# UK Consensus on Normal Tissue Dose Constraints for Stereotactic Radiotherapy

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**Highlights:**

- 6 UK studies investigating SABR are currently open or set to begin recruitment in 2016.
- A national agreement on SABR dose constraints has been produced.
- This will facilitate standardised implementation and permit meaningful toxicity comparisons.

**Abstract**

6 UK studies investigating SABR are currently open or set to begin recruitment in 2016. Many of these involve treatment of oligometastatic disease at many different locations in the body. Members of all the trial management groups collaborated to generate a consensus document on appropriate organs at risk (OARs) dose constraints. Values from existing but older reviews were updated using data from current studies. It is hoped that this unified approach will facilitate standardised implementation of SABR across the UK and will permit meaningful toxicity comparisons between SABR studies.

**Keywords:** SABR, SBRT, stereotactic radiotherapy, normal tissue, OAR, constraints.

## Introduction

Stereotactic ablative radiotherapy (SABR) is routinely used for the treatment of early stage lung cancer and is increasingly used to treat other primary or metastatic tumour sites [1-9]. There are currently a number of UK studies (of which 3 are randomised) investigating the utility of SABR in the treatment of oligometastatic disease (breast, lung, and prostate), lung, prostate, pancreas and hepatobiliary primary malignancies [10-12]. These are supported by Cancer Research UK (CRUK) and currently open or in set-up to begin recruitment in 2016. In addition, a NHS Commissioning through Evaluation (CtE) programme was commenced in 2015 to evaluate SABR in situations where clinical trials are not available [13].

The focus of many of these studies is the use of SABR in the treatment of oligometastatic disease. Inherent in the delivery of SABR to oligometastatic sites at any location in the body is an understanding of the local normal tissue dose constraints. It is recognised that as SABR is a relatively new treatment technique, definitively established dose constraints which directly correlate to risk of toxicity are rare. However, in order to standardise protocols and the associated radiotherapy planning, members of the various trial management groups collaborated to generate a consensus document on appropriate organs at risk (OARs) dose constraints associated with the various common SABR fractionations.

There are numerous publications which report toxicity following SABR at various sites. These have been summarised in a number of reports or reviews [14-17]. The most comprehensive of these reviews is the AAPM-101 report [15], but this is now over 5 years old, and newer data are available. Rather than conduct a primary systemic review, these values were revised where appropriate, by taking into consideration any updated or more robust data on a given dose constraint value in the opinion of the panel, as described below.

## General principles of dose constraint selection and application to clinical trials or routine practice

In choosing the most appropriate dose constraints for UK SABR treatments, the following principles in selecting and applying these dose constraints have been used:

1.) Both optimal and mandatory dose constraints were included, where appropriate;

2.) For body (extra-cranial) dose constraints, except for the spinal cord/canal, a near-point maximum dose volume of 0.5cc should be used across sites. This represents a volume which is both clinically realistic and comparable when calculated across different planning systems. For the spinal canal, as a surrogate for cord dose in most cases, a point maximum dose volume of 0.1cc should be used. It should be noted that where the area to be treated abuts the spinal cord, the spinal cord should be explicitly defined on both CT and MRI, and a margin for set-up errors added based on local specification;

3.) There are differences in the ways dose constraints are reported for serial and parallel organs. Care should be taken to distinguish between these and the key principles are listed in Table 1.

4.) For the purpose of these guidelines, single fraction treatment should not be given extra-cranially, and 3, 5 or 8 fraction regimes are recommended;

5.) Radiation Therapy Oncology Group (RTOG) normal tissue atlases should be used for delineation of OARs [18]. Specifically it is recommended to follow the RTOG guidance by contouring the spinal canal based on the bony limits of the spinal canal. The spinal cord should be contoured starting at the level just below cricoid (or at the level of the base of skull

for tumour of the lung apex) and continuing on every CT slice to the bottom of L2. Neural foraminae should not be included;

6.) The dose constraints described in this document are only applicable for patients receiving de novo SABR. For patients who have received recent or are receiving concomitant systemic therapy (and in particular anti-angiogenic agents and other biological agents) there may be an enhanced risk of normal tissue toxicity;

7.) These dose constraints are not applicable in the situation of a re-irradiation using SABR. For example, where there is overlap with previous radiotherapy treatment or where another part of the organ (e.g. lung or liver) has previous received radiotherapy;

8.) Where 2 separate GTVs are being treated in the same organ (e.g. two separate lung metastases) then the summed dose to both lesions and associated OARs should not usually exceed the given dose constraints;

9.) Where patients are having more than one lung lesion treated with SABR, it is recommended that these should be treated on alternate days and with the same dose/fractionation (usually the most conservative schedule). This reduces the dose per fraction to the whole lung. The only situation when both sites may be treated on the same day is if the tumours can be encompassed in a single field or when the combined V20 is below the tolerance for a single lesion. There is little published data on normal tissue tolerances for multiple lesions and ideally the standard thoracic constraints should be met. However, the OAR constraint which is most likely to be exceeded is V20Gy. In the case of treating two or three lung lesions, the following V20Gy lung constraints should be followed:

- Optimal <12.5%
- Acceptable in all cases <15%
- Acceptable in selected cases with good lung function <20%

Where the lung function parameters of forced expiratory volume in 1 second (FEV1) and transfer factor (DLCO) are below 40% of predicted, its strongly recommended that the V20Gy should be kept below 12.5% (optimal) or 15% (mandatory).

10.) Where patients are having more than one liver metastasis treated with SABR, it is recommended a 5 fractions regime is used and that all OAR constraints should be met as per single lesion, with at least 48 hours (alternative days) between treatments.

11.) These dose constraints are to be used as guidance only. Those using these dose constraints should note that the final responsibility for radiotherapy plan evaluation remains with the treating clinician and the treating institution.

12.) These constraints will be reviewed periodically as part of updates to the UK SABR Consortium guidelines.

**Table 1** – Description of dose constraint types.

| Organ type | Principle of Dose Constraint Descriptor | Example |
|---|---|---|
| **Serial** | Dose constraints are described as the maximum volume of the organ that can receive a threshold dose or more | The volume of small bowel receiving a dose of 25.2Gy or more should be less than 5cc (D5cc<25.2Gy) |
| **Parallel (Entire organ)** (.e.g. liver, kidneys and lungs) | Dose constraints may be described as a maximum percentage volume of the organ receiving a threshold dose or more. | The volume of lung receiving a dose of 20Gy or more should be less than 10% of the total lung volume (V20Gy<10%). |
| **Parallel (Minimum critical volume of an organ)** (.e.g. liver, kidneys and lungs) | For these, the constraint may be described as a minimum critical volume of the organ which must be spared from receiving a threshold dose (or more). | At least 200cc of kidney should receive a dose of 16Gy or less (Dose to ≥200cc ≤ 16Gy) |

## Specific principles for each anatomical site grouping

**CNS (Table 2) –** These constraints are primarily based on those described in the AAPM-101 report [15], with some modification to give consistent near-point maximum dose volumes for serial organs (0.1cc), and taking account of recent risk analyses for optics and spinal cord [19,20]. Cochlea volumes are usually so small than the mean dose may be considered as the near-point dose, and an optimal limit has been added to reflect recent studies [21]. Optimal limits have also been added for lens and orbit (as a surrogate for retina), though these should generally be kept as low as reasonable practicable. Single fraction treatments are recommended for CNS metastases, but multi-fraction constraints are also included in the rare event of skull bone metastases receiving SABR treatment. These constraints are not specifically designed for stereotactic radiosurgery (SRS), but may be useful in this regard also. However some centres have used higher tolerances successfully, or sought to spare other structures such as trigeminal nerve.

**Thoracic (Table 2) –** Updated constraints are taken from the UK SABR consortium guidelines (3 and 5 fractions) [17] and the LungTech trial (8 fractions) [22]. The LungTech protocol describes dose constraints for all OARs except the heart. When delineating the proximal bronchial tree for the purposes of dose reporting, both mediastinal and lung windows on CT should be used, as appropriate to each case.

**Gastro-Intestinal and Abdomen (Table 3) –** Updated constraints are taken from the ABC-07 trial (5 fractions) and the SPARC study [12,23]. These constraints incorporate revised AAPM constraints in light of published trials data [24-26]. For lower lobe lung treatments, significant irradiation of the abdominal structures is not a common clinical occurrence where co-planar delivery is employed. If there is a risk of significant irradiation of an adjacent intra-

abdominal organ (e.g. liver for right lower lobe lung tumours), then imaging of the entire organ should occur at simulation.

**Pelvis and Other (Table 4)** – Updated constraints are available from the PACE trial (5 fractions) [11], however these apply specifically to primary treatment of the prostate which allows potentially higher bowel toxicity that would be acceptable from treatment to a metastatic site. Therefore, the AAPM-101 constraints are retained for pelvic treatments in general and PACE study dose constraints are included for interest. At present, there is no clear indication for 8 fraction pelvic SABR treatments and hence these are not included. Optimal constraints on the skin are included based on AAPM-101 values.

## Conclusion

A national agreement on SABR dose constraints has been achieved. It is hoped that this unified approach will facilitate standardised implementation of SABR across the UK and will permit meaningful toxicity comparisons between SABR studies and further refinement of the constraints. Further SABR trials developed in the UK will aim to adopt this consensus.

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**Table 2 - CNS and Thoracic Dose Constraints**

| Description | Constraint | Single Fraction | | 3 Fractions | | 5 Fractions | | 8 Fractions | |
|---|---|---|---|---|---|---|---|---|---|
| | | Optimal (Gy) | Mandatory (Gy) | Optimal (Gy) | Mandatory (Gy) | Optimal (Gy) | Mandatory (Gy) | Optimal (Gy) | Mandatory (Gy) |
| Optic pathway | DMax (0.1cc) | - | < 8 | - | < 15 | - | < 22.5 | - | < 27.2 |
| Cochlea | Mean | < 4 | < 9 | - | < 17.1 | - | < 25 | - | < 44 |
| Brainstem (not medulla) | DMax (0.1cc) | < 10 | < 15 | < 18 | < 23.1 | < 23 | < 31 | < 27.2 | < 37.6 |
| Spinal canal* (inc. medulla) | DMax (0.1cc) | < 10 | < 14 | < 18 | < 21.9 | < 23 | < 30 | < 25 | < 32 |
| | D1cc | < 7 | - | < 12.3 | - | < 14.5 | - | - | - |
| Cauda equina & sacral plexus | DMax (0.1cc) | - | < 16 | - | < 24 | - | < 32 | - | < 38.4 |
| | D5cc | - | < 14 | - | < 22 | - | < 30 | - | < 36 |
| Normal Brain (Whole Brain - GTV) | D10cc | < 12 | - | - | - | - | - | - | - |
| | D50% | < 5 | - | - | - | - | - | - | - |
| Lens | DMax (0.1cc) | < 1.5 | - | - | - | - | - | - | - |
| Orbit | DMax (0.1cc) | < 8 | - | - | - | - | - | - | - |

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

| Description | Constraint | 3 Fractions | | 5 Fractions | | 8 Fractions | |
|---|---|---|---|---|---|---|---|
| | | Optimal | Mandatory | Optimal | Mandatory | Optimal | Mandatory |
| Brachial Plexus | DMax (0.5cc) | < 24Gy | < 26Gy | < 27Gy | < 29Gy | < 27Gy | < 38Gy |
| Heart | DMax (0.5cc) | < 24Gy | < 26Gy | < 27Gy | < 29Gy | < 50Gy | < 60Gy |
| Trachea and bronchus | DMax (0.5cc) | < 30Gy | < 32Gy | < 32Gy | < 35Gy | < 32Gy | < 44Gy |
| Normal Lungs* (Lungs-GTV) | V20Gy | - | < 10% | - | < 10% | - | < 10% |
| | V12.5Gy | - | < 15% | - | < 15% | - | < 15% |
| Chest Wall | DMax (0.5cc) | < 37Gy | - | < 39Gy | - | < 39Gy | - |
| | D30cc | < 30Gy | - | < 32Gy | - | < 35Gy | - |
| Great Vessels | DMax (0.5cc) | - | < 45Gy | - | < 53Gy | - | - |

*Normal Lung (Lungs-GTV) constraints for the treatment of two or three lung lesions in the same patient, should follow the guidelines in general point 9 above.

**Table 3 – Gastro-intestinal Constraints**

| Description | Constraint | 3 fraction | | 5 fraction | |
|---|---|---|---|---|---|
| | | Optimal | Mandatory | Optimal | Mandatory |
| Duodenum | DMax (0.5cc) | - | < 22.2Gy | - | < 35Gy |
| | D1cc | - | - | < 33Gy | - |
| | D5cc | - | < 16.5Gy | < 25Gy | - |
| | D9cc | - | - | < 15Gy | - |
| | D10cc | - | < 11.4Gy | - | < 25Gy |
| Stomach | DMax (0.5cc) | - | < 22.2Gy | < 33Gy | < 35Gy |
| | D5cc | - | - | < 25Gy | - |
| | D10cc | - | < 16.5Gy | - | < 25Gy |
| | D50cc | - | - | < 12Gy | - |
| Small Bowel | DMax (0.5cc) | - | < 25.2Gy | < 30Gy | < 35Gy |
| | D5cc | - | < 17.7Gy | < 25Gy | - |
| | D10cc | - | - | - | < 25Gy |
| Oesophagus | DMax (0.5cc) | - | < 25.2Gy | < 32Gy | < 34Gy<br>(Use <40 Gy for 8 fractions) |
| Large Bowel | DMax (0.5cc) | - | < 28.2Gy | - | < 32Gy |
| Common Bile Duct | DMax (0.5cc) | < 50Gy | - | < 50Gy | - |
| Parallel GI organs | | | | | |
| Normal Liver<br>(Liver minus GTV) | V10Gy | - | - | < 70% | - |
| | Mean liver dose | - | - | < 13Gy | < 15.2Gy |
| | D50% | < 15Gy | - | - | - |
| | Dose to ≥700cc | < 15Gy | < 19.2Gy | - | - |
| Kidneys (individual and combined) | Mean kidney dose | - | - | < 10Gy | - |
| | Dose to ≥200cc | - | < 16Gy | - | - |
| If solitary kidney or if one kidney mean dose >10Gy | V10Gy | - | - | < 10% | < 45% |

**Table 4 - Pelvic and Other Dose Constraints**

| Description | Constraint | 3 Fractions | | 5 Fractions | |
|---|---|---|---|---|---|
| | | Optimal (Gy) | Mandatory (Gy) | Optimal (Gy) | Mandatory (Gy) |
| Bladder | D15cc | - | < 16.8 | - | < 18.3 |
| | DMax (0.5cc) | - | < 28.2 | - | < 38 |
| Penile Bulb | D3cc | - | < 21.9 | - | < 30 |
| | DMax (0.5cc) | - | < 42 | - | < 50 |
| Ureter | DMax (0.5cc) | - | < 40 | - | < 45 |

| Description | Constraint | 3 fraction | 5 fraction |
|---|---|---|---|
| | | Optimal (Gy) | Optimal (Gy) |
| Skin | DMax (0.5cc) | < 33 | < 39.5 |
| | D10cc | < 30 | < 36.5 |
| Femoral Head | D10cc | < 21.9 | < 30 |

| Description | Constraint (**Prostate primary only**) | 5 Fractions | |
|---|---|---|---|
| | | Optimal | Mandatory |
| Rectum | D50% | - | < 18.1Gy |
| | D20% | - | < 29Gy |
| | D1cc | - | < 36Gy |
| Bladder | D40% | - | < 18.1Gy |
| | V37Gy | < 5cc | < 10cc |
| Prostatic urethra (if visible) | D50% | < 42Gy | - |
| Neurovascular bundle (if visible) | D50% | - | < 38Gy |
| Femoral head | D5% | - | < 14.5Gy |
| Penile Bulb | D50% | - | < 29.5Gy |
| Testicles | Avoid beam entry e.g. Blocking structure | | |
| Bowel | D5cc | - | < 18.1Gy |
| | D1cc | - | < 30Gy |