Stereotactic Body Radiotherapy for Inoperable Stage I Non-Small Cell Lung Cancer

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ABSTRACT

Stereotactic Body Radiotherapy (SBRT) is one kind of emerging advanced radiotherapy that uses a high dose of radiation delivered to a precise target. The results of treatment by SBRT in inoperable stage I non-small cell lung cancer (NSCLC) are very impressive from both retrospective and prospective studies. The local control is up to 85% and the result suggests improved overall survival with little toxicity compared to the conventional fractionation technique. With its excellent result and safety record, SBRT should be considered as an optional treatment for inoperable stage I NSCLC.

Keywords: Stereotactic Body Radiotherapy, Non-small cell lung cancer

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Lung cancer is the most common cancer worldwide and accounts for the most cancer-related deaths.[1] The most common lung cancer is non-small cell lung cancer (NSCLC), which accounts for 80% of all lung cancer cases. Approximately 15-20% of the diagnosed NSCLC patients present with early-stage (stage I) disease.[2] The International Early Lung Cancer Action Program Investigators[3] reported the results of their large, collaborative, 12-year lung cancer screening study using spiral CT. Of 31,567 symptomatic participants at high risk of lung cancer, 484 were found to have lung cancer, which was of clinical stage I in 85% of cases. The standard therapy for stage I NSCLC is surgical resection, consisting of either lobectomy or pneumonectomy, as well as nodal dissection, with a 5-year overall survival ranging from 50% to 70%.[4] An anatomic lobectomy is recommended in patients who are able to tolerate the procedure, because the locoregional recurrence rate was three times greater in the limited resection group (17%) than in the lobectomy group (6%).[5] The average 5-year survival rate for patients with stage I NSCLC is approximately 65% (range 55-90%).[6] Moreover, the estimated 10-year survival rate was 88% for stage I lung cancer patients who were diagnosed by CT screening and 92% for the patients who underwent surgical resection within 1 month after diagnosis.[3] In contrast, McGarry et al., reported that lung cancer was shown to be the cause of death in 53% of 49 stage I medically inoperable patients not receiving definitive therapy.[7]

However, there are patients with stage I NSCLC who cannot undergo surgery because of their poor lung function, cardiac function, bleeding tendency, or other co-morbidities. The alternative treatment options for these patients are limited surgical resection[8] or conventional radiotherapy (1.8 -2.0 Gy/fraction)[9], although, the outcomes appear to be inferior to anatomic resection.[5] Radiation treatment should be considered as one of the treatment options. In the past, conventional fractionated radiotherapy (60-66 Gy in 1.8-2.0 Gy fractions) was used, with reported 5-year local control and overall survival rates ranging from 30-50% and 10-30%, respectively.[10,11] Dosoretz and colleagues reported that the local control rates at 3 years were 77% for 4 cm lesions and 48% for those larger than 4 cm.[10] They also found that the intercurrent death rate in patients with inoperable stage I was quite high. Qiao et al.,[11] reported a high local recurrence rate (up to 70%) in patients with stage I NSCLC, receiving median radiation doses of 60 Gy in 30 fractions with conventional RT from 18 studies performed between 1988 and 2000. Even using modern techniques (smaller volumes and higher doses) of conventional radiotherapy, Sibley et al., demonstrated that overall and progression-free survival rates at 5 years were 48% and 28%, respectively for clinical stage I NSCLC.[9]

Since systemic metastasis is not inherited in early stage NSCLC, local control is essentially important. With conventional radiotherapy, local control is not impressive. Therefore, radiation dose escalation would potentially show a benefit in both local control and overall survival.[10,12-14] If local control is achieved, it might have a low incidence of distant metastasis. The rates of distant metastasis in early NSCLC were correlated to the size of the primary tumor. Incidences of metastasis in 3 years were 8% for cases with tumors smaller than 3 cm, 27% for tumors measuring 3-5 cm, and 50% for tumors larger than 5 cm.[10] Thus image-guided hypofractionated stereotactic

body radiotherapy (SBRT) with an escalated biological effective dose is an interesting and impressive treatment to treat inoperable stage I NSCLC patients.

Stereotactic Body Radiotherapy (SBRT) in inoperable stage I NSCLC

For definite diagnosis in this population, although pathologic confirmation is the gold standard, biopsy pathology is not available in many cases due to medical contraindications. In this situation, CT-based and more recently PET-based, staging has been used to characterize and clinically define the mediastinal lymph nodes. Although up to 30% of patients were non-biopsied SBRT patients, the results of treatment were similar to the biopsy-proven cases.[15]

SBRT is a kind of modern three-dimensional conventional radiotherapy (3D-CRT). Modern 3D-CRT improves clinical outcomes compared with two-dimensional radiotherapy in lung cancer.[16] SBRT combines multiple radiation beam angles to achieve sharp dose gradients and delivers a high radiation dose per fraction (Fig 1). Image-guided radiation therapy (IGRT) interventions are based on different types of images; Four-dimensional CT (4D-CT) images, gated static X-ray images and fluoroscopic images. IGRT technique allows a high precision localization. These systems provide smaller treatment volumes, facilitate hypo-fractionation with markedly increased daily doses, and substantially reduce overall treatment time. SBRT should be considered only for early stage (stage I T1-T2, N0, M0), selective stage II (T3 with chest wall involvement, N0M0), or isolated, peripherally located recurrent or metastatic NSCLC. The result of treatment is very impressive, especially stage I NSCLC. Nagata and colleagues reported in a phase I/II SBRT study that the 1-year and 5-year local relapse-free survival rates were 100% and 95% for stage IA (T1N0M0) and 100% for stage IB (T2N0M0).[17]

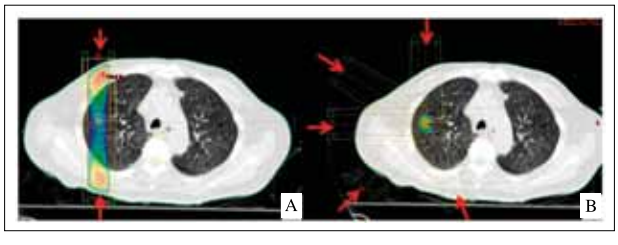

Fig 1. Radiotherapy (RT) planning showed stereotactic body radiotherapy (SBRT) achieved better dose coverage (color wash) of the tumor than conventional radiotherapy. A: conventional radiotherapy (2 RT beams) B: SBRT (multiple beams), red arrows = direction of RT beams.

Radiotherapy treatment planning

4 dimensional computed tomography (4D-CT) based SBRT planning

Precise and reliable immobilization devices with sophisticated 3D-CRT and IGRT are required to achieve SBRT. Immobilization is critical in SBRT to reduce daily setup uncertainty. The appropriate immobilization with arm up position should be chosen for each patient. Because a lung is a moving organ, the consideration of tumor motion in SBRT is very important. A four-dimensional computed tomography (4D-CT) image is a sequence of 3D-CT images spanning the phases of the breathing cycle. This collection of 3D-CT data sets describes the snapshots of a patients 3D anatomy over a periodic respiratory signal. Liu et al. demonstrated that by using 4D-CT, tumor movement of more than 1 cm during breathing was found in 13% of 72 lung cancer patients, particularly in those with small lower lobe tumors close to the diaphragm.[18] Thus each patient should be evaluated for regularity of breathing, responsiveness to feedback guidance, and breath-holding capability. Treatment delivery techniques could be (1) free-breathing approach (with or without feedback guidance), (2) respiratory-gated approach, (3) breath-holding approach (with or without feedback guidance), (4) abdominal compression, or (5) a combination of the above techniques. Patients who have tumor motion <5 mm can be treated with the free-breathing approach by using simple expansion of the tumor-motion margin. For patients with considerable tumor motion, particularly with tumor motion of >1 cm, the respiratory-gated approach can be used. An externally placed fiducial is used to track as the patient breathes in this technique. Patients receive radiotherapy at only the chosen phase of the respiratory cycle. They are usually treated at the end of expiration because it is the longest and most reproducible portion of the respiratory cycle.[19] Active breathing control and deep-inspiration breath-holding are techniques that require very cooperative patients who are able to hold their breath for at least 15 seconds. These techniques help patients to hold their breaths.[20,21] They limit patient respiratory excursion to fixed volumes and then limit diaphragm movement to about 5 mm instead of 10-15 mm. In some institutes, abdominal compression has been selected to reduce the diaphragm movement. With a 4D-CT, we can assess the organ/tumor motion and can have more accurate design for respiratory-gated or breath-holding SBRT using a breathing cycle-guided procedure. 4D-CT provides a collection of 3D-CT datasets which are created by either sorting or reconstructing the image data in a series of respiratory-phase bins. Then we use the average CT, a 3D-CT dataset created by performing a voxel-by voxel numerical averaging over all the breathing phases, to calculate the radiation dose in the treatment planning system. The maximum intensity projection (MIP), is a 3D-CT dataset created by assigning each voxel the value of the highest valued voxel at that location across the breathing phases, and all 10 respiratory-phase datasets are used for delineation of the internal target volume (ITV).

SBRT target volume delineation

To treat the precise lung tumor, delineating target volume is an important step. In general gross tumor volume (GTV), internal gross target volume (IGTV), internal target volume (ITV) and planning target volume (PTV) are contoured. The PTV is the final volume to be treated with radiotherapy. In the past, standard radiotherapy consisted of electively irradiated regional nodal areas and the primary tumor. However, many studies have shown that omitting prophylactic lymph node irradiation, does not reduce the local control rate for patients receiving definitive radiotherapy, who have isolated outside-field (field of radiotherapy) local recurrence rates of 3-8%, particularly in patients with stage I disease and in those patients who undergo PET for disease staging.[22-24] Thus the target to be treated might be only the primary tumor.

Gross tumor volume (GTV)

The GTV should be delineated on CT images. The pulmonary extension of the tumor should be evaluated on lung window images.

Internal gross target volume (IGTV)

The IGTV is the GTV which contains the extension throughout its motion during respiration. IGTV could be defined by using MIP or outlined on the expiratory phase of the 4D images if 4D-CT is available. In all cases the resulting IGTV contour should be evaluated across all phases. Another optional approach if 4D-CT is not available is contouring the GTV on the end of both inspiration and expiration breath-holding. For this technique, the composite volume of these two volumes is the final IGTV.

Internal target volume (ITV)

The ITV is defined as IGTV plus an 8-mm margin.[25] The ITV should be edited as necessary to account for physical boundaries.

Planning target volume (PTV)

The PTV consists of an ITV plus a margin for daily setup uncertainty. Daily image-guided SBRT delivery is very important to ensure adequate tumor coverage while sparing normal critical structures.[26] Discrepancies between the planned and actual tumor position during SBRT were larger than 3, 5, and 8 mm in 47%, 27%, and 8% of cases, respectively, as measured by daily cone-beam CT images. Moreover, displacements of tumor position relative to the bony anatomy were larger than 3, 5 and 8 mm in 29%, 12% and 3%, of cases respectively.[27]

Dose-volume constraints

The National Comprehensive Cancer Network (NCCN) recommendsthe SBRT dose depending on the site and size of tumors (Table 1).[28] The peripheral tumors are those located > 2 cm in all directions around the proximal bronchial tree.[29] The RTOG phase II SBRT study reported that with 60 Gy in three fractions, patients with tumors treated in the central lung had 2-year freedom from severe toxicity of only 54%[29,30] whereas central lesions have been safely treated with slightly lower dose (such as 50 Gy in five fractions) with similar local control and toxicity as seen in the treatment of peripheral lesions to higher doses.[15,17,31,32] In addition, the biological effective dose (BED) should be considered for the total dose of radiotherapy. The linear quadratic model shows that cell death from radiation increases exponentially according to a linear (α) and a quadratic (β) component of the dose.[33] The BED is calculated with the following linear quadratic equation: $BED = n \times d [1+ d/(\alpha/\beta)]$ (where n is the number of fractions, d is the dose per fraction, and n x d is the total dose delivered) using an α/β of 10 for acute effects and of 3 for late effects. The BED should be higher than 100 Gy_{10} (i.e. calculated for an α/β ratio of 10 Gy). Onishi et al.,[34] retrospectively studied 245 stage I NSCLC patients who were treated with hypo-fractionated high-dose SBRT and found that the local recurrence rate was 8.1% for those given a BED which was >100 Gy_{10} but was 26.4% when the BED was <100 Gy_{10} ($p < 0.5$). The 5-year overall survival rate in patients with medically operable NSCLC was 88.4% for those given a BED of >100 Gy_{10}, compared with 69.4% when the BED was <100 Gy_{10} ($p < 0.05$).

For the normal organ, Timmerman et al., recommended the SBRT dose constraints from investigators at the University of Texas Southwestern.[35] The NCCN[28] also has the recommendation for normal organs (Table 2), which was based on a combined consideration from ongoing multicenter trials (RTOG 0915).

Clinical outcome and toxicity

Although no randomized comparison between conventional fractionated radiotherapy and SBRT for early NSCLC is available, a recent meta-analysis revealed superior 5-year overall survival for SBRT as opposed to conventional radiotherapy (42% vs 20%).[36] Several prospective phase I/II trials and large single-and multicenter studies in early NSCLC have demonstrated that the local control rates are invariably reported and outstanding as 85-95%,[15,17,29-32,37-43] despite the use of a wide range of equipment, techniques and fractionation schemes. Recently, Timmerman et al., reported 3 years primary tumor control of 97.6% (95%CI, 84.3-99.7%) with SBRT for inoperable early stage lung cancer patients (T1/T2N0). The loco-regional failure rate was 87.2% (95%CI, 71-94.7%) and the overall survival at 3 years was 55.8% (95%CI, 41.6-67.9%).[44] However, a radiological complete response is generally observed in approximately 20% of patients, although the clinicians have to be familiar with the different patterns of fibrotic changes

TABLE 1. Stereotactic Body Radiotherapy regimens and indications for lung Tumors[28]

Regimen	Indications
30-34 Gy x 1 F	Peripheral small (< 2 cm) tumors, > 1 cm from chest wall
15-20 Gy x 3 F	Peripheral < 5 cm tumors, > 1 cm from chest wall
12-12.5 Gy x 4 F	Peripheral tumors, particularly those < 1 cm from chest wall
10-11 Gy x 5 F	Peripheral tumors, particularly those < 1 cm from chest wall

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TABLE 2. Normal tissue dose volume constraints for Stereotactic Body Radiotherapy[28]

Organ at risk (OAR)	1 Fraction Gy	3 Fractions Gy (Gy/fx)	4 Fractions Gy (Gy/fx)	5 Fractions Gy (Gy/fx)
Spinal cord	14	18 (6)	26 (6.5)	30 (6)
Esophagus	15.4	30 (10)	30 (7.5)	32.5 (6.5)
Brachial plexus	17.5	21 (7)	27.2 (6.8)	30 (6)
Heart/pericardium	22	30 (10)	34 (8.5)	35 (7)
Great vessels	37	39 (13)	49 (12.25)	55 (11)
Trachea/Large bronchus	20.2	30 (10)	34.8 (8.7)	40 (8)
Rib	30	30 (10)	31.2 (7.8)	32.5 (6.5)
Skin	26	30 (10)	36 (9)	40 (8)
Stomach	12.4	27 (9)	30 (7.5)	35 (7)

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that are now well characterized.[45,46] The mediastinal or hilar nodal failures rates were rare, ranging from 0-10% with primarily PET staging in most SBRT series[15,29-32,38,41] whereas distant metastasis occurs in 15-30% of stage I patients after SBRT treatment.[15,29-32,38,41]

The severe clinical toxicity from SBRT is reported to be less than 5%. However, the actual real risk of late toxicity may be higher than the reported risk due to a limited follow-up period from non-cancer related mortalities in medically inoperable patients. Moreover, pulmonary toxicity symptoms may be overestimated by being mixed, being combined with exacerbations of COPD and pneumonias. The incidence of grade >3 radiation-induced pneumonitis was reported to be 0-5%.[31,40,41,46] For peripheral tumors, chest wall symptoms have been reported in 5-15% and seem to be related to the treatment dose, fractionation and beam arrangement.[15,47,48] Dunlap et al., recommended that radiation doses less than 30 Gy in 3-5 fractions to a limited volume less than 30 cm^3 would reduce the risk of chest wall toxicity.[47] Other toxicities, soft-tissue fibrosis,[49] skin reaction,[50] and brachial plexopathy[51] have been observed, although these occur in less than 1% of treated patients and are likewise preventable with changes in treatment planning. Brachial plexus injury should also be considered if the tumor is at the apex of a lung. The actuarial two-year risk of brachial plexopathy symptoms was 46% when the BED was greater than 100 Gy_3 in a series of 37 apical lesions versus 8% for a BED <100 Gy_3 ($p = 0.04$).[51]

All of these studies have been reported according to 6th AJCC staging.[52] Although recently the 7th AJCC lung cancer staging was changed slightly, and stage IA and IB still include T1N0M0 (Tumor <3 cm) and T2aN0M0 (Tumor >3 cm, <5 cm), respectively.[53] In conclusion, SBRT and multiple 3D-CRT beam angles technique with IGRT system is an emerging advanced technique of radiotherapy. It provides the precise high radiation dose to pulmonary tumor per fraction. For medical inoperable stage I NSCLC patients, many studies demonstrated the excellent results of SBRT treatment which were better than conventional radiotherapy with acceptable safety. Thus SBRT should be considered as the option of treatment instead of conventional radiotherapy.

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