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A Case of Recurrent Esophageal Cancer Treated with Chemoradiation Combined with Long-term Hyperthermia Treatment

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Abstract : Hyperthermia is a less invasive treatment than chemotherapy, radiotherapy and surgery. However, there has been no report about the safety of administering repeated hyperthermia treatments over a long period. This report describes a patient who received 86 hyperthermia treatments over the course of four years.

A 65-year-old man was diagnosed with advanced esophageal cancer in the middle portion of the thoracic esophagus. He underwent a subtotal esophagectomy with gastric tube reconstruction. Five months after surgery, recurrent lesions were revealed on a computed tomography (CT) examination in the upper mediastinum and left supraclavicular region. Chemoradiation with a total dose of 60 Gy was performed in combination with hyperthermia as an initial treatment for these recurrences. Concurrent chemotherapy consisted of cisplatin (CDDP) and 5-fluorouracil (5FU). Hyperthermia was applied with an RF-capacitive heating apparatus (Thermotron RF-8, Yamamoto Vinita, Osaka, Japan) for 50 minutes twice a week. On a CT examination at the end of two months, both of the recurrent masses had decreased in size. Therefore, chemotherapy using CDDP and tegafur-uracil (TS-1), combined with twice-weekly hyperthermia, was performed as an adjuvant therapy for two weeks. Subsequently, he continued to receive hyperthermia once a week or once every three weeks for 3.5 years. At present he has had no adverse effects associated with the hyperthermia and no recurrence.

Key Words : hyperthermia, esophageal cancer, chemoradiation

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Introduction

Chemoradiation is frequently performed for recurrent esophageal cancer after surgery. The efficacy of chemoradiation is generally affected by the blood flow and oxygenation in the tumor. Lowered blood flow and hypoxia can decrease both the cytotoxic effect of chemotherapy and the tumor's sensitivity to radiation. In the case of a tumor with central necrosis like metastasis from esophageal cancer, it was found that chemotherapeutic agents had more difficulty reaching necrotic areas and radiation sensitivity in hypoxic necrotic areas was poor[1]. However, hyperthermia can increase tumor blood flow and consequently, improve tumor oxygenation[2]. Therefore, chemoradiation in combination with hyperthermia was able to improve the therapeutic effect by increasing the cytotoxic effect of chemotherapy and the radiation sensitivity of the tumor. These effects can be anticipated at a temperature range of 40-45°C[3].

Hyperthermia is a less invasive treatment than chemotherapy, radiotherapy and surgery. However, there is no report of long-term, repeated administration of hyperthermia. This report concerns a patient with recurrent esophageal cancer who received 86 hyperthermia treatments over the course of four years.

Material and methods

In 2006, 65-year-old man presented with esophageal obstruction and vomiting. Endoscopy revealed an esophageal mass with a tumor length of 3 cm at a 30-cm distance from the dental arch. A biopsy of the mass indicated moderately differentiated squamous cell carcinoma. On a computed tomography (CT) examination, no lymph node metastasis was found. Subtotal esophagectomy and D2 lymph node dissection with gastric tube reconstruction was undertaken for advanced esophageal carcinoma in the middle portion of the thoracic esophagus. In pathology after surgery the primary tumor was found to have spread to the adventitia and a peri-gastric lymph node metastasis (# 3) was found. Thus, the tumor was classified as pT3N1M0, using the 2009 UICC TNM classification system. No adjuvant treatment after surgery was performed.

Five months after surgery, a CT examination revealed recurrent lesions in the upper mediastinum and left supraclavicular region. F-18 fluorodeoxyglucose positron emission tomography / CT (FDG-PET/CT) showed high uptake (SUVmax: 8.9 in the supraclavicular l esion, 11.0 in the upper mediastinal lesion) (Fig. 1). A total-body examination revealed no other lesion. In

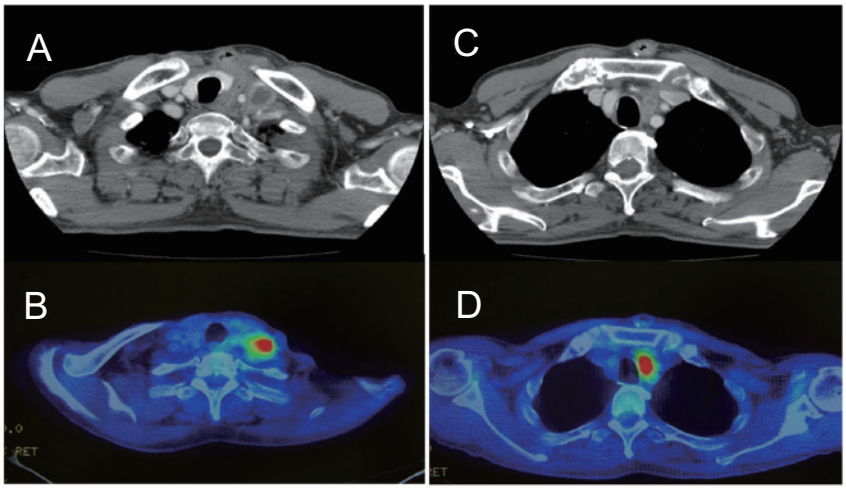

Fig. 1. CT and FDG-PET/CT images before chemoradiation with hyperthermia. **A**, left subclavian mass with central necrosis; **B**, high FDG uptake in left subclavian mass; **C**, upper mediastinal mass; **D**, high FDG uptake in upper mediastinal mass.

March 2007 chemoradiation with hyperthermia was started for the recurrent lymph node lesions. External beam radiation was delivered in 30 fractions of 2 Gy to a total dose of 60 Gy with 10 MV X ray. The initial field included the upper/ middle mediastinum and bilateral supraclavicular region to 40 Gy using a opposed technique. An additional 20 Gy was delivered with smaller fields to the recurrent lesions using the three-field technique. Chemotherapy consisted of concurrent cisplatin (CDDP) and 5-fluorouracil (5FU). CDDP (5 mg/m^2) and 5FU (300 mg/m^2) were given five days per week for four weeks. Hyperthermia was applied with a RF-capacitive heating apparatus (Thermotron RF-8, Yamamoto Vinita Co, Osaka, Japan) for 50 min twice a week for two months. The hyperthermia was administered at a power of 1,200-1,300 W for fifty minutes with the 30 cm electrodes.

Results

The patient had grade 1 esophagitis according to the Common Terminology Criteria for Adverse Events (CTCAE version 4). At the 40-Gy radiation dose, concurrent chemotherapy was discontinued because grade 2 thrombocytopenia and grade 3 leukopenia was detected. However, no adverse effect associated with the hyperthermia was found.

An post-treatment examination showed a decrease in size in the recurrent lesions. Therefore, chemotherapy with hyperthermia was performed as an adjuvant therapy. Chemotherapy consisted of CDDP (10 mg/m^2) and oral tegafur-uracil (TS-1) (80 mg/body). CDDP was given twice a week while TS-1 was given every day for two weeks. Hyperthermia was performed twice a week. No adverse effects from the adjuvant therapy were found. On a CT examination after the adjuvant therapy, the recurrent lesions were noticeably shrunken. The high pretreatment FDG uptakes for the recurrent lesions were reduced (Fig. 2).

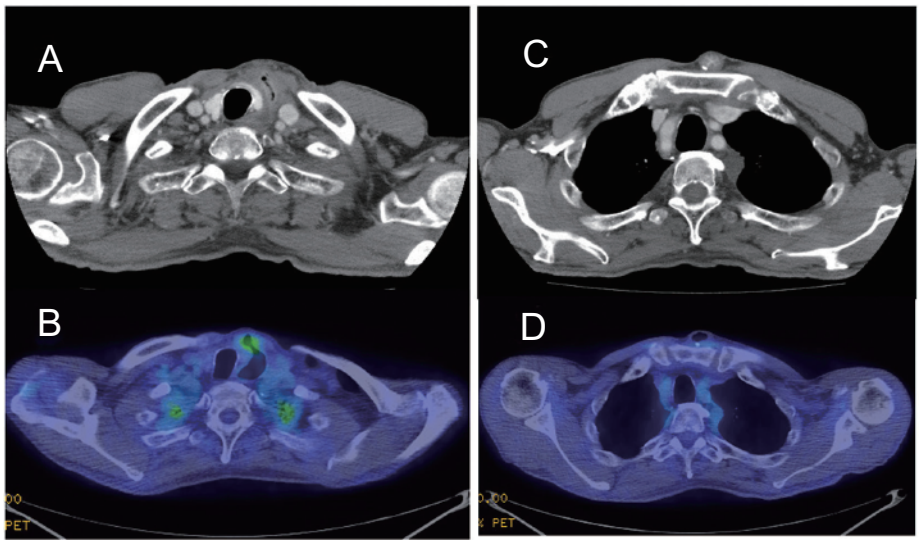

Fig. 2. CT and FDG-PET/CT image after chemoradiation with hyperthermia (May, 2007).
A, left subclavian mass markedly shrunken ; **B**, high FDG uptake in left subclavian mass was reduced ; **C**, upper mediastinal mass markedly shrunken ; **D**, high FDG uptake in upper mediastinal mass was reduced.

Hyperthermia was continued for relapse prevention once a week or once every three weeks after the series of treatments for recurrent lesions. The treatment schedule was influenced by the patient preference. Over four years 86 hyperthermia treatments were administered (Fig. 3). During this period no adverse effect associated with hyperthermia was found. On the latest CT examination, no recurrent lesions were found.

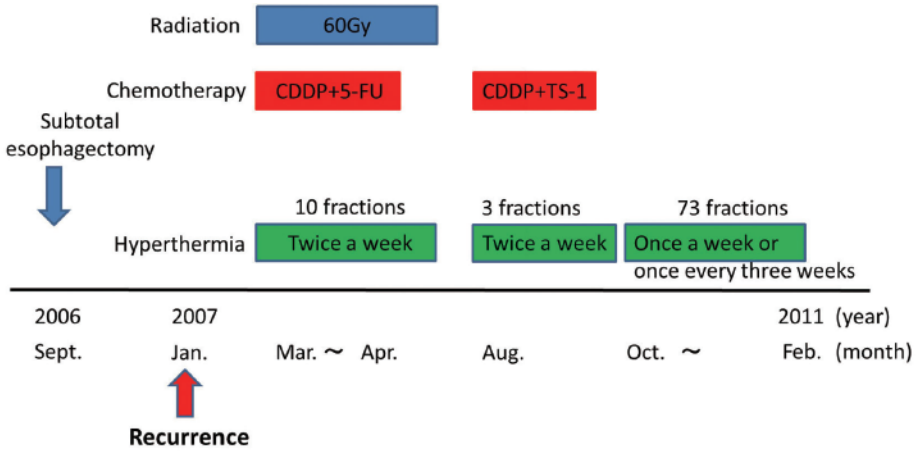

Fig. 3. Clinical course of the patient.

Discussion

Several authors have reported that a treatment combining hyperthermia and chemotherapy is useful[4–7]. Colombo reported long-term positive outcomes from a randomized controlled trial comparing thermochemotherapy with mitomycin-C alone for non-muscular invasive bladder cancer. The 10-year disease-free survival and bladder preservation rates for thermochemotherapy were higher than those for chemotherapy alone[8]. There have also been reports demonstrating the usefulness of intraperitoneal hyperthermic chemotherapy for peritoneal carcinomatosis. Scaringi suggested that intraperitoneal hyperthermic chemotherapy might be useful to improve the survival in selected patients with advanced gastric cancer when a complete cytoreduction can be achieved[4]. Verwaal also reported the usefulness of intraperitoneal hyperthermic chemotherapy for peritoneal carcinomatosis of colorectal cancer[5].

Reports on the additive effect of hyperthermia in combination with radiation have also been published. Franckena reported the usefulness of a combination treatment with radiation and hyperthermia for locoregionally advanced cervical cancer. In this result the local control and 12-year survival rates were better for radiation with hyperthermia than for radiation alone[9]. Jones reported that for local recurrence of breast cancer hyperthermia is considered to be useful as a radiation sensitizer[10]. Tilly reported that regional hyperthermia might increase the local effectiveness of radiotherapy based on an evaluation of 22 patients with locally advanced or recurrent prostate cancer who were treated by a standard irradiation regime in combination with regional hyperthermia[11].

Hyperthermia is frequently performed for recurrent tumors in combination with chemoradiation therapy. Previous reports have suggested the synergistic cytotoxicity-enhancing and radiosensitizing

effects of hyperthermia. Also, tumor blood flow and consequent tumor oxygenation are increased during hyperthermia[3,9,12,13]. The tumor response to irradiation and chemotherapy of well-oxygenated and vascularized tumors is in general superior to that of hypoxic tumors[2]. At our institution hyperthermia is performed to increase the therapeutic effects of chemotherapy or radiation therapy. In this case, initial treatment for recurrent lesions consisted of hyperthermia, chemotherapy and radiation therapy. This three-pronged approach resulted in a complete response in the long term. The synergistic cytotoxicity-enhancing and radiosensitizing effects of hyperthermia are likely to have been partly responsible for this treatment outcome.

The adverse effects of hyperthermia include skin burns, fat necrosis and so on. The toxicity associated with hyperthermia has been found to be acceptable and manageable[3,11]. Martine *et al*. compared radiation and hyperthermia with radiation alone for cervical cancer. They reported that hyperthermia did not significantly add to the radiation-induced toxicity compared with radiation alone[9]. Other authors also reported that hyperthermia was nontoxic and did not increase radiation-induced toxicity[3,11,14]. However, there has been no report on the safety of repeated treatments in the long term. In this report, a patient with recurrent esophageal cancer received hyperthermia many times over four years. During the treatment he showed no adverse effects associated with the hyperthermia. These results suggest that prolonged hyperthermia may be performed safely to suppress the growth of tumors.

Conclusion

We reported a case of recurrent esophageal cancer which achieved complete remission by chemoradiation, combined with hyperthermia over four years.

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