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Effect of different treatment plans on irradiated small-bowel volume in gynecologic patients undergoing whole-pelvic irradiation

Shih-Chen CHANG[1], Hsiao-Fei LEE[1], Hui-Min TING[1], Tzu-Chao PAN[2], Shu-Yu LIU[1], Chien-Fu CHEN[1], Teng-Yi WANG[1], Kuo-Jung JUAN[1], Tsung-I LIAO[1] and Eng-Yen HUANG[1,3,*]

[1]Department of Radiation Oncology, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung, Taiwan
[2]Department of Nuclear Medicine, Antai Medical Care Coorperation Antai Tian-Sheng Memorial Hospital, Pingtung, Taiwan
[3]School of Traditional Chinese Medicine, Chang Gung University College of Medicine, 259 Wen-Hwa 1st Road, Kwei-Shan Tao-Yuan 333, Taiwan
*Corresponding author. Department of Radiation Oncology, Kaohsiung Chang Gung Memorial Hospital, 123, Ta-Pei Road, Niao-Sung District, Kaohsiung 833, Taiwan. Tel: +886-7-731-7123 ext. 2600; Fax: +886-7-732-2813; Email: huangengyen@gmail.com

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To evaluate the effect of different treatment plans for whole-pelvic irradiation on small-bowel volumes (SBVs) in patients with gynecologic malignancies, 40 patients were enrolled in this study. Computed tomography (CT) simulations were performed, and the small bowel of each patient was outlined manually. Treatment plans with equal-weighted (EW) and non-equal-weighted (NEW) (70% in bilateral directions) techniques of four-field and intensity-modulated radiation therapy (IMRT) were performed. The V10–V100 represented the volume (cm^3) at different levels of the prescribed doses (10–100%). The V10–V100 was compared among the different treatment planning techniques, and patients who were suitable for IMRT or NEW were identified. IMRT and NEW significantly reduced the V50–V100 and V40–V60 levels compared with EW, respectively. NEW caused a significant reduction in the V30–V60 levels in patients with a BMI $\geq$26 kg/m^2. Patients with IMRT demonstrated lower V70–V100 levels compared with those with NEW. In patients with a BMI $\geq$26 kg/m^2 or an age $\geq$55 years, lower V20–V50 levels were noted using NEW compared with IMRT. Treatment planning with larger weighting in the bilateral directions in four-field radiotherapy reduces the low-dose SBV in patients with gynecologic malignancies, especially in those with a high BMI or the elderly. IMRT effectively reduces high-dose SBV, especially in patients with a low BMI.

Keywords: BMI; small bowel; non-equal weighting; IMRT; four-field radiotherapy

INTRODUCTION

The small bowel is one of the major organs at risk (OARs) during pelvic irradiation. The tolerance dose of the small bowel is lower than that of the colon, rectum, and urinary bladder. Hence, radiation can easily damage the small bowel. However, patients with gynecologic malignancies, such as cervical cancer or endometrial cancer, usually undergo whole-pelvic irradiation because the pelvic lymph nodes always fall within the clinical target volume (CTV). Hence, a high dose of radiation to the small bowel near the CTV is inevitable, and intestinal complications are possible. In patients with previous abdominal surgery, the fixed bowel loop increases the risk of bowel sequelae [1, 2]. Hence, the determination of techniques that decrease radiation-induced small-bowel damage is important. The conventional method used for whole-pelvic radiotherapy to treat gynecologic cancer employs a box-field technique. Computed tomography (CT)- based treatment planning offers accurate dosimetry at the CTV and the OAR. However, some of the bowel loop in the 'box' receives a full prescription dose. Intensity-modulated radiation therapy (IMRT) overcomes the box-field disadvantage and reduces the high-dose volume of a small-bowel dose. However, the

IMRT increases the irradiated non-target volume (low-dose volume) [3]. Some studies have demonstrated an effect of a low-dose volume on the small bowel [4–8]. The distribution of the small bowel is diverse. At places where the small bowel loop disperses in the pelvis, the IMRT may include a larger low-dose volume. The four-field technique with large bilateral weighting may aid in sparing the anterior portion of the small bowel and reduce the low-dose small bowel volume. The distribution of the small bowel may differ in elderly [9] or obese patients [10]. Therefore, the effect of advanced treatment planning may be different in these patients compared with young or slim patients. Hence, in the current study, we compared the equal weighting technique, the non-equal weighting technique, and IMRT techniques with respect to the prevention of radiation-induced complications in patients with different ages and BMIs.

MATERIALS AND METHODS

Patient characteristics and CT simulation

For the present study, we enrolled 40 patients with histologically proven gynecologic malignancies who were scheduled to receive whole-pelvic radiotherapy during the period from July 2008–November 2009. The institutional review board at our hospital (97-1370B) approved this study. Table 1 shows the patient characteristics. A computed tomography (CT) simulator (Lightspeed series, GE Medical Systems, Milwaukee, WI) was used to capture the images. Bladder emptying then drinking oral contrast solution (4% gastrograffin, Mallinckrodt Medical, St Louis, MO) to identify the small bowel sixty min before the simulations was required. At the time of intake of oral contrast solution, patients were encouraged to avoid emptying their bladders to control urination until completion of CT simulation. Each patient was asked to lie on the simulation couch in a supine position with the pelvis holder just before the CT simulations. A thermoplastic cast was used to immobilize the low abdomen-pelvis of the patient, and the therapist obtained axial images from the T10 spine to the upper thigh in 5-mm adjacent slices. After the CT simulation, the therapist exported the CT simulation images to the Pinnacle treatment planning system (version 8.0, ADAC Laboratories, Milpitas, CA) for 3D reconstruction and treatment planning.

Table 1. Characteristics of patients ($n = 40$)

Characteristics	No. (%)
Age (years)	
<40	4 (10%)
41–50	7 (17.5%)
51–60	17 (42.5%)
61–70	7 (17.5%)
>70	5 (12.5%)
BMI (kg/m^2)	
<18.5	1 (2.5%)
18.6–23.9	12 (30%)
24–26.9	14 (35%)
27–29.9	6 (15%)
30–34.9	6 (15%)
≥35	1 (2.5%)
Disease	
Cervical cancer	29 (72.5%)
Endometrial cancer	9 (22.5%)
Uterine sarcoma	2 (5%)
Abdominal surgery	
Abdominal total hysterectomy and BSO	12 (30%)
LAVH and BSO	1 (2.5%)
Radical abdominal hysterectomy and BSO	2 (5%)
Appendectomy	5 (12.5%)
Caesarean section	3 (7.5%)
Others	3 (7.5%)
No	14 (35%)
External beam techniques at treatment	
IMRT	16 (40%)
EW	1 (2.5%)
NEW (bilateral 30%)	2 (5%)
NEW (bilateral 60–70%)	10 (25.0%)
NEW (bilateral 70%)	9 (22.5%)
Refuse RT	2 (5%)

BMI = Body mass index, BSO = bilateral salpingo-oophorectomy, EW = equal weighting, NEW = non-equal weighting, IMRT = intensity-modulated radiation therapy.

Treatment planning

After importing the images into the treatment planning system, the physician manually outlined the CTV on all of the CT slices and the OARs, including the small bowel, the large bowel, the rectum, the femur head, and the urinary bladder. The CTV included the lymph nodes (internal, external, common iliac, and presacral), the intact uterus (or tumor bed), the proximal vagina, the parametrium, and the uterosacral ligament in those tumor cases without involvement of the lower half of the vagina. Distal vagina was included in fields while low vagina.was involved by tumor. The superior border of the pelvic CTV was typically 1 cm below L4–L5. The planned target volume (PTV) was expanded 1 cm from the CTV in all directions. Inter-observer variation in CTV was evaluated. The small bowel loop was contoured with exclusion of the peritoneal surface and mesentery, from the cul-de-sac to 1 cm above the PTV. Treatment planning was performed with different box-field weightings and IMRT. The plan evaluation was based on the dose-volume histograms (DVHs). We used a convolution/superposition algorithm for the dose model. We made no correction for contrast of small bowel in the dose calculation.

Plan categories

This is a study of plan exercise for comparison among three treatment techniques. The planned dose to the PTV was 39.6 Gy/22 fractions for 31 patients, and 45 Gy/25 fractions for 9 patients. IMRT plans were created with seven axial 10-MV beam angles (30°, 80°, 130°, 180°, 230°, 280° and 330°). The dose was then delivered using the step-and-shoot approach. A clinically optimized treatment plan was generated based on constraints that permitted delivery of the dose to the PTV while minimizing the dose delivered to the OARs with constraints (3% weighting) to limit the maximum dose to the rectum, bladder and small bowel to as low as 35 Gy, 35 Gy and 28 Gy, respectively. All of the IMRT plans were carried out with mean dose of PTV for prescription. Conventional equal weighting (EW) and non-equal weighting (NEW) were compared in four-field whole-pelvic planning. Based on our previous study showing that V40 (volume of small bowel receiving 40% prescribed dose) was important for acute small bowel toxicity in patients without abdominal surgery [6], in the present study, we attempted to reduce V40 of the small bowel using bilateral weighting (35%/35%) and anterior-posterior/posterior-anterior (AP/PA) (15%/15%) to spare the anterior small bowel as much as possible. We used the geometric center point of the PTV as the normalized point in each plan. The DVH was obtained for each plan, and the following criteria were used to judge the quality of our department's planning. The Out-PTV–$V_{110\%}$ is the volume outside of the PTV that received 110% of the dose. The present study used data from the plans for different weightings and IMRT. Our department's criteria for PTV coverage are PTV–$V_{100\%} \geq 95\%$, PTV–$V_{95\%} \geq 99\%$, PTV–$V_{110\%} \leq 20\%$, and Out-PTV–$V_{110\%} \leq 1\%$.

Small bowel volume

We define Vn as the volume of the small bowel receiving n % of the prescribed dose for each 10% dose increment in volume of the small bowel (V10–V100). The volume of the irradiated small bowel was obtained from DVH for doses between 10% (V10) and 100% (V100) of the prescribed dose at 10% intervals. According to the study in which V40 and V100 were identified as important parameters of the volume effect [6], in the present study, the volume change was compared between the EW four-field and another plan. We defined $V40_{EW-NEW}$ ($V40_{EW}$ minus $V40_{NEW}$) and $V100_{EW-IMRT}$ ($V100_{EW}$ minus $V100_{IMRT}$) as the absolute volume reduction by NEW or IMRT technique. $R40_{NEW}$ (defined as $V40_{EW-NEW}/V40_{EW}$) and $R100_{IMRT}$ (defined as $V100_{EW-IMRT}/V100_{EW}$) represented the corresponding relative volume reduction. Our goal herein was to evaluate the correlations of $V40_{EW-NEW}$, $R40_{NEW}$, $V100_{EW-IMRT}$, and $R100_{IMRT}$ with age and BMI.

Technique during radiotherapy

The technique used for radiotherapy was dependent on the hysterectomy and the SBV. In general, IMRT was chosen in patients undergoing hysterectomy, patients with both a history of abdominal surgery and a high V100 (>250 ml) using the EW plan, and patients without a history of abdominal surgery but with a high V100 (>400 ml) using the EW plan. Choice of weighting, i.e. EW or NEW, was dependent on lower V40 and V100 [6]. As a result, 1, 9 and 16 patients underwent EW, NEW and IMRT techniques, respectively; 12 patients received NEW other than 70% in bilateral directions; 2 patients withdrew from radiotherapy (Table 1).

Grading of treatment-related toxicities

The general principle of management for acute small bowel toxicity has been described previously [6]. We used common toxicity criteria [11] for acute small bowel toxicity, and RTOG/EORTC criteria [12] for late gastrointestinal (GI) and genitourinary (GU) toxicities.

Statistics

The effect of EW, NEW and IMRT on the mean of SBVs (V10–V100 as a continuous variable) in the same patient was compared using a repeated measurement analysis of variance (ANOVA). The Bonferroni *post hoc* comparison was used to compare SBVs between the groups. Correlations of the SBVs or SBV differences/ratios with age or BMI were calculated using the Pearson's correlation and multiple linear regression. Age and BMI cut-offs for grouping were established based on the median values. A P value < 0.05 was regarded as statistically significant. Statistical analyses were performed using the Statistical Package for Social Sciences, version 17.0 on a personal computer (SPSS Inc., Chicago, IL).

RESULTS

Dose homogeneity among different planning techniques

The 95% confidence interval of intraclass correlation coefficient for inter-observer variation in the CTV was 0.950–0.987. The PTV – $V_{95\%}$, PTV – $V_{100\%}$, PTV – $V_{110\%}$ and out-PTV – $V_{110\%}$ were 99.77 ± 0.05%, 96.86 ± 0.18%, 2.57 ± 0.61% and 0.21 ± 0.06%, respectively, in the EW planning. The corresponding data for NEW were 99.66 ± 0.52%, 96.26 ± 0.16%, 8.63 ± 1.28% and 0.85 ± 0.16%, and those for IMRT were 99.74 ± 0.31%,

Table 2. Small bowel volumes (SBVs) (cm^3) and planned target volume (PTV) for different plans

Parameters	EW	NEW	*P* value	IMRT	*P* value
PTV–$V_{95\%}$	99.77 ± 0.05	99.66 ± 0.05	0.002	99.74 ± 0.03	1.000
PTV–$V_{100\%}$	96.86 ± 018	96.26 ± 0.16	0.073	96.20 ± 0.17	0.002
PTV–$V_{110\%}$	2.58 ± 0.62	8.63 ± 1.29[a]	<0.001	1.03 ± 0.33	0.088
Out-PTV–$V_{110\%}$	0.21 ± 0.06	0.85 ± 0.16[a]	<0.001	0.001 ± 0.001	0.014
V10	486 ± 30	486 ± 30	1.000	496 ± 30	0.078
V20	450 ± 28	449 ± 28[b]	1.000	463 ± 28	0.031
V30	422 ± 27	420 ± 27[b]	0.526	439 ± 27	0.005
V40	402 ± 26	356 ± 26[b]	<0.001	406 ± 26	1.000
V50	382 ± 26	304 ± 25[b]	<0.001	343 ± 22	<0.001
V60	307 ± 24	282 ± 24	<0.001	276 ± 19	0.013
V70	245 ± 22	262 ± 23[a]	<0.001	204 ± 17	0.005
V80	223 ± 22	237 ± 23[a]	0.001	146 ± 15	<0.001
V90	202 ± 21	201 ± 21[a]	0.665	100 ± 11	<0.001
V100	177 ± 20	178 ± 20[a]	1.000	59 ± 7	<0.001

EW = equal weighting, IMRT = intensity-modulated radiation therapy, NEW = non-equal weighting, PTV = Planned Target Volume. Data represent the mean ± standard error of the mean (SEM).
[a]Statistically significant small SBV of IMRT compared with NEW.
[b]Statistically significant small SBV of NEW compared with IMRT.

96.20 ± 0.17%, 1.03 ± 0.33% and 0.001 ± 0.001%. The statistical comparisons are shown in the Table 2.

V40 and V100 reductions with different planning, and factors associated with the effective volume reduction

Table 2 shows the comparisons of different SBVs among different plans. V40–V60 were significantly reduced in the NEW plan compared with the EW plan. V50–V100 were significantly reduced in the IMRT plan compared with the EW plan. Figure 1 shows iso-dose curves among the different plans. The correlations between SBV-related parameter ($V40_{NEW-EW}$, $R40_{NEW}$, $V100_{IMRT-EW}$, or $R100_{IMRT}$) and patient-related factor (age or BMI) are shown in Table 3. Age was positively correlated with $V40_{EW-NEW}$ and $R40_{NEW}$, and BMI was positively correlated with $R40_{NEW}$ but inversely correlated with $V100_{EW-IMRT}$ (Fig. 2A). A multiple linear regression analysis confirmed the corresponding data correlation (Table 3). In addition, a correlation between uterine volume and age was noted ($r = –0.580$, $P = 0.004$).

Small bowel volumes in patients with different ages and BMIs

BMI ($r = –0.591$, $P < 0.001$) (Fig. 2B) but not age ($r = –0.144$, $P = 0.374$) was correlated with $V100_{EW}$. BMI ($r = –0.369$, $P = 0.019$) but not age ($r = 0.241$, $P = 0.135$) was correlated with $V40_{EW}$. Age ($r = 0.359$, $P = 0.023$) but not BMI ($r = –0.192$, $P = 0.236$) was correlated with $V10_{EW}$.

Age and BMI cut-offs were established based on the median values. The SBVs were compared for the EW plan as follows. In patients with a BMI <26 kg/m^2 (Fig. 3), NEW decreased V50 only, and IMRT decreased V50 and V80–V100. In patients with a BMI ≥26 kg/m^2 (Fig. 3), NEW decreased V30–V60, and IMRT decreased V50 and V70–V100. In patients with an age <55 years (Fig. 4), NEW decreased V40 and V50, and IMRT decreased V50 and V80–V100. In patients with an age ≥55 years (Fig. 4), NEW decreased V40–V60, and IMRT decreased V50 and V80–V100.

SBVs in patients with NEW and IMRT

Patients with IMRT had lower V70–V100 levels compared with those with NEW (Table 2, and Figs 3–4), irrespective of age or BMI. In patients with a BMI ≥26 kg/m^2 (Fig. 3) or an age ≥55 years (Fig. 4), lower V20–V50 levels were noted using NEW compared with IMRT. In other analyses, no differences in V20–V50 were noted between NEW and IMRT in patients with a BMI <26 kg/m^2 (Fig. 3), or an age <55 years (Fig. 4).

SBVs in patients undergoing radical and post-operative radiotherapy

Surgery previous to radiotherapy affects small-bowel distribution and can affect its DVH. It is necessary to analyze

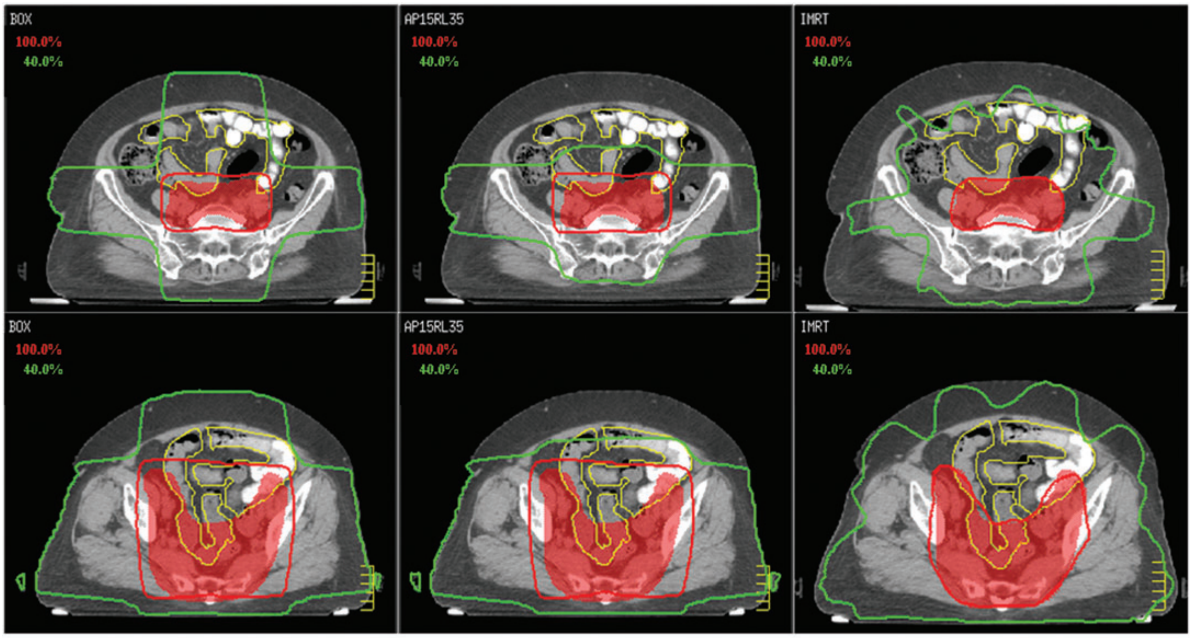

Fig. 1. Iso-dose curves for the different plans in a representative patient. IMRT and non-equal weighting in the four-field reduce the high-dose (V100: red curve) and low-dose (V40: green curve) volumes of the small bowel, respectively.

Table 3. Correlation and multiple linear regression to determine changes in the small bowel volume with age or BMI

Parameters		$V40_{EW–NEW}$	$R40_{NEW}$	$V100_{EW–IMRT}$	$R100_{IMRT}$
Pearson's correlation					
Age	*r* value	0.544	0.485	–0.062	0.187
	P value	<0.001	0.002	0.704	0.248
BMI	*r* value	0.237	0.353	–0.577	0.123
	P value	0.141	0.026	<0.001	0.448
Multiple linear regression					
Age	Coefficient	2.945	0.006	–0.010	
	P value	<0.001	0.002	0.939	NS
BMI	Coefficient	1.90	0.010	–12.201	
	P value	0.168	0.027	<0.001	NS

NS = non-significant.

data including surgical history as a factor. Table 4 shows the comparisons of different SBVs among different plans in patients undergoing radical radiotherapy. V40–V60 were significantly reduced in the NEW plan compared with the EW plan. V50 and V70–V100 were significantly reduced in the IMRT plan compared with the EW plan. Table 5 shows the comparisons of different SBVs among different plans in patients undergoing post-operative radiotherapy. V50–V60 were significantly reduced in the NEW plan compared with the EW plan. V80–V100 were significantly reduced in the IMRT plan compared with the EW plan.

Treatment-related toxicities

Two patients withdrew from radiotherapy, the remaining 6 (15.8%), 12 (31.6%), 13 (34.6%) and 7 (18.4%) patients had Grade 0, 1, 2 and 3 acute diarrhea, respectively. The corresponding rate was 0%, 37.5%, 37.5% and 25% using the NEW plan, and the rate was 31.3%, 25%, 31.3% and 19.4% using the IMRT plan.

No Grade 3 or greater late GI toxicity was noted. One patient died of an unknown cause during radiotherapy, the remaining 27 (73.0%), 8 (21.6%) and 2 (5.4%) patients had Grade 0, 1 and 2 GI toxicity, respectively. Neither the

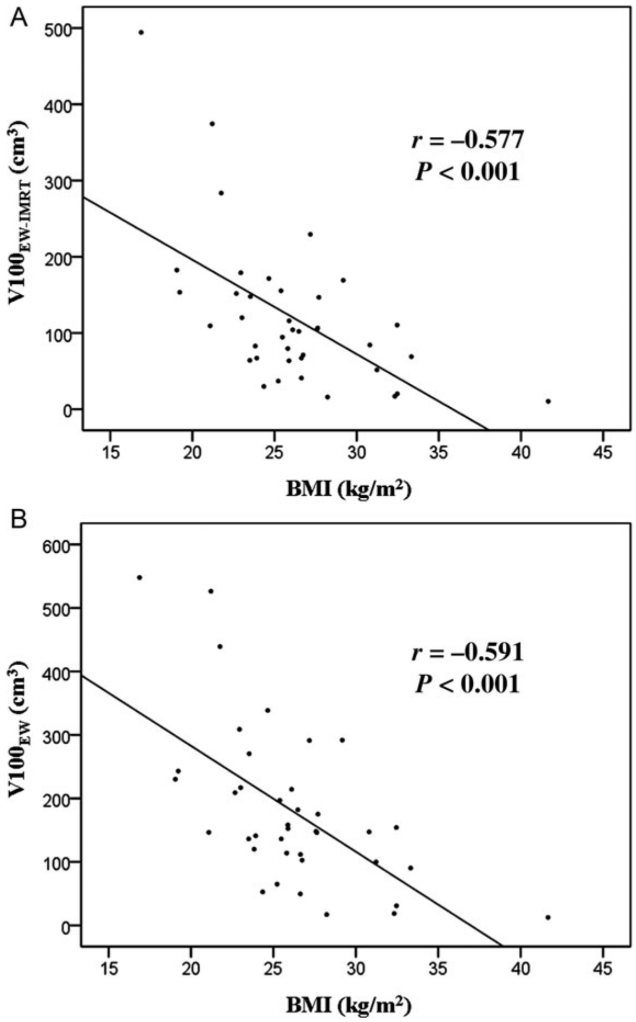

Fig. 2. Correlation of BMI with $V100_{EW–IMRT}$ (**A**) and $V100_{EW}$ (**B**).

patients undergoing the NEW technique, nor those undergoing the IMRT technique had Grade 2 or greater toxicity. The corresponding Grade 1 incidence was 12.5% (1/8) and 18.8% (3/16). No Grade 4 or greater late GI toxicity was noted.

Grade 1, 2 and 3 late GU toxicities were noted in 3 (8.1%), 0 (0%) and 1 (2.7%) patients, respectively. Neither the patients undergoing the NEW nor the IMRT technique had Grade 2 or greater toxicity. The corresponding Grade 1 incidence was 12.5% (1/8) and 6.25% (1/16). No pelvic or femoral bone complications were noted.

DISCUSSION

A reduction of the SBV to diminish acute and late enteric toxicity is the aim of advanced RT techniques for gynecologic patients. Dosimetric studies comparing conventional 4-field and IMRT favor IMRT for small-bowel sparing. D'Souza *et al.* compared four-field and IMRT techniques in 10 patients who were undergoing post-operative RT for cervical cancer [13]. They contoured the small bowel, including the volume surrounding the bowel loops to the edge of the peritoneum. Hence, a large volume of the small bowel was noted in their analysis. The volume of the small bowel at the level of 25, 30, 35, 40, 45 and 50 Gy decreased significantly in IMRT planning at the prescribed dose of 50.4 Gy. The approximate volume levels ranged from V50–V100, similar to the results of our comparison of EW and IMRT planning (Table 2). Ahamad *et al.* also reported similar results (30–45 Gy for prescription of 45 Gy) (i.e. V67–V100) in patients with hysterectomies [10]. Volumes receiving below 25 Gy (V56 in our definition) appeared to be similar between four-fields and IMRT planning. Roeske *et al.* also contoured the small bowel, including the peritoneal cavity, and they used the relative volume (percentage) of the small bowel for the analysis [14]. The low-dose volume of small bowel (20 Gy for a prescription of 45 Gy) (i.e. V44) was also significantly smaller in IMRT (76%) than in four-field planning (85%). However, the 30-Gy volume was not different. Taken together, the results show that IMRT decreases high-dose volumes in the small bowel in patients with gynecologic malignancies. The role of IMRT in the low-dose volume of the small bowel remains controversial.

Although IMRT reduced the high-dose volume of the small bowel, clinical data obtained for acute and late toxicities are limited. Mundt *et al.* reported that IMRT decreased acute GI and GU toxicities in gynecological patients [15]. However, they did not report the dosimetric data. Chen *et al.* reported similar results in patients who were undergoing post-operative CCRT for cervical cancer [16]. In addition, chronic GI toxicity also decreased in these patients. Although they noted a decrease in V50, V70, V90 and V100 for the SBV (%) in IMRT, they did not report the correlation of the SBV and the toxicity grade. Although the literature contains few reports concerning SBV effects on late complications, one of the aims of IMRT is to decrease acute and late complications through decreased dose volumes for OARs. Gallagher *et al.* noted a high-dose (>45 Gy) volume effect on the gastrointestinal tract [1]. Letschert *et al.* reported a high chronic diarrhea rate as an SBV effect in patients undergoing post-operative RT for rectal cancer [2]. The diarrhea rate increased from 32% (volume $<77\ cm^3$) to 41% (volume $>328\ cm^3$). Their analysis noted no volume effect on small bowel obstruction. Further studies of volume effects on late small bowel complications are encouraged.

Growing evidence for a low-dose volume effect on the small bowel in acute enterotoxicities demonstrates the importance of a low-dose volume [4–8]. Huang *et al.* demonstrated a low-dose volume (V40) effect on acute enterotoxicities in patients without prior abdominal surgery

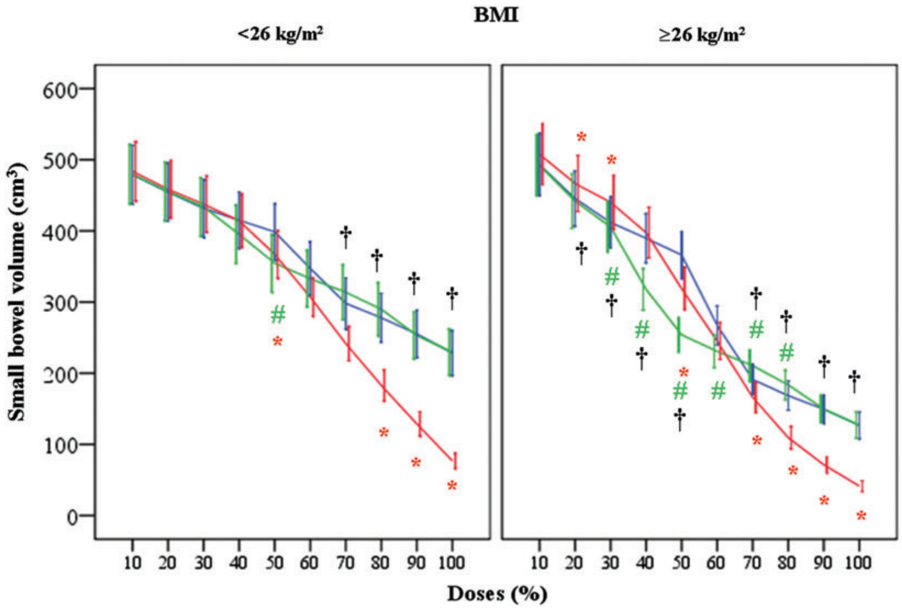

Fig. 3. Dose-volume relationships in patients with low and high BMIs. The asterisk represents a significant difference between the IMRT (red line) and EW (blue line) techniques. The hash sign denotes a significant difference between the NEW (green line) and EW techniques. The dagger indicates a significant difference between the NEW and IMRT techniques.

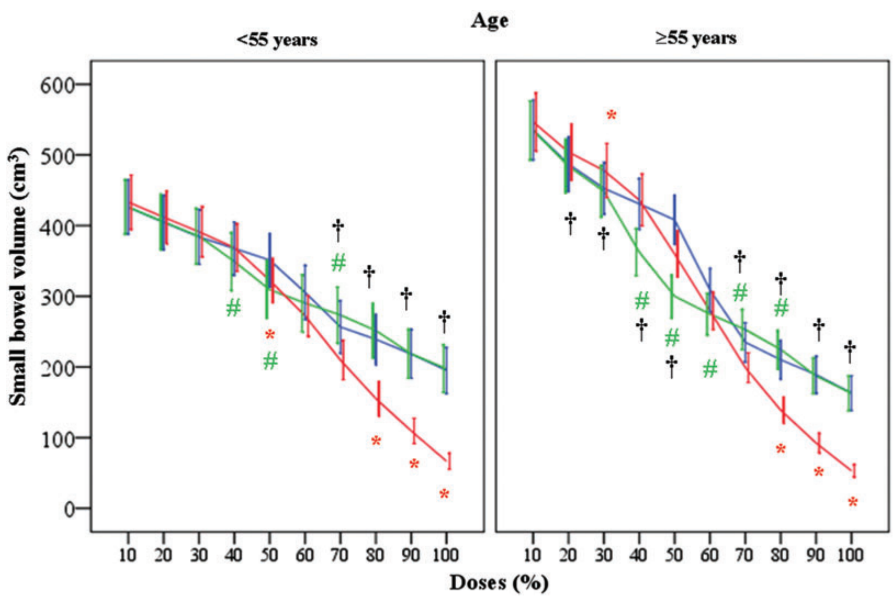

Fig. 4. Dose-volume relationship in young and old patients. The asterisk indicates a significant difference between the IMRT (red line) and EW (blue line) techniques. The hash sign denotes a significant difference between the NEW (green line) and EW techniques. The dagger indicates a significant difference between the NEW and IMRT techniques.

[6]. In addition, a high-dose volume (V100) effect was observed in those patients who had undergone abdominal surgery. Hence, techniques to minimize the low-dose volume remain a challenge. In the present study, attempts to reduce both high-dose and low-dose volumes of the small bowel provided conflicting results. IMRT seldom reduced the low-dose volume (<V50) of the small bowel in other studies and herein. Hence, appropriate planning to

Table 4. Small bowel volumes (SBVs) (cm^3) for different plans in patients undergoing radical radiotherapy ($n = 25$)

	EW	NEW	*P* value	IMRT	*P* value
V10	495 ± 38	494 ± 38	1.000	507 ± 37	0.204
V20	451 ± 35	449 ± 35[b]	0.635	470 ± 36	0.020
V30	419 ± 34	415 ± 34[b]	0.065	444 ± 36	0.002
V40	398 ± 33	329 ± 30[b]	<0.001	405 ± 34	0.497
V50	375 ± 32	279 ± 28[b]	<0.001	334 ± 30	<0.001
V60	275 ± 27	257 ± 27	0.016	259 ± 25	0.286
V70	215 ± 25	235 ± 26[a]	0.001	183 ± 20	0.031
V80	194 ± 24	209 ± 25[a]	0.004	127 ± 16	<0.001
V90	172 ± 24	172 ± 23[a]	1.000	88 ± 13	<0.001
V100	147 ± 22	148 ± 22[a]	0.706	52 ± 8	<0.001

EW = equal weighting, NEW = non-equal weighting, IMRT = intensity-modulated radiation therapy. Data represent the mean ± standard error of the mean (SEM).
[a]Statistically significant small SBV of IMRT compared with NEW.
[b]Statistically significant small SBV of NEW compared with IMRT.

Table 5. Small bowel volumes (SBVs) (cm^3) for different plans in patients undergoing post-operative radiotherapy ($n = 15$)

	EW	NEW	*P* value	IMRT	*P* value
V10	471 ± 49	472 ± 49	1.000	476 ± 49	0.232
V20	447 ± 47	448 ± 47	1.000	450 ± 43	1.000
V30	426 ± 46	428 ± 46	0.931	431 ± 42	1.000
V40	409 ± 44	402 ± 46	0.338	408 ± 39	1.000
V50	395 ± 43	346 ± 46	0.004	356 ± 34	0.052
V60	361 ± 42	324 ± 45	0.025	304 ± 30	0.062
V70	294 ± 41	306 ± 44	0.355	239 ± 30	0.165
V80	272 ± 39	284 ± 43[a]	0.291	177 ± 26	0.018
V90	253 ± 37	251 ± 38[a]	0.194	121 ± 20	0.001
V100	228 ± 35	229 ± 36[a]	1.000	71 ± 12	<0.001

EW = equal weighting, NEW = non-equal weighting, IMRT = intensity-modulated radiation therapy. Data represent the mean ± standard error of the mean (SEM).
[a]Statistically significant small SBV of IMRT compared with NEW.

reduce the low-dose volume is important if this parameter is a major concern. The specific aim of our study was to identify BMI and age as indices for patient selection. In patients with a BMI <26 kg/m^2 or an age <55 years, there was no superiority of NEW over IMRT at levels of V20–V50. Hence, we suggest IMRT for this group. In patients

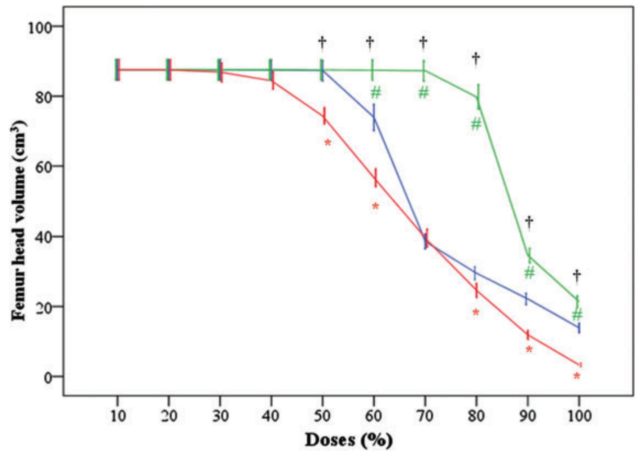

Fig. 5. Dose-volume relationships of femur head in different plans. The asterisk represents a significant difference between the IMRT (red line) and EW (blue line) techniques. The hash sign denotes a significant difference between the NEW (green line) and EW techniques. The dagger indicates a significant difference between the NEW and IMRT techniques.

with a BMI ≥26 kg/m^2 (Fig. 3) or an age ≥55 years (Fig. 4), NEW was superior to IMRT at levels of V20–V50 levels. IMRT was a superior solution for high-dose SBV in all of the patients who had undergone abdominal surgery. The results of the present study suggest that NEW should be used in patients without a history of abdominal surgery because late complications may be rare in this group, especially in patients with a BMI ≥26 kg/m^2 or an age ≥55 years.

Concerning V100 due to late complications, IMRT is the technique of first choice. With respect to the patient that demonstrated greater sparing of the small bowel, our results revealed an inverse correlation between $V100_{EW-IMRT}$ and BMI (Fig. 2). Patients with a low BMI demonstrated a greater amount of sparing (Fig. 3), from 228 cm^3 to 77 cm^3 (a difference of 151 cm^3 and a ratio of 66.2%). IMRT decreased V100 (Fig. 3) from 127 cm^3 to 41 cm^3 (a difference of 86 cm^3 and a ratio of 67.7%) in patients with a BMI ≥26 kg/m^2. Ahamad *et al.* also noted the effect of BMI on small-bowel sparing. The amount of sparing significantly increased as the BMI decreased [10]. The present data also revealed an inverse correlation between $V100_{EW}$ and BMI. We suggest that a large amount of fat accumulation in the mesentery results in bowel loop dispersion and a small $V100_{EW}$ in patients with a high BMI. Hence, the absolute volume of sparing by IMRT is limited. Reasons for the effects of age on anterior small bowel sparing by NEW remain elusive. A very low-dose volume (V10) can be represented as the amount of small bowel distribution in the whole pelvis. We noted an increase in V10 (Fig. 4) but not V100 in elderly patients. In addition, $V40_{EW-NEW}$ and uterine volume were correlated with age. Atrophy of the

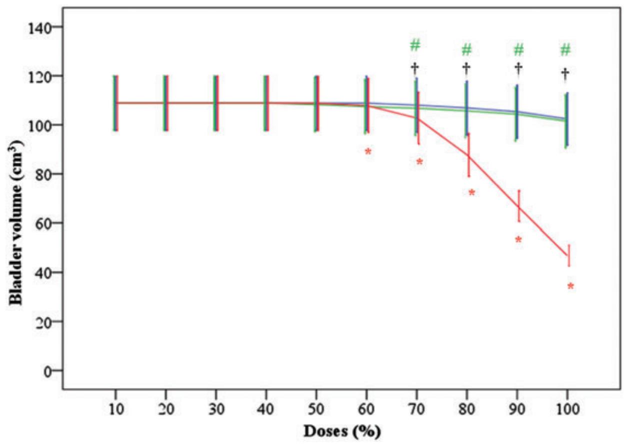

Fig. 6. Dose-volume relationships of the bladder in different plans. The asterisk represents a significant difference between the IMRT (red line) and EW (blue line) techniques. The hash sign denotes a significant difference between the NEW (green line) and EW techniques. The dagger indicates a significant difference between the NEW and IMRT techniques.

uterus in elderly patients may result in anterior displacement of the small bowel to a position in front of the uterus.

We also analyzed DVH analyses of the small bowel in different plans in patients undergoing radical radiotherapy and postoperative radiotherapy. Although the results are similar after stratification of hysterectomy history as a factor in the comparison of all patients, IMRT is more favorable in postoperative radiotherapy.

The limitations and concerns associated with NEW should be discussed. Enforced bilateral weighting could increase the doses delivered to the femoral head and pelvic bone, especially in obese patients. Hot spots may appear in bilateral hips. High-energy photons are suggested to reduce the volume of hot spots. The tolerance dose (TD 5/5) of the femoral head is estimated to be 52 Gy [17]. In our practice, we did not observe treatment-related toxicity although the NEW technique obviously increased the volume and dose of the irradiated femur head (Fig. 5) but not bladder (Fig. 6). The general pelvic dose of external beam irradiation was 39.6–50.4 Gy, and we noted few complications in the pelvic and femoral bones during the follow-up because most of the patients with pelvic bone complications received at least 50 Gy in the pelvis [18, 19]. The present work represents a treatment planning study to compare different plans. The ability to translate the volume reduction of V40 and V100 by NEW and IMRT, respectively, into a reduction of enterotoxicity remains unknown. Additional randomized studies are needed to prove the effectiveness of different techniques in patients with different BMIs or ages.

We believe that the small bowel distribution influences optimal planning selection. In cases in which the distribution of the small bowel is in front of the anterior margin of the box-field, we recommend the use of NEW planning to reduce V40. In contrast, we suggest that IMRT planning be employed to reduce V100 if the distribution is within the posterior cavity in hysterectomy patients. Before developing an optimal method for quantitative measurements of the small bowel distribution, studies are needed to determine the association of age and BMI with anterior or pelvic cavity sparing of the small bowel. In conclusion, the use of larger weighting in the bilateral direction of the box-field reduces the low-dose volume of the small bowel in patients with gynecologic malignancies, especially in those with a high BMI or old age. IMRT effectively reduces the high-dose volume of the small bowel, especially in patients with a low BMI.

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REFERENCES

1. Gallagher MJ, Brereton HD, Rostock RA *et al*. A prospective study of treatment techniques to minimize the volume of pelvic small bowel with reduction of acute and late effects associated with pelvic irradiation. *Int J Radiat Oncol Biol Phys* 1986;**12**:1565–73.
2. Letschert JG, Lebesque JV, Aleman BM *et al*. The volume effect in radiation-related late small bowel complications: results of a clinical study of the EORTC Radiotherapy Cooperative Group in patients treated for rectal carcinoma. *Radiother Oncol* 1994;**32**:116–23.
3. Palm A, Johansson KA. A review of the impact of photon and proton external beam radiotherapy treatment modalities on the dose distribution in field and out-of-field; implications for the long-term morbidity of cancer survivors. *Acta Oncol* 2007;**46**:462–73.
4. Minsky BD, Conti JA, Huang Y *et al*. Relationship of acute gastrointestinal toxicity and the volume of irradiated small bowel in patients receiving combined modality therapy for rectal cancer. *J Clin Oncol* 1995;**13**:1409–16.
5. Tho LM, Glegg M, Paterson J *et al*. Acute small bowel toxicity and preoperative chemoradiotherapy for rectal cancer: investigating dose-volume relationships and role for inverse planning. *Int J Radiat Oncol Biol Phys* 2006;**66**:505–13.
6. Huang EY, Sung CC, Ko SF *et al*. The different volume effects of small-bowel toxicity during pelvic irradiation between gynecologic patients with and without abdominal

surgery: a prospective study with computed tomography-based dosimetry. *Int J Radiat Oncol Biol Phys* 2007;**69**:732–9.

7. Gunnlaugsson A, Kjellén E, Nilsson P *et al*. Dose-volume relationships between enteritis and irradiated bowel volumes during 5-fluorouracil and oxaliplatin based chemoradiotherapy in locally advanced rectal cancer. *Acta Oncol* 2007;**46**:937–44.
8. Robertson JM, Lockman D, Yan D *et al*. The dose-volume relationship of small bowel irradiation and acute grade 3 diarrhea during chemoradiotherapy for rectal cancer. *Int J Radiat Oncol Biol Phys* 2008;**70**:413–8.
9. Huang EY, Hsu HC, Yang KD *et al*. Acute diarrhea during pelvic irradiation: is small-bowel volume effect different in gynecologic patients with prior abdomen operation or not? *Gynecol Oncol* 2005;**97**:118–25.
10. Ahamad A, D'Souza W, Salehpour M *et al*. Intensity-modulated radiation therapy after hysterectomy: comparison with conventional treatment and sensitivity of the normal-tissue-sparing effect to margin size. *Int J Radiat Oncol Biol Phys* 2005;**62**:1117–24.
11. Trotti A, Byhardt R, Stetz J *et al*. Common toxicity criteria: version 2.0. an improved reference for grading the acute effects of cancer treatment: impact on radiotherapy. *Int J Radiat Oncol Biol Phys* 2000;**47**:13–47.
12. Cox JF, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Biol Phys* 1995;**31**:1341–46.
13. D'Souza WD, Ahamad AA, Iyer RB *et al*. Feasibility of dose escalation using intensity-modulated radiotherapy in posthysterectomy cervical carcinoma. *Int J Radiat Oncol Biol Phys* 2005;**61**:1062–70.
14. Roeske JC, Lujan A, Rotmensch J *et al*. Intensity-modulated whole pelvic radiation therapy in patients with gynecologic malignancies. *Int J Radiat Oncol Biol Phys* 2000;**48**: 1613–21.
15. Mundt AJ, Lujan AE, Rotmensch J *et al*. Intensity-modulated whole pelvic radiotherapy in women with gynecologic malignancies. *Int J Radiat Oncol Biol Phys* 2002;**52**: 1330–7.
16. Chen MF, Tseng CJ, Tseng CC *et al*. Clinical outcome in posthysterectomy cervical cancer patients treated with concurrent Cisplatin and intensity-modulated pelvic radiotherapy: comparison with conventional radiotherapy. *Int J Radiat Oncol Biol Phys* 2007;**67**:1438–44.
17. Emami B, Lyman J, Brown A *et al*. Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys* 1991;**21**:109–22.
18. Huh SJ, Kim B, Kang MK *et al*. Pelvic insufficiency fracture after pelvic irradiation in uterine cervix cancer. *Gynecol Oncol* 2002;**86**:264–8.
19. Ikushima H, Osaki K, Furutani S *et al*. Pelvic bone complications following radiation therapy of gynecologic malignancies: clinical evaluation of radiation-induced pelvic insufficiency fractures. *Gynecol Oncol* 2006;**103**:1100–4.