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REVIEW

STEREOTACTIC BODY RADIOTHERAPY FOR LUNG TUMORS: BASIC PRINCIPLES AND CLINICAL RESULTS

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Abstract In stereotactic body radiotherapy (SBRT), extracranial primary tumors or metastases are treated with high doses of radiation in a few fractions. The precise and accurate delivery of multiple radiation beams to the target maximizes tumor cell death while keeping the dose to the surrounding normal tissue to a minimum. Much of the technology to overcome the barriers to applying this treatment to moving tumors was developed in Japan. This review defines SBRT and presents the history of its technical development for safe and effective administration, as well as the clinical results of using SBRT to treat early-stage non-small cell lung cancer and lung metastases.

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Key words: stereotactic body radiotherapy; non-small cell lung cancer; lung metastases; oligo-recurrence.

Introduction

Stereotactic body radiotherapy (SBRT) is a treatment technique with high efficacy for relatively small tumors, such as early-stage lung cancer and lung metastases. Stereotactic irradiation is differentiated from conventional radiotherapy mainly by the administration of high doses in hypofractionation, with the expectation of a high biological effect. To minimize adverse effects on normal tissues, it is important that the high-dose region is matched to the shape of the tumor and that the dose around the tumor diminishes sharply. SBRT now provides an alternative treatment to surgery for medically inoperable patients with early-stage non-small cell lung cancer (NSCLC) or lung metastases. Japan is one of the leading countries in the development and use of this high-precision external beam radiotherapy.

This review defines SBRT and describes the history of its technical development for safe and effective administration. It also summarizes the clinical results for SBRT in the treatment of early-stage NSCLC and lung metastases.

Definition of SBRT

SBRT is a technique in which the target is precisely irradiated from multiple directions; this is to improve local control and reduce adverse effects on the surrounding normal tissue. The technique is used for small tumors localized in the trunk. Specifically, SBRT is defined by the following three criteria[1)]:

1. Three-dimensional irradiation from a linear accelerator is used.
2. The deviation of the position of the irradiation center is noted and confirmed to be within 5 mm for every irradiation.
3. Either the patient is immobilized to prevent

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motion, such as by using a fixed frame or shell, or the irradiation is synchronized with the patient's motion by tracking physiological respiratory movement or the movement of internal organs, providing precision control.

The technical development of SBRT

SBRT was developed against the background of the great success of stereotactic irradiation for intracranial tumors. Several investigators have reported the efficacy of stereotactic radiosurgery or radiotherapy for patients with intracranial malignancies[2-5]. The success of these techniques resulted, in the mid-1990s, in considerable interest in their application for extracranial tumors. SBRT using CT-guided linear accelerator treatment, also called a FOCAL unit, was first pioneered in 1996 by Uematsu et al.[6] for the adjustment of tumor position. The FOCAL unit was composed of a linear accelerator, an X-ray simulator, a CT scanner, and a treatment table. It was confirmed that using the FOCAL unit reduced the set-up error to almost zero (within 0.5 mm)[7]. However, even when the location of a tumor can be accurately identified, the problem of its respiratory motion remains. Onishi et al.[8] developed a novel technique for lung cancer irradiation that combined a linear accelerator and CT with patient-controlled end-inspiratory breath-hold and radiation beam switching. The advantages of this technique included reduced set-up and internal margins, reduced tumor motion during irradiation without the need for a respiratory monitoring device, improved dose-volume histograms (DVHs) because of the breath-hold, and shorter treatment times. In addition, Onishi et al.[9] developed a simple respiratory monitoring device, the so-called Abches that did not include any electronic components.

Many further devices related to SBRT were developed in Japan. Shirato et al.[10] developed a linear accelerator synchronized with a fluoroscopic real-time tumor-tracking system in 1999; this allowed the location of a metallic marker in a tumor to be detected in three dimensions to an accuracy of within 2 mm. This dramatic improvement in the localization of a moving tumor made it possible to irradiate the tumor at a favorable phase of respiration. Kamino et al.[11] developed a four-dimensional image-guided radiotherapy system in 2006, which, uniquely, had an innovative gimbaled X-ray head; this enabled small-angle rotations along the two orthogonal gimbals, allowing accurate irradiation without stopping respiration. The majority of devices for SBRT developed in Japan have been commercialized and are currently widely used clinically.

Clinical studies of SBRT applied to NSCLC

NSCLC is a leading cause of mortality worldwide. With the recent increase in the use of CT examinations, NSCLC is now often detected at an early stage. The first-choice treatment for early-stage NSCLC is surgical resection; however, many patients are considered to be inoperable because of their advanced age, poor respiratory function or other chronic illness, the risk of complications, or refuse surgery. SBRT provides an alternative treatment for such patients. Table 1 lists the irradiation methods and local control rates for several institutions that performed SBRT for primary stage-I NSCLC[8, 12-16]. Although these institutions used different prescribed doses and reference points, the initial data appear promising, with local control rates of 87 % to 97 %.

Nagata et al.[17] surveyed the current status of SBRT in Japan and reported fractionation schedules. According to their survey, the most common schedules for primary lung cancer were 48 Gy administered in four fractions (used at 22 institutions), 50 Gy administered in five fractions (11 institutions), and 60 Gy administered in eight fractions (four institutions). The reason the first of these schedules is the

Table 1. Summary of studies reporting the use of stereotactic body radiotherapy for primary lung cancer

Author (Refs.)	Year	Number of patients	Total tumor dose (Gy)	Single dose (Gy)	Reference point	BED_{10} (Gy)	Local control (%)	Median follow-up (months)
Uematsu[12]	2001	50	50–60	5–6	PTV margin	75–96	94	36
Fukumoto[13]	2002	22	48–60	6–7.5	PTV margin	77–105	94	24
Timmerman[14]	2003	37	60	20	80% margin	180	87	15
Onishi[8]	2004	35	60	6	PTV margin	96	94	12
Nagata[15]	2005	45	48	12	Isocenter	106	97	30
Baumann[16]	2009	57	45	15	67% margin	113	92	35

BED_{10}, biologically effective dose; PTV, planning target volume.

most common in Japan may be related to the impact of a Japanese phase II clinical trial[18] (JCOG0403). This was the first Phase II clinical trial in the world for a medically operable case group. In JCOG0403, 48 Gy administered in four fractions was prescribed for the isocenter. Sixty-five patients were included between July 2004 and January 2007.The median observation period was 45 months, the 3-year overall survival rate was 76 % and the 3-year locally progression-free rate was 69 %. No cases of treatment-related toxicity of grade 4 or above were identified. However, many different SBRT fractionation schedules are currently used in other institutions in Japan, and there is a lack of consensus regarding the optimal fractionation schedule. Biologically effective dose (BED) values for tumoral and normal tissues have been used to compare the efficacy of various fractionation schedules, with many investigators reporting its utility[15, 19].

There have been several reports of a correlation between BED_{10} and local control. BED_{10} is defined as $nd\ [1 + d / (\alpha/\beta)]$, where n and d represent the number of fractions and fraction size, respectively, and α/β is assumed to be 10 Gy for tumors. Onishi et al.[19] evaluated clinical outcomes following stereotactic hypofractionated high-dose irradiation of stage-I NSCLC and found that local control rates were better with $BED_{10} \geq 100$ Gy than with $BED_{10} < 100$ Gy (91.9 % vs. 73.6 %, respectively). Similar findings regarding the importance of BED_{10} for local control have been reported by Nagata et al.[15]. BED_{10} also appears to be useful for comparing the efficacy of treatment protocols with different fraction sizes and total doses. Conversely, Shibamoto et al.[20] highlighted issues with the use of a linear-quadratic (LQ) model and BED for estimating the efficacy of radiation schedules in SBRT. The LQ model has utility for the conversion of the relatively low radiation doses used in conventional radiotherapy, but it may not be applicable to higher daily doses or smaller fraction numbers[21]. Further research is needed, focusing on the development of alternative mathematical models for SBRT.

Clinical studies of SBRT applied to lung metastases

Distant cancer metastases, which may, for example, form as a result of hematogenous metastases of the cancer, help define the advanced-stage disease. They are often associated with a poor prognosis and limited life expectancy. However, some patients have distant metastasis in only a few sites. In 1995, Hellman and Weichselbaum proposed an intermediate state of metastasis, which they called oligometastasis, in which there were only a limited number of metastatic tumors and sites[22]. The lungs are among the most common sites of metastasis fol-

lowing the radical treatment of a primary cancer. SBRT has been widely used as a treatment option for lung oligometastases worldwide[23].

Recently, Niibe et al.[24] addressed the states of oligo-recurrence, in which a patient shows one to several distant metastases/recurrences in one to several organs, and disease control at the primary cancer site. Several studies have reported favorable outcomes following SBRT for oligo-recurrence in the lungs. Inoue et al.[25] reported the results of SBRT for 22 patients with lung oligo-recurrence; with a median follow-up period of 25 months, the 3-year local control and overall survival rates were 100 % and 72 %, respectively. In a study of SBRT treatment for 42 patients with lung oligo-recurrence, Takahashi et al.[26] reported that, with a median follow-up of 20 months, the 2-year local control and overall survival rates were 87 % and 65 %, respectively.

Oligo-recurrence in the lungs following primary colorectal cancer has widely been considered a worse prognostic factor for local control than that following other primary cancers. Takeda et al.[27] compared outcomes for patients with oligometastatic lung tumors following colorectal cancer (21 tumors) and following other primary cancers (23 tumors); all were treated with SBRT of 50 Gy in five fractions. The 2-year local control rates for colorectal oligometastases and the oligometastases from other origins were 72 % and 94 %, respectively ($P < 0.05$). It is not known why the local control rate after SBRT is worse for lung metastases from colorectal cancer than from other cancer types, but there have been several further similar reports, including one from our institution[28-30]. Recently, Jingu et al.[31] reported an analysis of 93 patients that showed that dose escalation improved the local control rate of pulmonary oligometastases from colorectal cancer after SBRT. The median observation period was 28 months, the 3-year local control rates for higher BED_{10} (≥130 Gy for isocenter) and lower BED_{10} (<130 Gy for isocenter) were 95 % and 60 %, respectively ($P = 0.011$). For ≥ 130 Gy BED_{10} prescribed with the isocenter, standard prescribed doses for primary lung cancer in Japan (e.g. 48Gy/4, 50 Gy/5 or 60 Gy/8 fractions) are insufficient for pulmonary oligometastases from colorectal cancer. However, future studies are needed to establish the required extent of the dose increase.

Adverse events after SBRT for lung tumor

SBRT is associated with excellent local control and minimal toxicity; however, excessive pulmonary toxicity following SBRT has been reported with the use of hypofractionated regimens, especially for centrally located tumors. Timmerman et al.[32] reported the results of RTOG 0236, a phase II trial of SBRT in medically inoperable patients with T1 or T2 tumors who were treated with 60–66 Gy in three fractions of 20–22 Gy. The study enrolled 70 patients; Grade 3 to 5 toxicity occurred in 14 of these patients. The analysis of those 14 patients suggested that tumor location (hilar/pericentral vs. peripheral) was a strong predictor of toxicity. The authors suggested that this regimen should not be used for patients with tumors near the central airways because of the excessive toxicity.

Conversely, there have been several reports of adverse events after SBRT for peripherally located lung tumors. The largest study of radiation pneumonitis after SBRT to date found frequencies of around 10 % and 2 %–4 % for Grade 2 and Grade 3 radiation pneumonitis, respectively[33]. Radiation pneumonitis following SBRT usually appears after 2 to 7 months, mostly only as an image finding that is asymptomatic or involves only a mild cough. Other reported side effects of SBRT include radiation dermatitis[34], chest wall pain[35], and rib fractures[36]; however, high-grade toxicity (Grade

Table 2. Three-year local control rates and adverse events following stereotactic body radiotherapy, by fractionation schedule[39]

Fraction size (Gy)	Total dose (Gy)	BED_{10} (Gy)	Tumor size (n)		3-year LC (%)	Radiation pneumonitis (n)	
			≤3 cm	>3 cm		Grade 1	Grade 2
6	54	86.4	12	8	90	13	0
7	56	95.2	19	1	95	13	0
8	56	100.8	19	1	95	15	1
9	54	102.6	18	2	95	13	1
10	50	100.0	18	2	100	16	0

BED_{10}, biologically effective dose; LC, local control.

3 to 5) is rare.

For SBRT candidates with lung tumors, attention should be paid to the presence of comorbid interstitial pneumonia, even when findings are minimal. Takeda et al.[37] reported the case of a primary lung cancer patient with slight focal honeycomb changes of the lung on CT, who experienced acute exacerbation of subclinical idiopathic pulmonary fibrosis following SBRT. In their survey of SBRT in Japan, Nagata et al.[17] reported the frequency of Grade 5 radiation pneumonitis to be 0.5 %.

Clinical experience of SBRT for lung tumors at our institution

At Hirosaki University Hospital, we started using SBRT for lung tumors in May 2003. Our eligibility criteria for treatment with SBRT are as follows: (1) primary lung cancer (T1–2N0M0), or no more than three lung metastases without active primary cancer; (2) tumor size <50 mm across the maximum diameter; (3) tumor visible by fluoroscopy; and (4) performance status ≤2 according to the Eastern Cooperative Oncology Group performance scale. We have previously reported our initial clinical experience of SBRT in patients with early-stage NSCLC and lung metastasis, using a total dose of 54 Gy administered in nine fractions[38], and we have subsequently performed a dose escalation study of SBRT for localized lung tumor with increases in fraction size of 1 Gy.

We started our dose escalation study with a fraction size of 6 Gy. Although a fraction size of 12 Gy is now commonly used in Japan[18], the optimal fractionation schedule for SBRT was unknown at the time the study commenced. Table 2 summarizes the 3-year local control rates and adverse events according to almost uniform doses with five treatment schedules at our institution. Regardless of the fractionation schedule, SBRT with total doses between 50 and 56 Gy administered over five to nine fractions achieved acceptable tumor control without any severe complications[39].

The current treatment schedules for SBRT at our institution are as follows: a total dose of 50 Gy administered in five fractions for tumors <3 cm in diameter; 60 Gy administered in six fractions for tumors >3 cm in diameter or for lung metastasis from colorectal cancer, regardless of tumor size.

Between May 2003 and December 2017, 395 patients with 445 lung tumors (primary lung cancer, n = 327; metastases, n = 118) were treated by SBRT in our institution. The median follow-up period for all the patients was 27.5 months. The 3-year local control rates for stage-I lung cancer and lung metastases were 90.1 % and 87.1 %, respectively (Figure 1). The frequency of radiation pneumonitis after SBRT was 1.5 % (six patients) at Grade 2 and 0.3 % (one patient) at Grade 3. We observed no other adverse events after SBRT at Grade 2 or more

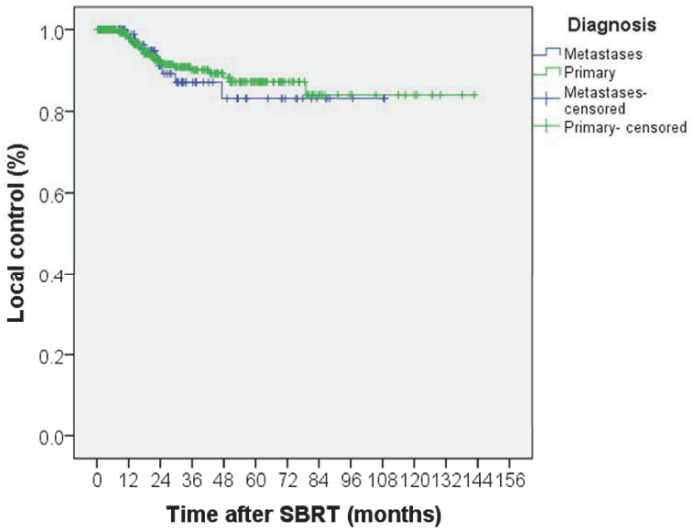

Figure 1 Kaplan-Meier curves of local control rates for stage-I lung cancer (n = 327) and lung metastases (n = 118) after stereotactic body radiotherapy (SBRT). The curves include all such tumors at Hirosaki University Hospital between May 2003 and December 2017.

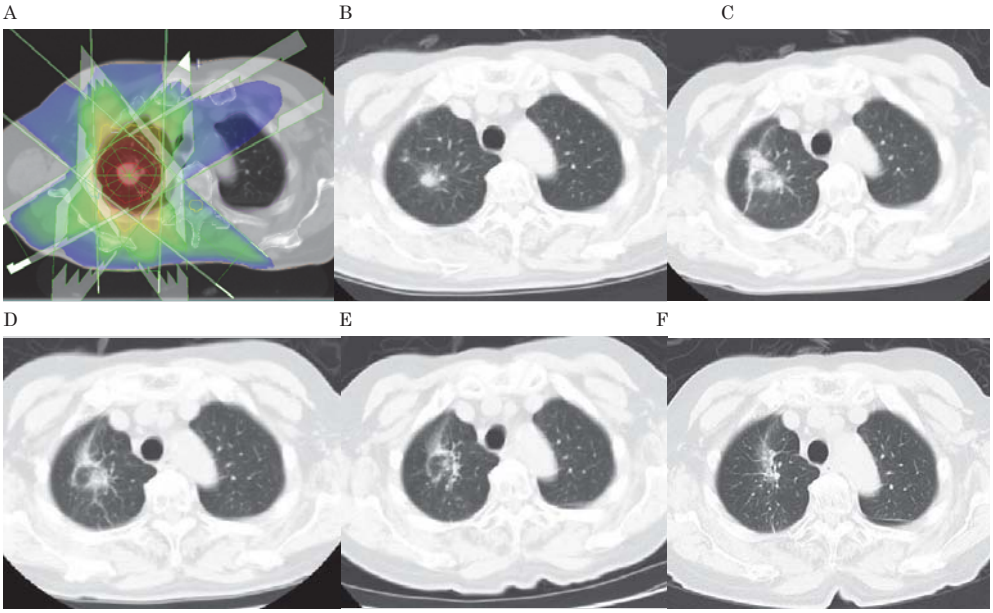

Figure 2 Clinical course of a patient treated with stereotactic body radiotherapy (SBRT). The patient was an 80-year-old woman with primary lung cancer (adenocarcinoma; cT1N0M0). (A) Pre-treatment CT scan with the dose distribution. (B–F) CT scans acquired at 3 months (B), 6 months (C), 1 year (D), 2 years (E), and 5 years (F) after the SBRT. Radiation pneumonitis was observed 6 months after the SBRT, which changed to radiation fibrosis. The tumor was controlled more than 5 years after the SBRT.

in our series. A typical case of a patient with early-stage NSCLC who responded well to this treatment is shown in Figure 2.

Conclusion

SBRT offers a high degree of local control with minimal toxicity for patients with early-stage NSCLC and lung oligo-recurrence. It is our

intention to refine this technology and adapt it for other malignant tumors, and we will continue to use it for the treatment of many patients.

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