UK SABR Consortium 2022 Consensus on Normal Tissue Dose Constraints for Stereotactic Radiotherapy

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UK 2022 consensus on normal tissue dose-volume constraints for oligometastatic, primary lung and hepatocellular carcinoma Stereotactic Ablative Radiotherapy

Highlights

- An updated consensus for OAR constraints for SABR is presented
- Constraints are based on the published literature and reflect international practice
- This consensus aims to support safe and consistent SABR practice across the UK

Abstract

The use of stereotactic ablative radiotherapy (SABR) in the UK has expanded over the past decade, in part as the result of several UK clinical trials and a recent NHS England Commissioning through Evaluation (CtE) programme. A UK SABR Consortium consensus for normal tissue constraints for SABR was published in 2017, based on the existing literature at the time. The published literature regarding SABR has increased in volume over the past five years and multiple UK centres are currently working to develop new SABR services. A review and update of the previous consensus is therefore appropriate and timely. It is hoped that this document will provide a useful resource to facilitate safe and consistent SABR practice.

Introduction

The use of stereotactic ablative radiotherapy (SABR or SBRT) in the UK has expanded over the past decade. Initially SABR was limited to early-stage primary lung cancer but, in part as a result of several UK clinical trials[1-7] and a recently completed NHS England Commissioning through Evaluation (CtE) programme (a single arm prospective registry study of patients treated with SABR for oligometastases)[8], its use has now extended to the oligometastatic setting as well as non-lung primary disease sites. Evidence suggests SABR is well-tolerated and achieves high rates of local control in multiple settings[5,8-11]. Phase II trials and pooled analyses indicate promise in terms of overall and progression-free survival endpoints[12-14], but phase III evidence confirming the overall survival benefit of SABR, in addition to standard of care in the oligometastatic setting, or as an alternative to surgery in the primary lung cancer setting, is still awaited. While well tolerated in the majority, cases of severe, and even grade 5, toxicity have been documented[9,15,16]. An appreciation of organ at risk (OAR) constraints is therefore essential to help ensure, as far as possible, that treatment is safe.

In 2017 we published a UK consensus for SABR constraints to encourage and facilitate uniform practice across the UK[17]. Many of the constraints were derived from the American Association of Physicists in Medicine (AAPM) Task Group (TG) 101 report from 2010[18], the most comprehensive list of constraints at the time. We recognised in our original publication that the constraints should be viewed as preliminary and would require to be reviewed and updated over time. Many more patients have now been treated with SABR, within and outside of clinical trials, and more clinical outcome data have been published. In addition, following the encouraging outcomes from CtE[8], SABR for oligometastases is currently being rolled out to multiple UK centres with less experience of this technique. It is therefore timely to review our original consensus in light of more recent information and the need for contemporary guidance for centres setting up new SABR services.

Here we present an updated UK consensus on constraints for SABR, taking into account published constraints and related works since our 2017 publication. Specifically, the HyTEC group (Hypofractionated Treatment Effects in the Clinic) was formed as an AAPM working group, with the aim of reviewing SABR dose-volume outcomes for normal tissues as well as tumours[19]. In May 2021, a special issue of the International Journal of Radiation Oncology, Biology and Physics brought together the publications of the HyTEC group, which included several organ-specific papers[20-24]. In addition, this year, a systematic review by Gerhard et al was published that examined normal tissue constraints from currently recruiting trials using SABR for the treatment of oligometastases (n=53), that helpfully summarised these as the modal, median and range[25]. Any constraints from our 2017 publication that were noted to be markedly different to those reported in the HyTEC publications or by Gerhard et al were reviewed particularly closely and justification sought if these were to be retained.

The authors are active or past members of the UK SABR Consortium and affiliates, and/or co-investigators in SABR/SRS clinical trials. Both clinicians and medical physicists contributed, all with clinical and research experience in SABR. Individuals participated in site-specific discussions, in their area of expertise, where OAR constraints were agreed for that anatomical region. In addition, all co-authors were involved in whole-group discussions to establish general principles for this update.

General principles

As with our original consensus, several general principles were adopted as well as some organ-specific principles. General principles are as follows:

1. Constraints are divided into anatomical region (thorax, abdomen, pelvis, spine and intra-cranial), with both optimal and mandatory dose constraints included, where appropriate.

2. For extra-cranial organs, near maximum doses previously applied to 0.5 cc (i.e. $D_{0.5cc}$) are now reported to 0.1 cc to become more in line with international practice. The volume of 0.1 cc was also chosen as this is considered a large enough volume to be reproducible between treatment planning systems (TPS) [26], acknowledging that ICRU report 91[27] and the AAPM TG-101 report[18] recommend that maximum dose constraints be applied to ≤0.035 cc. It is considered that, at present, there is insufficient high-quality prospective evidence to justify the ongoing use of $D_{0.5cc}$ as before. Moving to near maximum doses of $D_{0.1cc}$ from $D_{0.5cc}$ is less permissive and therefore a 'safe' change. Spinal cord, cauda equina and other CNS constraints (where OARs are often very small volume) are now applied to 0.035 cc (rather than 0.1 cc as before) to be closer to the volumes used for the modelling work that defined these dose limits[20].

3. There are differences in how constraints are reported for serial and parallel organs; key principles are listed in Table 1. Importantly, for parallel organs, $D_{\geq xxcc}$ constraints relate to **minimum critical volumes** or 'cold' constraints whereby the intention is to spare a specific volume or more of OAR (in this case xx cc) from a specified dose. Care must be taken not to confuse these with maximum dose or 'hot' (i.e. D_{xxcc}) constraints, as used for serial OARs.

Depending on the TPS, it may not be possible to directly evaluate minimum critical volume constraints and it may be necessary to determine the dose as for a maximum dose, or 'hot' constraint by using the $D_{VTOT-xxcc}$ notation, where 'VTOT' is the total OAR volume and 'xxcc' is the minimum volume that must be spared.

4. As before, constraints have been provided for 3, 5 and 8 fraction SABR. In addition, being aware of increasing uptake of single fraction SABR[28], one fraction constraints are also provided, largely derived from AAPM TG-101, which also align closely to the modal and median values reported in the Gerhard et al constraint systematic review[18,25]. In addition, we have added spinal cord constraints for 2-fraction SABR, in light of the recent HyTEC report and an awareness of increasing utilisation of 2-fraction spinal SABR internationally[20,29].

5. Delineation uncertainty can be a major cause of uncertainty. As such, atlases and guidelines as recommended by the UK SABR Consortium should be used to guide OAR contouring[30]. Contour peer-review is also strongly encouraged and auto-contouring algorithms, if available, should be verified manually for each patient. When uncertainties in delineation remain, advice should be sought from appropriate radiologists.

6. The dose constraints presented are only applicable for patients receiving SABR alone. For those who have received recent, or are receiving concomitant, systemic anti-cancer therapy (SACT; in particular anti-angiogenic agents, small molecule inhibitors or immunotherapy) there may be an enhanced risk of normal tissue toxicity.

7. These dose constraints are not applicable to the setting of re-irradiation.

8. Where 2 separate GTVs are being treated within the same organ (e.g. two separate lung metastases) during the same treatment course, the doses from the summed plan (if separate isocentres are used) will be used to assess OAR constraints.

9. The constraints are recommended for use for the treatment of oligometastases in any body site, primary lung tumours and hepatocellular carcinoma (HCC). Different constraints may, however, be more appropriate when treating other primary tumours with SABR and site-specific protocols should be sought in these circumstances. For example, in the setting of primary prostate cancer, where the intent of treatment is different to the treatment of oligometastases in the pelvis, more lenient rectal constraints are considered appropriate[5]. Similarly, different dose-volume constraints are recommended in the setting of SABR for primary renal cell[31] and pancreatic cancer[32-34].

10. In the accompanying tables, unless otherwise specified, all constraints are less than or equal to (i.e. ≤) the stated value. Where the Gerhard et al systematic review of constraints is cited, this reflects the modal and/or median constraint reported in this work and not the full range of constraints. Any constraints without a reference have been derived by group consensus.

Consensus was reached through the site-specific group discussions and reflect current UK practice.

11. These constraints are recommended for use in routine practice and may differ from those evaluated in current and future clinical trials.

12. These dose constraints are to be used as guidance only. Final responsibility for radiotherapy plan evaluation remains with the treating clinician and treating institution. Changes should be justified using good a priori medical reasons.

Thoracic constraints and skin (Table 2)

Several of the 8-fraction thoracic constraints in the previous consensus were based on the LungTECH trial[35]. Being aware that this trial closed early and has not yet reported, these constraints have been revised based on alternative sources, including the SABR-COMET trial, where the predominant treatment site was lung, and which has reported acceptable toxicity levels[9,12]. Such instances are discussed below.

It is acknowledged that UK practice differs in its use of V_{20Gy}, however it is in line with the lung-specific work reported by HyTEC[22]. The volumes to which V_{20Gy} was applied in the previous consensus, however, were considered very conservative and therefore have been relaxed to V_{20Gy} ≤10% and ≤15% for optimal and mandatory constraints, respectively, in line with the doses implied in the lung-specific HyTEC work[22]. In addition, optimal mean lung doses of ≤8 Gy in 3 and 5 fractions have been added, again based on the same publication[22]. Extrapolating from this work, the same constraints have been applied to single and 8-fraction schedules. The V_{20Gy} constraints will apply to SABR for both single and multiple lung lesions.

For the heart, the previous 3- and 5-fraction mandatory constraints were from the ROSEL study[36] but have been revised as considered too conservative. The new mandatory constraints are those used in the SABR-COMET trial[9], which are also consistent with AAPM TG-101[18] and the modal/median constraints reported in the Gerhard et al systematic review[25]. The ROSEL constraints have now been adopted as optimal[36], where appropriate. The new, more conservative, mandatory constraint for 8-fraction treatments has been adopted from the SABR-COMET trial[9], also the median/modal constraint reported by Gerhard[25]. Importantly, where the 8-fraction cardiac mandatory constraint cannot be met, the prescription dose should be reduced from 60 Gy to 50 Gy.

Great vessel mandatory constraints have been retained for 3 and 5 fraction schedules, based on AAPM TG-101[18], SABR-COMET[9] and consistent with the modal/median constraints reported in the Gerhard et al review[25]. For 8-fraction SABR, a mandatory great vessel constraint has been added, also based on SABR-COMET[9], which is also consistent with the modal/median in the Gerhard et al

review[25]. An optimal constraint of 60 Gy has been added, based on group consensus. It is also recommended for 8-fraction SABR that any hot spots are constrained to the PTV.

The mandatory brachial plexus, trachea and bronchus constraints for 3, 5 and 8 fractions, originally based on the ROSEL (3 and 5 fractions) and LungTECH (8 fraction) trials[35,36], have been modified to be in accordance to the SABR-COMET trial[9]. The 5- and 8-fraction brachial plexus optimal constraints have been based on the currently recruiting SABR-COMET-3 trial[37].

Chest wall constraints are optimal and retained for 3 fractions but modified to be more permissive for 5 fractions, in line with AAPM TG-101[18]. No optimal is given for 8 fractions, in line with a number of international trials. Clinically 8 fraction schedules are typically only used away from the chest wall or near the apical or posterior chest wall, where dose is optimised based on a more sensitive neighbouring OAR (e.g. brachial plexus or spinal canal). It is stressed that all chest wall constraints are optimal, and it is therefore accepted that these may not be met when a lesion is adjacent to the chest wall and, in this situation, the patient should be consented for an increased risk of chest wall toxicity.

Regarding the oesophagus, the 5-fraction mandatory constraint has been increased to 35 Gy (from 34 Gy), such that all 1-, 3-, and 5-fraction constraints are now consistent with AAPM TG101[18], with 5- and 8-fraction constraints also being those used in SABR-COMET[9] and the modal/median constraints reported by Gerhard et al[25].

Skin constraints, also optimal, have been retained from the previous report for 3 and 5 fractions and 8-fraction constraints added, based on SABR-COMET-3[37], which reflects the modal/median constraints reported by Gerhard et al[25]. In some scenarios it may be necessary to exceed these constraints in an effort to achieve coverage and in these cases the patient should be consented for increased risk of skin toxicity.

As for other sites, single fraction constraints have been included, mainly based on APPM TG-101 and also in line with the modal/median values reported in the Gerhard et al review[18,25]. However, where a more conservative constraint was used in the recently reported SAFFRON II trial[28], this has been used in preference, given that limited single fraction SABR outcome data are currently available.

Abdominal constraints (Table 3)

The multiple constraints previously recommended for stomach, small bowel and duodenum have been rationalised. For the all three structures, the 5-fraction D_{10cc} constraint (≤25 Gy) has been moved to become optimal, because this dose (EQD_2 40 Gy, based on α/β=3 Gy) has been delivered safely to much larger volumes of small bowel in clinical practice, without excessive short- or long-term toxicity[38,39]. In addition, the previous optimal 5-fraction D_{5cc} constraint (also EQD_2 40 Gy) has been removed for all three structures. For the duodenum, the 5-fraction D_{1cc} and D_{9cc} constraints have also been removed and, instead, the dose previously applied to D_{1cc} (≤33 Gy) made optimal for $D_{0.5cc}$ (i.e. $D_{0.5cc}$ ≤33 Gy). The values used are in line with the range of constraints reported in the Gerhard et al systematic review[25], accepting that the duodenal 5-fraction D_{10cc} constraint (≤25 Gy) is at the upper end of the range reported and also higher than that reported by AAPM TG-101 (D10 ≤12.5 Gy)[25]

but, as above, is a well-established dose for larger volume treatments. It is acknowledged that the luminal constraints presented here are more conservative than those that may be adopted when treating primary pancreatic cancer[32-34], where the risk: benefit ratio is different.

The constraints required to limit toxicity when irradiating central liver structures such as the common bile duct lack robust evidence, therefore these constraints have been retained at 50 Gy (now applied to 0.1 cc) for both 3- and 5-fraction schedules.

For the liver, an optimal 5-fraction $D_{\geq 700cc}$ has been added and the mandatory 3-fraction $D_{\geq 700cc}$ has been lowered from 19.2 Gy to 17 Gy, to reflect the recent liver-specific HyTEC work[23]. In addition, optimal and mandatory 3-fraction mean dose constraints have been added, also in accordance to HyTEC[23]. While we have opted to provide one set of constraints for the liver, it is acknowledged that patients with liver metastases represent a different disease entity than those with HCC, where underlying cirrhosis puts these patients at a greater risk of radiation-induced toxicity. As such, for HCC, the optimal 3-fraction mean liver dose should be considered mandatory. Of–note, the provided constraints are only appropriate for patients with, at worst, Child Pugh A6 liver disease. While all the liver constraints presented here are compatible with the range that the recent liver-specific HyTEC work considered acceptable, it is recognised that most of the HyTec work focused on 3- and 6-fraction SABR[23], whereas, in the UK, most liver SABR is delivered in 3 (metastases) or 5 (metastases or HCC) fractions. These constraints are also in line with those presented by Gerhard et al[25]. Of note, where patients are having more than one liver lesion treated with SABR, it is recommended a 5-fraction regime is used and that all OAR constraints should be met as per a single lesion, with at least 40 hours (alternate days) between treatments.

In terms of the kidneys, the previous guidelines applied the 3-fraction $D_{\geq 200cc}$ constraint to individual and combined kidneys. In practice, individual kidneys are frequently <200 cc in volume, making the $D_{\geq 200cc}$ less useful in this setting. Therefore the 3-fraction $D_{\geq 200cc}$ has been retained for combined kidneys only and, for consistency, a 5-fraction combined kidney $D_{\geq 200cc}$ has been added, based on AAPM TG-101 and in line with the modal/ median constraints reported in the Gerhard et al review[25]. The mean dose for 5-fraction SABR has been retained for both combined and individual kidneys and, also for consistency, a mean dose for 3-fraction SABR added, equivalent to the 5-fraction dose (α/β=3 Gy). In the previous consensus, for patients where the mean ipsilateral kidney dose was exceeded, or for patients with a solitary kidney, 5-fraction V_{10Gy} optimal and mandatory constraints for the contralateral kidney were specified. These have been retained and mandatory V_{10Gy} constraints added for 1 and 3 fractions, based on the constraints applied to the contralateral kidney in the FASTRACKII trial[40]. Of note, where patients have both kidneys but are known to have poor renal function or significant imbalance in kidney function, it may be most appropriate to observe the single kidney constraints for the better functioning kidney.

The spleen is increasingly recognised as a potential OAR, with patients who receive higher doses being at increased risk of infection and infection-related mortality[41,42]. While constraints for conventional fractionation have been proposed, no constraints for SABR have been defined to date. As such, contouring and reporting of mean spleen doses is now encouraged to facilitate future modelling work.

Pelvic constraints and skin (Table 4)

Pelvic constraints that were considered of little clinical value have been removed. These include D_{15cc} for both 3- and 5-fraction bladder, which were considered too low to be clinically relevant (EQD_2 28.9 Gy and 24.4 Gy for 3 and 5 fractions, respectively, based on α/β=3 Gy). In addition, the 5-fraction ureter constraint has been removed as, at 45 Gy, it is unlikely to be exceeded with prescription doses of 30 Gy. The 3-fraction ureter constraint has been retained, however, as, at 40 Gy, this could be exceeded with prescription doses of 30-40 Gy. Penile bulb constraints have been removed as it is unlikely that target volumes would be compromised to respect these.

Colon and rectal 5-fraction mandatory constraints have been revised to 38 Gy, such that all constraints are consistent with AAPM TG-101[18] and the modal/median constraints reported by Gerhard et al[25].

The lumbo-sacral plexus and cauda equina (see next section), which were previously considered as one structure, have now been separated and sacral plexus constraints are now considered optimal, rather than mandatory in the de novo oligometastatic setting. It remains mandatory for oligoprogressive disease. This change reflects the fact that decisions on lumbo-sacral plexus dose often require an individual value judgement. For example, in cases where a patient will likely experience prolonged survival and has multiple further lines of therapy available (e.g. a patient with hormone sensitive prostate cancer with a pelvic side wall nodal recurrence), then respecting lumbo-sacral plexus constraints is likely appropriate. In contrast, for a patient with few treatment options, a more limited prognosis and lumbo-sacral plexus invasion from recurrent disease, then a clinician might opt to prioritise target coverage over sacral plexus sparing, provided the risks have been discussed and the patient consented appropriately. The 3-fraction D_{5cc} constraint has been increased from 22 Gy to 22.5 Gy, such that all lumbo-sacral plexus constraints are now consistent with AAPM TG-101 as well as the modal/median constraints reported by Gerhard et al[18,25]. Guidelines are available for lumbo-sacral plexus delineation[43].

Recent work has highlighted the urethra as a potential OAR[44]. No international constraint for the urethra exists, however, and contouring of this structure is not routine. Where it is contoured, near maximum dose ($D_{0.1cc}$) reporting is recommended to facilitate future audit and modelling.

Femoral head constraints remain unchanged and, particularly with IMRT and arc treatments for more central disease, are rarely dose limiting. These constraints are optimal and so can be exceeded if the clinical scenario requires this and the patient consented as appropriate.

Spinal cord, cauda equina and spinal canal constraints (Table 5)

Constraints for the spinal cord have been modified in light of the recently published HyTEC report, which reviewed spinal cord dose/volume tolerance data from published data and modelled to

estimate the risk of radiation myelopathy (RM)[20]. Recommendations for spinal cord point maximum doses, associated with a 1-5% risk of RM were made for image-guided SABR delivered in 1 to 5 fractions[20]. Constraints for 1-, 2-, 3- 5- and 8-fraction constraints are included, in particular in light of the encouraging results of the phase III SC24 trial (24 Gy in 2 fractions SABR vs. 20 Gy in 5 fractions palliative radiotherapy), where little high grade toxicity was reported and which used the same spinal cord constraint as reported by HyTEC[20,29]. It is acknowledged that there are limitations inherent within the modelled data presented in the HyTEC paper and that the suggested constraints represent conservative estimates, however, these are considered the most appropriate starting point as spinal SABR services are expanded across the UK. The HyTEC report also summarises higher dose limits, based on protocols and expert opinion. There may be clinical circumstances such as high-grade epidural disease and/or radioresistant disease, where target coverage may be compromised if a more conservative constraint were to be applied. The risk of choosing a dose-escalated constraint must be judged by the treating clinician, taking into account the treating centre's experience, SABR platform(s) and the need for rigorous quality assurance (QA) in the set-up, planning and delivery of spinal SABR at their individual institution. The mandatory constraint for 8-fraction SABR is retained and is that used in the SABR COMET trial[9] as well as the modal/median reported in the Gerhard et al systematic review[25], now applied to 0.035 cc.

For the cauda equina, the 3-fraction mandatory D_{5cc} constraint has been lowered slightly such that all 1-, 3- and 5-fraction constraints are based on AAPM TG-101[18], which are also consistent with Gerhard et al[25]. The 2-fraction cauda equina constraint is the same as that used for the spinal cord[20,29].

For spinal targets at the level of the spinal cord, the spinal cord itself should be contoured based on the co-registered MRI and a planning organ at risk volume (PRV) added. The spinal cord constraint is applied to the spinal cord **PRV** and applied to a volume of 0.035 cc, to be more consistent with the modelling work that derived these constraints[20]. The appropriate PRV size should be determined by the individual treating centre and is typically 1-3 mm and can vary across treatment platforms.

For spinal targets below the termination of the spinal cord, the cauda equina becomes the relevant OAR. The thecal sac is contoured as a surrogate for the cauda equina using a co-registered MRI[45]. No PRV is added to the thecal sac. The cauda equina constraint should also be applied to 0.035 cc of structure.

For non-spinal targets, the bony canal should be used as a surrogate for the spinal cord/cauda equina throughout the length of the spine (neural foraminae should not be included) and the spinal cord/cauda equina constraint applied to 0.035 cc of this structure. No PRV should be applied.

Intracranial constraints (Table 6)

In the 2017 UK consensus, 0.1 cc was used as a small volume surrogate for maximum dose for central nervous system (CNS) structures, except for cochlea which can be smaller than this volume, in which case mean dose was recommended. However, it is recognised that optic structures such as chiasm, and lenses can also be smaller than 0.1 cc. Very small volumes or point doses should not be used for

dose reporting though, because of uncertainties in TPS volume and dose calculations. A multi-centre study of stereotactic radiosurgery (SRS) planning found differences of up to 0.05 cc for target volumes less than 1 cc, both between different TPS and between different centres with the same TPS[26]. Therefore 0.035 cc is now used as the near maximum volume in this guidance for optic structures, lens and brainstem (along with spinal cord as above). The cochlea constraints remain as mean dose constraints, acknowledging that the constraints presented for 3 and 5 fractions were originally intended as near maximum constraints (to 0.035 cc)[18]. Given the small volume of the cochlea, meaningful differences are not anticipated.

For optic structures, more recent evidence has suggested that increased mandatory tolerances compared to those listed in our previous publication may still be associated with a low risk of radiation-induced optic nerve/chiasm neuropathy (RION). Milano et al[24] projected a 1% risk of RION for patients without prior cranial radiotherapy in patients receiving < 10, 20 and 25 Gy, in 1, 3 and 5 fractions to the optic apparatus, respectively, and so these have been adopted in this current consensus as mandatory constraints.

Regarding brain as an OAR, both dose volume metrics and location of dose are important. Retrospective data report a range of toxicity endpoints and are often confounded by several pathology and treatment variables. Furthermore, toxicity in the form of radionecrosis can be difficult to discriminate from progression for tumour cases. This makes it challenging to recommend a universal dose/volume constraint. However, it is widely accepted that small volumes tolerate higher doses as reflected in the RTOG 90-05 phase I dose escalation study for brain metastases[46] and many subsequent series. Total tissue V_{12Gy}, that is the volume including target receiving 12 Gy, as opposed to normal brain V_{12Gy}, where the target volume is subtracted, emerged several years ago as a predictor of late radiation toxicity for arteriovenous malformations (AVMs)[47,48]. Brain V_{12Gy} was not significant on multivariate analysis. The value of this metric for other pathology including brain metastases remains unclear. For brain metastases the benefits from early local control, and in the situation of multiple brain metastases, a distribution of V_{12Gy} across the brain, raises uncertainty with regards to the optimal value of V_{12Gy}. To help address this issue HyTEC published a normal tissue complication model based on dose and volume[21]. The group estimated that a V_{12Gy} of 5 cc, 10 cc and >15 cc were associated with a symptomatic necrosis risk of 10%, 15% and 20% respectively with single fraction SRS for brain metastases. Estimated risks were slightly lower for AVMs. Metastases treated with 3 fractions and a V_{20Gy} <20 cc, or with 5 fractions and a V_{24Gy} <20 cc, were associated with a <10% risk of any radionecrosis or oedema, and a <4% risk of radionecrosis requiring surgery. The QUANTEC analysis also acknowledged increasing risk with using single fraction with a V_{12Gy} above 5-10 cc[49]. Table 5 has been updated taking into consideration this modelling and more importantly the advantages from standardised reporting. However, individual risk versus benefit, location of target and therapeutic goals should be considered when reviewing the metric locally on a per-patient basis.

Optimal limits are retained for lens and orbit (as a surrogate for retina). Although in most cases target volumes should not be compromised to achieve these values, the risk of damage from high doses to sensitive structures such as the cornea should be avoided. Doses to these structures should generally be kept as low as reasonably practicable. Likewise, cochlea constraints are now listed as optimal only. There may be occasional benign treatments where hearing preservation is the priority,

but for most treatments target coverage (and chance of local control) should not be compromised for this OAR.

Discussion

This document presents the current UK consensus on OAR constraints for the delivery of SABR. While the recent literature has been reviewed, and despite many more patients having been treated with SABR since 2017, several of the current constraints remain those from the AAPM TG-101 report[18]. Despite being over 10 years old and based on limited clinical experience and even "educated guessing", the AAPM TG-101 constraints are still in common use, as demonstrated by Gerhard et al in the recent systematic review of constraints used in currently recruiting trials of SABR for the treatment of oligometastases[25]. Hence, the constraints presented in this consensus also represent contemporary international practice and their ongoing use in prospective clinical trials will hopefully lead to their validation. To remain in line with international practice, we opted to reduce near maximum dose constraints to be to 0.1 cc for extracranial OARs, rather than $D_{0.5cc}$ used in the previous consensus and we have reduced CNS, spinal cord and cauda equina near maximum dose constraints to $D_{0.035cc}$. We have also included constraints for single fraction (all sites) and 2-fraction (spinal) SABR to reflect international SABR developments[28,29].

Of note, the systematic review by Gerhard et al included constraints used in 53 currently recruiting trials[25]. As such, it is possible that safety concerns relating to some of these constraints may become apparent when these trials report. Although substantial variability in some OAR constraints was noted in the review, the modal and median constraints reported are often closely aligned, if not identical, to those in the AAPM TG-101 report[18], again suggesting these have become more established over time, rather than being superseded by newer constraints. In addition, NRG/RTOG trial protocols are heavily represented in the Gerhard et al review[25] and the constraints used within these, and those reported in APPM TG-101[18], are all based on older versions of 'Timmerman's tables'[50,51]. While Timmerman acknowledges that the original versions were based on very limited experience [50], as our own consensus illustrates, these have become ingrained in ongoing practice. The more recent constraints from HyTEC[19], however, which are derived from pooled clinical data and modelling, are yet to become fully embedded in clinical practice.

Despite increasing SABR outcome data over the past few years, it remains challenging to accurately quantify the risk of severe toxicity related to individual OAR constraints. Modelling work has been performed, sometimes with differing results and often with acknowledgement that further data are required[20-24,52]. Large scale prospective clinical data are likely to provide the best source of individual risk quantification over time. That said, for the majority of patients, the reported overall risk of severe toxicity related to SABR appears relatively low but, in a small proportion, can result in treatment-related death[9]. Individual patient factors are also likely to have an impact on toxicity risk (e.g. vascular disease, previous surgery) but, to date, these also remain relatively poorly described in the literature. Similarly, the impact of systemic therapy, in particular small molecule inhibitors and immunotherapy, either close in time or concurrent with SABR, on side effect profile has not yet been thoroughly investigated. As such, the continuing efforts of groups such as HyTEC will be invaluable in

quantifying individual risk going forward, including by providing guidance on how systemic therapies may be safely and optimally combined with SABR.

We are aware that, while constraints are provided for different fractionations, these are rarely biologically equivalent. For example, the EQD_2 (α/β=3 Gy) for the mandatory cardiac constraints described here are 110 Gy, 78 Gy, 80.6 Gy for one, three and five fractions, respectively. This likely relates to the fact these were often developed based on limited clinical experience[18], without a particular radiobiological basis, and continue to be used in practice. There are also large uncertainties about the use of the linear-quadratic (LQ) model at high doses per fraction or the correct α/β value in this setting[53]. Until more complete modelling data can provide advice to the contrary, constraints consistent with those used by other centres worldwide and that largely appear acceptable, will be applied. Furthermore, the authors acknowledge that the traditional division of OARs into serial and parallel structures, and defining constraints based on these, is not entirely valid. Several OARs have both serial and parallel architectures (e.g. lung parenchyma is considered parallel, while the airways, including the very small bronchi that would be delineated as lung, are serial in nature; the heart contains both serial (coronary arteries) and parallel (myocardium) components[54]). That said, these divisions form a useful starting point and, over time, as toxicity and modelling data develop, constraints can be adjusted.

Given the current limitations in the available data, ongoing high-quality prospective data collection remains essential. While the outcomes from the recent NHS England CtE programme appear encouraging, and included over 1400 patients (the largest dataset for oligometastatic patients treated with SABR[8]), it is acknowledged that registry data are often incomplete, limiting their use for future modelling. Formal, funded prospective trials are therefore more likely to produce the most reliable outcome data to guide future iterations of constraints.

While this consensus provides UK guidelines for SABR OAR constraints, different constraints may be required in different clinical scenarios. The Gerhard et al review included trials using SABR for oligometastases and, as discussed, modal and median values closely aligned to the AAPM TG-101 constraints [18]. Over time, however, SABR for a variety of primary disease sites has developed further, where the intent of treatment is different, and therefore these constraints may be less appropriate. For example, in the setting of SABR for primary prostate cancer, more lenient rectal constraints have been necessary to facilitate meaningful coverage and have been shown to result in low levels of toxicity[5]. Similarly, in the setting of SABR for primary renal cancer, different constraints are recommended based on increasing clinical experience[31] and, for primary pancreatic cancer, less stringent luminal constraints have been adopted to allow better target coverage, with acceptable toxicity outcomes[32-34]. This current consensus should therefore be considered a general guide for SABR but site-specific protocols should also be available to guide clinicians in these settings.

Conclusions

As with the 2017 guidance, the current consensus will require to be reviewed and updated in the future as further data emerge and as SABR treatments continue to evolve. Further information is still outstanding including, for example, detailed data regarding risk quantification, the impact of other treatments and patient-related factors and appropriate constraints for SABR in the re-irradiation

setting. As more centres in the UK and worldwide begin to deliver SABR for increasing indications, however, we hope that this document provides a useful resource to facilitate safe and consistent practice.

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Table 1. Serial-like and parallel-like organs at risk

Organ type		Dose-volume constraint descriptor	Notation	Example
Serial-like (e.g. spinal cord and esophagus)	**Critical maximum volume[18]**	The threshold dose, or higher, that can be given to a specified (typically small) volume of the organ, with the remaining volume receiving less than the threshold dose – may be termed a 'hot' constraint	$D_{xxcc} \leq$ yy Gy	*The dose to 0.035 cc of the spinal cord should be less than or equal to 14 Gy ($D_{0.035cc} \leq 14$ Gy)*
Parallel-like (e.g. lungs, liver and kidneys)	**Critical maximum volume[18]**	The maximum critical volume (percentage or absolute) of the organ that can receive a specified threshold dose, or higher	$V_{xxGy} \leq$ xx% (or cc)	*The normal lung volume receiving 20 Gy or higher should be less than or equal to 10% (Lung $V_{20Gy} \leq 10\%$)*
	Critical minimum volume[18]	The minimum critical volume of the organ that must receive a specified threshold dose or lower (i.e. be spared from receiving a dose higher than the threshold dose) – may be termed a 'cold' constraint	$D_{\geq xxcc} \leq$ yy Gy (equivalent to $D_{VTOT-xxcc} \leq$ yy Gy†)	*For a combined kidney volume of 250cc, at least 200cc should receive a dose of 16Gy or lower ($D_{\geq 200cc} \leq 16$ Gy, used as a 'cold' constraint†; or $D_{50cc} \leq 16$ Gy, used as a 'hot' constraint†)*

†Some TPSs allow the user to record 'cold' constraints directly, however many do not and therefore these require adjusting into a 'hot' (standard) constraint format; VTOT Is the total volume of the organ

Table 2: Thoracic constraints

Structure	Metric	1 Fraction		3 Fractions		5 Fractions		8 Fractions		End point
		Optimal	Mandatory	Optimal	Mandatory	Optimal	Mandatory	Optimal	Mandatory	
BrachialPlex	$D_{0.1cc}$		15 Gy[28]		24 Gy[9,18,25,37]	30.5 Gy[18,25,37]	32 Gy[9,25]	35 Gy[25,37]	39 Gy[9]	Grade 3+ neuropathy
Bronchus_Prox	$D_{0.1cc}$		20.2 Gy[18,25]		30 Gy[9,18,25]	35 Gy[36]	38 Gy[9]		40 Gy[9]	Grade 3+ stenosis/fistula
Chestwall	$D_{0.1cc}$	30 Gy[18,25]		36.9 Gy[18]		43 Gy[18,25]				Grade 3+ fracture/pain
	D_{30cc}			30 Gy[18, 25]						
Esophagus	$D_{0.1cc}$		15.4 Gy[18,25]		25.2 Gy[18]		35 Gy[9,18,25]		40 Gy[9,25]	Grade 3+ stenosis/fistula
GreatVes	$D_{0.1cc}$		30 Gy[28]		45 Gy[9,18,25]		53 Gy[9,18,25]	60 Gy	65 Gy[9,25]	Grade 3+ aneurysm
Heart+A_Pulm	$D_{0.1cc}$		22 Gy[9,18,25]	26 Gy[36]	30 Gy[9,18,25]	29 Gy[36]	38 Gy[9,18,25]	40 Gy	46 Gy[9,25]†	Grade 3+ pericarditis
Lungs (non-lung lesions) & Lungs-ITV (lung lesions)	V_{20Gy}	10%[22]	15%[22]	10%[22]	15%[22]	10%[22]	15%[22]	10%	15%	Grade 3+ pneumonitis
	D_{mean}	8 Gy		8 Gy[22]		8 Gy[22]		8 Gy		
Skin	$D_{0.1cc}$		26 Gy[18,25]	33 Gy[18,25]		39.5 Gy[9,18,25]		48 Gy[25,37]		Grade 3+ ulceration
	D_{10cc}		23 Gy[18,25]	30 Gy[18,25]		36.5 Gy[18,25]		44 Gy[25,37]		
Trachea	$D_{0.1cc}$		20.2 Gy[18,25]		30 Gy[9,18,25]	35 Gy[36]	38 Gy[9]		40 Gy[9]	Grade 3+ stenosis/fistula

†If not achievable, drop prescription dose to 50 Gy

Table 3: Abdominal constraints

Structure	Metric	1 Fraction		3 Fractions		5 Fractions		End point (if available)
		Optimal	Mandatory	Optimal	Mandatory	Optimal	Mandatory	
BileDuct_Common	$D_{0.1cc}$		30 Gy[25]	50 Gy		50 Gy[2,4]		
Bowel_Small	$D_{0.1cc}$		15.4 Gy[18,25]		25.2 Gy[18,25]	30 Gy	35 Gy[18,25]	Grade 3+ enteritis/obstruction
	D_{5cc}		11.9 Gy[18,25]		17.7 Gy[18,25]			
	D_{10cc}					25 Gy[25]		
Duodenum	$D_{0.1cc}$		12.4 Gy[18,25]		22.2 Gy[18,25]	33 Gy	35 Gy[2,4]	Grade 3+ ulceration
	D_{10cc}		9 Gy[18,25]		11.4 Gy[18,25]	25 Gy[2,4]		
Kidney_Cortex (individual/combined)	D_{mean}			8.5 Gy[25]‡		10 Gy[2,4]		Grade 3+ renal function dysfunction
Kidney_Cortex (combined)	$D_{\geq 200cc}$		8.4 Gy[18,25]		16 Gy[18,25]		17.5 Gy[18,25]	
If solitary kidney or one Kidney_Cortex D_{mean} >10Gy	V_{10Gy}		33%[40]		33%[40]	10%[2,4]	45%[2,4]	
Liver (non-liver lesions) & Liver-GTV (liver lesions)†	$D_{\geq 700cc}$		9.1 Gy[18,25]	15 Gy[23,25]	17 Gy[23]	15 Gy[23]		Grade 3+ liver function dysfunction
	V_{10Gy}					70%[2,4]		
	D_{mean}			13 Gy[23]	15 Gy[23]	13 Gy[2]	15.2 Gy[2,25]	Radiation-induced liver disease (classic or non-classic)
Spleen	D_{mean}		report		report		report	
Stomach	$D_{0.1cc}$		12.4 Gy[18,25]		22.2 Gy[18,25]	33 Gy[2,4,25]	35 Gy[2,4]	Grade 3+ ulceration/fistula
	D_{10cc}		11.2 Gy[18,25]		16.5 Gy[18,25]	25 Gy[2,4.25]		
	D_{50cc}					12 Gy[2,4]		

†Patients with primary liver tumours are generally considered at greater risk of toxicity and so optimal constraints should be favoured, where applicable. For HCC, optimal D_{mean} for 3 fractions should be applied as mandatory.

‡Equivalent to 10 Gy for 5 fractions using α/β=3 Gy

Table 4: Pelvic constraints

Structure	Metric	1 Fraction		3 Fractions		5 Fractions		End point (if available, from AAPM[18])
		Optimal	Mandatory	Optimal	Mandatory	Optimal	Mandatory	
Bladder	$D_{0.1cc}$		18.4 Gy[18,25]		28.2 Gy[18,25]		38 Gy[18,25]	Grade 3 cystitis/fistula
Bowel_Large	$D_{0.1cc}$		18.4 Gy[18,25]		28.2 Gy[18,25]		38 Gy[18,25]	Grade 3+ colitis/fistula
FemurHeadNeck	D_{10cc}	14 Gy[18,25]		21.9 Gy[18,25]		30 Gy[18,25]		Grade 3+ necrosis
LumbSacPlex	$D_{0.1cc}$	16 Gy[18,25]		24 Gy[18,25]		32 Gy[18,25]		Grade 3+ neuritis
	D_{5cc}	14.4 Gy[18,25]		22.5 Gy[18,25]		30 Gy[18,25]		
Rectum	$D_{0.1cc}$		18.4 Gy[18,25]		28.2 Gy[18,25]		38 Gy[18,25]	Grade 3+ proctitis/fistula
Ureter	$D_{0.1cc}$		35 Gy[25]		40 Gy[25,57]			
Urethra	$D_{0.1cc}$		report		report		report	

Table 5: Spinal constraints

Structure	Metric	1 Fraction		2 Fractions		3 Fractions		5 Fractions		8 Fractions		End point
		Optimal	Mandatory	Optimal	Mandatory	Optimal	Mandatory	Optimal	Mandatory	Optimal	Mandatory	
CaudaEquina & SpinalCanal (below level of the cord)	$D_{0.035cc}$		16 Gy[18,25]		17 Gy[25,29]		24 Gy[18,25]		32 Gy[18,25]			AAPM[18]: Grade 3+ neuritis
	D_{5cc}		14 Gy[18,25]				21.9 Gy[18,25]		30 Gy[18,25]			
SpinalCord_PRV (vertebral lesions) & SpinalCanal (non-vertebral lesions)	$D_{0.035cc}$	12.4 Gy[20]	14 Gy[20,25]		17 Gy[20,25,29]		20.3 Gy[20]		25.3 Gy[20]		32 Gy[9,25]	Sahgal[20]: Radiation myelopathy (1-5% risk for 1-5#)

Table 6: Intracranial constraints

Structure	Metric	1 Fraction		3 Fractions		5 Fractions		End point
		Optimal	Mandatory	Optimal	Mandatory	Optimal	Mandatory	
Brain (including targets)†	**V_{12Gy}**	10-15 cc[21]						Milano[21]: Symptomatic radiation necrosis (1#), oedema/necrosis (3 & 5#)
	D_{20cc}			20 Gy[21]		24 Gy[21]		
Brainstem (not medulla)	**$D_{0.035cc}$**	10 Gy‡	15 Gy[18]	18 Gy‡	23.1 Gy[18]	23 Gy‡	31 Gy[18]	AAPM[18]: Grade 3+ cranial neuropathy
Cochlea	**D_{mean}**	4 Gy[56]		17.1 Gy		25 Gy		Grade 3+ hearing loss
Lens	**$D_{0.035cc}$**	1.5 Gy						Cataract formation
OpticPathway	**$D_{0.035cc}$**	8 Gy‡	10 Gy[18,24,25]	15 Gy[55]	20 Gy[24]	22.5 Gy[55]	25 Gy[18,24,25]	AAPM[18]: Grade 3+ optic neuritis; Hiniker[55]/Milano[24]: Grade 4 radiation-induced optic neuropathy
Orbit	**$D_{0.1cc}$**	8 Gy						Retinopathy

†Based on modelling by HyTEC[21], V_{12Gy} of 5cc, 10 cc and >15cc was associated with an approximate symptomatic necrosis risk of 10%, 15% and 20% respectively for brain metastases. Individual risk/benefit and therapeutic goals need to be considered when reviewing this metric locally on a per-patient basis.
‡Derived from AAPM[18] TG-101 $D_{0.5cc}$ constraints for brainstem and $D_{0.2cc}$ constraint for optic pathway.