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Research Article

Dosimetric Feasibility of Magnetic Resonance Imaging Guided, Tri-^{60}Co Stereotactic Body Radiotherapy for Non-Small Cell Lung Cancer

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Abstract

Purpose: To provide a dosimetric comparison of lung stereotactic body radiotherapy (SBRT) for NSCLC between an integrated three-source ^{60}Co, Magnetic Resonance Image Guided Radiation Therapy (MR-IGRT) system and traditional LINAC based planning.

Materials and Methods: Ten patients with NSCLC, previously treated with LINAC based SBRT, were included. Patients received prescription doses of 48Gy/4fx for peripheral lesions and 50Gy/5fx for central lesions. All LINAC-based SBRT plans were generated using volumetric modulated arc therapy (VMAT). Three-source ^{60}Co plans were generated using step-and-shoot IMRT and used Monte Carlo dose calculation including the magnetic field correction for 0.35T. The plans were evaluated using dose-volume indices for PTV and OARs.

Results: For peripheral lesions, the MR-IGRT met 86% of dose constraints while the LINAC plans met 89% of dose constraints (p=0.77). For central lesions, the MR-IGRT met 87% of dose constraints while the LINAC plans met 93% of dose constraints (p=0.29). Lung dose constraints were met for all peripheral lesions while 2 patients with central lesions were unable to meet the 13.5Gy<1000cc criteria with the MR-IGRT while all patients met the dose constraint with the LINAC plans. Regardless of location, on average, MR-IGRT based plans had larger low dose lung volumes compared the LINAC-based SBRT plans.

Conclusion: A three-source ^{60}Co integrated MR-IGRT system produced lung SBRT plans comparable with LINAC-based treatment. Further studies are needed to evaluate benefits of this novel MR-IGRT system for lung SBRT; especially examining its ability to image and plan in real time and adaptive treatment delivery.

Keywords: Lung cancer; Magnetic Resonance Imaging Guided; Stereotactic Body Radiotherapy

Introduction

Non-small cell lung cancer (NSCLC) is the leading cause of cancer death in the United States, with 224, 390 new cases reported and 158,080 deaths estimated in 2016. This disease represents 13% of all new cancer cases and 27% of all cancer deaths, with only 17.4% survival at 5 years [1] Approximately 16% of patients present with localized disease. Definitive treatment options for localized early stage NSCLC include surgery and Stereotactic Body Radiotherapy (SBRT). SBRT is increasingly being used across many sites in the body and its advantages include an ability to deliver conformal, high dose radiotherapy with minimal fractions [2-4]. Additionally, it may offer previously unrealized radiobiological mechanisms for cell killing involving destruction of the tumor microenvironment and release of tumor antigens [5]. SBRT is currently used for the treatment of inoperable NSCLC [6] and recent evidence has suggested that it may be of equivalent outcome in operable NSCLC patients [7].

Despite increasing utilization of SBRT, localization of the tumor during radiation treatment has remained a continual challenge. Current strategies include expanding the Clinical Tumor Volume (CTV) to an Internal Target Volume (ITV) to account for tumor motion, various 4D-CT acquisition techniques [8], PET/CT fusion, and the use of volumetric cone-beam computer tomography (CBCT). These methods however contribute to an increased total radiation dose and may be impractical for patients with compromised respiratory function due to increased time needed for acquisition and treatment.

The MRIdian® (ViewRay, Oakwood Village, OH) is a novel technology that addresses the problem of intrafraction and inter fraction motion management through continuous real time MR imaging during the delivery of radiation therapy. It has recently gained US-FDA approval for use in radiation therapy [9,10]. It consists of a vertically gapped, horizontal solenoidal superconducting 0.35-Tesla MRI scanner with three ^{60}Co sources mounted on a ring gantry enabling continuous MR imaging of soft tissue during radiation therapy (RT) delivery. The RT system provides a dose rate

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Table 1: Comparison of dosimetry between LINAC and ViewRay for Central NSCLC.

OAR	Constraints per RTOG 0813	Linac ± SD	ViewRay ± SD	p-Value
Spinal Cord	D_{max} ≤ 30 Gy	9.99 ± 7.87	12.18 ± 8.46	0.09
	$D_{0.25cc}$ ≤ 22.5 Gy	0.12 ± 0.28	0.06 ± 0.13	0.39
Both Lungs	D_{1500cc} ≤ 12.5 Gy	530.7± 340.63	916.00 ± 431.37	0.01
	D_{1000cc} ≤ 13.5 Gy	411.77 ± 300.26	736.64 ± 396.26	0.01
Heart	D_{max} ≤ 32 Gy	27.07 ± 18.25	29.78± 17.14	0.06
	D_{15cc} ≤ 32 Gy	0.47 ± 0.73	2.95 ± 5.15	0.28
Esophagus	D_{5cc} ≤ 27.5 Gy	0.0 ± 0.0	0.0 ± 0.0	N/A
Skin	D_{max} ≤ 36Gy	22.85± 6.55	28.74± 9.33	0.04
	D_{10cc} ≤ 33.2Gy	0.0 ± 0.0	0.18 ± 0.25	0.18

Table 2: Comparison of dosimetry between LINAC and ViewRay for Peripheral NSCLC.

OAR	Constraints per RTOG 0915	Linac ± SD	ViewRay ± SD	p-Value
Spinal Cord	D_{max} ≤ 26 Gy	8.37± 6.08	9.13± 4.73	0.58
	$D_{0.35cc}$ ≤ 20.8 Gy	0.00± 0.00	0.00 ± 0.00	N/A
Both Lungs	D_{1500cc} ≤ 11.6 Gy	369.66 ± 239.24	535.54 ± 256.56	0.005
	D_{1000cc} ≤ 13.6 Gy	312.97 ± 205.38	450.18 ± 220.53	0.007
Heart	D_{max} ≤ 34 Gy	12.01± 8.35	18.00± 6.48	0.08
	D_{15cc} ≤ 28 Gy	0.00± 0.00	0.00± 0.00	N/A
Ribs	D_{max} ≤ 40 Gy	37.77 ± 22.46	36.75 ± 21.66	0.65
	D_{1cc} ≤ 32 Gy	3.74 ± 5.54	15.34 ± 20.68	0.28
Skin	D_{max} ≤ 36Gy	20.16± 4.32	26.97± 4.25	0.01
	D_{10cc} ≤ 33.2Gy	0.00± 0.00	0.00± 0.00	N/A

comparable to that of conventional linear accelerators [9,10]. MR imaging is performed in real time during treatment delivery in 1 sagittal plane at 4 frames per second or 3 sagittal planes at 2 frames per second. Together, the RT system and real time MR imaging enables continuous tracking of soft tissue and ability to selectively deliver radiation when the target is within the radiation field with 300-ms latency. Use of the Magnetic Resonance Image Guided Radiation Therapy (MR-IGRT) system could enable PTV margin reduction without exposing the patient to additional radiation dose seen in contemporary imaging techniques. Moreover, the MRIdian treatment-planning system is integrated with IMRT planning and delivery software capable of auto contouring and dose computation using a Monte Carlo (MC) algorithm. With a fast MC dose calculation (30 seconds for a 9 field plan) and plan optimization, online adaptive radiotherapy is possible with the MRIdian based on the volumetric images acquired during the day of delivery [9,10].

The advantages of the MRIdian system include lack of MRI interference due to the use of ^{60}Co beams, small electron return effect due to the use of a low strength magnet and increased output with the use of three ^{60}Co sources. Its disadvantages include larger beam penumbra, lower treatment energies than typically used by modern MV machines and lower MRI resolution than typically experienced with more powerful MRI machines [10]. Given these advantages and disadvantages, it remains unclear if this MR-IGRT system is capable of generating comparable plans to current LINAC based SBRT in NSCLC. Our aim was to establish the dosimetric feasibility of the utilizing the MRIdian in central and peripheral NSCLC.

Materials and Methods

Patient characteristics

From an Institutional Review Board (IRB) – Exempt, anonymized retrospective patient database, ten patients with NSCLC were selected. All patients were replanned using the MRIdian system. Peripheral tumors were defined as being greater than 2 cm from the bronchial tree [11]. A total of five patients with peripheral tumors and five patients with central tumors were included in the study. The median age of the patients was 63 (range 49 to 79). 4/10 of the patients were men. The mean volume of the PTV treated was 54.27cc (range 16.02 to 130.72). Tumor locations in this patient population were left lower lobe (n = 1), left upper lobe (n=1), right lower lobe (n = 5), right middle lobe (n=2) and right upper lobe (n=1).

Treatment planning

Patient data, including computed tomography (CT) images and normal structure contours, were exported for all patients from the Eclipse (ver. 11) treatment planning system (TPS) (Varian Medical Systems, Palo Alto, CA) into MRIdian TPS (ViewRay Inc, Oakwood, OH) and assessed for accurate delineation. The clinical treatment plans were designed using the Eclipse TPS with a single isocenter utilizing coplanar arc treatment. Similarly in the MRIdian TPS, single-treatment isocenters were employed placed in the center of the GTV when possible; with consideration of the couch and patient clearance limitations. In MRIdian system, the three ^{60}Co sources are 120 degrees apart and rotate in concert; constituting a beam group of 3 beams at any specific gantry angle. A gantry angle in MRIdian system refers to the angle "source 1" makes to the MRIdian coordinate system [11]. In all plans, 15 groups of beams with 10-20 beam angles were employed. Calculation grid size of 0.25cm was used for all dose calculations. Beams passing through the edge of the couch were avoided. Treatment planning was performed in multiple iterations, and all the constraints as specified by RTOG 0813 and RTOG 0915 were attempted to be achieved. The normal tissue constraints for both of these trials are listed in the second columns of Table 1 and Table 2. MRIdian TPS employed Monte Carlo dose calculation while Eclipse TPS employed Acuros XB (ver. 11) dose calculation algorithm. The MRIdian plans were calculated with the consideration of the influence of 0.35T magnetic field to the radiation dose distribution. The optimized plans normalized such that 95% of the PTV covered by the 100% of the prescription dose for consistency to identical prescription target coverage as in Eclipse based plans. The detail of the dose optimization is described by Saenz et al [12] and will not be included here.

Plan assessment

To determine the feasibility of plan delivery, the treatment plans were reviewed in a blinded, matched comparison by a radiation oncologist specializing in the treatment of lung cancer. The physician reviewed both plans in MRIdian planning and delivery system. When reviewing the plans, isodose distributions, dose volume histograms and dosimetric statistics were made available. Plans were assessed on the basis of the PTV coverage, mean and maximum PTV doses, homogeneity index (HI) [13], conformity index (CI), [14] and organ of risk (OAR) dosimetry (Table 1 and Table 2). The practicing

Table 3: RTOG 0813 constraints- Central NSCLC Lesions.

Target	Mean Dose (Gy)		Homogeneity Index		Conformity Index	
	Linac	MRIdian	Linac	MRIdian	Linac	MRIdian
PTV_{50} (n=5)	52.84 ± 0.55	52.36 ± 1.19	1.12 ± 0.05	1.08 ± 0.04	1.03 ± 0.05	1.17 ± 0.17
p-value	0.64		0.21		0.11	

Table 4: RTOG 0915 Constraints- Peripheral NSCLC Lesions.

Target	Mean Dose (Gy)		Homogeneity Index		Conformity Index	
	Linac	MRIdian	Linac	MRIdian	Linac	MRIdian
PTV_{48} (n=5)	50.98 ± 1.17	50.96 ± 0.90	1.14 ± 0.05	1.12 ± 0.06	1.06 ± 0.08	1.15 ± 0.09
p-value	0.96		0.37		0.12	

radiation oncology clinician was asked to rate the plans as acceptable for delivery or reject the plans based on the dosimetric characteristics of each plan.

Statistical analysis

Dosimetric parameters of interest in the PTV were as follows: dose to the 5% of the volume (D5) of the PTV, dose to the 95% of the volume (D95) of the PTV, HI of the PTV and CI of the PTV. Normal tissue dose constraints attempted to be met are summarized in Table 1 and Table 2. Both data sets from MRIdian plans and Eclipse plans were assigned for a paired t-test. Total dose constraints met and not met were assessed for statistical significance with the chi-squared test. Individual comparisons were performed accordingly with correlation coefficient and p value < 0.05 as the threshold for statistical significance.

Results

PTV coverage comparisons between the MRIdian and Eclipse treatment arms are summarized in Tables 3 and 4. A representative plan for the same patient using the MRIdian and Eclipse planning systems is shown in Figure 1. The mean PTV D5 was 55.6Gy and 53.8Gy for all Eclipse and MRIdian plans respectively ($p > 0.05$). The mean PTV D95 was equivalent between the two treatment modalities since both plans were normalized such that 95% of the PTV received 100% of the prescription dose. The mean homogeneity indexes (HI) for PTV were 1.13 and 1.10 for all the Eclipse and MRIdian plans respectively ($p > 0.05$). The mean conformity indexes for PTV were significantly different with Eclipse plans being 1.05 and MRIdian plans being 1.16 ($p > 0.05$).

When performing a subgroup analysis of the central lung lesions, the mean PTV D5 was 56.2Gy and 53.8Gy for Eclipse and MRIdian plans respectively ($p > 0.05$). With central lesions, the PTV mean HI were 1.12 and 1.08 for the Eclipse and MRIdian plans ($p > 0.05$). Unlike the entire cohort, the CIs were not significantly different for central lesions with Eclipse plans being 1.03 and MRIdian plans being 1.17 ($p > 0.05$).

In the subgroup only involving peripheral lesions, the mean PTV D5 was 54.95Gy and 53.74Gy for Eclipse and MRIdian plans respectively ($p > 0.05$). For the same lesions, the mean PTV D95 was equivalent between the two structures. With peripheral lesions, the PTV HIs were 1.14 and 1.12 for the Eclipse and MRIdian plans respectively ($p > 0.05$). Similar to central lesions, for the peripheral subgroup, the differences in PTV CIs were not statistically significant, for Eclipse plans being 1.06 and MRIdian plans being 1.15 ($p > 0.05$).

For the subgroup of patients with central lesions, the average maximum cord dose in the Eclipse plans was 9.99Gy while the maximum average cord dose in the MRIdian plans was 12.2Gy. The absolute maximum dose to the cord received by any patient on the MRIdian was 21.3Gy, which was still within RTOG 0813 dose constraints. In patients with central lesions, the volume of lung receiving more than 12.5Gy was 530.7 cc and 916.00 cc in the Eclipse and MRIdian plans respectively ($p<0.01$). In patients with central lesions the volume of lung receiving more than 13.5Gy was 411.8 cc and 736.6 cc in the Eclipse and MRIdian plans respectively ($p<0.01$). Two patients who met criteria using the Eclipse planning system were not able to meet D1000cc ≤ 13.5Gy with the MRIdian plans. For central lesions, the mean maximum heart dose was 27.07Gy in the Eclipse plans and 29.78Gy in the MRIdian plans ($p=0.04$). The mean esophageal maximum dose was 11.96Gy in the Eclipse plans and 14.57Gy in the MRIdian plans ($p=0.06$), however both patient groups were within the dose limits of RTOG 0813. There was no significant difference between the amount of skin receiving more than 33.2Gy ($p>0.05$) but the average maximum dose to the skin was noted to be higher in the MRIdian plans (28.74Gy v. 22.85Gy; $p=0.04$). One patient did not meet the maximum skin dose criteria per RTOG 0813. Overall in patients with central lung lesions, dosimetric constraints were met in 93.3% and 86.7% of RTOG 0813 parameters using the Eclipse and MRIdian based plans respectively. The MRIdian plans did not meet 2 constraints for lung 13.5Gy<1000cc, 2 constraints with a heart maximum dose, 1 dose constraint for spinal cord and 1 constraint of a maximum skin dose. In a blinded comparison, 3/5 of MRIdian plans were deemed appropriate for treatment, while all Eclipse based plans were previously administered.

For patients with peripheral lesions, the average maximum cord dose was lower by about 50% in this set of patients. In the Eclipse plans, the mean maximum cord dose was 8.37Gy while the maximum average cord dose in the MRIdian patients was 9.13Gy ($p=0.58$). Similar to the patients with central lung lesions, the patients with peripheral lung lesions had higher doses of low level radiation to the lung in the MRIdian plans. In these patients, the volume of lung receiving more than 11.6Gy was 369.7cc and 535.54cc in the Eclipse and MRIdian arms respectively ($p<0.01$). The volume of lung receiving more than 13.6Gy was 312.97cc and 450.2cc in the Eclipse and MRIdian plans respectively ($p<0.01$). The mean maximum heart dose in patients with peripheral tumors was 12.00Gy in the Eclipse plans and 18.0 in the MRIdian plans ($p=0.05$). Unlike the group of

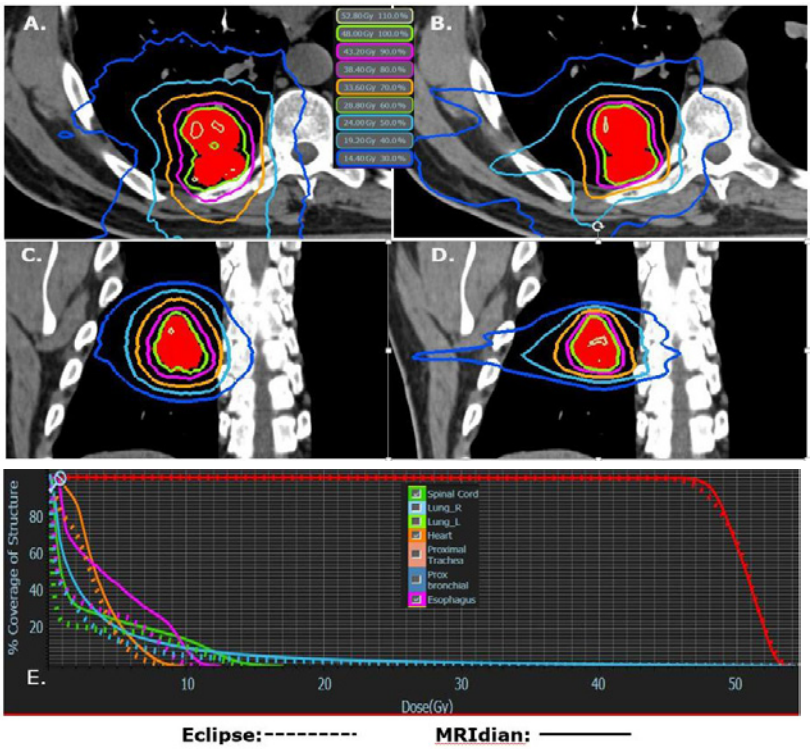

Figure 1: Representative axial views of a patient with peripheral NSCLC planned with MRIdian (a) and Eclipse (b). Representative sagittal views of the same patient planned with MRIdian (c) and Eclipse (d). The corresponding DVH of the patient is shown in (e).

patients with central lesions, we did not calculate the esophageal dose as suggested by RTOG 0915 and instead examined the rib dose. In patients with peripheral lung cancer, the mean maximum rib dose was 37.8Gy in Eclipse plans and 36.8Gy in the MRIdian plans ($p > 0.5$). All skin constraints were met per RTOG 0915, however the patients in the MRIdian group had higher average maximum skin doses (26.97Gy v. 20.16Gy; $p=0.01$). In patients with peripheral lesions, 89% and 86% of dosimetric constraints were met using the Eclipse and MRIdian based plans respectively. The dose constraints that were not met were maximum rib dose (<40Gy) and a constraints of less than <32Gy to 1cc for both patients groups. In a blinded comparison, 5/5MRIdian plans were deemed appropriate for treatment, while all Eclipse based plans were again previously administered.

Discussion

To our knowledge this is the first study examining the feasibility of tri-^{60}Co, MRI guided SBRT for both peripheral and central NSCLC lesions. Others have previously reported on the use of the MR-IGRT SBRT on extremity soft tissue sarcomas [15], malignant hepatic lesions [16], partial breast [17] and central lung tumors [11]. The results of our study indicate that MRIdian three source ^{60}Co plans are dosimetrically feasible for peripheral NSCLC and may be feasible for the majority of central NSCLC. All peripheral lesion MRIdian plans were found to be suitable for clinical delivery while 3/5 of central plans were deemed to be suitable for clinical delivery. PTV coverage of V100 >95 was achieved in all patients with the use of MRIdian three source ^{60}Co system regardless of location of the tumor. For central lesions, dose constraints were not met with selective lung, heart and skin constraints with MRIdian plans. With the exception rib constraints in peripheral patients, all dose constraints as described in RTOG 0915 were met with the MRIdian plans.

Although there was no statistically significant differences in the conformity index between either the central or peripheral lesions, larger portions of normal lung received low levels of radiation in the MRIdian three source ^{60}Co plans. For peripheral lesions, volumes of normal lung receiving 13.6Gy and 11.6Gy were noted to be significantly higher in the MRIdian plans but all plans met dosimetric constraints. In patients with central lesions, the volumes of lung receiving 12.5Gy and 13.5Gy, was similarly noted to be significantly higher in the MRIdian plans. In total, 2 patients had greater than 1000cc receiving 13.5Gy making their plans clinically inappropriate for delivery per RTOG 0813 dose constraints. Two patients with central lung NSCLC had heart dose maximum that was beyond the specified dose constraints. The increased areas of low dose radiation were expected as the ^{60}Co involves the use of 1.17MeV and 1.33MeV photons. In a blinded review by a radiation oncologist specializing in lung cancer, two MRIdian plans were deemed un-deliverable due to not meeting constraints.

A similar study from Merna et al. looked only at central NSCLC lesions [11]. In this study, the authors evaluated plans using the MD Anderson dose constraints and found that they were able to meet 97.4% of constraints in a cohort of 20 patients with central lung lesions. In our cohort, for central patients, we were able to meet 87% of dose constraints for central lesions and 93% of dose constraints for peripheral lesions. Unlike the study by Merna et al., our study found that 3/5 of plans for the central NSCLC were appropriate for delivery and 5/5 plans for peripheral lesion appropriate for

delivery. Our lower percentage of dose constraints met may be due to multiple reasons including different dose constraints, not having multiple levels of peer review of the dosimetry, lack of dosimetric experience and comparatively difficult anatomic location of certain tumors. Taken together, both our studies demonstrate the feasibility of MRIdian three source ^{60}Co SBRT in peripheral and central NSCLC when compared to LINAC-based SBRT plans despite the inherent dosimetric deficiencies of using ^{60}Co. However, there appears to more difficulty in meeting the dosimetric constraints of centrally located NSCLC compared to peripherally located NSCLC.

Treatment plan quality depends on multiple factors, including the delivery system, the planning system and experience of the user in optimizing these systems. Others have reported on the use of the MRIdian with IMRT in various clinical sites including, head, neck, prostate, lung, breast and CNS with comparable plans to what was achieved in 6-MV LINAC based plans [17,18]. The authors of these studies found that isodose distributions in these plans were comparable to 6-MV LINAC based plans with slightly higher low radiation doses to larger volumes. It should be noted however that the MRIdian system was compared to 6 MV plans as opposed to higher energy plans by both Adams & Warrington and Fox et al [18,19]. When evaluating the quality of IMRT plans with the MRIdian, Wooten et al [10] found that the mean OAR dose tends to be higher on average with MRIdian three source ^{60}Co plans with the difference not being clinically significant. Similar to their study, we found that when the MRIdian system delivered SBRT to peripheral lesions, there were largely comparable dose distributions with non-clinically-significant increases in average dose to the heart, lungs, skin and ribs. For central NSCLC, we found similar non-significant increases in dose to skin and heart. In contrast to other studies, lung dose constraints that were met with Eclipse plans were not met in the MRIdian plans in 2/5 of central plans. These two patients received significantly higher low dose radiation to larger volumes of lung, deeming their plans undeliverable. Despite these slightly larger low dose regions, it should be noted that the use of the MRIdian system in these patients would spare them dose from multiple cone beam CT, or on-board KV or MV imaging during the SBRT delivery.

Despite having slightly inferior dosimetry, the MRIdian three source ^{60}Co systems offers two key advantages. First, real time MR imaging represents a significant paradigm shift and may offer ability to decrease PTV expansion margins. This may lead to more clinically equivalent dosimetry in central lung lesions. Additionally, the real-time MR imaging would obviate the need for conventional low dose image dependent position verification and potentially offset the larger low dose regions. Secondly, the MRIdian system offers routine use of online adaptive RT workflow which allows for rapid image guidance, plan creation and plan verification in a time dependent manner [20]. The system offers potential dose reduction through the use of online adaptive radiotherapy and decreasing treatment volumes with subsequent fractions provided there is subsequent shrinkage of the tumor.

Conclusion

Our study demonstrates the feasibility of treating both central and peripheral NSCLC with the use of MRIdian three sources ^{60}Co based SBRT and being able to achieve similar dosimetry as LINAC based plans for peripheral lesions. More studies are needed to understand the full potential and limitations of MRIdian in treatment planning for NSCLC; especially in regards to central lesions, real-time MR imaging, online adaptive radiotherapy and PTV reduction.

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