Table 2. The mean, SD and minimum and maximum values of residual error in the left–right, superior–inferior and anterior–posterior directions and residual error for the Euclidean distance obtained by using the cross-correlation coefficient or mutual information, with or without a Sobel filter, for a test data set

		Residual error (mm)			
Method	**Direction**	**Mean**	**SD**	**Min**	**Max**
CC	LR	1.25	1.13	0.00	3.24
	SI	1.72	1.41	0.00	4.80
	AP	3.97	3.12	0.56	9.60
	Euclidean	5.18	2.52	0.97	9.76
CC + Sobel	LR	1.20	1.12	0.00	3.24
	SI	1.50	1.51	0.00	4.24
	AP	1.72	1.29	0.00	4.25
	Euclidean	3.10	1.49	0.56	5.03
MI	LR	0.97	0.77	0.00	2.68
	SI	2.22	2.64	0.00	8.71
	AP	6.45	3.34	1.13	9.60
	Euclidean	7.46	3.25	2.29	12.93
MI + Sobel	LR	1.20	1.01	0.00	3.24
	SI	1.38	1.56	0.00	4.24
	AP	1.77	1.25	0.00	4.25
	Euclidean	3.12	1.33	1.12	4.69

See Table 1 note for abbreviations.

Table 3. Statistical significance (P-value) in the residual error of the Euclidean distance between combinations of two similarity measures, that is, cross-correlation coefficient (CC) and mutual information (MI), with or without a Sobel filter for a training data set

	CC	**CC + Sobel**	**MI**	**MI + Sobel**
CC		–	–	–
CC + Sobel	0.000032		–	–
MI	0.408930	0.000001		–
MI + Sobel	0.000584	0.497856	0.000026	

See Table 1 note for abbreviations.

Table 4. Statistical significance (P-value) in the residual error of the Euclidean distance between combinations of two similarity measures, that is, cross-correlation coefficient and mutual information, with or without a Sobel filter for a test data set

	CC	**CC + Sobel**	**MI**	**MI + Sobel**
CC		–	–	–
CC + Sobel	0.046963		–	–
MI	0.114838	0.001802		–
MI + Sobel	0.043631	0.976325	0.001615	

See Table 1 note for abbreviations.

Table 5. Statistical significance (P-value) in the residual error between two directions using cross-correlation and mutual information with a Sobel filter for a training data set

	LR–SI	**SI–AP**	**AP–LR**
CC + Sobel	0.894853	0.415737	0.484603
MI + Sobel	0.894853	0.212833	0.236069

See Table 1 note for abbreviations.

Table 6. Statistical significance (P-value) in the residual error between two directions using cross-correlation and mutual information with a Sobel filter for a test data set

	LR–SI	**SI–AP**	**AP–LR**
CC + Sobel	0.638753	0.741841	0.638753
MI + Sobel	0.764862	0.565630	0.764862

See Table 1 note for abbreviations.

In this preliminary study, the proposed method was focused on translation in the LR, SI and AP directions so that we could investigate the usefulness of the localized pelvic templates. Because the prostate is located in the middle of the patient body, the proposed method based on the localized pelvic templates including regions close to the prostate would not be influenced by the patient rotation around the LR, SI and AP axes. Nevertheless, the proposed method should be expanded to the 3D localized pelvic templates in order to account for the patient rotation.

We dealt with the estimation of setup errors of prostate cancer patients in this study. In principal, the proposed method may be applied to other cancers, such as head and neck cancers. However, for cancers in mobile parts of the patient body or cancer deformation, we should incorporate non-rigid registration techniques into the template-matching technique using localized templates.

The purpose of this study was to investigate the usefulness of the proposed method based on the localized pelvic templates for detection of patient setup errors. To investigate the usefulness, we applied a whole-pelvic-template-based method, which used a different template from the proposed method but the same algorithm, to the same 11 training cases as used for development of the proposed method. The results showed that the average residual errors of the patient setup error using the whole and localized pelvic templates were 2.61 and 1.33 mm in the LR

direction, 2.36 and 1.28 mm in the SI direction, 2.47 and 1.58 mm in the AP direction, and 5.12 and 2.56 mm in Euclidean distance, respectively. We believe that the proposed method based on the localized pelvic templates could be useful for the detection of patient setup errors.

In this paragraph, we discuss the results of investigation of the effects of the following three parameters on the performance of the proposed method: (i) optimum size of the localized pelvic template; (ii) similarity measures; and (iii) enhancement of bony anatomical structures.

Optimum size of the localized pelvic template

As shown in Fig. 6, the optimum localized pelvic template size was 80% of the original localized template image, which was used in the proposed method for estimation of the patient setup errors. The 80% templates included a sufficient characteristic region of the bone structures around the prostate, such as the ischial tuberosity and obturator foramen for the pelvic template matching. In contrast, the 100% templates sometimes also contained the outside regions of ischial tuberosity, whose appearance in the EPID portal image could vary when the patient rolled on the treatment table, due to their distance from the body axis. Therefore, the larger pelvic template may not work well for estimation of patient setup errors. On the other hand, templates smaller than 80% relative size may not contain a sufficient characteristic region of the bone structures, and thus such templates might not be useful for pelvic template matching.

Similarity measures

As shown in Tables 1 and 2, the method using the CC can more correctly detect the patient setup errors than the method using MI regardless of whether or not the Sobel filter is applied. The CC is considered to be the degree of similarity between two images with respect to the spatial distribution of pixel values, and it could be useful for two images with similar image quality. The MI is based on a two-dimensional pixel value histogram, and is intuitively regarded as the shared information between two images, which can be used as a degree of similarity. MI is considered to be useful for evaluation of the similarity between two images with different image quality, such as CT and positron emission tomography images. In this study, because both the DRR and EPID portal images are based on the degree of attenuation of X-rays for the human body, the spatial distributions of pixel values of the two images are similar to each other. Therefore, the method with the CC would be better to obtain the patient setup errors.

Enhancement of bony anatomical structures

The method with the Sobel filter was better for evaluating setup errors than that without the Sobel filter, irrespective of the similarity measure, as shown in Tables 1 and 2. The reason for this result was considered to be that the pelvic template matching using the DRR and EPID portal images depends on the bone structures, because soft tissue structures were hardly imaged in the DRR and EPID portal images. Therefore, the enhancement of bone structures was useful for the detection of patient setup errors.

Since the localized pelvic DRR template was extracted from the patient's own DRR image produced from his planning CT images, the localized templates could reflect the patient's clinical condition, such as the degree of obesity, weight and the degree of bladder filling when imaging the planning CT. However, the patient's clinical condition at imaging of the planning CT is not exactly the same as that at the treatment time, and the patient condition could vary during the course of treatment, since the treatment often consisted of around 36 fractions (e.g. many patients lost weight during the treatment). Consequently, the condition of bone structures could change, and the localized templates would not be optimum. Therefore, in a future work we should incorporate non-rigid registration techniques into the template-matching technique using the localized templates in consideration of the change in the patient's condition.

To further confirm its robustness, the proposed method should be applied to many test cases, since we performed a validation test using only 10 cases in this study. In addition, we should employ test cases including portal images and CT images, which could be acquired from different equipment in different institutions. We believe that the proposed method can be improved by performing such validation tests as a next step, such that the method will ultimately be able to detect patient setup errors with high accuracy for many different types of cases.

CONCLUSIONS

We have developed a computerized method for estimation of patient setup errors in portal images based on localized pelvic templates for prostate cancer radiotherapy. The patient setup errors were estimated based on a template-matching technique between the portal image and a localized pelvic template image around a clinical target volume for each patient. The residual errors in the three directions (LR, SI and AP) obtained by the method were <2 mm in both tests. There were no statistically significant differences in the residual error between the test for training cases and the validation test ($P = 0.438$). The proposed method appears to be robust for the detection of patient setup error at a treatment session.

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APPENDIX A DETERMINATION OF THE ACTUAL CENTER OF AN IRRADIATION FIELD IN A PORTAL IMAGE

The actual center in an irradiation field on a portal image was determined by searching a measuring scale within the irradiation field in the portal image using a template matching technique based on the cross-correlation coefficient [15, 16]. A measuring scale was superimposed on the portal image for two clinical purposes: verification of the center of the portal image and comparison with the planned isocenter of the planning DRR image. Prior to this process, the irradiation field was extracted based on a pixel-value histogram analysis. First, the initial irradiation field in the portal image was roughly extracted by a threshold value, which was determined by subtraction of the SD of the largest peak in a portal image histogram from the pixel value of the corresponding largest peak [16]. Then, the final irradiation field was segmented by cropping a field 3-mm smaller than the circumscribed quadrangle of the initial irradiation field, because the near edge of the initial irradiation field was not segmented well. Figure A1a, b and c show a portal image with a measuring scale, an initial irradiation field and a final irradiation field, respectively.

The center of the measuring scale in the portal image was detected as an actual center of the irradiation field based on a template matching between the portal image and the standard scale point template. The actual center of the irradiation field was determined by finding a location with the maximum cross-correlation coefficient between the portal image and the template image. Figure A2 shows a standard measuring scale point template used for determination of the center of the irradiation field. This template was obtained from a portal image, which was acquired without any objects by mounting the measuring scale to a gantry head of the linear accelerator.

APPENDIX B REDUCTION OF SCALE POINTS IN THE PORTAL IMAGE

The measuring scale points should be reduced for more accurate template matching between the portal image and the localized pelvic template image. Therefore, the measuring scale points were reduced by inpainting each scale point with a mean filter and a measuring scale binary template. Figure A3 shows illustrations of the reduction of scale points in the portal image by inpainting the scale points with a mean filter. A measuring scale superimposed in an original portal image is shown in Figure A3a. To reduce the scale points in the portal image, the mean filter with the structure element of a circle (radius: nine pixels) was applied to each pixel within each circle scale point in the measuring scale binary template (Figure A3b), which was overlaid on the original portal image (Figure A3a) in the position of the actual center of the irradiation field. The mean value was calculated within the neighbor pixels in

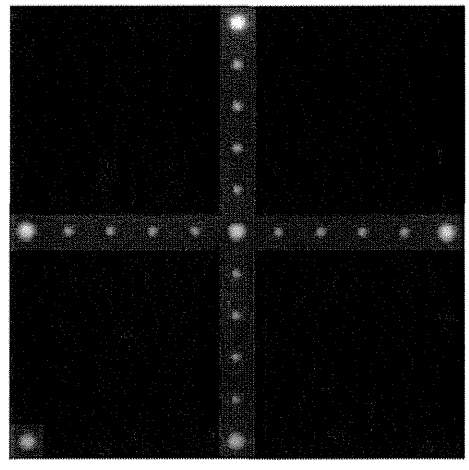

Fig. A2. Standard measuring scale point template image used for determination of the center of the irradiation field.

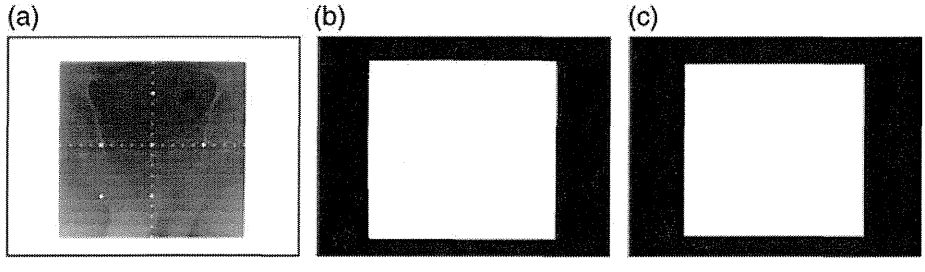

Fig. A1. Illustrations of (**a**) a portal image with a measuring scale, (**b**) an initial irradiation field and (**c**) a final irradiation field.

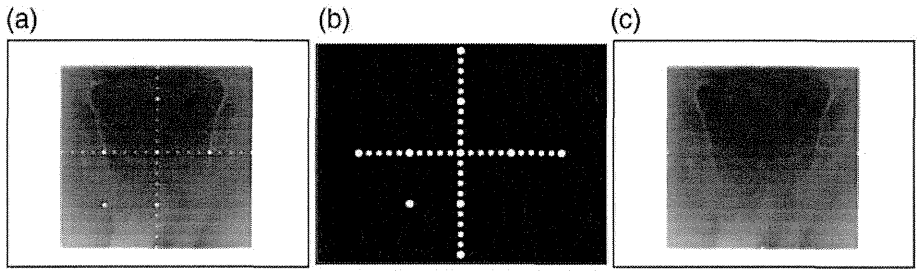

Fig. A3. Illustrations of the reduction of scale points in a portal image by inpainting of the scale points with a mean filter: (**a**) an original portal image, in which a measuring scale was superimposed, (**b**) a measuring scale binary template and (**c**) the portal image with reduced scale points.

the circle of the mean filter excluding the circle scale point region. Finally, a median filter with a 3×3 square structure element was used for removal of the very small amount of noise. Figure A3c shows the portal image with reduced scale points.

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Clinical results of stereotactic body radiotherapy for Stage I small-cell lung cancer: a single institutional experience

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The purpose of this study was to evaluate the treatment outcomes of stereotactic body radiotherapy (SBRT) for Stage I small-cell lung cancer (SCLC). From April 2003 to September 2009, a total of eight patients with Stage I SCLC were treated with SBRT in our institution. In all patients, the lung tumors were proven as SCLC pathologically. The patients' ages were 58–84 years (median: 74). The T-stage of the primary tumor was T1a in two, T1b in two and T2a in four patients. Six of the patients were inoperable because of poor cardiac and/or pulmonary function, and two patients refused surgery. SBRT was given using 7–8 non-coplanar beams with 48 Gy in four fractions. Six of the eight patients received 3–4 cycles of chemotherapy using carboplatin (CBDCA) + etoposide (VP-16) or cisplatin (CDDP) + irinotecan (CPT-11). The follow-up period for all patients was 6–60 months (median: 32). Six patients were still alive without any recurrence. One patient died from this disease and one died from another disease. The overall and disease-specific survival rate at three years was 72% and 86%, respectively. There were no patients with local progression of the lesion targeted by SBRT. Only one patient had nodal recurrence in the mediastinum at 12 months after treatment. The progression-free survival rate was 71%. No Grade 2 or higher SBRT-related toxicities were observed. SBRT plus chemotherapy could be an alternative to surgery with chemotherapy for inoperable patients with Stage I small-cell lung cancer. However, further investigation is needed using a large series of patients.

Keywords: stereotactic body radiotherapy; small-cell lung cancer; Stage I

INTRODUCTION

Small-cell lung cancer (SCLC) represents approximately 20% of all lung cancer and it is basically characterized by rapid growth and early metastasis [1]. Therefore, thoracic radiotherapy combined with systemic chemotherapy has been typically accepted as the standard treatment for patients with limited disease [2]. For patients with Stage I SCLC among limited-disease, however, surgical resection followed by chemotherapy is recommended in the clinical practice guidelines of the National Comprehensive Cancer Network (NCCN) [3] and also the Japan Lung Cancer Society [4]. Nevertheless, we sometimes experience patients with Stage I SCLC who are medically inoperable because of poor pulmonary function, cardiac disease and/or other co-existing diseases. However, an optimal treatment has not been established for medically inoperable patients with Stage I SCLC. Currently, stereotactic body radiotherapy

(SBRT) has been widely used as one of the curative treatment options for peripherally-located Stage I non-small cell lung cancer (NSCLC) [5–9]. Given that SCLC is generally more radiosensitive than NSCLC, we hypothesized that SBRT would also be effective for Stage I SCLC.

From 2003, at Kyushu University, we began using SBRT for Stage I SCLC patients who were not candidates for surgery. Here, we retrospectively analyse the treatment outcomes of SBRT for patients with Stage I SCLC in our institution, and evaluate the effectiveness and safety of SBRT for this disease.

MATERIALS AND METHODS

Patients

From April 2004 to September 2009, 269 patients with lung tumors were treated with SBRT at Kyushu University Hospital. Of these, eight patients with Stage I SCLC were treated with SBRT. In all patients, pathology of the lung tumors was confirmed as SCLC by transbronchial brushing cytology or CT-guided percutaneous fine needle aspiration cytology. The patients' age was 58–84 (median: 74) yeas. Tumor size range was 15–38 mm (median: 29) in diameter. The T-Stage of the primary tumor at the time of diagnosis was T1a in two, T1b in two and T2a in four patients. Serum levels of the pro-gastrin releasing peptide (ProGRP) and neuron-specific enolase (NSE) before treatment are shown in Table 1. Normal levels of ProGRP and NSE in our institution are less than 46.0 pg/ml and 12.0 ng/ml, respectively. All patients received 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) and brain magnetic resonance imaging (MRI) for staging in addition to chest-abdominal CT scan. Six of the patients were inoperable because of poor cardiac and/or pulmonary function, and two patients refused surgery. Patient characteristics are summarized in Table 1. All of the patients provided written informed consent.

Treatment planning for SBRT

All patients were fixed with a thermoplastic body cast combined with a vacuum pillow, arm and leg support, and a carbon plate (Engineering Systems Co., Matsumoto, Japan). The detail of this body fixation system has been described previously [10]. Treatment planning was performed using the 3D RTP machine (Eclipse 7.1.4). The gross target volume (GTV) was identified on relevant lung setting CT images. The internal target volume (ITV) was created individually according to the internal respiratory motion. The planning target volume (PTV) margin was 5mm in all directions. Seven to eight multi-leaf-collimator (MLC)-shaped non-coplanar static ports of 4- or 10-MV X-rays were selected to maintain target volume homogeneity within 10%, and to decrease the irradiated lung volume receiving 20 Gy or more (V20) to below 20%.

Table 1. Summary of the eight Stage I SCLC patients treated with stereotactic body radiotherapy

Cases	Age	Gender	T-stage	Primary sites	Tumor markers		SBRT	CTx (courses)	Timing of CTx	Prognosis	Recurrences (Sites)
					ProGRP (pg/ml)	NSE (ng/ml)					
1.	75	F	T1a	RUL	70.5	13.4	48 Gy/4 Fr	CDDP +CPT-11(3)	pre-SBRT	50M alive	none
2.	77	M	T2a	RLL	92.9	7.2	48 Gy/4 Fr	CBDCA +VP16 (3)	post-SBRT	15M dead	yes (lymph node)
3.	56	M	T2a	LUL	22.3	NA	48 Gy/4 Fr	none	none	18M dead	none
4.	79	M	T2a	RLL	56.0	NA	48 Gy/4 Fr	CBDCA +VP16 (3)	pre-SBRT	54M alive	none
5.	69	F	T1a	LUL	31.1	11.0	48 Gy/4 Fr	CBDCA +VP16 (3)	pre-SBRT	32M alive	none
6.	63	M	T1b	RUL	121.6	11.5	48 Gy/4 Fr	CBDCA +VP16 (3)	post-SBRT	59M alive	none
7.	84	M	T1b	RUL	32.0	NA	48 Gy/4 Fr	CBDCA +VP16 (4)	pre-SBRT	30M alive	none
8.	74	M	T2a	LUL	18.4	10.7	48 Gy/4 Fr	none	none	6M alive	none

RUL = right upper lobe, RLL = right lower lobe, LUL = left upper lobe, LLL = left lower lobe, ProGRP = pro-gastrin releasing peptide, NSE = neuron-specific enolase, NA = not available, CDDP = cisplatin, CPT-11 = irinotecan, CBDCA = carboplatin, VP16 = etoposide, SBRT = stereotactic body radiotherapy, CTx = chemotherapy.

Treatment

SBRT was given to the PTV with an isocenter dose of 48 Gy in four fractions. Total treatment duration ranged from 4–8 (median = 4) days. By using CT and portal images (anterior-posterior and lateral), the isocenter was verified in the first treatment session. In the second and following sessions, portal images (anterior-posterior and lateral) and/or CT images were used. When respiratory tumor motion was 1 cm or more, breath-holding irradiation was performed using a visual-feedback-guided breath-holding system developed at our institution [11, 12]. Chemotherapy using carboplatin (CBDCA) + etoposide (VP-16) or cisplatin (CDDP) + irinotecan (CPT-11) was performed for six patients before or after SBRT. Five of the patients received 3–4 cycles of CBDCA (AUC = 5 on Day1) + VP-16 (100 mg/m^2 on Days 1, 3 and 5 every 4 weeks), and one received three cycles of CDDP (20 mg/m^2 on Days 1, 8 and 15) + CPT-11 (60 mg/m^2 on Days 1, 8 and 15, every 4 weeks). Two patients with severe cardiac or liver dysfunction were treated with SBRT alone. The details are shown in Table 1. No patients received prophylactic cerebral irradiation (PCI) after completion of SBRT, with or without chemotherapy.

Patient follow-up and evaluation

After completion of SBRT, patients were evaluated by examinations including chest X-ray and CT every two to three months for two years, and every six months thereafter. Brain MRI and FDG-PET were also performed if needed.

Methods of data analysis

Survival rates (overall, disease-specific, progression-free), local control rate after SBRT, pattern of failures, and SBRT-related toxicities were evaluated. Overall, the disease-specific and progression-free survival rates, and local control rate were estimated with the Kaplan-Meier method. SBRT-related toxicities were graded according to the Common Toxicity Criteria for Adverse Effect version 3.0 [13].

RESULTS

The follow-up period for all patients was 6–60 months (median: 32). Six patients were still alive without any recurrence. One patient died from SCLC, and one died from another disease. The overall survival rate and disease-specific survival rate at three years were 72% and 86%, respectively (Fig. 1). There were no patients with local progression of the target lesion of SBRT. Only one patient, who was treated with SBRT alone, had nodal recurrence in the mediastinum at 12 months after treatment. This patient refused salvage treatment by radiotherapy or chemotherapy for the recurrence, and received best supportive care in another hospital. There were no patients with distant metastasis during the follow-up period. The progression-free survival rate and local control rate at three years were 71% and 100%, respectively (Fig. 2). No Grade 2 or higher SBRT-related toxicities were observed during follow-up in any patient.

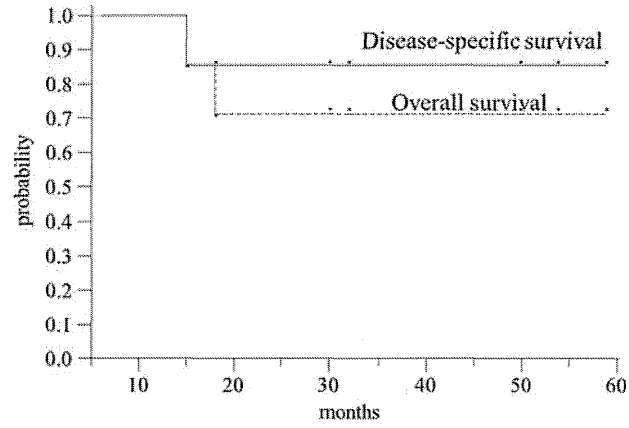

Fig. 1. Overall and disease-specific survival rates for eight patients treated with SBRT for Stage I SCLC.

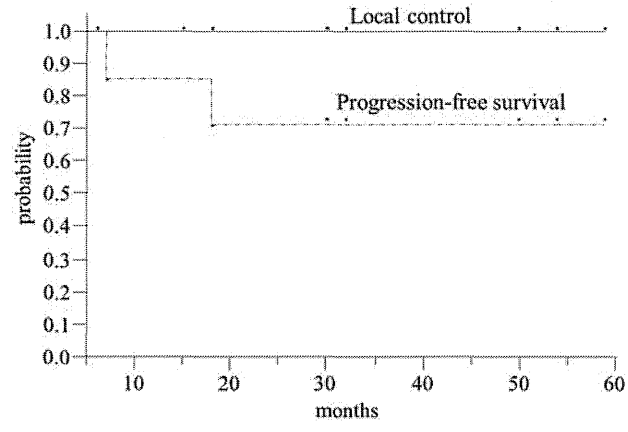

Fig. 2. Progression-free survival rate and local control rate for eight patients treated with SBRT for Stage I SCLC.

DISCUSSION

In the present study, favorable outcomes were achieved with SBRT of 48 Gy in four fractions with or without chemotherapy for patients with clinical Stage I SCLC; the 3-year survival rate and local control rate were 72% and 100%, respectively. The treatment was also considered well tolerable because no Grade 2 or greater toxicity was observed. Therefore, SBRT can be a safe and effective treatment option for Stage I SCLC.

Several reports have been published regarding the outcomes of surgery with or without chemotherapy for Stage I

SCLC. The 5-year overall survival rates after surgery for Stage I SCLC have been reported as approximately 50–70 % [14–17]. Although it is difficult to compare these results directly, mainly because of the difference between the pathological stage and clinical stage, the 3-year survival rate in our study using SBRT compared favorably to those of surgical series previously listed.

In previous reports of SBRT for NSCLC [6] and also metastatic lung tumors [18], favorable outcomes of survival and local control were reported in patients treated with a biologically effective dose, assuming the alpha/beta ratio to be 10 (BED10) over 100 Gy at the isocenter. In our present study of SBRT for Stage I SCLC, the prescribed dose of 48 Gy in four fractions (BED10 = 105.6 Gy) at the isocenter was used for all patients, the same as the commonly used SBRT dose for Stage I NSCLC in Japan, because there is no published information regarding the optimal dose of SBRT for SCLC. Complete local control was achieved with no severe toxicity in any patients. Therefore, this prescribed dose is considered sufficient for local control of T1-2a SCLC. However, given that SCLC is known to be more radiosensitive than NSCLC, the total dose of SBRT might be reduced slightly for SCLC. Considering that SCLC is also a rapid growth tumor, more fractionated scheduling may be advantageous in the point of cell cycle effects. Therefore, further investigation is necessary to determine optimal dose and fraction scheduling of SBRT for Stage I SCLC. However, it should be noted that BED based on the linear-quadratic (LQ) model has been shown to overestimate the effect of high fractional doses of radiation, and also not to take reoxygenation as well as cell cycle effect into account [19].

Chemotherapy has an important role in the treatment of SCLC because of its biological behavior, characterized by rapid growth and early dissemination. Generally, a chemotherapy regimen using CDDP (or CBCDA) plus VP-16 is combined with thoracic radiation therapy for limited-disease SCLC (LD-SCLC). Also, adjuvant chemotherapy is generally recommended after surgery for Stage I SCLC in order to reduce the risk of distant metastasis. In the present series, four patients initially received chemotherapy in other hospitals, and then were introduced to our institution because of residual tumors. Two patients received adjuvant chemotherapy after SBRT as planned treatment. In these patients who received neoadjuvant or adjuvant chemotherapy no Grade 2 or higher SBRT-related toxicity was observed. Although the number of patients is too small to draw a conclusion, the sequential combination (neoadjuvant or adjuvant) of chemotherapy may be safe in patients treated with SBRT. In SBRT for Stage I SCLC, therefore, it is better to combine chemotherapy with SBRT. However, the optimal timing of chemotherapy combined with SBRT (neoadjuvant, concurrent, vs adjuvant) is yet to be determined.

Recently, the role of PCI has been established in the treatment of SCLC, especially in LD-SCLC [20, 21]. In our series, no patients suffered from brain metastasis, despite not undergoing PCI. However, the number of patients in this series is too small to discuss whether PCI is essential or not in Stage I SCLC patients.

In conclusion, SBRT plus chemotherapy could be an alternative treatment option to surgery with chemotherapy for patients with Stage I small-cell lung cancer. However, further investigation is needed using a larger number of patients.

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Stereotactic Body Radiation Therapy for Stage I Non-small Cell Lung Cancer Patients with Chronic Respiratory Insufficiency Requiring Domiciliary Oxygen Therapy

TADAMASA YOSHITAKE[1], KATSUMASA NAKAMURA[2], YOSHIYUKI SHIOYAMA[1], TOMONARI SASAKI[2], SAIJI OHGA[2], TAKESHI NONOSHITA[2], KOTARO TERASHIMA[2], KAORI ASAI[2], KEIJI MATSUMOTO[2] and HIROSHI HONDA[2]

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Abstract. *Background: The efficacy of stereotactic body radiation therapy (SBRT) for patients treated with domiciliary oxygen therapy is not well known. Patients and Methods: We collected the clinical records of 15 patients with chronic respiratory insufficiency requiring domiciliary oxygen therapy at 1-3 l/min who were treated with SBRT for stage I non-small cell lung cancer. All patients were fixed with a thermoplastic body cast system. SBRT was given in 7-8 fields with an isocenter dose of 40-60 Gy in 4-10 fractions (median, 48 Gy in 4 fractions). Results: The overall 2-year and 5-year survival rates for all patients were 67.4% and 34.7%, while the disease-specific 2-year and 5-year survival rates were 90.0% and 72.0%, respectively. Pulmonary adverse effects were mild in the majority of the patients, although two patients had grade 2 radiation pneumonitis. The oxygen flow required increased slightly at follow-up periods greater than one year, but was still at an acceptable level. Conclusion: SBRT was feasible for patients requiring domiciliary oxygen therapy.*

Although surgical resection remains the present standard care for early-stage non-small cell lung cancer (NSCLC), stereotactic body radiation therapy (SBRT) is a worthwhile alternative. In particular, SBRT for NSLC is considered for patients who are medically inoperable because of pulmonary co-morbidities or other medical conditions (1-6). If a patient has severe lung function impairment, observation is a viable nonsurgical option (7) because possible radiation-induced pneumonitis or fibrosis may be critical for such patients. However, medically inoperable patients with untreated early-stage lung cancer have a poor prognosis, with >50% of patients dying of lung cancer (7). Although it has been shown recently that poor pulmonary function does not predict reduced survival or pulmonary function after SBRT (8, 9), the efficacy of SBRT for patients treated with domiciliary oxygen therapy has not been well known.

In this retrospective study, we investigated the feasibility of using SBRT to treat patients with stage I NSCLC with chronic respiratory insufficiency requiring domiciliary oxygen therapy, in particular focusing on changes in oxygen flow rate.

Patients and Methods

Patients. From April 2004 to April 2010, 259 patients with early lung cancer were treated with SBRT at the Department of Radiology of Kyushu University Hospital. Of these, we collected retrospectively the clinical records of 15 patients (5.8%) with chronic respiratory insufficiency requiring domiciliary oxygen therapy before SBRT. These patients had been treated with 1-3 l/min of oxygen to maintain an oxygen saturation of ≥88%, as measured by pulse oximetry.

Patient characteristics are presented in Table I. Pulmonary function tests were performed before treatment, with results as shown in Table II.

Treatment. The SBRT technique has been previously described (10). Briefly, the patients were fixed with a body cast system composed of a thermoplastic body cast, a vacuum pillow, arm and leg support, and a carbon plate (Engineering Systems Co., Matsumoto, Japan). The body cast restricted the chest and abdominal wall movement to immobilize the patients during planning and treatment. Respiratory movement was evaluated with an X-ray simulator for the diaphragm and the tumor. CT scans were performed at 2-mm intervals on the day of planning and the first treatment day for verification. CT volume data were transferred to a three-dimensional radiotherapy treatment planning (3D-RTP) system (Eclipse; Varian Medical Systems, Inc.,

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Key Words: Stereotactic body radiation therapy, non-small cell lung cancer, chronic respiratory insufficiency, domiciliary oxygen therapy, pulmonary adverse effects.

Table I. *Patient characteristics (n=15).*

	Number
Gender	
Male:female	10:5
Age	
Median, range (years)	75 (60-83)
Performance status	
0	0
1	3
2	8
3	3
4	1
Underlying disease	
COPD	12
Postoperative respiratory failure	1
Chronic pulmonary tuberculosis	1
Chronic heart failure	1
Histology	
Squamous cell carcinoma	8
Adenocarcinoma	1
Unknown	6
Clinical stage	
T1aN0M0	7
T1bN0M0	5
T2aN0M0	8
Tumor size	
Median, range (mm)	20 (8-48)

COPD, Chronic obstructive pulmonary disease.

Palo Alto, CA, USA). Seven to eight multi-leaf collimator-shaped static ports of 4- or 6-MV X-rays were selected. To maintain the isocenter setup accuracy, a comparison of the anterior, posterior (AP) and lateral digital portal images with the planning AP and lateral digitally reconstructed radiographs was performed daily. The dose was 48 Gy in four fractions to the isocenter for 13 of the tumors, 60 Gy in 10 fractions for one tumor, and 40 Gy in 4 fractions for 1 tumor. The linear accelerator used was a Clinac-21Ex (Varian Medical Systems, Inc.). The median percentage of total lung receiving more than 20 Gy (V20) was 4.8% (range 2.2-8.7%).

Follow up. In principle, patients were assessed after completion of SBRT every four weeks for the first six months, every three months for the next 36 months, and every six months thereafter. Toxicity was graded according to the Common Terminology Criteria Adverse Events version 3 (CTCAE v3.0) (11), and chest CT or x-ray was performed at every follow-up. Oxygen therapy continued after SBRT. Oxygen flow was moderated to achieve target oxygen saturation levels of ≥88%, based on pulse oximetry.

The overall and disease-specific survival rates were calculated using the Kaplan Meier method. The median follow-up was 23 months (range 6-69 months).

Results

Survival and patterns of failure. The overall 2-year and 5-year survival rates for all patients were 67.4% and 34.7%, while the disease-specific rates were 90.0% and 72.0%, respectively (Figure 1).

Table II. *Pulmonary function test values before stereotactic body radiotherapy.*

Test	Median, range
FEV_1 (l)	0.74 (0.38-1.85)
FEV_1 (%)	43.1 (21.1-77.7)
FVC (l)	1.81 (0.87-3.58)
FVC (%)	63.3 (43.3-116.2)

FEV, Forced expiratory volume in 1 second; FVC, forced vital capacity.

Six patients (40%) had disease recurrence. Three patients (20%) had a local recurrence, and one had a pleural dissemination. Two patients experienced disease relapse in the hilar lymph nodes. No patient developed distant metastases. During the observation time, three patients died of lung cancer; five patients died of concurrent disease (chronic obstructive pulmonary disease (COPD) in four patients, cardiovascular disease in one patient).

Adverse effects. Pulmonary adverse effects were mild in the majority of the patients. Although two patients had grade 2 radiation pneumonitis, medical management including steroid administration improved their symptoms. There were no severe complications for the remaining 13 patients.

Oxygen flow before and after treatment to maintain oxygen saturation levels of ≥88% are shown in Figure 2. No patient exhibited reduced oxygen flow levels after SBRT. Of five patients whose oxygen flow levels were evaluated at an interval less than one year after SBRT, only one patient exhibited an increase in the oxygen flow required. In contrast, the necessary oxygen flow increased slightly with follow-up periods of more than one year.

Discussion

To our knowledge, this is the first report of the feasibility of SBRT for patients with stage I NSCLC with chronic respiratory insufficiency requiring domiciliary oxygen therapy. Although the sample size was small, the treatment was well tolerated and the tumor control rate was high.

Recently, several reports have been published regarding pulmonary function after SBRT for patients with early-stage NSCLC. Henderson *et al.* reported that poor baseline pulmonary function did not predict reduced survival or pulmonary function after SBRT for patients with stage I NSCLC treated with a dose of 60–66 Gy in three fractions (9). Bishawi *et al.* reviewed collected data of stage I-II lung cancer prospectively, and demonstrated that SBRT did not have an effect on forced expiratory volume in 1 second

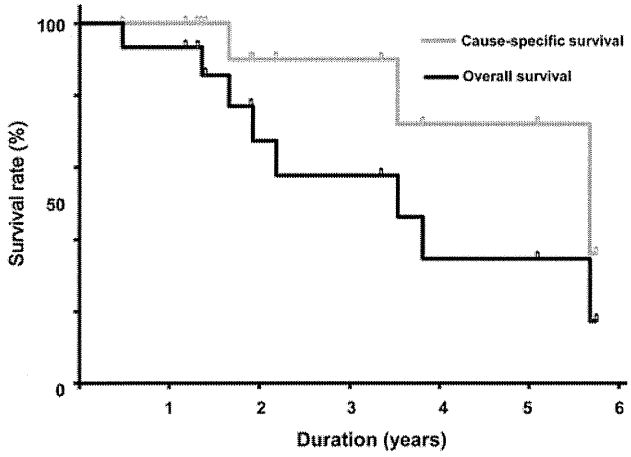

Figure 1. *Overall and disease-specific survival rates for 15 patients treated with stereotactic body radiation therapy for stage I non-small cell lung cancer.*

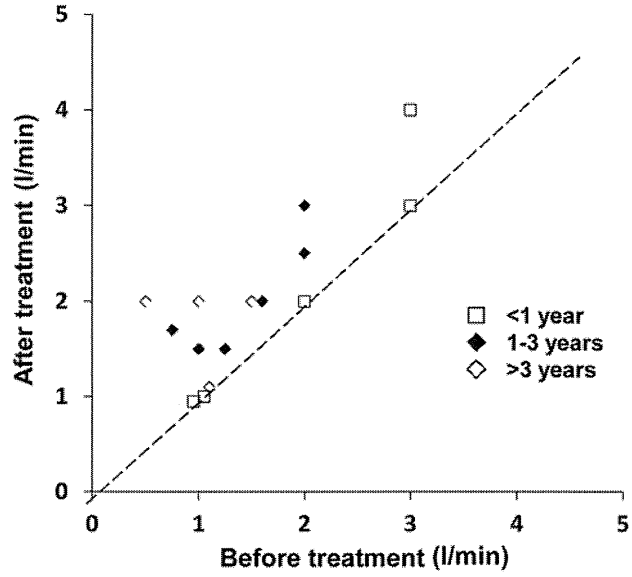

Figure 2. *Oxygen flow before and after stereotactic body radiation therapy (SBRT) to maintain oxygen saturation levels of ≥88%. In one patient, chronic respiratory failure acutely worsened; the oxygen flow levels necessary for this acute-on-chronic form of respiratory failure were excluded. The plots are divided into three categories according to the period between SBRT and the follow-up evaluation of oxygen flow (<1 year, 1-3 years, >3 years). The median follow-up period was 1.2 years (range 0.1-5.7 years).*

(FEV1) or forced vital capacity (FVC) at a mean follow-up time of four months (8). In our study, the oxygen flow required to maintain oxygen saturation levels of ≥88% increased slightly in most cases with follow-up periods of more than one year, but was still at acceptable levels.

In this study, we used a median total dose of 48 Gy with four fractions, which is the most frequently used schedule of SBRT in Japan for primary lung cancer (12), although it is smaller than the doses used in the United States (5). We were able to achieve very low V20 values for the lungs, but three patients (20%) had a local recurrence. Multi-institutional phase II trials of SBRT are currently underway in Japan (13), and patient enrollment for these trials has already closed. The results will hopefully validate the efficacy of this schedule of SBRT for NSCLC.

Patients with chronic respiratory insufficiency requiring domiciliary oxygen therapy have a poor prognosis. Crockett *et al.* examined the prognosis of patients treated with domiciliary oxygen therapy for COPD, and demonstrated that the overall crude survival was 75.1%, 51.3%, and 18.9% at 1, 2, and 5 years respectively (14). Therefore, observation alone may be a nonsurgical option for patients with severe lung function impairment (7). In our study, five patients (26.7%) died of concurrent diseases, and the overall 2-year and 5-year survival rates for all patients were 67.4% and 34.7%, respectively. However, McGarry *et al.* reported that medically inoperable patients with untreated stage I-II NSCLC have a poor prognosis, with >50% of patients dying of lung cancer; the median survival time for such patients with no treatment was 14.2 months (7). Therefore, based on the fact that poor pulmonary function does not predict reduced survival or pulmonary function after SBRT (8, 9), SBRT may be a treatment option for patients already requiring domiciliary oxygen therapy.

In this retrospective study, SBRT proved feasible for patients requiring domiciliary oxygen therapy. However, the number of patients was small, and this finding is in contrast to the situation after conventionally fractionated radiotherapy, where COPD and reduced FEV1 were associated with severe acute radiation pneumonitis (15). The exact benefit of SBRT for patients with domiciliary oxygen therapy may be elucidated by larger prospective observational studies.

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Title	重粒子線がん治療の現状と今後の展開
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総　　説

重粒子線がん治療の現状と今後の展開

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はじめに

放射線治療は，外科治療および化学療法とならんで「がん治療」の３本柱の１つである．これまではガンマ線やＸ線が主に用いられてきたが，体表近くでエネルギーが最大となり徐々に減衰はするものの体内を透過してしまう性質を持つため，線量の集中性が低いことが問題であった．そのため，近年，病巣へ多方向から集中して照射する３次元原体照射法（3D-CRT）や，更に放射線強度を部分的に変化させて線量分布を最適化する強度変調放射線治療（IMRT）など相対的に線量を集中させる照射技術が開発され，治療効果の向上および副作用の低減に寄与している．一方で，加速器技術の進歩とともに，シンクロトロンやサイクロトロンといった粒子加速器により光の速度の60-80％という超高速に加速された荷電粒子をがん病巣にピンポイントで照射する粒子線治療の研究および臨床応用が進み，その高い有用性が注目されている．粒子線治療は陽子を用いる「陽子線治療」とそれよりも重い荷電粒子を用いる「重粒子線治療」とに大別される．現在，重粒子線として実際に臨床応用されているのは炭素イオン線のみであることから，重粒子線治療と言えば，現時点では「炭素イオン線治療」を指すことになる．陽子線，重粒子線に共通する点は，従来のＸ線やガンマ線と比較して線量集中性が高いという物理学的特性である．一方，両者の大きな違いは生物学的特性であり，重粒子線はＸ線・ガンマ線，陽子線に比較して明らかに高い生物効果を持つという点である．

本項では，従来のＸ線・ガンマ線治療やもう１つの粒子線である陽子線治療と比較しながら，重粒子線治療の特徴，実際の治療法，治療成績，国内外の現状や今後の展開などを紹介する．

１．物理学的特性とがん治療上のメリット

炭素イオン線に代表される重粒子線の物理学的特徴は，文字通り「荷電粒子」であるため飛程を持つこと，また，超高速で飛び込んできた粒子は体表面および体表面近くでは小さなエネルギーしか与えないが，その速度を減じながら体内深部で停止する直前に急激にエネルギーを放出するという，いわゆるブラッグ・ピークを形成することである．この物理学的特性はがん治療において非常に有利な特徴であり，ブラッグ・ピークの位置を腫瘍の深さに一致させ，ピークの幅を腫瘍の大きさと合うように調節することにより，手前の正常組織に比べて腫瘍に遥かに高い線量を投与できるばかりか，腫瘍より奥の線量をほぼゼロにすることができる（図１）．つまり，Ｘ線やガンマ線では線量集中性を高めるのにどうしても多方向か

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ら照射する必要があり，その分，周囲正常臓器に低～中線量域が広がってしまうのに対して，重粒子線では，より少ない方向から効率よく腫瘍に線量を集中することができる．よって，周囲正常臓器に投与される線量およびその範囲を最小限に留めることができることになり，副作用や二次発がんリスクの低減という観点からも有利となる．類似の物理学的特性は陽子線も持ち合わせており，陽子線治療においても同様のメリットが期待できる．但し，生物効果を加味したブラッグ・ピーク部分と手前の平坦部分との比（ピーク/プラトー比）を比較すると，陽子線は重粒子線に比べてやや劣る．また，質量が小さい（炭素イオンの12分の1）ことから，側方に散乱する（拡がる）傾向があり，これらの点で線量分布は重粒子線の方がシャープである[1)]．重粒子線の場合にブラッグ・ピークより深部（飛程終末部分）で核破砕反応により僅かな低線量の尾を引くが，エネルギーも低く臨床的にはあまり問題とはならない．

2．生物学的特性とがん治療上のメリット

重粒子線（炭素イオン線）のもう1つの特徴は高い生物学的効果である．飛跡に沿って付与される単位長さ当たりのエネルギーを線エネルギー付与（linear energy transfer：LET）と呼ぶ．各種放射線は，この線エネルギー付与（LET）の大きさによって高LET放射線と低LET放射線とに大別され，生物学的効果も異なってくる．陽子線が従来の放射線（X線やガンマ線）と同様に低LET放射線に分類されるのに対し，重粒子線（炭素イオン線など）は高LET放射線に分類される．低LET放射線では，その生物作用はDNAに対する間接効果（電離によって生じたラジカルによるDNA 1本鎖切断）が主体であり修復されやすい．X線やガンマ線の生物学的効果を1としたときの，陽子線の生物学的効果比（relative biological effectiveness：RBE）は，1.1でとされ，陽子線の生物学的効果は従来の放射線（X線・ガンマ線）とそれほど変わらない．また，その効果が細胞周期や組織の酸素濃度に依存するという性質も同様と考えられている．一方，高LET放射線である重粒子線の生物作用は密な電離による直接作用（ラジカルを介さないDNA 2本鎖切断）が主体であるため，生物学的効果はRBEがX線・ガンマ線，陽子線と比べ2～3倍と高く，また，細胞周期や組織酸素濃度への依存性も低い[2)3)]．つまり，重粒子線治療では，従来の放射線治療では問題となっていた，がんの組織型や細胞周期，酸素濃度などの放射線感受性を規定する様々の因子に影響を受けにくいという大きなメリットがある．これらの生物学的特徴は1回照射や少分割照射を行う上でも非常に有利であり，治療期間の短縮にも寄与している．

3．治療の実際

重粒子線治療の方法を紹介する．もちろん，単に加速器で重粒子を加速し照射室に導くだけでは治療はできない．つまり実際の臨床においては，加速された単一エネルギーの重粒子線を病巣（腫瘍）の大きさ，形状および深さに応じて加工し照射する必要がある．これは照射野形成と呼ばれている．現在，標準的に行われている方法はパッシブ照射法（ワブラー法，散乱体法とも呼ばれる）という方法で，細いビームを電磁石や散乱体で広げ，様々なフィルターを通して照射する方法である．具体的には，ワブラー電磁石および散乱体により主に横方向にビームを広げた後，楔状の形をしたリッジフィルターを通過させることで深さ方向に拡大したブラッグ・ピーク（拡大ブラッグ・ピーク spread out Bragg peak：SOBP）を作り，更に，レンジシフターにてビームが届く距離を調節した後，マルチリーフコリメーターで広がったビームを腫瘍の形状に合わせ，最終的には，ボーラスという水等価物質でできた吸収体を通して腫瘍の遠位部の形に一致させて停止させる（図2）．もちろん，実際の標的体積は微視的ながん細胞の浸潤やセットアップ誤差などを加味して設定される．これら標的体積の設定や照射パラメーターの設定は，事前に治療計画CTを撮像し，線量分布の計算，標的体積やリスク臓器への線量評価等を含めて3次元治療計画コンピューターを用いて行われ，更に，実際に患者毎・照射野毎に測定されコンピューターによる計算に間違いがないかが確認された後に初めて治療が実施される．

重粒子線治療に限らず，高精度の放射線治療を行う上で重要な因子の1つが照射位置の再現性の確保である．特に重粒子線治療は線量分布がシャープ（標的体積辺縁部付近での線量勾配が急峻）であるため，

通常の放射線治療にも増して高い照射位置の再現性が要求される．その為，治療中の患者の動きを防止するために熱可塑性プラスチックを用いた患者固定とX線画像を用いた毎回の照射位置確認と微調整を行うシステム（画像誘導放射線治療システム）が必須である．また，体幹部病変の治療においては，呼吸による腫瘍の動きが問題となるため，呼吸に同期をかけて照射する「呼吸同期照射」という照射技術も必須となる．

4．重粒子線治療が有効な腫瘍

重粒子線治療は，その良好な線量分布と高い生物学的効果により，従来のX線やガンマ線を用いた治療では放射線抵抗性とされていた骨軟部肉腫，頭頸部の粘膜悪性黒色腫や腺癌系腫瘍，直腸癌の術後骨盤内再発などの難治性がんに対して良好な治療効果が得られることが臨床上も明らかとなった．これらの疾患で切除困難な場合には重粒子線治療の適応を優先して検討すべきと考えられている．また，脊索腫などの頭蓋底部腫瘍でも極めて高い局所制御が得られている．その他，肺癌，肝臓癌，前立腺癌などの一般的ながんでも，高い治療効果と安全性を維持しつつ，より短期間で治療できることが明らかとなっている．図3に，1994年6月から2011年7月までに放射線医学総合研究所・重粒子医科学センター病院にて治療が行われた症例数と疾患別内訳を示す．既に6000例を超える症例の治療が実施され，現在では年間700例近い症例の治療が実施されている．また，本治療法は2003年に現在の先進医療にあたる高度先進医療としての承認を受けており，先進医療として実施された症例も3000例を超えている．内訳では，前立腺が最も多く，次いで，骨軟部腫瘍，頭頸部，肺，肝臓，直腸癌術後再発の順となっており，これらで全体の約70%を占める．最近では，膵臓癌，術後のリンパ節転移（単発・少数個転移）などへも有効であることがわかってきており症例も増加傾向にある．

逆に，重粒子線治療が適応とならないものとしては，不規則なぜん動がある胃や小腸・大腸の腫瘍，血液腫瘍，全身に拡がった転移性腫瘍などである．

5．各疾患の治療成績

1）頭頸部・頭蓋底腫瘍

従来の放射線に抵抗性を示す腺癌系腫瘍や悪性黒色腫，頭頸部原発の肉腫，手術の困難な頭蓋底腫瘍などに対して高い治療効果が示されている．腺癌系腫瘍および悪性黒色腫に対して57.6～64.0GyE/16回/4週法の治療が行われた第II相試験では，5年局所制御率は腺癌79%，腺様嚢胞癌で81%，悪性黒色腫で78%と良好な長期局所制御が得られている[4)5)]．悪性黒色腫に関しては遠隔転移が高頻度に見られ，5年生存率36%と高い局所制御率に見合った生存率の向上が得られなかったことから[6)]，2001年から化学療法（DAV療法：DTIC，ACNU，VCR）との併用治療が開始され，5年生存率64%と生存率の向上がみられている[5)]．頭頸部領域の肉腫に対しては70.4GyE/16回/4週法程度のより高い線量が必要ではあるが，3年局所制御率92%，生存率74%と良好な治療成績が報告されている[7)]．頭蓋底部脊索腫に対する治療成績も良好で，48.0-60.8GyE/16回/4週法のI/II相試験では5年局所制御率85%，生存率88%，現在用いられている60.8GyE/16回/4週法に限っては5年局所制御率95-100%，生存率90-95%と報告されている[5)8)]．

2）非小細胞肺癌

局所進行期肺癌や中枢側I期肺癌などに対する治療も行われているが，ここでは最もエビデンスがある末梢型I期非小細胞肺癌に対して述べる．初期は18回照射や9回照射が行われていたが，近年，照射回数を更に減らした短期照射の有効性と安全性が確認されている．先進医療としてはT1（≤ 3 cm）：52.8GyE，T2（＞3 cm）：60.0GyEの4回/1週法が行われており，5年局所制御率90%（T1：98%，T2：80%），5年原病生存率68%，問題となる晩期有害反応もなく，良好な治療成績が報告されている[9)10)]．更に，究極の短期照射として1日で治療が終了する1回照射法による臨床試験が進行中である．28.0GyEか