Lung Metastases Treated by CyberKnife® Image-Guided Robotic Stereotactic Radiosurgery at 41 Months

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Objectives: Based on the reported success of stereotactic body radiotherapy in treating extracranial tumors, we used CyberKnife® (Accuray Incorporated, Sunnyvale, CA) to treat patients with metastatic lung cancer.

Methods: This is a retrospective report of treatment details and outcomes of 35 patients, ranging in age from 33 to 91 years, with 69 histologically proven pulmonary metastases, treated by image-guided robotic stereotactic radiosurgery at the CyberKnife® Center of Miami, between March 2004 and August 2007. Tumor volumes ranged from 0.7 mL to 152 mL. Total doses ranged from 5 to 60 Gy delivered in one to four fractions with an equivalent dose range from 6 to 110 Gy NTD delivered in 2-Gy fractions assuming an α/β of 20 Gy.

Results: All patients tolerated radiosurgery well with fatigue as the main side effect. Grade 3 and grade 4 pulmonary toxic reactions were observed in one patient who had undergone a repeat treatment. Of the 35 treated patients, 27 (77%) were still alive at a median 18-month (range 2–41 mo) follow-up. Local control was 71% with 25 tumors showing a complete response, 16 a partial response, and 7 stable with disease. Eight had progressive disease.

Conclusions: The delivery of precisely targeted radiation doses to lung tumors in a hypofractionated fashion is feasible and safe. image-guided robotic stereotactic radiosurgery of pulmonary metastases with the CyberKnife® achieves good rates of local disease control with limited toxicity to surrounding tissues and in many cases may be beneficial for patients for whom surgery is not an option.

Key Words: body radiation therapy (SBRT), CyberKnife®, hypofractionation, image-guided robotic stereotactic radiosurgery (IGR-SRS), pulmonary metastasis stereotactic

Historically, because of poor prognosis, radiotherapy has not been employed with curative intent for patients with pulmonary metastases. However, data exist to support aggressive local intervention for selected patients with pulmonary metastases.[1,2] Reports of stereotactic body radiotherapy (SBRT) for treatment of lung tumors have included patients treated for metastatic disease. Dose fractionation and techniques employed for these patients were similar to those used for primary lung tumors, and control rates ranged from 66 to 100% with minimal toxicity.[3–13] Given the high rates of local control and low toxicity demonstrated by SBRT, we postulated that similarly selected patients who are not eligible for surgery may benefit from treatment with the CyberKnife® Radiosurgery System (Accuray Incorporated, Sunnyvale, CA), a frameless, image-guided robotic stereotactic radiosurgery (IGR-SRS), capable of directing ablative doses to limited treatment volumes.[14] CyberKnife® can deliver the prescribed dose using radiation beams from many different angles converging on the tumors, with real-time target tracking through

Key Points

- Image-guided stereotactic radiosurgery provides an option for patients with resectable but medically inoperable metastatic lung tumors.
- In patients with limited pulmonary metastases, potent doses of image-guided robotic stereotactic radiosurgical system (IGR-SRS) are well tolerated with limited early toxicity.
- Local control rates are better than those obtained with conventional radiotherapy.
- Systematic research is necessary to clearly establish optimal treatment parameters.

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combined orthogonal radiograph imaging and optic motion tracking system Synchrony[15] and Xsight[16,17] skeletal patient alignment. This article summarizes our experience in using this system in the treatment of patients with pulmonary metastases of various pathologies who were ineligible for surgery or who refused surgery.

Patients and Methods

Patient Selection and Pretreatment Evaluation

Before acceptance for treatment, each patient was evaluated by both a thoracic surgical oncologist and radiation oncologist, and underwent a pretreatment clinical staging consisting of a computed tomography (CT) scan of the chest, abdomen, and pelvis; an integrated fluorodeoxyglucose (FDG) positron emission tomography (PET) combined in a PET-CT scan with standard uptake value reported; pulmonary function tests, complete blood count and chemistry, and screening for tumor markers such as carcinoembryonic antigen, if applicable.

All patients were determined to have a technically resectable lesion but were deemed ineligible for surgery because they lacked adequate respiratory reserve, had severe cardiac dysfunction or chronic heart disease, pulmonary hypertension, advanced diabetes mellitus with severe end-organ damage, vascular disease, general frailty, or severe cerebral disease. Tumors larger than 5 cm in diameter were excluded for treatment with curative intent. We did not exclude patients receiving other forms of antineoplastic therapy such as chemotherapy, biologic therapy, and vaccine therapy. On the contrary, all patients were evaluated by a medical oncologist to determine whether systemic therapy was indicated to control spread of the disease, although radiosurgery was used to treat the metastasis.

Treatment Preparation and Planning

Patients selected for treatment were sent for placement of gold fiducial markers into the tumor under CT guidance using preloaded needles introduced transthoracically. A single fiducial in the tumor is preferred. This reduces the number of entrances into the chest and lessens the chances of: pneumothorax, embolization, bleeding into adjacent lung parenchyma, migration of the fiducial, and finally the fewer fiducials in or around the target leads to less confusion in recognition of the target fiducial during treatment. This confusion in interpreting which fiducial to treat leads to emergency stop and requires remodeling before proceeding with treatment and increase treatment time. Non spheroid targets may require an addition fiducial. An interval of 5 to 7 days between fiducial marker placement and the treatment planning CT scan allowed fiducial markers to stabilize, edema to subside, and assured that the fiducial had not migrated. Thin-slice (1.5 mm contiguous axial slices) planning CT scans with contrast (125 mL Omnipaque 350) were obtained while patients held their breath in expiration. Three-dimensional treatment plans were subsequently developed and evaluated by each member of the

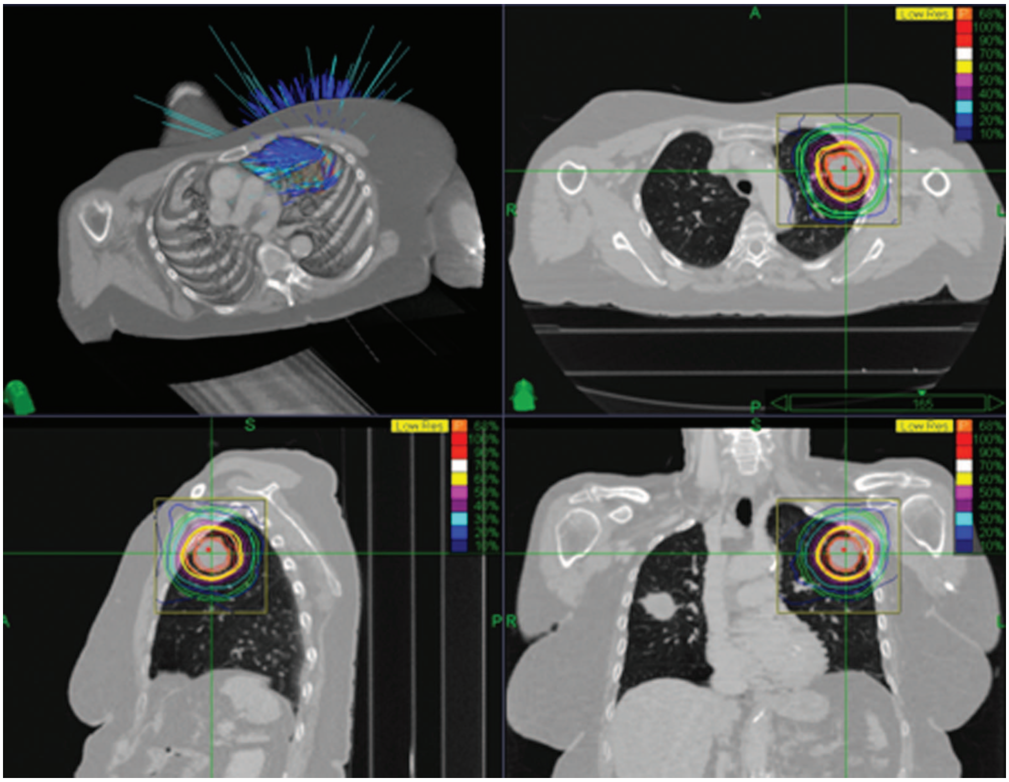

Fig. **A typical three-dimensional dose plan of treatment (64 beams used, 20 Gy × 3 prescribed to the 68% isodose level).**

team (Fig). Treatment doses and fractionation regimens were individualized for each patient depending on tumor volume, location, and proximity to vital structures, etiology, comorbid disease, and the physician's judgment.

The planning treatment volume (PTV) routinely included a margin of 3 to 5 mm beyond the gross tumor volume (GTV) to cover macroscopic disease, microscopic infiltration, and to account for targeting uncertainty. The dose was prescribed to the 60 to 85% isodose line enclosing 100% of the GTV and more than 95% of the PTV. The prescribed dose delivered a heterogeneous higher dose to the center of the tumor. The inverse planning module was used to maximize dose conformality. To ensure an acceptably steep dose gradient, over 50 noncoplanar beams were often required. Two treatment plans were generated, one with the orientation defined by Xsight Spine Tracking System (Accuray, Inc.,) and the other with the orientation defined by the tumor fiducial. During treatment, the Xsight setup plan was loaded first and the patient was aligned to the spinal structure in translations and rotations to replicate the position during CT acquisition. Then the second plan was loaded and the patient was moved to the new imaging center defined by the tumor fiducial. The treatment was then carried out by tracking the tumor fiducial continuously as the patient breathed using Synchrony (Accuray, Inc.,). Figure demonstrates a typical dose plan, in which 64 beams were used and 20 Gy × 3 was prescribed to the 68% isodose level.

We defined a complete response as a disappearance of the lesion determined by chest PET/CT scan with FDG negative status, and a partial response as the presence of a residual abnormality on PET/CT scan and a reduction of FDG. Stable disease was represented by no significant change of size of tumor or FDG level. Progressive disease was defined as an enlarging lesion on PET/CT or increasing FDG activity not attributable to radiation pneumonitis or fibrosis.

Results

Between March 2004 and August 2007, 35 patients—14 women and 21 men—ranging from 33 to 91 years of age, (mean age 59 years), with 69 histologically proven lung metastases, were treated. Fourteen patients (40%) had multiple metastases and were treated for two to eight pulmonary metastasis. Tumor volume ranged from 0.7 to 152 mL (median 12.10 mL). Thirty-five of the 69 metastatic tumors (50%) were less than 14.16 mL in volume. Forty-nine tumors were treated with 5 to 45 Gy, 19 tumors received from 45 to 60 Gy/2 to 3F (45 Gy/2F = BED_{20} 96 Gy to 45 Gy/3F = BED_{20} 79 Gy), 3 of 19 tumors received 60 Gy/3 fractions (BED_{20} 120 Gy), 21 tumors were treated with 5 to 24 Gy/1F to isodose line 58 to 70%, 7 tumors were treated with from 25 to 30 Gy/2F to a 65 to 70% isodose line, and the remaining 39 received from 30 to 60 Gy/3F to an isodose line from 70 to 84%. The patient characteristics and treatment are presented in Tables 1 to 4.

The follow-up ranged from 2 to 41 months with a median of 18 months. Twenty-seven (77%) of the 35 treated patients were still alive as of August 2007. Eighty-four percent of the treated metastatic tumors experienced a reduction in size or inhibition of growth: 24 tumors with complete response, 16 with partial response, 7 with stable disease, and 8 with progressive disease. There were eight deaths from disease and four lost to follow-up. Of those patients treated with a single fraction, (Table 1) there were four patients with from two to three metastases, and volume ranged from 1.7 to 151.4 cm, dose ranged from 5 to 25 Gy. There were five deaths in this group. In the group of seven patients treated with two fractions (Table 2) none had multiple metastases, volume ranged from 3 to 42.4 mL, and dosage ranged from 15 to 48 Gy. In this group, three patients have expired. In the group treated with three fractions (Table 3), 10 patients had multiple metastases ranging from 2 to 6, tumors volume ranged from 1.7 to 152 mL, dose ranged from 15 to 60 Gy. One death occurred in this group and it occurred in a patient with recurrent tumor who may have had a grade 5 toxic reaction as a result of retreatment of same PTV. Two patients were treated with four fractions (Table 4), volume 7 to 129 mL, dosage 20 and 30 Gy to a single metastasis in one patient and multiple metastases in the other patient.

One patient with three lung metastases in different lobes was treated in June 2005 by a single fraction of 10 Gy to a 9.1-mL metastasis, 25 Gy to a 1.7-mL metastasis, and finally, 22 Gy to a 24-mL lesion. Recurrent disease was detected between 6 and 9 months later and all three metastases were retreated successfully with 51 Gy/3 to the 10.9 mL; 51Gy/3 to the 12.2 mL, and 48 Gy/3 to the 86 mL tumor in March 2006. However, the patient developed grade 3 and 4 pulmonary toxicity during the final two treatments. Both events were successfully managed with full recovery and the patient is without any evidence of disease at 1-year follow-up. This highlights the difficulty in evaluating retreatment to the same PTV. No other major toxic events were observed; fatigue was the main side effect.

Discussion

Before SBRT or robotic radiosurgery can be used as an alternative to surgery in the treatment of metastatic or primary disease, they must yield survival results equivalent to surgical practice. Failure to obtain local control as the major obstacle and recurrent or persistent disease has been reported in patients treated by SBRT and robotic radiosurgery. The reasons for this may differ based upon the delivery system used. In a 72-patient phase II study,[18] SBRT actuarial 2-year local control for a potent dose regimen (60 Gy/3F) was predicted to be 95%; however, the overall 2-year survival for this population was poor at 54.7%. Twenty-eight patients died as a result of cancer, with most of the deaths related to comorbid illness rather than disease progression or toxicity. Isolated hilar or mediastinal nodal relapse was extremely rare despite clinical staging. In that study, grade 3 to 5 toxicity occurred in 14 patients.

The most widely accepted means of describing the relationship between radiation dose and cell survival for conventionally fractionated radiotherapy is the linear-quadratic formula.[33] The problem might have been the lesser degree of

Table 1. Single fraction SRS (Biological equivalent dose using tumor alpha/beta 20 Gy[a])

Patient number	Treatment date	Sex/Age	Histology	Location	Vol	Dose	%	BED	Comments
3	July 10, 2006	F80	Transitional	RML	6.9	12	70	19	PR new metastasis 4/06
4	October 1, 2004	M69	Renal cell	LUL	59.7	5	70	6	PD
8	October 8, 2004	F63	NSCLC	RUL	18.7	25	70	56	PR EXP 2.26.05 difficult walking Nov 2004 multiple metastasis
9	March 23, 2005	70F	Pharynx	RUL	22.4	20	80	56	PR EXP October 16, 2005 progression
10	December 16, 2004	M73	Sarcoma	LUL	5.7	20	84	40	PR both lesions treated
	December 20, 2004	M73	Sarcoma	LUL	11.9	20	84	40	PR 7.28.06 rec/failed chemo. Exp August 18, 2006
11	January 25, 2005	M61	Colon	LLL	4.8	20	80	40	Lost
	January 26, 2005	M61	Colon	LLL	12.1	15	60	40	Lost
	February 15, 2005	M61	Colon	LUL	9.2	20	70	26	CR had CNS mets
12	January 31, 2005	M33	Testicular	RUL	24.0	20	70	40	PD 1 wk post
	February 1, 2005	M33	Testicular	LLL	27.0	16	70	40	PD EXP 1 wk S/P progression
14	November 3, 2004	F65	NSCLC	RML	151.4	15	63	26	PR EXP metastasis to CNS
16	June 10, 2005	F49	Breast	LUL	9.1	10	72	21	PD recurred
	June 10, 2005	F49	Breast	LLL	1.7	25	80	56	PD recurred
	June 9, 2005	F49	Breast	RLL	24	22	76	67	PD recurred
18	October 13, 2005	F82	Rectal	LLL	24.1	24	81	40	CR
21	March 27, 2006	F77	NSCLC	RUL	11.94	15	70	6	PR
32	June 22, 2007	F59	Leiomyoma	RML	16	15	60	26	PR palliation
	June 26, 2007	F59	Leiomyoma	RUL	30.5	15	60	26	PR palliation
	June 27, 2007	F59	Leiomyoma	RLL	30	15	60	26	PR palliation

[a]*Tumor response: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; EXP, expired; F, female; M, male; NSCLC, non small cell lung cancer; LUL, left upper lobe; RML, right middle lobe; LLL, left lower lobe; RUL, right upper lobe; CNS, central nervous system; SRS, Stereotactic radiosurgery; Gy, gray.*

precision to which the linear-quadratic model predicted the treatment effect of ablative dosages.

In SBRT, a rigid frame, vacuum pillow and abdominal compression are used to limit respiratory motion. In addition, respiratory movement is compensated by the addition to GTV + 10 mm in the superior/inferior direction and GTV + 5 mm in transverse direction. The delivery of the 10 to 12 arcs or beams may be limited by the ridged frame. The respiratory motion requires a wider delivery margin, and so more normal tissue may be included in the treatment with possible increase of pulmonary toxicity. The inability to track respiratory motion during treatment can also lead to a geographic miss even with techniques of breathing suppression, which may account for some recurrence or persistence of disease. In our treatment of lower lobe metastasis we have observed superior/inferior motion of as much as 6 cm.

The flexible robotic system is capable of delivering many noncoplanar beams from a wider solid angle, resulting in a rather higher degree of dose fall-off gradient outside of PTV. This will lead to less normal tissue being included in the high-dose region and may lessen pulmonary toxicity. We had only one patient who experienced both a grade 3 and 4 toxicity after retreatment to the same PTV.

The average targeting uncertainty of the Cyberknife was reported to be 1.1 to 1.2 mm, with a standard deviation of 0.8

Table 2. Two-fraction IGR-SRS[a]

Patient number	Treatment date	Sex/Age	Diagnosis	Location	Vol	Dose	%	BED	Comments
2	May 12, 2004	F73	Esophageal	LUL	42.4	30	70	52	EXP 1/04/05 primary eso ca new NSCLC S/P new mediastinal nodes February 13, 2004
3	September 24, 2004	F78	Transitional	RLL	3.4	30	80	52	CR new metastasis 4/06
4	May 11, 2004	M69	Renal cell	RLL	33.3	30	70	52	PD increasing size + FDG
5	November 11, 2004	M57	Renal cell	LUL	4.3	30	58	52	CR FDG neg May 25, 2006
13	September 14, 2004	M53	Mesothelioma	RLL	23.5	15	65	20	PR IMRT EXP January 20, 2006
19	December 14, 2005	M91	Piriform CA	LUL	42.2	24	67	38	PR EXP Jan 2006 brain mets
27	March 31, 2004	M70	NSCLC	RLL	23.4	48	65	105	PR retreated

[a]*Tumor response: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; EXP, expired; IGR-SRS, image guided robotic-stereotactic radiosurgery; eso, esophageal; S/P, status post; CA, carcinoma; LUL, left upper lobe; RLL, right lower lobe; NSCLC, non small cell lung cancer; FDG, fluorodeoxyglucose; IMRT, intensity modulated radiation therapy.*

Table 3. Three-fraction IGR-SRS

Patient number	Treatment date	Sex/Age	Diagnosis	Location	Vol	Dose	%	BED	Comments
1	October 18, 2004	F68	NSCLC	RUL	4.7	45	70	78	SD
3	May 31, 2006	F80	Transitional	LUL	2.5	60	75	120	CR Transitional cell Rt FDG avid + FNA
	September 14, 2006	F80	Transitional	LLL	2.7	30	70	45	PR persisted RML FAILED 4/04/07 surgical resected. August 30, 2007? RU + LUL nodules on CT
4	September 29, 2004	M69	Renal cell	LUL	50.7	30	70	45	EXP 6/06 Grade 5 toxicity
5	September 30, 2004	M57	Renal cell	LUL	47.9	26	70	36	CR renal cell May 25, 2006. FDG negative
	December 12, 2006	M58	Renal cell	RUL	3.2	36	65	57	CR
	December 15, 2006	M58	Renal cell	LUL	1.7	36	70	57	CR
	January 22, 2007	M58	Renal	RUL	2.8	32	65	46	CR 2nd mass RUL
	May 17, 2007	M58	Renal	LUL	4.8	30	68	45	PD recurrent area 1st site Rx Sept 2004
	July 23, 2007	M58	Renal	RLL	6.4	30	60	45	New metastasis
6	February 7, 2005	M57	NSCLC	RUL	152.0	30	65	45	SD
7	March 9, 2005	M86	Renal cell	RLL	18.3	25	62	34	CR
15	May 25, 2005	M57	Testicular	RML	48	30	67	45	SD
	June 1, 2005	M57	Testicular	RML	55	30	67	45	SD
16	March 8, 2006	F50	Breast	LUL	12.2	48	81	86	CR repeat, treatment
	March 21, 2006	F50	Breast	RLL	86	51	82	86	CR repeat treatment
	March 23, 2006	F50	Breast	LLL	10.9	60	83	120	CR repeat treatment
17	October 11, 2005	M56	Tonsillar	LUL	3.7	37.5	78	57	CR Ca of tongue mets to chest CR, then
	October 19, 2005	M56	Tonsillar	RUL	15.4	20	77	24	PR developed new metastasis sent for IMRT
20	March 15, 2006	M80	NSCLC	LML	40	15	70	18	PD 12 Gy × 3; July 5, 2006 partial new RML + 3 liver metastasis
21	September 5, 2006	F78	NSCLC	RUL	30.2	30	65	45	PR retreated persistant FDG SUV 5.9
22	April 3, 2006	F58	Uterine	RLL	67.2	36	65	57	PR
23	April 12, 2006	M56	Esophageal	RML	10.9	42	65	64	CR New metastasis 7/06/07
24	April 18, 2006	F55	Small cell	RLL	0.7	36	80	57	CR Small cell metastasis 1.1 × 0.9; June 16, 2006 5 mm
25	February 22, 2006	F63	Leiomyoma	RLL	17.48	48	70	86	CR
	April 5, 2006	F63	Leiomyoma	LLL sup seg	3.6	48	70	86	CR
	June 14, 2006	F63	Leiomyoma	LLL	2.9	33	65	51	CR 4th mass left hilar leiomyoma
	June 19, 2006	F63	Leiomyoma	LLL hilum	3.8	48	65	86	CR stable new lesions
26	March 8, 2006	M60	NSCLC	RLL	4.2	48	65	86	PR failed at 3 mo SUV up 2.4–8.4 response at November 13, 2006
	March 15, 2006	M60	NSCLC	RUL	5.9	40	75	64	PR failed at 3 mo SUV up 2.5–7.8 improved November 13, 2006
28	January 18, 2006	M76	Laryngeal	RLL	4.51	30	74	45	SD stable
29	January 4, 2007	F35	Gastric	RML	5.17	60	70	120	SD mets liver lung palliation/stable June 13, 2007
	January 16, 2007	F35	Gastric	RUL	1.7	56	75	106	RP eff R April 18, 2007/June 13, 2007 recurrent nodule in PTV site
33	June 5, 2007	M82	NSCLC	RUL	1.4	45.1	70	78	CR of area Rx new metastasis left rib
34	May 18, 2005	M57	Meso	LML	48	47.3	67	86	CR mesothelioma two tumors in med rx same time
	June 1, 2005	M57	Meso	LML	55.5	35.5	67	57	Lost to follow-up
35	March 31, 2004	M57	NSCLC	RLL	23.4	24	65	33	Recurred
	March 16, 2005	M57	NSCLC	RLL	47.3	40.0	65	66	Recurred
	April 19, 2006	M72	NSCLC	RLL	19.3	48.0	70	86	New metastasis

[a]*Tumor response: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; EXP, expired; Rx, treatment; IGR-SRS, image guided robotic-stereotactic radiosurgery; SUV, standard uptake value; F, female; M, male; Dx, diagnosis; NSCLC, non small cell lung cancer; meso, mesothelioma; RUL, right upper lobe; LUL, left upper lobe; LLL, left lower lobe; RLL, right lower lobe; RML, right middle lobe; LML, left middle lobe; sup, superior; seg, segment; FNA, fine needle aspiration; FDG, fluorodeoxyglucose; IMRT, intensity modulated radiation therapy.*

mm.[19] Caution should be exercised when a small margin is used to define the PTV. For metastatic lung tumors we use a 5-mm margin beyond GTV to cover microscopic extension of tumor cells[20] and target uncertainty.

SBRTs dose is delivered in 30 to 45 minutes with a beam-on time of 20 minutes compared with the robotic system which often requires 50 to 100+ beams delivered over 60 to 90 minutes with an average beam-on time of 40 minutes.

Table 4. Four-fraction IGR-SRS

Patient number	Treatment date	Sex/Age	Diagnosis	Location	Vol	Dose	%	BED	Comments
30	April 26, 2007	M88	Merkel	RUL	129	56	95	95	CR Orig R axilla S/P sur + RT 6.07.07 no mass
5	March 6, 2007	M58	Renal	RUL	7	32	70	44	CR

[a]*Tumor response: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; EXP, expired; IGR-SRS, image guided robotic-stereotactic radiosurgery; M, male; RUL, right upper lobe; S/P, status post; RT, right.*

Based upon theoretical and experimental evaluation, the intermittent delivery of highly conformal radiation of the robotic system may contribute to increased cell survival secondary to cell repair during off-time of robotic delivery. The dosimetry delivery of the different systems may require different parameters.

With the addition of the respiratory tracking system to our CyberKnife® unit, after the treatment of the first few patients (four in this series) with the breath-hold technique, our treatment times were dramatically shortened from up to 4 hours down to 90 minutes. Therefore, our early results may have been affected by the potentially detrimental effect of lengthy individual treatment durations.[21–24] Benedict et al[22] have considered this problem from the prospective of Linac-based stereotactic radiotherapy. Their observation was that cell survival increased with increasing total irradiation time, presumably a consequence of cellular repair. Arnfield et al[21] provided experimental data supporting the concern of adverse effects when high-dose brachytherapy is prolonged. Fowler et al[14,19,25] addressed this problem regarding the presence of hypoxic cells. Just as tumor volume will have an effect on tumor control probability of a fractionation scheme, even a low percentage of hypoxic cells may reduce tumor control. Fowler et al[23] have suggested that a loss of biologic effectiveness in 1 hour may be 10 to 30%. Therefore, it is most advisable that treatment durations be as short as other requirements permit. Accordingly, we have altered our treatment time by reducing the number of beams to 50 to 80 from 100 to 150 whenever possible. The increase in the LINAC output rate is also desirable. The combined efforts should shorten total treatment to less than 1 hour where possible. In cases where the demand of high conformality requires a longer treatment time, a higher dose may be needed to compensate for the loss of biologic effect. Systemic research is necessary to clarify optimal dose parameters.

A significant difference in survival has been reported in patients treated by multifractionation versus a single fraction.[25] The most extreme form of hypofractionation is single-fraction IGR-SRS which Whyte et al[26] used in the first report of CyberKnife® treatment for lung cancer. However, there are good reasons to question the effectiveness of a single-fraction strategy. Single-fraction treatment offers no chance for reoxygenation of cells or for any cells to shift out of resistant phases of their cell cycle. If a single fraction is used, Hara et al[32] demonstrated that dose-response was improved with 30 to 32Gy/1F. However, such an ablative dose level could result in higher acute toxicity.

More fractions were used in some patient than others in our series to reduce the possibility of early and late toxicity, especially when the tumor was in close proximity to organs at risk.

It has been reported that local control and survival rates were better for patients with nonsmall cell lung cancer who received a BED equal to or greater than 100 Gy compared with those who did not. Particularly, in medically inoperable patients who received this dose, survival rates were excellent and potentially equivalent to those normally obtained with surgery.[27] In the patient series presented in this article, few tumors received such a dose. The primary limiting factors were the etiology, tumor sizes, and the proximity to organs at risk. The etiology influenced the prescribed dose based upon different α/β required by the pathology. Where possible, the dose was curative for tumors up to 3 cm in maximum dimension and we did not treat tumors larger than 5 cm in diameter for cure. Dose was reduced and number of fractions could be increased if a metastasis was too close to an organ at risk. In the article, for comparison purpose, we used 20 Gy for α/β to calculate BED for all tumors as were for the NSCL tumors. This is based upon speculation that the particularly oxygen-rich environment in the lung would result in an elevated α/β for all tumor types.

Fatigue was the most common side effect. None of our patients complained of esophagitis. Pneumonitis was observed in several posttreatment chest CT scans but all were asystematic with the exception of one patient as described above. Pneumonitis reactions can be kept mostly below grade 3, if the mean NTD to the pair of lungs minus the PTV (or the sum of the PTVs, if more than one lesion is treated) does not exceed 18 to 20 Gy (in 2 Gy fractions equivalent dose). Our mean normalized lung doses resulted in less than 18 to 20 Gy NTD for any single treatment. For dose fractions larger than 2 Gy, the old V_{20} criteria are less reliable as described in the literature,[34,28–31] and we have calculated our V_{15} (normal lung volume receiving 15 Gy and higher in three fractions) to range from 0.3 to a maximum of 11.2%. The dose of 15 Gy was derived assuming the same BED for 20 Gy delivered over 35 fractions of a conventional radiotherapy course. We speculate that the grade 3 and 4 pulmonary toxicity seen in one of the patients was the result of a cumulative effect and possibly overlap by the proximity of the tumors to each other; although each was in a different lobe.

Conclusions

IGR-SRS for lung metastases offers a very effective treatment option without significant complications in medically impaired patients who are not surgical candidates or refuse surgery. In patients with limited pulmonary metastases, radiobiologically potent doses of IGR-SRS are well tolerated with minimal early toxicity. Patient selection is of paramount importance, because those with a low risk of systemic progression are more likely to benefit from this approach with curative intent. We believe that IGR-SRS will add a wider dimension to this armamentarium. Further studies are needed to define the optimal dose and fractionation schedule.

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