1-5% risk for 1-5#)

† above table adapted from the UK 2022 Consensus on Normal Tissue Dose-Volume Constraints for Oligometastatic, Primary Lung and Hepatocellular Carcinoma Stereotactic Ablative Radiotherapy. Clinical Oncology. 2022. P. Diez et al. ***(3)*** *https://doi.org/10.1016/j.clon.2022.02.010*

†† In cases where the ipsilateral Kidney_Cortex D_{mean} is exceeded, the V_{10Gy} should be applied to the contralateral kidney ***(3)***

- If the mean dose to the spleen exceeds 10Gy consider placing the patient on the hyposplenism register.
- If a patient is being treated on a clinical trial then the trial overrides this protocol.
- If the treatment is off protocol, this should be noted and the correct local procedure for recording off protocol treatment followed.

9. Treatment

In vivo dosimetry as per local protocol.

Any other monitoring

Patients should be assessed for toxicity and new symptoms prior to each fraction. It is the responsibility of the treatment radiographers to carry out the review. Toxicity should be documented using the Common Terminology Criteria Adverse Events (CTCAEv4).

Side effects may include:

Acute: Skin reaction, tiredness, nausea, vomiting, dyspepsia, poor appetite, pain.

Late: GI bleeding, nausea, abdominal pain, liver dysfunction, adrenal insufficiency, diarrhoea, renal failure, pneumonitis, pulmonary fibrosis.

Patients should have FBC, U&E LFT and cortisol checked pre-treatment and then at each follow-up appointment as below.

Patients should be weighed prior to treatment and additional dietetics support if weight loss or difficultly eating.

Patients should be discussed with a clinician if ongoing nausea and vomiting or dyspepsia despite prophylactic PPI and Ondansetron.

On treatment imaging.

Daily 3D CBCT.

Bone match to check for gross rotational and positional errors and then soft tissue match to the tumour. Consult the treating clinician if the shift from bone is >5mm as the patient may need replanning.

If proximal OAR of concern, clinician to document acceptable shifts.

For centres newly treating SABR, consider post treatment offline CBCT to confirm treated position - this can be reviewed and likely discontinued after the first 10 patients.

For gaps in treatment follow local policy

Treat as category 2 for gaps in treatment. Ensure 40 hours between treatments.

On treatment review and follow-up

Patients should be assessed for acute toxicity 4-6 weeks post SABR.

Subsequently patients should be reviewed 3 monthly for the first year, then 6 monthly for subsequent years. However, this can be modified depending on the underlying primary cancer diagnosis and disease status. Follow-up (following the first post radiotherapy visit) should usually be with the primary site team. Review should include assessment of toxicity (using CTCAEv4) and symptom review.

The first post treatment CT should be done at 3 months and then repeated at least every 6-12 months depending on circumstances.

FBC, U&E, LFT and random cortisol should be checked at 3,6,9,12,18 and 24 months, then at least annually long-term.

10. References

1) R Mirr, S Kelly, Y XIAO et al. Organ at risk delineation for radiotherapy clinical trials: Global Harmonization Group consensus guidelines. Radiation and Oncology. 2020. 150; 30-39.

2) Stereotactic Ablative Body Radiation Therapy (SABR): A Resource. Version 6.1. UK SABR Consortium. Jan 2019.

3) P. Diez, G. Hanna, K Aitken et al. UK 2022 Consensus on Normal Tissue Dose-Volume Constraints for Oligometastatic, Primary Lung and Hepatocellular Carcinoma Stereotactic Ablative Radiotherapy. Clinical Oncology. 2022.

4) Stereotactic Ablative Radiotherapy for Oligometastatic Non-small cell lung cancer a Randomised Phase III Trial – Radiotherapy and QA guidelines V3.1. April 2021.