Genesis Care Protocol for Liver & Abdominal SABR

1. Introduction and purpose

The liver is a common site for metastases, especially from carcinomas of the lung, breast and colon. 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.

Autopsy studies show that 40% of colon cancer patients succumb with disease confined to the liver. 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).

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% and 14% in patients with poor prognostic factors. 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.

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%. Control rates from RFA are dependent on tumour size, with lesions under 3cm diameter having greater local control rates than larger lesions. 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.

2. Scope

To summarise the planning and treatment of patients receiving stereotactic body radiotherapy for intrahepatic and abdominal malignancies.

3. Inclusion/Exclusion Criteria

Inclusion Criteria

- Liver metastases unequivocally seen on contrast enhanced CT and /or MRI, previously confirmed pathologically as carcinoma, either:
    - The tumour must be unresectable

- The patient must be medically unfit for surgery,
- Extra-hepatic metastases are present (making hepatic surgery an inappropriate treatment option)
- Standard chemotherapy has failed or deemed unsuitable

- Hepatocellular carcinoma up to 6 cm in size arising in the context of liver cirrhosis are generally suitable for SABR. In certain situations it may be appropriate to treat larger lesions.

- Locally relapsed pancreatic cancer following radical surgery, as a consolidation treatment following a period of chemotherapy, or as definitive treatment in patients unfit for chemotherapy
- Locally advanced, inoperable pancreatic cancer, following a period of chemotherapy or as definitive treatment in patients unfit for chemotherapy
- Karnofsky performance status (KPS) > 60
- Patients must have recovered from the effects of previous surgery, radiotherapy or chemotherapy with a minimum of 2 weeks break
- Adequate organ function as follows: haemoglobin > 90 g/L, absolute neutrophil count > 1.5 x 10^9/L, platelets > 80 x 10^9/L, bilirubin < 3.0 times upper limit of normal range, INR < 1.3 or correctable with vit. K, AST or ALT < 5.0 times normal range, Creatinine < 200 umol/L
- There is no upper limit on tumour size. However the volume of uninvolved liver must be at least 700 cc
- Child A liver score. On occasion, cirrhotic patients with Child Pugh B7 liver function may be considered.
- Life expectancy >3 months
- No more than three liver lesions to be treated

<u>Exclusion Criteria</u>

- Patients with active hepatitis or clinically significant liver failure (encephalopathy, oesophageal varices, portal hypertension).
- Prior radiation therapy to the right upper abdomen, precluding re-irradiation of the liver. That is, any previous radiation therapy in which a mean dose to the liver of 15 Gy in conventional fractionation was delivered or previous doses to critical normal structures that would make re-irradiation unsafe. Prior pelvic radiation is permitted, as long as no overlap between pelvic and liver radiation fields occurs
- Clinically apparent ascites or other signs of metastatic disease

- Central nervous system metastases

Pre-Radiotherapy Investigations

- Baseline blood tests include FBC, Coag screen, U+E, LFT, Ca, tumour markers (if relevant).
- All patients *are recommended to* have a diagnostic liver MRI to aid tumour definition, in addition to a contrast-enhanced CT (*unless contraindications to MRI)*
- DMSA scan may be required if renal dose likely to be significant

Pre-Treatment considerations

- Patient supine with arms above the head on the chest board with a vac-bag and knee immobilization.
- Consider abdominal compression.
- Two hours nil by mouth prior to scan and treatment
- Intravenous contrast is standard.
- *Consider oral contrast to aid visualization of GI tract*

4. Preparation for Imaging

Bowel Prep

The treatment site location will dictate the requirements for patient specific preparation prior to imaging. The main guidance is around a low fibre diet for 1 week prior to imaging and during treatment to ensure minimal bowel gas and a consistently reproducible bowel and stomach contour. Patients should be advised not to eat anything 2-3 hours before the imaging appointment. This advice will be of particular importance for treatment sites close to the bowel, duodenum and stomach but should be discussed and agreed with the Oncologist at the point of referral.

Intravenous and Oral Contrast

A contrast-enhanced exhale breath hold CT should be used to outline the GTV. Injection and subsequent scan should be timed to capture the venous phase and/or arterial phase of contrast enhancement. If advised by the IR(ME)R practitioner, oral contrast should be administered approximately 10-15 minutes prior to CT scan to maximise the chance of capturing the contrast in the duodenum as well as the stomach.

Venous Contrast Phase	Characterisation	Time Delay (seconds)
1st Pass: Hepatic Arterial Phase (HAP)	Characterised by none/minimal admixture of enhanced PVP blood	15-20s
2nd Pass: Late Arterial Phase (LAP)	Portal venous inflow phase (PVIP) admixture of contrast	25-30s
3rd Pass: Hepatic Venous Phase (HVP)	Referred to on SSCT as portal venous phase	60-70s

Contrast CT fused with MRI is superior and wherever possible merged MRI based GTV definition should be used (T1W or T2W). The MRI should wherever possible be acquired on a flat couch in

the same immobilisation and treatment position as the planning CT. Due to the increased complexity of contouring abdominal soft tissue lesions and OAR, radiologist support is encouraged if available.

Contrast during Treatment
It may be advantageous on some patients to administer oral contrast for each fraction of treatment to aid visualisation of the stomach and duodenum. This should be discussed and agreed with the clinician to identify when this is required.

5. Motion Management

This is the most challenging aspect of overall treatment accuracy and is vital for the safe delivery of SABR to targets affected by respiratory motion. Suboptimal motion management can lead to under-dosing of the tumour and hence reduced local control, as well as increased organ at risk (OAR) doses. For this reason the addition of multiple or repeat scans that will have a significant dose implication to the patient such as 4DCT are entirely justifiable if it results in the full range of target motion being quantified. These associated radiation exposures are insignificant in comparison to delivering an ablative dose in the wrong geographical location.

To maximise the prescription dose and minimise the dose to critical structures it is ideal to have the smallest planning target volume achievable. Respiratory motion can lead to a larger PTV and consequential reduction in prescription dose to meet critical structure constraints. A consistent approach should be followed to ensure the motion quantified during the imaging session is then matched during treatment sessions. Where possible, consistent centre staff should be present at both the imaging session and Day 0 or #1 of treatment.

Optimal Motion Management
The most optimal approach to motion management is to isolate motion all together during imaging and treatment. This can be done by imaging the patient whilst they are holding in a specific phase of the respiratory cycle (most guidance is for an exhale phase as this helps raise the diaphragm and minimise OAR doses for liver or abdominal targets). This approach can only be utilised with FFF photon beams otherwise the number of CBCT required to complete the treatment delivery is impractical. With the patient held in ideally an exhale breathe phase a 4DCT scan can then be performed to confirm zero movement of the GTV. On treatment IGRT will then utilise the SGRT contour acquired at CT with smaller translational and rotational margins required for SABR.

Fast XVI scans and Partial Arc Imaging
All XVI presets now employ "Fast" CBCT scans but if these are still too long for the patient to remain in exhale position for then a partial arc could be used. The

Currently in GCUK SABR patients requiring motion management will fall into two categories:

1. Patients scanned with abdominal compression in an inhale and exhale phase
2. Patients scanned with 4DCT without abdominal compression

Both of the approaches mentioned above can be used to define an ITV (Internal Treatment Volume) which must incorporate patient respiration. For approach "**1**" the GTV/CTV can be contoured on both inhale and exhale scans and combined to create the ITV. For approach "**2**"

the GTV/CTV can be contoured on all 10 respiratory phases and again be combined to create the ITV.

1: Abdominal Compression
Local teams should have received onsite training with regards to the correct use of abdominal compression equipment. All information regarding setup and paddle position should be recorded to ensure a consistent setup on treatment.

Compression is used to minimise the patient's ability to move their abdomen and diaphragm during respiration. More specifically, the objective is to reduce the amplitude of respiratory induced tumour motion. Under full compression the patient will continue to breathe but with a reduced amplitude. For this reason CT scans should be acquired in both an inhale and exhale phase. The radiographers should spend time to coach the patient around a steady breathing cycle and during image acquisition request the patient goes into a medium inhale and medium exhale and maintains this until informed to continue breathing normally. There will be variation on what is achievable during this process based on how well compressed the patients are and also whether they are chest or abdomen breathers.

*For patients requiring abdominal compression it is essential to avoid the bridge, clamps and paddle of the compression equipment coinciding with the line of the treatment VMAT arc. Use the CT topogram, anatomical landmarks and any previous imaging to ensure the compression equipment will not coincide with slices containing PTV.

**It is common for the exhale scan under abdominal compression to be set as the primary data set where both an inhale and exhale scan have been acquired. This is justified from published literature demonstrating patients spend more time in exhale than inhale.

2: 4DCT (RPM or GateCT)
Local teams should have received onsite training with regards to the correct use of RPM and GateCT equipment. All information regarding setup and paddle position should be recorded to ensure a consistent setup on treatment.

4DCT allows for the full respiratory cycle to be imaged and binned to create a movie sequence of the patient. This enables the clinician to create contours and amend the contouring based on any movement during respiration. All 10 phased data sets are combined to create an average intensity projection (AIP) and maximum intensity projection (MIP). The AIP is usually set as the primary data set as each pixel represents the average density at a given point during respiration and is therefore most suitable for patient dose calculation.

If on 4DCT the target volume is seen to be moving greater than 10mm (maximum movement of any point on or within the GTV) during respiration then an attempt should be made to reduce this movement using abdominal compression.

6. Imaging Scan Limits

The 3D and 4D CT scan should encompass all abdominal and thoracic anatomy to ensure adequate coverage of the treatment area and inclusion of OAR for dose statistic calculation

such as the entire lung volume if the treatment site is close to the diaphragm. As discussed above, there is no justification in limiting the length of the 4DCT as the saving in exposure to the patient does not justify the loss in information to enable accurate assessment of movement of the patient during respiration.

7. PTV Margins

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

GTV-CTV: For liver metastases, a GTV to CTV margin of 0.5 cm is typically used. No such marginally is generated used for HCC.

CTV-PTV: Studies have tended to use larger margins in the superior-inferior direction to allow for respiratory motion. The most common practice has been to use 10mm with smaller margins when 4DCT has been used for image guidance. Radially, most studies have used margins of 5mm, again reduced when 4DCT is used.

8. Organs at Risk

Please refer to the following publication relating to the latest optimal and mandatory tolerances for organs at risk (OAR) with SABR. A copy of this publication can be found at:

Hanna GG, et al., UK Consensus on Normal Tissue Dose Constraints for Stereotactic Radiotherapy, Clinical Oncology (2017), https://doi.org/10.1016/j.clon.2017.09.007

Any organ that is traversed by part or all of a beam should be contoured so that the dose it receives can be assessed. The below is a guide but not an exhaustive list of reccomendations: Oesophagus, Stomach, Duodenum, Small bowel, Large bowel

Liver: The whole liver should be outlined , and for dose calculation this volume minus 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 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.

Lung: Outlined from apex to base, as a single structure.

9. Dose Prescriptions

The following is a list of accepted dose prescriptions for both liver SABR and broader abdominal/oligometastatic pathologies.

Liver

- 40-60Gy in 3 fractions
- 50-60Gy in 5 fractions

Abdominal soft tissue oligomets

- 27-45 Gy in 3 fractions
- 45-60 Gy in 5 fractions

10. Treatment Planning

Guidance on the planning of targets mentioned in this protocol cannot cover all clinical eventualities that may be faced by planners but some of the learning points experienced previously will be discussed here. Planners should start with standard single or dual arc 6MV photon beams depending on whether a mid CBCT will be used for IGRT. The Isocentre should be placed no greater than 2-3cm from midline otherwise onset verification of clearance with XVI must be confirmed prior to Day 0. The position of the isocentre will also dictate how much of the liver will be visualised on CBCT and this should be considered early in the planning process.

The plan should be prescribed to a point dose and to an isodose level between 70-90%. General consensus is to achieve exactly 95% coverage of the PTV by the full 100% prescription dose. The maximum dose (1.0cc) should not exceed 130%-140% of the prescribed dose.

Multiple targets

The complexity of multiple targets can be somewhat mitigated by using a single isocentre and optimising both targets within the same dual Arc VMAT delivery. The main clinical and computational advantage of this is being able to accurately model the contribution of the dose from one target to another and the sometimes "bridging" of 90-100% prescription dose between targets in close proximity.

The disadvantage depending on the location of the targets is a reduction is flexibility when performing IGRT. Although one GTV may show good alignment the other(s) may not and this is not acceptable when all targets are being treated simultaneously. The solution to avoid such problems is detailed assessment of previous and current by a MDT and agreement on the best solution for the specific case.

If multiple targets require treatment their geographical separation can dictate whether a combined treatment is possible or feasible. Usually a combined treatment is preferred when targets lay within the same VMAT arc plane as accurately modelling a combined plan later on can be problematic. For targets separated in the superior-inferior direction without overlap of PTV then a sequential may be preferred.

CT Slice and Dose Grid

For all non spine SABR plans a CT slice of 2mm and a dose grid of 2mm is sufficient.

Optimisation structures
Planners will optimise individual plans based on specific objectives relating to each case but generally the ring structures should be set to achieve a steep dose gradient away from the PTV and weighted sufficiently that Pinnacle has worked hard to ensure this occurs. Ring objectives on average will not deviate far (+/-5%) from the following fall of objectives:
Ring 1 (4-5mm) = 100%
Ring 2 (4-5mm) = 70%
Ring 3 (10mm) = 50%
Ring 4 "2cm Ring" (10mm) = 40%
Ring 5 (20mm) = 30%

PTV overlap with OAR
Where the PTV overlaps with OAR and prevents planners meeting tolerances a discussion with the clinician early in the process (ideally at the contouring stage) should be had to agree on whether compromising the PTV coverage is acceptable (using a PTV_prescribe approach) or whether the prescription dose should be amended to reflect the overlap. Any OAR tolerances requested by the clinician that deviate from the UK consensus document [1] should be clearly documented in Mosaiq.

Couch Density with Stradivarius Board
If abdominal compression has been used during the immobilisation process then the correct couch density must be applied in Pinnacle. The density values for couch inner and outer should be **0.21 and 0.6** respectively.

Contrast density
If significant amounts of IV and oral contrast are within the VMAT plane of the treatment volume then a density override should be considered. Planners should use the density measuring tool in Pinnacle and consult a physicist if any uncertainty of when this should be applied exists.

Plan Conformity
All SABR plans should set out to achieve a high degree of conformality and the Shaw, Gradient and Paddick conformity index should be calculated and displayed in the Tx plan for each case. For irregular shaped target volumes or volumes with compromised PTV coverage the conformity indices may be less meaningful but should still be quoted for review by the clinician. For plans using a PTV-prescribe the "TVpiv" and "TV" values should use the PTV_prescribe and not the full PTV.

11. CBCT matching guidance

As with any on treatment imaging within GCUK staff should refer to policy RT-POL-028 V13.0 for guidance on best practice for different treatment sites and types. RT-PRO-233 should also be referred to for the treatment and imaging workflows. The following is section is here to support existing policies and should not be regarded as a stand alone IGRT guidance.

Due to the reduced tolerances for CBCT matching during SABR treatments (<1mm) there may at times be an increased number of CBCT required at each fraction. The standard limit is 3 x CBCT per day and 10 x CBCT per week. For SABR patients the consultant should be onsite for Day 0/#1

and can provide immediate guidance on whether they approve further CBCT imaging. Subsequent fractions should not deviate significantly from the number required at Day 0/#1 unless approved by the consultant (i.e. within 1-2 CBCT of Day 0).

3 x CBCT per fraction

The current standard SABR IGRT approach in GCUK is to perform a pre, during and post CBCT at each fraction. With the imaging in many cases taking longer than the treatment delivery some clinicians may prefer to drop the mid CBCT from the IGRT process. If this is the case a local discussion should be had and this should be highlighted to the GCUK SABR team to ensure there are no objections. It should be highlighted though that some patients for a variety of reasons (e.g co-morbidities, comfort with setup) may be less stable during treatment delivery and in these cases the mid CBCT to assess intra-fraction movement is recommended.

CBCT Matching

General reccomendation for image matching abdominal targets for SABR is to utilise anatomical landmarks in close proximity to the target volume and use these as a surrogate for ensuring correct alignment with the reference CT. Examples of this include the alignment of the liver in its entirety, the inferior vena cava (IVC) for more central pathology

12. Treatment process Summary

	Optimal	Minimum
Treatment Prep	Low Fibre diet 1 week prior to treatment Nil by mouth 2-3 hours prior to CT	Nil by mouth 2-3 hours prior to CT
Immobilisation	Patient with arms up above head Abdominal compression to reduce diaphragm motion to <1cm. Vac bag if required but not mandatory Combifix & knee stocks if required	Patient with arms up above head. If unable to tolerate compression then 4DCT unless motion >1cm then question suitability of patient for SABR. Discuss suitability with Clinician.
Contrast	IV contrast (Venous phase) + Oral contrast Oral contrast 10-15 minutes prior to CT IV contrast 1 minute prior to CT	No recommended minimum but requirements should be discussed with clinician prior to imaging.
Imaging	Patient in exhale breath hold using SGRT to capture surface contour for use during treatment. Perform 4DCT to confirm zero GTV motion.	Abdominal compression (Inhale & Exhale Scans) or 4DCT to obtain ITV if patient unable to tolerate compression.
Treatment Planning	Mid-line Isocentre placement to avoid collisions with XVI on treatment Plan on average intensity projection like lung SABR as this will represent the average pixel density during respiration.	
Treatment	Patient in exhale breathe hold and being monitored with SGRT. Treatment delivered using 1-2 FFF Photon beams. Elekta response system monitoring SGRT contour and automatically gating treatment.	Mid, during and end CBCT with each fraction

IGRT	Anatomical surrogates can be used during IGRT such as the liver itself and IVC to confirm lack of rotations and translations. Start by assessing entire liver organ on CBCT first along with any other local OAR and then zoom in on XVI and assess local anatomical alignment. Make use of old clips and RFA cavities if available.	Start by assessing entire liver organ on CBCT first along with any other local OAR and then zoom in on XVI and assess local anatomical alignment.

13. Follow-up

Post treatment response imaging is usually done by contrast enhanced CT scan or MRI scan at frequent intervals generally starting at 3 months following treatment and then at least every 3 months for a year. After a year the follow-up imaging frequency can be reduced and/or rely on the use of PET-CT for assessing post SABR follow-up.

14. References

1. *Hanna GG, et al., UK Consensus on Normal Tissue Dose Constraints for Stereotactic Radiotherapy, Clinical Oncology (2017), https://doi.org/10.1016/j.clon.2017.09.007*
2. Stereotactic Ablative Body Radiation Therapy (SABR): A Resource, UK SABR Consortium Version 5.1, January 2016
3. Genesis Care Policy: RT-POL-028 IMRT and IGRT Treatment Standards
4. Genesis Care Policy: RT-PRO-233 Genesis Care Clinical Protocol for SABR