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Original research article

Influence of the contrast agents on treatment planning dose calculations of prostate and rectal cancers

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ABSTRACT

Aim: The aim of the present study is to quantify differences in dose calculations caused by using CA and determine if the resulting differences are clinically significant.

Background: The influence of contrast agents (CA) on radiation dose calculations must be taken into account in treatment planning.

Materials and methods: Eleven patients with pelvic cancers were included in this study and two sets of CTs were taken for each patient (without and with CA) in the same position and coordinates. Both sets of images were transferred to the DosiSoft ISOgray treatment planning system for contouring and calculating the dose distribution and monitor units (MUs) with Collapsed Cone and Superposition algorithms, respectively. All plans were generated on pre-contrast CT and subsequently copied to the post-contrast CT. Radiation dose calculations from the two sets of CTs were compared using a paired sample *t*-test.

Results: The results showed a statistically insignificant difference between pre- and post-contrast CT treatment plans for target volume and OARs ($p > 0.05$), except bladder organ in the prostate region ($p < 0.05$) but the relative mean dose and MU differences were less than 2% in any patient for 18 MV photon beam.

Conclusions: Treatment planning on contrasted images generally showed a lower radiation dose to both target volume and OARs than plans on non-contrasted images. The results of this research showed that the small radiation dose differences between the plans for the CT scans with and without CA seem to be clinically insignificant; therefore, contrast-enhanced CT can be used for both target delineation and treatment planning of prostate and rectal cancers.

1. Background

Cancer as a major neoplastic disease is an important global public health concern worldwide.[1] During the past decade, the incidence of pelvic cancers such as colorectal, prostate,

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and cervical cancers were increasing in many countries of the Asia-Pacific region such as China, South Korea, and Iran.[2,3] Nowadays, pelvic irradiation is an essential part of the curative treatment strategy of pelvic malignancies, including rectal, prostate, and cervical carcinoma.[4] One of the major limiting factors for radiotherapy is the lack of contrast in the absorption of ionizing radiation between healthy and cancerous tissues. Most current efforts to defeat this problem focus on methods which spatially conform the dose to the tumor volume through improvements in treatment planning facilities and imaging.[5] However, this situation can be further improved through the introduction of contrast agents (CAs) where they have been used extensively in conjunction with imaging techniques such as computed tomography (CT).[6] CA is commonly used in CT simulation to assist radiation oncologists in defining regions of interest (ROI), so that normal and malignant tissues can be better delineated.[7–9]

The tissue containing CA, includes high-Z radio-opaque materials, attenuates the CT X-rays more than normal. As a result, CT scan with CA causes the temporary increase in the CT number or Hounsfield unit (HU) and so the corresponding electron density (ρ_e).[9,10] Photon dosimetry in radiotherapy is a function of the ρ_e of irradiated tissues; therefore, altering the ρ_e of structures may affect photon dosimetry.

2. Aim

Dosimetric influences caused by using intravenous (IV) and/or oral plus intravenous CA in CT simulation were quantified and the results were examined to determine if these influences were clinically significant. The result may serve as a reference to justify the use of contrast-enhanced CT data sets for three-dimensional conformal radiation therapy (3D-CRT) planning, using DosiSoft ISOgray system, of pelvic region cancers.

3. Materials and methods

3.1. *Patient selection*

We have designed a prospective treatment planning study performed as self-controlled clinical trial with before/after method at Imam Reza Hospital, Kermanshah City, Iran, during the period from April 2015 till July 2015. The ethics committee of Kermanshah University of Medical Sciences (KUMS) approved the patient study (Grant No: kums.rec.1394.12). Also, this trial was registered with the Iranian Registry of Clinical Trials (IRCT) and allocated a unique code (Registration ID: IRCT2015051922319N1). A total of 11 non-metastasized patients (10 male and 1 female), with a mean age of 59.20 ± 14.14 were included in this study. Five patients undergoing radiotherapy for prostate cancer and six patients undergoing rectal irradiation were chosen for the present study. Cases with renal diseases, diabetes, asthma, and prior reactions to CA were excluded. The tumors were staged based on the American Joint Committee on Cancer (AJCC) staging system. Patient characteristics are shown in Table 1.

3.2. *Acquisition of computed tomography (CT)*

Treatment planning CT simulation was performed using a multi slice CT scanner (Aquilion 16 Slice; Toshiba, Japan).

Table 1 – Patient characteristics along with the CA type ($n = 11$).

Patient characteristics		Number of patients	Patients age distribution (year)	
			Median	Mean ± Std dev
Region	*Rectum*	6	45.00	49.20 ± 20.50
T stage	TX	0		
	T1	0		
	T2	3		
	T3	3		
	T4	0		
Lymph node (LN)	LN negative	3		
	LN positive	3		
Gender	Female	1		
	Male	5		
CA	IV	5		
	Oral + IV	1		
Region	*Prostate*	5	65.00	69.20 ± 10.50
T stage	TX	0		
	T1	0		
	T2	1		
	T3	3		
	T4	1		
Lymph node (LN)	LN negative	5		
	LN positive	0		
Gender	Female	0		
	Male	5		
CA	IV	0		
	Oral + IV	5		

Std dev, standard deviation; IV, intravenous.

Overall, two sets of CTs were performed for every patient. Primary study sets contained pre-contrast images; secondary study sets were performed post-contrast in the same position and with the same coordinates. The patients remained in the same immobilization device to minimize any positioning differences between the two CT scans and also they were instructed to hold their breath at the tidal inspiration level during the CT scan. The IV contrast agent contained 320 mg/ml of ionic CA iodixanol (Visipaque). The total dose of the CA was 1.2 ml/kg body weight or about 100 ml for patients with a body weight of over 80 kg and administered via an automatic injector. Oral contrast was 20–40 ml of meglumine compound (Gastrografin) with a concentration of 370 mg of iodine per ml diluted in 1.5 L of mineral water. Initially, CT images were taken without contrast. Then, patients having oral contrast were trained to drink the entire contents of the cup prior to the acquisition of secondary CT images. After the administration of oral contrast, the IV automatic injector was connected to the patient's angiocath. The scan started 65 s after the IV contrast injection. The same isocenter and scanning technique (120 kVp, 250–300 mAs, 512 × 512 pixel image size) were used and reconstruction of the images was performed with 4–5 mm intersection gap in cases.

3.3. *Treatment planning and radiation dose calculations*

All plans were generated in the treatment planning system (DosiSoft, France) which was adjusted to the linear accelerator (ELEKTA, England) with 6, 10 and 18 MV photon beams. ISOgray is a representative product of DosiSoft company for radiotherapy treatment planning, which is proven by the Food and Drug Administration (FDA). This treatment planning system is a convenient and comprehensive product that supports three dimensional conformal radiation therapy (3D-CRT), intensity modulated radiation therapy (IMRT), multi-field planning with an automatic registration suite and instrumental intelligent functions. DosiSoft ISOgray provides accurate dose distribution based on the Point Kernel and Collapsed Cone algorithms for photon beams, and the Superposition Convolution algorithm for monitor units (MU) calculations applying heterogeneity correction in both (pre- and post-contrast CT data sets) plans.

To compare the density difference between the two sets of CTs, changes in the electron density (ρ_e) between the non-enhanced and enhanced CTs were evaluated in ROIs on the DosiSoft ISOgray.

After the CT simulation, both sets of CT images were transferred to the radiotherapy planning system for contouring using digital imaging and communications in medicine (DICOM) 3RT format. The gross tumor volume (GTV), clinical target volume (CTV), and planning target volume (PTV), along with the other organs at risk (OARs), were delineated and contoured. ROIs were drawn on non-contrasted images and then copied to the contrasted images. The two CT data sets were already registered and shared the same ROIs and the same method was employed to analyze pre- and post-contrast CT data. Also, the beam characteristics of the radiotherapy plan generated in the non-enhanced CT data set were copied and applied to the enhanced CT data, which included the beam energy, treatment fields, fraction number and fraction size (dose per fraction) for each field. Radiation dose distributions in the enhanced CTs could be obtained by recalculation of each plan using the same parameters of the non-enhanced plans. Radiation dose calculations were performed for 18 MV photon beam of the linear accelerator. In current study the prostate and rectal irradiation was also planned by using four fields, which included anteroposterior (AP), posteroanterior (PA), right-lateral (RL), and left-lateral (LL) beams, as a box plan.

The prescription dose was 1.8 (Gy) per fraction for PTV. Therefore, the required MUs to deliver 1.8 (Gy) doses for each plan were calculated and the relative dose differences of PTVs and OARs between the 3D plans, with and without CA, were compared. Mean and standard deviation (SD) were used for quantitative data description. The data were analyzed using SPSS 16 and statistical tests such as paired sample *t*-test. The meaningless level of statistical tests was considered as $p < 0.05$.

The relative dose difference (%) between the pre- and post-contrast enhanced computed tomography (CECT) plans was defined as follows:

$$\text{Relative dose difference(\%)} = \frac{(\text{Dose[Gy]with post-CECT}) - (\text{Dose[Gy]with Pre-CECT})}{\text{Prescription Dose[Gy]}}$$

4. Results and discussion

The eleven patients (10 men and 1 woman) included in the study were eligible for analysis of the difference between the radiation dose of all volumes (PTVs and OARs) for CT pre- and post-contrast based calculations. The patient characteristics along with the contrast type are shown in Table 1.

Table 2 summarizes the degree of relative electron density (ρ_e) differences for tumor volume (PTV) and OARs due to the CA (IV and/or oral + IV) in CT scans for rectal and prostate plans. The results in these tables confirm the expected relationship of increasing attenuation, HU number and ρ_e with increased tissue density due to the CA.[7,8,12] The range of increase in ρ_e was from 0.006 to 0.004 and 0.008 to 0.013 for rectal and prostate plans, respectively. The magnitude of difference in the maximum ρ_e increase was in the range of 0.010–0.035 and 0.016–0.028 for rectal and prostate plans, respectively. In both plans, the prostate showed the largest difference in average ρ_e increase (because of the oral + IV CA), followed by the bladder and rectum, presumably due to the concentration of blood flow nearby. These three CA-sensitive ROIs showed an average increase of over 0.56% ρ_e (maximum 1.27%).

The comparison of 3D-CRT mean dose calculation from pre- and post-contrast agents by using percentage of relative mean dose difference and paired sample *t*-test for rectal and prostate regions (PTVs and OARs) are shown in Table 3. Because the post-contrasted images had higher HU and ρ_e, the photon beam attenuation was more than what was calculated based on pre-contrasted images. Treatment planning on post-contrasted images generally showed a lower dose to both targets and OARs than plans on pre-contrasted images.

Table 2 – Relative electron density (ρ_e) differences due to the contrast agent administration.

Region	Site	Relative electron densities (ρ_e)		p-Value*	Increase in ρ_e	Maximum ρ_e increase	Average ρ_e increase (%)
		Pre-contrast Mean ± Std dev	Post-contrast Mean ± Std dev				
Rectum	PTV	0.99 ± 0.03	0.99 ± 0.02	0.27	0.006	0.01	0.56
	Bladder	1.01 ± 0.01	1.02 ± 0.006	0.49	0.006	0.03	0.62
	LN	0.99 ± 0.007	0.99 ± 0.005	0.43	0.004	0.01	0.36
Prostate	PTV	1.01 ± 0.009	1.03 ± 0.02	0.41	0.010	0.02	1.27
	Bladder	1.01 ± 0.01	1.01 ± 0.02	0.50	0.008	0.01	0.79
	Rectum	0.92 ± 0.15	0.93 ± 0.12	0.88	0.005	0.02	0.43

PTV, planning target volume; LN, lymph node; Std dev, standard deviation.
* Significant values at $p < 0.05$.

Table 3 – Relative mean dose differences due to the contrast agents.

Region	Site	Mean dose		p-Value*	Relative mean dose difference (%)	Maximum mean dose increase (Gy)	Average mean dose increase (%)
		Pre-contrast Mean ± Std dev	Post-contrast Mean ± Std dev				
Rectum	PTV	45.98 ± 1.60	45.87 ± 1.72	0.38	−0.21	0.31	0.23
	Bladder	40.67 ± 7.10	40.19 ± 7.51	0.20	−0.97	0.81	1.19
	LN	47.72 ± 1.58	47.56 ± 1.82	0.44	−0.32	0.17	0.33
	Lt. Femur	22.56 ± 5.15	22.15 ± 5.96	0.54	−0.82	0.80	1.83
	Rt. Femur	21.68 ± 4.57	21.75 ± 5.47	0.89	0.14	1.23	0.32
Prostate	PTV	49.64 ± 0.79	49.38 ± 0.07	0.70	−0.52	0.25	0.52
	Bladder	45.12 ± 6.59	45.76 ± 6.63	0.03**	1.28	0.67	1.41
	Rectum	43.55 ± 9.41	44.13 ± 8.82	0.39	1.16	1.00	1.33
	Lt. Femur	28.78 ± 0.08	27.84 ± 0.61	0.31	−1.87	−0.44	3.24
	Rt. Femur	25.98 ± 3.83	27.34 ± 4.92	0.32	2.72	2.13	5.00

PTV, planning target volume; LN, lymph node; Std dev, standard deviation.
* Significant values at $p < 0.05$.
** Mean ± Std dev.

From Table 3, the percentage of relative dose difference for the rectum as tumor volume, bladder, lymph node, left and right femur are −0.21% (0.381), −0.97% (0.206), −0.32% (0.444), −0.82% (0.549) and 0.14% (0.897), respectively. The results show no significant difference between pre- and post-contrast CT images treatment plan.

From Table 3, the percentage of relative dose difference for the prostate as tumor volume, bladder, rectum, left and right femur are −0.52% (0.700), 1.28% (0.030), 1.16% (0.399), −1.87% (0.310) and 2.72% (0.328), respectively. The results show no statistically significant difference between pre- and post-contrast CT images treatment plan for the tumor volume (PTV), rectum, left and right femur, except the bladder. Statistically but not clinically significant difference in mean dose of the bladder as OAR of post-contrasted images was observed in the prostate plan as compared with pre-contrasted images ($p < 0.05$). Relative dose difference at the bladder is different between two plans because CECT image has a lot of contrast agent filled in the bladder with high concentration and enlarge region (Fig. 1); therefore, density at the bladder volume between pre- and post-contrast CT images treatment plans is more different than the other organs (ROIs). According to the results, the maximum difference in the mean dose was shown in Table 3 for the bladder as OAR. This result confirms the findings of Jabbari et al. study.[15] When using CECT data for multi-field planning, average increase in mean dose at the isocenter and in OARs were observed up to 0.23%, 1.19% and 0.52%, 1.41%, for rectal and prostate plans, respectively. Planning on post-contrasted images may result in an increase in dose of up to 0.23% and 0.52% for rectal and prostate plans, respectively at the isocenter, which would generally be regarded as clinically insignificant. Based on the results of this research and Liu et al. study,[8] it is obvious that the increased CT-number (HU) and ρ_e caused by CA did not change the dose distribution proportionally. The relative mean dose difference for the points of interest placed in the PTV and OARs rarely changed more than 2% in any patient. In this research, we found that there were not clinically significant differences in the mean dose of post-contrasted images, as compared with pre-contrasted images in prostate and rectal plans at the isocenter ($p > 0.05$). These results confirm the findings of similar studies.[7,8,11]

The total monitor units (MU) and also equivalent depth (mm) calculated from all fields in the two plans are compared in Table 4. No clinically significant difference is apparent between the numbers of MU and equivalent depth calculated from the pre- and post-contrasted CT images ($p > 0.05$). On account of the low increase in electron densities, the average differences in MUs as a result of CA administration was less than 2% for 18 MV photon beam. This indicates that the differences in MUs by the use of contrast agents are not clinically significant and may be considered negligible at the pelvic anatomical region. These findings are in agreement with the previous investigations.[13–16]

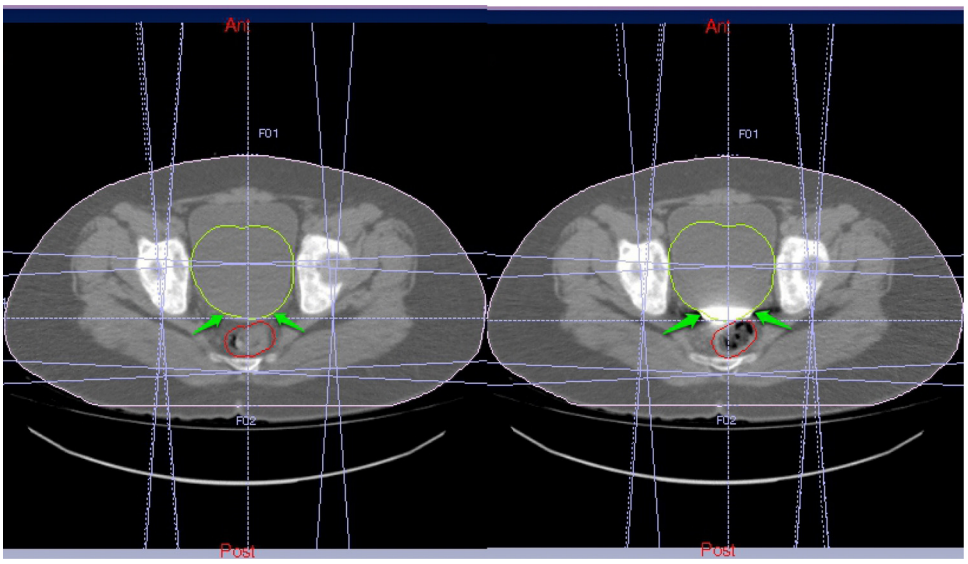

Fig. 1 – The pre-contrast CT (left) and the post-contrast CT (right).

Table 4 – Differences in equivalent depth (mm) and total monitor unit numbers due to the contrast agents for 18 MV photon beam.

Region	Equivalent depth (mm)		*p*-Value*	Monitor unit		*p*-Value*
	Pre-contrast Mean ± Std dev	Post-contrast Mean ± Std dev		Pre-contrast Mean ± Std dev	Post-contrast Mean ± Std dev	
Rectum	147.08 ± 5.75	147.48 ± 4.62	0.54	225.41 ± 6.87	225.57 ± 6.37	0.78
Prostate	130.93 ± 9.21	134.97 ± 5.51	0.36	206.05 ± 2.04	207.22 ± 0.445	0.48

Std dev, standard deviation.
* Significant values at $p < 0.05$.

5. Conclusions

The influence of contrast in the dosimetry of 3D-CRT for rectal and prostate cancers was evaluated. The radiation dose changed in accordance with the differences in ρ_e interpolated from the HU or CT-number. The 3D treatment planning dose calculations based on post-contrasted images do not show a clinically significant difference in the dose calculations compared to the standard 3D planning based on pre-contrasted images. Treatment planning by using of CECT had clinically insignificant effect on the dose calculations and monitor units. The difference is generally less than 2% due to the CA. Therefore, there is no need to expose the patients to additional radiation dose to obtain two CTs. In our opinion, only contrasted CT images need to be performed during the CT simulation for rectal and prostate cancers. CECT can be used for both target volume delineation and treatment planning of pelvic cancers because the radiation dose and monitor unit differences between the plans for the CT scans with and without CA seem to be clinically insignificant.

Conflict of interest

None declared.

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