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FULL PAPER

Dosimetric planning study for the prevention of anal complications after post-operative whole pelvic radiotherapy in cervical cancer patients with hemorrhoids

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Objective: Radiation-induced anal toxicity can be induced by low radiation doses in patients with haemorrhoids. The object of this study was to determine the dosimetric benefits of different whole pelvic radiotherapy (WPRT) techniques in terms of dose delivered to the anal canal in post-operative patients with cervical cancer.

Methods: The planning CT images of 10 patients with cervical cancer undergoing postoperative radiotherapy were used for comparison of three different plans. All patients had been treated using the conventional box technique WPRT (CV-WPRT), and we tried low-margin-modified WPRT (LM-WPRT), three-dimensional conformal techniques WPRT (CF-WPRT) and intensity-modulated WPRT (IM-WPRT) planning for dosimetric comparison of the anal canal, retrospectively.

Results: Mean anal canal doses of the IM-WPRT were significantly lower ($p < 0.05$) than those of CV-WPRT, LM-WPRT and CF-WPRT, and V_{10} , V_{20} , V_{30} and V_{40} to the

anal canal were also significantly lower for IM-WPRT ($p < 0.05$). The proportion of planning target volumes (PTVs) that received $\geq 98\%$ of the prescribed dose for all plans was $>99\%$, and the proportion that received $\geq 108\%$ of the prescribed dose for IM-WPRT was $<2\%$. Volumes of bladders and rectums that received ≥ 30 or ≥ 40 Gy were significantly lower for IM-WPRT than for three of the four-field WPRT plans ($p = 0.000$).

Conclusion: IM-WPRT can significantly reduce radiation dose delivered to the anal canal and does not compromise PTV coverage. In patients with haemorrhoids, IM-WPRT may be of value for the prevention of anal complications.

Advances in knowledge: Although tolerance of the anal canal tends to be ignored in patients undergoing post-operative WPRT, patients with haemorrhoids may suffer complications at low radiation doses. The present study shows IM-WPRT can be meaningful in these patients.

INTRODUCTION

Radiotherapy (RT) is an indispensable treatment modality for patients with cervical cancer.^{1–3} Conventional box technique whole pelvic RT (CV-WPRT) is widely used in patients with cervical cancer postoperatively to cover the whole pelvis, including the tumour bed and pelvic lymph node chains.^{4,5} Although the treatment benefit of RT is definite, radiation-induced complications are possible in near normal organs.^{6,7} Recently, intensity-modulated whole pelvic RT (IM-WPRT) was attempted in patients with pelvic cancer, because this technique makes it possible to reduce irradiated doses to critical normal organs, such as small bowel, bladder and rectum, while producing excellent target coverage.^{8,9}

The tolerance dose of the anal canal tends to be ignored during pelvic irradiation planning because prescription doses of 45–55 Gy in fractions of 1.8–2 Gy are considered safe for

this organ.¹⁰ Furthermore, total doses delivered during post-operative whole pelvic RT (WPRT) are relatively low and the anal canal is not considered an organ at risk. However, patients with haemorrhoids can suffer complications at low radiation doses. In particular, WPRT in patients with cervical cancer with haemorrhoids can cause acute aggravation, such as anal bleeding and pain.¹¹ This implies that careful WPRT planning is required in patients with haemorrhoids. Although empirical anal block is being used in such patients to reduce the dose administered to the anal canal in some institutions, IM-WPRT could possibly provide further dosimetric benefits. Published studies on IM-WPRT generally focus on small bowel, rectal and bladder complications,^{8,12} and studies on the anal canal are rare. On the other hand, in patients with haemorrhoids undergoing RT, dosimetric evaluation of the anal canal for different WPRT plans is considered indispensable.

The purpose of this study was to evaluate radiation doses administered to the anal canal, which can contribute to radiation-induced anal complications, for different WPRT plans. More specifically, we compared CV-WPRT, low-margin-modified WPRT (LM-WPRT) with IM-WPRT in postoperative patients with cervical cancer with haemorrhoids.

METHODS AND MATERIALS

The planning CT images of 10 patients with cervical cancer undergoing postoperative RT were used in the present analysis. All patients had undergone CV-WPRT, and we tried LM-WPRT and IM-WPRT planning for dosimetric comparison of the anal canal, retrospectively. To reduce the bias by different treatment volumes in comparison with IM-WPRT planning, three-dimensional conformal techniques WPRT (CF-WPRT) were also analysed. Colonoscopy was performed as a pre-treatment evaluation in all patients, and haemorrhoids were confirmed in four patients. Acute anal symptoms such as anal pain and bleeding, were observed at 1 month after RT completion. Details of patient characteristics are summarized in Table 1.

Simulation and anal canal contouring

All patients were simulated in the supine position without a custom immobilization device and underwent CT using a Toshiba Asteion helical CT scanner (Toshiba Medical Systems, Tokyo, Japan) with 3-mm slice thickness. The resulting CT images were transferred to the Eclipse™ treatment planning system (TPS; Varian® Medical Systems, Palo Alto, CA), and target volume and critical organs such as rectum and bladder were contoured. Clinical target volumes were contoured as described by the Radiation Therapy Oncology Group (RTOG).^{13–15} Clinical target volumes were uniformly expanded by 7 mm to produce planning target volumes (PTVs). Anal canal volume was defined as volume from the anal verge to 3 cm superior to the anal verge in planning CT images.^{11,16,17}

Four-field whole pelvic radiotherapy planning

All four-field (4F) WPRT plans were generated using the Eclipse TPS with 10-MV photons. The treatment field of CV-WPRT plan was based on conventional bony structures, and regional node

coverage was accessorially confirmed by delineated PTVs. The prescribed dose was 45 Gy in 25 fractions to the PTVs. The acceptable criteria of the plan were that at least 98% of the PTV should receive 98% of the prescribed dose and that no region should be exposed to a dose >110%. CV-WPRT plans were anteroposterior (AP), posteroanterior (PA) and two lateral fields, and all fields were coplanar. As shown in Figure 1a, the superior-inferior borders of AP/PA fields were determined by considering bony anatomy, PTV and beam penumbra. The two lateral borders were set 2 cm beyond the pelvic brim with standard corner blocking. For the left/right lateral fields (Figure 1a), the superior-inferior field border were the same as the AP and PA fields. The anteroposterior border of the fields was the anterior aspect of the symphysis pubis between the S2 and S3 vertebrae. Variable field weightings were used to optimize dose homogeneity.

LM-WPRT was originally devised to reduce irradiated dose to the anal canal and has been used clinically in patients with haemorrhoids to prevent haemorrhoid aggravation. As shown in Figure 1b, the LM-WPRT plan was the same as the CV-WPRT plan except for the custom anal block, which was created in to shield a portion of the anal canal using a multi-leaf collimator (MLC). The lower edge of the MLC block in the AP/PA fields was set at 1.0–1.5 cm below the PTV and the lower limit of the lateral fields was determined by considering the specific shape and location of the anus without compromising PTV coverage. As shown in Figure 1c, the treatment field of CF-WPRT plan was based on PTVs. In addition, the MLC margin of 1.5 cm was added to the PTVs considering the beam penumbra.

Intensity-modulated whole pelvic radiotherapy planning

For IM-WPRT planning, we used seven coplanar fields and the same PTVs used in CF-WPRT plans with 10-MV photons. All IM-WPRT plans used the sliding window technique of the Eclipse TPS and gantry angles of 75°, 110°, 145°, 180°, 215°, 250° and 285°. The prescribed dose (45 Gy in 25 fractions to PTVs) was also used for IM-WPRT plans and acceptability criteria of the plan were that at least 98% of the PTV should received 98%

Table 1. Clinical characteristics of the patients ($n = 10$)

Patients	Age (years)	Stage	WPRT (Gy)	Chemotherapy	Haemorrhoid	Acute anal toxicity
1	78	IIB	50.4	N	Y	N
2	41	IB	50.4	Y	N	N
3	52	IB	50.4	Y	N	N
4	55	IIIA	45	N	N	N
5	33	IIB	45	N	Y	Anal pain, bleeding
6	38	IIB	50.4	N	N	N
7	39	IIIB	45	Y	N	N
8	42	IB	45	N	Y	Anal pain, bleeding
9	49	IB	45	Y	Y	Anal pain, bleeding
10	67	IB	45	N	N	N

WPRT, whole pelvic radiotherapy.

Figure 1. Beam's eye views of anteroposterior and left field of three of the four-field whole pelvic radiotherapy (WPRT) plans. (a) Conventional WPRT, (b) low-margin-modified WPRT, (c) conformal WPRT. CTV, clinical target volume; PTV, planning target volume.

Figure 2. Comparison of irradiated isodose distributions in the transversal planes of the four whole pelvic radiotherapy (WPRT) plans for a single patient. (a) Conventional WPRT, (b) low-margin-modified WPRT, (c) conformal WPRT, (d) intensity-modulated WPRT. The circle represents the anal canal.

of the prescribed dose and that no region should received >110%. Anal canal dose constraints and the dose-volume constraints for the OARs (organs at risk) were incorporated in plan optimizations as follows: 15% volume of the anal canal <20 Gy and 30% volume of the anal canal <10 Gy; 25% volume of the bladder <35 Gy and 50% volume of the bladder <25 Gy; 17% volume of the rectum <35 Gy and 35% volume of the rectum <25 Gy; maximum dose to the small bowel <35 Gy; 10% volume of each femoral head <30 Gy, respectively. Dose constraints for the OARs were based on the RTOG 0126 and RTOG 0822 protocols, and they were modified according to the

prescribed dose (45 Gy) of our study. The anisotropic analytical algorithm v. 8.9.17 (Eclipse; Varian® Medical Systems, Palo Alto, CA) was used for IM-WPRT plan calculations and to determine all dose-volume histogram (DVH) values.

Dosimetric evaluation parameters

Several dosimetric factors were considered in plan comparisons. The anal canal DVHs of all WPRT plans obtained using the TPS and V_{10} , V_{20} , V_{30} , V_{40} and V_{45} were calculated from DVHs. V_{dose} represents the percentage volume of the anal canal that received at least the specified dose. Other dosimetric

Table 2. Dose-volume statistics of the anal canal for three of the four-field whole pelvic radiotherapy (WPRT) plans and intensity-modulated WPRT (IM-WPRT)

Variable	CV-WPRT	LM-WPRT	CF-WPRT	IM-WPRT	p -value ^a	p -value ^b	p -value ^c	p -value ^d
Mean (Gy)	34.89 ± 7.72	29.49 ± 6.94	32.36 ± 6.68	15.02 ± 4.68	0.123	0.000	0.000	0.000
D_2 (Gy)	45.31 ± 0.90	44.77 ± 0.88	44.81 ± 0.79	13.36 ± 4.19	0.165	0.000	0.000	0.000
D_{98} (Gy)	11.76 ± 12.79	6.30 ± 4.94	10.12 ± 10.31	2.85 ± 1.76	0.315	0.001	0.004	0.002
V_{10} (%)	86.80 ± 15.07	81.32 ± 14.69	88.90 ± 11.26	51.14 ± 19.44	0.315	0.000	0.003	0.000
V_{20} (%)	79.29 ± 17.65	68.18 ± 17.68	77.03 ± 16.84	28.18 ± 11.73	0.123	0.000	0.000	0.000
V_{30} (%)	72.82 ± 20.47	56.99 ± 18.76	63.45 ± 19.49	17.36 ± 9.87	0.089	0.000	0.000	0.000
V_{40} (%)	63.58 ± 23.68	43.01 ± 19.42	48.49 ± 21.30	9.02 ± 6.96	0.052	0.000	0.000	0.000
V_{45} (%)	20.17 ± 28.44	8.17 ± 16.65	9.67 ± 18.41	2.44 ± 2.53	0.247	0.912	0.165	0.315

CF-WPRT, conformal WPRT; CV-WPRT, conventional box technique WPRT; LM-WPRT, low-margin-modified WPRT.

Values are presented as mean ± standard deviation.

^aComparison of CV-WPRT and LM-WPRT.

^bComparison of CV-WPRT and IM-WPRT.

^cComparison of LM-WPRT and IM-WPRT.

^dComparison of CF-WPRT and IM-WPRT.

Figure 3. Average dose-volume histogram comparisons for the four whole pelvic radiotherapy (WPRT) plans. (a) Anal canal, (b) planning target volume (PTV), (c) bladder and (d) rectum. CF-WPRT, conformal WPRT; CV-WPRT, conventional box technique WPRT; IM-WPRT, intensity-modulated WPRT; LM-WPRT, low-margin-modified WPRT.

factors, such as mean, D_2 and D_{98} anal doses were also analysed. D_2 and D_{98} represent the doses received by 2% and 98% volumes of the anal canal, respectively. PTV coverages were calculated and estimated using percentage volumes of the PTV that received $>98\%$ and $>108\%$ of the prescribed dose, respectively. To compare irradiated dose for the OARs in all plans, the percentage volumes of the bladder and rectum that received 30 and 40 Gy (V_{30} and V_{40}) were generated from the DVHs. Total monitor units (MUs) for all WPRT plans were calculated and analysed. Data are presented as mean $\pm$ standard deviation.

Statistical analyses

The analysis was conducted using the Mann-Whitney U test in PASW® statistics 18 (IBM Corp., New York, NY; formerly SPSS Inc., Chicago, IL). p -values of <0.05 were considered statistically significant.

RESULTS

40 plans were generated to evaluate dosimetry of the anal canals of 10 post-operative patients with cervical cancer. Irradiated isodose distributions in transversal planes of the four techniques of WPRT plans for a specific patient are shown in Figure 2 and the comparison of anal canal parameters is provided in Table 2.

Although not statistically significant, irradiated doses administered to the anal canal were lower for LM-WPRT than for CV-WPRT. In fact, mean anal canal doses administered by IM-WPRT were significantly lower ($p < 0.001$) than those of CV-WPRT or LM-WPRT. In addition, D_2 , D_{98} , V_{10} , V_{20} , V_{30} and V_{40} for IM-WPRT were also significantly lower ($p < 0.05$) than those of two of the 4F-WPRT plans (Table 2 and Figure 3a). V_{45} of the anal canal were not significantly different for the WPRT plans ($p > 0.05$), whereas the mean V_{45} of IM-WPRT was $<3\%$. A summary of PTV coverage parameters is provided in Table 3 and Figure 3b.

Table 3. Dose coverage of the planning target volumes (PTVs) for the four different whole pelvic radiotherapy (WPRT) plans

Variable	CV-WPRT	LM-WPRT	CF-WPRT	IM-WPRT	p -value ^a	p -value ^b	p -value ^c
PTV $\geq 98\%$ of the prescribed dose (%)	99.63 $\pm$ 0.45	99.45 $\pm$ 0.54	99.60 $\pm$ 0.70	99.30 $\pm$ 0.29	0.052	0.393	0.023
PTV $\geq 108\%$ of the prescribed dose (%)	5.70 $\pm$ 6.96	5.54 $\pm$ 6.80	5.86 $\pm$ 8.34	1.73 $\pm$ 1.09	0.353	0.481	0.353

CF-WPRT, conformal WPRT; CV-WPRT, conventional box technique WPRT; IM-WPRT, intensity-modulated WPRT; LM-WPRT, low-margin-modified WPRT. Values are presented as mean $\pm$ standard deviation.

^aComparison of CV-WPRT and IM-WPRT.

^bComparison of LM-WPRT and IM-WPRT.

^cComparison of CF-WPRT and IM-WPRT.

Table 4. Dose-volume statistics of the bladder and rectum volumes for three of the four-field whole pelvic radiotherapy (WPRT) plans and IM-WPRT

Variable	CV-WPRT	LM-WPRT	CF-WPRT	IM-WPRT	<i>p</i> -value ^a	<i>p</i> -value ^b	<i>p</i> -value ^c
Bladder V_{30} (%)	100	100	99.27 ± 1.49	65.36 ± 11.85	0.000	0.000	0.000
Bladder V_{40} (%)	100	100	95.28 ± 5.12	35.65 ± 14.63	0.000	0.000	0.000
Rectum V_{30} (%)	99.95 ± 0.13	99.95 ± 0.13	99.96 ± 0.10	71.32 ± 5.72	0.000	0.000	0.000
Rectum V_{40} (%)	99.16 ± 1.49	99.16 ± 1.50	99.06 ± 1.76	38.81 ± 7.70	0.000	0.000	0.000

CF-WPRT, conformal WPRT; CV-WPRT, conventional box technique WPRT; IM-WPRT, intensity-modulated WPRT; LM-WPRT, low-margin-modified WPRT. Values are presented as mean ± standard deviation.

^aComparison of CV-WPRT and IM-WPRT.

^bComparison of LM-WPRT and IM-WPRT.

^cComparison of CF-WPRT and IM-WPRT.

All WPRT plans showed excellent PTV coverage. For all plans, 99% of PTVs received ≥98% of the prescribed dose. However, 5.70%, 5.54%, 5.86% and 1.73% of PTVs received ≥108% of the prescribed dose by CV-WPRT, LM-WPRT, CF-WPRT and IM-WPRT, respectively (Table 3, $p > 0.05$). The volume of PTV receiving ≥110% of the prescribed dose was not observed in all WPRT plans.

A comparison of the bladder and rectal volumes is provided in Table 4 and Figure 3c,d. The volumes of bladders and rectums receiving ≥30 and ≥40 Gy were significantly lower for IM-WPRT than for 4F-WPRT ($p = 0.000$). The mean total MUs and standard deviations were 212.9 ± 5.9, 213.4 ± 5.6, 212.7 ± 6.1 and 1309.4 ± 91.2 for CV-WPRT, LM-WPRT and IM-WPRT, respectively. In the present dosimetric study, IM-WPRT significantly reduced anal canal dosimetric factors as compared with 4F-WPRT. However, the MU of IM-WPRT was greater than that of 4F-WPRT.

DISCUSSION

WPRT using the box technique has been widely applied as an adjuvant treatment in post-operative patients with cervical cancer. However, the CV-WPRT technique includes the large and considerable volumes of normal organs, such as the small bowel, rectum and bladder. The exposure of OARs is an important issue during the treatment of prostate cancer, which requires high total radiation doses. For these reasons, the IM-WPRT technique has been used on a trial basis to reduce the dose delivered to OARs.^{18–20} Although post-operative IM-WPRT may be less attractive because total radiation dose is within the tolerable dose, we considered that post-operative IM-WPRT might be valuable in patients with haemorrhoids.

Generally, the anal canal is not considered an OAR during WPRT planning because it is believed that radiation-induced

anal complications are rare at the doses prescribed for post-operative WPRT. However, low levels of radiation exposure can induce acute anal complications in patients with haemorrhoids receiving WPRT.¹¹ Although these acute anal complications recover spontaneously, they cause continuous pain and are protracted in nature. Thus, because there is no definite treatment, careful WPRT planning is indispensable in patients with haemorrhoids to prevent radiation-induced anal complications.

The LM-WPRT approach using MLC block of the anal canal has been applied empirically in some institutions. However, the present study shows that the use of LM-WPRT did not induce a significant reduction in dosimetric parameters as compared with CV-WPRT. It is believed that this unsatisfactory result was caused by restrictive beam direction and high deviation of the anal canal. In the context of RT planning, the length and location of the anal canal show high deviation in the supine position.¹¹ Although it is widely known that the length of the anal canal extends approximately 3–5 cm from the anal verge,²¹ it is difficult to differentiate the anal canal and rectum on CT images for RT planning. Accordingly, the location of the anal canal is an important factor, and if the PTV is close to the anal canal, anal block cannot be applied appropriately.

In the present study, doses (mean, V_{10} – V_{40}) administered to the anal canal were significantly lower for IM-WPRT than for three of the 4F-WPRT plans (Table 2 and Figure 3a). In addition, IM-WPRT was able to effectively reduce the dose delivered to the anal canal regardless of anal canal location and length. Furthermore, IM-WPRT plans provided excellent PTV coverage and significantly improved OAR (bladder and rectum) dose sparing, as shown in Tables 3 and 4 and Figure 3b–d. However, IM-WPRT has some disadvantages. As shown in Table 5, the

Table 5. Total monitor units for the four different plans

Total MUs	CV-WPRT	LM-WPRT	CF-WPRT	IM-WPRT
Mean MU ± SD	212.9 ± 5.9	213.4 ± 5.6	212.7 ± 6.1	1309.4 ± 91.2
Minimum MU	202	203	205	1162
Maximum MU	222	222	224	1407

CF-WPRT, conformal WPRT; CV-WPRT, conventional box technique WPRT; IM-WPRT, intensity-modulated WPRT; LM-WPRT, low-margin-modified WPRT; MU, monitor units; SD, standard deviation; WPRT, whole pelvic radiotherapy.

mean MUs of IM-WPRT were approximately five times greater than that of three of the 4F-WPRT plans, which implies that the IM-WPRT approach increases total body scatter dose and treatment time. In addition, IM-WPRT requires more time to optimize planning and for quality assurance, and, thus, increases workloads as compared with 4F-box technique WPRT. Total body scatter dose can be reduced if the volumetric-modulated arc therapy (VMAT) technique can be applied. This technique can also reduce total MUs without compromising plan quality as compared with IM-WPRT.^{22–24} Therefore, despite its disadvantages, we believe IM-WPRT is suitable for the treatment of post-operative patients with cervical cancer with haemorrhoids to prevent acute anal toxicity.

There are some published studies^{25,26} about the displacement of vaginal vault. Unfortunately, the present study is a retrospective setting, and we did not use markers or cylinders to localize the vaginal vault, and there was no proper guideline about the dose constraint of the anal canal. Although there are several studies^{27,28} about the tolerance of the anal canal, they are just about late complications. Our study was focused on the acute anal complication in patients with haemorrhoids, and the published study¹¹ about acute anal toxicity is rare. A previous study²⁹

demonstrated that 34.1 Gy is the induction dose of acute anal symptoms in patients with haemorrhoids, and we conservatively chose the dose objective of the anal canal. To apply IM-WPRT plan in the clinical field, the accurate target delineation and the proper dose constraint of the anal canal is a requisite. Nevertheless, we thought that the present study is valuable to introduce the benefit of IM-WPRT for the prevention of acute anal complications.

In the clinical field, most institutions do not use workload IM-WPRT for post-operative RT regardless of the presence of haemorrhoids. Furthermore, because it increases workload and treatment time, IM-WPRT may not be attractive to clinicians. However, IM-WPRT makes it possible to reduce acute anal toxicity and increase the quality of life of patients with haemorrhoids. In the present study, we analysed the dosimetric parameters of RT treatments afforded to postoperative patients with cervical cancer by comparing different WPRT plans. We found that IM-WPRT can significantly reduce the dose administered to the anal canal without compromising PTV coverage compared with the 4F-WPRT plans. In our opinion, IM-WPRT is probably of value for patients with haemorrhoids and suggests that a clinical study be conducted on this topic.

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