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Dosimetric Comparative Study between Single and Dual Isocenter Stereotactic Body Radiotherapy Plans in Treatment of Multiple Lesions Non-Small Cell Lung Cancer Patients

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ABSTRACT

Introduction: stereotactic body radiotherapy (SBRT) is the most proper treatment for multi lesions non-small cell lung cancer (NSCLC) for enhanced good coverage and minimizing dose to organs at risk (OARs). This study aims to compare single and dual isocenter SBRT plans and discuss which technique we can use in multi lesions NSCLC.

Material and Methods: Ten patients with multi targets NSCLC underwent two different SBRT treatment planning techniques including single isocenter and dual isocenter. We quantitatively assessed plans qualities by dose-volume metrics. Conformity index (CI), Confirmation Number (CN), heterogeneity index (HI), gradient distance (GD), Gradient index (GI), and maximum percentage dose at 2cm all around PTV (D_{2cm}) were gathered, tallied, and statistically examined. OARs were evaluated and the dose to the normal lung was evaluated using V5, V10, V20, and mean lung dose (MLD).

Results: There is an insignificant difference between single and dual isocenter plans in CI, CN, HI, GD, GI, and dose spillage where the mean distance between two lesions was 5.50 ± 1.50 cm, and the mean total volume of the planning target volume (PTV) was 42.60±21.33cc. For single and dual isocenter plans, the median MLD was 4.5(2-16)Gy and 4 (2-16)Gy respectively (p=0.25).

Conclusion: Plan quality of single isocenter was equal to dual isocenter for SBRT treatment of multi lung lesions with maximum distances between them was 10 cm. Dual isocenter took time during setup and matching for cone beam computed tomography (CBCT).

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Introduction

Lung cancer is the most important cause of cancer-related death worldwide, with 1.8 million deaths every year [1]. In 2020, lung cancer would be the second most often diagnosed cancer and the leading cause of cancer death, accounting for about one in every ten (11.4%) cancer diagnoses and one in every five (18.0%) mortality [1].

Radiotherapy is an essential part of both therapeutic and palliative treatments for this disease. With recent technological developments, stereotactic body radiotherapy (SBRT) treatment for medically inoperable non-small cell lung cancer (NSCLC) patients with solitary primary or metastatic lung lesions is safe, reliable, and has a high cure rate comparable to surgery [2, 3].

SBRT has been defined by the American College of Radiology (ACR) and the American Society for Radiation Oncology (ASTRO) as the use of very large doses of radiation, more than 6 Gy per fraction given over few (five or fewer) fractions [4]. SBRT has precise radiobiologic characteristics, which could reason dramatic tumor response, main to the related term "ablative" radiotherapy. Several research have proven that properly turning in a better biologically effective dose (BED) to the lung lesions advanced the therapeutic ratio and local control rates [5-7]. Furthermore, when compared to monitor units (MUs) and the treatment time for different techniques like CyberKnife, intensity-modulated radiotherapy of lung SBRT treatment and volumetric modulated arc therapy (VMAT) planning without a flattening filter (FFF) beam [8]. VMAT enhance reduction MUs allow for speedier dose delivery time, which reduces patient

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discomfort, avoidance uncertainty setup motion, and support successful clinical efficiency. [9-12].

Organ movement because of respiratory and cardiovascular movement presents huge difficulties for the exact delivery of radiotherapy to both the chest and the upper abdomen. Present-day imaging methods during radiotherapy reproduction and delivery currently grant better evaluation of organ movement, which thus controls cancer and organ at risk uncertainties. These imaging propels, combined with respiratory-related radiotherapy delivery strategies, have prompted the advancement of a scope of ways to deal with overseeing respiratory movement. The internal movement during respiration is a significant challenge in defining robust PTV in lung-SBRT. The internal target volume (ITV) of a tumour is the volume at which it alternates in a breathing cycle. ITVs are created by combining gross target volume (GTV) and internal target motion (IM) plus a margin that account for microscopic disease[13].

SBRT for multiple lung lesions appears to be a safe and successful treatment [14,15]. single-isocenter VMAT plan for treating multiple primary or oligometastatic lung lesions can achieve high conformity with dose fall off and organs at risk (OAR) sparing by using jaw tracking with 6X-FFF beam [16,17]. A few studies have discussed the use of two-isocenter SBRT for multiple lung lesions [18-20], but still unknown when dual isocenter is a good choice for multitarget lesions of NSCLC so we discuss this topic with specific characteristics of patients.

This work aims to compare single and dual isocenter SBRT treatment planning when we use one full arc and two partial arc VMAT treatment planning for SBRT multiple lesions of non-small cell lung cancer with a maximum separation distance of 10 cm and total target volume does not exceed 90 ccs. We assessed plan qualities by target coverage, dose spillage, and evaluation of OAR dose.

Materials and Methods

Patients

We Included ten patients with non-small cell lung cancer fitting all the following criteria were included: patients had primary or oligometastatic with a separate distance between lesions do not exceed 10 cm and the maximum total targets volume was 90 cc (Table 1).

Treatment planning

All patients received a free-breathing scan followed by 10-stage 4-dimensional computed tomography (4DCT) using Varian's real-time positioning management (RPM) in Egypt. Gating System which consists of infrared-reflecting marker container that's placed at the patient's chest wall close to xyphoid process and a charge coupled device (CCD) digital digicam monitoring the vertical motion of the marker at a frequency of 30 frames in step with second. Gating technique represents "beam-on" during the precise respiration phases and "beam-off" during the other phases. Then 4DCT imported into Varian Eclipse treatment planning system (TPS) versions (15.6). Gross target volumes (GTV) and, internal target volumes (ITV) were delineated by the radiotherapist. Planning target volumes (PTV) were generated to account for patient setup concerns based on tumor size, location, and synchronous tumor movement, nonuniform margins were included in the ITV. Then delineation of the organ at risk (OAR) such as normal lungs (bilateral lungs) excluding GTV, spinal cord, chest wall, heart, and esophagus.

Table 1. Basic characteristics of the studied lung cancer patients.

	Number	Percent
Age (years)		
Mean±SD	66.80 ± 5.80	
Median (Range)	67 (57 – 75)	
Number of lesions		
Two lesions	8	80%
Three lesions	2	20%
Location		
Right lung	5	50%
Left lung	5	50%
Distance between two lesions (cm)		
Mean±SD	5.50 ± 1.50	
Median (Range)	5 (4 – 8)	

In addition to optimization ring structures, Dose-control tuning structures were created to help the planner interact with the optimizer, with the goal of a rapid falloff dose around each target for radiosurgery. These structures were three-dose level areas: The inner control had an inner edge at the PTV's border and an outer edge 5 mm away. The outer control had an inner edge at the boundary of the middle control and an outer edge of 1.5 cm away from the PTV (50 percent of the prescribed dose), whereas the middle control had an inner edge 0.5 cm from the PTV and an outside edge 1 cm away from the PTV.

In some cases, we use a "bridge breaker" tuning structure drawn between two targets when two lesions are close to each other, and undesired bridging is occurring.

All patients were applied to two different SBRT treatment planning techniques including single isocenter and dual isocenter. In each patient, a single isocenter was placed automatically between the tumors. A reverse VMAT optimization was performed using a full arc and 2non-coplanar partial arcs (angular range 5-30 degrees) for optimal target coverage and maximum sparing of normal tissue. A pair of collimator leaves are placed for each arc to minimize the opening of the multileaf collimator (MLC) between the cusps while the portal rotates around the patient to align with the target's lateral edge.

All clinical treatment plans were designed with Eclipse TPS using an anisotropic analysis algorithm (AAA) to calculate the dose with a 0.25 cm

grid. For each plan, all targets were treated at the same dose and a 70-80% isodose line is suggested to ensure that at least 95% of every PTV receive the recommended Dose (meaning that at least 95% of the PTV will receive prescribed dose). The dose of four patients is 54 Gy in three fractions, four patients are 50 Gy in five fractions and two patients are 30Gy in three fractions.

After that replanned the SBRT treatment plans for all patients with a conventional two-isocenter approach. Eight patients have two lesions, each lesion has an individual isocenter and two patients have 3 lesions. The plans were generated using one full arc and 2 non-coplanar partial arcs, like a single central plane. Rotate the collimator and monitor the applied jaw. All planning objectives used were the same as the single-point design, including OAR parameters and bypass structure. Dosimetry characteristics were assessed for target coverage and surrounding OARs, including normal lungs.

Plan evaluation

Numerical indices used for the evaluation of a radiosurgery plan are derived from dose-volume metrics and divided into target coverage and dose spillage indices. We quantitatively assessed plan qualities by the following parameter: - Radiation Therapy Oncology Group (RTOG) conformity index (CI) [21] is the prescribed treated volume divided by the target volume. Ideally, CI = 1.0, implying a perfectly conformal plan. The RTOG recommendation for the CI is<1.2 with 1.2-1.5 being acceptable with minor deviations.

Ian Paddick [22] proposed Paddick CI/Confirmation Number (CN) equal to the ratio between the square of target volume covered by the prescription isodose volume to the product of multiple the target volume (TV) and the prescription isodose volume (PIV). CN ideal value is 1 but is always<1 and approaches unity in increasing plan quality from below.

In addition, the heterogeneity index (HI) [23] as defined by RTOG is the ratio of D_{max} to the prescription dose. The Eclipse treatment planning system reports the gradient distance (GD), defined as the difference, in centimeters, of the equivalent spherically of the prescription isodose flow volume (PIV) at 50% and 100% [24]. The gradient index (GI) is a measure of intermediate dose reduction and is the ratio between the volume of one-half of the prescribed isodose and PIV [25]. The clinically viable GI depends on the size of the PTV [26]. Calculate the overflow dose and the maximum dose at 2cm around the PTV ($D_{2\ cm}$) in percent of dose perscriped. The dose-volume chart parameters were compared between the single-concentric and double-concentric designs. The dose for normal lung was assessed by percent volume of lung received 5,10, and 20Gy (V5, V10, V20), Mean lung Dose (MLD) and a maximum dose of for OAR assessed for the spinal cord, heart, esophagus, and chest wall according to RTOG guidelines.

Treatment Delivery

All single isocenter plans were treated on a Varian True Beam linear accelerator with an HD 120 multileaf collimator (MLC). By using 6 X-FFF energy (1400MU/min). Each clinical plan evaluates delivery parameters, the total number of monitor units (MU), and measured dose delivery time (DDT). DDT was calculated using sum MU divided by the mean delivered dose rate. The quality assurance (QA) for all plans were done on the machine before the patient's first treatment (before -treatment QA).

Statistical Analysis

All data were collected, tabulated, and statistically analyzed using SPSS 20 for windows (IBM Corp., Armonk, NY, USA) and Microsoft Office Excel 2010 for windows (Microsoft Cor., Redmond, WA, USA). Wilcoxon signed ranks test was used to compare two dependent groups of non-normally distributed variables. Differences were considered statistically significant at $p < 0.05$.

Results

Ten non-small cell lung cancer (NSCLC) patients with solitary primary or metastatic lung lesions with varying lesions size, number, and distance apart from each other were simulated in the supine position, arms above their head (table 1). Table 2 outlines details of the total volume of delineated targets and OARs.

Table 2. Total volume (cc) of delineated targets & organs at risk among lung cancer patients.

Total volume (cc) of delineated targets & organs at risk	The studied lung cancer patients			
	Mean	±SD	Median	(Range)
Combined GTV volume (cc)	16.40	±8.54	15	(5 – 30)
Combined PTV volume (cc)	42.60	±21.33	41	(18 – 81)
Lung volume (cc)	3536.9	±1246.63	3737.50	(1268 – 5486)
Heart volume (cc)	758.60	±117.93	773.50	(530 – 918)
Cord volume (cc)	54.50	±9.90	56.50	(39 – 72)
Esophagus volume (cc)	57.80	±12.48	58.50	(36 – 81)

Table 3. Comparison between single isocenter plan and dual isocenter plan as regards dose-volume histogram (DVH) parameters of target lesions. n. s.=, not significant values.SD= standard deviation.

parameters	Single isocenter plan	Dual isocenter plan	p-value
Target coverage parameters	Mean±SD Median (Range)		
CI	1.04±0.05 1.06(0.95-1.12)	1.05±1.04 1.01(0.95-1.30)	n. s.
Paddick CN	0.92±0.07 0.89(0.85-1.10)	0.90±0.45 0.89(0.86-1.02)	n. s.
HI	1.10±0.6 1.09(1.0-1.2)	1.09±0.05 1.1(1.0-1.18)	n. s.
Dose spillage parameters			
GI	6.23±1.31 6.15(4.8-9.3)	6.18±1.49 5.95(4.6-9.8)	n. s.
GD (cm)	1.78±0.2 1.76(1.4-2.1)	1.74±.24 1.72(1.24-2.07)	n. s.
Dose spillage	1.08±0.05 1.09(.95-1.16)	1.08±.03 1.08(1.03-1.14)	n. s.
D_{2cm} (%)	55.49±17.38 60.9(30.9-76)	54.72±17.47 62.1(27.9-72.7)	n. s.
Treatment delivery parameters			
MU	5390.5±1639 5126(3114-8284)	5971±1685 5759(3348-8752)	0.005
DDT(min)	3.42±1.13 3.16(1.94-5.4)	4±1.22 3.7(2.39-6.25)	0.02

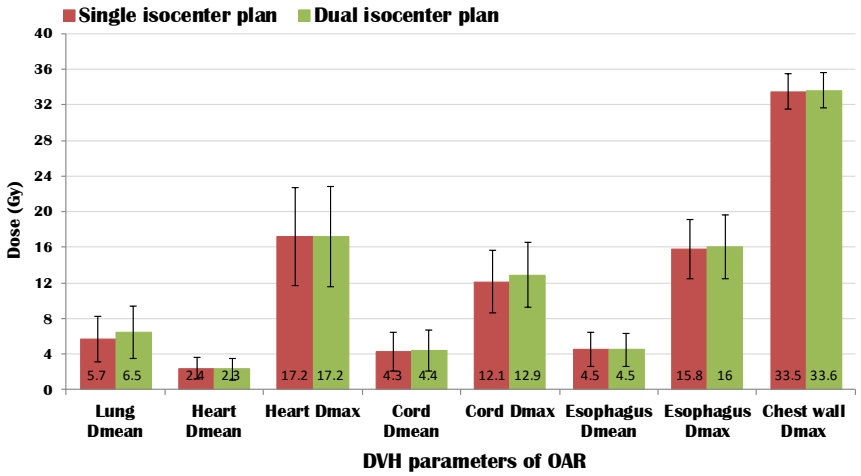

Figure 1. Error bar chart shows a comparison between a single isocenter plan and a dual isocenter plan as regards dose-volume histogram (DVH) parameters (mean of D_{mean} and D_{max}) of OAR among lung cancer patients; the bar represents the mean, Y-error bar represents 95%CI (confidence interval of mean).

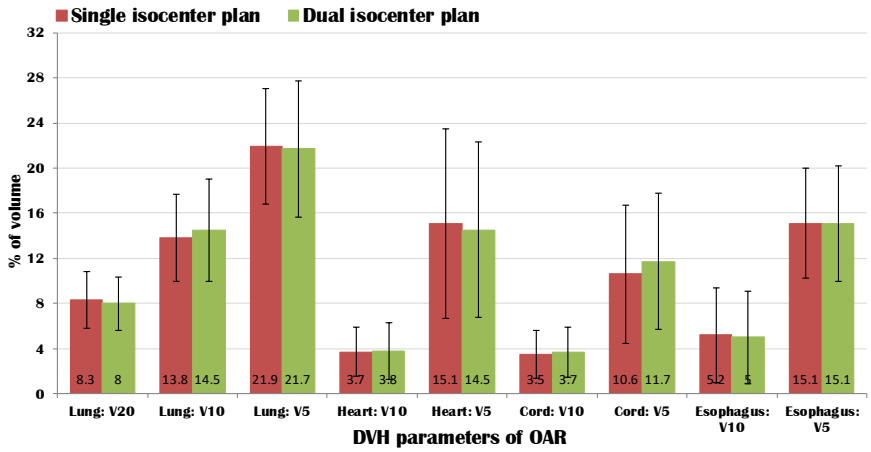

Figure 2. Error bar chart shows a comparison between a single isocenter plan and a dual isocenter plan as regards dose-volume histogram (DVH) parameters (mean of Volume limits) of OAR among lung cancer patients; the bar represents the mean, the Y-error bar represents 95%CI (confidence interval of mean).

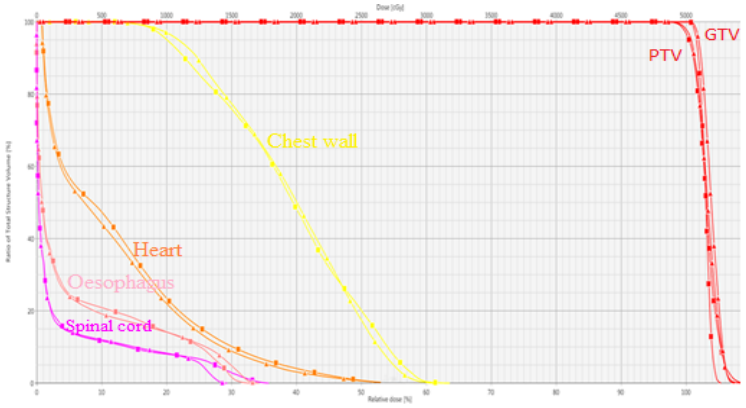

Figure 3. This shows the dose-volume histogram comparison for the target coverage (GTV (red) &PTV (red)) and a few OARs such as chest wall(yellow), heart(orange), Oesophagus (pink), and spinal cord (purple) are shown for a patient. The prescription dose was 50 Gy in five fractions. The square symbols represent the single-isocenter plan, and the triangle symbols represent the two-isocenter plan.

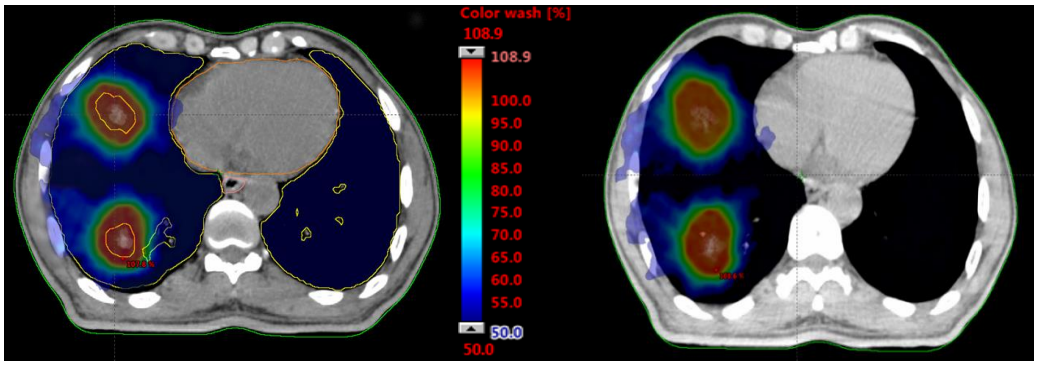

Figure 4. This shows the color wash of isodose distributions in a transverse view for a patient. In the right plane, a single-isocenter location (automatic between two lesions) is shown by the intersection of the cross-hair. The left plane for the dual isocenter plane.

Target coverage and dose spillage

All lung SBRT plans for single isocenter and dual isocenter were acceptable per RTOG guidelines for the high (CI, HI) and intermediate-dose spillage (GI and D_{2cm}). Table 3 reported a comparison between the two plans. There is an insignificant difference between the single and dual isocenter plans in CN, CI, HI, GD, GI, and dose spillage. In addition, the D_{2cm} values were slightly higher in a single isocentric plane, showing a slower dose reduction**.** However, the difference between the two techniques for the total MU and DDT was statistically significant**.** For unicentric VMAT planes**,** the median values for total MU were 5126.5 (range 3114–8284MU**).** For all patients described here, a maximum dosage rate of 1400 MU per minute for the beam energy 6X-FFF was used. For dual designs**,** the median of total MU is 5759 (range: 3348-8752MU).

Dosimetric parameter of normal lung and OARs

In every case, the OARs limitations satisfied their tolerance criteria for single and dual isocenter treatment plans (accepted by RTOG guidelines [27]). Figures 1 and 2 show the statistical results for mean lung dose (MLD), V20, V10, and V5 of the lung. For single isocenter plans, the median MLD was 4.5Gy, median of max. Heart dose was 22 Gy, median of max. The spinal cord was 14.5 Gy, median of max. esophagus dose was 17.5 Gy. In dual isocenter plans, the median MLD was 4 Gy, median of max. Heart dose was 22.5 Gy, median of max. the spinal cord was 16 Gy, median of max. esophagus dose was 17 Gy.

An example case patient who was treated for two lesions in the upper left lung with a separation distance of 8 cm. Combined planning target volume (PTV) was 57.8cc with lesion 1(PTV1) =33.4cc and lesion 2(PTV2)24.4cc. The patient received asynchronous SBRT treatment with a total dose 50Gy in 5 fractions for each lesion. The corresponding dose-volume histogram is shown in Figure 3. Figure 4 show isodose distribution in transverse view have slightly difference were more conformal with dual isocenter plan (CI = 1.05) and exhibited steep dose fall-off outside the combined PTV (GI = 5.6; GD = 1.91cm; and D_{2cm} =63%) compared to single isocenter plan (CI =1.06; GI = 6; GD =1.97 cm; and D_{2cm} = 61.0%) for this case.

Discussion

A comparative analysis of VMAT stereotactic body radiotherapy plan technique using single and dual isocenter for treatment multi lesions non-small cell lung cancer was investigated in this study and that's to determine the most efficient treatment technique in terms of good dose distribution (target coverage) and as

low as possible to all OARs to reduce acute and late toxicity effect of treatment. To remove any influence in treatment planning, all planning conditions were kept the same, while creating VMAT plan using single and dual isocenter. It was observed that the single isocenter technique is similar to double isocenter with normal tissue issues and target coverage.

The present work shows that the target coverage (CI, paddick CN, and HI) and dose spillage (GI, GD, and D_{2cm}) are similar between the two techniques of single and dual isocenter SBRT VMAT plans. This is compatible with Sanford et al. [18] founded that there is no clinically significant difference in CI, HI, GD, GI, and D_{2cm} and they showed absolute differences between single and two isocenter plans for normal lung V10, V5, and MLD, where there was no difference (p value=0.09) for the normal lung V20 between the two plans. Another significant difference was observed for the dose to 15cc of heart and dose to10cc of ribs.

The data presented in this report founded a statistically insignificant difference for evaluation of heart dose (V5, V10, D_{max}, and D_{mean}), cord dose (V5, V10, D_{max}, and D_{mean}), esophagus dose (V5, V10, D_{max}, and D_{mean}), and chest wall. In addition to, p value of normal lung tissue receive 20 Gy is equal to 0.1 and p value of V5, V10, and MLD is more than 0.05.

Our assessment of all OARs is not consistent with Sanford et al. [18] as we use one full arc and 2 noncoplanar partial arcs with isocenter to tumor distances were 1.8 to 4.2 cm (3D target distance was 3.6 to 8.5) which is the fundamental difference in our study, but they studied eight patients with two early-stage non-small cell lung cancer (NSCLC) lung tumors localized in the periphery and used 2-4 noncoplanar partial arcs with isocenter to tumor distance was 3.7 to 9.6 cm (3D target distance was7.4 to 19.2cm).

In previse studies for single isocenter, Liu et al. [28] reported the use of single-isocenter multisegmented dynamic conformal arc (SiMs-arc), full-arc VMAT, and partial-arc VMAT techniques for lung SABR in five patients. The use of single isocenter SBRT for numerous lung lesions has been considered in a few publications. Gulam et al. [20] reported that a single isocenter is satisfied for planning multitarget lung lesions, after evaluation of Six patients with RTOG study 0915 protocol but not all dosimetric parameters were discussed. Quan et al. [19] studied dosimetric comparison for eleven patients without any specific cutoff threshold for the distance between targets and don't use a specific technique for VMAT (no of arc) or IMRT. They showed no difference in multiple dosimetric parameters between single isocenter VMAT plans and multi isocenter intensity-modulated SBRT to the lung. Their single isocenter plans had similar or even smaller normal lung V20, V10, and V5 compared with multi isocenter plans.

For increase treatment efficiency for single isocenter multiple lesions VMAT lung SBRT Sanford and Pokhrel [29] used the photon optimizer (PO) MLC method. When the photon optimizer (PO) MLC technique was compared to the progressive resolution optimizer (PRO) for single isocenter/multiple lesions VMAT lung SBRT, the PO MLC approach improved treatment efficiency without sacrificing plan quality. By lowering the beam-on time, intra-fraction motion can be decreased.

The main objective of our study to investigate for difference in OARs dose when using single and dual isocenter VMAT plan for multiple lung lesions with short separate distance .There was an insignificant difference between both plans regarding almost all study parameters except the total number of MUs was significantly lower in the single-isocenter plan than dual isocenter plan (mean: 5390MU versus 5971MU respectively, p-value=0.005), also there was a significant difference regarding beam time on where the single-isocenter plan had a shorter beam time on than dual isocenter. Therefore, single isocenter plan is our treatment planning for all patients. A daily quality assurance assessment on kilovoltage to megavoltage imaging isocenter coincidence was done on each SBRT treatment before it was delivered.

Conclusion

Dosimetric parameters data and Plan quality of single isocenter was equal to dual isocenter for SBRT treatment of multi lesions with a mean distance between two lesions was 5.50 ± 1.50 cm and mean total PTV was 42.60±21.33cc. dual isocenter took time during setup, matching for cone beam computed tomography (CBCT), and treatment time. But in some cases, dual isocenter will provide good distribution and coverage for target volume and reduce doses to organs at risk with a very slight difference from the other treatment plan. Although the difference was decimal, we can recognize that the distance between lesions and their volumes has a more important impact on our choice of plan. Quality assurance for both plans is the same although the single isocentre takes less time for QA.

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