Original Article

Treatment Outcome of Stereotactic Body Radiotherapy for Patients with Lung Tumors: A Retrospective Study at Chulabhorn Hospital

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Background: Stereotactic body radiation therapy [SBRT] is a treatment option in several malignant diseases.

Objective: To assess the treatment outcome of SBRT in lung tumors in terms of response rates, local control, overall survival, and prognostic factors associated with response rate.

Materials and Methods: Twenty-one patients (32 lesions) with early-stage non-small cell lung cancer [NSCLC] or oligometastatic lung disease who received SBRT between January 2012 and March 2016 were included in this retrospective study. Overall survival and local control rate were calculated using the Kaplan-Meier method. Prognostic factors for response rate, including equivalent sphere diameter, tumor volume, biologically effective dose, and tumor type and location, were analyzed using Fisher's exact test.

Results: Median follow-up was 16.1 months; 59.4% of patients had complete response, 28.1% had partial response, and only 3.1% had progressive disease. Local control at 1, 2, and 3 years was 94.1%, 87.4%, and 87.4%, respectively. Overall survival at 1, 3, and 5 years was 90.2%, 90.2%, and 67.7%, respectively. In univariate analysis for response rate, tumor type (primary or metastatic) was the only significant factor.

Conclusion: SBRT in early-stage NSCLC and oligometastatic lung tumors produces promising outcomes in terms of response rate and local disease control.

Keywords: Stereotactic body radiation therapy [SBRT]; Treatment outcome; Early-stage NSCLCs; Oligometastatic diseases

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Stereotactic body radiation therapy [SBRT], also known as stereotactic ablative radiotherapy, is a form of external beam radiation therapy that precisely delivers very high doses of radiation to extracranial lesions using several intense beams from different angles. SBRT is usually administered as a single fraction, or not more than five fractions per course. Prescribed dose can vary depending on the type and location of the tumor and the patient's physical condition[1].

In patients with early-stage non-small cell lung cancer [NSCLC], the standard treatment is anatomical resection. However, patients with multiple comorbidities who cannot tolerate surgery are typically treated with conventional radiation therapy, which is associated with a poor outcome. According to a detailed analysis of 18 studies from 1988 to 2000 including a

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total of 1,680 patients, local failure was the dominant mode of treatment failure observed following conventional radiation therapy in lung cancer (ranging from 6.4% to 70% across the studies)[2]. Poor local control was associated with poor overall survival [OS], with 3- and 5-year cause-specific survival rates of 39% and 25%, respectively, and 3- and 5-year OS rates of 34% and 21%, respectively.

SBRT, an advanced radiation therapy technique, can deliver higher radiation doses than conventional techniques and represents a new treatment option for medically inoperable patients. Numerous single-institutional studies and pooled analyses have reported excellent outcomes with SBRT treatment in early-stage NSCLC[3-5]. The landmark RTOG 0236 study enrolled 59 patients with T1 or T2a peripherally located NSCLC[6] and used SBRT treatment of 54 Gy in three fractions, producing promising results. Local control of the primary site was 97.6% at 3 years, while regional and systemic control at 3 years was 87.2% and 77.9%, respectively.

Recent evidence suggests the existence of an intermediate disease state between localized and widespread systemic disease. The concept of oligometastatic disease was initially proposed by Hellman and Weichselbaum[7], who suggested that local treatment to reduce tumor burden might result in better disease control with prolonged survival. This observation has led to the increasing use of local therapy, including surgery and SBRT.

We performed a retrospective study to review the outcome of SBRT treatment of lung tumors at our institute in terms of response rate, local control, overall survival, and prognostic factors associated with response rate.

Materials and Methods

Patient characteristics

Patients with early-stage NSCLC or oligometastatic lung disease who received SBRT between January 2012 and March 2016 at Chulabhorn Hospital (Bangkok, Thailand) were included in this retrospective analysis. For early-stage NSCLC, we included patients with stage T1-T2N0M0 disease. For oligometastatic lung disease, we included patients with 1 to 3 pulmonary lesions of diameter size ≤5 cm and controlled primary tumor site. All patients had more than 18-years-old age and were evaluated by the hospital's tumor board, including a medical oncologist, a cardiothoracic surgeon, a radiologist, and a radiation oncologist. Two patients were excluded from the analysis because of short follow-up time (<3 months).

SBRT simulation; planning, dose prescription, and delivery

Patients were immobilized in a supine position with both arms above the head using a wing board and respiratory plate or respiratory belt. Four-dimensional computed tomography [4D-CT] scans with a slice thickness of 3 mm were performed on all patients. Gross tumor volume [GTV] was identified in both the lung and mediastinal window and internal target volume [ITV] was contoured using 10 phases of 4D-CT imaging. An additional margin for planning target volume [PTV] of about 5 mm was used. Organs at risk were contoured, including lung, heart, spinal cord, esophagus, and bronchi. Where target lesions were close to the chest wall or brachial plexus, the organs at risk were identified. SBRT protocols were optimized using the Analytical Anisotropic Algorithm [AAA] implemented in the Eclipse planning system version 10.0 to 13.6 (Varian Medical Systems, Inc., Palo Alto, CA, USA). A beam energy of 6 to 10 MV with un-flattened [FFF] photon beams was selected for some patients. Treatment was delivered using a True Beam linear accelerator (Varian Medical Systems, Inc).

Depending on tumor size and location, several different radiation schemes were used, including 60 Gy in three fractions, 45 Gy in three fractions, and 50 Gy in four fractions. These depended on locations and sizes of tumors. The dose was prescribed to the isodose line covering the PTV (typically the 70% to 100% isodose line). Prior to radiation delivery, cone beam CT scans were performed and physicians rechecked the areas of tissue affected in every radiation session.

Follow-up

Follow up visits were performed at 1 and 3 months after SBRT, and then every 3 months. Clinical assessment was performed at every visit, and chest CT scanning for response evaluation was performed at 3 months after SBRT and subsequently as clinically indicated. Local control was defined according to RECIST criteria 1.1[8]. Acute and late toxicities were scored according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.0[9].

Statistical analysis

Time to event was calculated from the date of the first day of treatment to the date that the event occurred. OS and local control rate were calculated using the Kaplan-Meier method. Prognostic factors for

response rate were analyzed by Fisher's exact test and included equivalent sphere diameter, tumor volume, biologically effective dose in Gy10 [BED Gy_{10}], tumor location, and type of tumor (primary or metastatic). The *p*-value <0.05 was defined as significant in all tests. The study was approved by the Ethics Committee involving Human Subjects, Chulabhorn Research Institute.

Results

Twenty-one patients (32 lesions) treated from January 2012 to March 2016 were included in the present study. Among these, 8 patients had early-stage NSCLC and 13 had metastatic lung tumors. The median follow-up was 16.1 months (range 3.8 to 57.5 months). Mean age of patients was 72.7 years. The SBRT dose varied depending on tumor location. Patient characteristics are shown in Table 1.

Among 32 lesions, 19 (59.4%) showed a complete response, 9 (28.1%) showed a partial response, and 3 (9.4%) had stable disease, and only 1 (3.1%) tumor had progressive disease. Table 2 shows the response rate at 3 months after radiation. Progressive disease was found in one patient with high-grade liposarcoma and lung metastasis; tumor volume was relatively large at 50.1 cm^3, with an equivalent sphere diameter of 4.6 cm. Most patients (42.9%) developed distant failure but some patients had recurrent disease at the primary and regional site (19% and 9.5%, respectively). Actuarial local control rates at the radiation site at 1, 2, and 3 years were 94.1%, 87.4%, and 87.4%, respectively. Recurrent tumor at the radiation site was recorded in two patients, one of which had NSCLC while the other had rectal cancer with metastatic lung disease. In both patients, doses were limited because of central lesions, and both had distant failure. No patients developed isolated radiation site failure.

At the time of analysis, 17 (81%) patients were alive and 4 (19%) were deceased. OS at 1, 3, and 5 years was 90.23%, 90.23%, and 67.67%, respectively. Figure 1 shows the local control rate at the SBRT site and OS.

Univariate analysis was performed for response rate (Table 3), tumor volume (<2.92 or ≥2.92), equivalent sphere diameter (<1.8 cm or ≥1.8 cm), BED Gy_{10} (>105 or ≥105), type of tumor (primary or metastatic), and location of tumor (central or peripheral). Type of tumor (primary or metastatic) was the only factor with statistical significant ($p = 0.039$). Sixteen of 24 (66.7%) lung metastatic tumors showed a complete response, while only 3 of 8 (37.5%) early-stage NSCLC tumors had a complete response. No acute or late toxicities of grade 3 or more were detected in any patient. However, 3 patients (14.3%) reported a grade 1 toxicity

Table 1. Characteristics of 21 patients and treatment feature

Patients characteristics	n	Percent
Age		
Mean ± SD	72.7±11.4	
Min-max	48 to 94	
Sex		
Male	12	57.1
Female	9	42.9
Performance status		
ECOG 0-1	16	76.2
ECOG 2-3	5	23.8
Type of tumor		
Primary lung cancer	8	38.1
Metastatic lung tumor	13	61.9
Colorectal cancer	5	
Head and neck cancer	2	
Gynecologic cancer	2	
Hepatocellular carcinoma	2	
Esophageal cancer	1	
Soft tissue sarcoma	1	
Histology		
Adenocarcinoma	10	47.6
Squamous cell carcinoma	5	23.8
Unspecified	6	28.6
Number of lesions		
1	13	61.9
2	6	28.6
3	2	9.5
Location	32	100.0
Rt. upper lobe	5	15.6
Rt. middle lobe	2	6.3
Rt. lower lobe	9	28.1
Lt. upper lobe	9	28.1
Lt. lower lobe	7	21.9
Volume (cm^3)		
Mean ± SD	10.6±19.01	
Median	2.9	
Min - max	0.3 to 88.8	
≥10	9	28.1
<10	23	71.9
Dose prescription (BED Gy_{10})	32	100.0
60 Gy/3 F (180)	7	21.9
60 Gy/5 F (132)	3	9.41
55 Gy/5 F (115.5)	4	2.5
50 Gy/4 F (112.5)	3	9.4
48 Gy/4 F (105.6)	3	9.4
50 Gy/5 F (100)	12	37.5

BED = biologically effective dose

of acute radiation pneumonitis.

Discussion

This retrospective study examined our experience using SBRT in lung tumors. The results indicate a good response, high rate of local control, and minimal toxicity associated with this treatment strategy, and a local control rate of 87.39% at both 2 and 3 years.

SBRT in early-stage NSCLC and oligometa static lung tumors is the treatment of choice in medically inoperable patients because of the high response rate associated with this treatment strategy. Navarria et al have demonstrated a high response rate with SBRT in oligometastatic patients. A complete response rate was recorded in 60% of patients, a partial response in 28.5%, stable disease in 3%, and progressive disease in 8.5%[10]. These results are consistent with those observed in our study, where a complete response was observed in 59.4% of patients, a partial response in 28.1%, stable disease in 9.4%, and progressive disease in 3.1%.

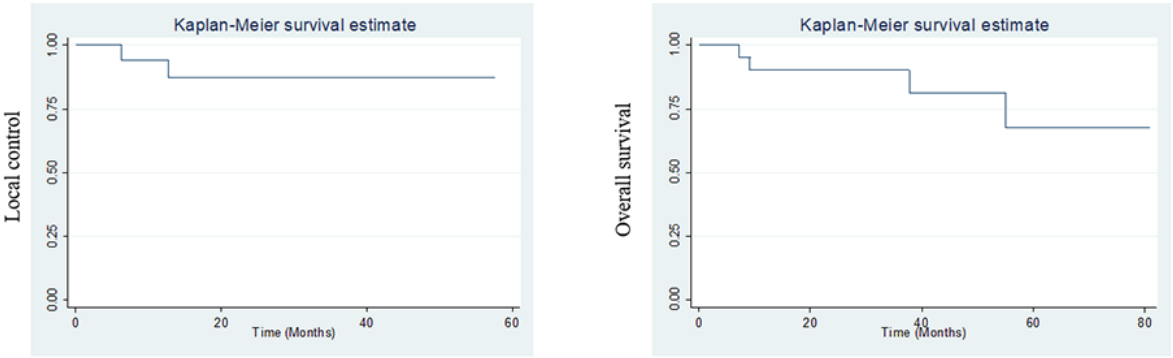
The most common pattern of failure in our study was distant failure, similar to other studies[11,12]. Senthi et al reported a 2-year distant failure rate of 14.7%, local failure of 4.9%, and regional failure of 7.8% in early-stage NSCLC patients who were treated with SBRT[13]. Franceschini et al. observed that 77.5% of patients treated with SBRT in radio-resistant lung metastasis had distant failure[14].

In the RTOG 0236 study, 3-year local control rate with SBRT in medically inoperable NSCLC patients was 97.6%, and a systematic review reported an excellent 2-year local control of 91%. However, local control for metastatic lung tumors was poorer than that for primary NSCLC. The reasons for this difference in local control rate in metastatic lung tumor are not well defined, but could be the result of anemia and tissue hypoxia[15] or genetic instabilities[16] associated with metastatic lung tumors. Franceschini et al. reported a 2-year local control rate of 84.9% in lung metastases from radio-resistant primary tumors[14]. Navarria et al. conducted a prospective study of SBRT in oligometastatic patients, and reported a 2-year local control rate of 89%[10]. Another study in patients with primary lung cancer and metastatic lung tumors showed a 3-year local control rate of 72.5%[17]. In our study, the 2-year local control rate was 87.4%, which was lower than the rate reported for primary lung cancer but comparable to that reported for metastatic lung tumors. Our study included both primary and metastatic lung tumors, and more than half of the patients had been diagnosed with metastatic lung tumors.

In univariate analysis, metastatic tumor type was the only significant factor associated with a better response. In our study, metastatic tumors tended to have smaller tumor volumes (mean 7 cm^3) compared with primary lung tumors (mean 21.5 cm^3). Ricco et al. reported a similar finding, and showed that tumors with smaller volumes had significantly higher local control

Table 2. Response rate at 3 months in 32 lesions of SBRT

Response rate at 3 months after RT	n	Percent
Complete response	19	59.4
Partial response	9	28.1
Stable disease	3	9.4
Progressive disease	1	3.1



(a) Local control rate (b) Overall survival

Figure 1. Local control of SBRT site and overall survival.

Table 3. Univariate analysis for response rate

Variables	Response rate		*p*-value
	Complete/partial	Stable/progression	
Tumor volume (cm^3)			1.000
<2.92	14	2	
≥2.92	14	2	
Equivalent sphere diameter (cm)			0.319
<1.8	16	1	
≥1.8	12	3	
BED Gy10			0.629
<105	12	1	
≥105	16	3	
Type of tumor			0.039
Primary	5	3	
Metastatic	23	1	
Location of tumor			0.303
Central	9	0	
Peripheral	19	4	

BED = biologically effective dose

and longer OS[18]. Ricardi et al also reported that tumor volume was significantly associated with survival[19]. In contrast, our study did not demonstrate that tumor volume or equivalent sphere diameter was statistically associated with response rate, but this might be attributable to our limited sample size.

Our study had some limitations. First was the retrospective design of our study, similar to most previous studies of this type. Second was the small sample size and relatively short follow-up time in which few events were detected.

Conclusion

SBRT for primary lung cancer and lung metastasis produces promising results in terms of response rate and local control rate, which were comparable with other studies.

What is already known on this topic?

Stereotactic body radiation is the guideline-recommended treatment of choice for early stage non-small cell lung cancer in patients who are medically inoperable. Moreover, there is growing evidence of metastatic lung tumors patients treated with SBRT.

What this study adds?

The present study is among the first to study clinical outcomes of SBRT in lung tumors in Thailand. The trial provides more evidence to support the SBRT in lung tumors treatment and has similar outcomes as others studies in term of response rate, local control and toxicities.

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Potential conflict of interest

None.

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