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ORIGINAL ARTICLE

The Outcome of CyberKnife Treatment for Primary or Metastatic Malignant Lung Tumors

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Background: To analyze the local control of malignant lung tumors and survival of nonsmall cell lung cancer (NSCLC) patients after stereotactic ablative radiotherapy with CyberKnife. **Materials and Methods:** Patients with malignant lung tumors treated by CyberKnife between July 2007 and October 2010 at our institute were retrospectively reviewed. A total of 55 patients with 110 malignant lung tumors were included. There were 32 men and 23 women, and the median age was 67 years. There were 11 early-stage NSCLCs, while the other 44 patients with 99 lesions were metastatic lung tumors. The median gross tumor volume was 13.3 ml. Radiotherapy schedules include 40-60 Gy in 4-5 fractions, 45-60 Gy in 3 fractions and 30 Gy in 1 fraction. **Results:** The median follow-up time for patients alive was 34 months. The local control rates for all tumors were 96% at 1-year and 80% at 2 years. Univariate analysis demonstrated that target volume was important for local control. Biologically equivalent dose (BED) ≥100 Gy provided significantly higher chance to achieve a complete response than BED <100 Gy. The disease-specific survival rates for early-stage NSCLC were 80% at 1-year and 60% at 2 years. Treatment related complications were acceptable. No grade 2-5 adverse events were noted. **Conclusions:** CyberKnife can be used for NSCLC and metastatic lung tumors, either peripheral or central location, with good local control and acceptable side-effects.

Key words: CyberKnife, lung cancer, lung metastases, stereotactic ablative radiotherapy, stereotactic body radiotherapy

INTRODUCTION

The standard therapy for early-stage nonsmall cell lung cancer (NSCLC) has been lobectomy with a local control rate of 80-90%.[1] However, radical surgery is impossible for medically inoperable patients. Treatment options for these patients are limited. Conventional radiotherapy (CRT) provides inferior outcomes with poor long-term survival of 15-30% and local failure rate up to 50%.[2-4] Because higher radiation dose comes with a higher dose to the lung and other normal tissues, dose escalation is difficult with CRT. The most commonly prescribed dose for definitive CRT is 60-70 Gy in 2 Gy fractions. Assuming a α/β of 10 Gy for lung cancer, the biologically equivalent dose (BED) is around 72-84 Gy for CRT.

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Stereotactic ablative radiotherapy (SABR), or stereotactic body radiotherapy, delivers a few large fractions of radiation to a well-defined small target with very steep peripheral dose falloff. It represents a non- or minimal-invasive alternative treatment for medically inoperable early-stage NSCLC, and the local control rate is 75-95% that is not inferior to lobectomy.[5-9] SABR has also been used for metastatic lung tumors with palliative intent.[10]

CyberKnife is a machine that is different from traditional linear accelerator. CyberKnife performs noncoplanar and nonisocentric irradiation with multiple pencil beam shots to the target. Due to its robotic arm and the synchrony system, CyberKnife can tract and treat moving targets real time. However, limited clinical reports are available.[11-15] We began treating malignant lung tumors, including primary and metastatic lung lesions, using the CyberKnife robotic radiosurgery system (Accuray Incorporated, Sunnyvale, CA) with synchrony respiratory motion tracking system in 2007. The treatment response was retrospectively investigated. The primary end point is local control for all patients, and the secondary endpoint is overall survival of the early-stage NSCLC patients.

MATERIALS AND METHODS

Patients with malignant lung tumors treated by CyberKnife between July 2007 and October 2010 at our institute were

retrospectively reviewed. Patients and targets were evaluated by chest surgeons and/or radiation oncologists before CyberKnife. According to cancer treatment guideline, early-stage NSCLC patients should receive radical surgery, either lobectomy or video-assisted thoracic surgery. We included patients who could not undergo surgery because of patients' refusal or medically inoperable disease. A total of 55 patients with 110 malignant lung tumors were enrolled in this study. Patient's characteristics, Eastern Cooperative Oncology Group performance status[16] and tumor volume were encoded prior to CyberKnife SABR. This study was approved by Institutional Review Board of the Tri-Service General Hospital.

CyberKnife is an image-guided radiotherapy system with 6 MV linear accelerator mounted on a robotic arm possessing 6° of freedom. Two diagnostic X-ray sources were mounted to the ceiling and were paired with amorphous silicon detectors to acquire live digital radiographic images of the patient. Three-to-five gold fiducial markers were implanted near the tumors under computed tomography (CT) guidance. When the lung tumor can be clearly identified by the paired X-ray sources, Xsight lung technique was used instead of fiducial placement for internal target tracking. The paired X-ray images are taken and registered every five shots during treatment.

The synchrony tracking system requires light-emitting diodes (LEDs) placed on the patients' anterior chest wall. LEDs motion with the respiratory cycle that represents external motion is registered by a camera array. The synchrony system identifies a corresponding model between the movement of the internal target and the LEDs. This model enables the linear accelerator to continuously track the motion of the internal target and adjusting automatically the position of the beam relative to the moving target. The tracking model is continuously updated throughout the treatment.

An interval of 7-10 days between fiducial marker placement and the treatment planning CT scanning allows fiducial markers to stabilize, edema to subside, and assured that the fiducial has not migrated. Contrast-enhanced thin-slice (1 mm continuous axial slices) planning CT scans were obtained while patients hold their breath in inspiration and expiration. Gross tumor volumes (GTVs) were contoured using lung windows. The GTV margin was expanded 3 mm to establish the planning target volume (PTV). The dose was prescribed to the 60-85% isodose line enclosing 100% of the GTV and more than 95% of the PTV. Multiplan® (Accuray Inc., Sunnyvale, CA, US) version 1.7.0 was used for the treatment plan before 2009 and version 2.1.0 after 2009.

Physical examination and contrast-enhanced CT scans were performed 1-2 months after CyberKnife and then 3 months follow-up interval. Tumor response of the lung lesions after CyberKnife was evaluated using serial CT scans. According to Response Evaluation Criteria in Solid Tumor committee,[17] complete disappearance of the lung tumor was defined as a complete response (CR), at least a 30% decrease in the sum of the longest diameter of the target as a partial response (PR), and at least a 20% increase in the sum of the longest diameter of the target as progressive disease (PD). Tumor response between PR and PD was defined as a stable disease (SD). When a tumor shrinks and then enlarges after treatment, PD is encoded. Local control is defined as stabilization or improvement of the treated lesion (CR, PR or SD).

Because acute radiation pneumonitis and late radiation fibrosis are still not well demarcated clinically after radiotherapy to the lung, we used the term radiation pneumopathy for this continuing process.[18] Radiation pneumopathy noticed by follow-up CT images was recorded, but only symptomatic radiation pneumopathy was designated as treatment-related complication. Acute and late side effects of the lung, heart, esophagus, skin and rib were recorded according to Radiation Therapy Oncology Group radiation morbidity scoring criteria.

All statistical analysis was performed using SPSS 16.0 software. The local control was calculated from the date of SABR to disease progression or last follow-up. Local control curve was computed using the Kaplan–Meier method, and prognostic factors were evaluated using the log-rank test. The significance of various factors was further analyzed using the Cox regression model. An α error of 0.05 was chosen for statistical significance.

RESULTS

A total of 55 patients with 110 malignant lung tumors were included in this study [Table 1]. The primary locations of the malignant lung lesions were NSCLCs in 37 patients (49 targets), colorectal cancers in 6 patients (29 targets), renal cell carcinomas in 5 patients (12 targets), head and neck cancers in 5 patients (17 targets), and other malignancies in 2 patients (3 targets). Seven patients failed after previous CRT with a median dose of 65 Gy (range, 54-74 Gy) before SABR. Of the 55 patients, 11 patients were diagnosed with early-stage NSCLCs and underwent SABR with curative intents.

Fiducials were implanted for 36 lesions (33%) while the others were treated with Xsight lung technique. No patients had complications after the fiducial implantation. Central lung tumors are defined as lesions located <2 cm in all directions to the proximal bronchial tree, and the others are peripheral lung tumors.[19] Thus, 46 lesions were central, and 64 were peripheral lung tumors. The following SABR schedules were used for treatment: 40-60 Gy in 5 fractions for 46 targets (median total dose, 42.5 Gy), 40-60 Gy in 4 fractions for 51 targets (median total dose, 48 Gy), 45-60 Gy

in 3 fractions for 6 targets (median total dose, 48 Gy) and 30 Gy in 1 fraction for 7 targets. BED to the target was calculated for comparison. The median maximal dose to the spinal cord was 10.88 Gy (range, 2.59-17.78 Gy), esophagus 16.29 Gy (range, 3.07-25.17 Gy), heart 18.4 Gy (range, 4.98-54.62 Gy), trachea 18.03 Gy (1.15-43.63 Gy) and skin 23.35 Gy (range, 9.67-38.45 Gy).

Table 1. Summary of patient and treatment variables

Characteristic	Value
Patients number	55
Targets number	110
Sex	
Male	32
Female	23
Median age, year (range)	67 (41-89)
Median GTV, mL (range)	13.3 (0.4-892.5)
ECOG performance status	
0-2	53
3	2
Histological type	
NSCLC	37 (49)
Colorectal cancer	6 (29)
Renal cell cancer	5 (12)
Head and neck cancer	5 (17)
Others	2 (3)
Prior radiotherapy	7
Location of targets	
Central lung area	46
Peripheral lung area	64
SABR schedule for targets	
40-60 Gy in 5 fx	46
40-60 Gy in 4 fx	51
45-60 Gy in 3 fx	6
30 Gy in 1 fx	7

ECOG = eastern cooperative oncology group; NSCLC = nonsmall cell lung cancer; fx = fraction; GTV = gross tumor volume; SABR = stereotactic ablative radiotherapy

Table 2. BED versus target response

Response	BED <100 Gy (n = 52)	BED ≥100 Gy (n = 58)	
Complete response (n)	5	26	
Partial response (n)	26	16	
Stable disease (n)	14	7	
Disease progression (n)	7	9	P<0.001

BED = biologically effective dose (the α/β is assumed to be 10 Gy for targets)

At the last follow-up, 37 patients died of disease, 1 patient died of traffic accident, and 17 patients were still alive. The median clinical and image follow-up times for patients alive were 34 months (range, 17-56 months) and 32 months (range, 17-49 months), respectively. The local control rates for targets were 96% at 1-year and 80% at 2 years [Figure 1]. Thirty-four targets achieved CR at 1-year, but three targets re-grew later. All these three targets received a dose of BED <100 Gy [Table 2].

The following factors were included in univariate analysis for local control: Target volume (<20 ml vs. ≥20 ml), target location (central vs. peripheral), cancer origin, treatment technology (fiducial tracking vs. Xsight lung), BED (<100 Gy vs. ≥100 Gy) and SABR schedules [Table 3]. Only target

Table 3. Univariate analysis of prognostic factors for local control

Factor (n, %)	1-year local control %	2 years local control %	P value
Target volume			
<20 mL (62, 56%)	95	89	P=0.006
≥20 mL (48, 44%)	96	68	
Target location			
Central (46, 42%)	100	75	P=0.697
Peripheral (64, 58%)	92	82	
Cancer origin			
NSCLC (49, 45%)	96	82	P=0.088
Colorectal cancer (29, 26%)	71	71	
Renal cell cancer (12, 11%)	100	100	
Head and neck cancer (17, 15%)	100	0	
Others (3, 3%)	100	81	
Treatment technology			
Fiducial tracking (36, 33%)	100	80	P=0.832
Xsight lung (74, 67%)	94	80	
SABR schedule			
40-60 Gy in 5 fx (46, 42%)	100	69	P=0.906
40-60 Gy in 4 fx (51, 46%)	92	82	
45-60 Gy in 3 fx (6, 5%)	100	100	
30 Gy in 1 fx (7, 6%)	100	100	
BED			
<100 Gy (52, 47%)	100	58	P=0.391
≥100 Gy (58, 53%)	93	90	

NSCLC = nonsmall cell lung cancer; fx = fraction; SABR = stereotactic ablative radiotherapy; BED = biologically effective dose (the α/β is assumed to be 10 Gy for targets)

volume is a significant prognostic factor for local control. Figure 2 showed that the 2 years local control rate for tumor size <20 ml and ≥20 ml was 89% and 68%, respectively (P = 0.006). However, 26 out of 58 targets had CR at BED ≥100 Gy group compared with 5 out of 52 CR at BED <100 Gy group (P < 0.001).

For the 11 early-stage NSCLC patients, the median age was 74 years (range, 58-85 years). Four lesions were central, and seven lesions were peripheral. The median GTV was 54.5 ml (range, 19-96 ml), and median BED was 150 Gy (range, 72-180 Gy). The median follow-up time was 24 months (range, 2-42 months). One patient died of traffic accident about 2 months after SABR, and this patient was considered having SD. There are two CR, four PR, two SD, and three PD. The local control rates were 88% at 1-year and 63% at 2 years. The overall survival was 73% at 1-year and 55% at 2 years. The disease-specific survival was 80% at 1-year and 60% at 2 years.

There is no immediate acute side effect during SABR. The incidence of radiation pneumopathy was 14% at 1-year and 43% at 2 years for all tumors, and symptomatic radiation pneumopathy was 11% at 1-year and 15% at 2 years for patients. The 1-year incidence of radiation pneumopathy was 72% and 24% for BED ≥100 Gy and BED <100 Gy, respectively [Figure 3]. The symptoms of radiation pneumopathy were all mild and could be controlled by antitussive agents and/or steroid. No Grade 2-5 adverse events of the heart, esophagus, skin or rib were noted.

DISCUSSION

The principle management for early-stage NSCLC is radical surgery. However, for patients with medically inoperable or unresectable metastatic disease, CyberKnife SABR is a feasible treatment modality with local control rates of 96% at 1-year and 80% at 2 years.

Hall and Giaccia described that the lung is an intermediate — to late-responding tissue.[20] Two waves of damage can be identified: Acute pneumonitis at 2-6 months after treatment, and fibrosis, which may develop slowly over a period of several months to years. However, it is difficult to cut the exact time point of these two effects in clinical setting. Barriger *et al*. analyzed radiation pneumonitis in NSCLC patients treated with SABR.[21] Radiation pneumonitis was diagnosed between 0.5 and 32.2 months. Graham *et al*. analyzed clinical dose-volume histogram for pneumonitis after 3 days treatment for NSCLC patients.[22] The actuarial development of Grade 2 or greater pneumonitis reached a plateau at about 15 months after treatment. Tsoutsou and Koukourakis speculate that between these two effects, an

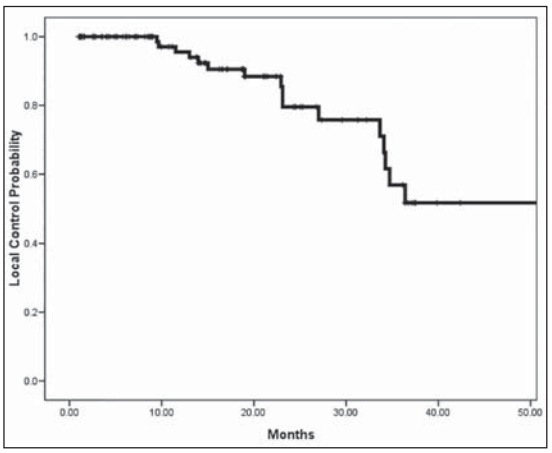

Figure 1. The local control curve for all tumors. The local control rates for all tumors were 96% at 1 year and 80% at 2 years

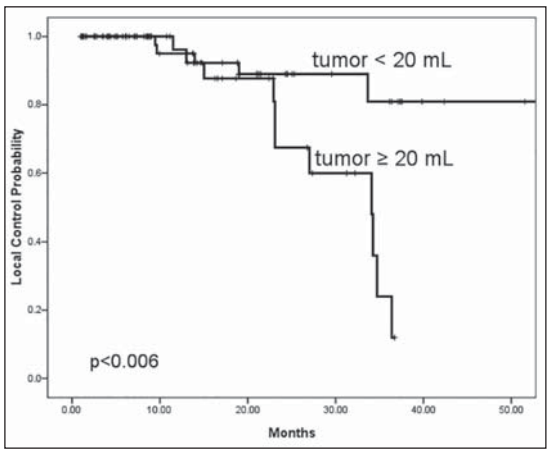

Figure 2. The local control curves for all tumors. The 2-year local control rates for tumor < 20 mL and ≥20 mL were 89% and 68%, respectively (P=0.006)

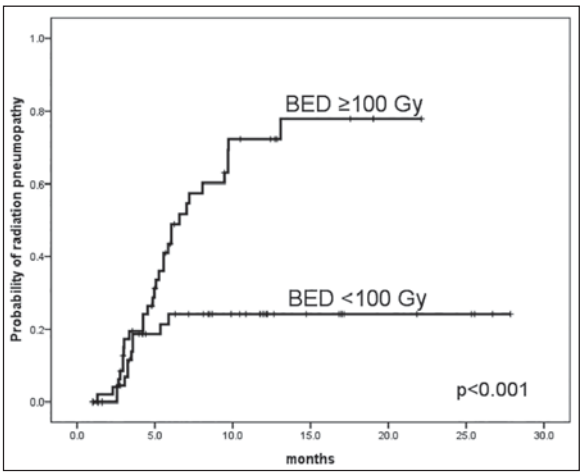

Figure 3. The probability of radiation pneumopathy for all tumors. The 1-year incidence of radiation pneumopathy were 72% and 24% for BED ≥100 Gy and BED <100 Gy, respectively

intermediate exudative phase may exist in the patient in whom acute pneumonitis fails to resolve completely.[18] The term "radiation pneumopathy" is used to describe this continuing process.

There are few potential biases in this study. First, the true tumor response could be obscured by radiation pneumopathy. Radiation pneumopathy leads to underestimation of CR and PR. It is difficult to evaluate tumor response until the progression of radiation pneumopathy stabilizes or subsides. Tumor responses were evaluated after reading a series of follow-up images in this study. Second, many patients received SABR for more than one tumor. For patients who had two or more irradiated lesions, the chance of symptomatic pneumopathy is higher than patients who had only one irradiated lesion. Therefore, radiation pneumopathy may be overestimated in our study because many patients had more than one tumor. Third, rapid disease progression, some leading to death, was noted outside CyberKnife treated area for patients with palliative intents. The lesions may keep shrinking if these patients had lived longer.

Only limited reports with limited patient numbers are available who were treated with CyberKnife. Brown *et al*. reviewed 35 patients with 69 pulmonary metastases treated by the CyberKnife.[11] The median GTV was 12.1 ml. Total doses ranged from 5 to 60 Gy delivered in one to four fractions. At a median 18 months follow-up, local control was 71%. Snider *et al*. reported 24 patients with biopsy-proven single-peripheral lung metastases treated by CyberKnife.[12] The mean maximum tumor diameter was 2.5 cm. At a median follow-up of 20 months, the 2 years local control rate was 87% and 2 years overall survival was 50%. Chen *et al*. reported 40 high-risk surgical patients with biopsy-proven Stage I NSCLC.[13] The median age was 76 years. The median maximum tumor diameter was 2.6 cm. A median dose of 48 Gy was delivered to the PTV. At a median 44 months follow-up, the 3 years Kaplan–Meier locoregional and overall survival rates was 91% and 75%, respectively. Collins *et al.* and Vahdat *et al*. enrolled 20 inoperable patients with small peripheral clinical Stage IA NSCLC.[15,23] A mean dose of 51 Gy (range, 42-60 Gy) was delivered to the PTV in three fractions using the CyberKnife. The average maximum tumor diameter was 2.2 cm. With a median follow-up of 43 months, the 2 years Kaplan — Meier overall survival was 90%, and the local control was 95%. They concluded that local control and survival following CyberKnife radiosurgery for Stage IA NSCLC is exceptionally high. Our study showed a 2 years local control rate of 80% that seems to be lower than Vahdat's result. However, metastatic lung lesions were also included in our series, and this may underestimate our results due to rapid systemic disease progression. Our study was made retrospectively, and patients were not highly selected. Compared to our study design, other series were done prospectively, patients were highly selected, and the GTV were relatively smaller than ours. This also may make our result inferior to other series.

Unger *et al*. accrued 20 patients with primary or metastatic hilar tumors treated by CyberKnife.[14] The median GTV was 73 ml. A prescribed dose of 30-40 Gy to the GTV was delivered in five fractions. At a median follow-up of 10 months, the 1-year Kaplan–Meier local control was 63%. He concluded that CyberKnife is an effective palliative treatment option for hilar tumors, but local control is poor at 1-year. However, the median GTV was relatively large in his study. When small targets were selected for palliative treatment and higher dose were used, local control rate may improve. CyberKnife with synchrony tracking system is an effective treatment for malignant lung tumors that moves. It also can be safely used for malignant hilar tumors, and the treatment result is not inferior to peripheral lung tumors.

There are several studies which used traditional linear accelerator based, image-guided SABR for lung tumors. The reports showed good local control rates around 75-95% for malignant lung tumors, and promising survival rates of 70-90% for early-stage NSCLC. Taremi *et al*. presented a prospective study of traditional SABR for medically inoperable patients with Stage I NSCLC.[8] One hundred and eight patients (114 tumors) received the following SABR schedules: 48 Gy in 4 fractions or 54-60 Gy in 3 fractions for peripheral lesions and 50-60 Gy in 8-10 fractions for central lesions. The mean tumor diameter was 2.4 cm. The median follow-up was 19.1 months. The local control rate at 1 and 4 years was 92% and 89%, respectively. The cause-specific survival rate at 1 and 4 years was 92% and 77%, respectively. Onishi *et al*. reviewed treatment outcomes for SABR in medically operable patients with Stage I NSCLC.[6] Eighty-seven patients were medically operable, but refused surgery. They were treated using SABR alone in 14 institutes. Total dose was 45-72.5 Gy at the isocenter, administered in 3-10 fractions. Median BED was 116 Gy. The local control rates for T1 and T2 tumors at 5 years were 92% and 73%, respectively. The 5 years overall survival rates for Stage IA and IB subgroups were 72% and 62%, respectively. He concluded that the survival rate for SABR is potentially comparable to that for surgery.

CyberKnife can be used for NSCLC and metastatic lung tumors, either peripheral or central location, with good local control and acceptable side effects. However, higher BED comes with a higher incidence of radiation pneumopathy.

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DISCLOSURE

No conflict of interest to declare.

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