Systematic review

Pelvic re-irradiation using stereotactic ablative radiotherapy (SABR): A systematic review

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ABSTRACT

Background and purpose: To perform a systematic review regarding the use of stereotactic ablative radiotherapy (SABR) for the re-irradiation of recurrent malignant disease within the pelvis, to guide the clinical implementation of this technique.

Material and methods: A systematic search strategy was adopted using the MEDLINE, EMBASE and Cochrane Library databases.

Results: 195 articles were identified, of which 17 were appropriate for inclusion. Studies were small and data largely retrospective. In total, 205 patients are reported to have received pelvic SABR re-irradiation. Dose and fractionation schedules and re-irradiated volumes are highly variable. Little information is provided regarding organ at risk constraints adopted in the re-irradiation setting. Treatment appears well-tolerated overall, with nine grade 3 and six grade 4 toxicities amongst thirteen re-irradiated patients. Local control at one year ranged from 51% to 100%. Symptomatic improvements were also noted.

Conclusions: For previously irradiated patients with recurrent pelvic disease, SABR re-irradiation could be a feasible intervention for those who otherwise have limited options. Evidence to support this technique is limited but shows initial promise. Based on the available literature, suggestions for a more formal SABR re-irradiation pathway are proposed. Prospective studies and a multidisciplinary approach are required to optimise future treatment.

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The primary treatment for many pelvic malignancies includes radiotherapy. The development of an isolated pelvic recurrence in the setting of prior pelvic radiotherapy often presents a challenge in terms of the optimal management approach. A variety of treatment interventions may be utilised including surgery, chemotherapy or radiotherapy, influenced by the site and volume of the recurrence, the location in relation to previously irradiated areas and the underlying disease biology. No standardised approach exists, and patients are evaluated on a case-by-case basis. While in some cases surgery can be curative, in others surgery may be considered impossible given the proximity of the recurrence to neuro-vascular structures or given concerns over potential surgical complications resulting from radiation-induced fibrosis. Where surgery is attempted, it may be extensive, resulting in significant morbidity, and/or leaving residual disease [1,2]. Alternatively, systemic therapy may be adopted with non-curative intent, using chemotherapy or other systemic agents, or androgen deprivation therapy in prostate cancer patients. The use of systemic chemotherapy for localised recurrences may risk toxicity with low potential for symptomatic benefit, and is often reserved for when widespread disease occurs. Where the recurrence is within or at the edge of the previously irradiated region, re-irradiation with conventionally fractionated radiotherapy is commonly avoided as the pelvis has often received doses considered near tolerance.

There is increasing interest in the use of stereotactic ablative radiotherapy (SABR) in extra-cranial sites [3]. SABR involves the very accurate delivery of a high radiation dose in a small number of fractions to a target with narrow margins [4]. In previously irradiated patients with small pelvic recurrences, the limited volume of normal tissue exposed to radiation in SABR is potentially attractive, as this may facilitate safe re-irradiation. The high dose, yet low number of treatment fractions, is also appealing. It has recently been highlighted, however, that SABR re-irradiation is an area that requires particular attention and further work [5]. This paper presents a systematic review of the literature regarding

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pelvic SABR re-irradiation. The limitations in the existing evidence are discussed to alert clinicians to the uncertainties that currently accompany this technique. Some practical considerations for the implementation of pelvic SABR re-irradiation are also presented.

Materials and methods

A systematic search was performed using MEDLINE (1996-present), EMBASE (1974-present) and the Cochrane Library. The search strategy included terms related to (i) SABR (and stereotactic body radiotherapy (SBRT)), (ii) re-irradiation and (iii) pelvic malignancies (including terms relating to individual primary sites, grouped sites (e.g. gynaecological malignancies) as well as pelvic malignancies as a whole). Reference lists of selected articles were also reviewed to identify additional papers. The last search was performed on 5th September 2016.

Only studies where re-irradiation involved overlap with previous radiotherapy were included (i.e. the re-irradiation volume was within, overlapping or close to the previously irradiated volume). Articles were excluded if they were: not in English, review articles or commentaries, concerned brachytherapy re-irradiation rather than SABR or conference abstracts or letters.

To meaningfully compare different dose and fractionations, the equivalent dose in 2 Gy fractions (EQD2) was calculated according to $EQD2 = D((d + \alpha/\beta)/(2 + \alpha/\beta))$ where D is total dose, d is dose per fraction and $\alpha/\beta = 10$ Gy for acute and tumour tissues, and $\alpha/\beta = 3$ Gy for late responding tissues. Different schedules can also be compared using the biologically equivalent dose (BED) which is calculated as $BED = D(1 + d/(\alpha/\beta))$. Corrections for repair or repopulation were not considered unless stated.

Study quality was scored according to relevant factors from the Quality Appraisal of Case Series Checklist produced by the Institute of Health Economics (IHE), Edmonton, modified for the specific subject of interest [6].

Results

Search

In total, 195 different articles were identified. Reasons for exclusion were: abstracts ($n = 29$), review articles and/or guidelines ($n = 53$), commentaries, editorials and letters ($n = 10$), not in English language ($n = 4$), therapies (principally ablative) for brain and base of skull lesions ($n = 28$), liver and colorectal cancer metastases ($n = 16$), lung and bone lesions ($n = 10$), and renal and germ cell tumours ($n = 14$), therapy for peritoneal carcinomatosis ($n = 1$), concerning cryotherapy for prostate cancer ($n = 1$), concerning SABR in the pelvis but not re-irradiation ($n = 5$), concerning brachytherapy ($n = 3$), concerning stereotactic biopsy ($n = 1$), overview of re-irradiation of multiple anatomical sites and/or doses without specific focus on the pelvis ($n = 2$) and concerning use of a radiotherapy system and not re-irradiation specifically ($n = 1$). Seventeen articles were therefore included. Using a modified Quality Assessment tool [6], the median study score was 16, out of a possible 22 (range 11–19; Supplementary Material Table 1).

Studies and patient numbers

Ten studies were identified in which all patients received pelvic SABR as re-irradiation (Supplementary Material Table 2). A further seven were identified in which a proportion of patients received SABR re-irradiation (Supplementary Material Table 3).

All studies involved low patient numbers with the largest including 31 patients re-irradiated in the pelvis [7]. Data were largely retrospective and from single institutions. In total, 205 patients were identified who were definitely re-irradiated using SABR within the pelvis. Most patients were re-irradiated for recurrent prostate cancer ($n = 86$ lesions, at least 82 patients), cervical or endometrial cancer ($n = 58$ lesions, at least 50 patients) and rectal cancer ($n = 50$ patients). Treatment intent (i.e. palliation versus cure) was generally not well described.

Follow-up

Median follow-up from re-irradiation in studies specifically examining re-irradiated patients ranged from 3 to 38 months, with seven of ten studies having <18 months median follow-up (Supplementary Material Table 2). In studies with mixed populations of re-irradiated and never previously irradiated patients, median follow-up was also relatively short, from 12.0 to 31 months (Supplementary Material Table 3).

Site of re-irradiation

Pelvic SABR re-irradiation was most frequently reported for local disease recurrence (predominantly in prostate cancer patients with intra-prostatic or anastomotic recurrences following previous radiotherapy or surgery and post-operative radiotherapy) and pelvic lymph node (LN) disease (i.e. oligometastatic relapse) (Supplementary Material Tables 2 and 3). Pelvic bony oligometastases were re-irradiated in ten patients and are included in this review, accepting that this adds to the diverseness of the data and that the toxicity profile may be different in this patient group, but this approach was considered justified given the intrinsic heterogeneity of the available data as a whole. The majority of patients had one lesion re-irradiated but occasional patients had two or three lesions treated. The degree of overlap between the former and re-irradiation plans was not well described. In almost all cases, the reported locations of re-irradiated lesions indicated the re-irradiation volumes were likely to have been contained within at least the 50% isodose of the previous radiotherapy plan and most often, wholly or partly, within the high dose region.

Interval to re-irradiation from first irradiation

The time between first and second irradiation, where reported, ranged from 3 to 336 months (excluding 5 cases where SABR was delivered as a boost immediately following external beam radiotherapy (EBRT)- these patients received previous brachytherapy [8,9]). The median time to re-irradiation was 22 months (based on reported median values). The previous conventionally fractionated radiotherapy dose in non-prostate cancer patients was usually 45–50.4 Gy but ranged from 20 to 100 Gy. In previously irradiated prostate patients, former doses of around 80 Gy were delivered (Supplementary Material Tables 4 and 5).

Localisation and immobilisation

Several studies performed Positron Emission Tomography (PET) to exclude additional disease [7,10–15]. In addition, seven studies used Magnetic Resonance Imaging-Computed Tomography (MRI-CT) co-registration to assist with target delineation [7,9,13,15–18]. Most studies used body frames, vacuum bags or cradles for immobilisation.

Irradiated volume

Re-irradiated volumes were variable. Gross Tumour Volume (GTV) and Planning Target Volume (PTV) volumes ranged from 6.6 cm³ to 1029.4 cm³ (median 38 cm³), and 7 cm³ to 1115 cm³ (median 154 cm³) respectively (based on Supplementary Material Table 2 (re-irradiated patients only)). Most studies delivered SABR

re-irradiation as an isolated treatment while in two studies involving gynaecological patients, SABR was delivered as a boost following conventionally fractionated pelvic radiotherapy in patients whose previous radiotherapy was brachytherapy alone ($n = 5$) [8,9].

Concurrent therapies

Androgen deprivation therapy was used in addition to SABR in some or all patients in three prostate cancer studies [7,10,11]. Chemotherapy was given concurrently with SABR re-irradiation in 9 patients [8,13,14].

Delivery technique

In terms of delivery technique, fourteen of seventeen studies delivered SABR using the Cyberknife (Supplementary Material Tables 2 and 3). Cyberknife use was associated with very tight margins (0 mm GTV-Clinical Target Volume (CTV), usually 3 mm CTV-PTV). In addition, fiducial marker insertion within or close to the target was usually performed to facilitate set-up and intra-fraction motion monitoring. In three Cyberknife studies, motion monitoring was performed using vertebral bodies instead of fiducials [10,13,16]. Studies using Cyberknife prescribed re-irradiation to a range of peripheral isodoses (40–86%).

For those four studies which included patients treated using a linear accelerator [7,8,15,19], GTV-CTV margins of 0–3 mm and CTV-PTV margins of 3–10 mm were adopted. Different prescription strategies were used (e.g. peripheral isodose [8] versus isocentric [19]). One study used tomotherapy [15] and another used arc techniques [7]. Only one of four linear accelerator-based studies performed intra-fraction motion monitoring in some patients [7]. Daily pre-treatment verification employed variable techniques (portal imaging [19], cone beam CT [7,8,15] and planning CT scanner [8]).

In three of the studies that reported re-irradiation for locally recurrent in situ prostate cancer, the CTV consisted of the whole prostate, rather than expansion of an image-defined GTV [7,11,17].

Re-irradiation prescription dose

Re-irradiation SABR prescription doses were variable, ranging from 15 Gy in 3 fractions to 60 Gy in 3 fractions (EQD2 to tumour ($\alpha/\beta = 10$ Gy); $EQD2_{10Gy}$: 18.8–150 Gy, EQD2 to late tissues ($\alpha/\beta = 3$ Gy); $EQD2_{3Gy}$: 24–276 Gy (Supplementary Material Tables 4 and 5). The selection of dose and fractionation was often stated as being based on recurrence size and location, interval since previous radiotherapy and previous radiotherapy dose [7–9,13,18,20–22]. The median physical SABR dose (i.e. without correction for fractionation and based on median values) delivered to definitely re-irradiated patients, was 30 Gy in a median of 4.5 fractions. The corresponding median dose to acute and late responding tissues was 41.7 Gy ($EQD2_{10Gy}$) and 58 Gy ($EQD2_{3Gy}$) respectively. Based on available information, the median cumulative dose to the acute and late responding tissues from previous and SABR irradiation was 105.3 Gy ($EQD2_{10Gy}$) and 111.9 Gy ($EQD2_{3Gy}$) respectively. Variations in prescription techniques (i.e. to different peripheral isodoses or isocentric) will result in further variations in doses actually received by the target.

Toxicity

Considering re-irradiated patients, ten of seventeen studies reported no grade 3+ toxicities (Supplementary Material Tables 6 and 7) [7,11–16,19,21,22]. In total, 9 episodes of grade 3 toxicity were reported in patients definitely re-irradiated in the pelvis: four acute (fatigue [9], worsening urinary incontinence [10], urethral obstruction [17] and enterocolitis [18]) and four late events (worsening urinary incontinence in the patient who had problems acutely [10], hydronephrosis secondary to ureteric stenosis requiring stenting [20], haemorrhagic cystitis in the patient who experienced acute grade 3 urethral obstruction [17] and urethral stricture [18]). The timing of the other grade 3 event was not reported (neuropathy) [20]. Six grade 4 events were also reported in definitely re-irradiated patients including five late events (small bowel ileus in a patient previously treated with EBRT and vaginal brachytherapy [8], intestino-vaginal fistula in a patient previously irradiated with vaginal brachytherapy who received conventionally fractionated re-irradiation then SABR [8], haemorrhagic cystitis requiring surgery [17] and two episodes of recto-vaginal fistulation in patients previously treated with pelvic surgery and whole pelvis external beam radiotherapy [18]). The timing of the sixth grade 4 event was not reported (small bowel perforation [20]). Three further episodes of grade 3 urinary toxicity were reported in two studies although whether these occurred in re-irradiated patients were not specified but seems unlikely as both studies highlighted other cases where toxicities occurred in re-irradiated patients [8,10]. One further study, which included re-irradiated and never previously irradiated patients, reported one potential grade 3 event (6%; thrombosis) and three late grade 4 events (vesico-vaginal fistula, recto-vaginal fistula and bowel obstruction), though specific outcomes for re-irradiated patients were not provided [23].

Organ at risk constraints

In terms of organs at risk (OARs), seven of seventeen studies reported constraints, mainly as maximum point doses [7,10,11,15,17,20,22] (Supplementary Material Tables 6 and 7). Only in one study, Abusaris et al., were constraints clearly based on cumulative doses from the previous irradiation and the re-irradiation [22]. Here original doses were subtracted from cumulative constraints to determine the normal tissue doses remaining for SABR re-irradiation. It was not reported how the values selected as cumulative constraints were determined. This group reported low toxicity, without grade 3+ events.

Response

In patients who were symptomatic prior to re-irradiation, improvements in pain were reported in 50–100% [13,20–22]. Bleeding improved in 75% in one study [22]. Beyond pain responses, other quality of life outcomes have not been widely evaluated. Deodato et al., however, reported no change in quality of life according to the Cancer Linear Analogue Scale (CLAS) scale between pre-SABR and first follow-up [19].

Radiological/clinical response rates appear variable. One study examining only re-irradiated patients reported no unequivocal responses according to Response Evaluation In Solid Tumours (RECIST) criteria [13]. Vascular changes were apparent, however, considered suggestive of response, leading the authors to suggest that alternative response measures might be appropriate. Indeed, another study examining re-irradiated patients alone reported no complete or partial responses but stable disease in 86% [21]. A complete response was, however, reported in two of five re-irradiated lesions in one study [19] and three of five in another [9]. Studies involving both re-irradiated and never previously irradiated patients reported complete and partial responses in 35–83% of patients, and stable disease in 5–40% [10,14,19,23].

Local control

In re-irradiated patients, local control (LC) at one year ranged from 51.4–100% (Supplementary Material Tables 6 and 7). Abusaris et al. observed that patients who received SABR doses of >60 Gy ($EQD2_{10}$) had improved LC compared to those who received lower doses (Two-year LC 100% with >60 Gy, 40% with 60 Gy or less, p = 0.04) [22]. Other studies that attempted statistical analysis to determine factors important for LC failed to identify significant factors, including re-irradiation volume and location (i.e. central vs. side wall) [8,14,21], although the numbers involved in such analyses were small. Local control in re-irradiated patients compared to never previously irradiated patients was evaluated in one study, where re-irradiated patients (some pelvic but also other sites of re-irradiation) had inferior LC compared to those who had not received prior radiotherapy ($p < 0.0001$), though re-irradiated patients received lower SABR doses (median BED re-irradiated: 79.2 Gy vs. 89.7 Gy in not previously re-irradiated) [18]. Similarly, Jereczek-Fossa et al. observed that most local failures occurred in prostate cancer patients who had re-irradiated intra-prostatic and anastomotic recurrences compared to patients who were treated for LN recurrences [10]. All patients with intra-prostatic and anastomotic recurrences were re-irradiated, while only 50% of LN recurrences were re-irradiated, and higher doses were prescribed for LN disease.

Survival

Progression free survival/disease free survival (DFS) was variable following SABR re-irradiation. Kunos et al. reported that all three patients progressed within 4 months of re-irradiation for vulvar disease [12] while Dewas et al. reported median DFS of 8.3 months in patients with a variety of diagnoses [13]. In patients re-irradiated for prostate cancer, the variable use of androgen deprivation therapy may impact progression. Vavassori et al. reported biochemical relapse at a median of 8.4 months in 4 of 6 patients and clinical progression at a median of 9.9 months in 3 of 6 prostate patients, 4 of whom received androgen deprivation alongside SABR [11]. Fuller et al., following salvage prostate SABR re-irradiation, reported 82% biochemical relapse free survival (bRFS) and 100% clinical relapse free survival at 2 years, respectively, with no patients receiving concurrent or adjuvant androgen deprivation [17]. No factors were identified which correlated with bRFS.

Overall survival (OS) following pelvic SABR re-irradiation was also variable, with median OS ranging from 11.5 to 14 months for re-irradiated patients with mixed primary tumour types [13,22], 26–40 months for re-irradiated colorectal patients [14,20] and 28 months for gynaecological patients [19]. One year OS in re-irradiated patients was reported as 46–52% in mixed primary tumour series [13,22], 77–90% for colorectal patients [20,21] and 60% for gynaecological patients [19]. When compared, Kim et al. found no significant difference in OS in re-irradiated and never previously irradiated patients with recurrent rectal cancer [14], while Park et al. observed inferior survival in re-irradiated compared to never irradiated cervical cancer patients (patients were irradiated in several sites, including the pelvis) [18]. Defoe et al. and Guckenberger et al. failed to identify any factors predictive of OS in re-irradiated rectal and gynaecological cancer patients respectively [8,21].

Patterns of failure

In terms of patterns of failure, where sufficient detail has been provided, when patients do relapse following SABR re-irradiation, more appear to relapse with distant metastatic disease rather than local disease [7,11,14,18,19]. Higher rates of LC compared to disease free survival [7,13], also support the suggestion that more patients experience distant, than local, recurrence.

Discussion

There is a paucity of evidence regarding pelvic SABR re-irradiation. Patients with isolated pelvic recurrences currently have limited options [24]. These include potentially extensive surgery, no surgery or systemic therapy with likely palliative intent for a localised problem. In suitable patients, pelvic SABR re-irradiation could potentially delay these alternatives and result in symptomatic benefit, long-term local control or even cure. Unfortunately existing studies investigating pelvic SABR re-irradiation have significant limitations: studies are small in number, patient numbers are too low for extensive analysis, follow-up is limited and data are largely retrospective and highly heterogeneous, sometimes considering re-irradiated and never previously irradiated patients as one. These factors make it difficult to draw conclusions regarding the most appropriate use of pelvic SABR re-irradiation. Several important points are, however, raised by the existing evidence.

Firstly, and perhaps surprisingly, pelvic SABR re-irradiation appears well tolerated: traditionally, Radiation Oncologists are wary of hypofractionation as late toxicity may be increased. And yet, despite combining re-irradiation with extreme hypofractionation, ten of seventeen studies reported no high-grade toxicity in re-irradiated pelvic SABR patients, and rates of grade 1/2 toxicity also appeared acceptable [7,11–16,19,21,22]. Six studies reported a total of nine grade 3 events and six grade 4 events in thirteen re-irradiated patients [8–10,17,18,20]. This gives a crude high-grade toxicity rate of 6.3% in definitely re-irradiated patients. Taking the worst case scenario, by presuming the additional high-grade toxicities reported by Yazici et al. [23] all occurred in re-irradiated patients, then the total number of grade 3 and 4 events would be ten and nine, respectively, in 17 patients, giving a 'worst case' crude high-grade toxicity rate of 8.3%. Both these estimates compare favourably with pelvic re-irradiation using hyperfractionated regimens (traditionally considered safer) where grade 3+ acute and late toxicity has been reported in up to 20% and 36% of patients respectively, following median doses of 30–40 Gy, usually delivered to the GTV with 2–4 cm margins [25]. Possible explanations for the observed lower toxicity rates include selection bias, shorter follow-up, smaller target volumes and potentially reporting bias and/or under-reporting of toxicities given the retrospective nature of most data. It may also be that technical developments and the use of tight margins around SABR targets markedly limit the volume of normal tissue re-irradiation. In addition, most SABR studies employ high quality image-guided radiotherapy (IGRT), thus ensuring accurate dose delivery and prescribe to a peripheral isodose, thereby facilitating rapid dose fall-off beyond the target [26].

In one of the seven studies where high-grade toxicity occurred, however, the overall high-grade toxicity rate was 25% at three years for all (re-irradiated and never previously irradiated) patients, which is unlikely to be acceptable in most settings [8]. In some studies where high-grade toxicity occurred, potential contributing factors can be identified. For example, in the study by Guckenberger et al., evaluating patients re-irradiated for recurrent gynaecological cancer, relatively large margins (7–8 mm) were employed and IGRT was less advanced in some patients than in other studies [8]. Both re-irradiated patients with grade 4 toxicity had received previous vaginal brachytherapy, leading to high local doses, potentially contributing to toxicity. Similarly, in one study investigating SABR re-irradiation for locally recurrent prostate cancer, one of two patients with high-grade urinary toxicity had

received previous low dose rate brachytherapy [17]. As well as receiving previous whole pelvis radiotherapy, both patients with grade 4 recto-vaginal fistulation in the series reported by Park et al. had received prior pelvic surgery, potentially increasing the risk of toxicity [18]. In one study, where one patient experienced acute and late grade 3 urinary toxicity, the patient had urinary problems pre-SABR, which likely contributed [10]. In another study, the development of grade 3 fatigue in one patient, was potentially multifactorial (EBRT and SABR as re-irradiation, grade 3 cystitis during EBRT) [9]. Additional clinical factors, such as previous surgery or co-morbidities, potentially contributing to the other high-grade events, are less obvious. Certainly, and particularly in gynaecological patients, the use of high cumulative radiotherapy doses, including that from brachytherapy, may increase the risk of toxicity from SABR re-irradiation. Previous pelvic surgery increases the risk of toxicity following a first course of radiotherapy [27], and so potentially also contributes to risk following subsequent courses. Numerous lines of previous systemic therapy, and the use of previous or subsequent anti-angiogenic therapies [28], may also impact. These factors require further investigation in the setting of SABR re-irradiation.

Whether the volume of re-irradiated tissue is important in influencing high-grade toxicity is unclear. For example, two studies re-irradiated lesions up to 5 cm and 8 cm in diameter without high-grade toxicity in 16 and 4 patients respectively [13,14], while lesions >1000 cm^3 have also been re-irradiated without high-grade toxicity [22].

In all studies where high-grade toxicity occurred, prescribed SABR doses did not appear particularly high compared to other studies (Fig. 1a Supplementary Material) [8–10,17,18,20]. It may be, however, that it is the cumulative dose from previous irradiation and SABR that is important. In addition, it is likely that it is normal tissue doses that are important rather than target (prescription) doses. Few studies, however, provide details of normal tissue doses from SABR or previous EBRT [22], and few [8] provide detailed dosimetric information about individual patients, which might be more useful when evaluating dosimetric contributors to toxicity. Examining the range of cumulative prescription doses between studies and high-grade toxicity, also does not demonstrate any obvious patterns (Fig. 1b Supplementary Material), suggesting that normal tissue and individual patient doses are more important.

In terms of determining the most appropriate re-irradiation SABR prescription dose and OAR constraints, the optimal approach is undefined. While Abusaris et al. [22] demonstrated that SABR doses >60 Gy (EQD2$_{10Gy}$) resulted in improved LC (total $n = 27$), not all patients will be suitable for such doses, based on previous radiation dose, location and volume of recurrence. Prescription doses should be influenced by previous and re-irradiation normal tissue doses. While seven studies reported re-irradiation constraints [7,10,11,15,17,20,22], only Abusaris et al. clearly employed cumulative dose constraints [22]. This strategy, together with tight margins and high quality IGRT, may have contributed to low toxicity rates. Approaches for OAR constraints are discussed further below.

Despite the relationship between dose and LC demonstrated by Abusaris et al., other groups have not demonstrated significant relationships between dose and outcome [14,18,21]. In addition, relationships between other conventional factors (e.g. volume and time to re-irradiation) and outcomes, have either not been evaluated or, where examined, significant associations have not been demonstrated [8,13,14,18,21]. This may well be multifactorial, reflecting the retrospective nature of most data, the limited statistical power of analyses with low patient numbers and the lack of information concerning, or inclusion of, other potential influencing factors, such as age, previous surgery, diabetes and

lines and types of systemic therapy. Furthermore, the heterogeneity of the data, including differences in case mix, case volume and levels of multidisciplinary expertise of those involved in delivering SABR re-irradiation between different centres, may also have an impact.

Based on current evidence, it is unclear whether some sites are more appropriate for re-irradiation than others. Patients have received re-irradiation for local recurrence of the primary and for oligometastases, which could have different biological characteristics. Jereczek-Fossa et al. observed improved LC and less toxicity in prostate cancer patients who received pelvic SABR for LN recurrences than for intra-prostatic or anastomotic recurrences [10]. Not all patients with LN recurrences, however, had received prior radiotherapy while all locally recurrent patients were re-irradiated, and doses were different, making firm conclusions difficult. It is conceivable that there is more limited capacity for re-irradiation in sites previously irradiated to very high doses (i.e. sites of primary disease) because of the doses previously received by surrounding normal tissues, and that such patients are at greater risk of toxicity from re-irradiation. It is also possible that tumours previously irradiated to high dose, which subsequently recur, may be inherently more radio-resistant. Larger patient numbers are required, however, to investigate if certain sites are more appropriate for SABR re-irradiation.

It is also uncertain if and how systemic treatments should be combined with SABR re-irradiation. A few patients have received chemotherapy concurrently with SABR but numbers are too few to determine how this influences outcomes [8,13,14]. Some patients received chemotherapy prior to SABR as an initial treatment for recurrence [13,14,23], and although the impact of this on outcome is unknown, it could be argued that for localised recurrences, chemotherapy may be better reserved for widespread symptomatic disease. Conversely, chemotherapy could potentially shrink an oligometastasis to render it more suitable for re-irradiation. Even less well understood, is the impact of newer systemic therapies (e.g. anti-angiogenic therapies, tyrosine kinase inhibitors, immune agents) on SABR re-irradiation outcomes, both disease control and toxicity. Such combinations have not been widely assessed in the setting of a first course of SABR, though increased toxicities have been observed in some cases [29], suggesting the need for caution if employing these agents around the time of SABR re-irradiation.

Despite the limitations of the existing evidence, there are signals of potential benefit from pelvic SABR re-irradiation, with encouraging LC and, generally, low toxicity rates. This supports the need for wider study, including high quality prospective studies using modern radiotherapy techniques. Such studies should include standard outcomes such as LC, progression free and overall survival and toxicity, but also quality of life/patient-reported outcomes. To maximise the knowledge that can be attained from future pelvic SABR re-irradiation, the process must be optimised as far as possible, with consideration of the issues illustrated by existing evidence. Based on the limited data available for SABR pelvic re-irradiation, and the strategies currently adopted for SABR in other (non-re-irradiation) settings, suggestions can be made [26,30]. These include:

Eligibility: time to re-irradiation

The impact of interval to pelvic SABR re-irradiation on outcome has not been widely assessed. In this review, times to re-irradiation from first radiotherapy ranged from 3 to 336 months. This may not, however, be completely reflective of the true disease free interval, as patients may have had additional interventions for recurrence between radiotherapy courses. Intuitively, a longer disease free interval would suggest less aggressive disease and, as such, a better
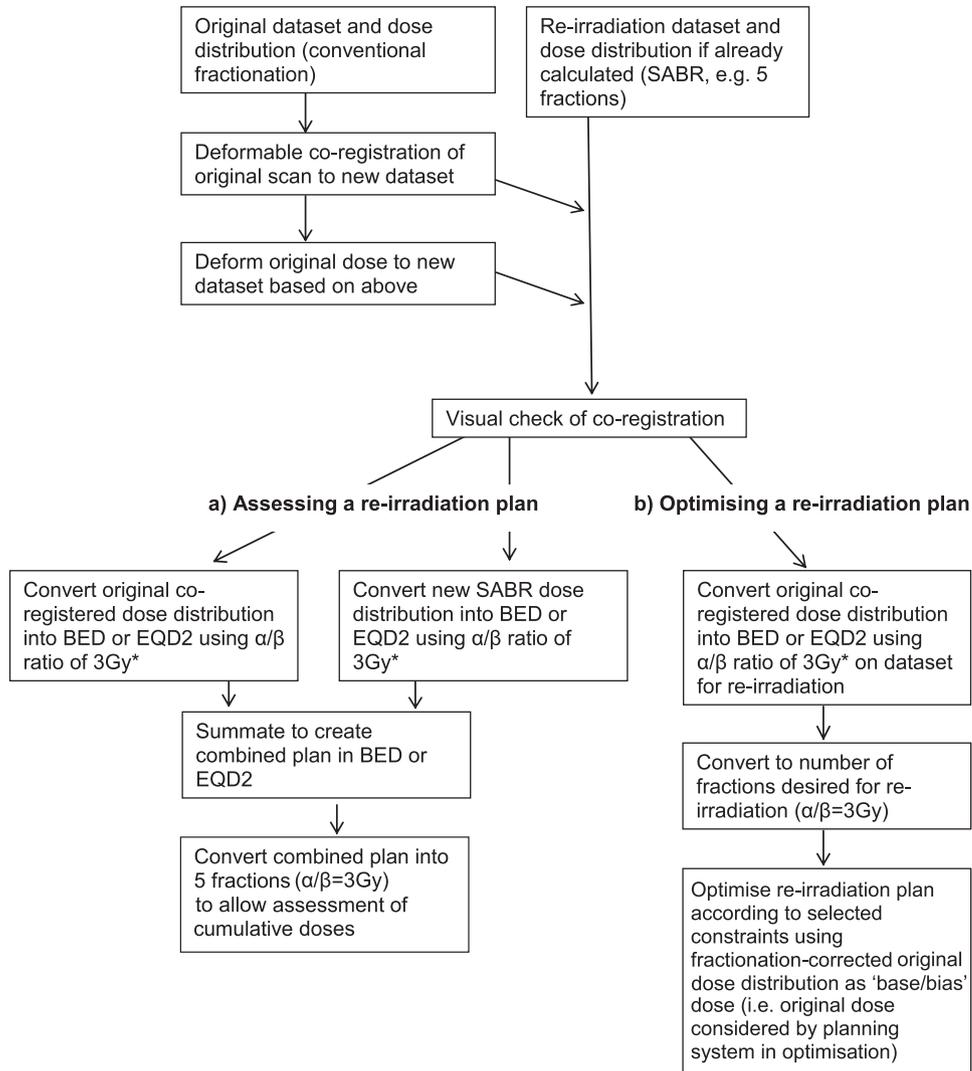
Fig. 1. Formal pathway for a) normal tissue plan summation of a former and already created 5 fraction re-irradiation plan and b) optimisation of a re-irradiation plan * A different α/β ratio (e.g. 2 Gy for spinal cord) could also be used. BED: biologically equivalent dose, EQD2: equivalent dose in 2 Gy fractions, SABR: Stereotactic Ablative Radiotherapy.

re-irradiation candidate, both in terms of tumour biology and normal tissue recovery. A lesion that recurs within a short period of initial radiotherapy could be considered radio-resistant and so the likelihood of meaningful response to re-irradiation would be low. The authors suggest a minimum disease free interval of 6 months for re-irradiation but accept this is not evidence based.

Eligibility: extent of disease, volume and location

When considering re-irradiation, the number, size and volume of lesions should be considered, together with the proximity to critical structures and degree of overlap with previous treatment.

Most evidence describes re-irradiation of a single lesion, although occasionally up to three lesions have been included [14,20]. More evidence is required to guide the number of lesions that can be safely and appropriately re-irradiated. A lower number of lesions could indicate less aggressive disease, and therefore a more suitable candidate. In practice, the authors do not re-irradiate more than three lesions but, again, accept that this is not evidence based. The total re-irradiation volume may, in fact, be more relevant for patient selection in terms of ability to meet OAR constraints.

Regarding lesion size/volume, optimal limits are unknown, with a wide range of lesion size and volume having been re-irradiated in practice. Similarly, a relationship between re-irradiated volume and toxicity has not been demonstrated. Meeting OAR constraints and delivering meaningful target doses will generally be more feasible when re-irradiating smaller lesions, though target location in relation to previous dose and OAR will also have an impact on the ability to meet constraints. Further evidence is required.

Work-up

- Occult disease should be excluded, therefore full staging (including PET where validated) should be performed
- Biopsy is appropriate where there is uncertainty regarding the nature of the lesion

Planning

Narrow treatment margins and high plan conformity are essential to limit the potential for normal tissue damage. As such:

- As with SABR in other sites, 0 mm GTV-CTV margins should generally be employed

Table 1
Remaining normal tissue doses for SABR small bowel re-irradiation based on variety of initial radiotherapy normal tissue doses and variety of cumulative constraints (based on α/β = 3 Gy).

Possible dose received by normal tissues at first irradiation	No. fractions	Dose per fraction	EQD2 (α/β = 3 Gy)	Remaining dose constraint (Gy) for 5 fraction SABR based on Abusaris et al. cumulative constraints [22] §	Remaining dose constraint (Gy) for 5 fraction SABR based on conventional first irradiation constraints used cumulatively, assuming no recovery *	Remaining dose constraint (Gy) for 5 fraction SABR based on conventional first irradiation constraints used cumulatively, assuming 50% recovery of original dose *	AAPM report constraints (Gy) for 5 fraction pelvic SABR as first irradiation, included for comparison only [35]
Small bowel							
30	15	2.00	30.00	37.8:max dose to 10 cm³	18.4 max point	24.8 max point	19.5 to <5 cm³/35 max point **
34	15	2.27	35.81	36.2:max dose to 10 cm³	15.4 max point	23.7 max point	19.5 to <5 cm³/35 max point **
34	28	1.21	28.66	38.2:max dose to 10 cm³	19.1 max point	25.1 max point	19.5 to <5 cm³/35 max point **
42	25	1.68	39.31	35.2:max dose to 10 cm³	13.4 max point	23.0 max point	19.5 to <5 cm³/35 max point **
45	25	1.80	43.20	34.0:max dose to 10 cm³	11.0 max point	22.2 max point	19.5 to <5 cm³/35 max point **
50.4	28	1.80	48.38	32.5:max dose to 10 cm³	7.1 max point	21.1 max point	19.5 to <5 cm³/35 max point **
50	25	2.00	50.00	31.9:max dose to 10 cm³	5.6 max point	20.7 max point	19.5 to <5 cm³/35 max point **
54	28	1.93	53.23	30.9:max dose to 10 cm³	2.0 max point	20.0 max point	19.5 to <5 cm³/35 max point **
70	39	1.79	67.13	26.1:max dose to 10 cm³	Nil remaining	16.6 max point	19.5 to <5 cm³/35 max point **
78	39	2.00	78.00	21.8:max dose to 10 cm³	Nil remaining	13.6 max point	19.5 to <5 cm³/35 max point **
80	39	2.05	80.82	20.5:max dose to 10 cm³	Nil remaining	12.8 max point	19.5 to <5 cm³/35 max point **

§ Abusaris et al. cumulative constraints [22] small bowel: no more than 10 cm³ of small bowel could receive this dose or higher: 110 Gy (as EQD2, α/β = 3).
* Conventional constraints: small bowel: e.g. maximum point dose 55 Gy [31], based on 28 fraction treatment.
** AAPM report constraints are those for ileum and jejunum, max: maximum.

- Techniques should be employed to ensure rapid dose fall-off beyond and escalation within the target (e.g. peripheral isodose prescription)
- Attention should be paid to the direction and volume of high and intermediate dose spill beyond the PTV, which should be minimised and directed to avoid higher dose regions from previous radiotherapy and more radiosensitive normal tissues

In addition:

- Prescription doses should be influenced by OAR doses from previous treatment
- OAR constraints should consider the original and re-irradiation plan (discussed below).

Simulation and treatment

- High quality immobilisation and IGRT are essential.

Other agents and treatments

- Until the toxicities from pelvic SABR re-irradiation are better understood, concurrent chemotherapy or newer systemic agents should be avoided, and there should be a gap of a few weeks between these agents and SABR. The use of concurrent androgen deprivation therapy is considered safe as it is standard of care in conventional radiotherapy with no increase in toxicity
- In patients who have had pelvic surgery, in addition to previous radiotherapy, re-irradiation may carry higher risks and so these patients should be approached with greater caution
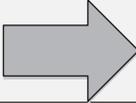
Other

- Prospective data collection regarding efficacy, toxicity and quality of life is essential to inform future treatments.
- Multidisciplinary input is critical for the safe and successful delivery of SABR in non-re-irradiation settings [30]. Similarly, multidisciplinary expertise in the further development of SABR re-irradiation is essential. This should include Radiation, Medical and Surgical Oncologists when determining which options are available to different patients. For SABR re-irradiation planning and delivery, Radiographers, Medical Physicists, Radiation Oncologists and, ideally, those with prior experience of delivering re-irradiation, should be involved. Input from Radiobiologists would also be valuable.

Organ at risk constraints and prescription doses

The optimal constraints for re-irradiation are unknown and form one of the most challenging aspects of re-irradiation. The doses that OARs are judged to be able to be receive are likely to influence prescription dose. The use of cumulative constraints, which take into account previous normal tissue doses and correct for fractionation, in a manner similar to Abusaris et al. [22], would be one radiobiologically supported approach. What the cumulative constraints should be, however, remains uncertain. The most conservative approach would be to use traditional first irradiation constraints (e.g. maximum point dose of 55 Gy in 28 fractions for small bowel [31]) and subtract the original normal tissue dose from this and so establish the dose that remains for SABR re-irradiation, corrected for fractionation. This is potentially the safest approach (accepting uncertainties in the use of the linear-quadratic equation for changing fractionations at high doses per fraction [32,33] and uncertainties in α/β ratios for late effects for different tissues) but may be prohibitive in delivering meaningful doses to the target

Table 2
Suggested pragmatic conservative approach for organ at risk constraint definition for SABR re-irradiation.

Organ at risk constraint determination				
First choice ('best case scenario')		**Second choice ('pragmatic compromise')**		
Subtract previous dose from traditional constraint, no repair permitted	**If first choice constraints not feasible** ⟹	Subtract previous dose from traditional constraint, allowing degree of repair	AND	Do not exceed AAPM report constraints for first irradiation[35], nor Abusaris et al[22] constraints

and unnecessarily conservative if there has been a degree of repair following the first irradiation.

Depending on the interval to re-irradiation, a degree of repair could therefore be permitted (e.g. if 50% repair assumed, then only 50% of the previous dose is subtracted from the cumulative constraint), thereby allowing a higher dose to be delivered. How much repair is appropriate, and after what period of time, however, also remain uncertain [34]. How the actual values for the cumulative constraints used by Abusaris et al. were determined is unclear [22]. The cumulative constraints used by Abusaris et al. are, however, generally more lenient than using traditional constraints in a cumulative manner, as shown in Table 1 (columns 5 and 6) using small bowel as an example. These also appear generally more lenient than when assuming 50% repair, based on traditional constraints (Table 1; column 7). Furthermore, the Abusaris et al. cumulative constraints are also more lenient than the constraints from The American Association of Physicists in Medicine (AAPM)-101 report for *first* SABR irradiation [35], a situation that could be considered excessively tolerant (Table 1; column 8). Further detail and discussion is provided in Supplementary Material. In brief, however, we suggest it is preferable to use traditional constraints in a cumulative manner, and so keep the combined original and re-irradiation doses within traditional tolerance limits. Where this is prohibitive to delivering a meaningful target dose, then a degree of repair could be assumed, influenced by time to re-irradiation, but we suggest that at no point should the AAPM constraints for first SABR irradiation be exceeded, nor those constraints used by Abusaris et al. Table 2 summaries this pragmatic approach. Based on this process, it seems likely that when patients have previously received conventionally fractionated pelvic doses of up to about 54 Gy, then there should be dosimetric capacity to deliver SABR re-irradiation doses of 25–30 Gy in 5 fractions while respecting at least the 'second choice' constraints and allowing 50% repair, as suggested in Table 2.

While a degree of recovery could be incorporated in determining re-irradiation constraints, it must be acknowledged that marked uncertainties remain regarding normal tissue recovery following first course irradiation and the radiobiological evidence to guide such factors, particularly in the pelvis, is severely lacking [34]. While 50% repair has been used in Table 1, this is merely an example and is not evidence based. We aim to illustrate options rather than provide definitive solutions, which require more evidence. It should also be noted that patient-related factors such as surgery, diabetes and vascular disease might also contribute to normal tissue re-irradiation tolerance, although there is insufficient evidence to know how such factors should be incorporated. The uncertainties merely highlight the importance of high quality prospective dosimetric and clinical evaluation of future patients.

Plan summation and re-irradiation planning

In practical terms, combining original and re-irradiation datasets poses challenges in the pelvis as deformation occurs between scans, including variability in rectal and bladder filling and the fact that some patients have undergone surgery. This may result in marked anatomical differences between original and re-irradiation imaging. Variations in position of individual bowel loops may pose a particular problem. The use of a bowel bag structure rather than individual loops, the same bowel and bladder preparation for both scans and deformable, as opposed to rigid, registration could help address these issues.

Furthermore, difficulties arise as high doses delivered to one part of an OAR (e.g. the inferior rectum) may be distant to the region of re-irradiation (e.g. near the superior rectum) and so it would be inappropriate to use the former whole rectum dose–volume histogram statistics to determine what dose should be received by the rectum at re-irradiation: 3-dimensional information is therefore ideally required, or at least a segmentation approach (e.g. separating the rectum into inferior, middle and superior thirds) when determining what doses remain for re-irradiation.

Radiobiology and differences in fractionation must also be considered when producing a re-irradiation plan or evaluating previously delivered re-irradiation. At present, however, commercial planning systems do not sufficiently incorporate these factors, alongside anatomical changes over time, to easily permit radiobiologically-informed plan summation. Similarly, while several planning systems allow the use of a former dose distribution to guide the optimisation of re-irradiation plan, none simultaneously permits the integration of the necessary fractionation corrections to make this a radiobiologically meaningful process. The use of a fractionation-corrected 'base dose' to guide the optimisation of a re-irradiation plan, within selected constraints, would represent an ideal scenario, where 3-dimensional information and anatomical changes are incorporated together with radiobiology. A suggested workflow for a) evaluating previously delivered re-irradiation and b) optimising re-irradiation are shown in Fig. 1 to illustrate a desirable future situation. Normal tissue repair could also be incorporated within this workflow.

The implementation of the above processes would assist in anatomically and radiobiologically appropriate assessment of delivered cumulative OAR doses. This could ultimately be correlated with toxicity to guide future radiobiologically and clinically informed cumulative OAR constraints.

Next steps

Prospective data collection is essential to optimise patient selection and delivery of pelvic SABR re-irradiation. This should include

detailed reporting of dosimetry from former and re-irradiation plans, including the degree of overlap between irradiated volumes, cumulative OAR doses and interval to re-irradiation. The creation of a pelvic re-irradiation 'minimum dataset', which specifies the necessary clinical and dosimetric information, would facilitate future analysis. A collaborative multi-centre and multidisciplinary approach, designed with consideration the issues discussed above, performed through either a registry study or clinical trial, would likely provide the optimal environment for gathering more uniform, high quality, and robust re-irradiation data. Simultaneously, improved methods for dose accumulation, which include 3-dimensional information and radiobiology, must be developed.

Conclusions

There is a lack of high quality evidence regarding pelvic SABR re-irradiation and definitive answers regarding its efficacy, tolerability and optimal delivery cannot yet be provided. There is a risk that selection bias within existing retrospective series, together with limited follow-up, results in over-estimation of efficacy and under-estimation of toxicity. That said, based on the available evidence, this treatment shows promise and wider study is warranted. The existing evidence raises several important issues, which require consideration for the optimal implementation of pelvic SABR re-irradiation. Based on this limited evidence and existing guidelines for SABR in non-re-irradiation settings, suggestions are provided. Determining optimal OAR constraints and prescription doses, together with accurate plan summation, form some of the more challenging elements of this process. High quality treatment delivery with rigorous QA, aggressive prospective data collection and consideration of previous treatment doses and intervals to re-treatment, are required to obtain better quality information.

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Conflicts of interest

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.radonc.2017.09.030.

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