Original Article

Impact of Dosimetric Parameters on Interplay Effects in 6 MV Flattening Filter-Free Photon Beams to Treat Lung Cancer

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Abstract

Context: Interplay effects have become the significant problem in lung cancer radiotherapy. Since these effects yield dose variation within the target and surrounding tissues. **Aim:** The aim of this study is to investigate the effect of the dosimetric parameters of interplay effects in 6 MV flattening filter-free (FFF) photon beams for lung cancer. **Settings and Design:** This study performed planning, measurement, and data analysis sections for examining different breathing amplitudes and phases, doses, dose rates, field sizes, and fractionations. **Subjects and Methods:** Standard and clinical plans were created on the eclipse treatment planning system. The static and dynamic measurements were performed using a robotic platform and two-dimensional (2D) diode array. The gamma passing rates were defined as the percent of dose variation caused by the interplay effects. **Statistical Analysis Used:** Unpaired *t*-test. **Results:** The outcomes showed three trends between gamma passing rates (γ) and dosimetric parameters. First, a decreasing trend was breathing amplitudes. The lowest γ of maximum amplitudes (2 cm) in both one dimensional and 2D were <25%. Second, an increasing trend was field sizes. The lowest γ of minimum field size (4 cm × 4 cm^2) was <55%. Third, constant outcomes were breathing phases, doses, dose rates, and a number of fractions. The γ values of these factors were 53.1%, 55.1%, 34.7%, and 36.7%, respectively. **Conclusions:** Lung tumor motion-induced interplay effects in 6 MV FFF photon beams are more pronounced for higher breathing amplitudes and smaller field sizes.

Keywords: Flattening filter free, interplay effects, lung cancer

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Introduction

Lung cancer is the most common malignancy in both genders worldwide. It is the leading cause of death, approximately 2.09 million cases in 2018.[1] Lung stereotactic body radiation therapy (SBRT) treatment has been widely used in recent years.[2-4] SBRT is the treatment technique that delivers extremely precise intense doses of radiation to cancer cells while minimizing damage to healthy tissue. Furthermore, the SBRT also provides large doses per few fractions together with a rapid fall-off of dose outside the target. Hence, the accuracy of dose delivery and conformity of dose is very essential. However, this technique still poses a challenge to the treatment of lung cancer. The most important concern is interplay effects due to patient breathing during irradiation. This interplay effect, the effects between tumor motion and multileaf collimators (MLCs) motion occurring at the same time, leads to heterogeneities within the target volume and/or unwanted dose to the surrounding tissue. The previous study of Mukhlisin *et al*. indicated that tumor motion during irradiation can bring dose validation inside the tumor target in both lung intensity-modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) treatment techniques.[5] Likewise, Adamczyk *et al*. study illustrated that lung three-dimensional conformal radiotherapy (3D-CRT) and IMRT treatment techniques could cause tumor underdosage due to the interplay effect.[6] In the same way, Kubo *et al*. showed the number of patient breathing induced by interplay effects also impact the dose variation in lung VMAT-SBRT.[7] Moreover, several studies revealed the blurring of dose distribution of tumor target during irradiation owing to the interplay effects when tumor was motioned in only craniocaudal (CC) direction (one dimensional [1D] motion).[8-11] However, in recent years,

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flattening filter-free (FFF) technique was utilized together with the SBRT technique to increase the efficiency of lung cancer treatment[12,13] and reduce the interplay effects.[9] It has several benefits such as providing a higher dose rate with shorter time treatment as well as allowing inhomogeneous dose distribution with reduced peripheral dose.[14-16] As a result, the goal of this study is to investigate the dosimetric parameters of interplay effects in 6 MV FFF photon beams with different breathing amplitudes and phases, doses, dose rates, field sizes, and fraction numbers using two-dimensional (2D) robotic platform together with the 2D diode array.

Subjects and Methods

Robotic platform: The MotionSimXY/four-dimensional (4D) platform from Sun Nuclear Corporation, Melbourne, FL was a precision instrument designed to use together with the 2D diode array for quality assurance study of motion effects in radiation therapy imaging and delivery by moving a phantom through programmable motion patterns (an operating system same as MapCHECK2). The options of the phantom were provided accuracy and precision of X-Y motor drive to move the MapCHECK2 in X and Y directions. Moreover, this platform also allowed a wide range of motor movement, which the maximum travel was 10.2 cm of each X-Y axis and the maximum velocity was 5.08 cm/s.

Robotic platform: The MapCHECK2 (Sun Nuclear Corporation, Melbourne, FL) is a 2D detector array for accurate and fast verifying planar radiotherapy dose distributions. It offers smaller 1,527 diode detectors placed uniformly throughout the array provide high sensitivity and proven stability in a large active field size 26 cm × 32 cm^2. A real-time electrometer measures every pulse with 50 ms updates.

Patient information: To test the interplay effects impact of the clinical plans, a retrospective group of eight patients with lung cancer who underwent 4D computed tomography (4DCT) at free-breathing conditions and 2–3 full arcs of SBRT-VMAT during 2017–2020 was chosen. The maximum intensity projection reconstruction image from ten phases of 4DCT images was transferred to Eclipse treatment planning system (TPS) (Varian Medical System, Palo Alto, CA) to be set as the planning image, where the irradiation targets were the planning target volume (PTV) that expanded margin from the clinical target volume of 0.5–1.0 cm. The range of total PTV volumes was 9.1–83.0 cm^3. The number of PTV was 1–6, which averages located on the middle and upper lobes of both sides of the lung. For organs at risk (OARs), the OARs were heart, esophagus, spinal cord, whole lungs (subtract PTV), and contralateral lung.

Planning preparation

This study investigated the interplay effects from two groups of the plans. There were the standard and the clinical plans groups; each group was defined as follows:

Standard plans group

The 6 MV FFF of photon beams plans were created on Eclipse TPS version 15.6.05 with an Anisotropic Analytical Algorithm. These standard plans were planned with anteroposterior field with the planning parameters of 500 cGy/fraction prescription dose, 1400 MU/min dose rate, 4 cm × 4 cm^2 field size, 100 cm source to axis distance, and 5 cm measurement depth.

Clinical plans group

The eight lung cancer plans were divided into two subgroups. There were four complex plans and four noncomplex plans. The complex plans refer to the plans with multiple targets. All clinical plans were optimized and calculated for VMAT partial arcs with a gantry angle from 70° to 290° to avoid the beams passing through MotionSimXY/4D platform. These eight clinical plans were also applied for 6 MV FFF photon energy with 1400 MU/min dose rate. The other planning parameters were similar to the original patient planning parameters such as the prescribed dose. The plans were evaluated by isodose distribution and dose-volume histogram. The standardized prescription isodose was chosen according to the following criteria: Ninety-five percentage of PTV was encompassed by the prescription isodose volume and 99% of PTV was covered by 95% of the prescription dose.[17] Finally, all plans were created into verification plans or QA plans for dose measurements. The prescription dose of each individual case was defined by a radiation oncologist. The range of total dose was 3,000–5,070 cGy in 3–6 fractions.

Dose measurement

The static and dynamic dose measurements were simulated on a robotic platform to examine the effects of different amplitudes and phases of the platform, which can represent the breathing pattern of the lung cancer patient. Moreover, this study also investigated on different doses, dose rates, field sizes, and number of fractions as illustrated in Table 1. All plans were irradiated on the robotic platform from TrueBeam linear accelerator (Varian Medical Systems, Palo Alto, CA, USA). The dose outcomes were measured by a 2D diode array positioned on the robotic platform and covered with 3 cm of the solid water phantom as shown in Figure 1. All measurements stipulated the robotic platform moving pattern in 1 cm of amplitude in the Y-axis and 4 s of phase that estimated from our patient breathing information. This motion was set according to these parameters

Table 1: Robotic platform and three-dimensional conformal radiotherapy planning parameters setting

Parameters	Conditions
Robotic platform	
Amplitude on X-axis (cm)	0, 0.5, 1, and 2
Amplitude on Y-axis (cm)	0, 0.5, 1, and 2
Amplitude on XY-axis (cm)	0, 0.5, 1, and 2
3D-CRT planning	
Dose (cGy)	500, 800, and 1200
Dose rate (MU/min)	400, 600, 800, 1000, 1200, and 1400
Field size (cm^2)	4×4, 6×6, 8×8, and 10×10
Number of the fraction	1 (1,000 cGy/1F), 2 (500 cGy/2F), and 5 (200 cGy/5F)

3D-CRT: Three-dimensional conformal radiotherapy, F: Fraction

except the amplitudes effect study because we have to vary the amplitudes to see the interplay effects outcomes. However, the phase still used at 4 s. The breathing velocity in all study was set to 0.5 cm/s.

Data analysis

The results of calculated and measured doses were compared using gamma analysis with 1%/1 mm criteria for standard plans. On the other hand, 3%/2 mm of criteria following the American Association of Physicists in Medicine Task Group number 218 recommendation was applied in the clinical part.[18] As for statistical analysis, an unpaired *t*-test was selected for checking of independent samples tests whether the mean values of two independent groups differed significantly. When the *P* value of the test is <0.05, it is assumed that there is a statistically significant difference in the variances between the two groups.

Results

The results of this research were presented in the following experimental steps: Standard plans dose measurement and clinical plans dose measurement, respectively.

Standard plans dose measurement

Table 2 displays a decreasing tendency between the gamma passing rates and amplitudes. The results show higher amplitudes received lower gamma passing rates in all moving patterns, especially for 2D motion (XY-axis). Nevertheless, these comparisons were not statistically significant differences in the results between 1D and 2D motion since all *P* values exceeded 0.05. The correlation between gamma passing rates and amplitudes was explained by a mathematical linear equation in form of negative direct variation as shown in Figure 2. The r-squared (R^2) of the three curves provided more than 0.90, which can confirm the good negative agreements between gamma passing rate and motion in different amplitude. Figure 3 exhibits an increasing tendency of gamma passing rates with different symmetric field sizes. The correlation curve illustrates the positive direct variation of the mathematical linear equation together with approximately R^2 of 0.92. Other parameters of phase, dose, dose rate, and number of fractions revealed a constant trend of the results as shown in Table 3.

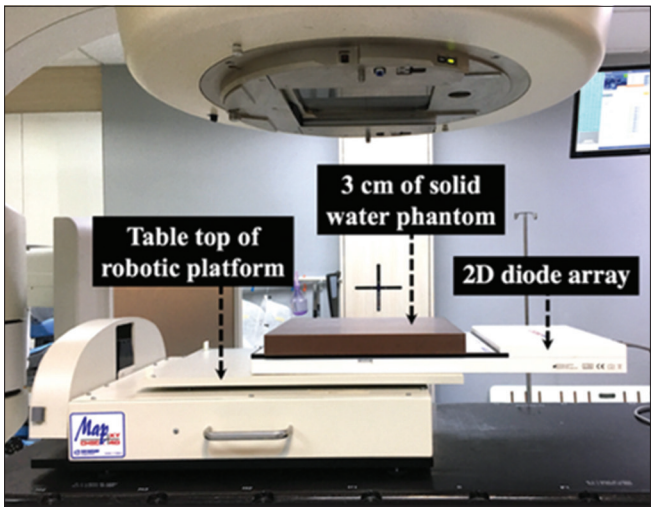

Figure 1: The setting up of robotic platform, MapCHECK2, and solid water phantom

Clinical plans dose measurement

Table 4 shows a reduction of gamma passing rates when the platform was moved. The noncomplex plans group received more than 84.0% of gamma passing rates whereas the complex plans group acquired <80.0%. Furthermore, both groups expressed dose blurring and changing in the shape of dose distribution as displayed in Figures 4 and 5 for noncomplex and complex plan, respectively.

Discussion

In this study, the percent of dose variation caused by the interplay effects were defined as the percent of the gamma passing rates. Thus, increasing the percent of gamma passing rates can be interpreted as a reduction of the impact of dosimetric parameters, which leads to an interplay effect. The results showed three tendencies of the standard plans dose measurement. First, the decrement trend was shown in amplitude outcomes. The results are in accordance with previous experimental research by Mukhlisin *et al*., Adamczyk *et al*., Kakakhel *et al*., and Edvardsson *et al*., which stated that the interplay effects were larger for higher breathing amplitudes of CC direction.[5,6,8,9] Besides, according to Figure 2, the slope value of the XY-amplitude correlation curve of this study showed higher the R^2 value more than the R^2 value of both X-amplitude and Y-amplitude slopes, whereas these two curves still receive the resemble outcomes. This point indicated that the 2D amplitudes motion has more impact on the interplay effects over 1D amplitude motions. Second, the interplay effects

Table 2: The gamma passing rates at 1%/1 mm criteria of standard plans irradiation with different amplitudes and unpaired *t*-test statistical analysis between 1D (X or Y-axis) and 2D (XY-axis) moving patterns

Amplitude (cm)	Moving platform in X-axis	Moving platform in Y-axis	Moving platform in XY-axis	Unpaired *t*-test (*P*)	
				X versus XY	Y versus XY
0.0	100.0	100.0	100.0	-	-
0.5	86.1	88.8	72.4	0.72	0.93
1.0	55.8	60.5	35.2	0.31	0.25
2.0	19.2	24.5	12.3	0.27	0.10

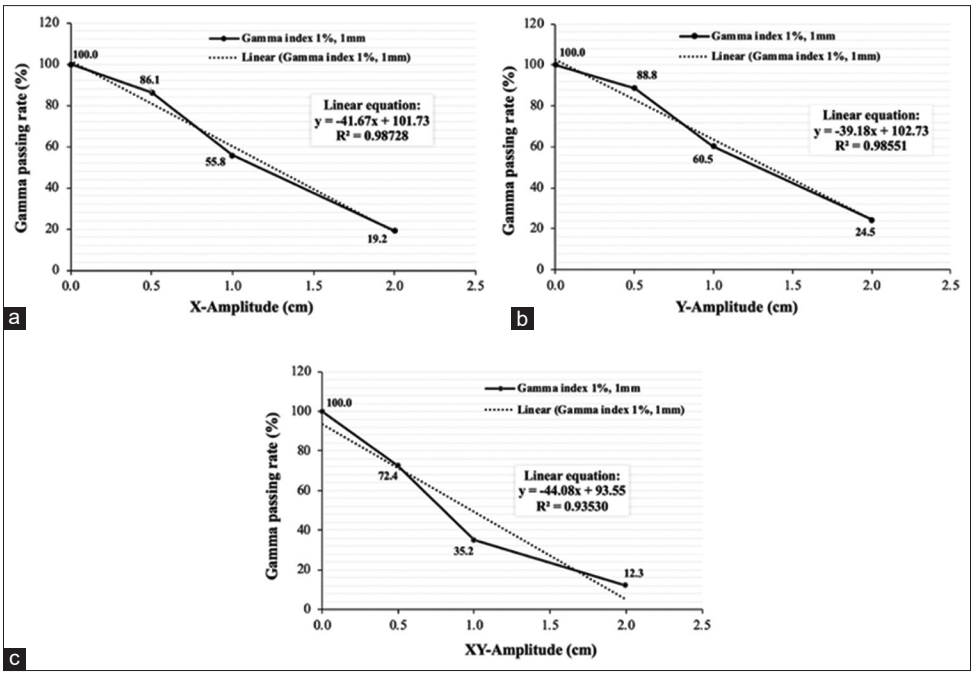

Figure 2: The correlation curves of all moving patterns between the gamma passing rates and the different amplitudes: (a) X-axis, (b) Y-axis, and (c) XY-axis

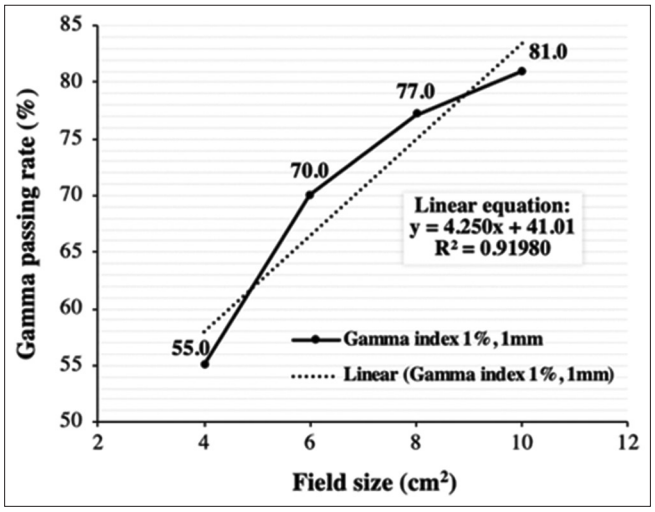

Figure 3: The correlation curve between the gamma passing rates and the different field sizes

were reduced by the larger field size. By cause of the larger expanding area allows more doses matching accuracy between calculated and measured doses. Kakakhel *et al*. also observed the increased gamma passing rates depended on the larger width of the field size.[8] Therefore, all findings mentioned above revealed that the longer distance and the larger number of directions of the tumor motion together with smaller treatment field size increase the interplay effects. Because the larger displacement leads to the larger area where the radiation doses do not overlap, furthermore, these problems easily provide tumor to escape from the beam trajectory.[6] Thereby, precise patient breathing and treatment field verification are the most important factor to ensure correct planning and delivery for lung cancer treatment. Third, the parameters of phases, doses, dose rates, and number of fractions were not affected by the interplay effects when compared dynamic phantom to the static phantom (phase was zero). All the static measurements showed 100% of gamma passing rate because

Table 3: The gamma passing rates from 1%/1 mm criteria and the linear equations of standard plans irradiation with different phases, doses, dose rates, and number of fractions

Dosimetric parameters	Gamma passing rate (%)
Phase (s)	
3	53.1
4	53.1
5	53.1
Dose (cGy)	
500	55.1
800	55.1
1,200	55.1
Dose rate (MU/min)	
400	36.7
600	34.7
800	34.7
1000	36.7
1200	34.7
1400	34.7
Number of fraction	
1	36.7
2	34.7
5	36.7

Table 4: The gamma passing rates for 3%/2 mm criteria and the planning target volume information of eight clinical plans irradiation to the static and dynamic mode of robotic platform motion

Number of clinical plan	PTV		Gamma passing rate (%)	
	Total volume (cm^3)	*n* is number of tumor	Static platform	Dynamic platform
1	83.0	1	100.0	85.9
2	71.3	1	100.0	90.8
3	15.0	1	100.0	84.1
4	9.1	1	100.0	84.3
5	31.8	2	100.0	79.7
6	30.2	2	100.0	75.6
7	28.6	6	99.5	71.0
8	9.7	2	98.5	69.7
Mean±SD			99.8±0.53	80.1±7.5

PTV: Planning target volume, SD: Standard deviation

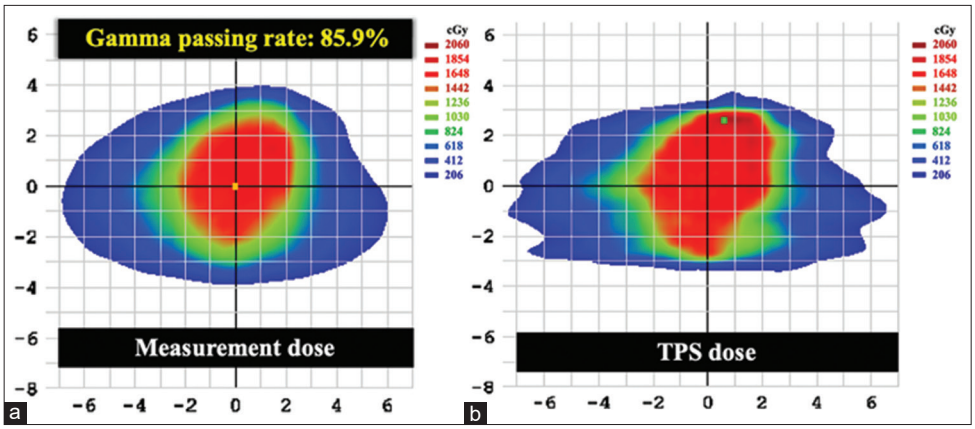

Figure 4: Examples of dose distributions of noncomplex lung stereotactic body radiation therapy plan delivered to MapCHECK2 placing on the robotic platform: (a) Dose distribution during dynamic platform measurement and (b) Dose distribution from the planning step

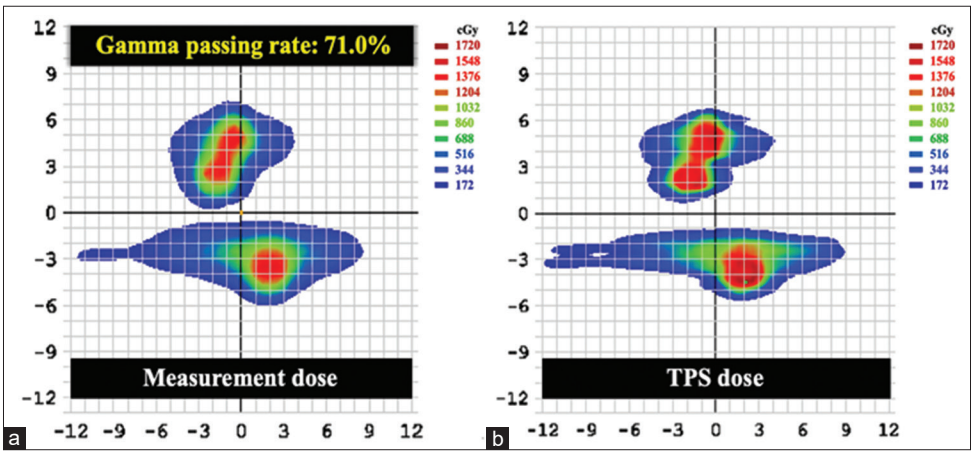

Figure 5: Examples of dose distributions of complex lung stereotactic body radiation therapy plan delivered to MapCHECK2 placing on the robotic platform: (a) Dose distribution during dynamic platform measurement and (b) Dose distribution from the planning step

the simple 3D-CRT planning technique was performed in this research. This technique provides a homogeneous field without any unchanging beam intensity. Furthermore, for number of fractions study, the phantom moving pattern and the homogeneous plans were similar in every fraction. Therefore, the results do not change. The other perspectives from Court *et al*., Ong *et al*., Rao *et al*., and Adamczyk *et al*. presented that the decrease in dose variation was associated with the decreasing in dose rate.[19-23] The 3D-CRT plans were generated with the dose rate of 300 MU/min, which was less than twice

dose rate used in IMRT and VMAT.[6] However, the lowering dose rate leads to prolonged treatment times, increasing the likelihood of patient motion during the treatment delivery[9] and necessitate more frequent patient monitoring with positional correction. The results of four factors, as shown in Table 3, were not significantly different in terms of interplay effects affecting factors. These results were taken by an uncontrolled of an initial phantom moving phase during irradiation. This event engendered an unequal of number of counting detectors. Therefore, the gamma passing rate of these four factors was different. In other words, if the starting time of phantom moving during irradiation can be identically set, the percentage of gamma passing rate will be the same for four effect studies.

The results of clinical plans showed that the interplay effects have more influence on large dynamic motion, high plan complexity, and small field size. The complex plans groups provide worst results than the noncomplex plans groups. This point showed the similarity to a study from Netherton *et al*., whom found the maximum and mean dose deviations increased with increasing plan complexity under tumor motion.[24] According to Table 4, clinical plan number one has a larger target volume than plan number two; however, the first patient was applied with a smaller field size (7.6 cm × 6.7 cm^2) than the second patient (9.5 cm × 7.7 cm^2). For this reason, the first clinical plan received a lower percentage of gamma passing rates. In addition, these clinical plans were created as the verification plans (QA plans). Thus, each plan was performed in only one fraction due to the limited practical time. However, we also anticipated that the number of fractions would be impacted to the interplay effect. This assumption was agreed with Stambaugh *et al*.[24] They revealed that the interplay effect was statistically significantly lower for the three-and five-fraction statistical simulations. Overall, the gradient effect dominates the clinical situation. Consequently, the interplay effect in clinical plans cannot be deliberated for some specific parameters but all dosimetric parameters of each case should be considered. Edvardsson *et al*. also indicated that the large interplay effect was observed for individual fraction and the extent varied with patient and machine-specific parameters. Each patient has a unique respiratory pattern that affects the particular planning parameters. These reasons make the different mutual movement between the target and the MLC, resulting in a different extent of the interplay effects.[9] For limitation of this study, because the 2D moving phantom applies with 2D diode array which can represent only planar doses. Thereby, this research cannot demonstrate an actual patient tumor motion and a tumor dose volume.

Conclusions

The interplay effects for 6 MV FFF photon beams in lung cancer are more pronounced for the higher amplitudes and the smaller field sizes. The breathing amplitudes above 0.5 cm lead to significant changes in the shape of dose distribution due to the interplay effects, especially for 2D movements. Nevertheless, the interplay effects in real clinical cases cannot be cogitated with just a single or both parameters since the individual patient has specific parameters for target shape, target volume, number of targets, the distance between targets, planning parameters/techniques, and patient breathing pattern. Therefore, the entire dosimetric parameters of clinical cases have a critical impact on the outcomes of the interplay effects.

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Conflicts of interest

There are no conflicts of interest.

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