Original Research Article

Dosimetric Comparison of Stereotactic Body Radiotherapy in Lung Cancers: CyberKnife Versus Helical Tomotherapy Versus Volumetric Modulated Arc Therapy

ABSTRACT

Aim: *Stereotactic body radiotherapy (SBRT) is widely used in the treatment of early- stage lung cancer. There are several SBRT techniques. We aimed to compare three planning techniques: CyberKnife (CK), Helical Tomotherapy (HT), and Volumetric Modulated Arc Therapy (VMAT).*
Material and Methods: *This study included 15 patients with early-stagelung cancer who were treated in our clinic. For this study, the images obtained were recontoured and replanned in CK, HT, and VMAT. Treatment plans were compared in terms of target volume and organ-at-risk doses.*
Results: *The HT plan differed significantly from the other plans in terms of conformity (CI), and gradient indexes (GI) ($p<0.001$). There was a significant difference between the plans in terms of homogeneity indexes (HI)favoring HT ($p<0.001$). VMAT plan reduced the monitor unit per fraction and beam on time per fraction values ($p < 0.001$). The lowest lung V5 (22.7%, $p = 0.046$), D_{max}, and the dose of 5 cc of trachea (499.4 cGy vs 252.4 cGy; $p=0.017$, $p=0.034$) and esophagus (673.9 cGyvs237.3 cGy; $p=0.014$ and $p=0.08$) were observed with the VMAT plan.*
Conclusions: *All plans met the organ-at-risk dose constraints and target volume doseswith acceptable limits. Each clinic should select an appropriate technique based on the available resources and experience.*

Keywords*: Lung cancer, Stereotactic body radiotherapy, CyberKnife, Helical tomotherapy, Volumetric modulated arc therapy*

INTRODUCTION

Lung cancer is the leading cause of cancer-related death (18%) globally.[1] Currently, stereotactic body radiotherapy (SBRT) is the standard treatment methodfor medically inoperable early-stage lung cancers. High SBRT doses can be safely delivered with advanced techniques that provide high coherent target coverage and strict protectionof adjacent normal tissues, and organs. Lee et al. reported that these techniques provided better local control with higher biologically effective dose values .[2], Prospective multi-institutional trials using SBRT have demonstrated local control and overall survival rates of approximately 85% and 60%, respectively.[3-5] SBRT is a treatment option without compromising the patient'squality of life,atolerable toxicityprofile, and with ahigherlocal diseasecontrol rate (≥ 90%).[6] A study evaluated the cost-effectiveness of treatment modalities in patients with stage I non-small cell lung cancer (NSCLC) and revealed that SBRT was more cost-effective in marginally operable patients, whereas lobectomy was more cost-effective in clearly operable patients.[7]

CyberKnife (CK) is a robotic arm-mounted 6-MV linear accelerator image-guided radiotherapy system. Mobile tumorscan be treated using this systemwith sub-millimeter accuracy in freely breathing patients. Helical tomotherapy (HT) is a technology that delivers image-guided intensity-modulated radiotherapy (IMRT), and treatment plans are generated in the Tomotherapy Hi-Art© planning system using 6-MV photons. Volumetric modulated arc therapy (VMAT) is an arc-based therapy that is delivered by a conventional linear accelerator.

This study aimed to compare the dosimetric differences between SBRT plans delivered with CK, HT, and VMAT in terms of quality and planning rationality for patients with early-stage NSCLC.

MATERIAL AND METHODS

In this study, the treatment of 15 patients with peripherally located early-stage NSCLC who had previously undergone SBRT in our radiation oncology department was replanned using three treatment planning systems (CK, HT, and VMAT) based on the same planning tomography. Patients breathed freely and consistentlyduring the procedure. Treatment planning usingcomputed tomography (CT) with a four-dimensional technique and 1.5-mm slice thickness was obtained for the delineation of target volumes and organs-at-risk(OARs) using a multislice CT scanner (Philips Big Bore BrillianceCT scanner (**Philips** Medical Systems, Cleveland, OH, USA)). After CT scanning, the CT data were sorted into 10 breathing phases. The obtained CT dataset was sent to CK's planning system. All patients were treated with CK. These CT data were transferred to the HT and VMAT planningsystems.Hi-ART® 5.1.4version of HT was used. All target volumes and OARs were recontoured for each patient by the same radiation oncologist. Gross tumor volume (GTV) indicated the gross demonstrable extent and location of the tumordefined in radiological screenings..

All patients underwentpositron emission tomography (PET) CT before treatment, and GTV was contoured using PET CT fusions. Internal target volume (ITV) was defined for all patients using the sorted breathing phases on planning CT. Subsequently, for all plans,planning target volume (PTV) was generated with 5-mm margins fromall directions to ITV. The lungs, esophagus, rib, heart, proximal bronchial tree, trachea, great vessels, and spinal canal were all at risk. Radiotherapy plans in the planning systems were performed by a physicist who were familiar with the systems used in this study. Three plans were performed for each patient in CK, HT, and VMAT. The prescription dose was 50 Gy in 5 fractions. The PTV was optimized to cover at least 95% of the targetvolume with 100% of the prescription dose. Treatment plans were designed to meet Timmerman's normal tissue dose constraints.[8]

CK plans were generated using sequential optimization in Multiplan version 3.5. Two fixed circular collimators and two to three shell constraints were used for each plan. The 76% to 80% isodose line interval was prescribed for treatment doses. During treatment, the tumor was tracked using the Xsight Lung Tracking System (XLTS).

VMAT plans were generated using the Varian Eclipse version 11.4 treatment planning system, and dose calculation was performed using the AAA algorithm. All plans were based on two coplanar partial arcs with multileaf collimators. The optimization resolution was 2.5 mm in all cases.

All contours and CT images for HT were transferred to the tomotherapy planning station (Accuray, Sunnyvale, CA, USA). Then plans were generated, using a fixed jaw mode with a modulation factor of 2.0, a field width of 2.50 cm, and a pitch factor of 0.15–0.18 cm.

Planning target volume, organ-at-risk doses, and treatment plan quality were used to compare treatment plans. D2, D50, D98, D_{min}, D_{max}, and D_{mean}were calculated from the dose- volume histograms (DVHs) of all plans for the planning target volume(PTV). V5, V10, V20, and mean lung dose for the lung; the dose of 0.35 cc of spinal cord volume; $D_{max}$and the dose of 5 cc of esophagus volume for the esophagus; D_{max} and the dose of 15 cc of heart volume for the heart; D_{max} of great vessel volume; D_{max} and the dose of 5 cc for the trachea and proximal bronchial tree; D_{maxi} and the dose of 5 cc for the rib were analyzed. The conformity index (CI), dose homogeneity index (DHI), gradient index (GI), beam-ontime per fraction (BOT/fx), and monitor unit per fraction MU/fx were used to evaluate treatment plan quality.

The CI was calculated as follows:

$$CI = \frac{V_{Rx}}{TV_{Rx}},$$

whereTV_{RX} indicates tumor volume receiving theprescribed dose and V_{RX} indicates prescription isodose volume.

The new CI (nCI) was calculated as follows:

$$nCI = \frac{TV}{TV_{RX}} x \frac{V_{Rx}}{TV_{Rx}},$$

where TV indicates tumor volume (cc), TV_{RX} indicates tumor volume receiving theprescribed dose,

and V_{RX} indicates theprescription isodose volume. [9] The reference value of CI and nCI is accepted as 1.

The DHI was calculated to quantitatively evaluate dose heterogeneity in the target tumor using the following formula:

DHI= $\frac{D_{maximum}}{D_{prescribe}}$,

where D_{maxi} indicates maximum dose to the target volume and $D_{prescribe}$ indicates prescription dose to the target volume.[9]

The GI was calculated as follows:

GI = $\frac{V_{\%50Rx}}{V_{Rx}}$,

where $V_{\%50Rx}$ indicates 50% of prescription isodose volume and V_{RX} indicates prescription isodose volume.[10]

Statistical analysis

Statistical Package for Social Sciencesv 16(SPSS, SPSS Inc., Chicago, IL,USA) was used for statistical analyses. from the target perspective, percentage and mean ± standard deviation (mean ± *sd*) in the course from the study perspective. The Shapiro–Wilk test was used to test the fitness of the variables to normal distribution. The reconstruction of the two alignments was performed using analysis of foci under normal conditions and analysis of variance for normal alignments.*P*-values of < 0.05 were set as the level of statistical significance.

RESULTS

All 15patients with lung cancershad peripherally located tumorsincluding tumors on the right upper (n=6), right middle (n=3), and left upper (n=6) lobes The mean PTV was 41.8 ± 32.5 cc (min = 8.9, max = 124.5).All OARs with comparable target coverage dose limitations met the Radiation Therapy Oncology Group [11] and/or Timmerman protocol limits.[8]

Significant differences were observed between the plans in terms of PTV_{mini}*and* PTV D98 (P < 0.01),which may be due to the differencesbetween VMAT and other plans. Moreover, there were significant differences among all plans in terms of PTV_{mean}, PTV_{max}, and PTV D2(*P* < 0.01). There was a significant difference between the plans in terms of PTV D50 (*P* < 0.01). which stemmedfrom the difference between CK plan and the other two plans (Table 1).

Table 1:Comparisons among CK, HT, and VMAT plans in terms of PTV , and DVH parameters

	CK	HT	VMAT	*P*-value
	Mean ± SD	Mean ± SD	Mean ± SD	
PTV_{min} (cGy)	4792.1 ± 109.7[a]	4692.9 ± 179.1[a]	4407.5 ± 156.5[b]	**<0.001**[*]
PTV_{mean} (cGy)	5483.1 ± 89.0[a]	5128.2 ± 60.9[b]	5225.7 ± 31.8[c]	**<0.001**[*]
PTV_{max}(cGy)	6320.8 ± 130.7[a]	5285.1 ± 92.8[b]	5570.4 ± 101.7[c]	**<0.001**[**]
PTV D98(cGy)	4990.7 ± 76.7[a]	4948.9 ± 37.7[a]	4864.1 ± 65.4[b]	**<0.001**[*]
PTV D50(cGy)	5444.6 ± 92.7[a]	5169.3 ± 112.4[b]	5246.2 ± 23.6[b]	**<0.001**[**]
PTV D2(cGy)	6085.2 ± 124.3[a]	5232.8 ± 88.2[b]	5376.7 ± 53.6[c]	**<0.001**[**]

[*]One way analysis of variance, [**]Kruskal-Wallis analysis, [a,b,c] Statistically significant differences between the groups

Abbreviations: DVH: dose volume histogram, CK: CyberKnife, HT: Helical tomotherapy, VMAT: volumetric modulated arc therapy, PTV: planning target volume.

The HT plan differed significantly from the other plans in terms of CI, nCI, and GI ($P < 0.001$). There was a significant difference between the plans in terms of HI ($P < 0.001$). This difference resulted from the difference between the CK plan and other plans. There was a significant difference between all plans in terms of MU/fx and BOT/fx (min, $P < 0.001$) (Table 2).

Table 2: Dosimetric results of CI, nCI, HI, GI, MU/fx, and bot/fx

	CK	HT	VMAT	*P*-value*
	Mean ± SD	Mean ± SD	Mean ± SD	
CI	1.16 ± .04[a]	1.25 ± .08[b]	1.15 ± .15[a]	**<0.001**
nCI	1.18 ± .05[a]	1.33 ± .12[b]	1.15 ± .05[a]	**<0.001**
HI	1.27 ± .03[a]	1.07 ± .06[b]	1.11 ± .03[b]	**<0.001**
GI	4.64 ± .53[a]	6.35 ± 1.01[b]	5.00 ± .72[a]	**<0.001**
mu/fx (mu)	6625.1 ± 858.0[a]	10071.9 ± 1692.6[b]	3352.8 ± 618.0[c]	**<0.001**
bot/fx(min)	35.8 ± 3.9[a]	11.7 ± 1.9[b]	6.4 ± .6[c]	**<0.001**

*One way analysis of variance, **Kruskal-Wallis analysis, [a,b,c] Statistically significant differences between the groups

Abbreviations: CK: CyberKnife, HT: Helical tomotherapy, VMAT: volumetric modulated arc therapy, HI: homogeneity index, CI: conformity index, nCI: new conformity index, GI: gradient index, MU/fx: monitor unit per fraction, bot/fx: beam- ontime per fraction.

Significant differences were noted between CK and VMAT plansin terms of lung V5 ($P = 0.046$), trachea D_{max} ($p = 0.017$), trachea 5 ($P = 0.034$), and esophageal 5 ($P = 0.008$) There was a significant difference between the VMAT and other plansin terms of esophageal D_{max} ($P < 0.014$). (Table 3).

Table 3: Dosimetric comparisons for OARs

	CK	HT	VMAT	*P*-value*
	Mean ± SD	Mean ± SD	Mean ± SD	
Mean lungs-ptv (cGy)	410.6 ± 223.0	448.5 ± 168.7	307.5 ± 149.5	0.104**
Lung V 5 (%)	34.3 ± 16.3[a]	32.1 ± 12.2[a,b]	22.7 ± 9.8[b]	**0.046****
Lung V 10 (%)	20.4 ± 13.3	23.9 ± 9.8	16.6 ± 9.0	0.136
Lung V 20 (%)	20.9 ± 42.1	12.0 ± 6.3	8.3 ± 6.1	0.069
Spinal cord D 0.35 cc (cGy)	731.7 ± 507.1	598.0±468.2	700.7 ± 358.4	0.828
Heart D_{max} (cGy)	847.1 ± 711.4	976.1 ± 1283.6	731.1 ± 1193.3	0.242
Trachea D_{max} (cGy)	992.0 ± 534.5[a]	790.5 ± 456.7[a,b]	499.4 ± 340.4[b]	**0.017****
Trachea D 5 cc (cGy)	600.3 ± 480.5[a]	441.4 ± 336.8[a,b]	252.9 ± 165.2[b]	**0.034****
PBT D_{max} (cGy)	727.7 ± 952.6	905.5 ± 633.8	800.3 ± 934.2	0.283
Rib D_{maxi} (cGy)	4441.3 ± 1477.3	4918.5 ± 726.6	4858.3 ± 873.0	0.800
Rib D 5 cc (cGy)	2106.5 ± 1533.0	2361.9 ± 1316.2	2354.9 ± 896.7	0.824**
Esophagus D_{max} (cGy)	1005.3 ± 422.8[a]	998.6 ± 341.1[a]	673.9 ± 209.1[b]	**0.014****

Esophagus D 5 cc (cGy)	585.7 ± 360.8[a]	445.8 ± 255.5[a,b]	257.3 ± 171.5[b]	**0.008**[**]

[*]One way analysis of variance, [**]Kruskal-Wallis analysis, [a,b,c] Statistically significant differences between the groups

Abbreviations: OAR: organ at risk, PBT: proximal bronchial tree, CK: CyberKnife, HT: Helical tomotherapy, VMAT: volumetric modulated arc therapy

DISCUSSION

SBRT is a treatment option for medically inoperable lung cancer. Thanks to technological advancements, SBRT can be currentlyapplied in modern radiotherapy clinics. This study has focused on three different SBRT techniques to determine target volumes and critical organ doses.

Three different RT devices (CyberKnife®, Helical Tomotherapy®, and VMAT) were compared, and evaluated ina study regarding the efficacy and toxicity of lung SBRT techniques.[12]The citedstudy compared theCKresults of 111 patients, with those of other plans (HT and VMAT), and demonstrateddosimetric benefit of CKwith reduced mean lung dose (2.6 vs. 4.1 Gy, $P < 0.001$), V5 (13.5% vs. 19.9%, $P = 0.002$), and V20 (2.3% vs. 5.4%, $P < 0.001$). The above-mentionedstudy did not report a clear-cut criterion for preferring one technique over the other, and the obtained dosimetric parameters had no effect on toxicity.[12] Our study evauated all OARs and revealed statistically significant differences between SBRT techniquesconcerninglung V5, $D_{maxi}$and dose of 5 cc of the trachea and esophageal volume. VMAT plan had lower lung V5 (P=0.046), $D_{max}$and trachea V5 (P=0.017, P=0.034) and esophagus V5 (P=0.014, P=0.08). However, we did not evaluate theplansregardingtheir toxicity profiles in order to assess the effect of dosimetric advantage on toxicity. However, a more comprehensive study evaluating the effect of dosimetric data can be done.

Desphande et al. conducted a comparative study and revealed that VMAT delivered higher maximum doses to the GTV and PTV and lower lung V5 than other plans. CK plans had higher CI compared to VMAT plans (median: 1.19 vs. 1.10, $P < 0.00001$), but VMAT plans had higher HI than CK plans (median: 1.30 vs. 1.25, $P < 0.001$).[13] In contrast to these findings, we reported higher CIs and HIs in HT and CK plans.The CK and VMAT plans are more heterogeneous; therefore, the maximum dose and DHI tend to increase as the dose is trapped more effectively in the PTV.

There have been numerous dosimetric comparison studies based on CK and VMAT plans on lung SBRT. Shao et al. evaluated SBRT plans and compared CK and Eclipse plans for lung SBRTin terms of duration of treatment. They reported that MU/fx and BOT/fx values were statistically higher in VMAT plans. The BOT/fx for VMAT plans was 8 min shorter than that for CK plans ($t = 7.23$, $P = 0.000$).[14] Although in our study VMAT plans have been realized within a shorter treatment periodcompared toCK plans, it is not preferred in clinical practice because of the absence of a tumor tracking system on the linear accelerator. In our clinic CK is the first choice for SBRT, because CK has a real-time tumor tracking system.

Yu et al. compared treatment planning systems for lung SBRT using the CK Multiplan and Varian Eclipse treatment planning systems as well as VMAT and knowledge-based VMAT and revealed that CK plans showed the highest MUs ($P < 0.001$). HI was higher for CK plans than for other plans ($P = 0.003$ and $P = 0.006$). Conversely, OAR sparing was superior in VMAT than in CK plans.[15] Our results were consistent with this study.

CONCLUSION

In this study all three SBRT systems used for lung tumors yielded optimalresults. The OAR and target volume doses were comparable in all plans. When we compared these three planning methods, only lung V10 was significantly better than VMAT in OARs, but it remained within the range of dose constraints according to the guidelines for all plans. Since in our patients the tumors were located inthe periphery of the lungs, the OAR values were within the limits stipulated by the guidelines and did not differ significantly among all three plans. Thus, these techniques can be used safely. For the selection of SBRT technique, each clinic should consider dosimetric results and the available resources for lung SBRT. Since CK has a real- time tumor tracking system, in our clinic we prefer to

use CK as lung SBRT, and recommend that clinics with available sources should evaluate priorily use of CK for lung SBRT.

ETHICAL APPROVAL

The study was approved by the Ethical Committee of Dr Abdurrahman Yurtaslan Oncology Training and Research Hospital, Ankara, Turkey (approval number 2022-05/109) on May 26, 2022.

Consent
As per international standard or university standard, patient(s) written consent has been collected and preserved by the author(s).

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