Local Control of Nonsmall Cell Lung Cancer by Radiotherapy Combined with High Power Hyperthermia Using an 8 MHz RF Capacitive Heating Device

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Original Contribution

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Abstract : We evaluated the effectiveness of radiotherapy combined with high-power hyperthermia with a radiofrequency output over 1500W for 13 patients with nonsmall cell lung cancer. An average total dose of 59.8 Gy by the conventional method, and an average of 12 sessions of hyperthermia during radiotherapy were employed. In addition, an average of 15 sessions of hyperthermia was administered after completing the radiotherapy. Complete response (CR, 100% regression) was achieved in 10/13 (77%) patients and partial response (PR, over 50% regression) in 3/13 (33%) for an overall response rate of 100%. Radiotherapy combined with high-power hyperthermia is especially advantageous for young patients with a thin subcutaneous fatty layer of the chest wall.

Key Words : hyperthermia, high output power, nonsmall cell lung cancer, radiotherapy

Introduction

A capacitive heating device is the main apparatus used in deep hyperthermia for thoracicoabdominal tumors in Japan [1]. At present, the upper limit of radiofrequency (RF) output of the capacitive heating device ranges from 500 to 1500W. However, the factors that must be considered to select the RF output upper limit of the device are uncertain.

The effectiveness of deep hyperthermia by the capacitive heating device for nonsmall cell lung cancer (NSCLC) has not yet been established [2-4]. In some studies, RF output was 1000W or less. We employed hyperthermia for NSCLC using the 8 MHz capacitive heating device in great numbers with high RF output. Hyperthermia for NSCLC resulted in excellent local control due to a high average RF output [5]. Many patients with a RF output around 1400-1500W were considered to have an allowance to further increase the RF output. Then, high-power hyperthermia over 1500W resulted in a higher therapeutic effect for 23 patients treated between 1995 and 1998. We previously reported that there were no serious side

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effects in hyperthermia with the RF output over 1500W [6]. Deep hyperthermia over 1500W by a capacitive heating device is possible, and it's usefulness must be examined. We investigated here, the local effect of hyperthermia over 1500W for 13 cases of NSCLC receiving curative radiotherapy.

Materials and Methods

Thirteen patients with unresectable NSCLC were treated with high power hyperthermia over 1500W. They received curative radiotherapy combined with hyperthermia at the hospital of University of Occupational & Environmental Health of Radiology between 1995 and 1997. The patient characteristics are shown in Table I. In all patients, tumors were deep-seated in the lung or the mediastinum and did not contact the chest wall. Ten patients had primary lung cancer and three patients had postoperative recurrence in the mediastinum. Ten patients had Stage IIIB disease and one patient had Stage IV disease in primary lung cancer. One patient with Stage IV underwent hyperthermia after solitary brain metastasis was curatively treated by radiosurgery. Three patients with recurrence had no metastases. The mean age of

Table I. Patient characteristics.
(PS: performance status, *Isolated brain metastasis was curatively irradiated by radiosurgery)

Case	Age	Sex	PS	Tumor size	TNM,stage	Pathology
1	36	M	0	22.1 cm^2	T2N3M0, IIIB	adenoca.
2	39	M	1	22 cm^2	T3N3M0, IIIB	adenoca.
3	44	M	1	14.3 cm^2	T4N2M0, IIIB	unknown
4	47	M	1	9 cm^2	T3N1M0, IV (brain*)	adenoca.
5	48	M	1	10.9 cm^2	postoperative recurrence	adenoca.
6	50	M	1	11.2 cm^2	T4N2M0, IIIB	SCC
7	54	M	1	12 cm^2	T2N3M0, IIIB	SCC
8	55	M	1	52 cm^2	T4N2M0, IIIB	adenoca.
9	56	M	1	13.9 cm^2	postoperative recurrence	SCC
10	57	M	0	15 cm^2	postoperative recurrence	adenoca.
11	59	M	2	52.5 cm^2	T4N3M0, IIIB	SCC
12	62	M	1	30 cm^2	T4N2M0, IIIB	SCC
13	62	M	2	21.8 cm^2	T2N3M0, IIIB	unknown

Table II. Methods of radiotherapy and hyperthermia.
(RTx: radiotherapy, HTx: hyperthermia)

Case	Radiotherapy		Hyperthermia			
	Medhod	Total dose	Heating time	Sessions during RTx	Sessions after RTx	Sessions Total
1	conformal	50 Gy	80 min.	16	18	34
2	field within field	80 Gy	80 min.	17	38	55
3	conformal	50.4 Gy	40 min.	10	5	15
4	conformal	60 Gy	40 min.	5	0	5
5	conformal	60 Gy	50 min.	11	4	15
6	conformal	70.2 Gy	40 min.	12	14	26
7	conformal	56.1 Gy	50 min.	8	27	35
8	field within field	52 Gy	60 min.	15	26	41
9	conformal	52.2 Gy	50 min.	12	0	12
10	field within field	66.2 Gy	50 min.	10	5	15
11	field within field	60.4 Gy	40 min.	11	46	57
12	conformal	60 Gy	50 min.	16	5	21
13	conformal	60 Gy	50 min.	14	7	21
Mean		59.8 Gy	52 min.	12	15	27

patients was 51 years and the performance status was two or less. All patients were men and had a thin subcutaneous fatty layer of the chest wall of less than 1.5 cm.

The details of hyperthermia and radiotherapy are shown in Table II. A Thermotron RF-8 capacitive heating device utilizing 8 MHz (Yamamoto VINITA Co., Osaka, Japan) was used for hyperthermia. The upper limit of the RF output of Thermotron RF-8 was set at 1500 W. By canceling the limiter of the supreme output, the maximum RF output was raised to 1679 W. Patients who showed no side effects by approximating 1500 W by hyperthermia at the first session, were selected as subjects. Hyperthermia over 1500 W was administered under sufficient monitoring with two doctors or more. Before the treatment, detailed descriptions of the possible side effects were provided to the patients.

Hyperthermia was performed just after the radiotherapy in two sessions per week. Total sessions of hyperthermia were 5 to 57 (average 27) depending on the therapeutic effects and the patients condition. In 11 out of 13 patients, hyperthermia alone was continued after the end of radiotherapy. Treatment time per session was 52 minutes on average. The RF output rapidly increased and reached the maximum level within 1 min.

In each case, the intraesophageal temperature was measured at once. The four-point thin Teflon-coated thermocouple was inserted in the 12F catheter filled sonojelly. It was inserted into the esophageal cavity at the level of the carina under the fluoroscopy. All patients were treated in the prone position, and both upper and lower electrodes were 30 cm in diameter with overlay bolus. As the overlay bolus circulating liquid, tap water was used in nine patients, and 0.5% NaCl was used in four patients. To reduce the thermoesthesia, sweating and fatigue, an external cooling unit and body earthing developed in our hospital were employed in six and four patients, respectively.

All patients were treated with megavoltage radiotherapy using a three-dimensional planning system. Conventional fractionation was used to total doses as shown in Table II. Total dose was decided by the therapeutic effects. In the four patients, the main lesion was irradiated by the field within field method. Local tumor response was measured as the maximum percentage of regression of the tumor on a CT image at least 1 month later by the criterion of the Japan Soc. for Cancer Therapy. The average observation period of 13 patients was 17 months.

Result

The treatment outcome is shown in Table III. Complete response (CR, 100% regression) was achived in 10/13 (77%) patients and partial response (PR, over 50% regression) in 3/13 (33%) for an overall response rate of 100%. The tumor regression rate was also over 80% for all PR patients. In two PR patients, the main tumors were over 50 cm^2. Hyperthermia alone was continued after the radiotherapy in 12 patients and CR was achieved in four patients following the additional hyperthermia. Furthermore, the residual tumor did not increase during the additional hyperthermia in PR patients.

Local recurrence was seen in two CR patients, 6 and 15 months after the end of treatment. Although the follow-up period after the treatment was short, eight patients survived, one of which survived for over 3 years, and the median survival was 26 months. Two of the four deaths were caused by liver metastases, and the other two deaths were caused by local recurrence and multiple bone metastases. One patient died due to lung abscess.

There was no problem with the blood pressure or pulse rate during hyperthermia. No patient developed

Table III. Treatment results.
(RTx: radiotherapy, HTx: hyperthermia, CR: complete response, PR: partial response, M: months)

Case	Intraesophageal temperature	Response after RTx	Response after HTx	Local recurrnce	Survival (cause of death)
1	44.8℃	PR	CR	non	38 M alive
2	44.6℃	PR	PR		11 M (liver metastases)
3	45.0℃	CR	CR	non	17 M alive
4	45.3℃	CR	CR	non	14 M alive
5	45.3℃	CR	CR	non	8 M alive
6	46.0℃	PR	CR	after 6 M	12 M alive
7	44.1℃	PR	CR	non	17 M alive
8	42.9℃	PR	PR		9 M (lung abscess)
9	44.9℃	CR	CR	non	15 M (bone metastases)
10	43.4℃	PR	CR	non	17 M alive
11	47.3℃	PR	PR		12 M alive
12	45.6℃	CR	CR	non	26 M (liver metastases)
13	48.1℃	CR	CR	after 15 M	25 M (local recurrence)

symptomatic radiation pneumonitis. Maximum intraesophageal temperature measured at the level of the carina was 42.9-48.1 ℃. The radiation esophagitis did not become serious even in the seven patients who demonstrated intraesophageal temperature exceeding 45 ℃. In addition, although hyperthermia over 2000 times was performed after the release of the limiter, there was no mechanical trouble in Thermotron RF-8.

Discussion

In our department, hyperthermia over 1000W has been employed since 1994, and we have gradually increased the RF output to 1500W. For patients whose subcutaneous fatty layer was 1.5cm or less, no side effects were observed even in the upper limit 1500W of Thermotron RF-8, so we judged that hyperthermia over 1500W was possible. Although we encountered 27 patients with a RF output over 1500W in 23 intrathoracic tumors including 13 patients described here, 2 hepatic tumors and 2 pelvic tumors, no side effects were observed. Our findings suggest that hyperthermia over 1700W is safe and the development of equipment which can generate a RF output of 2000W is desired.

The local tumor response by radiotherapy combined with hyperthermia over 1500W was marked as shown in Table III. Moreover, four patients achieved a CR following additional hyperthermia given after completion of radiotherapy. Our results indicated that residual tumors can be cured by high-power hyperthermia alone when radiotherapy can not be delivered due to the tolerance threshold of the normal tissues.

Direct measurement of the temperature is usually difficult in deep hyperthermia of intrathoracic tumors. We could not measure the tumor temperature in all patients, so the intraesophageal temperature was measured instead. Intraesophageal temperature measured here was the temperature in the tube inserted in the esophagus. It indirectly indicates the RF strength at the depth of the esophagus. In basic experiments on the measurement of the intraesophageal temperature by Thermotron RF-8, dissociation of the intraesophageal and the esophagus wall temperature was reported[7]. Since the esophageal mucosa is abundant in the capillary vessels, we proposed that a temperature increase in the esophageal mucosa is relatively lower than that of the intraesophageal catheter temperature. This hypothesis is supported by the finding that failure of the esophageal mucosa was not generated in any patients. However, the temperature increase of the tumor might be sufficient, because the changes in blood flow of the tumor are expected to be less in the course of treatment than that of the surrounding normal tissues. The excellent tumor regression rate proves this theory. Further studies to compare the temperature of the intrathoracic tumor with the intraesophageal temperature are needed.

Our findings suggest that high-power hyperthermia is possible due to the increased cooling ability of the overlay bolus and use of body earthing [8), 9)]. Furthermore, heating in the prone position allows better RF output elevation and diminishes the degree of thermoesthesia in hyperthermia for intrathoracic tumors using Thermotron RF-8 [10)]. High-power hyperthermia is particularly effective in young patients with a subcutaneous fatty layer under 1.5 cm.

We previously demonstrated that the efficiency of heating can be markedly improved using overlay bolus containing 0.5% NaCl as the circulation liquid [11)]. The intraesophageal temperature was 2℃ higher on average in four patients using the improved overlay bolus circulation liquid compared to nine patients using the conventional tap water circulation liquid. A higher deep-seated temperature using 0.5% NaCl for the overlay bolus circulation liquid is obtained at the equal output.

An excellent local effect was observed in 13 patients with NSCLC who were treated by radiotherapy combined with hyperthermia over 1500W. We introduced indications to achieve the high RF output treatment. The usefulness of hyperthermia over 1500W for treatment of other regions should be investigated.

Conclusion

Radiotherapy combined with high-power hyperthermia by Thermotron RF-8 seems to be a safe and effective therapy for NSCLC.

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8 MHz誘電加温装置を使用した高出力温熱併用放射線療法による非小細胞性肺癌の局所効果

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要　　旨：8MHz誘電加温装置によるRF出力1500W以上の温熱療法と放射線治療を施行した非小細胞性肺癌13例の局所効果を検討した．通常分割の平均総線量59.8Gyの放射線治療に平均12回の温熱療法を併用した．放射線治療後に平均15回の温熱療法が追加された．局所効果はComplete responseが10/13（77%），Partial responseが3/13（23%）と極めて高い奏功率（100%）を示した．年齢が若く，胸壁皮下脂肪の少ない肺癌患者に対して，1500W以上の高出力温熱療法は，有効な治療法である．