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Output-limiting symptoms induced by radiofrequency hyperthermia. Are they predictable?

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Abstract

Background: During radiofrequency (RF) hyperthermia treatment, hot-spot phenomena may occur and prevent treatment continuation if the output is not lowered. We previously reported a significant correlation between the initial energy output at which output-limiting symptoms occurred and patient status. Patients with a complete clinical response had significantly increased temperature, while some patients with partial clinical response and stable disease had increased temperature, depending on the occurrence of output-limiting symptoms. To predict the initial energy output at which output-limiting symptoms occur, we performed multiple regression analysis with the parameters of patients’ physical status.

Materials and methods: Hyperthermia alone or concomitant with chemotherapy and/or radiotherapy was applied in 62 patients with malignant disease for a total of 310 treatments with a Thermotron RF-8 between December 2011 and April 2014. Results: No output-limiting symptoms were shown in 65.5% of 310 treatments. Pain (29.7%), micturition desire (1.9%), skin discomfort (0.6%), subcutaneous induration (1.6%), cold sensation (0.6%), and nausea (0.3%) were reported in the 310 treatments. A good predictive equation for initial energy output at which output-limiting symptoms occur was determined with two parameters, initial time of an output-limiting symptom onset, and thickness of the fat of the abdominal wall. Multiple regression analysis showed an adjusted $R^2 = 0.99$ and variance inflation factor $< 2$. Conclusions: We present a good predictive equation for initial energy output at which output-limiting symptoms occur. It is critical to prevent RF hyperthermia-induced output-limiting symptoms and establish new prevention strategies.

Keywords

Output-limiting symptoms, physical status, prediction, radiofrequency hyperthermia

Introduction

Hyperthermia has been used for cancer therapy over the past three decades. There are numerous positive phase III trials indicating that it can enhance the efficacy of both radiotherapy and chemotherapy [1]. Although it has been proven effective in many circumstances, the treatment requires exposure of a portion of the body to externally applied power, such as radiofrequency. Under some circumstances pain that is associated with the treatment limits the amount of power that can be applied. In such circumstances it is possible that substandard hyperthermia application will result, thereby lessening its therapeutic effectiveness.

In our study of capacitively coupled RF hyperthermia, we found a significant positive correlation between the initial energy output at which output-limiting symptoms occurred and the time of an output-limiting symptom onset. Initial energy output also had a significant negative correlation to the patient’s physical status. Body mass index (BMI), visceral fat area, total fat area, thickness of the abdominal wall fat, subcutaneous fat area, abdomen girth and body weight were used to define physical status of patients. All patients with a clinical complete response (CR) had significantly higher skin temperatures than other groups. Output-limiting symptoms associated with energy output were correlated with occurrence of complete response (CR), clinical partial response (PR), stable disease (SD) or disease progression. Elevation of temperature was also associated with response [2].

The hot-spot phenomenon, thought to result from large RF reflections at the interface between soft tissue and bone or air, can also cause severe output-limiting symptoms, including pain, unpleasant sensations and burning at maximum power of the RF equipment [3–8]. Patients who experience these side effects may not receive optimal hyperthermia treatment.
because of limitations in applied power. If these output-limiting symptoms can be predicted and prevented, patients may be able to better tolerate application of hyperthermia, thereby maximising the likelihood that they will be effectively treated.

In this study we aimed to establish a predictive formula of the initial energy output at which output-limiting symptoms occur by using a multiple regression analysis with parameters such as the time of an output-limiting symptom onset and physical status of patients treated with hyperthermia.

**Materials and methods**

Hyperthermia alone (HT) or concomitant with chemotherapy (CT) and/or radiotherapy (RT) performed on 62 patients with malignant diseases (median age 65 years; range 33–89 years, male:female ratio 45:17, 48 primary and six recurrent rectal cancers, six recurrent colon cancers, one primary pancreas cancer, and one recurrent pseudomixoma), for a total of 310 abdominal treatments by using a Thermotron RF-8 (Yamamoto Vinita, Osaka, Japan) between December 2011 and April 2014.

**Hyperthermia**

Abdominal HT was applied five times per week for 50 min per treatment. From December 2011 to November 2012, a total of 26 patients began receiving CT and/or RT first through oral administration of fluoropyrimidine and/or a total dosage of 50 Gy by intensity-modulated radiotherapy. Patients then received RF thermal therapy either on the same day or on the next day, and continued to receive the same treatment cycle weekly. RF output was started from 300 W and increased by operators to 1200 W until output-limiting symptoms occurred. When these symptoms occurred, the output was decreased and increased again when symptoms reappeared, with output varying roughly from patient to patient. This method of adjusting power was recorded, but not standardised. To determine whether power adjustments affected treatment outcome, the data were retrospectively evaluated.

From November 2012 to January 2014, a total of 36 patients prospectively received a treatment with standardised power escalation principles. From retrospective evaluation of the data about output-limiting symptoms, we had noticed that patients with output-limiting symptoms showed greater thickness of the abdominal wall, internal organs fat area and total fat area than those without output-limiting symptoms. Therefore, we classified patients into two groups. Group A comprised patients with thickness of the fat of abdominal wall <16 mm, visceral fat area <100 cm², and total fat area <190 cm², and group B comprised patients with any one of the aforementioned factors. For patients in group A, the output increase was 50 W/min, while for those in group B it was 25 W/min. The operator started the output at 200 W and increased to 1200 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 standardised power escalation principles in this prospective study [2].

The study was approved by the ethics committee of Hidaka Hospital and Gunma University and each patient provided written informed consent before being accepted into the study. The physical status of all patients; thickness of the fat of the abdominal wall at the level of the navel, subcutaneous fat area, total fat area, and internal organ fat area were evaluated using computer tomography/magnetic resonance imaging (CT/MRI) before treatment. Height, body weight, body mass index (BMI), abdomen girth, body surface area calculated by the DuBois formula (BSA = \(W^{0.425} \times H^{0.725} \times 0.007184\)) and age were also recorded.

**Multiple regression analysis**

We analysed the correlations between the initial energy output at which output-limiting symptoms occurred, the initial time at which output-limiting symptoms occurred, and patients’ physical status such as body weight, height, BMI, and age as well thickness of the fat of the abdominal wall, internal organ fat area, total fat area and subcutaneous fat area, which were used as exploratory variables for multiple regression analysis. Variance inflation factor (VIF) was used to check for multicollinearity. The predictor equation was determined using a correlation analysis and executing a combination of stepwise and multiple linear regressions.

**Statistical analysis**

The SPSS Statistics package (IBM, Armonk, NY, USA), version 21, was used to analyse all data. For statistical efficiency we used a stepwise multiple regression method to predict the initial energy output at which an output-limiting symptom occurred. The correlations were evaluated using Pearson correlation coefficients (r) and significance values (p). Categorical data were analysed using the \(\chi^2\)-test. All reported p-values were two-tailed and considered significant if \(p < 0.05\).

**Results**

There was no significant difference between patients with and without output-limiting symptoms in gender and age (<65 years old and >66 years old). Output-limiting symptoms of 310 treatments occurred in 64.5% and 35.5% of patients <65 years old and >66 years old, respectively; this difference was significant (\(p = 0.013\)), and in 56.1% and 43.9% of patients without and with standardised power escalation principles, respectively (\(p < 0.001\)). There was no significant difference between patients with and without output-limiting symptoms in combination treatments (HT plus CT plus RT \((n = 56)\), HT plus RT \((n = 2)\), HT plus CT \((n = 3)\) and HT \((n = 1)\). Pain (29.7%), micturition desire (1.9%), skin discomfort (0.6%), subcutaneous induration (1.6%), cold sensation (0.6%), and nausea (0.3%) were reported for 310 treatments. The patients’ physical status with and without output-limiting symptoms in applied abdominal thermal therapy are summarised in Table 1. Patients with output-limiting symptoms had a
significantly higher body weight and thicker abdominal wall fat than those without output-limiting symptoms ($p = 0.05$ and $p = 0.028$, respectively). Table 2 shows the results of multiple regression analysis in patients who received abdominal thermal therapy with and without standardised power escalation principles. Adjusted $R^2$ were 0.99 and 0.90 in patients with and without standardised power escalation principles, respectively, and all VIF values were less than 2. There was no multicollinearity in the model. We attempted to use a forced entry multiple regression method to predict the initial energy output at which output-limiting symptoms occurred, but all the adjusted $R^2$ values were less than that obtained using stepwise regression.

Figure 1 shows the incidence of output-limiting symptoms during five RF treatment sessions. Patients with standardised power escalation principles developed output-limiting symptoms only once during five treatments, while those without standardised power escalation principles developed several output-limiting symptoms during five treatments. There was a significant difference in distribution between them ($p < 0.001$). No output-limiting symptoms during five treatments (310 abdominal thermal therapy) were observed in 73.9% and 53.8% patients with and without standardised power escalation principles, respectively. There was a significant difference between them ($p < 0.001$).

Figure 2 shows the relationship between the observed and expected initial energy output at which output-limiting symptoms occurred in patients receiving abdominal thermal therapy with standardised power escalation principles. There

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Table 1. Characteristics of patients’ physical status with and without output-limiting symptoms.

<table>
<thead>
<tr>
<th>Complication (-)</th>
<th>±SE</th>
<th>Complication (+)</th>
<th>±SE</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>68.0</td>
<td>1.7</td>
<td>64.8</td>
<td>1.5</td>
</tr>
<tr>
<td>Girth of abdomen (cm)</td>
<td>80.5</td>
<td>2.6</td>
<td>80.3</td>
<td>1.2</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>52.3</td>
<td>2.3</td>
<td>57.8</td>
<td>1.4</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>157.5</td>
<td>3.1</td>
<td>162.3</td>
<td>1.2</td>
</tr>
<tr>
<td>Body mass index</td>
<td>21.3</td>
<td>0.3</td>
<td>22.1</td>
<td>0.4</td>
</tr>
<tr>
<td>Internal organs fat area (cm$^2$)</td>
<td>56.5</td>
<td>12.9</td>
<td>93.4</td>
<td>7.8</td>
</tr>
<tr>
<td>Total fat area (cm$^2$)</td>
<td>138.9</td>
<td>29.4</td>
<td>183.9</td>
<td>13.0</td>
</tr>
<tr>
<td>Subcutaneous fat area (cm$^2$)</td>
<td>82.3</td>
<td>17.0</td>
<td>92.0</td>
<td>6.5</td>
</tr>
<tr>
<td>Thickness of the fat of the abdominal wall (mm)</td>
<td>11.3</td>
<td>1.9</td>
<td>15.3</td>
<td>0.9</td>
</tr>
<tr>
<td>Body surface area (m$^2$)*</td>
<td>1.5</td>
<td>0.0</td>
<td>1.6</td>
<td>0.0</td>
</tr>
</tbody>
</table>

*DuBois

Table 2. Results of multiple regression analysis in patients receiving abdominal irradiation with and without standardised power escalation principles.

<table>
<thead>
<tr>
<th>B</th>
<th>$\beta$</th>
<th>Adjusted $R^2$</th>
<th>$p$</th>
<th>Tolerance</th>
<th>VIF</th>
</tr>
</thead>
<tbody>
<tr>
<td>With standardised power escalation principles</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Constant)</td>
<td>967.995</td>
<td>-17.155</td>
<td>-0.822</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Initial time an output-limiting symptom occurred</td>
<td>6.162</td>
<td>0.413</td>
<td>0.986</td>
<td>&lt;0.001</td>
<td>0.958</td>
</tr>
<tr>
<td>thickness of the abdominal wall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without standardised power escalation principles</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Constant)</td>
<td>944.832</td>
<td>-15.826</td>
<td>-0.673</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Initial time an output-limiting symptom occurred</td>
<td>5.721</td>
<td>0.462</td>
<td>0.905</td>
<td>&lt;0.001</td>
<td>0.848</td>
</tr>
<tr>
<td>thickness of the abdominal wall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

VIF, variance inflammation factor.
was a good correlation between the observed and expected initial energy output obtained with the two parameters.

**Discussion**

In this study we demonstrated that a good predictor equation for initial energy output at which output-limiting symptoms occurred was determined with two parameters: time of an output-limiting symptom onset, and thickness of the fat of the abdominal wall. However, this conclusion is limited due to the small sample of this study.

It has been demonstrated in several prior clinical studies with deep hyperthermia that higher thermal doses are associated with better response. The achievement of optimal thermal doses requires deposition of adequate power, as we have reported previously [2], to the target tumour volume. To date, however, there have been no reports examining the relationship between RF output and thermal dose achieved in individual patients with deep-seated tumours, and no one has examined what factors might contribute to onset of pain during capacitive RF heating.

The hyperthermia group in Rotterdam reported that the Rotterdam method detailed a hyperthermia treatment planning system for which they calculated specific absorption rate (SAR) distributions and the successful outcomes of hyperthermia in patients with cervical cancer. They also reported that areas of pain correlated with modelled SAR peak locations [9–15].

SAR is a good parameter for standardisation of therapy and prediction of output-limiting symptoms with phased array devices. We show that time of onset of symptoms is associated with outcome. A future direction for those involved in phased array devices might be to examine this relatively simple tool. Fat thickness is an issue that is particularly limiting for capacitive RF devices. Whether or not this would be helpful with phased array devices would have to be tested.

**Conclusion**

In conclusion, we developed a good predictive equation for the initial energy output at which an output-limiting symptom will occur using the time of output-limiting symptom onset and thickness of the fat of the abdominal wall as parameters. Our results show that it is very important to prevent RF hyperthermia-induced output-limiting symptoms. New strategies need to be established for the prevention of output-limiting symptoms.

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**Declaration of interest**

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