Radiotherapy Protocol for the management of SABR to the liver for Oligometastatic disease

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

Document revision History

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1. Treatments to include

- Radical radiotherapy only

2. Indications for treatment

Inclusion criteria:

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

<u>All the following criteria must be met, unless within a clinical trial or agreed within the SABR MDT:</u>

- Confirmed histological diagnosis of metastatic cancer originating for any primary cancer in the body including carcinoma, sarcoma and melanoma
- Minimal disease-free interval of 6 months from primary treatment to the manifestation of metastases
- 1-3 sites of metastatic disease (oligometastatic) confined to 1-2 organs within the bones, spine, lymph nodes, liver, adrenal gland or lungs
- Tumour ≤5cm in any dimension
- Not suitable for surgical resection or RFA (technically not possible, patient not fit, patient declines surgery or the presence of extra-hepatic disease making surgery an inappropriate option)
- Child-Pugh Class A and adequate organ function (defined as >700cc normal liver, Hb ≥9g/dL, platelets >80, bilirubin <3x ULN, INR <1.3 or correctable with vitamin k (unless on warfarin), AST and ALT <5x ULN)
- Age ≥ 18 years
- Life-expectancy >6 months
- WHO performance status 0-2
- Normal liver (liver-GTV) volume of >700cc

FIgure 1: Child –Pugh scoring system (*extracted from SABR:A Resource V6.1 2019*) (1)

Measure	1 point	2 points	3 points
Total Bilirubin (µmol/l) (mg/dl)	<34 (<2)	34-50 (2-3)	>50 (>3)
Serum albumin (g/l)	>35	28-35	<28
INR	<1.7	1.71-2.20	<2.20
Acites	None	Mild	Severe
Hepatic Encephalopathy	None	Grade 1-2 (or suppressed with medication)	Grade 3 or 4

Points	Class	One Year Survival	Two Year Survival
5-6	**A**	100%	85%
7-9	**B**	81%	57%
10-15	**C**	45%	35%

Exclusion criteria:

- Active hepatitis or clinically significant liver failure (encephalopathy, oesophageal varices, clinically significant portal hypertension, clinically apparent ascites)
- Tumours >5cm in maximal dimension or >3 lesions
- Prior abdominal radiotherapy where the mean liver dose ≥15Gy in conventional fractionation or previous doses to OARs which would make re-irradiation unsafe (prior pelvic irradiation permitted as long as no overlap between pelvic and liver fields)
- Direct tumour extension into the stomach, duodenum, small bowel or large bowel
- Prior liver transplant
- Synchronous metastases or a disease-free interval of <6 months
- > 3 sites of metastatic disease in total
- Primary cancer in situ/active
- Haematological malignancies (myeloma, lymphoma)
- Systemic anti-cancer therapy administered within 28 days of SABR, or planned for 28 days following treatment
- Pregnant or lactating females
- Untreated brain metastases (patients should have received SRS or resection)
- Inability to comply with treatment requirements

3. Investigations required

Histological confirmation of malignancy

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

Diagnostic / staging imaging to include:

Multiphase CT abdomen and thorax

MRI Liver

PET-CT

Review of clinical history to include:

Current symptoms, including assessment for decompensated liver disease. Assessment of performance status.

Previous radiotherapy

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

Chronic conditions or disease that affects radiosensitivity

Ensure full assessment of past medical history, identifying conditions, which may confer increased radiosensitivity, affect delivery of radiotherapy or affect prognosis.

Ongoing medication that may affect response to radiotherapy

Identify medications, which may alter radiotherapy response. Stop potentially radiosensitising agents for a duration prior to and following SABR where possible.

Others as required

Patients should baseline renal and liver function (including coagulation) assessed prior to treatment.

4. Information given to patients

- Patients will have the rationale, technique and potential acute and long-term toxicities of liver SABR discussed with them in new patient or radiotherapy clinic. They should be provided with the appropriate information leaflet.
- Patients should have also had the opportunity to discuss the risks and benefits of surgical resection with a HPB surgeon if they are thought to be potentially suitable, albeit at a higher risk, in order to make an informed treatment decision.
- *Pre-treatment considerations:* consider prophylactic anti-emetics +/- PPI if stomach/small bowel are receiving significant dose

5. Consent

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

6. Trials Open

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

- SARON – synchronous oligometastatic NSCLC. Radical RT (SABR or conventional RT) to the primary lesion +/- nodes and SABR to the oligometastatic disease.
- HALT – 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 radiotherapy (and subsequently NBM 2 hours prior to each treatment).
- IV contrast to be administered unless contraindicated to aid target volume and OAR delineation – 70 seconds delay between contrast and imaging is optimal.
- Patients will receive dilute oral contrast prior to their planning scan to aid visualisation of the duodenum e.g. Omnipaque 150-200ml 4% solution, 10-15 minutes prior to scan.
- Scan limits: Apex of lungs to the inferior aspect of L5 vertebral body, ensure the whole kidneys are imaged.
- CT slices should be no greater than 2mm
- A MRI planning scan with contrast on a flat top couch should be performed, providing there are no contraindications. This should then be fused with the CT planning scan to aid delineation. Exact MRI protocols should be discussed within departments and individualised.

Motion control

- If tolerated (and available within the treatment centre), all patients should be scanned with one of the following techniques to limit liver motion:
    - ABC in exhale breath hold
    - Or 4DCT with abdominal compression (plus a contrast enhanced 3D-CT as below)
- 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 supine with arms above the head in a suitable immobilisation device such as a custom 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 visible, taking into account information from diagnostic imaging.

- If ABC is used then this will be on the contrast enhanced exhale ABC scan.
- If 4D-CT is used instead of ABC (+/- abdominal compression): GTV should be contoured on the 3D contrast scan and also on the maximum inhale and maximum exhale phases from the 4D-CT, these should then be amalgamated to create an ITV (to be outlined in violet).

b. GTV=CTV: no additional margin for microscopic spread usually required

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.
BileDuct_Common	Light blue	• The common bile duct is usually 8-10cm in length and 5-6mm in diameter. • The contour begins at the union of the common hepatic duct and the cystic duct and extends caudally to the second section of the duodenum. The common bile duct passes posterior and medial to the duodenum and joins with the pancreatic duct to form the ampulla of vater.
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 (2)
https://doi.org/10.1016/j.radonc.2020.05.038

e. The OARs should be inspected to ensure that wherever a treatment beam traverses an OAR it has been contoured adequately.
f. It is the responsibility of the clinical oncologist to outline and/or review all OAR outlines specified above.
g. Ideally the ITV and OARs should be peer reviewed by a least one other clinical oncologist.

8.2. Planning

a. Prescribed dose:

- There are RCTs comparing dose fractionation for SABR to liver metastases.
- Suggested schedules are:

Standard fractionation	40-60Gy in 3 fractions e.g. 45Gy in 3 fractions on alternate days	
Conservative fractionation	50-60Gy in 5 fractions on alternate days	May be used when a larger PTV is being treated in order to achieve OAR constraints or when PTV is within 1cm of small bowel/visceral OAR/bile duct or adjacent to chest wall/ribs

Very conservative fractionation	30-60Gy in 10 fractions Total dose to be individualised according to the effective liver volume treated: • 40-60Gy if <30% effective liver volume irradiated • 35-50Gy if 30-50% effective liver volume irradiated • 30Gy if 50-70% effective liver volume irradiated	Consider using when multiple lesions where unable to meet planning constraints or extra-hepatic disease

Effective liver volume = normal liver volume which, if irradiated to the reference dose, would be associated with the same normal tissue complication probability as the non-uniform dose actually delivered.

- All treatments should be delivered on alternate days with a minimum of 40 hours between treatments.
- The dose to different lesions may be different depending on their proximity to OARs.

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 smaller volumes (<40cc).

d. Conformity of PTV coverage will be judged as given in the tables below, incorporating constraints used in the ROSEL study. However, data from the CtE scheme found that R100% and R50% lose sensitivity to detect poor conformity with decreasing PTV coverage, therefore modified metrics with Prescription dose spillage (PDS) and Modified Gradient Index (MGI) need to also be calculated and reported as below

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

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

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. 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 OAR

Structure	Metric	1 fraction		3 fractions		5 fractions		End point
		Optimal	Mandatory	Optimal	Mandatory	Optimal	Mandatory	
Bowel_Large	$D_{0.1cc}$		18.4Gy		28.2Gy		38Gy	G3+ colitis/ fistula
Oesophagus	$D_{0.1cc}$		15.4Gy		25.2Gy		35Gy	G3+ stenosis/ fistula

Structure	Metric	1 fraction		3 fractions		5 fractions		End point
		Optimal	Mandatory	Optimal	Mandatory	Optimal	Mandatory	
Duodenum	$D_{0.1cc}$		12.4Gy		22.2Gy	33Gy	35Gy	G3+ ulceration
	D_{10cc}		9Gy		11.4Gy	25Gy		
Bowel_Small	$D_{0.1cc}$		15.4Gy		25.2Gy	30Gy	35Gy	G3+ enteritis/ obstruction
	D_{5cc}		11.9Gy		17.7Gy			
	D_{10cc}					25Gy		
Stomach	$D_{0.1cc}$		12.4Gy		22.2Gy	33Gy	35Gy	G3+ ulceration/fistula
	D_{10cc}		11.2Gy		16.5Gy	25Gy		
	D_{50cc}					12Gy		
BileDuct_Common	$D_{0.1cc}$		30Gy	50Gy		50Gy		
Chestwall	$D_{0.1cc}$	30Gy		36.9Gy		43Gy		G3+ fracture/ pain
	D_{30cc}			30Gy				
Lungs	V_{20Gy}	10%	15%	10%	15%	10%	15%	G3+ pneumonitis
	D_{mean}	8Gy		8Gy		8Gy		
Heart+A_Pulm	$D_{0.1cc}$		22Gy	26Gy	30Gy	29Gy	38Gy	G3+ pericarditis
Kidney_Cortex (individual/combined)	D_{mean}			8.5Gy		10Gy		G3+ renal function dysfunction
Kidney_Cortex (combined)	$D_{\geq 200cc}$		8.4Gy		16Gy		17.5Gy	
If solitary kidney or one Kidney_Cortex individual D_{mean} constraint exceeded†	V_{10Gy}		33%		33%	10%	45%	
Liver-GTV	$D_{\geq 700cc}$		9.1Gy	15Gy	17Gy	15Gy		G3+ liver

Structure	Metric	1 fraction		3 fractions		5 fractions		End point
		Optimal	Mandatory	Optimal	Mandatory	Optimal	Mandatory	
	V_{10Gy}					70%		dysfunction, radiation-induced liver damage
	D_{mean}			13Gy	15Gy	13Gy	15.2Gy	
Skin	$D_{0.1cc}$		26Gy	33Gy		39.5Gy		G3+ ulceration
	D_{10cc}		23Gy	30Gy		36.5Gy		
Spleen	D_{mean}		Report		Report		Report	
GreatVes	$D_{0.1cc}$		30Gy		45Gy		53Gy	G3+ aneurysm
SpinalCanal	$D_{0.035cc}$	12.4Gy	14Gy		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)

- If the mean dose to the spleen exceeds 10Gy consider placing the patient on the hyposplenism register.
- If the treatment is off protocol, this should be noted and the correct procedure for recording off protocol treatments followed.

9. Treatment :

In vivo dosimetry as per local protocol.

Patient review

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, dysphagia, poor appetite, pain, derangement of liver enzymes.

Late: GI bleeding, nausea, abdominal pain, liver dysfunction (liver enzyme disturbance, radiation-induced liver disease), adrenal insufficiency, diarrhoea, renal failure, rib fracture, pneumonitis, pulmonary fibrosis.

Patients should have FBC, U&E, LFT and coagulation screen checked pre-treatment and on the final fraction of treatment.

Patients should be weighed prior to treatment and additional dietetic support given if weight loss or difficulty eating.

Patient's should be discussed with a clinician if ongoing nausea and vomiting dyspepsia despite prophylactic PPI and Ondansetron.

On treatment imaging

Daily 3D CBCT if ABC/abdominal compression used. Otherwise a 4D CBCT (if available) on D1 and then 3D CBCT if no concerns regarding movement (otherwise continue with daily 4D CBCT)

Bone match to check for gross rotational and positional errors and then match to liver and tumour if visible.

If proximal OAR of concern, clinician to document acceptable shifts

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

For gaps in treatment

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

Follow up

Patients should be assessed for acute toxicity 4-6 weeks post SABR, including Child Pugh Score and performance status. All reviews should include assessment of toxicity (using CTCAEv4) and symptom review.

Subsequent review will depend on the underlying primary cancer diagnosis and disease status. Follow-up following the first post radiotherapy visit should be with the primary site team. A typical schedule in the absence of progressive disease might be 3 monthly for 2 years then 6 monthly reviews.

The first post-treatment imaging should be done at 3 months. Imaging may then be repeated as considered appropriate by the primary team depending on the circumstances. Multiphase CT is usually

able to differentiate focal radiotherapy reaction from disease. MRI may be superior in differentiating residual disease from normal tissue reaction and should be considered if pseudo-progression is suspected on CT.

FBC, U&E, LFT, clotting +/- tumour markers should be checked 3 monthly for the first 2 years, then 6 monthly.

10. References

1. Stereotactic Ablative Body Radiation Therapy (SABR): A Resource. Version 6.1. UK SABR Consortium. Jan 2019.
2. Organ at risk delineation for radiotherapy clinical trials: Global Harmonization Group consensus guidelines. Radiation and Oncology. 2020. 150; 30-39.

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.

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