

# Oral contrast agents lead to underestimation of dose calculation in volumetric-modulated arc therapy planning for pelvic irradiation

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## Abstract

**Background:** The effects of oral contrast agents (OCAs) on dosimetry have not been studied in detail. Therefore, this study aimed to examine the influence of OCAs on dose calculation in volumetric-modulated arc therapy plans for rectal cancer.

**Methods:** From 2008 to 2016, computed tomography (CT) images were obtained from 33 rectal cancer patients administered OCA with or without intravenous contrast agent (ICA) and 14 patients who received no contrast agent. CT numbers of organs at risk were recorded and converted to electronic densities. Volumetric-modulated arc therapy plans were designed before and after the original densities were replaced with non-enhanced densities. Doses to the planned target volume (PTV) and organs at risk were compared between the plans.

**Results:** OCA significantly increased the mean and maximum densities of the bowels, while the effects of ICA on these parameters depended on the blood supply of the organs. With OCA, the actual doses for PTV were significantly higher than planned and doses to the bowel increased significantly although moderately. However, the increase in the volume receiving a high-range doses was substantial (the absolute change of intestine volume receiving  $\geq 52$  Gy: 1.46 [0.05–3.99, cubic centimeter range: –6.74 to 128.12], the absolute change of colon volume receiving  $\geq 50$  Gy: 0.34 [0.01–1.53 cc, range: –0.08 to 3.80 cc]). Dose changes due to ICA were insignificant. Pearson correlation showed that dose changes were significantly correlated with a high intestinal volume within or near the PTV ( $\rho > 0.5$ ,  $P < 0.05$ ) and with the density of enhanced intestine ( $\rho > 0.3$ ,  $P < 0.05$ ).

**Conclusions:** Contrast agents applied in simulation cause underestimation of doses in actual treatment. The overdose due to ICA was slight, while that due to OCA was moderate. The bowel volume receiving  $\geq 50$  Gy was dramatically increased when OCA within the bowel was absent. Physicians should be aware of these issues if the original plan is barely within clinical tolerance or if a considerable volume of enhanced intestine is within or near the PTV.

**Keywords:** Oral contrast agents; Simulation; Dosimetry; Organ at risk; Volumetric-modulated arc therapy

## Introduction

Computed tomography (CT)-based simulation and planning form the backbone of modern three-dimensional (3D) radiotherapy. Contrast agents (CAs) are used during CT because they facilitate better structure discrimination. CAs contain materials with higher atomic numbers than those of biologic soft tissue, which increases the effective atomic number.<sup>[1,2]</sup> Therefore, dosimetry deviation is a concern, because while radiotherapy is planned using contrast-enhanced CT images, treatment is administered in the absence of CAs. The impact of CAs on dose calculation has been investigated using phantoms, animals, and clinical plans. In their phantom study, Ramm *et al*<sup>[3]</sup> showed that the relative dose difference increased linearly with BaSO<sub>4</sub>

concentration and the contrasted volume diameter. Clinical plan studies have been conducted for the head and neck,<sup>[4]</sup> lung and mediastinum,<sup>[5]</sup> breast,<sup>[6]</sup> abdomen, and pelvis,<sup>[7-12]</sup> and the overall results indicate that in routine practice, the absence of intravenous CAs (ICAs) induced a significant but clinically tolerable overdose of actual therapy, except in situations when the beams passed through a large volume with concentrated CA.<sup>[4-8]</sup>

Oral CAs (OCAs) are commonly used during simulation and planning of pelvic irradiation. They are mainly retained in the small intestine and are helpful for region of interest (ROI) contouring and beam arrangement.<sup>[4]</sup> Because of anatomical variations and possible bowel

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adhesions from previous surgeries, the volume with CA may get consolidated, resulting in a potential overdose and consequent toxicity. Studies focusing on OCAs are scarce, and overdose in the small intestine loops has not been specified.<sup>[4,5]</sup>

Volumetric-modulated arc therapy (VMAT) plans are widely used in radiotherapy because they enable better dose distribution and shorten treatment time.<sup>[6]</sup> OCAs may have a unique influence on VMAT plans which they will not have on other plans.<sup>[7]</sup> In the present study, we examined the effects of OCAs on dose calculation in VMAT plans and present our results regarding rectal cancer patients who received VMAT radiotherapy.

## Methods

### Ethical approval

The study was performed in accordance with the guidelines of our institutional review board as well as the Health Insurance Portability and Accountability Act, which waived the requirement for informed consent due to the retrospective nature of the study. All the patients signed the consent for possible future re-analysis of their data by the time of admission in our academic center.

### Patients

From 2008 to 2016, patients with rectal cancer receiving pre- or post-operative pelvic irradiation through 3D simulation and planning were eligible and allocated into three groups. Group 1 comprised patients who received neither OCA nor ICA during simulation ( $n = 14$ ), group 2 comprised those who received OCA but not ICA ( $n = 23$ ), and group 3 comprised those who received both OCA and ICA ( $n = 10$ ). Simulation was performed routinely using the Siemens SOMATOM Definition AS system (Siemens AG, Wittelsbacherplatz, DE-80333, Munich, Germany) or Philips Brilliance CT Big Bore system (Cleveland, OH, USA), and the scanning range was from 5 cm below the ischial tuberosity to the upper border of L2, with 5 mm slice thickness. The scan started 35 to 45 s after intravenous bolus injection of 88 mL of the CA (Xenetix®; 65.81 g in 100 mL; GUERBET, Lanester, France) using a power injector at a rate of 2.6 mL/s. The OCA was 20 mL iohexol containing 6 g iodine (Beilu Pharmaceutical Co Ltd, Beijing, China) and was diluted in 1000 mL of water. Patients took this solution 1 hour before simulation, during which they had a full bladder and lay in the prone position on a belly board.

### Establishment of a non-enhanced pool

CT Hounsfield unit (HU) data and electronic density (DENS) values from group 1 were recorded as the non-enhanced pool. The remaining two groups were established to investigate the impact of OCA and ICA on dose, respectively. Unlike studies in which the water density 1 g/m<sup>3</sup> or 0 HU was employed as the default non-enhanced value,<sup>[5,8,9]</sup> we applied the value obtained in actual patients, as described elsewhere.<sup>[10,11]</sup> In order to expand the non-enhanced pool for ICA, data of structures other

than the bowels in both groups 1 and 2 (without ICA) were included.

### Data and electronic density recording

ROIs were contoured as described in the Radiation Therapy Oncology Group consensus contouring atlas for anorectal cancer and in accordance with the guidelines of International Commission on Radiation Units & Measurements Report 83.<sup>[12,13]</sup> Normal structures in the pelvis and lower abdomen, namely, the entire intestine and colon loops, bladder, uterus, prostate, and kidney, were carefully delineated for measurement of CT number. The arteries and veins were also contoured from 5 cm above the planned target volume (PTV) to the peripheral branches as long as they were discernable. Additionally, the central part of the gluteus maximus was contoured as a cylinder of diameter 1 cm and length 5 cm. All CT numbers were recorded and converted to DENS. For reference, we used a translation table that we established and calibrated periodically on the basis of an electron density phantom composed of different tissue equivalent inserts (Computerized Imaging Reference Systems, Norfolk, VA, USA).

### VMAT plan and dosimetry evaluation

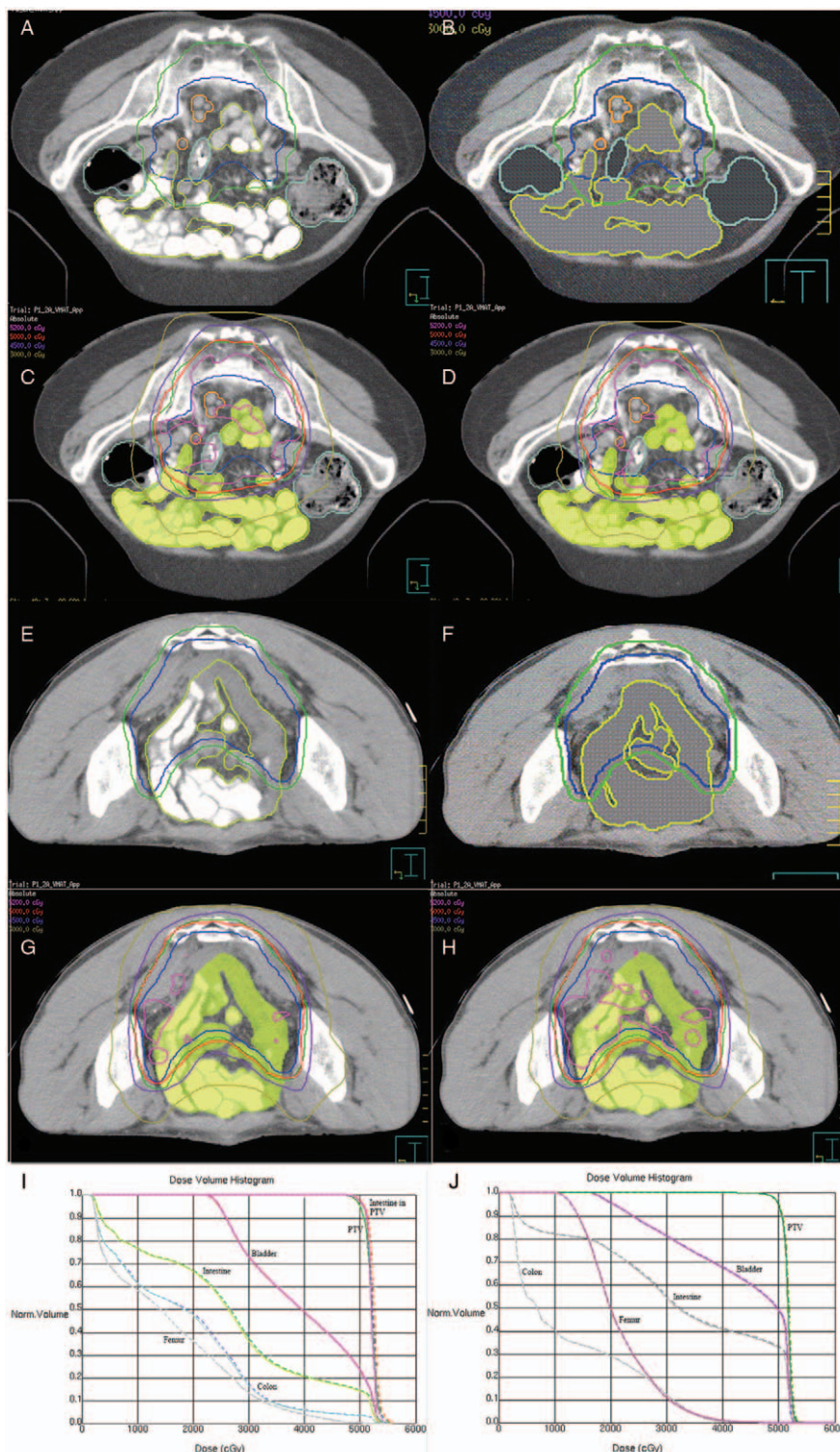
VMAT plans were designed using double arcs (181°–180° and 180°–181°) with the Pinnacle system (Philips Healthcare, Andover, MA, USA) with an adaptive convolution algorithm. An isotropic 4-mm dose calculation grid and a 6 MV photon beam from a linear accelerator (Synergy®; Elekta, Sweden) were employed. The prescription dose (Dp) for the PTV was 95% of the volume receiving 50 Gy at 2 Gy per fraction. The dose constraints on ROIs complied with our institutional criteria. For each patient in groups 2 and 3, the plans were first designed using the original CT images and then recalculated after DENS override using non-enhanced values. During the recalculation, all the other parameters were unchanged, such as beam weight, MU number, prescription dose, and leaf motions. The doses of the PTV, bowels, and other organs at risk between the original and modified plans were compared to determine the impact of OCA and ICA. For OCA alone, only the DENS values of the OCA-enhanced bowels were overridden in groups 2 and 3 [Figure 1]. For ICA alone, the DENS values of intravenously enhanced organs were overridden in the 10 patients who received both CAs. To improve the interpretability of the differences and establish clinical significance, we reported the relative change  $\Delta\%$ , as follows:

$$\Delta\% = \frac{\Delta}{\text{Dose}(\text{non-enhanced}) - \text{Dose}(\text{enhanced})} \times 100\%$$

$$= \frac{\Delta}{\text{Dose}(\text{enhanced})} \times 100\%$$

### Statistical analysis

Data such as CT HU, electronic density and dosage to the target volume or organs were recorded as continuous variables or percentages. Kolmogorov-Smirnov normality



**Figure 1:** Density over-ride of the OCA enhanced bowels and dose changes. (A and E) samples of simulation computed tomography images for two patients administered OCA; (B and F) the same images with density overridden by non-enhanced values. Green: planning target volume; blue: clinical target volume; light blue: colon; yellow green: intestine; orange: enlarged lymph node. (C and G) show the isodose lines from the original volumetric-modulated arc therapy (VMAT) plans. (D) and (H) show the isodose lines after the density replacement of the bowels; note the obvious expanding of the pink 52 Gy isodose line. Pink: 52 Gy dose line; red: 50 Gy dose line; purple: 45 Gy dose line; olive: 30 Gy dose line. (I) and (J) show the dose-volume histograms of the two patients; the semitransparent continuous lines represent the original doses and the dashed lines represent the recalculated doses. Note that the dashed lines for the intestine are always above the continuous lines and the distances between them pertains and increases when approaching the high-dose end (yellow green in I and dark gray in J). OCA: Oral contrast agents.

test was applied for all the data. Then the values were expressed as mean  $\pm$  standard deviation with or without ranges and analyzed using the paired *t* test if they obeyed normal distribution, otherwise, were expressed as median

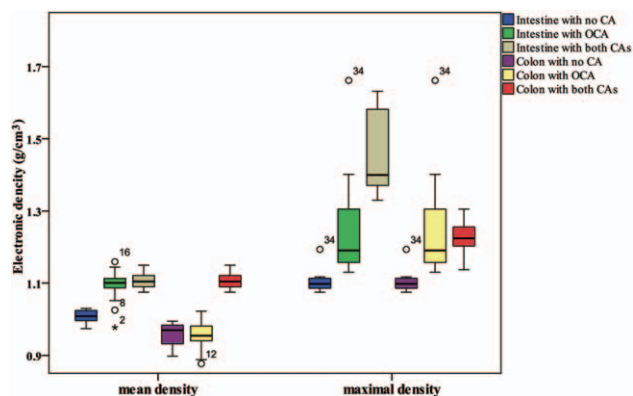
(P25, P75) or median (P25, P75, range) and analyzed with Mann-Whitney *U* test or Wilcoxon test. Spearman test was used to examine correlation between parameters and doses, and the correlation factor was represented as  $\rho$ . A



**Table 1: Computed tomography number (HU) for the bowels with (n = 33) and without contrast agents (n = 10).**

Items	Intestine	Colon
Maximum (HU)		
No contrast	1088.0 (1074.3, 1120.1)	1120.8 ± 43.7
With contrast		
Oral	1488.0 (1454.2, 1616.3)	1251.0 (1252.3, 1302.1)
Oral + IV	1558.1 (1524.0, 1780.2)	1314.4 (1285.6, 1358.1)
Minimum (HU)		
No contrast	162.0 (37.8, 396.5)	21.9 ± 20.0
With contrast		
Oral	101.0 (45.5, 233.0)	13.0 (7.0, 29.0)
Oral + IV	28.4 ± 51.3	11.5 (2.5, 15.5)
Mean (HU)		
No contrast	993.2 ± 24.5	931.1 (905.3, 959.8)
With contrast		
Oral	1105.9 ± 56.5	929.2 ± 39.2
Oral + IV	1120.8 ± 43.7	927.0 (896.8, 973.5)

Because the computed tomography values were obtained from two simulation machines, the *P* value is not given for possible systemic errors. Data are presented as mean ± standard deviation if they followed normal distribution, otherwise are presented in median (P25, P75). HU: Hounsfield unit; IV: With intravenous contrast; Oral: With oral contrast.



**Figure 2:** Boxplot for converted electron densities (DENS) of the bowels with and without CAs. The bars inside the box represent the median value of the corresponding densities. CA: Contrast agent; OCA: Oral contrast agent.

strong, moderate, and mild correlation was defined when  $\rho$  was more than 0.8, between 0.5 and 0.8 and between 0.3 and 0.5, respectively. A two-tailed *P* value less than 0.05 was considered statistically significant. SPSS 23.0 (IBM Corp, New York, NY, USA) and R studio 1.1.453 (Rstudio®, Boston, MA, USA) were used for data analysis.

**Results**

**CT numbers and DENS values**

The CT numbers in HU of the bowel with or without contrast enhancement are listed in Table 1. For the small intestine, OCA increased the mean CT number by over 110 HU and increased the maximum CT number by 400 HU. These differences were lower in the colon, probably because less OCA was collected in this organ and the distribution was uneven. The minimum CT number for the bowels did not change much, probably due to the existence

of gas in the lumen; therefore, the minimum values were excluded from subsequent analysis.

The DENS values of the bowel and other organs with or without contrast enhancement are shown in Supplementary Tables 1 and 2 <http://links.lww.com/CM9/A309> and Figure 2. OCA significantly increased the maximum and average values for the intestine from 1.10 and 1.01 mg/cm<sup>3</sup> to 1.43 and 1.10 mg/cm<sup>3</sup>, respectively. The maximum DENS values for the colon showed similar changes. The DENS change with or without additional ICA in the presence of OCA was not statistically significant.

In the case of ICA, both the maximum and average values of organs with abundant blood supply, such as the vessels and kidneys, increased significantly. However, for other structures such as the urogenital organs, only the average values increased. The changes in the DENS values of the gluteus maximus were non-significant.

**Influence of CAs on dosimetry**

The recalculated doses and modifications to the original plans are shown in Table 2 for PTV and Table 3 for organs at risks. For ICA, the dose changes were minimal and non-significant, and  $\Delta\%$  rarely exceeded 0.2%.

After the OCA over-ride, the PTV dose increased significantly but mildly:  $D_p$  (D95) increased by  $4.07 \pm 3.59$  cGy (range: -5.10 to 13.53 cGy,  $\Delta\%$ :  $0.08 \pm 0.07\%$ ), and  $D_{max}$  increased by 7.04 cGy (-0.10, 26.5 cGy, range: -16.5 to 74.8 cGy),  $\Delta\%$ : 0.14% (0, 0.48%). Changes in other indices, such as D2 to D98 and  $D_{mean}$ , were less than 0.2%. However, the increase in the PTV receiving a particular dose ( $V_x$ : PTV volume receiving  $\geq x$ Gy or  $x\%$  of the  $D_p$ ) was significant. The change in V105 (PTV volume receiving  $\geq 105\%$  of the  $D_p$ ) was 0.99% (0.08, 2.42%, range: -1.60% to 7.24%) of the PTV,  $\Delta\%$ : 10.08% (6.11, 27.86%, range: -4.0% to 1057.38%). The change in V107 was 0.09% (0, 0.32%,

**Table 2: Change in dose delivered to the planned target volume before and after the over-ride for oral or intravenous contrast agent.**

Parameters	Oral contrast agent (n = 33)					Intravenous contrast agent (n = 10)						
	Original	Over-riden	Δ	Δ%	Statistics	P	Original	Over-riden	Δ	Δ%	Statistics	P
<b>PTV</b>												
D <sub>max</sub> (cGy)	5407.3 ± 94.9	5422.4 ± 100.4	7.40 (-0.10, 26.5)	0.14 (-0.00, 0.48)	-4.139*	<0.001	5416.7 ± 113.4	5417.0 ± 116.1	0.29 ± 1.27	0.01 ± 0.02	-0.723*	0.490
D <sub>min</sub> (cGy)	4398.0 (4284.0, 4481.0)	4403.0 (4285.0, 4482.0)	0.00 (-0.20, 1.40)	0.00 (-0.01, 0.03)	154.5†	0.850	4423.1 (4270.2, 4458.9)	4423.0 (4269.2, 4458.1)	-0.26 ± 0.64	-0.01 ± 0.01	36.5†	0.358
D <sub>mean</sub> (cGy)	5155.7 ± 40.3	5159.8 ± 40.3	3.50 (1.30, 6.50)	0.07 (0.03, 0.13)	-5.852*	<0.001	5151.9 ± 42.9	5151.7 ± 44.4	-0.28 ± 0.43	-0.01 ± 0.01	2.052*	0.070
D98 (cGy)	4926.1 ± 18.7	4930.5 ± 18.6	4.39 ± 3.68	0.09 ± 0.07	-5.690*	<0.001	4929.8 ± 15.4	4929.6 ± 14.1	-0.17 ± 0.23	<0.01	2.339*	0.044
D95 (cGy)	4999.7 ± 7.1	5003.8 ± 7.3	4.07 ± 3.59	0.08 ± 0.07	-6.517*	<0.001	5000.9 ± 8.8	5000.8 ± 9.1	-0.17 ± 0.30	0.00 ± 0.01	1.788*	0.107
D90 (cGy)	5054.2 ± 16.0	5058.0 ± 16.3	3.77 ± 3.84	0.07 ± 0.08	-5.627*	<0.001	5053.2 ± 19.1	5053.0 ± 19.3	-0.17 ± 0.29	0.00 ± 0.01	1.808*	0.104
D50 (cGy)	5167.2 ± 42.7	5170.9 ± 42.7	2.73 (1.13, 5.29)	0.05 (0.02, 0.10)	-4.675*	<0.001	5160.8 ± 45.3	5160.5 ± 45.2	-0.32 ± 0.45	-0.01 ± 0.01	2.263*	0.050
D5 (cGy)	5268.39 ± 69.6	5276.01 ± 71.1	7.62 ± 7.09	0.14 ± 0.13	-6.169*	<0.001	5267.3 ± 77.4	5267.1 ± 77.6	-0.18 ± 0.62	0.00 ± 0.01	0.915*	0.380
D2 (cGy)	5294.3 ± 75.4	5303.4 ± 79.7	6.62 (2.26, 13.00)	0.13 (0.04, 0.24)	-4.852*	<0.001	5294.9 ± 85.9	5294.7 ± 86.3	-0.16 ± 0.48	0.00 ± 0.01	1.072*	0.311
V107 (%)	0.4 (0.0, 1.9)	0.4 (0.0, 2.9)	0.09 (0.00, 0.32)	31.94 (8.03, 46.08)	25.0†	0.001	0.6 (0.0, 3.6)	0.6 (0.0, 3.6)	-0.10 ± 0.05	0.00 (-0.01, 0.00)	10.0†	0.588
V105 (%)	8.3 (0.8, 24.7)	14.8 (1.4, 26.9)	0.99 (0.08, 2.42)	10.08 (6.11, 27.86)	31.0†	<0.001	11.3 (0.4, 24.7)	12.4 (0.4, 24.7)	0.00 (-0.18, 0.01)	0.09 ± 1.79	21.0†	0.180
V100 (%)	94.8 ± 0.5	95.1 ± 0.5	0.28 ± 0.25	0.29 ± 0.27	-6.393*	<0.001	94.8 ± 0.5	94.8 ± 0.6	-0.01 ± 0.02	-0.01 ± 0.02	2.091*	0.066
V95 (%)	99.8 ± 0.2	99.8 ± 0.2	0.01 (0.00, 0.02)	0.01 (0.00, 0.02)	3.99*	<0.001	99.8 ± 0.2	99.8 ± 0.1	<0.01	<0.01	-1.788*	0.107
V90 (%)	100.0 (99.9, 100.0)	100.0 (100.0, 100.0)	<0.01	<0.01	0†	0.125	100.0 (99.9, 100.0)	100.0 (99.9, 100.0)	<0.01	<0.01	0†	1.000
<b>HI</b>												
100 (D2-D98)/Dp	7.4 ± 1.7	7.5 ± 1.9	0.03 (0.01, 0.13)	0.44 ± 2.22	-2.712*	0.011	7.3 ± 1.8	7.3 ± 1.9	<0.01	0.02 ± 0.09	0.093*	0.928
100 (D5-D95)/Dp	5.4 ± 1.4	5.4 ± 1.4	0.07 ± 0.11	0.96 ± 2.24	-3.617*	0.001	5.3 ± 1.3	5.3 ± 1.4	<0.01	-0.01 ± 0.13	-0.084*	0.931

Data are presented as mean ± standard deviation if they followed normal distribution, otherwise are presented in median (P25, P75), D<sub>max</sub>: The maximal dose; D<sub>mean</sub>: The average dose of the volume; D<sub>min</sub>: The minimal dose; Dp: Prescription dose; Dx: The lowest dose of x% of the volume; HI: Homogenous index; PTV: planning target volume; cc: cubic centimeter; Vx: The percentage of the volume or the absolute volume receives ≥xGy; Δ: Change in the absolute value with the same unit as the left item (such as cc, cGy, or %); Δ%: The relative percentage of change obtained using the formula 100% × Δ/original value before density over-ride. † t value. ‡ V value for Wilcoxon signed rank test.

**Table 3: Changes in the dose delivered to normal organs before and after the over-ride for oral or intravenous contrast agent.**

Parameter	Oral contrast agent (n = 33)				Intravenous contrast agent (n = 10)			
	Original	Over-riden	Δ	Statistics	Original	Over-riden	Δ	Statistics
<b>Intestine</b>								
D <sub>max</sub> (cGy)	5306.0 (5207.0, 5383.0)	5342.0 (5240.0, 5423.0)	40.61 ± 34.55	9.0 <sup>†</sup>	5316.9 ± 108.4	5316.7 ± 108.7	-0.26 ± 1.23	0.0 ± 0.02
D <sub>min</sub> of intestine in PTV volume (cGy)	4606.5 ± 124.2	4635.0 ± 121.0	28.50 ± 17.17	9.390 <sup>*</sup>	4645.9 (4617.7, 4651.2)	4646.1 (4618.0, 4651.3)	-0.21 ± 0.55	0.0 ± 0.01
D <sub>mean</sub> of intestine in PTV volume (cGy)	5102.5 ± 81.1	5138.9 ± 85.3	36.36 ± 30.37	-6.773 <sup>*</sup>	5103.2 ± 67.0	5102.9 ± 68.3	-0.33 ± 0.48	-0.01 ± 0.01
V15 (cc)	327.9 ± 155.6 110.5	328.6 ± 155.7 113.7	0.66 ± 0.54 2.26	-7.057 <sup>*</sup> 0 <sup>†</sup>	401.1 ± 124.6 135.3	401.1 ± 124.9 153.8 ± 76.6	0.01 ± 0.01 0.02 ± 0.05	<0.01 -0.01 ± 0.02
V30 (cc)	(63.1, 153.3)	(63.4, 156.1)	(1.11, 3.21)	0 <sup>†</sup>	(110.9, 187.0)	(106.7 ± 59.9)	0.01 ± 0.02	-0.01 ± 0.02
V35 (cc)	(38.8, 103.6)	(39.8, 104.7)	(0.66, 1.73)	0 <sup>†</sup>	106.7 ± 60.0	106.7 ± 59.9	0.01 ± 0.02	-0.01 ± 0.02
V40 (cc)	49.8 (27.5, 80.6)	51.3 (28.1, 80.7)	1.03 ± 0.94	3.0 <sup>†</sup>	83.5 ± 52.4	83.5 ± 52.4	-0.01 (-0.01, 0.00)	-0.02 ± 0.02
V45 (cc)	36.4 (19.5, 67.8)	37.9 (20.0, 67.7)	0.99 ± 0.93	7.0 <sup>†</sup>	66.8 ± 47.6	66.8 ± 47.6	0.01 ± 0.06	1.037 <sup>†</sup>
V50 (cc)	19.4 (7.4, 55.3)	21.3 (8.1, 55.3)	1.91 ± 2.14	15.0 <sup>†</sup>	23.3 (18.3, 74.5)	23.3 (18.3, 74.5)	-0.03 ± 0.03	-0.17 ± 0.30
V52 (cc)	3.6 (0, 10.2)	6.1 (0.2, 14.2)	1.46 (0.05, 4.00)	64.0 <sup>†</sup>	3.7 (0.0, 9.3)	3.6 (0.0, 9.3)	0.00 (-0.07, 0.00)	-0.47 ± 0.83
<b>Colon</b>								
D <sub>max</sub> (cGy)	5306.0 (5231.0, 5372.0)	5303.6 ± 147.0	15.97 ± 20.49	38.0 <sup>†</sup>	5314.2 ± 95.7	5314.5 ± 95.7	0.31 ± 0.93	0.01 ± 0.02
D <sub>min</sub> of colon in PTV volume (cGy)	4608.7 ± 152.6	4639.3 ± 142.6	10.60 (0.50, 25.60)	-2.318 <sup>*</sup>	4630.1 ± 166.8	4629.8 ± 167.3	0.27 ± 1.00	-0.01 ± 0.02
D <sub>mean</sub> of colon in PTV volume (cGy)	5149.8 ± 52.8	5159.9 ± 54.5	10.04 ± 10.16	-5.502 <sup>*</sup>	5150.2 ± 61.8	5150.1 ± 61.8	-0.11 ± 0.43	<0.01
V35 (cc)	55.7 (36.5, 105.1)	56.0 (36.7, 105.4)	0.21 (0.08, 0.80)	0 <sup>†</sup>	52.9 (30.6, 74.6)	52.9 (30.6, 74.6)	<0.01	<0.01
V40 (cc)	43.4 (24.1, 81.9)	43.4 (24.1, 82.2)	0.43 (0.05, 0.46)	16.0 <sup>†</sup>	38.5 (26.7, 56.5)	38.5 (26.7, 56.5)	<0.01	0.00 ± 0.02
V45 (cc)	37.8 (21.7, 65.9)	38.0 (21.8, 66.1)	0.15 (0.03, 0.48)	19.5 <sup>†</sup>	34.0 (22.7, 40.6)	34.0 (22.7, 40.7)	<0.01	<0.01
V50 (cc)	34.4 ± 26.2	35.1 ± 26.6	0.38 (0.05, 0.82)	-4.226 <sup>*</sup>	26.2 (17.9, 31.2)	26.2 (17.9, 31.2)	-0.01 (-0.01, 0.00)	-0.03 ± 0.07
V52 (cc)	6.8 (0.2, 18.4)	7.3 (0.4, 18.8)	0.34 (0.01, 1.53)	76.0 <sup>†</sup>	12.1 ± 13.8	11.3 ± 26.6	0.02 ± 0.08	-0.02 ± 0.77
<b>Femur heads</b>								
D <sub>max</sub> (cGy)	4739.7 ± 311.2	4739.7 ± 311.1	-0.10 (-0.50, 0.30)	-0.129 <sup>*</sup>	4943.0 (4871.0, 4988.1)	4943.2 (4871.2, 4988.3)	-0.15 ± 0.85	0 ± 0.02
D <sub>mean</sub> (cGy)	1878.9 ± 230.1	1878.9 ± 230.1	0.00 (-0.01, 0.00)	-0.374 <sup>*</sup>	1858.6 ± 246.2	1858.5 ± 246.2	-0.10 (-0.18, -0.10)	-0.01 ± 0.01
V45 (%)	0.3 (0.0, 1.8)	0.3 (0.0, 1.8)	<0.01	16.5 <sup>†</sup>	1.84 ± 1.84	1.84 ± 1.84	<0.01	<0.01
V50 (%)	<0.01	<0.01	0.00 (-1.56, 0.00)	1.0 <sup>†</sup>	<0.01	<0.01	<0.01	<0.01
<b>Bladder</b>								
D <sub>max</sub> (cGy)	5329.6 ± 32.9	5325.2 ± 29.9	-0.90 (-4.8, -0.6)	-1.629 <sup>*</sup>	5317.2 ± 51.0	5317.4 ± 49.8	-0.42 (-1.70, -0.01)	-0.02 (-0.10, -0.00)
D <sub>mean</sub> (cGy)	3858.7 ± 126.4	3855.3 ± 126.9	-1.00 (-5.40, 0.20)	-1.904 <sup>*</sup>	3813.85 ± 221.1	3814.18 ± 227.0	-0.49 (-3.90, 0.15)	-0.05 (-0.22, 0.01)
V45 (cc)	139.3 ± 85.9	139.0 ± 85.7	-0.04 (-0.29, 0.01)	0.100	134.6 ± 89.1	134.7 ± 89.3	-0.03 (-0.19, 0.01)	-0.02 (-0.17, 0.01)
V50 (cc)	98.7 ± 68.2	98.0 ± 67.7	-0.08 (-0.78, 0.07)	-1.836 <sup>*</sup>	100.9 ± 59.3	100.0 ± 59.1	-0.04 (-0.36, 0.05)	-0.06 (-0.90, 0.04)
V52 (cc)	25.0 (15.1, 36.5)	26.2 (14.9, 33.5)	-0.71 (-1.58, 0.06)	12.0 <sup>†</sup>	39.5 (19.4, 40.1)	39.9 (19.0, 39.7)	-0.67 (-1.33, 0.10)	-2.21 (-8.77, 0.93)

Data are presented as mean ± standard deviation if they followed normal distribution, otherwise are presented in median (P25, P75). D<sub>max</sub>: The maximal dose; D<sub>mean</sub>: The average dose of the volume; D<sub>min</sub>: The minimal dose; Dp: Prescription dose; Dx: The lowest dose of x% of the volume; HI: Homogenous index; PTV: Planning target volume; cc: cubic centimeter; Vx: The percentage of the volume or the absolute volume receives ≥ xGy; Δ: Change in the absolute value with the same unit as the left item (such as cc, cGy, or %); Δ%: The relative percentage of change obtained using the formula 100% × Δ/original value before density over-ride. <sup>†</sup> Wilcoxon signed rank test for non-normal distribution (V value for statistics). <sup>\*</sup> t test for normal distribution.

range: -0.40% to 2.81%) of the PTV, Δ%: 37.93% (8.03, 46.08%, range: -7.38% to 750%), indicating that the maximum increase in the PTV volume receiving ≥52.5 and ≥53.5 Gy was 123.01 cubic centimeter [cc] and 35.87 cc, respectively [Figure 1].

The Vx of the bowels also increased significantly. In the low- and median-dose ranges, Δ% was less than 3%, but in the high-dose range (≥50 Gy), it mostly exceeded 10%. The increase in V50 (volume receiving ≥50 Gy) and V52 of the intestine was highly significant at 1.91 ± 2.14 cc (range: -0.66 to 8.78 cc), Δ%: 8.75% (4.04, 13.46%, range: -1.42% to 73.68%) and 1.46 cc (0.05, 4.00 cc, range: -6.74 to 128.12 cc), Δ%: 62.6% (32.0, 148.70%, range: -89.38% to 13,700.0%), respectively. Similarly, the increase in V52 for the colon was 0.34 cc (0.01 to 1.53 cc, range -0.77 to 12.13 cc), Δ%: 10.4% (1.98, 16.68%, range -26.6% to 146.67%). The D<sub>max</sub> for the intestine increased by >1.0 Gy in three patients while D<sub>max</sub> for the colon increase by >1.0 Gy in one patient. The doses for other organs were either mildly elevated but non-significantly or moderately reduced.

**Factors associated with dose alteration**

To further identify factors that critically affected OCA-induced dose uncertainty, Spearman correlation analysis was performed with the following factors: PTV volume, volume of the intestine (or colon) within the PTV, volume of enhanced intestine (or colon) within the PTV, volume of enhanced intestine (or colon) sharing slices with the PTV, previous surgery, and average DENS value of the intestine. The results are shown in Table 4. The volume of the enhanced intestine within the PTV was highly correlated with changes in the V45 to V52 of the intestine (ρ > 0.83), indicating a definite impact on the dose. It also correlated with changes in the D5, D2, and V100 of the PTV and the

V30 and V40 of the intestine (ρ were from 0.54 to 0.73), indicating a moderate effect. The volume of the enhanced intestine sharing slices with the PTV was also moderately correlated with most of the abovementioned changes (ρ were from 0.51 to 0.72), but the DENS value of the intestine with contrast enhancement was only slightly correlated (ρ were from 0.30 to 0.72). The PTV volume, previous surgery, and contrast enhancement of the colon showed negligible correlation with dose changes.

**Discussion**

In radiotherapy planning, CAs are helpful in ROI delineation but introduce dose uncertainties because while they are present during planning, they are not during treatment.<sup>[1,3]</sup> In the present study with 47 rectal cancer patients who received VMAT irradiation to the pelvis, we found that the influence of ICA on absolute dose was minor, which corresponds to the literatures.<sup>[4,9,11,14-27]</sup> However, with OCA, the actual dose administered to the PTV and bowels was significantly higher than planned. In contrast to ICAs, which get diluted in serum, OCAs accumulate almost exclusively in the bowel at considerable amounts, which makes a dosimetric re-evaluation necessary.

In the present study, the effects of OCA on dose were more remarkable for the bowels than for PTV. This difference could be explained by the main dosimetric change in the absence of OCA, which demonstrated a moderate increase in the absolute dose but a prominent expansion of the high dose area. Considering that only part of the bowel was within the PTV, the high-dose area expansion in PTV exerted a more obvious effect on the bowel. Since the volume of intestine receiving moderate to high dose was strongly associated with acute and long-term gastrointes-

**Table 4: Correlation of different factors with the dose matrix for pelvic irradiation.**

Parameter	PTV volume	Intestine in PTV	Intestine + C in PTV	Intestine + C at PTV layers	Intestine electronic density	Colon + C in PTV	Colon + C at PTV layers	Surgery
PTV D5	0.028	0.294	0.604 <sup>†</sup>	0.597 <sup>†</sup>	0.364 <sup>*</sup>	-0.029	0.143	0.524 <sup>*</sup>
PTV D2	0.115	0.286	0.563 <sup>†</sup>	0.559 <sup>†</sup>	0.359 <sup>*</sup>	-0.029	0.143	0.233
PTV V100	-0.147	0.334	0.538 <sup>†</sup>	0.513 <sup>†</sup>	0.404 <sup>*</sup>	-0.609	-0.429	0.383
Intestine ΔD <sub>max</sub>	-0.038	-0.038	0.409 <sup>*</sup>	0.31	0.721 <sup>†</sup>	0.116	0.257	0.233
Intestine ΔD <sub>min</sub> in PTV	-0.059	-0.124	0.133	0.21	0.177	0.029	0.143	0.163
Intestine ΔD <sub>mean</sub> in PTV	0.033	-0.116	0.459 <sup>†</sup>	0.306	0.682 <sup>†</sup>	0.029	0.257	0.299
Intestine ΔV30	0.285	0.404 <sup>*</sup>	0.549 <sup>†</sup>	0.724 <sup>†</sup>	0.457 <sup>†</sup>	-0.029	0.143	0.249
Intestine ΔV40	0.071	0.475 <sup>†</sup>	0.733 <sup>†</sup>	0.694 <sup>†</sup>	0.399 <sup>*</sup>	-0.116	0.257	0.262
Intestine ΔV45	0.095	0.596 <sup>†</sup>	0.857 <sup>†</sup>	0.710 <sup>†</sup>	0.265	-0.116	0.257	0.247
Intestine ΔV50	-0.076	0.550 <sup>†</sup>	0.878 <sup>†</sup>	0.639 <sup>†</sup>	0.301	-0.406	-0.086	0.39
Intestine ΔV52	0.046	0.426 <sup>†</sup>	0.839 <sup>†</sup>	0.566 <sup>†</sup>	0.362 <sup>*</sup>	-0.406	-0.086	0.324
Colon ΔD <sub>max</sub>	0.127	-0.092	0.130	0.168	0.347 <sup>*</sup>	0.029	-0.257	0.058
Colon ΔV50	-0.057	-0.248	-0.121	-0.026	0.331	-0.058	-0.086	0.175
Colon ΔV52	0.160	-0.229	-0.004	0.101	0.242	-0.116	-0.086	0.004
ΔHI	0.158	0.223	0.342	0.385 <sup>*</sup>	0.156	0.257	0.441	-0.001

The values in the table are Spearman ρ. D<sub>max</sub>: The maximal dose; D<sub>mean</sub>: The average dose of the volume; D<sub>min</sub>: The minimal dose; Dx: The lowest dose of x% of the volume; HI: Homogenous index; PTV: Planning target volume; Vx: The percentage of the volume that receives ≥x% of the prescription dose (for PTV) or the volume receives ≥xGy; Δ: Change in the absolute value; +C: With oral contrast. \* P < 0.05. † P < 0.01.



tinal toxicity,<sup>[28-32]</sup> the dose changes associated with the use of OCAs are greatly concerning.

We also found that the volume of enhanced intestine within the PTV or sharing slices with the PTV and the mean DENS value of the enhanced intestine were significantly correlated with the dose increase. Ramm *et al* and others, too, found that the changes in planned dose increased linearly with the concentration and expansion of CAs.<sup>[3,19]</sup> The increase in the CT number of the intestine by OCA found in the present study (over 110 HU) was similar to the increase in the CT number of blood pool by ICA.<sup>[14,17-19,22,23,33]</sup> Additionally, the volumes of enhanced intestine within the PTV or sharing slides with the PTV were considerable, at  $16.01 \pm 28.1$  cc (0–133.5 cc) and  $178.1 \pm 109.1$  cc (13.6–460.9 cc), respectively. These findings collectively indicate a more critical impact of OCA on dosimetry than that of ICA. Since iohexol administered orally was poorly absorbed into the circulation (0.3–0.5%), there should be little influence from OCA on the non-GI organs. Our findings also backup the theory that areas lying behind contrast-enhanced areas where the beams exit are exposed to more energy at the absence of the CAs.<sup>[14,32]</sup>

To our knowledge, the present study is among the few that examine the effects of OCA and is the first to show the increase in the high dose area induced by the absence of OCA. Rankine *et al*<sup>[4]</sup> studied the impact of CAs in six patients, including three with only OCA, using the “plan import method” and found that dose increase at the isocenter was less than 2.1%. Although they did not evaluate the doses to intestine, the conclusion that critical organs in close proximity to the PTV that receive the maximum permissible doses must be treated using plans designed on non-contrast-enhanced CT images supported our results. Joseph *et al*<sup>[34]</sup> evaluated the impact of OCA on pelvic irradiation in 13 patients by assuming 0 HU as the default non-enhanced CT number. They evaluated 4-field conventional, 7-field intensity modulated radiotherapy (7f-IMRT), and helical tomotherapy and found that the D95 of PTV was higher in the non-enhanced than enhanced plans, which was comparable to our  $\Delta D95$  for the PTV. For the bowel loops, Joseph *et al* evaluated doses to the peritoneal cavity instead and found that the differences in the mean D10 were 6.9 Gy (–1.73 to 15.61 Gy), 0.17 Gy (0.06–0.28 Gy), and 0.09 Gy (–0.09 to 0.26 Gy) for the three plans, respectively. However, in their study, only 21% length of the PTV volume shared slides with the enhanced bowel, while in our study, the volume of the enhanced intestine that shared slides with the PTV was 178 cc (109–461 cc). Further, the dose to the entire peritoneum may not represent that to the bowel loops for doses  $\geq 45$  Gy. Other studies that included a similar dose matrix as ours focused on ICA, and some also evaluated the dose to the bowels.<sup>[18,20]</sup> Their results showed subtle but significant dose changes (mean  $\Delta\%$  of  $D_{\max}$ : 0.13–0.95%), which were analogic to our ICA results (mean  $\Delta\%$ :  $0 \pm 0.02\%$ ), although higher. This difference might be explained by different radiation types (Cyberknife *vs.* VMAT), algorithms (collapsed-cone convolution *vs.* adaptive convolution), and ICA application strategies (multiphasic *vs.* pelvic enhancement), among other factors.

Our study included an appreciable sample size, with 33 plans, and carefully delineated the normal organs to build a CT number pool and modeled the actual treatment scenario by DENS replacement. We found that some aspects of overdose in the bowel were serious and could not be neglected, especially the volume of intestine receiving a high dose, which would possibly cause excessive morbidities beyond those predicted by the original dose-volume histogram. The larger the volume of the enhanced bowel near the path of the beams, the more significant is the dose underestimation in the calculation.

This study has some limitations. First, non-enhancement was simulated, using DENS over-ride. A more comprehensive method would be to scan patients in the same position twice, once before and once after CA application.<sup>[22,23,35]</sup> However, OCAs take time to reach the intestine, and volumes of the bowel and bladder change by minutes, which makes it impossible to repeat the scan with the same internal environment. Second, the non-enhanced data pool that we used for DENS collection was only from 14 patients for the bowels and from 37 patients for other organs, and this limit sample size may have introduced a bias and potential systematic error. Third, previous studies reported that density conversion and inhomogeneity correction were probably more accurately determined using dual-energy CT subtraction, a procedure still being investigated and not in routine use at our institution.<sup>[36-39]</sup> Fourth, our results must be validated before they can be applied to plans other than VMAT. Since it has been reported that the effects of CAs decrease as the number of incident beams increases, in IMRT plans with less control points, the underestimation might be even graver.<sup>[3,4,40]</sup>

In conclusion, the use of OCAs to simulate VMAT-based pelvic irradiation resulted in underestimation of the dose to the PTV and bowels. An actual overdose occurred in most ROIs, especially the intestine, of which the change was dramatic and serious. We recommend that if a large volume of small intestines is within the PTV or share slices with it, no OCAs or diluted OCAs be used.

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### Conflicts of interest

None.

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