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ORIGINAL RESEARCH

A novel strategy of radiofrequency hyperthermia (neothermia) in combination with preoperative chemoradiotherapy for the treatment of advanced rectal cancer: a pilot study

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Keywords
8 MHz radiofrequency capacitive heating device, capecitabine, hyperthermia, intensity-modulated radiotherapy, rectal cancer, reference point

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Abstract

The safety of weekly regional hyperthermia performed with 8 MHz radiofrequency (RF) capacitive heating equipment has been established in rectal cancer. We aimed to standardize hyperthermia treatment for scientific evaluation and for assessing local tumor response to RF hyperthermia in rectal cancer. Forty-nine patients diagnosed with rectal adenocarcinoma were included in the study. All patients received chemoradiation with intensity-modulated radiation therapy 5 days/week (dose, 50 Gy/25 times) concomitant with 5 days/week for five times of capecitabine (1700 mg/m^2 per day) and once a week for five times of 50 min irradiations by an 8 MHz RF capacitive heating device. Thirty-three patients underwent surgery 8 weeks after treatment. Three patients did not undergo surgery because of progressive disease (PD) and 13 refused. Eight (16.3%) patients had a pathological complete response (ypCR) after surgery. Among patients without surgery, 3 (6.1%) had clinical complete response (CR) and 3 (6.1%) had local CR but distant PD (CRPD). Ninety percent of ypCR + CR patients were shown in 6.21 W min^{-1} m^{-2}/treatment or higher group of average total accumulated irradiation output with 429°C min^{-1} m^{-2} or higher group of total accumulated thermal output. However, a patient with CRPD was in the higher total accumulated thermal output group. We propose a new quantitative parameter for the hyperthermia and demonstrated that patients can benefit from mild irradiation with mild temperature. Using these parameters, the exact output, optimal thermal treatment, and contraindications or indications of this modality could be determined in a multi-institutional, future study.

Introduction

In rectal cancer, the higher recurrence rate, especially the higher local recurrence rate after surgery compared to colon cancer, is a major problem. Since the National Comprehensive Cancer Network Practice Guidelines for treatment of stage II and III primary rectal cancer were specified in 2009, neoadjuvant chemoradiotherapy (CRT) has become the standard treatment for locally advanced cancer worldwide, except in Japan. Many studies have demonstrated that neoadjuvant CRT increases local control, but has no effect on overall survival [1, 2].

Bosset et al. recently reported that adjuvant fluorouracil-based chemotherapy after preoperative radiotherapy (with or without chemotherapy) does not affect disease-free survival or overall survival [3]. New treatment

strategies incorporating neoadjuvant therapy are required for rectal cancer.

Although hyperthermia has a long history as an oncological treatment and is widely used in clinical practice in several medical fields, unfortunately, this treatment modality has not been accepted widely in cancer therapy, because of an absence of strong scientific proof and stable, reproducible treatment quality. Since multicenter studies were difficult to perform, the clinical effect of hyperthermia was questioned [4, 5]. One of the reasons for these problems is the lack of standardized parameters for evaluation of the efficacy of this modality, that is, there is no reference point for this therapy. Consequently, interdisciplinary scientific analyses cannot be performed. In general, hyperthermia performed over five times was better in combination with chemotherapy, with or without radiation therapy than each modality or surgery alone. However, there was no indication whether each hyperthermic treatment was of the same quality. Moreover, troublesome problems such as the "hot-spot phenomenon" (specific acute to subacute side effects caused by the electrical interface) are reported to be present in up to 60% of cases, and cause pain during radiofrequency (RF) hyperthermia treatment. As a result, treatment cannot be continued without lowering the output [6].

We reported previously that in locally advanced rectal cancer, 5-fluorouracil-based CRT concomitant with RF hyperthermia can be performed safely and can improve the pathological complete response (ypCR) rate as well as tumor downstaging [7, 8].

The aims of this study, which was from the perspective of thermotherapy, were to define the quantitative parameters for standardized treatment and to evaluate the effects of RF hyperthermia device condition on local tumor control in rectal cancer patients who were treated with preoperative hyperthermochemoradiation therapy (HCRT).

Materials and Methods

Forty-nine consecutive patients diagnosed with rectal adenocarcinoma between December 2011 and January 2014 were included in this study. All patients received pre- and posttreatment diagnostic examinations at Hidaka Hospital. Staging for distant metastases was determined with computed tomography (CT) or positron emission tomography/computed tomography (PET/CT) of the abdomen and thorax, while tumor and node stage was classified mainly by magnetic resonance imaging (MRI). The extent and location of the tumor were classified according to tumor node metastasis (TNM) staging [9]. All patients underwent preoperative HCRT at Hidaka Hospital. CRT consisted of intensity-modulated radiotherapy (IMRT) five times weekly at a dose of 50 Gy/25 times and oral administration of capecitabine 1700 mg m^2 per day, 5 days/week for five times. Five thermotherapies were performed once a week with 8 MHz RF capacitive heating equipment (Thermotron RF-8; Yamamoto Vinita Co., Ltd., Japan). The study was approved by the ethics committee of the Hidaka Hospital and Gunma University, and each patient gave written informed consent.

Chemoradiotherapy

IMRT was administered conventionally once daily five times/week using TomoTherapy® (Hi-Art® Treatment System ACCURAY®, Accuray, Sunnyvale, CA, USA). Radiotherapy consisted of 50 Gy delivered to the posterior pelvis in 25 fractions of 2 Gy. The planning target volume included the clinical target volume plus a 2.5 cm caudal margin and a 1.5 cm ventrodorsal margin. Concurrent preoperative chemotherapy was delivered in 5-day courses during the first to fifth weeks of radiotherapy. Capecitabine was administered orally at a dose of 1700 mg/m^2 of body surface area per day.

Hyperthermia

Hyperthermia was administered after radiation. RF hyperthermia using an 8 MHz RF capacitive heating device was applied five times for 5 weeks with 50 min irradiation. From December 2011 to November 2012, 19 patients retrospectively received hyperthermic therapy by Thermotron RF-8. The output was increased until complications such as pain occurred, following which output was decreased and subsequently, increased when pain subsided. Consequently, the output varied patient by patient. This no-rule method of irradiation was not standard. From November 2012 to January 2014, 30 patients prospectively received standardized increasing output (we called this neothermia) based on preceding data, which were dependent on patients' characteristics before treatment, such as body mass index, thickness of the fat of the abdominal wall and internal organs fat area, total fat area, subcutaneous fat area, etc. Fat thickness of the abdominal wall and internal organs fat area, total fat area, and subcutaneous fat area were evaluated using CT. From retrospective data about complications, we had noticed that patients with complication showed bigger thickness of the abdominal wall, internal organs fat area, and total fat area than those without complications. Therefore, we classified patients into two groups as follows: (A) patients with <16-mm thickness of the abdominal wall fat, 100 cm^2 internal organ fat area, and 190 cm^2 total fat area, and (B) patients with any one of the factors previously described. For patients in group A, the output increase was 50 W/min, while in those in group B, it was 50 W/2 min. The operator started from 200 W and

increased the output until complications occurred and then decreased the output by 100 W. Most patients did not complain and continued the first irradiation treatment. Subtracting 100 W output was judged as the optimal output dose without complications. From the second to fifth irradiation treatment, this output was applied for 50 min. We think these our methods were the first time in hyperthermia community. First of all, by using the quartiles of frequencies procedure by SPSS (IBM, Armonk, NY, USA), we simply applied to the classification of patients into four groups according to the average total accumulated irradiation output (TAIO; average W min^{-1} m^{-2}/treatment). These were average TAIO of 6.2 or lower, 6.21–8.4, 8.41–10.43, and 10.44 or higher. Based on total accumulated thermal output (TATO; °C min^{-1} m^{-2}) patients were classified into four groups as follows: 428 or lower, 429–466, 467–548, 549, or higher. Finally, we concluded to be enough to be two to three groups of TAIO and TATO in clinical setting.

A sensor catheter with four temperature points was placed in the rectum in 12 patients while it was attached to the skin on the lateral abdominal side in 30 patients who received standardized therapy and in seven who did not. The accumulated surface skin thermal output of four temperature points was calculated from the estimated internal temperature of patients during the 50 min of each irradiation. An increased thermometry scale of the skin was added to the pretreatment axillar temperature of the patients to obtain a hypothetical internal body temperature that may be the possible core temperature. TATO was considered the heat effect of each treatment. Both temperature and output curves were recorded at 1-min intervals from 1 to 50 min. Body surface area was calculated by the DuBois formula ($BSA = W^{0.425} \times H^{0.725} \times 0.007184$) [10]. Figure 1 summarizes the protocol of this study. All patients received the same CRT and hyperthermic therapy with or without neothermia.

Evaluation of objective response

Each resected specimen was examined for histological changes after HCRT according to the histological criteria of the Japanese Classification of Colorectal Carcinoma [9].

Pathology

In resected specimens (n = 30), according to the Japanese Classification of Colorectal Carcinoma, grade 1a tumors show denaturation and necrosis of cancer cells in approximately <1/3 of the cancer; grade 1b have denaturation and necrosis in <2/3 of cancer cells plus fusion in >1/3 of the cancer; grade 2 shows significant denaturation, necrosis, fusion, and loss in >2/3 of the cancer; and in pathological complete response (ypCR), no cancer cell is observed in both primary and regional lymph nodes [9].

In nonresected/nonoperation cases (n = 19), the tumor size of rectal cancer was defined by Response Evaluation Criteria in Solid Tumors [11]. We classified patient response at 8 weeks after HCRT as follows: complete response (CR), that is, total disappearance of the lesions; partial response (PR), that is, 30% decrease in the sum of diameters of the lesions; stable disease (SD), that is, between 30% decrease and 20% increase; and progressive disease (PD), that is, 20% increase in the sum of diameters of the lesions or new distant metastasis. The CRPD (complete response, PD) group included patients where local tumors showed CR, but new distant metastasis appeared during HCRT.

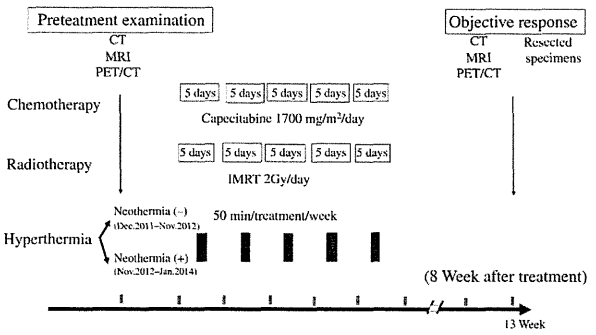

Figure 1. Protocol of this study. CT, computed tomography; MRI, magnetic resonance imaging; PET/CT, positron emission tomography/computed tomography; IMRT, intensity-modulated radiation therapy.

The main endpoint of this pilot study was the pathological and clinical response after 8 weeks of treatment. Adverse effects were evaluated according to the common terminology criteria for adverse events [12].

Results

Patient characteristics are shown in Table 1. All patients tolerated HCRT treatment without major adverse effects. One grade 3 patient had perianal dermatitis. Only two patients wanted to decrease the dose of capecitabine (complete treatment in 47/49 [95.9%] patients). No complication was observed in 64.9% patients during RF irradiation, but 29.7% suffered pain, and 2.1% had subcutaneous induration.

Thirty-three patients underwent surgery 8 weeks after HCRT, mainly at the Department of General Surgical Science, Gunma University, and the Division of Surgery at Hidaka Hospital. Each resected specimen was evaluated histologically at the Department of Pathology, Gunma University. Average and median anal verge distance were 2.76 cm and 3.0 cm, respectively. Abdominoperineal resection was performed in seven (14.3%) patients. One patient could not have the main tumor resected, 5 did not have surgery because of PD, and 11 refused surgery.

Table 1. Patients' characteristics.

	Number of cases (%)
Age (y)	
Median	62
Range	33–89
Gender	
Female	12 (24.5)
Male	37 (75.5)
Stoma	
(−)	41 (83.7)
(+)	8 (16.3)
Primary tumor	
T2	8 (16.3)
T3	36 (73.5)
T4	5 (10.2)
Regional lymph node	
N(−)	29 (59.2)
N(+)	20 (40.8)
Distant metastasis	
M0	44 (89.8)
M1	5 (10.2)
TNM stage[†]	
I	6 (12.2)
II	21 (42.9)
III	17 (34.7)
IV	5 (10.2)
Tumor differentiation	
Well differentiated	26 (53.1)
Moderately differentiated	20 (40.8)
Poorly differentiated	3 (6.1)

TNM, tumor node metastasis; CT, computed tomography; MRI, magnetic resonance imaging.
[†]Tumor staging was clinical, if available, by CT and MRI.

Table 2 summarizes the patients' status after 8 weeks of treatment. Local control of the tumor including CRPD was seen in 14 (18.5%) of 49 patients and in 17 (34.7%) patients with grade 3 or 2 cancer in this pilot study. Patients with less advanced tumors showed ypCR. In patients with preoperative stoma, which meant foreign matter was present in the radiation field, had an unfavorable outcome.

In all, 75% specimens showed a change from T2 to T0, 69.4% showed a change from T3 to T2 or T0, and 100% showed a change from T4 to T2 or T3. In all, 10.3% specimens showed a change from N0 to N1, and 70.0% showed a change from N1 or N2 to N0. Furthermore, 9.1% showed a change from M0 to M1 and 0% showed a change from M1 to M0.

Figure 2 shows the results of the correlation between objective response and average TAIO in 36 patients. Patients showed ypCR in 5 (19.2%) of 26 cases over 6.21 TAIO. In middle and higher TAIO patients, ypCR was seen, and one case of CRPD was seen in higher output patients. In 6.2 or lower and 6.2 or higher TAIO, histological grade 3 + 2 plus clinical CR were 2 (18.2%) and 20 (52.6%), others 5 (45.5%) and 15 (39.5%), and PD 4 (36.4%) and 3 (7.9%), respectively. There was a significant difference among them ($P = 0.028$).

Figure 3 shows the results of correlation between objective response and TATO in 36 patients. PD patients including CRPD and grade 2, 1b PD were observed in the lowest and highest TATO patients. There was no significant difference among them.

Figure 4 shows the correlation among objective response, TAIO and TATO in 35 patients. Consequently, ypCR patients were present in the middle TAIO and TATO group, while PD patients in lowest TAIO group. In 6.2 or lower TAIO and 429 or higher TATO, ypCR plus CR was shown in only one case, while 10 (27.0%) in 6.21 or higher TAIO, and also 9 (90%) patients of total 10 ypCR plus CR patients were shown in patients with 6.21 or higher TAIO and 429 or higher TATO. From these data, we think that 6.21 or higher TAIO and 429 or higher TATO are proper output and thermal dose.

Figure 5 shows the changes of possible body temperature during 50 min irradiation according to the correlation between TAIO (Fig. 5A: 10.44, Fig. 5B: 6.21–10.43, Fig. 5C: 6.2) and objective response. Patients received over 10.44 TAIO irradiation, and their body temperature increased, their outcomes were ypCR, but not increased, their outcome was CRPD (Fig. 5A).

Table 2. Summary of patients' outcomes.

	Grade 3 (%)	Grade 2, 1b, 1a (%)	CR (%)	PR, SD (%)	PD (CRPD-grade 2, 1b PD-PD) (%)	Total
Total no.	8 (16.3)	20 (40.8)	3 (6.1)	11 (22.4)	7 (3-2-2) (14.3)	49
Female	2 (16.7)	2 (16.7)	1 (8.3)	4 (33.3)	3 (2-0-1) (25.0)	12
Male	6 (16.2)	18 (48.6)	2 (5.4)	7 (18.9)	4 (1-2-1) (10.8)	37
Age						
–63	2 (7.7)	14 (53.8)	1 (3.8)	6 (23.1)	3 (1-1-1) (11.5)	26
64–	6 (26.1)	6 (26.1)	2 (8.7)	5 (21.7)	4 (2-1-1) (17.4)	23
Tumor differentiation						
Well differentiated	4 (15.4)	9 (34.6)	1 (3.8)	8 (30.8)	4 (2-1-1) (15.4)	26
Moderately differentiated	3 (15.0)	11 (55.0)	2 (10.0)	2 (10.0)	2 (0-1-1) (10.0)	20
Poorly differentiated	1 (33.3)	0 (0.0)	0 (0.0)	1 (33.3)	1 (1-0-0) (33.3)	3
Location of tumor						
Ra	1 (20.0)	0 (0.0)	0 (0.0)	2 (40.0)	2 (1-1-0) (40.0)	5
Rb	5 (17.2)	14 (48.3)	2 (6.9)	5 (17.2)	3 (0-1-2) (10.3)	29
RbP	2 (14.3)	6 (42.9)	0 (0.0)	4 (28.6)	2 (2-0-0) (14.3)	14
P	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0-0-0) (0.0)	1
Primary tumor						
T2	3 (37.5)	3 (37.5)	2 (25.0)	0 (0.0)	0 (0-0-0) (0.0)	8
T3	5 (13.9)	15 (41.7)	1 (2.8)	8 (22.2)	7 (3-2-2) (19.4)	36
T4	0 (0.0)	2 (40.0)	0 (0.0)	3 (60.0)	0 (0-0-0) (0.0)	5
Regional lymp						
	7 (24.1)	9 (31.0)	4 (13.8)	6 (20.7)	3 (1-1-1) (10.3)	29
N(–)						
N(+)	1 (5.0)	10 (50.0)	1 (5.0)	4 (20.0)	4 (3-1-0) (20.0)	20
Distant metast						
M0	8 (18.2)	19 (43.2)	3 (6.8)	10 (22.7)	4 (1-2-1) (9.1)	44
M1	0 (0.0)	1 (20.0)	0 (0.0)	1 (20.0)	3 (2-0-1) (60.0)	5
TNM stage[1]						
Stage 1 (T1, T2, N0)	3 (50.0)	1 (16.7)	2 (33.3)	0 (0.0)	0 (0-0-0) (0.0)	6
Stage 2 (T3, T4, N0)	4 (19.0)	8 (38.1)	1 (4.8)	6 (28.6)	2 (0-1-1) (9.5)	21
Stage 3 (N+)	1 (5.9)	10 (58.8)	0 (0.0)	4 (23.5)	2 (1-1-0) (11.8)	17
Stage 4 (M+)	0 (0.0)	1 (20.0	0 (0.0)	1 (20.0	3 (2-0-1) (60.0)	5
Stoma						
	8 (19.5	18 (43.9	2 (4.9)	8 (19.5)	5 (2-1-2) (12.2)	41
(–)						
(+)	0 (0.0)	2 (25.0)	1 (12.5)	3 (37.5)	2 (1-1-0) (25.0)	8
Operation						
LAR[2]	0 (0.0)	2 (66.7)	0 (0.0)	1 (33.3)	0 (0-0-0) (0.0	3
sLAR[3]	5 (45.5)	5 (45.5)	0 (0.0	0 (0.0)	1 (0-1-0) (9.1)	11
iSR[4]	1 (12.5)	6 (75.0)	0 (0.0)	1 (12.5)	0 (0-0-0) (0.0)	8
APR[5]	0 (0.0)	6 (85.7)	0 (0.0)	1 (14.3)	0 (0-0-0) (0.0)	7
Partial resection	2 (66.7)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0-0-0) (0.0)	3
No resection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0-1-0) (100.0)	1
No operation	0 (0.0)	0 (0.0)	3 (18.8)	8 (50.0)	5 (3-0-2) (31.3)	16

[1]Tumor staging was clinical, if available, by CT and MRI.
[2]Low anteriol resection.
[3]Super low anteriol resection.
[4]Intersphincteric resection.
[5]Abdominoperineal resection.

Figure 6 shows changes in body temperature during 50 min irradiation according to the correlation between TATO (Fig. 6A: 549, Fig. 6B: 429–548, Fig. 6C: 428) and objective response. In patients in whom body temperature increased, consequently had a good outcome (Fig. 6B), and patients in whom body temperature did not increase, still had a good outcome from this modality (Fig. 6C).

Discussion

In the pilot study presented here, we demonstrated that 8 (24.2%) of 33 patients who underwent surgery and 16.3% of total patients experienced ypCR and local CR, 6 (37.5%) of 16 patients who were not operated showed local tumor control, 14 (28.6%) of 49 showed ypCR, CR,

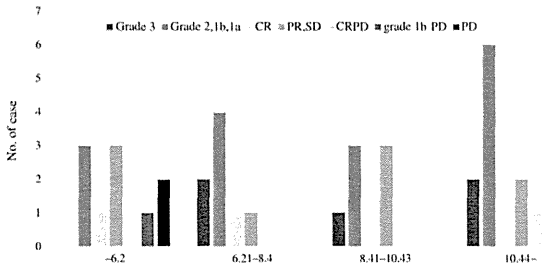

Figure 2. Correlation between objective response and average total accumulated irradiation output (TAIO) in 36 patients. Pathological complete response (ypCR) grade 3 and local complete response with distant progressive disease (CRPD) were seen in patients who could irradiate over 6.21 average TAIO, but not in those with 6.2 or lower average TAIO. ypCR was seen in 5 (19.2%) of 26 cases with over 6.21 TAIO. PR, partial response; SD, stable disease.

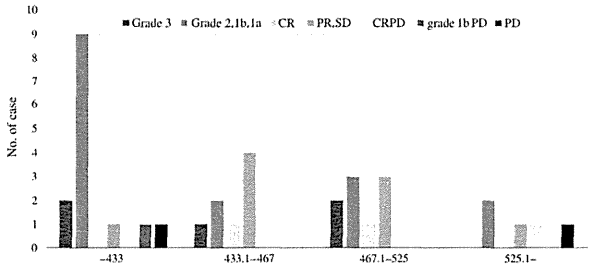

Figure 3. Correlation between objective response and total accumulated thermal output (TATO) in 36 patients. Local complete response with distant progressive disease (CRPD), grade 2, 1b progressive disease (PD), and PD were seen in patients with 6.2 or lower and 525.1 or higher TATO, but not in those with 433.1–525 TATO. PR, partial response; SD, stable disease.

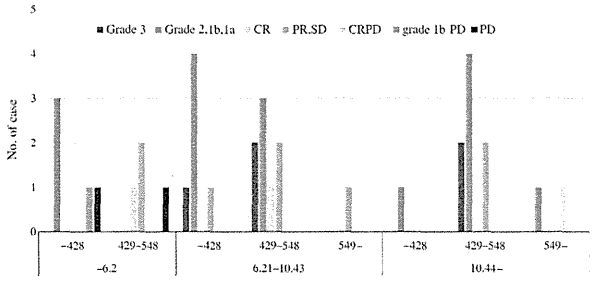

Figure 4. Correlation among objective response, total accumulated irradiation output (TAIO) and total accumulated thermal output (TATO) in 35 patients. In patients with 6.2 or lower TAIO, local complete response with distant progressive disease (CRPD), grade 2, 1b progressive disease (PD), and PD were seen, while in those with 10.44 or lower TAIO, one CRPD patient was present in those with 549 or higher TATO. PR, partial response; SD, stable disease.

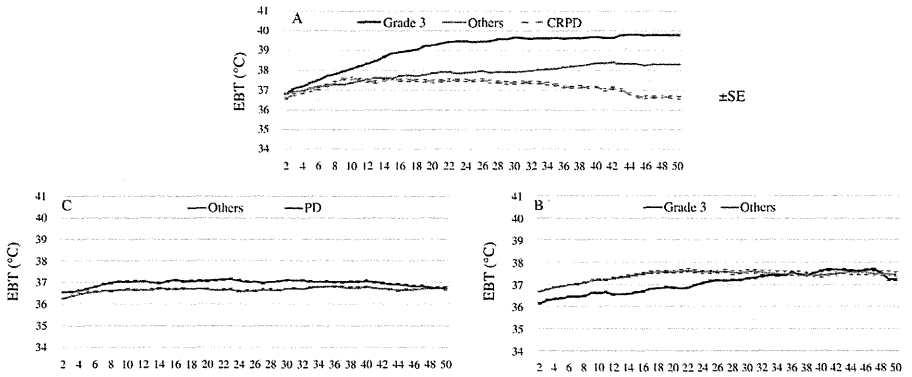

Figure 5. Changes in possible body temperature during 50 min irradiation based on the correlation between total accumulated irradiation output (TAIO) (A: 10.44, B: 6.21–10.43, C: 6.2) and objective response. In patients with 6.21–10.43 TAIO pathological complete response (ypCR) patients showed lower temperature (B), while in those with 10.44 or higher TAIO, ypCR patients showed higher temperature, but a CRPD patient showed lower temperature (A). Data in the figure are presented as means with standard error (SEM).

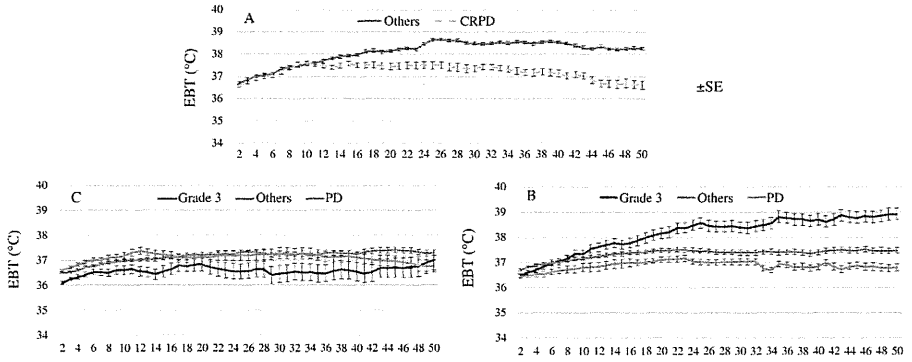

Figure 6. Changes in possible body temperature during 50 min irradiation according to the correlation between total accumulated thermal output (TATO) (A: 549, B: 429–548, C: 428) and objective response. In patients with 429–548 TATO, patients with pathological complete response (ypCR) showed significant increase in temperature (B), but there was no increase in those with 428 or lower TATO (C). Data in the figure are presented as means with standard error (SEM).

or CRPD, and 7 (14.3%) of 49 had clinical PD. In 11 patients who received surgery and could be 6.21 or higher TAIO and 429–548 TATO showed 4 (36.4%) ypCR patients. Moreover, 90% of ypCR plus CR patients show 6.21 or higher TAIO and 429 or higher TATO.

We concluded that patients with less advanced cancer (T2 > T3, T4) and those who could be treated with mild hyperthermia such as 6.21–10.43 TAIO and 429–548 TATO could be beneficial from RF hyperthermic treatment. But, because this study is a small sample, a conclusion has a limit.

All medical treatments are quantitatively characterized by defined parameters. It is essential to identify a parameter to quantify the effect of hyperthermia, as noted in other treatment modalities. If thermometry of one cancer cell is possible in a clinical setting, the true intracellular temperature can be measured, but this is impossible presently. Even in chemotherapy, the drug concentration in one cancer cell is impossible to determine because of tumor heterogeneity; consequently, the true intracellular drug concentration cannot be evaluated in relationship with its efficacy at present. As a result, the parameter in

chemotherapy, and in radiotherapy, mg/m^2 and Gy, respectively, is used for standardized treatment as a reference point. In clinical setting, multi-institute studies on both chemotherapy and radiotherapy have been performed using these parameters. Even the surgical treatment has no reference. For a long time, there was also no research for reference points in hyperthermic therapy.

Efforts had been made to standardize dosimetric measures of microwave/RF exposure as Watts per kilogram (W/kg) in 1981 by the National Council on Radiation Protection and Measurement [13], but there has been no new study until now.

We propose TAIO (W min^{-1} m^{-2}) as a quantitative parameter of the RF hyperthermia device, which can be used to determine the exact dose (output) of a RF hyperthermia device, contraindications or indications of this treatment, conditions of optimal thermal treatment, limits of the treatment, and treatment efficacy by multi-institutional studies. As for the thermal factor, a thermometer was placed on the skin on the lateral abdominal side for simple and reproducible assessment of body temperature in patients and the new parameter of TATO (°C min^{-1} m^{-2}) was defined as the hypothetical heat dosage in patients. In terms of hyperthermia therapy, the most important factor is the intratumor temperature of 42°C during treatment [14]. However, due to tumor heterogeneity, even adequate intratumor temperature is not enough to kill all cancer cells with heat. Hyperthermia itself has several cellular effects that should be synergistic with radiation-induced tumor cell death. Therefore, targeting a combination of tumor-specific and DNA repair pathways will not only enhance heat-induced radiosensitization in both chemotherapy and radiotherapy but will also decrease the overall level of normal tissue toxicity during radiotherapy, which could eventually help to improve the sequential use of heat and radiation treatment to obtain a better clinical outcome [15].

The term "mild" or "physiological range hyperthermia" is found sporadically in basic research, but there are no data regarding this in a clinical setting. Mace et al. reported that antigen-specific activation of naïve CD8$^+$ T cells and their differentiation into effector cells are temperature-sensitive events [16, 17]. These reports and our results have shown positive effects of mild/physiological hyperthermia on tumors when used along with chemoradiation. However, from our results, temperature is liable to depend on individuals. Our data suggest that certain individuals may be able to increase the set point of core temperature according to the output of RF irradiation.

On the other hand, side effects of hyperthermia are caused by large reflections at the interfaces between soft tissue and bone or air, which causes severe complications, including pain, unpleasant sensations, and burns, in 5–16% patients, and even prevents treatment from being efficacious [18–21]. It is necessary to accumulate high-quality evidence by performing a multicenter study to evaluate the relationship between adequate device condition, adequate total radiation dose, and adequate chemotherapeutic regimes and dose in cancer patients together with a study of prophylaxis for complications.

Radiation therapy has become a treatment modality for many types of cancer, but is associated with long-term adverse effects. Therefore, good local tumor control without good survival has been reported in patients after radiation therapy [22]. Gérard et al. [6] summarized four randomized trials of neoadjuvant treatment for rectal cancer, with ypCR ranging from 13% to 20% and grade 3 ranging from 6% to 25%. Chemotherapy consisting of oxaliplatin has also shown to increase ypCR rate and grade 3 toxicity [23–25]. Huang et al. [26] recently summarized the results from previously published studies on the efficacy of preoperative radiotherapy plus capecitabine (825–850 mg/m^2 twice daily, 5 days/week) in the treatment of locally advanced rectal cancer showing ypCR rates ranging from 6.7% to 31% and grade 3+ acute toxicities were noted in 5–15% of patients.

In this study, we used TomoTherapy® for treatment, which has potential advantages for rectal cancer patients, such as confirmation of the exact shape and location of a colorectal tumor, and decreased treatment-related side effects by minimizing damage to nearby healthy tissue. De Ridder et al. [27] first reported the efficacy of helical TomoTherapy® (23 fractions of 2 Gy within 5 weeks) on rectal cancer, with which only one patient developed grade 3, and this modality might decrease gastrointestinal toxicity.

The positive outcome of IRMT plus capecitabine was shown in ypCR rates ranging from 14.1% to 30.6% with grade 3 rates from 11.1% to 17.6% [26,28], but these reports did not mention PD cases. Lu et al. [29] only reported a ypCR of 20% with grade 3 at 22%, and PD in 17% of cases. Reports of controlled trials also did not mention PD. Thus, it is likely that PD cases were missed in these studies. Consequently, good local control outcomes did not correlate with good survival in patients. The timing of surgery after chemoradiation must be reconsidered in the future.

From our results and reports, the following two questions are raised:

1 Why did the body temperature of ypCR patients increase in patients who could be irradiated with a TAIO of 10.44 and higher, but not in CRPD patients?
2 Why was ypCR not seen in cases of a TAIO of 6.2 or lower?

Based on published literature, ypCR rate is less at 10–15% for rectal cancer patients treated with neoadjuvant

CRT. RF therapy may offset the chemoradiation effect in these patients.

In the former patients, those with low body temperature showed ypCR. This result may be help to predict the response of patients to hyperthermia. The set point of core temperature in an individual will be a key in predicting the RF response.

As for the latter, we must have fully defined strategies such as shifting patients who received low output irradiation because of complication at present to those with more output irradiation by preventing complications.

We conclude that standardization of RF hyperthermia using an 8 MHz RF capacitive heating device can be established as a potential new treatment for rectal cancer concomitant with chemoradiation therapy.

Adding RF hyperthermia has shown good local control and low toxicity [30], and if the aforementioned problems are solved, this new combined modality provides another potential treatment in patients with rectal cancer. A randomized control study can be planned for the future using a new strategy, which consists of lower Gy and lower chemotherapeutic dose than that currently concomitant with neothermia, which can lead to good survival of patients with rectal cancer.

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Conflict of Interest

None declared.

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CASE REPORT

Gastrojejunostomy for pyloric stenosis after acute gastric dilatation due to overeating

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Abstract

A 34-year-old woman presented at our hospital with abdominal distention due to overeating. Acute gastric dilatation was diagnosed. The patient was hospitalized, and nasogastric decompression was initiated. On hospitalization day 3, she developed shock, and her respiratory state deteriorated, requiring intubation and mechanical ventilation. Nasogastric decompression contributed to the improvement in her clinical condition. She was discharged 3 mo after admission. During outpatient follow-up, her dietary intake decreased, and her body weight gradually decreased by 14 kg. An upper gastrointestinal series and endoscopy revealed pyloric stenosis; therefore, we performed gastrojejunostomy 18 mo after her initial admission. The patient was discharged from the hospital with no postoperative complications. Gastric necrosis and perforation due to overeating-induced gastric dilatation are life-threatening conditions. Surgical intervention may be required if delayed pyloric stenosis occurs after conservative treatment. We report a case of pyloric stenosis due to overeating-induced gastric dilatation treated by gastrojejunostomy 18 mo after the initial presentation.

Key words: Acute gastric dilatation; Bulimia; Pyloric stenosis; Gastrojejunostomy; Gastric necrosis; Gastric perforation

Core tip: Acute gastric dilatation due to overeating may be life-threatening if gastric necrosis or perforation occurs. Therefore, emergency surgery is performed in most cases. This is the first report of a patient who underwent surgery more than a year after initial treatment. The number of patients with eating disorders, such as bulimia, has recently increased. For this reason in particular, physicians should be aware of acute gastric dilatation due to overeating.

Kimura A, Masuda N, Haga N, Ito T, Otsuka K, Takita J, Satomura H, Kumakura Y, Kato H, Kuwano H. Gastrojejunostomy for pyloric stenosis after acute gastric dilatation due to overeating. *World J Gastroenterol* 2015; 21(5): 1670-1674 Available from: URL: http://www.wjgnet.com/1007-9327/full/v21/i5/1670.htm DOI: http://dx.doi.org/10.3748/wjg.v21.i5.1670

INTRODUCTION

Although gastric necrosis or perforation following gastric dilatation is unusual because of the rich blood supply to the stomach, the occurrence of these conditions may be life-threatening. We report our experience with a patient who underwent gastrojejunostomy for pyloric stenosis after presenting with acute gastric dilatation due to overeating. Furthermore, we discuss the recent literature available on the subject.

CASE REPORT

A 34-year-old woman ate an overly large meal of curry, rice, and potatoes. She gradually developed abdominal distention for which she sought medical attention. The general physician decided on an expectant approach. However, she presented at our hospital because her symptoms did not improve. This patient had a history of episodes of bulimic binging, but she had failed to self-induce vomiting this time.

Physical examination at presentation revealed a blood pressure of 117/68 mmHg, a pulse rate of 100 beats/min, and a body temperature of 36.7 ℃. Her abdomen was distended, but there were no signs of peritoneal irritation. The significant laboratory test results were as follows: white blood cell count, 16700 cells/μL; C-reactive protein, 2.33 mg/dL; amylase, 1190 IU/L; serum creatinine phosphokinase, 4007 IU/L; blood urea nitrogen (BUN), 15.2 mg/dL; and creatinine, 2.33 mg/dL. Abdominal computed tomography scans revealed a massive dilation of the stomach reaching the pelvis but with no ascites or free air (Figure 1). We made a diagnosis of acute gastric dilatation due to overeating without gastric perforation or necrosis.

A nasogastric tube was inserted, and decompression and irrigation were initiated. On post-hospitalization day 3, the patient developed shock, and her respiratory state worsened. We then performed intubation and initiated mechanical ventilation. The inferior vena cava and diaphragm were compressed by her remarkably distended stomach. Further, decreased venous return and ventilatory impairment aggravated her condition. Although we considered emergency surgery, her general condition promptly improved after fluid resuscitation and respiratory care. Therefore, we continued conservative treatment. Seven days after intubation, we performed a tracheotomy. Her respiratory state gradually improved, and she was extubated 3 wk after intubation. The abdominal distention gradually improved by decompression. Thereafter, upper gastrointestinal (UGI) endoscopy and an UGI series were performed. The UGI endoscopy showed mucosal deciduation at the pyloric antrum (Figure 2A), but the UGI series showed no leakage and good passage of the contrast medium (Figure 3A). Thus, there was no evidence of pyloric stenosis. Tube feeding was initiated on hospitalization day 30 and continued until she was able to eat rice gruel. Three months after admission, she was discharged from our hospital.

While our patient was followed-up as an outpatient, her dietary intake gradually decreased. Although we recommended surgical treatment for her several times during the course of an outpatient, she rejected surgical treatment. Ultimately, she lost 14 kg from her original weight on admission. At present, her height and weight are 160 cm and 40 kg, respectively. However, because the UGI series and endoscopy revealed pyloric stenosis (Figures 2B and 3B), we performed Roux-en-Y gastrojejunostomy 18 mo after the first admission, with her consent. The postoperative course was uneventful, and she was discharged from our hospital 3 wk after surgery. The passage of contrast medium during the postoperative UGI series indicated that the anastomosis was accurate (Figure 4). At two years after surgery, the patient had gained 20 kg.

DISCUSSION

Acute gastric dilatation is a medical condition in which the stomach becomes progressively hypotonic and overstretched despite the absence of mechanical obstruction[1]. This condition can be caused by overeating, postoperative ileus, child birth, chronic debilitating affection, central nervous system damage, severe infection, and trauma[2]. Among these causes, acute gastric dilatation due to overeating is more common in females with underlying eating disorders, such as anorexia nervosa[3]. The rich collateral blood flow of the stomach generally protects the gastric wall from ischemia; gastric necrosis or perforation following gastric dilatation is unusual. However, a remarkable increase in the intragastric pressure by massive gastric dilatation can decrease the intramural blood flow, resulting in possible gastric necrosis or perforation[4]. Immediate nasogastric decompression and sufficient fluid resuscitation are necessary for the treatment of acute gastric dilatation[5]. These procedures can decrease the intragastric pressure and reduce the risk of necrosis and perforation; therefore, they should be implemented as early as possible. If gastric

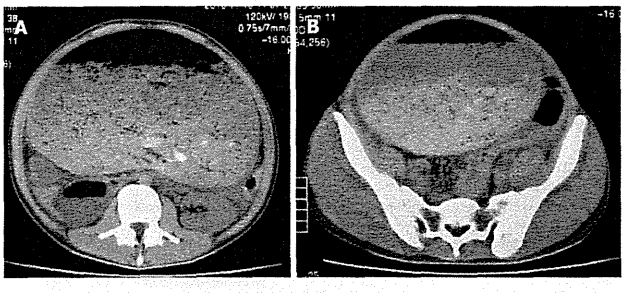

Figure 1 Computed tomography on initial admission. A. Upper abdomen B. Pelvis.

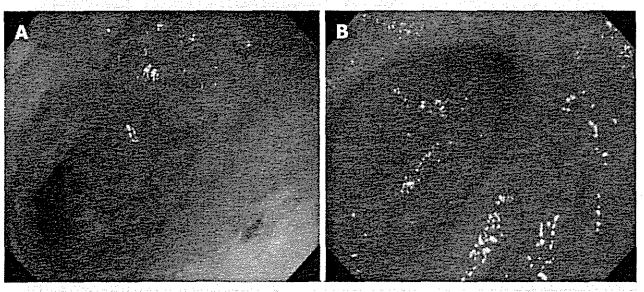

Figure 2 Gastrointestinal endoscopy revealed pyloric stenosis. A: One month after admission, gastrointestinal endoscopy revealed mucosal deciduation at the pyloric antrum, but there were no findings of pyloric stenosis; B: One year after discharge, gastrointestinal endoscopy revealed progressive pyloric stenosis.

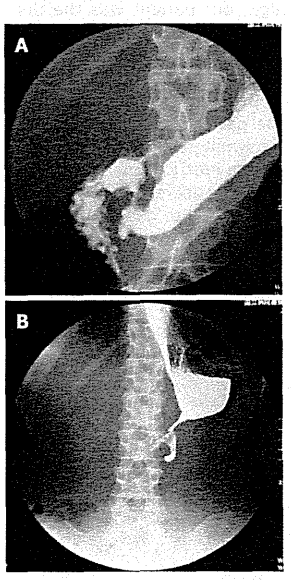

Figure 3 Gastrointestinal series showed pyloric stenosis. A: Two months after admission, an upper gastrointestinal series showed no leakage and a good passage of contrast medium; B: One year after discharge, a follow-up gastrointestinal series showed advanced pyloric stenosis.

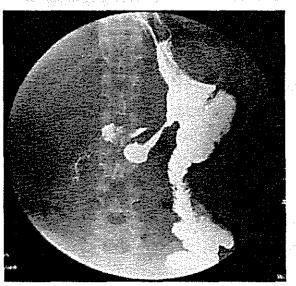

Figure 4 A postoperative gastrointestinal series showed improvement in the contrast medium passage through the stomach and intestine.

necrosis or perforation is suspected or if draining the gastric contents is difficult, immediate surgical intervention is required. Resection of the necrotic portion of the stomach is required in some cases, and total gastrectomy is required in others.

In our case, the pyloric stenosis progressed more than a year after initial treatment. The partial necrosis of the gastric wall may have been caused by acute gastric dilatation because the serum creatinine-phosphokinase level increased at onset. We promptly performed nasogastric decompression, which may have prevented complete gastric necrosis

Table 1 Reported cases of acute gastric dilatation due to overeating

Year	Ref.	Age (yr)	Sex	Underlying disease	Duration to surgery	Treatment	Outcome
2000	Nakao *et al*[5]	17	F	Anorexia nervosa	8 h	Proximal gastrectomy	Alive
2006	Barada *et al*[6]	24	F	Anorexia nervosa	NA	Nasogastric tube decompression	Alive
2011	Kim *et al*[7]	26	F	Eating disorder	NA	Nasogastric tube decompression	Dead
1987	Abdu *et al*[8]	14	F	None	Emergency	Partial gastrectomy	Alive
1987	Abdu *et al*[8]	17	F	Eating disorder	Emergency	Total gastrectomy	Dead
1987	Deret *et al*[9]	48	F	Schizophrenia	5 h	Total gastrectomy	Alive
1990	Trott *et al*[10]	17	F	Bulimia nervosa	Emergency	Gastric tube decompression (by laparotomy)	Alive
1992	Beiles *et al*[11]	24	F	Bulimia nervosa	Emergency	Partial gastrectomy	Alive
1995	Adson *et al*[12]	35	F	Eating disorder	2 d	Nasogastric tube decompression (with appendectomy)	Alive
1995	Adson *et al*[12]	30	F	Bulimia nervosa	NA	Nasogastric tube decompression	Alive
1996	Willeke *et al*[13]	19	F	Anorexia nervosa	Emergency	Partial gastrectomy	Alive
1998	Seligmann *et al*[14]	31	F	Bulimia nervosa	NA	Nasogastric tube decompression	Alive
2000	Qin *et al*[15]	12	F	None	NA	Oral gastric tube decompression	Dead
2000	Qin *et al*[15]	4	F	None	Emergency	Partial gastrectomy	Alive
2002	Holtkamp *et al*[16]	16	M	Anorexia nervosa	8 h	Aspiration of stomach contents (by laparotomy)	Alive
2003	Turan *et al*[17]	18	M	Mental retardation	Emergency	Total gastrectomy	Dead
2004	Sinicina *et al*[18]	19	M	Anorexia nervosa	NA	None	Dead
2004	Mathevon *et al*[19]	25	F	Anorexia nervosa	NA	Nasogastric tube decompression	Alive
2005	Luncă *et al*[20]	22	M	Mental retardation	NA	Nasogastric tube decompression	Alive
2006	Gyurkovics *et al*[21]	22	F	Eating disorder	Emergency	Gastrostomy	Dead
2009	Kashyap *et al*[22]	36	F	Eating disorder	Emergency	Gastrotomy	Alive
2010	García Salido *et al*[23]	16	Unknown	Anorexia nervosa	NA	Nasogastric tube decompression	Alive
2011	Hohenauer *et al*[24]	21	F	Psychosis	NA	Nasogastric tube decompression	Alive
2012	Mishima *et al*[25]	12	M	None	Emergency	Partial gastrectomy	Alive
2012	Franco-López *et al*[26]	31	F	Bulimia nervosa	Emergency	Gastrotomy	Alive
2012	Our case	34	F	Bulimia nervosa	1.5 yr	Gastrojejunostomy	Alive

NA: Not availiable.

and perforation. Because of the increase in the intragastric pressure caused by massive gastric dilatation, the intramural blood flow decreased, resulting in partial necrosis of the gastric mucosa and muscle scarring due to fibrosis. Together, these regenerative processes can lead to pyloric stenosis. In this case, acute gastric dilatation occurred only once. However, the dilatation of the stomach was severe, and it took approximately one month to drain the gastric contents completely. Therefore, delayed pyloric stenosis might have occurred.

From a literature search of the PubMed database between 1966 and 2013, in addition to our patient, we retrieved 25 cases of acute gastric dilatation due to overeating (Table 1). The mean age of these patients was 22.7 (range, 4-48) years, indicating a greater frequency among young patients. There were more female patients than males (n = 20 and 5 patients, respectively, with the gender of one patient being unknown). Eighteen patients had underlying eating disorders, such as anorexia or bulimia nervosa. Sixteen patients underwent laparotomy, three of whom underwent total gastrectomy. In contrast, eight patients were treated by nasogastric decompression alone. Eleven patients underwent emergency surgery: three within several hours and one within several days. In most cases, emergency or semi-emergency surgery was performed. To the best of our knowledge, our patient was the first to undergo surgery more than a year after initial treatment. According to our literature search, six patients died despite immediate treatment, including surgical intervention. Despite the many reports of young patients, some patients died shortly after surgery or the onset of symptoms. Therefore, gastric perforation following acute gastric dilatation may be more severe than usually considered.

In conclusion, although acute gastric dilatation due to overeating is rare, physicians should be aware of its potential complications, such as gastric necrosis or perforation. Moreover, if conservative treatment is preferred over surgery, physicians should be aware of the possibility of delayed pyloric stenosis.

COMMENTS

Case characteristics

A 34-year-old woman developed abdominal distention due to overeating.

Clinical diagnosis

The abdomen was distended, but there were no signs of peritoneal irritation.

Differential diagnosis

Gastric perforation, Ascites, Gastric dilatation.

Laboratory diagnosis

White blood cell count, 16700 cells/μL; C-reactive protein, 2.33 mg/dL; amylase, 1190 IU/L; serum creatinine phosphokinase, 4007 IU/L; blood urea nitrogen, 15.2 mg/dL; and creatinine, 2.33 mg/dL. The results of her liver function tests were within normal limits.

Imaging diagnosis

Abdominal computed tomography scans revealed a massively dilated stomach reaching the pelvis without ascites or free air.

Treatment

Initially, conservative treatment by nasogastric decompression was performed, and Roux-en-Y gastrojejunostomy was performed for delayed pyloric stenosis 18 mo after the first admission.

Related reports

Twenty-five cases of acute gastric dilatation due to overeating were retrieved from a literature search of the PubMed database of cases between 1966 and 2013.

Term explanation

Acute gastric dilatation is a medical condition in which the stomach becomes progressively hypotonic and overstretched, despite the absence of mechanical obstruction.

Experiences and lessons

This study not only presents the importance of immediate treatment for acute gastric dilatation but also describes the possibility of delayed pyloric stenosis after conservative treatment.

Peer-review

The article demonstrated a high mortality rate when performing emergency surgery for acute gastric dilatation due to overeating. Gastrojejunostomy is an interesting option in this situation.

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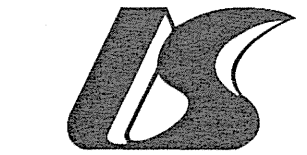

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Prognostic Role of Conversion Surgery for Unresectable Gastric Cancer

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ABSTRACT

Background. The prognosis of unresectable gastric cancer is poor. Chemotherapy occasionally converts an initially unresectable gastric cancer to a resectable cancer.

Methods. The responses of noncurative factors to initial chemotherapy and the outcomes of additional (conversion) surgery were retrospectively evaluated in 151 patients with unresectable gastric cancer receiving combination chemotherapy with S-1 plus cisplatin or paclitaxel from February 2003 to December 2013.

Results. Forty (26 %) of 151 patients underwent conversion surgery. After chemotherapy, R0 resection was accomplished in 32 patients (80 %). The 5-year overall survival (OS) rate among the 40 patients who underwent conversion surgery was 43 % (median survival time, 53 months). The 5-year OS rate in the 111 patients treated with chemotherapy alone was 1 % (median survival time, 14 months). Patients who underwent conversion surgery had significantly longer OS times than patients who underwent chemotherapy alone ($P < 0.01$). The 5-year OS rate among patients who underwent R0 resection was 49 % (median survival time, 62 months). Patients who underwent R0 resection had significantly longer OS times than those who underwent R1 and R2 resection ($P = 0.03$). Among patients who underwent conversion surgery, multivariate Cox regression analysis showed that one noncurative factor (odds ratio 0.49; 95 % confidence interval 0.28–0.88; $P = 0.02$) and R0 resection (odds ratio 0.52; 95 % confidence interval 0.28–0.95; $P = 0.03$) were significant independent predictors for favorable OS.

Conclusions. Patients with unresectable gastric cancer initially exhibiting one noncurative factor may obtain a survival benefit from chemotherapy and subsequent curative surgery.

Gastric cancer is the fourth most prevalent cancer worldwide.[1] Although the mortality rate associated with gastric cancer has decreased in many countries during the past few decades, it remains the second leading cause of cancer death worldwide.[2] Gastric cancer is generally diagnosed in the late stages and exhibits a high frequency of invasion or metastasis. The prognosis of highly advanced gastric cancer characterized by invasion or metastasis is usually very poor. Affected patients are currently not considered surgical candidates and are usually offered systemic chemotherapy.

Numerous randomized controlled trials of various treatment regimens have been described for patients with unresectable gastric cancer, including 5-fluorouracil (5-FU), doxorubicin plus mitomycin, epirubicin plus cisplatin, and 5-FU plus cisplatin.[3–5] However, these trials reported a median survival time of <1 year. The SPIRITS trial, a phase 3 study, established S-1 plus cisplatin as a standard first-line chemotherapy regimen for unresectable or metastatic gastric cancer in Japan.[6] Our previous phase-II trial noted that S-1 plus paclitaxel, an alternative drug combination, has similar efficacy but lower toxicity than does S-1 plus cisplatin.[7]

Several novel combined chemotherapy regimens occasionally allow for conversion of an initially unresectable gastric cancer to a resectable cancer in

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clinical practice. Additional surgery may result in long-term survival in selected patients. Several previous studies have evaluated the prognostic role of surgery after chemotherapy in patients with unresectable gastric cancer and one noncurative factor such as peritoneal metastasis, para-aortic lymph node metastasis, or positive peritoneal cytology alone.[8–10] However, few studies have investigated the prognostic role of conversion surgery for all patients with unresectable gastric cancer and one or more noncurative factors.[11,12]

In this study, we selected patients with initially unresectable gastric cancer who subsequently underwent conversion surgery after combination chemotherapy such as S-1 plus cisplatin or paclitaxel and retrospectively examined their clinicopathologic and survival data to evaluate the prognostic role of conversion surgery. Surgical resection was classified as curative (R0, complete resection with no residual tumor) or noncurative (R1 or R2, microscopic or gross residual tumor). We simplified this nomenclature by denoting additional surgery with a curative goal after a response to chemotherapy as "conversion surgery."

PATIENTS AND METHODS

Patients

We retrospectively reviewed a database of 151 patients with unresectable gastric cancer who underwent combination chemotherapy with S-1 plus cisplatin or paclitaxel at Saitama Medical Center of Saitama Medical University or Gunma University Graduate School of Medicine from February 2003 to December 2013. We selected 40 of these 151 patients who underwent conversion surgery. We retrospectively evaluated the responses of noncurative factors to combination chemotherapy and the outcomes of the subsequent surgery in all 40 patients. This retrospective study was approved by the local ethics committee of Saitama Medical Center of Saitama Medical University (No. 1059).

Patient Evaluation

A diagnosis of gastric adenocarcinoma was histologically proven in all patients. Before initial treatment, all patients underwent neck, abdominal, and pelvic computed tomography as well as upper gastrointestinal tract endoscopy and ultrasonography to determine the pretreatment clinical stage. Peritoneal lavage was performed as needed using 50 mL of saline during staging laparoscopy, and lavage fluid was collected from the pouch of Douglas for peritoneal cytology. Tumor staging and histopathologic grading were performed according to the International Union Against Cancer pathologic tumor, node, metastasis classification system staging guidelines, 7th edition.[13] Terminology defined by the Japanese Gastric Cancer Association was used to avoid unnecessary confusion.[14] Additionally, eligible patients were required to have an Eastern Cooperative Oncology Group performance status (PS) of 0–2.

Patients with unresectable gastric cancer were considered if they had at least one initially proven lesion with any noncurative factor such as tumor invasion of adjacent structures (T4b), peritoneal (P1), hepatic (H1) and distant metastasis (M1), or positive peritoneal cytology (CY1).

Chemotherapy Schedule

Patients assigned to the S-1 plus cisplatin group received oral S-1 (40 mg/m^2 twice daily) on days 1–21 plus intravenous cisplatin (60 mg/m^2) on day 8 of a 5-week cycle.[6] Patients assigned to the S-1 plus paclitaxel group received oral S-1 (40 mg/m^2 twice daily) on days 1–14 plus intravenous paclitaxel (60 mg/m^2) on days 1, 8, and 15 of a 4-week cycle.[7] Seventy-five patients enrolled in our previous trial were randomly assigned to one of the two treatment groups.[7] The remaining 76 patients were preferentially assigned to the S-1 plus paclitaxel group if they had renal dysfunction. Treatment was discontinued at the onset of disease progression, the development of severe toxic effects, or the patient's request. The tumor response was objectively assessed after each treatment course according to the Response Evaluation Criteria in Solid Tumors. Adverse events were evaluated according to the Common Terminology Criteria for Adverse Events, version 4.0.

Follow-Up Schedule

Disease progression and new lesion development were evaluated as needed by radiography and computed tomography, and the tumor markers carcinoembryonic antigen and CA 19-9 were measured at baseline and at least every 4–5 weeks during treatment.[7] Responses were evaluated every 8 weeks or earlier in patients with evidence of treatment failure. Physical examinations and laboratory tests were performed before treatment and at least every 2 weeks during treatment.

Indications for Conversion Surgery

The main indication for conversion surgery was the anticipation of curative resection on the basis of the response to chemotherapy, excluding patients which were unable to continue chemotherapy. Thus, the absence of any noncurative factors, including T4b, P1, H1, M1, and CY1, was considered as an indication. Another indication included the anticipation of curative resection despite little

response to chemotherapy, such as stable disease, if noncurative factors were absent. Chemotherapy mainly with S-1 agent was required after conversion surgery.

Statistical Analyses

Continuous variables are expressed as median or mean and range. Patient characteristics were compared using the χ^2 test, Fisher's exact probability test, and the Mann–Whitney U test, as appropriate. We calculated the cumulative overall survival (OS) and progression-free survival (PFS) rates by the Kaplan–Meier method and compared survival curves with the log rank test. OS was estimated from initial chemotherapy to the date of death or the last follow-up visit. We subjected significant variables from the log rank test with P values of <0.05 to multivariate Cox proportional hazard regression analysis to assess the independence of prognostic factors. In the multivariate analysis, we calculated odds ratios with 95 % confidence intervals (CIs). All statistical analyses were performed with JMP 5.0 software (SAS Institute Inc., Cary, NC, USA), and P values of <0.05 were considered statistically significant.

RESULTS

Clinical Factors of Patients Who Underwent Chemotherapy

The characteristics of the 151 patients who underwent chemotherapy with S-1 plus cisplatin or S-1 plus paclitaxel are presented in Table 1. These 151 patients comprised 108 male and 43 female patients with a median age of 66 years (range 31–79 years). In total, 77 patients were assigned to the S-1 plus cisplatin group, and 74 patients were assigned to the S-1 plus paclitaxel group. The characteristics of the assessable patients included median age; sex; PS; tumor location; histologic grade; tumor depth; nodal stage; absence or presence of P1, H1, M1, and CY1; number of noncurative factors; number of treatment cycles; toxicity; and surgery. The S-1 plus cisplatin group had significantly more cases of P1 than the S-1 plus paclitaxel group ($P = 0.01$), whereas the S-1 plus paclitaxel group had significantly more cases of H1 and number of cycles than the S-1 plus cisplatin group ($P < 0.01$). The other baseline characteristics were mostly balanced between the two treatment groups.

TABLE 1 Clinical factors of patients who underwent chemotherapy with S-1 plus cisplatin or S-1 plus paclitaxel

Characteristic	S-1 + cisplatin ($n = 77$)	S-1 + paclitaxel ($n = 74$)	P
Age, year, median (range)	66 (31–79)	66 (31–79)	0.79
Sex			
Male	54	54	0.70
Female	23	20	
Performance status			0.91
0	64	62	
1, 2	13	12	
Location			0.35
Upper	32	23	
Middle	34	36	
Lower	11	15	
Histologic grade			0.58
G1, G2	33	35	
G3	44	39	
Tumor depth			0.43
T2, 3, 4a	67	61	
T4b	10	13	
Nodal stage			0.93
N1, 2	40	39	
N3	37	35	
Peritoneal metastasis			0.01
No (P0)	60	42	
Yes (P1)	17	32	
Hepatic metastasis			<0.01
No (H0)	46	60	
Yes (H1)	31	14	
Distant metastasis			0.99
No (M0)	27	26	
Yes (M1)	50	48	
Peritoneal cytology			0.32
Negative	74	73	
Positive	3	1	
No. of noncurative factors			0.99
1	49	47	
2, 3	28	27	
No. of cycles, mean (range)	3.9 (1–12)	6.3 (1–35)	<0.01
Response rate, %	41.6	56.8	0.06
Grade 3 or 4 toxicity	18	19	0.74
Surgery	24	16	0.18

Characteristics of Patients Who Underwent Conversion Surgery

The characteristics of the 40 patients (26 %) who underwent conversion surgery are presented in Table 2. These patients comprised 29 male and 11 female patients with a median age of 65 years (range 42–76 years). All patients showed a PS of 0 or 1. Of all 40 patients with one

TABLE 2 Characteristics of 40 patients who underwent conversion surgery

Characteristic	Value
Age, year, median (range)	65 (42–76)
Sex	
Male	29
Female	11
Performance status	
0	36
1	4
Location	
Upper	11
Middle	16
Lower	13
Macroscopic types	
2	10
3	24
4	6
Histologic grading	
G1	7
G2	10
G3	20
Tumor depth	
T2	1
T3	10
T4a	23
T4b	6
Nodal stage	
N0	4
N1	12
N2	10
N3	14
Peritoneal metastasis	
No (P0)	29
Yes (P1)	11
Hepatic metastasis	
No (H0)	35
Yes (H1)	5
Distant metastasis	
No (M0)	14
Yes (M1)	26
Peritoneal cytology	
Negative	37
Positive	3
No. of noncurative factors	
1	33
2	7
Initial chemotherapy	
S-1 + cisplatin	24
S-1 + paclitaxel	16
No. of cycles, median (range)	4 (2–20)
Toxicity grade	
1	14
2	5
3	4
4	2
Response	
Partial response	34
Stable disease	6
Type of gastrectomy	
Distal	11
Total	29
Residual tumor classification	
R0	32
R1	3
R2	5
Pathologic response	
Grade 0	6
Grade 1a	11
Grade 1b	11
Grade 2	12
Second-line chemotherapy	
No	10
Yes	
S-1	24
Other	6

or two noncurative factors preoperatively, 6 (15 %), 11 (28 %), 5 (13 %), 26 (65 %), and 3 (8 %) had T4b, P1, H1, M1, and CY1 disease, respectively. In total, 24 patients (60 %) were assigned to the S-1 plus cisplatin group, and 18 patients (40 %) were assigned to the S-1 plus paclitaxel group. The median number of cycles administered per patient was 4 (range 2–20). All patients were assessable for response. No complete response was noted; 34 patients (85 %) had a partial response and 6 (15 %) had stable disease. All patients' cancers had been diagnosed as resectable with the goal of achieving no residual tumor after chemotherapy. However, among eight patients (20 %) with R1 or R2 disease, CY1, T4b, P1, and M1 were found in three, one, two, and two patients, respectively.

Survival

The 5-year OS rate of all 151 patients was 13 % (median time, 16 months) at a median follow-up time of 15.0 months (range 1.4–126.0 months). The 5-year PFS rate was 11 % (median time, 8 months). Among the 40