

Dosimetric Comparison of Pelvic Bone Marrow Preservation between Volumetric-Modulated Arc Therapy and Intensity-Modulated Radiotherapy in Radical Radiotherapy of High-Risk Prostate Cancer

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Background: Pelvic bone marrow (PBM) preservation is one of the factors that should be taken into consideration while choosing a technique for radiotherapy of pelvic malignancies.

Aim: To dosimetrically compare between volumetric-modulated arc therapy (VMAT) and intensity-modulated radiotherapy (IMRT) in PBM preservation in radical treatment of high-risk prostate cancer.

Methods: In 26 patients with high-risk prostatic carcinoma, dual arc VMAT and 7 fields IMRT plans were generated. In every patient, two targets were defined, clinical target volume (CTV) including the prostate and seminal vesicles (CTV-PSV) and CTV including pelvic lymph nodes (CTV-LN). The organs at risk delineated were the rectum, urinary bladder, small intestine, bulb of the penis, femoral heads bilaterally and PBM. The dose prescribed to the CTV-PSV was 76 Gy in 38 fractions given over 7.5 weeks and the dose to CTV-LN was 54 Gy in 38 fractions given over 7.5 weeks. Planning target volume (PTV) was created from the CTV with a margin of 5 mm in all direction. For assessment of PBM dose, V10, V20, V30, V40, V50 and mean dose were calculated. The dose volume histogram of PTV and PBM for both techniques was compared.

Results: The mean dose of PTV 54 Gy was achieved in both techniques adequately with better sparing of organs at risk with the VMAT technique. The mean dose for PBM in the VMAT technique was significantly less than that in the IMRT (21.7 Gy vs. 25.8 Gy, respectively; $p < 0.001$). The significant differences in PBM doses were in the range of 20 Gy to 40 Gy.

Conclusion: In radical treatment of prostate cancer, VMAT technique can offer comparable conformality to IMRT with better PBM preservation. Awareness of PBM delineation and reduction of its doses using VMAT can help to decrease the hematological toxicity.

Keywords: Prostate cancer, Radiotherapy, IMRT, VMAT, Pelvic bone marrow, Bone marrow sparing

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INTRODUCTION

Prostate cancer is considered the most common malignancy in males. It is the 4th leading reason of cancer-related death in the developed countries ¹. Prostatic radiation therapy concurrent with androgen deprivation has become the main treatment for locally advanced disease. The approved prescription dose for these patients is 70 to 78 Gy delivered in 1.8 - 2 Gy/fraction over 7-8 weeks with a pelvic lymph nodes (LNs) dose of 45-50 Gy ².

The escalation of the dose is now applicable using new radiotherapy techniques, such as intensity-modulated radiotherapy (IMRT), creating concave dose isodose lines around the target while protecting organs at risk (OARs) ³. Compared to 3-dimensional conformal radiation therapy (3-D CRT), IMRT delivers a lower dose to the rectum and bladder with better coverage of the target volumes ⁴. Comparison between volumetric-

modulated arc therapy (VMAT) and IMRT in different studies showed that VMAT has better efficiency. Many trials confirmed that the rectum and bladder are better spared by VMAT than IMRT. VMAT treatment time is less than IMRT as fewer motor units (MUs) are needed to deliver the same dose distribution by single arc ⁵⁻⁷.

At least 50% of the active bone marrow (BM) of the adults is present in the lumbar spine, sacral bone, ilium, ischium, pubic bones, and upper femur. Bone marrow is highly sensitive to radiation therapy due to its cytotoxic effect ⁸.

Androgen deprivation therapy (ADT) given concurrently with radiation therapy can increase its hematological toxicity. The hematological toxicity of ADT was not fully evaluated in prostate cancer clinical studies.

The blood lymphocytes are frequently assessed in radiobiological assays as it is easy to obtain and show high sensitivity to radiation ⁹. The preclinical data and

humans' limited information suggest that androgen hormones may have a role in regulating different hemopoietic cells. Limited data are available about the influence of ADT on immunity cells and platelets. In a trial evaluating 141 prostate cancer patients who received radiotherapy plus 4 months of combined androgen blockade, hemoglobin decreased by about 3.1 g/dl, and 81% of men developed hemoglobin drop of >2 g/dl¹⁰. Thrombopoiesis is also regulated by androgens, as the androgen receptor is expressed on megakaryocytes and regulated by androgens¹¹.

There is no specific recommendation regarding dose volume objectives for pelvic bone marrow (PBM) sparing to decrease the possibility of the hematological toxicities¹². However, many studies revealed a correlation between the hematological toxicity and the PBM dosimetric parameters in anal and cervical carcinoma patients. In anal cancer patients, the suggested dose constraints to the lumbo-sacral spine were $V_{10} \leq 80\%$. Keeping the mean dose of PBM < 22.5 Gy and < 25 Gy has been associated with 5% and 10% incidence of hematological toxicity, respectively¹³.

Studies that assessed cervical cancer suggested that PBM dose of $V_{10} \geq 90\%$ had higher incidence of grade 2 hematological toxicity rates than PBM dose $V_{10} < 90\%$ ¹⁴.

We assume that both dose escalation and the combined use of ADT with radiotherapy can increase the hematological toxicity. Proper selection of the best technique in radiation therapy can decrease the PBM dose, and consequently decrease the hematological toxicity. In this study, we compared the dosimetric results of PBM preservation between dual arc VMAT (Rapid Arc, Varian model) and 7 fields IMRT in radical radiotherapy for prostate cancer who received pelvic LNs irradiation.

METHODS

Study population

26 patients with high-risk localized carcinoma of prostate were selected for this study and all were treated by radical radiotherapy including the pelvic LNs. Luteinising-hormone releasing hormone (LHRH) agonist was given concurrently with radiotherapy.

Treatment planning

Each patient was simulated in head first supine position. Computed tomographic images with a thickness of 3 mm were taken from upper abdomen to 5 cm below the ischial tuberosities with immobilization by a custom vacuum immobilization device, and with state of full bladder and empty rectum condition.

In each patient, two targets were defined, clinical target volume (CTV) including the prostate and seminal vesicles (CTV-PSV) and CTV including the pelvic LNs (CTV LN) common iliac below L5-S1, external iliac, internal iliac and obturator; with 7mm around iliac vessels, carving out bowel, bladder and bone.

Based on standard Radiation Therapy Oncology Group (RTOG) guidelines, the OARs delineated were the rectum, urinary bladder, small intestine, bulb of the

penis, femoral heads bilaterally and PBM. Bone marrow was delineated as the marrow cavity 2 cm above and below the planning target volume (PTV).

Two set of plans, one set of dual Arc VMAT and another set of 7-beams IMRT were generated and optimized with similar planning objectives to each patient. For all patients, the dose prescribed to the CTV-PSV was 76 Gy in 38 fractions given over 7.5 weeks and the dose to CTV-LN was 54 Gy in 38 fractions given over 7.5 weeks. The PTV was created from the CTV with an additional margin of 5 mm in all direction.

The plans were analyzed according to the dose-volume histogram (DVH), and the coverage of the target volume $V_{95\%}$. Calculation of all plans was done by 10 MV photon using anisotropic analytical algorithm (AAA).

The PBM dose was analyzed with different dose volume objectives since there is no exact dose volume objective of sparing level has been recommended. For assessment of PBM dose, V_{10} , V_{20} , V_{30} , V_{40} , V_{50} and mean dose were calculated for both VMAT and IMRT plans.

Plan evaluation and acceptance

All plans were evaluated based on DVH scoring values of PTVs and OARs. The PTV was evaluated using the conformity index (CI), in association with the homogeneity index (HI) and dose gradient index of the distribution of the dose. Conformity Index equals V_{RI} / TV , where " V_{RI} " is reference isodose volume and " TV " is the target volume. Homogeneity Index equals I_{max} / RI , where " I_{max} " is maximum isodose in the target and " RI " is the reference isodose.

The statistical analysis was done with the use of SPSS (version 16.0.0, SPSS, Chicago, USA). P-value less than 0.05 was considered of significance statistically.

RESULTS

VMAT plans of most patients showed better DVH and CI than IMRT plans (table 1).

The mean dose of PTV 56 Gy for both techniques was satisfactory and comparable with better OARs (bladder and rectum) sparing using VAMT techniques.

The mean CI differed significantly between the VMAT and IMRT techniques, while the mean HI did not differ significantly between them (table 1).

The mean dose for PBM in the VMAT technique (21.7 Gy) was significantly less than that in the IMRT one (25.8 Gy) as shown in table 1.

The axial, sagittal and coronal views of dose distribution for one of the study patients by both techniques are illustrated in figures 1 (IMRT) and 2 (VMAT).

Figure 3 shows the DVH for PBM of patient's plans. The mean values of V_{30} differed significantly between the IMRT and VMAT techniques ($p < 0.05$). Similarly, the mean values of V_{40} differed significantly ($p < 0.05$).

Table 1: Comparison between volumetric-modulated arc therapy (VMAT) and intensity-modulated radiotherapy (IMRT) as regards conformity index (CI), homogeneity index (HI) and pelvic bone marrow (PBM) dose

Patient's No.	CI		HI		PBM mean dose (Gy)	
	IMRT	VMAT	IMRT	VMAT	IMRT	VMAT
1	1.08	1.05	0.072	0.084	26.65	24.46
2	1.11	1.06	0.086	0.082	27.3	23.4
3	1.06	1.035	0.092	0.12	26.4	22.6
4	1.035	1.023	0.062	0.084	25.4	22
5	1.092	1.053	0.102	0.1042	26.3	21.3
6	1.085	1.046	0.091	0.093	24	21.7
7	1.072	1.036	0.086	0.096	26.2	22.3
8	1.12	1.082	0.078	0.085	22.3	19.6
9	1.07	1.065	0.0692	0.078	27.3	22.1
10	1.06	1.0387	0.058	0.068	26.3	22.8
11	1.043	1.023	0.0762	0.087	28.4	21.3
12	1.112	1.085	0.074	0.086	28.3	22.3
13	1.034	1.03	0.086	0.092	25.38	19.6
14	1.0914	1.062	0.113	0.063	26.4	22.1
15	1.078	1.046	0.106	0.097	27.6	22.6
16	1.046	1.035	0.089	0.1	26.3	21.78
17	1.085	1.063	0.092	0.098	25.8	22.3
18	1.054	1.043	0.093	0.103	24.6	21.3
19	1.045	1.032	0.1	0.102	23.6	20.3
20	1.062	1.053	0.098	0.0995	22.3	20.5
21	1.132	1.057	0.086	0.092	28.6	23.5
22	1.068	1.083	0.078	0.083	27.4	22.35
23	1.022	1.018	0.076	0.0873	24.3	18.6
24	1.083	1.067	0.089	0.0973	25.3	21.8
25	1.138	1.069	0.068	0.0765	24.3	21.5
26	1.123	1.052	0.102	0.098	25.1	22.3
Minimum	1.022	1.018	0.058	0.063	22.3	18.6
Maximum	1.138	1.085	0.113	0.765	28.6	24.46
Mean	1.0769	1.0503	0.08548	0.09061	25.8396	21.7842
Standard deviation	0.03156	0.01871	0.01381	0.0121	1.70948	1.28113
t		3.708		- 1.425		9.68
p value		0.001		0.16		< 0.001

Bone marrow mean doses and different volumes start from V20, V30, V35 and V40 dose were 72.10 ± 2.31 , 65.32 ± 1.32 , 39.213 ± 0.86 and 24.8 ± 1.3 with IMRT and 18.6 ± 1.56 , 13.42 ± 1.22 , 11.18 ± 2.3 and 8.63 ± 1.5 with VMAT. The significant differences in PBM doses were in the range of 20Gy to 40Gy.

The other investigated BM volumes as V5, V10, V15, V45 and V50 showed no statistical significance between IMRT and VMAT.

The Dmax and mean dose for the rectum were significantly higher with IMRT (77.5 Gy and 42.1 Gy) than with VMAT (76.2 Gy and 38.7 Gy) ($p < 0.05$). Similarly, the Dmax and mean dose for the bladder were significantly higher with IMRT (77.6 Gy and 45.3 Gy) than with VMAT (76.4 Gy and 42.5 Gy) ($p < 0.05$).

For PTV 56 Gy Dmin, mean dose and Dmax were 55.4 Gy, 60 Gy and 78.2 Gy in IMRT plans respectively, while they were 57.3 Gy, 58.2 Gy and 77.6 Gy in

VMAT plans respectively, with statistically significant difference in favor of VMAT ($p < 0.05$).

For PTV 76 Gy Dmin, mean dose and Dmax were 70.8 Gy, 75.9 Gy and 80 Gy in IMRT plans respectively; while they were 71.8 Gy, 77.9 Gy and 78.6 Gy in VMAT plans respectively, with statistically significant difference in favor of VMAT ($p < 0.05$).

DISCUSSION

Both radiation and ADT are myelosuppressive, and combined treatment can lead to significant hematological toxicity. The irradiated bone marrow volume and the received dose affect the extent of injury as shown in clinical studies¹⁵.

A large volume of active PBM is affected using the 3-D conformal technique, especially in the pelvic bones and lower vertebrae, but using IMRT technique can decrease the bone marrow that receives 20 Gy or higher.

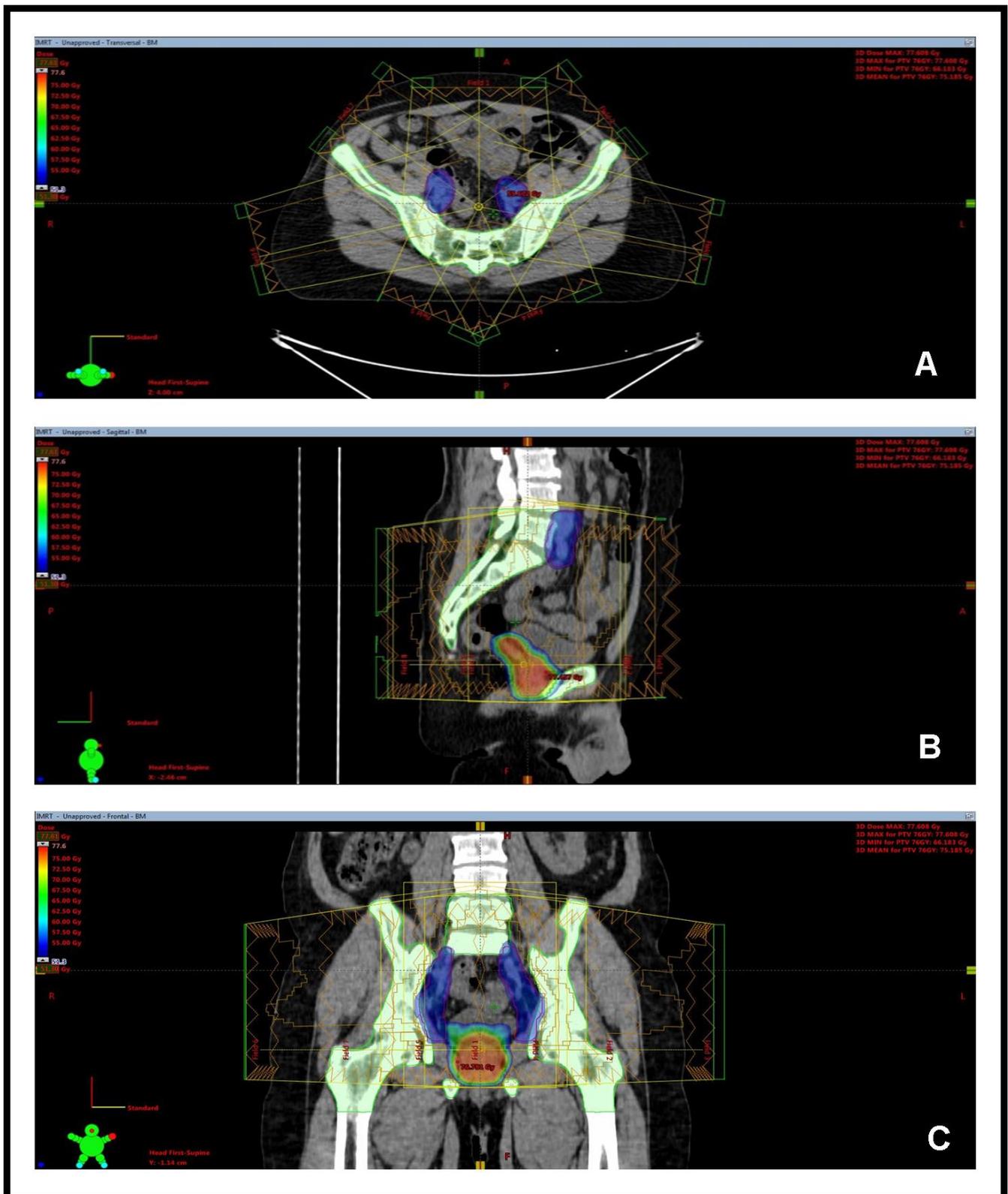


Figure 1: Dose distribution of intensity-modulated radiotherapy (IMRT) plan in one patient: A) Axial, B) Sagittal and C) Coronal views

The possibility of bone marrow sparing is limited by difficulties to avoid the large BM volume included in the radiation field¹⁶.

There is limited awareness of PBM delineation during the process of radiation, explained by the deficient data regarding the exact PBM tolerance doses

and limited data that translate the DVH scores into definitive hematological changes. Based on many studies showing better OARs preservation (rectum and bladder) by VMAT when compared to IMRT^{17, 18}, we hypothesized that VMAT may spare PBM better than IMRT with comparable PTV distribution.

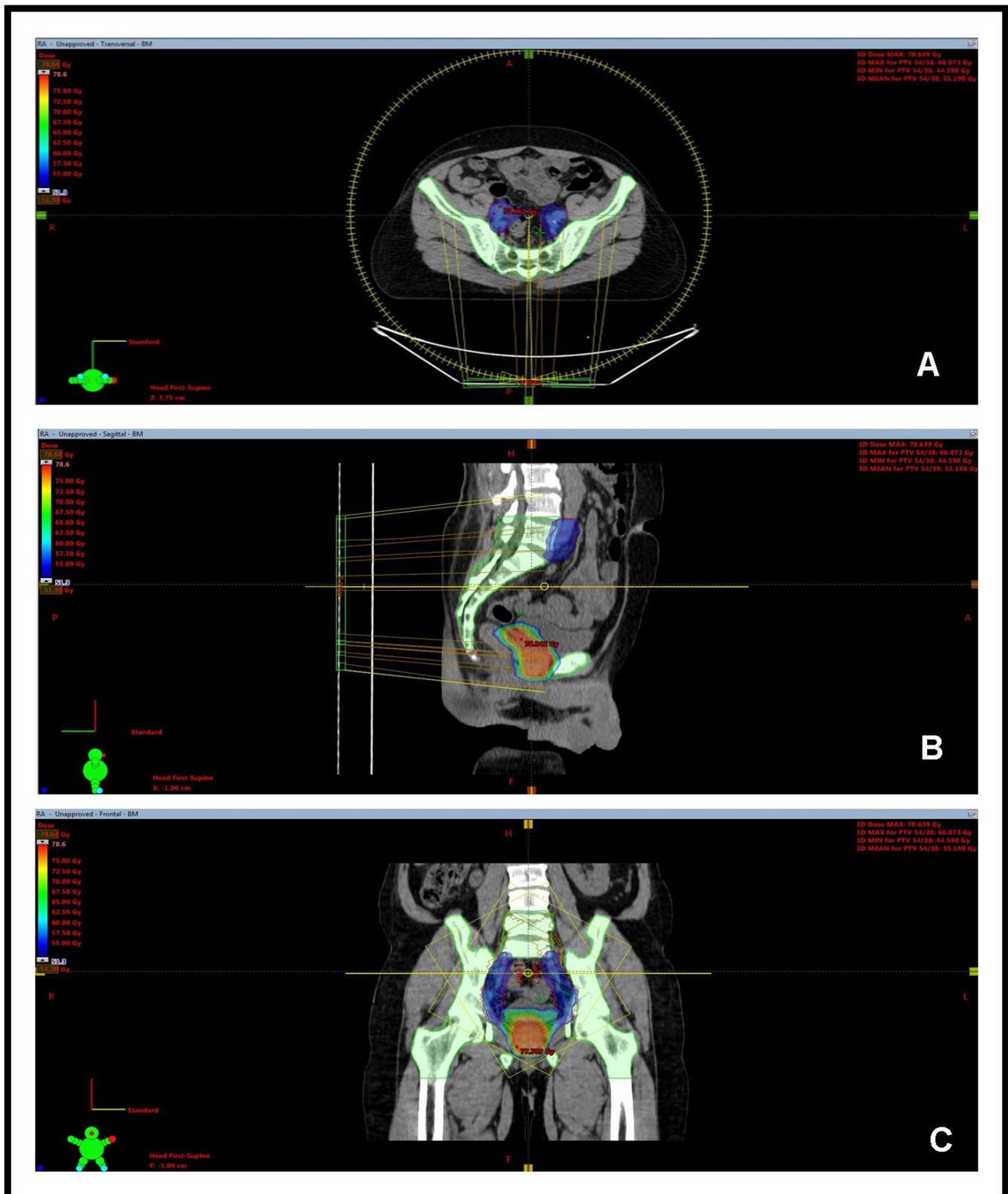


Figure 2: Dose distribution of volumetric-modulated arc therapy (VMAT) plan in one patient: A) Axial, B) Sagittal and C) Coronal views

In our study, Both VMAT and 7-fields IMRT showed satisfactory PTV 56 Gy and PTV 76 Gy coverage; however, VMAT showed higher PTV 56 conformity and homogeneity than IMRT.

Comparable results of PTV coverage were shown by Rao et al, who reported that more uniform plans were

provided by VMAT than IMRT with more rapid treatment delivery and less MUs⁵.

Our results showed statistically significant better PBM sparing by VMAT than IMRT in terms of PBM mean dose, V20, V30 and V40. The Mean dose for PBM by VMAT technique was significantly less than IMRT.

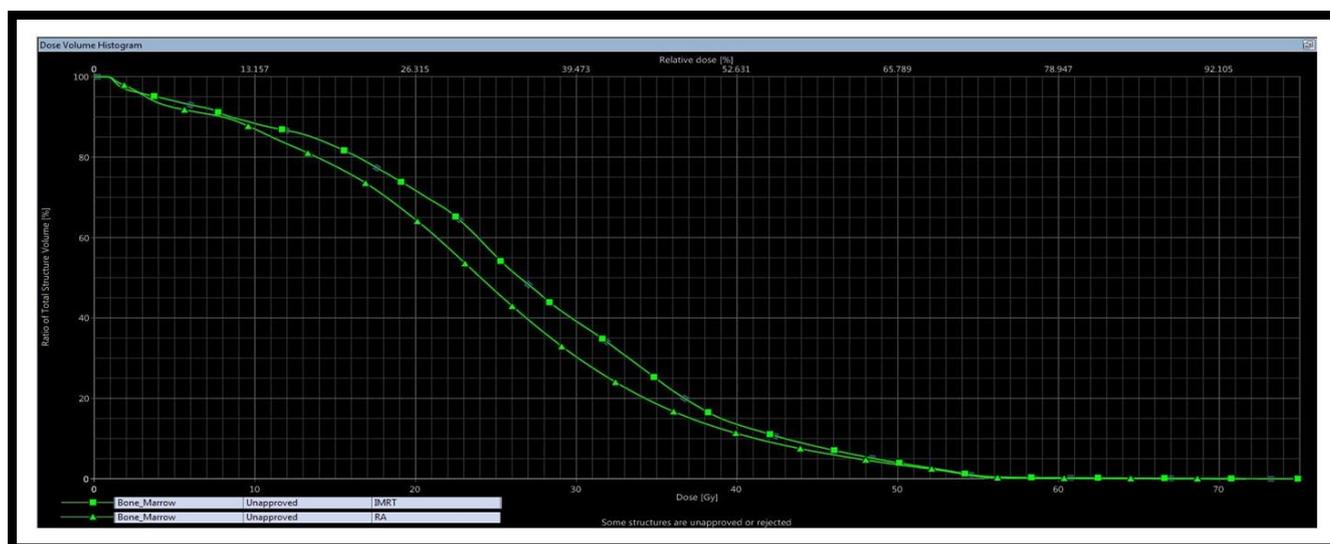


Figure 3: Dose-volume histogram (DVH) for pelvic bone marrow of patient's plans showing better sparing with volumetric-modulated arc therapy (VMAT) than intensity-modulated radiotherapy (IMRT)

Similar results were reported in another study, in which VMAT had better PBM preservation than IMRT in cervical cancer patients who received pelvic LNs irradiation, and the bone marrow mean and D40% dose with VMAT and IMRT were 30.128 ± 1.94 and 34.399 ± 2.09 ; 32.216 ± 2.72 and 37.397 ± 2.87 respectively¹⁹.

In this study, we observed that the difference between VMAT and IMRT was in the range including V20, V30 and V40 and also the mean PBM dose with a statistical significance. This observation raises the importance of the use of VMAT rather than IMRT, as according to RTOG 0418 phase II clinical trial, the higher the mean dose and more V40, the higher haematological toxicity of concurrent chemoradiotherapy in cervical carcinoma²⁰.

Other studies showed that delayed recovery of BM volumes with possible irreversible damage occurs with BM doses more than 30 to 50 Gy^{8,9}.

Our study showed that BM mean doses and different volumes start from V20, V30, V35 and V40 dose with IMRT and VMAT. This is comparable to another study that showed in which the mean of V10, V20, V30, and V40 of whole PBM were 80%, 36%, 77% and 36%, respectively. However, in that trial V30, V40 of sacral bone and ischial bone were higher due to its closeness to the planning target volumes. The iliac bone V30 was relatively higher as sparing of the bowel loops lead to higher dose accumulation in the iliac bone²¹.

The matched results of many studies correlating the acute hematological toxicities, with the BM mean dose and the range between V20 to V40 may give specific suggestions regarding BM tolerance dose during radiotherapy planning in pelvic lymph node irradiation for prostatic carcinoma.

According to our study, we suggest that the use of VMAT can lead to decrease in hematological toxicity through the reduction of specific clinically important PBM dose volume levels.

Further clinical trials are needed to correlate these PBM doses with clinical acute BM toxicity, as more

sparing of PBM can lead to less risk of hematological toxicity.

Conclusion

In high-risk prostate cancer patients receiving pelvic LNs irradiation, VMAT has better coverage of the target with better PBM sparing than IMRT. The toxicity of BM needs to be correlated with radiation dose and volume in future clinical trials. Increased awareness of PBM delineation and defining a clear BM tolerance can lead to decreased hematological toxicity.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare

REFERENCES

1. Heidenreich A, Bellmunt J, Bolla M, et al. EAU guidelines on prostate cancer. Part 1: screening, diagnosis, and treatment of clinically localised disease. *Eur Urol*. 2011; 59(1): 61-71.
2. Bolla M, Collette L, Blank L, et al. Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomised trial. *Lancet*. 2002; 360(9327): 103-106.
3. Martinez AA, Yan D, Lockman D, et al. Improvement in dose escalation using the process of adaptive radiotherapy combined with three-dimensional conformal or intensity-modulated beams for prostate cancer. *Int J Radiat Oncol Biol Phys*. 2001; 50(5): 1226-1234.
4. Luo C, Yang CC, Narayan S, et al. Use of benchmark dose-volume histograms for selection of the optimal technique between three-dimensional conformal radiation therapy and intensity-modulated radiation therapy in prostate cancer. *Int J Radiat Oncol Biol Phys*. 2006; 66(4): 1253-1262.
5. Rao M, Yang W, Chen F, et al. Comparison of Elekta VMAT with helical tomotherapy and fixed field IMRT: plan quality, delivery efficiency and accuracy. *Med Phys* 2010; 37(3): 1350-1359.

6. Sze HC, Lee MC, Hung WM, Yau TK, Lee AW. RapidArc radiotherapy planning for prostate cancer: single-arc and double-arc techniques vs. intensity-modulated radiotherapy. *Med Dosim.* 2012; 37(1): 87-91.
7. Wolff D, Stieler F, Welzel G, et al. Volumetric modulated arc therapy (VMAT) vs. serial tomotherapy, step-and-shoot IMRT and 3D-conformal RT for treatment of prostate cancer. *Radiother Oncol.* 2009; 93(2): 226-233.
8. Cao X, Wu X, Frassica D, et al. Irradiation induces bone injury by damaging bone marrow microenvironment for stem cells. *Proc Natl Acad Sci U S A.* 2011; 108(4): 1609-1614.
9. Grossmann M, Zajac JD. Hematological changes during androgen deprivation therapy. *Asian J Androl.* 2012; 14(2): 187-192.
10. Asbell SO, Leon SA, Tester WJ, Brereton HD, Ago CT, Rotman M. Development of anemia and recovery in prostate cancer patients treated with combined androgen blockade and radiotherapy. *Prostate.* 1996; 29(4): 243-248.
11. Khetawat G, Faraday N, Nealen ML, et al. Human megakaryocytes and platelets contain the estrogen receptor β and androgen receptor (AR): testosterone regulates AR expression. *Blood.* 2000; 95(7): 2289-2296.
12. Sini C, Fiorino C, Perna L, et al. Dose-volume effects for pelvic bone marrow in predicting hematological toxicity in prostate cancer radiotherapy with pelvic node irradiation. *Radiother Oncol.* 2016; 118(1):79-84.
13. Bazan JG, Luxton G, Mok EC, Koong AC, Chang DT. Normal tissue complication probability modeling of acute hematologic toxicity in patients treated with intensity-modulated radiation therapy for squamous cell carcinoma of the anal canal. *Int J Radiat Oncol Biol Phys.* 2012; 84(3): 700-706.
14. Mell LK, Kochanski JD, Roeske JC, et al. Dosimetric predictors of acute hematologic toxicity in cervical cancer patients treated with concurrent cisplatin and intensity-modulated pelvic radiotherapy. *Int J Radiat Oncol Biol Phys.* 2006; 66(5): 1356-1365.
15. Rose BS, Aydogan B, Liang Y, et al. Normal tissue complication probability modeling of acute hematologic toxicity in cervical cancer patients treated with chemoradiotherapy. *Int J Radiat Oncol Biol Phys.* 2011; 79(3): 800-807.
16. Liang Y, Messer K, Rose BS, et al. Impact of bone marrow radiation dose on acute hematologic toxicity in cervical cancer: Principal component analysis on high dimensional data. *Int J Radiat Oncol Biol Phys.* 2010; 78(3): 912-919.
17. Hardcastle N, Tomé WA, Foo K, Miller A, Carolan M, Metcalfe P. Comparison of prostate IMRT and VMAT biologically optimised treatment plans. *Med Dosim.* 2011; 36(3): 292-298.
18. Kopp RW, Duff M, Catalfamo F, Shah D, Rajecki M, Ahmad K. VMAT vs. 7-field-IMRT: Assessing the dosimetric parameters of prostate cancer treatment with a 292-patient sample. *Med Dosim.* 2011; 36(4): 365-372.
19. Deng X, Han C, Chen S, et al. Dosimetric benefits of intensity-modulated radiotherapy and volumetric-modulated arc therapy in the treatment of postoperative cervical cancer patients. *J Appl Clin Med Phys.* 2017; 18(1): 25-31.
20. Klopp AH, Moughan J, Portelance L, et al. Hematologic toxicity in RTOG 0418: a phase 2 study of postoperative IMRT for gynecologic cancer. *Int J Radiat Oncol Biol Phys.* 2013; 86(1): 83-90.
21. Lewis S, Chopra S, Naga P, et al. Acute hematological toxicity during post-operative bowel sparing image-guided intensity modulated radiation with concurrent cisplatin. *Br J Radiol.* 2018; 91(1092): 20180005.