ORIGINAL ARTICLE

Three-dimensional conformal reirradiation for locoregionally recurrent lung cancer previously treated with radiation therapy

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Abstract

Background: To evaluate the efficacy and toxicity of reirradiation using three-dimensional conformal radiotherapy (3D-CRT) in symptomatic patients with locoregionally recurrent lung cancer.

Methods: Between 2005 and 2012, 15 patients with locoregionally recurrent lung cancer were retreated with 3D-CRT after previously receiving thoracic radiotherapy. The median interval between the initial irradiation and reirradiation was 12 months (range, five to 41 months). The median initial radiotherapy dose was 63 Gy (range, 45–70 Gy), and reirradiation doses ranged from 25.2 to 45.2 Gy (median, 36 Gy), with daily fractions of 1.8–4 Gy (median, 2 Gy).

Results: After reirradiation, 80% of the patients experienced resolved or diminished symptoms for one or more of their symptoms, with an 83% improvement in a total of 24 symptoms. The overall tumor response rate to reirradiation was 46.7%, with progressive disease occurring in only one patient. The median overall survival (OS) time was 11 months (range, one to 27 months), and the one-year OS rate was 47%. The progression-free survival time ranged from one to 10 months (median, five months). In univariate analysis, the use of combined chemotherapy and a higher reirradiation dose showed a trend toward improved survival after reirradiation. Treatment-induced toxicity included grade 2 radiation pneumonitis in only one patient, and there were no other complications, such as radiation esophagitis or myelopathy.

Conclusions: Reirradiation using 3D-CRT with moderate doses for locoregionally recurrent lung cancer can provide palliative benefits without severe complications to the majority of selected patients with symptoms as a result of a regrowing tumor.

Introduction

Lung cancer is one of the most frequent and fatal cancers worldwide. Despite the recent biological and technological advances in lung cancer management, recurrence is frequently observed after initial lung cancer treatment. Although the time to recurrence and patterns of failure are not easily predicted, recurrent lung cancer has been judged as almost fatal with an extremely low cure rate and can also cause significant symptoms that result in a decline in quality of life. Retreatment options depend on previous therapies,

site of recurrence, and performance status of the patient at the time of relapse. In several large studies, approximately 1–2% of all recurrent lung cancers were managed by curative reoperation, with mostly discouraging results.¹

Most patients with lung cancer receive radiotherapy (RT) with a curative or palliative intent at some point during the course of their disease. However, despite advances in tumor localization, radiation dose escalation, and the use of combined chemotherapy, the rates of locoregional recurrence remain high in lung cancer patients. Locoregional failure after thoracic irradiation for lung cancer presents a clinical

challenge to radiation oncologists. One main reason for this challenge may be the fear or risk of excessive toxicity, primarily of the spinal cord and lung during reirradiation for recurrent lung cancer. Because reirradiation has the potential to exceed normal tissue tolerance, clinical judgment with regard to the risks and benefits of such treatment is important. Reirradiation has not been considered promising because the relapsed tumor often shows radioresistance, and high-dose reirradiation in an area that was previously irradiated with a full course of radiotherapy causes significant normal tissue damage. However, recent papers have reported on the usefulness of reirradiation for recurrent cancer in several sites, with the greatest clinical experience existing for head and neck cancers.^{2,3} For recurrent lung cancer, only a few reports have been published on reirradiation with a predominantly palliative aim.^{4–10} Researchers have reported encouraging relief rates for symptoms, such as hemoptysis, cough, dyspnea, and chest pain, with relatively low rates of toxicity. However, there are still no established guidelines for the reirradiation of recurrent lung cancer because of the retrospective nature and limited size of most available studies, large variety in the radiotherapy parameters used, and lack of prognostic factors.

We utilized reirradiation in selected patients with several symptoms that resulted from recurrent lung cancer who had no other effective treatments options remaining. To investigate the efficacy and toxicity of reirradiation using three-dimensional conformal radiotherapy (3D-CRT), we retrospectively reviewed the results of patients treated with reirradiation for locoregionally recurrent lung cancer previously treated with thoracic radiation and specifically assessed the effects of combined chemotherapy and reirradiation dose on outcomes.

Patients and methods

Patients

Between January 2005 and June 2012, 15 patients treated with thoracic reirradiation for locoregionally recurrent lung cancer following previous thoracic RT at our institution were retrospectively enrolled. Patients with a visible recurrent tumor on bronchoscopy and/or reappearance or enlargement of the primary lesion or regional lymph nodes on chest computed tomography (CT) and/or positron emission tomography (PET)-CT within the original irradiation volume, were eligible for the study. All patients underwent chest CT and PET-CT to visualize tumor regrowth at the initial site and to establish the diagnosis of recurrent disease. Recurrence was histologically confirmed in three patients. The study was approved by an independent review board at The Catholic University of Korea Daejeon St. Mary's Hospital (IRB approval number: DIRB-00102_1-001).

Radiotherapy

Three dimensional-CRT was performed with a 6- or 15-MV photon beam from a linear accelerator, both for the initial irradiation and the reirradiation. The total doses for the initial irradiation ranged from 45 to 70 Gy (median, 63 Gy), and those for the reirradiation ranged from 25.2 to 45.2 Gy (median, 36 Gy). Reirradiation was defined as RT delivered to an area that previously received a full RT dose of 45 Gy or more. Normalized tumor doses in 2 Gy fractions using an α/β ratio of 10 ($\text{NTD}(2)_{10}$) were calculated for the reirradiation course. Patients were immobilized in a Wing board and thorax Vac-Lok cushion (CIVCO Medical Solutions, Orange City, IA) with the arms above the head. Planning CT scans were obtained during quiet respiration with no attempt at breath holding or obtaining the scan during any particular phase of respiration, except for two patients who underwent a four-dimensional (4D) CT scan. After obtaining a planning CT scan that included the entire lung (slice thickness of 3 mm), the CT data were transferred to a commercial treatment-planning system (Pinnacle³ ver. 8.0 m; Philips Medical Systems, Fitchburg, WI) for 3D-CRT planning. Reirradiation fields included only the regrowing primary mass or the enlarged regional lymph node with a safety margin of 1–2 cm. No elective nodal irradiation was utilized in the reirradiation setting in any patient. In 6 patients with lung atelectasis, PET-CT scans were used for gross tumor volume (GTV) delineation, with thresholds of 40–50% the maximal standard uptake value (SUVmax) to define a tumor on ¹⁸F-fluorodeoxyglucose (FDG)-PET. In most cases, a direct GTV to planning target volume (PTV) expansion of 0.5–1 cm was utilized. The 3D-CRT plans used typical five to seven coplanar multileaf collimated beams and were normalized such that at least 95% of the PTV received the prescription dose, with heterogeneity corrections using the Collapsed Cone Convolution Superposition algorithm. We implemented weekly monitoring of patient position and tumor change using a megavoltage (MV) cone-beam CT (CBCT).

When designing the reirradiation plan, we were careful to minimize the dose to critical organs that had already been irradiated and to deliver doses that were as high as possible to the tumor. The dose to the spinal cord was restricted in the second RT course considering the initial RT dose to the spinal cord, the time interval between the initial RT and reirradiation, and the spinal cord tolerance for reirradiation.¹¹ Because a variety of fractionation regimens were used, the maximum spinal cord doses at reirradiation were converted into the biologically effective dose (BED), according to the linear-quadratic model, using an α/β value of 2 Gy to assess the possible maximal cord doses. The BED (Gy_2) is equal to $nd(1 + d/2)$, with n = number of fractions and d = dose per fraction. If possible, the same beam pathway used in the initial RT course was avoided to reduce lung

toxicity as a result of reirradiation. The dosimetric effects of reirradiation using 3D-CRT planning on a normal lung were analyzed via lung-dose parameters, such as the mean lung dose (MLD) and the percentage volumes of both lungs minus the GTV receiving specific doses of 10 and 20 Gy (V10 and V20), as estimated using dose-volume histograms.

Chemotherapy

Chemotherapy was delivered with the initial RT in 12 patients. At the initial irradiation, the chemotherapy regimens were vinorelbine, cisplatin, and carboplatin for non-small cell lung cancer (NSCLC) and etoposide and cisplatin for small cell lung cancer (SCLC). Of the 15 patients, six received chemotherapy either concurrently (three patients) or sequentially (three patients) with the reirradiation. At reirradiation, the chemotherapy regimens were carboplatin and gemcitabine, with a median of two cycles (range, 2–4).

Response, survival, and toxicity evaluation and statistical analysis

All patients were evaluated weekly during reirradiation, and follow-up visits were conducted two weeks after reirradiation completion, every one to two months for the first six months, and every three months thereafter. Tumor response to reirradiation was assessed with chest CT and/or PET-CT at one to two months after reirradiation using the Response Evaluation Criteria in Solid Tumors (RECIST).¹² To evaluate the symptom response, the physician scored relief of symptoms according to the patient's assessment of each symptom as resolved (complete resolution of the symptom), diminished (any improvement without complete resolution), stabilized (no change), or progressive (deterioration). The best response at any time was scored. Treatment-related toxicities were evaluated according to the National Cancer Institute-Common Terminology Criteria for Adverse Events version 3.0.

Overall survival (OS) was calculated from the first day of reirradiation to death by any cause. Progression-free survival (PFS) was calculated from the first day of reirradiation to the date of the first observation of disease progression or death. All survival distributions were calculated using the Kaplan-Meier method, and the log-rank test was used for univariate analysis. All statistical analyses were performed using SPSS ver. 15.0 (SPSS Inc., Chicago, IL), and *P*-values < 0.05 were considered statistically significant.

Results

Patient characteristics

The patients' characteristics are summarized in Table 1. All patients were male, and the median age at the time of

Table 1 Patient characteristics

Characteristics	No. of Patients (<i>n</i> = 15)
Gender	
Male	15
Female	0
Age at reirradiation (years)	
Range	59–80
Median	68
ECOG performance status	
0	2
1	13
Histological type	
Squamous cell carcinoma	13
Small cell carcinoma	2
Initial Stage	
I	1
II	2
III	10
Limited-SCLC	2
Combined chemotherapy at initial RT	
Yes	12
No	3
Combined chemotherapy at reirradiation	
Yes	6
No	9

ECOG, Eastern Cooperative Oncology Group; RT, radiotherapy; SCLC, small cell lung cancer.

reirradiation was 68 years (range, 59–80 years). The time interval between the end of the initial RT and the start of reirradiation ranged from five to 41 months (median, 12 months). The relapse patterns were local in three patients, locoregional in 11 patients, and both locoregional and distant failures in one patient. All patients had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0–1 at the time of reirradiation. At the time of the initial RT, the histological types were squamous cell carcinoma in 13 patients and small cell carcinoma in two patients (patient numbers four and eight), and of the 13 patients with NSCLC, 10 patients had stage III disease based on the American Joint Committee on Cancer (AJCC) 6th edition.¹³ Two patients (patient numbers nine and 10) had undergone surgical resection (pneumonectomy and lobectomy, respectively) as first-line treatment, and the initial RT was performed because of recurrence after surgery.

Treatment and clinical outcomes

Initial RT doses ranged from 45 to 70 Gy (median, 63 Gy) in 25–37 fractions (median, 32 fractions), with doses of 1.8–2.3 Gy (median, 2 Gy) per fraction. During reirradiation, the median total dose was 36 Gy (range, 25.2–45.2 Gy) delivered in a median of 16 fractions (range, 10–22 frac-

tions), with a median dose per fraction of 2 Gy (range, 1.8–4.0 Gy). A hypofractionation regimen was used in only two patients (patient numbers nine and 12). The cumulative doses ranged from 80.6 to 114.3 Gy (median, 96.6 Gy), and the median value of $NTD(2)_{10}$ for the reirradiation course was 36 Gy (range, 24.8–46.9 Gy). The median GTV at reirradiation was 78.8 cm³. At reirradiation, the dose to the spinal cord ranged from 6.8 to 26.6 Gy (median, 15.7 Gy), with a median BED of 24 Gy₂ (range, 9.0–48.4 Gy₂). Lung dosimetry at reirradiation using 3D-CRT planning showed that the MLD ranged from 0.6 to 9.8 Gy (median, 3 Gy) and that the values of V10 and V20 ranged from 0.3 to 31.9% (median, 7.4%), and 0 to 18.8% (median, 2.3%), respectively (Table 2). Figure 1 shows PET-CT images and 3D-CRT plans for patient number one at the initial RT and reirradiation.

Treatment outcomes after reirradiation are summarized in Table 3. Reirradiation was well tolerated by all patients, with a median follow-up of 10 months (range, one to 26 months). The overall response rate to reirradiation was 46.7%, with complete response (CR) achieved in two patients (patient numbers eight and nine), partial response (PR) in five patients, stable disease (SD) in seven patients, and progressive disease (PD) in one patient. After reirradiation, the median OS time was 11 months (range, one to 27 months) and the one-year OS rate was 47%. The PFS time ranged from one to 10 months (median, five months). Three patients (patient numbers eight, nine, and 13) were alive without symptoms at follow-up 15, 18, and 12 months after completing the reirradiation, respectively. The remaining 12 patients died of locoregional failure (10 patients) and both locoregional and distant failures (two patients). In univariate analysis, reirradiation with and without chemotherapy, the time interval between the end of the initial RT and the start of reirradiation, and reirradiation dose ($NTD(2)_{10}$) were not statistically significant factors affecting survival. However, the use of combined chemotherapy and a higher reirradiation dose showed a trend toward improved survival after reirradiation. The median OS time in patients who received combined chemotherapy was 14 months, while in patients who did not receive combined chemotherapy, the median OS time was eight months ($P = 0.112$). The median OS times associated with a $NTD(2)_{10}$ of less than 36 Gy and more than 36 Gy were six and 13 months, respectively ($P = 0.473$) (Table 4, Fig 2).

Twenty-four symptoms considered to be related to the recurrent tumor were observed in 15 patients. Of the 15 patients, seven patients had only one symptom, seven patients had two symptoms, and one patient had three symptoms at presentation. After reirradiation, 80% (12/15) of the patients experienced resolved or diminished symptoms for one or more of their symptoms. And 83% (20/24) of the symptoms had been resolved or diminished, with responses

Table 2 Treatment characteristics

Patient No.	Initial RT dose (Gy/fx)	Interval to RRT (months)	RRT dose (Gy/fx)	RRT dose ($NTD(2)_{10}$, Gy)	GTV at RRT (cm ³)	Spinal cord dose at RRT (Gy)	Spinal cord dose at RRT (BED, Gy ₂)	MLD at RRT (Gy)	V20 at RRT (%)	Combined CHT at RRT
1	68.8/32	33	37.5/15	39.1	180.4	15.7	24.0	5.8	8.0	
2	65.1/31	12	40/16	41.7	86.5	19.3	31.1	4.7	8.0	+
3	50/25	13	36/20	35.4	68.5	12.1	15.8	3.2	2.3	+
4	45/25	12	40/20	40.0	41.9	26.6	44.0	9.8	18.8	
5	63/35	41	30/15	30.0	78.8	19.7	32.5	4.3	4.8	
6	69.3/33	5	45/18	46.9	37.4	15.2	21.6	7.1	13.0	
7	66.6/37	30	30/15	30.0	71.1	9.9	13.2	2.7	3.3	+
8	50/25	8	30.6/17	30.1	7.5	7.4	9.0	1.7	1.5	+
9	70/35	9	40/10	46.7	6.8	6.8	9.1	0.6	0.0	
10	57.5/25	8	45.2/19	46.8	101.1	20.8	32.1	2.5	0.8	
11	64.8/36	17	44/22	44.0	8.1	19.9	29.0	5.7	9.1	+
12	39.3/33	20	30/10	32.5	107.1	13.0	21.5	3.0	1.3	
13	60/30	6	25.2/14	24.8	80.0	25.4	48.4	1.9	0.2	+
14	54/27	14	36/18	36.0	80.1	14.2	19.8	1.3	1.6	
15	63/35	7	30/15	30.0	143.2	19.4	31.9	1.5	1.0	
Median	63/32	12	36/16	36.0	78.8	15.7	24.0	3.0	2.3	

BED (Gy₂), biologically effective dose using an α/β value of 2 Gy; CHT, chemotherapy; fx, fractions; GTV, gross tumor volume; MLD, mean lung dose; $NTD(2)_{10}$, normalized tumor doses in 2 Gy fractions using an α/β ratio of 10; RRT, reirradiation; RT, radiotherapy; V20, percentage volumes of lungs receiving specific dose of 20 Gy.

Figure 1 Positron emission tomography-computed tomography (PET-CT) images and three dimensional conformal radiotherapy (3D-CRT) plans for patient number one at the initial radiotherapy (a) and reirradiation (b).

of 100% (4/4) for hemoptysis, 88% (7/8) for cough, 83% (5/6) for dyspnea, and 67% (4/6) for chest pain.

Grade 2 radiation pneumonitis occurred in only one patient (patient number eight). No grade 3 to 4 radiation pneumonitis or any grade of fibrosis was noted. There were no other complications, such as radiation esophagitis or myelopathy.

Discussion

The proportion of patients initially treated with thoracic RT who then undergo reirradiation for recurrent lung cancer is

not well known. In a single institution study, according to the medical records of more than 1500 patients with lung cancer, thoracic reirradiation was performed in only 23 patients (approximately 1.5%), mainly for symptomatic relief.¹⁴ The issue of how to retreat patients with locoregional recurrence after previous radical RT is controversial mainly because of concerns regarding the risk of reirradiation toxicity. Together with considerations for the possible increased risk of normal tissue damage, there are other factors to take into account in the reirradiation setting, such as the previously treated volume, dose fractionation schedule, interval from previous RT to reirradiation, extent of recovered and residual damages

Table 3 Treatment outcomes after reirradiation

Endpoints	No. of Patients (n = 15)
Tumor response	
CR	2/15 (13%)
PR	5/15 (33%)
SD	7/15 (47%)
PD	1/15 (7%)
Survival and disease progression	
OS (months)	1–27 (median 11)
One-year OS (%)	47
PFS (months)	1–10 (median 5)
Toxicity	
Grade 2 radiation pneumonitis	1/15 (7%)

CR, complete response; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

Table 4 Prognostic factors for overall survival by univariate analysis

Variables	No. of Patients (n = 15)	Median survival (months, 95% CI)	P-value
Combined CHT at RRT			0.112
Yes	6	14 (4.2–23.8)	
No	9	8 (2.2–13.8)	
Interval to RRT			0.580
>12 months	7	9 (1.3–16.7)	
≤12 months	8	11 (4.1–17.9)	
NTD(2) ₁₀ of RRT			0.473
>36 Gy	7	13 (7.9–18.1)	
≤36 Gy	8	6 (0.0–12.9)	

CHT, chemotherapy; CI, confidence interval; NTD(2)₁₀, normalized tumor doses in 2 Gy fractions using an α/β ratio of 10; RRT, reirradiation.

Figure 2 Kaplan-Meier analyses with the log-rank test for overall survival (OS). (a) OS curve in all patients after reirradiation. (b, c, and d) OS curves according to the use of combined chemotherapy (b), interval to reirradiation (c), and reirradiation dose (d).

to normal tissues in the reirradiation field after the first RT, patient performance at relapse, aim of reirradiation (curative or palliative), and any practical alternatives to reirradiation.² In most studies of recurrent lung cancer, symptom relief was the main goal of reirradiation. This goal, together with the

consideration of toxicity risk because of high doses, resulted in the administration of moderate doses, with a median of 16–51 Gy being used at reirradiation (Table 5).^{4–10} For relief of each symptom type after reirradiation of recurrent NSCLC, Cetingoz *et al.*⁹ reported that improvement (≥50%)

Table 5 Summary of reirradiation studies for recurrent lung cancer after previous irradiation

Study (reference)	No. of patients	Initial RT dose Gy (median)	Interval to RRT Months (median)	RRT dose Gy (median)	Symptomatic improvement (overall %)	MST (months)	One-year OS (%)	Toxicities (% of patients)
Okamoto <i>et al.</i> (4)	34	30–80 (60)	5–87 (23)	10–70 (50)	75% (of the patients)	8	43	G2 P (35%) G3 P (21%) G2 E (12%) G3 E (6%)
Wu <i>et al.</i> (5)	23	30–78 (66)	6–42 (13)	46–60 (51)		14	59	G1-2 P (22%) G1-2 E (9%)
Kramer <i>et al.</i> (6)	28	36–60	6–72 (17)	16 (16)	71% (of the patients)	5.6	18	P (4%) G2 E (4%)
Tada <i>et al.</i> (7)	19	50–70	5–60 (16)	50–60 (50)		7.1	26	G3 P (5%) G2 E (16%)
Ebara <i>et al.</i> (8)	44	50–70 (60)	5.8–47.2 (12.6)	30–60 (40)	74% (of the symptoms)	6.5	27.7	G2 P (7%) G3 P (7%)
Present study	15	45–70 (63)	5–41 (12)	25–45 (36)	80% (of the patients) 83% (of the symptoms)	11	47	G2 P (7%)

E, esophagitis; G, grade; MST, median survival time; OS, overall survival; P, pneumonitis; RRT, reirradiation; RT, radiotherapy.

regression of symptoms) was observed in 86% of the patients with hemoptysis, in 77% with cough, in 69% with dyspnea, and in 60% with thoracic pain. When global (i.e. any) symptom relief was considered, patients reported some benefit of treatment in 70–80% of cases.¹⁰ We also believe that reirradiation can be considered when recurrence in the thorax results in severe symptoms that worsen a patient's quality of life. The favorable palliative effects in our study may be associated with the results of tumor response to reirradiation, which showed PD in only one patient.

For reirradiation, various fractionations (i.e. 10–22 fractions and 1.8–4 Gy per fraction) were used, with total doses ranging from 25.2 to 45.2 Gy, depending on the initial RT dose, interval between initial RT and reirradiation, dose to spinal cord and lung, GTV, and severity of symptoms. In the 3D-CRT planning for the reirradiation in this study, we were careful to minimize the doses to the spinal cord and normal lung. Among the late responding tissues, the spinal cord and lung are capable of partial proliferative and functional recovery after several months.^{2,15} In addition to the considerable experimental evidence demonstrating significant recovery and increased reirradiation tolerance in the spinal cord, there are clinical data supporting spinal cord recovery and tolerance. Analyzing the clinical data of 40 patients published in eight different reports, Nieder *et al.*¹¹ came to the conclusion that the risk of myelopathy is low after a cumulative BED of $\leq 135.5 \text{ Gy}_2$ when the between-treatment interval is not less than six months and the BED of each course is $\leq 98 \text{ Gy}_2$. At the first RT course in our study, the dose to the spinal cord reached up to 45 Gy (BED $\leq 90 \text{ Gy}_2$) in all patients. Therefore, based on Nieder's clinical observation, we restricted the dose to the spinal cord to 45.5 Gy₂ for reirradiation performed within a median time interval of 12 months. After a median BED of 24 Gy₂ (range, 9.0–48.4 Gy₂) to the spinal cord during reirradiation, there was no radiation myelopathy, although the median follow-up time was only 10 months. Regarding lung toxicity after reirradiation, the risk of radiation pneumonitis was assessed in a mouse model with the whole thorax irradiated at a priming dose of 6–10 Gy and an interval of one to six months.¹⁶ Both the size of the priming dose and the between-treatment interval had a significant impact on the recovery after the initial doses and reirradiation tolerance in this experimental set-up. Although clinical data are limited and the median survival times after reirradiation were too short to enable an assessment of true late lung damage, recent studies support the experimental findings of a relatively large capacity for occult injury recovery, with relatively low rates of symptomatic pneumonitis (i.e. grade 3 pneumonitis: 5–21%) (Table 5).^{4,7,8,10} Various dosimetric parameters, such as MLD and the volume of lungs receiving a specific dose, have been suggested as predictors of symptomatic radiation pneumonitis after RT for lung cancer. In a prospective study using 3D-CRT planning, the risks of grade ≥ 2 radiation pneumoni-

tis were 8% for MLD $< 20 \text{ Gy}$ and 0% for V20 $< 22\%$.¹⁷ However, there were no precise quantitative data regarding the extent of occult injury repair and lung tissue tolerance at reirradiation. Considering the size of the initial dose and the elapsed time, we designed the fields to avoid the same beam path used in the first RT course and the value of V20 was kept to a minimum despite relatively low prescription doses of 25.2–45.2 Gy during reirradiation. Under the median values of 3 Gy and 2.3% in MLD and V20, only one patient (patient number eight) experienced grade 2 radiation pneumonitis at two months after reirradiation. The MLD and V20 of this patient were relatively low at 1.7 Gy and 1.5%, respectively. Therefore, the radiation pneumonitis in this patient may have resulted from the effect of combined chemotherapy or the short interval (eight months) from the initial RT, rather than the lung dose at reirradiation.

With respect to the prognostic factors for outcomes after reirradiation, the interaction of chemotherapy with reirradiation has not been investigated in any study. In addition, few studies used a radiobiological dose, such as the BED and NTD(2)₁₀, to describe the radiation dose and the dose response. Regarding the dose response, longer survival may result when higher doses are delivered at the time of reirradiation. Two studies examining high-dose reirradiation of more than 50 Gy in carefully selected patients reported median survival times of 14 to 15 months, in contrast to the median survival of 4.9–6.5 months in studies using median doses of 30–40 Gy.^{4,5,10} Novel technologies, such as stereotactic body radiotherapy, intensity modulated radiation therapy (IMRT), or proton therapy, could enable successful dose escalation while minimizing toxicity. IMRT can be used to produce dose distributions that are more conformal than those possible with conventional techniques, and a sharper fall-off of dose at the PTV boundary can be achieved. Proton therapy is an emerging RT technology with the potential to modulate radiation dose deposition along the beam path.¹⁸ These advances in RT delivery may be highly relevant in the setting of recurrent tumor in close proximity to an organ at risk where dose needs to be limited. For improved outcomes in highly selected patients, these techniques may play an important role in the reirradiation settings for lung cancer in the future. In our study, five of the seven patients who received a high NTD(2)₁₀ of $> 36 \text{ Gy}$ exhibited a tumor response $\geq \text{a PR}$ (CR in one patient and PR in four patients). Moreover, two patients (patient numbers two and 11) who received both combined chemotherapy and a higher reirradiation dose ($> 36 \text{ Gy}$) exhibited PR tumor responses, and the OS time in one patient (patient number 11) was the longest among all 15 patients (27 months). Although the median follow-up period was only 10 months and only a few patients were included, treatment-related toxicities were acceptable without severe consequences, and the median OS time (11 months) and the one-year OS rate (47%) after

reirradiation were favorable compared with the results in other studies (Table 5). At the time of reirradiation, the less aggressive biological behavior of most tumors (only one developed a distant metastases) and good ECOG PS scores of 0–1 in all patients may have served as additional factors associated with the relatively high survival outcomes in our study.

Conclusion

In conclusion, reirradiation using 3D-CRT with moderate doses of 25–45 Gy for locoregionally recurrent lung cancer can provide palliative benefits without severe complications to the majority of selected patients with symptoms resulting from a regrowing tumor. Based on our results regarding prognostic factors, longer survival time may be possible by increasing the reirradiation dose and combining the treatment with chemotherapy. Large prospective studies with longer follow-up periods are needed to confirm the efficacy and safety of reirradiation.

Disclosure

No authors report any conflict of interest.

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