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Microwave Interstitial Hyperthermia with Ablation Concept

Based on the Heating and Clinical Results of Five Cases

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Abstract: Interstitial hyperthermia using a single antenna would reduce invasiveness and expand indications. We developed an antenna with a nearly spherical temperature distribution, which is the ideal temperature distribution for single-antenna heating that matches the shape of common tumors. We also developed a means of inserting the antenna so that the center of the spherical temperature distribution matches that of the tumor. By increasing the antenna output, we considered the central region of the tumor could undergo thermal ablation while the peripheral region could be exposed to hyperthermia. Five patients were treated using microwave interstitial hyperthermia and radiation therapy with intent to cure. Four patients had supraclavicular or inguinal node metastasis, and one patient had a soft palate primary lesion. The mean follow-up time was 2 years and 2 months. The heated region was controlled in all patients during follow-up without evidence of tumor re-growth, in spite of the sizable tumors (3-7 cm, mean 4.5 cm).

Only one antenna was inserted into three patients. In all sessions with these three patients, the antenna output was set at 10-15 W (high) per antenna, which increased the temperature of the tissue near the antenna to 47-66°C. Coagulation necrosis should have occurred at this temperature range over a wide area around the tumor center in all three patients. The advantages of single-antenna interstitial hyperthermia are as follows: 1) it is less invasive than multiple antennas, and the indications are expanded. 2) from the viewpoint of combined radiotherapy, local control rates increase because the hypoxic radioresistant region at the tumor center can be ablated more effectively and 3) it can be safely applied when ablation is contra-indicated, such as when a tumor is adjacent to nerves, vessels or healthy tissues.
skin, because the temperature in the tumor periphery is lower. Interstitial hyperthermia with a single antenna is a “thermal therapy” that acts as both hyperthermia and ablation due to a longer period of heating and higher output power.

Key Words: microwave interstitial hyperthermia, thermal coagulation, thermal ablation, spherical SAR distribution, coaxial-slot antennas.

Introduction

Interstitial hyperthermia is one of the most useful hyperthermic methods, whereby it is possible to heat all the tumor volume at high enough temperature. Interstitial hyperthermia has been actively applied, but a prospective controlled randomized study that compared interstitial thermoradiotherapy with interstitial radiotherapy alone in 1996 did not verify its efficacy\(^3\). Since then, interstitial hyperthermia has been less popular. However, the present study found that that interstitial hyperthermia appeared ineffective because antennas were not properly positioned to sufficiently heat tumors. In fact, when we attempted to position antennas to surround a tumor using our previous 4-16 antenna array to acquire more homogenous temperature distribution\(^2\), difficulties with insertion were caused by interfering vessels, nerves and bones, and interstitial hyperthermia could only be performed on very few patients\(^3\).

If interstitial hyperthermia could be performed using a single antenna without adherence to homogenous temperature distribution, it would be less invasive and be available to a wider range of patients. To perform hyperthermia using a single antenna without surrounding a tumor with multiple antennas, the antenna should have an oval or spherical temperature distribution that reflects the shapes of common tumors. We developed an antenna with a more spherical temperature distribution than the previous antenna for hyperthermia. We also developed a means of inserting the antenna so that the center of the spherical temperature distribution matches that of the tumor. By increasing the antenna output, we considered that the central region could undergo thermal ablation due to a higher temperature and a longer period of heating, while the peripheral region could be exposed to hyperthermia at a lower temperature. This paper describes our method and considers the usefulness of single-antenna heating based on the findings of five patients who underwent interstitial hyperthermia.

Materials and methods

Patient characteristics

Five patients underwent microwave interstitial hyperthermia at Ichikawa General Hospital, Tokyo Dental College between August 2003 and January 2007 (Table Ia). Three of them were aged between 77 and 89 years. Four patients had supraclavicular or inguinal node metastasis, and one patient had a soft palate primary lesion (Fig. 1). Microwave interstitial hyperthermia was combined with radiotherapy (67.4-85.0 GY) as a curative strategy, because controlling the tumors by radiation alone was difficult due to radioresistibility and large size. Interstitial hyperthermia proceeded after 40 GY of irradiation as a general rule. Chemotherapy was not combined with this treatment in any of the patients. Tumor size ranged from 3.0 to 7.0 cm (mean: 4.5 cm).
Table I. Five cases treated with microwave interstitial hyperthermia.

a : Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, Sex</td>
<td>59y/o, female</td>
<td>69y/o, female</td>
<td>62y/o, male</td>
<td>77y/o, female</td>
<td>80y/o, female</td>
</tr>
<tr>
<td>Primary site</td>
<td>gingiva</td>
<td>soft palate</td>
<td>esophage</td>
<td>lip</td>
<td>corpus uteri</td>
</tr>
<tr>
<td>Pathology</td>
<td>squamous cell ca.</td>
<td>adeno ca.</td>
<td>squamous cell ca.</td>
<td>squamous cell ca.</td>
<td>adeno ca.</td>
</tr>
<tr>
<td>Heated site</td>
<td>supraclavicular node</td>
<td>soft palate</td>
<td>supraclavicular node</td>
<td>submandibular node</td>
<td>ilt. inguinal node</td>
</tr>
<tr>
<td>Maximum diameter</td>
<td>4.3 cm</td>
<td>3.0 cm</td>
<td>4.8 cm</td>
<td>3.5 cm</td>
<td>8.0 cm</td>
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</table>

b : Treatment results

<table>
<thead>
<tr>
<th></th>
<th>1) 14 min</th>
<th>1) 15 min</th>
<th>1) 11 min</th>
<th>1) 20 min</th>
<th>1) 31 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heated time</td>
<td>1) 19 min</td>
<td>2) 31 min</td>
<td>3) 25 min</td>
<td>4) 27 min</td>
<td>5) 31 min</td>
</tr>
<tr>
<td>&gt;42.5°C</td>
<td>3) 10 min</td>
<td>(&gt;47.5°C)</td>
<td>(&gt;47.5°C)</td>
<td>(&gt;47.5°C)</td>
<td>(&gt;47.5°C)</td>
</tr>
<tr>
<td>(total time)</td>
<td>14 min</td>
<td>44 min</td>
<td>115 min</td>
<td>42 min</td>
<td>123 min</td>
</tr>
<tr>
<td>Nearby antenna</td>
<td>65-66°C</td>
<td>56-57°C</td>
<td>43-49°C</td>
<td>47-50°C</td>
<td>43-50°C</td>
</tr>
<tr>
<td>power per antenna</td>
<td>10-15 W</td>
<td>10-15 W</td>
<td>5-6 W</td>
<td>10-15 W</td>
<td>3-10 W</td>
</tr>
<tr>
<td>Antennas</td>
<td>1</td>
<td>1</td>
<td>2-4</td>
<td>1</td>
<td>3-4</td>
</tr>
<tr>
<td>Sensors</td>
<td>3</td>
<td>3</td>
<td>3-4</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>RT dose (electron)</td>
<td>80.0 Gy (18 Gy)</td>
<td>67.4 Gy (8 Gy)</td>
<td>85 Gy (11 Gy)</td>
<td>72.4 Gy (16 Gy)</td>
<td>71.8 Gy (18 Gy)</td>
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ec : Clinical results

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<tr>
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<tbody>
<tr>
<td>Observation time</td>
<td>7.3 months</td>
<td>2 year 2 months</td>
<td>4 year 9 months</td>
<td>3 year 3 months</td>
<td>1 year 4 months</td>
</tr>
<tr>
<td>Tumor re-growth</td>
<td>non</td>
<td>non</td>
<td>non</td>
<td>non</td>
<td>non</td>
</tr>
<tr>
<td>Injury</td>
<td>non</td>
<td>non</td>
<td>numbness of arm (temporal)</td>
<td>non</td>
<td>local fibrosis, leg edema</td>
</tr>
<tr>
<td>Died of distant metastasis</td>
<td>Died of gastric ca.</td>
<td>Alive without disease</td>
<td>Dead of pneumonia</td>
<td>Alive without disease</td>
<td></td>
</tr>
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Antennas and heating device

We have been investigating a thin coaxial-slot antenna that is used for interstitial microwave hyperthermia\textsuperscript{4,5}. Fig. 2 shows the basic configuration of the antenna. Here, the operating frequency is 2.45 GHz, which is an ISM (Industrial, Scientific and Medical) frequency. This antenna is composed of a thin semi-rigid coaxial cable. Several ring slots are cut on the outer conductor of a thin coaxial cable, and the tip of the cable is short-circuited. Here, \( L_{15} \) is the length from the tip to the center of the slot close to the feeding point, and \( L_{15} \) is the length from the tip to the center of the slot close to the tip. Some structural parameters have been improved to generate a spherical heating region around the antenna tip using two slots; \( L_{15} \) and \( L_{15} \) are set to 20 and 10 mm respectively. In addition, we confirmed that the shape of heating region generated by this coaxial-slot antenna is independent of the antenna insertion
Fig. 1. CT scans of heated sites in five cases.

Fig. 2. Basic structure of coaxial-slot antennas.
depth. Fig. 3a and b compares the calculated distributions of SAR (specific absorption ratio) around improved and conventional antennas, respectively. Fig. 3a shows that the SAR distribution is centered almost in the same position as the lower slot, and is spherical around the antenna tip.

The treatment system consists of a microwave generator (AZM-550, Alfresa Pharma, Oosaka, Japan) signed for ablation with a maximum output power of 110 W, a microwave power reflection meter (NRT and NRT-Z44, Rohde & Schwarz, Munich, Germany), and custom made power dividers. The power dividers can divide microwave power in to eight ways in maximum.

**Thermometry**

After local xylocaine anesthesia followed by the insertion of closed-end catheters, antennas and thermosensors were introduced into the catheters (Fig. 4). A small incision was placed on the skin at each insertion site as required. Catheters for the antenna and thermosensor were 18-gauge and 21-gauge, respectively. Fluoroptic temperature probes (M-790, Laxtron, LumaSense Technologies, Santa Clara, US) were used as sensors for thermometry. At least three sensors were inserted to record temperature. We assumed that the “heated volume” completely covered the each tumor volumes. “Heated temperature” is defined as the minimum temperature of the heated volume at a point external to the tumor. We also measured the temperature at a point 5-10 mm from the antenna and adjacent skin (Fig. 5).
We adjusted the output to maintain the skin temperature below 42°C. The skin was cooled using wet gauze if necessary. The positions of the antennas and thermosensors were uploaded to a computer using an X-ray simulator, and after each session the three-dimensional positions of the tumor, antennas and thermosensors were verified (Fig. 6).
**Fig. 6.** Inserted antennas and sensors, AP (a) and lateral (b) views (case 4). Three-dimensional verification of these positions by computer (c).

**Unique techniques for single antenna heating**

a) Finding the center of the tumor

A $0.7 \times 2$-mm metallic marker was initially inserted into the estimated center of the tumor. The tumor was then examined by helical CT for volume scanning, and 2-mm slice images in the transverse, coronal and sagittal sections were obtained. We then measured the three-dimensional distance from the true to the estimated center of the tumor on CT images (Fig. 7a, b).

b) Matching the center of the tumor with that of spherical temperature distribution

We applied the techniques of conventional radiation therapy using an X-ray simulator. The metallic marker was visualized by fluoroscopy and the table was moved a known distance between the true center and estimated center of the tumor, to match the true center to the center of the light field and the isocenter. The antenna was then inserted vertically from the center of the light field of the simulator. The depth of insertion was the length determined by combining the distance from the tumor center to the insertion surface as measured by CT and the distance from the tip to the lower slot of the antenna. After insertion, metallic marker and antenna location were confirmed by fluoroscopy using the simulator and adjusted as necessary (Fig. 8).

**Results**

**Heating results**

Each patient underwent 1-5 interstitial hyperthermia sessions. Antennas were inserted at every
Fig. 7. CT scans of case 4, 1 month after interstitial hyperthermia. Inserted marker deviated several mm superiorly laterally and posteriorly from the true center of the tumor (a, b). Transverse section at the true center of the tumor with large central necrosis (c).

Fig. 8. Matching the center of the tumor with that of spherical temperature distribution. Adjustment of antenna location relative to metallic marker (arrow).

session of interstitial heating. We used only one antenna in three patients and 2-4 antennas in the other two. Table Ib summarizes the heating results for the five patients. All patients received heat above 42.5°C for 14 to 123 minutes (mean, 68 minutes). The use of multiple antennas in cases 3 and 5 ensure that the entire tumor volume was homogeneously heated at ≥ 42.5°C for 115 and 123 minutes, and the output per antenna was only 4 - 6 W (Fig. 5c and e). Case 3 underwent one 24-minute session at mean
temperature of 45.8°C. In cases 1, 2, and 4 in which only one antenna was applied, the average duration of heating at \( \geq 42.5^\circ \text{C} \) was 33 minutes. Several sessions were relatively short due to patient complaints of lumbar pain or heat pain. The output per antenna was notably higher at 10-15 W and the temperature of the tissue near the antenna reached 47-66°C (Fig. 5 line A) with large estrangement from the minimum heated temperature (Fig. 5 line M) in all three cases (Fig. 5a, b and d).

**Clinical results**

Follow-up ranged from 7.3 months to 4 years and 9 months (mean, 2 years and 2 months) and three of the cases died (Table Ic). Two died of another primary lesion and one died of distant metastasis after therapy. Two cases remain alive without disease. The heated region was controlled in all cases during follow-up without evidence of tumor re-growth, however imaging findings revealed PR in terms of early effects (Fig. 7c). One patient developed temporal numbness of the arm, and another developed severe focal fibrosis and slight leg edema. However, these side effects were considered within the allowable range.

**Discussion**

The five patients who underwent microwave interstitial hyperthermia were followed up from 7.3 months to 4 years and 9 months (mean, 2 years and 2 months) and the heated area was controlled in all of them. Two studies have documented that lymph node metastases of \( \geq 3 \) or 4 cm are hardly controlled by radiotherapy. The tumors in our series ranged from 3 to 7 cm (mean, 4.5 cm) and while the radiation dose tended to be high, the effects of interstitial hyperthermia were apparently considerable. The results obtained from our five patients showed that when more antennas are applied more stable and higher temperatures can be easily achieved (Fig. 5c and e, Table Ib). However, even when only one antenna was applied, the minimum temperature of heated volume could still be brought to \( \geq 42.5^\circ \text{C} \) by increasing the output. This strategy caused the temperature of the tissue near the antenna to reach 47-66°C for the duration of the procedure (mean, 68 minutes).

Thermal ablation heats tissue at temperatures of 48-100°C. In microwave coagulation therapy, tissue is heated at \( \geq 60^\circ \text{C} \) for about 5 minutes. Protein generally coagulates at 60-70°C, indicating that \( 60^\circ \text{C} \) is sufficient to induce coagulation necrosis. Stauffer et al. defined thermal ablation as \( \geq 50^\circ \text{C} \) for 4-6 minutes. They quoted one report indicating that these conditions produce vascular stasis, protein denaturation, cellular coagulation and tissue necrosis. Diederich prepared a plot of the temperature-time thresholds of acute thermal damage measured by Henriques and Moritz in pig and human skin in vivo bracketed by an iso-effect thermal dose of 240 EM 43°C and 900 EM 43°C and showed that 48-50°C for 5 minutes resulted in thermal coagulation. In the field of moderate temperature burn, Leach et al. reported that heating animal skin at 50-55°C for \( \geq 1 \) minute resulted in permanent and irreversible damage. On the other hand, temperature range for hyperthermia is \( \geq 42.5^\circ \text{C} \) up to about 45°C. This raises the issue of the temperature at which coagulation occurs during the 15-60 minute heating in conventional hyperthermia. Eddy heated animal tissues at 45°C for 30 minutes which is within the range of hyperthermia in temperature and time, and found that tumor circulation became static before the end of heating and progressed by the second day to coagulation necrosis.

The results suggest that heating at a borderline temperature between hyperthermia and ablation (45°C
or 50°C for 30 or 5 minutes, respectively) will induce coagulation. Because the temperature at a point 5-10 mm from the antenna increased to about 47-66°C (mean 68 minutes) in patients whose tumors were heated with only one antenna, coagulation necrosis must have occurred over a broad area beyond the temperature measurement sites. Since thermal ablation induces cell death more potently than hyperthermia, thermal ablation of the hypoxic radioresistant area at the tumor center mostly likely contributed to the favorable local control.

When comparing single-antenna interstitial hyperthermia with thermal ablation, thermal ablation is only an option when critical organs are not located near a tumor. For example, thermal ablation is often performed for liver, lung and kidney tumors with a safety margin of healthy tissue. On the other hand, the tumor situated near important nerves or vessels or covered by normal skin or mucosa can be safely treated by single-antenna interstitial hyperthermia because of the lower temperature range of hyperthermia. The advantages of interstitial hyperthermia with a single antenna are as follows: 1) it is less invasive than that with multiple antennas, and the indications are expanded. 2) from the viewpoint of combined radiotherapy, local control rates increase because the hypoxic radioresistant region at the tumor center can be more powerfully ablated and 3) it can be safely applied because of the lower temperature range when ablation is contra-indicated, such as when a tumor is adjacent to nerves, vessels or healthy skin.

Single-antenna interstitial hyperthermia is a “thermal therapy” that acts as both hyperthermia and ablation due to longer duration of heating and higher output of power. The technical foundation of the present method is the spherical distribution of an antenna and spatial accuracy. We estimated that the temperature distribution at the stable stage during the heating procedure was more spherical than that of the SAR pattern (Fig. 2a) due to accumulation of heat with time. For special accuracy, novel US or CT image guided techniques for interventional radiology may be applied. Thermal ablation is suitable if tumors can be ablated, and interstitial hyperthermia is suitable if multiple antennas can be properly positioned. However, if these techniques are not feasible, then our single-antenna thermal therapy can be useful. Even in interstitial hyperthermia with multiple antennas, a conventional antenna array might be gathered around the center of a tumor with higher output power to create an ablation effect (case 5, Fig 5e). Our method of thermal therapy can be flexibly applied to various situations and sizes of tumors.

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References


13) Aoyagi Y.: Different roles for cancer therapy of each heating methods —how are the tumors heated—. Sin-iryou, 18 : 76-80, 1991. (Japanese)