

Stereotactic Ablative Body Radiation Therapy (SABR): A Resource



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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 C. 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 the range of clinically-indicated sites, as listed in the NRIG Report 'Stereotactic Body Radiotherapy: Clinical Review of the Evidence for SABR'
- 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

Contents

I Quality assurance for SABR	5
II Peripheral lung cancer	11
III Liver metastases	31
IV Prostate cancer	55
V Other clinical sites	72
Appendix A: Suggested treatment protocols	73
Appendix B: Response Evaluation Criteria In Solid Tumours	74
Appendix C: Code of Practice for maintenance of guidelines	77

N.b. for sections II-IV the structure is as follows:

1. Review of clinical evidence
2. Patient selection criteria
3. Radiotherapy
 - 3.1. Pre-treatment image acquisition
 - 3.2. Delineation and treatment planning
 - 3.3. Treatment delivery clinical follow-up

I Quality assurance 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. 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' [3] and IPEM report 101 'Small Field MV Photon Dosimetry' should be adhered to [4]. Additional guidance may be found in AAPM report TG66 'Quality Assurance for computed-tomography simulators and the computed-simulation process' [5].

Standards for delivering SABR have been developed and are listed in Table I.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 [6-17].

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 RT 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 I.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. The results of these planning 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. The development of 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.
C.1	Tumour should be delineated on appropriate display settings.	Protocol documentation
C.2	Normal tissue structures should be delineated according to protocol. If needed, 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	Follow-up records for a sample of patients

	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.	
C.5	There shall be an electronic patient record for each SABR case consisting of planning images, structure sets, plan details and 3D dose-grids. 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. A SABR service should not be provided by centres unless a minimum activity of 25 patients per year can be maintained. Specialised services for rarer and complex cases should be developed only at selected centres serving catchment populations of at least 2 million.	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 QA reviews.	Records of QA reviews

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 MLC 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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II Peripheral lung cancer

II.1. Introduction and literature review

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.

Conventional Therapy and Outcome

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% [3]. 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 (or less) of those seen in surgical series [4]. The 2001 Cochrane review suggested that local recurrence rates in medically inoperable patients treated with external beam radiation therapy ranged from 6-70% [4]. 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 [5]. 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 [6].

Stereotactic Ablative Body Radiotherapy (SABR)

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. The treatment technique utilized is similar to that used for intracranial lesions, and employs multiple radiation beams to target a tumour with high precision, delivering an ablative dose of radiation. This is made possible by limiting the treatment volume, and the parallel structure of lung tissue.

Radiotherapy doses are prescribed to an isodose line covering the planning target volume (PTV), which means that within the PTV or to the ICRU dose reference point, the dose may be much greater. Various dose and

fractionation schedules have been used, ranging from a single to ten or more fractions [7, 8]. In some of these studies a body frame with stereotactic coordinates to aid set up and some form of respiratory management/compensation (e.g. to identify and take into account tumour motion in treatment planning and to limit motion and thereby reduce the amount of normal tissue irradiated) were used.

A large retrospective analysis of Japanese patients supported dose and fractionation regimens that delivered a BED of > 100Gy [9]. 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 [10,11]. The subsequent phase II study by Timmerman investigated a dose of 3 x 20 Gy and 3 x 22 Gy for T1-2 tumours, excessive toxicity was seen at a dose of 3 x 22 Gy and at 3 x 20 Gy for central tumours [12]. RTOG 0236 was a multicentre phase II study following on from the dose escalation study, which closed in October 2006. 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 two (3.6%) grade 4 and 7 (13%) grade 3 pulmonary/upper respiratory adverse events reported as related to protocol treatment [13, 14].

There is now considerable non-randomised evidence supporting SABR as superior to conventional RT with respect to local control and survival. This is biologically plausible. Lung SABR also appears to have an acceptable therapeutic index. Table II.1 summarises the outcome reported by these studies [15]. 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 [16,17]. The toxicity of this technique is relatively low when treating T1-2 tumours in the periphery of the lung [18]. It is important to bear in mind that a number of these studies were done prior to the era of on-line kilovoltage (kV) cone beam CT (CBCT) image guidance. The introduction of onboard imaging with kV CBCT has the potential to enhance target localisation and the safety of SABR treatments.

With regards to toxicity with SABR treatment, Lagerwaard et al [19] prospectively collected health-related quality of life (HRQOL) data in 382 consecutive patients with this technique. A SABR dose of 60Gy in 3, 5 or 8 fractions was delivered, resulting in a median survival of 40months and 2 year survival of 66%. 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. As chronic obstructive pulmonary disease (COPD) is present in 50-70% of people with lung cancer at the time of diagnosis [16], this potentially

represents the risk of significant toxicity from SABR. For this reason, the safety and outcomes of SABR in patients with severe COPD has also been reviewed by Palma et al [16] in their 2011 systematic review, finding 30day 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.

Table II.1 Reported survival outcome and local control in 35 studies [15]

	Studies with available data	Mean \pm SD		Median (range)
Overall survival (%)				
12 months	15	82.8	\pm 11.4	83.0 (52 – 100)
24 months	21	64.5	\pm 15.5	65.4 (32 – 91)
36 months	18	57.7	\pm 16.0	55.9 (32 – 91)
60 months	9	45.3	\pm 20.1	47.0 (18 – 77.5)
Cause-specific survival (%)				
12 months	7	93.7	\pm 2.7	94.0 (88 – 96)
24 months	15	77.3	\pm 9.9	82.0 (53.5–88)
36 months	14	72.0	\pm 11.9	70.0 (53 - 90.5)
60 months	7	56.9	\pm 16.2	50.0 (40 –78)
Local control (%)				
12 months	8	91.8	\pm 3.5	92.0 (85.3 – 96)
24 months	11	86.9	\pm 9.7	88.0 (67.9 – 96)
36 months	11	80.6	\pm 13.6	84.0 (57 – 95)
48 months	1	89.0	\pm 0.0	89.0 (n/a)
60 months	1	86.0	\pm 0.0	86.0 (n/a)

An important, but at present unanswered question, is whether SABR has comparable outcomes to surgery for early stage NSCLC. The ROSEL study was designed to attempt to answer this but unfortunately, due to poor recruitment, was closed early [20]. RTOG 0618, is a phase II trial of SABR for peripheral operable stage I lung cancer which completed accrual in 2010 [21] but has yet to report. There is recent published data reviewing outcomes of patients with early stage (AJCC stage I or II) NSCLC treated with surgical resection or SABR: Solda et al [22] performed a systematic review and comparison with a surgical cohort and found that the summary 2 year survival probability of patients with stage I NSCLC treated with SABR is 70% which is comparable to survival of a cohort of clinical stage I patients treated with surgery, while Varlotto et al [23] retrospectively analysed 2 databases which contained patients treated from 1999-2008 by lobectomy, sublobar resection and SABR, finding that patients with stage I NSCLC treated with SABR had similar total recurrence control and locoregional control as patients treated with surgery, but worse overall survival on a matched pair analysis. However,

after adjustment for treatment selection, overall survival was no longer significantly worse for patients treated with SABR.

Further studies and the results of ongoing prospective, randomised trials comparing SABR to surgery are awaited. The NCRIG Report (Stereotactic Body Radiotherapy: Guidelines for Commissioners, Providers and Clinicians in England 2011) recommends that SABR should be the treatment of choice for early-stage peripheral lung patients with contraindications to surgery.

Many of the comments in subsequent sections are consistent with, or drawn from, the RTOG 0236 trial (<http://www.clinicaltrials.gov/ct2/show/NCT00087438?term=rto0236&rank=1>) and the ROSEL trial protocol [19, 20].

II.2. Patient selection criteria

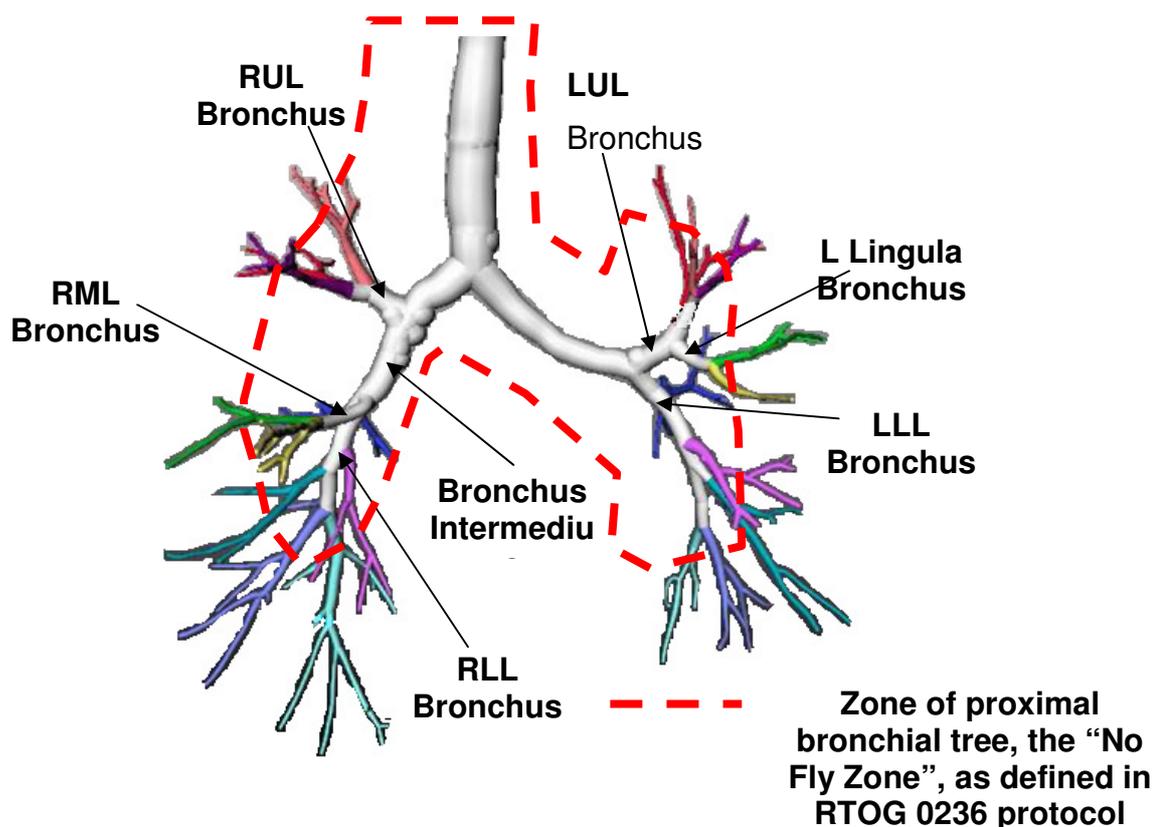


Figure II.1 Proximal bronchial tree as defined by RTOG 0236 protocol

Inclusion Criteria

- MDT diagnosis of NSCLC based on findings of positive histology, positive PET scan or growth on serial CT scan
- Clinical stages of T1 N0 M0 or T2 (≤ 5 cm) N0 M0 or T3 (≤ 5 cm) N0 M0 [radiologically N2 (CT or PET), patients only eligible if possible nodal disease is subsequently confirmed as histologically negative with mediastinoscopy or endoscopic bronchial or oesophageal ultra-sound biopsy]
- 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 outside a 2cm radius of main airways and proximal bronchial tree. This is defined as 2cm from the bifurcation of the second order bronchus e.g. where the right upper lobe bronchus splits (figure 2.1)
- Age ≥ 18 years

Exclusion Criteria

- NSCLC patients with T2 or T3 primary tumours > 5 cm.
- T3 primary NSCLC tumours involving the mediastinal structures or central T3 primary tumours.
- Metastatic lung tumours
- Any tumour that is not clinically definable on the treatment planning CT scan e.g. surrounded by consolidation or atelectasis.
- If tumour has respiratory motion ≥ 1 cm despite using techniques to reduce tumour motion, only proceed with treatment if target delineation is reliable and suggested normal tissue and tumour planning constraints can be achieved.
- Tumours within 2cm radius of main airways and proximal bronchial tree (figure II.1).
- Primary NSCLC tumours with clinical evidence of regional or distant metastasis after appropriate staging studies.
- Previous radiotherapy within the planned treatment volume
- Presence of pulmonary fibrosis (unless the increased risk of SABR has been fully considered and the patient has been appropriately consented)

- Chemotherapy administered within 6 weeks prior to study entry or planned for < 6 weeks following SABR.
- Pregnant or lactating females
- Inability to obtain informed consent or comply with treatment requirements

II.3. Radiotherapy

II.3.1 Pre-treatment image acquisition

Patient positioning

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. To this end, it is suggested that patients are positioned supine in a comfortable and reproducible position with their arms above their heads, although alternative positions may be required for individual patients.

Devices such as customized vacuum bags or thermoplastic moulds can be used to achieve patient comfort and stability. Custom devices can also be used for immobilisation and to facilitate abdominal compression. The immobilization device should allow for patient and tumour imaging as necessary using any required imaging techniques and not interfere with dose calculation or treatment delivery. In addition, analgesics +/- mild sedatives and oxygen can be considered to help the patient maintain the treatment position during each fraction.

The most popular immobilisation solution in the UK is the use of a wingboard with knee support, with or without vacuum immobilisation [24].

Minimum standard: Centres should assess the accuracy of immobilisation device/s used for positioning patients for SABR. Systematic setup errors should be within 3-5mm.

Tumour motion

Once the patient has been appropriately positioned it is highly recommended that the patient-specific tumour motion be incorporated into treatment either by using direct tumour tracking methods or by the use of 4DCT at the treatment simulation stage.

In some published series special consideration was given to tumours that moved more than 1cm in any direction. There are two main strategies to deal with mobile (>1cm) tumours.

(a) Motion Restriction to reduce tumour motion (to <1cm), e.g. by using one of the following methods:

1. Abdominal compression.
2. Respiratory gating.
3. Coached respiration
4. Active Breathing Control (ABC) device for patients with sufficient respiratory reserve to be able to breath hold for >20 seconds.

(b) Accounting for motion in RT planning:

1. Provided that the dose conformity, dose spillage and OAR constraints can be met the whole motion envelope may be included in the ITV and the patient treated whilst breathing normally (usually applies to small mobile tumours).
2. Planning using the mid-ventilation or time-weighted average image from 4DCT and accept that the ITV and PTV may not always include all tumour motion.

A patient may be deemed ineligible for SABR if:

- tumour motion is felt to be unacceptable or non-correctable with currently available respiratory immobilization techniques

AND

- dose conformity, dose spillage and OAR constraints cannot be met

It is the responsibility of each radiotherapy department to assess the reproducibility of their chosen method of managing tumour motion prior to commencing SABR treatments.

Pre-treatment imaging

Patients will undergo a treatment 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. As a guide, contiguous axial slices of $\leq 3\text{mm}$ will be obtained from the upper cervical spine to the lower edge of the liver, taking care to include all lung parenchyma on the planning scan.

More than one planning CT scan may be required for target definition/motion assessment. The planning CT scan(s) must allow for simultaneous viewing of internal organ anatomy as well as any fiducial systems if a stereotactic frame

is used for immobilisation, which will be identical for the treatment-planning phase and for each radiation fraction.

II.3.2. Delineation and treatment planning

Tumour Delineation

Gross Tumour Volume (GTV) = The GTV is defined as the radiologically visible tumour in the lung, contoured using lung settings. Mediastinal windows may be suitable for defining tumours proximal to the chest wall. Where available, information from PET/CT will be incorporated into delineating the GTV.

Clinical Target Volume (CTV) = The CTV is the GTV with no margin for microscopic disease extension. This is the accepted standard in the majority of SABR trials.

Internal Target Volume (ITV) = 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.

The margins from CTV to PTV will depend on the method of immobilisation, the assessment of tumour motion and methods for on treatment set-up verification/repositioning. Each centre will need to confirm the adequacy of the PTV margins with their immobilisation techniques. 3-5mm margins are typically chosen for 4DCT-based SABR planning, with the UK SABR Consortium survey [24] showing isotropic 5mm margins used in 13/15 centres.

All tumour and critical organ contours should be reviewed by 2 consultant oncologists with an additional review by a consultant radiologist highly recommended.

Organs at Risks (OAR)

It is recommended that the following organs at risk are delineated on the CT planning dataset.

Spinal cord

The spinal cord should be contoured on all slices based on the bony limits of the spinal canal.

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

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 protocol 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.

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.

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 (figure II.1)

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.

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.

Whole lung

Both lungs should be contoured as one structure using pulmonary windows. All inflated and collapsed lung should be included. However, GTV and trachea/ipsilateral bronchus as defined above should not be included.

Proximal bronchial tree plus 2cm

As part of adhering to the ineligibility requirements for not enrolling patients with tumours in the zone of the proximal bronchial tree listed in II.2 above, it is convenient to define an artificial structure 2 cm larger in all directions from the proximal bronchial tree. If the GTV falls within this artificial structure, the patient should not receive SABR outside the context of a clinical trial.

The OARs should be inspected to ensure that wherever a treatment beam traverses the OAR, it has been contoured. 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.

Treatment Planning

The constraints recommended in this report are based on those that have been safely used to treat > 500 patients at the VU centre in Amsterdam and subsequently implemented for the ROSEL study.

Beam selection

To achieve adequate target coverage using SABR whilst sparing critical structures, including the skin surface, typically at least seven beams are required, although rotational delivery solutions may also be appropriate. The beam configuration may be coplanar or non-coplanar, depending on the size and location of the lesion. The paradigm dictates that the high-dose region should be conformal to the PTV, the medium-dose region surrounding the PTV should be compact and the low-dose region is permitted to be relatively

large by comparison to the other regions. All dose calculations should be performed using heterogeneity correction.

Due to uncertainties in beam commissioning resulting from electronic disequilibrium within small beam apertures, individual centres should satisfy themselves of the veracity of their small-field dosimetry. Lower energy beams (e.g. 6MV) should be used due to the wide penumbra of high-energy beams, the small beam apertures used in SABR and the problems associated with build up. Analysis of the dose-volume histogram (DVH) for the PTV and critical normal structures forms the basis for selecting a particular treatment plan. It is therefore recommended that plans be calculated on a fine dose grid, with a separation no greater than 2.5mm, to ensure accurate calculations.

In addition, the dose to skin should be limited to minimise cutaneous and subcutaneous toxicity [25]. This is assisted by ensuring that beam entry points do not overlap on the skin.

Treatment Planning System

Inhomogeneity corrections have a large influence on the dose delivered to the PTV and OARs for SABR of lung tumours. Type A algorithms, which use an extended path length (EPL) calculation to account for heterogeneity, result in a wide range of errors relative to the actual dose distribution. This includes overestimation of the isocentric prescription dose and target coverage. The target coverage errors vary significantly depending on the location of the lesion, so a simple rescaling of prescription dose, as used in the RTOG and ROSEL studies, does not provide a reliable correction. Therefore Type B or Monte Carlo algorithms that consider changes in lateral electron transport should be used. [26,27]

Tumour Location/OAR doses

As defined above, the GTV must be outside the defined 2cm margin around the proximal airways (Figure II.1). Tables II.2 and II.3 lists the dose constraints used in the ROSEL study. These dose limits are based on the highest dose/fractionation regimes reported in lung SABR and therefore should be safe for lower biological equivalent dose regimes used.

Table II.2 Planning dose constraints

OAR	Volume (cm ³)	3#		5#		8-10#	
		Tolerance	Minor deviation	Tolerance	Minor deviation	Tolerance	Minor deviation
Spinal cord*	0.01	18Gy	18-22Gy	25Gy	25-28Gy	25Gy	25-28Gy
Oesophagus*	0.1	24Gy	24-27Gy	27Gy	27-28.5Gy	27Gy	27-28.5Gy
Brachial plexus*	0.1	24Gy	24-26Gy	27Gy	27-29Gy	27Gy	27-29Gy
Heart*	0.1	24Gy	24-26Gy	27Gy	27-29Gy	50Gy	50-60Gy
Trachea, bronchus*	0.1	30Gy	30-32Gy	32Gy	32-35Gy	32Gy	32-35Gy
Lungs-GTV		V20 < 10% V12.5 < 15%	N/A	V20 < 10% V12.5 < 15%	N/A	V20 < 10% V12.5 < 15%	N/A

*Taken from ROSEL study

Compliance with the following constraints may also be considered

OAR	Volume (cm ³)	3#		5#		8-10#	
		Tolerance	Minor deviation	Tolerance	Minor deviation	Tolerance	Minor deviation
Liver (valid only if >1000cc of liver imaged)		700cc<15Gy V33<21Gy V50<15Gy	N/A	700cc<15Gy V60<30Gy Mean <20Gy	N/A	V30<27Gy V50<24Gy	N/A
Chest wall	30.0 0.01	30Gy 37Gy	N/A	32Gy 39Gy	N/A	32-35Gy 39Gy	N/A

Note: when non-coplanar treatment beams are used additional organs may be irradiated (e.g. liver, bowel) – allowances must be made for this. It is recommended the entire liver be scanned, especially for lower lobe lesions and where non-coplanar beams are to be used.

Fractionation

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

Standard Dose Fractionation:	18Gy x 3 fractions (nb. 20Gyx3 not allowed)
Conservative Dose Fraction:	12Gy x 5 fractions or 11Gy x 5 fractions
Very Conservative Dose Fractionation:	7.5Gy (or as low as 6.25Gy) x 8 fractions

The conservative dose fractionation is recommended when any part of the PTV is in contact with the chest wall. It is recommended that the inter-fraction interval be at least 40 hours, with a maximum interval of ideally 4 days between fractions [15]

The very conservative fractionation schedules may rarely be used if the dose constraints cannot be met at 55Gy in 5 fractions and the patient has been discussed in the lung Q/A rounds. The conformity constraints are as per 5 fraction treatments.

Dose distribution requirements

Successful treatment planning can be achieved by a range of planning techniques [28-30] but will require accomplishment of all of the following criteria:

1. The dose prescription will be chosen such that 95% of the target volume (PTV) receives at least the nominal fraction dose (e.g. 18 Gy per fraction = 54 Gy total), and 99% of the target volume (PTV) receives a minimum of 90% of the fraction dose (e.g. 16.2 Gy per fraction = 48.6 Gy total for the standard fractionation)
2. The dose_{max} within the PTV should preferably not be less than 110%Gy (e.g. 59.4Gy for standard fractionation) or exceed 140%Gy (e.g. 75.6Gy for standard fractionation). A minor deviation will be scored in cases where the dose_{max} lies between either 105-110% (e.g. 56.7-59.4Gy) or 140-145% (e.g. 75.6-78.3Gy).
3. Conformity of PTV coverage will be judged as given in the tables below, which incorporate constraints used in the ROSEL study.

Table II.3 Dose conformity requirements for type B models

(i) 3 fractions

Vol(PTV) (cc)	Vol(100%) / Vol(PTV)		Vol(50%) / Vol(PTV)		Max dose >2cm		V20 (%) tolerance	
	tolerance	minor dev	tolerance	minor dev	tolerance	minor dev	tolerance	minor dev
<20	<1.25	1.25-1.40	<12	12-14	<35.1Gy	35.1-40.5Gy	<5	5-8
20-40	<1.15	1.15-1.25	<9	9-11	<37.8Gy	37.8-43.2Gy	<6	6-10
>40	<1.10	1.10-1.20	<6	6-8	<37.8Gy	37.8-43.2Gy	<10	10-15
60-90	<1.10	1.10-1.20	<5	5-7	<37.8Gy	37.8-43.2Gy	<10	10-15
>90	<1.10	1.10-1.20	<4.5	4.5-6.5	<37.8Gy	37.8-43.2Gy	<10	10-15

(ii) 5-8 fractions

Vol(PTV) (cc)	Vol(100%)/ Vol(PTV)		Vol(50%) / Vol(PTV)		Max dose >2cm		V20 (%)	
	tolerance	minor dev	tolerance	minor dev	tolerance	minor dev	tolerance	minor dev
<20	<1.25	1.25-1.40	<12	12-14	<35.8Gy	35.8-41.3Gy	<5	5-8
20-40	<1.15	1.15-1.25	<9	9-11	<38.5Gy	38.5-44.0Gy	<6	6-10
>40	<1.10	1.10-1.20	<6	6-8	<38.5Gy	38.5-44.0Gy	<10	10-15
60-90	<1.10	1.10-1.20	<5	5-7	<38.5Gy	38.5-44.0Gy	<10	10-15
>90	<1.10	1.10-1.20	<4.5	4.5-6.5	<38.5Gy	38.5-44.0Gy	<10	10-15

Vol(100%)/Vol(PTV): ratio of prescription isodose (eg 54Gy, 55Gy or 60Gy) volume to the PTV

Vol(50%)/Vol(PTV): ratio of 50% prescription isodose (27Gy, 27.5Gy or 30Gy) volume to the PTV

Max dose >2cm: maximum dose (% of nominal prescription dose) at least 2cm from the PTV in any direction

V20: percentage of total lung volume – GTV receiving >20Gy

Departments are urged to complete plan evaluation forms containing a minimum of the above data, for all patients. This will allow collection of dosimetric data that will be useful in the development of future guidelines.

II.3.3. Treatment delivery and clinical follow-up

Treatment Verification

Once the treatment plan has been generated, it is recommended that centres conduct a 'trial set up' session, prior to starting treatment, in order to confirm that all the beams are deliverable, that the patient can maintain the treatment position, to verify the patient setup procedure and, if the technology is available, use respiratory-correlation to assess margin adequacy.

It is suggested that centres verify patient setup before +/- during treatment using a procedure that can validate the position of the tumour relative to the patient anatomy for online image matching and correction. See App A1 for examples of verification process for CBCT-based imaging (an example process for kV planar imaging-based techniques will follow in a future version).

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 patient shifts if required. A verification image is suggested to ascertain that the shift was

made in the correct direction. Further imaging should be performed if there are concerns that the patient has moved during the treatment.

Treatment assessments & Follow Up

Tables II.4 and II.5 detail the suggested assessments to be undertaken. Patients should be reviewed prior to delivery of each fraction to review any symptoms and toxicity. We recommend using the CTCAE v4.0 (available from the link below) for assessing toxicity during and after RT, specifically the following symptoms: Atelactasis; Anorexia; Bronchospasm / wheezing; Cough; Dyspnoea; Fatigue; FEV1; Hypoxia; Nausea; Obstruction / stenosis of airway (bronchus, trachea); Pleural effusion; Pneumonitis; Pneumothorax; Pulmonary fibrosis; Pulmonary – other; Vital capacity; Vomiting.

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

Post-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 usually be done at 3-6 months 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 [31]. In addition a greater awareness of the potential for certain toxicities (e.g. chest wall/rib) is required [32-34]. If feasible full lung function tests should be considered annually. Response may be documented using the RECIST criteria (Appendix B). If possible patients should be followed for a minimum of five years.

Table II.4 Assessments at baseline and during radiotherapy.

Procedure	Base-line	During RT	4-6 weeks post RT
Medical History	X	X	X
Physical Examination	X	X	X
Weight	X		X
WHO PS score	X	X	X
FBC	X		
Biochemistry profile	X		
Lung function test	X		
Pregnancy test	X		
CT scan thorax and abdomen	X		
Chest Xray	X		X
CT/ MRI head	optional		
PET/CT	X		
Informed Consent	X		
Adverse event monitoring CTCAE v4.0	X	X	X
QOL (QLQ C30)	X		

Table II.5 Suggested Assessments during follow up post-SABR
(frequency to be decided locally but should ensure robust early and late response data)

Procedure	Months post RT											
	3	6	9	12	18	24	30	36	42	48	54	60
Medical History	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X
ECOG score	X	X	X	X	X	X	X	X	X	X	X	X
Lung function test		X		X		X		X		X		X
CT scan thorax and abdomen		X		X		X		X		X		X
Chest Xray	X		X		X		X		X		X	
Adverse event monitoring	X	X	X	X	X	X	X	X	X	X	X	X
QOL		X	X	X	X	X	X	X	X	X	X	X

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III 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.

III.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

Colorectal Carcinoma (CRC):

Colorectal cancer is the third most common cancer in the UK (2009), accounting for 13% of all new cases and the 2nd most common cause of cancer death in the UK (Cancer Research UK, 2012). 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 (number of lesions, size, primary tumour stage, 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 due to surgical factors (the site, size and distribution of metastases within the liver) or patient fitness. Chemotherapy may convert inoperable case in only around 10-20% of cases. [14]

Thermal destruction of tumours by radiofrequency ablation (RFA) is an alternative treatment. 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, with lesions under 3cm diameter having greater local control rates than larger lesions. [18] Again, not all patients will be suitable for this, due to the site of disease within the liver, especially the proximity to large blood vessels, the main biliary tract or dome of the diaphragm. [18]

Further, there are data to suggest that local control of CRC liver metastases is related to survival – Aloia et 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]

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]

Summary of evidence for SABR treatments of liver metastases

Evidence for Stereotactic Ablative Radiotherapy (SABR) for liver metastases are confined to retrospective series (table III.1), and prospective phase 1 and 2 trials (table III.2). A phase three trial (RAS trial, comparing RFA with SABR) is currently recruiting.

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
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. Due to geometric uncertainties and respiratory movement, treatment delivery requires image-guided-radiotherapy (IGRT), although the means by which this is achieved may vary
8. 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.
9. 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]
10. 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).
 11. The means by which liver SABR has been delivered in published series has been variable, but with generally good outcomes. There is no means of delivering SABR shown to have superior outcomes in terms of tumour control or toxicity, and centres have chosen to develop their own protocols based on their own resources.

Table III.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 III.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 III.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)

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

III.2. Patient Selection Criteria

Inclusion criteria:

- Patients may be considered for SABR if they have radiographic liver lesions most consistent with metastases on contrast enhanced CT and/or MRI and a histologically diagnosed carcinoma.

However, standard treatments should be considered and either:-

- The tumours must be considered unresectable after review by a Hepatobiliary (HPB) surgeon, in the context of a hepatobiliary MDT
- The patient is considered medically unfit for surgery
- Systemic chemotherapy has been completed
- Karnofsky performance status (KPS) of 70 or more
- Life expectancy of more than 3 months
- No, or limited and potentially treatable, extra-hepatic disease.
- 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)
- Up to 3 metastases, with no limitation on actual size of a given tumour provided organ at risk (OAR) dose constraints can be met
- volume of uninvolved liver must be at least 700 cc
- Adequate organ function, defined as: Haemoglobin 9.0 g/dL, absolute neutrophil count 1.5 bil/L, 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. Creatinine less than 200 umol/L (if creatinine is above the normal range consideration should be given to dynamic renal scintigraphy (renography) if there is anticipated to be any appreciable renal dose from the delivery of treatment.
- Class A from Child's Pugh Liver Score (see Table III.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 of 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.

- Any other severe comorbidity such as unstable angina, congestive cardiac failure or transmural MI requiring hospitalisation in the preceding 6 months, or acute bacterial/fungal infection requiring intravenous antibiotics
- CNS metastases
- Coagulopathy preventing safe insertion of fiducial markers and allergy to the metal component of the fiducial- If fiducial markers are to be placed

Table III.3: Childs-Pugh Liver Score

Measure	1 point	2 points	3 points
Total Bilirubin ($\mu\text{mol/l}$) (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
Ascites	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%

III.3. Radiotherapy

III.3.1. Pre-treatment image acquisition

Patient positioning

Reliable repositioning is vital for delivering SABR – use of immobilisation devices, such as stereotactic frames or individualised vacuum moulds are seen in all published studies. Patients are scanned with arms above the head, and every effort should be taken to optimise comfort to reduce intra-fraction motion.

Guidance Note: Use should be made of immobilisation devices (such as custom made vacuum moulds) and departments are encouraged to quantify the set-up errors associated with their chosen method of immobilisation.

Pre-treatment Imaging.

Treatment planning is usually CT based. However, contrast-enhanced CT often underestimates tumour volume in colorectal metastases, [35] and other primary sites. [36] MRI provides higher lesion-to-liver contrast and allows superior lesion detection and characterisation. [37]

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. [35,36] Retrospectively observed differences in mean tumour volume as defined on CT and MRI are significantly higher in patients showing local tumour failure ($p=0.002$). [35] The suggestion from this is that MRI may result in better tumour delineation and therefore, better local control.

FDG-PET is also 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. [38] 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. [39] However, incorporating PET for radiotherapy planning has not been validated.

Minimum standard: contrast-enhanced CT should be used to outline GTV for SABR (ideally dynamic contrast CT in exhale breath hold, capturing venous phase of contrast enhancement).

Contrast-CT fused with MRI is superior and wherever possible merged MRI-based GTV definition should be used (T1W or T2W). The MRI has to be acquired on a flat couch in the same immobilization and treatment position as planning CT). Radiologist support in outlining lesions and organs at risk is encouraged.

Tumour motion:

A major challenge for SABR for liver metastases is the management of respiratory motion, which can potentially lead to under-dosing of tumour, and hence reduced local control, as well as excess dose to organs at risk (OAR) as they move into the high dose region. The amplitude of respiratory motion may be assessed by kV fluoroscopy, [40] 4D-CT or cine-MRI. [42] Reports suggest that while the amplitude of breathing may be significant, the variability of respiratory amplitude is small [41]

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

Reducing Motion:

(i) *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. [43] It is the most commonly used means of respiratory motion control in published series. AC is also shown to reduce inter- and intra-fractional changes in liver position relative to bony anatomy. [40]

(ii) *Active Breathing Control (ABC):* This technique is a means of active respiratory gating and in effect produces a 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.[46] However, set-up errors can be reduced to less than 5mm (cranio-caudal) using ABC with image guidance. [44,45]

(iii) *Passive respiratory gating:* This technique allows patients to breathe freely, and co-ordinates the delivery of radiotherapy to 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. 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 [46].

Tracking motion:

Tumour tracking of implanted fiducial markers is shown to be feasible, but has the disadvantage of being invasive, requiring radiology time for insertion of the markers, potential for longer time for treatment time due to tracking and potential for marker migration. [47,48]

Planning with motion unrestrained:

A further means of managing respiratory motion is to plan radiotherapy simply allowing for the motion in adding margins. This may be appropriate if other means of motion management can not be applied or the tumour moves less than 5mm.

Minimum standard: a means of quantifying respiratory motion for individual patients before treatment must be available. For any observed respiratory motion of >5mm attempts should be made to reduce this.

III.3.2. Delineation and treatment planning

Tumour delineation

The PTV expansion margins used in published studies have varied considerably. Exact margins used are determined by the immobilization 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 expansion suggestions are 5mm radially and 10mm cranio-caudally. However, use of 4D CT scan technology may allow margins to be individualised, although a minimum of 5mm is suggested (radially and craniocaudally).

Organs at risk (OAR):

Any organ that is traversed by part or all of a beam should be contoured so that the dose it receives can be assessed. Organs should be outlined by the treating radiotherapist (or dosimetrist and checked by treating radiotherapist):-

Oesophagus, Stomach, Duodenum, Small bowel, Large bowel

Liver: The whole liver should be outlined, and for dose calculation this volume minus that of the PTV is used.

Kidneys: The entirety of each kidney should be outlined separately.

Spinal cord: Outlined using the bony limits of the spinal canal, including that section of the spinal cord 2cm above and below the extent of the PTV.

Heart: The heart and pericardial sac are outlined, defining the 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.

Lungs: Outlined from apex to base, as a single structure

Treatment planning:

Planning should be carried out by dosimetrists/physicists experienced in SABR.

In general, using larger numbers of beams increases conformality of dose to the target and the gradient of the dose distribution, at least up to a point. However, increasing the number of beams increases the integral dose of tissue treated and therefore, the risk of toxicity, as well as increasing treatment time. Liu et al have shown that in treating liver and lung lesion with SABR, the dose gradient is improved as the number of beams increases from 5-15, (for coplanar and non-coplanar treatments), and that the normal tissue complication probability (NTCP) decreases from 5-9 beams, but does not increase significantly when more than 9 beams are used, irrespective of the size of the target. They conclude that the optimal number of beams is 9. [49] Published studies have used generally 3-10 beams in generating plans (co-planar or non-coplanar depending on the exact scenario), but use of 6-8 beams is most common. Arc therapy can also be used.

Type B algorithms accounting for lateral electron scatter should be used, planning should endeavour to ensure that beams do not overlap on the skin (the optimum number of beams will depend on the exact clinical scenario)

It is advisable that two clinical oncologists trained in SABR evaluate each plan.

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, we can be sure of 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]

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 over 8-10 days

e.g. 45Gy in 3 fractions twice per week but not less than 8 days total treatment duration, e.g. Tuesday/Thursday/Tuesday. Mean dose to PTV will be at least 45Gy, maximum dose 60Gy or less (133%).

95% isodose should cover at least 95% of the PTV. Prescribe to covering isodose e.g. 80-95% if 95% does not provide adequate coverage, revise absolute max dose.

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 over 14 days

The target coverage goal is that a minimum of 95% prescribed dose will cover 99% of the PTV. The dose is prescribed to the isodose covering the PTV, which may range from 80% to 95%. Any hot spots should be within PTV, no greater than 1cc, and the maximum dose should be <120%. GTV should be covered by the 100% isodose.

(iii) 30-60Gy in 10 fractions over 14 days

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 more 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.

Prescription point:

Studies have varied considerably in the way in which dose is prescribed.

Prescribing to an isodose that covers the PTV generally results in a much higher dose (in some cases 35-40% higher than the prescription dose) within the PTV envelope. In instances such as this, extreme care is required to ensure the areas of high dose are contained within the PTV and that daily set up is optimised.

Guidance Note: The dose used in an individual case will depend on the clinical scenario and anticipated dose to OAR.

Table III.4: Organ at risk constraints

	3 Fractions	5 Fractions	10 Fractions
Normal Liver	700cc<15Gy V33<21Gy V50<15Gy	700cc<15Gy V60<30Gy Mean <20Gy	V30<27Gy V50<24Gy
Kidney (normal creatinine, both functioning)	Combined renal volume V35%<15Gy	33 % of combined renal volume <15Gy	33% of the combined renal volume may receive 18Gy
Kidney (one functioning)			10% of functioning kidney volume<10Gy
Spinal cord	Max 15Gy	Max 25Gy	Max 34Gy
Stomach	Less than 5cc>21Gy	1cc max 24Gy	1cc max 37Gy
Duodenum	Less than 5cc >15Gy	1cc max 24Gy	1cc max 37Gy
Small bowel	Less than 5cc >16Gy	1cc max 24Gy	1cc max 37Gy
Oesophagus	Less than 5cc>15Gy	1cc max 24Gy	1cc max 37Gy
Heart	Less than 1cc>24Gy	1cc max 27Gy	1cc max 40Gy
Lungs		V20 <10%	V20<10%

Normal Liver: The proportion of liver not radiographically involved by gross tumour (liver volume minus GTV).

Chest Wall: Maximum point dose 37Gy (in 3 fractions), and for no more than 30cm³ to receive more than 30Gy in 3 fractions.

Skin: Skin dose should be reviewed, and overlapping beams on the skin surface avoided to prevent skin necrosis.

III.3.3. Treatment Delivery and clinical follow-up

Treatment verification

III.3.1.1: Geometric Uncertainties, Inter-fraction and Intra-fraction variability:

The PTV for treatment is a volume in space into which we endeavour to place the tumour, for every treatment fraction. Errors in achieving perfect positioning arise from:-

- (i) *Base-line shifts* - Changes in liver tumour position relative to the bony anatomy that is used as a surrogate for image-guided pre-treatment set up (inter-fractional variation) and during treatment (intra-fraction variation).

Interfractional changes in base-line shift are estimated to be less than a mean of 5mm in medial-lateral (ML), cranio-caudal(CC), and anterior-posterior(AP) directions. However, vector translations can be significant (for 80% patients between 3.0 - 8.5mm, and in 10% of patients more than 8.5mm), although abdominal compression [40] and ABC [51] are demonstrated to reduce this. The degree of interfractional variability is not seen to correlate with the amplitude of respiration, as long as this is less than 19mm. [40]

Intrafractional variability, as assessed by cone beam kV-CT before and after delivery of a fraction of SABR, is measured to be small (assessed by Case et al to be 1.3 (RL), 1.6mm (CC), 1.5mm (AP) and 3.0mm (vector)). The magnitude is significantly less than interfractional baseline shift and again is reduced further by abdominal compression [40] and ABC. [51]

Treatment time: No correlation is observed between intra-fractional variation of exhale liver position and treatment time of less than 25 minutes for liver SABR [40], which correlates with similar experiences in lung SABR. [52] However, longer treatment times (> 34 minutes) are shown to increase intra-fractional variability. [53]

For this reason, treatment times are suggested to be less than 25 minutes wherever possible.

(ii) *Set up errors* – Departments planning to introduce SABR are encouraged to make an assessment of likely set up error according to the particular equipment used. With pre-treatment image guidance and correction, many centres report sub-3mm accuracy. The majority of patients are observed to require a positional correction, around two-thirds) [22] demonstrating the vital importance of image guidance.

III.3.3.2: Managing Base line shifts and set up errors: Image Guidance

Image guided delivery can compensate for errors in base-line shift and set up. There are several possible strategies:-

- (i) MV orthogonal imaging – this is shown to be better than no image guidance [45], but a residual error of more than 5mm in any direction (CC,ML, AP) is observed in 33% of patients in some studies. [54]
- (ii) Kv cone beam CT (CBCT) is thought to be superior – random errors (δ) estimated to be less than 3mm in any direction, and systematic errors (Σ) of 1-2mm. [54]
- (iii) Fiducial markers: These are more invasive, and can migrate, but have been used in several published series as means of image guidance. [32,33]

Of note, kV cone beam CT adds around 0.2-0.3 cGy (mean) per fraction. The time to acquire and analyse kV CBCT can be reduced to around 2-4 minutes with experience. [54]

It is advisable for treating clinical oncologists to be present when patients are treated, at least when liver SABR is first undertaken in a department.

Daily Image-guidance is mandatory in delivering liver SABR to reduce interfractional variability. Cone beam kV-CT (CBCT) is superior to other means of achieving this. Matching pre-treatment CBCT to the planning CT should be undertaken before each fraction of treatment

- the ideal is matching the soft tissues of the liver, but matching to vertebral bodies is a commonly used surrogate, although it is recognised that the liver moves between fractions relative to the vertebrae.

- errors of 3mm or more should be corrected

When using CBCT, a post-treatment scan is suggested, certainly when departments are starting SABR to assess intra-fractional variation. If no tracking or gating is used then a 4D-CT to confirm respiratory amplitude is advised.

Treatment assessments and 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 indeed the levels of toxicity reported in the studies herein reviewed are consistently low despite the heterogeneity of dose/fractionation schedules and differing prescription methods. The likely explanation is the limited dose delivered to uninvolved liver and the parallel functioning of liver parenchyma.

A syndrome of minor pain, fever and chills is observed in some patients (Grade 1, requiring no treatment, in 14%; grade 2, requiring treatment with analgesics/steroids, in 13%), usually occurs within 1-3 weeks of treatment. [22,24,26]

Rates of Gastritis/Oesophagitis are low (G2 7%, G3 in 3%) and many teams advise the use of prophylactic proton-pump inhibitors.[23]

Radiation-induced liver disease (RILD) is strictly 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. Childs Pugh B and HBC carriage associated with greater risks for 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]

- (ii) 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 reported as being low at around 2%-5%. [31, 33]

Late GI toxicity (grade 2 or less – ulceration/bleeding) is reported in 8% patients. [33]

Reported severe late toxicities are rare and include GI bleeding, rib fractures (2pts – calc % if 5 pts =7%). [22]

Patient Care on Treatment:

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

Use of proton pump inhibitors (PPI) to reduce the risk of GI ulceration and antiemetics for nausea are commonly used in published studies , especially if there isodose in proximity to the GI tract.

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] Some reports suggest MRI may be superior in differentiating residual disease from normal tissue reaction. [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. It should be particularly noted that the follow up of patients in published series is short (12-18 months) and therefore, the development of late effects poorly studied.

We recommend using the CTCAE v4.0 (available via the link below) for assessing toxicity during and after RT, specifically the following symptoms: Anorexia; Dyspnoea; Diarrhoea, Liver dysfunction and RILD, Fatigue; GI bleeding; Nausea; Pain, Pleural effusion; Pneumonitis; Pulmonary fibrosis; Vomiting

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

Suggested follow up schedule: Review at 4-6 weeks with a restaging CT, then 3 monthly to 2 years and 6 monthly thereafter. Follow up should include CT

assessment (especially if there is the potential of further treatment), bloods (FBC, U+E, LFTs, clotting and tumour markers as appropriate).

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.

Summary paragraph:-

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: 10mm cranio-caudally, and 5mm radially less if motion management techniques applied

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

- (i) 45-60Gy in 3 fractions over 8-10 days, 95% isodose covering at least 95% PTV
- (ii) 50-60Gy in 5 fractions over 14 days; to isodose covering PTV (80-95%)
- (iii) 30-60Gy in 10 fractions over 14 days (90% prescribed dose covering PTV)

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.(See *appendix 2.0/2.1*) 4DCT where available.

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

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

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IV Prostate Cancer

IV.1. Introduction and literature review

Conventional therapy and outcome

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 significant improvement in biochemical control of 10 to 20% at 5 years with 5 year freedom from biochemical failure rates of 64 to 80% reported [1-4]. 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 [1, 2, 4-6]. Trials comparing IMRT with CRT have revealed a significant reduction in acute and late gastrointestinal toxicity [7, 8]. 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 [9]. Recently 10 year outcomes were reported for a series of 170 patients who received 81Gy in 45 fractions with IMRT [10]. Median follow up was 99 months. Biochemical control was excellent 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 [10].

Dose escalating using conventional fractionation prolongs the overall treatment time which may have a negative effect on cancer outcomes [11]. 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 [12-15]. 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 [14, 16]. 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 iso-toxic levels of late rectal toxicity, or ii) by delivering an iso-effective hypofractionated dose to the prostate with the aim of a reduction in rectal toxicity. Clinical trials delivering prostate radiotherapy using moderate hypofractionation (e.g. up to 4Gy per fraction) have generally, but not exclusively, demonstrated that moderate hypofractionation offers equivalent biochemical outcomes with acceptable toxicity [17-20].

SABR delivers ultra-hypofractionated treatments and, in the treatment of prostate cancer, offers the potential for dose escalation and for harnessing the theoretical radiobiological advantages. Work has been done and continues to be done,

therefore, exploring the use of SABR in localised prostate cancer, but as yet the number of published results is relatively small.

It should be noted that the recent report of the National Cancer Action Team Radiotherapy Implementation Group regarding SABR have recommended that prostate SABR should only be implemented in the context of a clinical trial. To this end, prostate SABR delivered using the Cyberknife is currently being investigated in the PACE trial (International Randomized Study of Laparoscopic Prostatectomy vs Robotic Radiosurgery and Conventionally Fractionated Radiotherapy vs Radiosurgery for Early Stage Organ-Confined Prostate Cancer). Trials involving prostate SABR delivered using linear accelerators within the UK are likely to be set up over the next few years.

Stereotactic Ablative Body Radiotherapy (SABR)

A literature search using the search terms 'stereotactic' and 'prostate' revealed 21 studies where clinical data was presented [21-43]. These were either phase I/II trials or case series. Two trials dealt with recurrent disease, either locally and or isolated metastases [42, 43]. The remaining 19 trials dealt with primary localised prostate cancer. A summary of these publications is given in Table I.

Selection criteria in cited prostate trials was usually described as being 'localised' prostate cancer, usually stage T1/T2 but in at least one study eligible patients could have up to T4 N0 M0 disease [28].

Clinical studies of treatment of localised prostate cancer can be divided into two: firstly, those using conventional fractionation incorporating a SABR boost, and secondly, those using pure ultra-hypofractionation. Evidence from the five trials looking at conventional fractionation followed by a SABR boost suggest good biochemical disease free control and a small risk of increased urinary toxicity[31-33, 40, 41].

The ASTRO Emerging Technology Committee has produced a report entitled 'Stereotactic Body Radiotherapy (SABR) For Primary Management of Early-Stage, Low-Intermediate Risk Prostate Cancer' which overviews the available data [44]. It summarizes that preliminary results, primarily available only in abstract form and consisting of reports of clinical experiences from single institutions, show that SABR for the prostate is technically feasible with little reported acute morbidity. Very early results, of limited statistical power, suggest that treatment will induce an initial PSA response of a magnitude equivalent to that seen with conventionally fractionated radiotherapy. Data are not available regarding long-term disease control, survival, and chronic toxicity. In the absence of randomized trials and mature, long-term follow-up data, a conservative estimation of consequences of non-use of SABR would be a continuation of treatment following standard, accepted fractionation schemes with realization of the associated TCP and NTCP values.

The limited data available suggests that high dose hypofractionated SABR can achieve high rates of local control with low morbidity in low-, intermediate- and possibly high-risk localised prostate cancer. More robust data is required before

SABR can be recommended as a routine alternative for patients with localised prostate cancer and patients should only be treated within research protocols unless the alternative techniques of surgery, brachytherapy or external beam radiotherapy are suboptimal. This might include patients unfit or unwilling to undergo surgery who have significant urinary outflow symptoms or a recent TURP (contraindications to brachytherapy) or who have medical or other problems which might make conventional long-course external beam radiotherapy difficult or impossible, when SABR maybe considered the optimal means of delivering radical radiation therapy to the prostate.

The technique could only be used as routine if evidence was forthcoming demonstrating that it was at least as safe and as effective as existing treatments. If that was the case then SABR would become an acceptable alternative radiotherapy technique and could be used instead of conventionally fractionated external beam radiotherapy (either 3D conformal or IMRT) or brachytherapy. It could also be offered as an alternative to open, laparoscopic or robotic prostatectomy, for the same groups of patients.

A review of the equipment currently available to deliver SABR suggests that all systems which are SABR capable would be suitable for prostate treatment trials. There are differences between the various technologies, which could lead to differences in planning and treatment times, and to throughput, but there are no specific features which make one or more products clearly more or less suited to prostate SABR.

Table IV.1. Summary of studies using SABR in the treatment of localised prostate cancer

Study	Number of patients	Follow up (range)	Risk group (definitions given for each study)	Technique	Dose volume constraints	Dose and fractionation (BED; $\alpha/\beta=1.5$)	Duration	Use of androgen deprivation	Disease outcome	Toxicities
<i>SABR delivered using Cyberknife</i>										
Fuller et al 2008 ²¹	10	Maximum follow up 12 months	Low and intermediate	Cyberknife Fiducials Urinary catheter PTV: Prostate + up to 2cm of SV + 0-5mm	Rectal wall: Dmax= 38Gy Rectal mucosa: Dmax= 28.5Gy Urethra: Dmax= 45.6Gy Bladder: Dmax= 45.6Gy	38Gy / 4 # (279)	NR	NR	Fall in median PSA from 6.9ng/ml at baseline to 0.95ng/ml at 4 months (=86% reduction)	No acute rectal toxicity >RTOG Gd2
King et al 2012 ²²	67	2.7 years	Low	Cyberknife Fiducials PTV: Prostate + 5mm (3mm posteriorly)	Rectum: V50%<50%; V80%<20%; V90%<10%; V100%<5% Bladder: V50%<40%; V100%<10% Femoral heads: V40%<5%	36.25Gy / 5# (211)	5 consecutive days (n=22) or alternate days (n=45)	No	4 year biochemical relapse free survival 94% (95% CI 85-102%)	Late CTCAEv3 Gd2 GU: 5%, Gd3: 4%, Gd4: 0, Late CTCAEv3 Gd2 GI: 2%, Gd3+:0
Friedland et al 2009 ²³	112	24 months	Low, intermediate and high	Cyberknife Fiducials PTV: Prostate and proximal 1cm of SV + 5mm (3mm posteriorly)	Rectum: V36<1cc Bladder: V37<10cc	35 to 36Gy / 5# (198-209)	5 consecutive days	Yes- 19% (n=21)	Fall in mean PSA from 6.0ng/ml at baseline to 3.1ng/ml at one month. Mean PSA nadir of 0.6ng/ml at 18 months. 95% of patients with PSA nadir of \leq 1.0ng/ml at 3 years. 3 PSA failures	Gd3 rectal toxicity in 1 patient (not specified if acute or late)
Freeman and King 2012 ²⁴	41- selected cohort from Friedland et al ⁷⁵ and King et al ⁷⁷	60 months	Low risk	Cyberknife Fiducials PTV: As per Friedland et al ⁷⁵ and King et al ⁷⁷	As per Friedland et al ⁷⁵ and King et al ⁷⁷	35 or 36.25Gy / 5# (198-211)	5 consecutive days in 38 patients	No	5 year biochemical progression free survival 93% (95% CI 84.7-100%)	Late RTOG Gd3 GU: 2% Late RTOG Gd3+ GI: 0
Meier et al 2010 ²⁵	211	NR	Low and intermediate	Cyberknife Fiducials PTV: Prostate (+ SV if intermediate risk) Margins NR	NR	40Gy / 5# 36.25Gy / 5# to proximal SV if intermediate risk (253 to prostate, 211 to SV)	NR	No	Fall in median PSA from 5.2 at baseline to 0.9ng/ml at 12 months and 0.7ng/ml at 18 months. 1 PSA failure (Phoenix). Erectile dysfunction increased from 49% pre treatment to 58% at 12 months	CTCAEv3 Acute Gd2 GU: 20% (no Gd3+) CTCAEv3 Acute Gd2 GI: 9% (noGd3+) CTCAEv3 Late Gd2+ GU: 6.4% CTCAEv3 Late Gd2 GI: 1% (no Gd3+)
Aluwini et al 2010 ²⁶	10	5.1 months (2-13)	Low and intermediate	Cyberknife 4 fiducials Low fibre diet, Bowel prep, Urinary catheters in 8 patients PTV: Prostate +3mm	Rectal wall: Dmax<38Gy, Rectal mucosa: Dmax<28.5Gy, Whole rectum: 1cc<32.5Gy Bladder: Dmax=41.8Gy; D1cc<38Gy Urethra: Dmax=45.6Gy; D5%<45.5Gy; D10%<42Gy; D50%<40Gy Sigmoid/ intestine: 28.5Gy, Femoral head: 24Gy	38Gy / 4# (279)	4 consecutive days	No	Fall in mean PSA by 53% at 3 months and 81% at 6 months	RTOG Acute Gd1-2 GU: 50%, Gs3: 20% RTOG Acute Gd1-2 GI: 25%, Gd3:10% RTOG Late Gd1-2 GU: 25%, Gs3: 12% RTOG Late Gd1+ GI: 0

Table IV.1. Continued

Study	Number of patients	Follow up (range)	Risk group (definitions given for each study)	Technique	Dose volume constraints	Dose and fractionation (BED; $\alpha/\beta=1.5$)	Duration	Use of androgen deprivation	Disease outcome	Toxicities
Bolzicco et al (2010) ²⁷	45	20 months (6-42)	Low and intermediate	Cyberknife 4 fiducials Empty rectum Urinary catheter PTV: Prostate + 5mm (3mm posteriorly)	Rectum V38<5%, Bladder V40<5% Urethra V41<5%, Penile bulb V29<25%	35Gy / 5# (198)	5 consecutive days	Yes- 38% (n=17)	Fall in mean PSA from 4.7ng/ml at baseline to 0.35ng/ml at 2 years. No cases of biochemical failure	RTOG Acute Gd2 GU: 11%, Gd3+: 0% RTOG Acute Gd2 GI: 24%, Gd3+:0% RTOG Late Gd3 GU: 2%, Gd4: 0% RTOG Late Gd2 GI: 2%, Gd3+: 0%
Kang et al (2011) ²⁸ and Choi et al (2007) ²⁹	44	13 months (4-46)	T1c-T4b Low, intermediate and high	Cyberknife 6 fiducials in sacrum or prostate PTV: Low risk: prostate +4mm (2mm post) Intermediate or high risk: prostate and SVs+4mm (2mm post)	Rectum: V50%<50% V100%=0	32-36Gy / 4# (202-252)	4 consecutive days	NR	5 year biochemical free survival 93.6% (all failures in high risk group). Median PSA nadir 0.1ng/ml (range 0 to 1.13ng/ml)after median of 13 months	CTCAEv3 Acute Gd2 GU: 14%, Gd3+:0 CTCAEv3 Acute Gd2 GI: 9%, Gd3+:0 CTCAEv3 Late Gd2 GU: 7%, Gd3+:0 CTCAEv3 Late Gd2 GI: 11%, Gd3+:0
Oermann et al 2011 ³⁰	26	15 months (range 13-19)	Low and intermediate	Cyberknife 4 fiducials Enemas Low gas/motility diet. PTV: prostate and proximal SV plus 5mm (3mm posteriorly)	V50%<50%; V80%<20% V90%<10%; V100%<5% D1cc<36Gy Bladder: D10cc<37Gy Urethra: Dmax<133%	36.25Gy in 5 fractions (211)	Two weeks	No	Fall in median baseline PSA from 5.65ng/ml (range 2.3-10.3ng/ml) at baseline to 0.7ng/ml after 1 year	CTCAEv3 Acute Gd2 GU: 27%, Gd3+:0 CTCAEv3 Acute Gd2+ GI: 0 CTCAEv3 Late Gd2 GU: 23%, Gd3+:0 CTCAEv3 Late Gd2+ GI: 0
Townsend et al 2011 ³¹	48 SBRT alone: n=37 SBRT boost: n=11	11.5 weeks	Low, intermediate and high	Cyberknife 3-4 fiducials PTV: Prostate + 5mm (3mm posteriorly)	Rectum: D1cc<36Gy V50%<50Gy Bladder: D10cc<37Gy	SBRT alone: 35 - 37.5Gy /5# (198-225) Boost: 17.6-25Gy in 2-5 fractions- non-boost dose NR	NR	Yes- 25% (n=12)	Fall in median PSA from 9.34ng/ml at baseline to 2.41ng/ml (n=28 for this analysis)	CTCAEv3 Acute Gd2 GU: 10%, Gd3:8%, Gd4:0 CTCAEv3 Acute Gd2 GI: 27%, Gd3:9%, Gd4:0
Katz et al 2010 ³²	304 Group 1: n=50 Group 2: n=254	Group 1: 30 month (26- 37) Group 2: 17 month (8-27)	Low, intermediate and high	Cyberknife 4 fiducials Bowel prep: amifosidine PTV: Low risk: Prostate+5mm (3mm post at rectum) Intermediate risk: Prostate + proximal half SV+5mm (3mm post at rectum) High risk: Prostate + proximal half SV+5mm (3mm post at rectum + 8mm on affected side)	NR	Group 1: 35Gy in5 fractions (198) Group 2: 36.25Gy in 5 fractions (211)	NR	Yes- 19% (n=54)	Group 1: PSA nadir <1ng/ml after 24 months in 88% (n=38). PSA 0.11ng/ml after median 42 months ⁸² . No biochemical failures after median of 42 months ⁸² Group 2: PSA nadir <1.0ng/ml after 24 months in 81% (n=17). Biochemical failure in 1% (n=4 of 45; Phoenix definition), all in higher dose group	RTOG Acute Gd2 GU: 7%, Gd3+: 0% RTOG Acute Gd2 GI: 7%, Gd3+:0% RTOG Late Gd2 GU: 4%, Gd3: 1%, Gd4: 0% RTOG Late Gd2 GI: 8%, Gd3+: 0%

Table IV.1. Continued

Study	Number of patients	Follow up (range)	Risk group (definitions given for each study)	Technique	Dose volume constraints	Dose and fractionation (BED; $\alpha/\beta=1.5$)	Duration	Use of androgen deprivation	Disease outcome	Toxicities
Jabbari et al 2012 ³³	20	18.1 months (range 12.9-43.5)	Mainly low and intermediate	Cyberknife, 3 fiducials PTV: Prostate +/- Some or all SV on case by case basis 0-2mm margin, no overlap with rectum	NR	38Gy in 4 fractions (279)	Mostly 4 consecutive days	No	Median PSA nadir 0.47ng/ml, no evidence of progression	CTCAEv3 Acute Gd2 GU: 45%, Gd3+:0 CTCAEv3 Acute Gd2 GI: 5%, Gd3+: 0 CTCAEv3 Late Gd2 GU: 8%, Gd3: 5%, Gd4:0% CTCAEv3 Late Gd2 GI: 3%, Gd3+:0 (results combined with boost patients- below)
SABR delivered using linear accelerator										
Mantz et al 2007 ³⁴	22	NR (18 patients follow-up for a t least 1 months)	Low Prostate volume<60cc IPSS<18	Linear Accelerator-Trilogy (including CBCT) PTV: Prostate + 3mm	Rectum: Dmax:=85% Bladder: Dmax=100% Femoral heads: Dmax=50%	36.25Gy in 5 fractions (211)	Alternate days	NR	NR	CTCAEv3 Acute Gd1+ GU: 0 CTCAEv3 Acute Gd2 GI: 5%, Gd3+: 0
Mantz et al 2010 ³⁵	54	26 months	Low	Linear Accelerator-Trilogy (including CBCT) Calypso- electromagnetic tracking of fiducials PTV: NR	NR	40Gy in 5 fractions (253)	Alternate days	NR	Fall in median PSA from 6.9ng/ml at baseline to 1.0 and 0.3ng/ml at 12 and 24 months respectively	No difference in urinary or rectal symptom scores at one year compared to baseline
Pham 2010 ³⁶ and Madsen 2007 ³⁷	40	60 months (range 9-96)	Low	Liner accelerator Flex prone position 3 fiducials Low gas diet with simethecone PTV: NR	NR	33.5Gy in 5 fractions (183)	5 consecutive fractions for most patients	NR	5 year biochemical relapse free survival (Phoenix) 93% and 71% (ASTRO) 5 year overall survival 75%- no known prostate cancer related deaths	RTOG Acute Gd2 GU: 21%, Gd3: 3%, Gd4:0 RTOG Acute Gd2 GI: 13%, Gd3+:0% RTOG Late Gd2 GU: 13%, Gd3: 3%, Gd4: 0% RTOG Late Gd2 GI: 8%, Gd3+: 0%
Tang et al 2008 ³⁸	30	12 months	Low to intermediate Prostate volume <60cc IPSS<15	Linear accelerator IMRT 3 fiducials Vacuum lock bag PTV: Prostate + 4mm	Rectum: V20≤40% V32≤33% Bladder: V32≤40% Penile bulb: V20≤90%	35Gy in 5 fractions (198)	Once weekly fractions, over 29 days	Yes- 3% (n=1)	Fall in median PSA from 6.0ng/ml at baseline to 1.8ng/ml at 6 months	CTCAEv3 Acute Gd2 GU: 23%, Gd3+:0 CTCAEv3 Acute Gd2 GI: 50%, Gd3+:0 CTCAEv3 Late Gd2 GU: 13%, Gd3+:0 CTCAEv3 Late Gd2+ GI: 13%

Table IV.1. Continued

Study	Number of patients	Follow up (range)	Risk group (definitions given for each study)	Technique	Dose volume constraints	Dose and fractionation (BED; $\alpha/\beta=1.5$)	Duration	Use of androgen deprivation	Disease outcome	Toxicities
Boike et al 2011 ³⁹	45 Dose escalation trial- 15 patients in each of 3 dose levels	Group 1: 30months (3-36) Group 2: 18months (0-30) Group 3: 12 months (3-18)	Low to intermediate Prostate volume ≤ 60 cc.	Tomotherapy or linear accelerator based-Trilogy system. Fiducials or Calypso beacon implanted. Bowel prep including enema. Rectal balloon, full bladder PTV: Prostate +3mm	Rectum: Anterior rectal wall Dmax 105%, Lateral rectal walls V90% <3 cc Posterior rectal wall max: $\leq 45\%$ Bladder wall Dmax 105% and D10cc <18.3 Gy Prostatic urethra Dmax $\leq 105\%$	Group 1: 45Gy in 5 fraction (315;n=15) Group 2: 47.5Gy in 5 fractions (348;n=15) Group 3: 50Gy in 5 fractions (383)	One fraction at least every 36hours	Yes- 22% (n=10)	Biochemical failure free survival 100% (1 patient excluded from analysis as subsequently was found to have GS9 disease- this patient has relapsed)	CTCAEv3 Acute Gd2 GU: 22%, Gd3+:0 CTCAEv3 Acute Gd2 GI: 11%, Gd3+:0 CTCAEv3 Late Gd2 GU: 9%, Gd3: 4%, Gd4:0;CTCAEv3 Late Gd2 GI: 13%, Gd3:0, Gd4:7%(n=1)
<i>SABR delivered as a boost</i>										
Katz et al 2010 ³³	73	33 months (22-43)	Intermediate and high	Cyberknife 4 fiducials Bowel prep Rectal amifostine PTV: Boost: prostate + 5mm except 3mm posteriorly in region of the rectum	NR	45Gy in 25 fractions conformal + 18-21Gy in 3 fractions (189-218)	3 consecutive days (2 weeks after conformal radiotherapy)	Yes- 48% (n=36)	3 year biochemical relapse free survival of 89.5% for intermediate risk and 77.7% for high risk. PSA nadir of 0.5ng/ml achieved in 72% after 24 months. 10 PSA failures (Phoenix) at median 15 months.	RTOG Acute Gd2 GU: 4%, Gd3+:0 RTOG Acute Gd2 GI: 5%, Gd3+:0% RTOG Late Gd2 GU: 5%, Gd3: 0.3%, Gd4: 0%; RTOG Late Gd2 GI: 2%, Gd3+: 0%
Miralbell et al 2010 ⁴⁰	50	63 months (18-88)	Low, intermediate and high	Linear accelerator IMRT Rectal balloon External markers reflecting infrared (ExacTrac) Empty bladder PTV: For boost: "dominant tumour region within prostate" +/- SV + 3mm margin	Initial constraints: Rectum and bladder: V50% $<50\%$ V90% $<30\%$ Dmax=95% Urethra: NR but priority factor 100%	Conventional EBRT: 64-64.4Gy in 1.8 to 2Gy fractions Stereotactic boost: 10-16Gy in 2 fractions of 5 to 8Gy (185-250)	Boost:1 week between fractions	Yes- 66% (n=33)	5 year Biochemical relapse free survival 98% +/- 1.9% (Phoenix)	CTCAEv3 Acute Gd2 GU: 46%, Gd3: 4%, Gd4:0 CTCAEv3 Acute Gd2 GI: 8%, Gd3+: 0 CTCAEv3 Late Gd2 GU: 12%, Gd3+: 0 CTCAEv3 Late Gd2 GI: 10%, Gd3:10%, Gd4:0
Oermann et al 2010 ⁴¹	24	9.3 months (6.6-16.9)	Intermediate and high	Cyberknife 4 fiducials Enemas Low gas/motility diet. PTV: Prostate, regions of extracapsular spread, proximal SV plus 5mm (3mm posteriorly)	Rectum: V50% $<50\%$, V80% $<20\%$, V90% $<10\%$, V100% $<5\%$, D1cc ≤ 36 Gy Bladder: D10cc $<100\%$ Penile bulb: V15Gy $<50\%$ Membranous urethra: V18Gy $<50\%$ Bladder: D10cc <19.5 Gy Sigmoid colon and other bowel: D1cc <15 Gy	19.5Gy in 3 fraction boost then 50.4Gy in 28 fractions IMRT (215)	Consecutive or alternate days	Yes- 42% (n=10)	Fall in median PSA from 10.6ng/ml at baseline to 1.5ng/ml at 6 months in patients not receiving androgen deprivation	CTCAEv3 Acute Gd2 GU: 13%, Gd3+:0 CTCAEv3 Acute Gd2 GI: 4%, Gd3+:0 CTCAEv3 Late Gd2 GU: 8%, Gd3+:0 CTCAEv3 Late Gd2+ GI: 0%
Townsend et al 2011 ⁸¹	11	11.5 weeks	Low, intermediate and high	Cyberknife 3-4 fiducials PTV: Prostate + 5mm (3mm posteriorly)	Rectum: D1cc <36 Gy V50% <50 Gy Bladder: D10cc <37 Gy	Boost: 17.6-25Gy in 2-5 fractions- non-boost dose NR	NR	Combined with results from Townsend et al above	Combined with results from Townsend et al above	Combined with results from Townsend et al above

Table IV.1. Continued

Study	Number of patients	Follow up (range)	Risk group (definitions given for each study)	Technique	Dose volume constraints	Dose and fractionation (BED; $\alpha/\beta=1.5$)	Duration	Use of androgen deprivation	Disease outcome	Toxicities
Jabbari et al 2012 ³³	18	23.5 months (range 12.6-34.5)	Intermediate and high	Cyberknife, 3 fiducials PTV: Prostate +/- Some or all SV on case by case basis 0-2mm margin, no overlap with rectum	NR	Pelvic IMRT 45-50Gy (fraction size NR) 19Gy in 2 fraction boost	Mostly 2 consecutive days	Yes	Median PSA nadir 0.10ng/ml, no evidence of progression	Combined with results from Jannari et al above
SABR delivered for locally recurrent disease										
Vavassori et al 2010 ⁹³	6	11.3 months (9.6-18.6)	Locally recurrent prostate cancer following previous RT	Cyberknife 3 fiducials PTV: NR	Rectum: Dmax<75% Urethra: Dmax<125%	30Gy in 5 fractions (150)	5 consecutive days	Yes- 67% (n=4)	Biochemical progression in 67% (n=4) after median of 8.4 months (Phoenix definition; range 7-12 months)	No acute or late Gd3+ toxicities
Jereczek-Fossa et al 2012	15	9.5 months (3-28.9)	Locally recurrent prostate cancer following previous radiotherapy	Cyberknife 3 fiducials PTV: GTV + 1-2mm margin	Rectum: Dmax<100% Bladder and urethra: Dmax<120% Small bowel: D1cc<21Gy	30Gy in 5 fractions (150)	NR	Yes- 33% (n=5)	Complete biochemical response in 73% (n=11), partial in 20% (n=3) and stable PSA in 7% (n=1)- see text for definitions 30 months PFS: 22.2% (95%CI:--58.2)	RTOG Acute Gd2 GU: 6%, Gd3: 2%, Gd4:0 RTOG Acute Gd2+ GI: 0% RTOG Late Gd2 GU: 6%, Gd3: 6%, Gd4: 0% RTOG Late Gd2 GI: 3%, Gd3+: 0%

NR: not reported; GS: Gleason score; SV: seminal vesicles; CBCT: cone beam CT; IPSS: International Prostatic Symptom Score; IMRT: intensity modulated radiotherapy; PFS: progression free survival; CI: confidence interval

*: n=254: based on patients with at least one year of follow up

#: n= 64: based on patients with at least one year of follow up and patients who received androgen deprivation excluded

IV.2. Patient selection criteria

Inclusion and Exclusion Criteria

Although the published evidence for SABR in prostate cancer is sparse, there is no reason to think that the criteria for patients having SABR should be any different to those receiving other types of radical radiotherapy for prostate cancer (i.e. those with localised disease, stages T1-2, N0 M0). It is acknowledged that within these criteria are contained patients who may be at low, intermediate or high risk on the basis of their PSA and Gleason score and as such may require additional treatments such as hormone therapy (although it should be noted that few reports of SABR for prostate cancer included androgen deprivation as part of definitive therapy).

IV.3. Radiotherapy

IV.3.1 Pre-treatment image acquisition

Patient positioning and tumour localisation

The ASTRO Emerging Technology Committee state that technological advances such as stereotactic body radiotherapy combined with optimum immobilization and organ localization may allow refinements in dose delivery precision to achieve the goal of minimal margins around the target structure while permitting dose acceleration. Clinical implementation of this technique will require a consistent investment in new technologies capable of achieving this precision, or poorer local control rates will probably result. The authors of that report believe that further clinical trials addressing the uncertainties in the clinical implementation of this new approach to prostate cancer treatment should be conducted.

In the studies cited above, localisation of the prostate was achieved with the use of 3-4 fiducial markers (including electromagnetic transponders). Due to the duration of each treatment fraction, care should be taken to ensure patient comfort.

Minimum standard: All centres treating prostate patients with SABR must be able to visualise either the position of the prostate itself or a reliable surrogate in order to ensure accurate treatment delivery and allow reduction of margins. Monitoring of intra-fraction motion should be considered where available. N.b. evidence supporting the accurate positioning of the prostate during SABR treatments is currently only established for the use of fiducial markers. Other solutions should be used only in conjunction with thorough quality assurance procedures and evaluation within a clinical trial.

CT simulation

Care should be taken with bladder and bowel preparation prior to planning and treatment. Several of the existing studies have followed a variety of bowel and bladder protocols including low residue diets, enemas, rectal balloons and insertion

of a urinary catheter (to enhance visualisation of the urethra but would also allow bladder filling). Patients should have an empty rectum and full bladder.

Formal immobilisation devices are generally not required with patient set-up as for standard prostate radiotherapy, but formal immobilisation with vacuum bags can be used. Patients should be CT simulated, and conventionally this is performed at least 7 to 14 days after fiducial marker insertion to allow resolution of any oedema secondary to the insertion procedure.

IV.3.2. Delineation and treatment planning

Tumour delineation

GTV is generally defined as the prostate only with part of the seminal vesicles added to generate CTV in intermediate/high risk patients. There is variation in the existing studies regarding GTV to PTV margins largely dependent on whether intra-fraction motion monitoring and correction is available.

Studies using Cyberknife have commonly employed up to 5mm margins in all direction except for posteriorly where margins of up to 3mm have been employed (see table 1). Linear accelerator based systems utilising the Calypso electromagnetic tracking system have employed similar small margins [34, 35, 39]. 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 inclusion of the seminal vesicles within the treatment volume has differed between and within studies, with approximately half of the studies treating the prostate only and half sometimes or always including some or all (generally the proximal half or proximal 1cm) of the seminal vesicles, often in higher risk cases. It may well be feasible and appropriate to include the proximal 1cm of seminal vesicles in intermediate risk patients when treating with systems that require small CTV to PTV margins. With linear accelerator based systems that do not have intrafraction motion monitoring and correction capabilities, however, the necessary CTV to PTV margins may cause problems when trying to meet organ at risk constraints.

In Cyberknife centres recruiting patients to the PACE trial, for low risk patients the GTV consists of the prostate alone and in intermediate risk patients, the GTV is formed by the prostate plus proximal 1cm of seminal vesicles. A 1 to 2mm margin is added to form the CTV to account for regions of potential extra-capsular spread. The CTV to PTV margin depends on whether a heterogeneous or homogeneous dose distribution is desired. For homogeneous planning a 3mm margin is used with a 1mm margin posteriorly for all patients. For heterogeneous planning in low risk patients a 2mm CTV to PTV margin is employed with 0mm posteriorly. In intermediate risk patients for heterogeneous planning a 2mm margin is used in all direction except posteriorly where a 0 to 1mm margin is used. It should be noted that this trial mandates that a planning MRI scan is fused with the planning CT scan for volume definition, which is likely to influence the actual volume of prostate defined.

These volume definitions and margins are therefore only applicable to centres which a) use planning MRIs and b) use intra-fraction motion monitoring and compensation in line with the PACE protocol.

For linear accelerator based treatments no trial exists from which equivalent guidance can be drawn. The image guidance sub-study within the CHHiP trial (a randomised phase III trial comparing 74Gy in 37fractions, 60Gy in 20 fractions and 57Gy in 19 fractions), which did not require planning MRI scans or intra-fractional motion correction, used 6mm CTV to PTV expansion margins with fiducial markers. This margin was felt sufficient to encompass residual set up uncertainty as well as intra-fraction motion. A 6mm CTV to PTV margin may represent margin adequate to account for intra-fraction motion, and one that is feasible to respect organ-at-risk constraints for SABR, although individual centres must establish appropriate margins based on local facilities and processes.

Minimum standard: each centre must establish expansion margins that are appropriate for local practice. These margins should be audited regularly.

Organs at risk (OAR)

Guidance on OAR and tumour delineation should be consistent to allow accurate reporting and comparisons.

As a minimum, the following should be contoured as organs at risk:

- Rectum: from the anus to the recto-sigmoid junction
- Bladder (including wall and lumen)
- Femoral heads (excluding the femoral necks)
- Penile bulb
- Bowel (any present within 15cm of the PTV, excluding the rectum)

In addition, the following may be contoured:

- Urethra: only visible if patient catheterised for planning scan
- Testicles: for non-coplanar treatments
- Outer rectal wall and mucosa to generate rectal dose surface histograms

Treatment planning

Studies have used a variety of treatment techniques including 3D CRT and IMRT. Any technique that meets planning objectives can be used.

Two types of dosimetric approaches have been reported and are currently under further investigation – a relatively homogenous dose distribution within the PTV as would be desirable in conventional radiotherapy, or a simulated heterogeneous HDR brachytherapy plan.

Unlike the situation with peripheral lung cancer, as yet no comprehensive guidelines exist which standardise SABR delivery for prostate cancer. The ASTRO Emerging Technology Committee ‘Stereotactic Body Radiotherapy (SABR) For Primary

Management of Early-Stage, Low-Intermediate Risk Prostate Cancer' report recommends that [44]:

- conformity index should be less than 1.2 (defined in this report as “the ratio of the volume of the isodose shell that provides 95% PTV coverage to the PTV volume”). The most appropriate definition of conformity index, however, may vary depending on whether dose is prescribed to the isodose, the PTV as a whole, or to a peripheral isodose.
- Areas of high dose spillage are those that receive greater than 105% of the prescribed dose, and these should remain within the PTV
- Intermediate dose spillage should be evaluated by i) specifying a maximum dose permissible at 2cm from the PTV; this limit should be a function of the volume of the PTV, although no suggested values are provided, and ii) recording the ratio of the volume of the 50% isodose to the volume of the PTV. Again no suggested values are provided.

Although some investigators did not have firm DVH constraints, others reported that 95% [23] or 96% [32] of PTV had to receive the prescribed dose, or that all of the PTV had to receive at least 90% [37]. Fuller, who tried to mimic a HDR brachytherapy distribution using a dose of 38Gy in 4 fractions, used the following dose constraints: for the PTV, V100%, $\geq 95\%$ with a max dose of 200%, a max rectal dose of 100%, a max rectal mucosa dose of 75%, a max urethral dose of 120% and a max bladder dose of 120%[21].

The rectum was the main OAR; the rectal dose constraints documented by King (who delivered 36.25Gy in 5 fractions) were: V50%, <50% of rectum, V80%, <20% of rectum, V90%, <10% of rectum and V100%, <5% of rectum; Miralbell described a V36Gy of <1cc [22]. It is important to note that these constraints are not very rigorous, and it is not clear how they were determined. As a general principle, practitioners should aim to keep the rectal doses as low as possible.

Centres with Cyberknife participating in the PACE trial will adopt the dose-volume constraints used in this trial [‘International Randomized Study of Laparoscopic Prostatectomy vs Robotic Radiosurgery and Conventionally Fractionated Radiotherapy vs Radiosurgery for Early Stage Organ-Confined Prostate Cancer’ v3.0 trial protocol].

Fractionation

Although SABR can be used to deliver a high dose boost, most work is exploring its use in enabling extreme hypofractionated treatments. It is the latter which will be further examined here. The published experience has used a dose range from 33.5 to 50 Gy in 4 or 5 fractions, with fraction size varying from 6.7 to 10Gy. Treatment was usually daily 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, and so adopting an alternate day approach seems reasonable[22]. In all cases fiducial markers were used, usually either three or four.

For Cyberknife treatments, it is most likely that treatment will be prescribed within the context of the PACE trial, i.e. 36.25Gy in 5 fractions when aiming for a homogeneous dose distribution, and 38Gy in 4 fractions when aiming for a heterogeneous dose distribution. Since guidelines or consistent evidence are unavailable for linear accelerator based treatments, patients should only be treated within the context of a clinical trial.

IV.3.3. Treatment delivery and clinical follow-up

Treatment verification

Day 0 is generally not required for prostate SABR. Fiducials with either CBCT or planar imaging are recommended as a minimum to correct for daily inter-fraction motion. Where available systems to monitor and correct for intra-fraction motion are also advised particularly with treatment times > 30 min.

Minimum standard: All patients must be treated according to an established, comprehensive IGRT process appropriate to local practice.

Treatment assessments and follow-up

Biochemical control seems comparable to conventional treatment but clearly long term follow up is necessary to confirm the efficacy, and also assess result and late toxicity, and as such assiduous documentation of all outcomes, including early and late effects, is mandatory.

We recommend that toxicities are recorded according to CTC version 4 (available via the link below), with particular attention to the sections relating to genitourinary and gastrointestinal toxicities. Particular care should be made to assess

- i. Bladder: perforation, spasm, non-infective cystitis, haematuria
- ii. Urinary: fistula, frequency, incontinence, retention
- iii. Urinary tract: obstruction, pain, urgency
- iv. Anal: fistula, haemorrhage, mucositis, necrosis, pain, stenosis, ulcer, colitis
- v. Colonic: fistula, haemorrhage, obstruction, perforation, stenosis, ulcer, constipation, diarrhoea, faecal incontinence, lower GI haemorrhage, proctitis
- vi. Rectal: fistula, haemorrhage, mucositis, necrosis, obstruction, pain, perforation, stenosis, ulcer

In addition, the following should be recorded from the

- vii. Reproductive section: ejaculation disorder, erectile dysfunction, prostatic pain.

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

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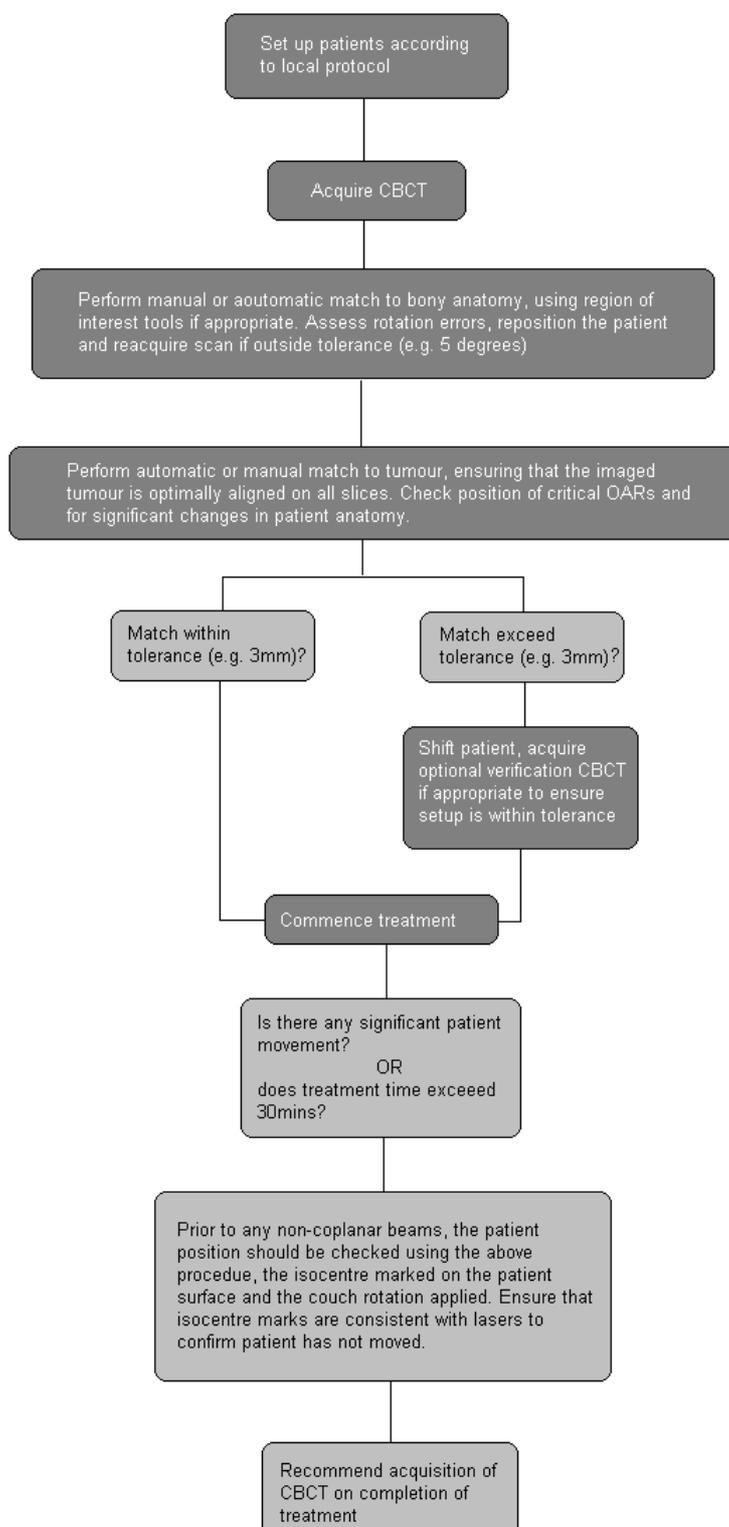
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V Other clinical sites

It is intended that in due course guidance will be developed by the Consortium for other clinical sites (i.e. central lung cancer, renal cancer, pancreatic cancer, head and neck cancer, spinal tumours, oligometastases) 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: Example treatment workflow when using volumetric imaging



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 calipers. 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 will 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

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

II. Peripheral lung

Introduced in December 2010 and reviewed for v4.1, due to be reviewed by January 2017

Sub-group membership

(i) Pooja Jain

(ii) Rob Stevenson

III. Liver metastases

Introduced in January 2013, to be reviewed by January 2016

Sub-group membership

(i) Maria Hawkins

(ii) David Wilson

IV. Prostate

Introduced in January 2013, to be reviewed by January 2016

Sub-group membership

(i) **Ann Henry**

(ii) Louise Murray

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

- Gareth Webster (email: Gareth.Webster@uhb.nhs.uk)
- Pooja Jain
- Maria Hawkins
- Ann Henry
- Stuart McCaighy
- Matthew Hatton

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.