Akita J Med **48** : 85-98, 2021

SAFETY AND TREATMENT OUTCOMES OF STEREOTACTIC BODY RADIOTHERAPY FOR PULMONARY TUMORS : A RETROSPECTIVE SINGLE-CENTER STUDY

Satoshi Kumagai[1)], Yuki Wada[1)], Akira Anbai[2)], Noriko Takagi[1)], Eriko Okuyama[1)] and Manabu Hashimoto[1)]

[1)]*Department of Radiology, Akita University Graduate School of Medicine*
[2)]*Department of Radiology, Omagari Kousei Medical Center*

(received 9 November 2021, accepted 13 December 2021)

Abstract
Stereotactic body radiotherapy (SBRT) uses hypofractionated and more precise irradiation methods, and has the advantages of shorter duration, better outcomes, and fewer side effects than conventional radiotherapy. However, the optimal dosage remains unclear. The purpose of the study was to analyze our preliminary treatment results and safety. We retrospectively analyzed 32 patients (primary cancer, 22 ; metastatic cancer, 10) who underwent SBRT for pulmonary tumors at our hospital from April 2015 to June 2020. SBRT was performed with escalated dose prescriptions (up to 55Gy in 4 fractions/64Gy in 8 fractions for peripheral/central lesions, respectively). We evaluated the local control rate (LC rate), overall survival (OS), progression-free survival (PFS), disease-specific survival (DSS), and adverse events. The target lesions comprised 22 primary lung cancers and 13 metastatic lung cancers. The 2-year LC, OS, PFS, and DSS rates were 82.5%, 68.3%, 50.5%, and 88.0% for primary lung cancer patients and 83.1%, 29.9%, 23.1%, and 48.6% for metastatic lung cancer patients, respectively. Five cases of radiation pneumonitis of grade 2 or higher, one of grade 1 dermatitis and 1 of esophagitis were observed as adverse events. We showed that the treatment outcomes of SBRT for primary and metastatic lung cancers were mostly acceptable.

Keywords : Stereotactic body radiotherapy, Stereotactic ablative radiotherapy, Lung cancer, Oligometastasis.

Introduction

Advancements in irradiation technology and the widespread use of devices facilitate "pinpoint" radiotherapy by ensuring high positioning accuracy and the application of radiation beams from several directions. This aforementioned method is termed stereotactic body radiotherapy (SBRT), also known as stereotactic ablative radiotherapy (SABR), in which a large dose of radiation of 7.5-20 Gy per fraction is delivered to a body lesion for image-guided, confirmed, and corrected precise position of the target lesion, while sparing the normal organs surrounding the target. In contrast, conventional irradiation methods only deliver 1.8-2 Gy dose per fraction. SBRT has advantages over three-dimensional conventional radiotherapy, including shorter treatment duration, higher local control (LC) rate, and lower frequency of adverse events[1)]. Currently, SBRT is used worldwide for various malignant tumors, including primary and metastatic lung cancer[2)], liver cancer, pancreatic cancer, and prostate can-

Corresponding Author : Yuki Wada
Department of Radiology, Akita University Graduate School of Medicine
1-1-1 Hondo, Akita-city, Akita, Japan
Tel : +81-18-834-1111
Fax : +81-18-836-2623 Mail ywada@med.akita-u.ac.jp

cer.

Some reports have demonstrated a good treatment outcome of SBRT for primary and metastatic lung cancer. In the treatment of early-stage lung cancer without lymph metastasis, SBRT had a higher control rate and fewer adverse events than conventional irradiation[3]. A prospective phase II trial of SBRT in Japan for inoperable cases of T1 lung cancer reported a 3-year LC rate of 87.3%, a 3-year overall survival (OS) rate of 59.9%, an adverse event (below Grade 4) rate of 12.5%, and no Grade 5 events[4]. For metastatic lung cancer, a Japanese multicenter retrospective study of SBRT showed a 3-year LC rate of 81.3% and a 3-year OS of 60.3%[5]. On the other hand, a retrospective analysis of 149 cases of conventional irradiation for inoperable stage I lung cancer reported a 3-year LC rate of 57% and a 3-year OS rate of 34%[6]. A randomized controlled trial of SBRT versus conventional RT for early-stage lung cancer reported that esophagitis was significantly more common with conventional RT, and other adverse events such as pneumonia, dyspnea, and pulmonary fibrosis also tended to be more common[3]. While the clinical features of SBRT are favorable, there is no established dose prescription. Our institution has been using the highest possible prescription dose within the dose constraints of normal tissue. This is because higher doses are more effective in SBRT for lung cancers[7,8]. SBRT applies an ablative dose to a narrow area, thus necessitating ensuring and evaluating the positioning and treatment planning techniques at each institution.

We initiated SBRT for primary lung cancer and lung metastasis at our hospital since 2015. We aimed to retrospectively analyze the treatment outcomes and adverse events in these patients.

Materials and Methods

This retrospective study was approved by the institutional review board of the Akita University Graduate School of Medicine (approval number : 2170).

Patients

A total of 34 patients underwent SBRT for primary or metastatic lung cancers at the Akita University Hospital from April 2015 to June 2020. Primary lung cancer includes clinically diagnosed lung cancer without pathological evidence, which comprises tumors with a consistent tendency to increase in size on computed tomography (CT) or those with highly suspicious ground-glass nodule (GGN), pleural involvement, or spicula on imaging as primary malignancies of the lung. It also includes tumors with failed or unavailable biopsy of the lung mass because of medical reasons and unknown histology. Two patients with no clinical follow-up after treatment were excluded. Eventually, we included 32 patients with 35 lung cancers in this retrospective study. Their medical information was obtained from the medical record system and radiation information system.

Treatment Techniques

SBRT was planned with Eclipse version 11.0 (Varian Medical System, USA), a three-dimensional radiotherapy planning system. Radiation planning CT images were acquired as four-dimensional (4-D) CT under respiratory synchronization using Aquilion LB (Canon Medical Systems Corporation, Japan). The irradiation system was TrueBeamSTX (Varian Medical System, USA). SBRT was performed with 6 MV or 10 MV X-ray of a linear accelerator. The respiration synchronizing intercept irradiation method was performed using Real-time Position Management (Varian Medical System, USA) system. Dose calculation was performed using AcruosXB or analytical anisotropic algorithms.

Radiotherapy planning was based on the 2016 or 2020 Japanese Society for Radiation Oncology guidelines for Radiotherapy Treatment Planning[9,10]. Briefly, the clinical target volume (CTV) was equal to the gross tumor volume, detected as a pulmonary lesion on planning CT images. The internal target volume (ITV) was based on merged CTV of 4-D CT images. The planning target volume (PTV) was created by adding 5 mm to the ITV in all directions. We set a leaf margin of 5 mm or 0-3 mm in case of an isocenter prescription method or volume prescription method to PTV, respectively, in all directions.

Dose prescription was guided by the isocenter prescription method from April 2015 to June 2018 and by the volume prescription method in which the prescribed dose

covered 95% of the target volume from July 2018 onwards.

The prescribed irradiation doses were different for the peripheral and central lesions, with 42–55 Gy in 4–5 fractions and 56–64 Gy in 7–8 fractions, respectively. Central tumors were defined according to a previous report[11].

While determining the prescription dose from April 2015 to June 2018, the dose was initially set at 48 Gy and 56 Gy in 4 and 8 fractions for peripheral and central tumors both guided by isocenter prescription, respectively. Starting from July 2018, the dose was set at 42 Gy and 56 Gy in 4 and 8 fractions for peripheral and central tumors guided by volume prescription and isocenter prescription, respectively. Dose prescription of 48Gy in 4 fractions guided by isocenter prescription and 42Gy in 4 fractions guided by volume prescription are approximately equivalent[12]. These dose prescriptions were in accordance with previous reports[4,13,14], and were defined as the standard dose. In central lesions, since important organs such as the trachea, bronchus, aorta, heart, and esophagus are close to the irradiation site, the number of irradiation fractions was increased and the amount of each single dose was reduced to maintain therapeutic efficacy. The standard dose was used from April 2015 to June 2018. The maximum dose was escalated to 55 Gy and 64 Gy in 4 and 8 fractions, respectively, in accordance with the results of phase I studies[14–16]. These doses were defined as the escalated dose, and within the range of dose constraints for healthy organs. The basic irradiation method for peripheral tumors involved 4–5 fractions. However, for cases with a history of thoracic irradiation or relatively large lesions adjacent to organs at risk, a larger number of fractions and a lower dose must be reluctantly adopted. In such cases, irradiation was performed at 48–49 Gy dose in 7–8 fractions. These dose prescriptions are defined as the reduced dose. This was in accordance with central tumors in consideration of the tolerable dose.

All patients did not receive chemotherapy or immunotherapy in combination with SBRT. However, in patients with metastatic lung cancer, SBRT was administered after primary treatment, such as surgery, radiotherapy, and chemotherapy, for the primary tumor.

Statistical Analysis and Assessments

We evaluated adverse events and the LC rate as primary endpoints for both primary and metastatic lung cancer. We also compared the OS, progression-free survival (PFS), and disease-specific survival (DSS) with those in previous studies and examined the prognostic factors. LC was defined as a state of similar or reduced tumor volume compared with that at the beginning of treatment. OS was defined as the time from the initiation of treatment until all deaths by current disease or other reasons. PFS was defined as the time from treatment initiation until disease worsening (local growth or metastasis) or death without progression. DSS was defined as the time from the beginning of treatment to death from current disease.

Treatment effects associated with SBRT were assessed by CT based on the Japanese version of the Response Evaluation Criteria in Solid Tumors version 1.1. as translated by the Japan Clinical Oncology Group (JCOG)[17]. We assessed adverse events by CT and physical assessment based on the Japanese version of the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 translated by the JCOG[18].

To compare the effects of various dose prescriptions and dose fractionation, we calculated the biological effective dose (BED) based on a linear-quadratic model[19] as described previously[7]. BED was defined as $nd(1+d/\alpha/\beta)$; where n is the number of fractions and d is the dose per fraction. α/β is set at 10 to evaluate anti-tumor effects ; BED is marked as BED_{10}, and the unit is Gy. The BED_{10} corresponding to each dose prescription used in SBRT for pulmonary cancers at our institution is shown in Figure 1.

We used the Kaplan-Meier method to plot the survival curves. We also assessed the prognostic factors for LC, OS, PFS, and DSS rate. We divided the patients into two groups according to sex, age, tumor size, and BED_{10} for each individual lesion and examined the differences in the LC, OS, PFS, and DSS rate using the log-rank test. For primary lung cancers, we divided the patients into two groups according to whether the lung cancer was GGN or not. For metastatic lung cancers, we divided the patients into two groups based on disease-free in-

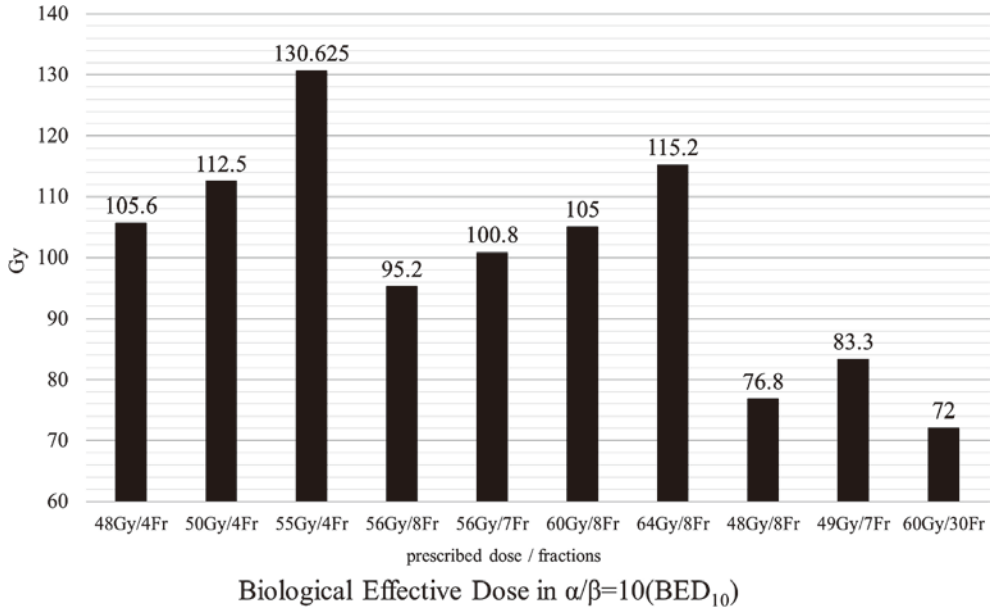

Figure 1. Biological effective dose in $\alpha/\beta=10$ (BED_{10}).
The BED_{10} based on the linear-quadratic model for each prescription dose. BED was defined as $nd(1+d/\alpha/\beta)$, where n is the number of fractions and d is the dose per fraction. α/β is set at 10 to evaluate anti-tumor effects. BED at $\alpha/\beta=10$ is marked as BED_{10}, and the unit is Gy. 48Gy/4Fr and 56Gy/8Fr are defined as the standard dose, while 50Gy/4Fr, 55Gy/4Fr, 56Gy/7Fr, 60Gy/8Fr, and 64Gy/8Fr are defined as the escalated dose. 48Gy/8Fr and 49Gy/7Fr are defined as the reduced dose. BED_{10} at 60 Gy/30 Fr, which is used in conventional radiotherapy, is shown on the far left.
BED, biological effective dose. Gy, Gray. Fr, Fractions.

terval (DFI). DFI was defined as the time between the completion of treatment for the primary tumor and the identification of metastasis or recurrence.

All statistical analyses were performed in BellCurve for Excel version 3.21 (Social Survey Research Information Co., Ltd. Tokyo, Japan). Statistical significance was set at $p<0.05$.

Results

Patients

A total of 32 patients were eligible for the study, and this comprised 35 lesions. Table 1 summarizes the patient characteristics. The participants comprised 17 men and 15 women. The median age was 77 years (range 51-89). While 22 patients had primary lung cancer, 10 had metastatic lung cancer. The number of treated lesions was one in 30 patients, two in 1 patient, and three in 1 patient. In patients with primary lung cancer, all 22 patients had one treated lesion. In patients with metastatic lung cancer, 8 patients had 1 treated lesion, 1 male patient had 2 treated lesions, and 1 female patient had 3 treated lesions. In metastatic lung cancers, 3 patients with esophageal cancer were treated with chemotherapy or immune checkpoint inhibitor (ICI) therapy for local or distant recurrence after SBRT. The chemotherapy and ICI therapy regimens included cisplatin+5-fluorouracil (5-FU), nedaplatin+5-FU, docetaxel, paclitaxel, tegafur-gimeracil-oteracil, irinotecan, and nivolumab, several of which were used sequentially.

Table 2 summarizes the tumor and treatment characteristics of the study participants. Of the 22 primary lung cancers, 9, 2, and 11 lesions were adenocarcinoma, squamous cell carcinoma (SCC), and clinically diagnosed lung cancer without histological proven data, all in re-

Table 1. Patient characteristics (N=32).

Characteristics		n
Age, years, median (range)		77 (51–89)
Sex		
male		17
female		15
Performance Status (ECOG)		
0		26
1		5
2		1
Origins of the tumor		
Primary		22
Metastasis		10
Number of targets		
1		29
2		1
3		1
Any chemotherapy/ICI therapy after SBRT in patients with metastatic lung cancer		
Yes		3
	Cisplatin+5-FU/Nedaplatin+5-FU	1/2
	Docetaxel/Paclitaxel	1/2
	Tegafur-gimeracil-oteracil	1
	Irinotecan	1
	Nivolumab	1
No		7

5-FU : fluorouracil
ECOG : Eastern Cooperative Oncology Group
ICI : immune checkpoint inhibitor
SBRT : Stereotactic body radiotherapy

spective order. The T classifications of clinical stages in primary lung cancers according to the Union for International Cancer Control classification eighth edition were Tis, T1mi, T1a, T1b, T1c, and T2a with 1, 2, 3, 3, 8, and 5 lesions, respectively. Of the 22 primary lung cancers, 5 were GGNs and 17 were solid tumors. Thirteen metastatic lung cancers consisted of 8 lesions spread from SCC in esophageal cancer, 2 from papillary thyroid cancer, 2 from sarcoma, and 1 from uterine/ovarian cancer. The lesions comprised 29 peripheral tumors and 6 central tumors. Isocenter and volume dose prescription was performed for 14 and 21 lesions, respectively. Eight and 13 peripheral lesions were administered the standard dose and escalated dose, respectively. In other lesions, including central lesions and those with a history of chest irradiation, 10 lesions were administered a standard dose, and 2 lesions each were administered an escalated dose and reduced because of dose constraints.

Local Control Rate and Adverse Events

The median follow-up was 15 months (range 1 to 34 months). The 2-year LC rates for primary and metastatic tumors were 82.5% and 83.1%, respectively (Figure 2), with no significant difference (p=0.8014). Of the 32 patients treated with SBRT, there were 10 recurrences of primary lung cancer and metastatic lung cancer (five cases each) comprising 5 cases of local enlargement, 3 cases of mediastinal lymph node recurrence, 1 case of distant lymph node recurrence, and 1 case of carcinomatous lymphangiomatosis. Twenty-two cases of primary

Table 2. Tumor and treatment characteristics (N=35).

Tumors	n
Histologic type	
Primary Lung Cancer	22
Adenocarcinoma	9
Squamous Cell Carcinoma	2
Clinical Lung Cancer (unknown histology)	11
Metastasis (type of primary cancer)	13
Esophageal squamous cell carcinoma	8
Thyroid Papillay Carcinoma	2
Sarcoma	2
Uterine/Ovarian carcinoma	1
T factor of clinical stage in primary lung cancer (UICC classification 8th edition)	
Tis	1
T1mi/a/b/c	2/3/3/8
T2a	5
Ground-glass nodule in primary lung cancer	
Yes	5
No	17
Location of tumors	
Peripheral	29
Central	6
Dose Prescription Method	
isocentric prescription	14
volume prescription	21
Dose Prescription	
Peripheral lesions	
Minimum dose (48Gy/4Fr or 42Gy/4Fr)	8
Escalated dose (48–55Gy/4Fr)	13
Central lesions / Lesions with history of chest irradiation	
Minimum dose (56Gy/8Fr)	10
Escalated dose (60–64Gy/8Fr,56Gy/7Fr)	2
Reduced dose (48Gy/8Fr, 49Gy/7Fr)	2
BED_{10} in Gy	
< 100	7
$\geqq 100$	28

BED : Biological Effective Dose
Fr : Fraction
UICC : Union for International Cancer Control

lesions comprised five (22.7%) cases of recurrences, including three (13.6%) local enlargement of the irradiated lesions and two (9.1%) mediastinal lymph node metastases. Thirteen cases of metastatic lesions comprised five (38.5%) cases of recurrences : two (15.4%) were enlargement of the irradiated lesions ; one (7.7%), mediastinal lymph node metastasis ; one (7.7%), distant lymph node metastasis ; and one (7.7%), carcinomatous lymphangiomatosis.

Radiation pneumonitis was the most frequently ob-

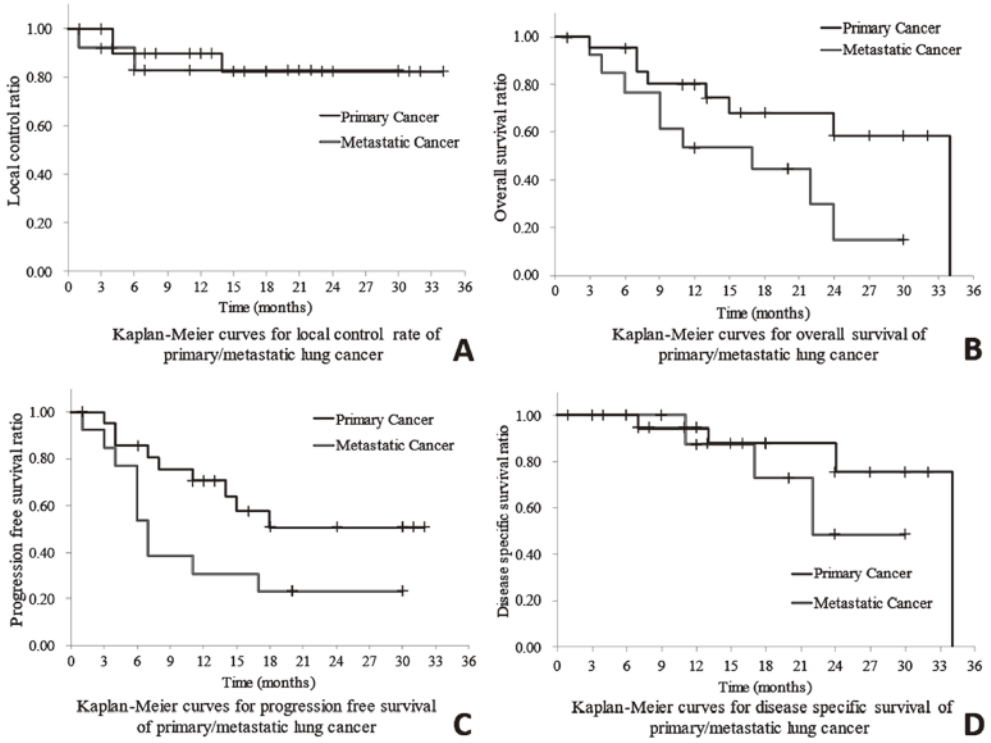

Figure 2. Kaplan-Meier curves of the local control, overall survival, progression-free survival, and disease-specific survival rates of patients with primary and metastatic lung cancer.
The figure depicts the LC (A), OS (B), PFS (C), and DSS (D) rates of patients with primary and metastatic lung cancer. Vertical lines indicate censoring. The 1-year and 2-year LC rates for primary and metastatic tumors are 90.0% and 83.1% and 82.5% and 83.1%, respectively, none of which reached the median. The 1-year and 2-year OS rates for primary and metastatic tumors are 80.2% and 53.9% and 68.3% and 29.9%, respectively, with a median OS of 34 months and 17 months, respectively. The 1-year and 2-year PFS rates for primary and metastatic tumors are 70.6% and 30.8% and 50.5% and 23.1%, respectively. While the median PFS rate for primary lung cancer has not reached the median, that for metastatic lung cancer is 7 months. The 1-year and 2-year DSS rates for primary and metastatic tumors are 94.7% and 87.5% and 88.0% and 48.6%, respectively. While the median DSS rate for primary lung cancer has not reached the median, that for metastatic lung cancer is 22 months. LC, local control. OS, overall survival. PFS, progression-free survival. DSS, disease-specific survival.

served adverse event following SBRT for pulmonary tumors. Grade 1 and 2 radiation pneumonitis was identified in 22 (64.7%) and 3 (8.3%) lesions, respectively. Two patients (6%) had grade 5 pneumonitis. One patient was a septuagenarian woman undergoing SBRT for three metastatic lung cancers following radical chemoradiation therapy (CRT) for esophageal cancer. SBRT was administered to each pulmonary tumor at dosages of 48 Gy, 56 Gy, and 56 Gy in 8 fractions each. The absorbed dose in the lung field was high, and the V20 Gy of the lung (volume percentage when irradiated with ≥20 Gy in a volume of the total lung) was 46.7% of the total dose. The other case involved a man in his 60s who was irradiated with 55 Gy in four fractions for one lesion of primary lung cancer, and the V20 Gy was 7.71%. However, a shadow suspicious for idiopathic pulmonary fibrosis was observed in the CT before irradiation.

Radiation dermatitis was not observed, excluding one case. One case of grade 1 dermatitis post-SBRT occurred after radical CRT for esophageal cancer, i.e., 60 Gy irradiation to the chest, and dermatitis occurred in areas where the total dose exceeded 80 Gy. However, it

Table 3. One and 2-year LC, OS, PFS, and DSS rates for primary ($n=22$) and metastatic lung cancers ($n=13$)

Characteristics	n	1-year LC rate (%)	2-year LC rate (%)	P value	1-year OS (%)	2-year OS (%)	P value	1-year PFS (%)	2-year PFS (%)	P value	1-year DSS (%)	2-year DSS (%)	P value
Primary Lung Cancer	22												
Sex													
male	12	100	90.1	0.4875	80.0	57.1	0.3481	60.6	48.5	0.7766	100	85.7	0.6813
female	10	100	74.1		80.0	80		80.0	50		88.9	88.9	
Age, years													
<75	8	100	100	0.1525	70.0	70	0.4883	87.5	52.5	0.4981	100	100	0.1705
≥75	14	100	71.4		75.5	67.1		59.8	49.9		90.1	53.9	
Tumor size, cm													
<3	20	100	88.9	0.2643	78.0	53.6	0.3213	67.4	51.3	0.9361	94.1	72	0.5104
≥3	2	100	50		100	100		100	50		100	100	
BED10, Gy													
<100	2	100	100	0.5759	100	100	0.3483	100	100	0.2924	100	100	0.5104
≥100	20	100	80.8		78.0	54.2		67.4	46.2		94.1	71.9	
GGN													
Yes	5	100	100	0.3173	100	66.7	0.4631	100	66.7	0.2641	100	100	0.3044
No	17	86.7	77		73.7	53		60.9	44.4		92.9	66.9	
Characteristics	n	1-year LC rate (%)	2-year LC rate (%)	P value	1-year OS (%)	2-year OS (%)	P value	1-year PFS (%)	2-year PFS (%)	P value	1-year DSS (%)	2-year DSS (%)	P value
Metastatic Lung Cancer	13												
Sex													
male	6	83.3	NR	0.9566	66.7	0.0	0.9784	33.3	NR	0.9373	100	37.5	0.8435
female	7	80.0	80.0		42.9	42.9		28.8	28.6		75.0	75.0	
Age, years													
<75	8	87.5	NR	0.6383	62.5	0.0	0.7925	37.5	NR	0.3983	83.3	33.3	0.3173
≥75	5	66.7	66.7		40.0	40.0		20.0	20.0		100	100	
Tumor size, cm													
<3	12	81.5	81.5	0.6595	58.3	32.4	0.5638	33.3	25.0	0.9695	100	55.6	0.0115*
≥3	1	0	NR		0	NR		0	NR		0	NR	
BED_{10}, Gy													
<100	5	80.0	NR	0.5184	40.0	0.0	0.1935	0	NR	0.0032**	100	50.0	0.7697
≥100	8	87.5	87.5		62.5	46.9		50.0	37.5		83.3	62.5	
DFI, months													
<15	8	87.5	NR	0.8695	25.0	0.0	0.0132*	12.5	NR	0.0609	66.7	33.3	0.2452
≥15	5	80.0	80.0		100	50.0		60.0	60.0		100	50.0	

LC: local control; OS: overall survival; PFS: progression-free survival; DSS: disease-specific survival; BED: biological effective dose; DFI: disease-free interval; NR: not reached. *$P < 0.05$; **$P < 0.01$.

was resolved shortly afterwards.

We also identified one case of grade 1 esophagitis post-SBRT. Esophagitis occurred after the irradiation of a lesion localized in the left lung apex adjacent to the esophagus. Nonetheless, it was resolved shortly afterwards.

Survival and Prognostic Factors

The 2-year OS, PFS, and DSS rates of 22 primary lesions and 13 metastatic lesions were 68.3%, 50.5%, and 88.0% and 29.9%, 23.1%, and 48.6%, respectively (Figure 2).

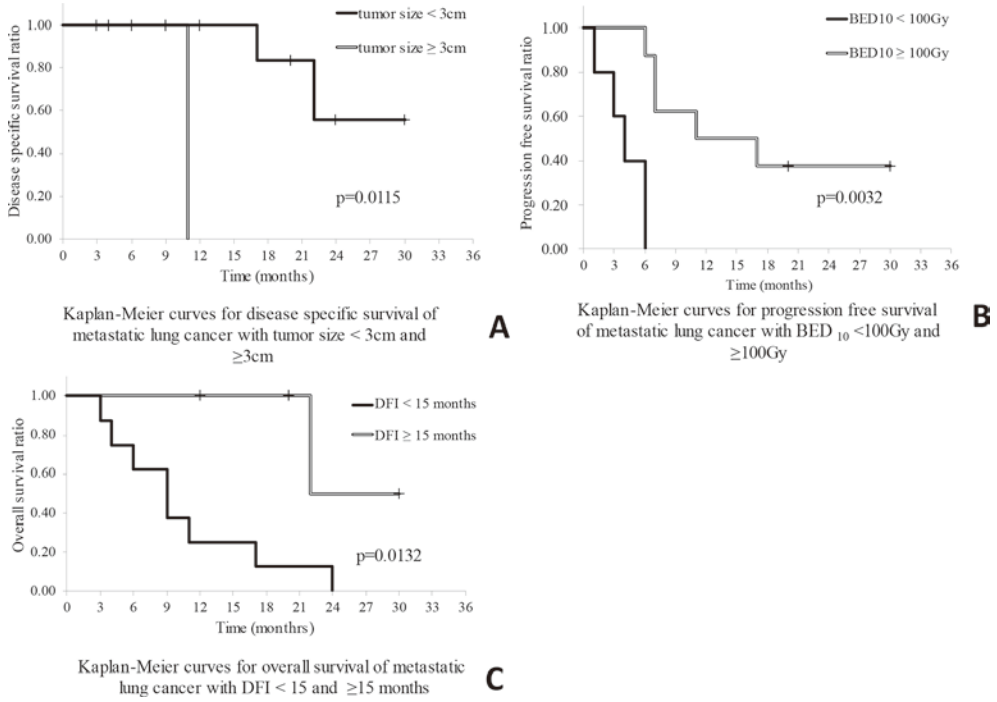

Figure 3. Kaplan-Meier curves of disease-specific survival in metastatic lung cancer with tumor size <3 cm and ≥3 cm (A), progression-free survival in metastatic lung cancer with BED_{10} <100 Gy and ≥100 Gy (B), and overall survival in metastatic lung cancer with DFI <15 months and ≥15 months (C).
The figure depicts the DSS (A), PFS (B), and OS (C) rates of patients with metastatic lung cancer with tumor size <3 cm and ≥3 cm (A), BED_{10} <100 Gy and ≥100 Gy (B), and DFI <15 months and ≥15 months (C), respectively. Vertical lines indicate censoring. In the log-rank tests of the Kaplan-Meier curves, there was a significant difference in DSS between patients with tumor size ≥3 cm and those with tumor size <3 cm (p=0.0115), in PFS between patients with a BED_{10} ≥100 Gy and a BED_{10} <100 Gy (p=0.0032), and in OS between patients with a DFI <15 months and those with a DFI ≥15 months (p=0.0132).
LC, local control. OS, overall survival. PFS, progression-free survival. DSS, disease-specific survival. DFI, disease-free survival.

Table 3 summarizes the prognostic factor analysis. Regarding primary lung cancers, no prognostic factors were identified. There was no significant difference in each outcome between GGN and other solid tumors, although the solid tumors showed a trend toward lower LC, OS, PFS, and DSS rates. Regarding metastatic lung cancers, smaller tumor size, higher BED_{10}, and longer DFI were associated with better DSS, PFS, and OS rates (Figure 3). Particularly, patients with tumor size ≥3 cm had poorer DSS than those with tumor size <3 cm (p=0.0115); those with a BED_{10} >100 Gy had better PFS than those with a BED_{10} <100 Gy (p=0.0032), and those with a DFI <15 months had poorer OS than those with a DFI >15 months (p=0.0132).

Discussion

We identified five cases of radiation pneumonitis ≥ grade 2 and one case each of grade 1 dermatitis and esophagitis. Of the ten recurrent cases, only five involved local recurrence. In addition, smaller tumor size, higher BED_{10}, and longer DFI were associated with better outcomes for metastatic lung cancers.

The 2-year LC rates were 82.5% and 83.1% for primary lung cancer and lung metastasis, respectively. A Japanese prospective phase II trial of SBRT for stage IA

non-small cell lung cancer (JCOG0403) reported 3-year LC rate of 85.4% and 87.3% for operable and inoperable cases, respectively[4]. For lung metastasis, an American prospective phase I/II multi-center study found a 2-year LC rate of 96%[20]. In Japan, a large multi-center retrospective study of 1,387 patients with lung oligometastases treated with SBRT reported a 3-year LC rate of 81.3%[5]. Despite the differences in patient characteristics among these studies, the LC rates of irradiated lesions we noted was similar to those in previous studies for both primary lung cancer and lung metastasis. The 2-year LC rate was not significantly different between primary and metastatic lung cancer. In a Japanese retrospective study of SBRT for GGN, including pathologically unconfirmed cases, a 3-year LC rate of 98.8%[21] was reported, which compared favorably with the results in primary and metastatic solid lung cacners[5,7]. In addition to these cases where better LC rate was expected, this study included relatively large solid primary pulmonary tumors of more than 2 or 3 cm in size. In such solid tumors, the results showed a trend toward relatively lower LC rates and survival rates compared with those of GGNs. Several studies have reported that LC rate decreases with tumor size[22-24], and phase I dose escalation studies for larger tumors have been conducted to confirm the safety of SBRT[15,16]. A phase III trial is currently conducted to compare normal and escalated doses[13]. In metastatic lung cancer, higher doses are associated with favorable LC rates[8]. Thus, escalating doses may be appropriate for improving the LC rate.

SBRT is linked to fewer adverse events than conventional irradiation[1]. However, radiation pneumonitis, dermatitis, rib bone fracture, intercostal neuralgia, bronchial hemorrhage, and esophagitis are major adverse events following SBRT for pulmonary tumors. In this study, two patients died due to grade 5 radiation pneumonitis (6%), and three patients had grade 2 radiation pneumonitis (8.3%). One patient each (3%) had grade 1 radiation dermatitis and esophagitis. Radiation pneumonitis is most frequently observed and can become fatal. The frequency of grade 2 and 3 radiation pneumonitis post-SBRT was reported to be 10% and 2-4%[25], respectively. Grade 5 radiation pneumonitis was observed in 0.5% cases in the 2006 and 2008 national surveys in Japan[26]. Risk factors for ≥grade 2 radiation pneumonitis include female sex, high or low cumulative smoking history, tumor size ≥3 cm, high V20 Gy of the lungs, a history of lung resection[27,28], and interstitial pneumonia detected on pretreatment CT[29,30]. Therefore, the risk of radiation pneumonitis and the benefits of SBRT should be carefully considered in patients with the aforementioned risk factors. Moreover, these patients require close follow-up post-SBRT. In this study, one of the patients with grade 5 pneumonitis was administered with high V20 Gy (46.7%) owing to a history of definitive 3-D conventional irradiation for chest malignancy. Moreover, SBRT was performed for three lung cancers. In the other patient with grade 5 pneumonitis, a shadow of suspected idiopathic pulmonary fibrosis in the CT before irradiation was noted. Excluding these high-risk patients, no serious side effects were reported, and we observed a significant correlation between the prescribed dose and outcome. Therefore, dose escalation within the dose constraints of healthy organs appeared to be a reasonable approach.

In this study, tumor size of less than 3 cm, BED_{10} of more than 100 Gy, and DFI of more than 15 months for metastatic lung cancers were associated with better DSS, PFS, and OS, respectively. Smaller tumor size[31] and higher BED_{10} (≥100 Gy)[7] have been associated with favorable LC rate for primary lung cancer. Moreover, higher BED_{10} was associated with favorable LC rate for lung metastasis[8]. An improvement in the LC rate of lung cancer/metastasis may necessitate the escalation of the radiation dose to at least BED_{10}=100 Gy within a safe range for a radiation exposure of the surrounding organs. Thus, it is necessary to escalate the dose within a reasonable range. Longer DFI is correlated with better prognosis for lung metastasis[32,33]. The European Society for Radiotherapy and Oncology/European Organisation for Research and Treatment of Cancer recommends classifying oligometastases into two groups, namely synchronous oligometastatic diseases and metachronous oligometastatic disease, based on the time from the initial diagnosis of primary lesion to recurrence is within 6 months or longer[34]. In the consensus recommendation, synchronous oligometastatic diseases display more aggressive disease phenotype and worse prognosis than the

metachronous type. In this study, a DFI of >15 months was associated with better prognosis. Previous studies have reported an association between longer DFI (≥36 months[32] and ≥30 months[33]) and better prognosis. Despite no consensus on an appropriate DFI to predict the OS after SBRT, longer DFI is favorable for the consideration of SBRT in patients with lung metastases.

In the prognostic analysis of primary lung cancer, male patients had a worse 2-year OS than female patients, despite having a better 2-year LC rate. The median age of eligible patients in this study was 77 years, which is close to the life expectancy of both males and females in Japan (81.41 years and 87.45 years, respectively[35]). The outcomes of the 12 male and 10 female patients with primary lung cancer were similar, with survival in 7 patients and deaths of 2, although there were 3 deaths from other diseases in the male patients compared with 1 in the female patients. The lower 2-year OS in male patients may be due to age and comorbidities. Primary lung cancer patients with a tumor size of less than 3 cm had a better 2-year LC rate than those with a tumor size of more than 3 cm, although those with a tumor size of less than 3 cm had a worse 2-year OS than those with a tumor size of more than 3 cm. A previous study has reported that larger tumor size is a prognostic factor for worse outcomes[22], and the results of this study were the opposite to what was expected. There were no deaths from other diseases in the group with a tumor size of more than 3 cm, while the group with a tumor size of less than 3 cm included 3 cases of death from other diseases. This may have caused a discrepancy between LC rates and OS.

In regard to the optimal dose of SBRT for peripheral tumors, on the basis of an early study[7], 48 Gy in 4 fractions (or 42 Gy in 4 fractions in the volume prescription) is the most common dose prescription currently given in Japan[9]. In an effort to improve the control rate, a phase III trial comparing 42 Gy in 4 fractions and 55 Gy in 4 fractions is currently ongoing[13]. In the U.S., the maximum tolerated dose was set at 60 Gy in 3 fractions (BED_{10} 180 Gy) in phase I trials[36,37], which comprises higher doses and more hypofractionation than that in Japan. For lung cancer with a clinical stage of T2 or higher, it has been suggested that better LC rates and OS can be obtained with a BED^{10} of 150 Gy or more[38], which is equivalent to 60 Gy in 4 fractions or 54 Gy in 3 fractions ; however, a phase I study in Japanese patients with clinically classified T2 lung cancer indicated that a dose prescription of 60 Gy in 4 fractions would be difficult to meet existing dose constraints[15]. For peripheral tumors, it is necessary to explore the optimal dose for each stage of disease. In SBRT for central tumors, it is common to use many fractions to reduce adverse events[9]. In the Japanese phase I trial of SBRT for central lesions, the recommended dose was 60 Gy in 4 fractions, not because higher dose caused higher toxicity, but because patients could not be included due to dose constraints and study time limitation[14]. A phase I/II trial in the U.S. for central lesions used a dose prescription of 57.5 Gy in 5 fractions (BED_{10} 123.6 Gy) and 60 Gy in 5 fractions (BED_{10} 132.0 Gy), which resulted in good LC and survivals comparable to SBRT for peripheral lesions. However, Grade 5 adverse events occurred in approximately 4% of patients in these high-dose groups[39]. For central lesions, dose escalation in the safe range should be considered. Prescribed doses of SBRT for metastatic lung cancer are set according to those for primary lung cancer. Better LC tends to be achieved with a higher dose, and it has been suggested that at least 48 Gy in 3 fractions (BED_{10} 124.8 Gy) or higher is required to achieve a 2-year LC rate of 90%[40]. Lung metastases from primary colorectal cancer (CRC) had a significantly lower LC rate than other primary cancers[5], although lung metastases from primary CRC tended to have a higher LC rate with a higher BED_{10}[8]. Optimal doses needs to be explored based on the histology, as well as the location of the tumor.

This study had a few limitations. First, we conducted a single-center, retrospective study with a limited sample size. Second, some of the treated patients demonstrated a short observation period. However, it was important to analyze the initial results after treatment initiation to evaluate and improve the quality of radiotherapy, particularly SBRT, which requires accurate treatment planning, advanced positioning, and irradiation techniques. Therefore, further studies examining more patients at a longer observation period should be carried out in the future.

Conclusion

The results of SBRT for pulmonary tumors performed at our institution were mostly acceptable. The frequency of adverse events, such as radiation pneumonitis, was low. Thus, dose escalating within the constraints was considered reasonable. However, the treatment of patients with high-risk factors for adverse events, such as those with a history of thoracic irradiation and intestinal pneumonitis, should be carefully determined. Smaller tumor size, higher BED_{10}, and longer DFI were correlated with more favorable outcomes.

Conflict of Interest : COI

The authors have no conflicts of interest to declare.

References

1) Palma, D. and Senan, S. (2011) Stereotactic radiation therapy : Changing treatment paradigms for stage I non-small cell lung cancer. *Curr. Opin. Oncol.,* **23**, 133-139.
2) Lewis, S.L., Porceddu, S., Nakamura, N., *et al*. (2017) Definitive stereotactic body radiotherapy (SBRT) for extracranial oligometastases : An International Survey of >1000 Radiation Oncologists. *Am. J. Clin. Oncol.,* **40**, 418-422.
3) Nyman, J., Hallqvist, A., Lund, JA., *et al*. (2016) SPACE - A randomized study of SBRT vs conventional fractionated radiotherapy in medically inoperable stage I NSCLC. *Radiother. Oncol.,* **121**, 1-8.
4) Nagata, Y., Hiraoka, M., Shibata, T., *et al*. (2015) Prospective trial of stereotactic body radiation therapy for both operable and inoperable T1N0M0 non-small cell lung cancer : Japan Clinical Oncology Group Study JCOG0403. *Int. J. Radiat. Oncol. Biol. Phys.* **93**, 989-996.
5) Yamamoto, T., Niibe, Y., Aoki, M., *et al*. (2020) Analyses of the local control of pulmonary oligometastases after stereotactic body radiotherapy and the impact of local control on survival. *BMC Cancer,* **20**, 997.
6) Morita, K., Fuwa, K., Suzuki, Y., *et al.* (1997) Radical radiotherapy for medically inoperable non-small cell lung cancer in clinical stage I : A retrospective analysis of 149 patients. *Radiother. Oncol.,* **42**, 31-36.
7) Onishi, H., Araki, T., Shirato., H., *et al*. (2004) Stereotactic hypofractionated high-dose irradiation for stage I nonsmall cell lung carcinoma : Clinical outcomes in 245 subjects in a Japanese multiinstitutional study. *Cancer,* **101**, 1623-1631.
8) Kobiela, J., Spychalski, P., Marvaso, G., *et al*. (2018) Ablative stereotactic radiotherapy for oligometastatic colorectal cancer : Systematic review. *Crit. Rev. Oncol. Hematol.,* **129**, 91-101.
9) Japanese Society for Radiation Oncology. JASTRO Guideline 2016 for Radiotherapy Treatment Planing. Available at : https://www.jastro.or.jp/medicalpersonnel/guideline/jastro/2016.html. (Accessed : 19th September 2021).
10) Japanese Society for Radiation Oncology. JASTRO official guidelines. Available at : https://www.jastro.or.jp/medicalpersonnel/guideline/jastro/. (Accessed : 19th September 2021).
11) Timmerman, R., McGarry, R., Yiannoutsos, C., *et al*. (2006) Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. *J. Clin. Oncol.,* **24**, 4833-4839.
12) Kawahara, D., Ozawa, S., Kimura, T., *et al*., (2017) Marginal prescription equivalent to the isocenter prescription in lung stereotactic body radiotherapy : Preliminary study for Japan Clinical Oncology Group trial (JCOG1408). *J. Radiat. Res.,* **58**, 149-154.
13) Kimura, T., Nagata, Y., Eba, J., *et al.* (2017) A randomized Phase III trial of comparing two dose-fractionations stereotactic body radiotherapy (SBRT) for medically inoperable Stage IA non-small cell lung cancer or small lung lesions clinically diagnosed as primary lung cancer : Japan Clinical Oncology Group Study JCOG1408 (J-SBRT trial). *Jpn. J. Clin. Oncol.,* **47**, 277-281.
14) Kimura, T., Nagata, Y., Harada, H., *et al*. (2017) Phase I study of stereotactic body radiation therapy for centrally located stage IA non-small cell lung cancer (JROSG10-1). *Int. J. Clin. Oncol.,* **22**, 849-856.
15) Onimaru, R., Shirato, H., Shibata, T., *et al*. (2015)

Phase I study of stereotactic body radiation therapy for peripheral T2N0M0 non-small cell lung cancer with PTV < 100 cc using a continual reassessment method (JCOG0702). *Radiother. Oncol.* **116**, 276-280.

16) Onimaru, R., Shirato, H., and Shibata, T., *et al*. (2017) Phase I study of stereotactic body radiation therapy for peripheral T2N0M0 non-small cell lung cancer (JCOG0702) : Results for the group with PTV ⩾ 100 cc. *Radiother. Oncol.,* **122**, 281-285.

17) Japan Clinical Oncology Group. RECIST guideline version1.1. Available at : http://www.jcog.jp/doctor/tool/recistv11.html. (Accessed : 18th September 2021).

18) Japan Clinical Oncology Group. Common terminology criteria for adverse events. Available at : http://www.jcog.jp/doctor/tool/ctcaev5.html. (Accessed : 18th September 2021).

19) Yaes, R.J., Patel, P., and Maruyama, Y. (1991) On using the linear-quadratic model in daily clinical practice. *Int. J. Radiat. Oncol. Biol. Phys.,* **20**, 1353-1362.

20) Rusthoven, K. E., Kavanagh, B.D., Burri, S.H., *et al*. (2009) Multi-institutional Phase I/II trial of stereotactic body radiation therapy for lung metastases. *J. Clin. Oncol.,* **27**, 1579-1584

21) Onishi, H., Shioyama, Y., and Matsumoto, Y., *et al*. (2012) Stereotactic body radiation therapy in 95 patients with lung tumors composed of ground-glass opacity (GGO) : Results of a retrospective multicenter study. *Int. J. Radiat. Oncol. Biol. Phys.,* **84**, S49.

22) Onimaru, R., Fujino, M., Yamazaki, K., *et al*. (2008) Steep dose-response relationship for Stage I non-small-cell lung cancer using hypofractionated high-dose irradiation by real-time tumor-tracking radiotherapy. *Int. J. Radiat. Oncol. Biol. Phys.,* **70**, 374-381.

23) Onishi, H., Shirato, H., Nagata, Y., *et al*. (2007) Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer : Updated results of 257 patients in a Japanese multi-institutional study. *J. Thorac. Oncol.,* **2**, S94-S100.

24) Shibamoto, Y., Hashizume, C., Baba, F., *et al*. (2012) Stereotactic body radiotherapy using a radiobiology-based regimen for stage i nonsmall cell lung cancer : A multicenter study. *Cancer,* **118**, 2078-2084.

25) Guckenberger, M., Baier, K., Polat, B., *et al*. (2010) Dose-response relationship for radiation-induced pneumonitis after pulmonary stereotactic body radiotherapy. *Radiother. Oncol.,* **97**, 65-70.

26) Nagata, Y., Hiraoka, M., Mizowaki, T., *et al*. (2009) Survey of stereotactic body radiation therapy in Japan by the Japan 3-D Conformal External Beam Radiotherapy Group. *Int. J. Radiat. Oncol. Biol. Phys.,* **75**, 343-347.

27) Baker, R., Han, G., Sarangkasiri, S., *et al*. (2013) Clinical and dosimetric predictors of radiation pneumonitis in a large series of patients treated with stereotactic body radiation therapy to the lung. *Int. J. Radiat. Oncol. Biol. Phys.,* **85**, 190-195.

28) Takeda, A., Kunieda, E., Ohashi, T., *et al*. (2012) Severe COPD is correlated with mild radiation pneumonitis following stereotactic body radiotherapy. *Chest,* **141**, 858-866.

29) Ueki, N., Matsuo, Y., Togashi, Y., *et al*. (2015) Impact of pretreatment interstitial lung disease on radiation pneumonitis and survival after stereotactic body radiation therapy for lung cancer. *J. Thorac. Oncol.,* **10**, 116-125.

30) Takeda, A., Enomoto, T., Sanuki, N., *et al*. (2008) Acute exacerbation of subclinical idiopathic pulmonary fibrosis triggered by hypofractionated stereotactic body radiotherapy in a patient with primary lung cancer and slightly focal honeycombing. *Radiat. Med.,* **26**, 504-507.

31) Matsuo, Y., Shibuya, K., Nagata, Y., *et al*. (2011) Prognostic factors in stereotactic body radiotherapy for non-small-cell lung cancer. *Int. J. Radiat. Oncol. Biol. Phys.,* **79**, 1104-1111.

32) Norihisa, Y., Nagata, Y., Takayama, K., *et al*. (2008) Stereotactic body radiotherapy for oligometastatic lung tumors. *Int. J. Radiat. Oncol. Biol. Phys.,* **72**, 398-403.

33) Aoki, M., Hatayama, Y., Kawaguchi, H., *et al*. (2016) Stereotactic body radiotherapy for lung metastases as oligo-recurrence : A single institutional study. *J. Radiat. Res.,* **57**, 55-61.

34) Guckenberger, M., Lievens, Y., Bouma, A.B., *et al*. (2020) Characterisation and classification of oligometastatic disease : A European Society for Radio-

therapy and Oncology and European Organisation for Research and Treatment of Cancer consensus recommendation. *Lancet Oncol.,* **21**, e18–e28.

35) Ministry of Health, Labor and Welfare. Summary of simplified life tables, 2020. Available at : https://www.mhlw.go.jp/toukei/saikin/hw/life/life20/index.html. (Accessed : 4th December 2021)

36) Timmerman, R., Papiez, L., McGarry, R., *et al.* (2003) Extracranial Stereotactic Radioablation : Results of a Phase I Study in Medically Inoperable Stage I Non-small Cell Lung Cancer. *Chest,* **124**, 1946–1955.

37) McGarry, R., Papiez, L., Williams, M., *et al.* (2005) Stereotactic body radiation therapy of early-stage non-small-cell lung carcinoma : Phase I study. *Int. J. Radiat. Oncol. Biol. Phys.,* **63**, 1010–1015.

38) Koshy, M., Malik, R., Weichselbaum, R., *et al.* (2015) Increasing radiation therapy dose is associated with improved survival in patients undergoing stereotactic body radiation therapy for stage I non-small-cell lung cancer. *Int. J. Radiat. Oncol. Biol. Phys.,* **91**, 344.

39) Bezjak, A., Paulus, R., Gaspar, L., *et al.* (2019) Safety and efficacy of a five-fraction stereotactic body radiotherapy schedule for centrally located non-small-cell lung cancer : NRG Oncology/RTOG 0813 trial. *J. Clin. Oncol.,* **37**, 1316–1325.

40) Tree, A., Khoo, V., Eeles, R., *et al.* (2013) Stereotactic body radiotherapy for oligometastases. *Lancet. Oncol.,* **14**, e28–37.