Current Treatment and Application of Hyperthermia for Squamous Cell Carcinoma of the Esophagus

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Abstract: Squamous cell carcinoma of the esophagus (ESCC) is a fairly aggressive disease with a poor prognosis. Surgical resection has been the gold standard of treatment for localized ESCC. However, this carcinoma is fairly sensitive to radiation, as well as chemotherapeutic agents such as cisplatin and 5-fluorouracil. Based on clinical trials conducted mainly by the Japan Clinical Oncology Group (JCOG), preoperative chemotherapy is regarded as the standard treatment for resectable ESCC in Japan. We have applied hyperthermia to ESCC mainly as a preoperative treatment associated with chemoradiotherapy since it has been experimentally proven to enhance the anti-tumor effects of chemotherapeutic agents and irradiation. The long-term survival as well as histological effectiveness was reported to be better in patients who received preoperative hyperthermochemoradiotherapy (HCR) than in those who received preoperative chemoradiotherapy (CRT). Definitive CRT is frequently performed even for resectable ESCC, and salvage treatment for either remnant or recurrent diseases remains an important clinical problem. We have applied hyperthermia simultaneously with chemotherapy as a salvage treatment for such patients, and complete response as well as stable disease was achieved in several patients. Hyperthermia is a promising modality as a salvage treatment and has recently been incorporated into regimens including taxanes. Potential enhancement of hyperthermia with certain drugs should be experimentally evaluated, and the clinical application of

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hyperthermia may be warranted with other newly-developed regimens.

**Key Words:** Esophageal cancer, hyperthermia, chemoradiotherapy, salvage therapy

**Current treatment strategies for resectable esophageal cancer**

Surgical resection has been the gold standard of treatment for localized esophageal cancer; however, this surgery is extremely invasive and is also associated with high rates of mortality and morbidity. The prognosis of patients with this cancer was extremely miserable and the 5-year survival was 10%-20% before 1990. Recently, the survival rate after esophagectomy has markedly improved due to multiple factors, such as an increase in the incidence of early-stage cancer, more accurate preoperative staging and improvements in surgical techniques as well as peri-operative management. The Comprehensive Registry of Esophageal Cancer in Japan 2009 revealed the 5-year overall survival rate to be 55.9%.

However, this carcinoma is fairly sensitive to radiation as well as chemotherapeutic agents such as cisplatin and 5-fluorouracil (5-FU) and multimodal therapy, including surgery, chemotherapy and radiotherapy, alone or in combination. To improve the prognosis, chemotherapy and/or radiotherapy have been applied preoperatively (as neo-adjuvant therapy) and postoperatively (as adjuvant therapy). In Western countries, the advantages of preoperative chemoradiotherapy (CRT) have been reported, and it is regarded as the standard treatment for resectable esophageal cancer. The superiority of preoperative CRT using carboplatin plus paclitaxel with 41.4 Gy of radiation over surgery alone was reported in a randomized controlled study ("CROSS" trial) for esophageal or junctional cancer. In addition, a meta-analysis including only randomized studies provided strong evidence for a survival benefit of neoadjuvant chemoradiotherapy over surgery with a hazard ratio for all-cause mortality of 0.78, and the survival benefit was similar to that with squamous cell carcinoma and adenocarcinoma.

Most esophageal cancer is histologically squamous cell carcinoma in Japan, and the standard treatment for resectable squamous cell carcinoma of the esophagus (ESCC) has been established based on clinical trials conducted mainly by the Japan Clinical Oncology Group (JCOG). The advantages of postoperative adjuvant chemotherapy for localized ESCC were examined in a multicenter randomized study (JACOG9204). In this study, the prognosis after esophagectomy was compared between patients who received surgery alone and those who received surgery and postoperative chemotherapy with cisplatin plus fluorouracil (CF regimen). The 5-year disease-free survival rates were 45% and 52%, respectively, and the reduction in the risk of recurrence was remarkable in the subgroup with node metastasis. These findings suggested that postoperative adjuvant chemotherapy might be able to prevent recurrence in patients with ESCC more effectively than surgery alone, especially in patients with positive node metastasis.

The JCOG9204 trial was then conducted in order to determine the perioperative timing (i.e. before or after surgery) for providing chemotherapy to patients with localized ESCC. The 5-year overall survival was 55% in the preoperative chemotherapy group, which was significantly better than that in the postoperative chemotherapy group (43%, $P=0.04$). Based on the results of this trial, chemotherapy with a CF regimen followed by surgery is currently considered the standard treatment in Japan. However, preoperative chemotherapy was not very effective in clinical stage III patients, although it was effective in stage II patients according to a subgroup analysis of the JCOG9204 trial. In addition, clinical experience requires more
intensive setting of preoperative therapy would be needed.

Docetaxel is a particularly promising drug, and recently, preoperative chemotherapy with docetaxel plus CF (DCF) has received focus, showing fairly good results. A three-arm phase III randomized trial, in which clinical results are compared between a preoperative CF regimen, DCF regimen, and CF plus radiation regimen, is being conducted as the JCOG1109 trial (NExT Study) in order to confirm the most effective preoperative therapy for localized ESCC.

Definitive chemoradiotherapy and salvage surgery for either remnant or recurrent disease

Since the results of the Radiation Therapy Oncology Group trial (RTOG85-01) were reported, definitive chemoradiotherapy regimens including radiotherapy using a total of ≥ 50 Gy plus cisplatin and 5-FU have been established as treatment strategies for advanced esophageal cancer. Definitive chemoradiotherapy is generally applied for far-advanced esophageal cancer and is the most effective treatment, especially for locally far-advanced (such as T4 or M1 lymph) esophageal cancer. Furthermore, definitive chemoradiotherapy is also applied for resectable ESCC, and satisfactory results regarding patients’ prognoses as well as the local control rate have been reported. For clinical stage I ESCC in particular, a phase II trial of definitive chemoradiotherapy was conducted as the JCOG9708 trial. In this trial, definitive radiotherapy of total 60 Gy plus a CF regimen was performed for 72 patients. Complete response was recognized in 63 patients (87.5%), and the 4-year relapse-free survival rate was 68%. Definitive chemoradiotherapy is considered a treatment option or stage I ESCC.

However, these increased opportunities for definitive CRT have resulted in several problems. One problem is long-term toxicities, such as radiation pneumonitis, pleuritis and pericarditis. Another problem is the need for treatment of residual lesions or recurrent tumors after definitive CRT. Although the complete response rates are high and the short-term survival is favorable after definitive CRT, locoregional disease persists or recurs in 40%-60% of patients. Salvage esophagectomy has been indicated for such lesions. The fairly good clinical results with definitive CRT for stage I ESCC, as shown in the JCOG9708 trial, were achieved under the hypothesis that salvage surgery was recommended for residual tumor or local recurrence. The long-term results of salvage surgery are acceptable when R0 resection can be achieved. However, the surgical risk is still considered to be extremely high, with high mortality and morbidity rate. To improve the clinical results of salvage esophagectomy, risk-reducing approaches appropriate for each case, such as two-stage operation, microvascular anastomosis for reconstructed conduit and musculocutaneous flap, should be applied in specialized high-volume centers.

Basic experiments regarding hyperthermia

The antitumor effect of hyperthermia has been studied in laboratory settings. We previously reported that hyperthermia in animal models enhances the effect of anti-tumor agents and radiation. We paid particular attention to the microcirculatory factors after hyperthermia. Matsuda et al. measured the regional blood flow of transplanted tumors in rabbit liver and reported a transitional decrease in the blood flow in the tumor. This decrease in the blood flow results in increased thermosensitivity, which may suppress...
thermo-tolerance induced by intermittent hyperthermia. In another experiment, an increased hyperthermic response was recognized on administration of the vasoactive agent prostaglandin E1\(^29\).

We established a cell line (KSE-1) of human ESCC and examined the basic evidence regarding the effects of hyperthermia itself and its synergistic effects on chemotherapy and radiotherapy\(^30\). We also performed \textit{in vitro} examinations to evaluate the efficacy of hyperthermia regarding the timing of anticancer drug administration\(^31\) and application of new sensitizers\(^32-34\). In addition, we recently examined the mechanism underlying the DNA damage mediated by the ATR-Chk1 and ATM-Chk2 pathways \textit{via} a biomolecular approach\(^35\).

Clinical application of hyperthermia for esophageal cancer and clinical investigations

Since we initially reported the clinical effects of hyperthermia combined with CRT (HCR) in 1983\(^36\), we have clinically applied hyperthermia to numerous patients with ESCC using a radiofrequency system with an endotract electrode (Endoradiotherm200A; Olympus, Tokyo Japan)\(^37,38\). HCR is mainly applied as a preoperative treatment, and the long-term prognosis as well as histological effectiveness was found to be better than after CRT alone\(^38-42\). Furthermore, a prospective randomized trial comparing the clinical results between patients who received preoperative HCR versus CRT revealed that the subjective symptoms were more frequently improved and both the clinical and histological effects were better in the HCR group than in the CRT group. HCR has also been applied as either definitive or palliative therapy for non-resectable ESCC due to far-advanced tumors and patients’ poor physical condition\(^43,44\).

We retrospectively examined the clinical results of preoperative CRT with or without hyperthermia, paying special attention to factors associated with the clinical response\(^5\). The survival of the patients who received preoperative CRT depended on the histological effectiveness, and the prognosis was favorable in patients who showed complete response (markedly effective based on the classification of the Japan Esophageal Society\(^45\), Fig.1). A multivariate analysis revealed that histological complete response was an independent prognostic

![Fig. 1. The overall survival after esophagectomy according to the histological effectiveness of preoperative chemoradiotherapy. The histological effectiveness is based on the classification of the Japan Esophageal Society: Grade 0-1, not effective; Grade 2, moderately effective; and Grade 3, markedly effective. The survival of patients in whom preoperative CRT was markedly effective (grade 3) was significantly better than in patients whose histological effect was moderately effective (grade 2) or not effective (grade 0 or 1, \(p<0.01\)).]
factor (Fig. 2). Furthermore, additional preoperative hyperthermia as well as the use of cisplatin was found to be an independent factor associated with complete response to preoperative CRT (Fig. 3). The 5-year

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Fig. 2. Independent factors associated with cancer recurrence, including the histological effectiveness of preoperative chemoradiotherapy (CRT), according to a multivariate analysis with a Cox proportional hazard model. The "95% C.I." indicates 95% confidential interval.

Fig. 3. Independent factors associated with a markedly effective histological response to preoperative chemoradiotherapy (CRT) according to a logistic regression analysis. The "95% C.I." indicates 95% confidential interval.

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overall survival was 36.4% and 29.0% in the preoperative HCR and CRT alone groups, respectively (Fig. 4).

Being able to predict the clinical effects of HCR is clinically important. We reported that patients with ESCC with a high DNA ploidy pattern tended to show positive effects for preoperative HCR therapy and that their prognosis was also significantly better than that of patients who received CRT alone\(^{40}\). We also reported that a succinate dehydrogenase inhibition test using a biopsy specimen before HCR correlated well with the effectiveness of HCR\(^{47}\). Furthermore, we immunohistochemically examined the expression of p53 and p21 in the biopsy specimens and compared the clinical effects of HCR for ESCC. The results showed that the combination of positive p53 and negative p21 expressions was an unfavorable marker of histological effectiveness of HCR. A multivariate analysis revealed the p21 expression to be an independent factor associated with the histological effectiveness\(^{48}\).

The immune response to CRT and hyperthermia was histologically evaluated by examining the lymphocyte infiltration in resected specimens of ESCC. This study suggested that the presence of lymphocyte infiltration might result in a favorable prognosis after CRT and that simultaneous hyperthermia may be able to stimulate lymphocyte infiltration\(^{42}\).

Current role and future perspective of hyperthermia for ESCC

Taxanes (docetaxel and paclitaxel) have recently been used as promising chemotherapeutic agents for ESCC. Nakajima et al.\(^{49}\) reported clinical results of preoperative HCR for ESCC. In this series, external hyperthermia using Thermotron RF-8 (Yamamoto Vinita, Osaka, Japan) was performed simultaneously with CRT including low-dose docetaxel. They reported the response rate to be 41.7% and pathological complete response rate to be 17.6%. The 5-year survival rate was reported to be 50%. For patients who showed pathological complete response, the 5-year survival rate was 66.7%.

Definitive CRT for ESCC is frequently performed; however, salvage treatment for either remnant or recurrent tumor after this treatment is usually difficult. In some cases, salvage surgery cannot be applied due to a high-risk operation, while additional irradiation cannot be performed because of previous definitive radiation. Thus far, systemic chemotherapy has been the only treatment for such patients. Hyperthermia increases the efficacy of chemotherapy. We have clinically applied hyperthermia simultaneously with salvage chemotherapy after definitive CRT. We reported the clinical results of 11 patients with ESCC who underwent "salvage hyperthermochemotherapy"\(^{50}\). Complete response was achieved in three patients\(^{51,52}\), while the
lesions were controlled as stable disease in five patients (Fig. 5). This treatment is usually performed for outpatients without severe adverse events and may be a potent treatment for salvage therapy after definitive CRT.

![Image](image_url)

**Fig. 5.** Neck and chest computed tomography findings of a patient who received salvage hyperthermochemotherapy for remnant lesions following definitive chemoradiotherapy for recurrent lymph nodes after esophagectomy. Neck and mediastinal node recurrence developed seven months after complete resection for clinical stage III squamous cell carcinoma of the lower esophagus. Both the neck and mediastinal nodes were enlarged even after definitive chemoradiotherapy using docetaxel. Hyperthermia combined with chemotherapy using S-1 was effective for these nodes, and the disease remains well-controlled.

Recently, the opportunity applying hyperthermia for esophageal cancer seems to decrease. The main reason may be that it takes much time and labor. Improvement of medical insurance supporting this treatment is essential to increase the opportunity for clinical application. Another reason is that esophageal cancer is fairly aggressive and that hyperthermia is considered to be no longer effective for such systemic disease. However, hyperthermia enhances the efficacy of chemotherapeutic agents and radiation without severe adverse effect, while it has been proved to be effective treatment for esophageal cancer. Hyperthermia should be, therefore, more aggressively indicated as a modality that enhances definitive CRT and salvage chemotherapy. On the other hand, potent chemotherapeutic regimens, such as chemotherapy with docetaxel plus CF, have recently applied, and immune therapies using immune check-point inhibitors are currently being explored as promising treatments for esophageal cancer (3). The potential enhancing effects of hyperthermia with respective drugs should be experimentally evaluated, as the clinical use of hyperthermia may be warranted with such newly-developed regimens.

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