Review

A Challenge for Non-small Cell Lung Cancer Using Hyperthermia

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Abstract : Recent randomized clinical trials on hyperthermia have shown promising results for not only superficial tumors but also deep-seated tumors. Local irradiation has been a traditional approach in non-small cell lung cancer (NSCLC). Local tumor control is an important goal of the primary treatment for NSCLC, but patients with unresectable NSCLC show an extremely poor prognosis. From recent clinical trials for NSCLC, chemoradiation provided more benefit in non-squamous cell carcinoma, while aggressive local treatment would be most beneficial in squamous cell carcinoma. Considering an application of hyperthermia, bulky squamous cell type NSCLC is a clinical challenge for hyperthermia combined with standard irradiation as a local aggressive treatment. Although clinical trial in western countries has not been reported, few Japanese researchers have investigated clinical benefit for combination of hyperthermia and irradiation in patients with NSCLC. In our study for unresectable NSCLC with chest wall invasion, hyperthermia combined with standard irradiation potentially improved the local control and might provide more long-term survivors without increasing adverse effect. Randomized clinical trial should be conducted mainly by Japanese Society of Hyperthermic Oncology.

Key words : non-small cell lung cancer, radiation, hyperthermia

1. Background

Hyperthermia is biologically known as an effective modality for the treatment of cancer. Recent randomized clinical trials on hyperthermia has shown promising results for various sites of tumor, for instance, recurrent advanced breast cancer, recurrent or metastatic melanoma, advanced head and neck cancer, glioblastoma multiforme and advanced intrapelvic malignancy 1-6). These positive results were initially confirmed in tumors arising from superficial sites, because it was easy to achieve intended temperature. Clinical trials for hyperthermia recently advanced to deep-seated tumors due to the improvement of the heating technique. The Dutch hyperthermia group conducted a prospective randomized trial for locally advanced tumors of the bladder, uterine cervix and rectum 8). They demonstrated
that the addition of hyperthermia to radiation therapy could improve local control and also improve overall survival in patients with advanced pelvic tumors. Complete response rates were increased for all tumor 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.

The standard treatment for primary non-small cell lung cancer (NSCLC) has been considered to be surgical resection, however, many tumors are unfavorable for surgical resection because of their locally advanced stage, age factor and additional medical problems. Although local irradiation has been a traditional approach in NSCLC, patients with unresectable NSCLC show an extremely poor prognosis. In such cases, patients have been generally treated with external beam irradiation to the primary tumor and/or regional lymph nodes with cytotoxic chemotherapy for the purpose of improvement of symptoms and for hopefully producing a rare long-term survivor. About two thirds of the patients with locally advanced NSCLC would die of locoregional disease with or without distant metastases. Local tumor control has been considered to be an important goal of the primary treatment, because local failure leads to major morbidity. In the present situation, more aggressive local treatment is emphasized for improvement of these poor prognoses.

In this review, we are going to discuss if regional hyperthermia combined with irradiation would be more beneficial than conventional irradiation alone for patients with NSCLC.

2. Patient selection for hyperthermia in combination with standard radiation

Because patients with advanced NSCLC often develop distant metastasis, many clinical trials have been performed worldwide comparing irradiation alone with irradiation and systemic chemotherapy for the purpose of improvement of survival. Some trials have been equivalent, but recent trials with cisplatin-based chemotherapy have shown positive results in favor of combined chemotherapy. Cancer and Leukemia Group B (CALGB) 8433 trial concluded that the patients who had been treated with induction chemotherapy followed by conventional radiation therapy showed a better survival rate than those who had received conventional radiation alone. The benefit was more emphasized in adenocarcinoma than that in squamous cell carcinoma. Phase III trial conducted by Radiation Therapy Oncology Group (RTOG) 88-08 and Eastern Cooperative Oncology Group (ECOG) 4588 also showed that the chemotherapy plus radiation were statistically superior to standard radiation alone in patients with non-squamous cell carcinoma, but not in squamous cell carcinoma. Other trials mainly including patients with squamous cell type NSCLC were not likely to show the survival benefit due to added cytotoxic chemotherapy. From these points, squamous cell carcinoma and non-squamous cell carcinoma are two distinct types of NSCLC, which have different natural histories and have 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. For the trial mostly including patients with squamous cell carcinoma, local aggressive treatment was emphasized in the report of continuous hyperfractionated accelerated radiation therapy (CHART), which showed improvement over standard fractionated irradiation. From these results, it was suggested that chemoradiation might provide more benefit in non-squamous cell carcinoma, while aggressive local treatment would be most beneficial in
squamous cell carcinoma. In our department, dose escalation study has been carried out for stage I - II squamous cell carcinoma, however, total dose at 80 Gy with conventional fractionation caused adverse chronic effects on the bronchus 19). Another study in our department suggested that tumor volume was an important prognostic factor for squamous cell type NSCLC 20). Considering an application of hyperthermia, bulky squamous cell type NSCLC is a clinical challenge for hyperthermia combined with standard irradiation as a local aggressive treatment.

3. Clinical researches

For the clinical researches of hyperthermia related to 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 21-26). For pleural dissemination from primary lung cancer, Kodama et al. demonstrated the survival benefit of postoperative hyperthermia combined the intrathoracic administration of cisplatin 21, 22). For the technical problem of heating of lung tissue, it was reported that normal lung tissue could be heated with RF capacitive heating devices in animal 27) and in human 28). Regarding hyperthermia plus conventional irradiation for primary lung cancer, Karasawa et al. treated 19 patients and concluded that thermoradiotherapy could increase resectability and improve long-term survival rates 24). For NSCLC invaded or in contact with the chest wall, Hiraoka et al. conducted the treatment of hyperthermia with irradiation 23). They demonstrated that thermal parameters were related to the appearance of low density areas observed with computed tomography (CT) but not to the tumor response, however, they did not refer to survival benefit. Terashima et al. treated patients with Pancoast tumor with full dose irradiation plus hyperthermia 25, 26). They showed good local response and survival benefit for combined treatment.

4. Phase I / II study for NSCLC with chest wall invasion in Gunma University

In our department, a prospective phase I / II study for NSCLC with chest wall invasion has been performed since 1995. Nine patients with advanced NSCLC directly invading the bony structure with no distant metastases were treated with full dose conventional radiation therapy (60-70 Gy) combined with hyperthermia. Majority of histology was squamous cell carcinoma. The method of radiation therapy has been reported previously 17, 20, 29, 30) The patients received 2 to 4 sessions of hyperthermia once weekly. Hyperthermia was performed immediately after irradiation fraction with radiofrequency devises (Thermox-1000, Omron Co. Ltd. and Thermotron-RF 8, Yamamoto Vinita Co. Ltd., Japan). The aim of hyperthermia was to continue treatment for 60 min after measured tumor temperature had reached 42°C. For overall 32 sessions of hyperthermia, intratumoral temperatures were obtained in 26 of 32 (81.3 %) sessions. The values of Tmin, Tay and Tmax ± standard error were 40.8 ± 0.22, 41.7 ± 0.26 and 42.5 ± 0.30 °C, respectively, with average duration for 49.9 ± 8.8 min.

Figure 1 shows survival curves in patients treated with radiation alone and with radiation plus hyperthermia. For 3 years in patient with radiation alone, there were no overall survivors and no recurrence-free survivors. The overall survival rates, recurrence-free survival and local recurrence-free survival rates for 3 years in patients treated with radiation plus hyperthermia were 44.4 %, 33.3 % and 76.2 %, respectively, whereas those with radiation alone were 0.0 %, 7.7 % and 16.9 %, respectively.
Fig. 1. Overall survival, recurrence-free and local recurrence-free survival curves in hyperthermia plus radiation and those in radiation alone. The survival rate was determined by Kaplan-Meier methods.
Local recurrence-free survival rates were statistically significant between both groups (p = 0.032). Four patients died of distant metastasis within 3 years in the hyperthermia group, but a disappearance of tumors even in the autopsy examinations was confirmed in 2 cases. For adverse effects, grade 3-4 severe pulmonary complications were not observed due to added hyperthermia.

Figure 2 shows a MR image in patient with squamous cell carcinoma of the lung. The tumor is found in right apex with direct invasion to vertebral body (arrows). The patient was treated with conventional irradiation total dose at 70 Gy and 3 sessions of hyperthermia.

![Figure 2](image)

Fig. 2. The initial finding of magnetic resonance imaging (T1-weighted) in patient with squamous cell carcinoma of the lung. The tumor is found in right apex with direct invasion to vertebral body (arrows). The patient was treated with conventional irradiation total dose at 70 Gy and 3 sessions of hyperthermia.

![Figure 3](image)

Fig. 3. A change in chest X-ray findings with squamous cell carcinoma of the lung treated with hyperthermia combined with radiation therapy.

Figure 2 shows a MR image in patient with squamous cell carcinoma with direct vertebral body invasion. This patient received 70 Gy of conventional radiation combined with 3 sessions of hyperther-
Hyperthermia for lung cancer • H. Sakurai et. al.

Average values of Tmax, Tav and Tmin were 42.1, 41.3 and 40.4°C for 50 minutes each, respectively. Figure 3 and 4 show radiograms and CT images in this patient. The tumor shadow remarkably decreased in size on CT images. The patient survived 38 months after the treatment without recurrence.

In conclusion, hyperthermia combined with standard irradiation potentially improves the local control and may provide more long-term survivors without increasing adverse effect for unresectable squamous cell type NSCLC. A randomized clinical trial should be conducted mainly by Japanese Society of Hyperthermic Oncology.

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Hyperthermia for lung cancer  •  H. Sakurai et al.


ハイパーサーミアを用いた非小細胞肺癌への挑戦

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要旨：近年のハイパーサーミアに関する無作為臨床試験から、表在性腫瘍だけでなく深在性腫瘍でもハイパーサーミアの有用性が明らかとなってきた。非小細胞肺癌に対し、局所の放射線治療が古くから行われている。腫瘍の局所制御は初期治療の重要な目標であるが、切除例の予後は極めて不良である。近年の非小細胞肺癌を対象とした無作為臨床試験から、非扁平上皮癌では放射線と化学療法の併用が有用であるが、扁平上皮癌には化学療法の併用よりも、強力な局所療法が有益であることが明らかになりつつある。非小細胞肺癌に対して放射線治療とハイパーサーミアを適応する場合、局所進行扁平上皮癌が対象として適していると考えられる。非小細胞肺癌を対象としたハイパーサーミアの臨床試験の結果は欧米から報告されていないが、少数ながら日本でその有用性を示した報告が認められる。非切除胸壁侵犯型肺癌を対象とした我々の研究でも、放射線治療とハイパーサーミアの併用により、副作用の増加なしに局所制御率が向上し、長期生存例が多く認められた。この領域では日本ハイパーサーミア学会を主体とした比較試験が望まれる。