Physics and Imaging in Radiation Oncology 23 (2022) 127–133

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

Lymphocyte-sparing pelvic radiotherapy for prostate cancer: An in-silico study

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ARTICLE INFO

Keywords:
Bone marrow
Hematologic toxicity
Intensity Modulated Radiotherapy
Prostate cancer

ABSTRACT

Background and Purpose: Evidence regarding radiation-induced lymphopenia and its negative impact on oncological outcome is incrementing. Therefore, the aim of this study is to evaluate the feasibility of lymphocyte-rich organs at risk (LOAR) sparing in pelvic irradiation for localized prostate cancer and to estimate its impact on the effective dose to circulating immune cells (EDIC).

Materials and Methods: Twenty patients with pelvic nodal and prostate or prostate bed irradiation were included. The following bone marrow (BM) structures were delineated as LOARs using semi-automatic segmentation: lumbosacral spine (Ls-BM), ilium (Il-BM), lower pelvis (Lp-BM), and the combined whole-pelvis (Wp-BM). Twenty new lymphocyte sparing treatment plans (LS plans) were calculated, optimizing doses to LOARs while maintaining strict coverage of the targets and respecting standard OARs dose constraints. Finally, we elaborated an EDIC calculation model for pelvic irradiation.

Results: LS plans showed a statistically significant dose decrease for LOAR compared to standard of care plans without compromising target coverage nor classic OAR dose constraints: in prostate plans, the V40Gy for Ls-BM, Il-BM, and Lp-BM was decreased by 23 %, 36 %, 52 % respectively. For prostate bed plans, the V40Gy for Ls-BM, Il-BM, and Lp-BM was decreased by 25 %, 59 %, 56 %, respectively. For Wp-BM, the V10Gy, V20Gy, and Dmean have been decreased by 3 %, 14 %, 15 %, and by 5 %, 15 %, 17 %, respectively for prostate and prostate bed plans. A statistically significant decrease in EDIC was seen for LS plans in both groups.

Conclusions: We successfully demonstrated the feasability of lympocyte-sparing treatment planning in pelvic irradiation, also proposing a model for EDIC calculation.

1. Introduction

In oncology, as we gain more and more interest in immunotherapy and its association with other treatments, radiation oncologists are confronted with a complex dual effect of radiotherapy (RT) on the immunological status, depending on the RT regimen [1]. On the one side, RT has an immunosuppressive effect, best illustrated by total body irradiation before stem cell transplantation in hematological oncology. On the other side, RT stimulates the immune system by the release of tumor antigens and cytokines that promote the recruitment of effector cells, like CD8 + *T*-cells, into the tumor micro-environment. In some cases, this may also stimulate an anti-tumor response outside of the RT treatment field, the so-called « abscopal effect » [2].

The immune system is composed of several types of cells, of which lymphocytes are known to be amongst the most radiosensitive through robust apoptotic pathways [3]. Until recently, radiotherapy-induced lymphopenia did not receive much attention despite being quite common [4]. Evidence regarding the negative impact of lymphopenia on oncological outcomes is incrementing. Firstly, radiation-induced lymphopenia has been associated with a decrease in overall survival (OS) and/or progression-free survival (PFS) which implies a reduced tumor control probability (TCP) [4–7]. Also, lower pretreatment lymphocyte counts have been associated with inferior outcomes for different tumor types [8,9]. Secondly, lymphopenia may represent a limiting or even life-threatening factor in patients receiving RT combined with immunosuppressive drugs because of the risk of opportunistic infections.

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https://doi.org/10.1016/j.phro.2022.07.006
Received 12 April 2022; Received in revised form 25 July 2022; Accepted 27 July 2022
Available online 30 July 2022

Finally, there is a growing interest in combining RT with immunotherapy and therefore the role of the immune response created by RT [10–14].

Lymphocytes are distributed in several compartments in the human body. The blood pool contains the circulating lymphocytes. Lymphoid organs, such as the lymph nodes or the spleen, are reservoirs of lymphocytes while the bone marrow is continuously producing new precursors of lymphocytes. For practical reasons, all these structures are called lymphocytes-rich organs at risk (LOARs).

The exact mechanism of radiation-induced lymphocytopenia is not yet fully understood. Hematopoietic toxicities can be acute, following damage to progenitor cells and mature lymphocytes, and chronic, due to structural changes into the hematopoietic organs such as the bone marrow [4,15]. In-vitro analyses on human lymphocyte colonies have demonstrated their radiosensitivity. The lethal dose required to reduce the surviving fraction of circulating lymphocytes to 10 % (LD10) is only 3 Gy and LD90 is around 0.5 Gy [16]. Based on these data, Yovino et al. found that for every fraction of RT during a standard glioblastoma treatment, 5% of the circulating cells receive > 0.5 Gy, resulting in > 99 % of circulating cells being exposed to > 0.5 Gy over the 6 weeks of RT treatment (60 Gy in 30 fractions). In this regard, circulating lymphocytes should be treated as a radiosensitive organ at risk [17].

The thorax was the first site for which a model has been developed evaluating the Effective Dose to circulating Immune Cells (EDIC), an estimation of the equivalent uniform dose to the entire blood during the RT course. A secondary analysis of the RTOG 0617 lung cancer dose-escalation trial showed an increasing EDIC to be associated with a decreasing local progression-free survival and overall survival [18]. It is to be mentioned that for prostate cancer patients, which are generally long-term survivors, there is no clear evidence that radiation-induced lymphopenia will have a clinical impact on their outcome [19].

For pelvic tumors, nodal irradiation results in the exposure of large volumes of LOAR, including iliac vessels, pelvic bone marrow, and pelvic lymph nodes. As we know, new lymphocytes are derived from the bone marrow (BM) and approximately 25 % of the bone marrow's hematopoietic activity takes place in the pelvis [20]. RT-induced lymphopenia is a phenomenon widely described in the literature for pelvic malignancies. Several observational studies assessed the risk of hematotoxicity in relation with the dose–volume parameters of the pelvic bones. Since most of these papers regard anal or cervical cancer, chemotherapy plays a confounding role but eventually these studies show that a higher volume of irradiated BM can significantly contribute to hematotoxicity [4,7–9,17,21–24]. However, a consensus regarding the dose–volume relationship is not yet reached [21,22,25]. Because a validated normal tissue complication probability (NTCP) model is not yet established, Lambin et al. proposed the ALARA principle for LOARs [26].

However, with emerging data on the negative impact of lymphopenia and the adoption of IMRT/VMAT treatment planning techniques, several authors investigated the feasibility of lymphocyte-sparing irradiation. In their study, Bao et al showed that the optimal strategy for BM sparing is to define BM structures as separate OARs for optimization without increasing the dose to other normal tissues [27]. Mell et al. studied the possibility to decrease the dose to the pelvic bone during whole-pelvis RT in gynecological cancers. In a phase II study on radiochemotherapy in 83 locally advanced cervical cancer patients, they showed a possible reduction in dose to the active BM (FDG-PET/CT based) while respecting classic constraints, as well as significantly lower grade ≥ 3 neutropenia [28].

As mentioned above, most of these studies are focused on radiation-induced lymphopenia occurring during cervical, anal or rectal cancer treatments, in which chemotherapy accounts for a substantial part, while in prostate cancer, there is a lack of data regarding this phenomenon compared with other pelvic malignancies [29].

In the current planning study, we aim to test whether a significant reduction of doses to the pelvic bones is technically possible without compromising on target coverage and classical OAR doses, and to estimate its impact on the circulating lymphocytes in terms of EDIC.

2. Materials and methods

2.1. Patient selection

Twenty patients treated in our department between March 2019 and October 2020 with pelvic nodal and prostate or prostate bed irradiation were included. Dose prescriptions were 77 Gy in 35 fractions for prostate patients and 70 Gy in 35 fractions for prostate bed patients. All patients received pelvic nodal irradiation with 56 Gy in 35 fractions. Exclusion criteria were hip prosthesis and any positive nodal boost irradiation for which respectively 2 and 3 patients were excluded with replacement.

The protocol of this in-silico planning study has been reviewed and approved by our institutional ethics committee.

2.2. Contouring

According to our department's protocol, delineation of the prostate, prostate bed, and pelvis nodal clinical target volume (CTV) was based on ESTRO ACROP guidelines [30], Latorzeff et al. [31], and Harris et al. [32], respectively. A 7 mm margin was applied to form the PTV.

The standard OARs (bowel bag, bladder, rectum, sigmoid and femoral heads) were delineated using the Male RTOG Normal Pelvis Atlas [33]. All of these contours were subsequently peer reviewed with the same radiation oncologist specialized in prostate treatment.

As a surrogate of hematopoietic active bone marrow (BM) and considering them as LOARs, The pelvic bones were systematically delineated using a semi-automated segmentation of the bones and divided into three sub-structures. First, the *lumbosacral spine* (Ls-BM) comprises vertebrae L4, L5 and the entire sacrum. Second, the *ilium* (Il-BM) structure includes the iliac crests down to the superior border of the femoral heads. Third, the *lower pelvis* (Lp-BM) is constituted of the ischium, pubis, acetabula, and proximal femora down to the small trochanter. The *whole pelvis* (Wp-BM) is defined as the union of these three sub-structures. Finally, for each structure, an inner margin of 2 mm was applied to exclude the cortical bone. This technique was chosen to be systematic and to eliminate any interobserver variability, as discussed in other papers [34,35]. For consistency, all pelvic bones were also delineated by the same investigator.

2.3. Treatment planning and deliverability

Each patient was treated with a standard-of-care plan (SOC), based on internationally accepted constraints [36] and internal planning protocols with two arcs of 360°, and different collimator angles (45° and 345°).

For each patient, a new, lymphocyte sparing (LS) treatment plan was optimized. For the LS strategy, we chose a set of dose constraints (Table 1) based on their dose–effect relationship on acute and late radiation-induced lymphopenia as previously demonstrated in pelvic RT for prostate cancer [37]. The priority was given to target volume

Table 1
Bone marrow dose constraints.

Structures	Constraints		
	Mandatory	Optimal	Wish
Ls BM	/	V40Gy < 50 %	V40Gy < 20 %
Il BM	/	V40Gy < 50 %	V40Gy < 20 %
Lp BM	/	V40Gy < 15 %	/
Wp BM	V10Gy < 90 % V20Gy < 75 %	/	Dmean < 20 Gy

Abbreviations: BM = bone marrow, Ls = lumbosacral spine, Il = ilium, Lp = low pelvis, Wp = whole pelvis.

coverage and the non-violation of classic OARs dose constraints. For consistency, all the LS treatment plans were calculated by the same medical physicist. All plans were generated with Monaco v5.51 treatment planning system (Elekta AB, Stockholm, Sweden), with 6MV photons. The number of control points per arc and angle increment were set to 90–120 and 30°, respectively. The grid size calculation varied between 0.3 and 0.4 cm.

The actual linac output was measured to evaluate the deliverability of the LS plans. For quality assurance (QA), the gamma index was used. All the plans were measured on an Elekta InfinityTM equipped with an AgilityTM head with the Delta4 + phantom. Global gamma evaluation was used with 3 %/3mm criteria above a 20 % of maximum dose threshold for 95 % of measured points.

2.4. Circulating lymphocytes and EDIC

In order to evaluate the dose delivered to the circulating lymphocytes, we would need to delineate an OAR structure taking into account the inherent difficulties of a continuously moving "organ". Alternatively, the EDIC calculation model uses high blood density organs as surrogates. This model was originally validated for thoracic irradiation with 25 fractions or more [20] taking into account mean doses to the lungs (MLD), heart (MHD) and to the remaining tissues. The vessels and small capillaries outside the lungs and heart are considered to be homogeneously distributed in the body. Integral total body dose (ITD) can then be used to replace the mean dose to these components. EDIC is then calculated as follows:

$$EDIC = B_1\% \times MLD + B_2\% \times MHD + \left[B_3\% + B_4\% \times k_1 \times \sqrt{\frac{n}{k_2}}\right] \times \frac{ITD}{62 \times 10^3}$$

where B% represents the percentage of blood volume contained in the organ at any time relative to the total body blood volume. B% is (1) 12 % for the lungs, (2) 8 % for the heart, (3) 45 to 50 % for the great vessels, and (4) 30 to 40 % for small vessels and capillaries. k_1 represents the dose losing factor, taking into account that a low percentage of the cardiac output goes to small vessels/capillaries, k_2 represents a dose saturation factor considering that the entire blood volume becomes irradiated when the number of fractions is sufficiently large, and n the number of fractions. 62×10^3 (cm^3) is the average total body volume, assuming an average weight and density of 63 kg and 1.02 g/cm^3.

In our study, we exported this EDIC model to the pelvic region. We considered the pelvic lymphatic vessels to be included in the target volume, hence they cannot be taken into account for any lymphocyte-sparing technique. Then:

$$EDIC = \left[0.45 + 0.35 \times 0.85 \times \sqrt{\frac{35}{45}}\right] \times \frac{ITD}{62 \times 10^3}$$

where B% and k have been replaced by their proper values, with n being 35 fractions. For the ITD calculation, which is simplified by the product of the body mean dose and the body volume, we subtracted the bladder from the body as we considered it is not a high blood density organ but could highly influence the mean organ dose.

2.5. Statistical analysis

The normality of all parameters was assessed using a Shapiro-Wilk test. As the normality condition was not met, dosimetric parameters and EDIC values were compared between SOC and LS plans using the non-parametric Wilcoxon signed-rank test, with a statistical significance level of $p < 0.05$. All tests were performed using the stats module of SciPy in Python.

3. Results

The LS plans showed a statistically significant decrease in all LOAR parameters compared to SOC plans: an absolute decrease of 13, 10, and 14 % for the V40Gy of Ls-BM, Il-BM, and Lp-BM respectively in prostate patients, and 14, 17, and 21 % in prostate bed patients. Also, for Wp-BM we observed a statistically significant reduction of the V10Gy, V20Gy, and Dmean (Table 2, Fig. 1). DVH representations for each new delineated bone marrow structure are illustrated in Fig. 1 for all prostate and prostate bed patients together. Also, Fig. 2 quickly shows these reductions to be present in all individual patients for almost all LOAR parameters.

There was no difference in coverage for PTV70-77 and PTV56 between both treatment plans. Considering the conventional OAR, the bladder and femoral heads showed no significant difference. Regarding the rectum, the V50Gy was lower for LS plans for prostate patients; the V70Gy was slightly higher in LS plans for prostate bed, while still maintaining the constraints within the tolerances. Although the V45Gy of the bowel bag was higher in LS plans, dose constraints remained respected as well (Table 2).

We found a statistically significant reduction in EDIC for LS plans compared to SOC in both prostate and prostate bed patients (Table 3). For prostate patients, EDIC values ranged from 3.4 to 8.8 Gy with a median of 4.9 Gy, and from 3.2 to 8.2 Gy with a median of 4.6 Gy for SOC plans and LS plans respectively. For prostate bed patients, the ranges were narrower, 3.9–6.6 Gy (median 4.2 Gy) and 3.5–6. Gy (median 3.9 Gy) for SOC plans and LS plans respectively. Furthermore, EDIC calculations did not show any correlation with the bladder volume.

Regarding their deliverability, all SOC and LS plans were satisfactory, always showing a gamma passing rate well above 95 %, with no statistically significant difference between both strategies.

After analysis of the results, we could adapt our BM dose constraints for future use (Table 4). These constraints are feasible in 90 % of the patients.

4. Discussion

In our study, we found that, while still respecting the classic OAR dose constraints as well as dose prescription to target volumes, we could considerably lower the dose to all bone marrow structures, especially in prostate bed plans.

On one hand, previous studies on hematotoxicity of pelvic radiochemotherapy indicate an influence of both low as intermediate-high doses to pelvic BM [21,24,25,29,38,39]. On the other hand, Sini et al found that medium to high doses (≥40 Gy) to BM were strongly correlated with both acute and late lymphopenia for prostate cancer patients only treated with radiotherapy [37].

In addition, we found a systematic reduction of EDIC values in favor of LS plans, which means that the dose to the circulating lymphocytes was probably also slightly reduced with our LS planning approach. This result could be explained by the V10Gy and V20Gy constraints applied to the Wp-BM. Reaching these low dose objectives on a large structure in the pelvis probably decreased the dose spillage in the body. The 6.7 % and 7.6 % respective decreases in EDIC values for prostate and prostate bed, yet statistically significant, might not be clinically relevant. Still, we demonstrated that the BM-sparing planning technique would not paradoxically increase the dose to the circulating lymphocytes. Due to a growing interest for the combination of radiotherapy with immunotherapy, and the impact of one on another, EDIC models were calculated in several studies. Based on these models which are now well established for thoracic and upper abdominal localizations [18,40–44], we could propose some explanations to our results. A trial including patients treated for stage III NSCLC reported a median EDIC of 6.1 Gy, which is higher than the EDICs we calculated [43]. The absence of heart and lungs, organs that process 100 % of the cardiac output, can explain the lower EDIC values in the pelvis compared to thoracic localizations. In

Table 2
Dose-volume parameters for pelvic bone marrow, PTVs and OARs.

VOI	Parameter	SOC (median)		LS (median)		Difference (LS-SOC)		p-value	
		P	PB	P	PB	P	PB	P	PB
Ls BM	V40Gy (%)	57.3	56.8	43.9	42.6	**−13.3**	**−14.2**	**0.002**	**0.002**
Il BM	V40Gy (%)	26.8	28.0	17.1	11.5	**−9.7**	**−16.6**	**0.002**	**0.002**
Lp BM	V40Gy (%)	27.9	38.4	13.5	17.1	**−14.4**	**−21.4**	**0.002**	**0.002**
Wp BM	V10Gy (%)	87.2	85.5	84.7	81.4	**−2.5**	**−4.1**	**0.002**	**0.027**
	V20Gy (%)	73.8	71.9	61.6	61.6	**−10.2**	**−10.4**	**0.002**	**0.002**
	Dmean (Gy)	31.4	32.9	26.6	27.2	**−4.8**	**−5.7**	**0.002**	**0.002**
PTV70-77	V95% (%)	95.3	95.3	95.3	95.3	0.0	0.0	0.813	1.000
PTV56	V95% (%)	96.5	96.2	95.9	96.1	−0.5	−0.1	1.000	0.625
Bladder	V70Gy (%)	14.2	2.4	12.7	12.7	−1.5	10.3	0.846	0.064
Rectum	V70Gy (%)	12.7	0.2	12.5	5.0	−0.2	**4.8**	0.064	**0.004**
	V50Gy (%)	49.5	44.9	44.5	46.6	**−5.1**	1.7	**0.037**	0.625
Bowel bag	V60Gy (cm^3)	0.0	0.0	0.0	0.1	0.0	0.1	0.173*	0.343*
	V45Gy (cm^3)	84.8	138.8	110.6	128.5	**25.9**	−10.3	**0.027**	0.375*

Abbreviations: P = prostate, PB = prostate bed, SOC = standard-of-care planning, LS = lymphocyte-sparing planning, BM = bone marrow, Ls = lumbosacral spine, Il = ilium, Lp = low pelvis, Wp = whole pelvis. Significant results are highlighted in bold. p-values marked by * should be considered carefully.

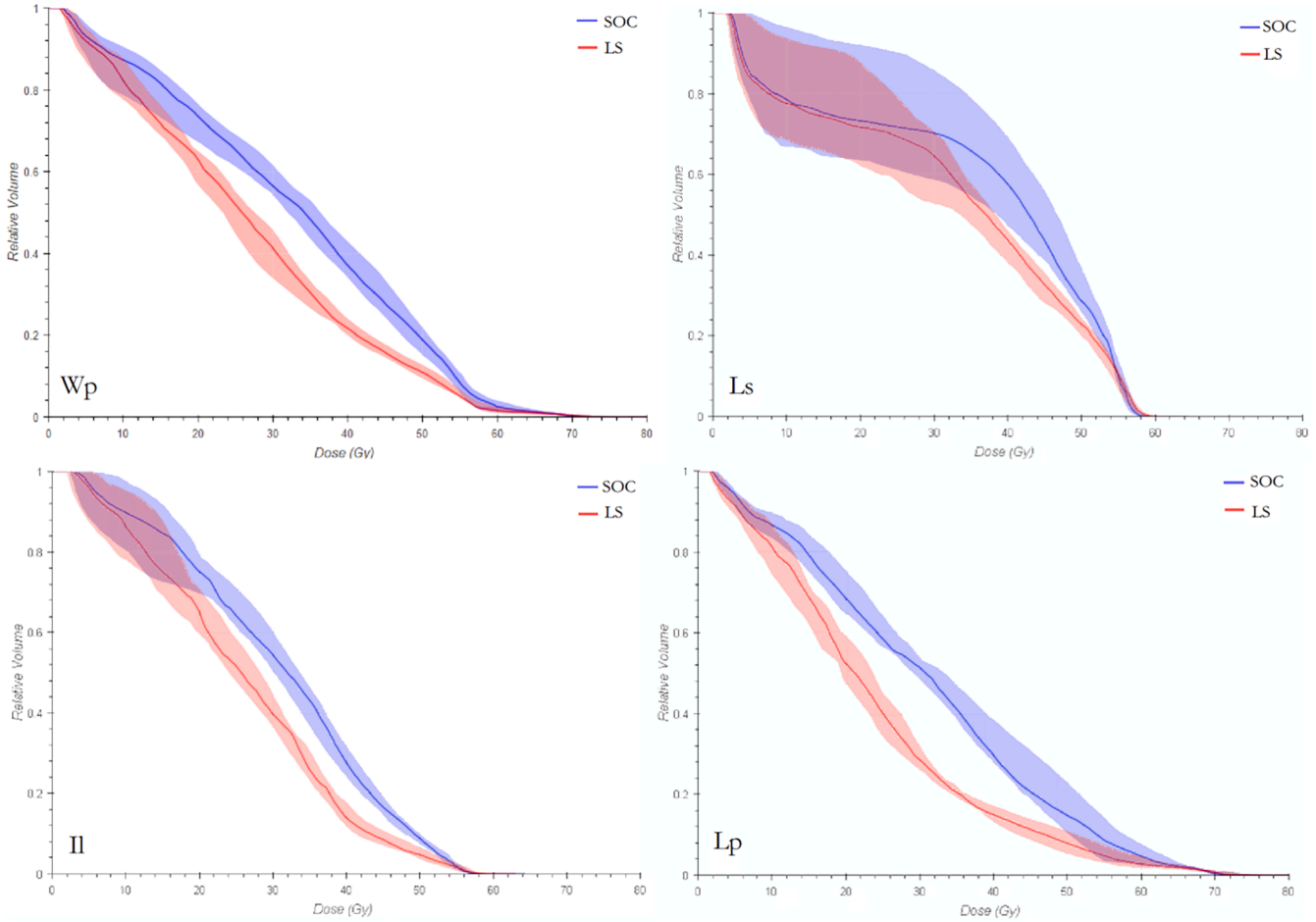

Fig. 1. Dose-volume histograms comparison for BM structures From left to right, SOC (blue) and LS (red) dose volume histograms for the Wp-BM, Ls-BM, Il-BM and Lp-BM respectively, in both prostate and prostate bed plans. The solid line represents the median and the colored spread is the interquartile range. Abbreviations: SOC = standard-of-care, LS = lymphocyte-sparing, BM = bone marrow, Ls = lumbosacral spine, Il = ilium, Lp = low pelvis, Wp = whole pelvis.

addition, theoretically these results could be partially explained by the strict bladder filling protocol implemented in our department for all pelvic treatments. A filled bladder provides a volume without circulating lymphocytes within the high-dose region of the plan. Therefore, we subtracted the bladder from the body volume for the EDIC calculation. Besides, a correlation between bladder volume and EDIC was not found. To our knowledge, this is the first study that proposes an EDIC model calculation in the pelvis.

One of the limitations of our study is the comparison between prospective dosimetric data and retrospective ones, as all of the twenty treatments plans were already delivered at the time of our investigation.

Secondly, the number of patients is limited, but is comparable to other dosimetric studies, particularly for feasibility purposes. Our cohort of patients is also homogeneously distributed and representative of real-life practice. Moreover, the results are very consistent and the number of patients allowed us to discern statistically significant differences.

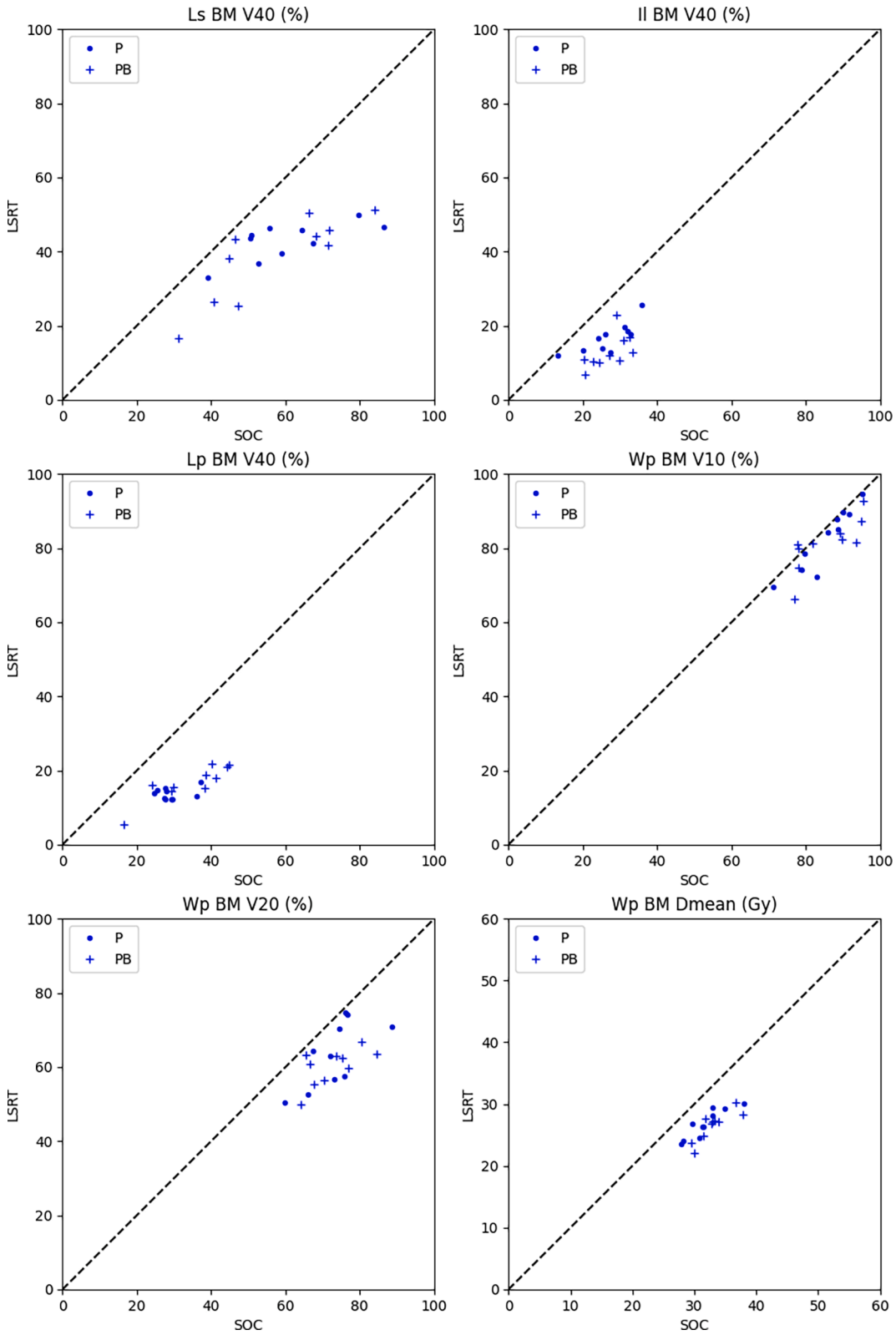

Fig. 2. Dosimetric parameters comparisons for bone marrow volumesAbbreviations: SOC = standard-of-care, LS = lymphocyte-sparing, BM = bone marrow, Ls = lumbosacral spine, Il = ilium, Lp = low pelvis, Wp = whole pelvis.

Finally, our EDIC calculation model includes some limitations. Our transposed model does not take into account some factors influencing circulating lymphocytes, such as regeneration from stem cells or variations in blood flow velocity. In the current study, this does not constitute a problem since two different planning approaches are compared within the same patient. Although this method is a simplified tool to evaluate the dose to circulating lymphocytes, we believe that this model provides an important basis for further investigations.

As mentioned before, the proposed BM dose constraints are reachable for 90 % of the patients. Therefore, the next step would be a

Table 3
EDIC comparison.

EDIC	SOC		LS		Difference (LS-SOC)		p-value	
	P	PB	P	PB	P	PB	P	PB
Median (Gy)	4.9	4.2	4.6	3.9	**−0.3**	**−0.3**	**0.002**	**0.002**

Abbreviations: EDIC = Effective Dose to Immune Cells, P = prostate, PB = prostate bed, SOC = standard-of-care planning, LS = lymphocyte-sparing planning. Significant results are highlighted in bold.

Table 4
Reviewed bone marrow dose constraints.

Structures	Constraints		
	Mandatory	Optimal	Wish
Ls BM	V40Gy < 50 %	V40Gy < 20 %	/
Il BM	V40Gy < 50 %	V40Gy < 20 %	/
Lp BM	/	V40Gy < 15 %	/
Wp BM	V20Gy < 75 %	V10Gy < 90 %	Dmean < 20 Gy

Abbreviations: BM = bone marrow, Ls = lumbosacral spine, Il = ilium, Lp = low pelvis, Wp = whole pelvis.

prospective study, randomizing prostate cancer patients to a lymphocyte-sparing versus a standard-of-care treatment planning, by which we would be able to highlight lymphopenia solely induced by irradiation. This would be an important step towards validating a NTCP model from chemo-naive patients' data. Findings of these dose-volume effects could then offer information and guidance for other pelvic RT indications.

In this work, we successfully demonstrated the feasibility of lymphocyte-sparing treatment planning for prostate cancer patients undergoing pelvic irradiation, without compromising target coverage or classic OAR dose constraints. Indeed, the study revealed a statistically significant dose reduction to pelvic bone marrow compared to standard-of-care treatment planning. We also proposed a model for EDIC calculation in the pelvis, for which LS treatment planning showed a systematic decrease in both treatment settings.

Declaration of Competing Interest

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.phro.2022.07.006.

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