Original Contribution

Challenge of Hyperthermia Combined with Chemotherapy or Chemo-radiotherapy for Unresectable Intrathoracic Malignant Tumors: A Preliminary Result

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Abstract: As prognosis after radiotherapy for patients with unresectable intrathoracic tumors is still extremely poor, such patients need intensive treatment. The aim of this study is to investigate the feasibility of hyperthermia combined with chemotherapy or chemo-radiotherapy for patients with advanced intrathoracic tumors. Our treatment regimen consisted of weekly concurrent thermo-chemotherapy using a low-dose of CDDP and CPT-11 with or without definitive radiation therapy. Our study has demonstrated that 2 out of 11 tumors showed a complete response and partial response was achieved in 3 tumors as the initial effects of the treatment. Furthermore, 2 patients with advanced Pancoast tumors survived for over 2 years without any indication of recurrence. All patients underwent the complete course of treatment without evidence of grade 3 or worse non-hematological toxicity, including pneumonitis. We have therefore concluded that thermo-chemo-radiotherapy with concurrent administration of CDDP and CPT-11 at a low dose may be tolerable and effective for unresectable intrathoracic malignant tumors.

Key words: intrathoracic tumor, lung cancer, thermo-chemo-radiotherapy

Introduction

Clinical outcomes of unresectable locally advanced primary or recurrent intrathoracic malignancies, such as lung cancer and malignant pleural mesothelioma, are disappointing because of a high rate of local recurrence after treatment by radiation therapy (RT) alone[1)2)]. As an aggressive therapy, concurrent chemo-radiotherapy has therefore been used for advanced lung cancer. Some recent clinical trials for locally advanced lung cancer using a combination of radiation therapy and chemotherapy have produced

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satisfactory results not only in terms of local control but also of survival[3-5]. Because local failure, however, leads to major morbidity even after the combined therapy, local tumor control remains an important goal in primary treatment.

It is well known that hypoxia is associated with a reduction in sensitivity to irradiation and thus adversely affects the success of RT treatment[6-8]. In experimental studies, the biological effect of radiation under hypoxic conditions was 2.5-3 times worse than that under oxygenated conditions[9]. Hyperthermia is effective for tumor cells under hypoxic conditions as well as under low pH and nutritionally deficient conditions that lead to radiation resistance. Moreover, cells in the late DNA synthesis phase of the cell cycle are most sensitive and resistant to hyperthermia and X-ray, respectively[10][11]. This has led to the assumption that hyperthermia combined with RT may offer a significant advantage in the treatment of locally advanced tumors in contrast to RT alone. Our previous study on patients with non-small cell lung cancer (NSCLC) with direct bony invasion demonstrated that a combination of radiation therapy and hyperthermia produces significantly better results than RT alone[12].

On the other hand, it has also been reported that the cytocidal potential of some anti-cancer drugs including Cisplatin (CDDP) and Irinotecan (CPT-11) was found, in experimental and clinical studies, to be enhanced by hyperthermic temperature elevation[9][13-18]. Furthermore, both CDDP and CPT-11 are useful drugs when combined with RT for the treatment of locally advanced tumors, including NSCLC[19-22].

Our protocol design consisted of combined thermo-chemotherapy, and a tri-modality schedule that also included definitive RT in addition to concurrent low-dose chemotherapy and weekly hyperthermia. The primary endpoint of this study was to establish the feasibility of this regimen, especially with regard to the appropriate dose of CPT-11, in view of the probability of severe lung toxicity arising from the combination with RT. The secondary endpoint was to determine the initial response and the local control.

Materials and Methods

Patients

Between March 2002 and March 2004, 11 patients with primary or recurrent intrathoracic malignancies were enrolled in this study. There were 2 primary Pancoast tumors, 4 recurrent lung cancers, 3 malignant pleural mesotheliomas, a lymph node metastasis from clear cell carcinoma of the ovary, and a pleural dissemination of lung adenocarcinoma. The patient characteristics are summarized in Table 1. Among 11 patients, 9 were male and 2 were female and the median age of the patients was 63 years (range: 49-73 years) at the initiation of the treatment.

Radiation Therapy

Fig. 1 shows our schedule of RT, chemotherapy and hyperthermia treatment. Weekly chemotherapy and hyperthermia were concurrently initiated from the third or fourth week after the start of RT. Definitive RT was performed on 7 of 11 patients of this study, while the remaining 4 tumors were not irradiated because of an existing RT treatment history (Table I). The patients were treated by EBRT

Table I. Characteristics of Patients with intrathoracic malignant tumors.

Characteristics	Number of Patients
Gender	
Male	9
Female	2
Age (years)	49-73 (median : 63)
Tumor types	
Pancoast tumor	2
Recurrent NSCLC	4
Malignant mesothelioma	3
LN metastasis of ovarian cancer	1
Pleural dissemination of NSCLC	1
Radiation therapy	
Yes	7
No	4

NSCLC : non-small cell lung cancer, LN : lymph node

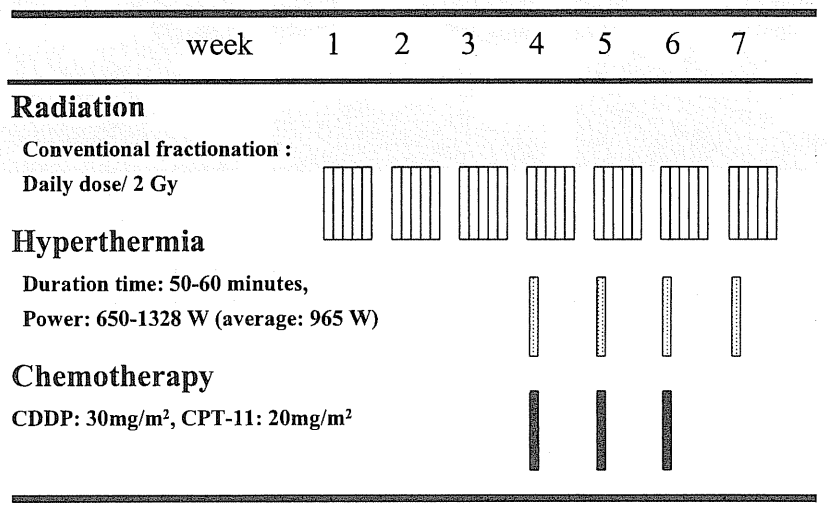


Fig. 1. Thermo-chemo-radiotherapy treatment schedule of the present study. Three cycles of weekly thermo-chemotherapy using 30mg/m² of CDDP and 20mg/m² of CPT-11 were concurrently given from the third or fourth week onwards after start of radiotherapy. Afterward, additional hyperthermia sessions took place during the final week.

using 10 MV X-rays with a conventional daily fractionation dose of 2 Gy. After a dose of 40-50 Gy had been delivered with parallel anterior-posterior opposed fields, boost therapy for the tumor was performed using more shrunken fields so that the total dose was in the range of 60-68 Gy. If the spinal cord was irradiated with the initial field, the shrunken field was planed to avoid irradiating the spinal cord.

Hyperthermia

The method of hyperthermia used in our department for lung cancer has been previously described elsewhere[12)23)]. In the present study, four sessions of weekly regional hyperthermia were undergone using

Table II. Initial response to the treatment.

Disease	Initial response (TCR cases / All cases)			
	CR	PR	NC	PD
Pancoast tumor (n=2)	0/0	2/2	0/0	0/0
Recurrence of NSCLC (n=4)	0/1	0/0	2/3	0/0
Malignant mesothelioma (n=3)	0/0	1/1	0/1	0/1
LN metastasis (n=1)	1/1	0/0	0/0	0/0
Pleural dissemination (n=1)	0/0	0/0	1/1	0/0
All	1/2	3/3	3/5	0/1

TCR: thermo-chemo-radiotherapy, NSCLC: non-small cell lung cancer, LN: lymph node

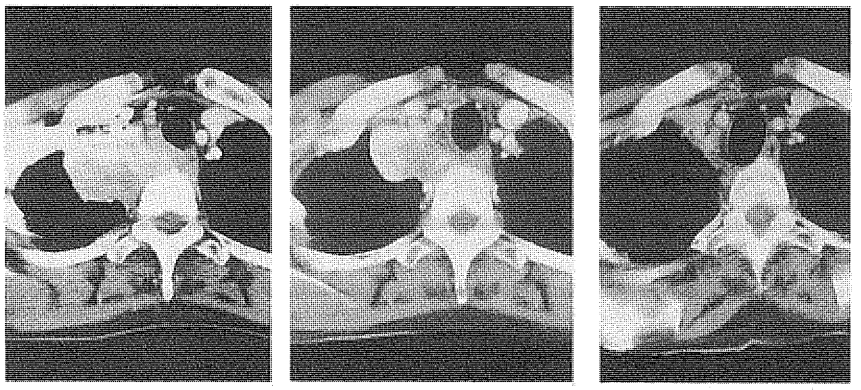


Fig. 2. Contrast-enhanced CT scan of a case of mediastinal lymph node metastasis from clear cell carcinoma of the ovary depicting a heterogeneous irregular enhanced tumor with tracheal compression and involvement of adjacent vessels before treatment. The tumor disappeared 12 months after thermo-chemo-radiotherapy.

8 MHz radiofrequency capacitive heating by Thermotron RF8 (Yamamoto Vinita Co., Ltd., Osaka, Japan). The initial 3 sessions were conducted in combination with simultaneous chemotherapy, while the final session consisted of hyperthermia alone. Hyperthermia was performed immediately after RT for 50-60 minutes and the average power was 965 W (range: 650-1328 W).

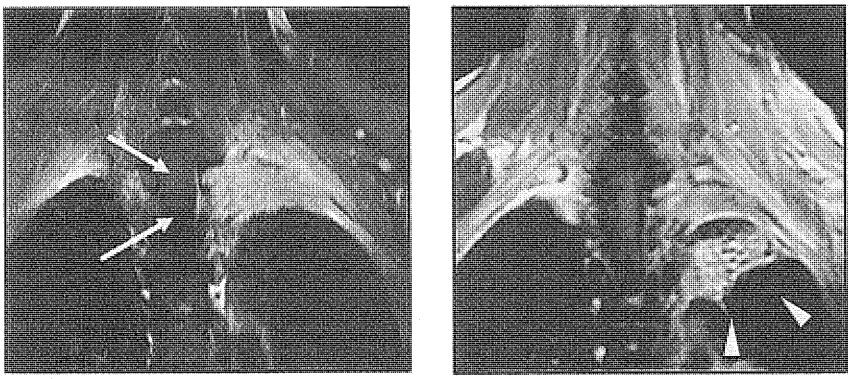
Chemotherapy

The weekly chemotherapy regimen consisted of 30mg/m^2 of CDDP and 20mg/m^2 of CPT-11 intravenously administered for all patients 3 times. These anti-cancer drugs were simultaneously infused during irradiation and hyperthermia.

RESULTS

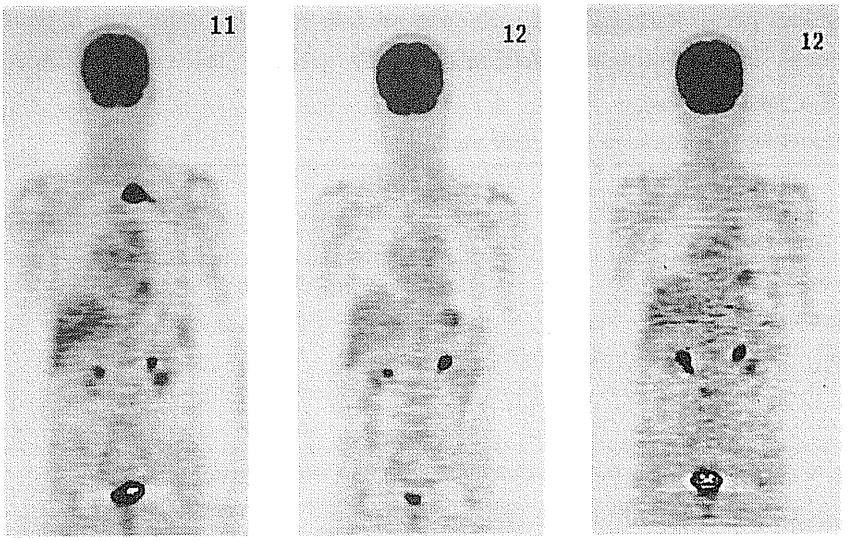
Response and Prognosis

Responses of the tumors in the current study are summarized in Table II. Complete responses (CR) were obtained in 2 patients (a recurrent lung cancer case and a case of mediastinal lymph node metastasis from an ovarian cancer) and 3 tumors (2 Pancoast tumors and a malignant mesothelioma) were judged



Before treatment　　4 months after treatment

Fig. 3A. MRI of a Pancost tumor detects an irregular enhanced tumor in the left apex of the lung. Prior to treatment, the tumor showed invasion on to the dura mater of the spinal cord (white arrows). The tumor shrank and lung fibrosis within the irradiated field was delineated 4 months after thermo-chemo-radiotherapy (arrowheads).



Before　　1 month after　　12 months after

Fig. 3B. Fluoro-2-deoxy-D-glucose positron emission tomography demonstrated an abnormal strong accumulation in the apex of left lung before treatment. No uptake was observed after treatment and no other site of abnormal accumulation was detected

as partial responses (PR), whereas the responses in 5 patients were regarded as no change (NC), and a remaining patient with malignant mesothelioma had a progressive tumor despite of receiving thermo-chemotherapy. Figure 2 showed a CR case with ovarian cancer and Fig. 3A and 3B demonstrated a PR case with Pancoast tumor. Responses (CR + PR) were obtained in 4 (57 %) of 7 patients treated with thermo-chemo-radiotherapy, and 1 (25 %) of 4 patients treated with thermo-chemotherapy.

Two patients with Pancoast tumors have survived without any finding of recurrence. One patient with pleuritis carcinomatosa from a lung adenocarcinoma received molecular targeting therapy using the EGFR inhibitor, gefitinib ("Iressa," ZD1839), because the tumor did not respond to the treatment. After

administration of Iressa, the tumor began to shrink rapidly and pleural effusion disappeared. This patient was still alive and she was alive without relapse of tumor at the time of the last follow-up. The remaining 8 patients were died of the diseases within 4-19 months (median: 12 months) after the treatment.

Toxicities

Acute and late toxicities related to the treatment were assessed in accordance with the National Cancer Institute-Common Toxicity Criteria (NCI-CTC) version 2[23] and the hematological and non-hematological toxicities encountered during the treatment are listed in Table III. In view of acute toxicity, grade 2 and 3 hematological toxicities were found in 3 (27 %) and 5 (45 %) patients, respectively, but no grade 3 or worse non-hematological toxicity was observed. Two patients developed grade 2 esophagitis due to irradiation of the upper thoracic esophagus and another patient presented with grade 2 nausea/vomiting. With a help of pre-medication support provided, there was no case of severe diarrhea, a side-effect peculiar to CPT-11. By way of late toxicity, there was a patient with grade 2 pneumonitis, which subsequently subsided resolved to grade 1 following a short course of oral administration of a steroid drug.

Table III. Toxicities according to treatment modalities.

	Grade (%)*			
Site	0	1	2	3
Bone marrow	1 (10)	2 (18)	3 (27)	5 (45)
Nausea/vomiting	7 (64)	3 (27)	1 (9)	0 (0)
Esophagus	7 (64)	1 (9)	2 (18)	0 (0)
Diarrhea	8 (73)	3 (27)	0 (0)	0 (0)
Lung	5 (45)	5 (45)	1 (10)	0 (0)

*According to National Cancer Institute-Common Toxicity Criteria version 2.0

Disucussion

It has been well known that the clinical use of regional hyperthermia as an adjuvant to RT has some advantages for radio-resistant tumors. One notion is that hypoxia induced by locally advanced tumors reduces radio-sensitivity[9], but tumor cells in hypoxic environment are more sensitive to hyperthermia than aerobic cells. Another notion based on experimental studies is that the cells in the DNA synthetis phase of the cell cycle are most resistant to X-ray, but most sensitive to hyperthermia[11]. Furthermore, it is thought that hyperthermia sensitizes radiation-induced cytotoxicity because it inhibits the repair of DNA damage induced by irradiation[11]. Based on this theory, combined therapy has been used as a local aggressive treatment for many locally advanced tumors in order to improve local tumor control. Our previous study on NSCLC with chest wall invasion also demonstrated that the survival and local control rates in the combined group were superior to those in the RT alone group[24]. In fact, the 3-year local control rate of the combined group was 76.2 %, whereas the corresponding rate in the RT alone group was 16.9 %. The difference between the survival rates of the two groups was statistically significant ($P=0.03$). In another investigation into NSCLC with direct bony invasion, we were also able to show

that hyperthermia combined with RT produced a much superior local control rate to RT alone[12].

CDDP is widely recognized as a representative sensitizer for RT. The treatment effect of RT has been found, in various experimental and clinical studies, to be enhanced by combination with CDDP[25-27]. As a matter of fact, concurrent chemo-radiotherapy (CRT) using CDDP is already a standard treatment method for unresectable NSCLC[28-30]. Recently, some experimental studies have also indicated that CPT-11, which is a new derivation of camptothecin, has a sensitization potential for RT and hyperthermia in vitro and in vivo[17][18]. CPT-11 has become one of the major anticancer drugs used in CRT for advanced or recurrent NSCLC and produces good treatment outcomes[19-22]. However, the prognosis for NSCLC after CRT is still unsatisfactory because it is difficult to achieve local tumor control. To improve survival prospects for these patients, it is therefore important to reduce the incidence of local tumor recurrence. On the other hand, the effect of hyperthermia is generally enhanced by chemotherapy[11]. From the foregoing results, it can be seen that the combination of RT, hyperthermia and chemotherapy produces a synergistic effect for locally advanced or extensive tumors contrary to CRT only if the event of severe adverse effect is not significantly increased.

Administration of CPT-11 in thoracic RT may cause severe pneumonitis. Some randomized trails have indicated that the recommended dose of CPT-11 should range from 50-60 mg/m^2/week[20][22]. In our study, the weekly doses of CPT-11 and CDDP were selected on the expectation that these drugs could enhance the effect of RT combined with hyperthermia and that the risk of severe toxicities that might necessitate the suspension or discontinuation of the treatment would not be increased. Therefore, the CPT-11 and CDDP doses were kept at 20 mg/m^2/week and 30 mg/m^2/week, respectively. In fact, no grade 3 non-hematological toxicity was observed and it was possible to fully complete the treatment courses for all of 7 patients receiving combined CRT and hyperthermia. It is believed that our treatment protocol consisting of CRT combined with hyperthermia can be tolerated even by patients subjected to chest irradiation.

The treatment effect of CRT combined with hyperthermia for Pancoast tumor seems quite satisfactory in our study, seeing that both patients had PR as the initial effect and they are still surviving 2 years after RT without tumor recurrence. It has been reported that the prognosis of unresectable Pancoast tumor is disappointing after RT alone and that it is difficult to achieve local control for the disease. Attar et al. reported that the median survival of their RT alone group of 37 Pancoast tumor patients was 6 months only[31]. To improve prognosis for the disease, it is therefore necessary to reduce local recurrence as well as distant metastasis using an aggressive treatment. Recently, chemotherapy has been concurrently used in RT for the unresectable Pancoast tumor and improvement of survival was observed compared with RT alone[32]. However, clinical outcomes of CRT without surgery have also remained poor[31][32]. On the other hand, regional hyperthermia is thought to be a typical aggressive local treatment modality. Terashima et al reported that a partial response was obtained in 4 (67 %) of 6 patients with Pancoast tumor treated by RT combined with regional hyperthermia[33]. Similarly, in a previous study on lung cancer with direct bony invasion, we pointed out that the combined therapy is useful for locally advanced lung cancer, including Pancoast tumor[12][24]. In view of these results, the tri-modality schedule consisting of radiation, chemotherapy and regional hyperthermia appears to confer distinctive benefit in terms of management for locally advanced malignant tumors such as Pancoast

tumor.

In conclusion, our thermo-chemo-radiotherapy protocol is effective for intrathoracic malignancies, and a weekly CPT-11 dose of 20 mg/m^2 and a weekly CDDP dose of 30 mg/m^2 can be tolerated by patients receiving thoracic irradiation combined with hyperthermia. The next step will be to ascertain the recommended dose of chemotherapy by a dose escalation study for these patients.

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References

1) Cox J. D., Yesner R., Mietlowski W., Petrovich Z.: Influence of cell type on failure pattern after irradiation for locally advanced carcinoma of the lung. Cancer, 44: 94-98, 1979.
2) Karasawa K., Kaizu T., Niibe Y., Ishikawa H., Okamura T., Tanaka Y.: Intrathoracic thermochemoradiotherapy for the treatment of locally-advanced malignant pleural mesothelioma: Treatment protocol and report of the three cases. Jpn J Hyperthermic Oncol, 17: 45-52, 2001.
3) Sause W. T., Scott C., Taylor S., Johnson D., Livingston R., Komaki R., mami B., Curran W. J., Byhardt R. W., Turrisi A. T., Rashid Dar A., Cox J. D.: Radiation Therapy Oncology Group (RTOG) 88-08 and Eastern Cooperative Oncology Group (ECOG) 4588: preliminary results of a phase III trial in regionally advanced, unresectable non-small-cell lung cancer. J Natl Cancer Inst, 87: 198-205, 1995.
4) Dillman R. O., Herndon J., Seagren S. L., Eaton W. L. Jr, Green M. R.: Improved survival in stage III non-small-cell lung cancer: seven-year follow-up of cancer and leukemia group B (CALGB) 8433 trial. J Natl Cancer Inst. 88: 1210-1215, 1996.
5) Furuse K., Fukuoka M., Kawahara M., Nishikawa H., Takada Y., Kudoh S., Katagami N., Ariyoshi Y.: Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. J Clin Oncol 17: 2692-2629, 1999.
6) Ishikawa H., Sakurai H., Hasegawa M., Mitsuhashi N., Takahashi M., Masuda N., Nakajima M., Kitamoto Y., Saitoh J., Nakano T.: Expression of hypoxic-inducible factor 1alpha predicts metastasis-free survival after radiation therapy alone in stage IIIB cervical squamous cell carcinoma. Int J Radiat Oncol Biol Phys, 60: 513-521, 2004.
7) Lyng H., Sundfor K., Trope C., Rofstad E. K.: Disease control of uterine cervical cancer: relationships to tumor oxygen tension, vascular density, cell density, and frequency of mitosis and apoptosis measured before treatment and during radiotherapy. Clin Cancer Res, 6: 1104-1112, 2000
8) Brizel D. M., Dodge R. K., Clough R. W., Dewhirst M. W.: Oxygenation of head and neck cancer: changes during radiotherapy and impact on treatment outcome. Radiother Oncol, 53: 113-117, 1999.
9) Hall E. J. Radiobiology fot the radiologist, 5 th ed. Lippincott Williams & Wilkins, pp91-111, 2000.
10) Westra A., Dewey W. C.: Variation in sensitivity to heat shock during the cell-cycle of Chinese hamster cells in vitro. Int J Radiat Biol, 19: 467-477, 1971.
11) Hall E. J.: Radiobiology fot the radiologist, 5 th ed. Lippincott Williams & Wilkins, pp257-288, 2000.
12) Sakurai H., Hayakawa K., Mitsuhashi N., Tamaki Y., Nakayama Y., Kurosaki H., Nasu S., Ishikawa H., Saitoh J. I., Akimoto T., Niibe H.: Effect of hyperthermia combined with external radiation therapy in primary non-small cell lung cancer with direct bony invasion. Int J Hyperthermia, 18: 472-483, 2002.
13) Davis R. K., Gibbs F. A., Sapozink M. D., Farver M., Harker G.: Thermochemotherapy in inoperable head and neck cancer. Otolaryngol Head Neck Surg, 103: 897-901, 1990.

14) Ohtsubo T., Saito H., Tanaka N., Noda I., Saito T., Kano E.: Effect of heat-drug sequences on thermoenhancement and uptake of cis-DDP in human pharyngeal carcinoma. Anticancer Res, 16: 297-300, 1996.
15) Mohamed F., Marchettini P., Stuart O. A., Urano M., Sugarbaker. PH. Thermal enhancement of new chemotherapeutic agents at moderate hyperthermia. Ann Surg Oncol, 10: 463-468, 2003.
16) Kowal C. D., Bertino J. R.: Possible benefits of hyperthermia to chemotherapy. Cancer Res, 39: 2285-9, 1979.
17) Katschinski DM, Robins HI.: Hyperthermic modulation of SN-38-induced topoisomerase I DNA cross-linking and SN-38 cytotoxicity through altered topoisomerase I activity. Int J Cancer, 80: 104-109, 1999.
18) Tamura K., Takada M., Kawase I., Tada T., Kudoh S., Okishio K., Fukuoka M., Yamaoka N., Fujiwara Y., Yamakido M.: Enhancement of tumor radio-response by irinotecan in human lung tumor xenografts. Jpn J Cancer Res, 88: 218-223, 1997.
19) Socinski M. A., Morris D. E., Halle J. S., Moore D. T., Hensing T. A., Limentani S. A., Fraser R., Tynan M., Mears A., Rivera M. P., Detterbeck F. C., Rosenman J. G.: Induction and concurrent chemotherapy with high-dose thoracic conformal radiation therapy in unresectable stage IIIA and IIIB non-small-cell lung cancer: a dose-escalation phase I trial. J Clin Oncol, 22: 4341-4350, 2004.
20) Oka M., Fukuda M., Fukuda M., Kinoshita A., Kuba M., Ichiki M., Rikimaru T., Soda H., Takatani H., Narasaki F., Nagashima S., Nakamura Y., Hayashi N., Kohno S.: Phase I study of irinotecan and cisplatin with concurrent split-course radiotherapy in unresectable and locally advanced non-small cell lung cancer. Eur J Cancer, 37: 1359-65, 2001.
21) Takeda K., Negoro S., Kudoh S., Okishio K., Masuda N., Takada M., Tanaka M., Nakajima T., Tada T., Fukuoka M.: Phase I/II study of weekly irinotecan and concurrent radiation therapy for locally advanced non-small cell lung cancer. Br J Cancer, 79: 1462-1467, 1999.
22) Yamada M., Kudoh S., Fukuda H., Nakagawa K., Yamamoto N., Nishimura Y., Negoro S., Takeda K., Tanaka M., Fukuoka M.: Dose-escalation study of weekly irinotecan and daily carboplatin with concurrent thoracic radiotherapy for unresectable stage III non-small cell lung cancer. Br J Cancer, 29: 258-263, 2002.
23) National Cancer Institute.: Common Toxicity Criteria Manual. Bethesda, Md: National Cancer Institute, 1999.
24) Sakurai H., Hayakawa K., Tamaki Y., Nakayama Y., Ishikawa H., Mitsuhashi N.: A challenge for Non-small cell lung cancer using hyperthermia. Jpn J Hyperthermic Oncol, 17: 23-30, 2001
25) Tsuchiya S., Ohe Y., Sugiura T., Fuwa N., Kitamoto Y., Mori K., Kobayashi H., Nakata K., Sawa T., Hirai K., Etoh T., Saka H., Saito A., Fukuda H., Ishizuka N., Saijo N., Japan Clinical Oncology Group Study.: Randomized phase I study of standard-fractionated or accelerated-hyperfractionated radiotherapy with concurrent cisplatin and vindesine for unresectable non-small cell lung cancer: a report of Japan Clinical Oncology Group Study (JCOG 9601). Jpn J Clin Oncol, 31: 488-494, 2001.
26) Nakamoto S., Mitsuhashi N., Takahashi T., Sakurai H., Niibe H.: An interaction of cisplatin and radiation in two rat yolk sac tumour cell lines with different radiosensitivities in vitro. Int J Radiat Biol, 70: 747-53, 1996.
27) Mitsuhashi N., Sakurai H., Takahashi T., Akimoto T., Higuchi K., Matsumoto H., Ebara T., Nozaki M., Niibe H.: Does AK-2123 (Senazole) have sensitizing effects on radiation, cisplatin and hyperthermia under aerobic conditions in vitro? Anticancer Res, 18: 3463-3467, 1998
28) Zatloukal P., Petruzelka L., Zemanova M., Havel L., Janku F., Judas L., Kubik A., Krepela E., Fiala P., Pecen L.: Concurrent versus sequential chemoradiotherapy with cisplatin and vinorelbine in locally advanced non-small cell lung cancer: a randomized study. Lung Cancer, 46: 87-98, 2004.
29) Cakir S., Egehan I.: A randomised clinical trial of radiotherapy plus cisplatin versus radiotherapy alone in stage III non-small cell lung cancer. Lung Cancer, 43: 309-316, 2004.
30) Komaki R., Seiferheld W., Ettinger D., Lee J. S., Movsas B., Sause W.: Randomized phase II chemotherapy and radiotherapy trial for patients with locally advanced inoperable non-small-cell lung cancer: long-term follow-up of

RTOG 92-04. Int J Radiat Oncol Biol Phys, 53: 548-557, 2002.

31) Attar S., Krasna M. J., Sonett J. R., Hankins J. R., Slawson R. G., Suter C. M., McLaughlin J. S.: Superior sulcus (Pancoast) tumor: experience with 105 patients. Ann Thorac Surg, 66: 193-198, 1998.

32) Komaki R., Roth J. A., Walsh G. L., Putnam J. B., Vaporciyan A., Lee J. S., Fossella F. V., Chasen M., Delclos M. E., Cox J. D.: Outcome predictors for 143 patients with superior sulcus tumors treated by multidisciplinary approach at the University of Texas M. D. Anderson Cancer Center. Int J Radiat Oncol Biol Phys, 48: 347-354, 2000.

33) Terashima H., Nakata H., Yamashita S., Imada H., Tsuchiya T., Kunugita N.: Pancoast tumour treated with combined radiotherapy and hyperthermia--a preliminary study. Int J Hyperthermia, 7: 417-424, 1991.

胸部腫瘍に対する温熱化学療法・温熱化学放射線療法の初期経験

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要　旨：切除不能の局所進行胸部悪性腫瘍に対する放射線治療成績は不良であり，こうした症例に対してはより強力な治療が必要と考えられる．我々は治療成績の改善を目的に原発・再発胸部悪性腫瘍に対して温熱化学療法もしくは温熱化学放射線療法を施行し，その有効性について検討したので報告する．対象は2002年3月から2004年3月までの11症例で，治療方法は毎週の少量CDDP (30 mg/m^2)・CPT-11 (20 mg/m^2) 併用温熱療法3クール (温熱療法のみ1クール追加し合計4クール) に照射可能7症例については同時に通常分割照射を用いた放射線療法を施行した．全症例で治療の完遂が可能であり，初期効果として11例中2例にCR, 3例にPRが得られた．特に，Pancoast腫瘍 (Stage IIIB) については2症例とも現時点で再発なく治療終了後2年以上経過している．毒性についてもGrade3以上の非血液毒性は認められず，本治療方法は切除不能進行胸部腫瘍に対して安全かつ有効な治療法と考えられた．