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Salvage Hyperthermo-chemotherapy for Local Recurrence of Cervical Esophageal Cancer after Definitive Chemoradiotherapy : A Case Report

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Abstract : Salvage treatment (treatment of recurrent or resistant tumors) is difficult in patients with either residual or recurrent cancer after definitive chemoradiotherapy for esophageal cancer. This report presents the first case of a patient, for whom hyperthermo-chemotherapy was markedly effective for recurrent cervical esophagus cancer after definitive chemoradiotherapy (CRT). The patient was a 66-year-old female, in whom an elevated cervical tumor was detected 10 years after an endoscopic mucosal resection for mid-thoracic esophageal cancer (cT1aN0M0 Stage I based on standards of the Japan Esophageal Society). The tumor was diagnosed to be a secondary primary squamous cell carcinoma of the cervical esophagus (cT2N1M0 Stage II). Definitive chemo-radiotherapy (a total 75.4 Gy of radiation plus docetaxel) resulted in a complete response. However, a local recurrence was recognized five months later. Although chemotherapy with nedaplatin and 5-FU was performed for 6 months, the recurrent tumor enlarged. Oral S-1 (100 mg/day) chemotherapy was administered on days 1-28 every 6 weeks. Concurrent with S-1, local hyperthermia delivered with a Thermotron RF-8 (50 minutes) was performed on days 1, 8, 15, and 22, every 6 weeks. After the first course of treatment, the tumor disappeared, and this treatment was repeated for 5 cycles on an outpatient basis without any critical side effects. The clinical course of this case suggests that hyperthermo-chemotherapy is a potent salvage treatment for either remnant or recurrent esophageal cancer disease after definitive CRT.

Key Words : cervical esophageal cancer, hyperthermia, chemotherapy, salvage treatment, S-1

Introduction

The prognosis for patients with esophageal cancer has gradually improved and in Japan, the 5-year survival rate is over 40% after an esophagectomy[1]. On the other hand, the resection rate for esophageal

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cancer is 70% according to the 2006 Annual Report by the Japanese Association for Thoracic Surgery[2], so 30% of these patients are candidates for non-surgical therapy. Recently, definitive CRT has been performed, not only for well advanced esophageal cancer[3], but also for resectable cancer[4], and fairly satisfactory results have been reported. However, long term toxic effects after definitive CRT, such as intractable pleural effusion and pericarditis, have also been reported[5].

Another problem with definitive CRT is how to treat either residual or recurrent lesions. Additional radiation is usually impossible since the previous radiation fields overlap at the residual or recurrent sites. A surgical resection defined as a salvage esophagectomy is one treatment strategy, however this is a high risk operation with high mortality and morbidity rates[6,7]. Moreover, in such patients, general conditions are often is too poor to permit the use of this approach for recurrent disease.

Hyperthermia is a treatment which can be directly cytotoxic to cancer cells. Furthermore, it enhances the effect of chemotherapeutic drugs such as platinum compounds and 5-FU through multiple mechanisms such as the acceleration of drug-induced apoptosis and the modification of reactive oxygen species generated by chemotherapy[8,9]. Therefore, endoluminal hyperthermia combined with either chemotherapy or CRT has been clinically adopted for the treatment of patients with esophageal cancer[10,11].

This report presents the case of a patient with recurrent cervical esophageal cancer after definitive CRT in whom salvage hyperthermo-chemotherapy was markedly effective.

Case report

A 66 year old Japanese female underwent an endoscopic mucosal resection for squamous cell carcinoma of the mid-thoracic esophagus (cT1aN0M0 Stage I based on standards of the Japan Esophageal Society[12], and cT1N0M0 Stage I based on the UICC-TMN classification[13]), and she received periodic endoscopic examinations, thereafter. Ten years later, an elevated tumor was detected in the cervical esophagus just distal to the esophageal oriphis. (Fig. 1*a* and *b*) and it was histologically diagnosed as a poorly differentiated squamous cell carcinoma (SCC). Computed tomography (CT) visualized swelling of the cervical paraesophageal node (Fig. 1*c*). Endoscopy suggested that the tumor had invaded the muscularis propria (cT2N1M0 Stage II based on the standards of the Japan Esophageal Society[12], and cT2N1M0 Stage IIB based on the UICC-TMN classification[13]). The patient elected to undergo definitive CRT to avoid the loss of vocal function associated with an operation requiring a laryngectomy and cervical esophagectomy. The definitive CRT consisted of a total dose of 75.4 Gy of radiation and a weekly drip infusion of docetaxel (10 mg/m^2, 6 times). External beam radiation was performed using 6 MV and 10 MV photons, and 41.4 Gy in 1.8 Gy daily fractions and was administered using a short T-shape field (two anterior-posterior opposed fields). In addition, 34 Gy in 2 Gy daily fractions of integrated booster radiation was delivered to the primary site (in two oblique fields to avoid the spinal cord). After these treatments, both esophagography and endoscopic examination revealed that the cervical tumor had completely disappeared (Fig. 2). Five months later, a follow-up endoscopic examination revealed a local recurrence (Fig. 2). The patient, therefore, was treated with chemotherapy with nedaplatin (80 mg/m^2) on day 1, and 5-FU (500 mg/body) on days 1-5, every 4 weeks. In spite of this systemic chemotherapy, the recurrent tumor continued to increase in size (Fig. 2).

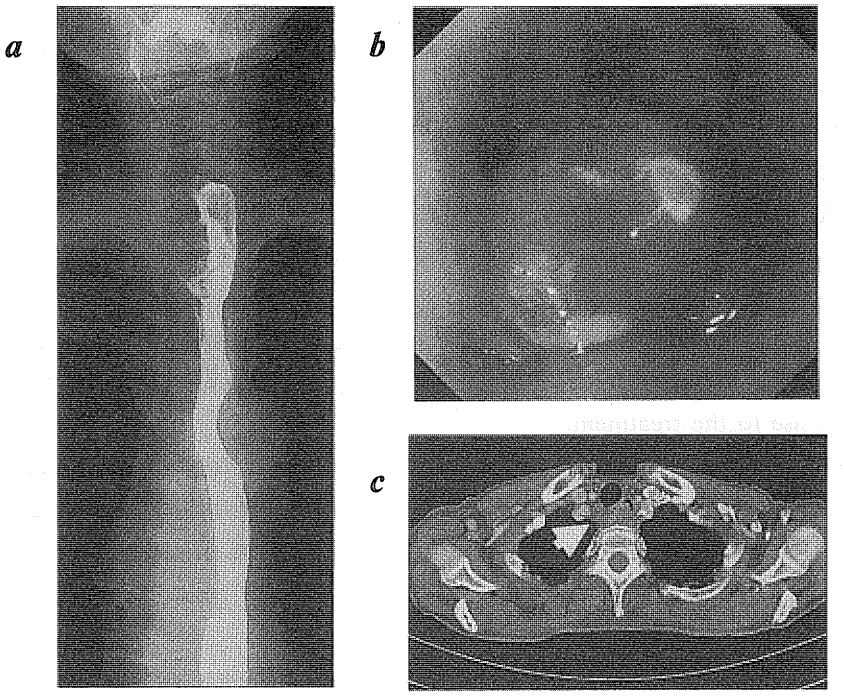

Fig. 1. Radiologic and endoscopic findings for the tumor at the initial diagnosis. Panel ***a***, Esophagography : A filling defect, measuring 30 mm in size on the upper esophagus is visualized. Panel ***b***, Endoscopy : An elevated tumor was found at the cervical esophagus just distal from the esophageal oriphis. Panel ***c***, Chest CT : Both the thickness of the cervical esophageal wall and swelling of cervical paraesophageal node are visualized.

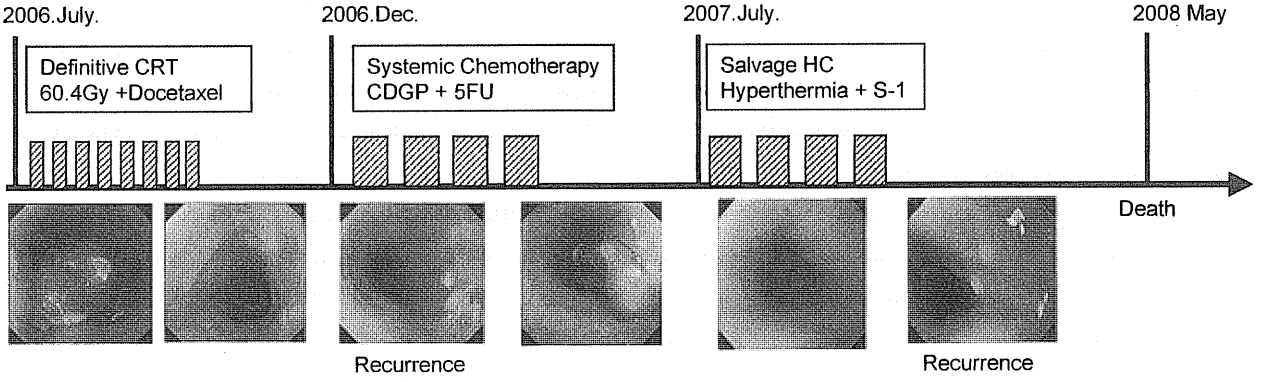

Fig. 2. The clinical course of endoscopic imaging of the cervical tumor. Just after definitive radiation combined with weekly docetaxel, the cervical tumor completely disappeared. At 5 months after definitive CRT, a local recurrence of type 0-IIa with a white moss appearance was found. Despite administering systemic chemotherapy with nedaplatin (CDGP) and 5-FU, the recurrent tumor continued to increase in size. After the first course of salvage hyperthermo-chemotherapy (Salvage HC), the recurrent tumor disappeared. However, the tumor recurred again, and the patient died 10 months after the beginning of salvage HC.

Hyperthermo-chemotherapy was indicated for this patient as a salvage treatment, *i.e.* a treatment used for a recurrent or non-responsive tumor. Hyperthermia was applied with a RF-capacitive heating apparatus (Thermotron RF8, Yamamoto Vinita Co, Ltd., Osaka. Japan) on days 1, 8, 15, and 22 every 6 weeks. This device uses 8 MHz radiofrequency electromagnetic waves as a source of heat. The heating time during hyperthermia therapy was 50 minutes, and 400 W was applied with a pair of electrodes 14 and 30 cm diameter in a supine position. For systemic chemotherapy, daily doses of 100 mg of S-1 was administered orally on days 1-28 every 6 weeks.

Just after the first course of hyperthermo-chemotherapy, an endoscopic examination revealed the disappearance of the recurrent tumor. The patient subsequently underwent four courses of treatment as an outpatient, and no definitive side effects with a magnitude greater than NCI-CTC grade III were observed in response to the treatment.

Subsequently, a follow-up endoscopic examination revealed a recurrence of the tumor. Although the patient eventually died 10 months after the initiation of the hyperthermo-chemotherapy, she was nevertheless able to lead an active daily life at home for 8 months during this period (Fig. 2).

Discussion

Definitive CRT for esophageal carcinoma is one treatment strategy used for squamous cell carcinoma of the esophagus. Since RTOG8501 studies revealed the superiority of definitive CRT in comparison to definitive radiotherapy alone[14], definitive CRT has been applied either to well advanced non-resectable esophageal cancer, or to the patients with a poor general condition. Since the 1990s, this therapy has been also been applied to resectable esophageal carcinomas. Hironaka et al. reported that the five year survival rates of T2 or T3 esophageal cancer patients treated with definitive CRT and with surgery were 46% and 51% respectively. The oral intake status of the definitive CRT group was better than the surgery group[4]. Although definitive CRT may offer a relatively good organ-preserving therapy, both residual disease and regrowth of the tumor frequently occur. A salvage esophagectomy could offer a chance for a cure in patients with a recurrent tumor, however, this operation is associated with a greater risk of prolonged mechanical ventilation, and an extended treatment time in the intensive care unit and hospital. Furthermore, in patients who have undergone a salvage esophagectomy after definitive chemoradiotherapy, critical postoperative complications, such as pneumonia and anastomotic leakage are more frequently observed than in patients treated with a conventional esophagectomy[6,7]. On the other hand, the late toxic effects of definitive CRT such as pleural effusion and pericarditis are critical : In such a situation, salvage surgery can not be performed and other treatment options should be selected.

Hyperthermia is utilized as a cancer treatment based on the principle that high temperatures can damage and kill cancer cells, usually with minimal injury to normal tissues[15]. Hyperthermia can also enhance the effects of certain anticancer drugs[8,9]. One of the mechanisms acting in combination therapy is an increase in DNA damage caused by an increase in drug uptake as a result of the disruption of membrane permeability from hyperthermia[8]. Reactive oxygen species (ROS) play an important role in cytotoxic activity[9]. The adverse effects of hyperthermia are nonfatal and consist of temporary effects such as burns, blisters, discomfort, or pain, and hyperthermia is applicable to patients with a low performance status[15,16]. Hyperthermo-chemo-radiotherapy has been found to be more effective than

CRT for patients with esophageal cancer and the efficacy of this therapy has been reported as a preoperative treatment, as well as a treatment for non-resectable carcinoma[11]. Furthermore, a randomized study which compared hyperthermia combined with chemotherapy (cisplatin plus bleomycin) to chemotherapy alone for esophageal cancer was conducted, and the findings showed that the assessed radiological improvements and histological effectiveness was better in the hyperthermo-chemotherapy group than in the chemotherapy alone group[10].

S-1 is a potent anti-cancer drug, based on the biochemical modulation of 5-FU and this drug can be administrated orally to outpatients. The response rate for gastric cancer is 53.6%[17], and clinical efficacy of S-1 combined with cisplatin is also reported for esophageal cancer[18]. In the current case, the salvage treatment with oral S-1 plus hyperthermia was effective for the recurrence of cervical esophageal cancer after definitive CRT. The treatment was performed as an outpatient treatment and was tolerated without any critical adverse effects. This treatment has never been previously reported, and this is therefore the first report of salvage hyperthermo-chemotherapy for a recurrent carcinoma after definitive CRT. The clinical course of this case suggests that hyperthermo-chemotherapy is a potent salvage treatment for either remnant or recurrent esophageal cancer after definitive CRT.

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Abstract in Japanese

サルベージ温熱化学療法が奏効した根治的化学放射線療法後再発食道癌の一例

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要　　旨：根治的放射線化学療法後に再発した食道癌に対して温熱化学療法が奏効した一例を報告する．頸部食道癌に対して根治的化学放射線療法によって腫瘍の完全消失後，5ヶ月で食道癌が再発した．化学療法 (5FU・ネダプラチン) を行ったが腫瘍はさらに増大した．その後，サルベージ (救済) 療法として温熱療法と S-1 による化学療法を行ったところ腫瘍の消失が得られ，4 クール，副作用なく外来にて治療を行った．根治的化学放射線療法後の食道癌再発に対する治療法の選択肢は限られていることから，サルベージ温熱化学療法は有効な治療法となりえる可能性が示唆された．