RESEARCH ARTICLE

Clinical Outcome of Helical Tomotherapy for Inoperable Non-Small Cell Lung Cancer: The Kyung Hee University Medical Center Experience

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Abstract

<u>Background</u>: Published studies on clinical outcome of helical tomotherapy for lung cancer are limited. The purpose of this study was to evaluate clinical outcomes and treatment-related toxicity in inoperable non-small cell lung cancer (NSCLC) patients treated with helical tomotherapy in Korea. <u>Materials and Methods</u>: Twenty-seven patients with NSCLC were included in this retrospective study. Radiotherapy was performed using helical tomotherapy with a daily dose of 2.1-3 Gy delivered at 5 fractions per week resulting in a total dose of 62.5-69.3 Gy. We assessed radiation-related lung and esophageal toxicity, and analyzed overall survival, locoregional recurrence-free survival, distant metastasis-free survival, and prognostic factors for overall survival. <u>Results</u>: The median follow-up period was 28.9 months (range, 10.1-69.4). The median overall survival time was 28.9 months, and 1-, 2-, and 3-year overall survival rates were 96.2%, 92.0%, and 60.0%. The median locoregional recurrence-free survival time was 24.3 months, and 1-, 2-, and 3-year locoregional recurrence-free survival rates were 85.2%, 64.5%, and 50.3%. The median distant metastasis-free survival time was 26.7 months, and 1-, 2-, and 3-year distant metastasis-free survival rates were 92.3%, 83.9%, and 65.3%, respectively. Gross tumor volume was the most significant prognostic factor for overall survival. No grade 4 or more toxicity was observed. <u>Conclusions</u>: Helical tomotherapy in patients with inoperable NSCLC resulted in high survival rates with an acceptable level of toxicity, suggesting it is an effective treatment option in patients with medically inoperable NSCLC.

Keywords: Helical tomotherapy - lung cancer - clinical outcome - Korea

Introduction

Radiotherapy (RT) is the standard treatment for medically inoperable or locally advanced non-small cell lung cancer (NSCLC). Several studies have shown that RT dose escalation improves locoregional control in NSCLC (Mehta et al., 2001, Rengan et al., 2004, Bradley et al., 2005, Rosenzweig et al., 2005, Ding et al., 2012, Lee et al., 2013, Liu et al., 2013, Zheng et al., 2013). Recently, intensity-modulated RT has been proposed as an effective modality to facilitate dose escalation to target volumes while sparing normal surrounding tissues. Many planning studies demonstrated the theoretical dosimetric advantages of intensity-modulated RT over 3-dimensional conformal RT (Grills et al., 2003, Liu et al., 2004, Murshed et al., 2004, Wu et al., 2004, Chang et al., 2005, Schwarz et al., 2005, Christian et al., 2007). However, few published studies have reported the clinical outcome of intensity-modulated RT in NSCLC (Sura et al., 2008, Liao et al., 2010, Govaert et al., 2012, Jiang et al., 2012).

In 2008, the Kyung Hee University Medical Center started treating patients with medically inoperable or locally advanced NSCLC with helical tomotherapy. Helical tomotherapy employs helical intensity-modulated RT in which a 6-megavoltage (MV) linear accelerator gantry rotates continuously 360° around the patient using tens of thousands of narrow beamlets (Mackie et al., 1993). While some planning studies reported dosimetric advantages of helical tomotherapy planning in lung cancer (Scrimger et al., 2003, Kron et al., 2004, Cattaneo et al., 2008), there are no published studies reporting the clinical outcome of helical tomotherapy in lung cancer. Here, we report the results of our retrospective study in which we evaluated the clinical outcomes and treatment-related toxicities in inoperable NSCLC patients treated with helical tomotherapy.

Materials and Methods

Patient eligibility criteria included the presence of pathologically confirmed inoperable NSCLC, receipt of definitive helical tomotherapy with or without

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chemotherapy, receipt of total RT dose ≥60 Gy, no prior history of thoracic RT and thoracic cancer, no other simultaneous cancer, no distant metastasis, and available follow-up data. From January 2008-January 2013, 57 patients received thoracic helical tomotherapy at Kyung Hee University Medical Center. Of those patients, 27 met the eligibility criteria and were included in this study.

Each patient underwent basic laboratory studies, liver function test, pulmonary function test, chest radiograph, chest computed tomography (CT), brain magnetic resonance imaging, and most patients also had whole-body positron emission tomography (PET). The cancer stage of each patient was assigned based on the American Joint Committee on Cancer (AJCC) staging system (7th edition). For all patients, we retrospectively reviewed hospital records, laboratory results, imaging studies, and extracted dose-volume histogram (DVH) data from computerized treatment planning records. The institutional review board of Kyung Hee University Medical Center approved this study, and all research was carried out in compliance with the Helsinki Declaration.

For CT simulation, all patients were immobilized in the supine position with arms above their head using posterior vacuum bags and anterior vacuum-sealed cover sheets (BodyFix, Medical Intelligence Medizintechnik GmBH, Schwabmünchen, Germany). To reduce movement of the lung by respiration, all patients were instructed to take shallow breaths. All patients received intravenous contrast agents, and axial CT images were acquired with 3-mm slice thickness. The simulation CT data were transferred to the Hi·Art Planning Station (TomoTherapy Inc., Madison, WI) for inverse planning.

The gross tumor volume (GTV) was delineated according to all detectable tumors and involved lymph nodes as determined from chest CT and PET information. Subsequently, a 6-8 mm margin was added to create the clinical target volume (CTV), and the planning target volume (PTV) was created by adding an additional 8-15 mm margin to the CTV, taking into account the target movement by respiration. Elective nodal irradiation was not performed. Normal structures were also delineated. The ipsilateral and contralateral lungs were delineated separately to attempt to constrain the radiation dose to the contralateral lung. The spinal cord, heart, and esophagus were also delineated.

The prescription dose was decided by the physician's own judgment according to PTV and patients' general condition. A daily dose of 2.1-3 Gy was delivered at 5 fractions per week, resulting in a total dose of 62.5-69.3 Gy. The most commonly prescribed (22 patients, 81.5%) dose fractionation schedules were a total dose of 63-66 Gy with a daily dose of 2.1-2.2 Gy.

We evaluated each treatment plan using a DVH and visually inspecting isodose curves. In general, we considered plans acceptable if the PTV was covered by 95% isodose curves, inhomogeneity of the PTV ranged from 95%-107%, and doses to normal structures were limited in their tolerances. Dose tolerances for normal structures were total lung $V20<40\%$, mean lung dose <20 Gy, maximum dose to spinal cord <45 Gy, heart $V40<50\%$, and esophagus $V55<30\%$. The

planners generally attempted to keep radiation doses to the contralateral lung low, although formal dosimetric constraints were not applied to this structure. Planning objectives were prioritized to give the greatest importance to achieving coverage of the PTV and avoiding spinal cord and normal lung, while trying to keep radiation doses in other normal structures as low as possible.

RT was performed using a TomoTherapy (TomoTherapy Inc., Madison, WI). Triangulation marks were used to make sure the patient did not roll and to quickly position the patient into the correct location. Before each treatment, a 3.5-MV fan beam CT image was acquired using a CT detector mounted on a ring gantry and matched to the planning CT image for comparison. Then, if necessary, the patient position was corrected. The implementation of chemotherapy was individualized based on tumor clinical stage, patient general condition and compliance.

Patients were evaluated with weekly chest radiographs during RT. Follow-up visits were scheduled 1 month after completion of RT and every 2-3 months thereafter. Visits were more frequent for those who experienced severe treatment-related complications or disease progression. At the time of follow-up visits, basic laboratory studies, liver function tests, chest radiographs, and chest CT scans were conducted. When needed, PET was also performed.

We assessed the radiation-related lung and esophageal toxicities according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The worst toxicity grade scored at any time was considered the final grade of toxicity. Because radiation-related toxicities could present during treatment, the time to toxicity was calculated from the date of RT start.

For the purposes of this study, local recurrence was defined as tumor progression within the high-dose radiation treatment volume (PTV). Actuarial survival rates were estimated using the Kaplan-Meier method, and comparisons among groups were performed using log-rank tests. Overall survival time and time to locoregional recurrence and distant metastasis were calculated from the date of NSCLC diagnosis. Parameters evaluated as potential prognostic factors for overall survival were age, gender, tumor histology, AJCC stage, GTV, total RT dose, RT interruption, and chemotherapy. For multivariate analysis, the Cox proportional regression hazard model was used. For all analyses, a p value <0.05 was considered statistically significant. All analyses were performed using SPSS version 18.0 (SPCC Inc., Chicago, IL).

Results

Patient characteristics

Patient and tumor characteristics are summarized in Table 1. Fourteen patients (51.9%) were stage I/II and 13 patients (48.1%) were stage IIIA/IIIB. Eight patients (29.6%) had underlying chronic obstructive pulmonary disease, 12 patients (44.4%) had hypertension, 10 patients (37.0%) had diabetes mellitus, and 4 patients (14.8%) had ischemic heart disease. The median PTV was 176.32 cc (range, 30.79-851.23). Twelve patients (44.4%) received chemotherapy, and the most common chemotherapy regimen was carboplatin plus paclitaxel (10 patients).

Eight patients (29.6%) experienced temporary RT interruption due to RT or chemotherapy-related toxicities, and the median duration of RT interruption was 3 days (range, 1-12). The median follow-up period was 28.9 months (range, 10.1-69.4) for all 27 patients and 38.1 months (range, 10.1-69.4) for the surviving patients.

Treatment outcome

Eighteen patients (66.7%) survived during the follow-up period. The median overall survival time was 28.9 months, and 1-, 2-, and 3-year overall survival rates were 96.2%, 92.0%, and 60.0%, respectively. Locoregional recurrence developed in 14 patients (51.9%). The median locoregional recurrence-free survival time was 24.3 months, and 1-, 2-, and 3-year locoregional recurrence-free survival rates were 85.2%, 64.5%, and 50.3%, respectively. Of the 14 patients who developed locoregional recurrence, 7 patients experienced local recurrence (recurrence within the high-dose radiation treatment volume). Distant metastasis developed in 8 patients (29.6%). Distant metastatic sites were contralateral lung in 2 patients, brain in 2 patients, contralateral lung and brain in 1 patient, contralateral lung and bone in 1 patient, bone in 1 patient, and liver in 1 patient. The median distant metastasis-free survival time was 26.7 months, and 1-, 2-, and 3-year distant metastasis-free survival rates were 92.3%, 83.9%, and 65.3%, respectively (Figure 1). Treatment outcomes were also analyzed according to clinical stages (stage I/II vs IIIA/IIIB), and summarized in Table 2.

Prognostic factors for overall survival were analyzed.

In univariate analysis, GTV (p=0.011) and RT interruption (p=0.040) were significantly associated with overall survival. In multivariate analysis, GTV remained a significant prognostic factor for overall survival (hazard ratio, 9.187; 95% confidence interval, 1.369-61.638; p=0.022) (Table 3, Figure 2).

Toxicities

Table 4 summarizes the radiation-related lung and
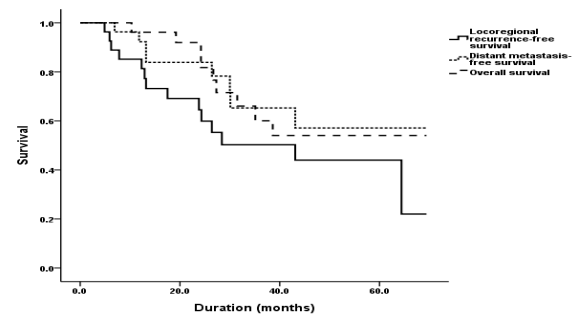
Figure 1. Locoregional Recurrence-free Survival, Distant Metastasis-free Survival, and Overall Survival Curves for 27 Non-Small Cell Lung Cancer Patients Treated with Helical Tomotherapy

Table 2. Treatment Outcomes of All Patients, Patients with Stage I/II Disease, and Patients with Stage IIIA/IIIB Disease

		All (27 patients)	Stage I/II (14 patients)	Stage IIIA/IIIB (13 patients)
OS (%)	1-year	96.2	92.3	92.3
	2-year	92	92.3	80.8
	3-year	60	73.8	43.3
LRFS (%)	1-year	85.2	85.7	84.6
	2-year	64.5	69.3	61.5
	3-year	50.3	51.9	49.2
DMFS (%)	1-year	92.3	88.9	84.6
	2-year	83.9	88.9	69.2
	3-year	65.3	66.7	69.2

*OS, overall survival; LRFS, locoregional recurrence-free survival; DMFS, distant metastasis-free survival

Table 3. Analysis of Prognostic Factors for Overall Survival

Variables	3-year overall survival (%)	Univariate	Multivariate
Age (years)			
≤70 vs >70	75.0 vs 53.6	0.886	0.673
Gender			
Male vs female	53.2 vs 80.0	0.189	0.317
Histology			
SqCC vs Adenocarcinoma	65.0 vs 54.7	0.936	0.385
Clinical stage			
I/II vs. IIIA/IIIB	73.8 vs 43.3	0.279	0.052
GTV (cc)			
≤15 vs >15	81.8 vs 32.2	0.011	0.022
Total RT dose (BED, Gy_{10})			
≤80.25 vs >80.25	33.3 vs 71.5	0.239	0.523
RT interruption			
Yes vs no	29.2 vs 68.4	0.040	0.149
Chemotherapy			
RT+CTx vs RT alone	66.7 vs 56.3	0.482	0.682

SqCC, squamous cell carcinoma; GTV, gross tumor volume; RT, radiotherapy; BED, biologically equivalent dose; CTx, chemotherapy

Table 1. Patient and Tumor Characteristics

Age (years)	Median 73.7	(range, 51.4-85.1)
Gender	Male	21 (77.8%)
	Female	6 (22.2%)
Smoking history	Never	5 (18.5%)
	Former	8 (29.6%)
	Current	14 (51.9%)
Underlying lung disease	Yes	8 (29.6%)
	No	19 (70.4%)
ECOG performance status	0	5 (18.5%)
	1	17 (63.0%)
	2	5 (18.5%)
Tumor location	Right	11 (40.7%)
	Left	16 (59.3%)
	Upper	19 (70.4%)
	Middle or lower	8 (29.6%)
Clinical stage	I	5 (18.6%)
	II	9 (33.3%)
	III	13 (48.1%)
Pre-RT FEV1 (L)	Median 2.18	(range, 0.55-3.54)
Histology	SqCC	17 (63.0%)
	Adenocaricnoma	10 (27.0%)
GTV (cc)	Median 15.29	(range, 3.85-215.63)
Total RT dose (Gy)	Median 66	(range, 60.0-69.3)
Daily RT dose (Gy)	Median 2.2	(range, 2.1-3.0)
Chemotherapy	Induction	1 (3.7%)
	Induction+concurrent	2 (7.4%)
	Induction+adjuvant	1 (3.7%)
	Concurrent	5 (18.5%)
	Concurrent+adjuvant	1 (3.7%)
	Adjuvant	2 (7.4%)
	RT alone	15 (55.6%)

*ECOG, Eastern Cooperative Oncology Group; RT, radiotherapy; FEV1, forced expiratory volume in 1 second; SqCC, squamous cell carcinoma; GTV, gross tumor volume

Table 4. Incidence of Radiation-Related Pulmonary and Esophageal Toxicities in All Patients

Toxicity grade	Acute pulmonary toxicity (pneumonitis)	Acute esophageal toxicity (esophagitis)	Late pulmonary toxicity (pulmonary fibrosis)	Late esophageal toxicity (esophageal stricture)
0	5/27 (18.5%)	19/27 (70.4%)	6/27 (22.2%)	26/27 (96.3%)
1	7/27 (25.9%)	1/27 (3.7%)	14/27 (51.9%)	0
2	14/27 (51.9%)	7/27 (25.9%)	6/27 (22.2%)	0
3	1/27 (3.7%)	0	1/27 (3.7%)	1/27 (3.7%)
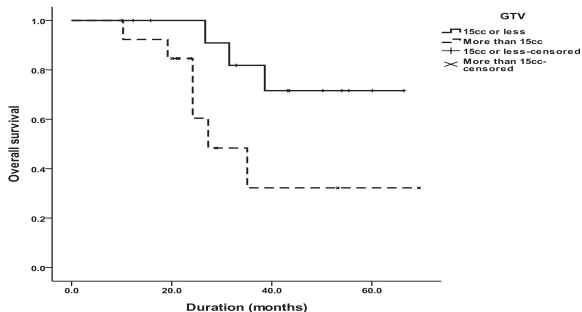
Figure 2. Overall Survival According to Gross Tumor Volume (GTV). The 36-month overall survival rates were 81.8% if GTV ≤15 cc and 32.2% if GTV >15 cc (p=0.011)

esophageal toxicities. We did not observe any grade 4 toxicity and no patients died of radiation-related toxicity. The median duration from the date of RT start to the development of toxicities was 3.2 months (range, 2.1-4.7) for pneumonitis, 1.2 months (range, 0.5-1.4) for esophagitis, and 10.4 months (range, 5.2-27.2) for pulmonary fibrosis. Only 1 patient experienced grade 3 esophageal stricture at 6.7 months after RT start, and this patient received esophageal balloon dilatation four times.

Discussion

This study is the first to report treatment outcomes in patients with inoperable NSCLC treated with helical tomotherapy. Some studies have reported treatment outcomes of linac-based intensity-modulated RT in inoperable NSCLC, and the reported median overall survival time ranged 16.8-29.7 months, and the reported 1- and 2-year overall survival rates ranged 57-71% and 46-58%, respectively (Yom et al., 2007, Sura et al., 2008, Liao et al., 2010, Govaert et al., 2012, Jiang et al., 2012). In our study, the median overall survival time was 28.9 months, and 1- and 2-year overall survival rates were 96.2% and 92.0%, respectively. Compared with previous studies, our study showed comparable median overall survival time, and favorable 1- and 2-year overall survival rates. Because of heterogeneous patient populations and tumor characteristics, various RT dose fractionation schedules and chemotherapy regimens, and different RT techniques and GTVs, it is hard to compare treatment outcomes among published studies. Nevertheless, the overall survival rates of our study seemed to be favorable. Our study also showed favorable locoregional recurrence-free survival rate compared with previous studies. The 2-year locoregional recurrence-free survival rate was 64.5% in our study compared to the 50-58% reported in previously published studies (Yom et al., 2007, Sura et al., 2008, Jiang et al., 2012). The most likely explanation for the favorable results in our study is the high number of patients with

early stage cancer. Table 5 shows that all patients had stage I/II NSCLC. In our study, patients with stage I/II NSCLC represented 22/27 of all patients in previously published studies (Yom et al., 2007, Sura et al., 2008, Liao et al., 2010, Govaert et al., 2012, Jiang et al., 2012). To confirm the favorable results of our study, additional studies with larger sample sizes and longer follow-up durations will be required.

There are studies and clinical trials comparing the clinical outcomes of 3-dimensional conformal RT and intensity-modulated RT in NSCLC. Liao et al. (2010) retrospectively analyzed the treatment outcomes of 318 NSCLC patients treated with 3-dimensional conformal RT and 91 NSCLC patients treated with linac-based intensity-modulated RT. In that study, the median overall survival times were 1.4 years for intensity-modulated RT group and 0.85 years for 3-dimensional conformal RT group, and overall survival was significantly better in patients treated with intensity-modulated RT. Our study showed a longer median overall survival time than those of Liao et al.'s study (2.4 years *vs* 1.4 years). However, in our study, there was no matched comparison group treated with 3-dimensional conformal RT. In the near future, we plan to conduct additional studies that compare the clinical outcomes of 3-dimensional conformal RT and helical tomotherapy in inoperable NSCLC.

There are some concerns with respect to the use of intensity-modulated RT in lung cancer. One such concern is the low-dose radiation exposure of unaffected ipsilateral and contralateral lung tissues. Because of increasing the number of radiation beams, intensity-modulated RT could expose a larger volume of healthy lung tissue to low-dose radiation. A number of studies have reported potential deleterious effects of low-dose radiation. Gopal et al. (2003) reported losses in the diffusing capacity of carbon monoxide in lung exposed to low-dose radiation. In addition, Hall (Hall, 2006) and Brenner et al. (2003) suggested that more radiation-induced secondary cancers might be expected in long-term survivors treated with intensity-modulated RT. Because of helical radiation delivery method, helical tomotherapy exposes almost all of the lung tissues to low-dose radiation. So, the low-dose radiation exposure of normal tissues is a bigger concern in helical tomotherapy. Our study showed favorable and acceptable acute and late toxicities after thoracic helical tomotherapy with a median follow-up time of 38.1 months. However, a longer follow-up duration will be necessary to detect potential long-term deleterious effects of low-dose radiation after helical tomotherapy in lung cancer patients.

There were some limitations in this study. First, this study was retrospective and may have inherent biases. For example, RT dose fractionation schedules varied widely because they were determined at the discretion of the

attending radiation oncologists rather than a predetermined protocol. In addition, we could not analyze some potential prognostic factors for overall survival, such as changes in body weight. Second, the sample size was small. Third, the patient and tumor characteristics were heterogeneous. However, despite these limitations and some concerns about helical tomotherapy, the clinical outcomes of our study are very promising and the toxicity results are favorable and acceptable. Therefore, we believe that our study provides evidence that helical tomotherapy is a useful treatment modality for the treatment of inoperable NSCLC.

In conclusion, helical tomotherapy in patients with inoperable NSCLC resulted in high survival rates with an acceptable level of toxicity. These findings suggest helical tomotherapy is an effective treatment option in patients with medically inoperable or locally advanced NSCLC.

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