Stereotactic Body Radiotherapy for Lung Tumors at the Pulmonary Hilum

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Background and Purpose: High-dose irradiation to the pulmonary hilar region is generally considered to be of high risk in causing bronchial injury. The aim of this retrospective study is to investigate the safety and efficacy of stereotactic body radiotherapy (SBRT) for patients with lung tumors in the pulmonary hilum.
Patients and Methods: 21 patients who underwent SBRT for lung tumors within 2 cm from a major bronchus were retrospectively analyzed. The total biologically effective doses ranging from 50.7 to 157.5 Gy (median, 100 Gy) were given to the tumors by SBRT.
Results: The overall survival rates at 1 and 2 years after SBRT were 90.0% and 62.2%, respectively. Nine patients were alive and 15 irradiated tumors were controlled during the follow-up period of 10–54 months (median, 20 months). Nine patients died of tumor progression and one patient each died of hemoptysis, infectious pneumonia, and epidural hemorrhage. Severe late toxicity (≥ grade 3) was seen in three patients of whom two had previously received repeated radiotherapy.
Conclusion: SBRT for lung tumors located in the pulmonary hilar region may be tolerable and acceptable, if multiple treatments to the same major bronchus are avoided, and irradiated volumes are carefully taken into consideration.

Key Words: Radiotherapy · Stereotactic body radiotherapy · Lung · Pulmonary hilum · Bronchial stenosis

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Stereotaktische Strahlentherapie bei Lungentumoren im Hilum pulmonis

Hintergrund und Ziel: Die hochdosierte Bestrahlung der Lungenhilusregion gilt im Allgemeinen als großes Risiko in Bezug auf die Verursachung von Bronchialverletzungen. Ziel dieser retrospektiven Studie ist die Untersuchung der Sicherheit und Wirksamkeit der stereotaktischen Strahlentherapie bei Patienten mit Lungentumoren im Hilum pulmonis.
Patienten und Methodik: 21 Patienten, die sich einer stereotaktischen Bestrahlung von Lungentumoren im Abstand von bis zu 2 cm zu einem Hauptbronchus unterzogen, wurden retrospektiv analysiert. Die Tumoren wurden mit biologisch wirksamen Gesamtdosen im Bereich von 50,7 bis 157,5 Gy (Median: 100 Gy) bestrahlt.
Ergebnisse: Die Gesamtüberlebensraten 1 und 2 Jahre nach der stereotaktischen Strahlentherapie lagen bei 90,0% bzw. 62,2%. Während des Nachuntersuchungszeitraums von 10–54 Monaten (Median: 20 Monate) waren neun Patienten am Leben, und 15 bestrahlte Tumoren wurden kontrolliert. Neun Patienten starben aufgrund von Tumorprogression und je ein Patient starb infolge von Hämoptysis, infektiöser Pneumonie und epiduraler Blutung. Schwere Spättoxizität (≥ Grad 3) wurde bei drei Patienten beobachtet, von denen sich zwei in der Vergangenheit mehreren Strahlentherapien unterzogen hatten.
Schlussfolgerung: Eine stereotaktische Strahlentherapie bei Lungentumoren in der Gegend des Lungenhilus ist möglicherweise verträglich und vertretbar, wenn mehrere Behandlungen des gleichen Hauptbronchus vermieden und bestrahlte Volumen sorgfältig berücksichtigt werden.

Schlüsselwörter: Strahlentherapie · Stereotaktische Bestrahlung · Lunge · Lungenhilus · Bronchostenose

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Introduction

Stereotactic body radiotherapy (SBRT) has been increasingly applied as an emerging modality for the treatment of early-stage non-small cell lung cancer (NSCLC) and metastatic lung tumors because of its efficacy in delivering high-dose radiation to the minimum area [3, 11, 14, 15, 17, 19, 21, 26, 29, 31, 33, 34]. However, the safety and efficacy of SBRT for pulmonary hilar tumors have not been well established yet. One of the reasons for this is that the risk of bronchial injury followed by secondary atelectasis has been reported to be higher when the pulmonary hilar region was irradiated with a high dose [26].

In our facility at the International Medical Center of Japan, SBRT for lung tumors including tumors at the pulmonary hilum was started in 1998. We herein describe our retrospective review of patients with pulmonary tumor located within 2 cm from the main bronchus to clarify the tolerance and feasibility of SBRT for patients with tumors in this region.

Patients and Methods

Patient and Tumor Characteristics

From August 1998 to January 2009, 181 patients with 229 malignant lung tumors were treated by SBRT at the International Medical Center of Japan. Patients were generally considered for SBRT if the tumors were ≤ 5 cm in the maximum diameter without evidence of lymph node metastases. Some patients who refused surgery and patients in whom surgery was not indicated were considered for SBRT, to achieve local control if prophylactic or lymph node irradiation was not required. By reviewing these 229 tumors, we could find that 22 tumors in 21 patients were located in the region within 2 cm from the major bronchus on computed tomography (CT) images, and they were retrospectively analyzed in this study.

The patient and tumor characteristics are shown in Table 1. There were eleven males and ten females with a median age of 71 years (range, 35–89 years). The Eastern Cooperative Oncology Group (ECOG) performance status [18] of these patients was as follows: 0–1: n = 15, 2: n = 5, 3: n = 1. Fourteen patients had NSCLC and 7 patients had metastatic lung tumors. The median maximum tumor diameter and planning target volume were 28 mm (range, 10–40 mm) and 34.3 cm^3 (range, 8.2–86.4 cm^3), respectively. The clinical stages of the 14 patients with NSCLC were as follows: stage IA: n = 1, stage recurrent (r)IA: n = 3, stage rIB: n = 1, stage rIIA: n = 1, and stage IV: n = 8, according to the TNM classification of the International Union against Cancer [22]. One patient with IA primary lung cancer was initially treated by SBRT because of severe chronic obstructive lung disease. Local control was aimed at in all cases, however, surgery was not considered due to advanced disease, poor respiratory function, or old age. Also conventional radiotherapy was not applicable because of the previous history of radiotherapy or long treatment periods. Written informed consent was obtained from all patients before starting SBRT.

Table 1. Patient and tumor characteristics.

Tabelle 1. Patienten- und Tumorcharakteristika.

Sex (n)	
Male	11
Female	10
Age (years)	
Median	71
Range	35–89
Performance status (n)	
0–1	15
2	5
3	1
Maximum tumor size (mm)	
Median	28
Range	10–40
Primary disease (n)	
Lung	14
Colon	4
Apocrine	1
Breast	2
TNM stage in patients with lung cancer (n)	
IA	1
rIA	3
rIB	1
rIIA	1
IV	8

Stereotactic Body Radiotherapy

From August 1998 to June 2004, SBRT was performed using Microtoron (Hitachi Medical Co., Tokyo, Japan) with 6-MV X-rays under respiratory gating. The details of the initial treatment methods have been described previously [6–8]. Briefly, simulation during the end-expiratory phase was performed with the patient lying on the cradle made for each patient after CT had been taken; then, multiportal, noncoplanar irradiation planning was conducted. The information concerning the respiratory movement detected by a laser displacement monitor (Keyence, Tokyo, Japan) placed on the patient's chest was sent to the respiratory gating system, and the treatment beams were delivered only during the end-expiratory phase. Since July 2004, SBRT has been performed with the CLINAC 21EX accelerator and a real-time position management system (RPM; Varian, Palo Alto, CA, USA) with patients immobilized by individually shaped body casts (Vac-Loc; Med-Tec, Orange City, IA, USA). CT images of 2 mm thickness were taken in the treatment position during the expiratory phase and the data were sent to a treatment planning system (Eclipse TM; Varian). The clinical target volume (CTV) was contoured as the gross tumor volume (GTV), and an additional 5- to 7-mm margin was added to cover the CTV as a PTV. Before daily treatment, gated kilovolt radiography was taken to verify the patient's position. The treatment beam was delivered during the expiratory phase with the RPM system using a 5-mm gating threshold.

Table 2. Radiotherapy to the thorax. BED: biologically effective dose; Conv: conventional radiotherapy; IBRT: intrabronchial radiotherapy (brachytherapy); SBRT: stereotactic body radiotherapy.

Tabelle 2. Thoraxbestrahlung. BED: biologisch wirksame Dosis; Conv: konventionelle Strahlentherapie; IBRT: intrabronchiale Strahlentherapie (Brachytherapie); SBRT: stereotaktische Strahlentherapie.

	Radiotherapy to thorax				SBRT to pulmonary hilum		
Patient #	1st	2nd	3rd	4th	Total dose (Gy)	Fractions (n)	BED (Gy) (α/β = 10)
1	SBRT[a]				60.0	10	96.0
2	Conv	SBRT[a]			60.0	10	96.0
3	SBRT[a]				40.0	4	80.0
4	SBRT[a]				50.0	5	100.0
5	SBRT	SBRT[a]			40.0	5	72.0
6	SBRT[a]	SBRT[a]			39.0	13	50.7
					50.0	10	75.0
7	SBRT[a]	SBRT	SBRT		50.0	5	100.0
8	SBRT[a]				50.0	5	100.0
9	Conv	SBRT[a]			50.0	5	100.0
10	SBRT	Conv	IBRT	SBRT[a]	50.0	5	100.0
11	SBRT[a]				48.0	4	105.6
12	Conv	SBRT[a]			60.0	10	96.0
13	SBRT[a]				35.0	1	157.5
14	Conv	SBRT[a]	IBRT		33.0	1	140.8
15	SBRT[a]	IBRT			48.0	8	76.8
16	IBRT	SBRT	SBRT[a]		25.0	1	87.5
17	SBRT[a]	SBRT			50.0	5	100.0
18	SBRT[a]	Conv			40.0	4	80.0
19	SBRT[a]				35.0	1	157.5
20	SBRT	SBRT[a]			30.0	1	120.0
21	SBRT	SBRT[a]	SBRT		26.0	1	94.7

[a]SBRT to pulmonary hilum

Patient Follow-Up and Evaluation Criteria

After the completion of SBRT, patients were evaluated by chest imaging studies (CT, X-ray, or positron emission tomography) every 2–3 months at the outpatient clinic in either our institute or their referring facilities. Local responses to treatment were classified according to the modifications of the Response Evaluation Criteria in Solid Tumors (RECIST) [10]. Acute and late toxicities associated with treatments were evaluated by the National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE) version 3.0 [28] and the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer late radiation morbidity scoring scheme, respectively [2, 18].

Statistical Analysis

Statistical analysis was performed on data including the maximum tumor diameter, dose-volume histogram, clinical and imaging follow-up, as well as overall survival rate and local control rate. The actuarial survival and disease control rates were calculated from the beginning of SBRT using the Kaplan-Meier method [13]. All statistical analyses were performed by the statistic software (SPSS Inc., Chicago, IL, USA).

Results

SBRT to the pulmonary hilum was the first thoracic radiotherapy in twelve patients, while it was not the initial radiation therapy in nine patients. Nine patients underwent additional radiation therapy (SBRT, conventional radiotherapy, or interstitial radiotherapy) to the thorax after SBRT to the pulmonary hilar region. One patient with apocrine cancer received SBRT to the bilateral pulmonary hilar region (Table 2).

Radiation Dose

Total doses ranging from 25 to 60 Gy in one to 13 fractions were given (median, 50 Gy in five fractions) to the patients. As various fractionation regimens were used, the biologically effective dose (BED) was calculated for comparison using the linear-quadratic model with α/β ratios assumed to be 10 (BED_{10}) for tumors and 3 (BED_3) for normal lung tissue [4]. The BED was not corrected by values for tumor doubling time or treatment term in this study. As a result, the calculated BED_{10} ranged from 50.7 to 157.5 Gy, with a median of 100 Gy (Table 2).

In addition, the ratios of lung volume receiving ≥ 20 Gy (V_{20}) ranged from 0.1% to 15.6%, with a median of 3.3%. However, V_{20} is usually assessed in conventional fractions of 2.0 Gy per fraction radiotherapy and its application to SBRT in the same way is controversial [5, 20]. Therefore, we calculated the BED_3 which corresponds to 20 Gy in 30 fractions in each patient; for example, it is almost equal to 13 Gy in five fractions, and to 7.2 Gy in one fraction. As a result, the alternative values for V_{20} calculated using this method ranged from 1.0% to 20.5%, with a median of 7.9%.

Toxicity

Radiotherapy-related acute toxicity > grade 1 was not observed in any case. Late toxicity is summarized in Table 3. Fibrotic reactions at the treated regions were noticed in follow-up CTs in every case. Mild toxicities were seen in five patients; three patients had grade 2 dyspnea and two patients grade 2 radiation pneumonitis. There were also three cases (14.3%) that showed ≥ grade 3 toxicity in respiratory function.

Table 3. Late radiotherapy-related toxicity.

Tabelle 3. Bestrahlungsassoziierte Spättoxizität.

	Grade				
	1 (n)	2 (n)	3 (n)	4 (n)	5 (n)
Pulmonary fibrosis	21	0	0	0	0
Dyspnea	0	3	1	0	0
Pneumonia	0	2	0	0	0
Bronchial obstruction	0	0	1	0	0
Hemoptysis	0	0	0	0	1

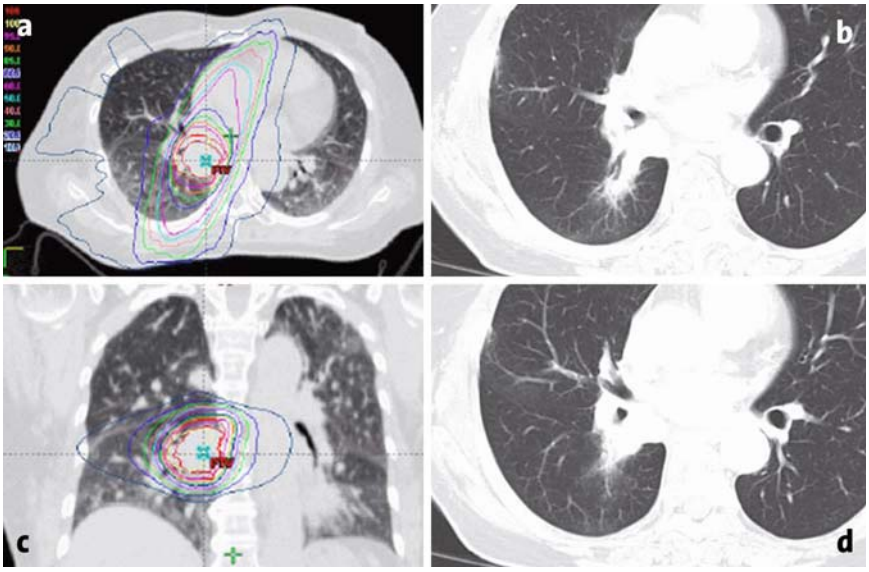
One patient who received SBRT of 96 Gy in BED_{10} demonstrated grade 3 bronchial stenosis (patient # 1 in Table 2). This patient suffered from intractable cough and sputum due to bronchial stenosis with secondary atelectasis 1 year after SBRT (Figure 1). Repeated balloon dilatation relieved these symptoms in 2 months.

Another patient who had previously received two courses of thoracic radiotherapies died of hemoptysis (grade 5) 18 months after SBRT with 87.5 Gy in BED_{10} (patient # 16 in Table 2). Previous treatments in this patient consisted of intrabronchial brachytherapy for the bilateral pulmonary hilar regions (BED_{10}: 38.4 Gy) and SBRT for apical lesion in the same lobe (BED_{10}: 120 Gy).

The third patient who received three courses of radiotherapy for bilateral lung tumors before SBRT for the hilar lesion suffered from grade 3 dyspnea and required domiciliary oxygen therapy 18 months after SBRT (patient # 10 in Table 2). There were no overlaps among these treatment fields. This patient had previously received SBRT to the right middle lung with a BED_{10} of 100 Gy, conventional radiotherapy followed by intrabronchial brachytherapy to the left lingular segment (BED_{10}: 89.4 Gy), and SBRT to the right pulmonary hilum (BED_{10}: 100 Gy).

Survival and Local Control Rates

At the time of the analysis in January 2009, nine patients were alive. The follow-up period ranged from 10.1 to 53.7 months with a median period of 19.8 months for all patients, and from 10.3 to 53.7 months with the median of 18.9 months for alive patients from the start of the first SBRT. The median overall survival time and progression-free survival time were 26.2 and 13.8 months, respectively. The overall survival rates at 1 and 2 years were 90.0% and 62.2%, respectively, and the progression-free survival rates at 1 and 2 years were 54.8% and 23.8%, respectively (Figure 2). There were four complete responses (CR), 13 partial responses (PR) and five stable diseases (SD) in 6 months, and the resulting objective response rate (CR plus PR) was 77%. 15 irradiated tumors (69%) were controlled during the observation period, and the local control rates at 1 and 2 years were 74.3% and 59.6%, respectively. Of the twelve patients who deceased during follow-up, nine died of cancer progression, and remaining three patients died of hemoptysis, infectious pneumonia, and epidural hemorrhage, respectively. Polymerase chain reaction of the sputum from the patient who died of infectious pneumonia showed a high level of *Pneumocystis jirovecii* DNA, and the serum level of *Aspergillus* antigen was high. The pneumonia shown on CT images was outside of the irradiated field, and the radiation fibrosis seen 2 weeks before he died had not changed for 6 months.



Figures 1a to 1d. Dose distribution at the planning (a: axial, c: coronal) and axial CT images (b, d) of the patient with bronchial obstruction after SBRT to the pulmonary hilum.

Abbildungen 1a bis 1d. Dosisverteilung bei der Planung (a: axiale Ansicht, c: koronale Ansicht) und axiale CT-Bilder (b, d) des Patienten mit Bronchialobstruktion nach stereotaktischer Bestrahlung des Lungenhilus.

Discussion

SBRT has been increasingly applied to primary NSCLC and metastatic lung tumors [14, 15, 19, 21, 26, 34], however, its feasibility to the pulmonary hilar lesions is still controversial. Tinnel et al. analyzed the correlation between the risk of interstitial pneumonia and the irradiated lung volume in rodent experiments [27]. They mentioned that the bronchus could tolerate therapy when a small volume was irradiated with a very high dose, such as a single fraction of 80–160 Gy. However, Timmerman et al. reported that the risk of severe toxicity associated with SBRT was elevenfold higher in patients with centrally located lung tumors in comparison to that of patients whose tumors were peripheral [26].

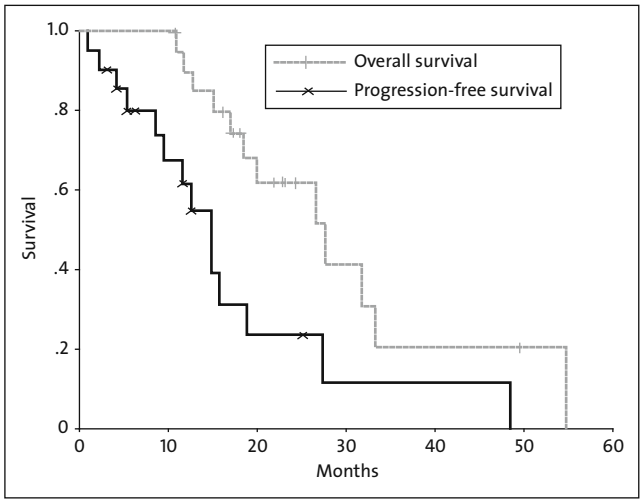


Figure 2. Overall survival and progression-free survival curves of the patients with tumors at the pulmonary hilum treated by SBRT.

Abbildung 2. Gesamtüberlebens- und progressionsfreie Überlebenskurven der Patienten mit Tumoren im Bereich des Lungenhilus, die sich einer stereotaktischen Strahlentherapie unterzogen.

After this landmark report cautioned us against using SBRT to tumors within 2 cm from the main bronchus, a few reports have been published recently which are affirmative for SBRT to the pulmonary hilum [1, 12, 27]. Joyner et al. treated nine patients who had centrally located lung tumors by SBRT with a dose of 36 Gy in three or six fractions (BED_{10}; 57.6 Gy or 46.8 Gy). Although their sample size is small, they mention that SBRT for centrally located lung lesions appears feasible. However, SBRT with their regimen may not be suitable in curative intent because long-term survival can frequently be associated with major airway injury [12]. More recently, Chang et al. reported on 27 cases with centrally and superiorly located NSCLC who underwent four-dimensional CT-based planning, and daily CT-on-rail-guided SBRT with doses of 40 Gy and 50 Gy in four fractions (BED_{10}; 80 and 112.5 Gy). This advanced image-guided technique yielded excellent local control, and was associated with a low incidence of severe toxicities within a median follow-up period of 17 months [1].

In our present study, radiation-induced bronchial obstruction was observed in one patient who underwent SBRT as a primary treatment, and there were two cases of ≥ grade 3 toxicities in re- or multitreated cases. It has been reported that the occurrence of bronchial stenosis is in a range from 7.5% to 80% in periods from 2 months to 4 years after high-dose-rate endobronchial brachytherapy and/or high-dose external radiotherapy [12, 16, 23, 24]. Based on these reports and outcomes observed in this study, the indication of SBRT to hilar lesions should be carefully determined when there is an overlap with the previous treatments even in palliative intent.

Our study is limited by its retrospective design and, as a result, comprises patients with both NSCLC and metastatic lung tumors with various stages of disease. Also, modes of treatment are primary or boost using different treatments regimens, and purpose is salvage in most of recurrent cases. However, the 1- and 2-year overall survival rates in our series could yield 90% and 62%, respectively. Considering that 20 of 21 patients had recurrent tumor or stage IV disease and surgery was indicated in none of them, the authors believe that SBRT to the pulmonary hilar region could potentially yield survival benefits. Especially when other treatment modalities including surgery are not indicated due to poor pulmonary function or other systemic complications, SBRT can be a final option.

As mentioned above, SBRT to pulmonary hilar lesions should currently be conducted with caution, because long-term follow-up in larger numbers of patients is lacking. However, we believe it is worth seeking methods to improve its potential efficacy. For example, more precise techniques such as image-guided SBRT monitoring both intra- and interfractional changes [9, 20, 25, 31, 32] are suitable candidates. With these improvements in techniques, SBRT can be a useful modality not only for primary lesions in curative intent but also for recurrent lesions with reducing treatment period in palliative intent. Although the sample size may be small, we believe that the data presented here can contribute to improving efficacy of SBRT in the future.

Conclusion

SBRT for lung tumors located in the pulmonary hilar region may be tolerable and acceptable, if multiple treatments to the same major bronchus are avoided, and irradiated volumes are carefully taken into consideration. Prospective studies of SBRT for lung tumors located in the pulmonary hilar region are strongly expected to prove its efficacy.

References

1. 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;72:967–71.
2. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys 1995;31:1341–6.
3. Ernst-Stecken A, Lambrecht U, Mueller R, et al. Hypofractionated stereotactic radiotherapy for primary and secondary intrapulmonary tumors: first results of a phase I/II study. Strahlenther Onkol 2006;182:696–702.
4. Fowler JF, Tome WA, Fenwick JD, Mehta MP. A challenge to traditional radiation oncology. Int J Radiat Oncol Biol Phys 2004;60:1241–56.
5. Graham MV, Purdy JA, Emami B, et al. Clinical dose-volume histogram analysis for pneumonitis after 3D treatment for non-small cell lung cancer (NSCLC). Int J Radiat Oncol Biol Phys 1999;45:323–9.
6. Hara R, Itami J, Komiyama T, et al. Serum levels of KL-6 for predicting the occurrence of radiation pneumonitis after stereotactic radiotherapy for lung tumors. Chest 2004;125:340–4.
7. Hara R, Itami J, Kondo T, et al. Stereotactic single high dose irradiation of lung tumors under respiratory gating. Radiother Oncol 2002;63:159–63.

8. Hara R, Itami J, Kondo T, et al. Clinical outcomes of single-fraction stereotactic radiation therapy of lung tumors. Cancer 2006;106:1347–52.
9. Hui Z, Zhang X, Starkschall G, et al. Effects of interfractional motion and anatomic changes on proton therapy dose distribution in lung cancer. Int J Radiat Oncol Biol Phys 2008;72:1385–95.
10. James K, Eisenhauer E, Christian M, et al. Measuring response in solid tumors: unidimensional versus bidimensional measurement. J Natl Cancer Inst 1999;91:523–8.
11. Jereczek-Fossa BA, Kowalczyk A, D'Onofrio A, et al. Three-dimensional conformal or stereotactic reirradiation of recurrent, metastatic or new primary tumors. Analysis of 108 patients. Strahlenther Onkol 2008;184:36–40.
12. Joyner M, Salter BJ, Papanikolaou N, Fuss M. Stereotactic body radiation therapy for centrally located lung lesions. Acta Oncol 2006;45:802–7.
13. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;31:457–81.
14. Koto M, Takai Y, Ogawa Y, et al. A phase II study on stereotactic body radiotherapy for stage I non-small cell lung cancer. Radiother Oncol 2007;85:429–34.
15. McGarry RC, Papiez L, Williams M, et al. Stereotactic body radiation therapy of early-stage non-small-cell lung carcinoma: phase I study. Int J Radiat Oncol Biol Phys 2005;63:1010–5.
16. Miller KL, Shafman TD, Anscher MS, et al. Bronchial stenosis: an underreported complication of high-dose external beam radiotherapy for lung cancer? Int J Radiat Oncol Biol Phys 2005;61:64–9.
17. Mirri MA, Arcangeli G, Benassi M, et al. Hypofractionated conformal radiotherapy (HCRT) for primary and metastatic lung cancers with small dimension. Efficacy and toxicity. Strahlenther Onkol 2009;185:27–33.
18. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649–55.
19. 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;101:1623–31.
20. Seppenwoolde Y, Shirato H, Kitamura K, et al. Precise and real-time measurement of 3D tumor motion in lung due to breathing and heartbeat, measured during radiotherapy. Int J Radiat Oncol Biol Phys 2002;53:822–34.
21. Sibley GS. Radiotherapy for patients with medically inoperable stage I non-small cell lung carcinoma: smaller volumes and higher doses – a review. Cancer 1998;82:433–8.
22. Sobin LH, Wittekind C, eds. Classification of malignant tumors, 6th edn. New York: Wiley-Liss, 2002.
23. Speiser BL, Spratling L. Remote afterloading brachytherapy for the local control of endobronchial carcinoma. Int J Radiat Oncol Biol Phys 1993;25:579–87.
24. Speiser BL, Spratling L. Radiation bronchitis and stenosis secondary to high dose rate endobronchial irradiation. Int J Radiat Oncol Biol Phys 1993;25:589–97.
25. Takayama K, Nagata Y, Negoro Y, et al. Treatment planning of stereotactic radiotherapy for solitary lung tumor. Int J Radiat Oncol Biol Phys 2005;61:1565–71.
26. 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;24:4833–9.
27. Tinnel B, Mendonca MS, Henderson M, et al. Pulmonary hilar stereotactic body radiation therapy in the rat. Technol Cancer Res Treat 2007;6:425–31.
28. 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;13:176–81.
29. Wang C, Nakayama H, Sugahara S, et al. Comparisons of dose-volume histograms for proton-beam versus 3-D conformal X-ray therapy in patients with stage I non-small cell lung cancer. Strahlenther Onkol 2009;185:231–4.
30. Wara WM, Phillips TL, Margolis LW, Smith V. Radiation pneumonitis: a new approach to the derivation of time-dose factors. Cancer 1973;32:547–52.
31. Wiehle R, Koth HJ, Nanko N, et al. On the accuracy of isocenter verification with kV imaging in stereotactic radiosurgery. Strahlenther Onkol 2009;185:325–30.
32. Wu J, Li H, Shekhar R, et al. An evaluation of planning techniques for stereotactic body radiation therapy in lung tumors. Radiother Oncol 2008;87:35–43.
33. Wulf J, Haedinger U, Oppitz U, et al. Stereotactic radiotherapy of targets in the lung and liver. Strahlenther Onkol 2001;177:645–55.
34. Wulf J, Haedinger U, Oppitz U, et al. Stereotactic radiotherapy for primary lung cancer and pulmonary metastases: a noninvasive treatment approach in medically inoperable patients. Int J Radiat Oncol Biol Phys 2004;60:186–96.

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