



Dosimetric Comparison of Three-Dimensional Conformal Radiotherapy with Hybrid Intensity-Modulated Radiotherapy Techniques for Treatment of Locally Advanced Lung Cancer

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OBJECTIVE

Radiation treatment planning for advanced lung cancer can be technically challenging, as the delivery of doses of ≥ 60 Gy is often associated with significant risk of normal tissue toxicities. We aimed to examine the effect of the hybrid technique combining three-dimensional compared radiotherapy (3DCRT) with intensity-modulated radiotherapy (IMRT) on target dose distribution and critical organ doses.

METHODS

The treatment plans of nine patients treated with 3DCRT were replanned using hybrid technique. 3DCRT consisted of 3-5 fields using 6-18 MV energies and IMRT plans consisted of 7-10 fields using 6 MV energy. In hybrid plans, 60% of the prescribed dose were delivered with 3DCRT and 40% with IMRT beams. Prescribed dose was 66 Gy in 2 Gy fractions.

RESULTS

Hybrid IMRT improved dose homogeneity in planning target volume (PTV). It was possible to reduce the hotspots that exceeded 107% of the prescribed dose with the hybrid technique compared to 3DCRT ($p=0.028$). Total and contralateral lung doses were found to be increased with hybrid technique. Hybrid IMRT decreased maximum esophagus and spinal cord doses.

CONCLUSION

Hybrid IMRT improved dose homogeneity in PTV and decreased hot spots but increased lung doses. The lower maximum point doses of esophagus and spinal cord were achieved with hybrid technique. Reducing the number of fields and contribution of IMRT fields might increase the advantage of hybrid technique by reducing lung doses.

Keywords: 3D conformal radiotherapy; hybrid IMRT; locally advanced lung cancer.

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Introduction

Lung cancer is the leading cause of cancer death worldwide.[1,2] Over 85% of lung cancer patients are histologically classified as non-small cell lung can-

cer (NSCLC) and only 15% of patients present with localized disease.[3] While surgery is curative treatment of these localized disease, chemoradiotherapy is standard treatment of locally advanced unresectable NSCLC.[4] Radiation treatment planning for ad-

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vanced lung cancer can be technically challenging, as the delivery of doses of ≥ 60 Gy with concurrent chemotherapy to large volumes is often associated with significant risk of normal tissue toxicities.[5] For the treatment of lung cancers, limiting dose to esophagus and normal lung can significantly reduce treatment-related morbidity. In meta-analysis studies, symptomatic pneumonia was reported as 30% and grades 2 and 3 esophagitis rates were reported as 32% and 17%, respectively.[6] The main factors that trigger the development of radiation pneumonia are advanced age, receipt of carboplatin and paclitaxel chemotherapy regimen, high V20 values, being located in lower lobes, and large fraction size.[6] Palma et al.[7] performed meta-analysis to examine predictors of radiation esophagitis for patients with locally advanced lung cancer and younger age, low performance status, being female, and concurrent chemotherapy were found to increase the risk of esophagitis. They found that the best predictor of esophagitis is the volume of esophagus receiving ≥ 60 Gy.

Transition from 2D radiotherapy to 3D radiotherapy was made possible by computerized tomography (CT) simulation and this allowed the radiation oncologist to determine the tumor volume more accurately. Three-dimensional compared radiotherapy (3DCRT) provides more conformal doses to the tumor compared to 2D radiotherapy. The advantage of intensity-modulated radiotherapy (IMRT) over 3DCRT is improved target conformity and sparing of organs at risk (OAR).[8] Compared to IMRT, volumetric modulated arc therapy (VMAT) and intensity-modulated arc therapy (IMAT) which are a form of VMAT further improve conformity of high dose and sparing of OARs.[8] While improving target coverage and sparing OAR, IMRT and related techniques such as VMAT and IMAT can increase low dose in lung which can be critical for radiation pneumonitis. Studies have shown an increased risk of pneumonitis when volume of lung receiving 5 Gy and more higher than 60%.[9-11] However, V_5 has not consistently been found to associate with the development of pneumonitis, and many practitioners currently give V_5 less priority during planning than V_{20} or MLD. Moreover, in the secondary analysis of RTOG 0617, IMRT was found to be associated with better preservation of quality of life compared with 3DCRT and to be associated with lower rates of grade 3 pneumonitis.[12] Mayo et al.[13] developed a novel technique combining 3DCRT and IMRT and called hybrid IMRT to reduce low-dose region in lung in breast cancer patients.

Later, this technique has been used for esophagus and lung cancers.[5,13]

In this study, we aimed to use hybrid technique that combines 3DCRT and IMRT to improve isodose distributions and reduce OAR doses. We replanned the treatment plans of the nine patients treated with 3DCRT and compared hybrid IMRT with 3DCRT for target coverage and sparing of OAR.

Materials and Methods

Patients

We retrospectively analyzed the treatment plans of nine patients treated with 3DCRT and replanned with hybrid IMRT technique. The patient characteristics are summarized in Table 1.

Contouring and Target Delineation

CT simulations were performed and all patients were scanned using Lightspeed RT 16 model CT with 2.5 mm thick slices during normal breathing. No specific measures were taken to control motion of lesions due to respiration. Gross tumor volumes (GTVs) were delineated according to F18-Fluorodeoxyglucose-positron emission tomography computed tomography. Clinical target volumes were obtained by adding 6 mm margin to GTV. Planning target volume (PTV) margins of 5-10 mm were specified by physician. The spinal cord, esophagus, lung, and heart were contoured.

Dose Prescription and Planning Technique

The treatment planning was carried out using the Precise (ELEKTA) treatment planning system. 3DCRT consists of 3-5 fields using 6, 10, and 18 MV energies, depending on the PTV location. 3DCRT plans were manually optimized using field in field technique considering cross-sectional dose distribution maps, beams-eye view images, and dose-volume histograms. IMRT plans consisted of 7-9 fields using 6 MV energy. Hybrid plans consisted of 3DCRT and IMRT beams that delivered 60% and 40% of the prescribed dose, respectively. 66 Gy in 2 Gy fractions was prescribed. PTV coverage was prescribed to 95%. The planning objectives were as follows: The maximum point dose to the spinal cord was < 45 Gy, volume of lung minus PTV receiving more than 20 Gy (V_{20}) $\leq 35\%$, 5 Gy (V_5) $\leq 65\%$, mean lung dose (MLD) ≤ 20 Gy, volume of heart receiving more than 30 Gy (V_{30}) $\leq 45\%$, mean heart dose ≤ 26 Gy, and volume of esophagus receiving more than 50 Gy (V_{50}) $\leq 40\%$.

Table 1 Patient characteristics

Patient	Gender	Age	Localization	Stage	PTV volume (cc)
1	E	71	Left upper	T3N2-IIIB	1182.3
2	E	65	Left upper	T3N2-IIIB	1.504.2
3	E	69	Left upper	T2N2-IIIA	658.1
4	K	52	Right lower	T2N2-IIIA	524.4
5	E	62	Left upper	T4N2-IIIA	597.8
6	E	56	Right upper	T2N2-IIIA	662.4
7	K	56	Right upper	T2N2-IIIB	330.9
8	E	69	Left lower	T4M0-IIIA	501.1
9	E	56	Left upper	T4M0-IIIA	587.1

PTV: Planning target volume

Homogeneity Index (HI)

HI is a data that give information about whether the absorbed dose is homogeneously distributed in the target volume. If this value is close to 0, it indicates that the dose distribution in PTV is homogeneous. [14] According to ICRU 83 formula, HI is calculated as $HI = (D2 - D98) / D50$.

D2, the dose of 2% of the volume; D98, the dose absorbed by 98% of the volume and D50 refers to the dose received by 50% of the volume.

Conformity Index (CI)

The CI is the ratio of the treated volume to the planned target volume and is defined by the formula:

$$CI = \frac{TV}{PTV}$$

According to the RTOG criteria, the ideal dose distribution is obtained when $CI = 1$. It means that when $CI > 1$, the irradiated volume is greater than PTV. In the case of $CI < 1$, there is partial irradiation of the target volume. [15]

Statistical Analysis

Statistical analysis of all data obtained from the study was performed in SPSS 23 program. Normality assumption was checked by Shapiro-Wilk test. Paired t-test was used when the normal distribution assumption was provided, and Wilcoxon pair test was used if it was not. If $p < 0.05$ in the evaluations made for all cases, the results were considered statistically significant.

Results

No statistically significant difference was found between the two techniques for D95. However, it was possible to

lower the maximum value of PTV with the hybrid technique (mean, 70.88 Gy vs. 72.10 Gy, $p = 0.080$).

PTV coverage was optimal and 95% of the prescribed dose covered at least 96% of the PTV volume with both planning techniques and there was no statistically significant difference between the two techniques. For the average dose values of PTV, prescribed dose of 66 Gy was slightly exceeded with 3BCRT and results were much closer to 66 Gy with hybrid technique (mean 65.98 Gy vs. 66.74 Gy, $p = 0.007$). This difference was found to be significant. It was possible to reduce the hotspots that exceed 107% of the dose, with the hybrid technique (mean 4.39 vs. 0.19 Gy, $p = 0.028$) and this difference between the two techniques was considered statistically significant.

HI and CI values were also examined in target volume comparisons and no statistically significant difference was found between the two techniques. On the other hand, since the results of mean HI value was closer to zero for the hybrid technique, it is possible to say that more homogeneous plans are obtained with this technique (0.115 vs. 0.151, $p = 0.057$). For the CI value, the results found with both techniques which are between 0.9 and 1, and it is possible to say that both techniques are close to the ideal plan (0.969 vs. 0.965, $p = 0.656$).

The $V_5, V_{13}, V_{20}, V_{30}$ and mean dose values for the total lung were evaluated. It seems that the low and intermediate lung doses increased in hybrid technique; hence, in comparison, the statistically significant rising both in V30 and mean dose values was obtained (20.44%, vs. 18.29%, $p = 0.007$ and 15.44 Gy vs. 14 Gy, $p = 0.031$, respectively).

The same evaluations were performed for contralateral lung and the rising of V_5 and mean dose values had a statistically significant increase toward hybrid technique (35.94% vs. 20.37%, $p = 0.015$ and 7.06 Gy vs. 5.01 Gy, $p = 0.011$, respectively). For other parameters, there was an increase in the plans made with hybrid technique, but this increase was not considered statistically significant.

When we examined the V_{35}, V_{50} , mean, and maximum dose values for the esophagus, it was possible to keep the maximum value of the esophagus lower with the hybrid technique, and this difference was considered statistically significant (63.70 Gy vs. 66.30 Gy, $p = 0.038$). There was no statistically significant difference in terms of other parameters. In our evaluation for the heart, no statistically significant difference was found between the two planning techniques for V30, V_{50} , and mean dose values, and the mean dose value was kept below the average reference dose of 26 Gy in both techniques (17.36 Gy vs. 17.71 Gy, $p = 0.630$).

Table 2 Dosimetric comparison of two planning techniques for locally advanced lung cancer

Dosimetric parameters	3DCRT mean±SD	h-IMRT mean±SD	p
PTV			
V ₉₅	96.49±2.45	96.47±1.94	0.678
V ₁₀₇	4.39±5.64	0.19±0.51	0.028
Mean dose (Gy)	66.74±0.70	65.98±0.30	0.007
Maximum dose (Gy)	72.10±3.91	70.88±3.91	0.080
HI	0.151±0.068	0.115±0.036	0.057
CI	0.965±0.024	0.969±0.026	0.656
Total lung			
V ₅	36.65±8.9	48.59±20.2	0.052
V ₁₃	29.03±8.7	33.71±10.7	0.100
V ₂₀	23.84±9.3	25.59±8.3	0.288
V ₃₀	18.29±7.8	20.44±7.7	0.007
Mean dose (Gy)	14±4.09	15.44±4.16	0.031
Contralateral lung			
V ₅	20.37±10.59	35.94±28.9	0.015
V ₁₃	14.59±7.07	18.79±14.51	0.594
V ₂₀	7.78±5.58	9.32±7.69	0.594
V ₃₀	3.88±4.31	4.56±5.02	0.214
Mean dose (Gy)	5.01±2.60	7.06±4.26	0.011
Esophagus			
V ₃₅	43.71±22.2	44.98±19.1	0.295
V ₅₀	31.23±17.4	28.73±14.3	0.282
Mean dose (Gy)	29.18±10.74	29.36±8.58	0.774
Maximum (Gy)	66.30±4.24	63.70±4.89	0.038
Heart			
V ₃₀	26.42±17.8	26.94±14.4	0.830
V ₅₀	13.95±8	13.90±8.2	0.935
Mean (Gy)	17.36±9.86	17.71±9.36	0.630
Spinal cord (Gy)			
Maximum dose (Gy)	43.09±3.91	39.69±5.95	0.314

DCRT: Dimensional compared radiotherapy; IMRT: Intensity-modulated radiotherapy; PTV: Planning target volume; HI: Homogeneity index, CI: Conformity index; Gy: Gray

For the maximum value of the spinal cord, there was no statistically significant difference between the two techniques, but it was possible to keep this value lower in the hybrid technique (39.69 Gy vs. 43.09 Gy, p=0.314). In Table 2, PTV and critical organs are dosimetrically compared with the two planning techniques.

Discussion

Lung cancers are often a difficult group of tumors to treat definitively since it is challenging to give high doses to the tumor without exceeding the tolerance doses of critical organs such as heart, esophagus, and spinal cord. The lungs are particularly radiosensitive and are susceptible to radiation pneumonitis. Esophagitis is common and affects patient quality of

life. Beyond acute pericarditis, late cardiac toxicities are increasingly being recognized and can affect overall survival. In a systemic review of articles from 1993 to 2010 reporting on predictors of grade ≥2 pneumonitis in 836 patients after chemoradiation to a median dose of 60 Gy, 29.8% of patients developed clinically significant pneumonitis and 1.9% of patients developed fatal pneumonitis.[6] Since there are limited effective treatments, the primary strategy to reduce its likelihood of development is through strict adherence to dose-volume constraints of the normal lung. The two dose parameters that have been most commonly reported to be associated with radiation pneumonitis are the normal bilateral lung volume receiving at least 20 Gy (termed V₂₀) and the MLD. Radiation plans are generally designed to limit the V₂₀ to ≤30-37% and the MLD

≤ 20 -21 Gy to achieve a grade ≥ 2 rate of under 25%. Other lung volumetric doses, such as V_5 , have been reported to influence pneumonitis development, and V_5 may be particularly important with IMRT, where a low dose of radiation can be delivered to proportionally greater lung volumes.[6]

As a result of technical developments, an IMRT technique that provides optimal modulation of beams has been developed and can provide a more conformal dose distribution compared to 3DCRT. However, while providing low doses of healthy tissues such as spinal cord and esophagus, it can expose large lung volumes to low dose compared to 3DCRT.

Mayo et al. developed the hybrid IMRT technique for locally advanced NSCLC by combining static and IMRT beams to reduce the low and medium lung dose volumes received by the normal lung with the IMRT technique.[5,13] In their study, 3D plans were found less conformal than IMRT plans and hybrid plans reduced significantly total and contralateral lung volumes. However, 3D technique had lower V_5 values than the hybrid method for both lung. In their study, PTV volumes were much smaller (average 179 cm³) compared to our study and they used smaller IMRT contribution (33%). Verbakel et al.[16] used hybrid IMRT to treat 14 consecutive patients with PTVs exceeding 500 cm³ and compared this technique with 3DCRT, full rapid arc, hybrid rapid arc, and six-field full IMRT. They found that hybrid IMRT and hybrid rapid arc plans achieved optimal PTV coverage while avoiding hot spots and reduced the total lung V_{20} and the contralateral lung V_5 .

In the present study, PTV coverages were optimal with both techniques. We found lower V_5 , V_{13} , V_{20} , and V_{30} values with 3DCRT compared to hybrid technique. In our study, the reason for the increase in low- and medium-dose volumes of the healthy lung with the hybrid technique can be explained by the high number of IMRT fields that we used while planning the hybrid technique. IMRT field number was recommended to be 5 or fewer in order not to increase the irradiated low dose volume.[17] Liu et al. demonstrated that equidistant nine-field IMRT improved target coverage but increased the lung volume receiving at least 5 and 10 Gy. Nine-field IMRT has been demonstrated to produce larger total and contralateral lung V_5 and V_{20} compared to 4- or 5-field IMRT and 3DCRT. Furthermore, in the present study, the contribution of IMRT was 40% and this may cause a high lung doses. Other two studies[13,16] comparing 3DCRT with hybrid IMRT used less IMRT contri-

bution (33% and 11%). In our study, maximum contralateral V_5 was 64.8 Gy and 30.96 Gy for h-IMRT and 3DCRT, respectively. Verbakel et al. reported that maximum contralateral V_5 was 55% which is 9-18% lower than other techniques. Our PTV volume was comparable to Verbakel's study which is 723 cm³ but larger compared to Mayo's study (123 cm³).[13,16] Chan et al.[8] compared 3DCRT with hybrid rapid arc and double VMAT and found superiority of hybrid rapid arc technique. In their study, hybrid rapid arc technique used 50% 3DCRT consisted of two static beams and achieved the lowest V20 and MLD.

In the literature, several studies investigated the effect of hybrid technique on lung cancer radiotherapy planning.[5,16,18-21] These studies combined different techniques such as VMAT, rapid arc, and IMRT. All studies showed the advantage of hybrid techniques in terms of PTV coverage, treatment time, and reduced organ at risk doses including lung doses. Silva et al.[21] used hybrid rapid arc radiotherapy technique with combining 40% rapid arc with 60% 3DCRT to treat 11 patients with locally advanced lung cancer and demonstrated advantages for reduction in low-dose lung volumes, esophageal dose, and mean heart dose compared to 3DCRT and rapid arc therapy. The study performed by Chan et al.[8] compared 3DCRT, rapid arc, and h- rapid arc and demonstrated superiority of hybrid plans in dosimetric outcomes. Saglam et al.[20] shown that if hybrid arc technique could combine the benefits of IMRT and VMAT and showed that hybrid plans can deliver fast, conformal and homogenous treatments without limitations of low dose bath.

Esophagitis is among major dose limiting acute side effects. In the present study, hybrid technique reduced esophagus maximum dose which could help to reduce esophagitis. Verbakel et al.[16] did not attempt to spare esophagus and heart since IMRT contribution is small. On the other hands, Mayo et al.[5] found that full IMRT plans improved heart sparing.

Since our main aim was to make comparison between 3DCRT and hybrid IMRT, we did not analyze dosimetric parameters of full IMRT. When we compare 3DCRT and h-IMRT higher lung doses obtained with hybrid technique, and this can be explained by the higher number of IMRT beams in this study. As a conclusion, hybrid IMRT can be used especially for locally advanced lung cancers since it improved target coverage and spare critical organs. However, contribution of IMRT ratio and the number of beams should be adjusted not to increase lung doses.

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