Pergamon

Int. J. Radiation Oncology Biol. Phys., Vol. 30, No. 5, pp. 1171–1177, 1994

0360-3016/94 $6.00 + .00

0360-3016(94)00386-6

● *Hyperthermia Original Contribution*

THERMORADIOTHERAPY IN THE TREATMENT OF LOCALLY ADVANCED NONSMALL CELL LUNG CANCER

KATSUYUKI KARASAWA, M.D.,*† NOBUHARU MUTA, M.D.,* KEIICHI NAKAGAWA, M.D.,* KENJI HASEZAWA, M.D.,* ATSURO TERAHARA, M.D.,*‡ YUZO ONOGI, M.D.,* KOH'-ICHI SAKATA, M.D.,* YUKIMASA AOKI, M.D.,* YASUHITO SASAKI, M.D.* AND ATSUO AKANUMA M.D.‡

*Department of Radiology, University of Tokyo, Hongo, Bunkyo-ku, Tokyo, 113, Japan; †Department of Radiology, Tokyo Metropolitan Komagome Hospital, Honkomagome, Bunkyo-ku, Tokyo 113, Japan;‡ National Institute for Radiological Science, Anagawa, Inage-ku, Chiba, 263, Japan

Purpose: To improve the treatment results of locally advanced non-small cell lung cancer (NSCLC), we have been conducting a clinical trial using regional hyperthermia combined with radiotherapy.
Methods and Materials: Between 1985 and 1990, 19 patients were treated. All cases except one were regarded as initially unresectable. There were 10 Stage IIIA cases and nine Stage IIIB cases. In 10 cases thermoradiotherapy was used definitively, and in the other nine cases preoperatively. Radiotherapy was administered with conventional fractionation. Total dose ranged from 42 to 80 Gy (mean 62.9 Gy) for definitive treatment cases, and 38 to 47 Gy (mean 40.6 Gy) for preoperative cases. Radiofrequency (RF) capacitive hyperthermia was administered twice weekly, immediately after radiotherapy. Total sessions of hyperthermia ranged from 5 to 16 times (mean 9.0) for definitive treatment cases and 3 to 8 times (mean 6.7) for preoperative cases.
Results: The results of thermoradiotherapy group (HTRT group) were compared with our historical control group (RT group); initially unresectable Stage III NSCLC irradiated definitively with 50 Gy or more (26 cases), or became resectable after radiotherapy and operated (4 cases). As for initial response, there were 5 complete responses (CRs), 13 partial responses (PRs), and 1 no change (NC) (CR rate 26%, response rate 95%) in the HTRT group, whereas there were no CR, 21 PRs, and 9 NCs in the RT group (CR rate 0%, $p < 0.005$, response rate 70%, $p < 0.05$). Overall 3-year local relapse-free survival and survival rate for the HTRT group was 73% and 37%, respectively, and 20% and 6.7%, respectively, for the RT group ($p < 0.01$, $p < 0.01$). The rate of death from uncontrolled primary disease for the HTRT group was significantly lower than for the RT group (21% vs. 53%, $p < 0.03$).
Conclusion: Although the number of cases is rather small, thermoradiotherapy in the treatment of locally advanced NSCLC is promising in raising resectability, local control, and, thus, long-term survival.

Nonsmall cell lung cancer, Radiotherapy, Hyperthermia, Thermoradiotherapy.

INTRODUCTION

The incidence of lung cancer has been increasing rapidly all over the world, and death due to this cancer has also been increasing. Despite the development of preventive medicine, more than half of the patients are detected to be Stage III or higher; that is, unresectable or inoperable. The mainstay of treatment for Stage III non-small cell lung cancers (NSCLC) is still radiation therapy. However, the survival results by definitive radiation therapy has been around 5% at 5 years, which is far from satisfactory. Many combined treatment regimens for Stage III NSCLC have been tried, such as multiagent chemotherapy containing cisplatinum, with modest success in improving survival rates (2, 8).

Hyperthermia has been used in combination with radiation therapy and/or chemotherapy and is considered to be effective for certain type of tumors. For instance, for superficial tumors such as lymph nodes in head and neck regions, there has been a statistically significant improvement in survival with the use of hyperthemia in combination with radiotherapy (1). When the initial response by hyperthermia in combination with radiotherapy was complete response (CR), there was a better long-term local control and patient survival results (6).

Since 1985, we have been conducting a clinical trial of

Presented at the International Congress of Radiation Oncology 1993, Kyoto, Japan, June 1993.

Reprint requests to: Katsuyuki Karasawa, M.D., Department of Radiology, Tokyo Metropolitan Komagome Hospital, 3-18-22, Honkomagome, Bunkyo-ku, Tokyo, 113, Japan.

Acknowledgements—The authors thank Professor C. W. Song and Dr. S. Jo for their critical review of this paper.

Accepted for publication 8 July 1994.

radiotherapy in combination with hyperthermia with or without surgery for unresectable locally advanced NSCLC patients, to see whether thermoradiotherapy can improve the treatment of NSCLC. In this report, thermoradiotherapy cases were compared with historical controls treated with radiotherapy with similar total radiation dose without hyperthermia during the same treatment period.

METHODS AND MATERIALS

Eligibility criteria

The criteria for selecting the candidates for thermoradiotherapy were Stage III NSCLC, Eastern Cooperative Oncology Group (ECOG) Performance Status between 0 and 3, preferably those with chestwall invasion by the tumor to perform direct thermometry, and those with bulky tumors that seem incurable by radiotherapy alone.

Among the historical control group (RT group), those whose total radiation dose was under 50 Gy without surgery were eliminated from this study as palliatively treated cases. We have had relatively small numbers of patient referrals; therefore, the total number of Stage III NSCLC patients treated between 1985 and 1990 was 72, and among them 23 were treated palliatively or postoperatively.

We dealt with preoperative cases and definitive treatment cases together because all except one case were initially unresectable, and our aim in this study was to see whether the resectability rate by the addition of heat to radiation would be improved over radiation therapy alone.

Table 1. Patient characteristics

	HTRT Group	RT Group
Treatment Period	1985–1990	1985–1990
No. of cases	19	30
Sex (male/female)	18:1	27:3
Age mean (range)	57.3 (16–76)	61.7 (29–80)
PS(ECOG) 0	0	4
1	6	8
2	9	14
3	4	4
4	0	0
Histology		
SqCC	8	11
Adeno Ca	6	13
Large Cell Ca	2	2
Undifferentiated	1	0
ACC	0	1
Subtype unknown	2	3
TNM		
IIIA	10	16
T1N2M0	0	1
T2N2M0	1	0
T3N0M0	6	6
T3N1M0	0	1
T3N2M0	3	8
IIIB	9	14
T2N3M0	0	5
T3N3M0	0	3
T4N0M0	2	1
T4N2M0	6	4
T4N3M0	1	0
TxN3M0	0	1
Use of XRT		
Definitive	10	26
Preoperative	9	4

HTRT: thermoradiotherapy; RT: historical control (radiation alone); XRT: radiotherapy; PS: performance status; and ECOG: Eastern Co-operative Oncology Group.

Table 2. Treatment method

	HTRT Group	RT Group
XRT Dose		
Definitive Tx cases		
mean dose	62.9 Gy	60.8 Gy
range	42–80	50–70
< 50 Gy	1	0
50 Gy $\leq <$ 60 Gy	0	7
60 Gy $\leq <$ 70 Gy	6	13
70 Gy $\leq$	3	6
Preoperative cases		
mean dose	40.6 Gy	45.0 Gy
range	38–47 Gy	40–60 Gy
< 40 Gy	1	0
40 Gy $\leq <$ 50 Gy	8	3
50 Gy $\leq$	0	1
Hyperthermia		
Definitive Tx cases		
mean times	9.0	—
range	5–16	—
Preoperative cases		
mean times	6.7	—
range	3–8	—

HTRT: thermoradiotherapy; RT: historical control (radiation alone); and XRT: radiotherapy.

HTRT cases

Patient characteristics of the thermoradiotherapy group (HTRT group) are listed in Tables 1 and 2. Between 1985 and 1990, a total of 19 patients were treated; the male to female ratio was 18:1, their age ranged from 16 to 76 with a median age of 59 (mean 57.3), and the follow-up period ranged from 34 months to 98 months. There were eight squamous cell carcinomas, six adenocarcinomas, two large cell carcinomas, one undifferentiated carcinoma, and two with unknown suptype. According to the International Union Against Cancer (UICC) TNM Stage (1987), there were 10 Stage IIIAs and 9 Stage IIIBs. Maximum tumor diameter ranged from 2.5 cm to 12 cm (mean 6.8 $\pm$ 2.4 cm). Tumor volume ranged from 4 to 618 cm^3 (mean 164 $\pm$ 178 cm^3).

RT cases

Patient characteristics of the control group (radiotherapy cases) are listed in Table 1 and Table 2. As the control group, we selected those Stage III cases treated in the same

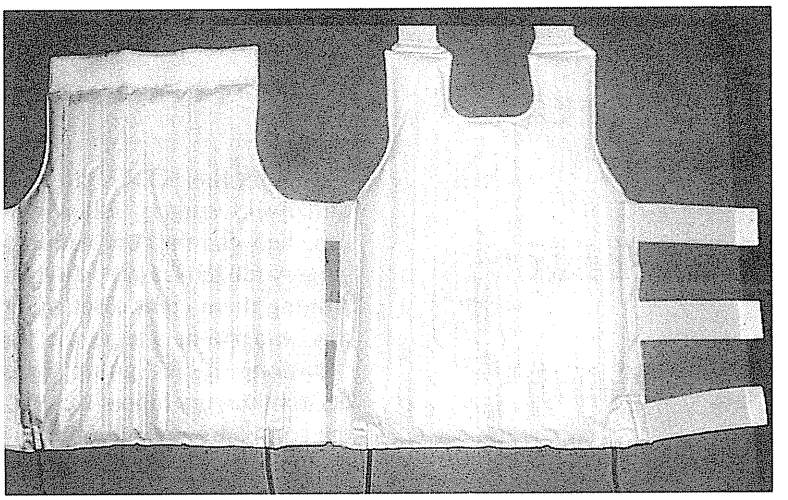

Fig. 1. Jacket-shaped overlay bolus. To fit the electrode to the body of the patient more smoothly and to avoid edge effect, the jacket-shaped bolus was developed. Since the introduction of the bolus, more steady heating was obtained.

treatment period who were regarded as initially unresectable and received radiotherapy up to 50 Gy or more, or those who were regarded resectable following radiotherapy. There were 30 such cases, and among them only 4 cases (13%) became resectable. Their age ranged between 29 and 80 (mean 61.7), and the male to female ratio was 27:3. Their performance status was not different from thermoradiotherapy cases. There were 11 squamous cell carcinomas, 13 adenocarcinomas, 2 large cell carcinomas, 1 adenoidcystic carcinoma, and 3 with unknown subtype. There were 16 Stage IIIA cases and 14 Stage IIIB cases. Maximum tumor diameter ranged from 2 cm to 10 cm (mean 6.1 ± 1.7 cm). Tumor volume ranged from 2.3 to 300 cm^3 (mean 84.8 ± 66.5 cm^3). Tumor volume in the RT group tended to be smaller than in the HTRT group ($p < 0.07$).

Radiotherapy

Radiotherapy was administered conventionally once a day five times a week. The fraction dose was 2 Gy in all cases except one, who was treated partly with 3 Gy fraction dose. The initial field covered primary tumor and regional lymphnodes with anteroposterior–posteroanterior (AP–PA) technique. Normally we covered one eschelon of lymphnodes further in the initial field. Then we shrunk the field at the doses of 40 Gy to the primary and enlarged lymphnodes for the boost doses of 10 Gy to 30 Gy. Normally we took 1 to 2 cm safety margins to avoid geographic miss.

Total radiation doses for definitive treatment cases ranged from 42 to 80 Gy (mean 62.9 Gy) and 38 to 47 Gy (mean 40.6 Gy) for preoperative cases in the HTRT group. By thermoradiotherapy protocol 40 Gy initial (preoperative) doses were given, and then the patient was evaluated for the resectability. If resectable, surgery was done 2 to 4 weeks afterwards. If still unresectable, the boost doses of 20 Gy were administered. Seven out of 9 preoperative cases (78%) and 6 out of 10 definitive treatment cases (60%) were treated this way.

Total radiation doses ranged from 50 Gy to 70 Gy (mean 60.8 Gy) for definitive treatment cases, and from 40 Gy to 60 Gy for preoperative cases in the RT group. There was no difference in radiation doses between the HTRT group and the RT group.

Hyperthermia

Hyperthermia was administered twice weekly immediately following radiotherapy. Usually it started within 15 min after the irradiation. The heating apparatus was RF capacitive heating device.[1] We placed a pair of electrodes with cooling bolus from front and back of the patient's chestwall and loaded the 8 MHz RF wave. The size of electrodes ranged from 14 cm to 25 cm. We administered heat to the patient to the maximum tolerable dose for the patient. The average dose (in watts) ranged from 452 to 971, mean 670 ± 145. We devised a new type of overlay bolus (jacket-shaped overlay bolus; Fig. 1) and placed it between the patient body surface and the electrodes. With the use of this bolus, the mean electrical power could be increased and the burden to the patient could be reduced. Direct thermometry was done with thermocouples by inserting 21 gauge Teflon catheters into the tumor whenever possible. Heating duration was between 45 min and 60 min. Number of heat treatments

[1] Thermotron RF8, Yamamoto Vinyta Co. Ltd., Osaka, Japan.

Table 3. Results of thermometry

Case no.	Stage (TNM)	Site	Histology	Tumor volume (ccm)	Average electrical power (Watt)	Average of				Response	
						T_{max} (C)	T_{ave} (C)	T_{min} (C)	T_{50} (C)	S/N	Histological
1	IIIA (320)	LUL	Adeno	26	452	41.8	41.0	40.0	41.1	PRa	PR
2	IIIA (320)	RUL	Squamous	70	632	41.9	40.7	39.9	40.6	PRb	*
3	IIIA (300)	RUL	Adeno	4	523	42.3	40.7	39.7	40.6	PRa	PR
4	IIIA (300)	RUL	Adeno	125	676	42.8	40.8	39.5	40.8	PRa	PR
5	IIIA (300)	LUL	Unknown	468	455	42.8	41.6	40.9	41.5	PRa	CR
6	IIIA (300)	RUL	Squamous	75	875	42.8	41.3	40.1	41.3	PRa	PR
7	IIIA (300)	RUL	Large	94	769	44.4	43.6	42.5	43.7	PRa	*
8	IIIB (420)	LUL	Squamous	442	798	41.6	40.7	39.9	40.7	PRb	CR
9	IIIB (400)	LLL	Squamous	75	609	42.2	41.1	40.1	41.1	PRa	PR
10	IIIB (420)	LUL	Squamous	374	563	42.3	40.6	39.2	40.5	PRb	PR
11	IIIB (420)	LUL	Adeno	33	716	43.3	42.0	41.0	42.0	PRa	PR

S/N: evaluation by size and necrosis by CT *Histological evaluation was not done; LLL: left lower lobe; LUL: left upper lobe; RUL: right upper lobe.

ranged from 3 to 8 times (mean 6.7), and 5 to 16 times (mean 8.0) for preoperative cases and definitive treatment cases, respectively.

Surgery

Among the HTRT group there were nine cases who underwent surgery following thermoradiotherapy. The time between the completion of thermoradiotherapy and surgery ranged from 10 days to 32 days (mean 19.2 days). Among them eight cases underwent lobectomy and one case underwent pneumonectomy.

Among the RT group there were four cases who underwent surgery following radiotherapy. The time between the completion of radiotherapy and surgery ranged from seven days to 37 days (mean 18 days). Among them, two cases underwent lobectomy, one case underwent pneumonectomy, and one case underwent only probe thoracotomy.

Response criteria

Tumor regression was graded as complete regression (CR), partial regression (PR; more than half of the tumor volume), and no change (NC) by imaging studies and/or histological specimen. To evaluate the relationship between the thermometry data and the response rate among the HTRT group, PR criteria was divided into two groups: PRa; more than 80% regression, PRb; more than 50%, and less than 80% regression. Among the HTRT group, in 17 cases, the response was evaluated by computed tomography (CT) scan, and in two cases, response was evaluated by chest x-ray film taken 1 to 4 weeks after thermoradiotherapy. Among the RT group, in 17 cases, the response was evaluated by CT scan, and in 13 cases, the response was evaluated by chest x-ray film taken 1 to 4 weeks after radiotherapy.

Statistical analysis

The maximum likelihood method was used for the calculation of the correlational relationship. Chi-square test was used for the test of the difference in the ratio. *T*-tests were used for the test of the difference in the mean value. The Kaplan–Meier method was used for the calculation of survival probability, and the log-rank test was used for the test of the difference in survival probabilities.

RESULTS

Thermometry

Eleven cases underwent direct tumor temperature monitoring. The results of thermometry for the 11 cases are listed in Table 3. The maximum temperature (T_{max}) ranged from 41.6°C to 44.4°C, with an average of 42.6°C ± 0.8°C. The average temperature (T_{ave}) ranged from 40.6°C to 43.6°C with an average of 41.3°C ± 0.9°C. The minimum temperature (T_{min}) ranged from 39.2°C to 42.5°C with an average of 40.3°C ± 0.9°C. In 78% of

the treatments T_{max} was higher than 41.5°C. In every case, T_{max} reached 41.5°C three times or more. There was no correlational relationship between mean electrical power and T_{max}, T_{ave}, T_{min} (r = 0.307, 0.242, and 0.334, respectively). There was no correlational relationship between tumor size and T_{max}, T_{ave}, T_{min} (r = −0.157, −0.103, and −0.276, respectively).

T_{50} (temperature that was exceeded in 50% of the measuring points) for each case was obtained, and the relationship between the T_{50} and the response rate is shown in Fig. 2. The T_{50} for PRa cases ranged from 40.6°C to 43.7°C, with an average of 41.5°C ± 0.9°C, whereas the T_{50} for PRb cases ranged from 40.5°C to 40.7°C, with an average of 40.6°C ± 0.1°C.

Initial responses

The initial responses for the treatment are listed in Table 4. As for the initial response for the HTRT group, among 19 cases there were 5 CRs, 13 PRs, and 1 NC (CR rate 26%, response rate 95%). As for the RT group, there were no CR, 21 PRs(70%), and 9 NCs (CR rate 0%, response rate 70%). The HTRT group showed better CR rate and response rate ($p < 0.005$, $p < 0.05$, respectively). Eight out of eight cases (100%) in the HTRT group who had had painful symptoms before treatment showed pain relief, whereas seven out of eight cases (88%) in the RT group showed pain relief. There was a tendency that pain relief occurs earlier in the HTRT group than in the RT group.

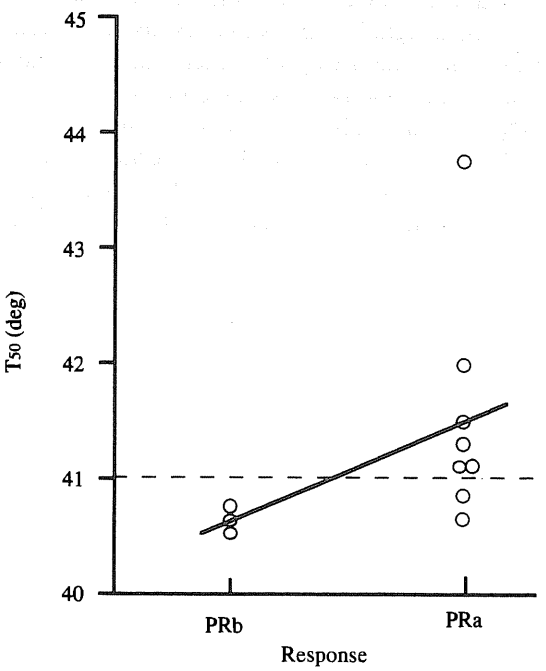

Fig. 2. Relationship between T_{50} and response. To see the relationship between T_{50} and the response rate, PR criteria was divided into two groups: PRa; more than 80% regression, PRb; more than 50% and less than 80% regression. In the PRa group, T_{50} was higher than 41.0°C in 75% of the cases, whereas in the PRb group there was no case whose T_{50} was higher than 41.0°C.

Table 4. Initial response

	HTRT Group	RT Group
CR	5	0
PR	13	21
NC	1	9
PD	0	0
CRR	26%	0% ($p < 0.005$)
RR	95%	70% ($p < 0.05$)

CRR: CR rate; RR: response rate; HTRT: thermoradiotherapy; and RT: historical control (radiation alone).

Long-term survival results

Overall local relapse-free survival curves of both treatment groups are shown in Fig. 3. Overall 1- and 3-year local relapse-free survival rates for the HTRT group were 73% and 73%, respectively. Overall 1- and 3-year local relapse-free survival rates for the RT group were 42% and 20%, respectively. The HTRT group showed better local control than the RT group ($p < 0.01$). Overall survival curves of both treatment groups are shown in Fig. 4. Overall 1- and 3-year survival rates for the HTRT group were 56% and 37%, respectively. Overall 1- and 3-year survival rates for the RT group were 30% and 6.7%, respectively. The HTRT group survived longer than the RT group ($p < 0.01$). Median survival time was 17 months for the HTRT group and 9 months for the RT group.

Patterns of failure and complication

Among the HTRT group, there were three cases who failed locally, one locally and distantly, and five distantly. As for the complications, there were three pneumonites and one pulmonary abscess among the HTRT group (21%). All cases endured the heat treatment well.

Among the RT group there were 12 cases who failed locally, 6 locally and distantly, and 5 distantly. As for complications, there were seven pneumonites (23%).

Causes of death

The causes of death of both treatment groups are listed in Table 5. As for the HTRT group, 13 cases have died; among them 4 (21%) died of local tumor progression, 5 (26%) of distant metastasis, 2 (11%) of complication, and 2 (11%) of intercurrent disease (1 second malignancy and 1 aplastic anemia). As for the causes of death for the RT group, there were 16 (53%) of local failure, 7 (23%) of distant failure, 5 (17%) of complication, and 2 (7%) of unknown causes. The rate of death from uncontrolled primary disease of the HTRT group was significanlty lower than the RT group (21% vs. 53%, $p < 0.03$). The rate of death from the disease was also lower in the HTRT group than in the RT group (47% vs. 77%, $p < 0.05$).

DISCUSSION

Lung cancers have been thought to be difficult to heat empirically. In addition, the lack of appropriate heating

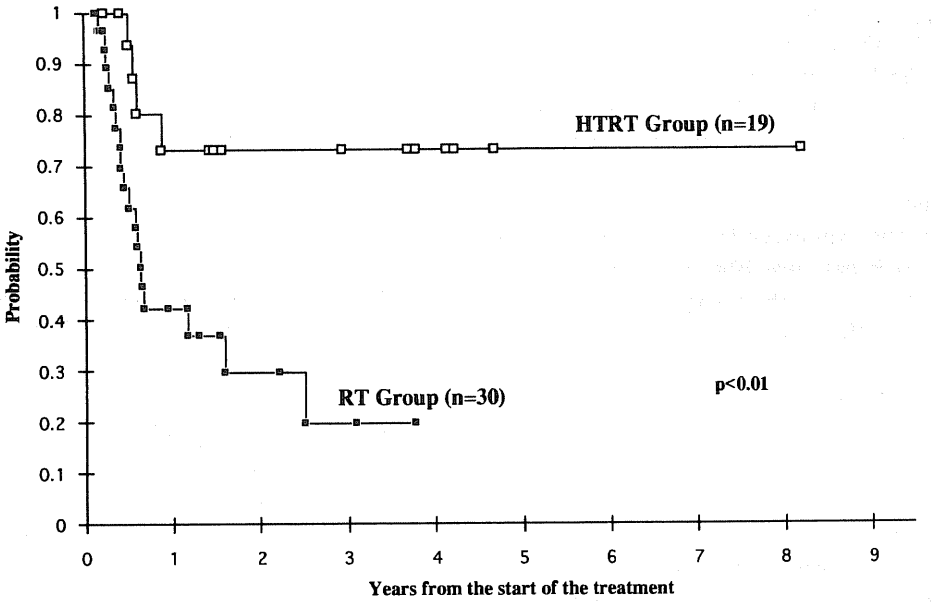

Fig. 3. Cumulative local relapse-free survival curve.

apparatus has made it difficult to heat lung cancers safely. Concerning the first point, lung tissue in fact has small heat capacity because of the existence of air in the bronchus and alveola. Therefore, the temperature of lung tumor can easily be raised with relatively small power input. Besides, in contrast to abdominal RF capacitive heating where intestinal gas causes significant feeling of pain to the patient, chest heating can be performed relatively easily to the therapeutic heat dose. In fact, in our cases, T_{max} greater than 41.5°C was obtained at least three times in every case.

Concerning the second point, there are few treatment apparatus that can heat deep tumors in the chest regions sufficiently. Microwave apparatus can only heat superficial tumors. Ultrasound apparatus is now under development. The RF capacitive heating apparatus used in our study, on the other hand, can heat deep-seated tumors in the chest without causing much discomfort to the patients. Using the jacket-shaped overlay bolus we developed in addition to the usual bolus, the edge effect is reduced markedly, and discomfort for the patients is further reduced. The mean electrical power could be raised as high as approximately 700 watt constantly.

Using the heating apparatus, we have been treating locally advanced NSCLC with thermoradiotherapy, and have obtained significantly better results compared with the radiation-alone group of rather smaller tumors for both the initial response (CR rate 26% vs. 0%; $p < 0.005$) and long-term survivals (3-year survival rate 37% vs. 6.7%; $p < 0.01$). The toxicity with hyperthermia was not increased (complication rate 21% vs. 23%). Reviewing the literature, the survival results were not worse than any

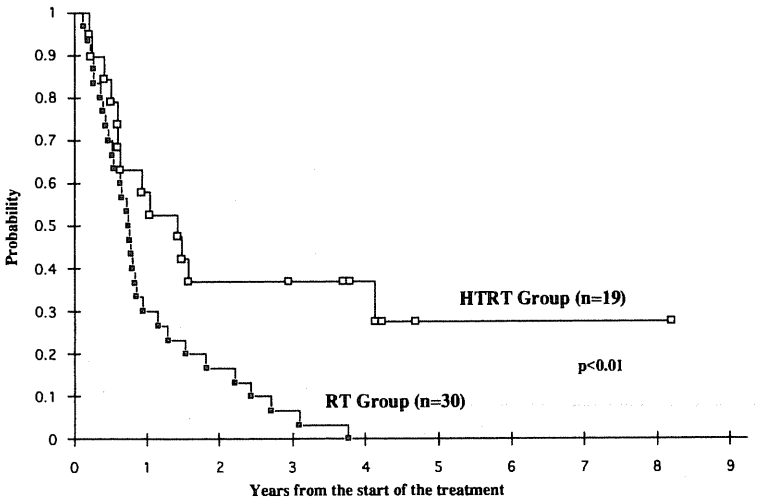

Fig. 4. Cumulative overall survival curves.

Table 5. Causes of death

	HTRT Group	RT Group
Primary	4 (21%)	16 (53%)
Distant Mets	5 (26%)	7 (23%)
Complication	2 (11%)	5 (17%)
Intercurrent	2 (11%)	0 (0%)
Unknown	0 (0%)	2 (7%)
Dead cases	13 (68%)	30 (100%)
Alive cases	6 (32%)	0 (0%)
DOP Rate	21%	53% ($p < 0.03$)
DOD Rate	47%	77% ($p < 0.05$)

DOP rate: death-of-primary rate; DOD rate: death of disease rate; HTRT: thermoradiotherapy; and RT: historical control (radiation alone).

other trial treating initially unresectable Stage III NSCLC (4, 5).

One may think that our HTRT group contains a relatively high percentage of T3N0M0 cases (6/19, 32%) that carry relatively favorable prognosis. However, in this study only 1 out of 5 CR cases (20%) was T3N0M0, which means that mediastinal nodes can be equally heated and cured by thermoradiotherapy. In our HTRT group there were relatively larger tumors compared with the RT group (mean of largest diameter 6.8 cm vs. 6.1 cm; $p < 0.07$). According to Bleehen and Cox (3) the largest size of the tumor that can be treated with curative intent may be 8 cm in diameter, and tumors with chestwall invasion cannot be a candidate for radical radiotherapy. Therefore, from a radiation oncological point of view, there were more unfavorable patients in our HTRT group compared with the RT group, and yet the HTRT group responded better than the RT group.

The average of T_{max}, T_{ave}, T_{min} were 42.6°C, 41.3°C, and 40.3°C, respectively, and comparable with other available data (7). There were no strong correlational relationships among tumor size, electrical power loaded, and intratumor temperature, although T_{50} tended to be correlated with responses. This might be because of the existence of necrosis within the tumor. With the development of special overlay boluses, steady heat treatment is now available. In the future, these factors together with other factors, such as the location of tumor, will have to be reanalyzed carefully with a large number of patients to seek the optimal treatment regimen.

CONCLUSION

Although the number of cases is rather small, thermoradiotherapy in the treatment of locally advanced NSCLC is highly promising in raising local control, which is the most critical issue for treating NSCLC and thus raising the long-term survival rate. Optimal dose, fractionation, number of treatments, and so on, need to be investigated in a Phase III randomized trial.

REFERENCES

1. Arcangeli, G.; Cividalli, A.; Nervi, C. Tumor control and therapeutic gain with different schedules of combined heat and radiation. Int. J. Radiat. Oncol. Biol. Phys. 9:1125–1134; 1983.
2. Bitran, J. D.; Golomb, H. M.; Hoffman, P. C. Protochemotherapy in non small cell lung carcinoma. Cancer 57: 44–53; 1986.
3. Bleehen, N. M.; Cox, J. D. Radiotherapy for lung cancer. Int. J. Radiat. Oncol. Biol. Phys. 11:1001–1007; 1985.
4. Choi, N. C. Curative radiation therapy for unresectable non small cell carcinoma of the lung: Indications, techniques, results. In: Choi, N. C.; Grillo, H. C., eds. Thoracic Oncology. New York: Raven Press; 1983:163–199.
5. Emami, B.; Perez, C. A. Lung. In: Perez, C. A.; Brady, L. W., eds. Principles and Practice of Radiation Oncology. 2nd ed. Philadelphia, PA: Lippincott; 1992:806–836.
6. Hiraoka, M.; Jo, S.; Dodo, Y.; Ono, K.; Takahashi, M.; Nishida H.; Abe, M. Clinical results of radiofrequency hyperthermia combined with radiation in the treatment of radioresistant tumors. Cancer 54:2898–2904; 1984.
7. Hiraoka, M.; Masunaga, S.; Nishimura, Y.; Nagata, Y.; Jo, S.; Akuta, K.; Li, Y. P.; Takahashi, M.; Abe, M. Regional hyperthermia combined with radiotherapy in the treatment of lung cancers. Int. J. Radiat. Oncol. Biol. Phys. 22:1009–1014; 1992.
8. Schaake-Koning, C.; van den Bogaert, W.; Dalesio, O.; Festen, J.; Hoogenhout, J.; van Houtte, P.; Kirkpatrick, A.; Koolen, M.; Maat, B.; Nijs, A.; Renaud, A.; Rodrigus, P.; Schuster-Uitterhoeve, L.; Schulier, J.-P.; van Zandwijk, N.; Bartelink, H. Effect of concomitant cisplatin and radiotherapy on inoperable non-small cell lung cancer. N. Engl. J. Med. 326:524–530; 1992.