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Dosimetric Comparison of Three-Dimensional Conformal Radiotherapy, Dynamic Intensity Modulated Radiation Therapy, and Hybrid Planning for Treatment of Locally Advanced Lung Cancer

Hamit Basaran♦, MD, Gokcen Inan, PhD, Osman Vefa Gul, PhD, Mürsel Duzova, MD

Department of Radiation Oncology, Faculty of Medicine, Selcuk University, Konya, Turkey

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Abstract

Background: The present dosimetric study aimed to evaluate the dosimetric benefits of using three-dimensional conformal radiotherapy (3D-CRT), dynamic intensity-modulated radiation therapy (D-IMRT), and Hybrid CRT/IMRT plans.

Method: In this dosimetric research, 10 patients with locally advanced lung cancer (Stage-IIIB) were selected. The patients with centrally located tumors were particularly chosen to underline the complexity of the treatment plans. We performed 3D-CRT, D-IMRT, and Hybrid CRT/IMRT treatment plans using Varian with the Eclipse treatment planning system. The treatment plans were compared with respect to the doses received by the organs at risk, including total lungs, contralateral lung, ipsilateral lung, heart, spinal cord, esophagus, the dose homogeneity index, and conformity indexes. Paired samples t-test was performed for statistical analyses.

Results: Hybrid method significantly advanced the target conformity index when compared with 3D-CRT and D-IMRT methods (P = 0.000). The total lung volume receiving 5 to 10 Gy was significantly lower in the 3D-CRT plans compared with that in D-IMRT and Hybrid plans (P = 0.025 and P = 0.003). V20 of the total lung was significantly lower in Hybrid plans (P =0.036). The average mean doses to heart in all the plans were similar with no significant differences. There was a statistically significant difference concerning the maximum doses for spinal cord, when D-IMRT plans were compared with 3D-CRT and Hybrid (P = 0.000).

Conclusion: Hybrid technique could be highly conducive to the treatment, while 3D-CRT and D-IMRT techniques are not adequate alone for maintaining the spinal cord, heart, and esophagus in the treatment of LALC patients.

Keywords: Three-dimensional conformal radiotherapy, Intensity-modulated radiotherapy, Lung neoplasms

♦Corresponding Author:
Hamit Basaran, MD
Department of Radiation Oncology, Faculty of Medicine, Selcuk University, Konya, Turkey
Tel: +90 543 607 61 65
Email: drhbasaran@gmail.com

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Introduction

Lung cancer is the most prevalent cancer with approximately 2 million cases annually[1,2] and the most common cause of cancer death worldwide.[3] Surgery is the most frequently applied treatment for patients with early or localized disease. Concurrent chemoradiotherapy continues the standard treatment for locally advanced lung cancer (LALCa).[4] Standard fractionated radiotherapy, especially accompanied by advanced treatment methods, is of great importance for the treatment process. The optimal tumor control can be obtained by adequate dose escalation. However, delivery of doses >60 Gy to large target volumes is associated with significant toxicities.[5] Thus, recognizing target delineation, improvement in dose delivery using new radiation technique, and reducing exposure of healthy lung and esophagus to radiation damage have become the fields of interest for researchers in this field over the last decade; three- dimensional conformal radiotherapy (3D-CRT) techniques are used to minimize normal tissue damage. These techniques, compared with conventional approaches, may require using more treatment fields and reduce the dose to the organs at risk (OARs).

IMRT has been implemented with the development of treatment planning programs and imaging systems. IMRT technique has shown that collective intensity-modulated beams from multiple directions can be designed to produce the same homogeneity within the tumor, but superior conformality for nearly OARs.[6] In addition, IMRT makes non-uniform dose distributions if required for the treatment of a volume within another defined volume known as concomitant boost techniques. On the other hand, the another advantage of IMRT has low doses in the tissues surrounding the target, such as critical organs.

For treatments of LALCa, limiting the dose to the esophagus and normal lung can significantly reduce the treatment-related morbidity. Esophageal volume receiving at least 60 Gy (V_{60}) during radiotherapy is a predictor of esophagitis.[7,8]

In similar studies, it has been observed that the risk of radiation-induced pneumonia increases in case of V_5 >60% for the lung.[9,10] However, meta-analysis has indicated symptomatic pneumonitis rate of 30%[11] and an incidence of grade 2 and 3 esophagitis of 32% and 17%, respectively.[7] For this reason, we require new methods of IMRT for treatment purposes and prescriptions regarding LALCa. Hybrid IMRT (H-IMRT) is a novel method in which the majority of the dose to the primary tumor (PTV) is delivered with traditional treatment of 3D-CRT, and the remainder with Dynamic intensity-modulated radiothery (D-IMRT).[12] The superiority of H-IMRT over the other techniques is the delivery of high dose to primary tumor volume (PTV), while reducing the low dose to the surrounding normal tissue.[13]

This study aimed to evaluate the dosimetric benefits of 3D-CRT, D-IMRT, and a combination of these techniques with hybrid-dynamic conformal D-IMRT (H-DCIMRT) technique concerning thorax radiotherapy treatment. The average percentage of irradiated volumes of adjacent non-cancerous organs include contralateral lung, heart, and esophagus, which were calculated and compared between various plans.

Material and Method

Patient selection

We recruited 10 thorax cancer patients in this dosimetric study. The local institutional board of Faculty of Medicine, Selcuk University (ethics code:2020/496) provided the ethical approval. The patients were immobilized in a supine position and a chest board was used to rest their arms over their heads. For the planning, computed tomography (CT) scans were generated via a CT scanner with a 3-mm slice thickness. The acquired image data from CT were transferred to the treatment planning system (TPS) (Eclipse, version 15.1; Varian Medical System Inc, Palo Alto, CA, USA).

Target and OAR delineation

The target and the critical organ volumes were outlined with the TPS work-station. CT images of the subjects were contoured by a radiation oncologist and controlled by the second specialist

Table 1. Dose statistic comparison for planning target volume

Parameters	3DCRT	IMRT	Hybrid	*P* value
PTV D_{mean} (Gy)	59.93 ± 0.47	60.38 ± 0.35	59.47 ± 0.66	0.002
PTV D_{max} (Gy)	64.31 ± 0.59	63.86 ± 0.65	63.06 ± 0.88	0.002
$D_{\%2}$	63.50 ± 0.49	61.65 ± 1.34	61.86 ± 0.68	0.000
$D_{\%98}$	54.15 ± 1.21	55.85 ± 1.27	54.77 ± 0.99	0.110
$D_{\%50}$	60.03 ± 0.52	60.03 ± 1.20	59.64 ± 0.47	0.469
HI	0.14 ± 0.01	0.80 ± 0.03	0.17 ± 0.21	0.243
CI	0.96 ± 0.19	0.59 ± 0.30	1.49 ± 0.53	0.000

3DRCT: Three-dimensional conformal radiotherapy; IMRT: Intensity-modulated radiotherapy; CRT/IMRT: Conformal radiotherapy- intensity-modulated radiation therapy; PTV: Planning tumor volume; HI: Homogeneity index; CI: Conformity index; D: Dose

according to the reports defined by the International Commission on Radiation Units and Measurements (ICRU) 62. The primary tumor and involved mediastinal node regions were contoured as the target organ volume. Additionally, bilateral lungs, heart, esophagus, and spinal cord were contoured as OARs volumes.

The Radiation Therapy Oncology Group (RTOG) atlases for OARs in Thoracic Radiation Therapy were utilized as a reference in the target volume drawing.[14] FDG-PET/CT was used to identify the mediastinal nodal gross tumor volume (GTVn) and primary gross tumor volume (GTVt). We performed contouring based on RTOG 1106 target atlas. To create the clinical target volume (CTV) that represents a volumetric expansion of the GTV to encompass microscopic disease, we used a 6-8-mm margin that was given around the GTV based on histology of squamous cell carcinomas and adenocarcinoma. Furthermore, to create planning target volume of PTV and planning target volume of mediastinal lymph node (PTVn), a margin of 20 mm was given from the superior /inferior and 10 mm from other directions.

3D-CRT, D-IMRT, and Hybrid CRT/IMRT techniques

For each of the treatments with 3D-CRT, D-IMRT, or a combination of them with hybrid 3D-CRT/D- IMRT, the plans were generated using Varian DHX linear accelerator, which is capable of delivering both static and dynamic IMRT. The prescribed dose for the planning target volume was 6000 cGy in 30 fractions. For 3D-CRT, four coplanar field plans were designed and the weights and directions for the plans were manually performed. We created 3D-CRT plans with 18 MV photons. For the D-IMRT, the plans were created with 6-7 coplanar fields. The optimal beam angles were selected to obtain the best target volumes and sparing critical structures. D-IMRT treatment plan optimization was generated employing the Dose Volume Optimizer algorithm using TPS. D-IMRT plans were created utilizing 6 MV photons. The treatment plans were optimized to provide the best PTV coverage and also OARs sparing. When the optimization process was over, the leaf motions, utilizing sliding window method, were used for the treatment plans. H-IMRT plans concurrently combined 3D-CRT (60%) and D-IMRT (40%) beams. This

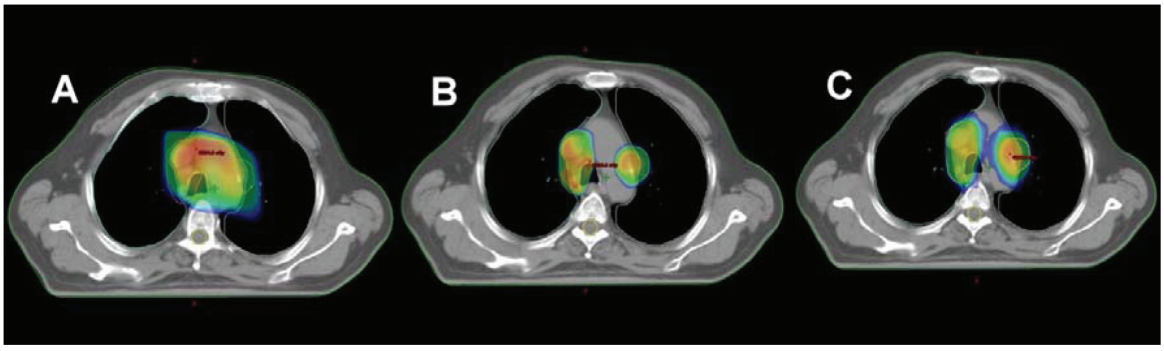

Figure 1. This figure shows the comparison among the dose distribution of all the plans A: Three- dimensional conformal radiotherapy (3D-CRT); B: Dynamic intensity-modulated radiation therapy (D-IMRT); C: Hybrid.
CRT/IMRT: Conformal radiotherapy- intensity-modulated radiation therapy

Table 2. Dose statistic comparison for organs at risk

Parameters	3DCRT	IMRT	Hybrid	*P* value
Total lungs				
D_{max} (Gy)	63.11 ± 0.87	62.92 ± 1.28	61.55 ± 0.81	0.003
D_{mean} (Gy)	16.34 ± 3.10	15.32 ± 1.86	13.66 ± 3.80	0.156
V_5	55.96 ± 6.34	64.74 ± 7.75	59.69 ± 6.06	0.025
V_{10}	39.57 ± 8.66	52.01 ± 6.70	43.64 ± 6.81	0.003
V_{20}	28.73 ± 8.22	30.92 ± 4.42	23.95 ± 7.38	0.036
V_{30}	23.02 ± 6.16	16.98 ± 3.83	19.60 ± 6.91	0.083
V_{45}	9.03 ± 5.39	7.19 ± 2.97	11.69 ± 4.43	0.087
V_{60}	1.23 ± 1.29	0.76 ± 0.75	0.48 ± 0.41	0.187
Contralateral lung				
D_{max} (Gy)	57.94 ± 9.75	59.65 ± 7.74	55.57 ± 10.00	0.615
D_{mean} (Gy)	11.14 ± 5.33	11.93 ± 2.50	10.21 ± 5.37	0.710
V_5	44.70 ± 16.47	60.30 ± 10.62	50.81 ± 12.73	0.049
V_{10}	32.49 ± 15.39	47.53 ± 10.34	30.89 ± 14.82	0.021
V_{20}	22.28 ± 13.85	21.09 ± 7.43	14.39 ± 11.73	0.264
V_{30}	17.16 ± 12.45	9.07 ± 3.96	9.89 ± 8.25	0.101
V_{45}	4.93 ± 5.40	2.66 ± 1.58	5.68 ± 5.00	0.288
V_{60}	0.40 ± 0.61	0.31 ± 0.38	0.08 ± 0.20	0.252
Ipsilateral lung				
D_{max} (Gy)	62.58 ± 0.57	62.43 ± 0.41	61.35 ± 0.94	0.124
D_{mean} (Gy)	20.10 ± 3.44	18.79 ± 2.33	19.32 ± 4.44	0.706
V_5	60.70 ± 12.58	65.09 ± 13.11	63.12 ± 13.60	0.757
V_{10}	52.45 ± 10.46	57.38 ± 10.90	48.85 ± 15.15	0.317
V_{20}	41.35 ± 7.54	40.86 ± 4.99	34.05 ± 1.93	0.183
V_{30}	33.26 ± 4.94	25.46 ± 3.75	28.30 ± 12.16	0.100
V_{45}	14.23 ± 8.06	11.68 ± 4.75	18.15 ± 7.63	0.132
V_{60}	2.38 ± 2.62	1.63 ± 1.54	0.76 ± 0.71	0.156
Heart				
D_{max} (Gy)	44.22 ± 28.31	45.58 ± 27.64	44.71 ± 27.15	0.994
D_{mean} (Gy)	11.16 ± 7.60	10.22 ± 6.35	10.94 ± 8.31	0.965
V_5	36.11 ± 27.79	40.78 ± 29.63	36.07 ± 25.23	0.908
V_{10}	29.21 ± 22.97	30.72 ± 21.72	23.56 ± 19.05	0.734
V_{20}	18.39 ± 14.45	16.68 ± 13.00	17.19 ± 15.12	0.963
V_{30}	12.84 ± 10.90	9.38 ± 8.20	13.33 ± 12.26	0.665
V_{45}	7.81 ± 7.44	5.55 ± 5.56	9.87 ± 10.35	0.495
V_{60}	1.26 ± 1.91	0.77 ± 0.90	0.35 ± 0.59	0.292
Spinal cord				
D_{max} (Gy)	38.61 ± 6.81	30.31 ± 7.21	44.36 ± 1.53	0.000
Esophagus				
D_{max} (Gy)	60.25 ± 3.83	61.56 ± 1.81	58.58 ± 3.42	0.126
D_{mean} (Gy)	25.62 ± 8.11	26.97 ± 4.53	23.97 ± 6.69	0.603
V_{60}	7.38 ±7 .50	7.05 ± 8.62	2.80 ± 5.38	0.309

3DRCT: Three-dimensional conformal radiotherapy; IMRT: Intensity-modulated radiotherapy; CRT/IMRT: Conformal radiotherapy- intensity-modulated radiation therapy; V: Volume

combination was based on an improvised decision ratio. The objective of combining the two plans with this fixed ratio was to direct OAR exposure within the fields. The 3D-CRT treatment plans were conducted to the opposing 2-field lateral coplanar beams (anteriorposterior-posterior-anterior (AP-PA). The treatment fields were optimally weighted to obtain the suitable PTV coverage. For 3D-CRT, beam shaping was accomplished with multileaf collimators (MLC) to shield the spinal cord and heart as needed using 18 MV photon beams.

Plan analysis

Three different plans were performed based

on the DVH (dose-volume histogram) according to the International Commission on Radiation Units and Measurements (ICRU) 83 evaluation of plans.[15] The maximum and mean dose (D_{max} and D_{mean}), dose homogeneity index (DHI), and conformity index (CI) were compared in terms of the PTV. For OAR, the values of interest in this study, which were compared, included D_{max}, D_{mean}, V_{5Gy}, V_{10Gy}, V_{20Gy}, V_{30Gy}, V_{45Gy}, and V_{60Gy} for the total lungs, contralateral lung, and ipsilateral lung, along with D_{max}, D_{mean}, V_{5Gy}, V_{10Gy}, V_{20Gy}, V_{30Gy}, V_{45Gy}, and V_{60Gy} for the heart, in addition to D_{max} for the spinal cord and D_{max}, D_{mean}, and V_{60} for the esophagus. For PTV, DHI was defined according to ICRU 83 dose homogeneity and evaluated through the DHI.[16]

$$HI = \frac{(D_{2\%} - D_{98\%})}{D_{50\%}}$$

D_{98} was the maximum dose absorbed with 98% of the PTV, with the lowest irradiation, and D_2 was the minimum dose absorbed with 2% of the PTV, with the highest irradiation. CI was defined by the ratio of reference isodose volume to target volume of PTV.

Statistical analysis

Statistical Package for Social Sciences, version 25.1 (SPSS, Inc., Chicago, IL, USA) was utilized for the statistical analysis. We used ANOVA test for analyzing the differences among the three methods. When there was a significant difference among them, Tukey test was applied in order to further determine the the ranking of each metod. A P value of < 0.05 was considered to be significant.

Results

Table 1 represents the mean of the PTV parameter results in 3D-CRT, D-IMRT, and Hybrid plans. For PTV, the average mean doses were 59.93 ± 0.47, 60.38 ± 0.35, and 59.47 ± 0.66 Gy in 3DCRT, D-IMRT, and Hybrid, respectively. Figure 1 demonstrates the evaluation of 3 DCRT, IMRT, and Hybrid plans. For PTV, smaller HI means more homogeneous dose distribution. Thus, the 3D-CRT technique showed better results compared with the D-IMRT technique. The CI was significantly lower in D-IMRT compared with that in 3D-CRT and Hybrid ($P = 0.000$).

Table 2 depicts the statistical dosimetric comparison for OARs. DVHs obtained from the plans are illustrated in terms of target volumes and critical structure in figure 2. For the lungs, the average mean doses were 16.34 ± 3.10, 15.32 ± 1.86, and 13.66 ± 3.80 Gy in 3D-CRT, D-IMRT, and Hybrid, respectively. In all the plans, the mean total lung doses were similar with no significant differences. The total lung volume receiving 5 to 10 Gy was significantly lower in 3D-CRT than that in D-IMRT and Hybrid plans ($P = 0.025$ and $P = 0.003$). However, V_{20} for the total lung were significantly lower in the Hybrid plans ($P = 0.036$). Comparing V_{30} and V_{45} of the total lung, in D-IMRT plans, they were lower than thos in 3D-CRT and Hybrid. Hybrid was

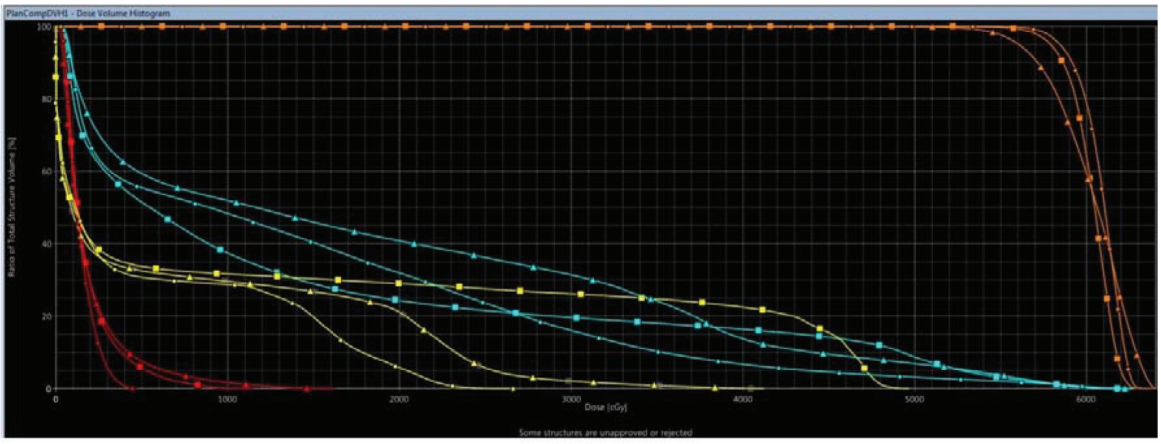

Figure 2. This figure shows the dose-volume histogram comparison of a patient; orange: PTV; blue: Total lungs; red: Heart; yellow: Spinal cord; ▲: 3D-CRT technique; ●: D-IMRT technique; ■: Hybrid-CRT/IMRT technique.
3D-CRT: Three- dimensional conformal radiotherapy; D-IMRT: Dynamic intensity-modulated radiation therapy; CRT/IMRT: Conformal radiotherapy- intensity-modulated radiation therapy

superior over D-IMRT concerning the maximum dose to contralateral lung. The contralateral lung volume receiving 10 to 20 Gy was significantly lower in Hybrid than that in 3D-CRT and D-IMRT treatment plans ($P = 0.049$ and $P = 0.021$). The average maximum doses to the ipsilateral lung were lower in Hybrid plan in comparison with those in 3D-CRT and D-IMRT.

The average mean doses to the heart were 11.16 ± 7.60, 10.22 ± 6.35, and 10.94 ± 8.31 Gy in 3D-CRT, D-IMRT, and Hybrid treatment plans, respectively. The mean dose to heart in all the plans was similar with no significant differences. For the spinal cords, the average maximum doses were 38.61 ± 6.81, 30.31 ± 7.21, and 44.36 ± 1.53 Gy in 3D-CRT, D-IMRT, and Hybrid, respectively. Comparing D-IMRT plans with 3D-CRT and Hybrid, there was a statistically significant difference in terms of the maximum doses to the spinal cord ($P < 0.001$). The esophagus average mean doses were 25.62 ± 8.11, 26.97 ± 4.53, and 23.97 ± 6.69 Gy, respectively, in 3 DCRT, D-IMRT, and Hybrid plans. The maximum dose to esophagus in all the plans was similar with no significant differences. Similar results were observed for the esophagus in volume-based criteria V_{60}.

Discussion

In this study, we investigated a Hybrid technique in which the combination of 3D-CRT (AP-PA) and D-IMRT techniques were compared. In the treatment plans, the beam fields significantly have the soft tissue of the mediastinum. Hence, we conducted this work to study the use of the technique of Hybrid plans for protecting the lung tissue. Radiotherapy has an important role in treating LALCa (Stage-IIIB) patients. For the LALCa radiotherapy, D-IMRT and Hybrid, compared with previous 3D-CRT methods, can provide higher doses to the tumor more conformably while minimizing the doses to OARs. Accordingly, these treattments are able to increase the local control and decrease morbidity. In this study, the treatment plans were developed to minimize the dose to surrounding normal organs. Thus, we aimed to limit the risk of treatment toxicity. Treatment plans can be developed using 3D-CRT or D-IMRT techniques and should include beams from multiple gantry angles.[17]

The most important obstacle in achieving the maximal dose deposition for lung tumors is the lung itself. Actually, radiation-related pneumonitis may cause a fatal disease. For lungs, the parameters of V_{20} are usually used for the evaluation of the probability of radiation pneumonitis.[18,19] When planning large volumes of the lung, it is vital to develop treatment plans that adhere to normal lung tolerance doses. Dose values, such as V_5 and V_{20}, must be observed to avoid treatment complications.[20] Evaluation of 3D-CRT and D-IMRT treatment plans requires careful assessment of DVHs.

Herein, V_{10} of the total lung in 3D-CRT plans were lower than that in D-IMRT and Hybrid plans. Kristensen et al. explained that V_{10} was a vital factor for the fatal lung toxicity.[21] Liu et al. and Chan et al. indicated that for the lung and thoracic tissue, an additional reduction in the >5-Gy and >10-Gy volume was more difficult with D-IMRT.[22,23] In this study, V_{20} for the total lung was significantly lower in Hybrid plans than that in 3D-CRT and D-IMRT. Sung Joon Kim et al. compared the dosimetric differences between Hybrid-dynamic conformal arc therapy (HDCAT) and 3D-CRT techniques in 20 lung cancer cases. They found that in HDCAT plans, V_{20} of the total lung was significantly lower than that in 3D-CDRT ($P < 0.001$).[24]

In the current study, V_5 and V_{10} for the heart were lower in Hybrid than those in the other plans. However, the volume-based criteria of V_{20}, V_{30}, and V_{45} of the heart were lower in D-IMRT. Sung Joon Kim et al. compared HDCAT to 3D-CRT. They found that V_{40} and V_{50} of the heart were lower in the HDCAT technique.[28] High-dose irradiation may cause radiation-induced cardiac complications for the heart; therefore, utilization of D-IMRT can minimize the risk of cardiac toxicities.[27]

Compared with 3D-CRT, D-IMRT decreases the dose in the spinal cord more easily. Compared with 3D-CRT and Hybrid techniques, the D_{max} of the spinal cord could reduce in the D-IMRT

technique. In 3D-CRT treatment, beams are limited for lung cancer treatment; thus, it is very challenging to minimize the dose to the spinal cord due to the proximity between PTV and OAR.

In this study, D_{mean} and V_{60} of the esophagus were lower in the Hybrid plan compared with those in 3D-CRT and D-IMRT treatments. We observed the mean esophageal doses to be similar to each technique. The maximum esophageal dose correlates with symptoms, as do multiple absolute dose and volume thresholds.[29] Esophagitis, for the radiation treatment fields of lung cancer, is an important dose-limiting acute side-effect directly related to the PTV.[30] QUANTEC analysis has concluded that the volumes treated above 40 to 50 Gy correlate with acute esophagitis and has further suggested that no dose above the desired prescribed dose should be allowed for small volumes of esophagus, in order to reduce the risk of severe ulceration or fistula.[17]

In the current study, we faced several limitations. This was a dosimetric study and did not include the vital aspects required for clinical use. This work was solely a dosimetric comparison between the planning options. The number of the subjects used for the comparison was limited to 10. This may be improved in further studies in order to obtain better results. We only aimed to investigate the Hybrid combination of 3D-CRT and D-IMRT for future planning. We did not intend to perform this combination as a standard treatment to all treatment plans. Nonetheless, we could suggest that this combination stands as a viable option once required.

Conclusion

D-IMRT enables us to produce a highly conformal dose to a PTV and steeper dose gradients around the target volume compared to 3D-CRT. It is eligible to administer a high dose to PTV volume while sparing OARs. According to the findings obtained in this study, Hybrid technique can be applicable in vital lung volume while protecting the spinal cord, heart, and esophagus within tolerance dose limits.

Conflict of Interest

None declared.

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