EARLY EXPERIENCE OF STEREOTACTIC BODY RADIOTHERAPY IN PATIENTS WITH PRIMARY AND METASTATIC LUNG TUMORS

SBRT for Primary and Metastatic Lung Tumors

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Purpose：To investigate the clinical outcomes of patients with primary and metastatic lung tumors treated by CyberKnife® (CK) stereotactic body radiotherapy (SBRT).

Methods：Between November 2005 and June 2008, we treated 19 patients with SBRT at Taipei Medical University-Wan Fang Hospital. The SBRT was delivered by CK tumor tracking system. Tumor response and treatment-related toxicity were evaluated by follow-up image study. Treatment-related toxicities were scored by Common Terminology Criteria for Adverse Events version 3.0. In this study, we reviewed their medical records retrospectively.

Results：We treated 47 lung tumors in 19 patients using CK SBRT. Eleven tumors in 8 patients were primary lung cancer, and 36 tumors in 11 patients were metastatic lung cancer. The locations of 9 tumors were central, whereas the others were peripheral. The tumor volumes were ranged from 1.1 to 110.5 ml (median, 9.5 ml). The radiation doses were ranged from 22 to 60 Gy, given in 2 to 4 fractions. The prescribed doses were normalized at 76% to 85% of the planned isodose. With a median follow-up interval of 12 months, we observed that grade 2 radiation pneumonitis (RP) occurred in 3 patients (1 central; 2 peripheral), whereas we found that grade 3 RP occurred in 2 patients with central lesions. According to the univariate analysis, female ($p = 0.038$) and central lesion ($p = 0.042$) were two predictive factors to the occurrence of grade $\geq$ 2 RP. One grade 4 tracheal complication (tracheoesophageal fistula) and one grade 5 bronchial complication (bronchial necrosis) were observed in two patients who had centrally located recurrent tumors and had been previous treated with external beam radiotherapy. Four of the evaluable patients (16 patients) had responded completely (25%), seven exhibited partial response to treatment (43.8%), and two had stable disease (12.5%). Three patients had tumor progression after SBRT (18.7%). The

1-year overall survival (OS) was 63%, and the 1-year local progression-free survival (PFS) was 84.2%. The 1-year local PFS was 87.5% for primary lung cancer and 81.8% for metastatic lung cancer (p = 0.87). The 1-year local PFS for central and peripheral lesions was 80% and 85.7%, respectively (p = 0.63).

Conclusion：Our study showed that SBRT using the CK system was effective for treating primary and metastatic lung tumors, providing better local control and shorter treatment course compared with those treated with conventional fractionated radiotherapy. Our study also showed two predicting factors for RP. Finally, using SBRT to treat centrally located tumor or re-irradiate recurrent tumor require additional caution due to higher risk of having complication. Thus, we suggest that more studies are needed in the future to confirm those findings in this study.

Key words：CyberKnife®, Stereotactic body radiotherapy, Lung tumor, Radiation pneumonitis

INTRODUCTION

Stereotactic body radiotherapy (SBRT) has been used to deal with tumors outside of the central nervous system for more than 10 years. Due to recent advances in imaging and radiotherapy technique, dose escalation for improving therapeutic gain has become feasible. Several clinical studies have been reported to have the efficacy of SBRT in treating primary or metastatic lung tumors, and promising local control rates of 80% or greater [12, 23, 26, 35, 38, 40].

The major concern is the tolerance of treatment-related normal tissue toxicities from prescription of a large fraction size. Less standard dose-volume constraints for organs at risk (OARs) in SBRT have been studied compared with those in conventional radiotherapy. When using SBRT in treating lung tumors, a new strategy of dose constraints needs to be investigated. Furthermore, care must be taken particularly when treating central lesions (i.e. tumors close to trachea or carina) [7].

This retrospective analysis was conducted to investigate the clinical outcome in patients with lung tumors treated with SBRT.

METHODS

Patient Eligibility

We reviewed the medical records retrospectively between November 1, 2005 and June 30, 2008 for lung cancer patients who received SBRT. We found that 47 lung tumors in 19 patients treated by CyberKnife® (CK, Accuray Inc., Sunnyvale, California, USA) at Taipei Medical University-Wan Fang Hospital. All cases were discussed by the multi-disciplinary thoracic oncology team.

In this study, the selection criteria for CK treatment included: (1) pathological confirmation of malignancy, (2) inoperable lung tumor due to excessive risk or patient's

refusal for surgery, (3) performance status being equal or smaller than 2 according to Eastern Cooperative Oncology Group (ECOG) scale, and (4) favorable pulmonary function with forced expiratory volume in the first second (FEV1) being greater than 70% or breath-holding time being more than 10 seconds.

Stereotactic Treatment

The CK stereotactic radiosurgery system is a frameless, image-guided robotic radiosurgery device which has a 6-MeV linear accelerator mounted on a robotic arm to deliver wide-ranged radiation beams at six degrees of freedom. CK is equipped with a real-time imaging tracking system to track for patient movement with sub-millimeter spatial accuracy and can compensate tumor movement.

Before the SBRT, we implanted three or more gold markers (fiducials, 5 mm in length and 0.8 mm in thickness) in the peripheral of the tumors through computed tomography (CT)-guided percutaneous needle approach performed by experienced interventional radiologists except in patients unsuitable for the procedure. The exclusion criteria for the fiducial implant included: (1) contraindication to anesthetic agents, (2) having bleeding tendency, and (3) tumor's proximity to major vessels. Unenhanced CT was performed after the procedure to evaluate markers location and immediate complications. We monitored patients without complications with chest radiograph in the coming morning and then being discharged from hospital, whereas patients with complications received further appropriate treatment in the hospital.

We did CT simulation at least seven days after markers implantation to allow the resolution of tissue inflammation and markers migration. Patients underwent a spiral treatment-planning CT scan using an individualized immobilization device in the treatment position on a flat table. We obtained contiguous CT slices of 1.25 mm thickness through the

gross primary tumor and the whole thoracic cavity. All critical thoracic structures and the lungs were contoured. Lung tumors seen in lung windows on enhanced CT were delineated as gross tumor volumes (GTV). A 0.5 to 1 cm margin was expanded to form the planning tumor volumes (PTV). The dose schemes and dose constraints (Table 1) were adapted based on clinical studies results [22, 33]. The conformity index (CI) was determined from the ratio of the prescription isodose volume (V^{Rx}) and the target volume (V_{PTV}): $CI = V^{Rx} / V_{PTV}$. The homogeneity index (HI) was determined by dividing the maximal dose (D^{max}_{PTV}) by the prescription dose to the PTV (D^{Rx}_{PTV}): $HI = D^{max}_{PTV} / D^{Rx}_{PTV.}$ The centrally located tumor was defined as their proximal margin within 2 cm from trachea or main bronchus on CT scan.

The Synchrony® Respiratory Tracking System (RTS) was a subsystem of the CyberKnife® robotic treatment device to irradiate extracranial tumors that move due to respiration. In the beginning of treatment, two orthogonal X-ray images were taken at different phases of the motion cycle. By registering these images with two digital reconstruction radiography images from the planning CT, the absolute position of the target relative to the fiducial markers was determined (Figure 1A). Three red light-emitting diodes (LED) were attached on the surface of the patient's anterior chest region with maximum respiratory motion. The camera array was continuously recorded the positions of the LED markers as a function of time. Immediately before the treatment delivery, we created an adaptive correlation model between the internal fiducial markers positions imaged by the X-ray targeting system and the external LED as continuously imaged by the camera array (Figure 1B). The RTS estimated the tumor positions by correlating the external LED motion and implanted fiducial locations. By using the Synchrony® RTS, the tumor motion could be real-time validated and updated during treatment [8, 21].

For eight patients with unsuitable condition for the implanted procedure, we did SBRT with the X-sight® Spine Tracking System, which used the neighboring spine structures to set up the global position of the target [15, 20].

Toxicity scoring and follow up

The primary endpoints were to analyze the local control and the treatment-related toxicities. We did follow-up evaluations for treatment response with history taking, physical examination and chest imaging every 3 months for the first year, every 6 months for the second year, and annually thereafter, or any time point when being recorded to have related pulmonary symptoms. Positron emission tomography (PET) scan was performed in selected patients whose clinical radiological findings were indefinite. Treatment-related acute and late toxicities were scored according to the Common Terminology Criteria for Adverse Events version 3.0 [34]. We evaluated tumor response with CT study basing on the Response Evaluation Criteria in Solid Tumors (RECIST) criteria [30].

Statistical analysis

The follow-up interval was defined as the duration between SBRT completion and the last follow-up. For patients with multiple tumors concurrently irradiated by SBRT, progression of any treated tumors was recorded as local failure. We used the Kaplan-Meier method to calculate the local control and survival rates. The chi-square test and independent *t*-test were applied to analyze the factors associated with grade 2 or greater radiation pneumonitis.

We computed the data with the Software Package for Social Sciences (SPSS Inc., Chicago, Illinois, USA) version 13.0 for statistical analysis. The differences between groups were considered significant if *p*-values were smaller than or equal to 0.05.

RESULTS

Patient and treatment characteristics

Forty-seven lung tumors in 19 patients were treated by CK SBRT. Eleven tumors in 8 patients were primary lung cancer (stage IIB: 2, IIIA: 1, IV: 5), and 36 tumors in 11 patients were metastatic lung cancer. The location of 9 tumors was central, whereas that of the other 38 tumors was peripheral. Table 2 lists the patient characteristics.

The median tumor volume was 9.5 ml (range, 1.1 ml to 110.5 ml). The radiation doses ranged from 22 to 60 Gy, given in 2 to 4 fractions. Most patients were treated with 36 to 45 Gy in 3 fractions, whereas dose was modified for small peripheral lesions (48 to 60 Gy in 3 fractions) and centrally located tumors (22 to 45 Gy in 2 to 4 fractions). The prescribed doses were normalized at 76% to 85% of the planned isodose. For patients with multiple tumors, lesions were treated concurrently in 1 or 2 SBRT courses in two weeks interval.

Complications and toxicities

Among the 11 patients who received fiducials implantation, two of them developed grade 2 pneumothorax. The pneumothorax recovered either spontaneously or after chest tube insertion within 10 days after the implant. The incidence of implant-related pneumothorax was 18%.

The median follow-up period for patients was 12 months. Grade 2 radiation pneumonitis (RP) was observed in 3 patients (1 central; 2 peripheral), whereas grade 3 RP occurred in 2 patients with central lesions. The median time of the pneumonitis occurrence was 4 months after the SBRT. According to the univariate analysis, female ($p = 0.038$) and central lesion ($p = 0.042$) were two predictive factors to the occurrence of grade $\geq$ 2 RP (Table 3). One patient developed tracheoesophageal fistula (grade 4 tracheal complication)

and one had bronchial necrosis (grade 5 bronchial complication). These two adverse events were observed at 5 months after their SBRT, and the treated tumors were categorized as centrally located tumors. Furthermore, both patients had received more than 50 Gy of thoracic external beam irradiation about 6 months before their SBRT and they had SBRT to relieve symptoms caused by the recurrent lung tumors. Table 4 summarizes the patients with grade 2 or greater toxicities.

Local control and survival

Three patients died within two months after SBRT, and they were excluded from the assessment of local control. Among these three patients, two suffered from hepatocellular carcinoma and they both died of intracranial tumor bleeding. The other one died of inter-current sepsis. Among the evaluable 16 patients, three patients had tumor progression after SBRT, eleven were recorded as response to treatment (4 complete response, 7 partial response) and 2 patients had stable disease. The overall local control rate to SBRT was 81.3%

The 1-year overall survival (OS) was 63%, and the 1-year local progression-free survival (PFS) was 84.2% (Figure 2). According to the tumor origin, the 1-year local PFS was 87.5% for primary lung cancer and 81.8% for metastatic lung cancer ($p = 0.87$). The 1-year local PFS for central and peripheral lesions was 80% and 85.7%, respectively ($p = 0.63$). Figures 3 and 4 depict the local PFS curves according to tumor origin and location. One patient with solitary lung metastasis showed progression free over 1 year was illustrated in Figure 5.

DISCUSSION

Although surgical resection continues to be the standard of care for patients with lung tumors, SBRT has become increasingly accepted as a viable alternative in patients for whom

surgery is not feasible or is medically contraindicated. SBRT, which is allowed for a highly precise irradiation is originally developed from stereotactic radiosurgery in the 1970s. Since, it has been used more and more in extracranial indications [36]. In the first study of SBRT for lung, reported in 1995 by Blomgren et al., the investigators enrolled 15 patients treated with total doses of 20 to 40 Gy, given in 1 to 3 fractions [3]. The study result has shown progression-free in all lesions after a median follow-up of 8 months.

Many innovative radiotherapy techniques, such as respiratory gating for tumor motion control, the image-guided radiation therapy, and robotic radiosurgery have been emerged recently. CK is one of the developments and has been proven to provide sub-millimeter accuracy in SBRT using an intra-fractional tumor tracking with its robot arm [9, 21]. Despites the potential risk of pneumothorax, bleeding, or the possibility of migration [18, 39], the fiducials were implanted to improve SBRT delivery accuracy in many patients. Our data showed lower incidence (18%) of pneumothorax when compared with other reports (25% to 30%) [27, 39], and no other implant-related toxicity was recorded after a two-year maximum follow-up. This might be attributed to the routine pretreatment multi-disciplinary team discussion and the skillful implant technique of our interventional radiologist.

With advanced imaging and radiotherapy technique, previous studies showed the feasibility of radiation dose escalation in unresectable non-small cell lung cancer (NSCLC) [14], and the local control rates seem to be improved further [2, 6, 40]. Wulf et al. reported a one-year local control rate of 76 % using three to four fractions of 7 to 10 Gy to treat primary and metastatic lung lesions [37]. In Japan series using SBRT treating stage I NSCLC, Onishi et al. reported an overall response rate (complete response and partial response) of 84.8 % in 245 patients and favorable local control and survival with BED $\geq$ 100 Gy [26]. Nagata et al. found that the 1-year local relapse-free survival is 100 % in 45 patients receiving 48 Gy in 4

fractions [23]. Currently, the use of SBRT in treating metastatic lung tumors is increasingly popular with variable schemes of radiation dose [12, 17, 25].

Despites that many patients had multiple lung tumors or extra-pulmonary metastases in our cohort, the local PFS curve for metastatic lung tumors was excellent and was nearly equivalent to primary NSCLC (Figure 3). From our study, the local control rates for primary and metastatic tumors approached 80% and this result is comparable with other SBRT reports [5, 10, 29, 32]. Except that three patients experienced early death during follow-up, cancer progression outside the irradiated field was still the main cause of mortality. Seven patients died of extra-pulmonary disease progression, 1 treatment-related bronchial necrosis, and 2 local failure. The other 6 patients were alive (1 local progression, and 5 local progression free) when they were seen at the last follow-up. In our study, many recruited patients were having metastatic condition and using SBRT was intended to be palliative rather than curative. Thus, to select suitable patients for SBRT is important to magnify the clinical benefits and optimize the treatment outcome. Considering the factors affecting local control in SBRT for lung tumors, there was a trend that primary or peripherally located lung tumor had a better local control, but the difference was not significantly different in our study. Nonetheless, comparing our data directly with the published results for local failure was difficult due to various treatment schemes, including single dose irradiation [11, 13], single dose combined with conventional fractionated radiotherapy [24], and hypofractionated irradiation [4].

Generally, the acute toxicity rate of stereotactic irradiation is relatively low. Therefore, SBRT could be used for outpatients. Rib pain and skin itching were two observed acute side effects in SBRT for lung tumors, and they were usually recovered within a few days [40]. Thus, the major concern was the risk of developing radiation pneumonitis (RP). Our result showed that CK SBRT for central lesions were associated with severe complications, which has been described elsewhere [1, 31]. Alternatively, one investigation showed that female

patients had higher rate of RP because they had smaller lung volume and smaller FEV1, which could result in having greater risk of lung injury in the equivalent radiation field [28]. Our data showed similar results regarding the risk factors for predicting grade 2 or greater RP (Table 3). But we did not have pretreatment pulmonary function data for every patient. In addition, Morgan and Breit proposed that hypersensitivity reaction has been increased in lung tissues of female patients because more autoimmune factors like lymphocytosis exist in women than those in men [19]. Further investigation is required to elucidate the gender difference in RP. Finally, two patients with re-irradiated central lesions experienced severe toxicities (one grade 4 tracheal and one grade 5 bronchial complications), even with lower SBRT treatment doses (28 Gy and 26 Gy, respectively). Therefore, using SBRT to re-irradiate recurrent centrally located tumor requires additional caution to minimize the treatment-related toxicities.

As the first SBRT report for lung tumor in Taiwan, our current treatment protocol has provided a feasible SBRT scheme in lung tumors treatment. But our study has three limitations. First, the median follow-up duration was short. Second, the sample size was relatively small. And finally, bias might exist due to the heterogeneity of our patient population. Further studies are imperative to investigate the treatment variables, including patient selection criteria, optimal dose and fractionation, treatment planning algorithms, uncertainty of respiratory motion, and the combination of other treatment modalities.

We are also looking forward to the result of multi-centered prospective phase III randomized trial which we have participated in. In that protocol, we are comparing CK SBRT with surgical resection in stage I NSCLC [16].

CONCLUSION

Our study showed that SBRT using the CK system was effective for treating primary and metastatic lung tumors, providing better local control and shorter treatment course compared with those treated with conventional fractionated radiotherapy. Our study also showed two predicting factors for radiation pneumonitis. Finally, using SBRT to treat centrally located tumor or re-irradiate recurrent tumor require additional caution due to higher risk of having complication. Thus, we suggest that more studies are needed in the future to confirm those findings in this study.

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REFERENCES

1. Ball D: Stereotactic radiotherapy for nonsmall cell lung cancer. Current Opinion in Pulmonary Medicine 2008; 14 (4): 297-302.

2. Baumann P, Nyman J, Lax I, et al.: Factors important for efficacy of stereotactic body radiotherapy of medically inoperable stage I lung cancer. A retrospective analysis of patients treated in the Nordic countries. Acta Oncologica 2006; 45 (7): 787-795.

3. Blomgren H, Lax I, Naslund I, Svanstrom R: Stereotactic high dose fraction radiation therapy of extracranial tumors using an accelerator. Clinical experience of the first thirty-one patients. Acta Oncol 1995; 34 (6): 861-870.

4. Brock J, Ashley S, Bedford J, Nioutsikou E, Partridge M, Brada M: Review of hypofractionated small volume radiotherapy for early-stage non-small cell lung cancer. Clin Oncol 2008; 20 (9): 666-676.

5. Brown WT, Wu X, Amendola B, et al.: Treatment of early non-small cell lung cancer, stage IA, by image-guided robotic stereotactic radioablation-CyberKnife. Cancer J 2007; 13 (2): 87-94.

6. Brown WT, Wu X, Fayad F, et al.: CyberKnife radiosurgery for stage I lung cancer: results at 36 months. Clinical Lung Cancer 2007; 8 (8): 488-492.

7. Chang JY, Balter PA, Dong L, et al.: Stereotactic body radiation therapy in centrally and superiorly located stage I or isolated recurrent non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2008; 72 (4): 967-971.

8. Chang SD, Main W, Martin DP, Gibbs IC, Heilbrun MP: An analysis of the accuracy of the CyberKnife: a robotic frameless stereotactic radiosurgical system. Neurosurgery 2003; 52 (1): 140-146; discussion 146-147.

9. Chen CP, Chiu JF, Huang YC, et al.: Acceptance test for Cyberknife unit. Therapeut Radiol Oncol 2006; 13 (3): 197-204.

10. Collins BT, Erickson K, Reichner CA, et al.: Radical stereotactic radiosurgery with real-time tumor motion tracking in the treatment of small peripheral lung tumors. Radiat Oncol 2007; 2 (1): 39.

11. Fritz P, Kraus HJ, Blaschke T, et al.: Stereotactic, high single-dose irradiation of stage I non-small cell lung cancer (NSCLC) using four-dimensional CT scans for treatment planning. Lung Cancer 2008; 60 (2): 193-199.

12. Fritz P, Kraus HJ, Muhlnickel W, et al.: Stereotactic, single-dose irradiation of stage I non-small cell lung cancer and lung metastases. Radiat Oncol 2006; 1: 30.

13. Hara R, Itami J, Kondo T, et al.: Stereotactic single high dose irradiation of lung tumors under respiratory gating. Radiother Oncol 2002; 63 (2): 159-163.

14. Hayman JA, Martel MK, Ten Haken RK, et al.: Dose escalation in non-small-cell lung cancer using three-dimensional conformal radiation therapy: update of a phase I trial. J Clin Oncol 2001; 19 (1): 127-136.

15. Ho AK, Fu D, Cotrutz C, et al.: A study of the accuracy of cyberknife spinal radiosurgery using skeletal structure tracking. Neurosurgery 2007; 60 (2 Suppl. 1): 147-156; discussion 156.

16. International randomized study to compare CyberKnife stereotactic radiotherapy with surgical resection in stage I non-small cell lung cancer (STARS). Available on line at: http://clinicaltrials.gov/ct2/show/NCT00840749. Accessed May 1, 2010.

17. Kavanagh BD, McGarry RC, Timmerman RD: Extracranial radiosurgery (stereotactic body radiation therapy) for oligometastases. Semin Radiat Oncol 2006; 16 (2): 77-84.

18. Kazerooni EA, Lim FT, Mikhail A, Martinez FJ: Risk of pneumothorax in CT-guided transthoracic needle aspiration biopsy of the lung. Radiology 1996; 198 (2): 371-375.

19. Morgan GW, Breit SN: Radiation and the lung: a reevaluation of the mechanisms mediating pulmonary injury. Int J Radiat Oncol Biol Phys 1995; 31 (2): 361-369.

20. Muacevic A, Drexler C, Wowra B, et al.: Technical description, phantom accuracy, and clinical feasibility for single-session lung radiosurgery using robotic image-guided real-time respiratory tumor tracking. Technol Cancer Res Treat 2007; 6 (4): 321-328.

21. Murphy MJ, Cox RS: The accuracy of dose localization for an image-guided frameless radiosurgery system. Med Phys 1996; 23 (12): 2043-2049.

22. Nagata Y, Matsuo Y, Takayama K, et al.: Current status of stereotactic body radiotherapy for lung cancer. Int J Clin Oncol 2007; 12:3-7.

23. Nagata Y, Takayama K, Matsuo Y, et al.: Clinical outcomes of a phase I/II study of 48 Gy of stereotactic body radiotherapy in 4 fractions for primary lung cancer using a stereotactic body frame. Int J Radiat Oncol Biol Phys 2005; 63 (5): 1427-1431.

24. Nakagawa K, Aoki Y, Tago M, Terahara A, Ohtomo K: Megavoltage CT-assisted stereotactic radiosurgery for thoracic tumors: original research in the treatment of thoracic neoplasms. Int J Radiat Oncol Biol Phys 2000; 48 (2): 449-457.

25. Norihisa Y, Nagata Y, Takayama K, et al.: Stereotactic body radiotherapy for oligometastatic lung tumors. Int J Radiat Oncol Biol Phys 2008; 72 (2): 398-403.

26. 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 2004; 101 (7): 1623-1631.

27. Prévost JBG, Nuyttens JJ, Hoogeman MS, Pöll JJ, van Dijk LC, Pattynama PMT: Endovascular coils as lung tumour markers in real-time tumour tracking stereotactic radiotherapy: preliminary results. Eur Radiol 2008: 1-8.

28. Robnett TJ, Machtay M, Vines EF, McKenna MG, Algazy KM, McKenna WG: Factors predicting severe radiation pneumonitis in patients receiving definitive chemoradiation for lung cancer. Int J Radiat Oncol Biol Phys 2000; 48 (1): 89-94.

29. Silvano G: New radiation techniques for treatment of locally advanced non-small cell lung cancer (NSCLC). Ann Oncol 2006; 17 (Suppl. 2): 34-35.

30. Therasse P, Arbuck SG, Eisenhauer EA, et al.: New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000; 92 (3): 205-216.

31. Timmerman R, McGarry R, Yiannoutsos C, et al.: 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 2006; 24 (30): 4833-4839.

32. Timmerman RD, Park C, Kavanagh BD: The North American experience with stereotactic body radiation therapy in non-small cell lung cancer. J Thorac Oncol 2007; 2 (7 Suppl. 3): 101-112.

33. Timmerman RD, Paulus R, Galvin J, et al.: Toxicity analysis of RTOG 0236 using stereotactic body radiation therapy to treat medically inoperable early stage lung cancer patients. Int J Radiat Oncol Biol Phys 2007; 69 (3 Suppl. 1): 86.

34. Trotti A, Colevas AD, Setser A, et al.: CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. Semin Radiat Oncol 2003; 13 (3): 176-181.

35. Uematsu M, Shioda A, Suda A, et al.: Computed tomography-guided frameless stereotactic radiotherapy for stage I non-small cell lung cancer: a 5-year experience. Int J Radiat Oncol Biol Phys 2001; 51 (3): 666-670.

36. Uematsu M, Shioda A, Tahara K, et al.: Focal, high dose, and fractionated modified stereotactic radiation therapy for lung carcinoma patients: a preliminary experience. Cancer 1998; 82 (6): 1062-1070.

37. Wulf J, Hadinger U, Oppitz U, Thiele W, Ness-Dourdoumas R, Flentje M: Stereotactic radiotherapy of targets in the lung and liver. Strahlenther Onkol 2001; 177 (12): 645-655.

38. Wulf J, Haedinger U, Oppitz U, Thiele W, Mueller G, Flentje M: Stereotactic radiotherapy for primary lung cancer and pulmonary metastases: a noninvasive treatment approach in medically inoperable patients. Int J Radiat Oncol Biol Phys 2004; 60 (1): 186-196.

39. Yousefi S, Collins BT, Reichner CA, et al.: Complications of thoracic computed tomography-guided fiducial placement for the purpose of stereotactic body radiation therapy. Clin Lung Cancer 2007; 8 (4): 252-256.

40. Zimmermann FB, Geinitz H, Schill S, et al.: Stereotactic hypofractionated radiotherapy in stage I (T1-2 N0 M0) non-small-cell lung cancer (NSCLC). Acta Oncologica 2006; 45 (7): 796-801.

Table 1. Dose constraints in lung tumor treated with CK

Organ	Dose Constraint
Spinal Cord	Max < 18Gy (6 Gy/fraction)
Esophagus	Max < 27Gy (9 Gy/fraction) Max < 30Gy (7.5 Gy/fraction)*
Trachea and Ipsilateral Bronchus	Max < 30 Gy (10 Gy/fraction)
Ipsilateral Brachial Plexus	Max < 24 Gy (8 Gy/fraction)
Heart	Max < 10 Gy/fraction
Whole Lung (GTV excluded)	V20 < 20%
PTV	CI< 1.5, HI < 1.5
Desired isodose	>75%
Desired target coverage	>95%

Abbreviation: Max = maximum dose; CI = conformity index; HI = homogeneity index

* For tumor close to esophagus (proximal margin < 2 cm in distance)

Table 2. Patient characteristics (n=19)

Characteristic	Value
Age (years)	15 ~ 85 (median: 59)
Gender	Male: 12; Female: 7
Performance status	
ECOG 0-1	8
ECOG 2	11
Origin	
Primary lung cancer	8
Metastatic lung cancer	11
Hepatocelluar carcinoma	4
Renal cell carcinoma	2
Breast cancer	1
Colorectal cancer	2
Uterus leiomyosarcoma	1
Chondroblastoma	1
Tumor features (total 47)	
Location	
Central	9
Peripheral	38
Volume (ml)	1.1 ~ 110.5 (median: 9.5)
Tumor number per patient	1 ~ 14 (median: 1)
Numbers of implanted marker	
0	8
3	3
4	1
6	6
10	1
Follow-up interval (month)	1 ~ 41 (median: 12)

Abbreviation: ECOG = Eastern Cooperative Oncology Group

Table 3. Univariate analysis of factors related to Grade ≥ 2 radiation pneumonitis after CK treatment

Factor	N	≥ Gr.2 RP (%)	OR	95% CI	*p*-value
Chi-square test					
Gender				1.161 – 185.235	0.038
Male	12	1 (8.33)	1		
Female	7	4 (57.14)	14.667		
Performance status				0.332 – 21.739	0.603
ECOG 0-1	8	3 (37.50)	2.70		
ECOG 2	11	2 (18.18)	1		
Origin				0.141 – 8.995	1.000
Primary lung cancer	8	2 (25.00)	1		
Metastatic lung cancer	11	3 (27.27)	1.125		
Tumor location				1.235 – 66.667	0.042
Central	9	3 (33.33)	9.009		
Peripheral	38	2 (5.26)	1		
Fiducial marker implant				0.332 – 21.977	0.603
Yes	11	2 (18.18)	1		
No	8	3 (37.50)	2.700		
Factor					*p*-value
Independent t-test					
Age					0.612
Tumor volume					0.210
Tumor number per patient					0.406

Abbreviation: RP = radiation pneumonitis; OR = odds ratio; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group

Table 4. Details for patients with symptomatic complications after CK treatment

Patient No.	Tumor Origin	Tumor Location	Tumor Volume (ml)	Dose Scheme	Treatment-related Toxicity	Post-treatment Interval (mo.)
1	Primary	Central	28.3	3 x 9.3 Gy	Gr. 4 tracheal complication*	5
2	Primary	Central	55.7	3 x 15 Gy	Gr. 3 RP	4
3	Primary	Central	33.6	2 x 13 Gy	Gr. 5 bronchial complication†	5
4	Primary	Central	110.5	4 x 15 Gy	Gr. 3 RP & Gr. 3 Esophagitis§	3
5	Metastatic	Peripheral	25.4	4 x 13 Gy	Gr. 2 RP	6
6	Metastatic	Peripheral	2.5	3 x 15 Gy	Gr. 2 RP	8
7	Metastatic	Central	21.7	3 x 12 Gy	Gr. 2 RP	3

Abbreviation: RP = radiation pneumonitis

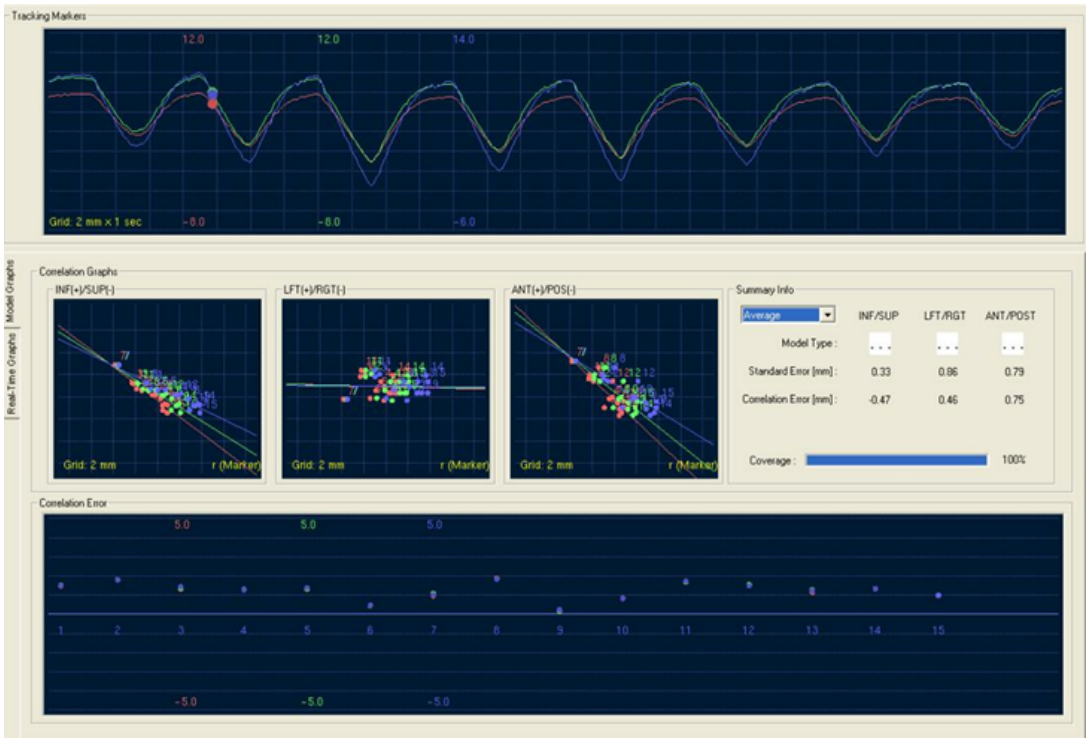
*Tracheoesophageal fistula

†Bronchial necrosis

§Esophageal stenosis

Figure 1. The Synchrony® Respiratory Tracking System (RTS) for lung SBRT:

(A) Registration of real time orthogonal X-ray images with digital reconstruction radiography images from the planning CT for fiducial markers tracking



(B) Building the adaptive correlation model for target position tracking and correction during continuous respiratory cycle

Figure 2. Progression free survival curve of patients with lung tumors treated with CK (n = 19)

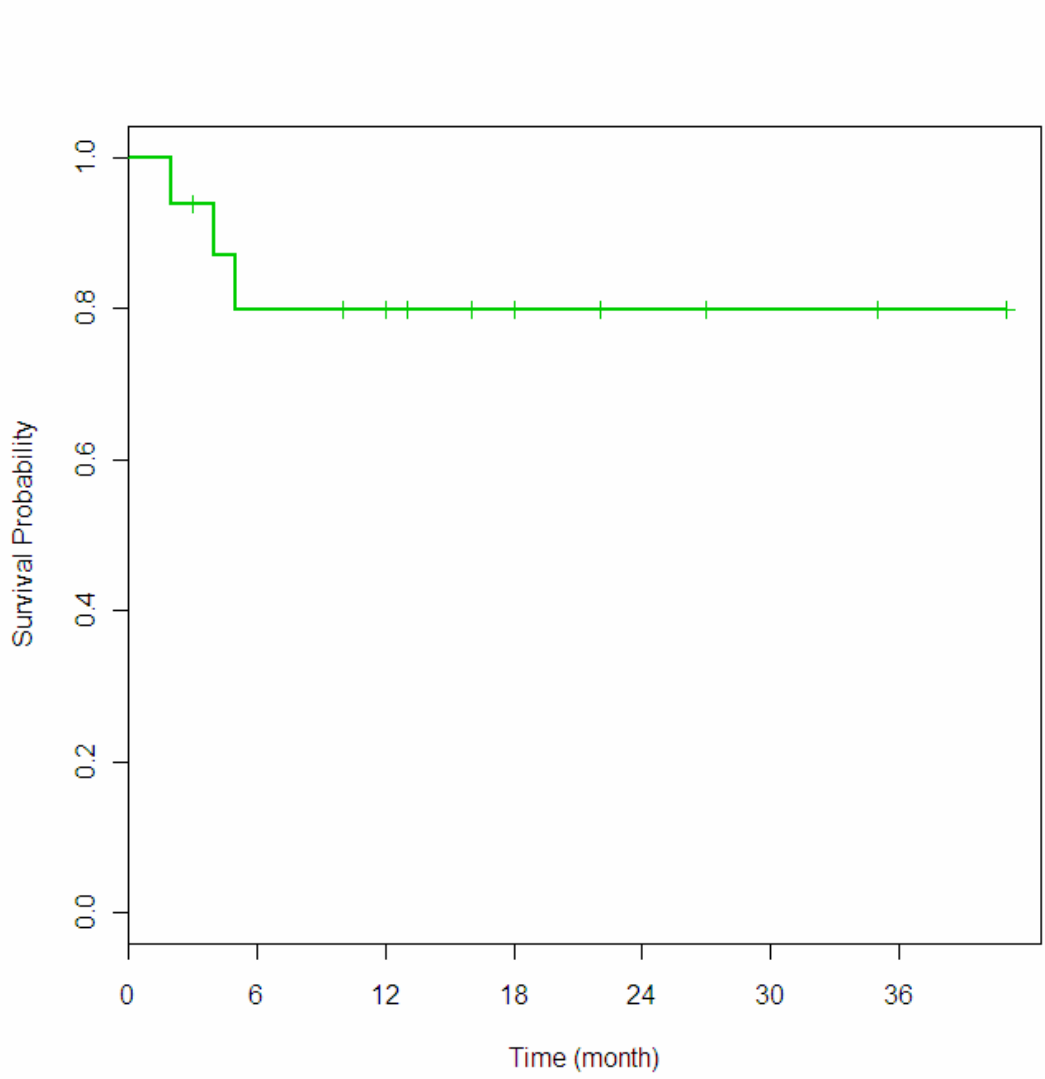


Figure 3. Progression free survival curves of patients with (1) primary and (2) metastatic lung tumors treated with CK (n = 19)

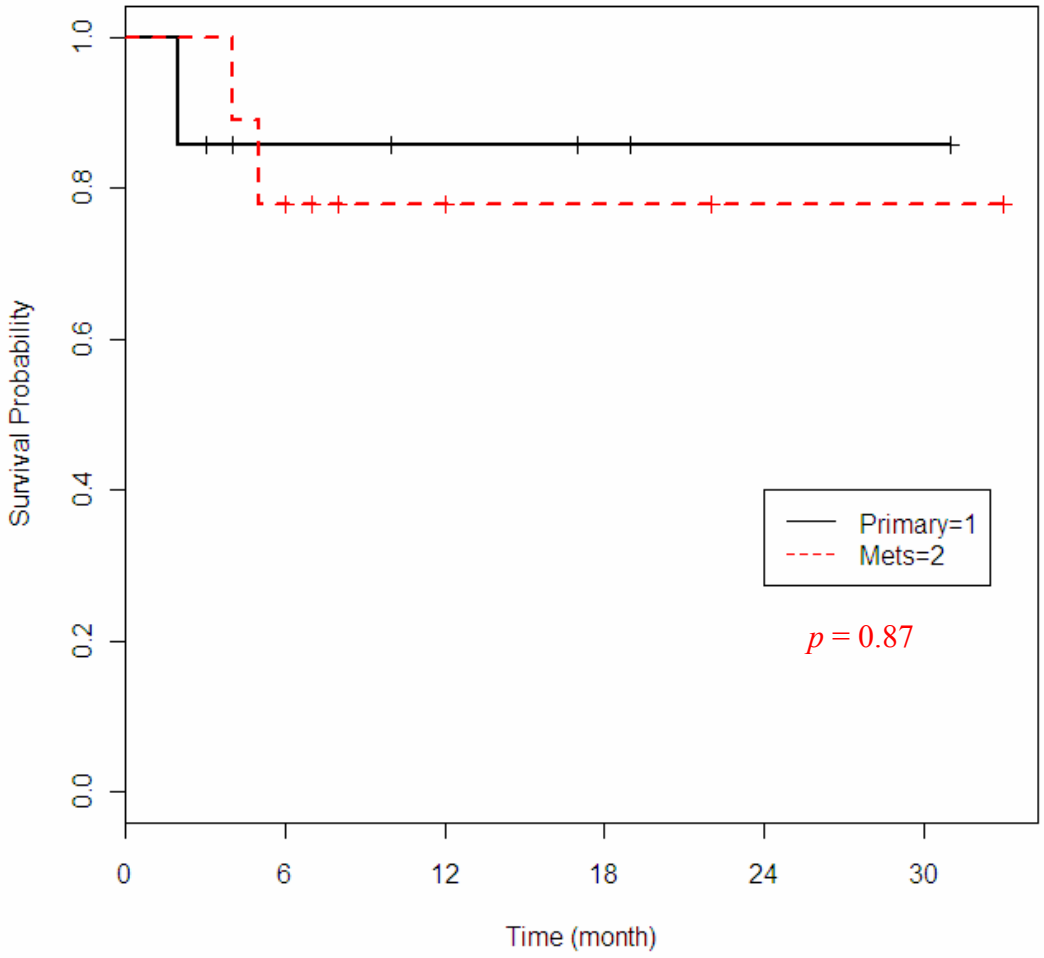


Figure 4. Progression free survival curves of patients with (1) centrally and (2) peripherally located lung tumors treated with CK (n = 19)

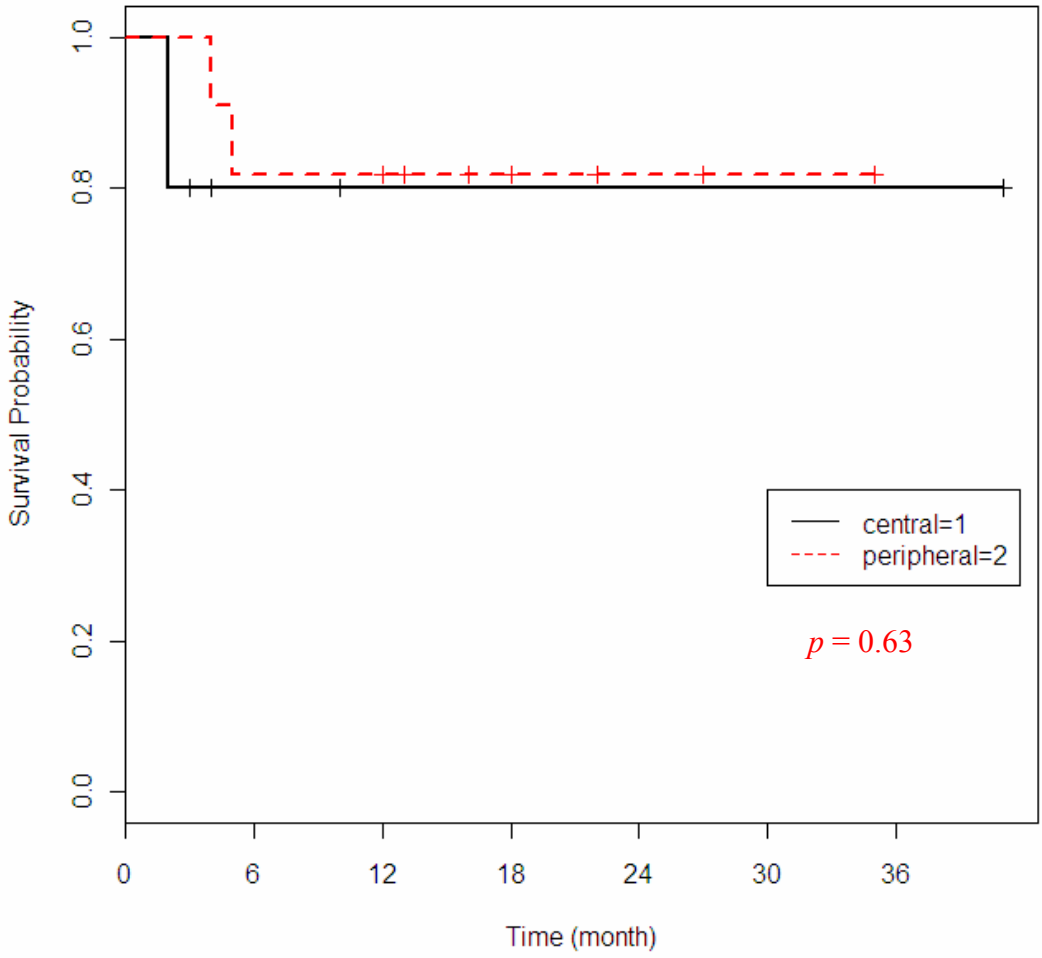
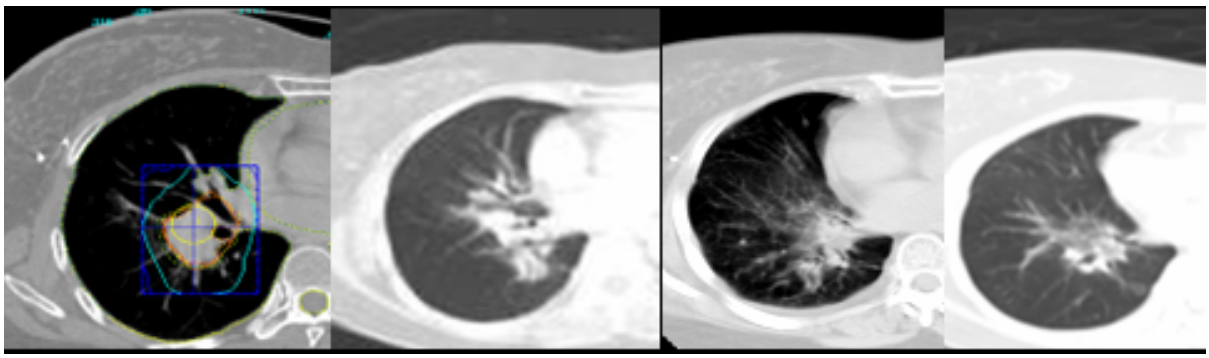


Figure 5. Serial follow-up CT images of a patient with solitary right lower lobe lung metastasis treated with CK SBRT, 36 Gy /3 fractions to 88% isodose



Before CK | Post CK 3 mo. | Post CK 6 mo. | Post CK 12 mo.

使用立體定位體部放射治療於原發性和轉移性肺腫瘤病患之早期經驗

目的：探討使用電腦刀立體定位體部放射治療 (SBRT) 於原發性和轉移性肺腫瘤病患之臨床結果。

方法：回溯性探討自 2005 年 11 月至 2008 年 6 月間於萬芳醫院接受 SBRT 之 19 位病患的醫療記錄。SBRT 是運用電腦刀之腫瘤追蹤系統來實行治療。治療後腫瘤反應和相關之副作用是以追蹤影像進行評估。治療相關副作用則以 Common Terminology Criteria for Adverse Events version 3.0 分級來記錄副作用之嚴重程度。

結果：於接受電腦刀 SBRT 之 19 位肺腫瘤病患（共 47 顆肺腫瘤）中，8 位（11 顆腫瘤）爲原發，11 位（36 顆腫瘤）爲轉移。9 顆腫瘤位於中央，其餘位於週邊。腫瘤體積介於 1.1 至 110.5 毫升（中位數, 9.5 毫升）。放射治療之劑量介於 22 至 60 Gy，歸一化於 76%至 85%之等劑量曲線，分 2 至 4 次給予。於 12 個月之中位追蹤時間中，共有 3 位病患發生 2 級放射性肺炎，另有 2 位病患發生 3 級放射性肺炎。分析其風險因子，女性（$p = 0.038$）和中央型肺腫瘤（$p = 0.042$）於單變項分析中有統計學上之差異。在兩位爲復發中央型肺腫瘤且先前已接受過肺部體外放射治療之病患中，觀察到氣管食道瘺管及支氣管壞死之治療相關副作用。於 16 位可供分析局部控制率的病患中，4 位（25%）爲 complete response，7 位（43.8%）爲 partial response，2 位（12.5%）爲 stable disease，3 位（18.7%）爲 progressive disease。病人一年之整體存活率爲 63%，一年之局部無病存活率爲 84.2%。比較原發性和轉移性肺癌之一年局部無病存活率（87.5% vs. 81.8%, $p = 0.87$），以及中央型和週邊型肺腫瘤之一年局部無病存活率（80% vs. 85.7%, $p = 0.63$），並無統計學上之差異。

結論：於我們的早期經驗中，電腦刀立體定位體部放射治療能有效局部控制原發性和轉移性肺腫瘤，然而，治療中心型或先前已照射過放射線之復發肺腫瘤時，應特別謹慎以避免較嚴重之副作用。

關鍵詞：電腦刀、立體定位體部放射治療、肺腫瘤、放射性肺炎