Thermal Therapy as Multidisciplinary Therapy Applied to Rectal Cancer: A New Perspective and Potential Role of This Treatment

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Abstract: To avoid colostomy, we try to improve local control, i.e. to perform pathological complete response (pCR) by the neoadjuvant chemoradiation (NACR) with concurrent thermal therapy, falling into a so-called "wait-and-see policy". The aim of this study is examined whether the treatment response of NACR with concurrent thermal therapy for rectal cancer can be predicted after the treatment completion and we showed the changing history of our treatment protocol, current results of our study and a new perspective and potential role of thermal therapeutic approaches in patients with rectal cancer. In this study, 81 patients with rectal cancers (54 resected, M:F = 61:20, median age 63 years old (33-89), from December 2011 to May 2015) were received intensity-modulated radiotherapy (IMRT) (total dose 50 Gy/25 fractions) with capecitabine (1,700 mg/m²/day) for five weeks. Thermal therapy was performed using the Thermotron-RF 8, once a week for 5 weeks with 50 min irradiation. Clinical complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) were shown in 33.4%, 38.3%, 12.3%, and 16.0% of the patients, respectively. Patients with a gross tumor volume (GTV) ≤ 32 cm³ and a radiofrequency (RF) output difference (RO difference) ≥ 0 Watt/min exhibited the rates of pathological complete response (pCR) 42.9% and complete response (CR) 71.4%, and those with RO difference < 0 Watt/min, 23.1% and 92.3%, respectively. While, patients with a GTV ≥ 80 cm³ and a RO difference ≥ 0 Watt/min exhibited the rates of pCR and CR 23.1% and 30.8%, and those with RO difference < 0 Watt/min, 0% and 0%, respectively. Skin temperature significantly changed in patients with a pathological grade 3 tumor compared both to those who had PD and other outcomes, in the
difference RO $\geq 0$ Watt group ($p < 0.05$), but not in the difference RO $< 0$ Watt group. These data suggest that patients with a small tumor ($GTV \leq 32$ cm$^3$) and a difference RO $< 0$ Watt are enough to treat by NACR only and those with a large tumor ($GTV \geq 80$ cm$^3$) and a RO difference $\geq 0$ Watt by NACR with concurrent with thermal therapy.

**Key Words:** thermal therapy, rectal cancer, chemoradiation therapy, multidisciplinary therapy, new potential role

**Introduction**

Recent advances of understanding tumor biology and molecular drug development are leading us to new cancer therapies. 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 improved local tumor control, but has no effect on overall survival\(^1\).\(^-\)^\(^9\) New treatment strategies incorporating neoadjuvant therapy are required for rectal cancer.

Hyperthermia has been used for cancer treatment for long and is widely used in various medical fields in a clinical setting. In addition, many phase II or III trials of hyperthermia have demonstrated a significant improvement in the clinical outcome for tumors of the head and neck\(^9\), breast\(^9\), rectum\(^9\), lung\(^7\), esophagus\(^8\), and melanoma\(^9\) and sarcoma\(^10\). The biggest improvements have been reported in gynecological malignancies\(^11^-\)^\(^13\).

Randomized trials with positive results, as mentioned above, have been performed mainly in Asia, Russia, and Europe, although studies performed mainly in the USA have not shown positive results\(^14^-\)^\(^17\). Therefore, it has received less attention in the oncological community of North America, and then the era of cancer hyperthermia therapy in gastrointestinal cancers is still in an inchoate stage.

We suppose that there may be an ethnic or haplotype of difference in the effect of hyperthermia \textit{[i.e. different response to heat/radiofrequency (RF)]} on cancers as is seen in other modalities.

This modality has had two major issues: (1) this has not been approved as a standardized treatment in oncology because each hyperthermic treatment is not stable, reproducible treatment i.e. the different quality of each thermic treatment, being difficult to perform multicenter studies and (2) there are risks for fatal hot spot phenomena, which are induced by the RF treatment itself, which could not increase and continue ideal RF output\(^18\)^\(^,\)^\(^19\). For these reasons, this treatment also has not been recognized as a standard oncological treatment worldwide.

As for the former, we used a treatment with standardized power escalation principles, each treatment had been of the same quality\(^20^-\)^\(^22\), improving the heating quality.

As for the latter, we reported previously that a good predictive equation for initial energy output at which output-limiting symptoms (OLS) occur was determined with two parameters: initial time of OLS onset and abdominal wall fat thickness, by using standardized power escalation principles\(^22\). This formula had an adjusted $R^2$ of 0.99, and all variance inflation factor (VIF) values were less than 2. The initial energy
output (initial RF output (IRO)) at which an OLS occurred (Watt) = initial time at which an OLS occurred (min) × 6.162 – abdominal wall fat thickness (mm) × 17.155 + 967.995; i.e. larger number of IRO means thinner thickness of the fat of the abdominal wall.

If power limiting hot spots are prevented, this makes high quality hyperthermia of utmost importance, resulting in significant improvements in treatment quality.

Here we show our history of thermal therapy and current results of our study and a new perspective and potential role of thermal therapeutic approaches in patients with rectal cancer.

Materials and Methods

Our study team started to treat rectal cancer by using radiotherapy from 1991 at (Department of Surgery, Gunma University), and had minor changes of protocol, and to perform to CRT with concurrent thermal therapy using Thermontron-RF8 (Yamamoto Vinita Co., Ltd., Osaka, Japan) from 1994 (Table I)23).

Table I. Historical change of treatment for rectal cancer.

| Year | Radiotherapy | Hyperthermia (/week) | Chemotherapy |
|------|--------------|----------------------|--------------|
|      | Total dose (Gy) | Daily (Gy) | Fraction |                      |
| 1991 | 30.6 | 1.8 | 17 | – | – |
| 1994 | 40 | 2 | 20 | 2 | 5FU+1-LV |
| 2002 | 50 | 25 | 5 | 2004 | 5FU+1-LV |
| 2006 | 50 | – | 3 | | |
| 2011 | 50 | – | 5 | | |

Fig. 1 shows our present protocol for rectal cancer. Between December

Hyperthermic chemoradiotherapy (HCRT)

Pre-treatment Examination

CT
MRI
PET/CT

Chemotherapy

Radiotherapy

Hyperthermia

Neothermia(-)

Neothermia(+)

Objective Response

CT
MRI
PET/CT

Resected Specimens

C: Oral administration of capecitabine 1700 mg/m²/day, 5 days/week for 5 times
R: Intensity-modulated radiotherapy (IMRT), 5 times weekly at a dose of 50 Gy/25 times
H: Five thermotherapies, once a week with 8 MHz radiofrequency capacitive heating equipment.

Fig. 1. Present protocol for rectal cancer.
2011 and May 2015, consecutive series of 81 patients with primary rectal adenocarcinoma localized in the rectum (up to 12 cm from the anal verge) (median age 62 with range 33-89, Female: Male = 20:61) were included in this study. Of these patients, 54 patients received surgery and were evaluated pathological response. Two patients did not resect because of widespread tumors and 25 did not undergo surgery; 4 because of clinical complete response (CR), 7 because of permanent ostomy, 6 because of poor general conditions (age and various complications) and 8 because of clinical progressive disease (PD); 3 lung metastases, 2 liver metastases and 3 growth of primary tumors or lymph nodes.

All patients received pre- and post-treatment diagnostic examinations, including computed tomography (CT), 18F-fluorodeoxyglucose (FDG) positron emission tomography/CT (18F-FDG 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 staging24).

All patients underwent NACR with concurrent thermal therapy at Hidaka hospital. Operations were performed at the Department of General Surgical Science, Gunma University, or at the Division of Surgery, Hidaka hospital.

The gross tumor volume (GTV) was contoured using the Focal Treatment Planning System (Focal, Eindhoven, Netherlands), taking into consideration clinical information from imaging modalities to identify the primary rectal tumor and enlarged regional lymph nodes. The clinical target volume (CTV) included the GTV plus a 15-mm margin in the anterior, posterior, and lateral directions and a 25-mm margin in the craniocaudal direction in addition to the entire mesorectum and internal iliac and presacral nodes. The cranial border was S2/3 interspace in order to reduce the irradiated small bowel volume. On the basis of our institutional setup data, the planning target volume (PTV) was determined by adding a 3-mm margin around the CTV.

Intensity-modulated radiotherapy (IMRT) was administered conventionally, once daily, 5 times/week using TomoTherapy® (Hi-Art® Treatment System, ACCURAY®, Sunnyvale, CA, USA) and neoadjuvant radiotherapy of 50 Gy delivered to the PTV in 25 fractions. The small intestines, bladder, and bilateral femur were contoured and defined as organs at risk (OAR). IMRT treatment plans were required to cover $\geq 98\%$ of the PTV with $\geq 45$ Gy, not delivering $\geq 52.5$ Gy to $15\%$ of the PTV, and not delivering $\geq 55$ Gy to $10\%$ of the PTV.

All patients receiving intersphincteric resection (ISR) were performed temporary ileostomy at surgery. Distance to anal verge mainly defined by digital examination, colonoscopy and MRI, and tumor location by the colonography, CT or PET/CT and MRI. Ra was defined from inferior level of second sacral vertebrae to inferior level of middle Houston’s valve, Rb from inferior level of middle Houston valve (Kohlrausch’s fold) (i.e. inferior reflection of the peritoneum) to the level of the puborectalis portion of the levator ani muscle, or the dentate line and RbP + Anal from the dentate line to the anal verge.

The study was approved by the ethics committees of the Hidaka hospital and Gunma University (No. 1143). Each patient gave written informed consent.

Evaluation of objective response

The timing of evaluation of objective response varied from weeks 2 to 18 with a median 8 weeks after completion of NACR with concurrent thermal therapy according to the response evaluation criteria in solid
tumors (RECIST) using MRI and CT or PET/CT\textsuperscript{25}. The timing of surgical resection varied from weeks 9 to 43 with a median of 16 weeks after completion of treatment.

Each resected specimen was evaluated histologically at the Department of Pathology, Gunma University according to the Japanese Classification of Colorectal Carcinoma\textsuperscript{24}. Tumor stages were defined with the combination of colonoscopy, barium enema, CT or \textsuperscript{18}F-FDG PET/CT, and MRI.

Statistics

SPSS Statistics (IBM, Armonk, NY, USA) version 21 was used to analyze all data. Mean values were compared using the Student’s t-test. The categorical data were analyzed using the $\chi^2$-test statistics. All reported P values are two-tailed and were considered significant if $P < 0.05$.

Thermal therapy

Thermic treatment was performed using the Thermotron-RF8 once a week for 5 weeks each with 50 min irradiation. Precise methods of thermal therapy were described elsewhere\textsuperscript{20-22}.

A sensor catheter with four temperature points was attached to the skin on the lateral abdomen of 68 patients. The average surface skin temperature of the four temperature points during each irradiation was measured to calculate the average surface skin temperature of the five thermal treatments. The skin temperature evaluated as a change of an increased thermometric scale of the skin temperature from before RF treatment.

Results

History of HCRT at Department of Surgery, Gunma University

There were a little bit change of the doses of Radiation, chemotherapy regimens, and the frequency of the thermic treatments using Thermotron-RF8. Table II shows our historical changes of strategies and outcomes for rectal cancer. We had performed phase 2 trial (HCR 1101 for Stage II-IVA) in Department of Surgery Gunma University and Hidaka hospital from 2011 to 2014 and are now performing multi-institutional study (Hidaka hospital, Department of Digestive Tract and General Surgery, Saitama Medical University, Department of Gastroenterological Surgery, Gunma Prefectural Cancer Center, Department of General Surgical Science, Gunma University Graduate School of Medicine, Department of Surgery I, Dokkyo Medical University) from 2014 to 2016 (OCD1401 for T3N(+)T2 of lower part of tumor).

| Year | Preoperative treatment | Surgery | Preserving anus |
|------|-------------------------|---------|-----------------|
| 1991 | RT ± intra cavity       | TME     | 33.3\%          |
| 1996 | RT + HT                | ANPS    | 50.0\%          |
| 2002 | RT(40 Gy) + HT, NCI    | ANPS    | 71.0\%          |
| 2006 | RT(50 Gy) + HT, NCI    | ISR     | 90.2\%          |
| 2011 | RT(50 Gy) + HT, Cap    | ISR     | 78.0\%          |
| Author (2011-2015) | IMRT(50 Gy), Cap | ISR | 41/54 = 75.9\% |

RT: radiation, HT: hyperthermia, NCI: night continuous infusion, Cap: Capecitabine, IMRT: intensity-modulated radiotherapy, TME: total mesorectal excision, ANPS: autonomic nerve preserving surgery, ISR: intersphincteric resection.
Standarization of thermic treatment, prediction of OLS induced RF, and difference radiofrequency output (RO difference) after treatment completion

To perform the same quality of thermic treatment of 5 each hyperthermic treatments, we used a treatment with standardized power escalation principles (we called this neothermia). Precise methods of thermal therapy were described elsewhere\(^2\). Fig. 2 shows the typical examples of the actual ROs (Watt) and temperatures (Y axis) during 50 min RF treatment (X axis) before and after neothermia. Fig.3 shows the average RO

**Before standardization**

**After standardized power escalation principles (Neo-thermia)**

![Fig. 2. Typical example of the actual ROs (Watt) and temperatures (Y axis) during 50 min RF treatment (X axis) before and after neothermia.
Y axis: ROs (Watt) (columns) and temperatures (lines), X axis: time of RF treatment.]

![Average Watt/treatment](average_watt.png)

![Fig. 3. Average RO (Watt/treatment) during 50 min RF treatment of the five RF treatment sessions before (thick columns) and after neothermia (thin columns).](average_watt.png)
during 50 min RF treatment before and after neothermia.

When we use the formula mentioned above, we considered 0 min as the initial time at which an output-limiting symptom occurred (predicted initial radiofrequency output [predicted IRO]). In this study the RO difference after treatment completion (Watt/min) is as follows: RO difference (Watt/min) = average actual observed RO (Watt/min) at treatment completion — predicted IRO (Watt).

**OLS and toxicity**

This 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 with 5 times thermal therapy. Grade 3 toxicities were shown in 8.8% patients with one palmar plantar erythrodysesthesia syndrome, 3 anal mucositis, 2 diarrhea and one anemia. RF-induced OLSs were experienced in 85.2% patients, experiencing pain 66.7%, including 5 patients who experienced subcutaneous induration.

Fig. 4 shows the incidence of output-limiting symptoms during the five RF treatment sessions before and after standardized thermic treatment. There was no significant difference in patients between with and without neotherma.

**Fig. 4.** Incidence of output-limiting symptoms during the five RF treatment sessions before and after neothermia.
Clinical outcomes

Table III shows the characteristics of the 81 patients. Patients with permanent colostomies and those without permanent colostomies made up 24.1% and 75.9%, respectively, of the patients in this study. Only one patient receiving pelvic exenteration had an abscess in the pelvic cavity after surgery.

| Total No. of patients | 81 (%) |
|-----------------------|--------|
| **Age-yr** | | |
| Median | 62 |
| Range | 33-89 |
| **Gender-no. (%)** | | |
| F | 20 (24.7%) |
| M | 61 (75.3%) |
| **Distance to anal verge-no. (%)** | | |
| 0-3.0 cm | 55 (67.90%) |
| 3.1-5.0 | 15 (18.50%) |
| 5.1- | 11 (13.60%) |
| **Tumor location-no. (%)** | | |
| Ra | 10 (12.3%) |
| Rb | 46 (56.8%) |
| RbP | 25 (30.9%) |
| **Tumor stage-no. (%)** | | |
| T2 | 20 (24.7%) |
| T3 | 45 (55.6%) |
| T4 | 16 (19.8%) |
| **Lymph node stage-no. (%)** | | |
| N0 | 40 (49.4%) |
| N1 | 38 (46.9%) |
| N2 | 2 (2.5%) |
| N3 | 1 (1.2%) |
| **Distant metastasis-no. (%)** | | |
| M(−) | 74 (91.4%) |
| M(+) | 7 (8.6%) |
| **Pretreatment TNM stage-no. (%)** | | |
| Stage 1 | 12 (14.8%) |
| Stage 2 | 24 (29.6%) |
| Stage 3 | 38 (46.9%) |
| Stage 4 | 7 (8.6%) |
| **Tumor differentiation-no. (%)** | | |
| Well differentiated | 38 (46.9%) |
| Moderately differentiated | 36 (44.4%) |
| Poorly differentiated | 6 (7.4%) |
| Undifferentiated | 1 (1.2%) |
| **Type of surgery-no. (%)** | | |
| Pelvic exenteration | 1 (1.2%) |
| APR | 12 (14.8%) |
| LAR | 13 (16.0%) |
| sLAR | 15 (18.5%) |
| ISR | 7 (8.6%) |
| local incision | 6 (7.4%) |
| No resection | 2 (2.5%) |
| No surgery | 25 (30.9%) |

ISR: intersphincteric resection, sLAR: super low anterior resection, LAR: low anterior resection, APR: abdominoperineal resection.
Table IV shows the results of the treatment response in correlation to neothermia and the incidence of OLSs. In 81 tested patients, CR, partial response (PR), stable disease (SD), and PD were shown in 30.9%, 39.5%, 12.3%, and 17.3% of the patients, respectively. Consequently, 11, 20, 19, 14, and 12 patients were pCR (i.e., grade 3), grade 2, grade 1-0 in resection and CR, PR-SD in no resection, respectively. There was no significant difference in neothermia and the incidence of OLS among objective response.

Table V shows the results of treatment response in correlation to GTV and RO difference.

Patients with a gross tumor volume (GTV) ≤ 32 cm³ and a radiofrequency (RF) output difference (RO difference) ≥ 0 Watt/min exhibited the rates of pathological complete response (pCR) 42.9% and complete response (CR) 71.4%, and those with RO difference < 0 Watt/min, 23.1% and 92.3%, respectively. While, patients with a GTV ≥ 80 cm³ and a RO difference ≥ 0 Watt/min exhibited the rates of pCR and CR 23.1% and 30.8%, and those with RO difference < 0 Watt/min, 0% and 0%, respectively.

There were significant differences according to RECIST ($\chi^2 = 34.102, p < 0.001$) in patients with RO difference < 0 Watt/min, but not in those with ≥ 0 Watt/min.

### Table IV. Results of treatment response in correlation to neothermia and the incidence of OLSs.

| Neothermia (+) | Neothermia (−) | Incidence of output limiting symptoms | Total |
|---------------|---------------|--------------------------------------|-------|
|               |               | 0/5 | 1/5 | 2/5 | 3/5 | 4/5 | 5/5 |       |
| Total No. of patients | 63 (100%) | 18 (100%) | 8 (100%) | 38 (100%) | 14 (100%) | 7 (100%) | 11 (100%) | 3 (100%) | 81 (100%) |
| RECIST CR      | 16 (25.4%) | 9 (50.0%) | 3 (37.5%) | 9 (23.7%) | 4 (28.6%) | 2 (28.6%) | 5 (45.5%) | 2 (66.7%) | 25 (30.9%) |
| PR             | 27 (42.9%) | 5 (27.8%) | 2 (25.0%) | 19 (50.0%) | 6 (42.9%) | 4 (57.1%) | 1 (9.1%) | 0 (0.0%) | 32 (39.5%) |
| SD             | 9 (14.3%) | 1 (5.6%) | 2 (25.0%) | 4 (10.5%) | 1 (7.1%) | 0 (0.0%) | 3 (27.3%) | 0 (0.0%) | 12 (14.8%) |
| PD             | 11 (17.5%) | 3 (16.7%) | 1 (12.5%) | 6 (15.8%) | 3 (21.4%) | 1 (14.3%) | 2 (18.2%) | 1 (33.3%) | 14 (17.3%) |

Resection* Grade3 CR: 8 (12.7%) | 3 (16.7%) | 2 (25.0%) | 6 (15.8%) | 2 (14.3%) | 0 (0.0%) | 1 (9.1%) | 0 (0.0%) | 11 (13.6%) |
| Grade2         | 16 (25.4%) | 4 (22.2%) | 1 (12.5%) | 8 (21.1%) | 2 (14.3%) | 4 (57.1%) | 4 (36.4%) | 1 (33.3%) | 20 (24.7%) |
| Grade1-0       | 15 (23.8%) | 4 (22.2%) | 2 (25.0%) | 10 (26.3%) | 3 (21.4%) | 1 (14.3%) | 2 (18.2%) | 1 (33.3%) | 19 (23.5%) |
| No resection   | CR: 3 (4.8%) | 2 (11.1%) | 1 (12.5%) | 6 (15.8%) | 3 (21.4%) | 1 (14.3%) | 2 (18.2%) | 1 (33.3%) | 14 (17.3%) |
| PR-SD          | 10 (15.9%) | 2 (11.1%) | 2 (25.0%) | 6 (14.3%) | 2 (18.2%) | 1 (14.3%) | 1 (33.3%) | 0 (0.0%) | 12 (14.8%) |

*: excluded PD

### Table V. Results of treatment response in correlation to GTV and RO difference.

| GTV                | < 0 Watt/min | 33-79 cm³ | ≥ 80 cm³ | Total |
|--------------------|--------------|-----------|----------|-------|
| Total No. of patients | 13 (100%) | 22 (100%) | 7 (100%) | 42 (100%) |
| RECIST CR           | 12 (92.3%) | 1 (4.5%) | 0 (0.0%) | 13 (31.0%) |
| PR                 | 1 (7.7%) | 9 (40.9%) | 4 (57.1%) | 14 (33.3%) |
| SD                 | 0 (0.0%) | 3 (13.6%) | 1 (14.3%) | 4 (9.5%) |
| PD                 | 0 (0.0%) | 9 (40.9%) | 2 (28.6%) | 11 (26.2%) |

Resection* Grade3 CR: 3 (23.1%) | 1 (4.5%) | 0 (0.0%) | 4 (9.5%) | 3 (23.1%) | 1 (5.6%) | 3 (23.1%) | 7 (18.4%) |
| Grade2             | 6 (46.2%) | 5 (22.7%) | 2 (28.6%) | 13 (31.0%) |
| Grade1-0           | 1 (7.7%) | 3 (13.6%) | 2 (28.6%) | 6 (14.3%) |

No resection CR: 3 (25.1%) | 0 (0.0%) | 0 (0.0%) | 3 (7.1%) | 2 (28.6%) | 0 (0.0%) | 0 (0.0%) | 2 (5.3%) |
| PR-SD              | 0 (0.0%) | 4 (18.2%) | 1 (14.3%) | 5 (11.9%) | 0 (0.0%) | 4 (22.2%) | 3 (23.1%) | 7 (18.4%) |

*: excluded PD
Fig. 5 shows the changes in the surface skin temperature in comparison to before RF treatment during the 50 min irradiation. Skin temperature significantly changed in patients with a pathological grade 3 tumor compared both to those who had PD and other outcomes, in the difference $\Delta \text{RO} \geq 0 \text{ Watt} \cdot \text{min}$ group ($p < 0.05$) (B), but not in the difference $\Delta \text{RO} < 0 \text{ Watt} \cdot \text{min}$ group (A).

The study demonstrated that patients who will respond well to RCT with concurrent with thermal therapy can be predict, as well as RCT from the evaluation of the consecutive series of rectal cancer patients who treated with the almost full dose of the same radio- (IMRT 50 Gy) and chemotherapy (Cap) with 5 times thermal therapy. This is the first report to demonstrate that tumor response can be predicted just after treatment complete in comparing a predicted IRO to an actual RO of the five RF treatment sessions.

Recently, there were many reviews about hyperthermia randomized trials and indicated that it can enhance the efficacy of both radiotherapy and chemotherapy, and also many non- and randomized clinical trials have demonstrated the significant improvement in clinical outcome from adding hyperthermia to standard treatment regimens of radiation and/or chemotherapy.

Maluta, et al. reported that hyperthermia along with 5-fluorouracil (5-FU) 200 mg/m$^2$ continuous infusion...
for 6 weeks plus weekly oxaliplatin (OXA) at 45 mg/m², and 50 Gy with 2-Gy fractions for 5 weeks, along with a 10-Gy boost, resulted in pCR for 23.6% patients, and 5.2% showed PD. The percentage of sphincter preservation amongst the patients was 73.7%\textsuperscript{35}.

Schroeder, \textit{et al}. compared neoadjuvant radiation with concurrent 5-FU-based chemotherapy, with and without hyperthermia, in rectal cancer. pCR was observed in 6.7% of patients in the chemoradiation group and in 16.4% of patients in the hyperthermia group. But, 34.4% of patients discontinued hyperthermia within the first three treatments. The rate of sphincter-sparing surgery was 57% in the hyperthermo-radiochemotherapy group in comparison to 35% in the radiochemotherapy group (\(p=0.077\))\textsuperscript{36}.

Asao, \textit{et al}. reported that preoperative HCRT was performed for lower rectal cancer, and 52.6% down-staging was achieved in the group who received a total dose of 50 Gy. The tumor regression effect was favorable, and clinical complete responses (cCR) and pCR were observed in 24 and 21.5%, respectively\textsuperscript{37,38}.

Although the publication of positive results from randomised clinical trials, it is difficult to recognized as a useful treatment for rectal cancer patients, because the reports were too heterogenous materials and methods among these reports. As mentioned above, method of thermic treatment is not standardized, resulting not be able to apply to multicenter study and also yet its exact techniques, dose, contraindications, limits and the conditions of optimal treatment are not determined.

In this study, we demonstrated that small size of tumor with GTV 32 cm³ showed good responses by CRT with concurrent thermal therapy without heatable condition, but the large tumor GTV 80 cm³ needed to produce heatable conditions by RF irradiation. There is no report refered to tumor size on which shows good response by CRT.

Perez \textit{et al}. referred to tumor size in patients with superficial measurable tumor of breast cancer that the complete response rate in tumours \(>3\) cm increased from 31% to 65% by using a better heating technique\textsuperscript{39}.

In general hyperthermia is mostly identified with an intratumor temperatures, we demonstrated that difference of skin temperature during RF irradiation can be evaluated the efficacy of this modality, and our method is very simple and applicable in clinical setting at general hospital.

In recently, there has been significant progress in the development and application of hyperthermia treatment planning software and non-invasive thermometry\textsuperscript{40-45}.

But, at present it is not generally available and restricted to a limited number of tumor sites; \textit{e.g.} moving tumors (abdomen) or for heterogeneous tissues.

**Perspective and possible important role of thermic treatment, moving to individual patient-oriented medicine (IPOM)**

Although there were no significant differences in both incidence of OLS and treatment response before and after standardization of HT irradiation in this study, we could demonstrate that the merit of standardization of HT irradiation is to be able to compare each other’s patients, and also their parameters of IMRT. We expect that a randomized multicenter study whether examine the merit or the demerit by adding thermic treatment will be able to perform by using our method, moving to IPOM in the future. We believe our idea might eventually yield an individual patient-oriented treatment with the highest possible tumor control probability and minimal risk of complications.

The present study has some limitations. First, the small sample size meant there was no comparison
group that received radiotherapy with concurrent Cap. Second, the post-treatment follow-up duration was short. Therefore, further studies based on predicted outpaintable/heatable conditions should be performed to confirm these results.

**Conflict of Interest Statement**

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Conflict of interest: none.

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