Introduction

Roussakow\(^{1}\) has reported the history of hyperthermia. Hyperthermia has been used for cancer treatment for long and is widely used in various medical fields in a clinical setting. In addition, many randomized trials and phase II or III trials of hyperthermia have demonstrated a significant improvement in the clinical outcome for tumors of the head and neck\(^{2}\), breast\(^{3}\), rectum\(^{4}\), lung\(^{5}\), esophagus\(^{6}\), and melanoma\(^{7}\) and sarcoma\(^{8}\). The biggest improvements have been reported in gynecological malignancies\(^{9, 10, 11}\). 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\(^{12, 13, 14, 15}\). Therefore, it has received less attention in the oncological community of North America. There may be an ethnic difference in the effect of hyperthermia on cancers as is seen in other modalities. For these reasons, this treatment has not been approved as a standard oncological treatment worldwide. Hyperthermia itself is associated with several problems as indicated by Roussakow\(^{16}\); there is no strong scientific proof or stable, reproducible treatment quality, and consequently, the clinical effect of hyperthermia is questioned. One of the reasons for these problems is that there is no reference point for this therapy, but the absence of reference point is similar to other modalities of cancer treatment such as chemotherapy (CT), radiotherapy (RT), and surgery\(^{17}\). In other words, these problems are due to the lack of standardization parameters, such as mg/m\(^2\) for CT or Gy for RT, for the evaluation of the efficacy of this modality. Consequently, clinical results for hyperthermia in cancer therapy are inconsistent, with doubts regarding its efficacy. Another
problem is that radiofrequency (RF) hyperthermia induces pain through the hot spot phenomenon, which does not allow prolonged treatment without lowering the output.

The aim of this retrospective and prospective study was to identify the quantitative evaluable parameters through standardization of treatment and to evaluate the relationship between these parameters and the clinical outcome and also between the initial irradiation output at which complications occurred and the physical status of patients with malignancies.

Materials and Methods

Hyperthermia treatment was administered either alone or concomitantly with CT and/or RT to 76 patients with malignancies (median age 65 years [male, 33-89 years; female, 28-48 years]), and a total of 341 irradiations were performed using Thermontron RF-8 (Yamamoto Vinita Co., Ltd., Japan) from December 2011 to April 2014. There were 52 primary cancer cases and 22 recurrent cancer cases. One patient with recurrent pseudomyxoma received RF irradiation 8 times. In this study, this female patient was evaluated as a single case.

This retrospective and prospective study was approved by the ethics committee of the Hidaka Hospital and Gunma University, and each patient gave written informed consent before study entry.

Hyperthermia

RF hyperthermia was administered 5 times for 5 weeks with 50 min irradiation in all patients. In general, patients started to receive CT and/or RT first (oral administration of fluoropyrimidine and a total of 50 Gy radiation through intensity-modulated radiotherapy) on a Monday. After CT and/or RT, they received RF irradiation on the same or next day, and then followed the same treatment cycle for 5 weeks. However, because of a national holiday and the radiation schedule, it was impossible to start these therapies on Monday. As a result, 9 patients received the therapy on the same day, 29 the next day, 11 after 2 days, 8 after 3 days, and 9 over 3 days after CT and/or RT. Between December 2011 and November 2012, a total of 27 patients received hyperthermia therapy. The output was increased to 1200 W by operators until complications such as pain occurred, and increased it to 1200 W 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 the fifth irradiation treatment, this output was applied for 50 min. These principles were maintained in patients treated prospectively with neothermia.

Temperature

A sensor catheter with 4 temperature points was placed in the rectum of 15 patients, while it was attached to the skin on the lateral abdominal side in 59 patients. The temperature of individual treatment expressed it as 4 temperature of average of a sensor. Two patients were not examined. The thermal output at the 4 temperature points was recorded for 50 min from the beginning as the potential estimated temperature of each irradiation. Increased thermometry scales were added to the pre-treatment axillar temperature of the patients to obtain a hypothetical internal body temperature that may be the core temperature. The thermometry scales of patients whose rectal temperatures were examined were one degree Celsius lower than the possible core temperature.

Hidaka output classification (HOC)

We think that we are the first to describe these methods in the hyperthermia community. First, using the quartiles of frequencies statistical method (SPSS [IBM, Armonk, NY, USA]), we simply classified the patients from retrospective study into 4 groups according to the total accumulated irradiation output (Watt/50 min). These were 26000 or lower, 26001-32600, 32601-39500, and 39501 or higher, which represent 1, 2, 3, and
4 Hidaka output points, respectively. Based on the sum of 5 treatments, the following 3 groups were defined according to the HOC: 9 points or lower, 10-16 points, and 17 points or higher.

**Evaluation of objective response**

We evaluated the objective response at 4 weeks for patients with recurrence and at 8 weeks for patients with primary disease, after hyperthermia treatment using positron emission tomography (PET)/computed tomography and magnetic resonance imaging (MRI) at Hidaka hospital. Response was classified based on response evaluation criteria in solid tumors (RECIST): clinical complete response (total disappearance of the lesions; CR), partial response (30% decrease in the sum of the diameters of the lesions; PR), stable disease (between 30% decrease and 20% increase; SD), and progressive disease (20% increase in the sum of the diameters of the lesions or new distant metastasis; PD). Briefly, we evaluated CR as the disappearance of cancer in computed tomography/MRI, and a positive to negative change in PET after treatment. Adverse effects were evaluated according to the criteria of Common Terminology Criteria for Adverse Events.

**Statistical analysis**

The IBM SPSS Statistics software (IBM, Armonk, NY, USA) version 21 was used to analyze all data. We analyzed the relationships between the initial irradiation output at which complications occurred, and the initial time at which complications occurred, as well as the body weight, height, BMI, abdominal girth, thickness of the fat of the abdominal wall and offal internal organs, total fat area, subcutaneous fat area, and age. The correlations were evaluated using Pearson correlation coefficients (r) and significance values (p). The results are presented as mean ± SE. Categorical data were analyzed using the χ²-test. All reported p values are two-tailed and were considered significant if p < 0.05.

**Results**

Table 1 shows the therapies used in this study. There were 61, 2, 11, and 2 patients who received hyperthermia treatment in combination with chemoradiotherapy, that is, hyperthermo-chemo-radiotherapy (HCRT), hyperthermo-radiotherapy (HRT), hyperthermo-chemotherapy (HCT), and hyperthermia alone (HT), respectively.

Two patients receiving HCRT rejected the full dose of chemotherapy with Grade 2 side effects. Complete treatment was received in 97.4% of cases. Grade 3 side effects were seen in 1 rectal cancer patient (perianal dermatitis) who received HCRT. All patients received 5 RF irradiations.

There were 18, 24, and 34 patients, respectively, with 9 points or lower, 10-16 points, and 17 points or higher according to HOC. CR, PR, SD, and PD were seen in 20 (26.3%), 22 (28.9%), 21 (27.6%), and 13 (17.1%) patients, respectively. Out of 54 patients with primary disease and 22 with recurrent disease, CR, PR, SD, and PD were seen in 19 (35.2%) and 1 (4.5%), 19 (35.2%) and 3 (13.6%), 9 (16.7%) and 12 (54.5%), and 7 (13.0%) and 6 (27.3%) patients, respectively. In patients treated with and those treated without neothermia, no complications were seen during irradiation in 76.7% and 54.8% of patients, pain occurred in 19.4% and 39.3% of patients, micturition occurred in 1.9% and 1.5% of patients, and subcutaneous induration was observed in 1.5% and 1.5% of patients, respectively.

Correlation coefficients between the initial irradiation output and initial time at which complications occurred, as well as body weight, height, body mass index (BMI), abdominal girth, thickness of abdominal wall fat, visceral fat area, total fat area, subcutaneous fat area, and age are shown in Table 2. There was significant positive correlation between the initial irradiation output and initial time at which complications occurred, and significant negative correlation among the initial irradiation output at which complications occurred and the BMI, visceral

<table>
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<tr>
<th>Disease</th>
<th>HCRT</th>
<th>HRT</th>
<th>HCT</th>
<th>HT</th>
<th>Total</th>
</tr>
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<tr>
<td>Primary rectal cancer</td>
<td>52</td>
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<td>0</td>
<td>53</td>
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<td>1</td>
</tr>
<tr>
<td>Recurrent rectal cancer</td>
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<td>1</td>
<td>1</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Recurrent colon cancer</td>
<td>2</td>
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<td>2</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Recurrent uterus cancer</td>
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<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Recurrent pseudomyxoma*a</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>61</td>
<td>2</td>
<td>11</td>
<td>2</td>
<td>76</td>
</tr>
</tbody>
</table>

*a same patient

[Abbreviations: HCRT, hyperthermo-chemo-radiotherapy; HRT, hyperthermo-radiotherapy; HCT, hyperthermo-chemotherapy; HT, hyperthermia alone]
Radiofrequency hyperthermia standardization

fat area, total fat area, thickness of the fat of the abdominal wall, subcutaneous fat area, abdominal girth, and body weight in patients receiving neothermia.

Fig. 1 shows the objective response according to HOC in 76 patients with malignancies. In the 10–16 HOC points group, complete response (CR) and partial response (PR) rates were higher than the stable disease (SD) and progressive disease (PD) rates.

Fig. 2 shows the objective response according to HOC in patients with colorectal cancer. Primary cancer cases showed higher rates of good objective response than recurrent cases. [CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease]

Fig. 3 shows the changes in body temperature during irradiation according to HOC. In the group with \( \leq 9 \) HOC points, body temperatures of CR patients significantly increased from 5 min to 50 min of irradiation, but not those of PR+SD and PD (Fig. 3A). In the 10-16 points group, CR but not PD increased from 13 min to 50 min irradiation, CR rather than PR increased from 14 min to 50 min, and PR rather than PD increased from 4 min to 50 min of irradiation (Fig. 3B). In the group with 17 or more points, CR and PR increased from 1 min to 50 min, and CR rather than PD increased from 16 min to 50 min of irradiation (Fig. 3C). CR patients showed significantly higher increased body temperature than the other patients, but in the group with 17 or more points, PD patients showed a significantly higher increased body temperature than PRSD patients.

Fig. 4 shows the results for the relationship between the objective response and complications. Patients with complications showed twice the CR and PD rates of those without complications. There was a significant difference between patients with and without complications (p=0.03).

Fig. 5 shows the results the relationship between the

| Table 2. Correlation coefficients for the relationship between initial irradiation output at which complications occurred, and other physical data examined in this study. |
|--------------------------------------------------|--------------------------------------------------|--------------------------------------------------|
|                                              | **Total**          | **Neothermia (+)** | **Neothermia (-)** |
|                                              | Correlation coefficient | p value | Correlation coefficient | p value | Correlation coefficient | p value |
| Initial time of complications                 | 0.543              | < 0.0001          | 0.610              | < 0.0001          | 0.568              | < 0.0001          |
| Body mass index                                | -0.379             | 0.0001            | -0.579             | < 0.0001          | -0.200             | NS                |
| Visceral fat area                               | -0.421             | < 0.0001          | -0.566             | < 0.0001          | -0.339             | 0.0081            |
| Total fat area                                  | -0.478             | < 0.0001          | -0.559             | 0.0001            | -0.424             | 0.0007            |
| Thickness of the fat of the abdominal wall     | -0.513             | < 0.0001          | -0.554             | 0.0001            | -0.496             | 0.0001            |
| Subcutaneous fat area                           | -0.453             | < 0.0001          | -0.480             | 0.0007            | -0.443             | 0.0004            |
| Abdominal girth                                | -0.351             | 0.0002            | -0.450             | 0.0017            | -0.279             | 0.0309            |
| Body weight                                    | -0.174             | NS                | -0.333             | 0.0221            | 0.026              | NS                |
| Height                                         | 0.200              | 0.0371            | 0.257              | NS                | 0.142              | NS                |
| Age                                           | 0.129              | NS                | 0.011              | NS                | 0.187              | NS                |
Fig. 3. Changes in body temperature during irradiation according to Hidaka output classification. Patients with complete response (CR) showed significantly higher increased body temperature than the others. [PR+SD, partial response and stable disease; PD, progressive disease]

Fig. 4. Results for the relationship between the objective response and complications. There was a significant difference between patients with and without complications (p=0.03). [CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease]

Fig. 5. Results for the relationship between the objective response and the timing of radiofrequency irradiation. Patients who received irradiation 3 days after chemotherapy and/or radiotherapy showed higher complete response (CR) rates. [PR, partial response; SD, stable disease; PD, progressive disease]

Fig. 6. Changes of body temperature during irradiation according to the objective response in patients with (A) and without (B) complications. Patients with complete response (CR) showed significantly higher increased body temperature than the other groups in spite of complications. The body temperature of the partial response and stable disease (PR+SD) group depended on whether complications occurred or not. [PD, progressive disease]
Patients who received irradiation 3 days after CT and/or RT showed higher CR rates than the others, while patients who received irradiation for 3 days or more after CT and/or RT did not show PD.

Fig. 6 shows the changes in body temperature during irradiation according to the objective response in patients with or without complications. In patients with complications, body temperatures of patients with CR increased significantly from 8 to 50 min, rather than those with PRSD and PD (Fig. 6A), while in patients without complications, body temperatures of those with CR and PRSD increased from 4 min to 50 min but not in those with PD (Fig. 6B). Patients with CR showed significantly higher increased body temperature than the other groups, while the irradiation effect in PRSD cases depended on the presence or absence of complications; the body temperature of PRSD patients with complications did not increase, while in those without complications, the increase was the same as in CR patients. Patients with complications showed significantly lower total RF Hidaka output points and total RF output than those without complications (p < 0.001 and p=0.01, respectively; Fig. 7).

Discussion

In this study, we demonstrated that 35.2% of patients gained CR in primary cancer cases, but only 4.5% achieved CR in recurrent cases. Higher CR rates were shown in patients with 10-16 HOC points; good responses resulted from timing the treatment 3 days after CT and/or RT. There was a significant positive correlation between the initial irradiation output and the initial time at which complications occurred, and a significant negative correlation with BMI, visceral fat area, total fat area, thickness of the fat of the abdominal wall, subcutaneous fat area, abdominal girth, and body weight in patients treated with neothermia. The most useful marker was the thickness of the fat of the abdominal wall for the early occurrence of hyperthermia complications (r=-0.513, p < 0.0001). All patients with CR showed significantly higher increased body temperature than the other groups, while the irradiation effect of PRSD depended on the presence or absence of complications. Therefore, we think that the standardization of radiofrequency hyperthermia, which induced lesser complication and was a more stable and reproducible treatment than the non-standardization hyperthermia, benefits patients with malignancies. In the group with 17 points or more, patients with PD showed significantly higher increased body temperature than those with PRSD. At present, the optimum temperature distribution for clinical purposes is unknown and because this study used a small sample, the conclusions are only valid up to a point.

The rationale for the use of hyperthermia in cancer treatment is based on a direct cell-killing effect at temperatures above 41–42°C. The rationale for the use of hyperthermia in combination with RT and/or CT is also based on microenvironmental factors such as high oxygen concentration through inducing blood flow and high pH in the tumor. Overall, hyperthermia is probably the most potent radiosensitizer known to date.

For the body temperature, we chose to use skin temperatures, which are dependent on a fundamental homeostatic function. Skin thermoregulation depends on a thermoregulatory center, which is located in the preoptic area, the anterior hypothalamic region of the hypothalamus. Thermoreceptors in the skin, which includes sweat glands and skin blood vessels, are dependent on sympathetic nerve-related adrenergic and cholinergic nerves. In general, the thermoregulatory center in the brain receives information through sensory afferent neuronal pathways; it receives information regarding environmental temperatures from thermoreceptors in the...
skin, regarding visceral temperatures from thermosensitive fibers in the abdominal cavity, and regarding central temperatures from thermosensitive neurons in the brain and spinal cord. In hyperthermia treatment, stimulation is thought to occur by mechanisms similar to the aforementioned mechanisms of visceral temperature maintenance in the abdominal cavity. However, there has been no study concerning whether the pathways of stimulation are similar or not.

Recently, a relationship between thermoregulation and the transient receptor potential (TRP) family of channel proteins has been reported in many medical fields. Recent studies of TRP show that transient receptor potential vanilloid (TRPV1) can be activated by a noxious range of heat (>34°C), by protons (pH ≤ 5.9), or by capsaicin.26,27 Yao et al. reported that the TRPV1 channel was activated by temperatures above 32°C at 0 mV.28

However, there are also no studies about the relationship between hyperthermia, forced fever, mechanically induced fever inside the body, and the TRP family.

Recent studies have also shown heat-dependent immunomodulatory reactions of human leucocytes, and specific effects on natural killer cells and cytokine depletion have been discovered.29 In the field of oncology, mild temperature seems to have a good effect on tumors. In our data, mild temperature seems to have a similar effect in the group with 10-16 HOC points.

In conclusion, significantly higher increased temperatures during RF irradiation were seen in patients with CR than in those with other responses, but some patients with higher increased temperature also showed PD. In the clinical setting, there were discrepancies between clinical responses and histological responses. In order to assess the response to therapy before and after the operation, in this study, we evaluated computed tomography/PET/MRI scans before the operation. These methods were not standardized for assessment of therapy responses, because it would be difficult to compare treatment response studies across institutes and clinical centers.30 We must examine this discrepancy by using a large sample of surgically resected cases and perform validate and reconfirm our results in the near future.

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References


