Original Article

Dosimetric comparison of helical tomotherapy and conventional Linac-based X-knife stereotactic body radiation therapy for primary lung cancer or pulmonary metastases

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Background: To compare helical tomotherapy (HT) with X-knife stereotactic body radiation therapy (HT-SBRT/X-SBRT) for primary or metastatic lung cancer regarding planning target volume (PTV) coverage, such as homogeneity index (HI), conformity index (CI) and dose-volume histogram (DVH) of organs at risk (OARs).

Methods: We retrospectively analyzed 21 patients receiving definitive radiation treatment for non-small cell lung cancer (NSCLC) or pulmonary metastases at our institution between March 2015 and October 2016. Tumors were irradiated with 4–10 Gy per fraction in 5–15 fractions. Plans were compared according to PTV coverage and OARs sparing.

Results: Significant differences between HT and X-knife were observed for both HI (P=0.003) and CI (P<0.001). The V5 (P=0.001), V10 (P=0.009), V20 (P=0.001), the mean lung dose (P=0.005) of total lung and maximum dose of the spinal cord (P=0.010) were significantly lower in the X-SBRT group than the HT-SBRT group. There were no significant differences for the V30 (P=0.075) and the mean heart dose (P=0.584) between the two groups.

Conclusions: X-SBRT was dosimetrically superior to HT-SBRT, when applied in these tumors' maximum diameters <5 cm. As HT resulted in increased low-dose volume, it is essential to optimize the patient selection in order to avoid severe radiation pneumonitis in HT-SBRT.

Keywords: Helical tomotherapy (HT); X-knife; stereotactic body radiation therapy (SBRT); primary or metastatic lung cancer

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Introduction

Lung cancer continues to be one of the most prevalent malignancies worldwide and is the leading cause of cancer deaths in both men and women. More than 80% of lung cancers are non-small cell lung cancer (NSCLC) (1). Treating early stage primary NSCLC still requires surgery, while not all of these patients are considered medically operable due to comorbidities, advanced age, or unwillingness to undergo surgery. Besides primary lung cancer, the lung is also one of most common metastatic sites for patients with various malignancies. However, the treatment options are limited for those patients with poor pulmonary function or previously receiving thoracic radiotherapy who are not appropriate for conventional external irradiation (2,3). Furthermore, conventional daily irradiation with a total tumor dose of 66 Gy is also not an adequate option, as it only achieves a 5-year survival rate of 10–30% (4,5).

As a promising new technique, stereotactic body radiation therapy (SBRT) has been introduced as a primary treatment for lung cancer, with promising results in excellent tumor control rates as well as limited toxicities to normal tissue. Since the essential characteristic of SBRT is to deliver a higher biologically effective dose (BED) to tumor target (6-10).

To our knowledge, there are few reports comparing the plans of HT-SBRT and X-SBRT for primary lung cancer or pulmonary metastases. In our study, to address this gap, dosimetric parameters including homogeneity index (HI), conformity index (CI) for planning target volume (PTV), dose and volume parameters of organs at risk (OARs) were compared between the plans of HT-SBRT and X-SBRT for the patients (n=21) with unresectable NSCLC or pulmonary metastases.

Methods

Patients

Our study included 21 patients with primary lung cancer and lung oligometastases from various primary sites who underwent SBRT by tomotherapy at our institution between March 2015 and Oct 2016. The enrolled criteria included: 18 years < age < 90 years; maximum diameters of irradiated lesions <5 cm; irradiated lesions ≤2. All patients were newly diagnosed and pathologically confirmed. Five out of the 21 patients were pathologically diagnosed with adenocarcinoma and squamous cell carcinoma. One patient with poor pulmonary function; another patient was 85 years old. Both of them were not suitable for surgery though diagnosed as T1 or T2N0M0 adenocarcinoma. Two patients were stage IV (AJCC 7th edition) adenocarcinoma (intrapulmonary metastasis). The last patient was diagnosed with stage IV squamous cell carcinoma with intrapulmonary recurrence after operation. The other 16 patients were with pulmonary metastases, diagnosed as stage IV. These primary malignances included hypopharynx carcinoma, esophageal cancer, gastric cancer, colon cancer, ovarian cancer, kidney cancer, bladder cancer and nasopharyngeal cancer (NPC). The lung nodules were located in the following areas: 11 patients had a solitary peripheral nodule, 4 had a single central lesion, and 6 had both central and peripheral nodules. All the patients were considered to be inoperable and provided written informed consents. The patients' characteristics were summarized in *Table 1*.

Table 1 The clinical and histopathological characteristics of the 21 patients

Characteristics	No. of patients (n=21), n (%)
Age	
<65 years	10 (47.6)
≥65 years	11 (52.4)
Gender	
Male	19 (90.5)
Female	2 (9.5)
PS (ECOG)	
0–1	17 (81.0)
2	4 (19.0)
Histology	
NSCLC	5 (23.8)
Adenocarcinoma	4 (19.0)
Squamous cell	1 (4.8)
Metastasis (primary tumor)	16 (76.2)
Gastric	1 (4.8)
Colon	1 (4.8)
Esophageal	4 (19.0)
Bladder	1 (4.8)
Nasopharyngeal cancer	4 (19.0)
Hypopharynx	1 (4.8)
Kidney	2 (9.5)
Ovarian	1 (4.8)
Other	1 (4.8)
Tumor location	
Central	4 (19.0)
Peripheral	11 (52.4)
Central and peripheral	6 (28.6)

NSCLC, non-small cell lung cancer.

Simulation and delineation of targets and OARs

The computerized tomography (CT) based simulation was

Table 2 The dose distribution of PTV by Tomo and X-knife plan (mean ± SD)

Dose	HT-SBRT	X-SBRT	P value
$Dose_{max}$ (Gy)	56.38±7.64	70.37±12.24	<0.001
$Dose_{min}$ (Gy)	49.25±6.99	49.28±5.39	0.582
$Dose_{mean}$ (Gy)	52.45±8.04	62.28±4.60	<0.001

PTV, planning target volume; SD, standard deviation; HT-SBRT, helical tomotherapy stereotactic body radiation therapy; X-SBRT, X-knife stereotactic body radiation therapy.

used to obtain pictures for the radiation oncologists to map out the tumor and OARs. The scanning range was the total lung, and the layer thickness was 3 mm. The simulation images were transmitted to Pinnacle^3 planning system for delineation of the gross tumor volume (GTV), clinical target volume (CTV), PTV and OARs by the same radiation oncologist. Only the primary tumors and metastases in lung were delineated as GTV, and regional (mediastinal) lymph nodes lesions were not included. The OARs included the lung, esophagus, heart and spinal cord.

Treatment planning

The CT images with delineated targets and OARs were transferred to the HI-ART Version 5.0.5.18 treatment planning system and X-knife treatment system (TuoNeng). Then, the physicists designed the HT-SBRT and X-SBRT treatment plans for 21 patients. The isocenter was placed within the tumor volume at the approximate center of mass. The range of collimator of X-knife treatment system was 0.5 to 5 cm. According to the size of the tumor, the range of collimator was selected. X-knife plans were generated using 2–3 coplanar or non-coplanar arcs, according to the location and numbers of the lesions. Such as for a solitary peripheral nodule located in right lower lung, plans angled between 150 and 330 degrees were customized. The computation dose grid size was 3.0 mm. Both groups were prescribed the same dose and fractions. Patients were treated with different fractionation schemes according to the tumor stage (T), tumor location (peripheral *vs.* central), and primary sites. Tumors were irradiated with 4–10 Gy per fraction in 5–15 fractions. The dose prescriptions were designed to cover at least 96% and 75–85% of the target volume for tomotherapy and X-knife plans, respectively. All plans were assessed and confirmed by senior physicians. The BED for tumor and normal tissues were estimated for each adopted fractionation plan. An α/β ratio equal to 10 Gy was used for primary and secondary tumors, while an α/β equal to 3 Gy was used for late-responding normal tissues. The BED was calculated using the equation $nD\,[1+ D/(\alpha/\beta)]$, n is a number of fractions, D is dose per fraction, and α/β was 2 Gy for the spinal cord and 3 Gy for the sparing organs. A median total BED_{10} was 90.1 Gy (84–100 Gy) at the margin of the PTV.

Dose evaluation

We compared planning parameters by the target dose distribution and OARs. Target coverage was analyzed using the maximum, minimum and mean dose of PTV, HI and CI. Dose distributions of OARs were analyzed using V5, V10, V20, V30 and mean lung dose (MLD), the maximum dose of the spinal cord and mean heart dose.

Statistical analyses

The results of this study were analyzed using the SPSS 16.0. The data were described as the mean ± standard deviation (SD). The paired *t*-test analysis was performed for comparison of the two groups. Two-sided $P \leq 0.05$ was considered statistically significant.

Results

Dose distribution for PTV

Dose-volume histograms (DVHs) were generated from each planning technique and used to compare PTV coverage and OARs. The dose distribution of PTV by HT and X-knife plan was shown in *Table 2* and *Figure 1*. PTV coverage with the 95% isodose was expected to be better for HT. The values of $Dose_{max}$ ($P<0.001$) and $Dose_{mean}$ ($P<0.001$) were statistically different between the two groups. The difference of $Dose_{min}$ was not statistically significant ($P=0.582$).

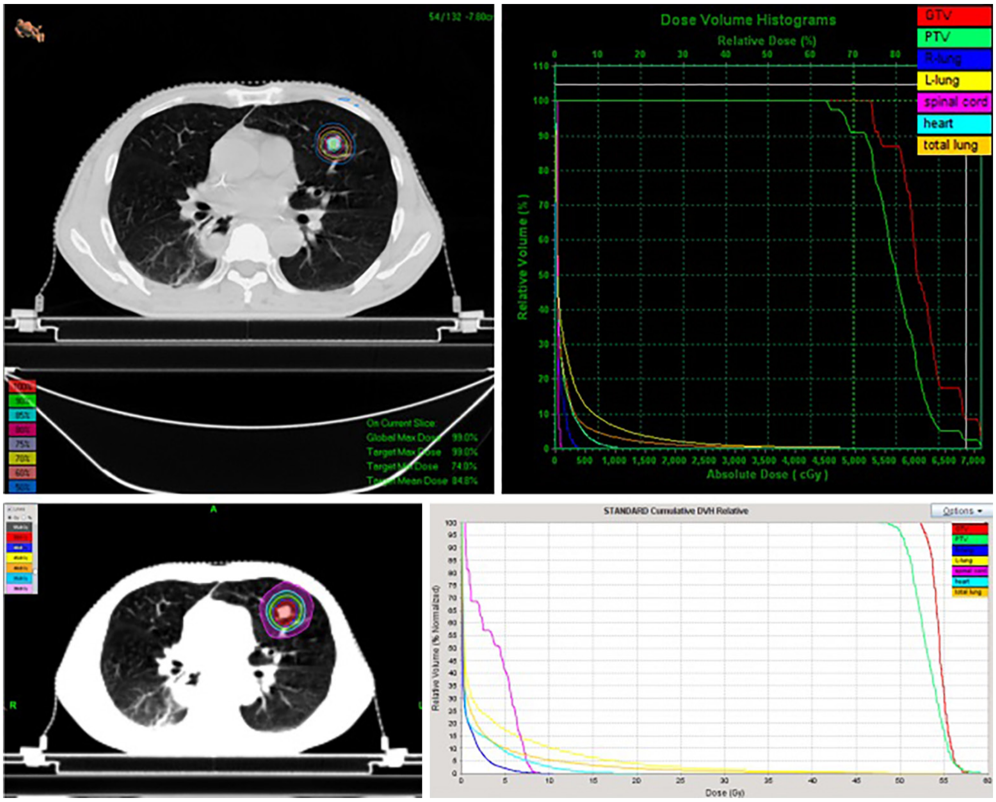

Figure 1 The dose distribution of PTV by tomotherapy and X-knife plan. This patient had lesions in the left upper that was treated to 50 Gy in 5 fractions. PTV, planning target volume.

Table 3 The HI and CI of PTV by HT and X-knife plan (mean ± SD)

Parameters	HT-SBRT	X-SBRT	P value
HI	1.02±0.08	1.35±0.05	0.003
CI	0.84±0.04	0.51±0.07	<0.001

HI, homogeneity index; CI, conformity index; PTV, planning target volume; SD, standard deviation; HT-SBRT, helical tomotherapy stereotactic body radiation therapy; X-SBRT, X-knife stereotactic body radiation therapy.

Homogeneity and conformity indices of PTV

The homogeneity and the conformal property of the target area of the two plans were shown in *Table 3*. HI = [D (V2) – D (V98)]/D_{pres}, where D (V2) and D (V98) equal the dose to 2% and 98% of the target volume respectively, and D_{pres} represents the prescribed dose. The lower the HI, the more homogenous the dose distribution in PTV. CI values close to 1 indicated a better conformal plan. Regarding the calculated HI and CI, HT was the technique with the most conformed and homogeneous (average values closer to the ideal) dose distribution. Significant differences were observed between the two plans for HI (P=0.003) and CI (P<0.001).

Dosimetric comparison for OARs

The dose volume parameters of total lung, spinal cord and heart are shown in *Table 4*. The V5 (P=0.001), V10 (P=0.009), V20 (P=0.001) and MLD (P=0.005) of lung and max spinal cord dose (P=0.01) were significantly lower in the X-SBRT group than the HT-SBRT group. There was no significant difference for the V30 (P=0.075) and mean heart dose (P=0.584).

Table 4 Dosimetric comparison for organs at risk (OARs) in two groups (mean ± SD)

Organs at risk	HT-SBRT	X-SBRT	P value
Total lung (%)			
V5	26.10±12.30	15.00±5.86	0.001
V10	14.49±7.34	9.83±4.49	0.009
V20	6.38±3.36	4.45±2.25	0.001
V30	3.24±1.82	2.66±1.28	0.075
Mean lung dose (Gy)	4.99±2.24	3.81±1.76	0.005
Max spinal cord (Gy)	9.17±4.58	3.42±1.87	0.010
Mean heart dose (Gy)	4.52±4.46	2.90±2.28	0.584

SD, standard deviation; HT-SBRT, helical tomotherapy stereotactic body radiation therapy; X-SBRT, X-knife stereotactic body radiation therapy.

Discussion

Standard radiation therapy regimens involving conventional fractionation schemes for early-stage primary lung cancer, advanced localized disease, and lung metastases have delivered only mediocre results so far. So many efforts have been made to achieve high BED while maintaining a sharp dose gradient fall outside the target, preventing dose to critical structures. Therefore, SBRT was developed. SBRT is a non-invasive treatment that can deliver a high dose of radiation in fewer fractions to thoracic or abdominal lesions, which can fully eradicate early-stage primary lung tumors and also can inactivate lung metastases or advanced localized disease. Therefore, it has exclusive advantages in the treatment of tumor peripheral dose change gradient large for pulmonary primary or pulmonary metastases (11-13).

To our knowledge, our study is one of the data to compare SBRT by HT and X-knife for primary lung cancer or pulmonary metastases. This work is an enlightenment to the coming studies and potentially useful for clinicians in making treatment choices for SBRT treatment of lung cancer patients. We found some dosimetric differences. Significant differences between HT and conventional X-knife were observed for HI and CI, and HT can achieve more conformed and homogeneous dose distribution. However, we can accept heterogeneities in SBRT. There was no difference of the V30 of total lung between these two plans. But low dose volumes including V5, V10, V20 and the MLD were significantly lower in the X-SBRT group than in the HT-SBRT group. While some studies also mentioned the volume of total lung with low-dose region (V5–V15) should be carefully regulated for NSCLC patients treated with HT (14). Low-dose irradiation to the lung has been reported to be a risk factor for pulmonary toxicity in lung cancer, especially when combined with chemotherapy (15,16). Our study found the V5 of the total lung in HT-SBRT plans were 26.10%+12.30%, higher than X-knife (*Figure 2*).

The reason and solution of increased low doses to a large volume of normal lungs have been explained as follows. A general conclusion summarized from previous reports was that advanced multi-beam treatment techniques could improve target homogeneity and reduce high doses, but the distribution of low doses would rise due to increased beam angles (17,18). X-knife use non-coplanar irradiation to protect normal tissue, and then improve the targets dose. However, the range of collimator of X-knife treatment system (TuoNeng) was 0.5 to 5 cm in our institution. So, limited by the diameter of collimator, when PTV diameter is greater than 5 cm, it cannot meet clinical requirements. Tomotherapy was able to achieve better HI and CI; however, this improvement was at the expense of increased volume of the total lung receiving low doses (19-21). In contrast, the conventional irradiation allows radiation to be delivered from only a few directions. The tomotherapy treatment system's linear accelerator (Linac) is mounted to a CT scanner-like ring gantry, which means it can be delivered continuously, from 360° angles around the patients. So, we use various "block" structures in our plans to reduce the low dose irradiation of lung. By contouring the specific vital structures and setting a "directional block" or "complete block", beam orientation can be limited to a local region and dose reduction to the normal lung. Directional blocking

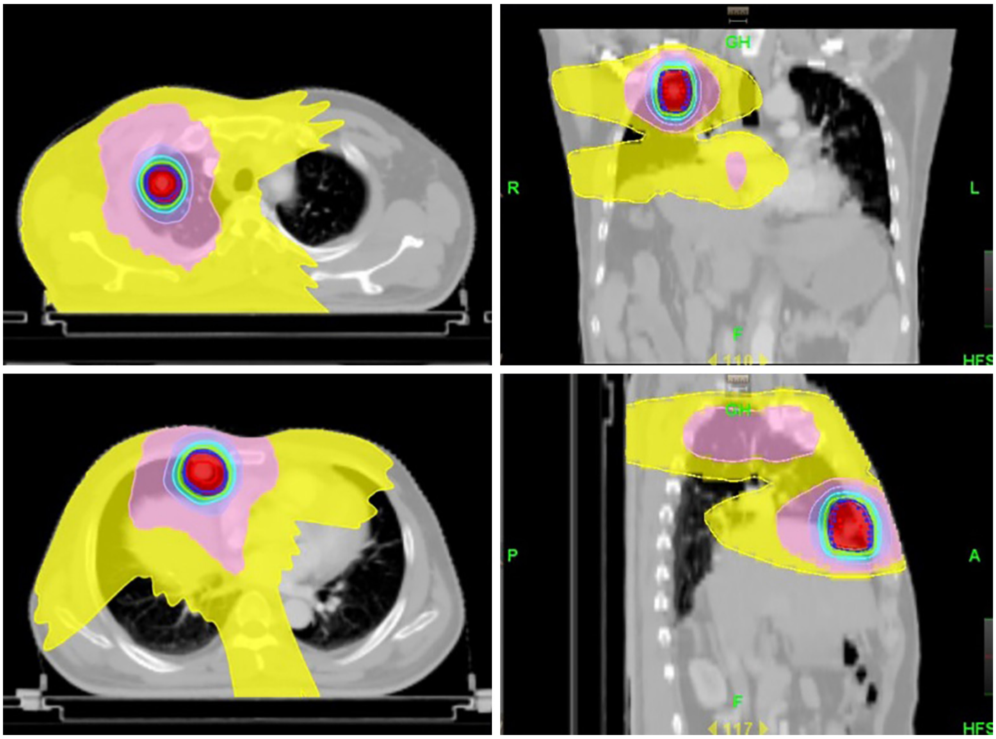

Figure 2 The V5 of total lung by tomotherapy plan.

the majority of the both lung drastically reduces the beam angles used for treatment, therefore, potentially reduces the conformity and normal tissues paring. The block is very helpful to reduce the low dose volume of the total lung. Previous studies also used these options to design other plans (22-24). Moreover, to avoid this inefficiency of beam usage, static ports (TomoDirect® mode) for the treatment of locally advanced lung cancer has been developed, making it possible to reduce the lung volume receiving low dose radiation (25,26). Meanwhile, it is essential to optimize equipment, a newly developed dynamic jaw technology (TomoEDGE) has been introduced. With this technology, radiation doses for the cranio-caudal edges of the target can be lowered by using narrower jaws around the edges (27). Attention to such detail is crucial in HT planning.

As one of the world's most advanced radiotherapy equipment, some clinical reports about HT-SBRT have demonstrated its feasibility, with a promising outcome and favorable tolerance, especially in the central or multiple targets (28-30). Helical tomotherapy is a novel form of intensity modulated and rotational radiotherapy and image-guided radiation therapy. It uses daily megavoltage computed tomography (MVCT) imaging to guide the treatment daily. During the radiotherapy for thoracic lesions, tumor volume may decrease during the treatment, while the irradiated normal lung tissue volume will increase. So, the application of MVCT can catch the change of tumor volume to achieve adaptive radiotherapy (31). Previous studies also confirmed the safety and effectiveness of tomotherapy for SBRT (32-34).

Conclusions

Helical tomotherapy results in increased low-dose volume of normal tissue and may cause a higher risk of radiation-induced toxicities. X-knife was able to achieve better results than tomotherapy especially in the tumors, maximum diameters of which are less than 5 cm, but had challenges for larger or multiple lesions. It is essential to optimize patient selection in order to reduce the risk of severe radiation pneumonitis in HT-SBRT.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This work was approved by the Ethics Committee of the Nanjing Drum Tower Hospital's (No. 2015-083-02). All the patients were considered to be inoperable and provided written informed consents.

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