Patient outcomes of monotherapy with hypofractionated three-dimensional conformal radiation therapy for stage T2 or T3 non-small cell lung cancer: a retrospective study

日本大学医学部放射線医学系放射線医学分野

坂口　雅州

申請年　2017 年

指導教員　天野　康雄

Sakaguchi et al. Radiation Oncology (2016) 11:3
DOI 10.1186/s13014-016-0582-1

Radiation Oncology

RESEARCH Open Access

Patient outcomes of monotherapy with hypofractionated three-dimensional conformal radiation therapy for stage T2 or T3 non-small cell lung cancer: a retrospective study

Masakuni Sakaguchi[1*], Toshiya Maebayashi[1], Takuya Aizawa[1], Naoya Ishibashi[1], Shoko Fukushima[1], Osamu Abe[1] and Tsutomu Saito[2]

Abstract

Background: Hypofractionated three-dimensional conformal radiation therapy (3D-CRT) is a treatment option for patients with early-stage non-small cell lung cancer (NSCLC) who are medically unable to tolerate surgery and who are not amenable to treatment with stereotactic body radiotherapy. This study assessed the efficacy and safety of 3D-CRT as a monotherapy in patients with localized stage T2 or T3 NSCLC.

Methods: This retrospective study consisted of 29 patients (20 males) aged 56–89 years (median, 76 years) with histologically confirmed NSCLC who underwent 3D-CRT between 2005 and 2014.

Results: The median duration of patient observation was 17.0 months (range, 1.0–64.0 months). Complete and partial responses occurred in 13.8 and 44.8 % of patients, respectively, and the overall response rate was 58.2 %. Meanwhile, the 1- and 3-year survival rates were 65.8 and 33.8 %, respectively. In T2 NSCLC, the median survival time (MST) was 12 months, and the 1- and 3-year survival rates were 62.4 and 21.4 %, respectively. In T3 NSCLC, the MST was 17 months, and the 1- and 3-year survival rates were 72.9 and 48.6 %, respectively. Severe toxicities (Common Terminology Criteria Grade 3) were not observed. The mean biologically effective dose required to improve local control exceeded 80 Gy (range, 67.2–96.0 Gy).

Conclusion: These findings support a role for 3D-CRT as a treatment option for patients who refuse or could not tolerate surgical therapy with early-stage NSCLC. Although this was a small, retrospective study, it may form the basis for future, larger controlled studies on 3D-CRT as a monotherapy for NSCLC.

Keywords: NSCLC, Radiation therapy, 3D-CRT, Radiotherapy

Introduction

Three-dimensional conformal radiation therapy (3D-CRT) delivers radiation to tumors while sparing surrounding normal tissue structures. The use of patient-specific 3D images allows for treatment planning in a manner that is distinct from conventional radiotherapy techniques. The complementary use of computed tomography (CT) and magnetic resonance imaging (MRI) of the lungs is performed to define the area of lung tumors. Identifying areas of tumor and normal lung tissue allows for selective and concentrated radiation therapy with less damage to normal lung tissue. Surgical resection is one treatment method for localized non-small cell lung cancer (NSCLC), and good outcomes are achieved with this method in stage I or II NSCLC [1–3]. While surgery is recommended for some patients with localized NSCLC, the proportion of operable patients declines with age [4, 5]. Radiation therapy is selected if pulmonary function is poor, if surgery is

* Correspondence: sakaguchi.masakuni@nihon-u.ac.jp
[1]Department of Radiology, Nihon University School of Medicine, 30-1, Oyaguchi Kami-cho, Itabashi-ku, Tokyo 173-8610, Japan
Full list of author information is available at the end of the article

contraindicated due to the patient's general condition, or if the patient refuses surgery. However, satisfactory results for patients with localized NSCLC have not been obtained with conventional irradiation at a dose of 2 Gy given in a single fraction [6–9]. In conventional radiation therapy, therapeutic effects are obtained on the basis of differences in the degrees of damage and recovery between normal and cancer cells. Damage to normal cells can be reduced by employing this irradiation method. Also, the treatment duration is prolonged to increase the dose, which may increase the risk of tumor regrowth. Further drawbacks include a low single radiation dose that reduces the antitumor effects and changes in the characteristics of cancer cells, especially their sensitivity to radiation, when the treatment duration is prolonged. For this reason, the duration of radiation treatment should be kept short, and the radiation dose should be increased for improved tumor control. Stereotactic body radiotherapy (SBRT) has also been established as a treatment option for localized NSCLC [10, 11]. SBRT results in improved patient outcomes compared with conventional irradiation, with results that rival surgery [12–14]. However, SBRT requires greater precision and accuracy than conventional radiotherapy, and it should be conducted according to a strict protocol [15]. Furthermore, patient characteristics such as tumor size, site, and general physical condition can make performing SBRT difficult. In such instances, hypofractionated 3D-CRT is an alternative treatment option [16, 17]. Some studies of hypofractionated radiotherapy (HFRT) using various radiation dose schedules have reported improved outcomes beyond those achieved with conventionally fractionated radiotherapy [16–19]. High-dose irradiation with a biologically effective dose (BED) of 100 Gy or more enables good localized disease control in SBRT, and thus, it may be assumed that not necessarily a mere increase in the total radiation dose, but increasing the BED as well will also lead to good localized control in 3D-CRT [12]. Previous reports indicated that when the radiation dose is increased to 4 Gy delivered in a single fraction, there are no severe adverse events and good localized control can be achieved [20]. There are few reports that describe 3D-CRT to treat patients with localized NSCLC without the use of combined anticancer agents. At our institution, we have recently administered radiation treatment to patients with stage T2 or T3 NSCLC, in whom we increased the radiation dose to more than 5 Gy delivered in a single fraction. In these patients, the radiation field is defined as the tumor plus margin, and the use of 3D-CRT is limited to patients for whom elective nodal irradiation was not conducted. This study investigated the safety and efficacy of 3D-CRT as a monotherapy in patients with T2 or T3 localized NSCLC and examined the factors influencing patient prognosis.

Methods

Patients studied

This retrospective study included 29 patients (20 males) aged 56–89 years (median, 76 years) with histologically confirmed NSCLC who received hypofractionated 3D-CRT between January 2005 and June 2014. Patients with severe heart and lung disease who required regular oxygen treatment were excluded. SBRT was indicated for patients with peripheral lung malignancies measuring 3 cm or less with a forced expiratory volume $(FEV)_{1.0}$ of 800 ml or more and a performance status (PS) of 0 to 1 and also for patients with lung cancer located 2 cm or more from the great vessels in the hilar region. Although there was no strict age limit, a cut-off of 85 years was used as the upper age limit for patients with PS 2. Even in patients who met the indications for SBRT, 3D-CRT was selected when they could not adequately synchronize respiration because lesions were located in the lower pulmonary lobes and there was marked fluctuation.

When postoperative $FEV_{1.0}$ was expected to be 800 ml or more, surgery was indicated in patients with PS 0 to 1 and localized lung cancer without complications. Although combination treatment with anticancer agents and radiation was the standard of care even for patients lacking indications for SBRT or surgery, the most common reason for selecting radiotherapy alone was renal impairment, followed by patient refusal and poor PS.

Staging investigations

Staging was performed using contrast-enhanced CT and positron emission tomography (PET), according to the recommendations of the current staging guidelines for NSCLC [21]. Tumors located no more than 2 cm from the pulmonary hilum were classified as the pulmonary hilum type. In seven patients, staging was performed using contrast-enhanced CT without PET. In addition to standard blood tests, the presence of NSCLC tumor markers was assessed, including monoclonal antibodies to squamous cell carcinoma antigen, carcinoembryonic antigen, and CYFRA 21.1 (a variant of cytokeratin 19) [22]. Radiography of the chest, MRI of the brain, and bone scintigraphy were performed. Staging, therapeutic effect, and the presence or absence of recurrence were determined by a radiologist, a respiratory medicine specialist, and a radiotherapist.

Radiation therapy

The treatment plan was performed with CT using a long scan time (3 s). Tumor motion was accounted once at the time of CT simulation. Scans were assessed in 3-mm sections at the lesion site and 10-mm sections elsewhere. The gross tumor volume was the volume of the area occupied by the tumor as measured by image diagnosis.

However, because a long scan time was used, the clinical target volume (CTV) was used to define the visible range of CT. The internal target volume (ITV) was the CTV plus the tumor margin for any organ movement. The ITV included a 5–7 mm 'set up' margin to establish the planning target volume (PTV). The radiation field was defined as the PTV plus a 5-mm leaf margin. Using a 6-MV X-ray beam, multifield irradiation to more than four fields (all noncoplanar irradiation) was administered under resting respiration. Each beam was created using PTV along the path of the beam with a margin. Additional techniques (for example field-in-field) were not used. Intensity-modulated radiotherapy (IMRT) was not used because our institution has no established policy of applying this treatment modality in patients with lung cancer. IMRT is not available in all institutions and is used for lung cancer only at a limited number of institutions. As 3D-CRT is an alternative treatment option for patients who are not suitable candidates for SBRT, it is reasonable to perform 3D-CRT at hospitals where SBRT, including IMRT, is not available. Thus, we believe that presenting data based on conventional 3D-CRT is both important and clinically relevant. The superposition method for the algorithm was used to calculate the irradiation dose. The minimum and maximum doses according to the PTV were 95 and 107 %, respectively (in the case of a large PTV, delivering a minimum dose of 90 % was acceptable). Elective nodal irradiation was not adopted for all patients. More recently, as long as no respiratory disturbance is present, irradiation is administered in our center in a single fraction at a total dose of more than 5 Gy, irrespective of tumor site and size.

Evaluation of the initial clinical response and toxicity

All patients underwent routine X-ray imaging and tests for serological tumor markers at 1 month after radiotherapy and every 3 months thereafter. In the event of poor X-ray results and positive tumor markers, a lung CT was performed. Routine lung CT was performed every 3–6 months following the completion of radiation therapy. A complete response (CR) was defined as the disappearance of all measurable disease and the absence of newly-developing lesions for 4 weeks. For measurable disease, a partial response (PR) was defined as a reduction in more than 30 % of the sum of the cross-sectional diameters of all measurable lesions over 4 weeks. Progressive disease (PD) was defined as either an increase of greater than 20 % of the sum of the cross-sectional diameters of all assessable lesions in 4 weeks or the appearance of new lesions. Stable disease (SD) was determined when there was an insufficient increase in tumor size to qualify as PD. SD also included the situation in which a tumor decreased in size enough to no longer meet the definition of PD. Responses were scored when the treatment was most effective. Local recurrence was defined as changes similar to those of PD. When tumor growth was difficult to assess because of radiation pneumonitis, tumor markers measured each month were used as reference values, and the date of recurrence was determined as the first day when levels began to rise. Adverse events were defined according to the Common Terminology Criteria (CTC) for Adverse Events, version 4.0, with toxicity graded as mild (CTC Grade 1), moderate (CTC Grade 2), severe (CTC Grade 3), or life-threatening (CTC Grade 4) [23].

Statistical analysis

Overall survival was calculated as the interval from the first day of treatment to the date of death or the last follow-up before June 2014. If they reach the end of the following period without having an event, patients were censored. Local tumor control (LC) was calculated as the period from the first day of treatment until local relapse. Patients who died with no evidence of recurrence were censored. Survival curves were generated using Kaplan–Meier analysis. Univariate survival comparisons were performed using the log-rank test. The analyzed prognostic factors for survival were age (<75 vs. ≥75), PS (≤1 vs. ≥2), T-stage (T2 vs. T3), location (lower lobe vs. middle and upper lobes, near the pulmonary hilum vs. peripheral), and pathology (squamous vs. adeno). Independent variables that appeared statistically significant on univariate analysis were tested by multivariate analysis. $P < 0.05$ indicated statistical significance. All calculations and survival displays were conducted using SPSS 15.0 J statistical software (SSPS Inc., Chicago, IL, USA).

Patient consent

The present study was a retrospective analysis of patient diagnostic and treatment data. Written informed consent was obtained from all patients, who were informed that their data would be included in the study.

Results

Patient and treatment characteristics

Baseline patient characteristics are listed in Table 1. Stage T2a NSCLC was present in 18 patients, whereas nine patients were diagnosed with stage T3 disease (thoracic invasion in eight patients and additional tumor nodules in the same pulmonary lobe in one patient). SBRT was proactively performed in most patients with stage T1 disease, and these patients were not included in the present study. The median tumor diameter was 31 mm (range, 25–60 mm) in T2 cancer and 42 mm (range, 26–60 mm) in T3 cancer. Tumors near the hilum, i.e., those defined as being located within 2 cm from the pulmonary hilum, were detected

Table 1 Clinical characteristics of patients

Characteristics		Number
Patients		29
Age, median (range)		76 (56–89)
<75		
≥75		
Gender		
	male	20
	female	9
PS		
	0	2
	1	22
	2	5
T-stage		
	T2a	18
	T2b	2
	T3	9
Location of the tumor 1		
	lower lobe	11
	middle, upper lobe	18
Location of the tumor 2		
	near the pulmonary hilum	8
	Peripheral	21
Pathology		
	squamous carcinoma	17
	adenocarcinoma	12
Dose (Gy), median (range)		60 (48–60)
	48Gy, 3Gy/f	1
	50Gy, 5Gy/f	3
	54Gy, 6Gy/f or 3Gy	2
	60Gy, 3Gy/f	2
	60Gy, 4Gy/f	8
	60Gy, 5Gy/f	10
	60Gy, 6Gy/f	3
BED (Gy), median (range)		84 (67.2-90)
	<80 Gy	14
	≥80 Gy	15
Fraction size (Gy)		
	3	7
	4	5
	5	15
	6	2
Chemotherapy		
TS-1	neoadjuvant	1
	concurrent	1
	adjuvant	1
UFT	concurrent	1

Abbreviations: *BED* biological effective dose

in 8 patients. Tumors growing in the lower lobes were found in 11 patients. Dose fractionation was higher in the most recent cases, with the highest dosage of 6 Gy per fraction administered to two patients. The most common dose was 5 Gy per fraction, administered to 15 patients. The treatment was given in three fractions per week in one patient because of the patient's general condition, and all other patients received conventional radiotherapy administered in a single fraction per day. No patients underwent accelerated HFRT. To compare the effects of different protocols with different fraction sizes and total doses, the BED was adopted using a linear quadratic model. The α/β ratio was assumed to be 10 for acute effects on normal tissue and lung tumors. The BED ranged from 67.2 to 96.0 Gy. The median BED was approximately 80 Gy. When 80 Gy was used as a cut-off value, BED was less than 80 Gy in 14 patients and more than 80 Gy in 15 patients.

Patient survival, response, and tumor recurrence

The median duration of observation was 17 months (range, 1–64 months). CRs and PRs were recorded in four (13.8 %) and 13 patients (44.8 %), respectively. SD occurred in four patients (13.8 %), and PD occurred in eight patients (27.6 %). The overall response rate was 58.6 %. The 1- and 3-year overall survival rates were 65.8 and 33.8 %, respectively (Fig. 1). There was no significant difference in OS between patients with T2 and

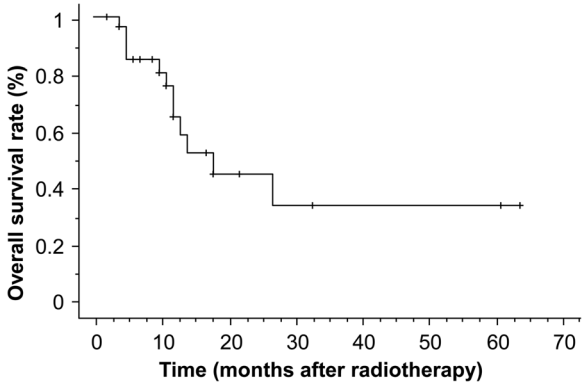


Fig. 1 The median survival time following radiotherapy with three-dimensional conformal radiation therapy was 17 months (range, 1–64 months), and the estimated 3-year survival rate was 38 %

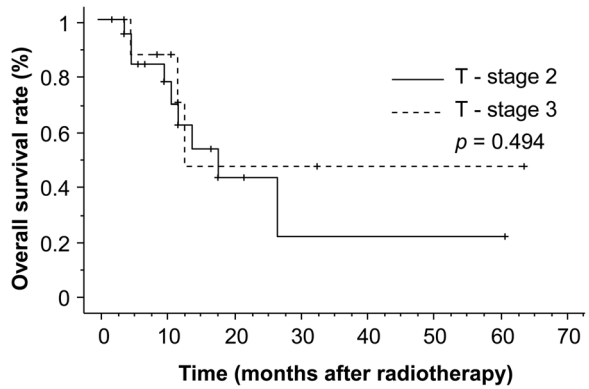


Fig. 2 Comparison of overall survival (OS) from radiotherapy with three-dimensional conformal radiation therapy. There was no significant difference in OS between patients with T2 and T3 non-small cell lung cancer

T3 (Fig. 2). The 1- and 3-year survival rates and prognostic factors identified by univariate analysis are listed in Table 2. However, there were no significant differences observed for any factors. During the follow-up, 11 patients died. The causes of death were primary disease in seven patients, brain metastasis in two, other diseases in two, and unknown in one. The 1- and 3-year cause-specific survival rate was 77.3 % and 49.7 %, respectively. Local tumor recurrence was observed in eight patients (two patients' imaging evaluation was difficult due to radiation pneumonitis, and local recurrence was identified by elevated tumor markers without metastasis to other sites) and the 1-year LC rate was 66.1 %. Upon univariate analysis, the BED (≥80 Gy vs. <80 Gy) and performance status (≤1 vs. ≥2) were significantly related to LC. Figures 3 and 4 illustrate the LC curves for NSCLC for each patient group. Upon multivariate analysis, only BED was a significant factor for LC ($P = 0.037$; hazard ratio = 10.10; 95 % confidence interval = 1.150–88.67) (Table 3).

Table 2 Univariate analysis to identify factors that affect survival and 1- and 3-year overall survival rates

Variables	*p* value	1-year	3-year
Age			
<75	0.958	58.3 %	38.9 %
≥75		70.3 %	35.2 %
PS			
≤1	0.163	70.5 %	45.7 %
≥2		33.3 %	–
T-stage			
T2	0.494	62.4 %	21.4 %
T3		72.9 %	48.6 %
Location 1			
Lower lobe	0.250	39.4 %	19.7 %
Middle and upper lobe		81.9 %	19.0 %
Location 2			
Near the pulmonary hilum	0.235	75.0 %	75.0 %
Peripheral		61.2 %	17.5 %
Pathology			
Squamous	0.728	61.4 %	28.1 %
Adeno		79.5 %	53.0 %
BED (Gy)			
<80 Gy	0.087	55.9 %	–
≥80 Gy		76.2 %	63.5 %

Abbreviations: *BED* biological effective dose

Radiation toxicity

Among acute toxicities, grade 1 pneumonitis was observed in three patients who received irradiation at a BED of 80 Gy or more and in two patients with a BED of less than 80 Gy. No patient was given oral steroid treatment or oxygen therapy. No patient developed esophagitis or macrovascular disease. No severe adverse events were observed.

Discussion

This retrospective study was performed to investigate a possible a role for 3D-CRT as a monotherapy for patients who refuse or could not tolerate surgical therapy with early-stage NSCLC. In this initial study, the 1-year survival rate for patients was 65.8 %, and the 3-year survival rate was 33.8 %. A significant difference in LC was observed with a BED of 80 Gy or more, and the side effects were deemed acceptable. Currently, surgery is the main treatment method for localized NSCLC, and it has achieved favorable outcomes. The Japanese Joint Committee of Lung Cancer Registry investigated prognosis in 6644 patients who underwent resection for NSCLC by

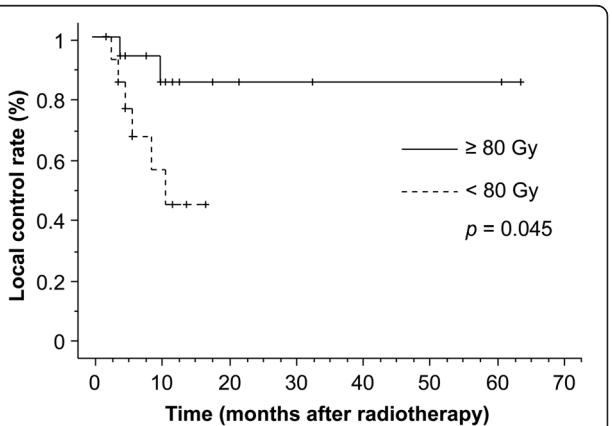


Fig. 3 Comparison of local control from radiotherapy with three-dimensional conformal radiation therapy. There was a significant difference between patients who received a dose of <80 Gy and those treated with a dose of ≥80 Gy ($P = 0.045$)

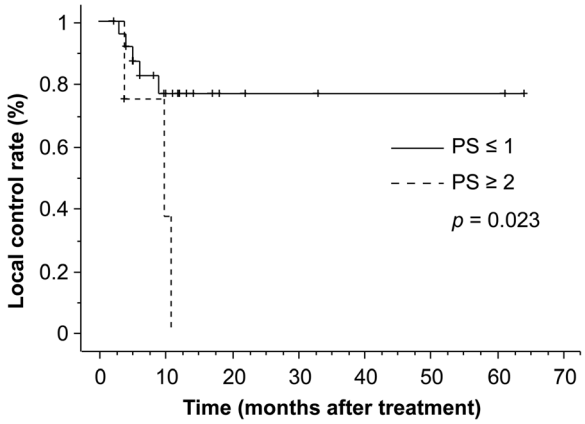


Fig. 4 Comparison of local tumor control (LC) from radiotherapy with three-dimensional conformal radiation therapy. There was a significant difference in LC between patients with a performance status (PS) of ≤1 and those with a PS of ≥2 ($P = 0.023$)

histologic type [24]. The 5-year survival rates for patients with clinical stages 1A and 1B NSCLC were 72 and 50 %, respectively. The 3-year survival rates for those with clinical Stages 1A and 1B were 82 and 63 %, respectively [24]. However, a limited number of patients have operable early-stage tumors, and elderly patients are at high risk from complications of surgery. The high long-term costs of surgery and postoperative care justify radiotherapy as a minimally invasive alternative treatment in NSCLC [4]. In our study, the 3D-CRT outcomes for survival was below what would be expected for potentially curative surgery, but none the less, represent an alternative to patients that lack a surgical option.

Table 3 Univariate and multivariate analysis of factors that affect local control (LC)

Variables	*p* value	Multivariate analysis		
		HR	95%CI	*p*
Age (years)	0.333	0.893	0.125–6.393	0.910
<75 vs. ≥75				
PS	0.023	9.773	0.778–122.7	0.077
≤1 vs. ≥2				
T-stage	0.700	0.212	0.017–2.671	0.230
T2 vs. T3				
Location 1	0.966	6.992	0.956–51.16	0.055
Lower lobe vs. middle and upper lobe				
Location 2	0.330	2.102	0.140–31.55	0.591
Near the pulmonary hilum vs. peripheral				
Pathology	0.505	0.303	0.034–2.680	0.283
Squamous vs. adeno				
BED (Gy)	0.045	10.10	1.150–88.67	0.037
<80 Gy vs. ≥80 Gy				

Abbreviations: *BED* biologically effective dose

Conventional methods of administering radiation at a dose of 1.8 or 2 Gy in a single fraction for a total of 60 to 66 Gy results in an LC rate of 50 % and a 3-year survival rate of 20 to 30 %, representing unsatisfactory outcomes [6–9]. Increasing the dosage prolongs the treatment period, which in turn results in increased patient burden and medical costs. Recent improvements in radiation therapy techniques have led to the widespread popularity of SBRT as an alternative therapy to radical surgery in NSCLC. In a recent systematic review, the 5-year survival rate in patients undergoing SBRT was estimated at 47 % (range, 18–78 %) and the LC rate was 80–100 % [25]. In patients with early-stage NSCLC, it is currently possible to achieve results comparable to those of surgery [13]. Thus, SBRT should be considered for patients with localized NSCLC who are inoperable. SBRT requires greater precision and accuracy than conventional HFRT and 3D-CRT, and it must be performed using a strict protocol that may not be available in all institutions [15]. A recent survey conducted in Japan reported that 44 % of replying institutions did not utilize SBRT [26]. SBRT can be deemed difficult due to varying patient factors, such as when stable respiration is not possible, when the tumor is close to major blood vessels or the hilar region, when respiratory function is poor, and when the patient is in poor general condition. In such instances, 3D-CRT could be an alternative treatment option. Despite the potential role for 3D-CRT in the treatment of NSCLC, there have been few treatment outcome studies. Past reports indicate that the radiation field varies from a field encompassing the tumor plus margin to a field in which elective nodal irradiation is performed, and irradiation techniques and schedules differ between reports [27]. Patients with T2 or T3 NSCLC have a higher incidence of lymph node metastasis, and therefore, many receive concurrent anticancer agents. Thus, irradiation monotherapy is limited to patients with T2 or T3 cancer without lymph node metastasis, and the irradiation field involves the tumor site only. At our institution, a total of 525 patients received radiotherapy for primary lung cancer during the observation period of January 2005 to June 2014. Of these patients, 29 with T2 or T3 localized lung cancer (approximately 5.5 %) underwent 3D-CRT monotherapy with the irradiation field set as the tumor plus tumor margin only. We believe that the results of the present study provide valuable data for future 3D-CRT treatment strategies. In the present study, the 3-year survival period following 3D-CRT for localized lung cancer was comparable with, or better than, those of previous reports [6, 8, 28]. This may be attributed to the difference in radiation distribution. Previous reports described irradiation performed with three

to five portals, whereas more than five irradiation portals are used at our institution [6, 8, 28]. The relatively small tumor size in the present study may also have contributed to the findings, with a T staging of T2a in 18 patients and T2b in two patients. Another reason for the findings in this study could be that patients who underwent thorough staging by PET were included. The reason that no difference in survival was observed between T2 and T3 patients is believed to be comparable median tumor diameter in the two groups of patients (T3, 42 mm and T2, 31 mm). It has been reported that patients with T2a (stage IB) disease who underwent SBRT had a 3-year survival rate of 63 % [29]. Based on our results, 3D-CRT appeared to have inferior outcomes to SBRT in patients with early-stage NSCLC. Thus, one conclusion of this present study is that although 3D-CRT may be a second treatment option for patients with early-stage NSCLC who are unable to undergo SBRT, it may not be an alternative treatment. A Japanese multi-institutional, retrospective survey revealed that a BED greater than 100 Gy resulted in significantly improved patient survival and LC than a BED of less than 100 Gy when SBRT was used to control stage I NSCLC [12]. Concerning BED, a radiation dose exceeding 100 Gy resulted in different control rates in T1 and T2 disease, whereas in the event of T2 lung tumors, a BED greater than 120 Gy was required [12]. In this study, LC was significantly improved in patients administered a BED of 80 Gy (range, 67.2–96.0 Gy). Previous reports of the use of 3D-CRT described treatment with a 3–3.5-Gy single fraction [16, 19]. More recently, it has been reported that good LC has been achieved with irradiation using a single 4-Gy fraction, and adverse events were within permissible ranges [20]. The total dosage is also reported to be an important factor [30]. This study has demonstrated that a BED greater than 80 Gy is an independent and significant prognostic factor in LC, using a linear-quadratic model and an α/β ratio of 10 to determine the acute effect on tumor and normal tissues. In a previous study using conventional fractionation, improved local PFS was observed in a subgroup of patients with no nodal disease who were receiving >73 Gy during 3D-CRT [30]. The LC rate in the present study is believed to be comparable with these earlier results. It has previously been reported that radiotherapy toxicities of CTC Grades 3–5 develop in 20 % of patients receiving SBRT with a single fraction that exceeds 20 Gy [31]. This same study concluded that the regimen should not be used for patients with tumors near the central airways because of excessive radiation toxicity [31]. Even for SBRT using approximately 12 Gy delivered in a single fraction, a tumor located near a major vessel or serial organ poses a concern for the occurrence of adverse events. In the present study, no severe adverse events (CTC Grade 2 or more) were observed with 3D-CRT and with irradiation given at a BED of more than 80 Gy. A previous report supports these findings, showing that no severe adverse events developed in 3D-CRT with a BED over 90 Gy [19]. The results of this study support the view that to improve LC in early-stage NSCLC, if the patient's respiratory function and general physical condition allow, the dose per fraction should be increased, and if possible, the BED should exceed 80 Gy. Furthermore, because this study has confirmed that there are no severe radiation toxicities associated with this regimen, it is possible that the dosage may be increased further. This consideration and other aspects of the role of 3D-CRT as monotherapy in early-stage NSCLC require investigation in further controlled studies with larger patient numbers. Because of current advances in therapy for NSCLC, as well as the increasing numbers of patients treated with combined anticancer agents, the number of patients receiving 3D-CRT within one center will be limited.

Our study limitations include lack of long-term follow up and small number of patients, because of which the results of multivariate analysis were unclear. This limitation may be addressed in the future by studies involving multiple centers in multiple countries.

Conclusions

The retrospective nature of this study and small number of patients who were available within a single center do not detract from the value of these preliminary findings. This study has demonstrated that 3D-CRT may be used as a monotherapy for patients with T2 or T3 NSCLC as a second treatment option for patients unable to receive SBRT. Although the therapeutic efficacy outcomes in this small study were inferior to those reported for SBRT, the safety outcomes were comparable. Furthermore, to improve LC in early-stage NSCLC, this study found that the BED should exceed 80 Gy, and it is possible that this dosage could be increased even further. These findings support a role for 3D-CRT as a treatment option for patients who refuse or could not tolerate surgical therapy with early-stage NSCLC, and they may form the basis for future, larger controlled studies on 3D-CRT as a monotherapy option for early-stage NSCLC.

Abbreviations

BED: Biologically effective dose; CTC: Common Terminology Criteria; CR: Complete response; CT: Computed tomography; CTV: Clinical target volume; HFRT: Hypofractionated radiotherapy; ITV: Internal target volume; MRI: Magnetic resonance imaging; MST: Median survival time; NSCLC: Non-small cell lung cancer; PET: Positron emission tomography; PR: Partial response; PTV: Planning target volume; SD: Stable disease; SBRT: Stereotactic body radiotherapy; 3D-CRT: Three-dimensional conformal radiation therapy.

Competing interests

The authors declare that they have no competing interest.

Authors' contributions
MS collected data and drafted the manuscript. OA evaluated Xp and CT data for staging. MS, TM, TA, NI, SF, and TS examined the patients, and MS, TM, and NI planned and administered the radiation therapy. All authors read and approved the final manuscript.

Author details
[1]Department of Radiology, Nihon University School of Medicine, 30-1, Oyaguchi Kami-cho, Itabashi-ku, Tokyo 173-8610, Japan. [2]Sonodakai Radiation Oncology Clinic, 4-1-12, Takenotsuka, Adachi-ku, Tokyo 121-0813, Japan.

Received: 24 June 2015 Accepted: 5 January 2016
Published online: 19 January 2016

References

1. Scott WJ, Howington J, Feigenberg S, Movsas B, Pisters K, American College of Chest Physicians. Treatment of non-small cell lung cancer stage I and stage II: ACCP evidence-based clinical practice guidelines (2nd edition). Chest. 2007;132:234–42.
2. Mountain CF. A new international staging system for lung cancer. Chest. 1986;89:225S233.
3. Dominioni L, Imperatori A, Rovera F, Ochetti A, Torrigiotti G, Paolucci M. Stage I non small cell lung carcinoma: analysis of survival and implications for screening. Cancer. 2000;89(11 Suppl):2334–44.
4. Haasbeek CJ, Lagerwaard FJ, Antonisse ME, Slotman BJ, Senan S. Stage I nonsmall cell lung cancer in patients aged > or =75 years: outcomes after stereotactic radiotherapy. Cancer. 2010;116:406–14.
5. Brown JS, Eraut D, Trask C, Davison AG. Age and the treatment of lung cancer. Thorax. 1996;51:564–8.
6. Kołodziejczyk M, Kępka L, Tyc-Szczepaniak D, Wierzchowski M. Outcome of three-dimensional conformal radiotherapy for early stage non-small cell lung cancer patients who met or not inclusion criteria for stereotactic-body radiation therapy. Pneumonol Alergol Pol. 2011;79:326–36.
7. Qiao X, Tullgren O, Lax I, Sirzén F, Lewensohn R. The role of radiotherapy in treatment of stage I non-small cell lung cancer. Lung Cancer. 2003;41:1–11.
8. Dosoretz DE, Katin MJ, Blitzer PH, Rubenstein JH, Galmarini DH, Garton GR, et al. Medically inoperable lung carcinoma: the role of radiation therapy. Semin Radiat Oncol. 1996;6:98–104.
9. Kaskowitz L, Graham MV, Emami B, Halverson KJ, Rush C. Radiation therapy alone for stage I non-small cell lung cancer. Int J Radiat Oncol Biol Phys. 1993;27:517–23.
10. Kim SS, Song SY, Kwak J, Ahn SD, Kim JH, Lee JS, et al. Clinical prognostic factors and grading system for rib fracture following stereotactic body radiation therapy (SBRT) in patients with peripheral lung tumors. Lung Cancer. 2013;79:161–6.
11. Timmerman R, Paulus R, Galvin J, Michalski J, Straube W, Bradley J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA. 2010;303(11):1070–6.
12. Onishi H, Araki T, Shirato H, Nagata Y, Hiraoka M, Gomi K, et al. Stereotactic hypofractionated high-dose irradiation for stage I nonsmall cell lung carcinoma: clinical outcomes in 245 subjects in a Japanese multi-institutional study. Cancer. 2004;101:1623–31.
13. Nagata Y, Takayama K, Matsuo Y, Norihisa Y, Mizowaki T, Sakamoto T, et al. Clinical outcomes of a phase I/II study of 48 Gy of stereotactic body radiotherapy in 4 fractions for primary lung cancer using a stereotactic body frame. Int J Radiat Oncol Biol Phys. 2005;63:1427–31.
14. Uematsu M, Shioda A, Suda A, Fukui T, Ozeki Y, Hama Y, et al. Computed tomography-guided frameless stereotactic radiotherapy for stage I non-small cell lung cancer: a 5-year experience. Int J Radiat Oncol Biol Phys. 2001;51:666–70.
15. Potters L, Kavanagh B, Galvin JM, Hevezi JM, Janjan NA, Larson DA, et al. American Society for Therapeutic Radiology and Oncology; American College of Radiology. American Society for Therapeutic Radiology and Oncology (ASTRO) and American College of Radiology (ACR) practice guideline for the performance of stereotactic body radiation therapy. Int J Radiat Oncol Biol Phys. 2010;76:326–32.
16. Bonfili P, Di Staso M, Gravina GL, Franzese P, Buonopane S, Soldà F, et al. Hypofractionated radical radiotherapy in elderly patients with medically inoperable stage I-II non-small-cell lung cancer. Lung Cancer. 2010;67:81–5.
17. Faria SL, Souhami L, Portelance L, Duclos M, Vuong T, Small D, et al. Absence of toxicity with hypofractionated 3-dimensional radiation therapy for inoperable, early stage non-small cell lung cancer. Radiat Oncol. 2006;1:42.
18. Ahmad E, Sandhu AP, Fuster MM, Messer K, Pu M, Nobiensky P, et al. Hypofractionated radiotherapy as definitive treatment of stage I non-small cell lung cancer in older patients. Am J Clin Oncol. 2011;34:254–8.
19. Thirion P, Holmberg O, Collins CD, O'Shea C, Moriarty M, Pomeroy M, et al. Escalated dose for non-small-cell lung cancer with accelerated hypofractionated three-dimensional conformal radiation therapy. Radiother Oncol. 2004;71:163–6.
20. Cheung PC, Yeung LT, Basrur V, Ung YC, Balogh J, Danjoux CE. Accelerated hypofractionation for early-stage non-small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2002;54:1014–23.
21. Mirsadraee S, Oswal D, Alizadeh Y, Caulo A, van Beek EJ. The 7th lung cancer TNM classification and staging system: Review of the changes and implications. World Journal of Radiology. 2012;4:128–34.
22. Pastor AI, Menendez R, Cremades MJ, Pastor V, Llopis R, Aznar J. Diagnostic value of SCC, CEA and CYFRA 21.1 in lung cancer: a Bayesian analysis. Eur Respir J. 1997;10:603–9.
23. U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE). Version 4.0. May 29th, 2009. http://ctep.cancer.gov/protocalDevelopment/electronic_applications/ctc.htm#CTC_40. Accessed 18th May 2015.
24. Goya T, Asamura H, Yoshimura H, Kato H, Shimokata K, Tsuchiya R, et al. Japanese Joint Committee of Lung Cancer Registry. Prognosis of 6644 resected non-small cell lung cancers in Japan: a Japanese lung cancer registry study. Lung Cancer. 2005;50:227–34.
25. Chi A, Liao Z, Nguyen NP, Xu J, Stea B, Komaki R. Systemic review of the patterns of failure following stereotactic body radiation therapy in early-stage non-small-cell lung cancer: clinical implications. Radiother Oncol. 2010;94:1–11.
26. Nagata Y, Hiraoka M, Mizowaki T, Narita Y, Matsuo Y, Norihisa Y, et al. Survey of stereotactic body radiation therapy in Japan by the Japan 3-D Conformal External Beam Radiotherapy Group. Int J Radiat Oncol Biol Phys. 2009;75:343–7.
27. Jeremic B, Classen J, Bamberg M. Radiotherapy alone in technically operable, medically inoperable, early-stage (I/II) non-small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2002;54:119–30.
28. Lee JH, Wu HG, Kim HJ, Park CI, Lee SH, Kim DW, et al. Hypofractionated three-dimensional conformal radiotherapy for medically inoperable early stage non-small-cell lung cancer. Radiat Oncol J. 2013;31:18–24.
29. Takeda A, Sanuki N, Kunieda E, Ohashi T, Oku Y, Takeda T, et al. Stereotactic body radiotherapy for primary lung cancer at a dose of 50 Gy total in five fractions to the periphery of the planning target volume calculated using a superposition algorithm. Int J Radiat Oncol Biol Phys. 2009;73:442–8.
30. Martel MK, Strawderman M, Hazuka MB, Turrisi AT, Fraass BA, Lichter AS. Volume and dose parameters for survival of non-small cell lung cancer patients. Radiother Oncol. 1997;44:23–9.
31. Timmerman R, McGarry R, Yiannoutsos C, Papiez L, Tudor K, DeLuca J, 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.

非小細胞肺癌の治療法には、ステージに応じて放射線単独治療や手術単独療法、術前後の化学放射線療法、分子標的薬を含めた化学放射線療法がある。治療方針を決定するためのステージングは、Union for International Cancer Control (UICC)による TNM 分類が広く用いられている。肺癌においては第 8 版が新たに報告され、T1 を中心にさらなる細分化がなされたが、それ以前の研究期間の検討には以下に示す第 7 版が広く用いられている。特徴として T 分類は大きさ、もしくは浸潤の程度や気管支との距離により分類がなされている。

1. 非小細胞肺癌のステージ分類

T-原発腫瘍

TX：原発腫瘍の存在が判定できない、あるいは、喀痰または気管支洗浄液細胞診でのみ陽性で画像診断や気管支鏡では観察できない

T0：原発腫瘍を認めない

Tis：上皮内癌（carcinoma in situ）

T1：腫瘍最大径≦30mm、肺か臓側胸膜に覆われている、葉気管支より中枢への浸潤が気管支鏡上なし

T1a：腫瘍最大径≦20mm　T1b：腫瘍最大径＞20mm でかつ≦30mm

T2：腫瘍最大径＞30mm でかつ≦70mm、または以下のいずれかであるもの

・主気管支に及ぶが気管分岐部より≧20mm 離れている

・臓側胸膜に浸潤

・肺門まで連続する無気肺か閉塞性肺炎があるが一側肺全体には及んでいない

T2a：腫瘍最大径＞30mm でかつ≦50mm　T2b：腫瘍最大径＞50mm でかつ≦70mm

T3：最大径＞70 mm の腫瘍；横隔膜、胸壁、横隔膜、横隔神経、縦隔胸膜、壁側心膜のいずれかに直接浸潤；分岐部より 2 cm 未満の主気管支に及ぶが分岐部には及ばない；一側肺に及ぶ無気肺や閉塞性肺炎；同一葉内の不連続な腫瘍結節

T4：大きさを問わず縦隔、心、大血管、気管、反回神経、食道、椎体、気管分岐部への浸潤、あるいは同側の異なった肺葉内の腫瘍結節

N-所属リンパ節

NX：所属リンパ節評価不能

N0：所属リンパ節転移なし

N1：同側の気管支周囲かつ/または同側肺門、肺内リンパ節への転移で原発腫瘍の直接浸潤を含める

N2：同側縦隔かつ/または気管分岐部リンパ節への転移

N3：対側縦隔、対側肺門、同側あるいは対側の前斜角筋、鎖骨上リンパ節への転移

M-遠隔転移

MX：遠隔転移評価不能

M0：遠隔転移なし

M1：遠隔転移がある

M1a：対側肺内の腫瘍結節、胸膜結節、悪性胸水、悪性心嚢水

M1b：他臓器への遠隔転移がある

表 1. 非小細胞肺癌の病期診断

	N0	N1	N2	N3
T1a（≦20mm）	IA	IIA	IIIA	IIIB
T1b（20mm＜, ≦30mm）	IA	IIA	IIIA	IIIB
T2a（30mm＜, ≦50mm）	IB	IIA	IIIA	IIIB
T2b（50mm＜, ≦70mm）	IIA	IIB	IIIA	IIIB
T3（＞70mm）	IIB	IIIA	IIIA	IIIB
T3（胸壁浸潤など）	IIB	IIIA	IIIA	IIIB

ステージングは computed tomography（以下 CT）や positron emission tomography（以下 PET）を用いて行われる。これらの検査でリンパ節転移のない限局型の非小細胞肺癌と判断された場合には、手術や放射線単独治療が考慮される。Stage I, II の治療方針を以下に示す。

2. 非小細胞肺癌、病期Ⅰ期、Ⅱ期の治療法

図 1. 病期Ⅰ期治療のフローチャート

(T1a (≦20mm)または T1b (20mm＜、≦30mm)または T2a (30mm＜、≦50mm)かつリンパ節転移など転移がない症例)

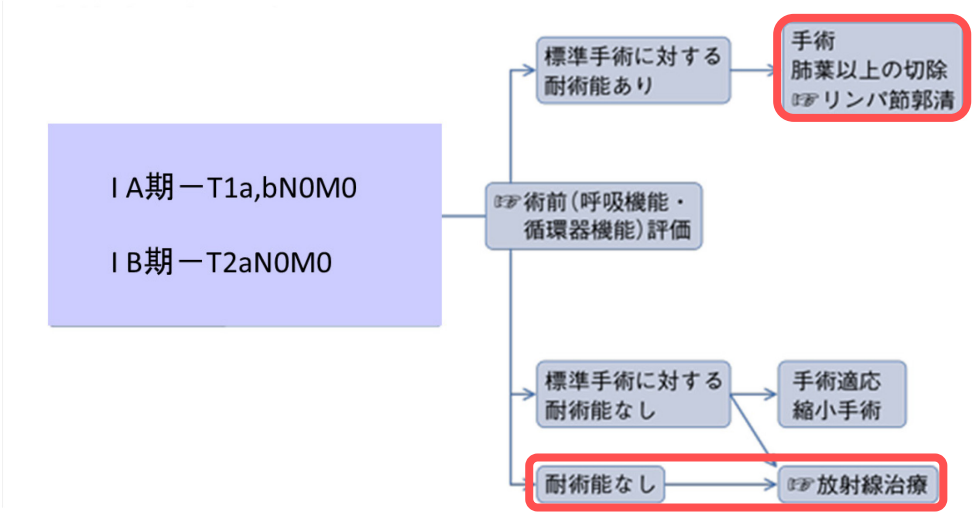
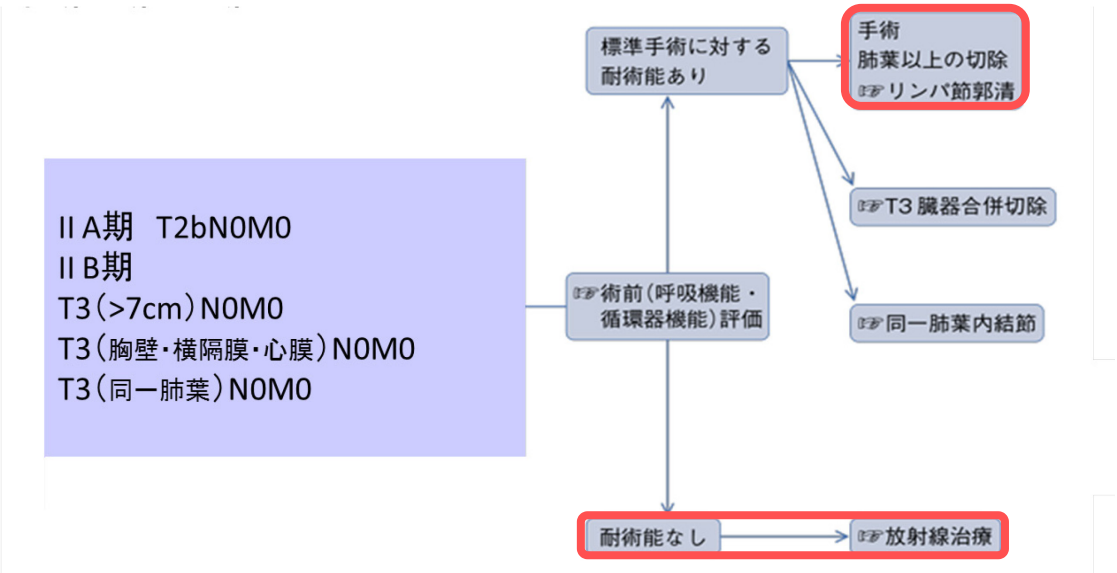


図 2. 病期Ⅱ期（リンパ節転移症例を除く)治療のフローチャート

(T2b (50mm＜、≦70mm)または T3 (＞70mm)または胸壁浸潤または同一肺葉内転移症例)



3. 放射線治療の適応

I, II 期に対する治療は、耐術能がある場合、手術が考慮される。医学的な理由で手術できない I, II 期非小細胞肺癌には、根治的放射線治療の適応があり、肺癌診療ガイドラインではグレード B（科学的根拠があり、行うよう勧められる）となっている。T1 症例に対する標準的手術療法と体幹部定位放射線治療(stereotactic body radiation therapy、以下 SBRT)

を直接比較した報告は一編のみであるが〔1〕、手術、SBRT それぞれの治療成績については、複数報告されている。手術に関しては、T1a, T1b (stage IA), T2a (stage IB)の 5 年生存率はそれぞれ 86.8%、73.9%と良好な成績が報告されている（Japanese Lung Cancer Registry）〔2〕。また、腺癌手術症例における病理組織別の成績が報告されており、最も成績の悪い組織型(solid adenocarcinoma with mucin)で 5 年生存率 54.4%とされている〔3〕。一方、耐術能のない患者、もしくは手術を拒否した患者は、放射線治療が選択される。I 期非小細胞肺癌に対する放射線治療の方法としては、体幹部定位放射線照射など線量の集中性を高める高精度放射線照射技術を用いることが勧められ、ガイドラインではグレード B となっている。JCOG0403 の結果では、手術可能な患者の 5 年生存率は T1a, T1b, T2a (stage IA, IB)では 54.0%、手術不能な患者 T1a,T1b, T2a (stage IA, IB)では 42.8%であった。手術可能な患者の 3 年局所制御率は 87.3%、手術不能な患者では 85.4%であった〔4〕。JCOG0702 では T2 症例の SBRT の線量増加試験が行なわれた。2 年生存率 83.3%であったが、耐容線量限界に達したため、限界線量は生物学的効果線量（biological effective dose、以下 BED）で 130.6Gy であった〔5〕。よって T2 に対する SBRT の成績は未だ議論が続いており、明確な結論は出ていない。T1 症例に対する放射線治療単独で、1 回線量を 2Gy とした通常分割照射では 5 年生存率 20%以下と成績が不良であることが知られている〔6〕。T1 において未治療にて経過観察した場合の 5 年生存率は以下に示すように 10%程度で、こちらも成績が不良であることが報告されている。

表 2. T1 症例における未治療の成績

	発表年	生存期間中央値	5 年生存率
Raz DJ et al〔7〕	2007	T1a, b：13 か月	T1a,b：9%
		T2a：8 か月	T2a：5%
Wisnivesky JP et al〔8〕	2005	T1a, b＋T2a：14 か月	T1a, b＋T2a：14%
Motohiro A et al〔9〕	2002		T1a, b＋T2a：17%
McGarry RC et al〔10〕	2002	T1a, b＋T2a：14 か月	

よって、体幹部定位照射が不適応の患者には代替治療として 3 次元原体照射（three dimensional conformal radiotherapy、以下 3D-CRT）が適切である。局所のみに多方向から照射することにより、周囲臓器の線量を減少させることができる。これにより 1 回線量の増加、BED の増加を達成することができる。1 回線量を増加させ、治療期間を短縮する照射方法は寡分割照射と呼ばれている。研究の進んでいる SBRT でも T2 以上の症例に対する治療成績や有害事象については報告が少ないため、以下に示すリスク臓器の耐用線量を考慮して治療を行なわれるのが一般的である。また、3D-CRT は SBRT より高線量にはならないため、SBRT の線量制約を厳守すれば問題ないと考えられ、当院では安全性に余裕をもたせるためにも SBRT の線量制約を参考にした。その他、呼吸機能や performance status

（以下 PS ）についても SBRT に準拠し、これらをもって、3D-CRT のガイドラインとした。

表 3. SBRT の線量制約

Organ	Dose	Volume	Dose	Volume
Lung	40Gy V15	<= 100cc <= 25%	MLD V20	<= 18cc <= 20%
Cord	25Gy	Max		
Esophagus	40Gy	<= 1cc	35Gy	<= 10cc
Pulmonary artery	40Gy	<= 1cc	35Gy	<= 10cc
Stomach	36Gy	<= 10cc	30Gy	<= 100cc
Intestine	36Gy	<= 10cc	30Gy	<= 100cc
Trachea, main bronchus	40Gy	<= 10cc		
Other organs	48Gy	<= 1cc	40Gy	<= 10cc

表 4. 通常照射における線量制約

		TD5/5 (5 年間で 5%に副作用を生ずる線量)			TD50/5 (5 年間で 50%に副作用を生ずる線量)			判定基準
	体　積	1/3	2/3	3/3	1/3	2/3	3/3	
頭頸部	中耳・外耳	30 Gy		30 Gy*	40 Gy		40 Gy*	急性漿液性耳炎
		55 Gy		55 Gy*	65 Gy		65 Gy*	慢性漿液性耳炎
	耳下腺	—	32 Gy*		—	46 Gy*		口内乾燥症 (TD100/5 は 50 Gy)
	喉　頭	79 Gy*	70 Gy*		90 Gy*	80 Gy*		軟骨壊死
		—	45 Gy	45 Gy*	—		80 Gy*	喉頭浮腫
胸部	肺	45 Gy	30 Gy	17.5 Gy	65 Gy	40 Gy	24.5 Gy	肺　炎
	心　臓	60 Gy	45 Gy	40 Gy	70 Gy	55 Gy	50 Gy	心外膜炎
	食　道	60 Gy	58 Gy	55 Gy	72 Gy	70 Gy	68 Gy	臨床的狭窄，穿孔
腹部	胃	60 Gy	55 Gy	50 Gy	70 Gy	67 Gy	65 Gy	潰瘍，穿孔
	小　腸	50 Gy		40 Gy*	60 Gy		55 Gy	閉塞，穿孔，瘻孔
	大　腸	55 Gy		45 Gy	65 Gy		55 Gy	閉塞，穿孔，潰瘍，瘻孔
	直　腸	100 cm^3 では体積効果なし		60 Gy	100 cm^3 では体積効果なし		80 Gy	高度の直腸炎，壊死，瘻孔，狭窄
	肝　臓	50 Gy	35 Gy	30 Gy	55 Gy	45 Gy	40 Gy	肝不全
	腎　臓	50 Gy	30 Gy*	23 Gy	—	40 Gy*	28 Gy	臨床的腎炎
	膀　胱	—	80 Gy	65 Gy	—	85 Gy	80 Gy	症候性の膀胱萎縮・体積減少

*50%以下の体積では明らかな変化は認めない

（放射線治療ガイドラインより）

4. 考察

寡分割照射にて 1 回 4Gy 程度の照射をおこなった報告は、以下に示すように 2 編ほどあるものの更に 1 回線量を増加させた成績はほとんどない。

表 5. T1-3 症例に対する原体照射の治療成績

	発表年	生存期間中央値	生存率
Joo Ho Lee et al〔11〕	2013	T1-3：27.8 か月	T1-3：2 年 54.3%
Milena Kotodziejczyk et al〔12〕	2011		T1-3：3 年 37.0%

SBRT では BED で 100Gy 以上の大線量を照射することで、局所コントロールが良好であることから、3D-CRT においても線量増加が良好な局所コントロールをもたらすと考えられる。今回の対象者は手術や SBRT が不適格であるという背景があるため、線量増加による局所制御の向上や有害事象の発生を主体に検討を行った。3D-CRT にて 1 回線量を増加させた点では初めての報告である。放射線治療は精度が向上しさらには患者の努力が必要となってしまっている。この検討は超高齢化社会がすすむことを予想し簡易的放射線治療の限界を知るうえで大切な研究となると考えられる。

文献

1. Chang JY, Senan S, Paul MA, et al. Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. Lancet Oncol. 2015;16(6):630-637.
2. Sawabata N, Miyaoka E, Asamura H, et al. Japanese Joint Committee for Lung Cancer Registration. Japanese lung cancer registry study of 11,663 surgical cases in 2004: demographic and prognosis changes over decade. J Thorac Oncol. 2011;6(7):1229-1235.
3. Sakurai H, Asamura H, Miyaoka E, et al. Japanese Joint Committee of Lung Cancer Registry. Differences in the prognosis of resected lung adenocarcinoma according to the histological subtype: a retrospective analysis of Japanese lung cancer registry data. Eur J Cardiothorac Surg. 2014;45(1):100-107.
4. Nagata Y, Hiraoka M, Shibata, et al. Prospective Trial of Stereotactic Body Radiation Therapy for Both Operable and Inoperable T1N0M0 Non-Small Cell Lung Cancer: Japan Clinical Oncology Group Study JCOG0403. Int J Radiat Oncol Biol Phys. 2015;93(5):989-996.
5. Onimaru R, Shirato H, Shibata T, et al. Phase I study of stereotactic body radiation therapy for peripheral T2N0M0 non-small cell lung cancer with PTV<100 cc using a continual reassessment method (JCOG0702). Radiother Oncol. 2015;116(2):276-280.

6. Qiao X, Tullgren O, Lax I, et al. The role of radiotherapy in treatment of stage I non-small cell lung cancer. Lung Cancer. 2003;41(1):1-11.
7. Raz DJ, Zell JA, Ou SH, et al. Natural history of stage I non-small cell lung cancer: implications for early detection.Chest. 2007;132(1):193-199.
8. Wisnivesky JP, Bonomi M, Henschke C, et al. Radiation therapy for the treatment of unresected stage I-II non-small cell lung cancer. T.Chest. 2005;128(3):1461-1467.
9. Motohiro A, Ueda H, Komatsu H, et al; National Chest Hospital Study Group for Lung Cancer. Prognosis of non-surgically treated, clinical stage I lung cancer patients in Japan. Lung Cancer. 2002;36(1):65-69.
10. McGarry RC, Song G, des Rosiers P, et al. Observation-only management of early stage, medically inoperable lung cancer: poor outcome. Chest. 2002;121(4):1155-1158.
11. Lee JH, Wu HG, Kim HJ, et al. Hypofractionated three-dimensional conformal radiotherapy for medically inoperable early stage non-small-cell lung cancer. Radiat Oncol J. 2013;31(1):18-24.
12. Kołodziejczyk M, Kępka L, Tyc-Szczepaniak D, et al. Outcome of three-dimensional conformal radiotherapy for early stage non-small cell lung cancer patients who met or not inclusion criteria for stereotactic-body radiation therapy. Pneumonol Alergol Pol. 2011;79:326-336.