Chemoradiotherapy and concurrent radiofrequency thermal therapy to treat primary rectal cancer and prediction of treatment responses

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Abstract. The present study aimed to evaluate a previously reported predictive formula of output-limiting symptoms induced by radiofrequency (RF) to determine the efficacy of this neoadjuvant chemoradiation (NACR) and concurrent RF thermal therapy. The present study included 81 consecutive patients with confirmed diagnoses of rectal adenocarcinoma that was localized in the mid-low rectum (up to 12 cm from the anal verge) who received NACR [intensity-modulated radiotherapy (IMRT), 50 Gy/25 fractions, capecitabine 1,700 mg/m^2/day for 5 days/week)] with concurrent thermal therapy (Thermotron-RF8, once a week for 5 weeks with 50 min irradiation). Patients with progressive disease (PD) did not receive RF outputs higher than the predicted value. Some patients who were predicted to receive more output in fact received more than the predicted output. In patients who were predicted to receive moderately higher outputs, 37.5% of the patients experienced pathological complete responses, which was the highest rate, while in those who did not receive more than the predicted output, 66.7% of the patients experienced PD, which was the highest rate in the present study. We speculate that RF thermal therapy may offset the chemoradiation effects in some patients. Adding thermal therapy as a multimodality therapy to NACR potentially affects patients with lower predicted outputs and actual observed outputs slightly higher than the predictive value. Our predictive equation for initial energy output, in which output-limiting symptoms can be used to predict treatment efficacy, consequently, can be used to decide whether to continue this treatment modality.

Introduction

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. Numerous studies have shown that NACR increases local control of the tumor, but no effect on overall patient survival has been reported (1-6).

Conversely, recent studies have shown the benefits of NACR, including good pathological responses to therapy and increased rates of disease-specific and overall survival (7-15).

However, pathologic complete response (pCR) rates are reported to be only 10-29.3%, and more than one-third of patients do not respond to treatment. New strategies to achieve complete responses using multimodality neoadjuvant therapy are required for rectal cancer. Therefore, the present study aimed to establish new strategies that may increase the pCR rate for patients treated with NACR with concurrent thermal therapy.

Radiofrequency (RF) hyperthermia using the Thermotron-RF8 has been performed mainly in Japan; however, it has two major issues: i) this modality has not been approved as a standardized treatment in oncology since each hyperthermic treatment is not of the same quality; and ii) there are risks for fatal hot spot or thermal runaway phenomena, which are induced by the RF treatment itself (16,17).

As for the latter, we previously reported that a good predictive equation for initial energy output at which output-limiting symptoms occur was determined with two parameters: initial time of output-limiting symptom onset and abdominal wall fat thickness, using standardized power escalation principles (18). This formula had an adjusted R^2 of 0.99, and all variance inflation factor (VIF) values were <2. The initial energy output [initial RF output (IRO)] at which an output-limiting symptom

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occurred (Watt) = initial time at which an output-limiting symptom occurred (min) x 6.162 - abdominal wall fat thickness (mm) x 17.155 + 967.995; i.e., larger number of IRO means thinner thickness of the fat of the abdominal wall. In the present study, we considered 0 min as the initial time at which an output-limiting symptom occurred and compared it to the actual observed output.

The primary endpoint was toxicity and locoregional tumor control and the main objective of the present study was to identify pretreatment clinical parameters that predict pCR and progressive disease (PD). We retrospectively evaluated whether or not our predictive formula of output-limiting symptoms could predict pCR and PD at the beginning of this modality.

Materials and methods

The present study included 81 consecutive patients who were diagnosed with primary rectal adenocarcinoma localized in the rectum [up to 12 cm from the anal verge: The National Cancer Institute Rectal Cancer Focus Group has defined the rectum as anything remaining within 12 cm from the anal verge (19)] between December 2011 and May 2015. All patients received pre- and post-treatment diagnostic examinations, including computed tomography (CT), positron emission tomography/CT (PET/CT), and magnetic resonance imaging (MRI) at Hidaka Hospital. The tumor extent and location were classified according to the tumor-node-metastasis (TNM) staging (20).

All patients underwent NACR with concurrent thermal therapy at Hidaka Hospital. Surgeries were performed at the Department of General Surgical Science at Gunma University or the Division of Surgery at Hidaka Hospital. Each resected specimen was histologically evaluated in the Department of Pathology at Gunma University. The present study was approved by the Ethics Committees of Hidaka Hospital and Gunma University. Each patient provided written informed consent.

Chemoradiotherapy. Intensity-modulated radiotherapy (IMRT) was conventionally administered once daily 5 times/week using TomoTherapy® (Hi-Art® treatment system; Accuray®). For neoadjuvant radiotherapy, 50 Gy of radiotherapy was administered to the posterior pelvis in 25 2-Gy fractions. Concurrent neoadjuvant chemotherapy was administered in 5-day courses during the first through fifth week of NACR. Capecitabine (Cap) was administered orally at a dose of 1,700 mg/m²/day for 5 days/week. Patients received Cap throughout the radiation therapy course, beginning and ending on the first and last days of radiation therapy administration, respectively.

Thermal therapy. Thermal treatment was performed using the Thermotron-RF8 (Yamamoto Vinita Co., Ltd., Osaka, Japan) and administered once a week for 5 weeks during a 50-min irradiation. Precise thermal therapy methods have been previously described (18,21-23).

Objective response evaluation. The timing of objective response evaluations according to the Response Evaluation Criteria in Solid Tumors (RECIST) using MRI and PET/CT varied from weeks 2-18 after completion of NACR with concurrent thermal therapy, with a median time of 8 weeks (24). We classified patient responses as follows: complete response (CR), which describes total resolution of the lesions; partial response (PR), which describes a 30% decrease in the sum of the diameters of the lesions; stable disease (SD), which describes changes between a 30% decrease and 20% increase; and PD, which describes an increase of at least 20% in the sum of the diameters of the lesions or new distant metastasis. We evaluated CR as the disappearance of the tumor on PET/CT and MRI and a positive to negative change by PET/CT. The CRPD group included patients who experienced local CRs, although new distant metastases appeared. Adverse effects of these treatments were evaluated based on the criteria defined by the Common Terminology Criteria for Adverse Events (Ver.4.0) (25).

Pathology. Resected specimens (n=54) were evaluated according to the Japanese Classification of Colorectal Carcinoma. According to this criteria, pathological grade 0 tumors have no fibrosis. Grade 1 tumors exhibit denaturation and necrosis of cancer cells in approximately <1/3 of the tumor (grade 1a) or denaturation and necrosis in <2/3 of cancer cells plus fusion in >1/3 of the tumor (grade 1b). Grade 2 tumors exhibit significant denaturation, necrosis, fusion and loss in >2/3 of the tumor. In grade 3 tumors [pathological complete response (pCR)], no cancer cell is observed in both primary and regional lymph nodes (19). The pathological grade 1-0PD group included patients in whom local pathological grade 1 to 0 had resolved even though new distant metastases appeared.

Statistical analysis. SPSS Statistics (IBM, Armonk, NY, USA) version 21 was used to analyze all data. Mean values were compared using Student's t-tests. Categorical data were analyzed using the χ^2 test statistics. All reported P-values are two-tailed and were considered significant when P<0.05.

From the thickness of the fat of the abdominal wall (mm), IRO Watt and RO difference Watt at their first thermal treatment were determined using the formulas below as follows:

IRO (Watt) = 967.995 - abdominal wall fat thickness (mm) x 17.155

Average RO difference at the first thermal treatment (Watt/min) = average actual observed RO (Watt/min) at the first thermal treatment - IRO (Watt)

Average RO difference after treatment completion (Watt/min/5) = average actual observed RO (Watt/min) at treatment completion - IRO (Watt)

For predicted IRO, the quartiles were ≤635, 636 to 720, 721 to 792 and ≥793 Watt. For RO differences, the quartiles were ≤-153, -152 to -77, -76 to 76, and ≥77 Watt at the first thermal treatment and ≤-135, -134 to -32, -31 to 132 and ≥133 Watt after treatment completion.

Results

Table I contains the characteristics of the patients. Of the 81 consecutive patients, 56 received NACR with concurrent

Table I. Patient characteristics.

Patient characteristics	Data
Total no. of patients	81
Age (years)	
Median	62
Range	33-89
Gender, n (%)	
Female	20 (24.7)
Male	61 (75.3)
Distance to anal verge (cm), n (%)	
0-3.0	55 (67.9)
3.1-5.0	15 (18.5)
5.1-	11 (13.6)
Tumor location, n (%)	
Ra	10 (12.3)
Rb	46 (56.8)
RbP	25 (30.9)
Tumor stage, n (%)	
T2	20 (24.7)
T3	45 (55.6)
T4	16 (19.8)
Lymph node stage, n (%)	
N0	40 (49.4)
N1	38 (46.9)
N2	2 (2.5)
N3	1 (1.2)
Distant metastasis, n (%)	
M0	74 (91.4)
M1	7 (8.6)
Pretreatment TNM stage, n (%)	
Stage 1	12 (14.8)
Stage 2	24 (29.6)
Stage 3	38 (46.9)
Stage 4	7 (8.6)
Tumor differentiation, n (%)	
Well-differentiated	38 (46.9)
Moderately-differentiated	36 (44.4)
Poorly-differentiated	6 (7.4)
Undifferentiated	1 (1.2)
Type of surgery, n (%)	
APR Miles	12 (14.8)
ISR	7 (8.6)
sLAR	15 (18.5)
LAR	13 (16.0)
Local incision	6 (7.4)
Pelvic	1 (1.2)
No resection	2 (2.5)
No surgery	25 (30.9)

Table I. Continued.

Patient characteristics	Data
Clinical response after completion of treatment, n (%)	
CR	26 (32.1)
PR	32 (39.5)
SD	10 (12.3)
PD	13 (16.0)

TNM, tumor-node-metastasis; APR, abdominoperineal resection; LAR, low anterior resection; sLAR, super low anterior resection; ISR, intersphincteric resection; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

thermal therapy followed by surgery. In total, 54 tumors were resected and evaluated for pathological responses. Two patients did not have their tumors resected since the tumors were widespread, and 25 patients did not undergo surgery. Reasons for not undergoing surgery included the surgery itself after CR (n=4), permanent ostomy (n=7), poor general conditions (age and various complications; n=6) and PD (n=8), which included 3 lung metastases, 2 liver metastases, and growth of tumors or lymph nodes in 3 patients. The timing of surgical resections varied from 8 to 42 weeks after NACR and thermal therapy, with a median of 15 weeks after treatment completion. The median distance to the anal verge was 3.0 cm (range, 0-12 cm). We avoided permanent ostomy in 41/56 patients (73.2%).

Reduced tumor burden was achieved in 37/54 patients (68.5%), specifically in 10/15 patients (66.6%) with preoperative T2 lesions, 20/31 patients (64.5%) with T3 lesions and 7/8 patients (87.5%) with T4 lesions. Sixteen of the 54 patients (29.6%) had postoperative yT0 lesions.

NACR with concurrent thermal therapy was well-tolerated, with 96.3% of our patients receiving the full dose of chemotherapy and 100% receiving the full dose of radiotherapy and 5 cycles of thermal therapy. Sixty-three patients (77.8%) and 18 patients (22.2%) received thermal treatments with and without standardized power escalation principles, which we called neothermia, respectively (21).

In 81 tested patients, CR, PR, SD and PD with the RECIST criteria were shown in 32.1, 39.5, 12.3 and 16.0% of the patients, respectively (Table I). Table II displays the treatment response results for 81 patients with rectal cancer after completion of NACR with concurrent thermal therapy according to tumor stage, lymph node involvement, distant metastasis and pretreatment tumor-node-metastasis (TNM) stage. In 54 resected tumor samples, pCR grade 3, grade 2, grade 1-0, grade 1-0PD was found in 20.4, 37.0, 35.2 and 7.4% of the samples, respectively. The PD ratio included clinical PD and pathological grade 1-0PD. Five patients (25.0%) and 3 patients (15.0%) who were diagnosed with pretreatment T2 tumors achieved pCRs and CRs, respectively, while 1 patient (6.2%) with T4 tumor achieved CR. Four patients (33.3%), and 3 patients (25.0%) who were diagnosed with pretreatment pTNM stage 1 tumors achieved pCRs and CRs, respectively,

Table II. Treatment response results after completion of NACR with concurrent thermal therapy, according to tumor stages, lymph node involvement, distant metastasis and pretreatment TNM stages in 81 patients with rectal cancer.

	Grade 3	Grade 2	Grade 1-0	CR	PR-SD	PD	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	Total
T2	5 (25.0)	6 (30.0)	3 (15.0)	3 (15.0)	1 (5.0)	2 (10.0)	20
T3	6 (13.3)	11 (24.4)	12 (26.7)	1 (2.2)	7 (15.6)	8 (17.8)	45
T4	0 (0.0)	3 (18.8)	4 (25.0)	1 (6.2)	4 (25.0)	4 (25.0)	16
N-	8 (20.0)	12 (30.0)	6 (15.0)	4 (10.0)	6 (15.0)	4 (10.0)	40
N+	3 (7.3)	8 (19.5)	13 (31.7)	1 (2.4)	6 (14.6)	10 (24.4)	41
M(-)	11 (14.9)	19 (25.7)	18 (24.3)	5 (6.8)	12 (16.2)	9 (12.2)	74
M(+)	0 (0.0)	1 (14.3)	1 (14.3)	0 (0.0)	0 (0.0)	5 (71.4)	7
Stage 1	4 (33.3)	2 (16.7)	2 (16.7)	3 (25.0)	0 (0.0)	1 (8.3)	12
Stage 2	4 (16.7)	9 (37.5)	3 (12.5)	1 (4.2)	6 (25.0)	1 (4.2)	24
Stage 3	3 (7.9)	8 (21.1)	13 (34.2)	1 (2.6)	6 (15.8)	7 (18.4)	38
Stage 4	0 (0.0)	1 (14.3)	1 (14.3)	0 (0.0)	0 (0.0)	5 (71.4)	7
Total	11 (13.6)	20 (24.7)	19 (23.5)	5 (6.2)	12 (14.8)	14 (17.3)	81

NACR, neoadjuvant chemoradiation; TNM, tumor-node-metastasis, CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Table III. Results according to the frequency of RF-induced output-limiting symptoms.

Patients		Grade 3	Grade 2	Grade 1-0	CR	PR-SD	PD
Scores	N	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
0/5	8	2 (25.0)	1 (12.5)	2 (25.0)	0 (0.0)	2 (25.0)	1 (12.5)
1/5	38	6 (15.8)	8 (21.1)	10 (26.3)	2 (5.3)	6 (15.8)	6 (15.8)
2/5	15	2 (13.3)	3 (20.0)	2 (13.3)	2 (13.3)	3 (20.0)	3 (20.0)
3/5	6	0 (0.0)	3 (50.0)	1 (16.7)	0 (0.0)	1 (16.7)	1 (16.7)
4/5	11	1 (9.1)	4 (36.4)	2 (18.2)	1 (9.1)	1 (9.1)	2 (18.2)
5/5	3	0 (0.0)	1 (33.3)	1 (33.3)	0 (0.0)	0 (0.0)	1 (33.3)
Total	81	11 (13.6)	20 (24.7)	18 (22.2)	5 (6.2)	13 (16.0)	14 (17.3)

0/5, No output-limiting symptoms during the 5 thermal therapies; 5/5, output-limiting symptoms occurred during each thermal therapy. RF, radiofrequency; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

while 5 patients (71.4%) diagnosed with TNM stage 4 disease experienced PD.

Table III displays the treatment response results according to the frequency of RF-induced output-limiting symptoms during the 5 thermal treatments. Patients who scored 0/5 experienced no output-limiting symptoms during the thermal treatments, while those who scored 5/5 experienced output-limiting symptoms during each thermal treatment. The highest pCR rate (25.0%) was seen in patients who had no RF-induced output-limiting symptoms during the thermal treatments.

As for RF-induced output-limiting symptoms during thermal therapy, 69 patients (85.2%) experienced RF-induced output-limiting symptoms, with 54 of those (66.7%) experiencing pain, including 4 patients (4.9%) who stopped RF due to severe symptoms, 8 experiencing skin discomfort,

5 experiencing subcutaneous induration, 1 experiencing micturition desire and 1 experiencing cold sensations.

Table IV summarizes the toxicity incidence among the 81 patients. Grade 3 toxicities were observed in 7/81 patients (8.6%), with 1 patient experiencing palmar-plantar erythrodysesthesia syndrome, 3 experiencing anal mucositis, 2 experiencing diarrhea and 1 experiencing anemia.

Fig. 1 shows the treatment response results according to the predicted IRO (Watt) of output-limiting symptoms. The highest proportion of patients with grade 3 disease (21.2%) was in the upper quartile (≥793 Watt), followed by 15.0% in the lowest quartile (≤635 Watt).

Fig. 2 shows the average of the RO difference (Watt) (Fig. 2A) and the treatment responses at the first RF thermal therapy (Fig. 2B). There was a significant difference in the RO difference between patients with pathological grade 1-0PD

Table IV. Summary of the toxicity in response to NACR with concurrent thermal therapy in 81 patients.

Toxicities	Negative response (-) n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Total
Palmar-plantar erythrodysesthesia syndrome	20 (24.7)	46 (56.8)	14 (17.3)	1 (1.2)	81
Peripheral sensory neuropathy	66 (81.5)	15 (18.5)	0 (0.0)	0 (0.0)	81
Anal mucositis	14 (17.3)	33 (40.7)	31 (38.3)	3 (3.7)	81
Nausea	68 (84.0)	10 (12.3)	3 (3.7)	0 (0.0)	81
Anorexia	75 (92.6)	4 (4.9)	2 (2.5)	0 (0.0)	81
Diarrhea	32 (39.5)	40 (49.4)	7 (8.6)	2 (2.5)	81
Fatigue	76 (93.8)	5 (6.2)	0 (0.0)	0 (0.0)	81
White blood cell count decrease	58 (71.6)	11 (13.6)	12 (14.8)	0 (0.0)	81
Anemia	51 (63.0)	22 (27.2)	7 (8.6)	1 (1.2)	81
Platelet count decrease	64 (79.0)	16 (19.8)	1 (1.2)	0 (0.0)	81

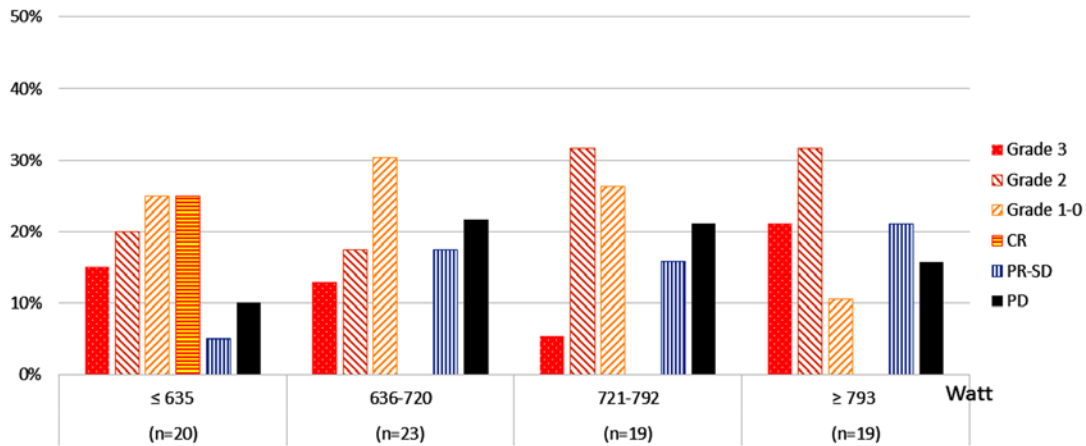NACR, neoadjuvant chemoradiation.

Figure 1. Treatment response results according to the predicted initial RF output (IRO) (Watt) of output-limiting symptoms.
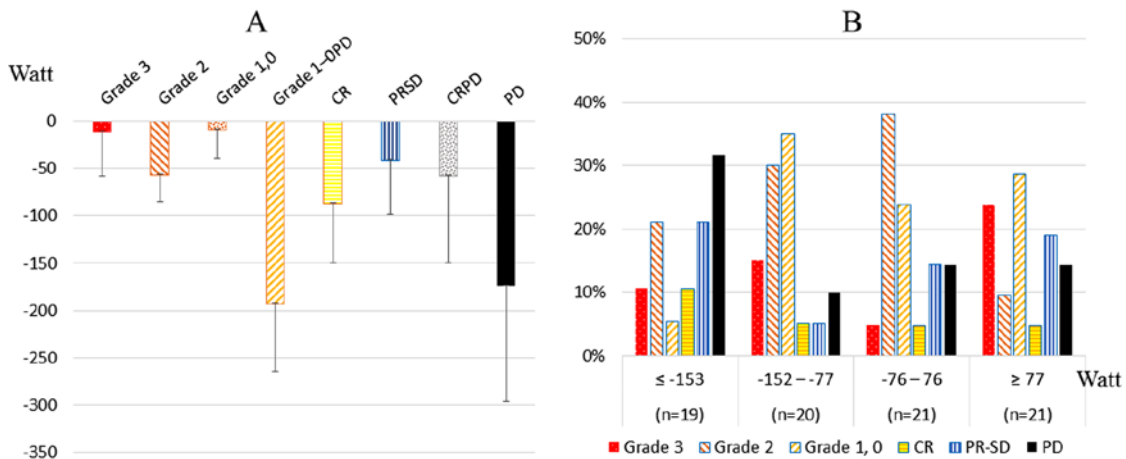

Figure 2. Average RO difference (Watt) and treatment response at the first radiofrequency (RF) thermal therapy. (A) Average RO difference. (B) Treatment response.

and grade 1-0 (p=0.021). All patients with PD had negative scores of RF outputs, as PD patients did not receive increased RF output over the predictive output. The highest proportion of patients with grade 3 disease (23.8%) was in the upper
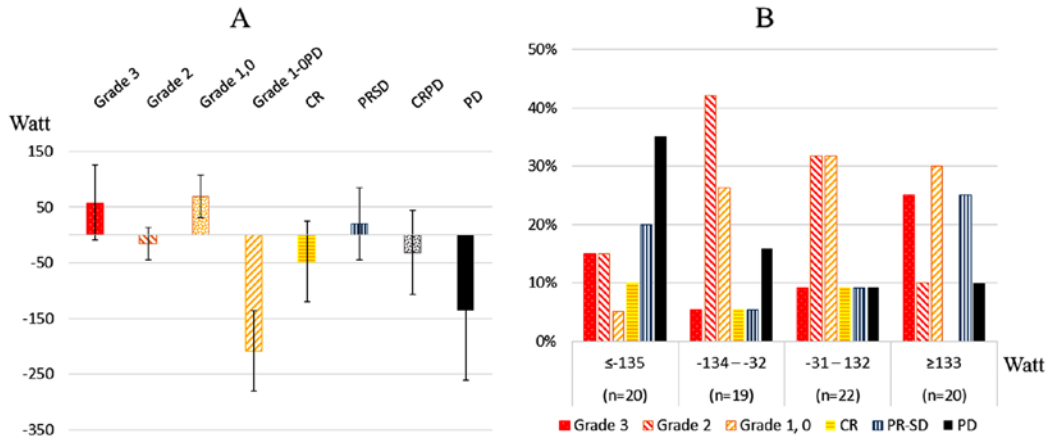
Figure 3. Average RO difference (Watt) and treatment response after the fifth thermal therapy. (A) Average RO difference. (B) Treatment response.
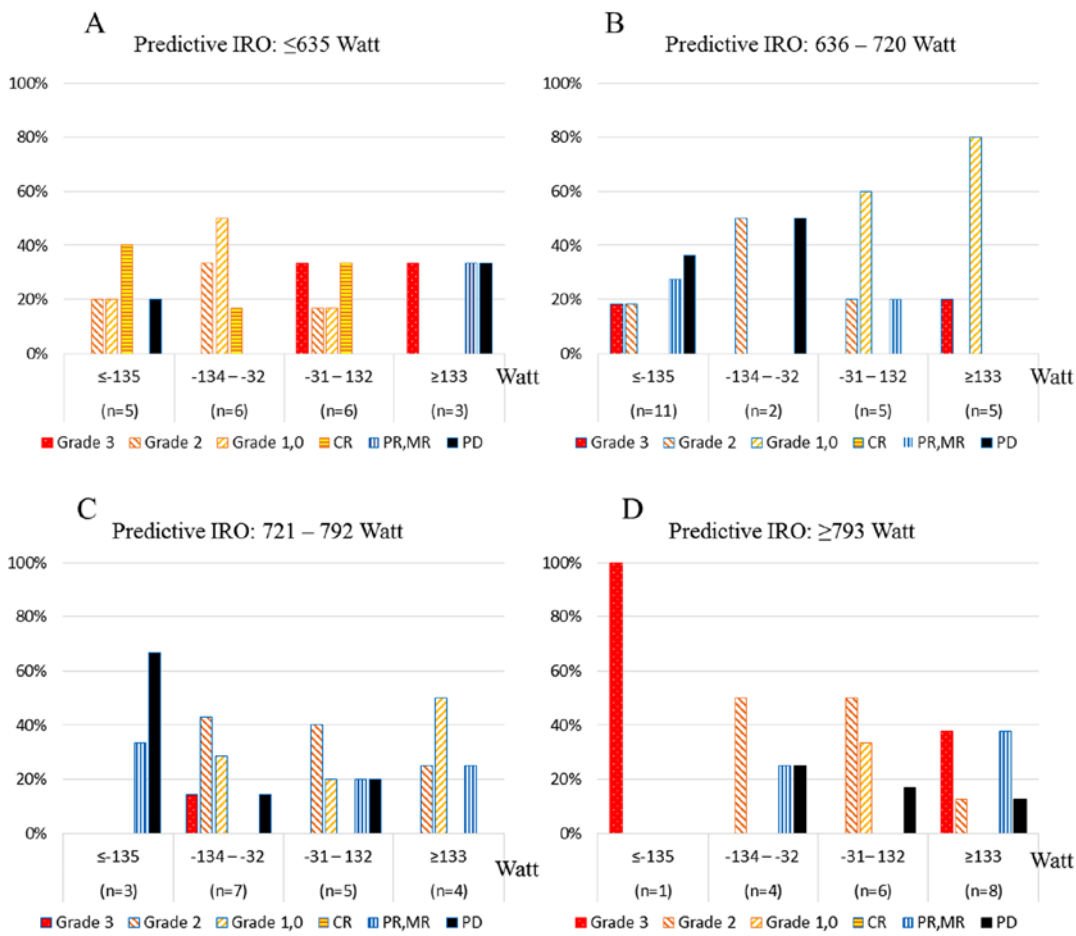

Figure 4. Correlations between predicted initial RF outputs (IROs) and the RO differences (Watt) or treatment responses after the fifth thermal therapy. (A) Predicted IRO, ≤635 Watt. (B) Predicted IRO, 636-720 Watt. (C) Predicted IRO: 721-792 Watt. (D) Predicted IRO, ≥793 Watt.

quartile (≥77 Watt) and the highest proportion of patients with PD (31.6%) was in the lowest quartile (≤-153 Watt).

Fig. 3 shows the average RO difference (Watt) (Fig. 3A) and treatment response after the fifth thermal treatment (Fig. 3B). There were significant differences between patients with grade 3, grade 2 and grade 1-0 disease and patients with pathological grade 1-0PD (p=0.046, p=0.016 and p=0.005, respectively). There was a weak relationship between patients with grade 3 disease and all patients with PD (p=0.054). The

highest proportion of patients with grade 3 disease (25.0%) was in the upper quartile (≥133 Watt), and the highest proportion of patients with PD (35.0%) was in the lowest quartile (≤-135 Watt).

Fig. 4 shows the correlations between both the predicted IRO and the RO difference (Watt) and treatment response after the fifth thermal treatment.

The highest proportion of patients with grade 3 disease (37.5%) were in the upper quartiles (predicted IRO ≥793 Watt
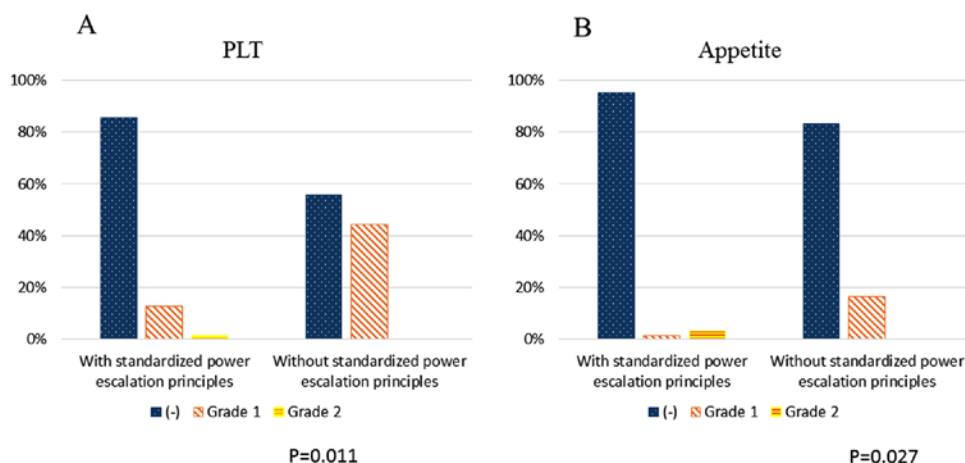
Figure 5. Toxicity (A) platelet count decrease and (B) anorexia in patients receiving thermal therapy with or without standardized power escalation principles.

and predicted IRO with ≥133 Watt) (Fig. 4D), and the highest proportion of patients with PD were in the predicted IRO 721-792 Watt quartile and the RO difference ≤-135 Watt quartile (Fig. 4C).

Fig. 5 shows the toxicities in patients receiving thermal treatment with or without standardized power escalation principles. There was no significant difference between patients who received treatments with or without standardized power escalation principles, with the exception of platelet (PLT) and anorexia, which patients who received treatment with standardized power escalation principles experienced with significant less frequency (p=0.011 and p=0.027, respectively).

Discussion

Although numerous studies support the use of capecitabine or infusional 5-FU, which are potentially radiosensitizing agents (26-28). as a standard of care in the neoadjuvant treatment of rectal cancer, the optimal preoperative chemotherapy regimen and radiation dose as a combined therapy for patients with rectal cancer are unknown. Recently, the National Surgical Adjuvant Breast and Bowel Project published its final study, in which the neoadjuvant Cap use was comparable to continuous 5-FU infusion when combined with radiation therapy (45 Gy/25 fractions) in 1,608 patients with stage II or III rectal cancer, and the addition of oxaliplatin (OXA) did not provide additional benefits with respect to toxicity (29,30). The reported pCR rate was 20.7% for patients receiving Cap (825 mg/m^2) 7 days a week beginning and ending on the first and last days of radiation therapy, respectively, which was similar to the rates in other studies (~15%) (2,3,15).

Craven *et al* reported results using similar regimens to the one described in the present study (radiation, 45 Gy/25 fractions; Cap, 900 mg/m^2 for 5 days/week vs. 7 days/week) in 70 patients with rectal cancer. The pCR and progressive disease (PD) rates were 9.2 and 6%, respectively. Sixty-two patients (88.6%) received the full dose of Cap without suffering significant grade 3 or 4 toxicities. Three patients (4.3%) had to discontinue Cap due to acute toxicities. Sixty-seven patients (96%) received the full 45-Gy dose of radiotherapy. Three patients (4.3%) suffered grade 3 diarrhea, while 1 patient developed severe abdominal pain and diarrhea.

Of the 65 patients who underwent resections, 33 were anterior resections, 26 were abdominoperineal resections, 5 were pelvic exenterations and in 33/64 (51.5%) the anus was preserved (31).

Gérard *et al* compared the Cap 45 group, which received 45 Gy/25 fractions with concurrent 800 mg/m^2 Cap twice daily 5 days/week, and the combined Cap and OXA group, which received 50 Gy/25 fractions with 800 mg/m^2 Cap twice daily 5 days/week and 50 mg/m^2 OXA once weekly. The present study of 597 patients with rectal cancer reported pCR rates of 13.9% for the Cap 45 group and 19.2% for the Cap + OXA group (32).

Positive outcomes due to IMRT plus Cap treatment have been observed, with pCR rates ranging from 14.1% to 30.6% in patients with grade 3 disease, who comprised 11.1% to 17.6% of the study populations (33-35), but these studies did not mention cases of PD. Lu *et al* (36) only reported a pCR in 20% of the cases with a 22% rate of grade 3 toxicity, and PD in 17% of the cases. Studies with controlled trials also did not mention PD. Thus, it is likely that PD cases were not analyzed in these studies.

To the best of our knowledge, Hernando-Requejo *et al* reported excellent pCR rates using the concomitant-boost IMRT dose fractionation scheme (35). Seventy-four patients were treated with concomitant-boost IMRT (57.5 Gy in 23 fractions and concurrent 825 mg/m^2 Cap bid), and the pCR and grade 3 toxicity rates were 30.6 and 17.6%, respectively.

Before the year 2000, there was no standardized thermal dose or standard hyperthermia treatment. Although the results were not comparable, the pCR rates were reported to range from 10 to 14%, in populations with 14% PD by adding hyperthermia to chemoradiotherapy in patients with rectal cancer (37,38). Since 2000, trials by the International Agency of Atomic Energy (IAAE) and Issels *et al* failed to show a synergistic effects between hyperthermia and radiotherapy (39-41).

Schroeder *et al* reported a retrospective study comparing neoadjuvant radiation with concurrent 5-FU-based chemotherapy with (n=61) and without (n=45) hyperthermia (90 min, 4-6 times) in 106 patients with rectal cancer, and pCR was achieved in 6.7% of the patients in the chemoradiation group and 16.4% of the patients in the hyperthermia group. The rate of sphincter-sparing surgery was 57% in the hyperthermo-radiochemotherapy group in comparison to

35% in the radiochemotherapy group, while, our rate of sphincter-sparing surgery was 73.2%. However, a total of 21 out of 61 patients (34.4%) discontinued hyperthermia within the first three treatments (42).

Maluta *et al* recently reported that hyperthermia plus chemoradiotherapy (200 mg/m^2 continuous 5-FU infusion for 6 weeks plus weekly 45 mg/m^2 OXA, and 50 Gy in 2-Gy fractions for 5 weeks plus a 10-Gy boost) resulted in pCRs for 18 out of 76 patients (23.6%), and 4/76 patients (5.2%) developed PD (43).

This series of patients receiving tumor resection and a 5-day/week schedule of Cap and radiotherapy with concurrent thermal therapy, shows higher compliance (96.3%), lower toxicity (8.6%), a better rate for preserving the anus (73.2%), better tumor burden (68.5%), and fairly good local control (20.4%) compared to previous studies.

We noticed that the rate of PD (17.3%) was higher than that of pCR in this series. Therefore, the specific patients who should be indicated to receive this therapy modality should be clarified. If we can discover or predict patients who received good outcomes using this treatment modality, this may add value in a clinical setting.

We reported that correlations between RF output and skin temperature from that RF output could be divided into three groups: low, median and high output, according to the occurrence of the output-limiting symptoms. From combination analyses of RF output and temperature output, patient temperature in the low RF output group did not increase. No patients achieved pCRs, and there was a high rate of PD. We think that these patients cannot respond to NACR with concurrent thermal therapy, and they possibly cannot respond to NACR alone. From these results and with the low pCR rate observed in these patients, additional and/or synergistic effects with NACR with concurrent thermal therapy were not observed. Consequently, the thermal therapy may offset the NACR effects in these patients. From our results, we found that patients with cT2, T3 and N0 lesions who were pretreated obtained good responses using this modality. However, those with T4, N(+) or M(+) lesions did not. This was similar to the results observed in other studies.

We also demonstrated in the present study that patients with PD actually could not receive higher RF outputs than the predicted output. We indicated the patient groups predicted to be able to receive more output that actually could receive more output than the predicted output as well as those who were predicted to receive lower to moderate output and could not receive more than the predicted output. The former group had a 37.5% pCR rate and the latter group had a 66.7% rate of PD. From previous and present data, we speculate that RF thermal therapy may offset the chemoradiation effects in patients who could receive more than the predicted output. Adding thermal therapy as a multimodality therapy to NACR has a potential filter effect on patients based on whether they experience potency with lower predicted outputs or higher predicted outputs as well as lower or higher RO differences. Thermal therapy, as a multidisciplinary therapy, may be used to evaluate patients that should be treated with NACR to determine whether they may experience true pCR or fallacious PD.

At present, unfortunately, we do not understand these mechanisms. One explanation for our results concerning the filter effects of RF thermal therapy is that RF thermal therapy and IMRT which provide electromagnetic treatment affect cancer cells with low energy and low-frequency waves (8-MHz) or high energy and high-frequency waves (>3x10^{19} Hz), respectively. Further study is needed to confirm these preliminary data in the future.

The need for suitable markers for the identification of patients who respond to cancer treatment is not limited to NACR with concurrent thermal therapy, and it is essential to reliably assess CRs and PD before or after completion of NACR treatment. Therefore, developing tools that predict responses has become exceedingly important, and a large number of studies have evaluated molecular parameters (44-46). To date, none have been validated in multi-institutional prospective trials. We may complete further studies to find suitable markers that may fit more with our predictive formula and offer more precise response to treatment assessments of this modality.

In conclusion, this treatment modality was beneficial for patients with T2, T3 and N0 rectal cancer in order to avoid permanent ostomy, and the predictive formula for output-limiting symptoms induced by RF is a good tool to predict CRs or PD. This formula may be able to identify patients in the clinical setting using chemoradiation treatment markers. These data suggest that RF with low/high output conditions, were correlated with output-limiting symptoms, which had a good or bad synergistic effect with chemoradiation regimens. Our predictive equation for the initial energy output at which output-limiting symptoms occur may also be able to use early assessment of treatment efficacy, and as a result, it can be used to decide on the continuation or cessation of this treatment modality.

The present study does have some limitations. We used a small sample size. Due to this, we did not have a group that received radiation therapy with concurrent Cap. We also did not perform long-term follow-up of the patients after therapy. Therefore, further studies should be performed to confirm these results.

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