



Re-irradiation plus regional hyperthermia for recurrent non-small cell lung cancer: A potential modality for inducing long-term survival in selected patients[☆]

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ABSTRACT

Purpose: The purpose of this study was to assess the toxicity and efficacy of re-irradiation plus regional hyperthermia for recurrent NSCLC and to identify the predictors of long-term survival.

Methods and materials: A total of 33 patients with recurrent NSCLC treated with re-irradiation plus regional hyperthermia were retrospectively analyzed. The median total dose of initial radiotherapy and re-irradiation were 70 Gy and 50 Gy, respectively. A median of 5 hyperthermia treatments using an 8-MHz radiofrequency-capacitive device were applied during re-irradiation in all patients.

Results: Toxicity of Grade 3 was seen in 3 (9%) patients, and no Grade 4 or 5 toxicity was observed. The median overall survival, local control, and disease progression-free survival times after re-irradiation were 18.1, 12.1, and 6.7 months, respectively. Eight patients achieved a long-term survival (more than 3 years after re-irradiation), and 4 of them underwent a third round of irradiation for re-recurrent tumors. Univariate analyses showed that a smaller tumor size (<4 cm) and the absence of distant metastases were significant predictors for a better overall survival. The absence of distant metastases was also found to be a significant predictor for better disease progression-free survival in the univariate analyses. In the subset analyses of 23 patients treated with hyperthermia using electrodes of 30 cm in diameter, the use of a higher radiofrequency-output power tended to be associated with a better prognosis in terms of the local control rate.

Conclusions: Re-irradiation plus regional hyperthermia for recurrent NSCLC appears feasible, with acceptable toxicity, and may be a promising treatment that can result in the long-term survival of patients without distant metastasis and larger recurrent tumors.

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1. Introduction

Previous results have shown that concurrent chemoradiotherapy (CRT) improves the survival in patients with locally advanced non-small cell carcinoma (NSCLC) [1–3]. However, the loco-regional recurrence rate was still as high as 31–48% [1–3]. Therefore, local recurrence at the primary site and the presence of a residual tumor continue to be major problems. There are few curative or palliative treatment options for recurrent NSCLC

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after definitive radiotherapy, and no general therapeutic guidelines have yet been established for these conditions. A subset of patients with recurrent loco-regional disease experience local failure without distant metastases. In such patients, curative local treatment may be selected. The management of patients with recurrent NSCLC after radiotherapy presents a challenge to radiation oncologists, because there is a higher incidence of complications in post-irradiation patients. Recently, re-irradiation has been successfully used in many recurrent tumors of various sites [4–7]. Modern three-dimensional conformal radiotherapy planning techniques allow the administration of a conformal dose distribution around the tumor, potentially minimizing the dose of radiation administered to adjacent critical structures, and permitting escalated dose delivery to the tumor. The combined use of re-irradiation and hyperthermia showed higher local control rates and a good palliative effect in patients with recurrent breast cancer and with rectal cancer [8–10]. Because the tolerated dose of

the organs at risk limits the prescribed dose for re-irradiation, the combined modality treatment may be ideal to obtain a sufficient anti-tumor effect for in-field recurrence after radiotherapy.

With this in mind, in the current study we performed combination therapy using re-irradiation plus regional hyperthermia, which were administered to improve the clinical outcomes in patients with recurrent NSCLC after initial radiotherapy. In our institution, combination therapy using re-irradiation with regional hyperthermia was started in 1992. To our knowledge, there are no clinical reports of such combination therapy. The purpose of our study was to evaluate the toxicity and efficacy of re-irradiation plus regional hyperthermia for recurrent NSCLC, and to identify the predictors of a long-term survival.

2. Materials and methods

2.1. Patients

From March 1992 to April 2009, 798 patients with NSCLC were treated with radiotherapy in the Division of Therapeutic Radiology at the authors' institution. There were 33 consecutive patients with recurrent NSCLC who were treated with re-irradiation plus regional hyperthermia during the same period. All 33 patients satisfied the following requirements and were included in the current retrospective study: recurrent NSCLC tumors after external radiotherapy, re-irradiation fields completely or partially-overlapping the initial irradiation fields, and more than a 1-month period between the initial and re-irradiation treatments. Patients with recurrent NSCLC which had infiltrated to the spinal cord or esophagus, did not undergo this therapy. Written informed consent for treatment was obtained from all patients. The study was approved by the Institutional Review Board of the University of Occupational and Environmental Health.

The characteristics and treatments of patients are listed in Tables 1 and 2. At the time of the initial irradiation, the clinical stages were as follows: Stage IB in 2 patients, Stage IIB in 4, Stage IIIA in 7, Stage IIIB in 10, Stage IV in 4, and postoperative recurrence in 6 patients. Fifteen (46%) of the 33 patients underwent regional hyperthermia during the initial irradiation. Although three of the 33 patients had biopsy-proven recurrent NSCLC,

Table 1
Patient clinical characteristics.

Variable	n = 33
Median age, years (range)	68 (45–85)
Gender	
Male/female	30/3
Performance status	
0/1/2	3/21/9
Histology	
Squamous cell carcinoma	16
Adenocarcinoma	15
Large cell carcinoma	1
Pleomorphic carcinoma	1
Purpose of initial irradiation	
As preoperative neoadjuvant	1
As postoperative adjuvant	4
As definitive therapy	21
For recurrence after resection	7
Median recurrent tumor size (cm) (range)	4 (2–9)
Type of recurrent tumor ^a	
Primary alone	24
T1/T2/T3/T4	3/9/6/6
Lymph node alone	5
N1/N2/N3	1/2/1
Primary + Lymph nodes	4
Distant metastasis	
Yes/no	9/24

^a International Union Against Cancer TNM classification, 6th edition.

Table 2
Treatment methods.

Variable	n = 33
Initial irradiation (median, range)	
Field size (cm ²)	112 (24–386)
Total dose (Gy)	70 (30–85)
Daily dose (Gy)	
1.6/1.8/2.0/3.0/1.5 bid	7/5/18/1/2
Re-irradiation (median, range)	
Field size (cm ²)	38 (16–170)
Total dose (Gy)	50 (29–70)
Daily dose (Gy)	
1.5/1.6/1.8/2.0/3.0/1.0 bid/0.8 bid	5/2/3/16/1/5/1
Cumulative dose (Gy) (median, range)	115 (70–146)
Hyperthermia	
Median applications (range)	5 (2–12)
Concurrent chemotherapy	15

Bid, twice a day.

the remaining were diagnosed as having recurrent NSCLC based on longitudinal computed tomography (CT), and in some cases, ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography and/or magnetic resonance imaging were also used. Although no specific chemotherapy protocol existed, 15 (46%) of the 33 patients underwent concurrent chemotherapy during the course of re-irradiation as follows: intravenous administration of carboplatin in 4 patients, irinotecan in 3, carboplatin in combination with paclitaxel in 2, cisplatin in 2, nedaplatin in one, cisplatin in combination with S-1 in 1, cisplatin in combination with 5-fluorouracil in 1, and carboplatin in combination with S-1 in 1 patient.

2.2. Radiotherapy

The field size and dose of the initial irradiation and re-irradiation are shown in Table 2. The interval between the initial irradiation and re-irradiation was a median of 7.9 months (range, 1.1–28.2 months). All patients underwent external beam re-irradiation with a 4-, 6- or 10-MV linear accelerator. CT-assisted three-dimensional treatment planning (Xio or FOCUS; CMS Japan, Tokyo, Japan) was used to determine the radiation fields in all patients except 3 patients who were treated in the early years of the current study. The gross tumor volume (GTV) was delineated, and a margin of 7–20 mm was extended from the GTV to the planning target volume (PTV) to cover subclinical invasion and to also account for the set-up uncertainty. No prophylactic nodal irradiation was administered. The principle for designing the re-irradiation plan was to minimize the dose to normal structures which were irradiated during the initial irradiation, and to deliver doses as high as possible to the PTV. The total cumulative radiation dose administered to the spinal cord and esophagus were limited up to the tolerance dose (45 Gy for the spinal cord and 60 Gy for the esophagus), and irradiation exposure to other organs at risk, such as the lungs, bronchus, great vessels and the heart were reduced as much as possible. If the spinal cord and esophagus had already been irradiated up to the tolerance dose during the initial irradiation, these were fully shielded during the re-irradiation. To limit and reduce the radiation dose for the organs at risk, 15 (46%) of 33 patients were treated with a three- or four-field beam arrangement or with conformational therapy, and the remaining 18 patients were treated with a one- or two-field beam arrangement. In addition, 4 (12%) of the 33 patients received a third round of irradiation of 36–66 Gy, with 1–3 Gy per fraction after re-irradiation. The total cumulative radiation doses to the spinal cord and esophagus were limited up to the tolerance dose, and the radiation exposure of other organs at risk was reduced in the same way as during the first re-irradiation.

Table 3

A summary of the characteristics of the long-term survivors.

Age	Tumor size (cm)	Interval ^a (mos)	Survival after re-RT (mos)	Cumulative dose (main re-irradiated organ)	Radiotherapy (total/daily dose) (Gy)		Toxicity (\geq Grade 2)
					Initial RT	re-RT	
64	2	11	38 (AWD)	92 Gy (rt. middle/inferior bronchus, rt. lung, rt. rib) ^b	46/2	46/2	None
60	3	7	55 (AWD)	136 Gy (rt. lung, rt. rib) ^c	70/2	50/1 bid	Radiation pneumonitis (Grade 2)
47	4	6	56 (DOD)	140 Gy (aortic arch, rt. lung)	80/2	60/2	None
54	3	1	60 (NED)	110 Gy (bil. brachiocephalic vein, trachea, rt. lung, rt. rib)	70/2	40/2	Brachial plexus neuropathy (Grade 3)
52	4	18	64 (DOD)	120 Gy (rt. lung)	60/2	60/2	None
81	1	6	73 (DOD)	90 Gy (rt. lung, rt. rib, heart)	60/2	30/2	None
45	3	17	76 (DOD)	120 Gy (trachea, superior vena cava, sternum, rt.rib) ^d	70/2	50/1 bid	Acute pleuritis (Grade 3)
68	2	21	119 (DOD)	88.2 Gy (aortic arch, rt. main bronchus, rt. lung) ^e	59.4/1.8	28.8/0.8 bid	None

RT, radiotherapy; AWD, alive with disease; NED, no evidence of disease; DOD, dead of disease; bid, twice a day.

^a Time between initial irradiation and re-irradiation.^b A third course of radiation with 36 Gy at 3 Gy per fraction was delivered to the rt. middle/inferior bronchus, rt. lung and rt. rib 33 months after re-irradiation.^c A third course of radiation with 66 Gy at 1 Gy per fraction (twice a day) was delivered to the rt. lung and rt. rib 13 months after re-irradiation.^d A third course of radiation with 50 Gy at 2 Gy per fraction was delivered to the trachea, superior vena cava, sternum and rt. rib 47 months after re-irradiation.^e A third course of radiation with 48 Gy at 2 Gy per fraction was delivered to the aortic arch and rt. lung 41 months after re-irradiation.

2.3. Hyperthermia

Heat was applied using an 8-MHz radiofrequency (RF)-capacitive regional hyperthermia device (Thermotron RF-8; Yamamoto Vinita, Osaka, Japan). The Thermotron RF-8 is a capacitive heating device operating at 8 MHz, in which the patient is placed between two electrodes connected to a high-power RF generator, and the use of this device has been reported previously [11–13]. In 23 of 33 patients, both the upper and lower electrodes were 30 cm in diameter, placed on opposite sides of the thoracic region, in 3 patients, both the upper and lower electrodes were 25 cm, in 4 patients, the upper electrode was 25 cm and lower was 30 cm, and in 3 patients, the upper electrode was 10 cm and the lower was 30 cm. The hyperthermia was applied immediately after radiotherapy once or twice a week. The goal of heating was to continue the treatment for least 30 min after RF-output power was increased until reaching the patient's tolerance threshold, and the heating duration was a median of 50 min (range, 40–60 min). The number of hyperthermia treatments during re-irradiation ranged from 2 to 12 (median 5).

In 7 patients treated during the early years of the current study, the intra-tumor temperature ($n=2$) or intra-esophageal temperature ($n=5$) were measured using a four-point microthermocouple sensor. The thermometric parameters measured included the maximum (T_{max}), minimum (T_{min}), and mean (T_{ave}) temperature during the steady-state and at the end of treatment. The steady-state was defined as 20 min after the start of hyperthermia, and the T_{max} , T_{min} , and T_{ave} of the intra-tumor/esophageal temperatures were 41.8 °C (range, 39.7–46.2), 40.2 °C (38.9–43.2) and 41.0 °C (39.3–44.3), respectively. In the remaining patients, the previous correlative data between the RF-output power and the intra-esophageal temperature in a large number of patients, were used to estimate the heating temperature if deep heating using this device was applied with the same size of electrodes and the same body posture, because the measurement of the direct intra-tumor or intra-esophageal temperature was clinically invasive or distressing [14–16]. The median RF-output power ranged from 650 to 1650 W (median 1150 W) in the 23 patients treated with both upper and lower electrodes of 30 cm in diameter.

2.4. Evaluation of the objective response, symptom relief and toxicity

The objective tumor response was evaluated by measuring the tumor size using CT before and after re-irradiation plus regional hyperthermia, and follow-up evaluations were performed by CT every 1–6 months. The treatment response was evaluated according to the World Health Organization criteria [17]. The tumor-related symptoms were also evaluated. Symptom relief was defined as follows; vanished (complete resolution of the symptom); diminished (any improvement without complete resolution); stabilized (no change); or progressive (deterioration), and the best response at any time was reported [18]. The National Cancer Institute Common Toxicity Criteria version 3 (CTCAE) was used to score the patient toxicity. The highest toxicity grade for each patient was used for the toxicity analysis. The toxicity was defined as acute (during therapy and up to 3 months after the combination therapy) or late (over 3 months after the completion of the combination therapy).

2.5. Statistical analysis

The overall patient survival, local (in-field) control and disease progression-free survival rates after re-irradiation were calculated from the first day of re-irradiation using the Kaplan–Meier method. To identify the prognostic factors for survival after re-irradiation plus regional hyperthermia, the univariate analyses were performed. The statistical significance of the differences between the actuarial curves was assessed using the log-rank test. Multivariate analyses using the Cox proportional-hazards model were also performed to evaluate the prognostic factors.

3. Results

The follow-up period was 2–119 months (median 11). Thirty-two (97%) of the 33 patients completed the planned re-irradiation dose. The remaining patient could not complete the planned dose due to worsening of an infectious disease. The acute toxicities \geq Grade 2 included hematological and non-hematological toxicity; thrombocytopenia of Grade 3, which occurred in 1 patient,

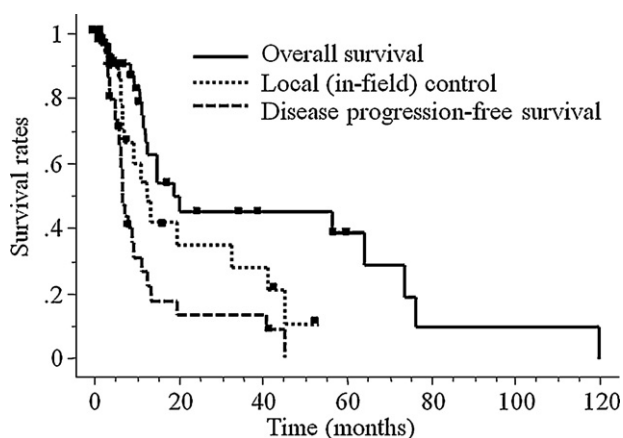


Fig. 1. The overall survival, local (in-field) control, and progression-free survival after re-irradiation of all patients.

neutropenia of Grade 2 in 2 patients, pleuritis of Grade 3 was observed in 1 patient, and radiation dermatitis of Grade 2 developed in 5 patients. Three patients experienced thermal burns, but they healed with conservative management. With regard to late toxicities, a brachial plexus neuropathy of Grade 3 occurred 16 months after re-irradiation in one patient, and radiation pneumonia of Grade 2 occurred in 3 patients at 3, 6 and 8 months after re-irradiation, respectively. There were no other serious complications, even in long-term survivors who lived for more than 3 years after re-irradiation (Table 3).

An objective tumor response was recognized in 14 (42%) of the 33 patients; CR in 3, PR in 11 and NC in 19. Sixteen (94%) of the 17 tumor-related symptoms in 13 patients were improved by the treatment. All 6 patients with pain, considered to be related to the recurrent tumor, had symptom relief (vanished in 2, diminished in 4). All 3 patients with hemoptysis, 3 patients with cough and 2 patients with dyspnea also showed symptom relief (vanished in 2, diminished in 6). An improvement in the numbness of an upper extremity was recognized in 2 of 3 patients (diminished in 2, stabilized in 1).

The median overall survival, local (in-field) control, and disease progression-free survival after re-irradiation in all 33 patients were 18.1 months, 12.1 months, and 6.7 months, respectively (Fig. 1). Table 3 summarizes the data of the long-term survivors (more than 3 years after re-irradiation); 4 (50%) of the 8 patients who achieved long-term survival after re-irradiation received a third course of irradiation with ($n=2$) or without ($n=2$) regional hyperthermia a median of 37 months after the re-irradiation. No third irradiation was performed in non-long-term survivors after re-irradiation.

Table 4 summarizes the results of the univariate and multivariate analyses for the survival rates after re-irradiation. The univariate analyses showed that the absence of distant metastasis was a significant predictor for overall ($p=0.02$; Fig. 2a) and disease progression-free survival ($p=0.008$; Fig. 2b). Tumor size was also a significant predictor for the overall survival rates ($p=0.0002$; Fig. 2c). The multivariate analyses showed that the tumor size (<4 cm) and non-squamous cell carcinoma were significant predictors of a better overall survival, and non-squamous cell carcinoma was a significant predictor for the local (in-field) control rate. In the subset analyses of the 23 patients treated with regional hyperthermia using both upper and lower electrodes of 30 cm in diameter, the use of a higher median RF-output power (≥ 1200 W) tended to be a better prognostic indicator for local (in-field) control ($p=0.08$; Fig. 2d).

Table 4
The results of the univariate and multivariate analyses of certain factors for survival after re-irradiation.

Variable	n	Overall		Local (in-field) control		Disease progression-free						
		Univariate		Univariate		Univariate						
		1-y (%)	p	1-y (%)	p	1-y (%)	p					
Age												
	14	84	0.83	82	0.006	0.89	29	0.61	-	-	-	-
	19	51	-	33	-	1.1 (0.9–3.3)	24	-	-	-	-	-
Performance status												
	24	78	0.05	61	0.39	-	29	0.91	-	-	-	-
	9	40	-	0	-	0.03	0	-	-	-	-	-
Histology												
	16	47	0.09	35	0.04	3.7 (1.2–12.0)	26	0.71	-	-	-	-
	17	85	0.0002	69	0.36	-	27	0.08	1.8 (0.6–5.3)	0.28	-	-
Recurrent tumor size (cm)												
	15	92	0.02	55	0.46	-	43	0.008	2.7 (0.8–8.4)	0.10	-	-
	18	47	-	61	-	2.3 (0.7–7.7)	0	-	-	-	-	-
Distant metastasis												
	9	58	0.12	63	0.83	-	30	0.88	-	-	-	-
	24	70	-	56	-	-	29	-	-	-	-	-
Interval ^a (mos)												
	15	83	0.88	67	0.90	-	24	0.76	-	-	-	-
	18	54	-	41	-	-	33	-	-	-	-	-
Dose of re-RT (Gy)												
	18	68	0.25	58	0.07	2.0 (0.7–5.6)	18	0.64	-	-	-	-
	15	63	-	48	-	-	29	0.04	1.7 (0.7–4.2)	0.28	-	-
Objective tumor response after re-RT												
	14	76	0.55	76	0.89	-	25	-	-	-	-	-
	19	60	-	46	-	-	14	-	-	-	-	-
Concurrent chemotherapy												
	15	64	-	50	-	-	14	-	-	-	-	-
	18	69	-	59	-	-	40	-	-	-	-	-

OR, odds ratio; CI, confidence interval; SqCC, squamous cell carcinoma; RT, radiotherapy; CR, complete response; PR, partial response; NC, no change.
^a Time between initial irradiation and re-irradiation.

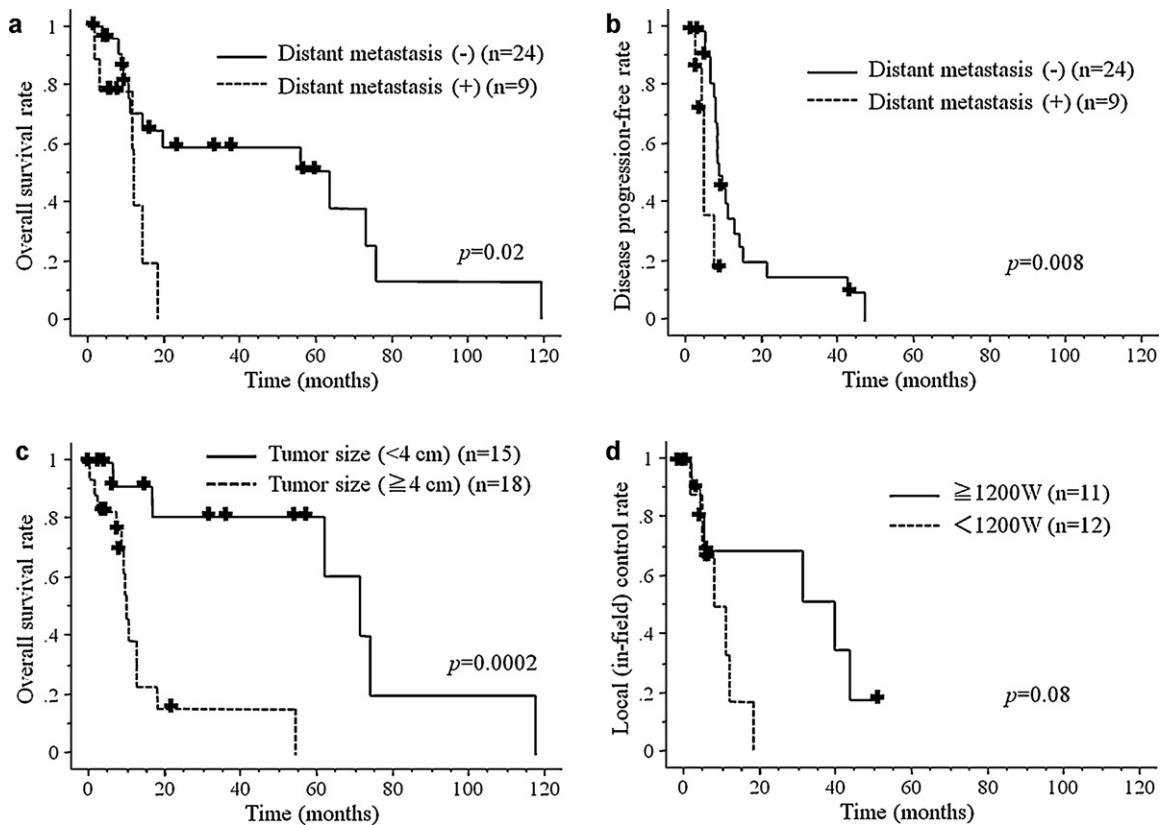


Fig. 2. (a) The absence of distant metastasis had a significantly better overall survival rate after re-irradiation ($p=0.02$). (b) The absence of distant metastasis also had a significantly better progression-free survival rate after re-irradiation ($p=0.008$). (c) The tumor size (<4 cm) was a significant predictor for a better overall survival rate after re-irradiation ($p=0.0002$). (d) The use of a higher median RF-output power (≥ 1200 W) tended to result in a better local (in-field) control rate after re-irradiation in the 23 patients treated with regional hyperthermia using both upper and lower electrodes of 30 cm in diameter ($p=0.08$).

4. Discussion

The current study is the first report of a new treatment option: re-irradiation plus regional hyperthermia for in-field recurrent NSCLC tumors after initial radiotherapy. The incidence of loco-regional recurrence after primary radiotherapy is still high, although concurrent CRT improves the survival time after the treatment of locally advanced NSCLC. Previous reports have shown that re-irradiation monotherapy can be successfully used in recurrent NSCLC with encouraging results, especially for symptomatic improvement. However, we delivered a combination therapy using re-irradiation plus regional hyperthermia for not only palliation of symptoms, but also for curative intent. Our selection of patients for re-irradiation is unique in this respect. There are only a few previous studies of re-irradiation with the aim of achieving a cure or prolongation of survival in patients with recurrent NSCLC [6,19]. Okamoto et al. reported 34 patients with recurrent NSCLC treated with re-irradiation to have a median survival time of 8 months, and there were 6 long-term survivors who lived for more than 20 months without severe toxicity [6]. Tada et al. also demonstrated that in 19 patients with recurrent NSCLC treated with salvage re-irradiation, the median survival time was 7 months [19]. In the current study, we found that re-irradiation plus regional hyperthermia was feasible, with acceptable toxicity, and is a promising treatment that can result in long-term survival, especially for the patients without either distant metastasis or large recurrent tumors. In addition, the median survival of 18 months in the current study was superior to those reported in the previous studies of re-irradiation alone, which may have been due to the effect of the hyperthermia.

As mentioned in the Introduction, modern radiotherapy planning techniques allow for more accurate delivery of the radiation

dose and the potential to escalate the dose without increasing morbidity. Jereczek-Fossa et al. reported the outcome of re-irradiation using three-dimensional conformal or stereotactic techniques in 108 patients with various malignant tumors; the median overall survival was 33 months, and was longer in patients treated with curative intent without severe toxicity [20]. In the current study, re-irradiation using CT-assisted three-dimensional treatment planning was used for all but 3 patients who were treated early in the study in order to limit the total cumulative radiation dose to the spinal cord and esophagus to the tolerance dose, and to reduce the radiation exposure of the other organs as much as possible. Because severe late toxicities of \geq Grade 3, except for a brachial plexus neuropathy of Grade 3 in one patient, were not seen even in the long-term survivors, we believe that these modern techniques are therefore essential for re-irradiation, and that the above-mentioned methods to limit and reduce the re-irradiation dose to the organs at risk in patients with recurrent NSCLC are promising.

An interesting result observed in the current study was that 4 (50%) of 8 long-term survivors after re-irradiation received a third course of irradiation after the re-irradiation (Table 3). The interval between re-irradiation and the third irradiation was a median of 37 months. Okamoto et al. also reported a long-term survivor who was treated with a third course of irradiation 12 months after re-irradiation for recurrent NSCLC [6]. For these delayed re-recurrent tumors, a third course of irradiation may be useful to achieve long-term survival, although the radiation exposure to the organs at risk should be limited and reduced using the same methods as used for the re-irradiation. Further studies are needed to investigate the relationship between the toxicity of each organ, the total cumulative radiation dose, and the interval of irradiation.

Hyperthermia is known to cause direct cytotoxicity to cancer cells, while also acting as a radiation sensitizer [21]. Deep regional hyperthermia-related toxicity in prior studies consisted of subcutaneous fat burns observed in 3–12% of patients. In general, these healed spontaneously and did not result in discontinuation of treatment [22,23]. The randomized phase III study of deep regional hyperthermia did not show any increases in acute or late toxicity from radiotherapy [24]. Several promising results have been reported regarding radiotherapy plus regional hyperthermia for primary NSCLC [15,25–28]. Recent studies indicated that the administration of radiotherapy combined with regional hyperthermia using a higher RF-output power could contribute to better clinical outcomes in patients with Stage III NSCLC [15,16]. The current study shows that re-irradiation plus regional hyperthermia for recurrent NSCLC is well tolerated and the use of a higher median RF-output (≥ 1200 W) may result in a better local control rate.

Regarding limitations associated with this study. Due to the fact that the current study was a small retrospective case series with heterogeneous treatment, the possibility of some selection bias with regard to the prognostic factors could not be ruled out, although we did perform both the univariate and multivariate analyses for the survival rates. A formal prospective trial is consequently needed to determine the efficacy and prognostic factors of this combined therapy in patients with recurrent NSCLC.

In summary, this is the first report that attempted to assess the toxicity and efficacy of re-irradiation plus regional hyperthermia in patients with recurrent NSCLC. This combination therapy showed promising results and acceptable toxicity, and appears to be a feasible treatment modality. Longer-term survival is possible in patients without distant metastasis and larger recurrent tumors. Regional hyperthermia with a higher RF-output power might contribute to better local control. A formal prospective trial with detailed treatment protocols and further investigation of the relationship among the toxicity, radiation dose, thermal parameters, and interval of irradiation are warranted to determine the efficacy and toxicity for this combination therapy for recurrent NSCLC.

Conflict of interest statement

Potential conflicts of interest do not exist in this study.

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