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CLINICAL INVESTIGATION **Lung**

RADIOTHERAPY WITH 8-MHz RADIOFREQUENCY-CAPACITIVE REGIONAL HYPERTHERMIA FOR STAGE III NON–SMALL-CELL LUNG CANCER: THE RADIOFREQUENCY-OUTPUT POWER CORRELATES WITH THE INTRAESOPHAGEAL TEMPERATURE AND CLINICAL OUTCOMES

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Purpose: To assess the efficacy of radiotherapy (RT) combined with regional hyperthermia (HT) guided by radiofrequency (RF)-output power and intraesophageal temperature and evaluate the potential contribution of HT to clinical outcomes in patients with Stage III non–small-cell lung cancer (NSCLC).

Methods and Materials: Thirty-five patients with Stage III NSCLC treated with RT plus regional HT were retrospectively analyzed. Twenty-two of the 35 patients underwent intraesophageal temperature measurements. Patients with subcutaneous fat of 2.5 cm or greater, older age, or other serious complications did not undergo this therapy. The 8-MHz RF-capacitive heating device was applied, and in all patients, both the upper and lower electrodes were 30 cm in diameter, placed on opposite sides of the whole thoracic region, and treatment posture was the prone position. The HT was applied within 15 minutes after RT once or twice a week.

Results: All thermal parameters, minimum, maximum, and mean of the four intraesophageal temperature measurements at the end of each session and the proportion of the time during which at least one of the four intraesophageal measurements was 41°C or higher in the total period of each session of HT, of the intraesophageal temperature significantly correlated with median RF-output power. Median RF-output power (≥1,200 W) was a statistically significant prognostic factor for overall, local recurrence–free, and distant metastasis–free survival.

Conclusions: The RT combined with regional HT using a higher RF-output power could contribute to better clinical outcomes in patients with Stage III NSCLC. The RF-output power thus may be used as a promising parameter to assess the treatment of deep regional HT if deep heating using this device is performed with the same size electrodes and in the same body posture. © 2009 Elsevier Inc.

Regional hyperthermia, Radiotherapy, Non–small-cell lung cancer, Intraesophageal temperature, Locally advanced lung carcinoma.

INTRODUCTION

Lung cancer is currently the most common cause of cancer death in many countries, including Japan. Non–small-cell lung cancer (NSCLC) accounts for approximately 75% of all lung cancers. More than one third of patients with NSCLC have Stage IIIA or IIIB at presentation. A proportion of these patients are amenable to surgical resection; however, the majority have unresectable disease. For many years, the mainstay of treatment for patients with unresectable NSCLC has been radiotherapy (RT) alone. However, the 5-year overall survival rate for definitive RT has been around 5%. Several clinical trials showed that the combination of chemotherapy and RT was superior to RT alone (1). Despite advances in treatment modalities, the 5-year overall survival rate for patients with locally advanced NSCLC remains less than 15% (2).

Hyperthermia (HT) is known to cause direct cytotoxicity for cancer, while also acting as a radiation sensitizer and chemosensitizer. The efficacy of RT plus HT in patients with advanced head and neck cancer, locally recurrent breast carcinoma, and cervical cancer of the uterus was shown and confirmed by randomized Phase III clinical trials (3). Promising results have also been reported regarding RT plus regional HT for Pancoast tumors or lung cancers in contact with the chest wall (4–6). Conversely, lung cancers not contacting

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the chest wall have rarely been attempted for regional HT (7), probably because treatment of those lesions would involve the physical difficulties associated with the delivery of heat and measurement of temperature. In most treatments for patients with lung cancer, direct intratumor measurements tend to be clinically difficult to manipulate, invasive, or uncomfortable for patients. van der Zee *et al.* (8) reported that direct intratumor measurements for deep-seated tumors also had the possibility of causing severe complications (*e.g.,* subcutaneous or deep infection, intolerable pain, and bleeding) while providing information of limited disproportional clinical value. Conversely, intraluminal thermometry (*e.g.,* intravaginal, intrarectal, and intravesical thermometry) provides sufficient information to apply deep regional HT to patients with pelvic tumors (8, 9). The Thermotron RF-8 system (Yamamoto Vinita Co., Osaka, Japan) is a capacitive heating device operating at 8 MHz, in which the patient is placed between two electrodes connected to a high-power radiofrequency (RF) generator. Hamazoe *et al.* (10) reported that patients with pancreatic or bile duct tumors were treated with chemotherapy plus regional HT using this device. There was a strong positive correlation between maximum RF-output power and maximum temperature of the tumors if deep heating was applied with the same size of electrodes and same body posture, and the objective response rate increased with RF-output power (10).

In this context, we added regional HT to RT to enhance the effect of RT in patients with Stage III NSCLC and assumed the tumor temperature indirectly by measuring the intraesophageal temperature and/or RF-output power. However, to our knowledge, there are no clinical reports regarding this strategy. The purpose of our study is to evaluate the efficacy of RT combined with regional HT and the potential contribution of regional HT guided by intraesophageal temperature and RF-output power to clinical outcomes in patients with Stage III NSCLC.

METHODS AND MATERIALS

Patients

From Oct 1993 to April 2002, a total of 35 patients (34 men, 1 woman; age range, 36–75 years; median, 64 years) with Stage III NSCLC were treated with RT with regional HT. Tumor temperature was indirectly estimated by measuring the intraesophageal temperature and/or RF-output power, and results were retrospectively analyzed. Characteristics and treatments of patients are listed in Tables 1 and 2. Twenty-two of 35 patients underwent measurement of intraesophageal temperature. In the remaining 13 patients, intraesophageal temperature was not measured, and RF-output power alone was used to estimate tumor temperature. Eastern Cooperative Oncology Group performance status and tumor, node, metastasis (TNM) stage (International Union Against Cancer TNM classification, 5th edition) were evaluated at the start of this treatment. Patients with subcutaneous fat thickness greater than 2.5 cm, which causes a decrease in the effectiveness of the RF-capacitive device, older age (>75 years), or other serious complications did not undergo this therapy. After this combined therapy, 34 of 35 patients underwent best supportive care, at least until disease progression. The remaining patient received adjuvant systemic chemotherapy with carboplatin and regional HT. Preoperative or postoperative cases were not included in this study.

Table 1. Patient characteristics

Characteristics	All patients (n = 35)	Patients* (n = 22)
Median age, y (range)	64 (36–75)	64 (36–75)
Gender		
Men/women	34/1	21/1
Performance status		
0/1/2	3/23/9	2/16/4
Histologic type		
Adenocarcinoma	12	11
Squamous cell carcinoma	21	9
Others	2	2
Tumor location		
Predominant lobe involved		
Right upper lobe	16	11
Right middle lobe	1	1
Right lower lobe	7	3
Left upper lobe (and lingula)	8	5
Left lower lobe	3	2
Centrally located tumors	25	15
Peripherally located tumors	10	7
Tumor size		
0–3.0	2	2
3.1–5.0	17	11
5.1–8.0	13	7
≥8.1	3	2
Tumor, node, metastasis†		
IIIA	5	2
T1N2M0	1	1
T2N2M0	2	1
T3N1M0	1	0
T3N2M0	1	0
IIIB	30	20
T1N3M0	1	1
T2N3M0	6	5
T3N3M0	4	3
T4N0M0	2	1
T4N1M0	2	0
T4N2M0	13	8
T4N3M0	2	2
Subcutaneous fat (mm)		
0–4	14	10
5–25	21	12
Thickness of thorax (cm)		
15–17	13	8
18–22	22	14

* Patients who underwent measurement of intra-esophageal temperature.

† International Union Against Cancer tumor, node, metastasis classification, 5th edition.

Although no specific chemotherapy protocol existed, 17 of 35 patients (49%) received induction chemotherapy as follows: a bronchial arterial infusion of cisplatin in 9 patients, carboplatin in combination with etoposide administered intravenously in 3 patients, cisplatin in combination with vindesine administered intravenously in 3 patients, cisplatin in combination with carboplatin administered intravenously in 1 patient, and cisplatin alone administered intravenously in 1 patient. In only 4 patients (11%), carboplatin was also administered concurrently with RT.

Hyperthermia

The HT was applied within 15 minutes after RT once or twice a week. The heat was applied using an 8-MHz RF-capacitive

Table 2. Treatment methods

Treatment methods	All patients (n = 35)	Patients* (n = 22)
Radiotherapy		
Median total dose (Gy)	61.2	60.4
Range (Gy)	45.0–80.0	45.0–80.0
Daily dose (Gy)	1.5–3.4	1.5–3.4
BED Gy10		
≥50 and <60 Gy10	3	1
≥60 and <70 Gy10	7	6
≥70 and <80 Gy10	12	9
≥80 and <90 Gy10	8	3
≥90 Gy10	5	3
Chemotherapy	19	13
Induction chemotherapy	17	13
Concurrent chemotherapy	4	0
Hyperthermia during radiotherapy		
Median times	11	12
Range	3–17	5–17

Abbreviation: BED = biologically effective dose.
* Patients who underwent measurement of intraesophageal temperature.

regional HT (Thermotron RF-8). Physical features of the RF-8 clinical HT machine and thermal distribution characteristics in a phantom, as well as in the human body, when heating with this device have been reported previously (11, 12). Heating duration was adjusted from 40–70 minutes based on the patient's tolerance (median, 50 minutes). The goal of heating was to continue the treatment for least 30 minutes after RF output was increased until reaching the patient's tolerance threshold, and maximum total treatment duration was 70 minutes. The number of HT treatments during RT ranged from three to 17 (median, 11 treatments). In all cases, both the upper and lower electrodes were 30 cm in diameter and placed on opposite sides of the whole thoracic region, and treatment posture was the prone position to reduce the degree of pain caused by heating (13). Patients were carefully instructed to mention any unpleasant sensation suggestive of a hot spot. The RF output was increased to the maximum level tolerated by the patient after appropriate adjustments of the treatment setting. For reduction of the preferential heating of subcutaneous fat tissue, the overlay boluses were applied in addition to regular boluses attached in front of the metal electrodes. In 13 of 35 patients (37%), HT alone was continued three to 26 times (median, 12 times), once or twice a week after the completion of RT.

Intraesophageal temperature was measured in 22 patients using a four-point microthermocouple sensor, which was inserted into the esophagus at the level of the bifurcation of the trachea through a 12-Fr catheter under x-ray fluoroscopy. The thermometric parameters measured included minimum (T_{min}), maximum (T_{max}), and mean (T_{ave}) of the four intraesophageal temperature measurements at the end of each session, and the proportion of the time during which at least one of the four intraesophageal measurements was 41°C or higher in the total period of each session of HT ($\%T \geq 41°C$). The number of measurements was one (n = 21) or two (n = 1) times. Median RF-output power was obtained during the steady state, defined as 20 minutes after the start of HT, and at the end of treatment.

Radiotherapy

The RT was administered conventionally once daily five times/week and performed using a 4-, 6-, or 10-MV linear accelerator, and computed tomography–assisted three-dimensional treatment planning (FOCUS; CMS Japan, Tokyo, Japan) was used in 33 of 35 patients (94%). For each patient, computed tomography planning was used to determine the radiation fields, with clinical target volume defined as the primary lung tumor and regional lymph nodes. The planning target volume (PTV) included the clinical target volume plus a 1–2-cm margin for daily set-up variation in the cranial-caudal dimension to account for the ventilatory motion of the lung. The initial field covered the PTV with anteroposterior-posteroanterior technique. Normally, the field was then shrunk at the dose of 40–50 Gy to the primary and enlarged lymph nodes for the boost doses of 10–30 Gy. The spinal cord was also spared when total dose reached 40–50 Gy. The irradiated lung volume was to be kept as small as possible. The RT was given during 36–64 days (median, 50 days). Total radiation dose ranged from 45.0–80.0 Gy (median, 61.2 Gy), and a daily dose was 1.5–3.4 Gy (median, 2.0 Gy). In 11 of 35 patients (31%), the PTV (including primary lung tumor and regional lymph nodes) was given a daily dose of 1.5–2.2 Gy (to 15.0–45.0 Gy; median, 32.0 Gy), with a 0.5–1.4-Gy concomitant boost (field within a field) for an additional 5.0–23.4 Gy (median, 15.2 Gy) to the primary lung tumor.

The biologically effective dose (BED) can be used to compare the efficacy of various dose-fractionation regimens in providing tumor control (14, 15). The BED (total dose) × (1 + daily dose/[α/β]) using a linear quadratic model with α/β ratios of 10, ranged from 51.5–107.0 Gy10 (median, 75.4 Gy10; Table 2).

Evaluation of objective response and toxicity

Tumor response was evaluated by measuring tumor size using computed tomography before and after RT with regional HT. Treatment response was evaluated according to World Health Organization criteria (16). A complete response (CR) was defined as complete disappearance of all clinically detectable tumors for at least 4 weeks. A partial response (PR) required at least a 50% reduction in the sum of the products of the longest perpendicular diameters of all measurable lesions. Progressive disease required a 25% increase in measurable lesions or the appearance of any new measurable or nonmeasurable lesion. Patients who did not meet the definitions of response or progression were classified as having no change.

Toxicity was scored according to criteria of the Radiation Therapy Oncology Group, except for the HT-related toxicity of skin burn (17). The highest toxicity grade for each patient during and after RT with regional HT was used for the toxicity analysis.

Statistical analysis

Overall, local recurrence–free, and distant metastasis–free survival rates were calculated from the start of RT by using the Kaplan-Meier method. The statistical significance of the difference between the actuarial curves was assessed using log-rank test. To identify prognostic factors, univariate analyses were performed using age, performance status, tumor size, histologic characteristics, subcutaneous fat, thickness of thorax, total radiation dose (BED), induction chemotherapy, concurrent chemotherapy, median heating duration, number of HT treatments during RT, median RF-output power, and continuation of HT alone. In addition, the univariate Cox proportional model was fit to assess the influence of median RF-output power on overall, local recurrence–free, and distant metastasis–free survival rates. Associations between certain factors, including thermal parameters, subcutaneous fat, thickness of the thorax, and median RF-output power, were evaluated using a linear regression analysis.

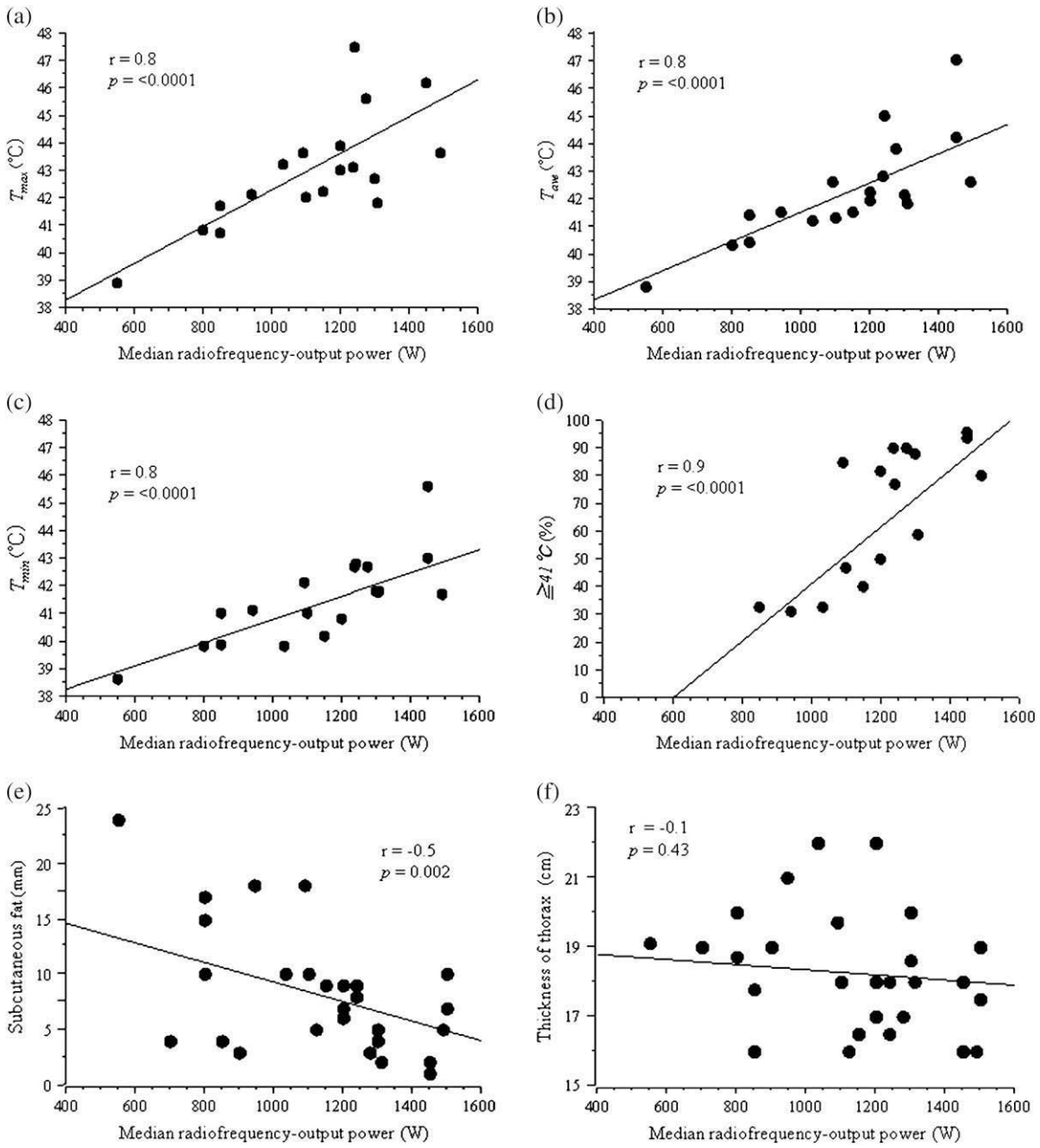

Fig. 1. All thermal parameters, (a) maximum (T_{max}), (b) average (T_{ave}), and (c) minimum (T_{min}) of the four intraesophageal temperature measurements at the end of each session, and (d) the proportion of the time during which at least one of the four intraesophageal measurements was 41°C or higher in the total period of each session of hyperthermia ($\%T \geq 41°C$), significantly correlated with median radiofrequency (RF)-output power. (e) Subcutaneous fat inversely correlated with median RF-output power. (f) There was no correlation between thickness of the thorax and median RF-output power.

RESULTS

Thermometry results

Intraesophageal T_{max} in the 22 patients who underwent measurement of intraesophageal temperature ranged from 38.9–48.1°C, with a median of 43.2°C. The T_{ave} ranged from 38.8–47.0°C, with a median of 42.2°C. The T_{min} ranged from 38.6–45.6°C, with a median of 41.7°C. The $\%T \geq 41°C$ ranged from 0–96%, with a median of 79%. Median RF-output power ranged from 548–1,660 W, with a median of 1,220 W in all 35 patients. Figure 1 shows the relationship between median RF-output power and intraesophageal temperature in the 22 patients who underwent measurement of intraesophageal temperature. All thermal parameters, T_{min}, T_{max}, T_{ave}, and $\%T \geq 41°C$, of intraesophageal temperature significantly correlated with median RF-output power. The thickness of subcutaneous fat in all 35 patients inversely correlated with median RF-output power. There was no correlation between thickness of the thorax and median RF-output power.

Objective tumor response and survival

Tumor response was CR in 7 patients, PR in 23 patients, and no change in 5 patients. The CR plus PR rate was 86%.

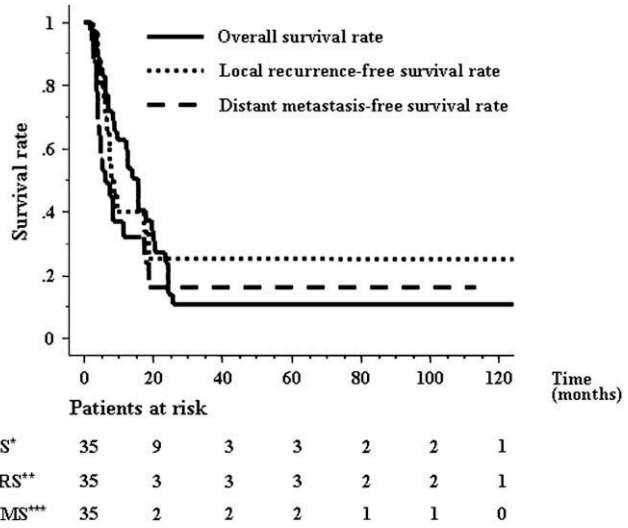

Fig. 2. Overall survival (OS), local recurrence–free survival (LRS), and distant metastasis–free survival (DMS) of all patients. The number of patients at risk at each period in each survival rate is shown below the survival curve. *OS; **LRS; ***DMS.

Follow-up ranged from 2–151 months (median, 14 months). Median overall, local recurrence–free, and distant metastasis–free survival times were 14.1, 7.7, and 6.1 months, respectively (Fig. 2). The first site of relapse is listed according to the respective histologic type in Table 3. Table 4 lists univariate analysis for the three survival rates in all patients. Median RF-output power (≥1,200 W) was a significantly good prognostic factor for all three survival rates (Fig. 3). Younger age (<65 years) was also a significantly good predictor for all three survival rates. Median RF-output power (≥1,200 W) was also found to be a statistically significant prognostic factor according to a univariate Cox proportional model on the overall (p = 0.01), local recurrence–free (p = 0.004), and distant metastasis–free (p = 0.02) survival rates.

Acute and late toxicity

Acute toxicity was generally mild. Grade 2 or more toxicity was seen at five sites in 5 patients (14%); Grade 3 dermatitis (n = 2), Grade 2 dermatitis (n = 1), and Grade 2 esophagitis (n = 2). In 1 patient, a skin burn was seen that disappeared spontaneously after completion of combined therapy. Insertion of the microthermocouple sensor into the esophagus caused some discomfort, which disappeared rapidly after the heating session without complications. Late toxicity was seen in 6 patients (17%). All those involved radiation pneumonitis/pulmonary fibrosis. Grade 4 toxicity of pneumonitis/pulmonary fibrosis was observed in 1 patient. In the remaining 5 patients, Grade 2 pneumonitis/pulmonary fibrosis was observed.

DISCUSSION

The use of regional deep heating has been investigated, especially for the treatment of patients with pelvic tumors and soft-tissue sarcoma (3). Randomized trials of RT with or without regional HT for patients with cervical cancer showed positive results concerning survival (18, 19). There is little information reported in the literature on the use of regional HT for the treatment of patients with lung cancer, probably because most available devices for regional deep heating are structurally difficult to apply to the thoracic region. In addition, the use of thermometry is more invasive when used to treat lung cancer than when used for pelvic tumors or a soft-tissue sarcoma of an extremity. The present study is the first to try to assess a combination therapy of RT and regional HT without direct tumor thermometry, guided by intraesophageal temperature and/or RF-output power, in patients with Stage III NSCLC. This study shows that the combined therapy was feasible, and RF-output power significantly correlated with intraesophageal temperature while, in addition, higher RF-output power predicted longer survival, improved local control, and improved the metastasis-free rate. We believe that regional HT using higher RF-output power acted strongly as a radiosensitizer and contributed to better clinical outcomes.

Table 3. First site of disease progression

Histologic type	Sq (n = 21)	Ad (n = 12)	Others (n = 2)
Local	5	0	0
Distant	7	7	0
Local + distant	2	3	0

Abbreviations: Sq = squamous cell carcinoma; Ad = adenocarcinoma.

Some reports described the feasibility and efficacy of regional HT using an 8-MHz RF-capacitive heating device with RT for patients with lung cancer (4–7). Hiraoka *et al.* (5) reported that 20 patients with locally advanced lung cancer in contact with the chest wall were treated by means of RT plus regional HT such that transcutaneous insertion of thermal probes into the tumor was possible, and higher thermal parameters were closely related to the appearance of low density on posttreatment computed tomography. The tumor temperature by direct measurements tended to correlate with an objective tumor response of NSCLC in another report using a similar approach (7). However, Fatehi *et al.* (9) recently reported that intraluminal thermometry provided sufficient information to apply deep HT to individual patients with pelvic tumors because intratumor and intraluminal temperatures during individual treatments highly correlated, and average intratumor and intraluminal temperatures were not different. In our study, because RF-output power correlated significantly with intraesophageal temperature, RF-output power and intraesophageal temperature may be used as a promising parameter to assess the treatment of deep regional HT for patients with NSCLC, if deep heating using an 8-MHz RF-capacitive heating device is enforced with the same size of electrodes and the same body posture. This strategy of regional HT, which is less invasive and causes less distress, may be suitably incorporated into the clinical combined-modality therapy.

One of the well-known disadvantages of an RF-capacitive device is the preferential heating of subcutaneous fat tissue, whereas Asian patients are considered to be relatively suitable

Table 4. Univariate analyses of certain factors for survival rates in all patients

		Overall survival rate		Local recurrence–free survival rate		Distant metastasis–free survival rate	
	Pt.(n)	MST (mo)	*p*	MST (mo)	*p*	MST (mo)	*p*
Age (median, 64 y)							
<65	18	18.7	0.02	17.2	0.02	9.4	0.01
≥65	17	12.4		5.3		4.0	
Performance status							
0–1	26	13.5	0.58	8.9	0.09	5.3	0.65
2	9	13.0		6.0		7.0	
Tumor size (cm)							
<5	14	19.0	0.14	18.8	0.18	7.2	0.37
≥5	21	12.2		7.3		5.3	
Histologic type							
Squamous cell ca.	21	13.5	0.54	7.3	0.20	6.3	0.69
Others	14	12.1		18.8		5.6	
Subcutaneous fat (mm)							
0–4	14	14.6	0.25	7.3	0.92	5.1	0.37
5–25	21	13.5		7.9		6.6	
Thickness of thorax (cm)							
15–17	13	14.0	0.93	12.0	0.68	3.9	0.10
18–22	22	12.3		7.5		7.5	
Total radiation dose (BED, Gy10)							
<74	16	12.1	0.22	16.6	0.12	8.3	0.03
≥74	19	13.7		6.7		4.0	
Induction chemotherapy							
Yes	17	10.5	0.97	8.3	0.28	6.3	0.76
No	18	14.7		6.6		5.2	
Concurrent chemotherapy							
Yes	4	7.6	0.03	5.4	0.53	4.9	0.91
No	31	14.9		8.2		5.9	
Median heating duration (minutes)							
<50	12	15.2	0.61	6.2	0.12	3.9	0.14
≥50	23	12.2		9.1		7.6	
No. of HT treatments during RT							
<9	13	12.2	0.56	6.1	0.13	5.7	0.40
≥10	22	14.6		14.1		6.0	
Median RF-output power (W)							
<1,200	15	7.8	0.009	5.6	0.001	4.4	0.01
≥1,200	20	19.3		18.8		11.0	
Continuation of HT alone*							
Yes	13	18.5	0.05	8.6	0.18	10.7	0.07
No	22	12.2		7.4		4.7	

Abbreviations: BED = biologically effective dose; MST = median survival time; HT = hyperthermia; RT = radiotherapy.
* After the completion of RT.

because of their slender constitution. The excessive power deposition in fatty tissue limits the effectiveness of the capacitive technique. There is a depth limit to the skin-cooling ability of the overlay bolus in the 8-MHz RF-capacitive heating device (20, 21). Therefore, we did not apply regional HT to patients with subcutaneous fat thickness greater than 2.5 cm, and the thickness of subcutaneous fat inversely correlated with RF-output power, even in patients with subcutaneous fat thickness less than 2.5 cm. It therefore may be necessary to assess the effect of regional HT on patients with such limited indications.

A concern in applying regional HT to lung tumors has been the presence of air in the thorax. In previous animal and human studies, normal lung tissue could be heated using an RF-capacitive heating technique (22, 23). Hatano *et al.* (23) measured thermal distributions of the tumor and surrounding normal tissue in the lung using an RF-capacitive heating technique, and the maximum temperature of normal lung tissue could be decreased about 1–3°C even if the maximum temperature in the tumor was maintained at 42–44°C. The RF-capacitive regional heating may increase tumor temperature in the lung without serious damage of normal lung tissue. In our study, regional HT also did not show significant HT-related toxicity in the lung.

In recent years, in patients with locally advanced NSCLC, two randomized studies that compared concurrent vs. sequential chemoradiotherapy showed that the concurrent approach provided a superior outcome (24, 25). In our study, improvement in outcomes by using chemotherapy was not confirmed. However, because only 4 patients were treated with concurrent chemotherapy and no specific chemotherapy protocol

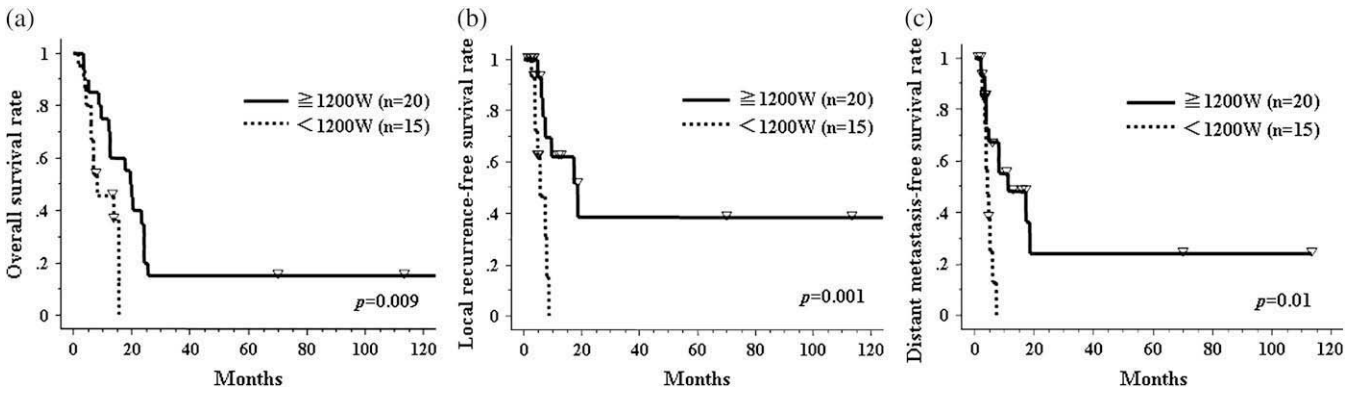

Fig. 3. Overall survival, local recurrence–free survival, and distant metastasis–free survival of patients with median radiofrequency-output power of 1,200 W or greater compared with less than 1,200 W using the Kaplan-Meier method and analyzed using log-rank test. Inverted triangles indicate censored cases. (a) Median survival times for overall survival were 19.3 months for the patients with median radiofrequency-output power of 1,200 W or greater and 7.8 months of less than 1,200 W ($p = 0.009$). (b) Median survival times for local recurrence–free survival were 18.8 months of 1,200 W or greater and 5.6 months of less than 1,200 W ($p = 0.001$). (c) Median survival times for distant metastasis–free survival were 11.0 months of 1,200 W or greater and 4.4 months of less than 1,200 W ($p = 0.01$).

existed, the effect of chemotherapy was not considered to have been adequately evaluated. Triple-modality therapy consisting of chemotherapy, RT, and regional HT for patients with rectal and cervical cancer has shown promising results (26, 27). Additional studies using chemoradiotherapy plus regional HT are necessary in patients with NSCLC.

In summary, this is the first report to attempt to assess the combination therapy of RT and regional HT without direct intratumor thermometry in patients with Stage III NSCLC, and we confirm that the combined therapy is feasible and regional HT using higher RF-output power may positively contribute to better clinical outcomes in such patients. Because RF-output power significantly correlated with intraesophageal temperature, it may be used as a promising parameter to assess the treatment of deep regional HT if deep heating using an 8-MHz RF-capacitive heating device is enforced with the same size of electrodes and same body posture. This strategy of regional HT, which is less invasive and well tolerated, therefore may be suitably incorporated into the combined clinical therapeutic modality.

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