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ORIGINAL ARTICLE

Dosimetric analysis of tomotherapy-based intensity-modulated radiotherapy with and without bone marrow sparing for the treatment of cervical cancer*

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Abstract

Objective The aim of the study was to compare tomotherapy-based bone marrow-sparing intensity-modulated radiotherapy (BMS-IMRT) with intensity-modulated radiotherapy (IMRT) without entering the pelvic bone marrow as a planning constraint in the treatment of cervical cancer after hysterectomy.

Methods BMS-IMRT and IMRT plans were designed for a cohort of nine patients. The prescribed dose was 45 Gy in 1.8 Gy daily fractions, and 95% of the planned target volume received this dose. The doses were computed using a commercially available treatment planning system with the convolution/superposition algorithm. Plans were compared according to dose-volume histogram analysis in terms of planning target volume homogeneity and conformity indices (HI and CI) as well as organ at risk dose and volume parameters.

Results BMS-IMRT had advantages over IMRT in terms of CI, but was equivalent to the latter in HI. V5, V10, V20, V30, and V40 of pelvic bone marrow in BMS-IMRT decreased by 0.06%, 17.33%, 22.19%, 13.85%, and 16.46%, respectively, compared with IMRT. Except for V30 of the small bowel and V30 and V40 of the bladder, no statistically significant differences were found between BMS-IMRT and IMRT in the small bowel, bladder, and rectum.

Conclusion For cervical cancer patients receiving tomotherapy-based radiotherapy after hysterectomy, BMS-IMRT reduced pelvic bone marrow volume receiving low-dose radiation, and it may be conducive to preventing acute hematologic toxicity.

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Key words: cervical neoplasm; helical tomotherapy; intensity-modulated radiotherapy (IMRT); dosimetry

Radiotherapy (RT) is an important therapeutic approach to treat cervical cancer before or after hysterectomy [1]. Although highly efficient, RT can cause numerous side effects, one of which is bone marrow (BM) toxicity; therefore, sparing BM as much as possible has become a priority in delivering precision RT [2]. Previous studies have shown that the volumes of pelvic BM (PBM) and lumbosacral BM receiving 10 or 20 Gy are associated with the development of acute BM toxicity in patients undergoing concurrent chemotherapy and RT or treated with RT alone [3–8]. Therefore, reducing the volume of BM receiving low-dose RT may prevent or reduce acute toxicity.

Intensity-modulated RT (IMRT) reduces radiation dose received by normal tissues during whole pelvic RT [1, 9–11]. Helical tomotherapy (HT) is a new CT-based rotational IMRT, which provides highly conformal dose distributions and simultaneous sparing of critical organs [12–16]. However, PBM sparing is not a constraint in the IMRT planning process in many clinics, and is only evaluated in terms of dose-volume when the treatment plan is completed. Then, a new question arises: if PBM sparing is set

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as a constraint in the HT planning process, then to what extent this type of IMRT can reduce radiation, particularly low-dose radiation, received by PBM? The purpose of this study was, therefore, to quantify the expected dosimetric benefits of BM-sparing IMRT (BMS-IMRT) compared with routine HT planning technique.

Patients and methods

Patient selection, positioning, and CT scanning

Nine cervical cancer patients treated with routine HT after hysterectomy between April and December 2012 were chosen for retrospective analysis. The mean and median ages were 49.1 and 48.5 years, respectively. A CT image of each patient in the treatment position was obtained using our departmental scanner (Brilliance Bigbore CT, Philips Medical systems, Cleveland, OH, USA) with slice interval and thickness of 5 mm. The CT scans were obtained from the L2 vertebral body to 5 cm below the ischial tuberosity and imported to the planning system (Pinnacle3, version 9.2, Philips Radiation Oncology systems, Madison, WI, USA). Oral and intravenous contrast agents were administered to all patients before CT scanning. In addition, to minimize setup variability, a custom immobilization device, i.e. a thermoplastic mold (MedTec) was fabricated for each patient in the supine position.

Target volumes

The delineation of target and critical structures for all patients was done by a single radiation oncologist with extensive experience in the treatment of cervical cancer on individual CT slices. According to the ICRU 62 report [17] and published studies [9, 11, 18], the clinical target volume (CTV) included the upper half of the vagina and stump, parametrial tissue, and pelvic lymph nodes. Because nonenlarged lymph nodes are poorly visualized on CT, contrast-enhanced vessels plus a 2-cm margin were used to define the common, external, and internal iliac nodal regions to the level of the L4–5 interspace. The presacral region was included to the bottom of the S3 vertebral body to ensure coverage of the presacral lymph nodes and attachment of the uterosacral ligament. The planning target volume (PTV) was generated using a 1.0-cm uniform expansion of the CTV. The prescribed dose to the PTV was 45 Gy in 1.8-Gy daily fractions.

Critical structures

Organs at risk (OARs) include the rectum, bladder, bowel, and PBM, which comprises the lumbosacral, iliac, ischium, pubis, and proximal femoral BM, and femoral heads. The rectum was defined from the level of the sacral promontory to the ischial tuberosity. The contour of the full bladder was also delineated. The peritoneal cavity (excluding the rectum and bladder) from the L4–5 level was used to define the small bowel region; the individual loops of the small bowel were not separately contoured [9].

Table 1 Dose-volume constraints for targets and critical structures

Structures	Volume (%)	Dose (Gy)
PTV	95	45
PBM	≤ 80	20
	≤ 85	10
Small bowel	≤ 30	25
Bladder	≤ 50	30
Rectum	≤ 10	45

Treatment planning

HT planning was conducted using the Hi-Art®4.1.2 treatment planning system (version 4.1.2; TomoTherapy Inc., Madison, WI, USA). For HT planning, the parameters affecting dose conformity and treatment times were the field width (FW), pitch, and modulation factor (MF). The FW is defined by the fan beam width in the longitudinal direction, the pitch is defined as the ratio of the couch travel per gantry rotation to the field width and required to be < 1.0, and the MF is defined as the intensity ratio between the most intense beamlet and the average of all beamlets. In our study, we utilized the FW of 2.5 cm, the pitch of 0.287 or 0.43, and the MF of 2.5. The prescribed dose to the PTV was 45 Gy in 1.8-Gy daily fractions. The dose-volume constraints used for the targets and critical structures listed in Table 1 were based on those used in our clinic and were the same for all plans. For each patient, two plans were generated using an identical set of PTV and OAR dose-volume constraints with the exception of PBM, which was entered as a separate constraint in BMS-HT. All plans were normalized to cover 95% of the PTV with the prescription dose.

Plan comparisons

Dosimetric comparison of the plans was performed based on the following parameters extracted from the dose-volume histogram (DVH): homogeneity index (HI), conformity index (CI), V5, V10, V20, V30, and V40 of the PBM, V10, V20, V30, and V40 of the small bowel, V20, V30, and V40 of the bladder, and V10, V20, V30, and V40 of the rectum (V5, V10, V20, V30, and V40 indicate the fraction of OAR volume receiving > 5 Gy, 10 Gy, 20 Gy, 30 Gy, and 40 Gy, respectively). The HI used to analyze dose uniformity is defined as D_5/D_{95} (minimum dose in 5% of the PTV/minimum dose in 95% of the PTV), and is inversely proportional to dose homogeneity. The CI, which indicates the degree of conformity, was calculated as the ratio of the PTV volume receiving at least 45 Gy to the total volume receiving 45 Gy [19]; the closer the CI

Table 2 Homogeneity and conformity index of BMS-IMRT and IMRT

	BMS-HT	HT	*t* value	*P* value
HI	1.03 ± 0.01	1.03 ± 0.01	1.48	0.176
CI	0.73 ± 0.04	0.70 ± 0.06	2.15	0.063

value is to 1, the better dose conformity. Fig. 1 showed isodose distributions on a transverse plane of the two RT modalities for a typical patient.

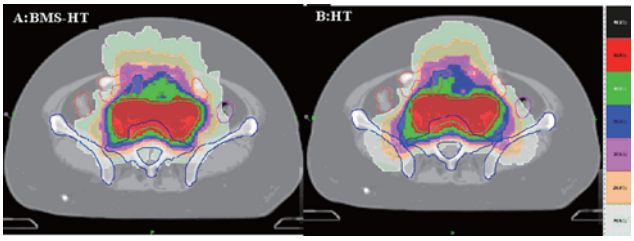

Fig. 1 Isodose distribution on a transverse plane of the two modalities for a typical patient (A: BMS-HT, B: HT)

Statistical analysis

Statistical analysis was performed using the SPSS software (version 12.0, SPSS Inc., Chicago, IL, USA). Quantitative data were expressed as the mean ± standard deviation ($\overline{\chi} \pm s$). The significance of differences was tested by using the paired two-tailed Student *t*-test. The 95% confidence intervals were calculated. A P value ≤ 0.05 was considered statistically significant.

Results

Comparison of the HI and CI of the PTV

The HI and CI were used to compare the two techniques in Table 2. No significant difference in these indexes was found.

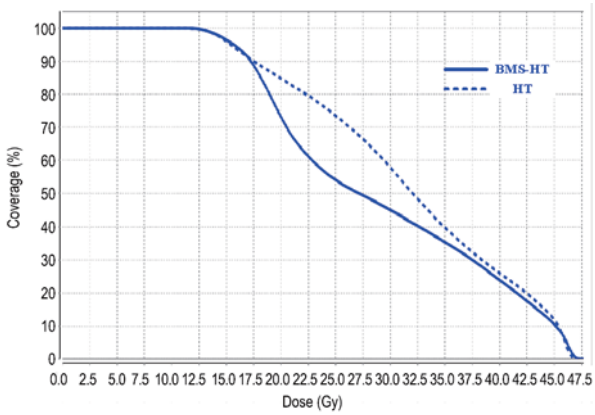

Fig. 2 The DVH of PBM in the two modalities for a typical patient (solid line: BMS-HT; dashed line: HT)

Comparison of dosimetric parameters of OARs for two modalities

Dosimetric parameters of normal tissues, including PBM, the small bowel, bladder, and rectum were presented in Table 3. V10, V20, and V30 of PBM showed significant differences between BMS-HT and routine HT (P = 0.000, P = 0.000, and P = 0.017, respectively). BMS-HT reduced the irradiated volume of PBM in both low and high dose areas. The DVH of PBM for a typical patient was shown in Fig. 2. For V30 of the small bowel, significant difference was observed (P = 0.007), while no significant differences were detected for V10, V20, and V40 (P = 0.347, P = 0.080, and P = 0.054). In addition, no significant difference was observed between BMS-HT

Table 3 Comparison of dosimetric parameters of OARs for BMS-HT and HT

OARs	Dosimetric parameters	BMS-HT	HT	*t* value	*P* value
PBM	V5	99.94 ± 0.18	100 ± 0	–1.01	0.342
	V10	81.65 ± 2.66	98.77 ± 2.05	–15.21	0.000
	V20	65.54 ± 2.15	84.23 ± 3.41	–24.95	0.000
	V30	51.26 ± 3.58	59.50 ± 9.56	–3.02	0.017
	V40	27.00 ± 5.89	32.32 ± 9.68	–1.78	0.112
Small bowel	V10	69.78 ± 21.76	73.09 ± 25.85	–1.00	0.347
	V20	48.06 ± 14.83	42.52 ± 14.91	2.01	0.080
	V30	18.02 ± 7.46	21.28 ± 7.46	–3.63	0.007
	V40	8.73 ± 5.68	9.64 ± 5.79	–2.26	0.054
Bladder	V20	71.03 ± 12.52	85.12 ± 17.76	–1.85	0.102
	V30	45.69 ± 5.71	58.73 ± 17.86	–2.36	0.046
	V40	31.01 ± 5.03	36.42 ± 8.60	–2.48	0.038
Rectum	V10	97.77 ± 2.51	98.81 ± 2.16	–1.15	0.284
	V20	87.77 ± 8.80	89.08 ± 10.46	–0.54	0.605
	V30	75.56 ± 14.43	74.90 ± 21.96	0.13	0.901
	V40	58.31 ± 21.35	53.55 ± 30.20	1.17	0.277

Note: V5, V10, V20, V30, and V40 indicated the fraction of OAR volume receiving > 5 Gy, 10 Gy, 20 Gy, 30 Gy, and 40 Gy, respectively

and HT in V20 of the bladder ($P = 0.102$). For the rectum, no significant differences were found between the two techniques in V10, V20, V30, and V40 ($P = 0.284$, $P = 0.605$, $P = 0.901$, and $P = 0.277$, respectively).

Discussion

The purpose of our study was to compare BMS-HT and routine HT planning methods with the aim to further reduce radiation dose received by PBM, which could be an important contributor to acute BM toxicity [3, 4, 20].

Several lines of evidence indicate that the reduction of low-dose radiation received by BM may decrease acute BM toxicity in patients undergoing pelvic RT. Multiple *in vitro* and *in vivo* studies have demonstrated high radiosensitivity of hematopoietic stem cells. Damage to these cells results in significant myelosuppression and low peripheral blood cell counts [21]. Up to 50% of patient's active BM is located in the os coxae, proximal femora, sacrum, and lower lumbar spine, i.e., within the conventional pelvic RT treatment ports [22]. Even at low doses, radiation causes acute and chronic pathologic changes in the BM [23–24], which can be further increased with radiation dose and volume [25–28].

IMRT is a strategy to reduce radiation dose received by BM. Several studies have examined IMRT with respect to BM irradiation and acute toxicity in gynecologic and other cancers [1, 29–30]. In their retrospective study, Brixey *et al* and Lujan *et al* [1, 11] have found that acute BM toxicity is reduced in gynecologic cancer patients treated with IMRT compared to the four-field box or AP-PA techniques. Other studies have shown that IMRT plans can be optimized to reduce BM irradiation compared to the conventional methods using extended-field and whole abdomen RT [31–32].

In our study, BMS-HT reduced irradiation of PBM compared with routine HT at all isodose levels. V5, V10, V20, V30, and V40 of PBM in BMS-HT decreased by 0.06%, 17.33%, 22.19%, 13.85%, and 16.46%, respectively, compared with those in HT, indicating that BMS-HT could help in lowering acute BM toxicity. BMS-IMRT also reduced V10, V30, and V40 of the small bowel, and a significant difference was observed in V30. V30 and V40 of the bladder decreased by 22.20% and 14.85%, respectively, compared to HT, demonstrating a significant difference. Although V30 and V40 of the rectum in BMS-IMRT increased by 0.88% and 8.89%, respectively, compared with HT, the effect was less than that in the study of Mell *et al*, who reported 86.7% and 83.7% increase, respectively [2].

In addition, there are still two major problems to be addressed. One is to identify the regions of PBM necessary and sufficient for sparing. Hematopoietically active BM is not distributed uniformly throughout the pelvis; thus, contouring the entire PBM may impose unnecessarily constrains to the IMRT planning process [33]. Magnetic resonance imaging technologies may be useful in contouring active BM on planning CT scans, where it is not visualized well [33–34].

Another issue is the degree of sparing necessary to significantly reduce the toxicity. Limiting low-dose radiation to normal tissues is a difficult problem for HT using conventional planning margins and current algorithms. Reducing the planning margins would likely improve BMS, but a significant problem is created by organ motion, which needs to be better understood and quantified. In other words, the conformal dose distributions and steep dose gradients generated around the target volumes created by HT planning require an accurate treatment setup and repeated monitoring to prevent geographic miss during RT. HT may supplement the existing approaches to allow safe reductions in planning margins, which could improve BMS-HT with its image guidance function.

Up to now, we still do not exactly know the correlation between the amount of spared volumes and toxicity reduction in RT for postoperative cervical cancer patients, which should be investigated using a larger cohort of patients and adequate follow-up.

Conclusion

For patients with cervical cancer after hysterectomy, tomotherapy-based BMS-HT reduced PBM volume receiving low-dose radiation. Therefore, BMS-HT may be conducive to preventing the occurrence of acute BM toxicity and may be a promising treatment approach. However, further investigation of BM toxicity reduction in RT using BMS-HT is required, and prospective studies are necessary to prove its clinical efficacy.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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