**Original Article**

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# Response Evaluation after Stereotactic Ablative Radiotherapy for Lung Cancer

Ji Hoon Choi

Department of Radiation Oncology, Kosin University Gospel Hospital,
Kosin University College of Medicine, Busan, Korea

We retrospectively reviewed lung cancer patients who were treated with stereotactic ablative radiotherapy (SABR). We investigated the value of response evaluation after treatment by measuring the volume change of tumors on serial chest computed tomography (CT) examinations. The study included 11 consecutive patients with early-stage (T1-T2aN0M0) non-small cell lung cancer (NSCLC) who were treated with SABR. The median dose of SABR was 6,000 cGy (range 5,000～6,400) in five fractions. Sequential follow-up was performed with chest CT scans. Median follow-up time was 28 months. Radiologic measurement was performed on 51 CT scans with a median of 3 CT scans per patient. The median time to partial response ($T_{PR}$) was 3 months and median time to complete remission ($T_{CR}$) was 5 months. Overall response rate was 90.9% (10/11). Five patients had complete remission, five had partial response, and one patient developed progressive disease without response. On follow-up, three patients (27.2%) developed progressive disease after treatment. We evaluated the the response after SABR. Our data also showed the timing of response after SABR.

**Key Words**: Lung cancer, Stereotactic ablative radiotherapy, SABR, SBRT

## Introduction

During the past decade, the standard therapy for operable, early-stage (T1-T2aN0M0), non-small cell lung cancer (NSCLC) has been lobectomy.[1] Conventionally fractionated radiotherapy for patients with early-stage NSCLC who are medically inoperable has traditionally been regarded as superior to no treatment but not able to achieve levels of local control (LC) or overall survival (OS) similar to those of surgical resection. During the past decade, stereotactic ablative radiotherapy (SABR; also called stereotactic body radiotherapy) has become standard of care for patients with early-stage NSCLC who are clinically unable to tolerate a surgical procedure or refuse surgery. SABR has resulted in LC in excess of 90% for tumors that are medically inoperable and operable tumors in clinical stage INSCLC[2-13] and overall survival after SABR was better than that achieved after conventional fractionated radiotherapy.[14] SABR delivers ablative doses of radiation (biologically effective dose [BED] ＞100 Gy) to tumors in 1～10 fractions with a high degree of accuracy. Accurate evaluation of tumor response after radiotherapy is essential to determine the efficacy of treatment. De Rose et al. analyzed a radiological response was defined according to RECIST criteria in non-small cell lung cancer oligometastatic patients who had undergone SABR for lung metastatic lesions. Local control was 92% of the treated lung lesions. Complete remission was 66% of cases and partial remission or persistent stable disease in 34% with assessment of radiological response.[15]

We investigated the value of response evaluation after treatment by measuring the size change of tumors on serial chest CT examinations.

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**Correspondence:** Ji Hoon Choi (1stdr@naver.com)
Tel: 82-51-990-6399, Fax: 82-51-793-0660

## Materials and Methods

### 1. Patients

This retrospective study included 11 consecutive patients with early-stage (T1-T2aN0M0), non-small cell lung cancer (NSCLC) who were treated with stereotactic ablative radiotherapy (SABR) between January 2011 and March 2015. Inclusion criteria were patients with pathologically proven early-stage (T1-T2aN0M0), non-small cell lung cancer (NSCLC) who were medically inoperable or who refused surgical resection. For this study, we excluded patients with TNM stage other than T1-T2aN0M0 and those who had previously received other treatments of surgery or chemotherapy for the tumor. All of patients underwent a PET-CT scan with chest CT examination and MRI of brain prior to initiation of treatment. Post treatment follow-up consisted of contrast enhanced CT scans of the thorax at 1, 3 and 6 months post-SABR, followed by 6 months until 2 years after treatment and annually thereafter. The patients' characteristics are listed in Table 1. The most common primary tumour histology was squamous cell carcinoma (54.5%). Median tumor size was 26 mm (range: 15～46).

Table 1. Patient characteristics.

| Parameter | N |
|---|---|
| Sex | |
| Male | 8 (72.7%) |
| Female | 3 (27.3%) |
| Median age (years) | 78 (52～87) |
| Location of tumor | |
| RUL | 4 (36.4%) |
| RML | 0 (0%) |
| RLL | 3 (27.3%) |
| LUL | 3 (27.3%) |
| LLL | 1 (9.0%) |
| Histology | |
| Adenocarcinoma | 5 (45.5%) |
| Squamous cell carcinoma | 6 (54.5%) |
| Stage | |
| T1 | 6 (54.5%) |
| T2 | 5 (45.5%) |
| Peripheral | |
| No | 2 (18.2%) |
| Yes | 9 (81.8%) |
| Median tumor size (mm) | 26 (15～46) |

### 2. Treatment

The patients underwent 4DCT scans for treatment planning. The 4DCT images were obtained using a 4DCT scanner (Light Speed RT, General Electric Co., Waukesha, WI, USA) with RPM (Real-time Position Management™, Varian Medical Systems, Inc., Palo Alto, CA, USA) system. The 4DCT images were sorted and reconstructed by an Advantage Workstation (General Electric Co.). Phases were sorted into 0%～90% (all phases) from 4DCT images and reconstructed using the maximum intensity projection (MIP) method. Gross tumor volumes (GTVs) and internal target volume (ITV) around the GTV, accounting for tumor motion were manually delineated on each of the 10 phases of reconstructed CT image by a radiation oncologist using the treatment planning system (Eclipse 8.1, Varian Medical Systems, Inc.) with the lung CT window setting (WW; window width: 1600 HU, WL; window level: −600 HU). All fractionation schemesBED of ≥100 $Gy_{10}$ prescribed to the planning target volume (PTV). The median dose of SABR was 6,000 cGy (range 5,000～6,400) in 5 fractions. The SABR dose was prescribed to deliver 100% of the prescribed dose to >99% of the ITV and 95% of the prescribed dose to >99% of the PTV. The PTV consisted of the ITV plus a 5 mm margin uniformly. The treatment dose schedule is shown in Table 2.

Post-SABR follow-up consisted of contrast enhanced CT scans of the thorax and PET-CT. Sequential follow-up was performed in our institution. Time-to-event outcomes were analyzed.

### 3. Response criteria

For 2-dimensional (2D) measurement, the tumor mass in the axial plane of the CT scan was measured at the longest cross-sectional diameter and the longest diameter perpendicular

Table 2. Treatment characteristics.

| Treatment characteristics | Median | Range |
|---|---|---|
| Prescription dose (Gy) | 60 | 50～64 |
| Fractions | 5 | 4～5 |
| BED dose ($Gy_{10}$) | 132 | 100～166.4 |

to it. Response criteria were defined as follows: complete response (CR), complete resolution; partial response (PR), decrease of at least 30%; progressive disease (PD), increase of at least 20%; and stable disease (SD), neither PR nor PD. Fisher's exact test was performed to examine the influence of variables on response.

## Results

### 1. Radiologic tumor size change

Over a median follow-up of 28 months (range, 2～50 months), the 3-year overall survival rate of all 11 patients was 80.0% (Fig. 1). Radiologic measurement was performed on 51 CT scans (11 pre-radiotherapy and 40 post-SABR CT scans) with a median number of 3 CT scans per patient. For all 11 patients, the mean pre-RT maximum diameter of tumor was 29 mm. Detailed RT-related parameters are listed in Table 2.

The relative values of the maximum diameter of the tumor on follow-up CT scans with reference to pre-SABR values were obtained. The median time to partial response ($T_{PR}$) was 3 months and median time to complete remission ($T_{CR}$) was 5 months.

### 2. Response rates and patterns of failure

The response rates (RRs) are listed in Table 3. Overall RR measured by the 2D-method was 90.9% (10 of 11 patients). Five patients had CR, five had PR, and one developed progressive disease without response.

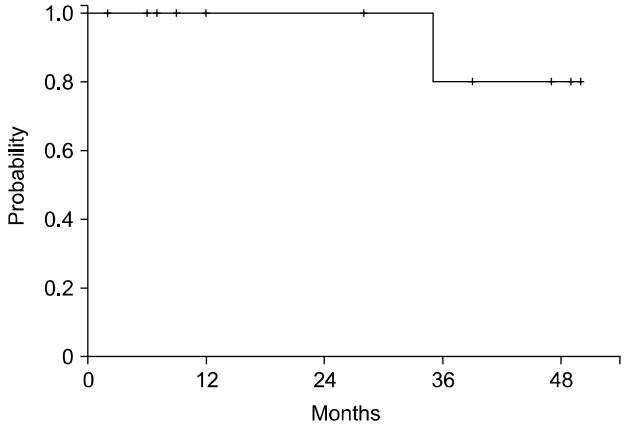


**Fig. 1.** Overall survival after SABR.

Three patients (27.2%) developed progressive disease after treatment. Among the three patients with progression, two (18.2%) had in-field failure with metastatic nodules and one (9.1%) had local failure with regional lymph node metastasis. Patients with higher-stage disease tended to undergo recurrence more frequently with disease progression, but the difference was not statistically significant (p=0.490).

## Discussion

Many studies have shown that stereotactic ablative radiotherapy (SABR) is effective for the treatment of early-stage non-small cell lung cancer and SABR has become the standard of care for medically inoperable NSCLC.[2-13] Chang et al. assessed overall survival for SABR versus surgery by pooling data from two independent, randomized, phase 3 trials of SABR in patients with operable stage I NSCLC. Overall survival at 3 years was 95% in the SABR group compared with 79% in the surgery group (p=0.037). Recurrence-free survival at 3 years was 86% in the SABR group and 80% in the surgery group (p=0.54).[16] Heal et al. retrospectively analyzed the rates of tumor control and toxicity following SABR treatment with the Cyberknife system for primary early-stage NSCLC. With a median follow-up of 27.5 months, 3-year local control rates were 84.33% and there was no grade 3 toxicity.[17] In our study, the median follow-up was 28 months (range, 2～50 months), overall survival rate was 80.0%. T-stage did not show as an independent predictor of overall survival. After SABR, the initial response rate to treatment was 81.8%. Table 3 lists the response rates (RRs). The overall response rate was 90.9% and 5 of 11 (45.4%) patients had complete remission of the tumor.

The patients treated with SABR in our study experienced few toxicities. One patient experienced a rib fracture (grade

**Table 3. Summary of response rates by measurement of tumor size.**

| | CR N (%) | PR N (%) | PD N (%) |
|---|---|---|---|
| ALL | 5 (45.5%) | 5 (45.5%) | 1 (9.0%) |
| T1 stage | 2 (18.2%) | 4 (36.4%) | |
| T2 stage | 3 (27.4%) | 1 (9.0%) | 1 (9.0%) |

≥3 toxicity) after SABR to a peripheral lung tumor within 1 cm of, but not abutting, the chest wall. Otherwise, all toxicities were grade 2 or lower. Observed toxicities were primarily pneumonitis. There were no cases of esophagitis, spinal cord toxicity, or hemorrhage of mediastinum. Chaudhuri et al. retrospectively analyzed outcomes in 68 patients with single lung tumors, 34 central and 34 peripheral tumors, who were treated with SABR consisting of 50 Gy in 4～5 fractions. The authors reported their experience in treating patients with central and ultra-central lung tumors with SABR. Toxicity rates were low and tolerable in both groups. There were two cases of grade 3 toxicity with chest wall pain, and one case of grade 4 toxicity of pneumonitis. They suggested that SABR dosed at 50 Gy in 4～5 fractions is safe and effective for treatment of early-stage non-small lung cancer, even for centrally located lung tumors.[18)]

Response evaluation of tumors is not easy because of the lack of distinct borders and irregular shape and growth patterns. There are some publications evaluating radiographic response using axial CT scan measurements. Shah et al. reported methodological issues in their publications comparing 2D and volume measurements for assessment of tumor response in adult high-grade gliomas.[19)] Force et al. analyzed 25 patients with thymic cancer and evaluated tumor responses using CT-based response evaluation criteria in solid tumors (RECIST), World Health Organization (WHO) criteria, modified RECIST, and 3D volumetrics with computer-assisted software. The authors found that use of volumetrics showed 22% discordance compared to RECIST, 15% versus modified RECIST, and 22% versus WHO criteria.[20)] Although they found a generally good correlation among modalities with some discordance, the primary purpose of their studies was to validate different measurement methods of assessing response, rather than to evaluate the efficacy of radiation therapy by assessing response.

In the current study we analyzed the timing of treatment response. The results of our study showed that the initial response became evident as early as 1 month after RT. The median time to partial response ($T_{PR}$) was 3 months. Five of 11 patients had complete remission of tumor. The median and mean time to complete remission ($T_{CR}$) was 5 months and 6.4 months respectively. Two patients showed response at the time of the first CT scan at 1 month after treatment. There was no correlation between T stage and tumor response. Eight of 11 patients showed a partial response at the time of the first CT scan after RT. Of these eight patients, four eventually showed complete remission of the tumor.

The median time to progression of disease was 10.5 months. Three patients (27%) had local failure with metastatic nodules and one patient (9%) had local failure with regional lymph node metastasis. Only one patient showed a PD response at the initial CT scan. The mean number of CT scans performed after SABR was 3.6 and the median time of the first CT scan from the end of treatment was 1 month (range, 1～6).

There are some limitations associated with the nature of this study, which was a single-institutional retrospective study with a small number of enrolled patients with SABR treatment.

## Conclusion

The overall response rate after SABR was 90.9%. Our data suggest that some patients could have a response as early as 1 month after RT. In addition, we evaluated the timing of the response after SABR. Our results may help clinicians with treatment planning for patients with early-stage non-small cell lung cancer.

## References

1. Shimkin MB, Connelly RR, Marcus SC, et al: Pneumonectomy and lobectomy in bronchogenic carcinoma. A comparison of end results of the Overholt and Ochsner clinics. J Thorac Cardiovasc Surg 44:503-19, 1962
2. Onishi H, Araki T, Shirato H, et al: Stereotactic hypofractionated high-dose irradiation for stage I nonsmall cell lung carcinoma: clinical outcomes in 245 subjects in a Japanese multiinstitutional study. Cancer 101:1623-31, 2004
3. Lagerwaard FJ, Haasbeek CJ, Smit EF, et al: Outcomes of risk-adapted fractionated stereotactic radiotherapy for stage I non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 70:685-92, 2008
4. Chang JY, Liu H, Balter P, et al: Clinical outcome and predictors of survival and pneumonitis after stereotactic ablative radiotherapy for stage I non-small cell lung cancer. Radiat Oncol 7:152, 2012
5. Crabtree TD, Denlinger CE, Meyers BF, et al: Stereotactic body radiation therapy versus surgical resection for stage I non-small cell lung cancer. J Thorac Cardiovasc Surg 140: 377-86, 2010

6. **Iyengar P, Westover K, Timmerman RD**: Stereotactic ablative radiotherapy (SABR) for non-small cell lung cancer. Semin Respir Crit Care Med 34:845-54, 2013
7. **Lagerwaard FJ, Verstegen NE, Haasbeek CJ, et al**: Outcomes of stereotactic ablative radiotherapy in patients with potentially operable stage I non-small cell lung cancer. Int J Radiat Oncol Biol Phys 83:348-53, 2012
8. **Onishi H, Shirato H, Nagata Y, et al**: Stereotactic body radiotherapy (SBRT) for operable stage I non-small-cell lung cancer: can SBRT be comparable to surgery? Int J Radiat Oncol Biol Phys 81:1352-8, 2011
9. **Palma D, Visser O, Lagerwaard FJ, et al**: Treatment of stage I NSCLC in elderly patients: a population-based matched-pair comparison of stereotactic radiotherapy versus surgery. Radiother Oncol 101:240-4, 2011
10. **Shirvani SM, Jiang J, Chang JY, et al**: Lobectomy, sublobar resection, and stereotactic ablative radiotherapy for early-stage non-small cell lung cancers in the elderly. JAMA Surg 149:1244-53, 2014
11. **Taremi M, Hope A, Dahele M, et al**: Stereotactic body radiotherapy for medically inoperable lung cancer: prospective, single-center study of 108 consecutive patients. Int J Radiat Oncol Biol Phys 82:967-73, 2012
12. **Timmerman R, Paulus R, Galvin J, et al**: Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA 303:1070-6, 2010
13. **Verstegen NE, Oosterhuis JW, Palma DA, et al**: Stage I-II non-small-cell lung cancer treated using either stereotactic ablative radiotherapy (SABR) or lobectomy by video-assisted thoracoscopic surgery (VATS): outcomes of a propensity score-matched analysis. Ann Oncol 24:1543-8, 2013
14. **Palma D, Visser O, Lagerwaard FJ, et al**: Impact of introducing stereotactic lung radiotherapy for elderly patients with stage I non-small-cell lung cancer: a population-based time-trend analysis. J Clin Oncol 28:5153-9, 2010
15. **De Rose F, Cozzi L, Navarria P, et al**: Clinical Outcome of Stereotactic Ablative Body Radiotherapy for Lung Metastatic Lesions in Non-small Cell Lung Cancer Oligometastatic Patients. Clin Oncol (R Coll Radiol), 2015
16. **Chang JY, Senan S, Paul MA, et al**: Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. Lancet Oncol 16:630-7, 2015
17. **Heal C, Ding W, Lamond J, et al**: Definitive Treatment of Early-Stage Non-Small Cell Lung Cancer with Stereotactic Ablative Body Radiotherapy in a Community Cancer Center Setting. Front Oncol 5:146, 2015
18. **Chaudhuri AA, Tang C, Binkley MS, et al**: Stereotactic ablative radiotherapy (SABR) for treatment of central and ultra-central lung tumors. Lung Cancer 89:50-6, 2015
19. **Shah GD, Kesari S, Xu R, et al**: Comparison of linear and volumetric criteria in assessing tumor response in adult high-grade gliomas. Neuro Oncol 8:38-46, 2006
20. **Force J, Rajan A, Dombi E, et al**: Assessment of objective responses using volumetric evaluation in advanced thymic malignancies and metastatic non-small cell lung cancer. J Thorac Oncol 6:1267-73, 2011

# 초기 폐암의 정위방사선치료후 반응평가 분석

고신대학교 복음병원 방사선종양학과, 고신대학교 의과대학 방사선종양학교실

**최지훈**

정위 방사선치료를 받은 폐암환자에서 결과를 후향적으로 분석하고자 하였다. 연속된 흉부 컴퓨터단층촬영(CT)의 종양의 크기변화 분석을 통해 치료 반응 평가를 조사하였다. 11명의 초기 비소세포폐암환자를 대상으로 정위 방사선치료 선량의 중앙값은 6,000 cGy이고 분할 조사 회수의 중앙값은 5회였다. 경과 관찰기간의 중앙값은 28개월로 치료후 종양의 크기 변화는 총 51회의 CT를 통해 분석하였고, 각 환자당 중앙값 3회의 CT 촬영이 시행되었다. 본 연구에서 치료의 총 반응률은 90.9%로 5명의 환자에서 완전관해와 5명에서 부분관해가 관찰되었다. 부분관해와 완전관해까지의 기간의 중앙값은 각각 3개월과 5개월이었다. 경과관찰에서 3명의 환자가 병의 진행양상을 나타내었다. 본 연구에서 초기 폐암의 정위방사선치료후 CT 분석을 통해 반응 평가와 함께 치료 반응 시점을 확인할 수 있었다.

**중심단어**: 폐암, 정위 방사선치료, SABR, SBRT