



Dosimetric Impact on Bone Marrow Sparing with Dual Energy Vmat in Treatment of Cervical Cancer



Nameer PV¹, Shambhavi C^{2*}, Shrinidhi G Chandraguthi³, Jyothi Nagesh³ and Sarath S Nair³

¹Medical Physics intern, Manipal College of Health Profession, Manipal Academy of Higher Education, India

²Assistant Professor-senior scale in Medical Physics, Manipal College of Health Profession, Manipal Academy of Higher Education, India

³Senior grade lecturer in Medical Physics, Department of Radiotherapy and Oncology, India

Submission: May 24, 2023 Published: June 26, 2023

*Corresponding author: Ms Shambhavi C, Assistant Professor-senior scale in Medical Physics, Manipal College of Health Profession, Manipal Academy of Higher Education, Manipal, Karnataka, India

Abstract

Background: To investigate the dosimetric impact on bone marrow sparing using VMAT of dual arc using dual energy in treatment of cervical cancer.

Methods: Twenty patients with cervical cancer were chosen retrospectively. Bone marrow was contoured to all the cases. Four VMAT (Volumetric Modulated Arc Therapy) plans were generated like Dual Arc (DA) with 6MV energy of x-ray photon, DA with 10MV, DA of dual energy with (6MV and 10MV) and DA of dual energy with (6MV and 15MV) and were optimized using similar planning objectives and dose calculation was done using Monte Carlo algorithm. The dosimetric results were compared to find significance difference using Repeated Measures ANOVA with significance level set at 5%.

Results: All the plans achieved acceptable coverage with little differences in Conformity Index (CI) and Homogeneity Index (HI). The sparing of bone marrow at various dose volumes was achieved significantly ($p < 0.05$) with DA of dual energy plans (6MV and 10MV combination).

Conclusion: DA of dual energy VMAT plan (6MV and 10MV) combination showed better sparing of bone marrow at various dose and volume levels without compromising the target coverage. The energy combination in VMAT plans can help to improve the therapeutic index, by reducing the Haematological Toxicity (HT) and thereby potentially decreasing treatment interruptions.

Keywords: VMAT; Pelvic Bone Marrow; Cervical Cancer; Haematological Toxicity

Abbreviations: ANOVA: Analysis of Variance; CI: Conformity Index; DA: Dual Arc; HI: Homogeneity Index; HT: Haematological Toxicity; MU: Monitor Units; OAR: Organs at Risk; VMAT: Volumetric Modulated Arc Therapy

Introduction

Cervical cancer is considered as one of the most common cancers among women worldwide [1]. Concurrent chemo-radiotherapy is the standard treatment protocol along with intracavitary brachytherapy in the treatment of cervical cancer [2]. Few studies have shown that concurrent chemo-radiotherapy can increase Hematologic Toxicity (HT), this can interrupt the course of the treatment and limit the dose to the tumor which results poor therapeutic index [3,4].

Pelvic Bone Marrow (BM) is one among the major Organs

at Risk (OAR) in radiotherapy for cervical cases. The bone marrow is a fat yet spongy tissue which consists of stem cells and is found in the hollow spaces in the interior of bone. It is also a vital element effectively taking part in the functioning of Hematopoietic and Immune system. In case of adults, the primary site for the blood formation is pelvic bone. Since most of the bone marrow (More than 50%) [5] resides in the region of pelvis and the stem cells responsible for haematopoiesis are exceptionally radio-sensitive, it procures serious dose from radiation in the course of radiotherapy treatment techniques for pelvic treatment

and results in blood counts dropping. Hence much importance should be given to sparing of bone marrow during radiotherapy procedures for pelvic treatments of cancer.

In radiotherapy, the popularity of 3DCRT technique for the treatment of cervical cancer has been reduced due to poor dose conformity, it results in irradiating a large volume of healthy tissue. Especially, the irradiation of high dose to BM leading to Hematological Toxicity (HT) [5,6]. A few studies found intensity modulated technique was appropriate technique to reduce the volume of BM irradiation [5-7]. These techniques achieve enhanced dose conformity to the target as well as sparing of OARs with the help of numerous beam angles or arcs in the case of pelvic tumor [8,9].

A study found that VMAT plan delivered lesser dose to BM than IMRT (Intensity Modulated Radiation Therapy) especially the higher dose received volume and mean dose of BM were reduced

significantly [10]. RTOG 0418 phase II trial [11] recommended that higher dose received volume and mean dose to be reduced as low as possible to minimize HT. However, some studies recommended that low dose received volume to be reduced to minimize the HT [12]. Hence, there are two different kind of recommendations exists in the sparing of BM while treating pelvic tumour. Thus, we intended to carry out this retrospective study to identify that whether any energy combination VMAT plan would help to achieve both the dosimetry recommendations to minimize HT.

Methods and Materials

Patient Selection

The CT image data of twenty patients with cervical cancer were randomly chosen for this retrospective study from the group of treated cases in our centre. Descriptive details of the cases are shown in (Table 1).

Table 1: Summary of the selected patients.

Diagnosis	Cancer of Cervix	
Sex	Female	
Radiation Dose Prescription	50Gray in 25 Fractions	
Age (Years)	Median (Range)	57 (51-70)
Stage	II	11
	III	9

Computed Tomography Simulation and Contouring:

All patients had followed Bladder protocol and positioned in the flat couch with simulation done in headfirst supine position and immobilised by a thermoplastic mould (ORFIT by ORFIT Industries). Axial CT images of thickness 3mm was acquired for the study using Philips Brilliance Big Bore CT. By using MONACO (Version 5.11) (Elekta Medical Systems, Crawley, UK) Treatment Planning System (TPS), Bone marrow was delineated. BM was drawn based on the standard guideline [11,12], in that relatively low density within the bone in pelvic area from the superior border of PTV to the inferior border of PTV was recommended. Targets and OARs were already delineated in the image dataset as this is a retrospective study.

Treatment Planning

Four VMAT plans were generated in MONACO TPS (version 5.11) for Elekta Versa HD) (Elekta Medical Systems, Crawley, UK) Linear Accelerator equipped with 160 Agility Multi Leaf Collimators (MLC) with leaf width of 5mm at the isocentre. The four plans were, (i) DA VMAT of 6MV (ii) DA VMAT of 10MV (iii) DA VMAT of dual energy (one arc with 6MV and other arc with 10MV) and (iv) DA VMAT of dual energy (6MV and 15MV). All the plans were made with two coplanar arcs, clockwise (CW) and Counterclockwise (CCW) of 360 degrees with control points set

at 200. All the plans were optimised to ensure that 95% of the dose is received by 95% of the target volume and this acceptance criteria were set uniform for all cases. The other plan objectives are shown in (Table 2), with prescribed dose of 50 Gy(Gray) to the PTV in 25 fractions. Dose calculation was done using Monte Carlo algorithm with the grid size of 3mm. Monte Carlo algorithm is a statistical approach for performing numerical integrations in mathematical phantoms. This algorithm employs a system where the x-ray interactions are mathematically simulated to execute dose calculations to organs.

Plan Evaluation

The plans were evaluated by means of Dose Volume Histogram (DVH) analysis with respect to the given planning objectives based on QUANTEC guidelines for OARs and ICRU 83 recommendations for target conformity and homogeneity [14] using the following equations.

$$CI = V_{Ri} / TV$$

Where, Conformity Index (CI), V_{Ri} is the volume covered by the reference isodose and TV is the Target Volume. Ideal value for CI was zero. If the value is closer to zero, the plan is considered more conformal.

$$HI = (D2\% - D98\%) / D_p$$

Table 2: Planning criteria for Planning Target Volume (PTV) and Organs at Risk.

Structure	Criteria
PTV 50	$D_{95\%} \geq 47.5\text{Gy}$
Bladder	$V_{50\text{Gy}} < 50\%$
Rectum	$V_{50\text{Gy}} < 50\%$
Bowel bag	$V_{45\text{Gy}} < 195\text{cc}$
Bone Marrow	$V_{40\text{Gy}} < 20\%$
Femoral Heads	Max Dose < 50 Gy

$D_{95\%}$: dose received by 95% PTV; $V_{x\text{Gy}}$: Volume receiving x dose; Gy: Gray; Max Dose: Maximum Dose.

Where, Homogeneity Index (HI), D2% and D98% are minimum doses to 2% and 98% of target volumes respectively and D_p being Prescribed Dose. Ideal value for HI was set to be 1. The results were tabulated and compared using repeated measure of ANOVA test. The p value <0.05 was considered as significant. The statistical tests were carried out using SPSS Software (Version 16).

Results

(Figure 1) shows dose distribution of 4 different plans for a case. (Table 3) shows the dosimetric results of PTV, where $V_{107\%}$ and required number of Monitor Units (MU) were significantly better with 10MV VMAT plan(p<0.05). However homogeneous dose with acceptable coverage was achieved by all the plans

without compromising in the conformity. (Table 4) shows the statistical results of OARs. The sparing of OARs was achieved by all the plans and no significant difference was observed among them. However, the sparing of BM at various dose-volume level was achieved significantly better with dual energy DA plan (6MV and 10MV). The BM sparing achieved by dual energy VMAT plan (6MV and 10MV) in all the dose-volume range was better than other VMAT plans. In all the cases dose volume objectives like D_{Mean} , D_{40} , D_{20} and V_{10} to V_{50} were achieved significantly lesser(p<0.05). (Figure 2) shows average of various dose received volume of BM in percentage of all the plans. In this figure, (6MV and 10MV) combinations plan shows that the low dose received volume as well as the high dose received volume of BM are lesser

Table 3: Statistical comparison of dosimetric parameters for PTV.

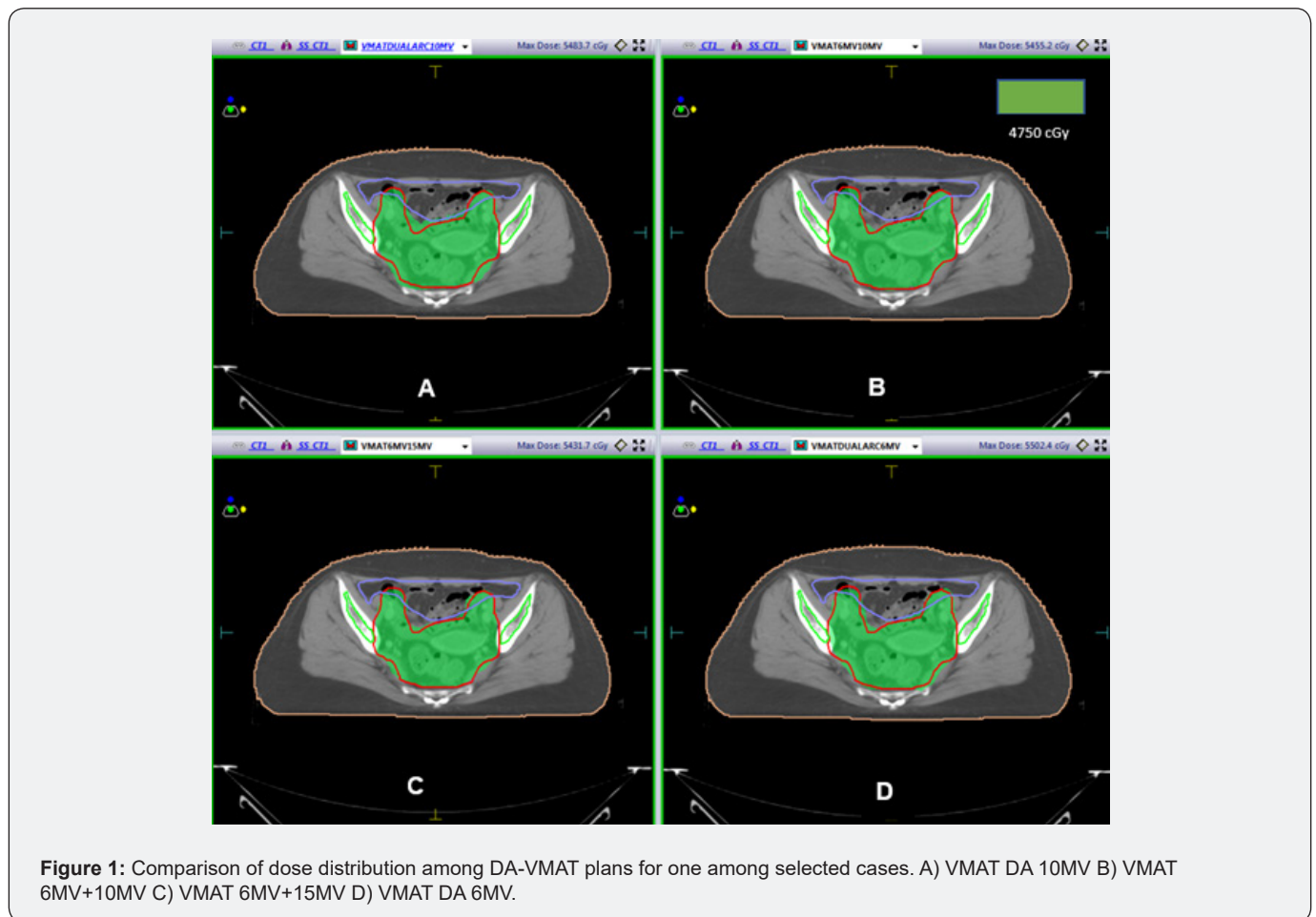
	DA VMAT Plans				P(<0.05 is significant)
	6 MV	6 MV + 10 MV	6 MV + 15 MV	10 MV	
HI	0.09 ± 0.13	0.09 ± 0.14	0.10 ± 0.19	0.09 ± 0.01	0.185
CI	1.14 ± 0.05	1.13 ± 0.07	1.13 ± 0.07	1.11 ± 0.06	0.097
D_{Max} (Gy)	54.85 ± 0.26	54.71 ± 0.51	54.52 ± 0.49	54.53 ± 0.68	0.102
D_{Mean} (Gy)	50.36 ± 0.12	49.97 ± 0.55	50.21 ± 0.25	50.13 ± 0.25	0.049
D_{95} (%)	97.46 ± 1.01	97.40 ± 1.08	96.46 ± 1.56	96.47 ± 1.05	0.187
V_{107} (%)	1.03 ± 0.50	0.49 ± 0.26	0.62 ± 0.30	0.26 ± 0.04	0.001
MUs	1377.47 ± 92.57	1337.02 ± 104.67	1308.22 ± 161.53	1277.18 ± 96.64	0.040

CI: Conformity Index, HI : Homogeneity Index, D_{Max} : Maximum Dose, D_{Mean} : Mean Dose, V_{95} : Volume receiving 95% of prescribed dose, V_{107} : Volume receiving 107% of prescribed dose, MU : Monitor Units are expressed as mean value (±SD).

Table 4: Statistical comparison of dosimetric parameters for Organs at Risk.

Organ at Risk	Parameters	DA VMAT Plans				P(<0.05 is significant)
		6 MV Dual Arc	6 MV + 10 MV	6 MV + 15 MV	10 MV Dual Arc	
Bladder	Mean Dose (Gy)	43.81 ± 1.58	44.08 ± 1.53	44.14 ± 1.51	44.25 ± 1.98	0.082
Bowel Bag	Mean Dose (Gy)	26.11 ± 1.96	26.15 ± 2.30	26.09 ± 2.08	26.07 ± 1.79	0.985
Rectum	Mean Dose (Gy)	44.68 ± 1.71	44.76 ± 1.87	44.98 ± 1.89	45.62 ± 2.03	0.319
Right Femoral Head	Max. Dose (Gy)	47.90 ± 1.94	47.74 ± 2.32	47.79 ± 2.35	47.73 ± 2.38	0.969
Left Femoral Head	Max. Dose (Gy)	45.34 ± 2.64	46.05 ± 2.98	46.42 ± 3.81	46.16 ± 3.13	0.429

Values are expressed in terms of mean dose (±Standard Deviation). Max. Dose: Maximum Dose.



Discussion

Cervical cancer is one the most prominent cancer among females worldwide [1]. Treatment for cervical cancer have been evolved from conventional Radiotherapy (RT) to modulated conformal RT. Many studies have been reported that this evolution helps in the sparing of OARs with conformal adequate dose coverage to the target to increase the therapeutic index [8]. Concurrent chemo-radiotherapy which is a standard treatment protocol for the cervical cancer, improved the survival rates with additional cost of HT [15,16]. Few of the studies recommended

that, if sparing of BM increases further the HT can be minimised hence helps in avoiding treatment interruption. Moreover, increased sparing of BM helps to deliver planned dose completely [3,4]. The RTOG 0418 Phase II Clinical Trial had concluded that mean dose and 40Gy received the volume of BM are directly associated with HT while treating cervical cancer patients with concurrent chemo-radiotherapy [11]. Loren K Mell et al reported that, using Intensity Modulated techniques BM sparing can be achieved better than conventional techniques [17]. Few other studies from their dosimetric study between VMAT and IMRT

reported that VMAT was achieved significantly higher sparing of BM than IMRT [10,18]. In our study also the coverage of tumour and sparing of the OARs were achieved with additional sparing of BM. Especially the combination of (6MV and 10MV) DA VMAT

plan reduced both the low doses as well as high doses irradiating BM volume. This study has evidence that dose sparing at all the dose-volume ranges can be possible which was not achieved in earlier mentioned studies [10,21].

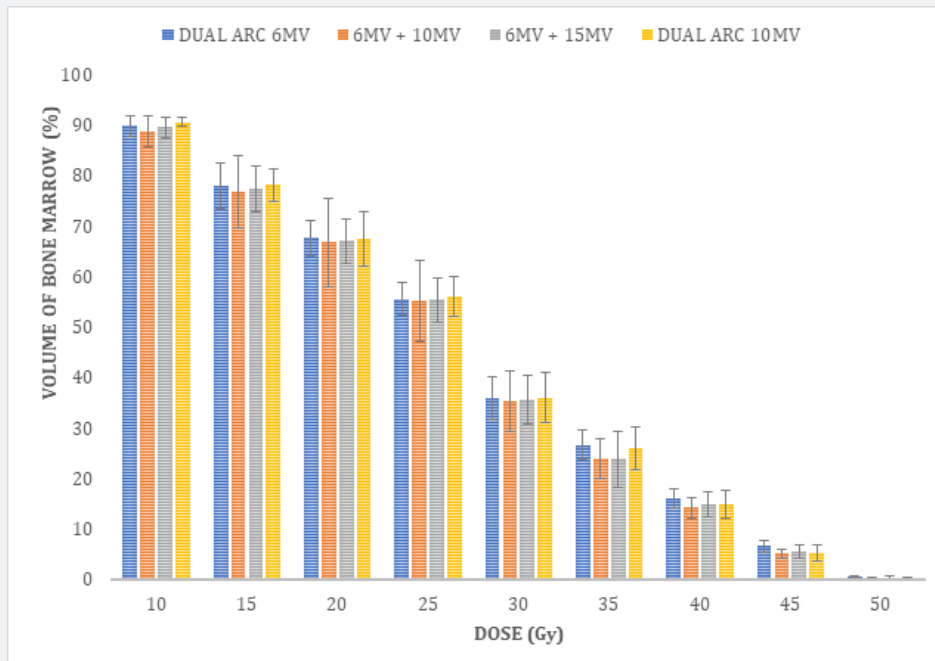


Figure 2: Graphical representation with error bar of dose received by BM in different volume levels in the different plans used in the study.

Table 5: Average Bone marrow dose of different volumes.

Dose/Volume	DA VMAT Plans				P(<0.05 is significant)
	6 MV	6 MV+10 MV	6 MV+15 MV	10 MV	
Mean (Gy)	26.66 ± 0.80	25.74 ± 1.73	26.38 ± 0.95	26.72 ± 1.50	0.015
D ₄₀ (Gy)	28.01 ± 1.34	27.66 ± 2.26	28.20 ± 1.50	28.37 ± 1.87	0.039
D ₂₀ (Gy)	36.94 ± 1.44	36.19 ± 1.82	36.72 ± 1.77	37.05 ± 1.65	0.008
V ₁₀ (%)	89.75 ± 1.98	88.69 ± 3.13	89.40 ± 2.17	90.46 ± 0.91	0.020
V ₁₅ (%)	77.86 ± 4.40	76.65 ± 7.08	77.21 ± 4.59	78.04 ± 3.15	0.025
V ₂₀ (%)	67.54 ± 3.50	66.64 ± 8.65	66.96 ± 4.43	67.38 ± 5.37	0.005
V ₂₅ (%)	55.51 ± 3.30	55.04 ± 8.03	55.32 ± 4.35	56.00 ± 4.01	0.013
V ₃₀ (%)	35.73 ± 4.23	35.13 ± 5.99	35.42 ± 4.86	35.93 ± 4.91	0.040
V ₃₅ (%)	26.54 ± 2.97	23.86 ± 3.95	23.80 ± 5.55	25.82 ± 4.29	0.014
V ₄₀ (%)	15.93 ± 1.81	14.08 ± 2.15	14.76 ± 2.43	14.86 ± 2.79	0.003
V ₄₅ (%)	6.48 ± 1.05	5.03 ± 0.82	5.44 ± 1.21	5.13 ± 1.64	0.000
V ₅₀ (%)	0.41 ± 0.21	0.16 ± 0.23	0.26 ± 0.23	0.16 ± 0.14	0.040

D_{x%}: dose received by x% Bone Marrow; V_{xGy}: Volume receiving x dose; Gy: Gray; Max Dose: Maximum Dose, Values are expressed in terms of mean ± Standard Deviation.

The pelvic region BM acts as a vital organ in producing platelet, leucocyte, and erythrocyte. Therefore, the sparing of BM is one of the higher priorities to minimize toxicity during the course of treatment [5,19,20]. In recent years, there has been some studies determining the dose volume relationship between the risk of HT and amount of PBM volume irradiated. It was found out by Mell et al. [22] that if BM receives dose more than that of 10Gy, there are high chances of Grade 2 or worse leukopenia as well as neutropenia. Adding, in a study done by Albuquerque K et al, it was shown that when the volume of bone marrow receiving 20Gy is more than 80% of its entire volume, the risk of toxicity will elevate by a factor of 4.5 [20]. Based on these findings, it is safe to assume that BM stem cells are highly sensitive to low dose radiations. The results obtained from our study indicates that the plans generated with energy combination (6MV and 10 MV) had better sparing in V10 and V20 in comparison to other plans with maximum significance shown in V20 with p-value of 0.005 (Table 5). There are other studies which reports contrary in assuming V10-V20 as predictors. For example, it was reported in RTOG 0418 trial that the chances of \geq grade 2 Haematological Toxicity is found to be more when 40Gy receiving volume of PBM is greater than 37% of its total volume [11]. Also, several other studies [21] had addressed the fact that the bone marrow volumes receiving dose of 30-50Gy required a longer period for recovery or can even experience permanent and irreversible damage to its functioning. So, it was mandatory to bring down the volumes receiving the above-mentioned dose limits. Taking this also in consideration, as we compare it with our study, all VMAT plans were successful in bringing down the volume receiving doses of 30 to 50Gy as visible in (Table 5). In comparison, DA VMAT plan (6MV and 10MV) had an upper hand among other plans in marginally reducing PBM volumes receiving dose of 30 to 50Gy.

X-ray photons of energy more than 10MV can produces neutron contamination. Dual energy DA VMAT plan with 10MV and DA VMAT plan with (6MV and 15MV) may produce slightly higher neutron contamination than dual energy DA VMAT plan with (6MV and 10MV). Energy related neutron contamination may be considered as a limitation however this optimum combination provides better dosimetric result and it can be used for the treatment of cervical cancer.

Conclusion

Dual energy DA-VMAT plan (6MV and 10MV) combination shows better sparing of bone marrow at various dose and volume levels without compromising the tumour coverage in treatment of cervical cancer. This energy combination VMAT plans helps to improve therapeutic index by reducing the Haematological Toxicity (HT) and avoiding the treatment interruption.

Conflict of Interest

Nil.

References

- Hoskins WJ, Perez CA, Young RC (2005) Principles and practice of gynecologic oncology (4th edn), Lippincott Williams and Wilkins, Philadelphia, PA, USA.
- Green JA, Kirwan JJ, Tierney J, Vale CL, Symonds PR et al. (2005) Concomitant chemotherapy and radiation therapy for cancer of the uterine cervix. *Cochrane Database Syst Rev* 20(3): CD002225.
- McGuire SM, Menda Y, Ponto LL, Gross B, Juweid M et al. (2011) A methodology for incorporating functional bone marrow sparing in IMRT planning for pelvic radiation therapy. *Radiother Oncol* 99(1): 49-54.
- Bazan JG, Luxton G, Kozak MM, Anderson EM, Hancock SL et al. (2013) Impact of chemotherapy on normal tissue complication probability models of acute hematologic toxicity in patients receiving pelvic intensity modulated radiation therapy. *Int J Radiat Oncol Biol Phys* 87(5): 983-991.
- Mell LK, Kochanski JD, Roeske JC, Haslam JJ, Mehta N et al. (2006) 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* 66(5): 1356-1365.
- Vale C, Tierny JF, Stewart LA, Brady M, Dinshaw K et al. (2008) Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systematic review and meta-analysis of individual patient data from 18 randomized trials. *J Clin Oncol* 26(3): 5802-5812.
- Hui B, Zhang Y, Shi F, Wang J, Wang T et al. (2014) Association between bone marrow dosimetric parameters and acute hematologic toxicity in cervical cancer patients undergoing concurrent chemoradiotherapy: Comparison of three-dimensional conformal radiotherapy and intensity-modulated radiation therapy. *Int J Gynecol Cancer* 24(9): 1648-1652.
- Yang B, Zhu L, Cheng H, Li Q, Zhang Y et al. (2012) Dosimetric comparison of intensity modulated radiotherapy and three-dimensional conformal radiotherapy in patients with gynecologic malignancies: a systematic review and meta-analysis. *Radiat Oncol* 7: 197.
- Ferrigno R, Santos A, Martins LC, Weltman E, Chen MJ et al. (2010) Comparison of conformal and intensity modulated radiation therapy techniques for treatment of pelvic tumors. Analysis of acute toxicity. *Radiat Oncol* 117.
- Krishnan J, Shetty J, Rao S, Hegde S, Shambhavi (2017) Dosimetric Advantage of VMAT Technique in Bone Marrow Sparing Than IMRT in Treatment of Cervical Cancer. *International Journal of Health Sciences and Research* 7(8): 102-109.
- Klopp AH, Moughan J, Portelance L, Miller BE, Salehpour MR et al. (2013) Hematologic toxicity in RTOG 0418: a phase 2 study of postoperative IMRT for gynecologic cancer. *Int J Radiat Oncol Biol Phys* 86(1): 83-90.
- Mahantshetty U, Krishnatry R, Chaudhari S, Kanaujia A, Engineer R et al. (2012) Comparison of 2 contouring methods of bone marrow on CT and correlation with hematological toxicities in non-bone marrow-sparing pelvic intensity-modulated radiotherapy with concurrent cisplatin for cervical cancer. *Int J Gynecol Cancer* 22(8): 1427-1434.
- Atiq A, Atiq M, Iqbal K, Shamsi QA, Buzdar SA (2018) Evaluation of various dose homogeneity indices for treatment of patients with cervix cancer using intensity-modulated radiation therapy technique. *J Radiother Pract* 18(1):1-6.
- Grégoire V, Mackie TR (2011) State of the art on dose prescription, reporting and recording in Intensity-Modulated Radiation Therapy (ICRU report No. 83). *Cancer/Radiothérapie* 15(6-7): 555-559.

15. Morris M, Eifel PJ, Lu J, Grigsby PW, Levenback C et al. (1999) Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. *N Engl J Med* 340(15): 1137-1143.
16. Rose PG, Bundy BN, Watkins EB, Thigpen JT, Deppe G et al. (1999) Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. *N Engl J Med* 340(15): 1144-1153.
17. Mell LK, Tiryaki H, Ahn KH, Mundt AJ, Roeske JC et al. (2008) Dosimetric comparison of bone marrow-sparing intensity-modulated radiotherapy versus conventional techniques for treatment of cervical cancer. *Int J Radiat Oncol Biol Phys* 71(5): 1504-1510.
18. Chigurupalli K, Vashistha A, Patel D, Purohit R, Peter S et al. (2019) Retrospective Dosimetric analysis of Bone marrow sparing vs non bone marrow sparing Image Guided Volumetric Modulated Arc Therapy in intact Carcinoma Cervix patients. *Curr Med Res Opin* 2(10): 288-292.
19. Mell LK, Schomas DA, Salama JK, Devisetty K, Aydogan B et al. (2008) Association between bone marrow dosimetric parameters and acute hematologic toxicity in anal cancer patients treated with concurrent chemotherapy and intensity-modulated radiotherapy. *Int J Radiat Oncol Biol Phys* 70(5): 1431-1437.
20. Albuquerque K, Giangreco D, Morrison C, Siddiqui M, Sinacore J et al. (2011) Radiation-related predictors of hematologic toxicity after concurrent chemoradiation for cervical cancer and implications for bone marrow-sparing pelvic IMRT. *Int J Radiat Oncol Biol Phys* 79(4): 1043-1047.
21. Mauch P, Constine L, Greenberger J, Knosp W, Sullivan J et al. (1995) Hematopoietic stem cell compartment: acute and late effects of radiation therapy and chemotherapy. *Int J Radiat Oncol Biol Phys* 31(5): 1319-1339.
22. De Martino F, Clemente S, Graeff C, Palma G, Cella L (2021) Dose Calculation Algorithms for External Radiation Therapy: An Overview for Practitioners. *Applied Sciences* 11(15): 6806.



This work is licensed under Creative Commons Attribution 4.0 License
DOI: [10.19080/CTOIJ.2024.23.556138](https://doi.org/10.19080/CTOIJ.2024.23.556138)

**Your next submission with Juniper Publishers
will reach you the below assets**

- Quality Editorial service
- Swift Peer Review
- Reprints availability
- E-prints Service
- Manuscript Podcast for convenient understanding
- Global attainment for your research
- Manuscript accessibility in different formats
(Pdf, E-pub, Full Text, Audio)
- Unceasing customer service

Track the below URL for one-step submission
<https://juniperpublishers.com/online-submission.php>