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Dosimetric effect of intra-fractional and inter-fractional target motion in lung cancer radiotherapy techniques

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Technical Report

Abstract

Purpose: The purpose of present study was to experimentally evaluate the dosimetric uncertainties in 3-dimensional conformal radiotherapy (3DCRT), dynamic intensity modulated radiotherapy (D-IMRT), step-shoot (SS-IMRT), and volumetric modulated arc therapy (VMAT) treatment delivery techniques due to intra- and inter-fractional target motion. **Methods:** A previously treated lung patient was selected for this study and was replanned for 60 Gy in 30 fractions using four techniques (3DCRT, D-IMRT, SS-IMRT, and VMAT). These plans were delivered in a clinical linear accelerator equipped with HexaPOD™ evo RT System. The target dose of static QUASAR phantom was calculated that served as reference dose to the target. The QUASAR respiratory body phantom along with patients breathing wave form and HexaPOD™ evo RT System was used to simulate the intra-fraction and inter-fraction motions. Dose measurements were done by applying the intra-fractional and inter-fractional motions in all the four treatment delivery techniques. **Results:** The maximum percentage deviation in a single field was -4.3%, 10.4%, and -12.2% for 3DCRT, D-IMRT and SS-IMRT deliveries, respectively. Similarly, the deviation for a single fraction was -1.51%, -1.88%, -2.22%, and -3.03% for 3DCRT, D-IMRT, SS-IMRT and VMAT deliveries, respectively. **Conclusion:** The impact of inter-fractional and intra-fractional uncertainties calculated as deviation between dynamic and static condition dose was large in some fractions, however average deviation calculated for thirty fractions was well within 0.5% in all the four techniques. Therefore, inter- and intra-fractional uncertainties could be concern in fewer fraction treatments such as stereotactic body radiation therapy, and should be used in conjunction with intra- and inter-fractional motion management techniques.

Keywords: Respiratory Motion; Dynamic Phantoms; Dosimetry; Intra-fraction Motion

Introduction

Treatment of upper abdomen and thorax using ionizing radiation is challenging issue in the radiotherapy due to inter- and intra-fractional movement.[1] Intra-fraction motion is caused mostly by the respiratory, cardiac, and gastrointestinal system. Apart from respiratory motion which varies from day to day, tumor and normal tissues can also shrink, grow and shift in response to radiation therapy and potentially to other concomitant therapies.[2] Studies on respiratory induced tumour motion have indicated that major movement is in superior-inferior (SI) direction and tumors located in the lower lobe of the lung exhibited the greatest amount of motion along the SI axis.[3,4] The motion of the lung in SI direction play important role in dosimetric uncertainties compared to lateral and anterior-posterior (AP) motions during lung cancer radiotherapy.[5] The inter-fractional setup errors which arise as a result of deviation of anatomic structures between the pre-treatment position and planning computed tomography (CT), produce deviation of delivered dose from planned dose affecting the treatment accuracy.[6] Apart from these, relative movement of target and multileaf collimator (MLC) known as interplay effect is an important factor to be considered in treatment delivery techniques that involve intensity modulation. The interplay effect can also produce cold/hot spots within the target. These sources of error become limiting factor in achieving the goal of the radiotherapy.

Technical advances resulted in various techniques to manage the inter- and intra-fractional motion such as breath-hold[7,8,9] gating[10,11,] and tracking.[12,13] Hence it is important to investigate the dosimetric effect of techniques used for delivery of radiotherapy treatments in context of respiratory motion. The purpose of this study was to experimentally evaluate the dosimetric uncertainties in 3-dimensional

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conformal radiotherapy (3DCRT), dynamic intensity modulated radiotherapy (D-IMRT), step-shoot (SS-IMRT), and volumetric modulated arc therapy (VMAT) treatment delivery techniques due to intra- and inter-fractional target motion

Methods and Materials

6-dimensional (6D) patient setup couch

HexaPOD™ evo RT System (Elekta Medical systems, USA) was used in this study that enables to correct the setuperrors in translational as well as in rotational direction (roll, pitch, and yaw). **Table 1** shows the range of movement of 6D hexapod evo RT system. The 6D setup errors used in this study were acquired from the daily portal verification images of a real patient. The inter setup error was simulated by these six directional shifts using Hexa POD 6D couch [**Table 2**]. The setup errors (mean ± SD) used was RL: 0.34 ± 0.53 cm, SI: 0.05 ± 0.30 cm, AP: 0.046 ± 0.33cm, Pitch: 0.43 ± 1.39, Roll: -0.63 ± 1.22deg and Yaw: 0.79 ± 1.13 deg. This helps in achieving the dose delivery to an accuracy of ±5% and spatial agreement of planned to delivered isodose lines of ±3 mm.

Quasar respiratory motion phantom

The intra-fractional respiratory motion was simulated using the QUASAR™ (Modus Medical Devices Inc., London) respiratory motion phantom, a state-of-the-art breathing simulator [**Figure 1**]. It is comprised of programmable drive unit, body oval and cylindrical inserts etc. The body oval with dimension 30 cm × 20 cm × 12 cm weighs 20 kg to approximate the average thorax region of human body. The cylindrical inserts provide the means for dose measurement. The insert can accommodate ionization chamber, thermo luminescence dosimeters (TLD), gafchromic films, gel dosimeter and optically stimulated luminescence etc. In this study 0.6 cc ionization chamber (PTW Freiberg, Germany) was used for the measurement of absorbed dose. The movement of the insert was in the superior- inferior direction as per the wave form acquired from Real-time Position Management ™ (RPM) system.

TABLE 1: Treatment range of 6D Hexapod evo System.

Translational treatment range at start position					
Axis	**Translations from the zero position**	**Movement**	**Axis**	**Rotation**	**Movement**
X	Lateral	±30 mm	Pitch	Around the x-axis	$\pm3^0$
Y	Longitudinal	±30 mm	Roll	Around the y-axis	$\pm3^0$
Z	Vertical	±30 mm	Yaw	Around the Z-axis	$\pm3^0$

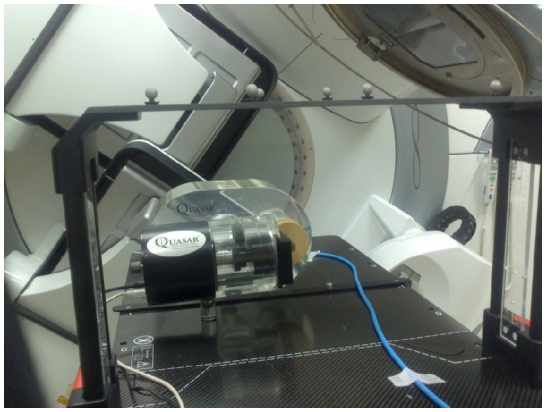

FIG. 1: Experimental setup: The QUASARTM respiratory phantom having insert connected to drive system on the Hexapod.

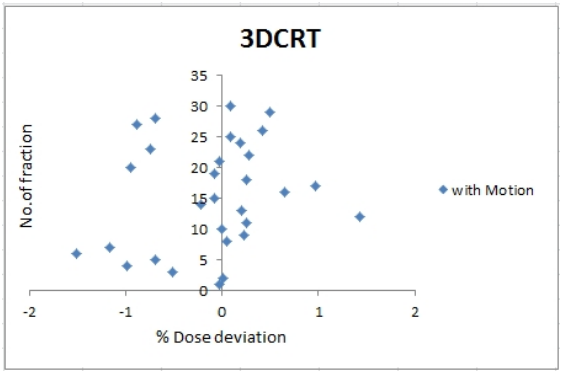

FIG 2: % Deviation in dose (with motion) from static in 3DCRT.

TABLE 2: Patients setup error for 30 fractions.

No. of fraction	X	Y	Z	Yaw	Pitch	Roll
1	0.7	0.5	-0.1	0.1	-2.4	2.3
2	1.2	0.2	0.1	-0.6	-0.3	1.9
3	0.5	0.2	0.4	2.1	-0.6	-0.1
4	0.1	-0.2	0.1	1.4	-0.4	1
5	-0.7	0.3	0.1	2.5	-0.9	2.5
6	0.8	-0.6	0.1	-2.4	0.1	2
7	0.5	0.4	0	0.5	-1.6	-0.7
8	-0.3	0	0.4	1.7	-0.5	-1.2
9	0.4	-0.4	0.3	-1	0.2	-1.1
10	1.2	-0.3	0.5	1.2	-1	0.7
11	1	0.2	-0.5	-1.9	0.3	1.7
12	0.4	0.2	-0.1	1.7	2.3	-0.5
13	0.1	0.2	-0.2	-0.3	-1.4	0.4
14	0.3	-0.5	-0.7	-0.6	-0.3	1.3
15	0.9	0.3	-0.2	0.2	-0.1	0.6
16	0.3	0.1	-0.1	2.5	-0.3	-0.2
17	0.8	-0.3	0.2	1.9	-1.0	0.7
18	0.5	0.00	-0.4	-0.2	-2.6	-0.5
19	-0.3	-0.2	0.3	-0.1	-2.6	-0.5
20	0.2	-0.4	-0.2	0.1	-2.3	2.2
21	0.1	0.2	-0.2	-0.3	-1.4	0.4
22	0.4	0.2	-0.1	1.7	2.3	-0.5
23	0.8	-0.4	0.8	2.5	-0.4	1.6
24	-0.6	0.5	0.4	0.7	-2.0	-0.4
25	1.0	0.2	-0.5	-1.9	0.3	1.7
26	-0.3	0.1	0.4	-0.3	-2.1	1.5
27	0.2	0.2	-0.1	-1.2	-.20	1.8
28	-0.5	0.4	0.2	2.1	0.9	1.3
29	1.0	0.2	0.1	-0.5	-0.4	2.0
30	0.6	0.2	0.4	0.8	-0.6	1.8

A previously treated lung cancer patient was selected for this study and was re-planned for 60 Gy in 30 fractions using four treatment delivery techniques viz 5 field 3D CRT, seven fields each in D-IMRT & SS-IMRT and single arc VMAT. The 3D CRT plan was generated using CMC XiO (version 4.64.00; Computerized Medical System, St.Louis, MO) and inverse planning was performed using Monaco (version 3.2; CMS Inc., St. Louis, MO) treatment planning system (TPS). Pre-treatment verification plans with maximum dose rate of ~ 700MU/min at the isocenter for 6 MV photon beam, were created and exported to RV system Mosaiq, Elekta, Mountain View, CA) for the treatment delivery using clinical linear accelerator (Infinity, Elekta Medical systems, USA) equipped with MLCi2, iViewGT, XVI (version 4.64.00) and HexaPOD™.

The QUASAR™ phantom with the insert having 0.6 cc ionization chamber, was placed on the HexaPOD™ evo RT System and connected to drive system that was responsible for the movement of target in SI direction as per the given breathing waveforms. Treatment plan of a real lung cancer patient was retrieved to the treatment delivery workstation. This plan was executed in two arrangements.

Target dose in static condition

Treatment plan of each technique was executed on the QUASAR™ phantom in static condition (without any intra-fractional and inter-fractional motion) keeping center of the chamber and center of the field along the central beam line with source to axis of the chamber distance (SAD) 100 cm. As shown in the [**Table 3**] dose values in each field of each fraction were recorded from the electrometer reading corrected for temperature, pressure, etc.

Target dose in dynamic condition

To incorporate the effect of inter-fractional (inter setup) and intra-fractional (target) motion, each fraction was delivered after introducing the inter setup error [**Table 2**] in the HexaPOD™ evo RT system couch along with the intra-fractional target motion according to individual patient waveform. Thus, target moves around the isocentre in SI direction during the delivery of radiation. In each fraction initial breathing phases were introduced randomly. This was done for 30 fractions in all the four techniques. Dose received was calculated as done in Static condition for each field of each fraction [**Table 3**]. The cumulative target dose from each fraction in all the technique was compared with the corresponding static doses to calculate percentage deviations.

Results

Dosimetric effect of intra- and inter-fractional target motion was studied for 3DCRT, SS-IMRT, D-IMRT, and VMAT treatment deliveries. The target dose measured for 120 fractions (30 fractions in each modality) using the 0.6 cc ionization chamber with inter- and intra-fractional motion in superior and inferior (SI) direction only, as well as for static reference condition as depicted in [**Table 3 (a), (b), (c) and (d)**]. Variation was found in daily fraction of each technique between static dose and dose in dynamic condition. There was large variation among the various techniques. The maximum percentage deviation in dose in dynamic condition compared to static doseina single field was -4.3%, 10.8% and -12.2% for 3DCRT, D-IMRT, SS-IMRT respectively. Similarly the % deviation for a single fraction was (-1.51 ± 0.64%), (-1.88 ± 0.80%), (-2.22 ± 0.83%) and (-3.03 ± 1.28%) for 3DCRT, D-IMRT, SS-IMRT and VMAT as shown in the [**Figure 2, 3, 4 and 5**]. On the other hand the percentage deviation of all the techniques was reduced to less than 0.5% for the entire 30 fractions. Difference in doses delivered by different techniques was found statistically significant (p = 0.331, at confidence level 0.05) using ANOVA One-way analysis of variance of means of % deviation from dose in static condition. Compared to 3DCRT the maximum deviation in dose was found in VMAT technique (p = 0.800).

TABLE 3(a): Measured dose (cGy) in 5 fields of each fraction in three dimensional conformal radiotherapy in static and dynamic condition.

No. of Fractions	1CRT	2CRT	3CRT	4CRT	5CRT
	Static(cGy)				
1	50.34	30.23	37.86	52.70	28.46
	Dynamic(cGy)				
1	50.33	30.20	37.78	52.73	28.49
2	51.20	30.30	36.80	52.84	28.47
3	49.58	30.56	37.96	52.05	28.39
4	48.91	30.98	38.27	51.29	28.17
5	50.24	30.48	37.40	51.90	28.18
6	48.57	31.30	38.26	50.52	27.93
7	48.911	31.33	39.03	50.30	27.69
8	50.85	30.51	37.11	52.74	28.49
9	50.45	30.51	38.11	52.57	28.39
10	50.23	30.53	38.39	52.17	28.26
11	50.85	30.28	37.64	52.80	28.53
12	51.35	29.59	37.51	54.86	29.13
13	50.66	30.75	36.95	52.95	28.68
14	50.34	30.83	37.47	52.19	28.32
15	49.19	30.12	38.89	52.64	28.60
16	51.35	30.17	36.47	53.99	28.90
17	51.11	29.86	36.61	54.78	29.17
18	50.57	30.27	37.38	53.18	28.69
19	50.52	30.86	36.97	52.56	28.53
20	48.99	31.02	38.75	51.02	27.94
21	50.66	30.60	36.74	52.91	28.64
22	49.54	30.20	37.93	53.50	28.97
23	50.46	30.13	37.61	51.75	28.15
24	50.67	30.24	37.30	53.27	28.50
25	50.97	29.85	37.61	52.96	28.37
26	50.74	29.62	37.44	53.86	28.78
27	49.41	30.40	38.87	51.21	27.93
28	49.74	30.47	38.02	51.81	28.19
29	50.33	30.83	39.22	51.80	28.39
30	49.24	31.28	37.58	52.33	29.34

TABLE 3(b): Measured dose (cGy) in 7 fields of each fraction in dynamic intensity modulated radiotherapy in static and dynamic condition.

No. of Fractions	1DIMRT	1DIMRT	1DIMRT	1DIMRT	1DIMRT	1DIMRT	1DIMRT
	Static(cGy)						
	48.20	32.98	18.16	27.59	36.88	40.60	35.54
	Dynamic(cGy)						
1	49.58	32.34	18.65	29.41	36.79	40.56	34.55
2	50.60	33.08	18.37	27.82	37.02	39.12	35.54
3	47.03	31.41	17.70	27.98	37.29	41.30	33.48
4	47.80	31.33	18.10	27.79	35.16	40.90	36.85
5	48.56	32.06	18.19	27.24	39.13	37.44	34.21
6	47.91	31.078	17.50	27.22	38.98	41.36	34.43
7	47.21	34.22	18.02	29.50	37.33	40.27	32.40
8	45.95	33.15	18.15	27.08	36.96	40.66	35.61
9	46.56	32.89	18.33	28.55	34.36	37.45	37.31
10	48.64	33.43	18.28	28.22	36.29	41.40	34.31
11	48.19	34.08	18.01	27.32	37.85	39.82	34.87
12	43.66	34.53	17.63	28.01	40.98	43.09	35.26
13	50.31	33.45	18.23	25.05	40.28	41.38	33.76
14	47.94	32.52	17.64	27.11	37.62	41.18	35.86
15	48.86	31.42	18.00	28.21	38.00	41.72	35.08
16	48.17	32.73	18.52	26.04	38.94	39.94	37.68
17	46.36	32.63	18.10	28.06	40.49	40.34	34.44
18	47.97	32.31	17.98	27.72	38.29	42.56	34.50
19	49.16	32.84	18.34	27.18	36.54	39.48	36.70
20	45.97	31.33	18.46	27.85	36.00	41.24	37.53
21	51.78	32.19	19.12	25.65	37.21	38.56	34.62
22	48.94	31.57	17.32	27.99	36.99	40.85	33.10
23	44.46	32.74	18.08	27.47	37.12	42.70	36.43
24	50.09	33.15	19.28	27.02	38.71	38.04	35.53
25	48.31	36.26	17.35	26.46	35.65	39.14	35.07
26	47.67	33.55	17.47	27.84	38.98	39.81	35.05
27	48.25	32.65	18.12	28.67	35.26	41.01	35.44
28	50.02	32.96	18.25	27.95	37.59	37.46	34.48
29	46.51	33.56	18.29	27.46	37.34	41.13	35.88
30	47.79	32.43	17.59	27.04	37.52	41.05	35.67

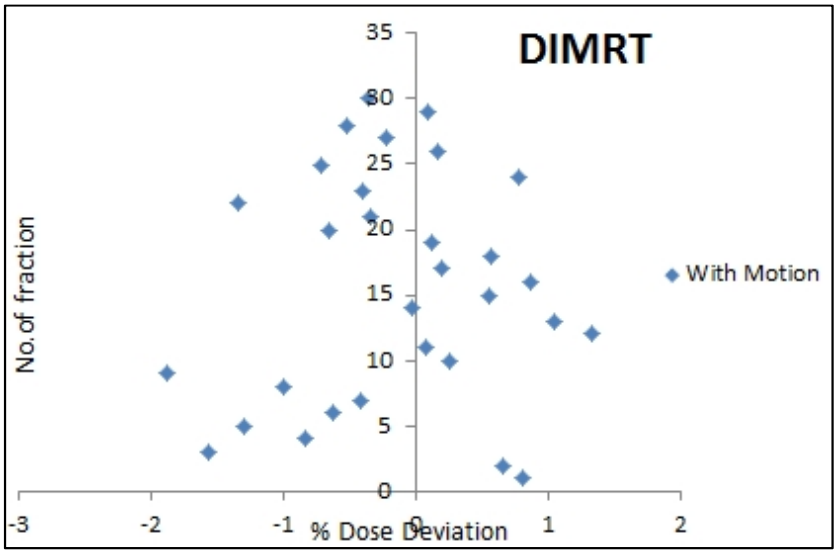

FIG. 3: % Deviation in dose (with motion) from static in DIMRT.

TABLE 3(c): Measured dose (cGy) in 7 fields of each fraction in step & shoot intensity modulated radiotherapy in static and dynamic condition.

No. of Fractions	1SSIMRT	2SSIMRT	3SSIMRT	4SSIMRT	5SSIMRT	6SSIMRT	7SSIMRT
	Static (cGy)						
	38.56	48.90	17.47	22.49	31.01	40.37	38.47
	Dynamic (cGy)						
1	38.90	49.00	17.63	22.52	31.20	40.17	37.99
2	38.95	50.07	17.62	21.86	31.10	42.71	36.45
3	39.71	49.51	17.63	22.96	31.751	39.11	37.81
4	39.62	47.80	17.86	22.88	31.97	38.33	36.72
5	40.26	51.21	18.04	22.53	31.00	39.88	33.76
6	39.28	47.69	18.26	23.67	32.61	37.47	36.21
7	39.80	47.64	18.16	24.44	32.78	37.70	36.63
8	39.77	52.39	17.98	22.27	30.63	40.83	36.09
9	39.62	48.77	17.62	22.90	31.39	40.15	37.63
10	40.40	50.55	17.66	22.74	31.62	40.26	38.63
11	39.07	49.41	17.48	22.23	31.35	41.17	35.41
12	37.61	48.52	17.20	21.77	31.77	42.40	40.21
13	38.67	50.44	17.85	21.82	31.07	40.16	38.80
14	40.29	50.76	17.95	23.03	31.31	39.84	36.36
15	38.66	46.17	17.63	22.77	32.14	39.09	38.90
16	36.89	51.04	17.48	21.17	31.27	42.05	39.32
17	38.94	49.71	17.33	21.47	32.90	40.99	41.17
18	37.67	50.87	17.59	21.79	31.01	40.51	38.76
19	39.12	49.08	17.99	22.04	31.23	39.73	38.12
20	39.64	47.87	17.95	23.94	32.00	38.12	36.04
21	38.62	51.11	17.60	21.72	30.95	39.97	38.38
22	36.87	47.01	17.88	22.15	31.60	39.13	40.99
23	40.58	51.54	17.74	22.63	31.33	40.00	37.31
24	37.58	49.40	17.50	22.65	30.87	40.51	38.77
25	38.47	49.33	17.04	22.45	30.32	41.36	37.63
26	36.61	50.38	17.42	21.86	31.12	41.20	38.70
27	39.99	47.57	17.87	24.23	31.61	38.59	36.22
28	40.09	50.21	17.79	23.24	31.50	39.01	35.65
29	39.50	49.57	17.88	22.15	31.51	39.92	36.10
30	39.55	48.14	17.40	22.70	31.62	39.56	38.41

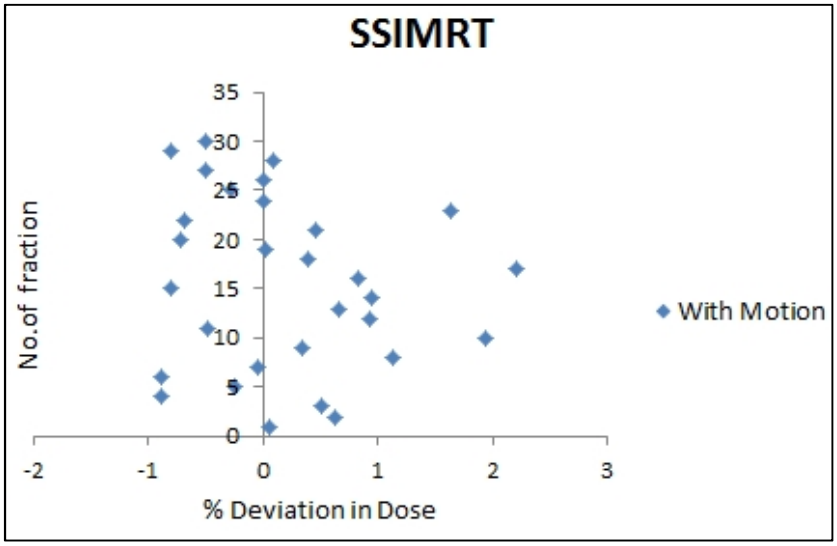

FIG. 4: % Deviation in dose (with motion) from static in SSIMRT.

TABLE 3(d): Measured dose (cGy) in each fraction in single arc of Volumetric Arc Modulated Radiotherapy in static and dynamic condition

No. of Fractions	VMAT
	Static
	237.596
	Dynamic
1	240.15
2	230.38
3	235.99
4	238.50
5	236.68
6	240.09
7	235.48
8	234.71
9	236.61
10	234.15
11	238.75
12	241.11
13	240.43
14	237.05
15	232.83
16	233.93
17	241.76
18	240.40
19	239.15
20	238.94
21	238.35
22	239.33
23	236.52
24	241.35
25	233.68
26	239.82
27	234.89
28	231.42
29	234.89
30	239.02

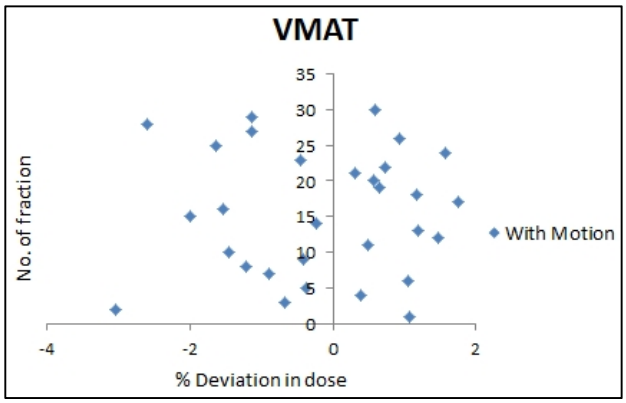

FIG. 5: % Deviation in dose (with motion) from static in VMAT.

Discussion

Both inter-fraction and intra-fraction motion affects the delivered dose distribution. Patients breathing pattern can vary during imaging and therapy in terms of amplitude and period etc.[14] in the present study, authors used the ionization chamber for the measurement of deviation in dose in dynamic condition from the static one in different techniques and deviation up to 2.22% in SS-IMRT was found. Schaefer *et al.*[15] made a study to find out whether breathing induced organ motion may cause over dosing or under dosing in the step-shoot IMRT of lung cancer. The measurement of dose was performed using ionization chambers in different places inside the phantom. The dose differences between static and moving target was from –2.4% and +5.5%. They concluded that at least in step-shoot IMRT the breathing effects are of secondary importance.

To manage inter- and intra-motions, a conventional and most popular method of adding the margin to gross tumour volume (GTV) is used. The treatment plan used in this study was created using 5 mm margin to GTV to produce the clinical target volume (CTV). Planning target volume (PTV) was created by adding 10 mm margin in CTV[16], besides these margins, a significant deviation up to 3.03% (VMAT) in a single fraction was found in dynamic dose compared to static one. At the same time these margins causes irradiation of normal tissue that results in the form of complications.

In the present study, difference in static dose and dose in dynamic condition was recorded though margins were present in GTV and CTV. The choice of adding more margins is always not a good way of practice especially for patients having wide range of tumour motion.[17] Nøttrup *et al.* found that method of margin is not always sufficient to overcome the problem of inter-fraction and intra-fraction motion. In their study they quantified the breathing variations over full course of radiotherapy and found that margins to account respiratory motion in lung tumour should include inter-fraction variations in breathing on the basis of individual assessment.[18]

In this study two modes of treatment were used viz conventional or non-modulated (3DCRT) and modulated (SS-IMRT, D-IMRT, and VMAT). The total error in position of tumor, is sum of relative movement between tumour-bone (intra-fraction) and bone-treatment room (inter-fraction). Intra-fractional motion causes averaging of the dose distribution whereas inter-fraction motion causes shift of dose distribution.[19] In case of 3DCRT technique intra-fraction motion is found to be a cause behind the dose deviation as the dose gradient at the center of field is very small. In case of modulated beam (IMRT), in addition to intra-fraction motion dose gradient within the field is also present. This is evident from the results of this study as least deviation (~1.5%) in dose in dynamic condition from static dose was found in 3DCRT compared to techniques involving modulation of beams (~3.0%) such as VMAT. The relative motion between multileaf collimator and tumour known as interplay effect can be a cause of dose difference. From the results of this study it was found that interplay effect dose

not play significant role in techniques involving large no. of fractions as for as total delivered dose is concerned. In this study, deviation in dose delivered in dynamic condition from dose in static condition in individual fractions was recorded similar to other studies using other means of dose measurement.[20, 21]

Similar to this experimental study, Bortfeld *et al.*[22] modeled (mathematically) the effects of intra-fraction motion on IMRT dose delivery and found that over all dose was just weighted average of static one. They concluded that one should not concern so much for the intra-fraction motion in highly fractionated IMRT treatment delivery. As a consequence, techniques for the management of organ motion reduces margin that enables dose escalation that is the one of the goals of radiotherapy. The accuracy of the results presented in this study may vary for different clinical conditions such as complexity of treatment plan, dose rate, etc. As dose was measured using large volume ion chamber, i.e. 0.6 cc for a single patient, it is required to extend this study to understand the three dimensional dose variations in relations to target and critical organs in cohort of patients. It is also recommended to further investigate the intra- and inter-fractional errors in the lung cancer patients treated with the stereotactic body radiation therapy (SBRT) VMAT technique.[24, 25]

Conclusion

The impact of inter-fractional and intra-fractional uncertainties calculated as deviation between dynamic and static condition dose was large in some fractions, however average deviation calculated for thirty fractions was well within 0.5% in all the four techniques. Therefore, inter- and intra-fractional uncertainties could be concern in fewer fraction treatments such as SBRT and should be used in conjunction with intra- and inter-fractional motion management techniques.

Conflict of interest

The authors declare that they have no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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