Radiotherapy Protocol for the management of SABR to the spine for Oligometastatic disease.

Document revision History

Version Number	Date	Document History.
1.0	22/11/22	Dr Sarah Taylor
1.1	April 22	Verified through- LJ
1.1	09/06/23	Ratified at NOG

1. Treatments to include

- Radical radiotherapy – SABR for oligometastatic disease to the spine

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 lesions in total within a maximum of 2 organs) histologically-proven malignancy with spinal metastasis on imaging
- Not more than 2 consecutive spinal vertebral bodies involved or > 2 tumours within the spine
- Tumour ideally 3-5mm from the cord
- Well-defined lesion(s) on MRI imaging
- Minimal interval from the primary treatment of 6 months and primary disease controlled
- Neurosurgical opinion documented if SINS score >6
- Absent, or potentially treatable extra-spinal disease
- WHO performance status 0-2
- Age ≥ 18 years
- Life-expectancy >6 months

Exclusion criteria:

- Patients with spinal instability (SINS score 13-18) or unable to lie flat/tolerate treatment
- Significant or progressive neurological deficit such that emergency surgery or radiation is required, including spinal cord compression or impingement
- Disease free interval between primary treatment and manifestation of metastases of <6 months
- Systemic anti-cancer therapy administered within 28 days of SABR, or planned for <28 days following treatment
- Haematological primary malignancy such as lymphoma or myeloma
- Pregnant or lactating females
- Inability to comply with treatment requirements
- Previous SABR to the same site
- Untreated brain metastases (patients should have received SRS or resection)

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

Table 1: Spinal instability Neoplastic Score (SINS) System (adapted from Fisher et al): (1) https://doi.org/10.1186/1748-717x-9-69

Component	Score
Location	
Junctional (O-C2; C7-T2; T11-L1; L5-S1)	3
Mobile Spine (C3-6; L2-4)	2
Semirigid (T3-10)	1
Rigid (S2-S5)	0
Mechanical pain	
Yes	3
No	2
Pain free lesion	1
Bone Lesion	
Lytic	2
Mixed (lytic/blastic)	1
Blastic	0
Radiographic spinal alignment	
Subluxation/translation present	4
Deformity (kyphosis/scoliosis)	2
Normal	0
Vertebral body collapse	
>50% collapse	3
<50% collapse	2
No collapse with >50% body involved	1
None of the above	0
Posterolateral involvement	
Bilateral	3
Unilateral	1
None of the above	0

	Score (Total = 0-18)		
	1-6	7-12	13-18
Clinical categories	Stable	Potentially unstable	Unstable
Binary scale	Stable	Currently or potentially unstable = possible surgical intervention	

3. Investigations required

- Histological confirmation of malignancy. Biopsy from malignancy not necessary if known primary cancer and MDT are in agreement that imaging is consistent with metastasis.
- Diagnostic / staging imaging to include:

-CT chest, abdomen and pelvis

-MRI spine

-PET-CT

- Review of clinical history to include:
  Current symptoms including pain and neurological impairment, mobility and performance status.
- Previous radiotherapy :
  Assess whether the patients had 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:
  Ensure full assessment of past medical history, identifying conditions that may confer increased radiosensitivity or risk, affect delivery of radiotherapy or affect prognosis
- Ongoing medication that may affect response to radiotherapy:
  Identify medications, which alter radiotherapy response. Stop potentially radiosensitising agents for a duration prior to and following SABR where possible.
- Others as required:
  Analgesia should be prescribed if patients are experiencing pain.

4. Information given to patients

- Patients will have the rationale, technique and potential acute and long-term toxicities of spinal SABR discussed with them in a new patient or radiotherapy clinic. They should be provided with the appropriate information leaflet.
- Patients should have also had the opportunity to discuss the risk and benefits of surgical intervention if they are potentially suitable.
- It is important that patients are educated regarding the signs and symptoms of metastatic spinal cord compression and are given appropriate contacts.

<u>Pre-treatment preparation</u>

- Patients should be commenced on Dexamethasone 4mg OD starting the same day as SABR and finishing with the last SABR fraction.
- Whilst on Dexamethasone patients should receive a PPI eg Lansoprazole 30mg
- Patients should have a pain assessment and be prescribed adequate analgesia. If stomach or bowel is receiving significant dose, prescribe prophylactic anti-emetics +/- anti-diarrhoea agents.

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 – 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 vs continuation of the TKI

7. Position and immobilisation

All patients will be CT scanned as per local protocol

- Patients should receive analgesia 30 minutes prior to planning scans (and subsequent treatments) if pain is present.
- The 3D planning CT should include at least 10cm superior and inferior to the treatment volume. It should cover all relevant vertebral bodies and OARs (if part of the lung, liver or kidney is likely to receive a clinically significant dose, the whole organ must be included in the imaging as there are volumetric dose constraints).
- Ideally 1mm slice thickness will be used with spacing
- IV contrast is not required routinely, but can be used at the clinician's request if it would aid OAR delineation
- Centres should use the advanced scanner features to reduce image artefact produced in patients with metalwork

<u>Planning MRI</u>

- Patients should have a planning MRI scan performed in the treatment position with a flat table top and using the same immobilisation as the planning CT, if available. This should ideally be done on the same day as the planning CT.
- It should cover one vertebra above and below the spinal abnormality, typical MRI length ~15cm.
- T1 and T2 weighted axial images with contrast and 2mm slice thickness should be regarded as essential scans. T1 images are used for GTV delineation and T2 for cord. Consideration could also be given to T2 sagittal scans. T1_pre-Gad are unlikely to useful.
- Subject to the patient's comfort and compliance, a Spine Coil should be used for patients with metalwork (assuming spine flexion is locally prevented by the metalwork), but other coils (together with the flat table top) should be used for patients without metalwork.

Immobilisation as per local protocol:

- Due to the proximity of the spinal cord, it is crucial that patients are robustly immobilised.
- T4 and above: Immobilise with customised head/shoulder support, indexed knee support, arms down
- T5 and below: Immobilise with an indexed wingboard with arms elevated, custom body vacuum bag, knee and foot supports

8. Planning

8.1. Volume Definition:

a) **GTV** (to be outlined in turquoise) = gross tumour using all available imaging

b) **CTV** (to be outlined in violet) should contain GTV and include bony CTV expansion to account for subclinical spread. Include abnormal marrow signal suspicious for microscopic invasion. See diagram and table below for further details:

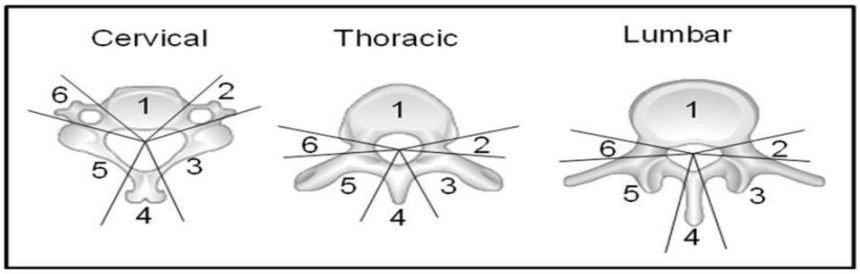


Figure 1: Anatomic classification for consensus target volumes for Spine SABR (taken from SABR: A Resource V6.1) (2)

Figure 2: Guidelines for SABR bony CTV delineation (taken from SABR: A Resource V6) (2)

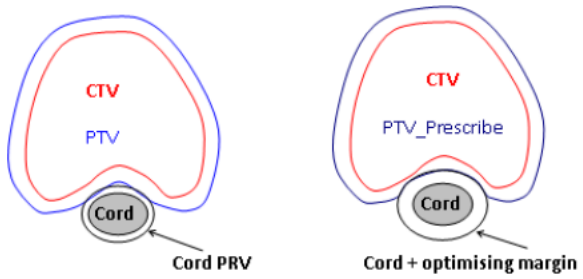
GTV involvement	ISRC GTV anatomic classification	ISRC bony CTV recommendation	CTV description
Any portion of the vertebral body	1	1	Include the entire vertebral body
Lateralized within the vertebral body	1	1,2	Include the entire vertebral body and the ipsilateral pedicle/transverse process
Diffusely involves the vertebral body	1	1,2,6	Include the entire vertebral body and the bilateral pedicles/transverse processes
GTV involves vertebral body and unilateral pedicle	1,2	1,2,3	Include entire vertebral body, pedicle, ipsilateral transverse process and ipsilateral lamina
GTV involves vertebral body and bilateral pedicles/transverse processes	3	2,3,4	Include entire vertebral body, bilateral pedicles/transverse processes and bilateral laminae
GTV involves unilateral pedicle	2	2,3 +/- 1	Include pedicle, ipsilateral transverse process and ipsilateral lamina, _ vertebral body
GTV involves unilateral lamina	3	2,3,4	Include lamina, ipsilateral pedicle/transverse process, and spinous process
GTV involves spinous process	4	3,4,5	Include entire spinous process and bilateral laminae

- Circumferential CTVs encircling the cord should be avoided except in rare circumstances where the vertebral body, bilateral pedicles/lamina, and spinous processes are all involved, or when there is extensive metastatic disease along the circumference of the epidural space without cord compression.

c) **PTV** (use blue colour) = CTV plus 2-3mm depending on equipment and experience, use local audit data

d) In order to allow for unavoidable under-dosing of the PTV in close proximity to the spinal cord, whilst maintaining consistency in the treatment prescription, a volume (PTV_Prescribe) should be created, which restricts the PTV by spinal cord PRV+2mm. If it is different from the PTV, this volume should be used for prescribing and additional dose reporting.

Figure 3: Illustration of PTV_Prescribe volume (taken from SABR: A Resource V6.1) (2)



i.e. PTV_Prescibe =PTV- (cordPRV+2mm)

- PTV_Prescibe volume may be generated or edited appropriately in treatment situations where the GTV extends beyond this volume, with consideration given to the achievable dose gradient.

e) Organs at risk (OAR) to be outlined:

- Spinal dose constraints must be met. The spinal cord *(SpinalCord)* should be contoured using the fused T1 and T2 weighted MR scans and should extend to at least one vertebra superior and inferior to the PTV. At the level of the cauda equina, the thecal sac should be considered to represent the relevant OAR
- A PRV margin will be generated to create SpinalCord_XX (where XX is the size of the margin in mm). This margin is for set-up error alone. In cases where good image quality allows confident co-registration and delineation, an isotropic margin of 2-3mm may be appropriate. However, if image quality is compromised, it is recommended that the larger volume of either a further 1mm isotropical expansion or the thecal sac be used instead.

- Any OARs which are traversed by a treatment beam should be contoured. Where OAR constraints are based on the dose received by the whole organ, the OAR should be outlined completely. Otherwise OARs should be contoured at least 2cm superiorly and inferiorly to the PTV for coplanar techniques.
- OARs requiring delineation may include oesophagus, stomach, lungs, heart, kidneys, liver, bowel, thyroid, larynx, trachea, chest wall.
- OARs should be outlined according to the Global Harmonization group consensus guideline (3): https://doi.org/10.1016/j.radonc.2020.05.038. Refer to the East Midlands lung/lymph node SABR protocols for OAR guidance for thoracic/lumbosacral lesions respectively.

f) It is the responsibility of the clinical oncologist to outline and/or review all the OAR outlines specified above

g) Ideally the ITV and OARs should be peer-reviewed by at least one other clinical oncologist

8.2. Planning

a) Prescribed dose:
   - There is little consensus in the literature regarding the optimal dose–fractionation, but the following have shown good outcomes with acceptable toxicity:
     - **Preferred fractionation:** 27Gy in 3#
     - If unable to meet dose constraints, reduce to 24Gy in 3#
     - Re-irradiation fractionation: 30Gy in 5#, however this needs to be considered on an individual patient basis to asses previous spinal cord doses delivered
     - Treatment should be delivered on alternative days with at least 40 hours between each fraction. The maximum interval between fractions is 4 days.

b) Treatment should be prescribed so that 95% of the PTV (or PTV_Prescribe where appropriate) should be covered by the prescription isodose, unless there is a need to accept less coverage to achieve the OAR tolerances.

c) Hot spots should be within the PTV and ideally 110-120% of the prescription dose, mandatory 110-130%.

d) 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:

Prescription dose spillage = Vol (100%)

PTV V100%

Modified Gradient Index = Vol (50%)

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 OARs: The relevant anatomical SABR protocol should be referred to regarding constraints or refer directly to the UK 2022 Consensus on Normal Tissue Dose-Volume constraints for Oligometastatic Primary Lung, and Heptacellular Carcinoma Stereotactic Ablative Radiotherapy (5). https://doi.org/10.1016/j.clon.2022.02.010

- If a patient is being treated within a clinical trial then the trial protocol overrides this protocol
- If the patient is off protocol, this should be noted and the correct local procedure for recording off protocol treatments followed

9. Treatment

9.1. In vivo dosimetry as per local protocol

9.2. 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:
  - All: Skin reaction, Tiredness, Pain flare, loss of appetite
  - C-spine: Mucositis
  - T-Spine : Oesophagitis, nausea, chest pain
  - L-Spine : Diarrhoea, nausea

- Late: Increased risk of vertebral compression fracture or collapse, which could require surgical intervention, rib fracture, small long-term risk of trachea-oesophageal fistula/stricture formation, small risk of myelopathy or nerve damage, bowel damage, thyroid dysfunction (depending on level)

9.3. On treatment imaging as per local protocols

- Use Hexapod/ equivalent if available
- Daily 3D CBCT
- Match to bone. Maximum acceptable shift 5mm, above this re-set-up/discuss with clinician.
- 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.

9.4. For gaps in treatment follow local policy

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

9.5. Follow up post SABR

- Patients should be assessed for acute toxicity 4 weeks post SABR
- Subsequently patients should be reviewed at 3, 6 and 12 months post SABR, then annually thereafter, but 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. Review should include assessment of toxicity (using CTCAEv4) and symptom review (including pain).
- The first post-treatment CT (typically CAP) should be done at 3 months and then repeated as determined by the patient's primary oncology team.

10. References

1. Fisher C, Schouten R, Versteeg a et al. Reliability of the Spinal Instability Neoplastic Score (SINS) among radiation oncologists: an assessment of instability secondary to spinal metastases. Radiat Oncol. 2014 Mar 4;9:69.
2. Stereotactic Ablative Body Radiation Therapy (SABR): A Resource. Version 6.1. UK SABR Consortium. Jan 2019.
3. Organ at risk delineation for radiotherapy clinical trials: Global Harmonization Group consensus guidelines. Radiation and Oncology. 2020. 150; 30-39.
4. Stereotactic Ablative Radiotherapy for Oligometastatic Non-small cell lung cancer a Randomised Phase III Trial – Radiotherapy and QA guidelines V3.1. April 2021.
5. 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.