Radiofrequency thermal treatment with chemoradiotherapy for advanced rectal cancer

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Abstract. We previously reported that patients with a clinical complete response (CR) following radiofrequency thermal treatment exhibit significantly increased body temperature compared with other groups, whereas patients with a clinical partial response or stable disease depended on the absence or presence of output limiting symptoms. The aim of this study was to evaluate the correlation among treatment response, Hidaka radiofrequency (RF) output classification (HROC: termed by us) and changes in body temperature. From December 2011 to January 2014, 51 consecutive rectal cancer cases were included in this study. All patients underwent 5 RF thermal treatments with concurrent chemoradiation. Patients were classified into three groups based on HROC: with ≤9, 10-16, and ≥17 points, calculated as the sum total points of five treatments. Thirty-three patients received surgery 8 weeks after treatment, and among them, 32 resected specimens were evaluated for histological response. Eighteen patients did not undergo surgery, five because of progressive disease (PD) and 13 refused because of permanent colostomy. We demonstrated that good local control (ypCR + CR + CRPD) was observed in 32.7% of cases in this study. Pathological complete response (ypCR) was observed in 15.7% of the total 51 patients and in 24.2% of the 33 patients who underwent surgery. All ypCR cases had ≥10 points in the HROC, but there were no patients with ypCR among those with ≤9 points in the HROC. Standardization of RF thermal treatment was performed safely, and two types of patients were identified: those without or with increased temperatures, who consequently showed no or some benefit, respectively, for similar RF output thermal treatment. We propose that the HROC is beneficial for evaluating the efficacy of RF thermal treatment with chemoradiation for rectal cancer, and the thermoregulation control mechanism in individual patients may be pivotal in predicting the response to RF thermal treatment.

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Introduction

Hyperthermia has a long history and is widely used in various medical fields (1). Radiofrequency (RF) hyperthermia (HT) has been performed in Japan and is associated with two major issues: i) this modality has not been approved as a standardized treatment in oncology, and ii) there is a risk of a fatal complication, the hot spot phenomenon, which is induced by RF thermal therapy itself (2,3). Many randomized trials of HT have demonstrated a significant improvement in clinical outcome for several tumor types (4-6). However, due to the lack of standardization parameters, and absence of a reference point for this therapy, clinical studies have had contradictory outcomes, thereby raising doubts about efficacy.

Conversely, rectal cancer shows higher local recurrence rates than colon cancer after surgery (7-9). Since the National Comprehensive Cancer Network Practice Guidelines for treatment of primary rectal cancer were specified in 2009, neoadjuvant chemoradiation (NACR) has been accepted as the standard therapy worldwide, except in Japan. Many studies have demonstrated that NACR increases local control but exerts no influence on overall survival (10-12). New strategies that incorporate neoadjuvant therapy are required for rectal cancer.

We reported that hyperthermo-chemoradiotherapy (HCRT) for rectal cancer is performed safely (13). The main endpoint of this study was the evaluation of the pathological and clinical responses after HCRT using the Hidaka RF output classification (HROC: termed by us).

Materials and methods

Between December 2011 and January 2014, 51 consecutive patients with primary rectal cancers were included in this

study. Patients received pre-treatment and post-treatment diagnostic examinations, including computed tomography (CT), positron emission tomography/CT (PET/CT), and magnetic resonance imaging (MRI), at Hidaka Hospital. The extent and location of the tumor were classified according to the tumor-node-metastasis TNM staging (14). Patients underwent HCRT at Hidaka Hospital. Operations were performed at the Department of General Surgical Science, Gunma University, or at the Division of Surgery, Hidaka Hospital. Each resected specimen was evaluated histologically at the Department of Pathology, Gunma University. The study was approved by the Ethics Committees of the Hidaka Hospital and Gunma University. Each patient gave written informed consent prior to enrollment in the study.

Chemoradiotherapy. Intensity-modulated radiotherapy was administered conventionally once daily 5 times/week using TomoTherapy® (Hi-Art® treatment system; Accuray). Neoadjuvant radiotherapy (NART) consisted of 50 Gy delivered to the posterior pelvis in 25 fractions of 2 Gy each. Concurrent neoadjuvant chemotherapy was delivered in 5-day courses during the first to fifth weeks of NART. Capecitabine was administered orally at a dose of 1,700 mg/m^2/day.

Hyperthermia. RF thermal treatment was performed using the Thermotron-RF 8 (Yamamoto Vinita Co., Ltd., Japan) and administered once a week for 5 weeks with a 50-min irradiation. From December 2011 to November 2012, 19 patients underwent abdominal hyperthermia treatment and the RF output was retrospectively evaluated and from November 2012 to January 2014, 32 patients prospectively received a standardized increasing output method (which we termed neothermia) based on retrospective data. Details of the method for increasing output have been reported previously (15). Briefly, group A included patients with a thickness of fat of the abdominal wall <16 mm, visceral fat area <100 cm^2 and total fat area <190 cm^2, and group B included patients with either one of the aforementioned factors. For patients in group A, the output was increased to 50 W/min, whereas patients in group B received 25 W/min. The operator started the output from 200 W and increased to 1,200 W until output limiting symptoms occurred and then decreased the output by 100 W. Most patients did not complain and continued the first RF thermal treatment. Subtracting 100 W output was judged as the optimal energy output dose without output limiting symptoms. From the second to fifth RF thermal treatment, this output was applied for 50 min. These principles were maintained in patients with neothermia in this prospective study.

Thermal output. A sensor catheter with 4 temperature points was placed in the rectum of 12 patients while it was attached to the skin on the lateral abdominal side, as well as in 39 patients who received neothermia and in 7 who did not. The accumulated thermal output was calculated from the estimated internal temperature of patients during the 50-min duration of each irradiation. An increased thermometric scale of the skin and the rectum was added to the pretreatment axillary temperature of the patients to obtain a hypothetical internal body temperature. Temperature and output curves were recorded at 1-min intervals from treatment initiation to completion (50 min).

Table I. Patient characteristics.

Characteristics	Data
Total no. of patients	51
Age (years)	
Median	62
Range	33-89
Gender, n (%)	
Female	13 (25.5)
Male	38 (74.5)
Stoma, n (%)	
(-)	41 (83.7)
(+)	8 (16.3)
Tumor location, n (%)	
Ra	5 (9.8)
Rb	30 (58.8)
RbP	15 (29.4)
P	1 (2.0)
Primary tumor, n (%)	
T2	9 (17.6)
T3	36 (70.6)
T4	6 (11.8)
Regional lymph node status, n (%)	
N(-)	30 (58.8)
N(+)	21 (41.2)
Distant metastasis, n (%)	
M0	46 (90.2)
M1	5 (9.8)
TNM stage[a], n (%)	
Stage 1	7 (13.7)
Stage 2	21 (41.2)
Stage 3	18 (35.3)
Stage 4	5 (9.8)
Tumor differentiation, n (%)	
Well differentiated	27 (52.9)
Moderately different	21 (41.2)
Poorly differentiated	3 (5.9)
A-V distance (cm)	
Median	3.0
Average (± SE)	2.70 (0.33)

[a]Pretreatment tumor staging was clinical, if available, by CT and MR.

RF output. Details of the HROC have been reported previously (15). Briefly, the total accumulated irradiation output (W/min) was classified into four groups: ≤26,000, 260,001-32,600, 32,601-39,500, and ≥39,501, as 1 point, 2 points, 3 points, and 4 points, respectively. The HROC was further classified into three groups: ≤9, 10-16, and ≥17 points, which were the sum of the five treatments.

Evaluation of objective response. All patients were evaluated according to the Response Evaluation Criteria in Solid

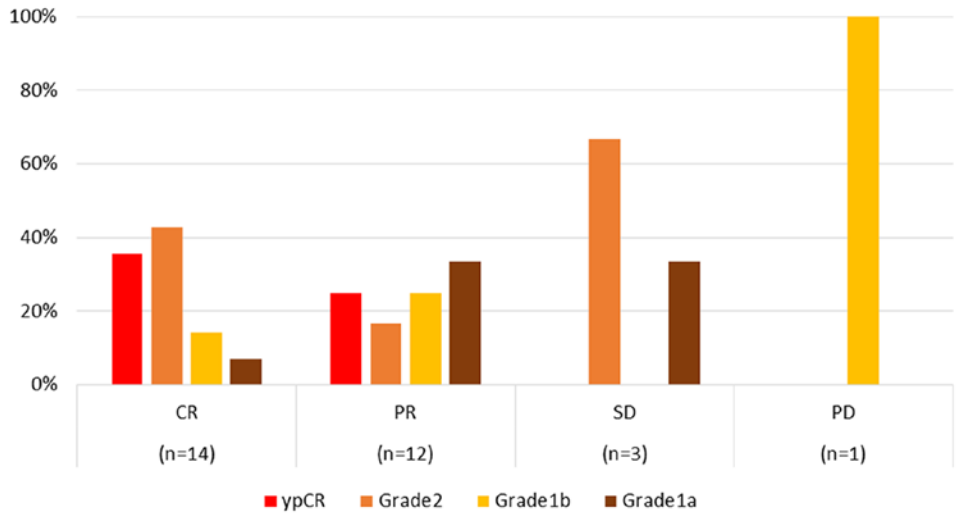


Figure 1. Discrepancies between clinical and histological objective responses. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ypCR, pathological complete response.

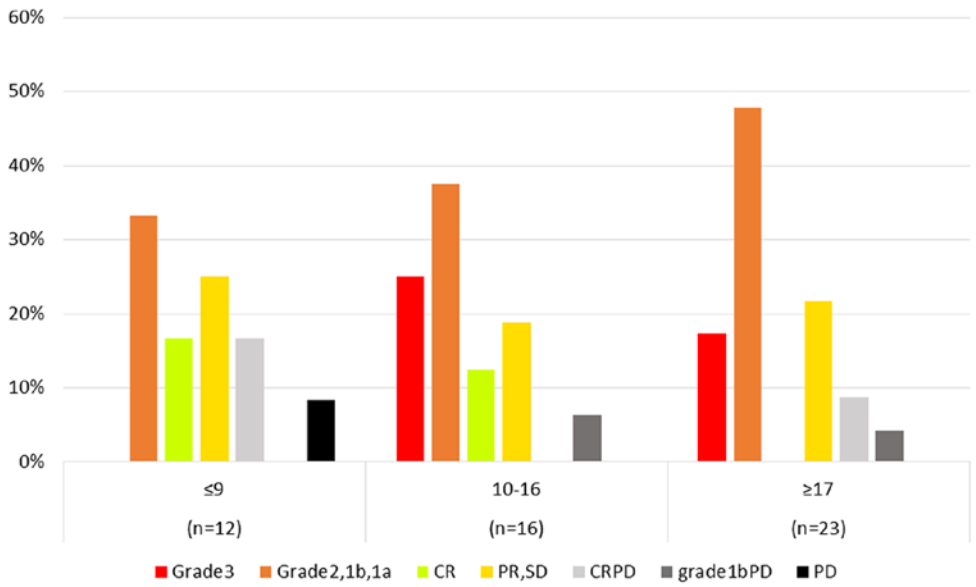


Figure 2. Results of the correlation between the objective response and the Hidaka RF output classification (HROC). CR, complete response; PR, partial response; SD, stable disease; CRPD, local CR but distant PD; PD, progressive disease. Grade; pathological complete response (pCR), grade 1bPD; local grade 1b but PD.

Tumors using MRI and PET/CT (16). Each resected specimen was examined for histological changes based on the histological criteria of the Japanese Classification of Colorectal Carcinoma. The CRPD group included patients in whom local tumors showed a complete response (CR), although new distant metastasis appeared. For the response assessment 8 weeks after HCRT, we evaluated CR as disappearance of the tumor on PET/CT and MRI and a positive to negative change in PET/CT. Adverse effects of these treatments were evaluated based on the criteria defined by the Common Terminology Criteria for Adverse Events (17).

Statistical analysis. SPSS Statistics (IBM, Armonk, NY, USA) version 21 was used to analyze all data. Mean values were compared using the Student's t-test. All reported p-values are two-tailed and were considered significant at $P<0.05$.

Results

Table I shows the patient characteristics. One patient had grade 3 perianal dermatitis. Only 2 patients with grade 2 disease wanted to decrease the dose of capecitabine (complete treatment, 96.1%). No output limiting symptoms were observed in 63.5% of the patients, whereas 30.2% suffered pain, and 2.0% had subcutaneous induration.

Good local control (ypCR + CR + CRPD) was observed in 32.7% of the patients in this study. Pathological complete response (ypCR) was observed in 15.7% of the total 51 patients and in 24.2% of the 33 patients who underwent surgery. Patients underwent surgery 8 weeks after HCRT. Abdominoperitoneal resection, lower anterior resection, intersphincteric resection, and partial resection were performed in 25, 43.7, 21.9, and 9.4% of the patients, respectively. One patient could

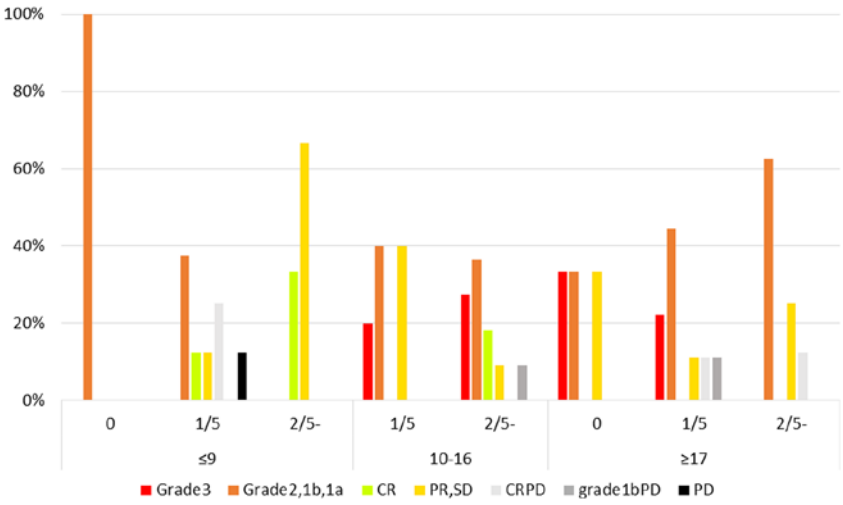
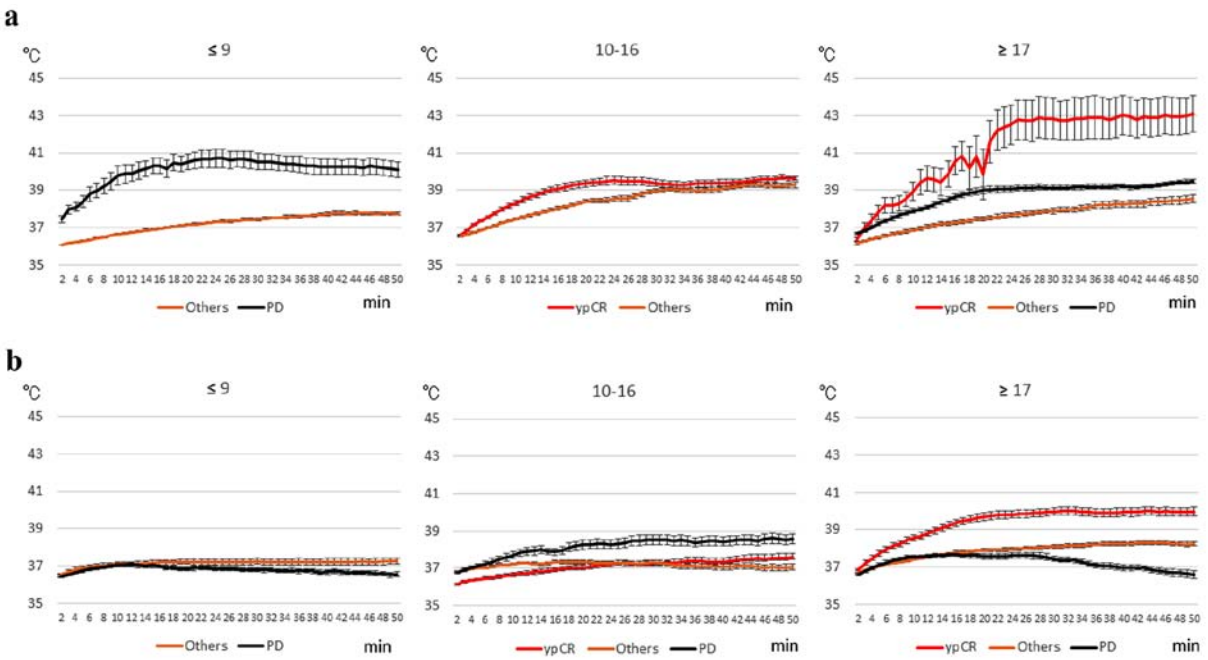


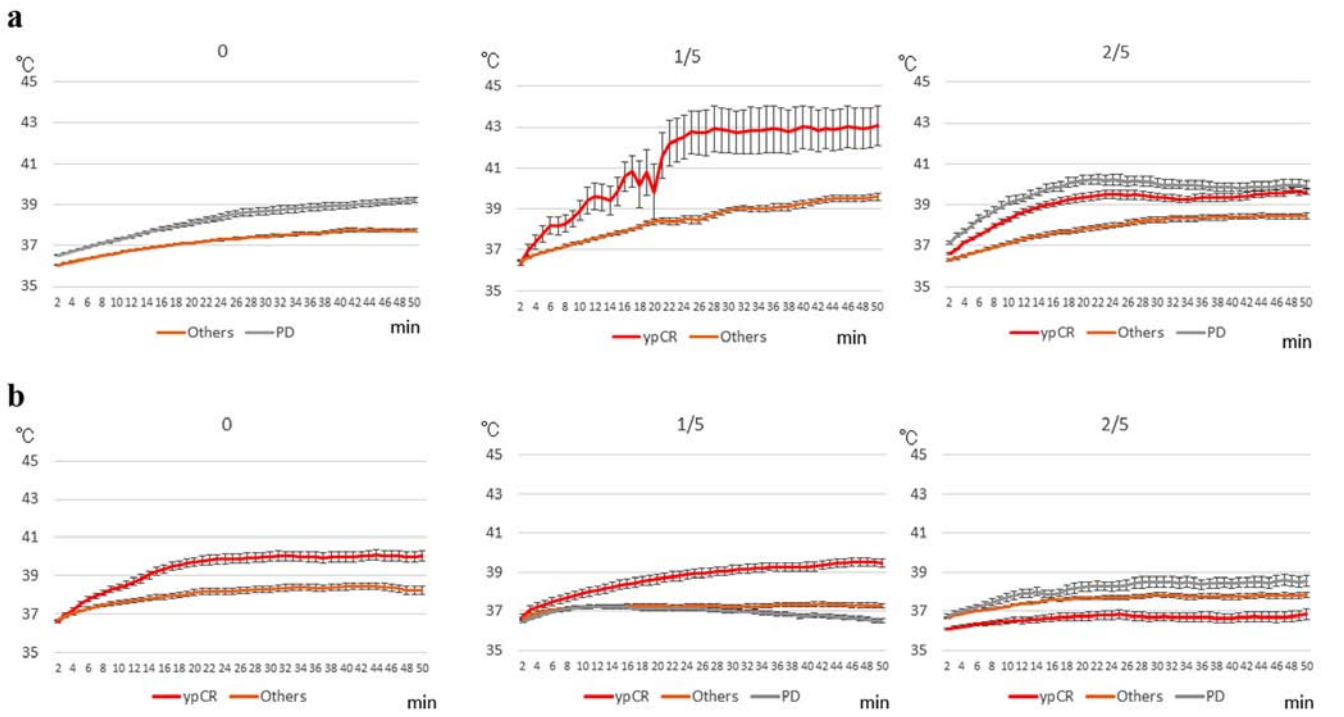
Figure 3. Results of the correlation among the objective response, the Hidaka RF output classification (HROC), and the incidence of output limiting symptoms. No output limiting symptoms, 1 output limiting symptoms, and ≥2 output limiting symptoms during the 5 thermal treatments are represented as 0, 1/5 and 2/5, respectively. CR, complete response; PR, partial response; SD, stable disease; CRPD, local CR but distant PD; PD, progressive disease. Grade; pathological complete response (pCR), grade 1bPD; local grade 1b but PD.



		Rectum	Time (min)	Skin	Time (min)
HROC	≤9	Others vs. PD	0-50	Others vs. PD	48-50
	10-16	ypCR vs. others	1-29	PD vs. ypCR	0-50
				PD vs. others	0-50
				ypCR vs. others	1-17
	≥17	ypCR vs. PD	0-50	ypCR vs. PD	0-50
		ypCR vs. others	0-50	ypCR vs. others	0-50
		Others vs. PD	0-50	Others vs. PD	31-50

Figure 4. Changes in rectal and skin temperatures during RF thermal treatment. (a) Rectal temperatures and (b) skin temperatures. Others: minor response [grade 2 + 1b + 1a + complete response (CR) + partial response (PR) + stable disease (SD)]. The results are presented as means ± standard errors. Significant differences were achieved (see table above) ($P<0.05$). PD, progressive disease; ypCR, pathological complete response.

not undergo resection of the primary tumor, and 5 patients could not undergo surgery due to progressive disease (PD); 13 (3 CR and 10 PR, SD) patients refused surgery mainly due to a permanent colostomy. Complete pathological response



		Rectum	Time (min)	Skin	Time (min)
Incidence of output limiting symptoms	0	PD vs. others	0-5	ypCR vs. others	0-50
	1/5	ypCR vs. others	0-50	ypCR vs. others	0-50
				ypCR vs. PD	0-50
				Others vs. PD	36-50
	2/5	PD vs. ypCR	1-34	PD vs. ypCR	0-50
		PD vs . others	0-50	PD vs. others	-
		ypCR vs. others	0-50	PD vs. others	8-15

Figure 5. Changes in rectal and skin temperatures during irradiation (50 min) based on the incidence of output limiting symptoms and the objective response. (a) Rectal temperatures and (b) skin temperatures. The results are presented as means ± standard errors. Significant differences were achieved (see table above) (P<0.05). PD, progressive disease; ypCR, pathological complete response.

(ypCR), grade 2, grade 1b, and grade 1a were observed in 25.0, 31.3, 21.9, and 18.8% of 32 patients, whose tumors were resected, respectively. Two patients with grade 1b showed PD. A change from T2 to T0 was observed in 66.7%, T3 to T2 and T0 in 69.4%, T4 to T2 and T3 in 50.0%, N(+) to yN(-) in 66.7%, and M0 to M1 in 8.7% of the patients.

Fig. 1 illustrates the discrepancies between clinical and histological responses; CR and partial response (PR) were observed in 35.7 and 25.0% of patients showing ypCR, respectively, whereas no ypCR was observed in patients with both stable disease (SD) and PD.

Fig. 2 illustrates the results of the correlation between objective response and the HROC. Eight patients with ypCR presented with ≥10 points, whereas 4 patients with PD also presented with ≥10 points. There was no patients with ypCR among those with ≤9 points in the HROC.

Fig. 3 shows the results of the correlation between objective response, the HROC, and the incidence of output limiting symptoms. Patients with ypCR either experienced output limiting symptoms or were free of output limiting symptoms. PD was not observed in patients with ≥17 points without output limiting symptoms, whereas ypCR was not observed in patients with ≤9 points. Three patients with PD (CRPD+grade 1bPD) and output limiting symptoms presented with ≥17 points.

Fig. 4 illustrates the changes in rectal (Fig. 4a) and skin (Fig. 4b) temperatures during RF thermal treatment for 50 min, based on the HROC and objective response. For ≤9 points, the rectal temperature of PD patients was increased significantly when compared with the rectal temperature of the others, while, skin temperature of the others was slightly increased. For 10-16 points, the rectal temperature of the ypCR patients was significantly increased when compared with the rectal temperature of the others, while, skin temperatures of the PD patients was significantly increased when compared with skin temperatures of patients with pyCR and others (P<0.05). In regards to ≥17 points, rectal and skin temperatures of the ypCR patients were significantly increased when compared with these temperatures of others and PD (P<0.05).

Fig. 5 shows the changes in rectal (Fig. 5a) and skin (Fig. 5b) temperatures during RF treatment for 50 min, based on the incidence of output limiting symptoms and objective response. In patients without output limiting symptoms, rectal temperature

of the PD patients was significantly increased than those of others, while skin temperature of the ypCR patients was significantly increased when compared with the skin temperature of the others (P<0.05). In patients who suffered output limiting symptoms once during the 5 treatments, both rectal and skin temperatures of the ypCR patients were significantly increased when compared with those of the other responses (P<0.05). However, in patients who experienced output limiting symptoms ≥2 times, both rectal and skin temperatures of the PD patients showed significantly higher temperature increases than those with others and ypCR (P<0.05).

Based on the results of Figs. 4 and 5, two types of patients were identified: patients with or without increased temperatures, and consequently, those who benefited or those who did not; and patients with or without increased temperatures in both the ypCR and PD groups, even though they received similar RF outputs.

Discussion

In this retrospective and prospective study, we aimed to establish a standardized protocol for RF hyperthermia safety, and 15.7, 7.8, and 7.8% of patients experienced ypCR, CR, and CRPD, respectively; 31.4 and 13.7% of patients showed good local control (ypCR + CR + CRPD) and PD (CRPD + grade 1b PD + PD), respectively. All ypCR cases had ≥10 points, while no ypCR patients presented with ≤9 points according to the HROC. We also demonstrated that there were two types of patients: patients with or without increased temperatures and who consequently received a benefit or not from treatment, even though they received similar RF outputs. Previously, we had reported that all patients with clinical CR showed significantly higher increases in temperatures than those with other responses, whereas in PR + SD patients the increase of temperature or not depended on whether the patients experienced any output limiting symptoms or not, and consequently, had good or poor outcomes (15). Our results indicate that increased temperatures correlate with the clinical response but not the histological response; increased temperatures served to control tumors but not kill tumor cells.

Randomized NART for rectal cancer showed a ypCR rate ranging from 13 to 20%, with grade 3 toxicity ranging from 6 to 25% (18). Oxaliplatin-based neoadjuvant chemotherapy resulted in an increase in ypCR rates and grade 3 toxicity (19-21). For rectal cancers, NART plus capecitabine showed a ypCR rate ranging from 6.7 to 31%, with grade 3 toxicity ranging from 5 to 15% (22). Capecitabine plus IRMT showed a ypCR ranging from 14.1 to 30.6%, with grade 3 toxicity ranging from 11.1 to x17.6% (23). Lu *et al* reported a ypCR rate of 20%, grade 3 toxicity of 22%, and PD rates of 17% (24). Whereas NACR showed superior local tumor control and higher rates of side effects than our results, most studies failed to report PD cases.

The correlation between the efficacy of hyperthermia and temperature has been reported (25). Based on our results and other reports of NART, the following two questions were raised: i) no ypCR was observed among patients with ≤9 points, and ii) ypCR patients did not have increased temperature, but had a good outcome. These questions may be pivotal in predicting the response to hyperthermia based on the control mechanism of a set point of core temperatures and thermoregulation in individual patients.

In this study, we analyzed skin temperature as a simple reproducible marker. Thermal control of skin temperature depended on a fundamental homeostatic function. Therefore, skin thermoregulation depends on the thermoregulatory center and thermoreceptors on the skin (26). Recently an association was observed between thermoregulation and the transient receptor potential (TRP) family; TRP vaniloid-1 was one of the important factors for thermoregulation and was activated at a noxious heat range (>43˚C) or at temperatures above 32˚C, and it was correlated with pain threshold (27-29). The correlation between the TRP family and thermal treatment will be considered in the future.

In conclusion, we proposed a standardization of RF thermal treatment safety. Neothermia with chemoradiation is a potential new treatment for rectal cancer; further studies on preventing output limiting symptoms and evaluating thermoregulatory control mechanisms in individual patients are needed in the future.

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