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Effect of hyperthermia combined with external radiation therapy in primary non-small cell lung cancer with direct bony invasion

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Purpose: Local control in lung cancer directly invading the bone is extremely poor. Effects of regional hyperthermia combined with conventional external beam radiation therapy were evaluated.

Materials and methods: Thirteen patients with non-small lung cancer (NSCLC) with direct bony invasion were treated with hyperthermia plus irradiation (hyperthermia group). The treatment outcome was compared with the historical treatment results in 13 patients treated with external radiation therapy alone (radiation alone group). In patients with no distant metastasis, radiation therapy at a total dose of 60–70 Gy was administered to both groups. Hyperthermia was performed for 45–60 min immediately after irradiation for two–four sessions with radiofrequency capacitive heating devices.

Results: For primary response, 10 of the 13 tumours responded to the treatment (3 CR, 7 PR) in the hyperthermia group, whereas seven tumours responded (1 CR, 6 PR) in the radiation alone group. The 2-year local recurrence-free survival rate for clinical M_0 patients in the hyperthermia group and that in the radiation alone group were 76.1 and 16.9%, respectively. Three patients died of distant metastases within 2 years in the hyperthermia group, but two out of three tumours histologically disappeared, even in the autopsy examination. The 2-year overall survival rate for clinical M_0 patients in the hyperthermia group and that in the radiation alone group were 44.4 and 15.4%, respectively. No severe pulmonary complication was observed in either group.

Conclusions: Regional hyperthermia combined with conventional irradiation could be a tool to improve local control in patients with NSCLC deeply invading the chest wall.

Key words: Lung cancer, radiation therapy, hyperthermia, chest wall.

1. Introduction

Non-small cell lung cancer (NSCLC) with direct bony invasion is characterized as deep involvement of the chest wall and, in most cases, as a relatively large volume tumour. The standard treatment for this type of disease has been considered to be surgical resection[1]; however, many tumours are unsuitable for surgical resection because of the advanced age of the patient, poor general condition, accompanying medical problem, and involvement of the vertebral bones. Locoregional irradiation has represented the traditional approach in these patients; however, patients with regionally advanced, surgically unresectable NSCLC have an extremely poor prog-

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nosis. In general, patients have been treated with external beam irradiation applied to the primary tumour and regional lymph nodes, with cytotoxic chemotherapy for the purpose of symptom alleviation and in the hope of producing a rare long-term survivor. Approximately two thirds of patients with locally advanced NSCLC will die from intrathoracic disease, with or without distant metastases[2]. Local tumour control is an important goal of primary treatment because local failure leads to major morbidity. At present, more aggressive treatment applied to locoregional sites is advocated to improve prognosis.

Experimental research shows that hyperthermia has a mechanism which selectively kills tumour cells, especially cells in hypoxic, poor perfusion and low pH environments, conditions that are specifically found in tumour tissue. It has been clearly shown that hyperthermia in combination with radiation therapy increases the cytotoxic effect, in so-called hyperthermic radiosensitization. Furthermore, recent randomized clinical trials on hyperthermia have produced the promising results for tumours in various sites[3–8]. However, there are few clinical reports in the literature on NSCLC treated with irradiation combined with hyperthermia[9,10].

This study presents the effect of regional hyperthermia in combination with conventional irradiation for NSCLC with direct bony invasion.

2. Materials and methods

2.1. *Patient*

During the period 1995–1999, 13 consecutive patients with primary NSCLC directly invading the bony structure were treated with external radiation therapy combined with hyperthermia (hyperthermia group). Metastases in the distant sites were observed in four of the 13 patients who were treated with palliative intent. To compare with the hyperthermia group, radiation therapy was assessed alone as an historical control in patients without distant metastasis from 1976–1994 (radiation alone group). The patients characteristics are summarized in table 1. Most histology was squamous cell carcinoma in both groups. Larger tumours in the advanced T stage were included in the hyperthermia group, whereas the patients with a poor performance status and in the advanced N stage were likely to be treated with radiation alone.

Table 1. Patient characteristics.

	Hyperthermia + radiation		Radiation alone
	Curative ($n = 9$)	Palliative ($n = 4$)	Curative ($n = 13$)
Gender (M/F)	7/2	4/0	13/0
Age	40–77 (median 62)	57–79 (median 64)	61–80 (median 69)
PS (0–1/2–3)	7/2	0/4	4/9
Pathology (Sq/Ad/others)	6/1/2	4/0/0	11/1/1
T factor (3/4)	3/6	2/2	9/4
N factor (0/1/2/3)	5/2/1/1	3/0/1/0	6/1/4/2
Stage (2B/3A/3B/4)	1/2/6/0	0/0/0/4	4/4/5/0
Tumour size (cm)	8.2 (4.6–12.5)	6.8 (6.0–8.0)	6.3 (4.5–8.0)
Total radiation dose (Gy)	67.6 (60–70)	64.5 (56–70)	66.8 (60–70)

PS: performance status, Sq: squamous cell carcinoma, Ad: adenocarcinoma.

2.2. *Treatment*

The radiation therapy method was reported previously[11–13]. All patients were treated with 10 MV X-rays by using conventional fractionation of 2 Gy once a day for 5 days per week. The radiation field in the first treatment utilized antero-posterior parallel opposed fields which included the primary tumour and regional lymph nodes besides the primary tumour. After 40 Gy, an additional dose was delivered with the boost fields by using the exact field determination of the tumour response. Uninvolved mediastinal lymph nodes were irradiated with up to 40 Gy, and involved nodes were irradiated up to 60 Gy. In most patients with stage N0, N1 and ipsilateral N2 disease, the spinal cord was avoided by means of antero-posterior portals after 40 Gy. In patients with metastases to the subcarinal lymph node and N3 disease, the primary tumour and involved lymph nodes were irradiated with oblique fields to diminish the dose to the spinal cord. The majority of patients were given a total dose of 60–70 Gy in 6–7 weeks. Combination chemotherapy was not performed in this series.

The first hyperthermia treatment was started when the total irradiation dose reached 40 Gy or more. In this series, the patients received two-to-four sessions of hyperthermia once weekly. Hyperthermia was performed immediately after the irradiation fraction with radiofrequency devices (Thermox-1000, Omron Co. Ltd. and Thermotron-RF 8, Yamamoto Vinita Co. Ltd., Japan). Coupling of the applicator to the patient was usually achieved with plastic bags filled with deionized water. For temperature monitoring of the tumours, a fine plastic needle containing a thermocouple thermometer was directly inserted into the tumour under local anaesthesia with guidance by means of echography. Multiple locations inside the tumour were monitored with a single needle containing a multisensor probe. For each monitored location, temperatures were recorded every minute during hyperthermic treatment. Active skin cooling at 5°C was applied to most patients during the treatment. The treatment was conducted with vital signs monitored at least every 10 min by a nurse in the Radiation Oncology Department. Power outputs were increased to patients' tolerance level. The aim was to continue treatment for 60 min after the measured tumour temperature had reached 42°C. Minimum, average, maximum intratumoral temperatures (T_{min}, T_{av} and T_{max}) and T_{50}, T_{90} were taken at the end of each hyperthermic session.

2.3. *Evaluation and statistics*

The endpoints of this study were primary response, local control, overall survival and complication rate. In all patients, primary response and early complications were evaluated. The local control rates, survival rates and late complications were assessed in patients with clinical M_0. The primary response was assessed at 1 month after completion of the treatment as follows: CR (completely regressed); PR (over 50 regression of the tumour); and NC (less than 50% regression). The tumour was considered controlled if it remained stable until the patient's death or until the last follow-up. Significance levels between thermal parameters and local response were determined by Student's *t*-test. Locoregional recurrence-free and overall survival rates were determined by means of Kaplan-Meier survival curves. Significance levels between curves were calculated by the generalized Wilcoxon test. Early pulmonary complications were assessed by the National Cancer Institute–Common Toxicity Criteria (NCI-CTC). Late pulmonary and late spinal complications were assessed by the Late Radiation Morbidity Scoring Scheme of the Radiation Therapy

Oncology Group and the European Organization for Research and Treatment of Cancer (RTOG/EORTC)[14].

3. Results

3.1. *Quality of hyperthermia*

For a total of 32 sessions of hyperthermia, intratumoural temperatures were obtained in 26 of 32 (81.3%) sessions. The values for T_{min}, T_{av} and $T_{max} \pm$ standard error were 40.8 ± 0.22, 41.7 ± 0.26 and 42.5 ± 0.30°C, respectively, with an average duration of 49.9 ± 8.8 min.

3.2. *Primary response*

For primary response, 10 of the 13 tumours responded to the treatment (3 CR, 7 PR) in the hyperthermia group, whereas seven responded (1 CR, 6 PR) in the radiation alone group. The complete response (CR) and overall response rates of the hyperthermia group were higher than those of the radiation alone group; however, there was no statistical significance. Figure 1 shows the correlation between thermal parameters and responses in the hyperthermia group. In the CR group, T_{min} and T_{90} values looked higher than those in the NC group, but there were no statistical significance.

3.3. *Survival*

Figure 2 shows locoregional recurrence-free survival in both groups. The 2-year local recurrence-free survival rates were 76% in the hyperthermia group and 17% in the radiation alone group. Two out of three patients in the hyperthermia group who died of distant metastasis within 2 years were autopsied and the tumours had disappeared even in the histological examinations. Figure 3 shows 2-year overall survival in both groups. The survival rates for 2 years were 44% in the hyperthermia group and 15% in the radiation group, with no statistical significance.

3.4. *Complications*

Table 2 shows complication rates of both groups. There was no grade 3–4 severe pulmonary complication in either group, but one patient developed grade 4 myelopathy in the radiation alone group.

3.5. *Short case reports*

Figure 4 shows radiograms and CT images for treatment of large squamous cell carcinoma with direct vertebral body invasion. This patient received 70 Gy of conventional radiation combined with two sessions of hyperthermia. After the treatment, the tumour had decreased in size. The primary response in this case was assessed as partial response. However, the tumour continued to decrease in size. As a result, the patient survived for 42 months after the treatment with no locoregional recurrence. Another patient had primary squamous cell carcinoma in the left upper lobe (figure 5). This patient also received 70 Gy of conventional radiation with two sessions of hyperthermia. The tumour had decreased in size just after the treatment, and the primary response was assessed as PR. However, the patient survived for 4 years after the treatment with no obvious recurrence. Table 3 shows the patients with good clinical courses in the hyperthermia group. There were four long-term survivors with no apparent recurrence.

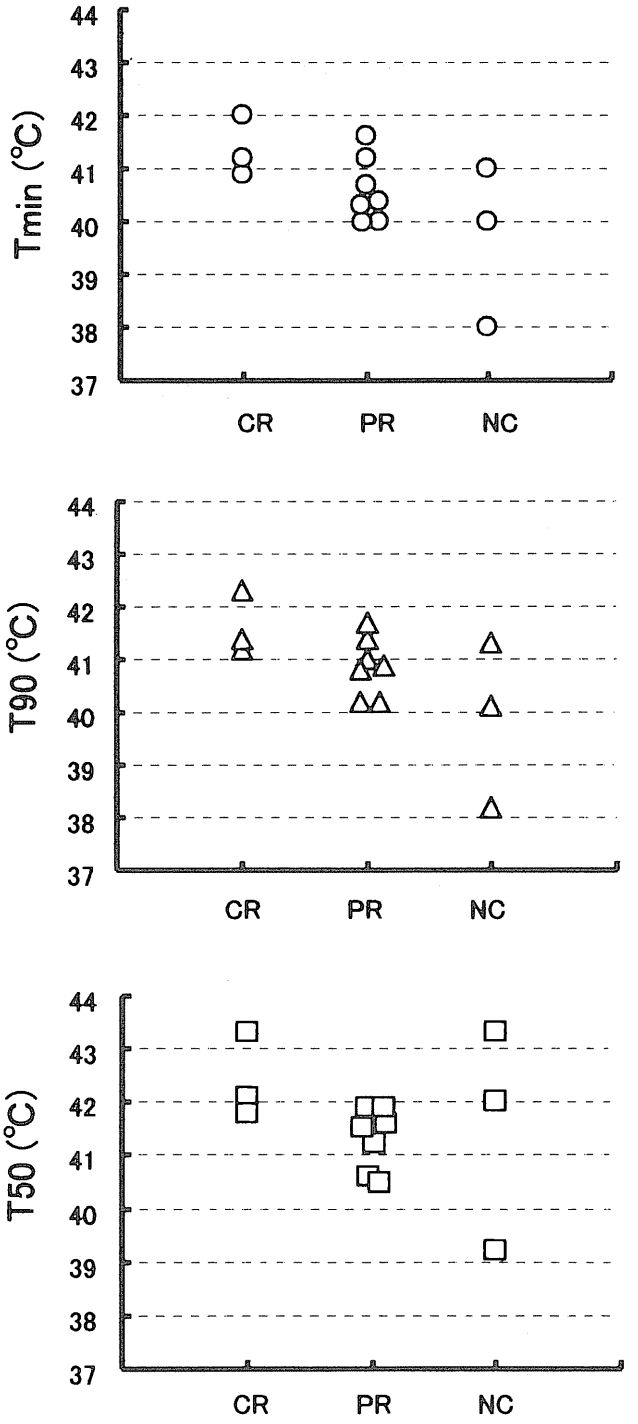

Figure 1. The correlation between thermal parameters (T_{min}, T_{90}, T_{50}) and primary response. There are no statistical significance in the response groups.

4. Discussion

This study was conducted to evaluate the hypothesis that regional hyperthermia combined with irradiation would provide not only local control but also survival superior to conventional irradiation for NSCLC with deep invasion of the chest wall. The result showed improved local control and survival, even if the recent improvement of patient management would be considerably contributing to the improvement of survival of the hyperthermia group. In this study, the majority of patients had squamous cell tumours which were treated without cytotoxic chemotherapy.

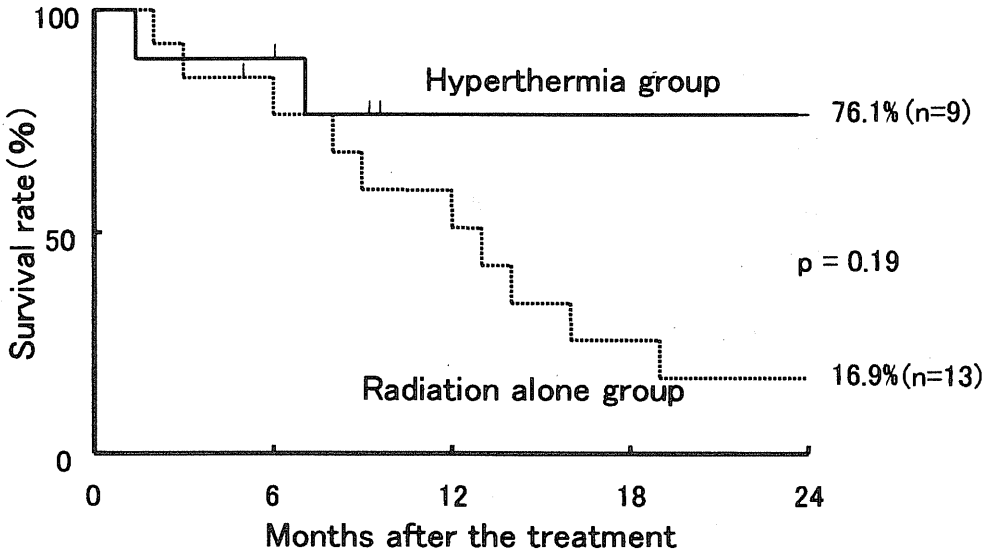

Figure 2. Local recurrence-free survival curves of curative patients in the hyperthermia group and in radiation alone. The survival rate was determined by the Kaplan-Meier method. The *p*-values were estimated with the generalized Wilcoxon test.

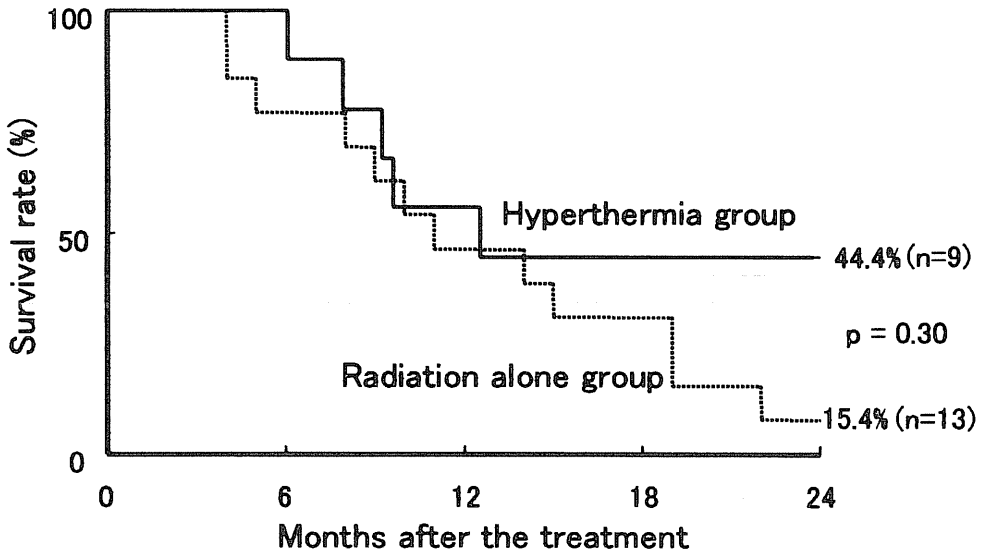

Figure 3. Overall survival curves of curative patients in the hyperthermia group and for radiation alone. The survival rate was determined by the Kaplan-Meier method. The *p*-values were estimated with the generalized Wilcoxon test.

Table 2. Complication rates in two groups.

	Hyperthermia group			Radiation alone group		
grade	0	1–2	3–4	0	1–2	3–4
early pulmonary (NCI-CTC)	10/13	3/13	0/13	12/13	1/13	0/13
late pulmonary (RTOG)	6/9	3/9	0/9	9/13	4/13	0/13
late spinal (RTOG)	9/9	0/9	0/9	12/13	0/13	1*/13

* Grade 4 radiation myelopathy (dose of spinal cord at 60 Gu).

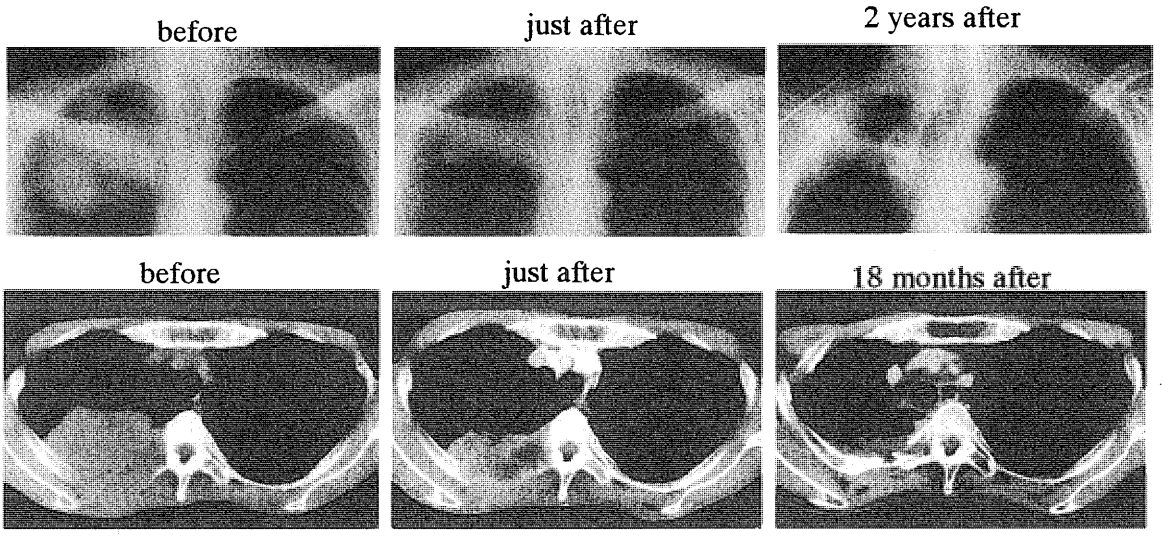

Figure 4. A change in chest X-ray findings and CT images in a 66-year-old male with squamous cell carcinoma of the lung treated with hyperthermia combined with radiation therapy. After the combined treatment, the tumour shrank and showed low density area, which is speculated as the effect of hyperthermia.

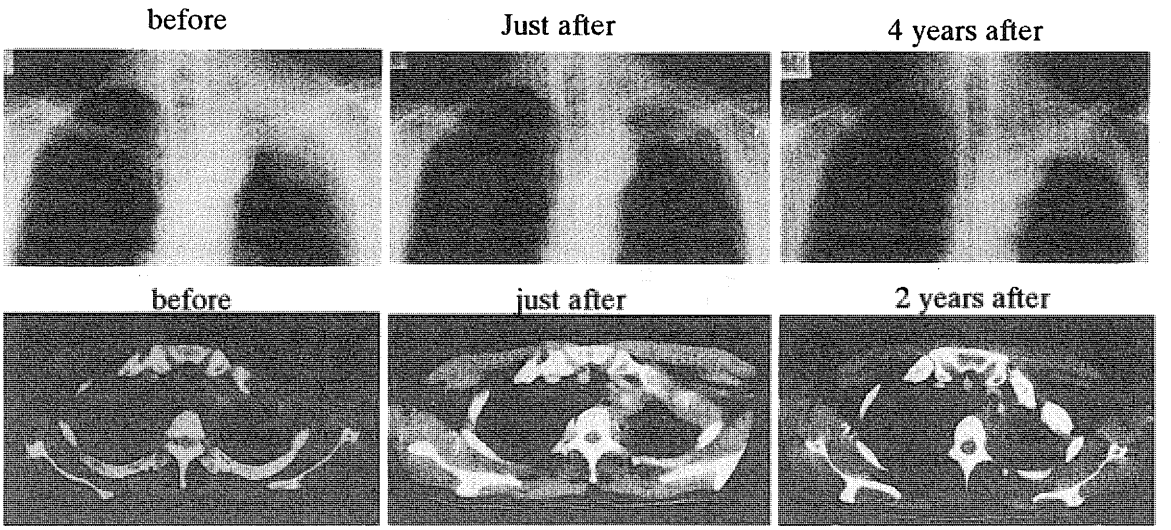

Figure 5. A change in chest X-ray findings and CT images in a 50-year-old male with squamous cell carcinoma of the lung treated with hyperthermia combined with radiation therapy.

Regarding locally advanced NSCLC, several clinical trials have been conducted worldwide comparing irradiation alone with irradiation and cytotoxic chemotherapy. Some trials have been similar to each other[15–18], but recent trials with cisplatin-based chemotherapy have shown positive results in favour of combined chemotherapy[19–21]. In recent randomized clinical trials, the benefit of induction chemotherapy was more emphasized in adenocarcinoma than that in squamous cell carcinoma[20,21]. From these results, squamous cell carcinoma and non-squamous cell carcinoma are two distinct types of NSCLC, which have different natural histories and require different methods of optimum treatment. For peripheral or chest wall lesions in squamous cell type NSCLC, about half of the patients developed recurrence in primary or intrathorax[22,23]. For the trial mostly including patients

Table 3. Long-term survivors in hyperthermia group.

Age Gender	Pathology	Stage	Tumour size (cm)	Radiation dose (Gy)	No. of HT session	T_{90}(°C)	T_{50}(°C)	Response	Survival time (Mo)	Outcome
66 M	Sq	3B	9.0	70	2	40.2	40.6	PR	41.8	Dead (cerebral infarct)
50 M	Sq	3B	10.0	70	2	40.2	40.5	PR	49.3	Alive
68 M	Sq	3B	8.0	70	3	40.8	41.3	PR	32.5	Alive
68 M	Sq	3B	4.8	70	3	41.4	41.8	CR	28.6	Alive

Sq: squamous cell carcinoma, Mo: month, HT: hyperthermia.

with squamous cell carcinoma, local aggressive treatment was emphasized in the report on continuous hyperfractionated accelerated radiation therapy (CHART) which was achieving better than standard fractionated irradiation[24]. In this department, a dose escalation study had been performed for stage I–II squamous cell carcinoma. However, a total dose at 80 Gy with conventional fractionation had adverse chronic effects on the bronchi[25]. Another study in this department demonstrated that tumour volume was an important prognostic factor for squamous cell type NSCLC[11]. Since patients with NSCLC involving direct bony invasion often have bulky tumours, these patients treated with conventional irradiation alone had never survived for more than 3 years in the department. On the basis of these studies, the project using regional hyperthermia combined with conventional irradiation has been performed as a local aggressive treatment.

Hyperthermia is known to be an effective biological method for the treatment of cancer. Recent randomized clinical trials on hyperthermia have provided promising results for tumours in various sites, for instance recurrent advanced breast cancer, recurrent or metastatic melanoma, head and neck cancer, glioblastoma multiforme and intrapelvic malignancy[3–8]. These positive results were initially confirmed in tumours arising in superficial sites, because it was easy to achieve the required temperature and to measure the intratumoural temperature. In this study, NSCLC with chest wall invasion was selected as a candidate for hyperthermia plus irradiation treatment, because it was located in a relatively superficial site. Clinical trials on hyperthermia have recently advanced to treating deep-seated tumours, made possible because of improvements in heating devices. The Dutch hyperthermia group conducted a prospective randomized trial for locally advanced tumours of the bladder, uterine cervix and rectum[8]. They demonstrated that the addition of hyperthermia to radiation therapy could improve local control and overall survival in patients with advanced pelvic tumours. Complete response rates were increased for all tumour sites and overall survival was improved for cervical and bladder cancer. They also concluded that the improved local control rates were not accompanied by increased toxic effects.

On clinical research into hyperthermia and lung cancer, few reports by Japanese investigators are available because of the physical difficulties associated with the delivery of heat and the measurement of temperature[9,10,26,27]. Kodama *et al.*[26,27] demonstrated the survival benefit of post-operative hyperthermia combined with the intrathracic administration of cisplatin for NSCLC with pleural dissemination. Regarding hyperthermia plus conventional irradiation, Karasawa *et al.*[10] treated 19 patients and concluded that thermoradiotherapy could increase resectability and improve long-term survival rates. For NSCLC invading or in contact with the chest wall, Hiraoka *et al.*[9] conducted treatment with hyperthermia and irradiation. Although they did not refer to the survival benefit of hyperthermia, they demonstrated that thermal parameters were related to the appearance of low density areas observed with computed tomography.

The best combined hyperthermia and irradiation methods still remain unproved. In this study, hyperthermia sessions were performed in the latter half of conventional radiation therapy, because hyperthermia could cause tumour necrosis due to injury to the tumour vessels. From this point of view, if hyperthermia causes necrosis in the initial phase of conventional radiation therapy, it becomes less effective because of numerous hypoxic tumour cells. On the other hand, a biological research conducted by Song *et al.*[28] showed that mild temperature hyperthermia around 41.5°C

improved the oxygen status in a murine tumour model. They speculated that hyperthermia at mild temperatures is easily achieved by using presently available clinical hyperthermia devices and may be an effective means for overcoming hypoxic protection in the treatment of human tumours. Many factors, such as temperature, the duration of hyperthermia and the tumour environment, complicate the best combination in hyperthermia and irradiation treatment.

In conclusion, regional hyperthermia combined with external radiation therapy could improve local control in patients with non-small cell lung cancer deeply invading the chest wall without increased adverse effects.

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