Stereotactic Ablative Body Radiation Therapy (SABR): A Resource

Version 6.1

Endorsed by

The Faculty of Clinical Oncology of The Royal College of Radiologists

This document is intended to provide guidance on the clinical implementation of stereotactic ablative body radiotherapy (SABR) across the range of indicated clinical sites. Since the knowledge, experience and expertise available, as well as the clinical and technical issues to be addressed, can vary considerably between different clinical sites, each site is addressed separately within the report with the aim being to establish minimum requirements for safe clinical implementation.

This document has been prepared by the membership of the UK SABR Consortium as detailed in Appendix D. The time required has been kindly provided by individuals and their employers with no financial reimbursement. There are no conflicts of interest declared. There has been no lay involvement in the preparation of these guidelines to date.

Stereotactic ablative body radiotherapy (SABR) refers to the precise irradiation of an image-defined extra-cranial lesion with the use of high radiation dose in a small number of fractions.

The report contains:

- An Introduction to Quality Assurance that may be used to inform discussions of SABR QA criteria. Specific criteria for individual clinical sites may also be established.
- Literature reviews of key SABR publications for a range of clinically-indicated sites.
- An overview of patient selection criteria for different clinical sites
- Examples from literature of radiotherapy dose/fractionation schedules and associated planning guidelines

Implementation of SABR is a team effort and requires that a clear clinical process be defined. It is essential that these suggestions be read in conjunction with published guidelines and other scholarly texts.

Disclaimer: This document is an information resource only. It does not constitute an instructional document for the carrying out of SABR, nor does it represent a legal standard of care. It is the responsibility of each treating team to ensure that they have received adequate and appropriate training and that their equipment is fit for purpose. Due to the varying technical equipment and systems available at radiotherapy centres it is advisable that each centre must determine the appropriate treatment selection and conduct of treatment for each of their patients and gain approval of their own institution's clinical governance body.

Version history

Version	Reason for amendment	Date approved
1.0	Establish guidance for Lung SBRT	2010
2.0	Update to guidance	2011
3.0	Restructure to accommodate guidance for sites other than peripheral lung	April 2012
4.0	Inclusion of guidance for prostate and liver SABR, rewording to allow alternative methods of treatment verification	January 2013
4.1	Inclusion of RCR endorsement, update to existing peripheral lung guidelines	April 2014
5.0	Inclusion of guidelines for spinal metastases	January 2015
5.1	Inclusion of guidance for adrenal SABR and combined OAR tolerance table in App.A	January 2016
6.1	Update to guidance. Inclusion of guidance for central lung, HCC, separation of generic technical sections	January 2019

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6. Treatment planning

7. Treatment verification

8. Lung cancer – Peripheral, Central and Ultra-central

9. Liver metastases

1. Quality assurance for SABR

1.1. Suggested Standards for SABR

Centres carrying out Stereotactic Ablative Radiotherapy (SABR) should adhere to the recommendations detailed in the NPSA report 'Towards Safety in Radiotherapy' [1]. In particular the staff involved need to be appropriately trained, competent and have the experience required. Local procedures need to be documented and there should be good multidisciplinary communication and team working. All procedures should be part of departmental QART procedures in accordance with ISO9001:2000 or similar. The linear accelerators used should be commissioned in line with IPEM report 94 'Acceptance Testing and Commissioning of Linear Accelerators' [2]. To ensure that the planning and treatment process is safe the appropriate recommendations in IPEM report 81 'Physics Aspects of Quality Control in Radiotherapy' 2nd edition [3], IPEM report 103 'Small Field MV Photon Dosimetry' [4] and IAEA 'Dosimetry of small static fields used in external beam radiotherapy' [5] should be adhered to. Additional guidance may be found in AAPM report TG66 'Quality Assurance for computed-tomography simulators and the computed-simulation process [6].

Standards for delivering SABR have been developed and are listed in Table 1.1. A list of publications specifically dealing with quality assurance related to CBCT and other issues relevant to SABR is provided at the end of this section [7-18].

QA should also be undertaken to ensure that appropriate patients for each particular SABR indication (i.e. meeting relevant inclusion/exclusion criteria) are being selected by meeting of the clinical oncology team. Contours and Radiotherapy plans should be reviewed by two clinicians to ensure that planning constraints are met as detailed in this protocol. It is the responsibility of the clinicians who agree to treat patients with such a regimen to follow these patients in order to document local control and toxicity. It is recommended that all patients for SABR in the UK should be asked to give consent for the anonymised data to be collected for use in audit and service development.

Table 1.1: Suggested Standards for SABR

Standard No.	Standard	Examples of evidence
A.1	Before commencement of SABR treatments the centre shall have carried out a number of planning studies and completed 'dummy-runs' of treatment planning and delivery (End-to-end testing). The results of these studies should be compared with those obtained by published data / another department experienced in the use of the same equipment and techniques to ensure that adequate plan quality and accuracy is being achieved.	Records of test cases and results of inter-comparisons with other departments.
A.2	Within 6 months of commencing SABR the centre should undergo an independent external audit of its SABR processes and in-house quality assurance. Such external audit would ideally take place within the context of a suitable clinical trial, but could also be arranged on an ad-hoc basis with another department which is delivering SABR. Participation in a national reference dosimetry programme is recommended	Records of an independent external audit.
A.3	Before commencing SABR treatments the centre should have assessed any relevant immobilisation devices, online image guidance technology and proposed method of respiratory compensation to ensure they are adequate to maintain patients well immobilised in a comfortable position, and that scans used for image-guidance are of sufficient quality to allow matching of the tumour or a suitable surrogate.	Staff training record for tumour matching, Record of tumour motion after using technique for respiratory motion compensation.
A.4	A full risk assessment of the SABR process should be completed and appropriate QA should be put in place to mitigate the identified risks.	Risk assessment
C.1	Tumour should be delineated on appropriate display settings.	Protocol documentation
C.2	Normal tissue structures should be delineated according to protocol, radiology input may be beneficial.	Protocol documentation
C.3	Target volume and dose reporting procedures should comply with departmental protocol and the UK guidelines for SABR.	Protocol documentation.

C.4	All patients receiving SABR shall have clinical follow-up for a minimum of 2 years, and ideally for at least 5 years. Full records must be kept of all late toxicity using CTCAE v4.0. Any local recurrences should be documented and fully investigated to determine if they represent in-field or marginal failures.	Follow-up records for a sample of patients
C.5	There shall be an electronic patient record for each SABR case consisting of planning images, structure sets, plan details, 3D dose-grids and on-set imaging data. Ideally these records should be stored in the form of DICOM-RT objects within an organisational PACS system.	Details of the electronic records system used.
M.1	Each department shall establish a SABR core multi-disciplinary team consisting of, as a minimum, a clinical oncologist, a therapy radiographer and a radiotherapy physicist who will each act as professional lead for the relevant components of the service. The team will consist of named individuals agreed by the Head of Service. The lead clinical oncologist will act as overall clinical lead for SABR and will be responsible for ensuring that the other standards are met.	Document agreed by the Head of Service with named individuals.
M.2	Implementation of SABR shall be part of an agreed service development within the organisational business plan to ensure adequate resources are made available. It is recommended that a minimum activity of 25 patients per year is required to maintain expertise. In applying this recommendation to rarer indications and complex SABR cases it is advised that these services are developed on a regional basis across networks.	Business plan agreed by Head of Service and senior management
M.3	There should be detailed documents defining consistent processes involved in selecting, outlining, planning, QA and delivering SABR and follow up of patients.	Process documents agreed by the Head of Service
M.4	There will be regular multi-disciplinary review of all SABR cases.	Minutes of review meetings
QA.1	Individual patient specific QA measurements must be made for at least the first 10 patients.	Records of patient QA
QA.2	There should be regular, documented reviews of both the risk assessment and QA, taking into account any relevant changes in	Records of risk assessment and QA reviews

	circumstances or clinical service.	
QA.3	There should be a documented procedure to be followed after software updates, upgrades or other significant changes to the SABR system. The procedure will detail the additional QA required.	Procedure agreed by the HoS.
QA.4	There should be documentation supporting the choice of QA tolerance values e.g. data from an initial period of measurements with the local QA kit	Documentation
QA.5	There should be sufficient machine-based delivery QA to support the chosen level of patient specific QA, especially if per patient QA is an independent calculation, and vice versa	Details of machine specific SABR QA procedures.
TE.1	Each member of the SABR core team must demonstrate appropriate specialist training in use of SABR. Such training could be attendance at an approved SABR course or visit to a centre established in delivering SABR to observe the various processes. Significant clinical experience in the application of advanced 3D conformal or intensity-modulated radiotherapy (as appropriate to local SABR process) and relevant image-guidance technology is recommended.	Records of attendance at suitable courses/sites CVs of core team members
TE.2	In addition to a broad knowledge and experience of advanced radiotherapy, members of the core team should have received detailed training relevant to the equipment that will be used within the centre.	Records of attendance at manufacturers approved training courses

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2. Patient positioning and immobilisation

2.1 Immobilisation considerations

Given the additional length of each treatment fraction, more consideration needs to be given to patient comfort, positional stability and the reproducibility of set-up. It is recommended that centres quantify and monitor the positional uncertainty associated with the reproducibility and stability of their chosen method of immobilisation.

Immobilisation equipment must interfere minimally with dose calculation and treatment delivery. Ideally, all immobilisation equipment will be compatible with pre-treatment imaging modalities to enable scanning in the treatment position.

Centres may consider using additional markers on the immobilisation equipment which are visible on different imaging modalities (e.g. oil capsules) which may reduce the risk of mis-registering images taken with a small field of view.

Consideration should be given to the immobilisation equipment's effect on skin dose, both in terms of increasing surface dose build-up through contact, and introducing or exacerbating skin folds within the treatment field.

2.2 Setup uncertainties

Systematic setup uncertainties of <3mm are achievable; however this should be evaluated locally and be factored into the treatment verification process.

Consideration should be given to immobilisation that is indexable to the treatment couch. Recommendations are:

- Abdominal targets; customisable vac bags, knee support and foot stock, arms out of field,
- Lower and mid thoracic (T5 and below) and all lung patients – wingboard, knee support and foot stock, vac bag optional
- Upper thoracic (~ above T4) – Immobilised with a 9 point cast and customised head/shoulder support, indexed knee support, arms down

Minimum standard: Centres should assess the accuracy of immobilisation device/s used for positioning patients for SABR, especially if changes are made to the equipment used. Systematic setup uncertainties should be within 5mm, preferably within 3mm.

3. Tumour motion

3.1 Assessing motion

Without mitigation, tumour motion can result in unnecessarily large target volumes (and correspondingly greater normal tissue irradiation), potential underdosing of the target, difficulties setting up the patient and reduced dosimetric accuracy. In cases where there is a large internal motion adjacent to the target (e.g. spine adjacent to the diaphragm), motion must also be accounted for.

The amplitude of respiratory motion may be assessed by kV fluoroscopy, [1] 4D-CT or cine-MRI [2]. For liver treatment, reports suggest that while the amplitude of breathing may be significant, the variability of respiratory amplitude is small [3].

Minimum standard: the motion of mobile tumours (or their surrogate) must be assessed for each patient, either through fluoroscopy or 4DCT.

3.2 Managing motion

There are several means of managing motion in published data:-

3.2.1 Reducing & controlling Motion:

3.2.1.1 Abdominal compression (AC):

Abdominal compression is shown to reduce liver motion, leaving small excursions (less than 10mm and in many cases less than 5mm) that are reproducible between cycles [4]. It is the most commonly used means of respiratory motion control in liver treatment in published series. AC is also shown to reduce inter- and intra-fractional changes in liver position relative to bony anatomy [1], however this should be verified with soft tissue matching where possible. Use of AC for other abdominal sites should be considered.

3.2.1.2 Active Breathing Control (ABC):

This technique is a means of active respiratory gating and uses forced breath hold during radiation delivery. A disadvantage is that it requires a breath-hold of 20-35 seconds, and experience of some centres has suggested that one third to one half of patients are unable to manage this technique [5]. However, set-up errors can be reduced to less than 5mm (cranio-caudal) using ABC with image guidance for liver [6,7].

3.2.1.3 Coached respiration;

This technique uses a visual display to feedback to patients the speed and amplitude of their breathing. With coaching, patients can voluntarily breath hold, or better control the amplitude and rhythm of their breathing.

3.2.2 Mitigating motion:

3.2.2.1 Passive respiratory gating:

This technique allows patients to breathe freely and co-ordinates the delivery of radiotherapy to the tumour during that part of the respiratory cycle when the tumour is within the treatment beam. The phase of respiration around the end of expiration is often chosen as this is the phase when the tumour is, on average, expected to spend most time, but this needs to be determined for each patient. It has the advantage of being better tolerated, but requires additional time, equipment and therefore additional training and expense. However, its use has been shown to allow significant margin reduction and escalation of tumour dose for the same level of normal tissue toxicity [5].

3.2.2.2 *Tracking motion:*

Tumour tracking with or without of implanted fiducial markers is shown to be feasible for different treatment sites especially lung, prostate and liver.

There is existing clinical experience with RF-transponders such as Calypso for prostate cancer [8,9,10,11] which demonstrates that unpredictable intra-fraction prostate motion of considerable amplitude is both detectable and correctable.

There is some emerging data from limited clinical studies that have investigated the use of intra-fraction tumour monitoring and correction using implantable radio-opaque fiducial markers for prostate cancer [12]. However, this is complex as it necessitates automated real-time marker detection software and the marker(s) may be shielded behind MLCs during IMRT / VMAT delivery. Despite this some groups have proven feasibility [13,14,15,16] but is not in routine clinical use at this time.

CyberKnife (Accuray Inc.) is the only clinical device that is in routine use for tracking mobile targets with semi-predictory modelling. This uses radio-opaque fiducial surrogates for pelvic, abdominal and lung targets. Tracking lung tumours directly using their contrast to surrounding low density lung tissue is also possible. Tracking mobile targets using CyberKnife allows for reduction in systematic and random components of set up error to <2mm end-to-end.

3.2.3 Planning with motion unrestrained:

A further means of managing respiratory motion is to plan radiotherapy simply allowing for the target motion within an ITV, usually informed by a 4DCT scan. This may be appropriate if other means of motion management cannot be applied or the tumour amplitude is <10mm for lung or <5mm for liver/abdominal sites.

3.3 Fiducial markers

If targets are not distinguishable on imaging for motion assessment on treatment, implantable fiducial markers should be considered but have the disadvantage of being invasive [17], requiring radiology time for insertion of the markers, potential for longer treatment time due to tracking and potential for marker migration [12,16]. Further, any oedema caused by the marker insertion should be allowed to resolve prior to acquiring planning scans, the standard recommendation is to leave 7-10

days between insertion and planning CT. Systems which combine on-set soft tissue imaging with fiducial tracking throughout treatment delivery get closer to the optimal solution; evaluation and evidence for their use is being gathered.

If a surrogate marker is used as a proxy of tumour position, it is highly recommended that the target-surrogacy is tested and quantified in at least the pre-treatment setting.

For mobile targets, where the amplitude and mean position of the target is critical to accurate treatment delivery, it is highly recommended that there exists a system for assessing target (or surrogate, if appropriate) motion at treatment and correlating that motion with the pre-treatment imaging and dosimetric plan.

Minimum standard: a means of quantifying respiratory motion for individual patients in the pre-treatment and treatment setting must be available. For any observed respiratory motion of amplitude >10mm for lung or >5mm for liver or abdominal sites, attempts should be made to reduce, control or mitigate this.

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4. Pre-treatment imaging

4.1 CT

Patients undergo a planning CT scan in the treatment position within the chosen immobilization device. The extent of the scan must be sufficient to include all potential organs at risk, especially when non-coplanar beams are used. Where OAR constraints are based on the dose received by a whole organ (e.g. lung, liver, kidney), the whole organ should be included in the scan.

4.1.1 CT technical standards

CT scans should have high resolution; in-plane voxel size preferably ≤1mm, although ≤1.4mm is acceptable where a larger field of view is required (in this instance consideration should be given to retrospectively reconstructing the CT at a smaller field of view as a co-registered study to improve the in-plane resolution). Slice thickness generally should be ≤3mm, with consideration given to higher resolutions for spine (≤2mm recommended) and when fiducial markers are used to reduce the uncertainty in their sup-inf position. Finer slice thickness will allow for more precise contouring of target volumes and will improve DRR resolution, reducing uncertainty if verifying patient position against planar images (e.g. Exactrac, linac kV, Cyberknife), however attention should be paid to contrast-to-noise ratio if the reconstructed CT slice thickness is <2.5mm. There appears to be little benefit to the accuracy of CBCT on treatment verification imaging when reducing slice thickness below 2-3mm [1].

4.1.2 Contrast CT

Contrast CT should be used for liver (dynamic contrast CT in exhale breath hold, capturing venous phase of contrast enhancement) and adrenal sites (exhale breath hold). There is no recommendation for contrast to be used generally for lung, spine or prostate, however this is at the clinician's discretion.

Centres should be aware of the change in Hounsfield Units caused by contrast and assess the effect this has on the accuracy of dose calculation and patient setup if DRRs are used based on a contrast CT dataset.

4.1.3 4DCT

Accounting for the full range of tumour motion and the movement of surrounding OARs is essential, and therefore the use of 4DCT for clinical sites subject to respiratory motion (e.g. lung, liver, adrenal, mediastinal nodes etc.) is highly recommended. It may be necessary to combine a 4DCT with a 3D scan if scan length in 4D is an issue.

4.2 MRI

The use of MRI is recommended and ideally should be performed with the patient in the treatment position. If this is not possible, consideration should be given to optimise the patient set up in the region of the disease to enable rigid image co-registration to a usable level of accuracy.

Appropriate QA should be carried out, to ensure geometric accuracy of the MR images.

MRI is strongly recommended for liver and adrenal sites, as contrast-enhanced CT alone often underestimates tumour volume in colorectal metastases [2] and other primary sites [3].

Attempts should be made to reduce the effects of motion over the lengthy MRI acquisition times for mobile targets. This can be achieved by a variety of means depending on the scanner and potential sequences. Options are: proactive respiratory triggering, retrospective binning, or breath-hold (if the patient is able to). It is recommended that the same respiratory phase is acquired as the primary planning CT phase.

MRI provides higher lesion-to-liver contrast and allows superior lesion detection and characterisation [4]. Use of MRI (plain T1W or T2W sequences) merged with CT to delineate tumour increases the CTV, potentially including tumour cell congregations missed using CT-based volume definition [2,3]. Retrospectively observed differences in mean tumour volume as defined on CT and MRI are significantly higher in patients showing local tumour failure ($p=0.002$) [2]. The suggestion from this is that MRI may result in better tumour delineation and therefore, better local control.

MRI is highly recommended for bone (including spine) lesions, the extent of which are sometimes difficult to assess by CT alone. For spine, Transaxial T1(weighted)+Gad and T2(weighted) should be regarded as essential scans, T1+Gad may also be useful and consideration could also be given to T2 transaxial and sagittal scans. T1_pre-Gad is unlikely to be useful.

The use of MRI for prostate SABR is recommended for contouring the prostate as a whole [5]. It is required for the PACE trial and is necessary if a focal boost is to be attempted (e.g. PIVOTAL boost trial). The use of MRI (together with other factors) will affect the CTV to PTV margin used (see target outlining section).

4.3 PET

PET has an important role in staging patients being considered for SABR though its role in tumour delineation during radiotherapy planning has not yet been validated. FDG-PET is shown to increase the volume of CTV delineated when merged with CT and also MRI, in treating colorectal liver metastases. When compared to CT-defined CTV, incomplete dose coverage of additional PET-positive tumour regions are associated with local progression [6]. PET is observed to be particularly useful in accurately determining GTV in previously treated liver tumours, where it is able to more accurately delineate active tumour from scar tissue [7]. PET scanning should ideally be done with the patient in the treatment position.

As with MRI, special consideration should be given to the blurring effect of mobile PET-avid lesions, acquired over many respiratory cycles. Additional consideration should be given to the specific-uptake-value window/levels or thresholding if using the PET data to define the periphery of the lesion. If possible 4DCT PET should be considered.

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4.4 Table 4.1 Summary of pre-treatment imaging recommendations for specific clinical sites

	Lung	Liver	Adrenal	Prostate	Spine
Un-enhanced 3D planning CT	Exhale breath-hold if tolerated , additional assessment of motion is necessary (e.g. using 4DCT or fluoroscopy)	-	-	**Free-breathe or expire breath-hold recommended slice thickness <3mm**	**Recommended slice thickness <2mm.**
3D planning Contrast CT	-	**Exhale breath hold, acquired in venous phase for GTV delineation**	**Exhale breath hold for GTV delineation, include lung and kidneys**	-	-
4DCT	**Recommended MIP or individual phases for contouring tumour, AVIP or representative phase contouring OARs and for dose calculation**	**Recommended for assessing tumour motion**	Recommended for assessing tumour motion.	-	Recommended if treating around level of the diaphragm
MRI		Strongly recommended T1W or T2W, transaxial and sagittal (or 3D isotropic sequences with <2mm resolution	Recommended T1W or T2W, transaxial and sagittal (or 3D isotropic sequences with <2mm resolution	**T1W+Gad, T2W transaxial and sagittal (or 3D isotropic sequences with <2mm resolution**	**T1W+Gad, T2W transaxial and sagittal (or 3D isotropic sequences with ~1mm resolution.** Diffusion MRI can be useful for visualising the lesions
PET	FDG-PET with 4DCT in the treatment planning position (where possible). PET(3D)CT can be used to assist target delineation.	Consider FDG-PET	Not validated, but if chosen, do on same day as CT and in treatment position	-	-

Minimum standards highlighted in bold. Additional scans are at clinician's discretion.

5. OAR Outlining

5.1 OAR outlining standards and descriptions

In general, any OARs which are traversed by a treatment beam should be contoured. Where OAR constraints are based on the dose received by a whole organ (e.g. lung, liver, kidney), the whole organ should be contoured. Otherwise, a volume of OAR should be outlined, sufficient to show that the OAR constraints have been met, with particular care paid to the volume receiving the highest doses.

Appropriate CT windowing or 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.

The body contour should also be contoured wherever the beams traverse it. The skin should be inspected to ensure that beams do not overlap, producing excessive skin dose, especially where there is a skin fold.

5.1.1 Spinal cord/Spinal canal

For clinical sites other than spine, a contour based on the bony limits of the spinal canal, ≥2cm superior and inferior of the PTV, will sufficiently allow for a conservative estimate of spinal cord dose.

For spine treatments, contouring the spinal canal may result in the unnecessary compromise of the target volume, and a contour based on the true cord should be used. Spinal cord should be contoured using the fused T1 and T2 weighted MR scans (plus CT myelogram where appropriate) and should extend to at least 1 vertebra superior and inferior to the PTV. On the level of the cauda equina, the thecal sac should be considered to represent the relevant OAR.

The required margin for PRV expansion will be dependent on local processes and should be carefully established and audited. In cases where good image quality allows confident co-registration and delineation, an isotropic margin around the spinal cord of 2-3mm may be appropriate in creating the spinal cord PRV. However, if image quality is compromised, it is recommended the larger volume of the thecal sac be used at the discretion of the treating clinician.

5.1.2 Brachial Plexus

The defined ipsilateral brachial plexus originates from the spinal nerves exiting the neural foramina on the involved side from around C5 to T2. However, for the purposes of this guide only the major trunks of the brachial plexus will be contoured using the subclavian and axillary vessels as a surrogate for identifying the location of the brachial plexus. This neurovascular complex will

be contoured starting proximally at the bifurcation of the brachiocephalic trunk into the jugular/subclavian veins (or carotid/subclavian arteries), and following along the route of the subclavian vein to the axillary vein ending after the neurovascular structures cross the 2nd rib. Use of contrast at CT may assist with outlining.

5.1.3 Oesophagus

The oesophagus will be contoured using mediastinal windowing on CT to correspond to the mucosal, submucosa, and all muscular layers out to the fatty adventitia.

5.1.4 Heart

The heart will be contoured along with the pericardial sac. The superior aspect (or base) for purposes of contouring is defined as the superior aspect of pulmonary artery (as seen in a coronal reconstruction of the CT scan) and extended inferiorly to the apex of the heart.

5.1.5 Trachea and proximal bronchial tree

The trachea and bronchial tree can be contoured either as a single structure or as two separate structures using lung windows. For this purpose, the trachea can be divided into two sections: the proximal trachea and the distal 2 cm of trachea. The proximal trachea will be contoured as one structure, and the distal 2 cm of trachea will be included in the structure identified as proximal bronchial tree. Differentiating these structures in this fashion will facilitate the eligibility requirement for excluding patients with tumours within 2 cm of the proximal bronchial tree.

5.1.6 Proximal trachea

Contours should begin 10cm superior to superior extent of PTV or 5cm superior to the carina (whichever is the more superior) and continue inferiorly to the superior aspect of the proximal bronchial tree.

5.1.7 Proximal bronchial tree

This will include the most inferior distal 2cm of trachea and the proximal airways on both sides as indicated in diagram 1. The following airways will be included: distal 2cm trachea, carina, right and left mainstem bronchi, right and left upper lobe bronchi, the bronchus intermedius, right middle lobe bronchus, lingular bronchus, and the right and left lower lobe bronchi. Contouring of the lobar bronchi will end immediately at the site of a segmental bifurcation.

5.1.8 Great Vessels

The great vessels (aorta and vena cava, not the pulmonary artery or vein) will be contoured using mediastinal window to correspond to the vascular wall and all muscular layers out to the fatty adventitia. The great vessel should be contoured at least 10 cm above and below the extent of the PTV. For right

sided lesions, the vena cava will be contoured, and for left sided lesions, the aorta will be contoured.

5.1.9 Whole lung

Both lungs should be contoured from apex to base as one structure using pulmonary windows. All inflated and collapsed lung should be included. For lung patients, GTV and trachea/ipsilateral bronchus as defined above should not be included. OAR constraints are based on lungs-minus-GTV.

5.1.10 Chest wall (for peripheral lesions)

The chest wall will be defined as the 3 cm rind of the ipsilateral hemi-thorax outside the lungs and contoured at least 5 cm superiorly and inferiorly to the PTV.

5.1.11 Liver

The whole liver should be outlined, excluding the gall bladder and hepatic vessels. For liver patients, normal liver should be taken as “whole liver” minus the GTV. Care should be taken not to inadvertently include the liver vasculature and/or gall bladder.

5.1.12 Common bile duct (CBD) and bifurcations

These ducts should be identified as tubular structures (lumen density equivalent to water). The expected location of the bile ducts is, the CHD (common hepatic duct) is anterior to the portal vein, lateral to the hepatic artery, and surrounded by fat in the porta hepatis, and the CBD was within or adjacent to the parenchyma of the pancreatic head. If there is uncertainty on the location, the portal vein can be contoured from the splenic confluence to the first bifurcation of the left and right portal

5.1.13 Skin

Defined as a 3-5 mm inner rind of body contour contoured if adjacent to PTV and in regions receiving more than 10Gy.

5.1.14 Kidneys

The entirety of each kidney should be outlined separately to allow evaluation of individual kidney dose. A summation of the two volumes should also be created to evaluate total kidney dose.

5.1.15 Stomach

The stomach should be contoured from gastro-oesophageal junction to duodenum using mediastinal windowing.

5.1.16 Duodenum

The duodenum will be contoured to include the mucosal bowel wall and contents.

5.1.17 Bowel

The use of a single bowel bag is an alternative to outlining individual loops of bowel which may move. Extra care should be taken when outlining the bowel nearest the target if this method is used.

5.1.18 Ureter

The ureter will be contoured as a solid structure from the renal pelvis down to the insertion into the bladder wall. The delineation limit is the outer wall of the ureter.

5.1.19 Bladder

The whole bladder will be contoured to include the bladder wall and lumen.

5.1.20 Lumbo-Sacral Plexus

At the L4 and L5 levels, the entire respective foramina will be contoured. The L4 root will be contoured by including the space defined by the psoas muscle anterior and laterally, and the facet joint/posterior vertebral body elements posteriorly. The L5 root will be contoured using the common iliac vein and psoas muscle anteriorly, the iliacus muscle laterally, and vertebral body and sacrum posteriorly. Below the level of the L5 foramen, the sacro-iliac joint should serve as the lateral border as well. Beginning at the level of the S1 foramen, the lumbo-sacral plexus (L4/L5) and S1 lie in the area bounded by the iliac vessels anteriorly, the iliacus muscle / sacro-iliac joint laterally, the sacral ala posteriorly, and medial margin of the S1 foramen medially. Beginning at the level of origin of the pyriformis muscle, the lumbo-sacral plexus will be contoured in the space bounded by the iliac vessels anteriorly, iliacus muscle / iliac wing laterally and pyriformis muscle posteriorly. At the lower margin of the greater sciatic foramen, the space bounded by the obturator internus muscle / ischial spine anteriorly, pyriformis muscle laterally and gluteus maximus muscle posteriorly will be contoured. The medial portion of the obturator internus muscle will serve as the medial extent. Below the pyriformis muscle, the space between the obturator internus muscle anteriorly and the gluteus maximus muscle posteriorly will be contoured. The medial and lateral extent should be 1 to 2 cm in length. Contouring will end at the level of the superior portion of the femoral neck.

5.1.21 Femoral heads

Femoral heads will be contoured from their most cranial aspect to the bottom of the curvature of the femoral head (i.e. exclude the femoral neck).

5.2 Use of PRVs

Consideration should be given to expanding serial OARs to Planning Risk Volumes (PRVs) to account for uncertainties in setup (both translational and rotational), delineation, inter-fractional anatomical changes, etc. As with PTV expansion margins, the magnitude of these margins should be appropriate to local practice and use of enhanced immobilisation, robotic couch or real-time tracking should be considered.

The position of OARs with respect to the tracked target (or appropriate surrogate) can vary, and therefore should be geometrically accounted for in the OAR PRV. It may well be larger than the PTV margin for highly mobile OARs such as bowel.

The concept that mobile OARs will be at different positions at each treatment fraction, and the received dose will therefore "average out" is only applicable to hyperfractionated treatments and is not compatible with SABR.

The careful choice of beam angles (for CyberKnife), arc entry and exit angles or avoidance sectors (for VMAT delivery) and their effect on plan robustness in the presence of mobile OARS or organs such as the diaphragm is highly recommended.

Minimum standard: OARs should be contoured ≥2cm superiorly and inferiorly to the PTV for coplanar techniques and up to 15cm of the PTV if non-coplanar techniques are used. Sufficient OARs should be contoured to show that the OAR constraints have been met; this may require the entire organ to be outlined. Careful consideration should be given to the magnitude of PRVs based on local data on set up uncertainties and per organ in the presence of anatomical changes with respiratory motion etc.

6. Treatment planning

6.1 Treatment modalities

VMAT, IMRT or modalities such as Cyberknife are all acceptable for delivering SABR treatments. The effect of immobilisation equipment and patient's limbs outside the FOV of the planning CT and CBCT must be considered.

6.2 Algorithms and dose calculation

Type B or Monte Carlo algorithms are mandatory for lung patients and preferred for all other indications. Dose grid resolution on the final dose calculation must be ≤2mm.

TPS settings need to be optimised for SABR plans and should be verified by measurement or audit. Notably:

- Calculation resolution for arc treatments. Some investigations into dosimetric errors produced by the Pinnacle TPS when calculating highly modulated plans showed the angular resolution of dose calculation for arcs to be significant (2 degree calculations significantly more accurate than 4 degree calculations).This should be verified locally.

- Dose grid resolution differences for OAR dose reporting. Unpublished data (provided by Clatterbridge Cancer Centre) showed that there are differences in the cord and cord PRV doses calculated when using 2.5mm and 1.0mm dose grid resolutions in Eclipse: in a sample of 5 patients, cord $D_{0.1cc}$ were 6.2 ± 2.1 (1 S.D) % lower and cord PRV (2mm margin) $D_{0.1cc}$ were 1.9 ± 4.4 (1 S.D) % lower with the 1.0mm dose grid resolution. This effect should be verified at each centre and compared with QA results to establish the most appropriate dose grid resolution.

- Small field or segment accuracy of the treatment planning system algorithm data. SABR plans generally treat small targets with a higher degree of modulation than standard treatments. This may result in treatment fields where a higher proportion of dose is delivered through smaller apertures than the beam model was originally commissioned for. Individual centres should satisfy themselves of the veracity of their small-field dosimetry. Evidence from national audits for the link between plan modulation and dosimetric accuracy is varied, with some audits reporting a correlation [1] and others not [2]. Single centre studies have shown reducing plan modulation does not significantly decrease plan quality, but can improve dosimetry verification results [3].

- Awareness of the radiation beam modulation limits. Different planning systems achieve the necessary beam modulation in different ways; biasing the burden on the linac differently [4].Care should be taken when changing planning systems that QA and commissioning methods are reviewed.

6.3 Metal-work and Density overrides

Particularly for spine, where metalwork is present the Hounsfield Unit conversion table must extend sufficiently high to accurately account for heterogeneity. The use of beam entry avoidance sections and appropriate density overrides should be considered where necessary.

Titanium implanted in a water equivalent material, when irradiated with a single 4MV beam (similar energy to Varian 6FFF) creates an 'upstream' ~20% increase in dose due to increased backscatter and 'downstream' ~10% decrease in dose due to frontscatter.[5]. The effect reduces to below 10% within 1mm and 5% within 2-3mm from the titanium surface. Some averaging-out will occur with full-arc VMAT treatments, with a net effect of increasing the dose to the material surrounding the titanium implants. Some implants may be screwed into surgical cement, which may limit the clinical significance of the dosimetric effect.

Exogenous IV Contrast within planning CT scans should be accounted for either by density overrides, or (for specific sites) work may be done to show contrast has a negligible effect on dosimetric accuracy.

6.4 Beam energies and dose rates

In general, the use of FFF beams is encouraged to minimise treatment time and the consequent risk of patient intra-fraction movement [6]. The UK SABR Consortium Lung Dosimetry Audit [7] found no difference between the dosimetric accuracy of flattened and unflattened beams, however the audit was conducted in a static phantom and included only a few centres using FFF. Local validation of dosimetry (and plan quality) is required when changing energy.

6.5 Planning structures

Some centres have found that ring structures around the PTV are useful to improve the conformity of the plan at all dose levels. Structures within the PTV may also be useful to ensure there are no cold spots at the centre of the target, which can occur when the dose gradient outside the target is over weighted during optimisation.

6.6 Prescribing and dose normalisation

In general, the dose distribution should be normalised so that 95% of the target volume (PTV or PTV_Prescribe where appropriate) receives at least 100% of the quoted prescription dose (e.g. 54Gy/3#).

For lung, 99% of the target volume should receive a minimum of 90% of the prescription dose.

6.7 Evaluation of plan quality

Particularly for non-coplanar techniques, the dose distribution as a whole should be evaluated to check that dose to normal tissues far from the target (limbs, skin folds etc.) is acceptable. Medium (~50% of prescription) isodose lines should exhibit a fairly isotropic distribution relative to the target volume, unless deliberately skewed to avoid dose to a particular OAR. If medium level isodoses extend away from the target, ensure that variation in patient setup or movement of OARs would not cause the OAR dose to exceed the constraints.

6.7.1 Evaluation of dose conformity

Good conformity of the prescription isodose to the target volume and a steep dose gradient surrounding the target volume are the hall-marks of SABR planning. Dose conformity levels from the ROSEL study [8] have been useful in evaluating lung plan quality by giving "tolerance" and "minor deviation" values for the R100% and R50% metrics.

Data from 147 patients reviewed in the SABR CtE QA programme indicated that the ROSEL "tolerance" and "minor deviation" levels for R100% are appropriate for both lung and non-lung sites (compared to the median +1S.D. and median +2S.D. of the CtE data). However, the R50% ROSEL levels are set too high for small volume targets, to usefully indicate that a plan has not been optimally planned and to ensure consistency between centres. The CtE data and others [9] also showed that plan quality metric values used by RTOG 0813 [10] are also unsuitable for use in evaluating dose conformity.

The SABR CtE QA data showed that for non-lung oligometastatic sites, approximately a quarter (16/68) of patients would have compromised target coverage (prescription dose covering <90% of PTV). The R100% and R50% metrics lose sensitivity to detect poor conformity with decreasing PTV coverage, so modified metrics are suggested and reported:

$$R100\% = \frac{Vol\ (100\%)}{Vol\ (PTV)} \quad \Rightarrow \quad Prescription\ dose\ spillage = \frac{Vol\ (100\%)}{PTV\ V100\%}$$

$$R50\% = \frac{Vol\ (50\%)}{Vol\ (PTV)} \quad \Rightarrow \quad Modified\ Gradient\ Index = \frac{Vol\ (50\%)}{PTV\ V100\%}$$

Where: "Vol(100%)" and "Vol(50%)" are the volumes of the patient receiving at least 100% and at least 50% of the prescription dose respectively and "PTV V100%" is the volume of PTV receiving at least 100% of the prescription dose. When PTV coverage is 100%, "PTV V100%" will equal "Vol (PTV) and each pair of metrics becomes equivalent.

Table 6.1. Prescription dose spillage requirements for lung and non-lung sites

Vol(PTV) (cc)	Vol(100%) / PTV V100%		
	Target	Tolerance	Minor Dev
<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

Table 6.2. Modified Gradient Index and other requirements for lung sites

Vol(PTV) (cc)	Vol(50%) / PTV V100%			Lung-GTV V20 (%)	Max dose >2cm	
					3 fractions	5-8 fractions
	Target	Tolerance	Minor Dev	Tolerance	Tolerance	Minor deviation
<20	7*	9*	9 – 11*	<5	<35.1Gy	<35.8Gy
20-40	5.5*	6.5*	6.5 - 7.5*	<6	<37.8Gy	<38.5Gy
40-60	5*	6*	6 – 7*	<10	<37.8Gy	<38.5Gy
60-90	4**	5	5 – 7	<10	<37.8Gy	<38.5Gy
>90	4**	4.5	4.5 – 6.5	<10	<37.8Gy	<38.5Gy

Table 6.3. 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

*Tables 6.1 – 6.3. Dose conformity levels for single lung and non-lung targets. "Target" values are based on the median data recorded in the SABR CtE QA Programme. Tolerance and Minor Deviation levels are from the ROSEL Study unless updated with values based on the median +1 S.D. and median +2 S.D. from the SABR CtE QA Programme (indicated by *), or based on literature reports **[11]*

"Target" values should be achievable for roughly half of all patient plans. It should be noted that the levels presented above are based on what has been found to be achievable in SABR planning and are therefore relevant for consistency and quality of planning. The levels are not related to clinical outcomes; comparing the planned dose with the published OAR constraints should be used for this purpose.

Many other conformity indices have been proposed [12], mostly without suggested values of what may be practically achievable. Other, more complicated methods for evaluating the optimality of the dose distribution have also been proposed [13], however the necessary data is not readily available from commercial treatment planning systems. Scripting and coding

modules within modern treatment planning systems may enable these measures to be more widely utilised in the future.

Anecdotal evidence suggests that lower lung density (<0.2 g/cc) limits the dose fall-off achievable around the target in lung plans.

6.7.2 Evaluation of target dose inhomogeneity

The maximum dose within the target volume should be between 110 to 140% of the prescription dose. Collated lung and non-lung plans from the SABR CtE QA programme indicated that there was a benefit to dose conformity by planning with greater dose inhomogeneity (130-140%), particularly for smaller volumes (<40cc). In larger volumes targets (>40cc) there was no correlation between dose inhomogeneity and dose conformity, however individual cases when re-planned with greater dose inhomogeneity may benefit.

When treating bone, the benefit of higher dose inhomogeneity should be balanced with the risk of compromising the mechanical properties of the bone, such as restricting the maximum dose (1cc volume) to 120-130% of the prescribed dose. (Clinical data shows a vertebral compression fracture rate of 23% following 20-23Gy/1#, 8.5% following 24Gy/2# treatment, but insufficient data for a 3# constraint [14], so caution is advised). The accuracy of the algorithm used for dose calculation within bone should also be considered.

Minimum standards: plans must be evaluated and meet at least the tolerance levels in the tables 6.1-6.3 in order to indicate good quality, beyond achieving acceptable target coverage and meeting OAR constraints.

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7. Treatment verification

7.1 Uncertainties and baseline shifts

Departments planning to introduce SABR are encouraged to make an assessment of likely set up uncertainties according to the particular immobilisation equipment used. With pre-treatment image guidance and correction, many centres report sub-3mm accuracy. Image guidance is vital for SABR treatment verification as patients often require a positional correction prior treatment [1].

Base-line shifts are changes in the relative position of the tumour and other anatomy compared to the planning images. Set up errors can arise from base-line shifts relative to the bony anatomy if the bony structures are used as a matching surrogate for soft tissue tumours. Base-line shifts between the tumour and normal tissues may introduce a difference between the planned and actual doses received by OARs. Imaging protocols should clear whether soft or bony anatomy will be used for matching and be sufficiently thorough to allow both types of base-line shift to be quantified and compensated for. This data should be used to help inform PTV and PRV margins.

7.2 Imaging and tolerances

Tolerances and associated action levels for on-line correction protocols should be established before deciding PTV and PRV expansion margins. The use of a robotic couch to correct both translations and rotations can allow reduction of such tolerances.

Regardless of treatment delivery platform, SABR treatments must be image guided prior to each fraction using on-line imaging and real time assessment. The required translational and rotational setup errors should be quantified and any anatomical or positional changes should be identified at the treatment verification stage. The common IGRT methods include using 2D planar kV imaging (with or without fiducial markers), 3D kV cone beam CT (CBCT), MVCT, and a combined approach of using both fiducial markers with CBCT. For soft tissue indications, CBCT should be used as the gold standard. This should include 4D-CBCT for moving tumours.

It is suggested that centres verify patient setup before and (optionally) during treatment using a procedure that can validate the position of the tumour relative to the patient anatomy for online image matching and correction. Anatomical changes should be observed throughout the course of treatment and centres should develop site-specific decision making protocols to determine the actions to take – both from clinical and dosimetric perspectives [2].

Consideration of the treatment time for each fraction should be made, and where possible, flattening filter free (FFF) modalities should be investigated to reduce the treatment time. This should reduce the intra-fraction variability and

improve patient comfort. For linac-based SABR delivery, longer treatment times (>34 minutes) are shown to increase intra-fractional variability [3] although this magnitude is significantly less than inter-fractional baseline shift. Changes in mean tumour position during the delivery of a treatment fraction can be assessed by (e.g.) cone beam CT (CBCT) before and after delivery of a fraction of SABR.

It is suggested that individual centres develop experience in online lung imaging/registration prior to commencing SABR. The patient should have an initial image acquisition, followed by image registration and online correction using an appropriate action level.. For linac SABR, further imaging intra-fractionally should be performed if there are concerns that the patient has moved during the treatment. If 4D-CT data has been used at the planning stage, 4D-CBCT should ideally be acquired at 1# (or using a day 0 appointment) and checked prior to treatment to ensure tumour movement has not changed [4]. The use of 4D-CBCT at all treatment fractions is recommended for lower lobe tumours and should be considered for other sites. For gated lung SABR treatments, 4D-CBCT should be used at each fraction to ensure that the tumour motion remains consistent with the planning 4D-CT and the associated gated window. Where real-time fiducial tracking is available, the effects of intra-fractional motion are directly accounted for.

Minimum standard: All patients must be treated according to an established, comprehensive IGRT process including online image guidance. Anatomical changes should be observed throughout the course of treatment and centres should develop site-specific decision making protocols to determine the actions.

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8. Lung cancer - Peripheral, Central and Ultra-central

8.1. Introduction and literature review

8.1.1 Early Stage Lung Cancer Patient Population

Lung cancer is responsible for 1 in 7 new cases of cancer and is responsible for 22% of all cancer deaths [1,2]. Approximately 80% of these patients have non-small cell lung cancer (NSCLC), of whom about 20% have early-stage disease (AJCC Stage I, TNM Stage T1-2N0M0) which is associated with the best chance of cure. Unfortunately, as lung cancer is more common in elderly patients and smokers, who have a higher incidence of medical co-morbidity, surgery may be regarded as too risky. Such patients are termed 'medically inoperable'. Some other patients may be inoperable for technical reasons, or decline surgery of their own volition. An effective, non-surgical treatment is needed for all of these scenarios as without treatment the prognosis is poor. Furthermore, population-based data supports increased active treatment resulting in improved outcomes [3].

8.1.2 Conventional Standard of Care

The time-honoured gold standard for the treatment of Stage I lung cancer is surgical resection. This is associated with five-year overall survival rates in the range of 60-70% [4]. For those patients who are not operable or who decline surgery, external beam radiation therapy (RT) is an alternative treatment approach. It is difficult to accurately compare survival rates in patients treated with surgery (resulting in accurate pathological staging) or radiation therapy (when patients may be under-staged by clinical investigations). However, long-term survival rates with radiation therapy alone (5 year survival 10-30%), seem to be about half of those seen in surgical series [5]. The 2001 Cochrane review suggested that local recurrence rates in medically inoperable patients treated with external beam radiation therapy ranged from 6-70% [5]. Even with a dose of 84 Gy administered in 1.8-2.0 Gy fractions over 8 weeks a third of patients may recur locally [6]. Furthermore, attempts to escalate the radiation dose beyond this, to 90 Gy or more, in standard fractionation, have been associated with unacceptable toxicity in some series [7]. Therefore, the UK has focused on accelerated radiotherapy schedules with meta-analysis demonstrating improvement in outcome when compared to conventional fractionations [8]. However, results reported for patients with stage I NSCLC, median survivals of 33 months for stage 1A and 25 months for stage 1B [9] suggest other radiotherapy approaches need to be explored.

8.1.3 SABR and the Importance of Lesion Location within the Thorax

With improvements in radiation technology, a number of groups began to investigate the use of hypofractionated stereotactic ablative body radiotherapy (SABR) for lung tumours, both primary NSCLC and metastatic carcinomas.

A large retrospective analysis of Japanese patients supported dose and fractionation regimens that delivered a BED of > 100Gy [10]. These were associated with a 5–year overall survival of approximately 70% in medically operable patients. In 2003 Timmerman published a phase I dose escalation study which confirmed 3 x 20 Gy as a safe dose for T1-2 peripheral lung tumours. Local failures were seen below a median dose of 3 x 12 Gy [11,12].

The subsequent phase II study by Timmerman et al was the first to report high toxicity after SABR to centrally located lesions with doses of 60-66 Gy in 3 fractions without heterogeneity correction (equivalent to 54 Gy in 3 fractions with heterogeneity correction, BED $\alpha/\beta 10$ = 151 Gy, BED $\alpha/\beta 3$ = 378 Gy) in 2006 [6]. The analysis of peripheral compared central tumours showed that the 2-year incidence of grade ≥ 3 toxicity was 17% and 46% respectively. The risk of developing grade 3–5 toxicity in patients with central tumours was 11-fold that of patients with peripheral tumours. Six patients out of 70 died, likely from treatment-related causes. Grade 5 events that occurred in 5 patients were respiratory: 1 fatal haemoptysis, which was associated with a local recurrence and 4 infectious pneumonias; a sixth patient died of complications from a pericardial effusion. These deaths occurred after a median of 10.4 months following SABR (range 1-20 months).

Another high-profile paper alerting the international community about the toxicity of SABR for central tumours is a case report published in 2012 by the University of Pennsylvania reporting on fatal central airway necrosis 8 months after SABR (50 Gy in 5 fractions) for a central lung lesion [13].

Such reports highlighted the importance of location of the tumour within the thorax and associated toxicity with SABR. The major difference between peripherally and centrally located NSCLC is the spatial relationship to critical organs as risk (OARs).

For peripherally located tumours, the pulmonary tissue around the target is the only relevant critical OAR and is well-known to show parallel organ radiobiological behaviour, associated with the safe delivery of SABR treatments in peripheral tumours [4,5]. The function of parallel organs (e.g. lung, bone marrow) is not severely compromised if only a small sub volume is exposed to high dose radiation. In contrast, severe damage to a sub-volume of serial organs will lead to the loss of function of the whole organ. In the context of SABR to centrally located tumours, several serial OARs need to be considered including main bronchi, trachea, blood vessels, oesophagus, spinal cord, brachial plexus and the heart. With the alpha/beta (α/β) ratio of these serial structures being low, dose escalated hypo-fractionated irradiation to centrally located tumours can lead to severe toxicity.

8.1.4 Defining central and ultra-central tumours

The Timmerman phase II study published the initial guidance on defining 'central' versus 'peripheral' tumour location [6] (Figure 8.1). The proximal bronchial tree (PBT) includes the following: the carina, right and left main bronchi, right and left upper lobe bronchi, intermedius bronchus, right middle lobe bronchus, lingular bronchus and right and left lower lobe bronchi.

Since then, there has been additional appreciation of the importance of centrally placed OARs other than the proximal bronchial tree, including the oesophagus, great vessels and heart. The RTOG 0813 study protocol from 2008 included a broader definition of 'central' lesions, including lesions within 2 cm around the proximal bronchial tree and lesions immediately adjacent to mediastinal or pericardial pleura (specifying any PTV rather than GTV touching the pleura). A similar definition has also been used as an exclusion criterion for the CHISEL trial comparing SABR to conventional radiotherapy for 'peripheral' lesions [14] and in the EORTC LungTech trial of SABR for 'central lesions' [15].

The recently published IASLC recommended definition of 'central' lesions is more cautious, including all lesions within 2 cm of the proximal bronchial tree and mediastinal and pericardial pleura and brachial plexus [10] (Figure 8.2). There has also been more recent recognition that the tumours of highest risk with SABR are those located 'ultra-centrally'. There are several different definitions of 'ultra-central' in the literature, including the one given below (Figure 8.3).

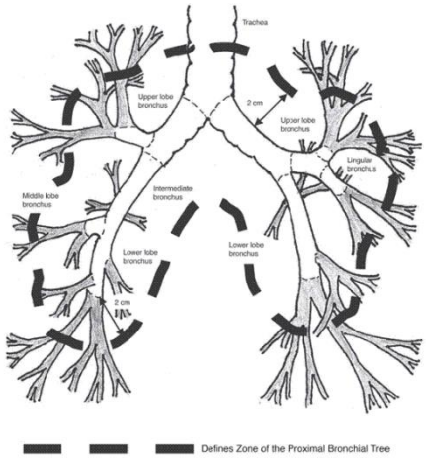

Figure 8.1: Timmerman 'central' zone definition: Any GTV within the 2 cm zone surrounding the proximal bronchial tree (PBT) [6].

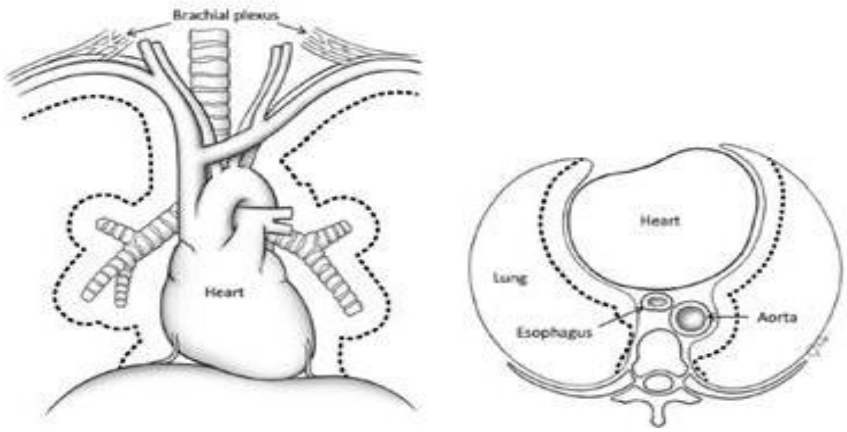

Figure 8.2: IASLC 'central' zone definition: Any GTV within the 2 cm zone around bronchial tree, major vessels, heart, oesophagus, spinal cord, phrenic & recurrent laryngeal nerve, brachial plexus [10].

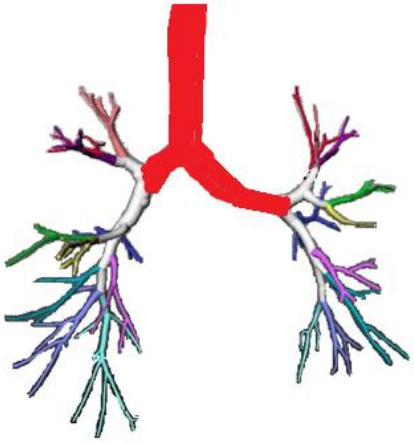

Figure 8.3: Nordic HILUS trial 'ultra-central' zone definition: Any GTV ≤1 cm from the proximal bronchial tree overlapping the trachea or main bronchi [16].

8.1.5 SABR for Peripheral Primary Lung Tumours

RTOG 0236 was a multicentre phase II study following on from the dose escalation study for patients with tumours more than 2 cm from the PBT. 55 (44 T1 and 11 T2 tumours) patients received 3 x 18 Gy, and when the 3-year results were reported disease free and overall survival were 48.3% and 55.8% respectively. The rates of acute toxicity were acceptable, with 2 (3.6%) grade 4 and 7 (13%) grade 3 pulmonary/upper respiratory adverse events reported as related to protocol treatment [17,18]. The long-term results have been published in abstract form with rates of disease free and overall survival at 5 years of 26% and 40%, respectively with a median overall survival of 4 years[19]. Late failures were observed particularly in the involved (untreated) residual lobe; however, an excess of late-appearing toxicity was not.

The body of evidence supporting the use of SABR for early stage peripherally located NSCLC has grown steadily over the last 15 years and has recently been reviewed by Murray et al [20]. The studies are heterogeneous with

varying dose/fractionation schedules but include outcomes for 4570 patients treated with SABR. Overall local control rates were excellent at 1 year (92.7% (64.7-100)), 2 years (89.9% (77.4-98.5)), 3 years (86.7% (40-97.6)), and 4-5 years (89.6% (83-95)) with corresponding overall survival rates of 87% (78-100), 82.9% (48-96), 59.6% (32-95) and 39.6% (17-83) with a mean follow-up of 29.4 months. In a large retrospective series Stahl et al have provided further evidence (in abstract form) for the effect of biologically effective dose on overall survival [21]. In a series of 747 patients after adjusting for confounding variables, BED_{10} ≥105 Gy versus <105 Gy remained significantly associated with improved OS (hazard ratio 0.78, 95% confidence interval 0.62-0.98, P = 0.03). Patients receiving ≥105 Gy BED_{10} had a median survival of 28 months compared with 22 months in those receiving BED_{10} <105 Gy.

As the population ages so the incidence of lung cancer is increasing and often these patients have multiple medical co-morbidities precluding surgical resection or may decline surgery. Several recent studies have reviewed the efficacy and toxicity of SABR in elderly populations reporting favourable outcomes [22,23,24,25]. In the largest of these Giuliani et al reviewed 1083 patients treated with SABR for early stage lung cancer across 5 centres [24]. Of these 305 patients were aged <70 years (28%), 448 aged 70 to 79 years (41%), and 330 aged ≥80 years (30%). They reported no difference in 2-year local recurrence (4.2% vs 5.4% vs 3.7%, respectively, P = 0.7), regional recurrence (10.4% vs 7.8% vs 5.3%, P = 0.1), distant metastases (12.2% vs 7.7% vs 9.5%, P = 0.2), or cause-specific survival (90.6% vs 90.3% vs 90.4%, P = 0.6) though those aged ≥80 years had significantly lower 2-year OS. Treatment was well tolerated with no difference observed in grade 3+ pneumonitis rates or 90-day mortality between the 3 age groups. Furthermore, Klement et al have evaluated factors which may predict early (within 6 months) death following SABR to identify a sub-group of medically inoperable patients who may not benefit from SABR [26].

The following variables were used to build the probability model; age, sex, Eastern Cooperative Oncology Group performance status, operability, forced expiratory volume in 1 second, and Charlson comorbidity index. The predictive performance of their model was too low for clinical application and at present SABR should be considered for all medically inoperable patients with peripheral tumours irrespective of their comorbidities.

8.1.6 SABR vs Surgery for Peripheral Primary Lung Tumours

An important question is whether SABR has comparable outcomes to surgery for early stage NSCLC. The ROSEL and STARS studies were designed to attempt to answer this but unfortunately, closed early due to slow accrual. A pooled analysis of these 2 trials in the intention-to-treat population using overall survival as the primary endpoint was published by Chang et al in 2015 [[27]]. Fifty-eight patients were randomised between surgery (27) and SABR (31). Estimated overall survival at 3 years was 95% (95% CI 85–100) in the SABR group compared with 79% (64–97) in the surgery group (hazard ratio [HR] 0·14 [95% CI 0·017–1·190], log-rank p=0·037). Recurrence-free survival

at 3 years was 86% (95% CI 74–100) in the SABR group and 80% (65–97) in the surgery group (HR 0·69 [95% CI 0·21–2·29], log-rank p=0·54). Although these results are encouraging and are used to support clinical equipoise between the treatment modalities, caution should be applied in interpretation due to the failure of either trial to complete accrual and the small numbers in each arm. Further randomised data are needed to definitively answer this question.

At present patients with standard operative risk and stage I NSCLC, SABR is not recommended as an alternative to surgery outside of a clinical trial (ASTRO/ASCO guidelines 2017 [28]). For patients with high operative risk stage I NSCLC, discussions about SABR as an alternative to surgery are encouraged within the multidisciplinary team [28]. For patients with early-stage peripheral lung tumours with contraindications to surgery, SABR is considered as the standard of care.

8.1.7 SABR vs Conventional Radiotherapy for Peripheral Primary Lung Tumours

There is considerable non-randomised evidence supporting SABR as superior to conventional RT with respect to local control. In addition, Dutch population data suggests that the availability of SABR has reduced the number of elderly patients with early NSCLC who are not offered potentially curative treatment with a documented improvement in survival across the population [29,30].

More recently, 2 randomised trials have reported outcomes of patients randomised between SABR and conventional fractioned radiotherapy. In the phase 2 SPACE trial 102 patients with stage I medically inoperable NSCLC were randomized to receive SABR (66 Gy in 3 fractions over one week prescribed to the 100% isodose) or 3DCRT (70 Gy over 7 weeks) [31]. The median follow-up was 37 months with a 1, 2 and 3-year PFS of: SABR: 76%, 53%, 42% and 3DCRT: 87%, 54% 42%, HR = 0.85 (95% CI 0.52–1.36) with no difference between the groups and no difference in OS (HR = 0.75, 95% CI 0.43–1.30). A trend towards an improved disease control rate was observed in the SABR group. Patients treated with SABR experienced better health-related quality of life and less toxicity (pneumonitis (any grade) 19% (SABR) vs 34% (3DCRT, p = 0.26), and oesophagitis 8% vs 30% (p = 0.006)).

The CHISEL trial has been reported in abstract form. This phase III trial randomised 101 patients with biopsy proven NSCLC who were medically inoperable or declined surgery to SABR (54 Gy in 3 fractions, or 48 Gy in 4 fractions), or conventional fractionated radiotherapy (66 Gy in 33 fractions or 50 Gy in 20 fractions) in a 2:1 ratio [14]. Patients randomized to SABR had superior freedom from local failure (HR = 0.29, 95% CI 0.130, 0.662, P = 0.002) and longer overall survival (HR = 0.51, 95% CI 0.51, 0.911, P = 0.020). Grade 4 toxicity was experienced by 1 patient (SABR arm) and grade 3 toxicity 11 patients (2 CRT, 9 SABR). This is the first randomised trial to demonstrate a survival benefit for SABR over alternative treatments though the full peer reviewed publication is awaited.

8.1.8 Fatigue, Lung, Chest Wall Toxicity and HRQOL following SABR for Peripheral Lesions

SABR for early stage peripheral lung cancer is generally a well-tolerated treatment and toxicity has been well documented and reviewed in the literature [20]. Grade 1-2 toxicity, particularly fatigue is very common though tends to be self-limiting. In 30 studies reporting toxicity outcomes grade 3-4 toxicity (pneumonitis, dyspnoea, chest pain and pneumonia) occurred in 2.7 - 27% of patients and was also often self-limiting. Treatment-related grade 5 toxicity is rare in treatment of peripherally located tumours.

Chronic obstructive pulmonary disease (COPD) is present in 50-70% of people with lung cancer at the time of diagnosis [30], and therefore potentially represents a risk of significant toxicity from SABR. The safety and outcomes of SABR in patients with severe COPD was reported in a systematic review by Palma et al [30] in 2011, finding a 30-day surgical mortality of 10% but 0% 30-day mortality following SABR. They also found that survival at 1 and 3 years were comparable between the 2 treatments. In a more recent analysis of the RTOG 0236 study baseline pulmonary function tests were not predictive of any pulmonary toxicity following SABR and poor baseline pulmonary function tests did not predict decreased overall survival [32].

Pneumonitis, both radiological and symptomatic (≥ grade 2) is observed following both conventionally fractionated and SABR to the lung. In a recent pooled analysis of 88 studies by Zhao et al [33] rates of ≥ grade 2 and ≥ grade 3 radiation induced lung toxicity were 9.1% (95% CI 7.15-11.4) and 1.8% (95% CI 1.3-2.5), respectively. Among the factors analysed, older patient age and larger tumour size were significantly correlated with higher rates of lung toxicity. Among studies that provided detailed dosimetric data, the pooled analysis demonstrated a significantly higher mean lung dose (P = 0.027) and V_{20} (P = 0.019) in patients with ≥ grade 2 toxicity than in those with grade 0 to 1. Reports of dosimetric factors which predict pneumonitis are varied within the literature and some studies found no association [32,34,35,36].

Although rates of clinically significant lung toxicity following SABR are low there is growing evidence that patients with underlying lung fibrosis at baseline are at increased risk [37]. Bahig et al reported that pre-existing radiological interstitial lung disease (ILD) was identified in 6% of 504 patients treated with SABR for Stage 1 lung cancer [38]. A 4% rate of ≥ grade 3 radiation pneumonitis was observed in the entire cohort. ILD was associated with increased risk of ≥ grade 3 radiation pneumonitis (32% in patients with ILD vs 2% in those with no ILD, P <0 .001). Five patients (21%) with ILD developed grade 5 radiation pneumonitis. Although several factors were predictive of ≥ grade 3 pneumonitis on univariate analysis, only FEV1 remained predictive on multivariate analysis.

In a further series of 71 primary or metastatic lung tumours, subclinical ILD was the only factor significantly associated with the occurrence of radiation pneumonitis ≥ grade 2 ($p < 0.001$). 2 patients with grade 5 radiation pneumonitis had ILD with honeycombing visible on imaging [39]. Pre-existing

ILD was retrospectively identified in 20 of 157 patients treated with SABR in a Japanese series reported by Ueki et al. The incidence of ≥ grade 2 or ≥ 3 pneumonitis was significantly higher in those with ILD than those without (55% vs 13.3% and 10% vs 1.5% respectively). On multivariate analysis the presence of ILD and volume of irradiated lung was as risk factor for ≥ grade 2 or ≥ 3 pneumonitis. Despite no difference being observed in the disease progression or local progression rates, the overall survival rate tended to be worse in patients with ILD than without (3-year OS, 53.8% versus 70.8%; p = 0.28).[40]

Although SABR may be used for peripherally located early lung cancers in patients with underlying ILD, patients must be appropriately counselled regarding the potential risks including fulminant pneumonitis which may be fatal. In addition, patients with subclinical ILD should be carefully monitored for the occurrence of severe radiation pneumonitis after SABR.

Chest wall toxicity from SABR may include rib fractures or pain. Chest wall pain is reported in approximately 10% of patients with grade 3 toxicity in about 2.0% [20] and a median time to onset of ≥ 6 months following treatment. Multiple studies have demonstrated a correlation between treatment factors and the incidence of chest wall toxicity with an increase in dose and treatment volume the most consistent radiation factors reportedly associated with toxicity [41,42,43]. An increased likelihood of developing side effects has also been correlated with patient factors such as body mass index, female gender, tumour location, and age.

In an elderly patient population with multiple co-morbidities, treatment toxicity and quality of life need to be balanced against potential benefits of disease control. Lagerwaard et al prospectively collected HRQOL data in 382 consecutive patients receiving a SABR dose of 60Gy in 3, 5 or 8 fractions with a resultant median survival of 40 months and 2-year survival of 66% [44]. They found that patients referred for SABR have substantially worse baseline HRQOL than those reported in surgical series; however clinically relevant deteriorations in HRQOL scores were not observed after SABR. In a review of 9 SABR series with HRQOL data, few clinically significant changes in patient-reported HRQOL scores were reported after SABR [45]. Clinically and statistically significant deteriorations in fatigue and dyspnoea were individually reported in 2 studies, but these findings were not replicated by other studies.

8.1.9 SABR for Central Primary Lung Tumours: Retrospective data

Several authors have reported retrospective studies showing favourable outcomes with regards to local control and toxicity for patients with central tumours treated with SABR as summarised below. However, the retrospective nature of these studies is associated with a few major flaws. Firstly, there is no certainty that the patients have been treated as described in the paper due to the lack of quality assurance and quality checks. Secondly, patients are not always followed up in the treating centre, with regular and rigorous assessment including imaging to assess response, toxicity and patterns of

relapse. This can lead to the underestimation of relapse rates and treatment-related toxicities. This issue is of concern in the context of SABR as toxicity could be higher than currently recognized because of competing risks of death in these patients (comorbid conditions and progressive disease). Thirdly, many of the published retrospective studies only included a short follow-up which again can lead to the underestimation of late toxicities. Severe side effects can indeed continue to appear 1 to 2 years after treatment. Furthermore, most of these retrospective studies come from single centres which are generally assumed to have more bias.

One of the most favourable clinical results with SABR for central lung tumours has been published by the VU University Medical Centre group with the dose-adapted 60 Gy in 8 fraction regimen prescribed at the 80% PTV encompassing isodose (BED α/β10 = 105 Gy, BED α/β3 = 210 Gy) [46]. This is consistent with the consideration that toxicity related to normal tissues with a low α/β ratio may be lower with more fractionated regimens. They reported 63 patients with centrally located tumours (37 patients with central hilar location and 26 patients with tumours abutting the pericardium or mediastinal structures). With a median follow up of 35 months, the local control rate at 3 years was 93%. No grade 4 or 5 toxicities were reported, and no dose volume-constraints were provided or suggested.

The MD Anderson group reported outcome and proposed OAR constraints for central lesions in 2008. The SABR regimen was 40–50 Gy in four fractions on consecutive days [47]. When 50 Gy in four fractions was delivered (BED α/β10 = 112.5 Gy, BED α/β3 = 258 Gy), the local control rate at 2 years was 100% and no fatal toxicity was reported. In contrast, 40 Gy in four fractions was associated with poor local control (57%) and one patient who had received 40 Gy to the brachial plexus experienced severe brachial plexus neuropathy. This regimen was therefore abandoned. An updated report in 2014 describing the use of SABR with 50 Gy in four fractions for 100 patients with tumours near the bronchial tree, other critical mediastinal structures and brachial plexus, showed that median survival time (58 months) and local control rates (96% at 2 years) were comparable to those for peripheral lesions treated with SABR to 50 Gy in four fractions [48]. The incidence and severity of radiation pneumonitis and chest wall pain were also similar; no grade 4 or 5 toxicities were reported. Patients in whom these dose-volume constraints could not be met were treated with 70 Gy in 10 fractions (BED α/β10 = 119 Gy, BED α/β3 = 233 Gy), which led to similar local control with tolerable toxicity [49]. This 70 Gy in 10 fractionation reduced late chest wall and brachial plexus toxicity, but it was not clear if it also minimized acute radiation pneumonitis and oesophagitis. It should be noted that a patient with a tumour invading the hilum treated with 70 Gy in 10 fractions (hilar Dmax = 83 Gy) developed fatal haemoptysis, which led to the recommendation that tumours that invade central structures should not be treated with high-BED schedules.

The Stanford group also reported low toxicity rates in patients with peripheral (n=34), central (n=34) and ultra-central lung tumours (n=7) treated with 50 Gy in 4–5 fractions [50]. With a median follow-up time of 18.4 months, 2-year

overall survival and local failure was similar in all 3 groups. Reported toxicity rates were low and comparable between the three groups, with only two cases of grade 3 toxicity (chest wall pain), and one case of grade 4 toxicity (pneumonitis) observed. There were no symptomatic toxicities reported in treated patients with ultra-central tumours.

Xia et al reported using 70 Gy in 10 fractions prescribed to the gross tumour volume (GTV) (BED α/β10 = 119 Gy, BED α/β3 = 233 Gy) and achieved a local control rate of 93% at 3 years [51]. No grade 3 or higher toxicity was reported for either central or peripheral lesions.

Investigators at the William Beaumont Hospital compared clinical outcomes for 125 patients treated with doses ranging from 48 to 60 Gy in four to five fractions (BED α/β10 = 100–132 Gy, BED α/β3 = 240–300 Gy) for central versus peripheral lesions using propensity-matched analysis [52]. No significant differences were found in overall survival or severe toxicity.

However not all retrospective series report reassuring rates of acute and late toxicity. The Memorial Sloan Kettering group reported on 108 patients treated with SABR (mostly 45 Gy in five fractions (α/β10 = 85.5 Gy, BED α/β3 = 180 Gy); the local control rate at 2 years was 79% [18]. However, severe oesophageal toxicity, including fistula in a patient with an oesophageal Dmax of 46 Gy, was reported. Six of 12 patients for whom the median oesophageal Dmax was 30 Gy developed grade ≥ 2 oesophagitis when the PTV overlapped the oesophagus. Two patients developed fatal haemoptysis, one with tumour involving the hilum and a maximum dose to the right bronchial tree of 47 Gy in five fractions, and the other with tumour encasing the left superior segmental bronchus with a maximum bronchial tree dose of 48 Gy in five fractions. Others have reported with similar doses (40–60 Gy in five fractions) fatal haemoptysis when a Dmax of greater than 50 Gy was delivered to the pulmonary artery and bronchus [53,54]. The Cleveland Clinic group also reported a case of oesophageal fistula when the oesophageal point dose exceeded 51 Gy and the V48 was >1 cm^3 [54].

The VU University Medical Centre group has recently reported on clinical outcomes of 47 patients with single primary or recurrent ultra-central NSCLC treated with SABR (60 Gy in 12 fractions over 3 weeks) [55]. They defined ultra-central lung tumours as planning target volumes overlapping the trachea or main bronchi. At a median follow-up of 29.3 months, median overall survival was 15.9 months, and 3-year survival was 20.1%. No isolated local recurrences were observed. Grade 3 or higher toxicities were recorded in 38% of patients, with 10 patients (21%) assessed as having a “possible” or “likely” treatment-related death. Importantly Grade 5 fatal pulmonary haemorrhage was observed in 15% of patients.

In a further paper, the same group modelled the normal tissue complication probability (NTCP) of pulmonary toxicity after SABR and hypo-fractionated radiotherapy for central lung tumours (≤12 fractions at two centres) [56]. A total of 585 bronchial structures were studied in 195 patients who were mainly treated using 5 or 8 fractions. Clinical grade 3 or higher toxicity was observed

in 24 patients (12%), and radiographic bronchial toxicity in 55 patients (28%). On multivariate analyses, significant predictors for grade 3 or higher toxicity were a planning target volume overlapping the trachea or main stem bronchus (p = 0.005), COPD (p = 0.034), and the oesophageal total $V_{130Gy,EQD}$ (p = 0.012).

8.1.10 SABR for Central Primary Lung Tumours: Prospective data

In contrast to most of the retrospective studies showing the safety of the administration of SABR regimens for centrally located tumours, prospective studies have reported severe toxicity such as bronchial stenosis, fatal haemoptysis, and central fistula after SABR to central tumours when ablative doses were delivered to critical structures. The Timmerman study, which was the first to raise the issue of toxicity after lung SABR for central tumours, was summarised above [6]. Additionally, Bral et al reported grade 5 toxicity in 1 out of 17 patients with central tumours after treatment with 60 Gy in 4 fractions [57].

The phase II Nordic HILUS trial included 42 patients with tumours close to a main stem bronchus (group A), and 31 patients with tumours close to a lobar bronchus (group B) [58]. Patients were treated with 60 Gy in 8 fractions prescribed to the 65-70% isodose line. Dose limits were mandatory for the spinal cord, trachea and contralateral main bronchus (Dmax, EQD = 89 Gy). However, dose guidelines to the ipsilateral main stem bronchus were recommended but not mandated (Dmax, EQD = 112 Gy). Severe toxicity of grade 3 or higher was reported in 28% of patients, and grade 4 and 5 toxicity occurred in 19% of patients in group A and 3% in group B. Six out of the 7 grade 5 events were due to fatal lung haemorrhage. PTV overlap with main stem bronchus or trachea was found to be significantly correlated with both grade 3 or higher clinical toxicity and high grade radiographic toxicity. A PTV overlap was present in 33% of all patients, and in 70% of patients who developed grade 3 or higher pulmonary bleeding.

A dose escalation Phase I/II study in small central NSCLC lesions was also recently reported by RTOG [59]. The dose was escalated from 50 Gy to 60 Gy, in five fractions delivered every other day (except over weekends), with at least 40 hours between treatments. Preliminary results reported that with a follow-up of 33 months, grade 3 or higher toxicity was 16% in the 5x11.5 Gy group and 21% in the 5x12 Gy group. Moreover, grade 5 pulmonary bleeding occurred in 4%, with three out of four patients being treated in the highest dose groups of 11.5 and 12 Gy per fraction. No optimal fractionation schedule has been assigned yet. This trial permitted a maximum point dose of 105% for the main bronchi, corresponding to a Dmax, EQD of ±197 Gy for a regimen with 5 fractions of 12 Gy. No data on the outcome of patients with central compared to ultra-central locations are available.

8.1.11 SABR for Central Primary Lung Tumours: The need for clinical trials

Given the contradictory and controversial data on SABR to central lesions in the literature, there are important unresolved issues which need to be addressed with prospective studies including:

- Multicentre assessment of efficacy and safety of SABR in centrally located tumours.
- Standardization of dose description and calculation in centrally located tumours.
- Definition of the patient population who might benefit from SABR (e.g. co-morbidity, tumour size).
- Establishing clinically validated dose / volume / topography data on normal tissue toxicity.

NTCP modelling in these trials will eventually provide us with the urgently needed dose constraints for central OARs. However, anticipated caveats are the limited number of severe events reported thus far, making a NTCP model less robust as in general a high number of events and multi-institutional data will build the best model.

In addition to the RTOG 0813 and the Nordic Hilus trials described above, which are only available in abstract form, the EORTC LungTech trial NTC01795521 has recently closed to recruitment and will be reporting shortly. These phase II trials investigated the safety of SABR for central tumours and other relevant trails that are recruiting include SUNSET (***NCT03306680)*** and a phase II randomized clinical trial comparing proton versus photon-based SABR for centrally located or recurrent lung parenchymal early stage NSCLC is currently ongoing (NCT01511081) [60].

8.2. Patient selection criteria

Inclusion Criteria

- MDT diagnosis of NSCLC based on findings of positive histology or a positive PET scan when predictive models (e.g. Herder, Brock) indicate a > 70% risk of malignancy (Callister et al BTS guidelines [61]).
- Clinical stages of T1 N0 M0 or T2 (≤5cm) N0 M0 or a subset of T3 (by virtue of chest wall invasion only) (≤5 cm)
- Not suitable for surgery because of medical co-morbidity, lesion is technically inoperable or patient declines surgery after surgical assessment (or option of assessment)
- WHO performance status 0-2
- Peripheral lesions, defined as outside the IASLC 'central' zone. (figure 8.2)
- Age ≥ 18 years

Exclusion Criteria

- Any tumour that is not clinically definable on the treatment planning CT scan e.g. surrounded by consolidation or atelectasis.
- Previous radiotherapy within the planned treatment volume
- Pregnant or lactating females
- Inability to obtain informed consent or comply with treatment requirements

Relative Contra-Indications

- Target motion due to respiration ≥ 1cm despite using techniques to reduce tumour motion
- Presence of pulmonary fibrosis (consider and consent for the increased risk of significant toxicity)

8.3 Radiotherapy for lung cancer

8.3.1 Tumour delineation

Gross Tumour Volume (GTV) is defined as the radiologically visible tumour in the lung, contoured using lung settings using information from all staging investigations including the PET-CT (ideally acquired within 4 weeks of planning scan). Mediastinal windows may be suitable for defining tumours proximal to the chest wall or mediastinum.

Motion adapted GTV is the tumour volume obtained using a 4DCT scan. This is defined as tumour contoured using either the (i) maximum intensity projection scan, (ii) maximum inspiratory and expiratory scans or (iii) as contoured on all 10 phases of a 4DCT scan.

Clinical Target Volume (CTV) is the motion adapted GTV with no margin for microscopic disease extension.

8.3.2 Recommendations for Dose Fractionation Schedules

For **peripherally located lesions**, there is strong evidence that SABR is superior to conventional radiotherapy for efficacy and safety with substantial clinical benefit. The two recommended dose fractionation schedules are:

- Schedule for PTV not abutting chest wall: 18 Gy x 3 fractions
- Schedule for PTV abutting or overlapping chest wall: 12 Gy x 5 fractions or 11 Gy x 5 fractions

It is recommended that this is an alternate day treatment however a minimum of 24 hours is required between fractions, with a maximum interval of ideally 4 days between fractions [62].

For **centrally located tumours (Figure 8.2, not invading central structures and not ultra-centrally located tumours),** there is limited evidence for efficacy compared to more conventional fractionation. There is also limited evidence that the benefit outweighs the risk compared to more conventional fractionation. Therefore, caution should be taken when using SABR in this patient population and decisions should be made on an individual patient basis. If SABR is being used, the recommended schedule is:

- Schedule for motion adapted GTV abutting or within central zone but outside ultra-central zone: 7.5 Gy x 8 fractions

For **ultra-centrally located lesions (Figure 8.3, motion adapted GTV within 1cm of proximal bronchial tree) and tumours invading central structures** (e.g. Large blood vessels, oesophagus, trachea) SABR treatment is not recommended outside of clinical trials. CHART, conventional or moderately hypo-fractionated (55 in 20 or 66 Gy in 24 fractions) have been used safely in locally advanced NSCLC therefore should be safe in early stage ultra-centrally located NSCLC.

Individual centres may choose to prescribe dose fractionation regimes other than those suggested above, however they must ensure that the BED is less than the highest dose recommended for the tumour location in these guidelines, and that all the appropriate OAR tolerances are met.

8.3.3 Treatment assessments & Follow Up

We recommend using the CTCAE v 4.0 (available from the link below) for assessing toxicity during and after RT.

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Following lung SABR we suggest that the first follow up should be at 4-6 weeks post radiotherapy to assess acute toxicity. Patients should have a repeat chest x-ray at each follow up visit. Subsequent follow up visits should be of the order of 3 monthly for the 1st year, and 6 monthly for subsequent years. Consideration should be given to collecting quality of life data if possible. First post treatment CT scan should be done at 3-4months and then repeated at least every 3-12 months depending on circumstances. Due attention must be given to the difficulty that can arise in differentiating local recurrence from tumour progression in certain scenarios [63]. In addition, a greater awareness of the potential for certain toxicities (e.g. chest wall/rib) is required [64,65,66]. If feasible full lung function tests should be considered annually. Response may be documented using the RECIST criteria (Appendix B). Ideally, patients should be followed for a minimum of five years.

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9. Liver metastases

The following guidelines are compiled purely as guidance in delivering SABR to liver metastases. It is the responsibility of each department to ensure adequate processes and training for all staff groups.

9.1. Introduction and literature review

The liver is a common site for metastases, especially from carcinomas of the lung, breast and colon [1]. For a population of patients, the liver will be the only site of metastases.

9.1.1 Colorectal Carcinoma (CRC):

Colorectal cancer is the fourth most common cancer in the UK (2015), accounting for 12% of all new cases and the 2nd most common cause of cancer death in the UK (Cancer Research UK, 2015). About 25% of patients present with stage IV CRC (synchronous metastases) and 50% of patients overall develop liver metastases. About 85% of patients with stage IV CRC have liver disease considered unresectable at presentation [2,3].

Autopsy studies show that 40% of colon cancer patients fail with disease confined to the liver [4,5,6]. Such oligometastatic disease may be amenable to aggressive local therapy with potential long term disease control [7,8] even in patients with poor prognostic factors (multiple lesions, larger tumour size, short disease free interval) [9,10]. The data to support such an approach is generally retrospective series and prospective phase 2 trials, with no prospective trials comparing aggressive local therapy with no treatment.

Surgery is usually the preferred treatment, with retrospective series reporting 5 year survivals of 25-47% [,9,10,11,12,13] and 14% in patients with poor prognostic factors [9,10]. However, only 10-25% of patients will be suitable for surgery, either due to anatomical factors (site, size and distribution of metastases within the liver), patient fitness or the presence of extrahepatic disease. Chemotherapy may convert inoperable cases to operable in 10-20% of cases [14].

Radiofrequency ablation (RFA) or microwave ablation are alternative local treatment modalities. Retrospective data of RFA for CRC liver metastases report 3 year survival rates of 30-46% [15,16,17]. Control rates from RFA are dependent on tumour size. RFA is most effective when reserved for treating three or fewer lesions, <3.5 cm in diameter, which are not in close proximity to large blood vessels due to the heat-sink effect [18]. Lesions situated in the dome of the liver or in close proximity to the biliary tract are technically unfavourable for RFA.

Further, there are data to suggest that local control of CRC liver metastases is related to survival. Aloia et al report a seven fold increase in the risk of local failure and a 3-fold increase in the risk of death, in patients treated with radiofrequency ablation (RFA) rather than resection, despite similar rates of distant intrahepatic and extrahepatic failure in both groups [19]. Chang et al report also a strong correlation

between local control and survival in patients treated with SABR for liver metastases. [20]

9.1.2 Other primary sites:

Surgical data for resection of non-CRC liver metastases are more limited. However, a large (n=1,452) retrospective, multi-institutional series has reported a 5 year survival of 36% and 10 year survival of 23% for carefully selected non-CRC, with metastases from breast cancer having the best and melanoma and squamous cell cancers the poorest survival [21]. There are also reports of non-CRC having better local control and survival than CRC when treated with SABR [22,23].

9.1.3 Summary of evidence for SABR treatments of liver metastases

Evidence for Stereotactic Ablative Radiotherapy (SABR) for liver metastases are confined to retrospective series (table 9.1), and prospective phase 1 and 2 trials (table 9.2). There is no prospective comparison of SABR and RFA and attempts to run such a trial have failed due to poor recruitment.

Reviewing the evidence as a whole, there is a significant heterogeneity in the patients selected for SABR, the size and number of lesions treated, dose-fractionation schedule delivered, prescription points and planning criteria.

Nonetheless, a number of observations regarding patients receiving SABR can be made:-

1. Patients are often heavily pre-treated before they come to receive SABR. (Several studies report the use of SABR in patients who have previously undergone surgery or RFA) [28,30].

2. SABR is used when the liver metastases are not amenable to surgery or other liver directed therapy such as RFA/microwave ablation.

3. Patients included have good performance status (KPS>70)

4. Treatment is considered if >700cc of normal liver is present and delivered only when it leaves a significant volume of liver spared (a common stipulation being to leave at least 700ml receiving less than 15Gy)

5. Most studies have used vacuum bags or stereotactic body frames for immobilisation and either abdominal compression (AC) or active breath control (ABC) to limit respiratory motion

6. Volumes are outlined using contrast enhanced CT with/without fused MRI or PET

7. Local control rates are 70-100% at 1 year, and 60-90% at 2 years [1] Several factors predicting local control (LC) may be identified, which may help in patient selection for treatment:-

    (i) The most consistently observed association with improved local control is baseline tumour volume. [35,39,40,45,46] For example, Rusthoven et al report a superior LC rate for tumours less than 3cm (100% vs 77% at 2

years, p=0.015) [31]. Number of tumours <3 and size <6cm is better. Also, delivered BED10>117Gy is associated with improved local control at 1 yr [20].

(ii) Natural history. Metachronous occurrence of CRC liver metastases with respect to primary disease [30]

(iii) Risk of extrahepatic disease and occult metastases e.g. tumour histology (breast, colorectal, etc.) and resistance to chemotherapy.

8. Overall survival is difficult to determine, particularly due to the heterogeneity of studies, spectrum of histology treated, and differences in further treatments, especially systemic chemotherapy. Median overall survival is 10-34 months, and 2 year survival ranges from 30-83%[1]. For CRC specifically, Hoyer et al report a median survival of 1.6 years from SABR [30]. Out-of-field progression of disease is observed to occur in a substantial proportion of patients, although this is also reported after hepatic resection[7].

   A number of predictors of overall survival may be identified and long term survival is seen after treatment. Factors associated with increased survival are:-

   (i) The absence of extra-hepatic disease (35.8 months vs 11.3 months [22,30]).

   (ii) Primary histology. Favourable primary histology includes breast, CRC, renal, carcinoid and GIST. Unfavourable primary sites include lung, ovary and non-CRC gastro-intestinal. Rusthoven et al report median survival for favourable primary sites as 32 months vs 12 months for unfavourable primaries ($p<0.001$, log rank test)[31]. Lee et al report superior 1 year survival for CRC (63%) and breast cancers (79%) compared to other primary sites (38%)[23].

   (iii) Tumours <3cm diameter are associated with improved overall survival [23,28].

9. Liver SABR is generally well tolerated, both in terms of acute and late toxicity, and may be used safely after other liver directed therapy (surgery or RFA) [5]

Table 9.1: Retrospective Studies of SABR for Liver metastases

Study	n	Vol / no mets	Histology	Immobilisation / Resp Motion	Dose	Prescription point	Toxicity	Outcome
Blomgren 1995 [24]	14	3-260mL	CRC(11); Anal Canal(1); Kidney(1);Ovarian (1)	SBF/AC	7.7-45Gy (1-4 frx)	Periphery of PTV	2 Cases of haemorrhagic gastritis	50% Response rate
Wada 2004 [25]	5	NR	NR	VM/AC	45Gy (3 frx)	90-100% isodose	No serious toxicity, no RILD	2 year LC 71.2%
Wulf 2006 [26]	44	9-355mL	CRC (23);Breast(11); Ovarian (4);Other (13)	SBF/AC	30-37.5Gy (3 frx); 26Gy 1 frx	30Gy: 65% isodose ; Others – 80% isodose (covering 95% of PTV)	No grade 2-4 toxicity	1 year LC 92%;2 year LC 66% 1 year OS 72%;2 year OS 32% (LC for 37.5Gy: 1 year 100%; 2 year: 82%)
Katz 2007 [27]	69	0.6 – 12.5 cm; (median 2.7cm)	CRC (20);Breast (16);Pancreas (9) Lung (5);Other (19)	VM/ Resp. gating	30-55 Gy (5-15 frx) 50Gy/5frx preferred	100% isodose with 80% covering PTV	No Grade 3-4 toxicity	10 months LC 76% 20 month LC 57% Median OS 14.5 months
Van der Pool 2010 [28]	20	0.7 – 6.2cm (median 2.3cm)	CRC (20)	SBF/AC	37.5-45Gy (3frx)	95% of PTV received prescribed dose	2 grade 3 late liver enzyme changes; 1 grade 2 rib fracture	1 year LC 100% 2 year LC 74% Median survival 34 months

Abbreviations: SABR (Stereotactic Ablative body radiotherapy); Mets = metastases; RT = radiotherapy; CRC = colorectal cancer; SBF= stereotactic body frame, VM=Vacuum Mould, AC = abdominal compression; ABC = Active breath control; NR; Not reported; LC = local control, OS = overall survival; frx = fractions

Table 9.2: Prospective Studies of SABR for Liver metastases

Study	Design	n	Vol/no mets	Histology	Immobilisation /Resp Motion	Dose	Prescript. point	Toxicity	Outcome
Herfath 2004 [22]	Ph 1-2	35	1-132mL (median 10ml)	CRC(18); Breast (10); Other (7)	SBF and VM/AC	Dose Escalation: 14-26Gy (1 frx)	Isocentre, with 80% covering PTV	No significant toxicity reported	1 year LC 71%; 18 month LC 67% (18 month LC 81% for Ph2) 1 year OS 72%; Med 25 months
Mendez Romero 2006 [29]	Ph 1-2	25 (17 liver mets)	1.1-322mL (med = 22.2mL)	CRC (14); Lung (1); Breast(1); Carcinoid (1);	SBF/AC	37.5Gy (3frx) 30Gy (3frx) in 3 patients to spare OAR	65% Isodose	2x G3 GammaGT elevations; 1x G3 asthenia; 1x late portal hypertension	2 year LC 86% 2 year OS 62%
Hoyer 2006 [30]	Ph 2	64 (44 liver)	1-8.8cm (median 3.5cm)	CRC only	SBF or VM/ AC	45Gy (3frx)	ICRU ref-95% to CTV and 67% PTV	1 liver failure; 2 severe late GI toxicities	2 year LC 79% (by tumour) 2 year LC 64% (by patient);
Rusthoven 2009 [31]	Ph 1-2	47	0.75-98mL (median 14.93mL)	CRC(15); Lung(10); Breast(4); Ovarian (3); Oes(3) ;HCC (2); Other (10):	VM/ ABC or AC	Dose Escalation: 36-60Gy (3frx) Ph2 60Gy(3frx) – 36 pts	Isodose covering PTV (80-90%)	No RILD Late Grade 3 / 4 <2%	1 year LC 95%; 2 year LC 92%; Median survival 20.5 months (32 months for breast and CRC p<0.001). 2 year OS 30%

Abbreviations: SABR (Stereotactic Ablative body radiotherapy); Mets = metastases; RT = radiotherapy; CRC = colorectal cancer; SBF= stereotactic body frame, VM=Vacuum Mould, AC = abdominal compression; ABC = Active breath control; NR; Not reported; LC = local control, OS = overall survival; frx = fractions

Table 9.2 (continued): Prospective Studies of SABR for Liver metastases

Study	Design	n	Vol/no mets	Histology	Immobilisation /Resp Motion	Dose	Prescript. point	Toxicity	Outcome
Lee 2009 [23]	Ph 1-2	68	1.2 – 3090ml (Med. 75.9mL)	CRC(40); Breast(12); Gallbladder(4); Lung(2); Anal(2); Melanoma(2); other(6)	VM/ ABC or AC (AC if resp excursion>5mm)	Individualised Dose 27.7-60Gy (6frx)	Isodose covering PTV (Max 140% in PTV)	No RILD 10% grade 3/4 acute toxicity No grade 3/4 late toxicity	1 year LC 71% Median survival 17.6 months
Ambrosino 2009 [32]	Prospect cohort	27	20-165mL (median 69mL)	CRC (11); Pancreas (10); Breast(2); 1 each of gallbladder,gastric, ovary, lung	Cyberknife™ (with synchrony™ to track US-placed gold fiducials)	25-60Gy (3 frx)	80% of prescribed dose covered PTV	36.2% CRC cases – mild-moderate transient hepatic dysfunction. 3.7% GI bleed; 3.7% portal vein thrombosis	Crude LC rate 74%
Goodman 2010 [33]	Ph 1 (HCC and liver mets)	26 (19 liver mets)	0.8-146.6 mL (Median 32.6mL)	CRC (6); Pancreas (3); Gastric (2); Ovarian(2); Other (6)	Alpha-cradle. Cyberknife™ (with synchrony™ to track US-placed gold fiducials)	18-30Gy (1frx)	Isodose that covered PTV (65-90%)	4 cases grade 2 late toxicity (2GI, 2 soft tissue/rib)	1 year local failure 23% Median survival 28.6Months 2 year survival 49% (mets only)
Scorsetti 2013 [58]	Prospective phase II	61	1.8-134 cc (Median 18.6)	CRC (29) Breast (11) Gynae (7) Other (14)	Linac	52.5-75 Gy (3 frx)	Mean dose to PTV	1 case late G3 toxicity	1 year LC 94% 1 year OS 84%

Abbreviations: SABR (Stereotactic Ablative body radiotherapy); Mets = metastases; RT = radiotherapy; CRC = colorectal cancer; SBF= stereotactic body frame, VM=Vacuum Mould, AC = abdominal compression; ABC = Active breath control; NR; Not reported; LC = local control, OS = overall survival; frx = fractions

9.2. Patient selection criteria

Inclusion criteria:

- 1-3 liver metastases unequivocally seen on contrast enhanced CT and/or MRI in patients with previously histologically diagnosed carcinoma.
- Metastases unresectable, patient unfit or declines surgery, or presence of extra-hepatic disease making surgery an inappropriate treatment option
- ECOG Performance Status ≤2
- Discussion in Hepatobiliary (HPB) MDT with agreement that SABR is the most suitable local treatment modality. It should be confirmed that the patient is unsuitable for surgery and/or RFA.
- Predicted life expectancy > 6 months
- Recovered from any previous therapy (such as surgery, chemotherapy or radiotherapy to other areas) with a minimum of 2 weeks break (anthracycline based chemotherapy should be completed 4 weeks before SABR)
- For 3-5# SABR: up to 3 metastases, maximum size of a single metastasis ≤ 6cm. For those with larger volume disease, consider treatment with 10# regimen.
- Adequate organ function, defined as: >700 cc normal liver (liver-GTV), Haemoglobin 9.0 g/dL, platelets >80 bil/L, bilirubin <3.0 times upper limit of normal, INR <1.3 or correctable with vitamin K and unless the patient is taking warfarin, AST or ALT <5.0 times upper limit of normal.
- Class A from Child's Pugh Liver Score (see Table 9.3)

Exclusion criteria:

- Active hepatitis or clinically significant liver failure (encephalopathy, portal hypertension, varices)
- Clinically apparent ascites
- Any previous radiotherapy where the mean dose to the liver ≥15Gy (conventional fractionation), where beams would be likely to overlap with those used to deliver SABR, or where previous doses to other critical normal structures would make re-irradiation unsafe.
- If fiducial markers are to be placed, coagulopathy preventing safe insertion of fiducial markers and allergy to the metal component of the fiducial.

Table 9.3: Childs-Pugh Liver Score

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%

The following guidelines are compiled purely as guidance in delivering SABR to liver metastases. It is the responsibility of each department to ensure adequate processes and training for all staff groups.

9.3. Radiotherapy

9.3.1. Tumour Delineation and OARs

The PTV expansion margins used in published studies have varied considerably. Exact margins used are determined by the immobilisation device and means by which respiratory motion is managed.

GTV-CTV: The most common practice in published studies has been to add no margin between GTV and CTV, (range 0-8mm).

CTV-PTV: Studies have tended to use larger margins SI to allow for respiratory motion. The most common practice has been to use 10mm (mean 8.3mm), although less when 4D CT has been used for image guidance. Radially, most studies have used margins of 5mm (mean 7.2mm), again reduced when 4D CT is used.

Guidance Note: Suggested margins are GTV-CTV – 5mm in all directions within the liver, with contours edited outside liver. CTV to PTV margins should be individualised according to motion management technique employed, although a minimum of 5mm is suggested (radially and craniocaudally) for Linac treatment. If using real-time

tracking e.g. CyberKnife, 3-5mm dependent on number of fiducials and proximity to lesion.

Organs at Risk

Appropriate dose limits for OARs are given in Appendix A, with the following structures being recommended for reporting:

Mandatory: spinal cord, oesophagus, kidney, heart, normal liver (i.e. liver-GTV), stomach, lungs, duodenum, small bowel

Recommended: Chest wall, skin, common bile duct

9.3.2 Fractionation

To date, there are no randomised, controlled trials comparing dose-fractionation regimens for SABR in liver metastases. The data that are published show considerable heterogeneity in the dose-fractionation schedules delivered. Nonetheless, there is a clear dose-response relationship.

McCammon et al report 3 year local control rates of 89.3% for lesions receiving 54-60Gy in 3 fractions, compared to 59% (36-53.9Gy/3 fractions), and 8.1% (less than 36Gy). [50] Similarly, Chang estimate that the dose required to achieve a 90% likelihood of local control at 1 year is 46-52Gy in 3 fractions (or a BED (assuming an α/β of 10) of more than 75Gy) [20].

A 10 fraction regimen may be useful for the palliation of larger volume disease and has been shown to be effective and well tolerated, even in heavily pre-treated patients [60].

However, in comparing dose regimen, it is important to note that the use of biological effective dose (BED) calculations when using small number of large fractions may not be as reliable as when used for conventionally fractionated radiotherapy.

Suggested fractionations and dose distribution requirements:

(i) 40-60Gy in 3 fractions (Alternate days)

e.g. 45Gy in 3 fractions.

Prescribed to the prescription isodose covering at least 95% of the PTV (usually 80-95%). DMax within PTV<133%.

If OAR constraints are not met, then the 95% isodose can be relaxed or total dose can be reduced according to clinical discretion.

(ii) 50-60Gy in 5 fractions (Alternate days or daily)

This may be used when a larger PTV volume is being treated in order to achieve OAR constraints (≤ 6cm), when the PTV is within 1 cm of small bowel/visceral OAR/bile duct or adjacent to chest wall/ribs. ≥95% of the PTV will receive the prescription dose.

(iii) 30-60Gy in 10 fractions

Consider use when target volume does not meet true SABR eligibility criteria (e.g. single lesion >6cm, multiple lesions where unable to meet 5# planning constraints or extrahepatic disease).

10 equal fractions delivered over 2 weeks. The total dose prescribed will be individualised according to the effective liver volume treated as follows:-

- 40-60Gy if less than 30% of effective volume of liver irradiated
- 35-50Gy if between 30%-50% of effective volume of liver irradiated
- 30Gy if between 50%-70% of effective volume of liver irradiated

N.b. Effective liver volume is defined as the 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.

9.3.3. Treatment assessments and clinical follow-up

(i) ACUTE TOXICITY:

Overall, rates of G1-2 toxicity are reported to range from 0-27% and grade 3-4 toxicities observed in around 5% [27] The rate of morbidity for liver radiation is reported to be independent of dose-fractionation schedule [55], and the levels of toxicity reported in the studies are consistently low.

Rates of Gastritis/Oesophagitis are low (G2 7%, G3 in 3%). Consider the use of prophylactic proton-pump inhibitors if stomach and/or small bowel are receiving significant dose [23]. These should be continued for 3 months after SABR. Consider prophylactic anti-emetics with 5HT3 antagonists to reduce the incidence of nausea.

Radiation-induced liver disease (RILD) is defined as anicteric elevation of alkaline phosphatase (ALP) to greater than twice the upper limit of normal, with non-malignant ascites (*Classical RILD*), or elevation of transaminases to more than 5 times the upper limit of normal or pre-treatment levels (*Non-classical RILD*). The rates of RILD are notably very low in all published series (<1% in modern series). Childs Pugh B and Hep B/C carriage is associated with a higher incidence of RILD [29].

Rates of liver enzyme derangement are similarly low. For example, Grade 1/2 elevation of liver function tests were observed in 28% patients treated with 30-55Gy (median 48Gy) by Katz et al. [27] and transient elevation of liver enzymes described as mild-moderate is noted in 31-36% of patients receiving 25-60Gy in 3 fractions. [32]

Several studies have reported the use of liver SABR in patients who have previously undergone surgical resection and/or RFA, and reported low levels of toxicity, suggesting SABR is safe to use in this context. [28,30]

LATE TOXICITY: Caution should be noted regarding late effects since several studies of liver SABR have observed poor survival. Only one study has durable follow up – 4.3 years [30]. Most others have follow up of around 16-18 months and, therefore, the extent of late radiation effects may be underestimated. However, the rates of high grade toxicity (G3 or worse) are generally low (2-5%) [31, 33]. Reported severe late toxicities are rare and include GI bleeding and rib fractures.

Patient Care on Treatment:

Review weekly on treatment – physical examination, full blood count, urea and electrolytes, liver function and coagulation screen.

Consider proton pump inhibitors (PPI) to reduce the risk of GI ulceration and anti-emetics for nausea.

Assessment of Response:

After SABR, a local reaction develops in the liver which can sometimes be difficult to differentiate from residual disease [1]. Multiphasic CT is reported to differentiate focal radiotherapy reaction from disease [56]. Distinct patterns of enhancement, shrinkage of hypodensity, and displacement of vessels are indicative of local response [57]. MRI may be superior in differentiating residual disease from normal tissue reaction and should be considered if pseudo-progression is suspected on CT [29]. The use of CT-PET has not been demonstrated, so far, to provide additional tumour response information [31].

Follow-up:

The purposes of follow up are early detection disease progression so as to intervene early in managing this, and to accurately document toxicity.

Suggested follow up schedule: Review at 4-6 weeks (clinical review only), then 3 monthly to 2 years and 6 monthly thereafter including bloods (FBC, U+E, LFTs, clotting and tumour markers as appropriate) and toxicity assessment. Follow up imaging assessments (CT and/or MR liver) should be performed routinely at 3, 6, 12 months post SABR and 6 monthly thereafter.

Prospective Collection of Audit Data:

Departments undertaking Liver SABR are encouraged to prospectively collect data relating to types of patients and tumours treated, dose-fractionations used, acute and late toxicities and outcome in terms of local control and survival.

9.4 SUMMARY FOR LINAC BASED SABR FOR LIVER METASTASES

Patient Selection: Discussion with Hepatobiliary MDT to consider suitability for liver SABR/alternative treatments

Consent: Explanation of procedure and likely risks

Immobilisation: Treat supine, arms above head, in suitable immobilisation device. Respiratory managed by ABC/AC/ gating as appropriate to resources and experience.

Pre-treatment imaging: Contrast enhanced CT/fused with MRI (+/- PET) wherever possible.

Volume Definition: Radiotherapist +/- radiologist. PTV and OAR.

Margins: Suggestions: GTV-CTV: 5mm; CTV-PTV: individualised according to motion management technique applied but minimum of 5mm

Dose: 3 dose-fractionations suggested: Dependant on clinical scenario and clinician choice:-

(i) 45-60Gy in 3 fractions

(ii) 50-60Gy in 5 fractions

(iii) 30-60Gy in 10 fractions over 2 weeks

Planning: Evaluated by two SABR trained clinical oncologists

Daily pre-treatment procedures: Ideally, cone beam CT, matched with pre-treatment CT with PTV outlined. Correct any errors. Repeat CT at end of fraction.

Pre-medication: PPI (e.g. Lansoprazole/Omeprazole) and antiemetic

Follow up: Weekly during treatment, 4-6 weeks after completion, 3 monthly to 2 years then 6 monthly to 5 years. Assessments to include history, examination, FBC, U+E, LFTs, clotting CEA (and/or other tumour markers as appropriate), CT/MRI at 3, 6, 12 months and 6 monthly thereafter.

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10. Hepatocellular carcinoma

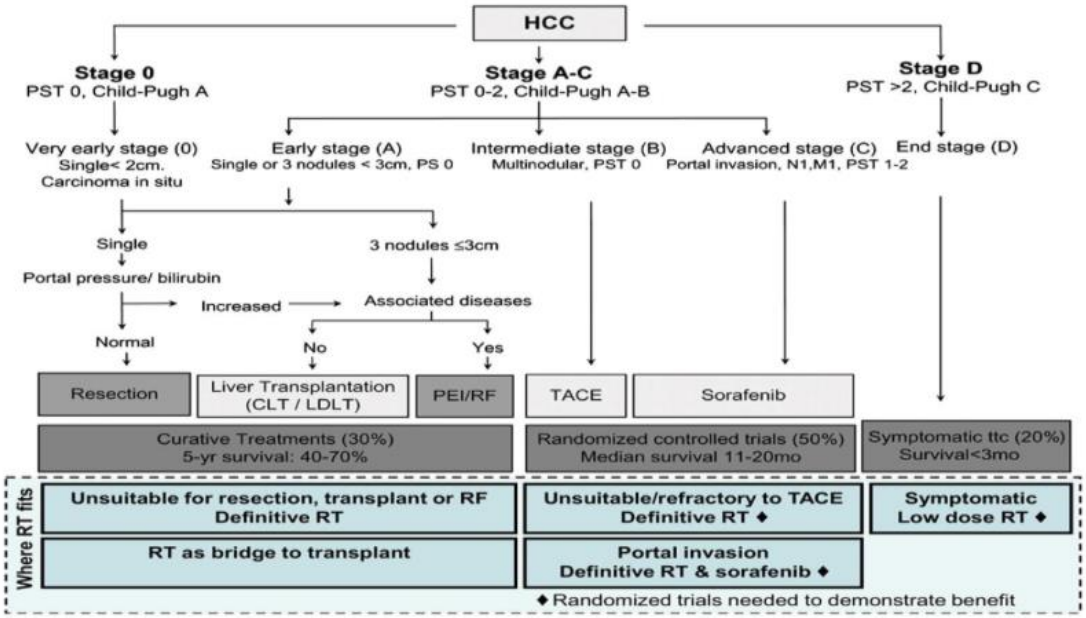
10.1. Introduction and literature review

All patients with hepatocellular carcinoma (HCC) being considered for SABR should be discussed in a specialist hepatobiliary MDT with the expertise to select the most appropriate therapy from the range of options available; these include transplant, resection, radiofrequency ablation (RFA), trans-arterial chemo-embolisation (TACE), ethanol injection, selective internal radiotherapy (SIRT), and palliative systemic therapy. Given that HCC usually arises in a cirrhotic liver, care must be taken with regard to patient selection to ensure that an appropriate balance of potential benefit vs potential harm is maintained.

Hepatocellular carcinoma (HCC) is rapidly rising in incidence 5550 new cases diagnosed in the UK every year [1]. Liver transplant is a curative option, although few patients prove suitable for this approach. There are several treatment options for localised disease but recurrence is common and systemic therapy options are limited in efficacy and number [2-10].

HCC usually arises in people with liver cirrhosis, the common causes of which include alcohol consumption, metabolic syndrome, and chronic viral infections. Patients who are eligible are offered liver transplant; the remainder are usually treated with RFA and/or TACE [2]. Disease recurrence and progression after these treatments is common. These patients are offered palliative systemic therapy if performance status is permissive [6]. A proportion of patients with HCC are not suitable for invasive ablation procedures or palliative systemic therapy due to co-morbid illnesses, despite retaining a good performance status. Patients with progressive disease after RFA/TACE, those who are not suitable for these techniques for anatomical or other reasons, or those who decline these treatments, and who have a good performance status and acceptable liver function, are potentially suitable for SABR.

The diagram below gives an integrated view of the various modalities available:



There is growing evidence that HCC is highly sensitive to radiation therapy. Early published series using conventionally fractionated radiotherapy showed good rates of tumour control [11]. Advances in the technology of radiation delivery have allowed the development of SABR regimes that have low rates of acute and late toxicity in patients with good liver function [12]. Multiple retrospective series and dose escalation studies have indicated that SABR offers equivalent local control to RFA, particularly for larger lesions, and can effectively treat recurrent or multifocal lesions not amenable or refractory to TACE, including those with branch or main portal venous invasion [13]. SABR also appears promising as a bridge to liver transplant with a better toxicity profile than TACE [14].

10.2. Patient selection criteria

Inclusion criteria

1. Either (a) pathologically or cytologically confirmed diagnosis of HCC, or (b) at least one solid liver lesion or vascular tumour thrombus (involving portal vein, inferior vena cava and/or hepatic vein) with arterial enhancement and delayed washout on computed tomography (CT) or magnetic resonance (MR) imaging, in the setting of cirrhosis or chronic viral hepatitis
2. Unsuitable for resection. SABR may be considered as a bridge to transplant if discussed within a transplant MDT
3. Unsuitable for, or failed, or declines, RFA or TACE. SABR may be used as consolidation treatment after either RFA or TACE if there is evidence of incomplete response on the first response assessment.
4. ECOG performance status 0-2
5. Adequate organ function, including Child-Pugh A liver function
6. Maximum single tumour size ≤10 cm, including any associated thrombus. No more than three intra-hepatic foci of radiologically confirmed active HCC
7. Patients with oligometastatic HCC, with or without liver involvement, may be considered for SABR

8. Liver-GTV volume of >700cc
9. Life expectancy from any associated co-morbidity >6 months

Exclusion criteria

1. Clinically significant liver failure (encephalopathy, actively bleeding oesophageal varices, clinically significant portal hypertension)
2. Prior upper abdominal radiotherapy, or whole-liver Y-90 SIRT
3. Direct tumour extension into stomach, duodenum, small bowel or large bowel
4. Radiologically confirmed metastatic disease, unless amenable to ablative techniques. Patients with indeterminate lung nodules or abdominal lymph nodes may be treated provided the hepatobiliary MDT confirms that there is no definite evidence of metastatic involvement.

10.3 Radiotherapy

10.3.1 Tumour delineation

GTV delineation in HCC SABR is often challenging and should be done with all diagnostic imaging available and with radiology assistance where possible. HCC is typically best visualized on contrast-enhanced CT, with hyperintensity being seen in the arterial phase and hypointensity being seen in the venous or delayed phases. Tumour thrombus is usually best seen as hypointensity compared to the contrast in the vessel on the delayed phase. The GTV comprises all active areas of HCC, including any definite tumour vascular thrombus. Bland thrombus is not included. A clinical target volume (CTV) for microscopic spread is not typically used. PTV margin selection and OAR delineation should be as per the liver metastasis section.

10.3.2. Fractionation

The total dose does not appear to be as important for tumour control in HCC as it is for liver metastases [20[. Until lower doses are proven non-inferior, however, clinicians should aim to deliver the highest dose feasible whilst respecting OAR constraints. In patients who meet the above inclusion criteria, a therapeutic dose can generally be achieved over five fractions delivered on alternate days. The prescription dose may be 50 Gy, 45 Gy, 40 Gy, 35 Gy or 30 Gy in five fractions. The dose to multiple PTVs may be different; for example, if the GTV in question is in close proximity to a visceral OAR, it may prove more practical to reduce the prescription dose to that particular PTV than to compromise on PTV coverage to meet the relevant constraint. The mean liver dose (MLD) is defined as the mean dose to the structure ‘liver-GTV’. The final prescription dose is determined by the following risk adaptation method:

Prescription dose (in 5 fractions)	Mean liver dose to be achieved	If the maximum MLD is exceeded at this dose
50 Gy	13 Gy	Reduce to 45 Gy and re-evaluate
45 Gy	15 Gy	Reduce to 40 Gy and re-evaluate
40 Gy	15.2 Gy	Reduce to 35 Gy and re-evaluate
35 Gy	15.5 Gy	Reduce to 30 Gy and re-evaluate
30 Gy	16 Gy	Not suitable for SABR

10.3.3 Treatment assessment & follow-up

Care on treatment

This is as per the liver metastasis section. It is recommended that Child Pugh status and performance status are reassessed 4-6 weekly for six months after SABR so that early investigation and management of any hepatic decompensation can be undertaken by hepatologists with an interest in HCC.

Post treatment imaging

Unless there is strong clinical evidence of disease progression, the initial response assessment imaging should be no earlier than 12 weeks after the final fraction.

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11. Prostate Cancer

11.1. Introduction and literature review

11.1.1 Conventional therapy and outcome

Treatment options for early prostate cancer include radical prostatectomy, external beam radiotherapy (EBRT), brachytherapy, or active surveillance in selected patients. In the ProtecT trial over 1600 men were randomised between active monitoring, prostatectomy and EBRT with no significant survival difference, although a higher rate of disease progression and development of metastases was recorded in the active monitoring group [1].

Radical external beam radiotherapy is accepted as a highly effective radical treatment for localised prostate cancer. Randomised trials have demonstrated that dose escalation to 74 to 79.2Gy in 1.8 to 2Gy per fraction, delivered using conformal EBRT, compared to doses of 64 to 70Gy, results in a 10 to 20% improvement in biochemical control at 5 years, with 5 year freedom from biochemical failure rates of 64 to 80% reported [2,3,4,5,6]. The data is suggestive of a dose-response relationship demonstrating increasing biochemical control with increasing dose. The increase in dose has been accompanied by an increase in both acute gastrointestinal and genitourinary toxicity together with an increase in late rectal toxicity when radiation is delivered using 3D conformal treatment [2,3,5,7,8]. Trials comparing IMRT with CRT have revealed a significant reduction in acute and late gastrointestinal toxicity [9,10]. This has allowed further dose escalation. One series of 772 men demonstrated that dose escalation to 81 to 86.4Gy with IMRT was feasible, with acute and late toxicities lower than would be expected with 3D-conformal radiotherapy [11]]. Recently 10 year outcomes were reported for a series of 170 patients who received 81Gy in 45 fractions with IMRT [12]. Median follow up was 99 months. Biochemical control was good with 10 year biochemical relapse free survival (Phoenix definition) of 81%, 78% and 62% for patients considered low, intermediate and high risk respectively. Toxicity rates were low with a 10 year likelihood of 9% and 5% for developing CTCAEv3 grade 2 and 3 late genitourinary toxicity and 2% and 1 % for developing grade 2 and 3 late gastrointestinal toxicity [12].

Dose escalating using conventional fractionation prolongs the overall treatment time which may have a negative effect on cancer outcomes [13]. An alternative means of delivering a higher total dose (i.e. a higher biological effective dose; BED) is with hypofractionation. There is good rationale for adopting this approach in the treatment of prostate cancer as there is evidence that prostate cancer has a low α/β ratio, meaning it is theoretically more sensitive to large dose per fraction treatments [14,15,16,17]. Importantly, evidence also suggests that the α/β ratio of the rectum for late toxicity is higher than the α/β ratio of the prostate with values in the region of 3 to 6Gy [16,18]. This allows exploitation of the potential biological advantage of the low alpha-beta ratio of prostate cancer in one of two ways: i) by delivering larger hypofractionated doses to the prostate (thus improving tumour control) for isotoxic levels of late rectal toxicity, or ii) by delivering an isoeffective hypofractionated dose to the prostate with the aim of a reduction in rectal toxicity.

There is substantial evidence advocating the use of moderate hypofractionation in prostate cancer. In the CHHIP trial, 3216 men were randomised between conventionally fractionated radiotherapy at a dose of 74 Gy in 37 fractions, and two moderately hypofractionated schedules of 60 Gy in 20 fractions or 57 Gy in 19 fractions [19]. The majority of patients had intermediate-risk prostate cancer and 97% received androgen deprivation therapy (ADT). This demonstrated the 60 Gy in 20 fraction schedule to be non-inferior compared to conventional fractionation, however the same could not be claimed for the 19 fraction schedule. 5-year biochemical/ clinical failure free rate was 88.3%, 90.6% and 85.9% for the 74 Gy, 60 Gy and 57 Gy groups respectively. The acute GI toxicity rate (RTOG ≥ grade 2) was higher in the hypofractionated arms, but late GI and GU toxicity rates were low, with no significant difference between the groups. Following publication of these results, moderately hypofractioned radiotherapy with 60 Gy in 20 fractions, in combination with ADT, has been adopted as standard practice in the UK for the treatment of localised prostate cancer.

More extreme hypofractionation has been evaluated in HYPO, a phase II randomised trial which randomised 1200 intermediate-risk patients to receive either conventional fractionation (78 Gy in 39 fractions) or a highly fractionated schedule of 42.7Gy in 7 fractions, without concomitant ADT [20]. No significant difference in toxicity was found between the two arms at 2 years follow up, which included 866 patients. RTOG ≥ grade 2 GU was 5.4% and 4.6% for the hypofractionated and conventional arms respectively, and GI toxicity 2.2% versus 3.7%. As presented at ESTRO 2018 by Widmark et al, the highly hypofractionated schedule was shown to be non-inferior to conventional fractionation in terms of freedom from biochemical or clinical failure at 5 years, with no significant difference in toxicity rate at 4 and 6 years.

11.1.2 SABR for prostate

SABR delivers ultra-hypofractionated treatment, usually in five fractions or less, and, in the treatment of prostate cancer, offers the potential for dose escalation and for harnessing the theoretical radiobiological advantages of hypofractionation. There is now a wealth of published data from non-randomised trials demonstrating efficacy and toxicity rates to be comparable with standard treatment in low- and intermediate-risk disease. In the United States, the American Society for Radiation Oncology (ASTRO) and National Comprehensive Cancer Network (NCCN) include SABR as a treatment option for localised prostate cancer [21,22]. However, the clinical commissioning policy from NHS England concludes that there is currently not enough evidence to allow SABR to be available as a standard treatment option (clinical commissioning policy 16031/P), and is therefore only available for NHS patients in the context of a clinical trial [23]. Published data does need to be interpreted with caution in view of diverse study methodology, including a number of retrospective studies and short follow in some cases. Randomised trials are required to accurately evaluate any benefit from SABR in comparison to standard therapy.

PACE is an international multicentre phase III trial based at the Royal Marsden Hospital [24]. The trial consists of two parallel randomisation processes, in order to directly compare SABR with radical prostatectomy (PACE A), and with standard radiotherapy (PACE B). SABR delivery is with CyberKnife or linac-based techniques, at a prescribed dose of 36.25Gy in 5 fractions to the PTV. Patients in the standard

radiotherapy arm are treated with either 78 Gy in 39 fractions or 62 Gy in 20 fractions, following the CHHIP trial publication. Low- and favourable intermediate-risk patients are eligible and are treated without ADT. The primary objective of PACE A is to determine whether there is improved quality of life with SABR compared to prostatectomy, and in PACE B it is to demonstrate non-inferiority of SABR compared to standard radiotherapy in terms of biochemical progression-free survival (bPFS). Given the difficulties of a surgery versus radiotherapy randomisation, PACE A recruitment has been slower than anticipated. In contrast, PACE B has recruited exceptionally well, and met the accrual target of 858 by the end of November 2017.

A literature search using the search terms 'stereotactic' and 'prostate', revealed over 120 publications with clinical data presented, evaluating SABR in primary localised prostate cancer. These consist of either phase I/II trials or cases series. The majority of studies are investigating the use of SABR as monotherapy, the larger of which are summarised in Table 11.1. Others using SABR as a boost following conventional radiotherapy will not be included in the scope of these guidelines.

Long-term results from a multi-institutional consortium study were published in abstract form this year by Kishan et al [25]. It is the largest study of prostate SABR monotherapy to date, involving 1644 patients with medium follow-up of 7.2 years. This included 54% low risk and 46% intermediate-risk patient, with 3.6% of patients receiving short-term ADT. SABR techniques varied, using a dose fractionation of 33.5 Gy–40 Gy in 4-5 fractions. Overall treatment was well-tolerated with low rates of grade 3 and above toxicity (see Table 11.1). The 5-year bDFS was 98% and 95% for low- and intermediate–risk patients respectively. For low-risk patient the bDFS at 10 years was 94%, and 91% for intermediate-risk patients.

Early results from a randomised trial (RTOG 0938) by Lukka et al, were published in abstract form in 2016 [26,27]. In this trial, 255 low-risk prostate cancer patients were randomised between SBRT with 36.25 Gy in five fractions, and a hypofractionated schedule of 51.6 Gy in 12 fractions. At 1 year post treatment, both schedules were well tolerated in terms of toxicity and patient-reported outcomes. Also in abstract form, Meier et el have reported 5 year outcomes from a large prospective multicentre trial in the US involving over 300 patients from 21 centres treated with Cyberknife [28]. Eligibility for this trial was limited to low (56%) and intermediate (44%) risk patients, without the use of ADT. With median follow up of 61 months, they demonstrated an overall biochemical failure free survival of 97.1% (97.3% and 97.1% in the low and intermediate risk groups respectively). There were no cases of grade 3 or above acute toxicity, 26% grade 2 genitourinary (GU) and 8% grade 2 gastrointestinal (GI) toxicity. With regard to late toxicity, 12% grade 2 and 2% grade 3 GU toxicity was reported; and 2% grade 2 GI toxicity with no grade 3 or above.

Although less established, prostate SABR experience in the UK is rapidly growing. Prospective data from the initial CyberKnife cohort from the Royal Marsden and Mount Vernon Hospitals has been published, most recently at 2.5 years median follow up. This analysis included 81 patients, 94% of which had low-or intermediate-risk [29,30]. The dose fractionation was 36.25 Gy in 5 fractions prescribed to the PTV, on consecutive or alternate days. 30% genitourinary (GU) and 22% gastrointestinal (GI) RTOG acute ≥G2 toxicity was reported. Late ≥ G2 GU and GI toxicity occurred in 11% and 10% of patients, with grade 3 GU and GI toxicity

occurring in 2% and 1%, respectively. Follow up was too short to assess efficacy and it will be highly informative to assess bDFS and long-term toxicity rates after at least 5 years follow up, confirming consistency with other studies internationally.

11.2. Patient selection criteria

Current evidence for SABR in prostate cancer relates mainly to patients with low- and intermediate-risk disease, although definitions may vary between studies. Within PACE, trial eligibility is limited to low- and intermediate-risk patients, as defined by NCCN criteria [21], including only those with Gleason score ≤ 3+4 (Grade group 2).
Evidence for SABR in high-risk prostate cancer is more limited. Theoretically, hypofractionation should be just as biologically advantageous in high risk disease, although it is acknowledged that this may be in combination with other treatments such as hormone therapy. A few studies involve a mixed population which include a small percentage of high risk patients. For example, a pooled multi-institutional analysis published in 2013 by King et al included 11% high-risk patients, demonstrating encouraging results with 5-year bPFS of 81% in this group [31]. The use of ADT was relatively low in 14% of the total population, and 38% in the high-risk group. King et al are conducting a multicentre phase II trial to evaluate efficacy and safety of SBRT specifically in the high-risk group, expecting to recruit 220 patients [32]. Preliminary results recently published in abstract form include 73 patients with median follow up of 13.8 months [33]. SBRT to the prostate was delivered at a dose of 40 Gy in 5 fractions and of note, 32% received SBRT to the pelvic nodes at a dose of 25 Gy in 5 fractions, and 63% received ADT. Treatment was well tolerated with no grade 3 toxicity, and evidence of biochemical failure in 2.7%, however longer follow-up is needed to evaluate efficacy of treatment.

The role of ADT in combination with SABR for localised prostate cancer is unclear. Evidence for using ADT with standard radiotherapy in low and intermediate risk patients is unconvincing, particularly now in the context of dose-escalated radiotherapy [34,35]. In view of this, many of the current prospective SABR trials in this group, such as PACE, do not include ADT. Zelefsky et al, have recently commenced recruitment to a multicentre phase III randomised trial to compare SBRT alone or in combination with hormones, in intermediate risk patients.

11.3. Radiotherapy

Presently, NHS patients with localised prostate cancer only have access to SABR within the context of the PACE trial. Any treatment platform capable of extra-cranial SABR delivery, is permissible within the PACE trial.

11.3.1 Tumour delineation and OARs

Tumour delineation

The CTV should include the whole prostate gland +/- proximal seminal vesicles. The inclusion of seminal vesicles within the treatment volume differs between and within studies, with some including the prostate alone and others including some or all (generally the proximal half or proximal 1-2 cm). Pathological studies indicate that it is reasonable to omit the seminal vesicles in low-risk patients, and to include the

proximal 1cm and 2cm seminal vesicles in intermediate- and high-risk patients respectively [36,37,38,39]. In the PACE trial, the CTV for low-risk patients consists of the prostate alone, and for intermediate-risk patients, the prostate plus proximal 1cm of seminal vesicles. It is strongly recommended that a planning MRI scan is fused with the planning CT scan to aid volume definition.

There is variation in the existing studies regarding CTV to PTV margins largely dependent on whether intra-fraction motion monitoring and correction is available. Commonly, 5mm margins in all directions have been applied, except for posteriorly where margins are reduced to 3mm due to the proximity of the rectum. Linear accelerator based systems utilising the Calypso electromagnetic tracking system have employed similar small margins [40,41,42]. Within PACE, the PTV is formed by applying 4-5mm margin to the CTV, reduced to 3 -5 mm posteriorly.

Where intra-fraction tracking and correction is not available then margins should be larger taking this into account together with any remaining set up uncertainties. The image guidance sub-study within the CHHiP trial, which did not require planning MRI scans or intra-fractional motion correction, used 6mm CTV to PTV expansion margins for the largest PTV, using fiducial markers, which was felt sufficient to encompass residual set up uncertainty as well as intra-fraction motion.

Minimum standard: each centre must establish expansion margins that are appropriate for local practice. These margins should be audited regularly and should be similar to those used in the literature.

Organs at risk (OAR)

The following OAR should be contoured:

Mandatory: rectum (anus to rectosigmoid junction), bladder (including wall and lumen), femoral heads (excluding femoral necks), penile bulb, bowel (within 2cm of PTV for linac and 15cm for CyberKnife)

Recommended: Urethra (if visible), testicles (to be used as a “blocking structure” for Cyberknife planning)

11.3.2 Dose and Fractionation

For prostate SABR, the dose used in published studies ranges between 33.5 Gy and 50 Gy in 4 or 5 fractions, with fraction size varying from 6.7 to 10Gy. As used in the PACE trial, 36.25 Gy in 5 fractions is the most commonly prescribed dose within the literature.

Dose escalation up to 50 Gy in 5 fractions has been evaluated by the Timmerman group, however significant toxicity was recorded in patients receiving higher doses. Six percent of patients developed high grade toxicity including 5 patients who required a colostomy. There is not a clear argument for escalating to this dose level, particularly in low risk patients. If the α/β of prostate cancer is as low as 1.5, then a SABR dose of 36.25 Gy in 5 fractions has a biologically effective dose (BED) of 211 Gy, which is higher than 78 Gy in 39 fractions (BED 182 Gy), but has a slightly lower BED (124 Gy vs 130 Gy) in terms of late rectal toxicity, assuming an α/β of 3.

Escalating the SBRT dose to 50 Gy in 5 fractions markedly increases the tumour BED to 385 Gy but at the cost of increasing normal tissue BED to 216 Gy, hence increasing the risk of significant rectal toxicity.

Limiting dose escalation to MRI-defined tumour within the prostate may be a method of improving efficacy in higher-risk patients while minimising toxicity, however this remains investigational. Recently reported results from the FLAME phase III trial demonstrate no significant increase in toxicity up to 2 years from combining an integrated boost up to 95 Gy to MRI-defined tumour with fractionated radiotherapy 77 Gy in 35 fractions to the entire prostate [43]. Aluwini et al, treated 50 patients with SABR at a dose of 38 Gy in 4 fractions to the PTV, and in 14 of these patients delivered an integrated boost to dominant tumour nodule visible on MRI, to a mean dose of 47.8 Gy [44]. Although the number of patients receiving the tumour boost was very small, no increase in toxicity was reported in this group at 23 months follow-up. The SPARC trial aims to boost dominant tumour nodules up to 47.5Gy in 5 fractions, while delivering 36.25 Gy to the prostate and proximal SV [45].

Treatment duration varies, usually delivered over consecutive days, but in some studies treatment has been given over longer periods of time, from alternate day treatments to once weekly fractions. King et al demonstrated that an alternate day treatment approach resulted in less late grade 1 or 2 rectal and bladder toxicity [46]. Henderson et al [30] however demonstrated no significant difference in grade 2 acute toxicity rates between alternate daily vs daily fractionation. Early results from the PATRIOT trial which randomised 152 patients to receive prostate SABR 40 Gy in 5 fractions either over 11 days or 29 days, found the 29-day arm to be superior in terms of patient-reported acute bowel and urinary toxicity, although no significant difference in late toxicity was found between the two schedules at median follow-up of 13.1 months [47].

DVH constraints

Although some investigators did not report the DVH constraints used, others reported that 95% [48] or 96% [49] of PTV had to receive the prescribed dose, or that all of the PTV had to receive at least 90% [50]. In PACE, 36.25 Gy in 5 fractions is prescribed, aiming to achieve a PTV V36.25 Gy ≥ 95%, and a CTV V40 Gy ≥ 95%. For CyberKnife planning, dose inhomogeneity should be kept to 120-130% of the prescription dose (or 120-150% if the urethra is contoured). For gantry-based SBRT, the following dose objectives should be met with respect to the PTV: D98% ≥ 34.4 Gy, Dmax < 48 Gy, aiming for D2% ≤ 42.8 Gy, where possible. Fuller, who tried to mimic a HDR brachytherapy distribution using a dose of 38Gy in 4 fractions, aimed for a PTV V100% ≥95 % and a max dose of 200% [51].

The PACE OAR constraints outlined in Appendix A are based on those used in the early US experience and are similar to those used in a large number of the published studies [46]. It is important to note that these constraints are theoretical derivations of conventional fractionation constraints and have yet to be validated following long-term follow-up. As a general principle, practitioners should aim to keep doses as low as possible.

The rectum is the organ traditionally considered the most important OAR for prostate radiotherapy. The high dose constraint of 36 Gy to <1cc rectum has been frequently described in the literature[52,48,53,28,54,55,56]. The Timmerman group, (delivering an escalated dose of 45 Gy to 50 Gy in 5 fractions), aimed for an anterior rectal wall Dmax of ≤105%, lateral rectal wall V90 % <3cc, and posterior rectal wall Dmax of ≤45%. They noted that a high rate of severe rectal toxicity occurred when > 3cc of contiguous rectal wall received 50 Gy. In addition they found that a high rate of high grade delayed rectal toxicity occurred when >35% of the rectal circumference received >39 Gy and the rate of ≥G2 acute rectal injury. Studies delivering 38 Gy in 4 fractions have aimed to constrain the rectum to a maximum dose of 100% prescription dose, and a maximum dose to the rectal mucosa of 75%. In terms of bladder, the PACE constraints are consistent with the majority of studies. Fuller et al have applied a maximum bladder dose constraint of 120% prescription dose, which was 38 Gy in 4 fractions [51].

11.3.3 Clinical follow-up

Biochemical control seems comparable to conventional treatment but clearly long term follow up is necessary to confirm efficacy and assess toxicity; in particular genitourinary, gastrointestinal and sexual function. In PACE, patients are assessed for acute toxicity within the first 12 weeks following treatment completion. Patents are then followed up every 3 months for the first 2 years, every 6 months to 5 years and annually to year 10, with PSA measurement and late toxicity assessment. Clinical reported toxicity is recorded according to the RTOG criteria and CTC version 4 (available via link below), and patient reported outcomes using IIEF-5, IPSS, Vaizey score and EPIC-26 instruments.

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Appendix 11.1. Summary of studies using SABR in the treatment of localised prostate cancer.

Study	Number of patients	Median follow-up (months)	Risk group (L / I /H)	Technique	CTV – PTV margin	Dose and fractionation	Schedule	ADT use	bDFS	Median PSA nadir	Toxicity
Prospective Studies											
Meier (US) 2016[28] **Error! Bookmark not defined.** and 2010[57] Multicentre	309	61	L and I	CK fiducials	NR	36.25 Gy / 5 # to PTV; 40 Gy / 5 # to CTV	NR	No	97.1% at 5 yrs L 97.3%; I 97.1%	0.7ng/ml 18 mnths (baseline 5.2ng/ml)	CTCAE v3. Acute: GU Gd 2 26%; GI Gd 2 8%. Late: GU Gd2 12%; Gd 3 2%; GI Gd2 2%.
Fuller (US) 2017[51] Multicentre	259	60	L (112) I (147)	CK fiducials	0 - 5mm	38Gy / 4 fractions Heterogenous planning	NR	No	L 100% 5yrs I 88.5% 5 yrs	0.1ng/ml 5 yrs; 0.035ng/ml 7 yrs	CTCAE v3 Late GU: Gd 2 13.7%; Gd 3 3%; Gd4 1 case. GI: Gd2 4.5%; Gd3 0.
Helou (CA) 2017[58] 3 trials	259	38 33 (40 Gy) 54 (35 Gy)	L and I	Linac/ fiducials	5mm (4mm initial trial)	40Gy/ 5# to CTV (68.3%) 35Gy/ 5# to CTV (31.7%)	11-29 days	Yes 4.6%	NR	35 Gy 0.64 ng/ml at 3 yrs 40 Gy 0.27 ng/ml	RTOG late Gd2 GU 32.6%; GI 12%; Gd 3 GU 1.9% GI 0.8%; Gd4 GI 1.1% Higher in 40Gy group
Loblaw (CA) 2017[59] 2 trials	114 Trial 1: 84 Trial 2: 30	102	Trial 1: L Trial 2: L and I	As above	4-5mm	Trial 1: 35Gy /5# to CTV Trial 2: 40 Gy/ 5# to CTV		1 pt	97.3% and 94.9% at at 5 and 8yrs	Trial 1: 0.39ng/ml at 7.67 yrs Trial 2: 0.12ng/ml at 5.95yrs	NR
Mantz (US) et al 2014[60] Prospective	102	Min 60	L	Linac / Calypso/ CBCT	NR	40Gy / 5 #	Alt days	NR	No BF at 5yrs; one at 6yrs	0.16ng/ml 5 yrs (baseline 7.3ng/ml	CTCAEv3. No G3 toxicity.
Bolzicco (IT) 2013 [61]	100	36	L (41) I (42) H (17)	CK fiducials	5mm /3mm post.	35Gy / 5#	Daily	29%	94.4% at 3 yrs	0.6ng/ml 18 mnths (baseline 6.9ng/ml)	RTOG Acute Gd2 GU: 12%, GI: 18% Late Gd2 GU 3%, GI 1%; Gd3 GU: 1%
Kim (US) 2014[62] and Hannan et al 2016[63] Multicentre	91	54	L and I	Tomo or linac Fiducials or Calypso. Rectal balloon,	2 - 3mm	Phase 1: 45 - 50 Gy / 5 # Phase II: 50 Gy / 5 #		16.5%	98.6% at 5 yrs 90.9% 45 Gy 100% 47.5 Gy and 50 Gy	0.125ng/ml at 42 months (baseline 5.4ng/ml	CTCAEv3 Acute Gd2 GU 22% GI 21%; Gd3 GI 1% Late Gd2 GU 21% GI 13%; Gd 3; GU 4% GI 4%; Gd4 ; GU 1% GI 2%
D'Agostino (IT) 2016[64]	90	28	L (53) I (37)	VMAT CBCT/ fiducials	5mm/ 3mm post	35 Gy / 5 #	Alt days	12 pts	BF 2 patients at 2 yrs	0.6ng/ml (baseline 6.9ng/ml)	CTCAEv4. Acute: GU Gd2 32.2%; GI Gd2 5.5%. Late: GU Gd 2 2.2%; GI Gd2 0%
Henderson (UK)2015[30] and Tree 2014[29]	81	30	L, I, H (6%)	CK fiducials	5mm /3mm post.	36.25Gy / 5 # PTV 40Gy / 5 # CTV	Daily/ alt day	12%	NR	0.3ng/ml 2 yrs (baseline 9ng/ml)	RTOG Acute Gd2+ GU 30%; GI 22%; Late Gd2+ GU 13%; GI 11%; Gd 3 GU 2% GI 1%

Study	Number of patients	Median follow-up (months)	Risk group (L / I /H)	Technique	CTV – PTV margin	Dose and fractionation	Schedule	ADT use	bDFS	Median PSA nadir	Toxicity
Rucinska (PL) 2016[65]	68	24	L and I	IMRT/ Fiducials/ CBCT	CTV: prostate/ 1cm SV + 3mm / 2mm (post) PTV: CTV+ 2mm	33.5 Gy / 5 #	Twice weekly	76.5%	No PSA failure	0.03ng/ml 0.6ng/ml (no ADT)	RTOG Acute gd2 GU: 35.3%, Gi: 10.3%; gd3 GU 1.5%. Late gd 2 GU: 11.8%, GI 4.4%. No late gd3 toxicity
King (US) 2012[46]	67	32.4	Low	CK fiducials	5mm /3mm post.	36.25Gy / 5#	Daily / alt day	No	94% at 4 yrs	0.5ng/ml at last follow-up	Late CTCAEv3 Gd2 GU: 5%, Gd3: 4%; Gd2 GI: 2%, Gd3+:0
Boyer (US) 2017[66]	60	27.6	L (20) I (40)	IMRT Calypso/ fiducials/ CBCT/ Exactrac	5mm / 3mm post.	37 Gy / 5 #	Alt days	No	NR		CTCAEv4 Acute Gd2 GU: 25%, GI: 5% Late Gd2 GU: 6.7%, GI: 8.3%; Gd3+ GI: 1.7%
Aluwini (NL) 2013[44]	50	23	L and I	CK fiducials	3mm	38Gy / 4# and 11Gy/ # boost to MRI-defined tumour (28%)	Daily	No	NR	0.6 ng/ml ≥ 24 mnths; 1.1ng/ml ≥ 12 mnths	RTOG Acute Gd2 GU 15%, Gd3: 8%; GI: 12%, Gd3:2% Late Gd2 GU 10%; Gd3 6%; Gd2 GI 3%
McBride (US) 2012[56] Freeman et al[67] Multicentre	45	44.5	Low	CK fiducials	5mm /3mm post.	36.25 - 37.5 Gy /5#	7 days	No	97.7% at 3 yrs	0.2ng/ml at final follow-up (baseline 4.9ng/ml)	Acute (CTCAEv4) Gd 2 GU: 19%, G2 GI: 7%; Gd 3+: 0 Late (CTCAEv4) G2 GU: 17%; G3: 2%; G2 GI: 7%, G3: 5%
Kotecha (US) 2016[68]	24	25	I 46 %, H 54%	Platform NR Heterogenous planning	Low Dose PTV: 3mm/0mm post	36.25 Gy / 5 # to Low Dose PTV 50 Gy / 5 # to High Dose PTV	Alternate days	Yes 67 %	NR	0.09ng/ml at last follow-up	CTCAEv4. Acute GU Gd2 frequency 38%, retention 16%; GI Gd2 0%. Late GU Gd2 cystitis 4%, frequency 4%; proctitis 8%; no Gd3 toxicity
Retrospective Studies											
Kishan (US/ CA) 2018[25] Multi-institutional consortium	1644	86.4	L (54%)) I (46%)	NR	NR	33.5-40Gy / 4-5#	NR	3.6%	L 98% ad I 95% at 5 yrs L 94% and I 91% at 10 yrs	NR	CTCAEv3 or RTOG.. Acute: GU Gd3 0.3%; Late: GU Gd3 2%, Gd4 1 patient; GI Gd 4 1 pt.
King (US/ IT) 2013[31] Pooled analysis	1100	36	L (58%) I (31%) H (11%)	CK fiducials	5mm/ 3mm post. or 2mm/ 0mm post (heterogenous planning)	Median 36.25 Gy / 5 # (range 35 – 40 Gy)	Daily (>95%)	14%	93% at 5 yrs L 95%; I 84%; H 81%	0.2 ng/ml 3 yrs	NR
Katz (US) 2017[69]	230	108	L	CK Amifostine	5mm/ 3mm post.	35–36.25 Gy / 5 #	Daily	NR	93.7% at 10 yrs	0.1ng/ml 4yrs (baseline 5.6ng/ml)	RTOG. Late: GU Gd2 9%; Gd3 3%; GI Gd 2 4%, no Gd3/4

Study	Number of patients	Median follow-up (months)	Risk group (L / I /H)	Technique	CTV – PTV margin	Dose and fractionation	Schedule	ADT use	bDFS	Median PSA nadir	Toxicity
Katz and Kang (US) 2016[70]	515	84	L (63%) I (30%) H (7%))	CK fiducials	5mm / 3mm post.	35Gy-36.25 Gy / 5 #	Daily	14%	L 93.6%, I 84.3%, H 65% at 8yrs	NR	NR
Katz (US) 2013[71]	304	60	L (69%), I (27%) H (4%)	CK fiducials	5mm / 3mm post. (8mm side of high risk disease)	35- 36.25 Gy / 5 #	Daily	19%	L 97%; I 90.7%; H 74.1% at 5 yrs	0.12ng/ml 5 yrs	RTOG. Acute: GU Gd2+ 14; GI Gd2+ 11. Late: GU Gd2+ 4% (35 Gy); 9% (36.25 Gy); Gd3 2% (36.25 G)y; GI Gd2+ 2% (35 Gy), 5% (36.25 Gy)
Oilai (US) 2016[72]	263 142 SBRT 121 IMRT	51 43 SBRT 34 IMRT	L / I / H	SBRT CK/ fiducials	SBRT 5mm / 3mm post. IMRT 8mm/ 5mm post	SBRT 35Gy - 37.5Gy / 5# IMRT 75.6 Gy/ 42 #	NR	SBRT 28.2% IMRT 71.9%	89.7% SBRT, 90.3% IMRT at 5 yrs	NR	RTOG. Persistent toxicity. GU Gd 2 SBRT 14%; IMRT 12%; GI Gd 2 SBRT 3%; IMRT 1%. All Gd 3 subsided
Oilai (US) 2013[55]	70	31	L (51%) I (31%) H (17%)	CK/ fiducials	5mm/ 3mm post.	35Gy - 37.5Gy / 5 #	Daily 17%	33%	94.5% at 3 yrs L 100%; I 95%; H 77.1%	0.2ng/ml 37 mnths (baseline 5.6ng/ml)	RTOG. Acute: Gd2 GU 19% GI 4%; Gd3 GU4% Late Gd2 GU29% GI 4%; Gd3 GU 3%
Kataria (US) 2017[73]	145	67.2	L (65) I (80)	CK fiducials	5mm (3mm post)	35 - 37.5 Gy / 5 #	Alt days	No	L 98.5%; I 95.5% at 5 yrs	0.2ng/ml	NR
Chen (US) 2013[54]	100	27.6	L (37) I (55) H (8)	CK/ fiducials	5mm (3mm post)	35 – 36.25 Gy / 5#	Alt days	11	99% at 2 yrs	0.49 ng/ml 2yrs	CTCAEv3. Acute: GU Gd2 35%; GI Gd2 5%. Late: GU Gd2 30%; Gd3 1%; GI Gd2 1%;
Rana (US) 2015[74]	102	51.6	L(36.3%) I (54.9%) H (7.8%)	CK fiducials	5mm /3mm post.	36.25 Gy / 5#	Daily	8.9%	100% at 3yrs	0.3ng/ml 3 yrs (baseline 5.8ng/ml)	RTOG G2 GU 9.9%, GI G2 3%; No G3/4
Freeman and King (US) 2011[67] Pooled cohort	41	60	Low risk	CK fiducials	5mm /3mm post.	35 or 36.25Gy / 5#	Daily (38)	No	92.7% at 5 yrs	0.3ng/ml at last follow-up (baseline 5.4ng/ml)	Late RTOG Gd3 GU: 2%; Gd3+ GI: 0
Friedland (US) 2009[75]	112	24	L /I /H	CK fiducials	5mm /3mm post.	35 to 36Gy / 5#	Daily	19%	3 PSA failures	0.6ng/ml at 18 months	Gd3 rectal toxicity in 1 patient (not specified if acute or late)
Pham (US) 2010[76] and Madsen 2007[77]	40	60	L	Linac/ fiducials Simethecone	NR	33.5Gy / 5 #	Daily	NR	93% at 5 yrs	0.65ng/ml at 2 yrs	RTOG. Acute: GU Gd2 21%, Gd3 3%, Gd4:0%; GI Gd2 13%, Gd3+ 0%. Late GU Gd2 13%, Gd3 3%, Gd4 0%; GI Gd2 8%, Gd3+ 0%

L, low-risk; I, Intermediate-risk; H, high-risk; CK, CyberKnife; NR, not recorded; GU, genitourinary; GI, gastrointestinal

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12. Spinal metastases

12.1. Introduction and literature review

Spine metastases are a common complication of malignancy, occurring often in patients with primary breast, prostate or lung malignancies [1]. They usually involve the vertebral body, often with an associated paraspinal soft tissue mass and may grow into the epidural space resulting in compression of the spinal cord with potentially devastating neurological consequences. Spinal oligometastases are expected to become increasingly observed as a result of a number of factors including earlier detection through better imaging techniques, improvements in systemic therapy and longer survival rates [2]. If left untreated spinal metastases can cause a number of symptoms which may have a detrimental effect on a patient's quality of life. For example, most patients will suffer with pain, which may be severe and can develop neurological complications due to the close proximity of disease to the spinal cord or cauda equina.

Spinal metastases are an incurable complication of malignancy but with better systemic therapies patients now may live for longer and therefore suffer a longer duration of spinal pain and neurological symptoms. Conventional management of spinal metastases includes the use of analgesia, such as opiates, surgical intervention (e.g. decompression, debulking or spinal stabilization) and conventional external beam radiotherapy techniques. All these modalities offer a limited duration of symptom control and better techniques are required to offer this select group of patient's better longer term local disease and symptom control to improve their quality of life.

12.1.1 Conventional Radiotherapy and Outcomes

External beam radiotherapy can palliate pain in 50-70% of cases of spinal column metastases and is widely used. A number of trials have considered the role of fractionated external beam radiotherapy versus single fraction treatment for pain control. Two large meta-analyses in the early 2000s revealed no difference in pain control with single versus multiple fraction regimes, most commonly 8 to 10Gy in a single fraction versus multi-fraction regimes comprising 20Gy in 5 fractions or 30Gy in 10 fractions; however those treated with a single fraction required significantly more re-treatments than the multiple fraction regime patients [3, 4]. The level of pain relief is rarely complete and other related endpoints are less well investigated.

A further updated meta-analysis published in 2007 also found no difference in response rates with multiple versus single fractions but again a significant 2.5 fold increase was seen in the number of patients needing re-irradiation after a single fraction [5].

Conventional radiotherapy techniques are limited by the tolerance of the critical organ at risk, the spinal cord. This is particularly important in patients who have previously received external beam radiotherapy as the risk of radiation induced myelopathy is greater in this group.

12.1.2 SABR for spinal metastases

SABR offers the ability to safely deliver a high biological equivalent dose in a hypofractionated regime to disease in close proximity to the spinal cord. Early data (see Table 12.1 below) suggests that by delivering a higher dose of radiation, it is possible to achieve higher levels of control of both pain and disease, which should in turn result in a better quality of life for possibly a longer duration of response. According to a recent review, local control using SABR has been achieved in 87% of previously unirradiated patients, 96% of re-irradiated patients and 94% of post-operative patients [6].

Indications for spinal SABR include: for patients with oligometastases of the spine with little systemic disease or at least controlled disease elsewhere with a reasonable duration prognosis (at least 3 months); patients with oligoprogression of a spinal metastasis in the presence of controlled systemic disease to avoid the need for a change in systemic therapy; for cases of progression following previous external beam radiotherapy (at least 3 months prior to SABR) with a reasonable prognosis. These have been detailed in the 2011 ASTRO guidelines for the treatment of bone metastases [7].

The technique has become widely used around the world, particularly in North America. A recent survey of US radiation oncologists revealed that spinal SABR was the second most common indication for the use of SABR within the USA [8]. Despite this, to date there is little high quality evidence to define the most appropriate role of spinal SABR and the techniques and schedules currently in use vary widely. For example, a survey of five centres in North America showed great variation in the dose / fractionation schedules used [9], with regimes ranging from a single fraction to 10 fractions. Furthermore, even within the single fraction treatment regimes, the doses delivered ranged between 16-24 Gy.

12.1.3 Indications for Spinal SABR

Patients who have not received prior external beam radiotherapy

SABR to spinal oligometastases as the initial treatment for patients without prior radiotherapy offers the opportunity to deliver the maximum possible dose to the tumour volume while taking the spinal cord dose to the maximum safe acceptable dose. Research is ongoing to define the maximum safe dose to the spinal cord, also accounting for the potential radiobiological effects of hypofractionation. Sahgal et al have reviewed nine recognised cases of radiation induced myelopathy post spinal SABR [10] and compared them to 66 cases where no radiation induced myelopathy was observed. The individual irradiated volumes were compared and a significant difference was observed between the mean maximum 2Gy normalized biological equivalent dose (nBED) for those who went on to develop radiation induced myelopathy and those who did not. A risk of radiation induced myelopathy of ≤5% was observed when limiting the thecal sac point maximum volume doses to 12.4 Gy in a single fraction, 17.0 Gy in 2 fractions, 20.3 Gy in 3 fractions, 23.0 Gy in 4 fractions, and 25.3 Gy in 5 fractions [10].

As spinal SABR becomes more widely available and with an increasing number of patients being diagnosed with spinal oligometastases this may well become the main

indication for treatment once robust data has confirmed the benefits of sustainable pain and local disease control.

Patients who have received prior external beam radiotherapy

In the current clinical setting this is likely to be the most commonly used indication for spinal SABR as patients are living longer with metastatic cancer. It seems likely that more and more patients will require re-irradiation of their spinal metastases following prior external beam conventional radiotherapy and evidence to date suggests that spinal SABR may offer a longer duration of symptom control than re-irradiation using conventional external beam radiotherapy at a lower dose due to the tolerance of the spinal cord. By sparing the spinal cord, SABR will allow further dose escalation potentially resulting in better disease and symptom control.

Many questions regarding this treatment remain unanswered, including how long the minimal interval between conventional radiotherapy and re-irradiation using SABR should be. Early data, the majority of which has been collected retrospectively, seems to support this treatment (see Table 12.1) although again further robust trial data is required to confirm the benefits of SABR over conventional re-irradiation before this is implemented into everyday practice. The radiobiology of the spinal cord is still not thoroughly understood with ongoing research considering time intervals between treatments and the propensity of the cord to recover and tolerate re-irradiation.

12.1.4 Optimal Dose Fractionation Schedule

Spinal SABR has been delivered via a range of fractionation schedules ranging from a single fraction (8 to 24Gy), through to hypofractionated regimes such as 30Gy in 5 fractions, 24-27Gy in 2 or 3 fractions and 35Gy in 5 fractions. To date there is no definite evidence to recommend one regime over another.

12.1.5 Treatment Outcomes

At present there is a lack of high quality evidence for treatment of spinal metastases with SABR. There are a number of reasons: firstly, patients with spinal metastases are a difficult group of patients to study due to the heterogeneity of the population, for example the metastases may arise from many different primary tumour types which will all have different intrinsic radiosensitivity; secondly, outcomes from this type of targeted radiotherapy are difficult to measure and require in depth quality of life analysis and objective pain response assessment, alongside defining an accurate measure of disease control using imaging techniques; thirdly, patients at this stage in their disease process may be less reluctant to partake in clinical trials if it may deny them access to a more advanced modern radiation technique; fourthly, the difficulty of adequately blinding patients and researchers when carrying out trials in this setting to minimize unwanted bias.

Table 12.1 summarizes the published literature to date on the use of spinal SABR. The majority of this data is limited by small numbers and/or the retrospective nature of the data collection. Some small prospective studies have been published but are

again limited by the heterogeneity of the populations studied with the majority of the data presented including patients who have both received and not received prior radiotherapy. Results are awaited from the RTOG 0631 trial [11] which has completed accrual, randomizing between conventional external beam radiotherapy to a dose of 8Gy in 1 fraction versus a 16Gy in 1 fraction SABR treatment. The trial included good performance patients with painful metastases affecting up to 3 spinal sites with a maximum of two consecutive levels at any one site. Patients were stratified according to whether their tumour was deemed to be a radio-resistant (e.g. sarcoma, renal cell carcinoma or melanoma) or a radio-sensitive tumour. Hopefully the results of this trial will provide further evidence to guide the future use of spinal SABR services and research.

12.1.6 Local Control

Tumour control following spinal SABR is difficult to define with no real consensus on which imaging modality is best to monitor this and how frequently these scans should be done. Indeed, it may be that different tumours are better monitored with different imaging modalities or tests and that as such the best way to define response should be based upon a number of individual patient characteristics. Examples would include: disease control, for example defined by RECIST criteria on serial scans or tumour markers, or PSA biochemical response for isolated prostate cancer spine metastases.

Despite these limitations, the published data (see table 12.1) does suggest that spinal SABR improves local control with rates ranging from 60 to 95% in the first few years following treatment. Again further prospective studies are needed to confirm this and to properly assess the impact local control has on other outcomes including quality of life, symptom control and survival.

12.1.7 Pain and Symptom Control

Across the literature reviewed here, pain control is achieved in 40-90% of patients. The definition of pain control varies, making comparisons between individual publications difficult. Pain control can be measured using scoring tools such as the brief pain inventory score [12]. Limitations with current data may be that the majority of it was collected retrospectively and in this setting defining adequate pain score outcomes is difficult. It seems reasonable to conclude that pain control may be improved for a number of patients but until high quality prospective pain control data post spinal SABR is published the exact benefits of this technique remain unknown. In addition, the heterogeneity of the population studied may also affect these outcomes given that pain is affected by a number of factors including the level of bone destruction, nerve root compression and neuropathic component, individual pain threshold and co-existing treatments such as analgesia.

12.1.8 Treatment Complications:

Acute Complications

Little data has been published on the acute complications of spinal SABR (e.g. mucositis, dysphagia, diarrhoea and transient radiculopathy) but the current data suggests that this technique is well-tolerated. This of course may be subject to publication bias and again a robust prospective trial is needed to confirm these results.

Published data suggests that if patients are treated without steroid cover then they may suffer a high incidence of pain flare in the days post spinal SABR with a peak at 24 hours post treatment [13]. All patients should therefore be offered high dose steroid cover when undergoing spinal SABR.

Similarly, vertebral compression fracture is a well-documented complication of spinal SABR [14], in comparison to conventional radiotherapy where the risk is <5% [15]. Published retrospective data in non-selected patients have revealed rates from 11-39% [16-18]. It is well recognised that all patients undergoing spinal SABR should have their risk of vertebral compression fracture assessed prior to treatment, including assessment using the Spine Instability Neoplastic Score (SINS) [19]. If the spine is deemed to be unstable a surgical review prior to SABR is essential.

Late Complications

Follow up time is relatively short in patients undergoing spinal SABR so little knowledge of the late effects of this treatment is currently available. Whilst this may be mostly because the majority of these patients do not survive for more than a few years post treatment, there are likely to be some outlying patients who do survive in the long term post SABR. It is crucial these patients are monitored closely to thoroughly assess the late toxicities of this new technique.

The incidence of radiation induced myelopathy following spinal SABR appears to be a rare event. Sahgal et al reviewed nine cases after an international review and as a result of this defined safe spinal cord limits [10]. Again this may be subject to publication bias and ideally a large prospective trial with substantial follow up is needed to confirm that these constraints are indeed safe.

Table 12.1: Summary of Studies Using SABR in the Treatment of Spine Metastases

Study	Number of patients	Median Follow up (range) / months	Technique	Spinal Cord Dose constraints	Dose and fractionation (BED α/β =10)	Duration	Imaging outcomes – Local control rate (%)	Pain outcomes	Toxicities
Schipani et al 2011 [20] (retro)	124	7 (1-50)	Linac	10 Gy to <10% cord volume	18Gy / 1# (50.4)	1 day	92% achieved control	92% achieved control	No grade 2-4 RTOG acute or late toxicities
Ryu et al 2011 [21] (prosp ph2 feasibility RTOG0631	44		Multi-centre study	1) 10 Gy to <10% cord volume or 2) 10 Gy to <0.35 cc of cord	16Gy / 1#	1 day			No G4 [CTCAE 3.0]; G1-2 acute (n=11); G3 acute (neck pain, n=1)
Chang et al 2007 [22] (prosp)	63	21.3 (0.9-49.6)	Linac	a) cord ≤10Gy b) cord ≤9Gy	a) 30Gy / 5# (n= 32) b) 27Gy / 3# (n=31)	Daily fractions		Narcotic usage fell to 36% at 6 mths (baseline 60%)	
Degan et al [23] (retro)	51 (38 with previous RT)	Mean 12	CyberKnife	Maximum 27.1Gy	Mean 21.2Gy (10.0-37.5) Mean dose/#: 6.45Gy (1-5#)	Daily fractions		First FU: decreased pain (84%), 74% pain free	No G3-4
Gerszten et al [24] (prosp)	393 (500 lesions, 344 with prior RT)	21 (3–53)	CyberKnife	Maximum dose 10Gy	Maximum intratumoral dose 12.5-25 Gy (mean 20) in 1 fraction	1 day	88% long term radiographic tumour control	Long term pain decrease (86%), neurological improvement (84%)	Nil reported
Wang et al 2012 [25] (prosp)	149	15.9 (1.0-91.6)	Linac	10Gy to <0.01cc of cord	27–30 Gy in 3 fractions	Every other day	Actuarial tumour 2 year PFS = 72.4% (95% CI 63.1%–79.7%),	Significant reduction in pain score and opiate use between baseline and 6 months post SBRT	G3 nausea (n=1),vomiting (n=1), diarrhoea (n=1), fatigue (n=1), non-cardiac chest pain (n=3), dysphagia (n=1), neck pain (n=1), diaphoresis (n=1), pain with severe tongue edema and trismus (n=2). No G4
Yamada et al 2008 [26] (prosp)	93	15 (2–45)	Linac	14Gy maximum dose	18–24 Gy in 1 fraction	1 day	90%	Not reported	Vertebral fracture (n=2) No G3-4

Study	Number of patients	Median Follow up (range) / months	Technique	Spinal Cord Dose constraints	Dose and fractionation (BED α/β =10)	Duration	Imaging outcomes – Local control rate (%)	Pain outcomes	Toxicities
Nguyen et al 2010 [27] (retro)	48	13.1 (3.3–54.5)	Linac	Max cord dose 9–10 Gy	24 Gy / 1# 27 Gy / 3# 30 Gy / 5#	Daily fractions	1 year PFS 82%	52% pain free at 12 months	G3 anaemia (n=1), G3 pain (n=1), no G4
Gagnon et al 2009 [28] (prosp)	151 (125 with prior RT)	12 (1–51)	CyberKnife	Unknown	1. Mean dose =26.4Gy/3# (if no prior RT) 2. Mean dose =21.05Gy/3# (if prior RT).	Daily fractions	Not reported	Significant decrease in mean pain score, continuing up to 4yrs post	Mild acute toxicities. Vertebral fracture (n=2), wound breakdown (n=1)
Gibbs et al 2007 [29] (prosp)	74	9 (0–33)	CyberKnife	Max 10Gy (for single fraction)	16–25 Gy in 1–5#	Daily fractions	N/A	84% improvement	Severe myelopathy (n=3)
Tsai et al 2009 [30] (retro)	69 (15 had prior RT)		CyberKnife		Mean 15.5Gy / 2# (10-30Gy)	Daily fractions	96.8% radiographic local control (10 months)	88% pain control	
Sahgal et al 2009 [31] (retro)	39 (60 mets, 37 with prior RT)	8.5 (1-48)	CyberKnife	Median maximum dose: No prior RT 16.8 (10.7–26) Prior RT 12.8 (5.4–27)	24Gy/3# to 67% and 60% isodose for unirradiated and irradiated respectively	Daily fractions	85% 1 year, 69% 2year	85% pain improvement	No G3-4
Chang et al 2009 [32] (retro)	129 (52 with prior RT)	14.3 (1-63)	CyberKnife	N/A	16-39 Gy / 1-5#	Daily fractions	69%	91%	No G3-4
Sheehan et al 2009 [33] (retro)	40	12.7 (4-32)	TomoTherapy	<10 Gy to 10% spinal volume	Mean 17.3 Gy / 1-5# (range 10-24 Gy)	Daily fractions	82%	85%	Worsening segmental kyphosis in 73%
Amdur et al 2009 [34] (prosp ph2)	25 (12 had prior RT)			12Gy to 0.1cc (no prior RT) 5Gy to 0.5cc (with prior RT)	15Gy / 1#	1 day	95%	43%	G1-2 dysphagia or nausea, vertebral body compression (n=3)
Shin et al 2009 [35] (retro)	9	10	Linac	Decided on an individual patient basis	Mean 13.8Gy (10–16Gy) in 1#	1 day	89%	80%	Nil reported
Wowra et al 2008 [36] (prosp)	102	15	CyberKnife	Unknown	Median 19.4 Gy /1# (range: 15–24 Gy) to 70% (range: 50%–85%) isodose	1 day	98% (95% CI: 89 –99%) at 15 months	Significant reduction in pain score (P<0.001)	Vertebral fracture (n=1), segmental neuropathy due to haemorrhage (n=1)
Ryu et al 2004 [37] (retro)	49	6-24	Linac	Unknown	10-16Gy / 1#	1 day	95%	85%	Unknown
Bishop et al 2015 [38] (retro)	285 (332 mets)	19 (0-111)	Linac	Unknown	18Gy/1# 24Gy/1# 27Gy/3#	Daily or alternate day fractions	1 year LC 88% 3 year LC 82%	Not reported	Unknown

Tao et al 2016 [39] (prosp. review of Ph1/2 trials)	66 (69 mets) post-op	30 (1-145)	Linac	Single #: 0.01cm^3 max. dose 10Gy Multiple #: max. 9Gy/3#	16-24Gy/1# 30Gy/5# 27Gy/3#	Alternate day fractions	1 year LC 85%	Not reported	No grade 3 or higher toxicities
Guckenburger et al 2014 [40] (retro)	301 (387 mets)	11.8 (0-105)	Linac	Max. point dose PRV spinal cord (EQD2/2 Gy) 2 – 112 Gy (median 22.4Gy)	Median 24 Gy (10 – 60 Gy) in a median of 3# (1-20)	Daily or alternate day fractions	1 year LC 89.9% 2 year LC 83.9%	Pain free at last assessment in 76.8% (pain-free pre-SABR), 56.3% (mild/ moderate pain pre-SABR) and 43.8% (severe pain pre-SABR)	2 patients suffered grade 3 pain. No other grade 3 or above toxicity.
Bernard et al 2017 [41] (retro)	127 (148 mets)	22.6	Linac	Unknown	27Gy/3# 18Gy/1# 24Gy/1# 16Gy/1# 30Gy/5# 24Gy/3#	Daily or alternate day fractions	1 year LC 82.6% 2 year LC 75.8%	Not reported	10 patients suffered compression fractures. No other Grade 3 or above toxicity
Thibault et al 2014 [42] (prosp)	37 (71 mets)	12.3 (1.2–55.4)	Linac	Median cord PRVmax. point dose (EQD2 QD2oi = 28.41 Gy2 (0.02–59.58)	Median 24 Gy (18–30 Gy) in 2# (1–5)	Daily or alternate day fractions	1 year LC 83%	Not reported	No grade 3 or more toxicity reported
Chang et al 2017 [43] (retro)	60 (72 mets)	21 months	Linac		20Gy/1# 24Gy/2# 24Gy/3#	Daily or alternate day fractions	1 year freedom from local progression = 92% 2 year freedom from local progression = 86%	Not reported	4 cases of vertebral compression fracture
Yoo et al 2017 44	33 (42 spinal segments)	7 months (1-43)	Linac	maximum dose of 14 Gy (0.03 cc) 10 Gy (0.35 cc)	16-20Gy/1# 18-45Gy/3#	Not stated	1 year LC 68.3% Radiographic cord comp ≤ II, 1-year LC rate w as 92.9%	73.3% Median duration 7 months	28.5% at 1 year
Gestaut et al 2017 [45]	73 (95)	12.7 months (1-56)	Linac		20Gy single fraction		LC 97% at median FU	mean 81% decrease in subjective pain score. 77% of patients had decrease in narcotic pain medication use. Pain completely resolved for 69%	Need full text
Summary: 24 studies	2528						Mean = 86.6%	Mean = 78.2%	

12.2 Patient selection criteria

Inclusion Criteria

- Spinal oligometastatic disease
- Performance status 0-2
- Limited systemic disease
- Not more than 2 consecutive spinal vertebral bodies involved
- Tumour at least 3-5mm from the cord
- Well defined lesions on imaging
- Age > 18 years old
- Histological confirmation of neoplastic disease

Exclusion criteria

- Patients with spinal instability (SINS score 13-18) or unable to lie flat / tolerate treatment
- Contraindication to MRI e.g. pacemaker in situ
- Prognosis < 3 months
- Significant or progressive neurological deficit such that emergency surgery or radiation required
- Radiosensitive histologies such as myeloma or lymphoma tumour type
- Spinal cord compression or impingement

All spine SABR patients should ideally be treated as part of a clinical trial.

12.3 Radiotherapy

Consent

Patients should be consented in line with DOH guidance [43] and will be given a spinal SABR patient information sheet.

Specific side effects to be consented for include:

All: Fatigue, skin reaction, pain flare, increased risk of vertebral compression fracture or vertebral collapse which could require surgical intervention and small risk of myelopathy or nerve damage.

C spine: Mucositis

T spine: Oesophagitis, nausea, chest pain, rib fracture, small long term risk of tracheo-oesphageal fistula / stricture formation

L spine: Diarrhoea, nausea, small risk of bowel damage (<5%)

12.3.1 Tumour delineation and OARs

Tumour Delineation should follow International Guidelines [44] and can be summarised as follows:

Fig 12.1. Anatomic classification system for consensus target volumes for spine SABR.

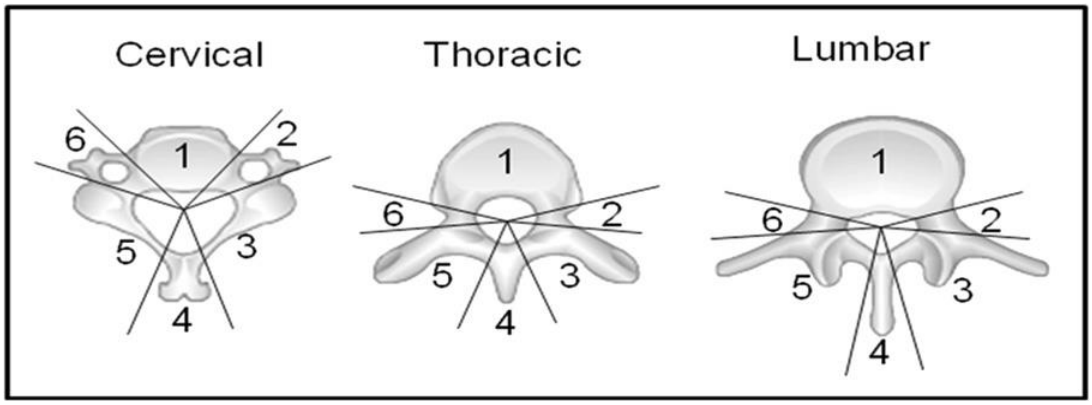
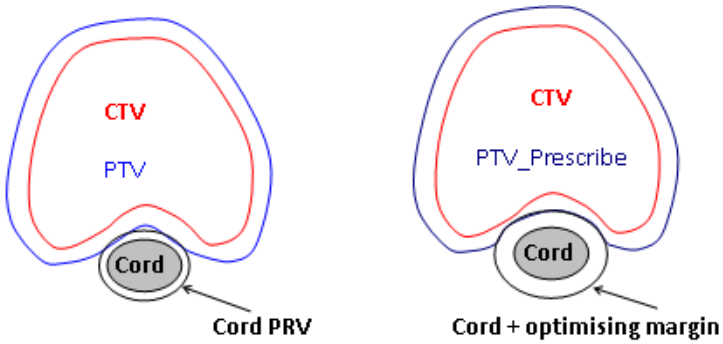


Table 12.2. Guidelines for spinal SABR bony CTV delineation

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

Figure 12.2. Illustration of PTV_Prescribe volume



In delineating the target volume, the recommendations of ICRU62 [47] should be followed, with an additional volume, here termed *PTV_prescribe*, recommended to account for the proximity of the spinal cord.

GTV	Contour gross tumour using all available imaging. Include epidural and paraspinal components of tumour
CTV	Should contain GTV and include bony CTV expansion to account for subclinical spread. Include abnormal marrow signal suspicious for microscopic invasion, as indicated in Fig 12.1 and Table 12.2. Circumferential CTVs encircling the cord should be avoided except in rare instances where the vertebral body, bilateral pedicles/lamina, and spinous process are all involved or when there is extensive metastatic disease along the circumference of the epidural space without spinal cord compression
PTV	The expansion margin from CTV to PTV should be established dependent on local practice but should reflect the geometric accuracy with which a centre can confidently delineate a target volume, setup a patient and deliver the planned dose distribution, verified with QA. A margin of 2-3mm may be appropriate. Dose to this volume should be reported in all circumstances.
PTV_Prescribe	In order to allow for unavoidable underdosing of the PTV in close proximity to the spinal cord, while maintaining consistency in treatment prescription, it is recommended that a volume be created (PTV_Prescribe, see Figure 12.2) that restricts the PTV by spinal cord PRV+2mm. If it is different from PTV, this volume should be used for prescribing and additional dose reporting. i.e. PTV_Prescribe = PTV – [cord PRV+2mm] N.b. PTV_Prescribe volume may be generated or edited appropriately in treatment situations where GTV extends beyond this volume, with consideration given to the achievable dose gradient.

Spine dose constraints must be met. Other constraints may be compromised at the clinician's discretion.

12.3.2 Fractionation

There is little consensus in the literature about the optimal dose for spinal metastases SABR but the following have been shown to produce good outcomes with acceptable levels of toxicity, although alternative schedules are also being investigated:

- 24Gy in 2 fractions
- 27Gy in 3 fractions
- Re-irradiation fractionation 30Gy in 5 fractions, however this needs to be considered on an individual patient basis to assess the previous cord dose delivered.

It is recommended that the treatment be prescribed so that 95% of the PTV (or PTV_prescribe where appropriate) should be covered by the prescription isodose unless there is need to accept less coverage to achieve the OAR tolerances. Hot spots should be within the PTV and ideally should not exceed 130% of the prescribed dose.

It is recommended that the inter-fraction interval be at least 40 hours, with a maximum interval of 4 days between treatment fractions.

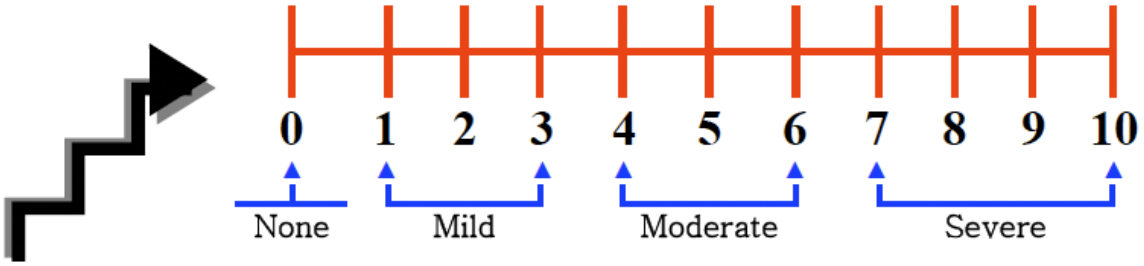
12.3.3. Treatment delivery and clinical follow-up

Table 12.3. Suggested Assessments at baseline and during radiotherapy.

Procedure	Base-line	During RT	1 month post RT
Medical History	X	X	X
Physical Examination	X	X	X
Weight	X		X
WHO PS score	X	X	X
FBC	X		
MRI scan	X		
Informed Consent	X		
Adverse event monitoring CTCAE v4.0	X	X	X
Pain assessment (NPRS)	X	X	X
QOL (QLQ C30)/	X		X

Follow up is suggested at 1, 3, 6 and 12 months, then annually thereafter. At each follow up visit local control, defined as tumour shrinkage or no tumour progression, will be assessed using serial MR imaging. Pain will also be assessed using NPRS (see Fig 12.3) and Quality of life data should be collected using QLC-30.

Figure 12.3. NPRS scale for pain assessment



	Months post RT						
Procedure	3	6	12	24	36	48	60
Medical History	X	X	X	X	X	X	X
Physical Examination	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X
MRI scan	X	X	X	X	X	X	X
Pain assessment	X	X	X	X	X	X	X
Adverse event monitoring	X	X	X	X	X	X	X
QOL		X	X	X	X	X	X

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13. SABR for adrenal metastases

13.1. Introduction and literature review

Adrenal glands are a site of metastatic disease in patients with lung cancer, breast cancer and melanoma. Adrenal metastases cause pain and are a significant detriment to the quality of life of cancer patients. Median survival without treatment in this group is 3 months [1]. While a majority of these cases are seen in the setting of disseminated disease there appears to be an intermediate oligometastatic state where resection leads to advantage in terms of survival [2-5]. An overall survival of 25% at 5yrs is quoted in this selected group of patients after complete surgical resection.

Evidence for this oligometastatic state is particularly apparent in lung cancer where the route of spread may be lymphatic (i.e. regional rather than hematogenous), with the implication that aggressive “regional” management may improve overall survival outcome [6].

While surgical resection remains the treatment of choice in selected patients, the advent of Stereotactic ablative radiotherapy (SABR) and radiofrequency (or microwave) ablation provides localised therapy options for the patients with oligo-metastatic disease where surgery is not considered feasible or appropriate.

13.1.1 Evidence for SABR for adrenal metastases

The evidence for SABR in the treatment of adrenal metastases is replicated in Table 13.1 from Gunjur et al [16] and is seen to consist mostly of retrospective series with one prospective study [14]. Due to the heterogeneous group of patients, treated with a variety of doses and fractionations, no robust evidence-based conclusions can be drawn. However some common themes emerge from the literature review.

- Non-small cell lung cancer is the most common primary site.
- SABR is used when the adrenal metastases are not amenable to surgery.
- SABR appears to produce inferior 2-year overall survival compared to surgery (19% vs 44%) in pooled series. However, this is biased by patient selection, both in terms of inclusion of isolated adrenal disease (48% in SABR compared to 75% in surgical series) and performance status / comorbidities.
- Patients of good performance status (KPS >70 ECOG 2 or better) were included.
- Synchronous metastatic disease appears to have a poorer outcome compared to metachronous metastatic disease (arising 6 months or more after primary diagnosis).
- Most studies used vacuum bags for immobilisation with a knee roll. Some older studies used a stereotactic frame.

Table 13.1: Summary of evidence for adrenal SABR

Study (year) Ref no.	Patients (lesions)	Histology	Median Dose (Range) Gy	Fractions	Median FU months	Local control
Katoh et al (2008) *(7)*	8 (9)	56% NSCLC 11% SCLC 22% HCC 11%RCC	48 (30-48)	8(8)	16	1 & 2Yr -100%
Chawla et al (2009) *(8)*	30 (30)	66% LungCa 10% HCC% 10%Brst Ca 3%Pancr Ca 3% Melanoma	40 (16-50)	4(4-10)	9.8	1yr – 55% 2yr – 27%
Torok et al (2011) *(9)*	7 (9)	57% NSCLC 14% SCLC 29% HCC	22 (10-36)	1 (1-3)	14	1yr – 63%
Oshiro et al (2010) *(10)*	11(11)	74% NSCLC 26% SCLC	45 (30-60)	5 (1-27)	10.1	6 months 94.7%
Holy et al (2011) *(11)*	18(18)	100% NSCLC	40 (20-40)	5 (5)	12	1yr - 94.4% 2yr -78.7%
Casamassima et al (2011) *(12)*	48(48)	50% Lung Ca 25% CRC 8% Melanoma 6% Br.Ca 6% RCC	36 (21-54)	3(3)	16.2	1yr and 2yr 90%
Goiou et al (2011) *(13)*	9 (10)	44% NSCLC 56% SCLC	25 (20- 37.5)	5 (5)	7.3	1yr and 2yr 44%
Ahmed et al (2012) *(14)*	13 (13)	31% NSCLC 8% SCLC 15% RCC 15% SKIN	45 (33 – 60)	5 (5)	12.3	Crude- 100%
Scorsetti et al (2012) *(15)*	34 (36)	64% NSCLC 7% SCLC 7% Melanoma	32 (20-45)	(4 (4-18)	41	1yr- 66% 2yr-32%
Rudra S et al (2013) *(17)*	10 (13)	60% NSCLC 20% SCLC 20% RCC	36 (24-50)	3(3)	14.9	1 yr -73%
Chance W et al. (2015) *(18)*	41 (47)	89% Lung Ca 5% Ovarian Ca 2% Bladder ca 2% Esoph ca 2% Skin ca	60 (50-60)	10(4-10)	11	1 yr -87%

- Most recent studies have used 4D CT for treatment planning with contrast, often with some form of respiratory motion management.
- Tumour volumes were outlined either on the MIP of the 4DCT or the co-registered end expiratory breath hold CT volumes and in some series PETCT / MRI.
- The GTV/ITV was expanded to PTV by either an isotropic 5mm margin or a centre-specific margin (3-5mm in different directions)
- Treatment delivery was with image-guided-radiotherapy (IGRT), usually with cone-beam CT as most of the published series were linac-based.
- Local control rate in the largest series (n=48) was 90% at 2 years [12] with 36Gy/3#, while the only prospective series used 45Gy/5# with a local control rate of 100% at 2 years [14]. There was an indication that higher BED could lead to better local control although most doses used lead to good palliation of symptoms [16].
- Acute toxicity was limited to grade 2 or below gastro-intestinal symptoms (nausea /dyspepsia) ranging from 0-17% [16]. Rates of gastritis / duodenitis are low (2-6%).
- Caution should be exercised regarding late effects due to generally short follow up (range 10-41 months, median 16 months). Late GI toxicity (grade 1-2, mainly ulceration / bleeding) is reported in 0-27% patients. Grade 2 adrenal insufficiency and grade 1-2 fatigue is reported in 5% of patients.
- Overall survival quoted ranged from 39-78% at 1 year with a median survival range 8 to 22 months. A pooled analysis showed a 19% 2 year survival [16]
- The means by which SABR was delivered in published series has been variable, but with generally good outcomes. There is no SABR delivery platform which is shown to have superior outcomes in terms of tumour control or toxicity.

13.2. Patient selection criteria

Inclusion criteria:

- Metastatic histologically-proven malignancy with adrenal metastasis on imaging.
- Tumour surgically unresectable or inappropriate after discussion in specialist uro-oncology MDT, or patient has declined surgery.
- Karnofsky performance status (KPS) of $\geq$70 or WHO PS $\geq$2.
- Life expectancy of > 6 months
- Absent, or limited and potentially treatable, extra-adrenal disease.
- Systemic therapy completed, or discontinued 4 weeks before SABR.
- Lesion <6cm in any dimension
- Able to provide informed consent and comply with radiotherapy.

Exclusion criteria:

- Single functional kidney on the same site as metastatic adrenal disease
- Any previous radiotherapy to the site likely to overlap with SABR, or where previous doses to other critical normal structures may make re-irradiation unsafe.

The risk of SABR treatment for a particular patient should be made by the local MDT considering factors such as, biochemical profile, FBC and Random cortisol. A DMSA scan can be considered for all patients, with PET/CT staging scans acquired as required according to the MDT decision.

13.3 Radiotherapy

13.3.1 Tumour delineation

GTV: the extent of gross tumour as visualised in the contrast-enhanced exhale phase breath hold CT scan (or individual phases of the 4DCT scan with a summed ITV generated after), ideally delineated in conjunction with a radiologist to define boundaries.

ITV: where tracking is unavailable or patients are unable to tolerate breath hold delivery of treatment (or where this or similar facility is unavailable) a 4D CT scan should be used to delineate the ITV as the full range of target position during respiration either on the MIP or the individual phases of the 4DCT scan with a summed ITV generated after this.

CTV: the most common practice in published studies has been to add no margin between GTV and CTV, (range 0-8mm).

PTV: although older studies have tended to use larger superior-inferior margins to allow for respiratory motion, these have been largely superseded by the use of 4D CT, gated deliveries or target tracking. Expansion margins to PTV, which should be established locally based on achievable delivery accuracy, are typically 3-5mm.

Organs at risk (OAR)

Organs should be outlined by the treating radiotherapist (or dosimetrist and checked by treating radiotherapist) and should include stomach, duodenum, small bowel, large bowel, kidneys, oesophagus (each of which should be outlined on *abdominal / kidney* windows), liver (entire volume), spinal canal (*bone* windows, to ≥2cm above and below the PTV), heart (including pericardial sac, with superior extent as the CT slice where the pulmonary trunk and right pulmonary artery are seen as separate structures, and continued down to the cardiac apex) and lungs (entire volume).

13.3.2. Fractionation

To date, there are no randomised, controlled trials comparing dose-fractionation regimens for SABR in adrenal metastases. The data that are published show considerable heterogeneity in the dose-fractionation schedules delivered. There does however appear to be a similar dose-response relationship as with other sites treated with SABR.

Suggested fractionations and dose distribution requirements:

(1) 30-36Gy in 3 fractions over 6-7 days
(2) 45Gy in 5 fractions over 10 days

The plan should be prescribed so that 95% of the PTV receives the nominal prescribed dose. The maximum (0.1cc) dose should be ≤140% of the prescribed dose. If OAR constraints cannot be met then reduction of either the prescribed dose, or the required dose coverage, should be considered.

13.3.3. Treatment Assessment and clinical follow-up

Patient Care on Treatment: weekly on-treatment review of full blood count, urea and electrolytes, liver function and random cortisol. Use of proton pump inhibitors (PPI) to reduce the risk of GI ulceration and 5HT3 antagonists for nausea are commonly used in published studies.

Follow-up: the purposes of follow up are early detection disease progression so as to intervene early in managing this, and to accurately document and respond to toxicity. Assessment as indicated in Table 13.2 is recommended at 3, 6, 12, 18 and 24 months and annually thereafter, with CTCAE v4.0 being recommended for toxicity assessment before and after RT, specifically the following symptoms: anorexia, dyspnoea, diarrhoea, liver dysfunction and RILD, fatigue, GI bleeding, nausea, pain, pleural effusion, pneumonitis, pulmonary fibrosis and endocrine dysfunction.

Assessment should also include radiological response (RECIST, see App.B) where appropriate, using CT or other imaging modalities such as MRI or PET/CT. For Symptomatic patients (usually pain), response of symptoms to treatment as assessed as outlined in Table 13.2 using the NPRS score and ED-D5 QoL data is advisable.

Table 13.2. Suggested assessments before, during and after radiotherapy.

Procedure	Base-line	During RT	Post RT
Medical History	X		X
Physical Examination	X	X	X
Weight	X		X
WHO PS score	X	X	X
FBC	X	X	
Informed Consent	X		
Adverse event monitoring CTCAE v4.0	X		X
Pain assessment (NPRS)	X		X
QOL (EQ-5D)	X		X
RECIST (see App.C)			X
CT scan			X

13.4 SUMMARY FOR SABR FOR ADRENAL METASTASES

Patient Selection: Discussion at Urology MDT to consider suitability for adrenalectomy / SABR / alternative ablative treatments

Consent: Explanation of procedure and likely risks

Immobilisation: For linac delivery - Treat supine, arms above head, in suitable immobilisation device. Respiratory movement management by ABC / AC/ passive gating - as appropriate to resources and experience. **For Cyberknife delivery –** Treat supine arms typically by the sides using appropriate immobilisation.

Pre-treatment imaging: For linac delivery - 4DCT scan with or without contrast plus expiratory breath-hold scan with contrast if 4DCT is without contrast. **For Cyberknife delivery –** expiratory breath-hold scans both with and without contrast.

Volume Definition: Radiotherapist +/- radiologist. GTV, PTV and OAR.

Margins: Suggestions: GTV-CTV: 0mm; CTV-PTV: 3-5mm isotropic dependant on IGRT and respiratory motion management techniques used..

Dose: 2 dose-fractionations suggested:
30-36Gy in 3 fractions over 6-7 days
45Gy in 5 fractions over 10 days

Planning: Evaluated by two SABR trained clinical oncologists

Daily pre-treatment procedures: For linac delivery - Cone beam CT, matched with treatment planning CT with PTV outlined. Correct any errors. Repeat CBCT at end of fraction.4DCBCT where available. **For Cyberknife delivery –** Direct Synchrony tracking of implanted fiducial.

Pre-medication: Consider PPI (e.g. Lansoprazole 30mg or equivalent) and anti-emetics (ondansetron 8mg or equivalent)

Follow up: Weekly during treatment, follow-up assessments at 3, 6, 12, 18 and 24 months then annually thereafter. Assessments suggested to include history, examination, FBC, U+E, LFTs, random cortisol (and/or other tumour markers as appropriate), and CT scan/MRI as appropriate.

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14. Other clinical sites

It is intended that in due course guidance will be developed by the Consortium for other clinical sites (i.e. renal cancer, pancreatic cancer, head and neck cancer) as clinical evidence is established, as recommended by NRIG. However, the Consortium currently feels that the evidence-base is currently too weak to establish safe guidance for these sites outside of the context of a controlled clinical trial. As the evidence base increases, additional sections may be introduced to these guidelines

Appendix A: Organ-at-risk dose constraints

Tables and data are copied from Hanna et al[1] with permission. *Values not in [1], carried over from previous document version.

Thoracic dose constraints

Description		3 Fractions		5 Fractions		8 Fractions		Source	Endpoint (and magnitude of risk where quantified)
		Optimal	Mandatory	Optimal	Mandatory	Optimal	Mandatory		
Brachial Plexus	DMax (0.5 cc)	< 24Gy	< 26Gy	< 27Gy	< 29Gy	< 27Gy	< 38Gy	3 and 5 fractions plus Optimal constraints for 8 fractions: UK SABR Consortium[2] 8 fractions Mandatory constraints from LungTECH trial[3] (excluding heart and great vessels)	Grade 3+ neuropathy
Heart	DMax (0.5 cc)	< 24Gy	< 26Gy	< 27Gy	< 29Gy	< 50Gy	< 60Gy	As above (8 fraction heart constraints from UK SABR Consortium[2])	Grade 3+ pericarditis
Trachea and bronchus	DMax (0.5 cc)	< 30Gy	< 32Gy	< 32Gy	< 35Gy	< 32Gy	< 44Gy	As above	Grade 3+ stenosis/ fistula
Normal Lungs* (Lungs-GTV)	V20 Gy	-	< 10%	-	< 10%	-	< 10%	As above	Grade 3+ pneumonitis
Chest Wall	DMax (0.5 cc)	< 37Gy	-	< 39Gy	-	< 39Gy	-	As above	Grade 3+ fracture or pain
	D30 cc	< 30Gy	-	< 32Gy	-	< 35Gy	-	As above	
Great Vessels	DMax (0.5 cc)	-	< 45Gy	-	< 53Gy	-	-	As above (8 fractions great vessels constraints from UK SABR Consortium[2])	Grade 3+ aneurysm

*Normal Lung (Lungs-GTV) constraints apply for the treatment of two or three lung lesions in the same patient

CNS dose constraints

Description	Constraint	Single Fraction		3 Fractions		5 Fractions		8 Fractions		Source	Endpoint (and magnitude of risk if previously quantified)
		Optimal (Gy)	Mandatory (Gy)	Optimal (Gy)	Mandatory (Gy)	Optimal (Gy)	Mandatory (Gy)	Optimal (Gy)	Mandatory (Gy)		
Optic pathway	DMax (0.1 cc)	-	< 8	-	< 15	-	< 22.5	<27.2*	<29.6*	AAPM[4]/ Hiniker[5]	AAPM: Grade 3+ optic neuritis Hiniker: 3 fraction: 0.8% and 5 fraction: 1.6% risk grade 4 radiation-induced optic neuropathy when limited to 0.05 cc
Cochlea	Mean	< 4	< 9	-	< 17.1	-	< 25	-	<44*	AAPM[4]/ Tamaru[6]	AAPM: Grade 3+ hearing loss
Brainstem (not medulla)	DMax (0.1 cc)	< 10	< 15	< 18	< 23.1	< 23	< 31	<27.2*	<37.6*	AAPM [4]	Grade 3+ cranial neuropathy
Spinal canal* (inc. medulla)	DMax (0.1 cc)	< 10	< 14	< 18	< 21.9	< 23	< 30	< 25	< 32	AAPM[4]/ Grimm[7]/ UK SABR Consortium [2]/ LungTECH[3]	AAPM: Grade 3+ myelitis Grimm: single and 3# optimal doses to 0.1cc limit risk of grade 2-4 myelopathy to ≤0.4%
	D1 cc	< 7	-	< 12.3	-	< 14.5	-	-	-		AAPM: Grade 3+ myelitis
Cauda equina & sacral plexus	DMax (0.1 cc)	-	< 16	-	< 24	-	< 32	-	-	AAPM[4]	Grade 3+ neuritis
	D5 cc	-	< 14	-	< 22	-	< 30	<36*	-	AAPM[4]	
Normal Brain (Whole Brain - GTV)	D10 cc	< 12	-	-	-	-	-	-	-		Radiation necrosis Cognitive deterioration (Group Consensus)
	D50%	< 5	-	-	-	-	-	-	-		
Lens	DMax (0.1 cc)	< 1.5	-	-	-	-	-	-	-		Cataract formation (Group Consensus)
Orbit	DMax (0.1 cc)	< 8	-	-	-	-	-	-	-		Retinopathy (Group Consensus)

*For treatments of the spine itself, these constraints should be applied to the cord PRV.

Gastro-intestinal Constraints

Description	Constraint	3 fraction		5 fraction		Source	End point
		Optimal	Mandatory	Optimal	Mandatory		
Duodenum	DMax (0.5 cc)	-	< 22.2Gy	-	< 35Gy	3 fraction: AAPM[4] 5 fraction: ABC-07[8]/ SPARC protocols[9]	Grade 3+ ulceration
	D1 cc	-	-	< 33Gy	-		
	D5 cc	-	< 16.5Gy	< 25Gy	-		
	D9 cc	-	-	< 15Gy	-		
	D10 cc	-	< 11.4Gy	-	< 25Gy		
Stomach	DMax (0.5 cc)	-	< 22.2Gy	< 33Gy	< 35Gy	As above	Grade 3+ ulceration/ fistulation
	D5 cc	-	-	< 25Gy	-		
	D10 cc	-	< 16.5Gy	-	< 25Gy		
	D50 cc	-	-	< 12Gy	-		
Small Bowel	DMax (0.5 cc)	-	< 25.2Gy	< 30Gy	< 35Gy	As above	Grade 3+ enteritis/ obstruction
	D5 cc	-	< 17.7Gy	< 25Gy	-		
	D10 cc	-	-	-	< 25Gy		
Common Bile Duct	DMax (0.5 cc)	< 50Gy	-	< 50Gy	-	As above	
Oesophagus	DMax (0.5 cc)	-	< 25.2Gy	< 32Gy	< 34Gy (<40 Gy for 8 fractions)	As above plus LungTECH for 8 fraction schedules[3]	Grade 3+ stenosis/ fistula
Large Bowel	DMax (0.5 cc)	-	< 28.2Gy	-	< 32Gy	As above	Grade 3+ colitis/ fistula
Rectum	Dmax (0.5 cc)	-	<28.2Gy	-	<32Gy	AAPM[4]	Grade 3+ colitis/ fistula

Parallel GI organs							
Description	Constraint	3 fraction		5 fraction		Source	End point
		Optimal	Mandatory	Optimal	Mandatory		
Normal Liver (Liver minus GTV)	V10Gy	-	-	< 70%	-	3 fraction: AAPM[4]/ Wulf et al[10,11]/ Rusthoven et al[12] 5 fraction: ABC-07[8]/ SPARC [9] protocols	Grade 3+ liver function dysfunction/ radiation-induced liver disease (classic or non-classic)
	Mean liver dose	-	-	< 13Gy	< 15.2Gy		
	D50%	< 15Gy	-	-	-		
	Dose to ≥700cc	< 15Gy	< 19.2Gy	-	-		
Kidneys (individual and combined)	Mean kidney dose	-	-	< 10Gy	-	3 fraction: AAPM[4] 5 fraction: ABC-07[8]/ SPARC [9]protocols	Grade 3+ renal function dysfunction
	Dose to ≥200cc*	-	< 16Gy	-	-		
If solitary kidney or if one kidney mean dose >10Gy	V10Gy	-	-	< 10%	< 45%	ABC-07[8]/ SPARC[9]protocols	

*If total kidney volume <200cc, or treating renal or adrenal lesions, then total dose to contralateral kidney should be <16Gy and minimise spillage into ipsilateral kidney if possible.

Pelvic dose constraints (for non-prostate primary irradiation)

Description	Constraint	3 Fractions		5 Fractions		Source	Endpoint
		Optimal (Gy)	Mandatory (Gy)	Optimal (Gy)	Mandatory (Gy)		
Bladder	D15 cc	-	< 16.8	-	< 18.3	AAPM[4]	Grade 3+ cystitis/ fistula
	DMax (0.5cc)	-	< 28.2	-	< 38		
Penile Bulb	D3 cc	-	< 21.9	-	< 30	AAPM[4]	Grade 3+ impotence
	DMax (0.5cc)	-	< 42	-	< 50		
Ureter	DMax (0.5cc)	-	< 40	-	< 45	BR001[13]	

Other dose constraints

Description	Constraint	3 fraction	5 fraction	Source	Endpoint
		Optimal (Gy)	Optimal (Gy)		
Skin	DMax (0.5 cc)	< 33	< 39.5	AAPM[4]	Grade 3+ ulceration
	D10 cc	< 30	< 36.5		
Femoral Head	D10 cc	< 21.9	< 30	AAPM[4]	Grade 3+ necrosis

PACE trial [14] constraints for primary prostate radiotherapy only

Description	Constraint (**Prostate primary only**)	5 Fractions		Source
		Optimal	Mandatory	
Rectum	D50%	-	< 18.1Gy	PACE trial[14]
	D20%	-	< 29Gy	
	D1 cc	-	< 36Gy	
Bladder	D40%	-	< 18.1Gy	As above
	V37Gy	< 5 cc	< 10 cc	
Prostatic urethra (if visible)	D50%	< 42Gy	-	As above
Neurovascular bundle (if visible)	D50%	-	< 38Gy	As above
Femoral head	D5%	-	< 14.5Gy	As above
Penile Bulb	D50%	-	< 29.5Gy	As above
Testicles	Avoid beam entry e.g. Blocking structure			As above
Bowel	D5 cc	-	< 18.1Gy	As above
	D1 cc	-	< 30Gy	

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Appendix B: Response Evaluation Criteria In Solid Tumours

(i) (RECIST) – Quick Reference Eligibility

Measurable disease - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Measurable lesions - lesions that can be accurately measured in at least one dimension with longest diameter >20 mm using conventional techniques or >10 mm with spiral CT scan.

All measurements should be taken and recorded in metric notation, using a ruler or callipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

METHODS OF MEASUREMENT

CT is the best currently available and reproducible method to measure target lesions selected for response assessment in lung cancers. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumours of the chest, abdomen and pelvis. Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

BASELINE DOCUMENTATION OF "TARGET" LESIONS

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).

A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumour.

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

RESPONSE CRITERIA

Evaluation of target lesions	
* Complete Response (CR):	Disappearance of all target lesions
* Partial Response (PR):	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
* Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
* Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

EVALUATION OF BEST OVERALL RESPONSE

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target lesions	Non-Target lesions	Evaluation of non-target lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

(ii) 'GREEN' Criteria

The complete disappearance of all evidence of malignant disease or residual radiographic abnormalities assessed by chest CT-scan at 3 and 6 months after completion of RT, which then remains stable for an additional 6 months or more, qualifies as controlled local disease

Given that the RECIST criteria may be difficult to classify after SABR the 'Green' criteria may be more appropriate and should be recorded in addition to RECIST.

Lung cancer, 2004; 11 (suppl 3) S11-13

Radiother Oncol, 2004. 71(2): p. 139-46 (EORTC guidelines)

Appendix C: Code of practice for maintenance of guidelines

Each section of the guidelines should be reviewed and updated at a minimum frequency of every 3 years to ensure that the guidance remains relevant and appropriate. This will involve

1. A systematic literature review by member(s) of the site-specific sub-group
2. Evidence reviewed by site-specific sub-group and Guidelines sub-group and changes drafted to the appropriate section of the guidelines
3. Changes reviewed by Consortium membership and, if necessary, guidance amended by Guidelines sub-group
4. Changes endorsed at Consortium meeting
5. Changes endorsed by Royal College of Radiologists

Additional site-specific sections being introduced into guidelines will undergo the same process.

The date on which the next update of each section of the guidance is due to be reviewed, as well as the membership of each sub-group, will be stated in this appendix

VIII. Peripheral lung

Introduced in December 2010 and reviewed for v6.1, due to be reviewed by January 2022

Sub-group membership

(i) Ceri Powell

(ii) Matthew Hatton

VIII. Central and Ultra-central lung

Introduced in December 2018 (v6.1), due to be reviewed by January 2022

Sub-group membership

(i) Fiona McDonald

(ii) Corinne Faivre-Finn

IX. Liver metastases

Introduced in January 2013 and reviewed for v6.1, to be reviewed by January 2022

Sub-group membership

(i) Katharine Aitken

(ii) Maria Hawkins

X. HCC

Introduced in December 2018 (v6.1), due to be reviewed by January 2022

Sub-group membership

(iii) James Good

(iv) Maria Hawkins

XI. Prostate

Introduced in January 2013, and reviewed for v6.1, to be reviewed by January 2022

Sub-group membership

(i) Kirsty Morrisson

(ii) Alison Tree, Nick van As

XII. Spinal metastases

Introduced in January 2015, and reviewed for v6.1, to be reviewed by January 2022

Sub-group membership

(iii) Jenny Sherriff

(iv) Anoop Haridass, Merina Ahmed,

XIII. Adrenal metastases

Introduced in January 2016, and reviewed for v6.1, to be reviewed by January 2022

Sub-group membership

(i) Anoop Harridass

The Guidelines sub-group, to whom the draft guidelines will be circulated prior to being dispersed to the general membership of the Consortium, currently consists of

- Jonny Lee (email:jonathan.lee11@nhs.net)
- Pooja Jain
- Maria Hawkins
- Ann Henry
- Anoop Harridass
- Matthew Hatton
- Jenny Sherriff
- Chris Dean
- Jenny Marsden
- John Lilley
- Gail Distefano
- Yat Tsang
- Angela Baker

The membership of this group is intended to minimise any bias in these guidelines by representing the range of relevant professional disciplines, as well as representatives experienced in the use of a range of suitable equipment. Any member of the wider SABR Consortium is free to join the Guidelines sub-group if they feel that their perspective would be beneficial.