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Clinical experiences in the thermoradiotherapy for advanced gastric cancer

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Recurrent and/or inoperable gastric cancer has been treated by thermoradiotherapy at Kyoto University Hospital since 1983. In the present study, the efficacy of hyperthermia (using radiofrequency capacitive heating) plus radiotherapy for gastric cancer was evaluated in 21 patients with local recurrence, abdominal wall metastases, peritonitis carcinomatosis or paraaortic node metastases. The intratumour temperature was measured using a microthermocouple thermometer. The means of the maximum, average, and minimum intratumour temperature were 43·5, 42·1, and 41·1°C respectively. The local tumour response was evaluated using computed tomography (CT). The local response rate (complete regression plus partial regression/all tumours) was 88·9%, which seemed to be higher than that of other reports using thermochemotherapy or radiotherapy alone. The one-year cumulative survival rate was 39·1%.

Keywords: Radiotherapy, hyperthermia, gastric cancer, thermometry, thermoradiotherapy

1. Introduction

Gastric cancer is a leading cause of cancer-related death in Japan. The first choice for treatment is surgery, but some patients are found to be inoperable due to the advanced stage of the disease. In addition, some patients develop tumour recurrence after surgery. For such patients, multi-drug chemotherapy and conventional radiotherapy have been occasionally indicated. However, their results have not been satisfactory (Gastrointestinal Tumor Study Group 1982, Gunderson *et al.* 1986, Tsukiyama *et al.* 1988).

At Kyoto University Hospital, radiofrequency (RF) capacitive heating equipment has been used since 1979 for the treatment of deep-seated tumours. We have applied it to the patients with inoperable advanced gastric cancer to enhance local tumour response with radiation since 1983. Our studies have demonstrated that our system could be applied to deep-seated tumours (Abe *et al.* 1986). Our clinical experience with RF hyperthermia in combination with radiotherapy in patients with advanced or recurrent gastric cancer was evaluated in this study and compared to previous reports.

2. Materials and Methods

2.1. *Subjects*

Since 1983, 21 patients with advanced or recurrent gastric cancer have been enrolled in this study. The ages ranged between 35 and 83 years (average: 54·7 years); there were 17 males and four females. Primary inoperable cancer was present in four patients, local recurrence in six, abdominal wall metastases in four, peritonitis carcinomatosis in four and paraaortic lymph nodal metastases in four, for a total of 22 different lesions because one patient had both paraaortic metastases and peritonitis carcinomatosis. We have evaluated

the local therapeutic effect in 18 lesions except peritonitis carcinomatosis, and survival in all 21 patients in this study.

2.2 *Hyperthermia*

An 8 MHz RF capacitive heating system (Thermotron RF-8, Yamamoto Vinitar Co. Ltd., Osaka, Japan) was used for hyperthermia treatment. In general, two opposing 25-cm diameter electrodes were selected for heating the gastric tumours. To prevent surface burning, a cooling pad was used during hyperthermia through which 0·9% saline cooled to 5°C was circulated. Pretreatment cooling was used 5–10 min before each treatment. The power level which could be tolerated by the patients was generally between 800 and 1300 W. Patients were treated with hyperthermia for 40–50 min once a week immediately after radiotherapy, and received 4–11 treatments (mean 5·3). During hyperthermia, the blood pressure, pulse rate and body temperature were monitored at 5 min intervals.

2.3 *Tumour temperature measurement*

The tumour temperature was measured using thin Teflon-coated copper-constantan microthermocouple probes (Physitemp, Clifton, NJ, USA). With the use of ultrasonography, the microthermocouple was inserted into the tumour percutaneously through a 15 cm long 21-gauge angiocatheter. Catheters were inserted into the peritoneal cavity in patients with peritonitis carcinomatosis. During and immediately after hyperthermia, the probe was withdrawn in 1 cm increments, and the temperature at each point was measured through the catheter. When the RF device interfered with the temperature measurement, it was temporarily switched off to allow data to be obtained during treatment.

T_{max}, T_{min}, and T_{mean} are the maximum, minimum, and average temperatures of all recorded intratumour temperatures during a steady state and at the end of treatment. A steady state was defined 20 min after the start of hyperthermia even if the temperatures showed slight, gradual increase in some tumours. T_{mean} was both spatial and temporal averages in hyperthermia sessions in which thermal distributions were obtained, although T_{mean} was just a temporal average in hyperthermia sessions in which tumour temperatures were monitored at a single point. All the parameters were determined for each hyperthermia session, and averages of these parameters were calculated over all treatments for a given tumour (T_{max}, T_{min}, T_{mean}). F(41°C) is a sampling fraction of the thermal mapping temperature measurements at the end of treatment which exceeded 41°C within a particular thermometry probe tract.

2.4. *Combination therapy*

Radiotherapy was performed with 10 MV X-rays using a linear accelerator (Mitsubishi Electronics, Tokyo, Japan), and 1·8 Gy was given daily five times a week for a total of 50–72 Gy except one case received 40 Gy (mean 52·6 Gy). The dose was determined by the patient's condition. For small tumours, >60 Gy was administered. A localized field including the tumour (mean 73·5 cm^2) was used and was established using our 3-D treatment planning machine. Hyperthermia was administered once a week immediately after radiotherapy. Because of operation findings of positive cancer cells in ascites, four patients with peritonitis carcinomatosis and two patients with primary unresectable tumours received concomitant systemic chemotherapy consisting of Cisplatin (50–200 mg), Doxorubicin (10–50 mg) and Mitomycin C (10–30 mg). In addition, one patient whose case is described in the 'Representative Case Report' section underwent surgery 2 months after thermoradiotherapy.

Table 1. Clinical and thermometry data.

Age	Sex	Tumour site	HT. sessions	Thermometry	T_{max}(°C)	T_{min}(°C)	T_{mean}(°C)	F(41)%	Local response
83	M	abd. wall	6	5	45·1	42·1	43·1	100	CR
35	M	peritonitis	4	3	42·8	41·4	41·8	95	
70	M	peritonitis	7	3	45·7	42·8	43·5	100	
50	M	abd. wall	11	5	44·9	41·9	42·5	100	PR
54	M	local rec.	5	2	45·4	40·4	43·1	40	PR
59	M	peritonitis	7	7	43·2	40·5	41·2	74	
46	M	peri + lymph	7	5	43·3	41·8	42·4	82	PR
56	M	local rec.	5	5	40·8	39·4	40·3	7	PR
53	F	abd. wall	4	1	43·2	42	42·1	100	PR
75	M	abd. wall	5	1	43	40·5	41·5	75	PR
55	M	primary	7	3	42·1	40·1	41·6	91	CR
66	M	primary	7	7	42·2	39·5	40·7	28	PR
48	F	primary	10	4	44	41·4	43	53	PR

Abbreviations: abd. wall = abdominal wall; peritonitis = peritonitis carcinomatosis; local rec. = local recurrence; primary = primary tumour; CR = complete regression; PR = partial regression.

Table 2. Site-specific tumour response.

	Local recurrence	Abdominal wall metastases	Primary unresectable	Paraaortic lymph node metastases	Total
CR	0	1	1	1	3
PR	5	3	2	3	13
NC	1	0	1	0	2
PD	0	0	0	0	0

Abbreviations: CR = complete regression; PR = partial regression; NC = no change; PD = progressive disease.

2.5. *Assessment of response*

The response was evaluated from the change in tumour volume (assessed by computed tomography) within 3 months of treatment. Complete regression (CR) was defined as complete disappearance of the tumour and partial regression (PR) was 50–100% tumour regression. No change (NC) was defined as between 50% tumour regression and 25% tumour progression, while progressive disease (PD) was defined as a $>25\%$ increase in tumour volume. The evaluation of the treatment effect to peritonitis carcinomatosis was difficult because CT and barium examination could not clearly visualize it. Therefore, the local treatment effect was evaluated in the lesions except peritonitis carcinomatosis. Survival was evaluated in the lesions including peritonitis carcinomatosis.

3. Results

3.1. *Temperature profiles*

The tumour temperature could be measured in only 13 patients (62%) out of 21 (Table 1). Thermometry was unsuccessful especially in patients with paraaortic lymph node metastases (1/4, 25%) and local recurrence (2/6, 33%). These tumours were so deeply seated around large vessels that insertion of the needle into the tumour was difficult. The temperature in the patients with peritonitis carcinomatosis was monitored at a point in the peritoneal cavity. Thermometry data was measured at 51 times.

The temperature was measured at 1–4 points (mean 2·5) through a single catheter within the tumour. The T_{max} was 40·8–45·7°C (43·5 ± 0·7°C, mean ± SD), and 12 out of 13 tumours reached a maximum temperature of >42°C. The T_{mean} was 40·3–43·5°C (42·1 ± 1·0°C) for all cases. The T_{mean} was 42·3°C for the abdominal wall metastases, 41·3°C for the primary unresectable tumours, 41·7°C for the local recurrences, and 42·2°C for the peritonitis carcinomatosis. The T_{mean} was >41°C in 11 (84%) out of 13 tumours. The T_{min} was 39·4–42·8°C (41·1 ± 1·1°C). Six out of 13 tumours could be heated to >41°C (F(41)%) in $>90\%$ of the entire tumour.

The mean of F(41) of those abdominal wall tumours and intraperitoneal carcinomatosis was 92%, even though the temperature measured by a single catheter may not represent the entire temperature of the intraperitoneal carcinomatosis. However, thermal distribution of deep-seated tumours, including primary tumours and local recurrence, was not as good and the average of F(41) was 43·8%.

3.2. *Local Response*

Of the six patients with local recurrence, five achieved PR and one showed NC. Of the four with abdominal wall metastases, one achieved CR and three showed PR. Of the four with primary unresectable tumours, one achieved CR, two achieved PR, and one showed NC. Of the four with paraaortic node metastases, one achieved CR and three showed PR. The local response rate was 16/18 (88·9%) (Table 2). In addition, five patients with severe pain experienced pain relief subjectively after thermoradiotherapy.

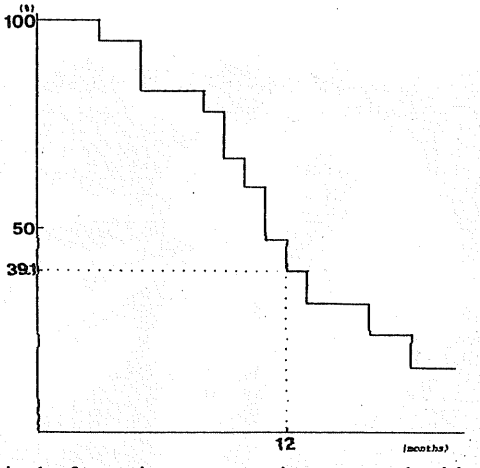

Figure 1. Cumulative survival of gastric cancer patients treated with thermoradiotherapy. (The relationship between survival months and cumulative survival rate using the Kaplan-Meyer method.)

3.3. *Survival*

Figure 1 shows the cumulative survival of these patients treated by thermoradiotherapy. The one-year cumulative survival rate was 39·1%. The median survival period of the patients with CR was 18·0 months, and was $>9{\cdot}0$ months of the patients with PR and NC.

3.4. *Toxicity*

The mean blood pressure (diastolic blood pressure plus 1/3 of the pressure difference) showed a change ranging from $-6{\cdot}4$ to 42 mmHg ($9 \pm 18{\cdot}7$ mmHg, mean ± SD) with hyperthermia. The pulse rate was markedly elevated in most patients with an increase ranging from 8 to 27 beats/min ($17{\cdot}8 \pm 7{\cdot}6$ beats/min, mean ± SD). The body temperature increased by 0·3 to 0·7 °C ($0{\cdot}5 \pm 0{\cdot}18$°C) during hyperthermia, but it decreased again within one h after the treatment. Most patients showed profuse sweating during and after hyperthermia. These findings were similar to those previously reported in patients with liver tumours (Nagata *et al.* 1990). Slight pain and a mild sensation of heat were observed in all cases. No severe complications were encountered except for localized fat burns in four cases. The burns occurred more frequently in the obese patients with the subcutaneous fat of >2 cm in thickness.

3.5. *Representative case report*

A 57-year-old man with epigastric pain was diagnosed by a barium study to have a pyloric tumour in the stomach. Endoscopic biopsy revealed the tumour to be a gastric adenocarcinoma. Surgical resection was attempted, but was abandoned during surgery because the tumour had invaded the pancreas (Figure 2a). Therefore, radiotherapy (Figure 2b) was delivered at a dose of 1·8 Gy, 5 times a week, for a total dose of 61·2 Gy, combined with hyperthermia immediately after radiotherapy twice a week for 40–50 min for a total of 8 sessions. The tumour decreased markedly in size and could then be clearly distinguished from the pancreas (Figure 2c). The tumour was subsequently resected and was clearly delineated from pancreas. No malignant cells were detected in the resected specimen. The patient remained free of disease for 2 years, but developed peritonitis carcinomatosis thereafter and died.

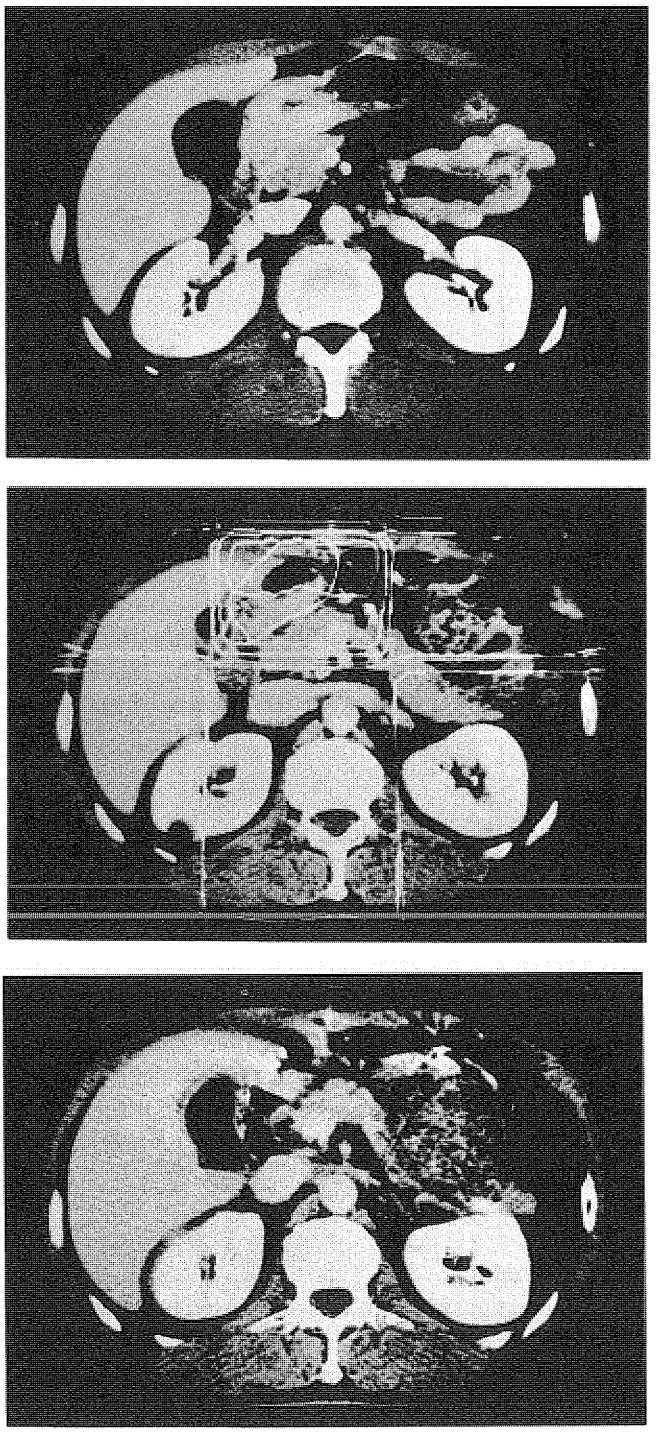

Figure 2. A patient with gastric cancer: (a) A CT scan obtained before thermoradiotherapy; (b) CT simulation. The dose distribution curves are superimposed over the CT image; (c) A CT scan obtained after thermoradiotherapy. The tumour has markedly decreased in size.

4. Discussion

The efficacy of hyperthermia for deep-seated tumours has been evaluated by several studies (Hiraoka *et al.* 1984, Kakehi *et al.* 1990, Nishimura *et al.* 1992). We have experience in treating >150 patients with liver tumours, and the temperature of hepatic lesions could be elevated to $>41°C$ in 60% of the cases by our hyperthermia method (Nagata *et al.* 1990). However, the heating capability of RF capacitive hyperthermia has not been evaluated for gastric cancer.

The average of F(41) of those abdominal wall tumours and intraperitoneal carcinomatosis was 92%, however, that of deep-seated tumours, including primary tumours and local recurrence, was 43·8%. Therefore, the thermal distribution of gastric cancer should be considered separately between superficial tumours including abdominal wall metastatsis, peritonitis carcinomatosa and deep-seated tumours including primary tumours, local recurrences. The thermal distribution of deep-seated tumours was previously reported to be nonhomogeneous (Hiraoka *et al.* 1984).

The relationship between the intratumour temperatures and the tumour response was not apparent in this study. A case with a maximum tumour temperature of 40·8°C showed partial response and a case with a minimum temperature of 41·4°C showed no change. The thermometry procedure used in this study was limited because of the difficulty in frequent and complete thermocouple insertion, and the thermal profiles obtained did not cover the entire tumour. Therefore, non-invasive thermometry to know the accurate entire intratumour temperature is waited.

Previous hyperthermia study for advanced gastric cancer has generally involved either total body hyperthermia including intraperitoneal hyperthermic perfusion or thermochemotherapy. Maeda *et al.* (1987) used whole body hyperthermia to treat advanced gastric cancer. The response rate reported by Maeda *et al.* (1987) was 16·7% (5 PRs in 30 patients). Fujimoto *et al.* (1989) found that surgery and intraperitoneal hyperthermic perfusion were effective for treating peritoneal recurrence of gastrointestinal cancer. The mean survival of patients with gastric cancer was 12·5 months when treated with hyperthermia, and only 3 months without hyperthermia treatment. Fujimura *et al.* (1989) performed continuous hyperthermic peritoneal perfusion with cisplatin and MMC to treat intraperitoneal carcinomatosis or prevent intraperitoneal recurrence in gastric cancer patients without intraperitoneal carcinomatosis. The 1 year survival rate of the patients with intraperitoneal carcinomatosis thus treated was 37%, which was mildly higher than the 30% survival of the patients without hyperthermia.

Kakehi *et al.* (1990) reported the results of thermochemotherapy for advanced gastric cancer using a Thermotron RF-8 in combination with MMC and 5FU. The response rate was 39%, including three CRs and 10 PRs out of 33 patients. Mukojima *et al.* (1990) also reported on the results of chemohyperthermia (RF capacitive hyperthermia with MMC and UFT). Their response rate, confirmed by endoscopic examination, was 40% (8/20). The effect of chemotherapy could not be evaluated in our study because of a small number of patients.

Radiotherapy is an effective method for selected cases of primary advanced and recurrent gastric cancer. Table 4 summarizes the result of radiotherapy for gastric cancer so far reported (Caudry *et al.* 1987). The complete regression (CR) rate of radiotherapy in the previous reports varied between 8 and 17% and the local response rate of 70% was only noted by Tsukiyama *et al.* (1988). The survival period was also mentioned only by Tsukiyama *et al.* (1988). The median period was 26·5 months in CR group, 7·3 months in PR, and 3·2 months in NC. All total, the 50% survival period of the radiation was 7·6 months.

Table 3. Clinical trials of hyperthermia for advanced gastric cancer.

Author (year)	Number of patients	Method of hyperthermia	Chemotherapy	Radiotherapy	Response rate (%)	1-year survival (%)
Kakehi (1990)	33	RF capacitive	MMC, 5FU	no	13/33 (39)	
Mukojima (1990)	20	RF capacitive	MMC, UFT	no	8/20 (40)	
Maeda (1987)	30	Total body	CDDP, ADR, MMC	no	5/30 (17)	17.8
Fujimura (1989)	30	Intraperitoneal	MMC	no		37
Nagata (1992)	21	RF capacitive	CDDP, ADR, MMC	50–72Gy	18/22 (82)	39.1

Abbreviations: MMC = Mitomycin C; 5FU = 5-fluorouracil; CDDP = cis-Platinum; ADR = Adriamycin; UFT = 1, 2-tetrahydrofuryl-5-fluorouracil with uracil.

Table 4. Clinical trials of radiotherapy for advanced gastric cancer.

Author (year)	Number of patients	Radiotherapy	Chemotherapy	Complete response rate (%)
Tsukiyama (1988)	75	40–70Gy	MMC, 5FU	6/75 (8)
Gunderson (1986)	46	45–50Gy	5FU	8/46 (17)
Caudry (1987)	45	45–60Gy		7/45 (16)

Abbreviations: MMC = Mitomycin C; 5FU = 5-fluorouracil.

As far as we know, there have been no previous reports on the treatment of gastric cancer with thermoradiotherapy except ours (Nagata *et al.* 1992). Our response rate was quite high at 88·9% (16/18), including three CRs and 13 PRs. Our local response rate (88·9%) was superior to the thermochemotherapy studies (39–40%) and radiation only study (70%). The 50% survival period (11 months) was superior in our study compared to the radiation only study (7·6 months) (Tsukiyama *et al.* 1988). We experienced the patient of case report who was free of disease at the primary site, as shown by surgery after thermoradiotherapy.

RF capacitive hyperthermia appears to be a safe treatment for patients with gastric cancer based upon the general condition of the patients. No severe cardiac complications occurred and the increase in body temperature during and after hyperthermia was only moderate.

The number of patients we treated was too small to draw conclusions about the therapeutic efficacy of thermoradiotherapy. However, the present study suggests that hyperthermia combined with radiotherapy can be effective for the treatment of advanced or recurrent stomach cancer. Further clinical trials of thermoradiotherapy for gastric cancer appear to be warranted.

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