Original Article

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Feasibility and Efficacy of Adaptive Intensity Modulated Radiotherapy Planning according to Tumor Volume Change in Early Stage Non-small Cell Lung Cancer with Stereotactic Body Radiotherapy

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The purpose of this study is to evaluate efficacy and feasibility of adaptive radiotherapy according to tumor volume change (TVC) in early stage non-small cell lung cancer (NSCLC) using stereotactic body radiotherapy (SBRT). Twenty-two lesions previously treated with SBRT were selected. SBRT was usually performed with a total dose of 48 Gy or 60 Gy in four fractions with an interval of three to four days between treatments. For evaluation of TVC, gross tumor volume (GTV) was contoured on each cone-beam computed tomography (CBCT) image used for image guidance. Intensity modulated radiotherapy (IMRT) planning was performed in the first CBCT (CBCT1) using a baseline plan. For ART planning (ART), re-optimization was performed at 2nd, 3rd, and 4th CBCTs (CBCT2, CBCT3, and CBCT4) using the same angle and constraint used for the baseline plan. The ART plan was compared with the non-ART plan, which generated copying of the baseline plan to other CBCTs. Average GTV volume was 10.7 cc. Average TVC was -1.5%, 7.3%, and -25.1% in CBCT2, CBCT3, and CBCT4 and the TVC after CBCT3 was significant ($p<0.05$). However, the nine lesions were increased GTV in CBCT2. In the ART plan, $V_{20\ Gy}$, $D_{1500\ cc}$, and $D_{1000\ cc}$ of lung were significantly decreased ($p<0.05$), and $V_{30\ Gy}$ and $V_{32\ Gy}$ of the chest wall were also decreased ($p<0.05$). While D min of planning target volume (PTV) decreased by 8.3% in the non-ART plan of CBCT2 compared with the baseline plan in lesions with increased tumor size ($p=0.021$), PTV coverage was not compromised in the ART plan. Based on this result, use of the ART plan may improve target coverage and OAR saving. Thus ART using CBCT should be considered in early stage NSCLC with SBRT.

Key Words: Stereotactic body radiotherapy, Lung cancer, Tumor volume, Adaptive planning

Introduction

The standard treatment for early stage non-small cell lung cancer (NSCLC) is lobar resection, however a portion of patients are medically inoperable. Stereotactic body radiotherapy (SBRT), with a 3-year local control rate of 80~90%, has been suggested as an alternative treatment option in these patients.[1,2] In recent series, the results of SBRT were comparable or better than those for sublobar resection.[3-5] Several studies reported that higher biologically equivalent dose was related to improved local control and survival.[6,7] However, large fraction size may increase the toxicities of organs at risk (OARs), including the lung,[8] chest wall[9,10] and large bronchus.[11] Therefore, a smaller margin around the tumor is warranted in order to reduce radiation-induced normal tissue toxicities.

In the course of SBRT, there are several uncertainties related to tumor geometry, motion and volume, hindering the reduction of the margin. For adjustment of tumor geometry and motion, an on board imager such as cone-beam computed tomography (CBCT) and 4-dimensional computed tomography are widely used. Tumor volume change (TVC) can be easily observed in CBCT images using image guidance. TVC during the course of radiotherapy in NSCLC is well established in the case of conventional radiotherapy.[12,13] TVC has also been reported even in SBRT despite its short overall treatment time.[14-18] However, the tumor volume could decrease or increase during the course

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of SBRT, while the tumor generally regresses during conventional radiotherapy. An increase in tumor volume might jeopardize the target coverage. A decrease in tumor volume might result in over-irradiation of the surrounding normal tissue, meaning that the margin should be reduced to decrease the dose of OARs.

Adaptive radiotherapy (ART) is defined as modifying the initial plan according to the change of the situation, such as tumor size and weight during the course of radiotherapy. A previous study reported that ART was useful in reducing the dose of OARs in the conventional radiotherapy for NSCLC.[19] Thus, we evaluated the TVC in the course of SBRT in patients with early-stage NSCLC and assessed the efficacy and feasibility of ART.

Materials and Methods

1. Patients

A total of 36 lesions in 34 patients treated with SBRT for early-stage NSCLC at Yeungnam University Medical Center were reviewed retrospectively. SBRT was usually performed with a total dose of 48 Gy to 60 Gy in four fractions with an interval of three to four days between treatments using Novalis TX (Varian Medical Systems Inc., Palo Alto, CA). CBCT was performed in each fraction for image guidance. Of these patients, those with an ill-defined tumor margin were excluded in order to reduce error in the analysis of the TVC. Thus, 22 lesions in 20 patients were selected for this study.

2. Contouring

Gross tumor volume (GTV) and OARs were delineated in four CBCT datasets per patient (CBCT1, CBCT2, CBCT3, and CBCT4, corresponding to first through fourth treatment) by an experienced radiation oncologist using Eclipse (Varian Medical Systems Inc., Palo Alto, CA). To reduce error, tumor was delineated under the same window width/level of -90/900 Hounsefield units. Planning target volume (PTV) was generated by addition of 3-mm margin to GTV. The chest wall and whole lung were delineated as OARs. The chest wall was delineated up to 1 cm superiorly and inferiorly from PTV.

3. Planning procedure

The rigid image registration was performed between CBCT1 and other CBCTs. A baseline intensity modulated radiotherapy (IMRT) plan was generated on CBCT1 with an analytic anisotropic algorithm. Dose prescription was normalized for 90% of PTV to receive 100% of a prescribed dose. Maximal point dose must be in PTV and not over 125% of a prescription dose. For generation of a non-adaptive plan, the baseline plan including MLC leaf motion, beam parameters and angles was copied to CBCT2, CBCT3, and CBCT4 with adjustment of the isocenter, and the dose distribution was calculated without optimization. The treatment isocenter was adjusted based on 3-dimensional registration data of each CBCT using the Varian offline review program (Varian Medical Systems Inc., Palo Alto, CA). For the adaptive plan, re-optimization was performed using the same beam angles and constraints of the baseline plan. The entire procedure is shown in Fig. 1.

4. Dosimetric parameters and statistical analysis

Differences in the GTV between CBCT1 and other CBCT datasets were evaluated using both absolute and relative values. Dosimetric parameters of PTV and OARs were compared between non-adaptive and adaptive plans. Minimum dose (D_{min}), mean dose (D_{mean}), maximum dose (D_{max}) and $V_{95\%}$ (volume receiving at least 95% of the prescription dose) were analyzed for PTV coverage. In terms of normal organ sparing, the following dosimetric parameters used in the study of RTOG 0915 were compared: $V_{20\ Gy}$ (volume receiving at least 20 Gy), $D_{1000\ cc}$ (dose to 1000 cc of target volume), and $D_{1500\ cc}$ of the lung; $V_{30\ Gy}$, $V_{32\ Gy}$, and $D_{30\ cc}$ of the chest wall. Because the range of CBCT scan was limited, all volume parameters were described in absolute value (cc). Paired T-test was used for comparison of the GTV volume and dosimetric parameters using SPSS version 21.0 (IBM, Armonk, NY). A p-value of less than 0.05 was considered significant.

Results

The locations of lesions were right upper lobe in 10 patients, right middle lobe in 1, right lower lobe in 6, left upper lobe in 3, and left lower lobe in 2. The histologic types were adenocarcinoma in 11 lesions and squamous cell carcinoma in 8. Biopsy was not performed on three lesions because of severe comorbidity. The average volume of GTV in CBCT1 was 10.7 cm^3 (range: 1.9 to 51.5 cm^3). All patients were treated in four

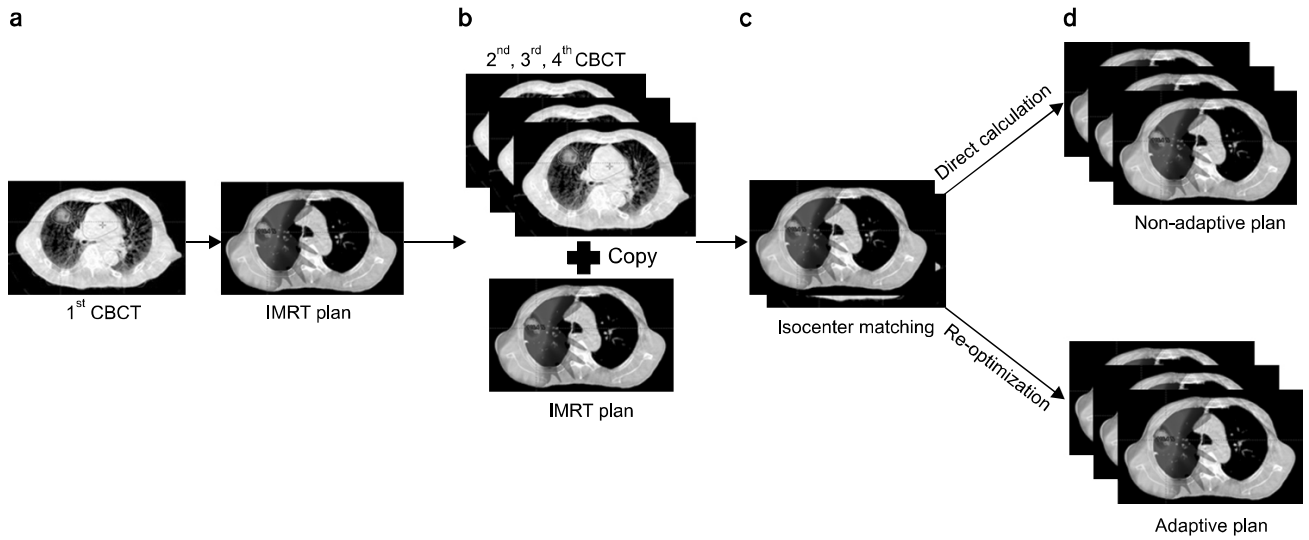

Fig. 1. Schematics of the planning procedure. (a) The intensity modulated radiotherapy (IMRT) plan was performed in 1st CBCT (baseline plan). (b) The beam angle and MLC motion of baseline plan was copied to other CBCTs. (c) The treatment isocenter was adjusted based on 3-dimensional registration data of each CBCT using the Varian offline review program (Varian Medical Systems Inc., Palo Alto, CA). (d) Non-adaptive plans were generated by direct calculation. Adaptive plans were generated by re-optimization process.

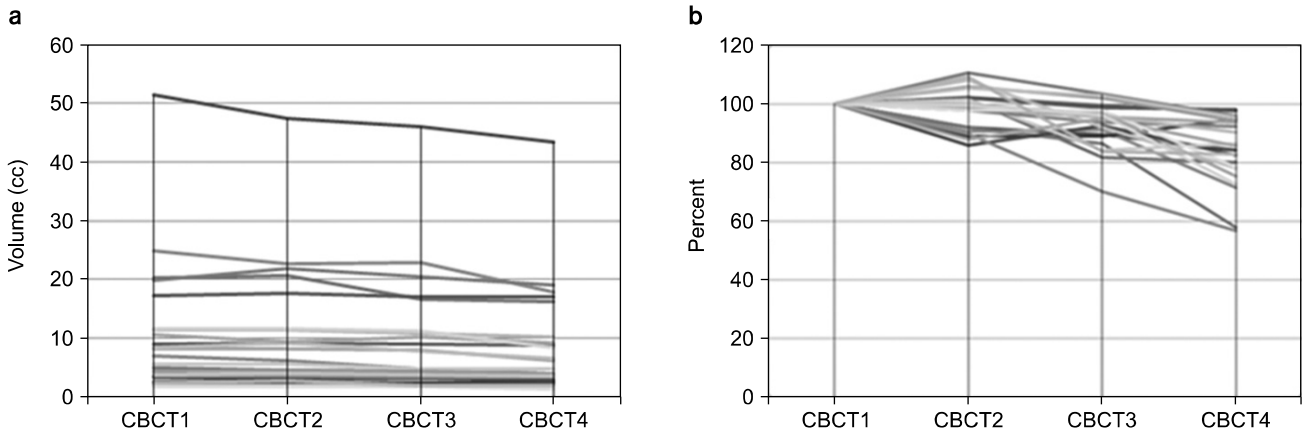

Fig. 2. The absolute and relative volume of GTV in all studied patients. (a) absolute GTV. (b) relative GTV.

fractions with the following fraction sizes: 12 Gy in 11 patients, 13 Gy in 1, and 15 Gy in 12.

1. Tumor volume change

Changes of GTV are shown in Fig. 2 and Table 1. TVC was not statistically significant in all patients in CBCT2, but the GTV was increased in nine lesions. However, the GTV was significantly smaller in CBCT3 (92.7%) and CBCT4 (83.9%) than in CBCT1. Fig. 3 shows the gradual decrease of the GTV volume.

Fig. 4 shows the change of GTV according to fraction size. Lesions treated with 15 Gy per fraction tended to increase in CBCT2 and their volume in CBCT2 was significantly larger than the volume of tumors treated with less than 15 Gy per fraction (p=0.005).

2. Dosimetric comparison between non-ART versus ART

Dosimetric parameters are summarized in Table 2. In the

Table 1. Absolute and relative volume of GTV in the course of stereotactic body radiotherapy.

Group		CBCT1	CBCT2	CBCT3	CBCT4
Absolute volume (cc)					
All	Mean (SD)	10.7 (11.2)	10.6 (10.6)	9.9 (10.2)	8.9 (9.5)
	p-value*	-	0.341	0.012	0.001
<60 Gy	Mean (SD)	10.8 (14.3)	10.1 (13.2)	9.8 (12.9)	9.0 (12.3)
	p-value*	-	0.124	0.089	0.031
60 Gy	Mean (SD)	10.6 (7.8)	10.7 (7.6)	9.9 (7.2)	8.9 (6.2)
	p-value*	-	0.664	0.08	0.025
Relative volume (%)					
All	Mean (SD)	100 (0)	98.5 (7.2)	92.7 (7.9)	83.9 (11.9)
	p-value*	-	0.346	<0.001	<0.001
<60 Gy	Mean (SD)	100 (0)	94.5 (6.3)	92.1 (8.6)	81.8 (14.3)
	p-value*	-	0.016	0.012	0.002
60 Gy	Mean (SD)	100 (0)	102.6 (5.8)	93.4 (7.4)	86.1 (9.0)
	p-value*	-	0.173	0.015	<0.001

*p-value was the result of independent T test compared between the first CBCT and other CBCTs. CBCT: cone beam computed tomography, SD: standard deviation.

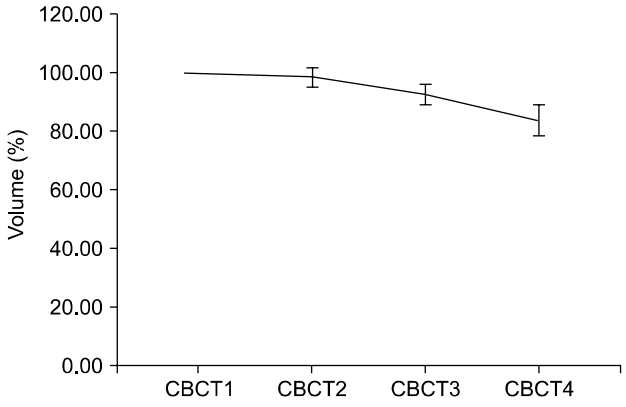

Fig. 3. The gradual decrease of the average GTV volume.

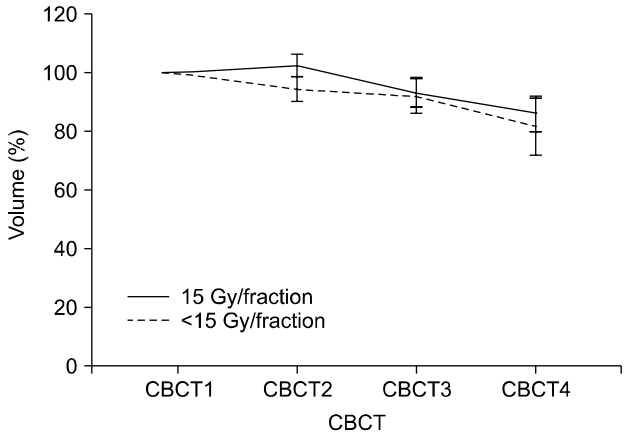

Fig. 4. Differences of GTV change according to dose schedule. GTV in lesions treated with 15 Gy per fraction was significantly larger than the volume of tumors treated with less than 15 Gy per fraction (p=0.005).

adaptive plan, there was a significant decrease in $V_{20\ Gy}$, $D_{1500\ cc}$, and $D_{1000\ cc}$ of the lung, and $V_{30\ Gy}$ and $V_{32\ Gy}$ of the chest wall ($p<0.05$). In peripheral tumors within 2 cm from the chest wall, $V_{30\ Gy}$ and $V_{32\ Gy}$ decreased by approximately 1.0 and 1.6 cc.

The coverage of PTV in CBCT2 was evaluated in the lesions that grew in CBCT2 (Table 3 and Fig. 5). D_{min} was decreased by approximately 8.3% in non-ART. However PTV coverage was not compromised compared with the initial plan in the ART plan.

Discussion

Our study showed a significant change of tumor volume during the course of SBRT. The tumor volume was usually reduced except on the second treatment day. Despite a short treatment time, tumor regression during the course of SBRT has been reported. Yi et al.[18] reported that mean overall reduction was 21.1% during the course of SBRT with three to five fractions over two weeks. In addition, increase of the tumor volume at a certain time during the course of SBRT has been reported, whereas the tumor volume decreased in the conventional fractionation.[12,13,20-22] In our study nine lesions showed increased tumor volume at the second CBCT. Saito et al.[16] re-

Table 2. Dosimetric parameters comparing non-adaptive versus adaptive plan.

Parameter	Non-adaptive		Adaptive		p-value
	Mean (SD)	Range	Mean (SD)	Range	
All patients (n=21)					
$V_{20\ Gy}$_lung (cc)	131.1 (68.2)	23.6～337.7	122.9 (63.1)	22.1～301.6	0.003
$D_{1500\ cc}$_lung (cGy)*	65.0 (72.2)	5.5～261.4	59.9 (65.8)	6.2～223.7	0.019
$D_{1000\ cc}$_lung (cGy)	158.9 (160.3)	17.6～696.5	148.7 (150.6)	17.2～548.3	0.013
$V_{30\ Gy}$_chest wall (cc)	11.5 (9.3)	0～32.8	10.6 (9.3)	0～33.9	0.001
$V_{32\ Gy}$_chest wall (cc)	9.0 (7.8)	0～25.8	7.9 (7.9)	0～25.7	0.020
$D_{30\ cc}$_chest wall (Gy)	20.6 (5.3)	10.5～30.2	20.2 (5.8)	10.0～31.1	0.328
Peripheral tumor (n=14)					
$V_{30\ Gy}$_chest wall (cc)	16.5 (7.7)	7.8～32.8	15.5 (8.0)	6.7～33.9	0.013
$V_{32\ Gy}$_chest wall (cc)	13.5 (6.0)	6.4～25.8	11.9 (7.2)	0.0～26.6	0.035
$D_{30\ cc}$_chest wall (Gy)	21.0 (6.4)	10.5～30.2	20.9 (7.1)	10.0～31.1	0.725

*2 cases were excluded from analysis because lung volume in the range of CBCT scan was not sufficient for analysis of D1500 cc.

Table 3. Comparisons of PTV coverage of non-adaptive and adaptive plans in CBCT2 compared with CBCT1.

	Baseline (CBCT1)	Non-adaptive (CBCT2)		Adaptive (CBCT2)	
	Mean (SD)	Mean (SD)	p-value	Mean (SD)	p-value
D_{min} (%)	88.7 (3.2)	80.4 (10.9)	0.021	87.1 (4.7)	0.172
D_{mean} (%)	107.7 (0.9)	108.9 (1.7)	0.062	107.7 (1.0)	0.858
D_{max} (%)	120.6 (2.9)	121.1 (3.9)	0.261	119.0 (2.3)	0.018
$V_{85\%}$ (%)	100.0 (0.0)	99.5 (1.1)	0.245	100.0 (0.2)	0.171
$V_{90\%}$ (%)	99.9 (0.15)	99.0 (1.9)	0.167	99.8 (0.2)	0.150
$V_{95\%}$ (%)	98.2 (1.0)	97.3 (2.9)	0.354	98.2 (0.6)	0.068
$V_{100\%}$ (%)	90.0 (0.0)	90.6 (4.3)	0.706	90.0 (0.0)	0.992
$V_{110\%}$ (%)	36.5 (8.4)	46.6 (11.5)	<0.001	36.8 (13.6)	0.895

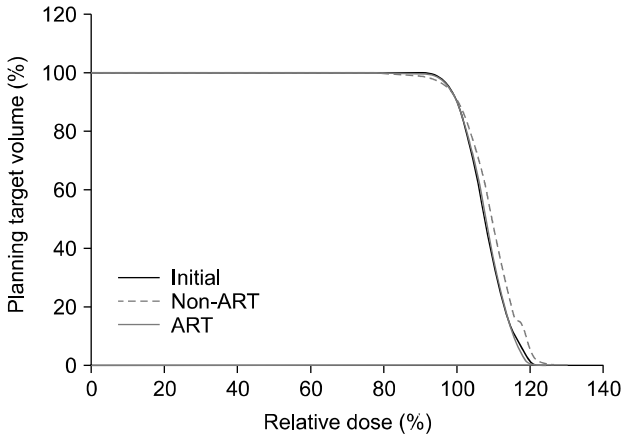

Fig. 5. The dose-volume histogram of PTV coverage on the baseline plan in CBCT1, non-adaptive plan and adaptive plan of CBCT2. While D_{min} was decreased by approximately 8.3% in non-ART ($p<0.021$), PTV coverage was not compromised compared with the initial plan in the ART plan.

ported that the median tumor size was larger on the third treatment day compared to the first day with a median enlargement of 1.53 cm^3 during the course of SBRT of 48 Gy over four consecutive days. Gunter at al,[15] who studied TVC in 25 NSCLC with SBRT during the course of SBRT of 50 Gy divided into 5 fractions, reported that the GTV of 4 lesions had increased on the second treatment day. Tatekawa at al.[17] reported that volume expansion of over 10% was observed in 32% of patients on the third treatment day with 48 Gy for T1 tumors and 52 Gy for T2 tumors divided into 4 fractions over a two-week schedule. This temporary increase of the tumor volume could be explained by the fact that tumor volume may increase due to edema induced by large fraction size and subsequently decreased by early response.

The factor of GTV enlargement was studied. Our study showed that tumor size of the 15 Gy fraction size group with

larger fraction size was more frequently increased compared with the <15 Gy group. The pain flare phenomenon in radiotherapy might explain this finding. The pain flare may be caused tumoral edema[23] and the incidence increased in spine SBRT with higher fraction size.[24]

Our study showed that PTV coverage was decreased with increasing tumor size. Dmin was significantly reduced by approximately 8.3%. Shirata et al.[25] reported that minimal dose could affect local control in stage I NSCLC with SBRT. The 3-year local control rates were 100% in patients with D_{min} for PTV of more than 89.88% versus 79.2% in those with dose for PTV less than 89.88%. However, the impact of the temporary increase of tumor volume on local control is uncertain.

When tumor size decreases, ART could be useful for decreasing the dose of OARs. Chest wall toxicity was significantly related to dose-volume parameters[9,10] and in our study, $V_{30\ Gy}$ and $V_{32\ Gy}$ of the chest wall were significantly reduced in the adaptive plan. Bhatt et al.[14] reported that the doses of the chest wall and left ventricle were reduced in adaptive plans compared with initial plans. And, in our study, $V_{20\ Gy}$, $D_{1500\ cc}$, and $D_{1000\ cc}$ of the lung, which are related to lung toxicity, were also significantly decreased in the adaptive plan. Barriger et al.[26] reported that radiation pneumonitis of grade 3 or more was observed in 4.3% of patients with $V_{20\ Gy}$ of less than 4% compared with 16.4% of patients with $V_{20\ Gy}$ of >4% (p=0.03).

There are several concerns regarding use of the adaptive plan using CBCT. The first is dosimetric feasibility of planning using CBCT images. Yoo et al.[27] reported that dosimetric error of the CBCT-based plan was only up to 3% compared to the CT-based plan with an inhomogenous phantom. Yang et al.[28] also concluded that CBCT-based dose calculation was acceptable in prostate cases. Therefore, adaptive planning using CBCT appears to be acceptable. The second is the contouring error. Altojai et al.[29] reported an interobserver reliability coefficient of 0.97 in CBCT contouring for early-stage NSCLC and concluded that CBCT imaging is an effective tool for target volume delineation. Finally, adaptive target delineation based on tumor regression could cause under-dose in the microscopic disease. However, Gukenberger et al.[30] reported that ART did not compromise dose coverage in the microscopic disease.

Conclusion

Our results showed significant change in tumor volume during the course of SBRT. Gradual regression of the tumor volume was also observed during the course of SBRT, except on the second treatment day in some tumors treated with 15 Gy per fraction. Increased tumor size may compromise minimum dose of PTV in the non-ART plan. When applying the adaptive plan, doses of OARs such as the chest wall and lung were significantly decreased. Thus, ART should be considered in early-stage NSCLC treated with SBRT.

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폐암의 정위적체부방사선치료에서 육안적종양체적 변화에 따른 적응방사선치료의 효용성 및 가능성 연구

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이 연구는 조기 폐암의 정위방사선치료에서 육안적종양체적(Gross tumor volume, GTV) 변화에 따른 적응방사선치료(ART)의 효과 및 가능성을 보기 위해 시행되었다. 영남대학교 의료원에서 정위방사선치료를 시행한 22개의 종양을 대상으로 연구를 진행하였다. 정위방사선치료는 2주에 걸쳐 48 혹은 60 Gy를 4회에 나누어 조사하는 방법으로 시행되었다. 종양체적 변화를 측정하기 위해 매 콘빔시티마다 육안적종양체적에 대한 윤곽선 그리기를 시행하였다. 그 다음 첫 번째 콘빔시티에 기준 치료계획으로 사용할 세기조절방사선치료 계획을 시행하였다. 적응방사선치료 계획을 하기 위해, 2, 3, 4번째 콘빔시티에 기준 치료계획과 동일한 빔 각도와 제약을 적용하여 각각 재 최적화 과정을 진행하였다. 이후 적응방사선치료 계획은 기준치료계획을 각각의 콘빔시티에 복사하여 생성한 비적응방사선치료 계획과 비교되었다. 평균 육안적종양체적은 10.7 cc였다. 평균 종양체적 변화는 두 번째, 세 번째, 네 번째 콘빔시티에서 각각 −1.5%, 7.3%, 25.1%였으며 세 번째 이후 변화는 통계적으로 유의하였다($p<0.05$). 하지만 두 번째 콘빔시티에서는 9개의 종양 체적이 증가하였다. 적응방사선치료 계획을 시행하였을 때, 폐에서 $V_{20\ Gy}$, $D_{1500\ cc}$, $D_{1000\ cc}$가 유의하게 감소하였으며, 흉벽에 대한 $V_{30\ Gy}$와 $V_{32\ Gy}$ 역시 유의하게 감소하였다($p<0.05$). 두 번째 콘빔시티의 종양체적이 증가한 환자들에서, 기준치료 계획에 비해 적응치료방사선치료 계획을 시행하지 않았을 때, 계획용 표적체적에 대한 선량 범위 변수 중 D_{min}은 8.3% 감소한 반면($p=0.021$), 적응방사선치료계획을 시행한 경우에는 차이가 없었다. 이러한 결과를 보았을 때, 적응방사선치료 계획을 함으로서 표적 선량 커버는 개선시키면서 손상위험장기에 대한 선량을 감소시킬 수 있을 것이다. 그러므로, 콘빔시티를 이용한 적응방사선치료 방법은 조기 폐암의 정위방사선치료에서 고려되어야 하겠다.

중심단어: 정위방사선치료, 폐암, 종양체적, 적응방사선치료계획