ORIGINAL ARTICLE

Pencil-beam scanning proton therapy for anal cancer: a dosimetric comparison with intensity-modulated radiotherapy

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ABSTRACT

Background. Concurrent chemoradiotherapy cures most patients with anal squamous cell carcinoma at the cost of significant treatment-related toxicities. Intensity-modulated radiotherapy (IMRT) reduces side effects compared to older techniques, but whether proton beam therapy (PBT) offers additional advantages is unclear.

Material and methods. Eight patients treated with PBT for anal cancer were chosen for this study. We conducted detailed plan comparisons between pencil-beam scanning PBT via two posterior oblique fields and seven-field IMRT. Cumulative dose-volume histograms were analyzed by Wilcoxon signed-rank test, and plan delivery robustness was assessed via verification computed tomography (CT) scans obtained during treatment.

Results. Compared to IMRT, PBT reduced low dose radiation (< 30 Gy) to the small bowel, total pelvic bone marrow, external genitalia, femoral heads, and bladder (all p < 0.05) without compromising target coverage. For PBT versus IMRT, mean small bowel volume receiving ≥ 15 Gy (V 15) was 81 versus 151 cm³, mean external genitalia V 15 was 14 versus 40%, and mean total pelvic bone marrow V 15 was 66 versus 83% (all p = 0.008). The lumbosacral bone marrow dose was higher with PBT due to beam geometry. PBT was delivered with ≤ 1.3% interfraction deviation in the dose received by 98% of the clinical target volumes.

Conclusion. Pencil-beam scanning PBT is clinically feasible and can be robustly delivered for anal cancer patients. Compared with IMRT, PBT reduces low dose radiation to important organs at risk in this population. While the clinical benefit of these differences remains to be shown, existing data suggest that limiting low dose to the small bowel and pelvic bone marrow may reduce treatment toxicity.

Concurrent chemoradiotherapy is standard treatment for anal squamous cell carcinoma [1]. This regimen cures most patients at the cost of significant gastrointestinal, dermatologic, and hematologic toxicities. Minimizing side effects is an important goal – not only to reduce patient morbidity but also because breaks during therapy appear to compromise overall treatment effectiveness [2]. Previous dosimetric studies in anal cancer suggested superior sparing of normal tissues with intensity-modulated radiotherapy (IMRT) compared to conventional conformal photon/electron techniques [3,4]. These benefits translated to reduced side effects in a phase II trial, establishing IMRT as the standard radiotherapy modality for anal cancer [5]. Acute morbidity was still common, however, with high rates of adverse events reported for patients on the IMRT arm (77% grade ≥ 2 gastrointestinal, 73% grade ≥ 2 hematologic, and 23% grade ≥ 3 dermatologic) [5].

Proton beam therapy (PBT) is a particle-based treatment with theoretical advantages over IMRT. While photons enter, traverse, and exit a patient – delivering radiation along their entire path – protons can stop within the body, depositing almost no radiation past the tumor target. To our knowledge, no quantitative data have been reported on whether PBT might benefit anal cancer patients. Therefore, the purpose of this study was to dosimetrically compare PBT with IMRT and to assess whether PBT can be robustly delivered for anal cancer treatment.
Material and methods

Patient population

From 2013 to 2014, eight patients with anal squamous cell carcinoma were enrolled onto a proton registry study and treated with PBT and concurrent chemotherapy (5-fluorouracil and mitomycin C) with definitive intent. Table I highlights disease and treatment characteristics of the cohort. Tumor T category ranged from T1 to T4. Half of patients had positive lymph nodes, most frequently in the inguinal region. The most common prescription was 45 Gy to the uninvolved pelvic and inguinal lymph nodes and 54 Gy to the primary tumor and any positive nodes [6,7].

A pure dose-painted technique – with each target volume receiving different daily fraction sizes over the same total number of fractions – was used for two patients, while sequential conedowns were used for five patients, and a combination of dose-painting followed by a conedown for one patient.

Target contouring

For the current study, we generated new PBT and IMRT plans for each patient using consistent planning techniques. The original clinical target volumes (CTVs) and planning target volumes (PTVs) – drawn at the time of treatment by one of three gastrointestinal radiation oncologists (J.M.M., E.B.J., J.P.P) – were maintained. These volumes encompassed the primary tumor, pelvic nodes, and inguinal nodes in a fashion similar to the Radiation Therapy Oncology Group consensus atlas [8]. CTVs were typically expanded by 5 mm to generate the corresponding PTV, with further modification for proton planning as discussed below. To ensure uniform assessment of the organs at risk, a single radiation oncologist (E.O.) retrospectively delineated these structures in a systematic manner for all patients; each PBT and IMRT plan was optimized using these uniform structure sets. The small bowel was contoured in tight loops on all 3-mm slices of the computed tomography (CT) simulation scan (Philips Gemini TF Big Bore). The bladder was contoured from the dome to the neck. The femoral heads were contoured from the most superior aspect of the head to the most inferior aspect of the lesser trochanter. The total pelvic bone marrow – composed of iliac, lower pelvic, and lumbarosacral subdivisions – was outlined as described by Mell and colleagues [9]. The external genitalia began at the inferior labia or scrotum and continued superiorly to the inferior-most aspect of the symphysis pubis. Laterally, the contour extended to the edge of the labia or scrotum in the inferior portion of the structure and to the lateral edge of the mons pubis in the superior portion of the structure. Anteriorly, the contour was bordered by the front of the labia or scrotum in the inferior portion of the structure and the front of the mons pubis in the superior portion of the structure. The cumulative CTV, PTV, and organ at risk volumes for each patient are listed in Supplementary Table I (to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.1002570).

IMRT and PBT treatment planning

Radiotherapy plans were generated in a consistent manner by a single planner (M.L.K.) using current institutional standard techniques. For seven-field

| Pt No. | T | N | Involved node(s) | Primary (Gy) | Pelvic nodes (Gy) | Inguinal nodes (Gy) | Fractionation (Gy) |
|--------|---|---|------------------|--------------|------------------|--------------------|-------------------|
| 1      | T2 | N2 | R inguinal       | 54           | 45               | R – 54             | Dose painted:     |
|        |    |    |                  |              |                  | L – 45             | 1.8/2.16 x 25 fx  |
| 2      | T4 | N3 | Presacral L inguinal | 54           | 45               | R – 45             | Sequential conedown: |
|        |    |    |                  |              |                  | L – 54             | 1.8 x 25 fx; 1.8 x 5 fx |
| 3      | T1*| N0 | N/A              | 50           | 36 high 45 low   | 36 both            | Dose painted:     |
|        |    |    |                  |              |                  |                    | 1.44/1.8/2.0 x 25 fx |
| 4      | T2 | N0 | N/A              | 54           | 39.5 high 45 low | 39.5 both          | Dose painted then sequential conedown: |
|        |    |    |                  |              |                  |                    | 1.58/1.8 x 25 fx; 1.8 x 5 fx |
| 5      | T1b| N0 | N/A              | 54           | 36 high 45 low   | 45 both            | Sequential conedowns: |
|        |    |    |                  |              |                  |                    | 1.8 x 20 fx; 1.8 x 5 fx; 1.8 x 5 fx |
| 6      | T2 | N0 | N/A              | 54           | 36 high 45 low   | 45 both            | Sequential conedowns: |
|        |    |    |                  |              |                  |                    | 1.8 x 20 fx; 1.8 x 5 fx; 1.8 x 5 fx |
| 7      | T2 | N1 | Perirectal       | 54           | 45               | 45 both            | Sequential conedown: |
|        |    |    |                  |              |                  |                    | 1.8 x 25 fx; 1.8 x 5 fx |
| 8      | T3v | N3 | Bilateral inguinal | 54           | 45               | 45 both            | Sequential conedown: |
|        |    |    |                  |              |                  |                    | 1.8 x 25 fx; 1.8 x 5 fx |

*p cauterization/fulguration; b/p excision with positive margin; c/p partial debulking. Fx, fractions; Gy, gray; L, left; N, nodal category; N/A, not applicable; No., number; Pt, patient; R, right; T, tumor T category.
sliding-window IMRT plans, gantry angles were approximately evenly spaced and adjusted based on patient anatomy, with a range of 30–70° between each beam. The collimator setting for all beams was 0°, and the average field size was 22.1 ± 0.8 cm × 20.6 ± 1.5 cm. The plans used mixed energies of 6 and 15 MV, which were chosen per gantry angle based on optimal target coverage and dose uniformity (see Supplementary Table II, to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.1002570).

Beam angles between ±50° of patient anterior and ±50° of patient posterior were most frequently assigned 6 MV energy, while all lateral and lateral oblique beams outside of these ranges used 15 MV beams. The average modulation factor for photon beams (total monitor units divided by dose per fraction) was 7.7 ± 0.8. The dose rate was 400 monitor units per minute for all beams.

Pencil-beam scanning PBT plans consisted of left and right posterior oblique fields to cover volumes encompassing the primary tumor, pelvic nodes, and inguinal nodes. Any separate sequential conedown to the primary tumor alone was achieved using opposed lateral beams in an attempt to spare skin. A distal margin to account for proton range uncertainty was calculated as 3.5% of the water equivalent range to the most distal aspect of the CTVs. An additional 1 mm was applied in the direction of proton delivery for beam uncertainty. No modifications were made to the PTVs in any other direction. Plans were optimized using single-field uniform dose technique, allowing each field to uniformly cover the target in order to ensure plan robustness. The Eclipse planning system Version 10 was used, with anisotropic analytical algorithm and proton convolution superposition algorithm for IMRT and PBT dose calculation, respectively. All plans were inversely optimized to achieve the clinical objectives found in Supplementary Table III (to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.1002570) for the targets and organs at risk.

Clinical treatment delivery and robustness assessment

Patients were positioned supine with arms crossed at the chest and immobilized with a knee and foot lock. PBT was delivered on a universal gantry via pencil-beam scanning. Daily image-guidance consisted of kV-kV films matched to the bony pelvis. Periodic verification CT scans were performed during the course of treatment for quality assurance. The frequency of scans varied, although they were generally obtained every 1–2 weeks. The total number was apt to be less for patients with minimal interfraction variability on the first few scans. These verification images were matched via bony anatomy to the original simulation CTVs based on the daily alignment images approved by the treating physician. Target and normal tissue contours were then overlaid on the verification CT, reviewed by the physician, and the dose was forward re-calculated. To assess robustness of clinical PBT delivery, these verification scans were reviewed for all patients. The dose received by 98% of each CTV volume (CTV D98%) was compared between verification scans and original plans.

Dose-volume histogram comparison and statistical analysis

Dose-volume histogram (DVH) data for the targets and normal tissues were exported at 0.05 Gy resolution from Eclipse and analyzed using the RadOnc package for R statistical software [10]. Cumulative DVHs were generated from the IMRT and PBT plans for all eight patients. Groupwise differences between the curves for the entire dose range at 0.05 Gy intervals were computed by the Wilcoxon signed-rank test. P < 0.05 was considered statistically significant, and p-values smaller than 0.001 were truncated and reported as <0.001. For the analysis, V X−Y denoted that Y% of a structure received at least X Gy, and V X = Y denoted that Y% of a structure received between X and Y Gy.

Results

Representative dose color wash images comparing IMRT and PBT plans are shown with axial slices through the low, mid, and high pelvis (Figure 1) for a patient with T2N2 anal cancer prescribed 45 Gy to the pelvic nodes and left inguinal nodes and 54 Gy to a right inguinal node and the primary tumor in a dose-painted technique.

Coverage of the CTVs and PTVs did not significantly vary by modality, but examination of the organs at risk revealed differences between IMRT and PBT (see Supplementary Tables IV and V, to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.1002570).

The volume of irradiated small bowel was reduced with PBT for all doses up to 35 Gy (minimum p = 0.008) and was not significantly different at higher doses (Figure 2A). The small bowel V15, V20, and V25 with PBT versus IMRT were 81 versus 151 cm³ (p = 0.008), 75 versus 134 cm³ (p = 0.008), and 69 versus 105 cm³ (p = 0.002), respectively. PBT also reduced the irradiated volume of external genitalia for all doses up to 29 Gy (minimum p = 0.008) without significant differences at higher doses (Figure 2B). External genitalia V20 for PBT versus IMRT was 14 versus 40% (p = 0.008). Mean
external genitalia dose was 7.4 Gy with PBT and 19.4 Gy with IMRT ($p = 0.008$).

PBT reduced the irradiated volume of the cumulative femoral heads for all doses up to 34 Gy (minimum $p < 0.001$) and was not significantly different at higher doses (Figure 2C). Mean femoral head dose was 16.7 Gy with PBT and 25.4 Gy with IMRT ($p = 0.008$). PBT also spared the bladder volume receiving all doses up to 33 Gy (minimum $p = 0.008$) without a significant difference at higher doses (Figure 2D). Mean bladder dose was 27.6 Gy with PBT and 34.3 Gy with IMRT ($p = 0.04$).

For the total pelvic marrow, PBT reduced the irradiated volume for all doses up to 30 Gy (minimum $p = 0.008$) without significant differences at higher doses (see Figure 3A). The total pelvic marrow $V_{37}, V_{40}, V_{43}$, and $V_{20}$ for PBT versus IMRT were 77 versus 94%, 72 versus 89%, 66 versus 83%, and 54 versus 75%, respectively (all $p = 0.008$). Overall mean total pelvic marrow dose was 22.8 Gy with PBT and 27.7 Gy with IMRT ($p = 0.008$). For the iliac and lower pelvic subdivisions, PBT reduced the irradiated volumes receiving all doses up to 34 and 33 Gy, respectively (minimum $p = 0.008$ for both) without significant differences at higher doses (Figure 3B,C). In contrast, for the lumbosacral subdivision, no differences were seen between PBT and IMRT for doses up to 20 Gy (Figure 3D). However, from 20 to 45 Gy, PBT yielded increased irradiated volumes (minimum $p = 0.008$). The lumbosacral marrow $V_{20}$ was 89% with PBT and 86% with IMRT ($p = 0.04$), and the overall mean was 35 Gy with PBT and 32.7 Gy with IMRT ($p = 0.008$).

Table II shows the robustness analysis from verification CTs. Patients underwent up to five scans (mean = 3). For the entire cohort over all scans, the mean absolute CTV D98% deviation from the original plan was 0.24 ± 0.28%. For individual patients, the mean absolute CTV D98% deviation ranged from 0.1 ± 0.08% to 0.43 ± 0.61%. The largest single interfraction difference was -1.3%. The individual measurements were negative – indicating a decrease in CTV coverage – in 18 of 38 instances (47%), positive in 11 (29%), and unchanged in nine (24%). The largest difference in bladder volume between simulation and any verification scan was 456 cm$^3$; on that day, the CTV D98% deviation for the 36 Gy volume was $-0.2%$. 

![Figure 1. Dose color wash images comparing IMRT and PBT for a patient with T2N2 anal cancer prescribed 45 Gy to the pelvic nodes and left inguinal nodes and 54 Gy to a right inguinal node and the primary tumor. Representative axial slices are shown for the low pelvis (A: IMRT, B: PBT), mid pelvis (C: IMRT, D: PBT), and high pelvis (E: IMRT, F: PBT).](image-url)
Proton beam therapy for anal cancer

Discussion

This study demonstrates that pencil-beam scanning PBT can be successfully delivered in a robust fashion for patients with anal cancer. In this population, PBT reduces low dose radiation exposure (≤ 30 Gy) to nearly all organs at risk compared with IMRT, while the higher dose regions are equivalent. Similar conclusions have been drawn in studies of PBT for rectal cancer [11,12]. This normal tissue sparing highlights a fundamental difference between photon- and proton-based planning. With IMRT, attempts to limit radiation to any one organ may deposit dose elsewhere in the pelvis. However, because protons have virtually no exit dose, careful selection of beam angles allows sparing of many normal tissues simultaneously. Are these low dose reductions clinically meaningful? What benefits might be expected from PBT for these patients?

Multiple retrospective investigations suggest that limiting low dose radiation to the pelvic bone marrow may be beneficial in anal cancer. The total pelvic bone marrow V_{5–20} and the lumbosacral subdivision V_{5–20} appear to be independently correlated with both decreased blood count nadirs [13] and grade ≥ 3 hematologic toxicity [14,15]. In this dose range, the total pelvic marrow is better spared with PBT compared to IMRT. No differences were seen between the two modalities for the lumbosacral subdivision up to 20 Gy. Likely due to our posterior oblique beam arrangement, the lumbosacral marrow V_{20–45} was higher with PBT. However, the absolute difference at 20 Gy was small (3%), and most studies have not found a dose-volume correlation with hematologic toxicities for doses over 20 Gy [13–15].

Low dose radiation to the small bowel also appears to be clinically relevant. Much of the literature on
Figure 3. Cumulative dose-volume histograms for the total pelvic bone marrow (A) and its iliac (B), lower pelvic (C), and lumbosacral (D) subdivisions. Groupwise medians are plotted as bold central lines for IMRT (blue) and PBT (red), with surrounding shading representing the median absolute deviation. The upper panels show corresponding p-values on an inverse logarithmic scale with a yellow region highlighting \( p < 0.05 \).

Table II. Verification scan deviations in CTV D98% compared to initial plan.

| Pt No. | Scan 1 (Gy: %) | Scan 2 (Gy: %) | Scan 3 (Gy: %) | Scan 4 (Gy: %) | Scan 5 (Gy: %) | Mean absolute deviation ± SD |
|--------|----------------|----------------|----------------|----------------|----------------|-----------------------------|
| 1      | 45: 0.0        | 45: +0.5       | 54: +0.2       | 54: +0.2       | N/A            | 45 Gy: 0.25 ± 0.35%         |
| 2      | 45: 0.0        | 45: −1.0       | 45: +0.6       | 45: −0.2       | 54: +0.2       | 54 Gy: 0.4 ± 0.4%           |
| 3      | 36: +0.1       | 36: −0.2       | 36: +0.1       | 36: 0.0        | N/A            | 36 Gy: 0.1 ± 0.08%          |
|        | 45: +0.1       | 45: −0.4       | 45: −0.3       | 45: +0.1       | N/A            | 45 Gy: 0.23 ± 0.15%         |
|        | 50: 0.0        | 50: −1.3       | 50: −0.4       | 50: 0.0        | N/A            | 50 Gy: 0.43 ± 0.61%         |
| 4      | 39.5: +0.4     | 39.5: 0.0      | 39.5: −0.1     | 39.5: −0.2     | N/A            | 39.5 Gy: 0.18 ± 0.17%       |
|        | 45: +0.2       | 45: −0.1       | 45: 0.0        | 45: −0.1       | N/A            | 45 Gy: 0.1 ± 0.08%          |
| 5      | 36: −0.1       | N/A            | N/A            | N/A            | N/A            | 36 Gy: 0.1, N/A             |
| 6      | 36: −0.4       | 45: −0.4       | N/A            | N/A            | N/A            | 36 Gy: 0.4, N/A             |
| 7      | 45: 0.0        | 45: −0.1       | 45: 0.0        | 45: −0.4       | N/A            | 45 Gy: 0.13 ± 0.19%         |
| 8      | 45: −0.4       | 45: −0.4       | N/A            | N/A            | N/A            | 45 Gy: 0.4 ± 0%             |
|        |                |                |                |                |                | Total: 0.24 ± 0.28%         |

CTV D98%, dose received by 98% of the CTV; Gy, gray; No., number; N/A, not applicable; SD, standard deviation; X Gy indicates the CTV volume prescribed X Gy.
this question comprises retrospective studies in rectal cancer patients receiving chemoradiotherapy with three-dimensional (3D) conformal techniques. In total, these investigations suggest acute Grade ≥ 2 diarrhea is associated with the absolute volume of small bowel exposed to doses from 5 to 40 Gy [16–20]. A dose-volume relationship is apparent at each dose in this range, and the most predictive region seems to be V_{15-25} [19,20]. In our study, PBT was superior to IMRT in sparing small bowel for all doses up to 35 Gy. Absolute reductions in irradiated bowel of 70 cm³, 59 cm³, and 36 cm³ were seen with PBT at 15, 20 and 25 Gy, respectively.

Radiation to the genitalia is a significant issue for anal cancer patients, as highlighted by the recent prospective toxicity and quality of life study. In a cohort treated with IMRT, patient-reported skin soreness rose sharply by the end of therapy, and high rates of acute radiation dermatitis were documented at the genital skin (57% grade 2, 26% grade 3, 2% grade 4) [21]. In the long term, survivors frequently report sexual dysfunction [22,23]. Despite these data, dose-volume correlations for external genitalia toxicity are lacking. This is perhaps in part because no general consensus has been reached on how to define the volume at risk [24]. Our genitalia planning objectives (see Supplementary Table III to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.1002570) are similar to those used in the prospective IMRT trial [5] and are based on clinical experience. In this study, PBT significantly decreased the irradiated volume of external genitalia for doses up to 29 Gy, and the mean dose was reduced by nearly two thirds. These differences are visually apparent in Panels A and B of Figure 1 for a representative patient. While the exact impact of this dose reduction and the role that the external genitalia play in long-term sexual function are unclear, sparing of this region appears to be a promising potential benefit of PBT.

There are no good data correlating dose-volume parameters to clinically meaningful endpoints for the femoral heads [25]. Emami and colleagues suggested limiting the entire femoral head to < 52 Gy to avoid necrosis or fracture, a recommendation acknowledged as imprecise and based partially on clinical experience [26]. Other authorities have proposed keeping the V_{50} < 5% or V_{52} < 10% [27,28]. Femoral head complications appear rare in the modern era, although a review of 207 patients receiving pelvic radiotherapy via older techniques yielded a 4.8% fracture rate – none with doses under 42 Gy [29]. In this study, PBT and IMRT were not significantly different above 34 Gy. In the absence of dose-volume data, the implications of reducing low dose to the femoral heads are unclear. However, in certain

clinical scenarios (e.g. sickle cell disease, long-term corticosteroid use, or osteoporosis) limiting dose to this region may be desirable.

Perhaps because of significant variation in filling and position during treatment, most studies of radiation effects on the bladder have failed to establish a dose-volume correlation with toxicity [25,30,31]. A minority of studies with a positive finding tend to suggest that high doses to small volumes are most relevant [31]. Therefore, the current literature does not suggest that the low dose bladder sparing seen with PBT in this study would translate to a clinically meaningful benefit.

The robustness analysis revealed that all patients experienced interfraction deviations in CTV D98% compared to the original plans, with the majority of these being a decrease in coverage. However, these deviations were small in magnitude and not clinically meaningful (see Table II). Although interfraction anatomic changes (e.g. marked differences in bladder filling) have the potential to alter PBT coverage of pelvic targets [32], the plans in this study were robustly delivered. The posterior oblique PBT field design takes advantage of the fact that the radiation targets for anal cancer are generally posterior and lateral to the bladder. When it fills, the bladder tends to push anteriorly and superiorly in the pelvis. Therefore, although some patients had large variations in interfraction bladder volume, there was no significant alteration in target coverage.

We acknowledge several limitations to this study. First, the total number of patients included was relatively small. However, the cohort represented patients who were actually treated with PBT and captured a wide extent of disease (T1–T4 primary tumors, half node-positive and half node-negative). The major findings were also reproduced individually for every patient in addition to the group. Second, small bowel contrast was not used during simulation CTs, making delineation of the bowel more challenging. This was a practical limitation secondary to planning concerns – namely that small bowel contrast would increase uncertainty in the simulation CT Hounsfield units and affect beam calculations for both photons and protons. Third, PBT and seven-field IMRT were analyzed in this study; how PBT would compare to other techniques, such as volumetric modulated arc therapy (which may decrease treatment time and monitor units over IMRT [33]) or a brachytherapy boost [34], is a question left for future investigations. Finally, patients were treated supine due to limitations on shallow targets with pencil-beam scanning and to reduce set-up variation during proton treatment. It is therefore unclear whether prone positioning with a belly board and bolus would change
our findings, although this would likely only impact the small bowel analysis.

In light of these data, we continue to accrue anal cancer patients onto our proton registry. Clinical toxicity will be reported in the future as patient numbers and follow-up increase, and we are beginning to incorporate quality of life questionnaires to assess functioning over the long term. These initial results should encourage clinicians to consider enrolling anal cancer patients into an ongoing prospective PBT pilot study (ClinicalTrials.gov Identifier NCT01858025).

In conclusion, pencil-beam scanning PBT is clinically feasible and can be robustly delivered for anal cancer patients. Compared with IMRT, PBT reduces low dose radiation (≤ 30 Gy) to most organs at risk in this population. While the clinical benefit of these differences remains to be shown, existing data suggest that limiting low dose to the small bowel and pelvic bone marrow may reduce treatment toxicity.

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Supplementary material available online

Supplementary Tables I-V to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.1002570.