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REVIEW ARTICLE

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Current status of stereotactic body radiotherapy for lung cancer

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Abstract Stereotactic radiotherapy (SRT) for extracranial tumors has been recently performed to treat lung and liver cancers, and has subsequently been named stereotactic body radiotherapy (SBRT). The advantages of hypofractionated radiotherapy for treating lung tumors are a shortened treatment course that requires fewer trips to the clinic than a conventional program, and the adoption of a smaller irradiated volume allowed by greater setup precision. This treatment is possible because the lung and liver are considered parallel organs at risk. The preliminary clinical results, mostly reported on lung cancer, have been very promising, including a local control rate of more than 90%, and a relatively low complication rate. The final results of a few clinical trials are awaited. SBRT may be useful for the treatment of stage I lung tumors.

Key words Stereotactic body radiotherapy · Conformal radiotherapy · Lung cancer · Stereotactic body frame · Stereotactic radiotherapy · Extracranial tumors

Introduction

Stereotactic radiotherapy (SRT) for extracranial tumors has been recently performed to treat extracranial tumors, mainly lung and liver cancers, and has subsequently been named stereotactic body radiotherapy (SBRT) or extracranial stereotactic radiotherapy (ESRT). The advantages of hypofractionated radiotherapy for treating lung tumors are a shortened treatment course that requires fewer trips to the clinic than a conventional program, and the adoption of a smaller irradiated volume allowed by greater setup precision. This treatment is possible because the lung and liver are considered parallel organs at risk (OAR). The disadvantages of SBRT are the uncertain effects of altered fractionation and the theoretical risk of worsening the ratio of normal tissue to tumor tissue through the use of a high dose per fraction. In this article, the technical procedures and clinical results of SBRT, especially in lung cancer, are reviewed.

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Biology

The biological background of SBRT is important. There is no past clinical evidence for this kind of hypofractionated regimen to extracranial tumors; therefore, most clinical regimens should be based on biological estimations.

The two great issues in hypofractionated regimens are dose response for tumor control and toxicity to normal tissue. Can the conventional linear-quadratic (LQ) model be applied in the SBRT dose range? Can repopulation be avoided in the SBRT regimen? How great is the effect of hypoxia in SBRT?

Fowler et al.[1] answered these questions, which are mostly applicable to SBRT; however, they recommended that SBRT be performed three to five fractionated schedule rather than using single SRS. These biological speculations should be reconfirmed in the clinical setting.

Body fixation

The first body fixation device was introduced in clinical practice as a stereotactic body frame by Bromgren et al.[2] and Lax et al.[3] Patients were fixed in the stereotactic frame, using a vacuum pillow. The concept of this frame is to utilize the cranial SRT coordinates for extracranial SBRT. The difference between cranial SRT and extracranial SBRT is the accuracy of the setup. The Japanese national guidelines for SRT state that the allowance of setup error is 2 mm for cranial tumors and 5 mm for extracranial tumors.

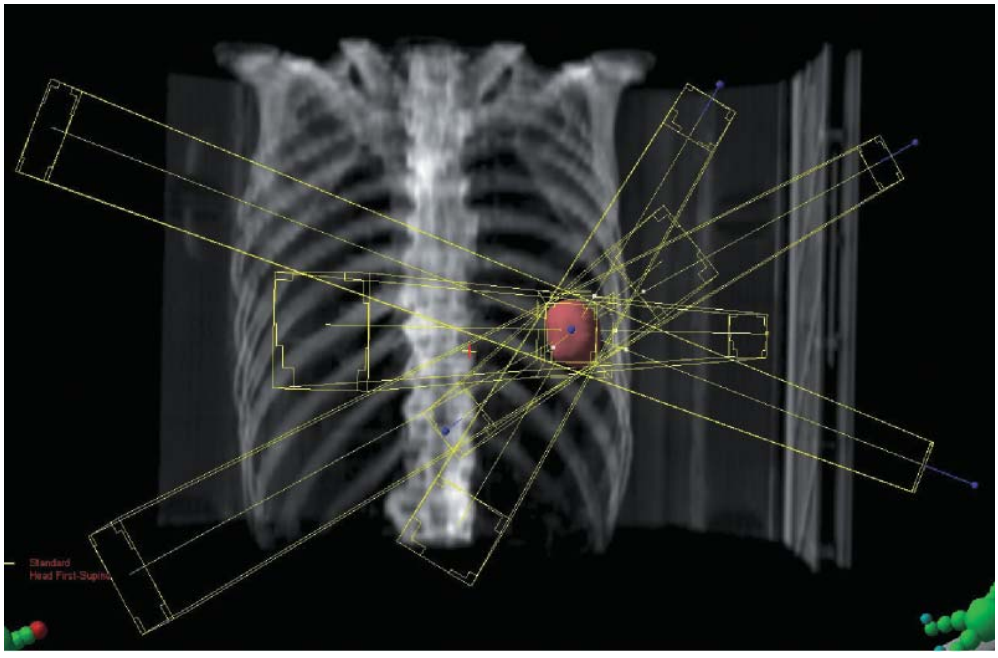

Fig. 1. Stereotactic body radiotherapy (SBRT) for lung cancer. In this image for treatment planning for left lung cancer, five beams are focused on the target

Some other fixing apparatuses using a vacuum sheet or thermoplastic shell are clinically available.

Respiratory monitoring

In the clinical practice of SBRT, the regulation of respiratory movement is essential. There are three ways to regulate the respiration of patients: respiratory holding, respiratory regulation, and respiratory gating.

The respiratory holding method is to ask patients to hold their breath for about 10 s during radiation; therefore, radiation is performed intermittently four to ten times. Theoretically, this method can reduce the internal target volume (ITV). Holding can be done either voluntarily by patients or by using devices such as an active breathing control (ABC).

Respiratory regulation can be performed by exerting pressure on the abdomen using a plate like our diaphragm control or an abdominal belt.[4]

The respiratory gating method was originally developed in Japan. The gating sensors are a respiratory flow monitor, abdominal wall fiducials, and implanted gold fiducials.

Target definition

In computed tomography (CT) images taken under free-breathing long-scan (4–8 s) conditions, the target outlines of the ITV are delineated. These CT images include the respiratory movement of the target. ITVs and Clinical Target Volume (CTV)s were not edited for anatomy.

If patients are irradiated with gated radiotherapy, the target outlines of CTV could be delineated under gating conditions.

The setup margins between the ITV and the planning target volume (PTV) must be determined at each institution. Our margins are 5 mm for the anteroposterior (AP), 5 mm for the lateral, and 8–10 mm for the craniocaudal directions. Overlapping the outlines under inhale and exhale conditions is an alternative choice.

Treatment planning

There are two different concepts of Radiotherapy Treatment Planning (RTP) for SBRT. One concept, mainly used in Japan, is to maintain dose homogeneity within the target. In this case, the dose is usually prescribed at the isocenter. The other concept, mainly used in the United States, is not to maintain dose homogeneity. In this case, the dose is prescribed at the PTV margin. Our method adheres to the former concept, with selection of the optimal direction of noncoplanar beams, with the goal of the RTP being 6–10 portals for noncoplanar static beams, as shown in Fig. 1. The beam energy used was 6 MV and the isocenter was single for all beams. Four single treatments with 12 Gy of radiation were prescribed at the isocenter. Using an LQ model,[5] the Biological Effective Dose (BED) was here defined to be nd (1 + d / alpha-beta) Gy, where n is the fractionation number, d is the daily dose, and the alpha-beta ratio for tumors was assumed to be 10. The value was 105.6 Gy-BED for 48 Gy in four fractions. The most important issue for RTP in SBRT is to maintain the dose constraints of OAR to avoid serious complications. The dose constraints of the OAR, including the spinal cord, pulmonary artery, bronchus, and heart, under the Japan Clinical Oncology Group (JCOG) 0403 protocol, are shown in Table 1.

Verification before radiation

In the clinical practice of SBRT for lung cancer, verification before each treatment is mandatory. In our institute, before each treatment, AP and lateral portal films are taken for verification. The position of each patient is verified by three experienced oncologists and technologists for each treatment. When the setup errors are larger than 2 mm between the X-ray simulation film and portal film in any direction, the patient is repositioned and portal films are taken and verified again. CT on rails and FOCAL units are also useful materials for verification before each treatment.

Clinical indications for SBRT

Currently, the eligibility criteria for patients with primary lung cancer are: (1) tumor size less than 5 cm in diameter without nodal and distant metastases (T14N0M0); (2) surgery was contraindicated or refused; (3) the patient could remain stable in the body frame for longer than 30 min (WHO performance status <=2); (4) no active interstitial pneumonitis; and (5) written informed consent was obtained. The criteria for patients with secondary lung cancer are: (1) tumor size less than 5 cm in diameter; (2) tumor number three or less; (3) no other metastases, and (4) local tumor is controlled.

Tumor size is an important factor when dose homogeneity within the target should be maintained. The dose constraints of mediastinal organs should be maintained; therefore, a central tumor could be less suitable for SBRT indications than a peripheral tumor.

Table 1. Dose constraints of various organs at risk, according to the JCOG 0403 protocol

Organ	Dose	Volume	Dose	Volume
Lung	40 Gy	<=100 cc	MLD	<=18 cc
	V15	<=25%	V20	<=20%
Spinal cord	25 Gy	Max		
Esophagus	40 Gy	<=1 cc	35 Gy	<=10 cc
Pulmonary artery	40 Gy	<=1 cc	35 Gy	<=10 cc
Stomach	36 Gy	<=10 cc	30 Gy	<=100 cc
Intestine	36 Gy	<=10 cc	30 Gy	<=100 cc
Trachea, main bronchus	40 Gy	<=10 cc		
Other organs (heart, etc)	48 Gy	<=1 cc	40 Gy	<=10 cc

18-Fluoro-deoxy-glucose (FDG)-positron emission tomography (PET)

18-Fluoro-deoxy-glucose (FDG)-PET scanning is an important examination both for the staging and the follow-up of lung cancer. For lung cancer staging, occult mediastinal and hilar lymph nodes, and distant metastases, are frequently found by FDG-PET.

In the follow-up of lung cancer after SBRT, radiation fibrotic change cannot be distinguished from residual tumor. FDG-PET is also useful in this situation.[6]

Clinical results

Local tumor response

The local control rates of primary lung cancer with SBRT have been previously reported by several authors, as shown in Table 2: 94 % (47/50) for 50–60 Gy in five fractions with a median follow-up of 36 months,[7] 92 % (22/24) for 60 Gy in 8 fractions with a median follow-up of 24 months,[8] 81% (30/37) for 60 Gy in three fractions with a median follow-up of 15 months,[9] 80% for 48–60 Gy in eight fractions with a median follow-up of 17 months,[10] 95% for 45–56.2 Gy in three fractions with a median follow-up of 10 months,[11] 90% for 30–40 Gy in four fractions with a median follow-up of 21 months,[12] and 98% (44/45) for 48 Gy in four fractions with a median follow-up of 30 months.[13] However, the definition of local control after radiotherapy is difficult because local tumor failure and Radiation Induced Lung Damage (RILD) cannot be clearly delineated. Even though the definition of local control is different in various trials, a BED larger than 100 Gy may be effective for the SRT of solitary lung cancer with a local control rate of above 85%.

Survival

The survival rates of stage IA (T1N0M0) lung cancer and stage IB (T2N0M0) lung cancer have not been separately reported by several authors. In our stage IA series, the 1-year and 5-year local relapse-free survival rates were 100% and 95%. The isease-free survival rates after 1, 3, and 5 years were 80%, 72%, and 72%, respectively, and the overall survival rates were 93%, 83%, and 83%, respectively. In our stage IB series, the 1-year local relapse-free survival

Table 2. Local control rates of stereotactic radiotherapy for primary lung cancer

Author (year)	Total dose (Gy)	Daily dose (Gy)	Reference point	Local control	Median follow-up (months)
Uematsu[7] (2001)	50–60	10	80% Margin	94% (47/50)	36
Arimoto[8] (1998)	60	7.5	Isocenter	92% (22/24)	24
Timmerman[9] (2003)	60	20	80% Margin	81% (30/37)	15
Onimaru[10] (2003)	48–60	6–7.5	Isocenter	80% (20/25)	17
Wulf[11] (2004)	45–56.2	15–15.4	80% Margin	95% (19/20)	10
Nagata[13] (2005)	48	12	Isocenter	98% (44/45)	30
Lee[12] (2003)	30–40	10	90% Margin	90% (8/9)	21

Table 3. Clinical toxicities after stereotactic radiotherapy for primary lung cancer

Author (year)	Number of cases	Lung >=grade 3	Lung grade 5	Other grade 5
Uematsu[7] (2001)	50	0%	0	
Arimoto[8] (1998)	24	NA	0	
Lee[12] (2003)	28	0	0%	
Onimaru[10] (2003)	45	2%	0%	Esophagus
Wulf[11] (2004)	61	0	0%	
Nagata[13] (2005)	45	0	0	
Timmerman[16] (2006)	70	20%	9%	Hemoptysis, pericarditis
J-CERG[5] (2006)	2106	NA	0.50%	Esophagus, hemoptysis

NA, not available

rate was 100%. The disease-free survivals after 1, 3, and 5-years were 92%, 71%, and 71%, respectively, and the overall survival rates were 82%, 72%, and 72%, respectively.[13] Onishi et al.[14] recently reported the results for 13 institutions in Japan, which summarized findings for 245 patients: 155 with stage IA lung cancer and 90 with stage IB lung cancer. There were 87 operable and 158 inoperable patients, and their results showed that the intercurrent death rate was especially high in the inoperable patient group. Moreover, the 5-year survival rates of operable patients irradiated with more than BED=100 Gy was 90% for stage IA and 84% for stage IB, and their clinical results were as good as those for surgery.

These survival rates should be compared with the results of surgery; however, the results of SBRT may differ depending on how many of the group are operable and how many are inoperable, and how many of the tumors are central and how many, peripheral.

Toxicities

The great concern of pulmonary toxicity with this SBRT treatment was relieved by the very low rates of complications in early studies. Most pulmonary complications were less than National Cancer Institute common toxicity criteria (NCI-CTC) version 2.0 grade 2. No other serious complications were reported, except for rib fracture, intercostals neuralgia, and mild dermatitis. However, recently, a few serious complications have been reported by several institutions in Japan.[15] These complications include grade 5 pulmonary complications, radiation pneumonitis, hemoptysis, and radiation esophagitis. Most cases of grade 5 radiation pneumonitis were associated with interstitial pneumonitis. Cases of interstitial pneumonitis should be carefully considered. Thoraco-cutaneous fistula was reported in a patient with previous tuberculosis history. Acute cholecystitis was reported in a patient with gallstones who had been pressed with an abdominal press board at the time of SBRT.

Another toxicity concern was the effect on the central bronchus, pulmonary artery, esophagus, heart, and spinal cord. The effects of a hypofractionated dose on the main bronchus, pulmonary artery, heart, and esophagus have not been followed up for a sufficiently long time. Lethal pulmonary bleeding and esophageal ulcer have been reported previously by several authors. Timmerman et al.[16] recently reported a series of complications with SBRT. Central hilar tumors adjacent to mediastinal organs should be carefully considered.[17] Table 3 shows the toxicities reported by various groups.

Ongoing clinical trials

Recently, a multi-institutional phase II study of SBRT for T1N0M0 non-small cell lung cancer under JCOG (http://www.jcog.jp/) protocol 0403 was started in Japan. Sixteen institutions entered together and started the same 48-Gy SBRT dose at the isocenter in four fractions for T1N0M0 lung cancer. One hundred patients have been registered. The results of SBRT for both inoperable and operable stage I lung cancer patients are awaited.

A new dose-escalation study of SBRT for T2N0M0 lung cancer is also planned, under the JCOG.

Timmerman et al.[9] concluded that a 60-Gy marginal dose in three fractions was the limiting dose, and the Radiation Therapy Oncology Group (RTOG) study 0239 for inoperable patients is already closed. There are a few other reports so far.[18–23] The coming RTOG protocols for operable patients, central tumors, and lung metastases are awaited.

Future directions

Both a new IGRT technique and four-dimensional RTP are future directions of SBRT. Systemic chemotherapy may be considered when the local tumor is well controlled and regional/distant metastases are frequent.

The primary indication for stereotactic radiotherapy in lung cancer could be a stage 1A (T1N0M0) patient. Very early-stage lung cancer can now be detected by screening CT examination, and these cases are also good indications for SRT; however, the issue in these cases is histological confirmation. In our clinical experience, 7 of a total of 95 SRT cases could not be finally confirmed histologically. Of course, these 7 cases were not included in our study.[13] They could not be histologically confirmed because of failure or difficulty in CT-guided biopsy or transbronchoscopic lung biopsy (TBLB). Currently, CT screening has revealed very early-stage lung cancer with ground glass opacity (GGO) and some patients with severe emphysema could be contraindicated for biopsy. Therefore, the indication for SRT for

these cases without histological confirmation should be discussed in the future. When the tumor is larger than 3 cm in diameter, which corresponds to stage 1B (T2N0M0), SRT is possible; however, the intratumor dose becomes less homogeneous, and the rate of occult distant metastases may increase. Therefore, extension of the indication of this technique for T2 tumors requires more consideration for dose escalation or adjuvant chemotherapy.

The current standard choice for stage IA lung cancer treatment is lobectomy;[24] however, for many patients this is not indicated because of accompanying diseases, such as chronic obstructive pulmonary disease (COPD), cardiac disease, and diabetes. For such patients, various minimal surgical techniques are indicated, including wedge resection and video-assisted thoracoscopic surgery (VATS), as well as ablation. The local control rates of various other modalities for primary stage I lung cancer previously reported were 93% for wedge resection and 83%-95% for VATS, and the 5-year survival rates were 82% and 50%-70%, respectively. A further randomized trial comparing SBRT with surgery should be considered.

Conclusion

SBRT is a safe and effective treatment method for stage I lung tumors. Further clinical studies are therefore warranted.

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