Hyperthermia Combined with Chemotherapy for Patients with Residual or Recurrent Oesophageal Cancer After Definitive Chemoradiotherapy

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Abstract. *Background/Aim: Definitive chemoradiotherapy (dCRT) is frequently administered in oesophageal cancer. We carried out hyperthermochemotherapy (HCT) for residual or recurrent cases after dCRT for oesophageal cancer. The aim of this study was to elucidate the usefulness of salvage HCT for these patients. Patients and Methods: Salvage HCT after dCRT was performed in 11 patients with residual or recurrent oesophageal cancer. We used an 8-MHz radiofrequency capacitive heating system for hyperthermia. The combined chemotherapy comprised of cisplatin/5-fluorouracil, an oral fluoropyrimidine and irinotecan. Results: There were no severe adverse events caused by hyperthermia. Complete response and stable disease was achieved in three and five patients, respectively; symptoms were improved in the remaining three patients. The median survival time after HCT was 12 (range=3-88) months. Conclusion: HCT is a feasible and potent salvage therapy for patients with residual or recurrent oesophageal cancer after dCRT, unless salvage surgery is indicated.*

Oesophageal cancer is highly aggressive and is usually associated with a dismal prognosis (1). Oesophageal resection is one curative treatment strategy (2) and remains a candidate treatment strategy in advanced oesophageal cancer (3). However, definitive chemoradiotherapy (dCRT) was shown to contribute to higher survival rates and milder toxicity compared to surgery in patients with stage I oesophageal cancer enrolled in the JCOG9708 trial (4). dCRT is considered as a curative treatment strategy for locally advanced oesophageal cancer (5, 6). However, there are no established strategies for the treatment of residual or recurrent oesophageal cancer after dCRT.

We reported the usefulness of hyperthermochemoradiotherapy (HCRT) as a preoperative therapy for oesophageal cancer (7-9). Some researchers have found that hyperthermic temperatures between 42.5˚C and 44.0˚C induced necrosis and apoptosis of cells (10, 11), de-stabilized cell membrane integrity, induced protein denaturation, and inactivated the DNA repair system (12). There exist certain studies that reported a synergistic effect between hyperthermia and chemoradiotherapy (CRT) (9). CRT is generally affected by tumor blood flow and oxygenation (13). Low blood flow and hypoxia reduce both the cytotoxic effect of chemotherapy and tumor sensitivity to radiotherapy (14). Hyperthermia can increase tumor blood flow and improve tumor oxygenation (13). Therefore, it is hoped that the combination of hyperthermia and chemotherapy will be effective for local disease.

We performed HCT for residual or recurrent oesophageal cancer after dCRT. To the best of our knowledge, this is the first report to demonstrate the long-term outcomes of HCT as a salvage treatment.

Patients and Methods

Salvage HCT after dCRT was performed for 11 patients with oesophageal squamous cell carcinoma between 2005 and 2009 at the Departments of Surgery and Science and Clinical Radiology, Kyushu University Hospital. Patient characteristics are summarized in Table I. Six patients were inoperable cases, and the other five patients were postoperative recurrent cases. The median patient age was 62 (range=53-72) years. Cases were inoperable for the following

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Table I. *Patients' characteristics*.

Case	Sex	Stage definitive CRT	Reasons for undergoing
Inoperable cases			
1. 68	M	cStage I	Post partial gastrectomy, thoracotomy
2. 66	F	cStage II	Declined laryngectomy
3. 53	M	cStage IV	Thoracic invasion, pleural dissemination
4. 54	M	cStage IV	Thoracic invasion, multiple LN metastasis
5. 72	M	cStage IV	Emphysema, thoracic invasion, LN metastasis
6. 61	M	cStage IV	Aortic Invasion
Residual or recurrent cases after oesophagectomy			
7. 57	M	fStage IIIB	Postoperative recurrence
8. 56	M	fStage IIIC	Postoperative recurrence
9. 70	M	fStage IIIA	Postoperative recurrence
10.62	F	fStage IIIC	Postoperative recurrence
11.66	M	fStage IIIA	Postoperative recurrence

There were six inoperable cases and five recurrent cases. CRT: chemoradiotherapy; F: female; M: male; cStage: clinical Stage; fStage: final Stage .*The numbers in the first column are case number common in all tables.

reasons: the occurrence of cStage IV disease in four patients; difficulty in performing oesophagectomy because of a past history of thoracotomy as a result of surgical treatment for pulmonary tuberculosis and gastrectomy for gastric cancer (cStage IA) in one patient; and refusal of oesophagolaryngectomy in one patient (cStage IIB). The other five patients were cases of recurrence after oesophagectomy; their pathological stage was IIIA-IIIC.

Extracorporeal hyperthermia was clinically applied using a 8-MHz radiofrequency, capacitive heating system (Thermotron RF-8; Yamamoto Vinita Co., Ltd, Osaka, Japan) (15). HCT regimens in each period are summarized in Figure 1. HCT was delivered at temperatures ranging from 42.5˚C to 44.0˚C at 400-1400 W (median 1200 W) for 50 min once or twice per week. Patients received combined chemotherapy using cisplatin/5-fluorouracil (5-FU) (cases 3, 4, and 6), irinotecan (case 5) or oral fluoropyrimidine (S-1) (the remaining cases). Three patients who underwent hyperthermia with dCRT were excluded from our study. The clinical and pathological TNM system stage was defined according to the Union for International Cancer Control (UICC) version 7.0 (16). Endpoint is overall survival.

Results

dCRT was performed in patients as a first-line treatment; it involved radiotherapy at a total dose of >60 Gy and chemotherapy consisting of 5-FU and cisplatin or docetaxel (Table II). Seven patients had recurrent disease, while the remaining four patients had residual tumour after dCRT. Hyperthermia was performed as the second- and the third-line treatment in these patients. S-1 was administered to eight patients as combined chemotherapy. HCT was administered to eight patients in an outpatient setting, maintaining their quality of life.

The long-term outcomes after HCT are summarized in Table III. The best responses to HCT were as follows: a complete response (CR) was achieved in three patients and stable disease (SD) was noted in five patients. The median time of SD was 8 (range=8-16) months in these five patients. We evaluated the patients using computed tomography and endoscopy. Symptoms, such as dysphasia, were improved in the other three patients. Dietary intake had increased and their quality of life had improved.

The treatment was conducted for 2-26 cycles. We continued treatment for as long as possible. The median survival time after dCRT/HCT was 20/12 (range=6-93/3-88) months. One patient, who achieved a CR, is still alive with no recurrence

Table II. *Details of the therapeutic protocol used for each patient after definitive chemoradiotherapy (CRT)*.

Case	First-line therapy	Residual disease/recurrence	Second-line therapy	Best effect
1	CRT(61.2 Gy,CDGP/5-FU)	Recurrence	Docetaxel→hyperthermia+S-1	Improvement of symptoms
2	CRT (61.2 Gy, Docetaxel)	Recurrence	CDGP/5-FU→hyperthermia+S-1	CR
3	CRT (61.6 Gy,CDGP/5-FU)	Residual	Hyperthermia+CDDP/5-FU	Improvement of symptoms
4	HCRT (61.2 Gy, CDDP/5-FU)	Residual	Hyperthermia+CDDP/5-FU→hyperthermia+S-1	SD
5	CRT (61.4 Gy, CDGP/5-FU)	Residual	Hyperthermia+CPT-11	SD
6	CRT (60 Gy, unknown)	Residual	Hyperthermia+CDDP/5-FU	SD
7	CRT (60 Gy, Docetaxel)	Recurrence	Hyperthermia+S-1	SD
8	HCRT (60 Gy, CDDP/5-FU)	Recurrence	Hyperthermia+S-1	CR
9	CRT (66 Gy, CDDP/5-FU)	Recurrence	Hyperthermia+S-1	Improvement of symptoms
10	CRT (66 Gy, CDDP/5-FU)	Recurrence	Hyperthermia+S-1	SD
11	HCRT (60 Gy, CDDP/5-FU)	Recurrence	Hyperthermia+S-1	CR

HCRT: Hyperthermochemoradiotherapy, CR: complete response, SD: stable disease, S-1: oral fluoropyrimidine, CDGP: nedaplatin, CDDP: cisplatin, 5-FU: 5-fluorouracil, CPT-11: irinotecan.

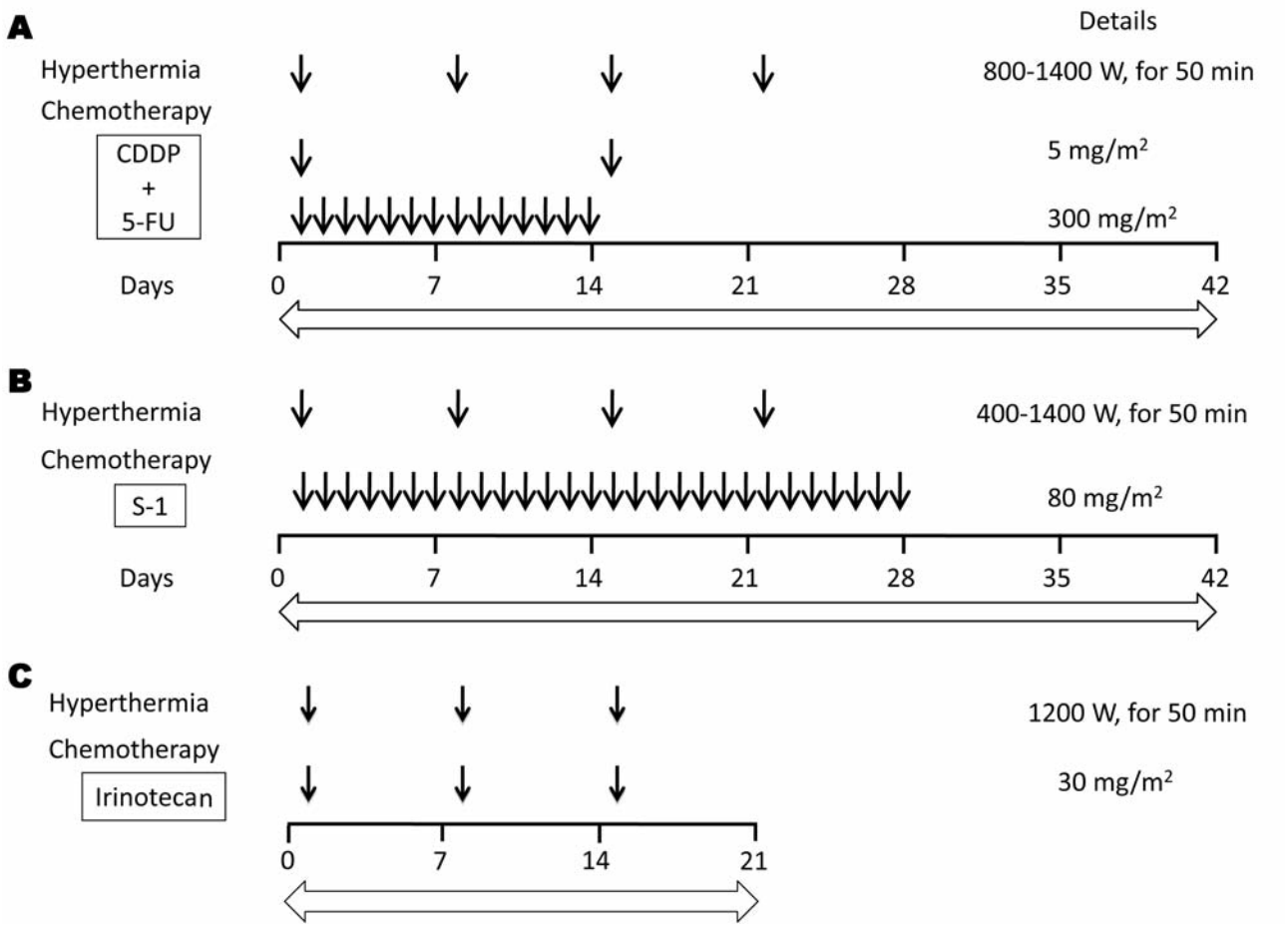

Figure 1. *Hyperthermochemotherapy protocol. The three patterns of treatment using the hyperthermochemotherapy regimens are shown. a: Hyperthermia with cisplatin and 5-fluorouracil, b: hyperthermia with oral fluoropyrimidine, and c: hyperthermia with irinotecan. Hyperthermia was administered once a week (black arrows).*

at 88 months after hyperthermia and is being followed-up as an outpatient. No patient was withdrawn from HCT because of adverse events. The overall survival rates at 1, 2, and 5 years after dCRT were 72.7%, 54.5%, and 9.1%, respectively.

Discussion

dCRT is an initial treatment for inoperable oesophageal cancer (17, 18). Recently, dCRT has been administered not only for non-resectable oesophageal cancer, but also for resectable oesophageal cancer; this has increased the opportunities to treat residual or recurrent tumour after initial dCRT. Although a useful treatment strategy is required for patients who have residual or recurrent oesophageal cancer after initial dCRT, there is still no established therapy. Chemotherapy-alone sometimes fails as a treatment, especially for local disease (19).

It is often difficult to determine the most appropriate treatment after failure of dCRT. When there exist recurrences in remote organs, the general approach is to perform systemic chemotherapy, palliative radiotherapy, or best supportive care. In cases without distant metastasis, such as local recurrence or localized lymph-node metastasis, it is important to determine whether or not the recurrent/remnant disease is located outside or inside the radiation field used for dCRT. In cases without metastasis, resection or CRT should be considered as a local treatment. In cases with recurrences in remote organs, salvage endoscopic resection or salvage oesophagectomy is the only potentially curative treatment strategy (10, 20, 21). However, salvage oesophagectomy is not yet an established therapy because dCRT increases the surgical risk (22). When both salvage endoscopic resection and oesophagectomy are contraindicated, systemic chemotherapy is often chosen. However, chemotherapy-alone is usually ineffective regarding local disease control (23). We expect that hyperthermia could enhance the local control effect achievable using chemotherapy.

Table III. *Outcomes of treatment of hyperthermochemotherapy.*

Case	Best effects 1st-line Tx/hyperthermia Tx	Survival from of HCT	Outcome
1	Improvement in swallowing (Outpatient)	10 months/ 3 months	Cancer death
2	CR (Outpatient)	20 months/ 9 months	Cancer death
3	Improvement in swallowing	6 months/ 3 months	Cancer death
4	SD for 8 months (Outpatient)	9 months/ 9 months	Cancer death
5	SD for 16 months (Outpatient)	26 months/ 20 months	Cancer death
6	SD for 8 months	20 months/ 8 months	Cancer death
7	SD for 12 months (Outpatient)	20 months/ 14 months	Cancer death
8	CR (Outpatient)	26 months/ 21 months	Cancer death
9	Increased food intake	24 months/ 5 months	Cancer death
10	SD for 8 months (Outpatient)	27 months/ 12 months	Cancer death
11	CR (Outpatient)	93 months/ 88 months	Alive
Overall	CR: 3	Median 20 months/ 12 months	Cancer death: 10
SD: 5 Improvement of symptoms: 3			Alive: 1

Eight patients were treated as outpatients; one is still alive but the others have died. The median survival time after hyperthermia treatment was 12 months. CR: Complete response, SD: stable disease; TX: therapy.

Second- or later-line chemotherapy should have lower toxicity because the general status of the patients is often poor. The Thermotron RF-8 can be used for the treatment of superficial and deep seated tumours (24). Patients treated with hyperthermia can develop chemosensitivity as a result of increased tumor blood flow and improved tumor oxygenation, which can increase the drug dose to the tumor (25). As a result, toxic side-effects of drugs in patients can be reduced and their quality of life preserved. In the present study, maintenance of a good quality of life in the patients might have contributed to their tolerance of long-term treatment and their favourable prognosis.

In our study, we demonstrated the advantages of external hyperthermia combined with chemotherapy for inoperable localized lesions. The median survival time after second-line therapy was 12 months; it was reported that the median survival time after relapse following dCRT for advanced oesophageal cancer was 4.0 months (26). Taking into consideration that our data included metastatic cases, treatment outcomes were considered to be sufficient. In addition, five patients achieved an improvement in their symptoms, suggesting that HCT is effective as a palliative treatment. HCT can be performed in an outpatient setting using an oral fluoropyrimidine drug and the toxicity of hyperthermia is generally mild (*e.g.* thermal blistering and thermal pain) (27). No significant adverse event (NCI-CTC grade 3 or 4) occurred in the current study. To our knowledge, this is the first report showing the usefulness of HCT as a second- or later-line treatment after failure of dCRT.

However, hyperthermia treatment has some limitations. Firstly, a special device and well-trained hyperthermia oncologists are required for treatment. In fact, very few institutes possess the required hyperthermic device and consequently many patients never have the opportunity to receive hyperthermic treatment. In addition, the effects of hyperthermia are influenced by patient body-size parameters, and it is difficult to measure the temperature at the tumour location (28). An inevitable technical problem associated with the use of hyperthermia is the difficulty in heating only the local tumor region to the intended temperature without damaging the surrounding healthy tissue (29). There is also no clinical evidence for the best combined chemotherapy for use with hyperthermia. It is considered that HCT will require further development if these problems are to be overcome.

We demonstrated that hyperthermic therapy for patients with residual or recurrent oesophageal cancer after dCRT can be safely performed. Hyperthermia achieved sufficient local treatment efficacy in combination with chemotherapy; it contributed to local disease control after dCRT for oesophageal cancer and improved the symptoms while maintaining quality of life. To our knowledge, this is the first report regarding the long-term outcome of salvage HCT. Our results highlight the possibility that hyperthermia therapy might be a useful modality for use as a salvage therapy for residual or recurrent oesophageal cancer after dCRT.

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