Radiotherapy Protocols

Stereotactic Ablative Body Radiotherapy (SABR) for Oligometastatic / Oligorecurrent disease

This document is the standardised Thames Valley and Wessex Radiotherapy Network SABR treatment protocol for oligometastatic/ oligorecurrent disease developed collaboratively by the SABR Oligometastatic Disease Protocol Working Group:

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Document History

Date of Issue	Version Number	Date Approved	Responsible for Change	Nature of Change	Ratification/ Approval
14/05/2021	1.1 Draft		ODN SABR Oligometastatic Disease Working Group	The existing OUH protocol used as a base for development a standardised Network-wide protocol	
24/06/2021	1.2 Draft		ODN SABR Oligometastatic Disease Working Group	Continued developing the Network-wide protocol	
07.07.2021	1.3 Draft		ODN SABR Oligometastatic Disease Working Group	Dose calculation equations added	
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25.08.2021	2.0 Final				Network Overview Group
23.09.2021	2.1		ODN SABR Oligometastatic Disease Working Group	Amendments as per the new consensus guideline for bony lesions	
09.11.2022	3.0 Final		ODN SABR Oligometastatic Disease Working Group	Changes in normal tissue dose-volume constraints as per the new UK 2022 Consensus for SABR	

Contents

1. Indications

SABR delivers ablative doses of radiotherapy to oligometastatic and oligorecurrent disease with the aim of:

1) Potential local control in oligometastatic / oligorecurrent disease.
2) Improved overall survival.
3) Delaying the use of systemic therapy.
4) Maintain QOL.

For every patient, consider if there are any appropriate trials. Within a trial, the trial protocol will be followed.

2. Links to Other Protocols

- For further information on SABR to primary tumours such as lung, HCC, renal, cholangiocarcinoma, pancreas etc. please see individual protocols
- For further information on SABR to lung metastasis please refer to lung protocol.
- Many SABR treatments will have national guidance from UK SABR Consortium on which this protocol is based.

3. Primary Objective & Scope

To summarise the planning and treatment of patients receiving stereotactic body radiotherapy for oligometastatic disease.

4. Inclusion/Exclusion Criteria

4.1. Inclusion Criteria for Oligometastases:

As per NHS England Commissioning Document, patients meeting **all** the following criteria will be eligible for treatment with SABR:

1) Confirmed histological diagnosis of metastatic cancer originating from any primary cancer in the body, including carcinoma, sarcoma and melanoma.
2) A disease-free interval between primary treatment and manifestation of metastases of at least six months.
3) One to three sites of extracranial, metastatic disease only at the time of disease presentation, confined to one to two organs (defined after appropriate imaging) in the following: bone, spine, lymph node, liver, adrenal gland, and/or lung.
4) Maximum size of 5 cm for any single metastasis.
5) In addition, patients eligible for SABR must have: A life expectancy of at least 6 months AND World Health Organisation (WHO) performance status ≤ 2.
6) Patients may only receive treatment with SABR for a maximum of three sites. Should further metastases develop, alternative treatment options should be sought.
7) For patients being treated for spinal metastases, a maximum of 2 sites in the spine can be treated with SABR.

4.2. Exclusion Criteria for Oligometastases:

As per NHS England Commissioning Document, treatment with SABR is unsuitable in people with:

1) Haematological malignancies (e.g., lymphoma, myeloma).
2) Evidence of intracranial disease.
3) Evidence of spinal cord compression or spinal instability.
4) Evidence of severe interstitial lung disease (for lung metastases).
5) Poor liver function and a Child-Pugh score B and above (for liver metastases).
6) More than three sites of metastatic disease or development of new metastases <6 months post treatment of a maximum of three lesions.
7) A disease-free interval between primary treatment and manifestation of metastases of less than six months.
8) A life expectancy of less than six months.
9) Severe co-morbidities or WHO performance status > 2.
10) Patients who require irradiation of whole nodal field (e.g., supra-clavicular recurrence for breast cancer).
11) Patients who have had previous treatment with SABR to the same site of the metastases.

4.3. Inclusion Criteria for SABR Reirradiation for Oligorecurrence

As per NHS England, patients meeting **all** the following criteria will be eligible for treatment with SABR:

1) Initial histologically confirmed primary pelvic tumour (all types) which has recurred in the pelvis.
2) Previous course of radiotherapy within the pelvis with no enduring significant toxicity.
3) Ineligible for surgery with curative intent or surgery with curative intent is declined by the patient or surgery has resulted in positive surgical margins.
4) More than 6 months since initial radiation treatment.
5) World Health Organisation (WHO) performance status ≤ 2; and life expectancy of more than 6 months.

4.4. Exclusion Criteria for SABR Reirradiation for Oligorecurrence

As per NHS England, treatment with SABR is not suitable in people:

1) With previously irradiated pelvic bone metastases or spinal metastases.
2) Receiving concurrent targeted therapies or systemic therapies.
3) In whom less than 6 months have elapsed since initial radiation treatment; or
4) With a life expectancy of less than 6 months.

Additional factors that will affect SABR reirradiation decisions of appropriateness for treatment include:

1) Previous doses delivered to disease and organs at risk.
2) If previous brachytherapy was delivered it may be challenging to calculate doses to OARs therefore proceed with caution.
3) If the tumour is in the lumen of an organ e.g., bowel lumen, there is no evidence for SABR in this setting so proceed with caution.

4.5. Beyond CTE

Although not commissioned, there are additional indications where there is emerging evidence of benefit as per indications above. These include but are not confined to (defined in [1]):

1) Induced oligorecurrence – patients who have had previous systemic therapy for multiple metastases and while most metastases are stable, only 1-3 lesions are growing or appearing, to delay restarting starting systemic therapy.
2) Induced oligoprogression – patients on systemic therapy where only 1-3 lesions are growing or appearing, to maintain the systemic therapy.
3) Synchronous oligometastatic disease or metachronous oligorecurrence – only after effective treatment of the primary and a period of systemic therapy following which there are no further sites of metastatic disease.

It is appropriate to treat patients beyond NHS Commissioning if the case has been discussed both in the site-specific MDT and the SABR MDT and both agree it is appropriate for that patient.

Factors that offer a favourable outcome in oligometastatic disease should be considered for all patients [2]. These include:

1) Smaller number of lesions.
2) Smaller number of involved organs.
3) First episode of metastatic disease.
4) Longer disease-free interval.
5) Metachronous disease.
6) Absence of cranial disease.
7) Good performance status.

5. Pre-Radiotherapy Investigations

(As per departmental guidelines, to be completed prior to radiotherapy procedures)

- Case reviewed at tumour specialised MDT and SABR MDT.
- Patients will be assessed and consented in clinic.
- An information sheet regarding SABR should be made available during clinic with documentation of late or potentially serious effects specific to their case in format available to patient (handwritten on consent or in letter).
- Baseline blood tests include FBC, U+E, LFT, Ca, tumour markers (if relevant) baseline random cortisol for adrenal lesions (if low, endocrinology input should be sought).
- Consider further axial imaging for fusion with planning scan e.g., axial MRI for bony lesions, PET for lymph nodes.
- Consider imaging to rule out additional metastasis e.g., PET-CT.
- DMSA scan may be required if renal dose likely to be significant.
- If overlap with previous radiotherapy, the previous plan must be sourced from previous treating centre.
- If SABR target within the thorax, lung function tests within last 6 months or after most recent lung directed therapy if this has occurred in last 6 months.

6. Pre-Treatment

6.1. Patient Simulation and Immobilisation:

- CT slices should be <3mm.
- Patients should be nil by mouth for 90-120 mins prior to scanning for upper GI disease.
- If IV contrast planned, screen patient for contra-indications prior to injection.
- IV and oral contrast timing will depend on target site and local OARs e.g., portal phase IV contrast for liver metastases. Oral contrast may be required when treating sites near the stomach, duodenum or small bowel.
- If 4DCT planned, helical scan should be taken in exhale for liver matching purposes where available.
- If SABR reirradiation planned and historic plan is not CT planned, ensure details of radiotherapy are available so a mock plan can be created on the planning scan from old tattoos and radiotherapy instructions.
- Immobilisation will be centre dependant. One option is documented below:
    1) Thoracic lesions: Supine with knee immobilisation; arms down if lesion is in superior thorax (lung apex, shoulder) and arms up if mid/lower thorax.
    2) Abdominal lesions: Supine with arms above the head and knee immobilisation.
    3) Pelvic lesions: Supine, hands on chest with knee immobilisation.
    4) Spine lesion: Supine with arms at sides and knee immobilisation.

- These factors should be discussed at SABR MDT when the patient is accepted for treatment and documented:
    - Patient position and immobilization as it is dependent on circumstances of patient and tumour site.
    - Whether abdominal compression or breath-hold is required. Ideally used in all upper GI disease, adrenal lesions and in lower lobe lung tumours.
    - Whether intravenous contrast should be considered. Ideally in all patients although some lung patients may not require.
    - Whether oral contrast is required to aid visualization of GI tract at planning and on treatment; and the timing to highlight different areas of the GI tract.
    - Whether a 4DCT is required. Always required in liver, pancreatic, adrenal, chest metastases. Suggested for abdominal lymph nodes. Helical scan should be taken in exhale for liver matching purposes where available.
    - Consider bladder filling; depending on site of treatment, it may be more appropriate to have full or empty bladder.
    - Consider enemas for e.g., mesorectal nodes.

7. Treatment Planning

7.1. Image Import and Registration

- Where required, appropriate diagnostic images (MRI / PET-CT / diagnostic CT) can be registered to the planning CT scan for use during delineation. Not useful when abdominal compression has been used due the different position of the patient.
- All registrations are to be reviewed prior to contour approval.
- If SABR reirradiation planned the initial planning scan with doses should be imported.

7.2. Volume Definitions

7.2.1. GTV

This will be defined by planning CT with information available from MRI / PET-CT / diagnostic CT as appropriate.

7.2.2. ITV

- This is required in all patients where a 4DCT has been considered to be required.
- This is the movement of the tumour throughout the 4DCT. If the metastasis cannot be seen on the 4DCT, this can be estimated by the motion of diaphragm or suitable surrogate structure.

7.2.3. CTV margin

- Liver metastases require a 5mm GTV to CTV margin.
- Vertebral CTV should be delineated using RTOG guidance [3] which is in keeping with UK SABR Consortium guidance.
- Sacral CTV can be delineated using international published guidance available [4] or as per non spine bones.
- Post-operative spines can be delineated following international consensus [5].
- Non-spine bones – based on consensus statement [9]. Two options (1) GTV based on MRI and CT, CTV = GTV + 3-5mm. (2) GTV based on CT alone, CTV = GTV + 5-10mm.
- Lymph nodes and lung metastasis do not usually require CTV, if this is added there should be documentation of the size and the reason.
- In soft tissue recurrence CTV margin may be appropriate depending on site.
- The CTV margin should be edited back from anatomical borders being careful to ensure it is edited back using 4DCT when appropriate, not just helical scan.

7.2.4. PTV margin

- This will depend on local kit and set up errors but an example of what is currently used in Oxford is given below:
    - For bony lesions a margin of 3mm is standard.
    - For soft tissue lesions a margin of 5mm is standard although with consideration at the SABR MDT can be reduced to 3mm in circumstances where movement is likely to be limited.
    - A symmetrical or asymmetric margin of up to 1cm can be used at the discretion of SABR MDT is cases where immobilisation is a significant challenge such as shoulders or changing bladder or rectal filling.
    - Slice thickness may affect the superior and inferior margin.

7.2.5. Organs at risk

- See section 4.4 for full list of OARs. Contour OARs as appropriate for treatment area. For contouring guidance of OARs, please consult green paper [6], appropriate RTOG atlas [7, 8] and/or UK SABR Consortium Guidelines.
- Nomenclature should be in keeping with green paper as above [6].
- Appropriate information from other imaging modalities should be used.

- OARs should be contoured ≥2cm superiorly and inferiorly to the PTV for coplanar techniques and within 15cm of the PTV if non-coplanar techniques are used.
- OARs should be contoured on primary dataset (Ave-IP in lung; helical in other areas). Where appropriate consider reviewing other images in the 4DCT dataset to inform the OAR e.g., when voluming brachial plexus on lung, please refer to helical scan; when voluming bowel in lymph node where it appears very far away and benefit is marginal, review Ave-IP to ensure it doesn't appear adjacent to target).
- For clinical sites other than vertebra, spinal canal may be used. For vertebral treatments, spinal cord should be contoured using T1 and T2 weighted MRI sequences. Please use local PRV protocol as needed. Cauda equina does not require PRV. Consider PRV for other organs as per local protocol, further discussion of PRV given in [6].

7.3. Dose and Prescribing

7.3.1. Dose

As per NHS England commissioning document, it is expected that one, three, five or eight fractions of SABR are used in the treatment of oligometastases. The dose and fractionation are dependent on the site of the oligometastatic disease and clinical scenario.

Indication	Dose (Gy)	Fractions	Dose per #	Schedule
Lung	18 or 26*	1	18 or 26	NAD
	54	3	18	Inter-fraction interval should be a minimum of 24 hours, keeping to alternate days where possible, with a maximum interval of ideally 4 days between fractions.
	55-60	5	11-12	
	60	8	7.5	
Adrenal	30-36	3	10-12	Daily or alternate days
	50-60	5	10-12	Alternate days
Liver	45	3	15	Alternate days
	50-60	5	10-12	Daily or alternate days
Spine	24-27 30-50	3 5	8-9 6-10	Alternate days
Bone	30-40 30-50	3 5	10-13.3 6-10	Alternate days
Lymph nodes	30-40	3	10-13.3	Alternate days
	50-60	5	10-12	Alternate days
Re-irradiation	30-45	5	6-9	Daily or alternate days

*18Gy single fraction for central tumours, 26Gy for peripheral tumours.

- Tumour control is maximised by lower number of fractionations. It is appropriate to consider higher fractionations in:
  - Weight-bearing bones [8].
  - Where the PTV abuts or involves chest wall, 5 fractions should be used [9].
  - Where the "no-fly zone" in the lung is penetrated by GTV, 8 fractions should be used [9].
  - In large targets.

- Where the target is adjacent to an OAR e.g., cases where PTV overlaps with GI tract. Suggest BED calculations to ascertain whether 3 fraction plan maintaining OAR constraints results in lower BED than 5 fraction plan maintaining OAR constraints.

- Target coverage: aim for PTV D95≥100% and D99>90%. It is expected that the PTV is covered by the 100% isodose and that this does not break up within the PTV. However, PTV coverage should be compromised where needed to remain within OAR tolerance at the physician's discretion.
- Maximum dose will be $D_{0.1cc}$ >110% and <130% of prescription and must be within PTV.

Modified Gradient Index requirements for non- lung sites

Vol(PTV) (cc)	Vol(50%) / PTV V100%		
	Target*	Tolerance*	Minor Dev*
<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

- Priorities:
  - OAR constraints should be given priority over PTV in most cases.
  - If clinically indicated it may be appropriate to prioritise PTV: clinician should document the order of priorities for planner (e.g., where lumbosacral plexus is already damaged by tumour, prioritise small bowel, then PTV, then lumbosacral plexus).
- If PTV is receiving <70% of the prescribed dose, consider whether a higher proportion can be treated with alternative fractionation, or a lower dose would be appropriate. If not, consider whether there is clinical benefit in treating.

7.3.2. Scheduling Issues

- If >1 lesion is to be treated, try to treat both on the same day due to capacity issues. There may be clinical scenarios where treatment of one lesion then a 6–8-week interval before treating the second lesion may be more appropriate e.g., concerns about pneumonitis if lesions in patient with poor lung function or bilateral adrenal lesions.
- If two lesions are being treated in the same organ, try to use the same fractionation as this will allow more accurate calculations of OAR constraints.
- If two lesions are being treated with the same isocentre, one treatment slot will suffice.
- If two lesions are being treated with different isocentre, ensure sufficient time on machine is booked for the two treatments.

7.4. OAR Limits

7.4.1. OAR constraints

For organ at risk constraints, please refer to the publication "UK 2022 Consensus on Normal Tissue Dose-Volume Constraints for Oligometastatic, Primary Lung and Hepatocellular Carcinoma Stereotactic Ablative Radiotherapy" [10].

7.4.2. OAR constraints in reirradiation

The optimum dose constraints in reirradiation are unknown because the percentage recovery for each organ and how time affects the recovery for each organ is unknown. It is therefore up to individual clinicians to weigh up the benefit risk ratio in each individual patient.

UK SABR Consortium Guidance recommends OAR constraints are maintained for the cumulative dose to OARs with recovery dependant on the number of months since initial treatment.

- For patients with 6 – 18 months from their previous XRT, a 30% recovery will be incorporated into the original dose delivered, when performing calculations for OAR constraints.
- For patients with >18 months from their previous XRT, a 50% recovery will be incorporated into the original dose delivered, when performing calculations for OAR constraints.

There are worked examples of how to calculate the cumulative OAR constraint in the UK SABR consortium guidance document.
An excel sheet will be made available for initial calculations using alpha-beta for each OAR is as follows: Small bowel – 3, Large bowel/Rectum – 3, Bladder – 3, Femoral Head – 3, Lumbosacral plexus - 2. Details on the previous max dose to each individual OAR from initial radiotherapy and the time since initial radiotherapy will be input. **This excel sheet is a guide and when determining constraints, it is not for clinical use. It remains the responsibility of each clinical team to recalculate a desired BED or EQD2 from the determined constraint per fraction and total dose.**

The calculation of constraints and the priorities for optimisation should be documented by the clinician for the planner as they will vary in each individual case.

7.5. Beam Arrangement / Treatment planning

Planning to be performed on primary data set, see section 6.1.

There is no standard beam arrangement. Use 6MV, 10MV, 6FFF 10FFF (and/or 15MV if conformal) coplanar or non-coplanar as required with the aim of minimising the path through OARs. Typically planned using VMAT however, hybrid VMAT, DCA and IMRT techniques can be used.

For liver plans, consider placing the isocentre such that the CBCT field-of-view encompasses the superior-most aspect of the liver in both max-exhale and max-inhale liver positions if possible.

Ideally place the isocentre(s) as centrally as possible to enable CBCT acquisition and reduce the risk of collision during treatment delivery.

Isodose matching / tolerance structure to be created if an OAR could potentially move on treatment is to be informed at SABR MDT or at planning. An isodose structure can be created from the isodose of concern and labelled as per local practise.

8. Quality Assurance and Approval Criteria

- This will vary in each individual centre.

9. Treatment Delivery

Patient set up as per local protocols. Replicate bladder volume, nil by mouth timings etc from CT planning. If oral contrast has been given at planning, ensure same volume of liquid is given at treatment to achieve similar filling.

Patient care on treatment

- Anti-emetics must be prescribed prophylactically before treatment commences if a large volume of stomach and/or duodenum is in the field. 5HT3 inhibitors are recommended.
- Patients whose PTV is close to the stomach/duodenum must be prescribed proton pump inhibitors (omeprazole or lansoprazole) unless there are any contraindications as GI ulceration is a recognised complication.

10. Treatment Verification

Daily CBCT or kV online imaging is required in all SABR patients, the type will depend on hardware available at each centre and the site being treated. 6DoF correction should be considered for spine treatments.
Matching structures should be agreed at the appropriate SABR MDT or /image review meeting as appropriate, prior to treatment and may be patient specific. Oral contrast should be considered where visualisation of the GI tract is required.
Matching priorities may include:

1) GTV if visible.
2) Bone if the target is in, close to or fixed to bony anatomy.
3) Clips if they are considered unlikely to move.
4) Contour of a normal organ e.g., dome of liver if lesion is superior liver, inferior border of liver if it is inferior.
5) OAR e.g., where a lung lesion is adjacent to the heart, match to heart border and assess GTV coverage.

An assessment of target coverage and OAR position should be performed.
If an OAR is abutting the GTV, then matching may need to be prioritised to this GTV/OAR edge to ensure dose to OAR is not exceeded. An isodose matching / OAR tolerance isodose structure may be useful.
SGRT, where available, should be used to guide initial patient setup and monitor intra-fraction motion.

11. Follow Up after Treatment

- This will vary in different centres, but patients should be reviewed 6-8 weeks after their treatment and tumour markers and imaging scheduled accordingly.
- Consider checking for late toxicity of treatment if symptoms dictate e.g., cortisol for adrenals, lung function for lung treatments, heart investigations etc.

Appendix 1: Abbreviations and acronyms

Abbreviation or acronym.	Definition
6 DoF	6 degrees of freedom e.g., Hexapod couch
BED	Biologically effective dose
CBCT	Cone beam computed tomography
CTV	Clinical target volume
DCA	Dynamic conformal arc
FFF	Flattening-filter free (high dose rate)
GTV	Gross target volume
Hybrid RA	Hybrid RapidArc
IGRT	Image guided radiotherapy
IMRT	Intensity modulated radiotherapy
ITV	Internal target volume
kV image	Kilo voltage image
MRI	Magnetic resonance imaging
OAR	Organ at risk
PET CT	Positron emission tomography-computed tomography
PRV	Planning organ at risk volume
PTV	Planning target volume
SABR	Stereotactic ablative body radiotherapy
VMAT	Volumetric modulated arc therapy

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