

Original Article

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Journal Pre-proofs

## An international Delphi consensus for pelvic Stereotactic Ablative Radiotherapy re-irradiation

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## **Abstract**

### *Introduction*

Stereotactic Ablative Radiotherapy (SABR) is increasingly used to treat metastatic oligorecurrence and locoregional recurrences but limited evidence/guidance exists in the setting of pelvic re-irradiation. An international Delphi study was performed to develop statements to guide practice regarding patient selection, pre-treatment investigations, treatment planning, delivery and cumulative organs at risk (OARs) constraints.

### *Materials and Methods*

Forty-one radiation oncologists were invited to participate in three online surveys. In Round 1, information and opinion was sought regarding participants' practice. Guidance statements were developed using this information and in Round 2 participants were asked to indicate their level of agreement with each statement. Consensus was defined as  $\geq 75\%$  agreement. In Round 3, any statements without consensus were re-presented unmodified, alongside a summary of comments from Round 2.

### *Results*

Twenty-three radiation oncologists participated in Round 1 and, of these, 21 (91%) and 22 (96%) completed Rounds 2 and 3 respectively. Twenty-nine of 44 statements (66%) achieved consensus in

Round 2. The remaining 15 statements (34%) did not achieve further consensus in Round 3. Consensus was achieved for 10 of 17 statements (59%) regarding patient selection/pre-treatment investigations; 12 of 13 statements (92%) concerning treatment planning and delivery; and 7 of 14 statements (50%) relating to OARs. Lack of agreement remained regarding the minimum time interval between irradiation courses, the number/size of pelvic lesions that can be treated and the most appropriate cumulative OAR constraints.

### *Conclusions*

This study has established consensus, where possible, in areas of patient selection, pre-treatment investigations, treatment planning and delivery for pelvic SABR re-irradiation for metastatic oligorecurrence and locoregional recurrences. Further research into this technique is required, especially regarding aspects of practice where consensus was not achieved.

### **Keywords**

Stereotactic Ablative Radiotherapy; Stereotactic Body Radiotherapy; Pelvic Cancer; Re-Irradiation; Consensus

### **Introduction**

Radiotherapy is frequently used in the management of pelvic malignancies. A recurrence after primary treatment within/at the edge of a previously irradiated volume presents a potential challenge as to the optimum therapeutic approach. Decision-making depends on factors relating to the patient, primary disease, previously delivered treatment and the recurrent lesion[1, 2]. Surgery may be morbid and challenging due to post-radiation fibrosis[2-4]. Systemic anti-cancer therapies are non-curative and may provide limited symptomatic relief for localised recurrences. Re-irradiation to organs at risk (OARs) may increase or cause unexpected toxicity[2, 5].

Stereotactic Ablative Radiotherapy (SABR), also called Stereotactic Body Radiotherapy (SBRT), is increasingly used to treat limited sites of metastatic relapse after primary treatment (so-called oligorecurrence) and locoregional recurrences[2, 6, 7]. The use of SABR to maximise dose to the

target and/or minimise dose to surrounding OARs could have a therapeutic advantage especially in the setting of re-irradiation. However, no high level evidence exists concerning this approach, with little formal guidance. Uncertainties remain regarding several aspects of the treatment pathway, including patient selection, planning and treatment delivery techniques and cumulative OAR constraints[2, 8, 9].

To determine current international practice, highlight areas of agreement and identify aspects of uncertainty which require further research, a Delphi study was undertaken. The purpose was to develop consensus statements to guide the practice of pelvic SABR re-irradiation for metastatic oligorecurrence and locoregional recurrence. The Delphi was restricted to SABR re-irradiation, since the intention was to develop specific statements which would provide a framework for SABR re-irradiation implementation by centres not currently delivering this and support its development by those already using it, including across different healthcare systems with varying access to resources.

## **Materials and Methods**

### *Organising group*

The study was led by XX, XX, XX, XX, XX and XX, all of whom have clinical experience of pelvic SABR re-irradiation in the UK.

### *Participants*

Radiation/clinical oncologists who had published articles about pelvic SABR re-irradiation, or who were considered by the organisers to be international experts in the field through their international profile, publications and academic collaborations, were approached by e-mail. If unable to participate, they were asked to nominate another appropriate individual. Only one oncologist from any research group was included. Forty-one invitations were made for the first round and participants who completed this were invited to complete subsequent rounds. All participants consented to participate prior to each round. Authorship was offered to participants, since they met the criteria through their substantial contribution to the data in the study and review of the draft manuscript.

### *Questionnaires*

A modified Delphi technique employing online questionnaires was used as a structured, transparent and iterative approach to obtain anonymous feedback and to allow participants to reassess their own judgements based on the feedback provided[10, 11]. A web-based survey platform was used (Online surveys, Jisc, Bristol, UK). The organisers were blinded to participant responses and did not complete any questionnaires. Three rounds took place.

Round 1 used mainly open-ended questions to gather information regarding participants' practice (**Supplementary Material 1**). Data were reviewed to identify themes and assemble statements to guide practice including: definition of pelvic SABR re-irradiation, patient selection, pre-treatment investigations, target volume/OAR delineation, treatment planning and delivery and cumulative OAR constraints.

In Round 2, statements were presented alongside summary data from Round 1 (**Supplementary Material 2**). Participants were asked to indicate their level of agreement with each statement using a 5-point Likert scale (strongly agree, agree, neither agree/disagree, disagree, strongly disagree). They were asked to consider how each statement might apply in general to patients treated with pelvic SABR re-irradiation, rather than for exceptional cases. Where participants did not agree/strongly agree, they were asked to provide an explanation in an accompanying free text box. Consensus was defined *a priori* where  $\geq 75\%$  of participants indicated that they either agreed/strongly agreed with the statement[11]. For cumulative OAR constraints, a table was provided which summarised published constraints (approaches include either relatively large cumulative maximum constraints or the subtraction of previously delivered dose from a traditional constraint with/without allowance for recovery), alongside participant information provided in Round 1[12-15].

In Round 3, statements without consensus in Round 2 were re-presented unmodified alongside the level of agreement of the whole group and a summary of free text comments from Round 2 (**Supplementary Material 3**). Participants were asked to indicate their level of agreement for these re-presented statements, taking into account Round 2 results. Statements with  $< 75\%$  agreement after Round 3 were considered not to have achieved consensus.

## Results

Twenty-three radiation oncologists (56% of 41 initial invitations) participated in Round 1. Of those who did not participate, the majority did not respond to the e-mail invitation. We are unaware whether all e-mails which were sent were actually received, given the potential, for example, for e-

mails to be blocked by hospital firewalls or otherwise not reach the intended recipient. Countries represented by the 41 initial invitations were: Australia (1 participant), Belgium (2), Canada (3), France (3), Germany (1), Italy (6), Netherlands (2), South Korea (2), Switzerland (2), Turkey (1), UK (5) and USA (13). Of the 23 participants, 21 (91% of 23 Round 1 participants) and 22 (96%) participated in Rounds 2 and 3 respectively. Countries represented by participants were: Canada (2 participants), France (1), Italy (6), South Korea (1), Switzerland (2), UK (4) and USA (5). Sub-specialty interests were: genitourinary (19, 83%), lower gastrointestinal (11, 48%) and gynaecological (8, 35%). Some experts practice in >1 sub-specialty. The median number of cases (range) treated each year per participant was 10 cases (10-100).

Round 1 opened 27/10/2020 and Round 3 closed 22/03/2021. A study schema is shown in **Figure 1**. After Round 1, 44 practice statements were produced. In Round 2, 29 of these achieved consensus and 15 statements without consensus were re-presented in Round 3. Of these, none achieved consensus in Round 3. Final lists of statements with and without consensus are shown in **Tables 5** and **6** respectively.

#### *Definition of pelvic SABR re-irradiation, patient selection and pre-treatment investigations*

Statements in this section and corresponding levels of agreement are shown in **Table 1**. After Round 3, absence of consensus remained for 7/17 statements. This included statements concerning the number (statement 5) and size (statement 6) of lesions considered appropriate for treatment. The location of lesions/proximity to OARs was considered more relevant than the number/size of lesions for 9 and 6 participants respectively. Despite this lack of agreement, statement 4 (which recommended that these each of these factors be considered as part of clinical decision making) achieved consensus (86%). There was no consensus regarding a lesion in contact with a critical/luminal OAR (statement 8): despite 90% agreeing that SABR was inappropriate where there was direct invasion of such an OAR (statement 7), only 50% agreed it may not be appropriate where there was contact rather than invasion. In such a scenario, delivery of a lower total dose/compromise of PTV coverage and close intra/inter-fraction monitoring were alternative approaches suggested by 3 and 2 participants respectively. A number of related objections were made for statements 16 and 17, which described scenarios where non-SABR re-irradiation (defined as conventionally or hyperfractionated radiotherapy) might be preferred, and which failed to achieve consensus.

No consensus was reached regarding a minimum time interval of 12 months from prior radiation (statement 9). Only 43% of participants agreed with this interval; comments included that previously delivered OAR doses (3 participants) and primary disease type (2 participants) were of greater importance or suggested alternative time intervals (3 participants). Regarding diagnostic imaging

(statement 14), 19 participants (83%) agreed that positron emission tomography-computed tomography was recommended but, among those who disagreed, 3 (13%) considered that magnetic resonance imaging might be unnecessary for nodal staging.

#### *Target volume/OAR delineation and treatment planning and delivery*

Statements in this section and corresponding levels of agreement are shown in **Table 2**. After Round 3, absence of consensus remained for 1/13 statements. Although 73% of participants agreed that the point maximum dose within the PTV should not exceed 140%, 2 participants indicated that proximity to OARs would determine the maximum acceptable dose and 1 participant considered that a lower maximum (115-125%) would be more appropriate. There was agreement for statements which concerned aspects of multidisciplinary team decision-making (statement 30), patient set-up (statements 18-19), target volume/OAR delineation (statements 20-21 and 24-25), treatment planning and delivery (statements 22 and 26-27) and documentation of disease/toxicity outcomes (statement 29).

#### *Proposed cumulative OAR dose constraints*

Statements in this section and corresponding levels of agreement are shown in **Table 3**. After Round 3, absence of consensus remained for 7/14 statements and these primarily described cumulative OAR constraints. Based on the information from Round 1 (with the exception of CaudaEquina/SacralPlex where most participants did allow recovery), approximately half of participants did not allow recovery from prior radiation, while the remainder did (by varying amounts/after varying time intervals). Therefore, 2 statements were produced per OAR: an optimal constraint in equivalent dose in 2 Gy fractions (EQD2) (without recovery) and a higher mandatory maximum cumulative constraint that might be appropriate once 12 months had elapsed from prior radiation. A summary of published data used to develop these is shown in **Table 4**. Optimal constraints were based on traditional de novo SABR American Association of Physicists in Medicine (AAPM) report 101 constraints in 5 fractions used cumulatively[13]. Mandatory cumulative maximum constraints were based on the mean value of constraints derived from published literature and which either used a large cumulative constraint (without recovery) or a traditional constraint incorporating recovery[12-15].

Only statements for mandatory maximum cumulative dose to bladder of 110 Gy<sub>3</sub> (statement 35) and optimal dose to CaudaEquina/SacralPlex of 67 Gy<sub>2</sub> (statement 38) achieved consensus. The percentage agreement for each of the remaining OAR constraint statements after Round 3 was ≥50%, except for maximum cumulative dose to Bowel\_Small (statement 37, 40.9%). Where consensus was not achieved for OAR constraint statements, small but broadly comparable numbers

of participants indicated that they considered the constraint to be too high or too low (**Supplementary Material 3**). Despite absence of consensus for most constraints, there was agreement both that published constraints should be used and that the previously delivered dose should be reviewed and a calculation of the maximum allowable dose for SABR re-irradiation (either in EQD2 or biologically effective dose (BED)) should be performed. Consensus was also obtained that OAR constraints should be prioritised over target volume coverage; participants would accept compromise in PTV dose and proceed with a minimum of 70% coverage by the prescribed dose.

## Discussion

This study has developed statements to guide pelvic SABR re-irradiation practice; 66% of these achieved consensus from an international group of radiation oncologists. Agreement was reached for statements about patient selection, treatment planning and delivery. Consensus was not reached for statements about minimum time interval between irradiation courses, maximum number/size of lesions and cumulative OAR constraints. Statements which achieved agreement form a useful guide for practice. In particular, statements that did not reach consensus highlight the lack of robust evidence, variation in practice and areas that require further research.

Of note, this study was based on expert opinion and was not necessarily evidence-based. Limited published literature exists concerning pelvic SABR re-irradiation. Most studies are small, single centre, retrospective and non-comparative, with modest follow up[2]. Many examined multiple tumour types with variation in dose-fractionation schedules, treatment techniques and endpoints. Reported rates of local control and survival outcomes vary considerably between histological subtypes (e.g. 1-year local control and overall survival range from 51-100% and 46-100% respectively[2, 15-17]). It remains uncertain whether control of the re-irradiated lesion influences patterns of further metastatic spread and survival.

### *Definition of pelvic SABR re-irradiation*

Agreement was reached regarding a definition, although there was no consensus regarding a statement which quantified a pre-specified overlap (e.g. a defined isodose or dose) to qualify a treatment as re-irradiation. Similar challenges in agreeing a definition which quantified overlap were encountered in a thoracic re-irradiation Delphi study[18]. This was considered to be due to

heterogeneity between patients and a lack of data to support a pre-specified overlap in OARs, and these same factors may well apply here.

#### *Patient selection*

Despite the majority of participants indicating that the number/size of pelvic lesions influenced decision making, consensus was not gained for specific statements relating to these factors. This likely reflects uncertainty regarding the most appropriate limits which maintain clinical utility but also the intent of treatment. In the non-re-irradiation oligorecurrence setting, often up to 3 or 5 lesions have been considered appropriate for SABR[6, 19]. Ongoing studies, such as SABR-COMET 10, will investigate the value of treating a greater number of lesions[20]. Of note, locoregional recurrence is a separate entity to oligorecurrence and, in the setting of isolated locoregional recurrence, equivalent limits on numbers of treated lesions may not apply[21]. Indeed, for both scenarios (i.e. local recurrence or oligorecurrence), several participants indicated that OAR dosimetry was of greater relevance or highlighted the potential for the statement to exclude a patient with >3 small closely-related lesions. However, there is likely to be a technical limit to the number/size of pelvic treatment volumes for which acceptable target coverage can be achieved while conformality is maintained/OAR constraints are respected. In addition, the complexity of treatment delivery including internal motion management also increases with each additional volume treated[22].

Consensus was not achieved concerning the time between prior radiation and SABR, which likely reflects uncertainty regarding what the acceptable minimum interval should be. Indeed, among participants who did not agree with a 12 month minimum interval, there was no majority view as to whether this should be shorter or longer. Similar to a smaller number of lesions, a longer interval might suggest less aggressive disease and a potentially better outcome from SABR re-irradiation[2]. On the other hand, the clinical need to obtain disease control/improve symptoms for a patient with, for example, an aggressive rectal cancer recurrence with associated poor prognosis, differs to a patient with a small volume prostate cancer recurrence[23-27]. The time interval could also influence whether an allowance for normal tissue recovery is made from prior radiation, although the extent to which this occurs and time intervals required are uncertain for most OARs[28, 29]. While individual case assessment should be made regarding the appropriate time interval from prior irradiation, a conservative approach for patients with a better prognosis may be to use a 12-month minimum interval (especially where allowance for recovery is to be made).

#### *Proposed cumulative OAR constraints*

Considerable uncertainty remains regarding the most appropriate constraints for SABR re-irradiation and whether any recovery should be incorporated. Reported rates of grade 3+ toxicity following SABR re-irradiation are typically <15%, although the observational nature of many of existing studies and limited use of patient-reported outcome measures (PROMs) restricts interpretation[2, 15-17]. When severe toxicity is reported, this may include potentially life-threatening conditions such as bowel obstruction or fistulae[2]. Few studies clearly report the use of cumulative dose constraints but there was clear consensus in this Delphi that previously delivered dose should be reviewed and the maximum permissible dose to each OAR calculated[12, 15].

Although few statements relating to optimal constraints gained consensus, it is likely that combined treatment plans which meet these, without an allowance for recovery, are safe, since the use of these traditional constraints (intended for first SABR irradiation) in a cumulative fashion is likely conservative. This approach may necessitate lower total doses (e.g. ~30 Gy in 5 fractions), especially in order to meet bowel constraints. It may be particularly appropriate for patients with better prognosis, other established treatment options and potential to survive to develop significant late toxicity, such as in prostate cancer. In addition, regarding prostate cancer, if the  $\alpha/\beta$  ratio is as low as thought, relatively 'low' SABR doses (e.g. 30 Gy in 5 fractions) deliver relatively high (>100 Gy) BEDs, although no high-level evidence exists to support a minimum acceptable BED[30-32].

Conversely, using traditional constraints cumulatively, without repair, may restrict the delivery of meaningful dose, especially for other histological subtypes or where the target is in close proximity to an OAR. This may be unnecessarily conservative and ignores potential for some recovery. Where a higher dose is considered necessary, maximum cumulative constraints, such as those reported by Abusaris et al and Smith et al, or incorporation of increasing amounts of recovery with time to traditional constraints, as described by Paradis et al, may need to be adopted, accepting the limited data to support this approach[12, 14, 15]. It should be noted that the cumulative constraints reported by Abusaris might be considered considerably lenient, given that they tend to be less restrictive than traditional constraints, even when 50% recovery is incorporated and also, in practice, may greatly exceed more accepted de novo SABR constraints, such as those of the AAPM (see **Table 4**)[12, 13]. Regardless of the approach, there was clear consensus that SABR re-irradiation should use highly conformal techniques and daily online image guidance and that SABR re-irradiation should be a shared decision between clinician and patient. This discussion should emphasise current uncertainties regarding OAR constraints and need for further research.

#### *Future directions*

The promising data associated with SABR for oligometastatic disease, particularly related to local control, are justification for further investigation specifically concerning SABR in the re-irradiation setting[6]. High-quality prospective studies of pelvic SABR re-irradiation are needed to evaluate disease outcomes alongside robust methods of toxicity assessment (including PROMs). Radiotherapy

quality assurance should include standardised methods of dose prescription, as per ICRU 91[33]. Priorities for studies are to determine appropriate time intervals to re-irradiation/magnitude of normal tissue recovery, maximum number/size of treated lesions and cumulative OAR constraints. Clinical trials in such a heterogenous population are likely to be challenging. An alternative approach is to define a minimum dataset for pelvic SABR re-irradiation to standardise data collection across multiple centres or from cancer registries[2]. Indeed, the ReCare registry study, currently in the design stage, aims to gather real-world data from re-irradiated patients[34]. There could, however, still be an advantage to obtaining multicentre data specifically relating to pelvic SABR re-irradiation. The statements developed in this study could be a helpful starting point in determining the patient, disease and treatment parameters to be investigated.

### *Limitations*

We focused on SABR re-irradiation to develop statements with specific recommendations. This approach excludes non-SABR re-irradiation and therefore limits the generalisability of our statements. Our selection criteria for the Delphi focussed primarily on radiation oncologists who had published articles on pelvic SABR re-irradiation. We considered this approach to be pragmatic but it could exclude those who are unpublished but have extensive clinical experience. Not everyone who was invited agreed to participate, but we consider that we obtained a reasonable response rate. We were not disease-specific in our inclusion criteria, meaning that some statements may not be applicable to all disease sites. Our aim was instead to produce technical guidance should a clinician consider that pelvic SABR re-irradiation is indicated. The maximum allowable dose with the PTV (for which no consensus could be obtained) would depend on the prescribed dose and so perhaps this statement is open to interpretation.

### **Conclusion**

This study has established consensus, where possible, in areas of patient selection, pre-treatment investigations, treatment planning and delivery for pelvic SABR re-irradiation. Important areas for future research include the minimum time interval between irradiation, number/size of pelvic lesions that can be treated and the most appropriate cumulative normal tissue constraints.

### **Figure caption**

Figure 1: Study schema.

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#### Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

✓ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

FA reports speaker honoraria and consultancy for Varian and Elekta. BAJF reports institutional research funding grants from Italian Association for Cancer Research (AIRC), FIEO-CCM & FUV and Accuray, outside of the submitted work. BAJF reports travel expenses/speaker fees from Janssen, Ferring, Bayer, Roche, Astellas, Elekta, Carl Zeiss, Ipsen, Accuray and IBA, outside of the submitted work.

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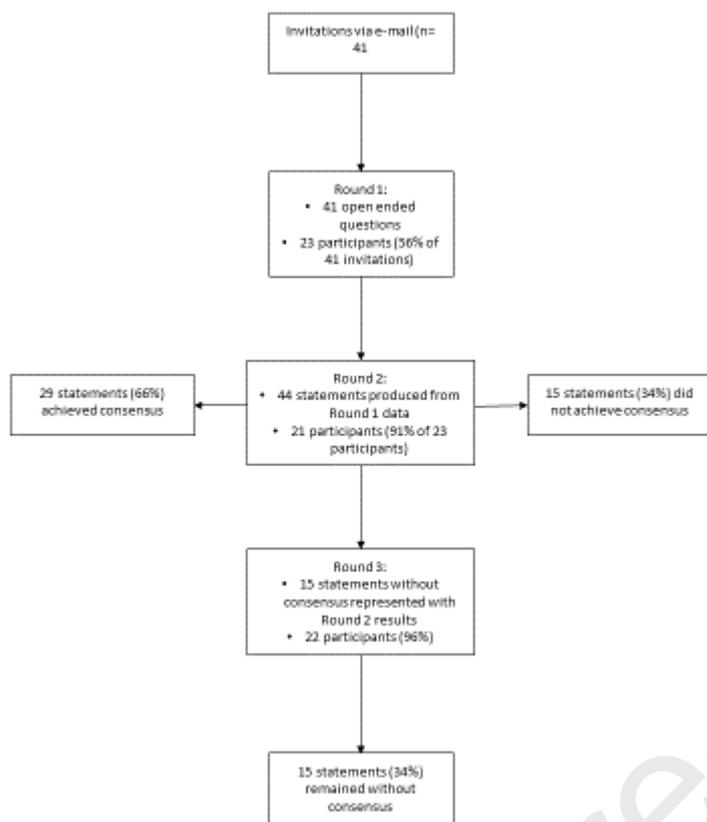


Table 1: Consensus for statements regarding definition of SABR re-irradiation in the pelvis, patient selection and pre-treatment investigations. Statements which achieved consensus are highlighted in bold

<i>Statement</i>	<i>Number of participants</i>	<i>Round</i>	<i>Strongly agree</i>	<i>Agree</i>	<i>Neither agree/disagree</i>
<b>1. Definition of SABR re-irradiation in the pelvis: Delivery of SABR, after initial radiotherapy to the pelvis, and where there is overlap of previously delivered dose with the new treatment that could result in excess dose to an OAR and/or significant toxicity</b>	21	2	38%	52%	5%
<b>2. SABR re-irradiation in the pelvis can be considered as an alternative to surgical exenteration following an appropriate multidisciplinary team discussion which takes into account individual patient and disease factors and the respective feasibility/risks of SABR and surgery</b>	21	2	29%	62%	5%
<b>3. SABR re-irradiation in the pelvis may be considered in the presence of extra-pelvic oligometastatic disease where this extra-pelvic disease can be controlled with metastasis-directed therapy</b>	21	2	33%	57%	5%
<b>4. When considering the feasibility of SABR re-irradiation in the pelvis it is necessary to take into account the number of lesions, the size of the target, and the target's location and proximity to OARs</b>	21	2	57%	29%	10%
5. The maximum number of pelvic lesions treated by SABR re-irradiation should not exceed 3	21 22	2 3	5% 0	38% 27%	14% 5%
6. The maximum size of an individual pelvic lesion treated by SABR re-irradiation should not exceed 6 cm in maximum dimension	20 22	2 3	15% 9%	45% 46%	10% 9%
<b>7. SABR re-irradiation in the pelvis is not usually appropriate where there is</b>	21	2	33%	57%	5%

<b>direct invasion of a luminal OAR</b>					
8. SABR re-irradiation in the pelvis may not be appropriate where the lesion is in contact with a luminal/critical OAR	21	2	9.5%	38%	19%
	22	3	5%	46%	14%
9. A minimum time interval of 12 months should have elapsed between a previous course of radiotherapy in the pelvis and SABR re-irradiation in the pelvis	21	2	0	38%	24%
	21	3	10%	33%	19%
<b>10. Patients otherwise eligible for SABR re-irradiation in the pelvis should, in general, have a minimum WHO performance status score of 2 (or equivalent)</b>	21	2	24%	62%	5%
<b>11. Previous acute radiotherapy toxicity that was expected/transient should not in itself preclude SABR re-irradiation in the pelvis, unless it was particularly severe or unexpected</b>	21	2	19%	81%	0
<b>12. SABR re-irradiation in the pelvis should be used with caution in the presence of moderate (e.g. CTCAE grade 2) previous/persistent late radiotherapy toxicity</b>	21	2	33%	62%	0
<b>13. SABR re-irradiation in the pelvis should be avoided in the presence of severe (e.g. CTCAE grade 3 or greater) previous/persistent late radiotherapy toxicity</b>	21	2	35%	55%	0
14. Diagnostic staging imaging prior to SABR re-irradiation in the pelvis should include MRI pelvis and PET-CT	21	2	24%	48%	5%
	22	3	18%	55%	5%
<b>15. Histological confirmation of recurrence prior to SABR re-irradiation in the pelvis may not always be possible or necessary and treatment may be appropriate based on a clinical and radiological</b>	21	2	33%	48%	10%

<b>diagnosis of recurrence</b>					
16. Non-SABR re-irradiation in the pelvis (e.g. using conventionally or hyperfractionated radiotherapy) is preferred for lesions >6 cm	21	2	14%	33%	29%
	22	3	9%	55%	14%
17. Non-SABR re-irradiation in the pelvis is preferred for lesions infiltrating or in contact with a luminal/critical OAR	21	2	10%	43%	29%
	22	3	5%	50%	18%

CTCAE, Common Toxicity Criteria for Adverse Events; MRI, magnetic resonance imaging; OAR, organ at risk; PET-CT, positron emission tomography-computed tomography; SABR, Stereotactic Ablative Radiotherapy; WHO, World Health Organisation

Table 2: Consensus for statements regarding SABR re-irradiation planning and treatment delivery. Statements which achieved consensus are highlighted in bold

<b>Statement</b>	<b>Number of participants</b>	<b>Round</b>	<b>Strongly agree</b>	<b>Agree</b>	<b>Neither agree/disagree</b>
<b>18. For SABR re-irradiation in the pelvis, patients should be positioned supine with the use of a device offering reproducible immobilisation (such as a vacuum bag or equivalent)</b>	21	2	29%	57%	10%
<b>19. During SABR re-irradiation in the pelvis, bladder preparation (filling/emptying) and rectal emptying should be determined on an individual patient basis, taking into account the position of the OAR during the prior treatment and the proximity of the OAR to the new target volume</b>	21	2	48%	48%	0
<b>20. Image co-registration with MRI or PET-CT to the planning CT should be used where it will improve target or OAR delineation</b>	21	2	48%	48%	0
<b>21. Intravenous contrast should be used (unless contraindicated) where it would improve target volume or OAR</b>	21	2	40%	55%	5%

delineation					
<b>22. Acceptable dose fractionation schedules for SABR re-irradiation in the pelvis are 30-37.5 Gy in 5-6 fractions or 21-27 Gy in 3 fractions with treatment delivered on alternate days</b>	21	2	19%	57%	5%
23. For conventional linear accelerator-based SABR, the maximum allowable dose within the target volume for SABR re-irradiation in the pelvis should not exceed 140% of the prescribed dose	21	2	0	71%	5%
	22	3	0	73%	14%
<b>24. Target volume and OAR nomenclature should be based on the recommendations in American Association of Physicists in Medicine (AAPM) report TG-263</b>	21	2	19%	71%	5%
<b>25. As a minimum, the following OARs should be delineated for SABR re-irradiation in the pelvis: Bladder, CaudaEquina, Femur_Head_L/R (with/without neck), Rectum, SacralPlex and a small and large bowel structure (e.g. Bowel_Small, Colon, Colon_Sigmoid)</b>	21	2	19%	57%	5%
<b>26. SABR re-irradiation in the pelvis should use IMRT (or similar high conformity techniques)</b>	21	2	52%	43%	0
<b>27. Daily online treatment verification using volumetric imaging or fiducial markers should be used for SABR re-irradiation in the pelvis</b>	21	2	48%	48%	0
<b>28. The concurrent administration of systemic anticancer therapies with SABR re-irradiation in the pelvis, aside from hormone therapy, is not recommended</b>	21	2	10%	81%	0
<b>29. Long term disease</b>	21	2	33%	52%	10%

<b>outcomes and toxicity data should be prospectively recorded for patients treated with SABR re-irradiation in the pelvis</b>					
<b>30. A multidisciplinary team including a radiation/clinical oncologist, medical physicist and radiographer/RTT, experienced in the practice of SABR re-irradiation in the pelvis, should be involved in determining the technical suitability of SABR re-irradiation cases and in the review of the treatment plan</b>	21	2	29%	62%	5%

CT, computed tomography; IMRT, intensity modulated radiotherapy; MRI, magnetic resonance imaging; OAR, organ at risk; PET-CT, positron emission tomography-computed tomography; RTT, radiation therapist; SABR, Stereotactic Ablative Radiotherapy

Table 3: Consensus for statements regarding cumulative organ at risk constraints. Statements which achieved consensus are highlighted in bold

<b>Statement</b>	<b>Number of participants</b>	<b>Round</b>	<b>Strongly agree</b>	<b>Agree</b>	<b>Neither agree/disagree</b>
<b>31. Treatment planning for SABR re-irradiation in the pelvis should include a review of the previously delivered dose to each OAR and calculation of the maximum allowable dose to each OAR during the new treatment (in EQD2 or BED)</b>	21	2	48%	38%	14%
32. Where there has been previous delivery of gynaecological brachytherapy, SABR re-irradiation is not recommended where there would be overlap of the planning target volumes	21 22	2 3	10% 9%	52% 41%	5% 18%
<b>33. External peer-reviewed guidance/literature should be used to guide cumulative OAR constraints for SABR re-irradiation in the pelvis</b>	21	2	10%	71%	10%

34. Optimally, the Bladder should receive no more than a cumulative dose of 80 Gy <sub>3</sub> EQD2 to 0.5 cc (assuming no recovery)	21	2	10%	62%	10%
	22	3	0	50%	14%
<b>35. The degree of recovery of Bladder after radiotherapy is uncertain but if 12 months or more have elapsed it is reasonable to assume some recovery and the Bladder may receive up to a maximum cumulative EQD2 of 110 Gy<sub>3</sub> to 0.5 cc</b>	21	2	5%	76%	14%
36. Optimally, Bowel_Small should receive no more than a cumulative dose of 70 Gy <sub>3</sub> EQD2 to 0.5 cc (assuming no recovery)	19	2	5%	47%	11%
	22	3	0	55%	5%
37. The degree of recovery of Bowel_Small after radiotherapy is uncertain but if 12 months or more has elapsed it is reasonable to assume some recovery and Bowel_Small may receive up to a maximum cumulative EQD2 of 90 Gy <sub>3</sub> to 0.5 cc	21	2	5%	48%	29%
	22	3	0	41%	23%
<b>38. Optimally, the CaudaEquina/SacralPlex should receive no more than a cumulative dose of 67 Gy<sub>2</sub> EQD2 to 0.1 cc (assuming no recovery)</b>	19	2	11%	68%	16%
39. The degree of recovery of CaudaEquina/SacralPlex after radiotherapy is uncertain but once 12 months or more have elapsed it is reasonable to assume some recovery and CaudaEquina/SacralPlex may receive up to a maximum cumulative EQD2 of 85 Gy <sub>2</sub> to 0.1 cc	19	2	11%	58%	16%
	22	3	0	64%	14%
40. Optimally, the Colon/Colon_Sigmoid/Rectum should receive no more than a cumulative dose of 80 Gy <sub>3</sub> EQD2 to 0.5 cc (assuming no recovery)	21	2	0	62%	10%
	22	3	0	59%	5%

41. The degree of recovery of Colon/Colon_Sigmoid/Rectum after radiotherapy is uncertain but once 12 months or more have elapsed it is reasonable to assume some recovery and Colon/Colon_Sigmoid/Rectum may receive up to a maximum cumulative EQD2 of 100 Gy <sub>3</sub> to 0.5 cc	21	2	5%	48%	14%
	22	3	0	55%	9%
42. OAR constraints should usually take priority over target volume coverage for SABR re-irradiation in the pelvis	21	2	19%	71%	0
43. If PTV coverage is compromised in order to meet an OAR constraint, a minimum of 70% of the PTV should receive the prescribed dose in order to proceed with SABR re-irradiation in the pelvis	21	2	0	81%	5%
44. The accepted risk of toxicity associated with SABR re-irradiation in the pelvis will depend on the prognosis and availability of effective alternative treatments and should be a shared decision with the patient	21	2	67%	29%	0

BED, biologically effective dose; EQD2, equivalent dose in 2 Gy fractions; OAR, organ at risk; SABR, PTV, planning target volume; Stereotactic Ablative Radiotherapy

Table 4: A summary of published OAR constraints: maximum cumulative dose in EQD2 to 0.5 cc for each OAR is shown based on first treatment of 45 Gy in 25 fractions (EQD2 43.2 Gy<sub>3</sub>) with/without allowance for recovery

<i>OAR</i>		<b>Abusaris [14]</b>	<b>Smith [17]</b>	<b>Paradis* [16]</b>	<b>AAPM* [15]</b>
<b>Conservative approach, based on use of a traditional constraint in a cumulative manner (may prevent delivery of meaningful r</b>					
Bladder	Constraint (no recovery; used cumulatively)	-	-	85 Gy	80 Gy
Bowel_Small	Constraint (no recovery; used cumulatively)	-	-	54 Gy	70 Gy
CaudaEquina/SacralPlex	Constraint (no recovery; used cumulatively)	-	-	70 Gy	67 Gy
Colon/Colon_Sigmoid/Rectum	Constraint (no recovery; used cumulatively)	-	-	70 Gy	80 Gy
<b>Less conservative approach, allowing larger cumulative dose and/or incorporating recovery into traditional constraint</b>					
		<b>Abusaris*†‡ [14]</b>	<b>Smith*†‡ [17]</b>	<b>Paradis*§ (50% recovery after 12 months) [16]</b>	<b>AAPM*# (25% recovery after 12 months) [15]</b>
Bladder	Cumulative constraint (includes additional recovery where	120 Gy	120 Gy	106.6 Gy	91.4 Gy

	appropriate)				
Bowel_Small	Cumulative constraint (includes additional recovery where appropriate)	110 Gy	98 Gy	64.8 Gy	80.8 Gy
CaudaEquina/SacralPlex	Cumulative constraint (includes additional recovery where appropriate)		74.4 Gy	91.5 Gy	77.9 Gy
Colon/Colon_Sigmoid/Rectum	Cumulative constraint (includes additional recovery where appropriate)	110 Gy	110 Gy	91.5 Gy	91.4 Gy

\* $\alpha/\beta$  ratio for all OARs of 3 used except for CaudaEquina/SacralPlex ( $\alpha/\beta$  of 2) and Paradis et al ( $\alpha/\beta$  of 2.5)

†Larger cumulative constraints used in Abusaris et al and Smith et al for Bladder, Bowel\_Small and Colon/Colon\_Sigmoid/Rectum, with no additional recovery permitted

‡No grade 3+ toxicity reported in Abusaris et al after a median follow up duration of 15 months (range 2-52 months). One patient experienced grade 3 pain but no other grade 3+ toxicity was reported in Smith et al after a median follow up duration of 24.5 months (IQR 17.8-28.8 months)

§50% recovery for all OARs for Paradis et al except Bowel\_Small (25% recovery)

#Recovery not specified by AAPM but included as illustrative of practice

Table 5: Summary of statements which achieved consensus

1. Definition of SABR re-irradiation in the pelvis: Delivery of SABR, after initial radiotherapy to the pelvis, and where there is overlap of previously delivered dose with the new treatment that could result in excess dose to an OAR and/or significant toxicity
2. SABR re-irradiation in the pelvis can be considered as an alternative to surgical exenteration following an appropriate multidisciplinary team discussion which takes into account individual patient and disease factors and the respective feasibility/risks of SABR and surgery
3. SABR re-irradiation in the pelvis may be considered in the presence of extra-pelvic oligometastatic disease where this extra-pelvic disease can be controlled with metastasis-directed therapy
4. When considering the feasibility of SABR re-irradiation in the pelvis it is necessary to take into account the number of lesions, the size of the target, and the target's location and proximity to OARs
7. SABR re-irradiation in the pelvis is not usually appropriate where there is direct invasion of a luminal OAR
10. Patients otherwise eligible for SABR re-irradiation in the pelvis should, in general, have a minimum WHO performance status score of 2 (or equivalent)
11. Previous acute radiotherapy toxicity that was expected/transient should not in itself preclude SABR re-irradiation in the pelvis, unless it was particularly severe or unexpected
12. SABR re-irradiation in the pelvis should be used with caution in the presence of moderate (e.g. CTCAE grade 2) previous/persistent late radiotherapy toxicity
13. SABR re-irradiation in the pelvis should be avoided in the presence of severe (e.g. CTCAE grade 3 or greater) previous/persistent late radiotherapy toxicity
15. Histological confirmation of recurrence prior to SABR re-irradiation in the pelvis may not always be possible or necessary and treatment may be appropriate based on a clinical and radiological diagnosis of recurrence
18. For SABR re-irradiation in the pelvis, patients should be positioned supine with the use of a device offering reproducible immobilisation (such as a vacuum bag or equivalent)
19. During SABR re-irradiation in the pelvis, bladder preparation (filling/emptying) and rectal emptying should be determined on an individual patient basis, taking into account the position of the OAR during the prior treatment and the proximity of the OAR to the new target volume
20. Image co-registration with MRI or PET-CT to the planning CT should be used where it will improve target or OAR delineation
21. Intravenous contrast should be used (unless contra-indicated) where it would improve target volume or OAR delineation
22. Acceptable dose fractionation schedules for SABR re-irradiation in the pelvis are 30-37.5 Gy in 5-6 fractions or 21-27 Gy in 3 fractions with treatment delivered on alternate days
24. Target volume and OAR nomenclature should be based on the recommendations in American Association of Physicists in Medicine (AAPM) report TG-263
25. As a minimum, the following OARs should be delineated for SABR re-irradiation in the pelvis: Bladder, CaudaEquina, Femur_Head_L/R (with/without neck), Rectum, SacralPlex and a small and large bowel structure (e.g. Bowel_Small, Colon, Colon_Sigmoid)

26. SABR re-irradiation in the pelvis should use IMRT (or similar high conformity techniques)
27. Daily online treatment verification using volumetric imaging or fiducial markers should be used for SABR re-irradiation in the pelvis
28. The concurrent administration of systemic anticancer therapies with SABR re-irradiation in the pelvis, aside from hormone therapy, is not recommended
29. Long term disease outcomes and toxicity data should be prospectively recorded for patients treated with SABR re-irradiation in the pelvis
30. A multidisciplinary team including a radiation/clinical oncologist, medical physicist and radiographer/RTT, experienced in the practice of SABR re-irradiation in the pelvis, should be involved in determining the technical suitability of SABR re-irradiation cases and in the review of the treatment plan
31. Treatment planning for SABR re-irradiation in the pelvis should include a review of the previously delivered dose to each OAR and calculation of the maximum allowable dose to each OAR during the new treatment (in EQD2 or BED)
33. External peer-reviewed guidance/literature should be used to guide cumulative OAR constraints for SABR re-irradiation in the pelvis
35. The degree of recovery of Bladder after radiotherapy is uncertain but if 12 months or more have elapsed it is reasonable to assume some recovery and the Bladder may receive up to a maximum cumulative EQD2 of 110 Gy <sub>3</sub> to 0.5 cc
38. Optimally, the CaudaEquina/SacralPlex should receive no more than a cumulative dose of 67 Gy <sub>2</sub> EQD2 to 0.1 cc (assuming no recovery)
42. OAR constraints should usually take priority over target volume coverage for SABR re-irradiation in the pelvis
43. If PTV coverage is compromised in order to meet an OAR constraint, a minimum of 70% of the PTV should receive the prescribed dose in order to proceed with SABR re-irradiation in the pelvis
44. The accepted risk of toxicity associated with SABR re-irradiation in the pelvis will depend on the prognosis and availability of effective alternative treatments and should be a shared decision with the patient

BED, biologically effective dose; CT, computed tomography; CTCAE, Common Toxicity Criteria for Adverse Events; EQD2, equivalent dose in 2 Gy fractions; IMRT, intensity modulated radiotherapy; MRI, magnetic resonance imaging; OAR, organ at risk; PET-CT, positron emission tomography-computed tomography; PTV, planning target volume; RTT, radiation therapist; SABR, Stereotactic Ablative Radiotherapy; WHO, World Health Organisation

Table 6: Summary of statements without consensus

5. The maximum number of pelvic lesions treated by SABR re-irradiation should not exceed 3
6. The maximum size of an individual pelvic lesion treated by SABR re-irradiation should not exceed 6 cm in maximum dimension
8. SABR re-irradiation in the pelvis may not be appropriate where the lesion is in contact with a luminal/critical OAR
9. A minimum time interval of 12 months should have elapsed between a previous course of

radiotherapy in the pelvis and SABR re-irradiation in the pelvis
14. Diagnostic staging imaging prior to SABR re-irradiation in the pelvis should include MRI pelvis and PET-CT
16. Non-SABR re-irradiation in the pelvis (e.g. using conventionally or hyperfractionated radiotherapy) is preferred for lesions >6 cm
17. Non-SABR re-irradiation in the pelvis is preferred for lesions infiltrating or in contact with a luminal/critical OAR
23. For conventional linear accelerator-based SABR, the maximum allowable dose within the target volume for SABR re-irradiation in the pelvis should not exceed 140% of the prescribed dose
32. Where there has been previous delivery of gynaecological brachytherapy, SABR re-irradiation is not recommended where there would be overlap of the planning target volumes
34. Optimally, the Bladder should receive no more than a cumulative dose of 80 Gy <sub>3</sub> EQD2 to 0.5 cc (assuming no recovery)
36. Optimally, Bowel_Small should receive no more than a cumulative dose of 70 Gy <sub>3</sub> EQD2 to 0.5 cc (assuming no recovery)
37. The degree of recovery of Bowel_Small after radiotherapy is uncertain but if 12 months or more has elapsed it is reasonable to assume some recovery and Bowel_Small may receive up to a maximum cumulative EQD2 of 90 Gy <sub>3</sub> to 0.5 cc
39. The degree of recovery of CaudaEquina/SacralPlex after radiotherapy is uncertain but once 12 months or more have elapsed it is reasonable to assume some recovery and CaudaEquina/SacralPlex may receive up to a maximum cumulative EQD2 of 85 Gy <sub>2</sub> to 0.1 cc
40. Optimally, the Colon/Colon_Sigmoid/Rectum should receive no more than a cumulative dose of 80 Gy <sub>3</sub> EQD2 to 0.5 cc (assuming no recovery)
41. The degree of recovery of Colon/Colon_Sigmoid/Rectum after radiotherapy is uncertain but once 12 months or more have elapsed it is reasonable to assume some recovery and Colon/Colon_Sigmoid/Rectum may receive up to a maximum cumulative EQD2 of 100 Gy <sub>3</sub> to 0.5 cc

EQD2, equivalent dose in 2 Gy fractions; MRI, magnetic resonance imaging; OAR, organ at risk; PET-CT, positron emission tomography-computed tomography; SABR, Stereotactic Ablative Radiotherapy

An international Delphi consensus for pelvic Stereotactic Ablative Radiotherapy re-irradiation

#### Highlights

- International expert survey of optimum practice for pelvic SABR re-irradiation
- Consensus established regarding multiple aspects of the treatment pathway
- Further research needed, especially concerning cumulative normal tissue constraints