Physics and Imaging in Radiation Oncology 21 (2022) 78–83

Contents lists available at ScienceDirect

Physics and Imaging in Radiation Oncology

journal homepage: www.sciencedirect.com/journal/physics-and-imaging-in-radiation-oncology

Original Research Article

A treatment planning comparison of photon stereotactic ablative radiotherapy and proton beam therapy for the re-irradiation of pelvic cancer recurrence

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ARTICLE INFO

Keywords:
SABR
Proton beam therapy
Re-irradiation
Pelvic recurrence

ABSTRACT

Background: Patients who experience a pelvic cancer recurrence in or near a region that received initial radiotherapy, typically have few options for treatment. Organs at risk (OAR) have often reached their dose constraint limits leaving minimal dose remaining for standard re-irradiation (reRT). However, photon based stereotactic ablative radiotherapy (SABR) has been utilised for reRT with promising initial results although meeting OAR constraints can be challenging. Proton beam therapy (PBT) could offer an advantage.
Materials and methods: SABR plans used for treatment for ten pelvic reRT patients were dosimetrically compared to PBT plans retrospectively planned using the same CT and contour data. PBT plans were created to match the CTV dose coverage of SABR treatment plans with V100% ≥95%. An 'as low as reasonably achievable' approach was taken to OAR tolerances with consideration of OAR dose from the initial radiation (using equivalent dose in 2 Gy fractions).
Results: Dosimetric comparison of relevant OAR statistics showed a decrease in OAR dose using PBT over SABR in all patients, with equivalent target coverage. The largest statistically significant reduction was seen for the colon D0.5 cm^3 with a median reduction from 13.1 Gy to 5.9 Gy. There were statistically significant dose reductions in the median dose to small bowel, sacral plexus and cauda equina.
Conclusion: PBT has the potential for significant dose reductions for OARs in the pelvic reRT setting compared to SABR. However, it remains unclear if the magnitude of these OAR dose reductions will translate into clinical benefit.

1. Introduction

Pelvic cancers make up a significant proportion of the 18 million plus new primary cancer diagnoses globally each year, with colorectal and prostate alone making up 9.8% and 7.3% respectively [1]. The majority of these patients will receive photon radiotherapy, as at least part of treatment for the disease. However, recurrence rates have been quoted between 5 and 20% [2,3]. When the recurrence occurs within or very near to the area previously irradiated these patients currently have limited treatment options [4].

Whilst for some patient groups surgery is favoured, the feasibility of surgery can be lower than 50% due to associated morbidities [5,6], and for others, surgery can be extensive and/or leave involved resection margins [7]. Systemic treatments such as chemotherapy are often given

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https://doi.org/10.1016/j.phro.2022.02.010
Received 24 November 2021; Received in revised form 16 February 2022; Accepted 17 February 2022
Available online 23 February 2022

only with palliative intent and for more widespread disease [8]. Re-irradiation with conventional fractionation photon radiotherapy techniques has typically been avoided due to concern over breaching OAR dose tolerances when the dose is summed over both the original and re-irradiation treatments (reRT).

For small recurrences (typically up to 5–8 cm in diameter [4]) stereotactic ablative radiotherapy (SABR) has recently been investigated as a treatment option due to the good conformality and high peak doses associated with this technique. In the UK the use of SABR for pelvic re-irradiation has been assessed through NHS England's Commissioning through Evaluation (CtE) program [9]. Initial results suggest that this technique is well tolerated, with local control ranging from 53% to 100% at 2 years [4].

As these patients have had previous radiotherapy treatment the 'dose remaining' OAR tolerances should be determined on a patient-by-patient basis. One approach is to radiobiologically subtract the previous OAR dose from the cumulative tolerance, using the equivalent dose in 2 Gy fractions (EQD2) to account for different fractionations [10,4]. However, significant uncertainties remain, including what cumulative tolerances should be, and using a traditional approach often leaves limited scope for re-irradiation [11].

Proton beam therapy (PBT) is a potential alterative that may offer improvements over photon SABR for these patients. The sharp distal dose fall off associated with PBT has been shown to reduce OAR doses compared to conventionally fractionated Intensity Modulated Radiotherapy (IMRT) for recurrent rectal cancer [12,13]. Therefore using PBT may enable more patients with recurrence to receive re-irradiation. Berman et al [12] previously used a passive scatter PBT technique to deliver conventionally fractionated re-irradiation for patients with locally recurrent rectal cancer and demonstrated that this resulted in reduced OAR doses. As far as the authors are aware, the impact of PBT on OAR doses in comparison to photons in the setting of SABR re-irradiation has not yet been evaluated.

The aim of this retrospective planning study was to compare OAR doses between SABR and PBT plans for a given prescription dose and coverage criteria.

2. Materials & methods

2.1. Patient selection

This study included the first ten patients treated for a single lesion at a centre with photon SABR for a pelvic recurrence under the CtE program [9]. Local approval was granted for this work and written informed consent was obtained from all patients. All patients included had >25 month interval between first irradiation and reRT, and a recurrence target diameter <6 cm. All ten commenced SABR reRT treatment between March 2016 and September 2017. The median interval between first radiation and commencement of reRT was 51.2 months with a range of 25–76 months. Median age at the time of reRT was 67.5 years, ranging from 56 −78.1 years. The primary disease was prostate for six patients and rectal for four patients. The doses given in the first course of radiotherapy ranged from 25 Gy to 76 Gy (median = 51.2 Gy) and between 1.6 and 5 Gy/fraction (median = 2.34 Gy/fraction). Eight of ten patients received nodal re-irradiation and 2 received treatment for bone metastases close to or within the previous treatment field.

2.2. Data acquisition and contouring

Patients were CT-simulated in the supine position with an empty bladder using 2 mm slice thickness. Contouring was performed using Monaco (v5.1, Elekta AB, Stockholm, Sweden) where the CTV was an expansion of the GTV + 3 mm for bone metastases and 0 mm for nodal disease. The PTV was a 5 mm isotropic expansion of the CTV. Depending on the location of the target the following OARs were contoured by the clinician: spinal canal, cauda equina, sacral plexus, small bowel, colon, femoral heads, vessels, bladder and rectum following the CtE protocol [9]. Parallel organs were outlined in full and serial organs were outlined 2–3 cm superior and inferior of the PTV. The CT, structures and dose from original treatment were registered to reRT CT scan to assess which OARs were involved in both cases and hence which were important for reRT.

2.3. Determination of OAR dose limits

The maximum cumulative dose tolerances used for OARs were taken from the CtE service specification and the UK SABR consensus guidelines and are shown in Table 1 [9,14]. A patient specific dose tolerance for the re-irradiation was calculated by rigidly registering the reRT CT to the original planning CT in Monaco. The registration was performed using mutual information initially as a global registration and then using a region of interest around the target. All registrations were performed by clinical scientists specialising in imaging with experience of performing these clinically.

The initial dose received was subtracted from those shown in Table 1 in equivalent dose in 2 Gy fractions (EQD2), converting the remaining dose into the number of fractions used for re-irradiation [4]. An alpha/beta ratio of 3 Gy was used for all OAR except for nerves where 2 Gy was employed. The previous OAR dose was considered as the maximum dose received by the portion of the OAR in closest proximity to the re-irradiation PTV (once registered). This was determined as the maximum dose to 0.1 cm^3 of the OAR within a 1 cm expansion of the re-irradiation PTV for vessels and nerves (relatively fixed structures), and within a 2 cm expansion of the re-irradiation PTV for bladder and bowel (more mobile structures). For larger volume constraints (e.g. 5 cm^3), with the exception of the femoral heads D10 cm^3, the same sphere approach was used, with additional 1 cm spherical expansions being added to the PTV until the required volume was encompassed within a sphere. For femoral heads, the D10 cm^3 was recorded from the previous treatment (without the use of spheres) and this dose used to determine the 'dose remaining' from the cumulative constraints.

This provides a conservative pragmatic solution, allowing for a degree of mis-registration between datasets and also a degree of organ motion in the case of more mobile organs (bowel and bladder). Both the SABR and PBT plans were planned using these remaining doses as guidance, taking an ALARA approach based on clinical judgement when these very conservative limits could not be met.

2.4. SABR treatment planning

Photon SABR plans were created to deliver 30 Gy in 5 fractions to the re-irradiation PTV (PTV_reRT), as per the CtE reRT service specification.

Table 1
Maximum OAR tolerances for 5 fraction SABR treatments as per CtE service specification and UK SABR consensus [9,14,15].

OAR	Volume	5 Fractions	
		Mandatory Constraint (Gy)	Optimal Constraint (Gy)
Bladder	0.5 cm^3	<38	
	15 cm^3	<18.3	
Cauda Equina	0.1 cm^3	<32	
	5 cm^3		<30
Colon	0.5 cm^3	<32	
Femoral Heads	10 cm^3	<30	
Rectum	0.5 cm^3	<32	
Sacral Plexus	0.1 cm^3	<32	
	0.5 cm^3		<30
Small Bowel	0.5 cm^3	<35	<30
	5 cm^3		<25
	10 cm^3	<25	
Vessels	0.5 cm^3	<53	

The PTV was created using a uniform 5 mm expansion of the re-irradiation CTV (CTV_reRT). Plans were produced in Monaco with a SABR VMAT technique using 6 MV flattening filter free with 200 degree arcs starting at gantry angle 180 degrees and covering the patients left or right side depending on PTV location. Dose was calculated with a Monte Carlo model with a 2 mm grid spacing and a 1% statistical uncertainty per calculation. Maximum doses within the PTV were ≤120% or ≤130% of prescription dose for bone and nodal targets respectively.

2.5. Proton beam treatment planning

The retrospective PBT plans were also prescribed to 30 Gy in 5 fractions prescribed to the re-irradiation CTV (CTV_reRT) with assessment under uncertainty conditions of ±5 mm shifts in all three axes to imitate the SABR CTV to PTV margins [16,17], plus an additional ±3.5% uncertainty in the proton range. The PBT plans were created within Eclipse (v13.7 Varian Medical Systems, Palo Alto) on the same planning CT data as the SABR plans. As per contemporary practice, Intensity Modulated Proton Therapy (IMPT) was used for planning. An IMPT dose distribution is created from many individual pencil beam 'spots' varying in energy and location.

The planning aim was to match target dose and coverage of the CTV_reRT in the PBT plans in both the nominal and worst case uncertainty scenario, with that achieved for the PTV in the SABR plans [17]. The doses to OARs were also only considered acceptable if they were acceptable in both the nominal and worst case scenarios. The worst case uncertainty scenario is the uncertainty condition (for example −5 mm sup) that gave the worst dose statistics for that structure. The proton prescription was kept equivalent to the SABR 30 Gy, accounting for the radiobiological equivalence (RBE) of 1.1 as currently commonly accepted for clinical PBT planning [18], for clarity Gy (RBE = 1.1) has been omitted from the rest of the paper.

An active scanning (pencil beam) technique was used and plans were created using single field optimisation (SFO) with two beams, such that each field was optimised independently, so that each beam aimed to achieve uniform coverage of the target. All plans were rescaled so that 100% of the dose covered 100% of the CTV_reRT. All PBT plans were reviewed by a consultant physicist working in PBT to ensure the plans were clinically appropriate and acceptable.

Where possible, beam directions through regions of anatomical uncertainty were avoided. This included directions clipping high density structures such as bone, long path lengths through mobile bowel, areas of significant gas, and avoiding regions prone to body contour uncertainties (particularly in larger patients). The closest angle of approach between the two beams was kept to ≥30° where possible to help reduce the risk of skin toxicities and to help counteract uncertainties in RBE so the areas of potentially increased RBE do not overlap.

The position of the PTV and CTV and PBT beam angles for all ten patients are shown in Fig. S2 in the supplementary material.

2.6. Dose comparison and statistical testing

Clinically relevant dose statistics defined in CtE, were extracted from the dose volume histogram (DVH) files of both the SABR plans, and the nominal case of the robustly planned PBT plans. For PBT plans the target doses to the CTV_reRT have been reported due to the need for the PBT plan to be created without using a PTV approach. OAR doses have been compared by subtracting the OAR dose in the PBT plan away from that received in the SABR plan. The DVH statistics for both the PBT and SABR approaches were extracted after the plans were rescaled.

A side by side plan comparison was performed with three consultant oncologists coming to a consensus view as to which plan was most acceptable. A score between 1 and 3 was given where 1 indicated that the PBT plan was clinically more desirable, 2 that there were no expected clinical differences between the SABR and PBT plans and 3 indicated that the SABR plan was clinically more desirable

Due to the high variance in patient cases, not every OAR listed was of clinical relevance in each plan. A Wilcoxon signed rank test was performed to determine if the differences between the SABR and PBT plans were significant, considered to be when $p < 0.05$. A Bonferroni correction was additionally carried out considering the 18 different DVH statistics that were compared.

2.7. Robustness comparison

The PBT plans were all planned considering robustness of the plan to changes in patient position whilst the SABR plans used the CTV to PTV margin to account for this. For a single representative patient (Patient 6 in Table S1 a dosimetric comparison of the SABR and PBT plans recalculated with ±5 mm shifts applied in x, y and z directions was determined, to test the robustness of both approaches. The PBT plans had an additional ±3.5% proton range uncertainty applied but this was not relevant for SABR. Dose statistics from the DVH's of the recalculated shifted SABR plans were extracted to find the 'worst case' dose found for each statistic. This was then compared to the worst case PBT dose for the same OARs.

3. Results

Collective scores from three oncologists in a side-by-side plan comparison are shown in Table S1 in the supplementary material. For four out of ten patients the PBT plan was preferred, for five out of ten there was no expected clinical difference between the plans and for one in ten the SABR plan was considered more desirable. For the patient (patient 9) where the SABR plan was preferred, this was due to a more anterior tumour, high BMI and hip replacement limiting the PBT beam angles.

A side-by-side comparison of the dose distributions and DVH plot for a representative patient (Patient 4) is shown in the supplementary material (Fig. S1). This illustrates the differences in dose and especially the large differences in the lower doses given using each method.

3.1. Target coverage

The CTV_reRT V100% achieved with SABR was 100% in all cases. The CTV_reRT coverage achieved by PBT for the V100% was 100 % for all patients in the nominal case (see Fig. 1). For PBT plans in the worst case scenarios three cases achieved a V100% < 95% for the CTV_reRT volume despite planning aims. These were for patients six, eight and ten with a V100% of 93.1%, 93.5% and 94.8% respectively. The maximum dose to 0.1 cm^3 was significantly ($p = 0.005$) lower in all the PBT plans compared to the SABR plans. The minimum dose to 0.1 cm^3 of the CTV_reRT was also significantly ($p = 0.047$) lower in the PBT plans compared to the SABR plans (median difference = -0.8 Gy, range 30.1 to 32.66 Gy) as a result of the different planning approaches. These were no longer significant once the Bonferroni correction was applied. The maximum dose was not peaked for the PBT plans as it was for the SABR plans, such that maximum dose to 1 cm^3 for the CTV was below 106% (median value) for PBT and 117% for SABR.

3.2. OAR doses

With PBT there was a marked decrease across all OAR doses, for both the mandatory (Fig. 2) and optional (Fig. 3) statistics, with the median consistently lying below zero. There was some variation in dose difference, which in part was due to the wide variation in presentation of the recurrence.

The largest statistically significant reduction was seen for the colon D0.5 cm^3 with a median reduction of 6.2 Gy. There were statistically significant dose reductions of at least 3 Gy (median) for small bowel D10 cm^3, D0.5 cm^3 and D5 cm^3, sacral plexus D0.1 cm^3 and cauda equine D0.1 cm^3, where the median dose reduction was 5.4 Gy, 3.2 Gy,

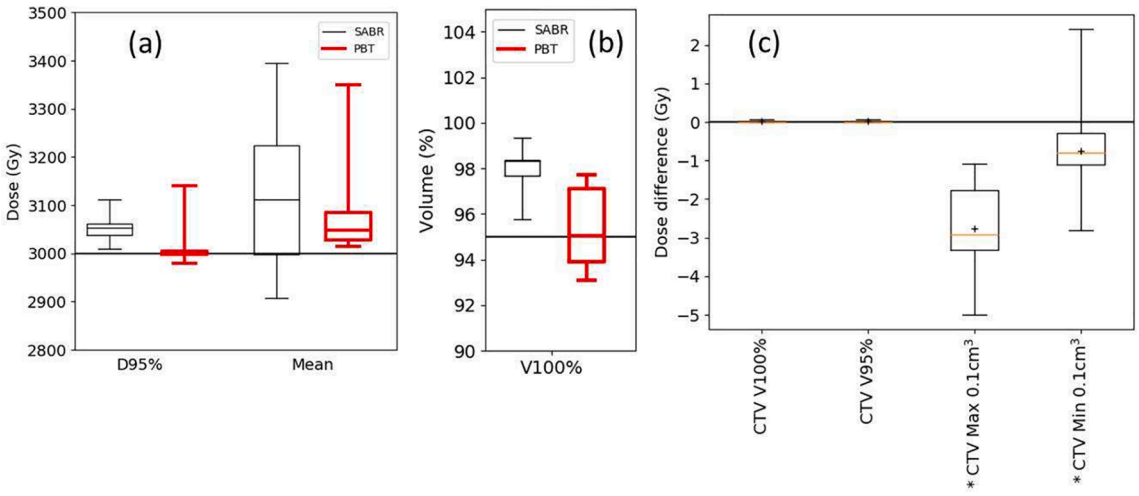

Fig. 1. (a) Box and whisker plots comparing the dose to the PTV_reRT for SABR (black) with the dose to CTV_reRT in the worst case scenario for PBT (red) for ten patients. This is shown for the dose being received by 95% of the volume (D95%) and mean dose, and (b) shows the percentage of the volume receiving 100% of the prescription. (c) Differences in CTV dose: PBT dose – SABR dose in Gy for the V100%, V95%, max dose to 0.1 cm^3 and minimum dose to 0.1 cm^3. Negative values indicate the doses were lower for PBT. A * indicates statistically significant differences between the SABR and proton doses at $p < 0.05$. The + indicates the mean value. The box shows the interquartile range, the orange line the median and the whiskers the minimum and maximum dose differences. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

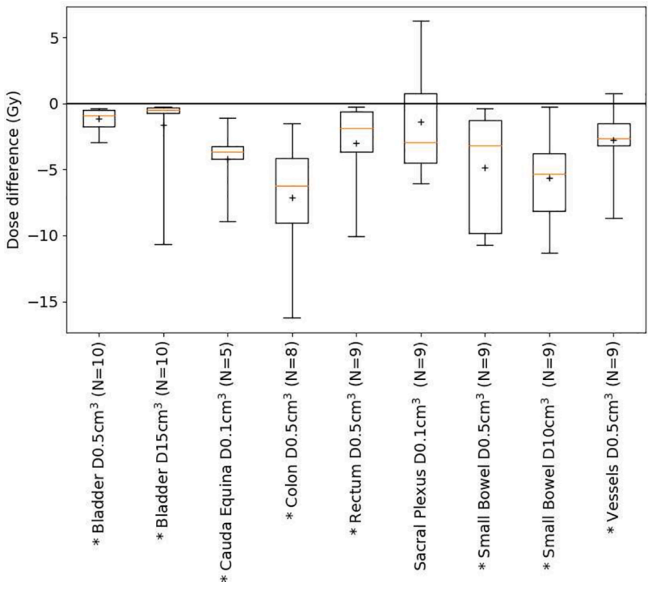

Fig. 2. The difference in achieved OAR dose: PBT dose – SABR dose in Gy for the mandatory constraints. Values below the zero line were lower for PBT. Values in brackets show the number of patients with that OAR contoured. * indicates statistically significant difference between the SABR and proton doses at $p < 0.05$. + indicates the mean value. The box shows the interquartile range, the orange line the median and the whiskers the minimum and maximum dose differences. The numbers of patients in the cohort contributing to each OAR statistic are denoted in brackets. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

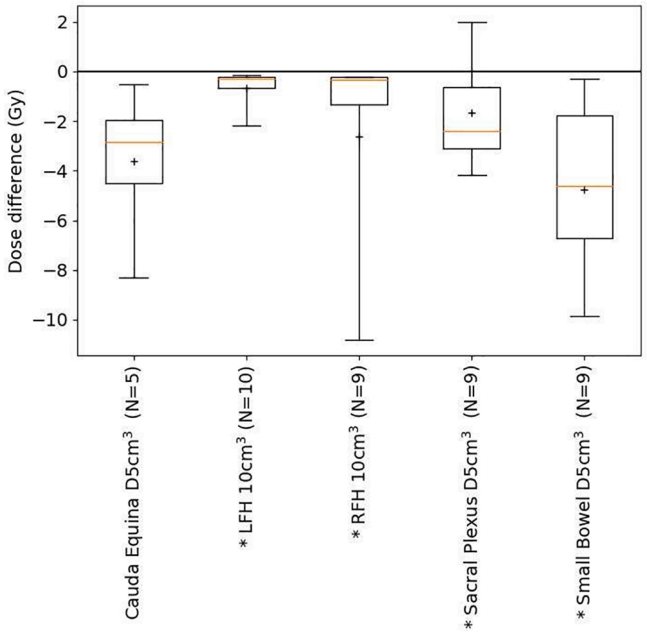

Fig. 3. The difference in achieved OAR dose: PBT dose – SABR dose in Gy for the Optional constraints. Values below the zero line were smaller for PBT. Values in brackets show the number of patients with that OAR contoured and a * indicates statistically significant difference between the SABR and proton doses at $p < 0.05$. The + indicates the mean value. The box shows the interquartile range, the orange line the median and the whiskers the minimum and maximum dose differences. LFH = left femoral head and RFH = right femoral head. The numbers of patients in the cohort contributing to each OAR statistic are denoted in brackets. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4.6 Gy, 3.0 Gy and 3.6 Gy respectively. These were no longer significant once the Bonferroni correction was applied.

There were some increases in OAR dose using PBT for individual patients. These increases were seen for 4 patients with the sacral plexus D0.1 cm^3 and D5 cm^3, and vessels D0.5 cm^3 between 6 Gy and 1 Gy higher in the PBT plan (see Table S1). For all these cases this is due to the sacral plexus and vessel being adjacent to or within the CTV, and the limited choice of beam angles for PBT treatment.

3.3. Robustness comparison

The robustness comparison for a single representative patient showed that for the CTV D95% for SABR reduced by 2.8% from the nominal case to the worst case scenario, whereas for the PBT plan the reduction was 1.4%. A comparison of the doses to the OARs for the

nominal plan and the worst case plan for SABR and PBT are shown in Fig. 4. The mandatory dose statistics are shown in Fig. 4a showing that the worst case SABR plan was always worse than for the worst case PBT plan. The same was true for the optional dose statistics shown in Fig. 4b, where the PBT doses were very small.

4. Discussion

To our knowledge this is the first study to compare SABR and PBT treatments for the treatment of recurrence in the previously irradiated pelvis. We have shown that reductions in doses to OARs could be achieved using PBT rather than SABR in the majority of cases. Although these statistically significant differences were no longer maintained after a Bonferroni correction was applied. Side by side plan review by three oncologists suggested that some of the dose differences could be clinically significant.

Other studies in the pelvis have reported dose reductions by PBT against photon VMAT and IMRT for several OARs which were most pronounced for lower dose statistics and mean doses, with less improvement seen for high dose statistics [13,19,20]. These studies demonstrated a mean dose reduction to the small bowel from 34 Gy for VMAT to 18.6 Gy for IMPT and the low dose bath (V10Gy) to bowel reduce by about 50% from VMAT to IMPT.

A similar result was observed in a study by Berman et al. [12] with large reductions in cauda equina, femur and bladder doses. However, a statistically significant reduction was only observed for bowel V20, V10, D200 cm^3 and D150 cm^3 with median reduction of 13.7 and 15.4 Gy for the D200 cm^3 and D150 cm^3 respectively. These are larger than was observed in this study, possibly the result of the differing treatment sites and techniques but the conclusions remain the same.

One potential limitation of this study is that the patients included had differing primary disease types and therefore received a variety of primary courses of radiotherapy. In addition, both nodal and bony re-irradiation were considered. Additionally 4 out of the 10 patients had undergone surgery between the two courses of radiotherapy, adding to the heterogeneity and complicating the image registration process. However, these reflect the cases encountered in routine practice and represent one of the challenges of clinical re-irradiation, where individualised approaches are often required.

The wide variation in recurrence presentation proved a challenge for creating a PBT planning approach. CTV_reRT targets ranged in volume (0.6 cm^3 to 48 cm^3), depth from patient surface, and the anatomy and nearby OARs. This required different planning approaches for each patient. The general approach of a (near to) posterior beam and a lateral oblique beam caused some of the dose statistics to be higher in PBT cases than SABR cases. Patient 2 was one of four patients that had higher doses to the sacral plexus with PBT than with SABR. In this case the CTV_reRT was immediately adjacent to the vessels, with the sacral plexus within the beam and the small bowel distal. This may have been avoided by moving the posterior beam more obliquely but to keep a reasonable angle between the two beams would have meant moving the lateral field closer to anatomy that is susceptible to set-up issues.

For the PBT plans the dose was not peaked as in the SABR plans. SABR plans need to peak the dose to achieve conformality [21,22] but this is not necessary for PBT plans. Therefore the prescription was matched rather than the dose peak.

The estimation of the dose from the previous treatment is complex and has large uncertainties. The approach taken here is a pragmatic approach and is one that is used clinically to determine the pervious doses for patients.

It is worth noting that whilst uncertainty conditions for the robust comparison and PBT planning utilised 5 mm axes shifts to imitate the 5 mm CTV-PTV expansion in SABR, the on treatment imaging protocol at the treating SABR centre matches to <2 mm. Here the imaging protocol consisted of: imaging the patient, aiming to match to 0 mm, accepting it within 2 mm, repeating the image, treating and acquiring a post

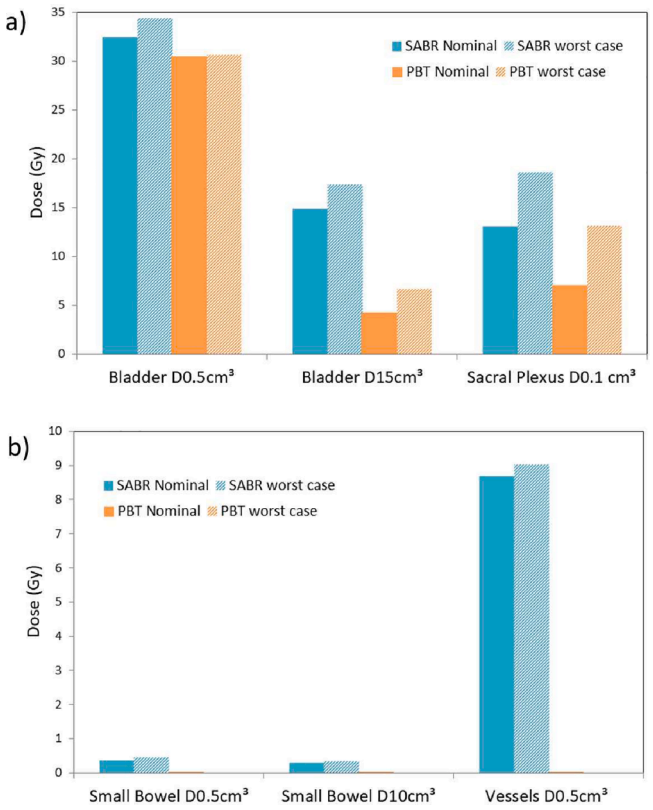

Fig. 4. Comparison of the nominal SABR and PBT dose statistics to the worst case scenario dose statistics. The mandatory dose statistics are shown for this case (a) along with the optional dose statistics (b).

treatment image. As such what has been presented here could be considered a conservative approach. However, a 5 mm margin is in line with other studies [13,19,20].

Further work investigating if specific patient characteristics can be used as a predictor for where PBT may provide most benefit could also be conducted. Including other OARs such as the bone marrow may also be of interest as Moningi et al. [23] found that PBT resulted in significantly less dose to the pelvic bone marrow, potentially decreasing haematological toxicity. In addition as this is a retrospective planning study, prospective studies with follow-up would be required to establish whether the dosimetric advantages observed with PBT translate into a clinically relevant reduction in toxicity.

The safety and efficacy of SABR up to four years [24] has been shown to be encouraging, so it is not clear that there would be significant clinical benefit to using PBT. Clinical trials are therefore required to evaluate the actual clinical benefit of PBT in the re-irradiation setting.

In conclusion, the results of this study indicate that PBT for the re-irradiation of pelvic recurrences can achieve statistically significant dose reductions across clinically relevant OAR statistics. Although these statistically significant differences were no longer maintained after a Bonferroni correction was applied. A side-by-side review showed that in four out of ten cases the PBT plan was deemed clinically more desirable.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Murray reports grants from Medical Research Council Confidence in Concept and grants from Yorkshire Cancer Research, during the conduct of the study. The rest of the authors have nothing to disclose.

Acknowledgements

RC and RS are supported by a Cancer Research UK Centres Network Accelerator Award Grant (A21993) to the ART-NET consortium. EG was supported by NIHR Manchester Biomedical Research Centre (BRC-1215-20007). LM is funded by Yorkshire Cancer Research (award number L389LM). This work was also supported by the Medical Research Council (Grant number MC_PC_16050). The authors would also like to acknowledge Cancer Research UK funding for the Leeds Radiotherapy Research Centre of Excellence (RadNet; C19942/A28832).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.phro.2022.02.010.

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