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● *Clinical Investigation*

CLINICAL RESULTS OF RADIOFREQUENCY HYPERTHERMIA FOR MALIGNANT LIVER TUMORS

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Purpose: To evaluate thermometry and the clinical results of radiofrequency (RF) hyperthermia for advanced malignant liver tumors.

Methods and Materials: One hundred seventy-three patients with malignant liver tumors treated between 1983 and 1995 underwent hyperthermia. The 173 tumors consisted of 114 hepatocellular carcinomas (HCCs) and 59 non-HCCs (47 metastatic liver tumors and 12 cholangiocarcinomas). Eight-megahertz RF capacitive heating equipment was used for the hyperthermia. Two opposing 25-cm electrodes were generally used for heating the liver tumors. Our standard protocol was to administer hyperthermia 40–50 min twice a week for a total of eight sessions. The liver tumor temperature was measured by microthermocouples when possible. Transcatheter arterial embolization, radiotherapy, immunotherapy, and chemotherapy were combined with hyperthermia treatment in accordance with each patient's liver function.

Results: One hundred forty (81%) of the 173 patients who underwent more than four sessions of hyperthermia were evaluated in this study. Thermometry was performed in 77 (55%) of these 140 patients. The maximum tumor temperature, average tumor temperature, and minimum tumor temperature in the HCC were (mean ± standard error) 41.2 ± 0.2°C, 40.3 ± 1.3°C, and 40.1 ± 0.2°C, respectively. The same thermometry results for non-HCC were 42.3 ± 0.2°C, 41.2 ± 0.2°C, and 40.9 ± 0.2°C, respectively. The maximum and minimum temperatures (41.8 ± 0.2°C and 40.3 ± 0.4°C) in the patients with a complete or partial response (CR or PR) were higher than those in the patients with no response or progressive disease (NR or PD) (41.3 ± 0.5°C and 39.8 ± 0.4°C), but the difference was not significant. Of the 73 cases with HCC who were evaluated by computed tomography (CT), CR was achieved in 7 (10%), PR in 15 (21%), NR in 37 (51%), and PD in 14 (19%). Of the 45 cases involving liver metastases evaluated by CT, CR was achieved in 3 (7%), PR in 17 (38%), NR in 12 (27%), and PD in 13 (29%). The 1-year cumulative survival rate for HCC patients was 30.0%, and the 5-year survival rate was 17.5%. The 1-year survival of non-HCC patients was 32.5%, and the longest survival was 30 months. The sequelae of hyperthermia included focal fat necrosis in 20 patients (12%), gastric ulceration in 4 (2%), and liver necrosis in 1 (1%). The sequelae of thermometry were severe peritoneal pain in seven patients (11%), intraperitoneal hematoma in one (1%), and pneumothorax in one (1%).

Conclusion: Even though the thermometry results for liver tumors were not satisfactory, the treatment results are promising. Further clinical trials of RF capacitive hyperthermia for the treatment of advanced liver tumors should be encouraged.

Radiofrequency hyperthermia, Liver tumor, Hepatocellular carcinoma, Thermometry.

INTRODUCTION

The number of patients with malignant liver tumors is increasing in Japan. Most such patients are not candidates for curative surgery because of multiple liver tumors. However, the many other chemotherapeutic regimens and other modalities currently in use have not shown remarkable satisfactory effects.

At Kyoto University Hospital, radiofrequency (RF) capacitive heating equipment was developed in 1979 for the treatment of deep-seated tumors. We have applied it to liver tumors since 1983. We have already reported our preliminary results (1–3, 7–9). Here we report our clinical results of RF thermotherapy for liver tumors followed-up as long as 12 years.

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METHODS AND MATERIALS

Patient profile

One hundred seventy-three patients with malignant liver tumors were administered hyperthermia between 1983 and 1995. The 173 tumors consisted of 114 HCCs and 59 non-HCC tumors. The HCC tumors consisted of 70 massive type, 24 nodular type, and 20 diffuse type. The non-HCC tumors consisted of 12 cholangiocarcinomas and 47 metastatic liver tumors. The 47 metastatic liver tumors consisted of 20 colon cancers, 5 gall bladder cancers, 5 stomach cancers, 4 pancreas cancers, and 13 other tumors. The 114 patients with HCC consisted of 98 males and 16 females. Their average age was 57.6 ± 10.1 years. The 59 patients with non-HCC consisted of 37 males and 22 females. Their average age was 56.0 ± 11.1 years.

Heating methods

Radiofrequency capacitive heating equipment (8MHz, Thermotron RF-8; Yamamoto Vinyter Co. Ltd., Osaka, Japan) was used for hyperthermia. Two opposing 25-cm electrodes were generally used for heating the liver tumors. The electrodes were covered with a water pad. Heat was applied through a pair of electrodes placed on opposite sides of the hepatic regions. Hyperthermia was usually applied from the anterioposterior (AP) direction. If the patient complained of severe epigastric focal heat pain, the hyperthermia was changed to the lateral direction. After 1986, all patients were surrounded by an overlay water bolus under the electrode to eliminate the focal heat hot spot. As much power as the patient could endure was administered. The maximal power of the machine was 1500 W. Our standard protocol was to administer hyperthermia for 40–50 min twice a week for a total of eight sessions when combined with transcatheter arterial embolization (TAE) or immunotherapy, or used alone. When combined with radiotherapy or chemotherapy, the protocol was once a week for a total of four or five sessions. Blood pressure and pulse rate were monitored every 5 min during hyperthermia. Body temperature was measured twice before and after hyperthermia.

Thermometry

Temperatures of the liver tumor were measured by thin Teflon-coated probes of copper-constantan microthermocouples (Physitemp, Inc., Clifton, NJ). The temperature distributions in the tumor and normal liver during hyperthermia were investigated. In each patient, a single catheter was inserted into the liver tumor through the normal liver with the aid of ultrasonography. The position of the catheter was checked using CT after the hyperthermia treatment. A thermocouple was placed in the catheter and the temperature in the liver was scanned during heating. At 20 min during hyperthermia and immediately after treatment, the probe was removed by 1-cm increments and the temperature at each point was measured through the single catheter.

We defined the maximum tumor temperature as the maximum temperature obtained in the tumor during the steady state and at the end of treatment. The steady state was defined at 20 min after the start of hyperthermia. The minimum intratumor temperature was defined as the minimum tumor temperature obtained by the same method. All parameters were determined for each treatment session, and the averages of these parameters were calculated over all treatments for a given tumor (T_{max}, T_{min}).

Combination therapy

Transcatheter arterial embolization, radiotherapy, immunotherapy, and chemotherapy were combined with hyperthermia treatment in accordance with each patient's liver function.

Of the HCC patients, most who were referred to our department were not only inoperable but also not indicated for TAE. TAE was combined in only 12 patients with HCC and in 15 patients with non-HCC. The feeding arteries were embolized with gelatin sponge particles to decrease the tumor blood flow, except when the tumor was accompanied by portal thrombus or arteriovenous shunting.

When the tumor was located in the lateral segment of left lobe or posterior segment of right lobe, radiotherapy was combined. Radiotherapy was combined with hyperthermia in 15 cases of HCC and 8 cases of non-HCC. Radiotherapy was performed with 10- or 15-MV X rays using a linear accerelator, and 1.8–2.0 Gy was given daily five times a week for a total of 50–60 Gy. The total dose was determined by the patient's condition. The field margin was 1 cm and the average field size was 99 cm^2. The field direction was usually anterorposterior or anteriolateral.

Most of the patients who were not indicated for either TAE or radiotherapy received treatment combined with immunotherapy. Because of the limitation of the external hyperthermia, systemic or intraarterial immunotherapy was combined to increase body temperature. A total of 0.5–5 KE U of picibanyl (OK-432; Chugai Pharmaceuticals, Tokyo, Japan) (12, 13) was used for the purpose of systemic hyperthermia in 22 patients, either intravenously or intraarterially. Picibanyl is an endotoxic agent derived from *Streptococcus,* which usually increases the body temperature of a patient injected, by about 1°–3°C. In two patients whose intraliver tumor temperature was measured, the temperature was 39.0°C even before hyperthermia.

When neither TAE, radiation, nor immunotherapy was indicated, only chemotherapy was combined with hyperthermia (18 HCC patients and 9 non-HCC patients). Doxorubicin (10–20 mg) and mitomycin (4–6 mg) were infused either intraarterially or intravenously every 2 weeks for a total of four to six sessions.

When all of these combination therapies were not indicated, we applied hyperthermia alone (16 HCC patients and 8 non-HCC patients).

Therapeutic effects

The therapeutic efficacy of each treatment regimen was evaluated by the change in tumor size assessed by CT 3 months after the completion of treatment.

The criteria proposed by the Japanese Society of Cancer Therapy were used for evaluation. A complete response (CR) was defined as the complete disappearance of the tumor. A partial response (PR) was 50–99% tumor regression in the product of two orthogonal diameters. No response (NR) was between 50% tumor regression and 25% tumor progression. Progressive disease (PD) was defined as a >25% increase in tumor size.

Survival was evaluated using the Kaplan–Meier method. The significance of differences between survival curves was determined by the generalized Wilcoxon test. Probability (p) values < 0.05 were considered significant.

RESULTS

Treatment results

The average number of hyperthermia sessions for the HCC patients was 6.5 ± 3.9. The average duration of each session was 40.5 ± 3.4 min. The average maximum power of the RF machine used was 830 ± 220 W.

The average number of hyperthermia sessions for the non-HCC patients was 7.1 ± 4.6. The average duration of each session was 41.4 ± 2.6 min. The average maximum power used was 906 ± 170 W.

For 173 patients, we applied hyperthermia treatment 1154 times. The number of the patients treated more than four times with hyperthermia was 140 (90 cases with HCC and 50 with non-HCC). Twenty-four patients with HCC and nine with non-HCC could not be treated more than four times with hyperthermia. Six cases with HCC and three with non-HCC could not continue hyperthermia because of focal heat pain. All of these patients were obese, with a subcutaneous fat tissue thickness > 20 mm. Eighteen patients with HCC and five patients with non-HCC could not continue hyperthermia because of their poor liver function. These patients had massive ascites, jaundice, or ruptured esophageal varices. These symptoms were caused by progressive liver cirrhosis. One non-HCC patient could not continue hyperthermia because of vasovagal shock during thermometry in the second hyperthermia treatment.

Of the 140 patients who were treated with hyperthermia more than four times, thermometry was performed 51 times in 45 cases with HCC, and 45 times in 32 cases with non-HCC. The 45 other HCC patients and 18 non-HCC patients did not receive thermometry; bleeding tendency because of poor liver function was the reason in 22 HCC and 7 non-HCC patients. The tumor location made thermometry impossible (superficial protruding tumor with a risk of rupture) in 11 HCC patients and 1 non-HCC patient. Massive ascites was the reason for two patients with HCC and two with non-HCC. Other causes such as insertion failure and patient refusal were the reasons for the other 10 HCC patients and 8 non-HCC patients.

Patients who could not tolerate more than four sessions of hyperthermia or whose follow-up CT could not be scanned were excluded from this study. Finally, of the patients who received hyperthermia more than four times, 73 (81%) of the 90 HCC patients, and 45 (90%) of the non-HCC 50 patients were clinically evaluated for the therapeutic effect of hyperthermia.

Thermometry results

The thermometry results for the HCC cases were tumor maximum temperature of 41.2 ± 0.2°C, tumor average temperature of 40.3 ± 0.3°C, and tumor minimum temperature of 40.1 ± 0.2°C. The temperature results were separated into three tumor subtypes. The tumor maximum and minimum temperatures were 41.1 ± 0.2°C and 40.0 ± 0.2°C, respectively, for massive-type, 41.0 ± 0.3°C and 40.0 ± 0.4°C, respectively, for nodular-type, and 42.1 ± 0.6°C and 40.6 ± 0.5°C, respectively, for diffuse-type tumors (Figs. 1 and 2).

The thermometry results for the non-HCC cases were tumor maximum temperature of 42.4 ± 0.2°C, tumor average temperature of 41.8 ± 0.2°C, and tumor minimum temperature of 40.7 ± 0.2°C.

The maximum temperature of normal liver for all patients was 39.6 ± 0.2°C, and that of subcutaneous fat was 40.3 ± 0.3°C.

Toxicity results

Blood pressure was compared before and after hyperthermia. The systolic blood pressure and diastolic blood pressure changed after hyperthermia, but not significantly. The average systolic blood pressure was 126.8 ± 1.2 mm Hg (Mean ± SE, $n = 189$) before hyperthermia, and 124.5 ± 1.3 mm Hg after hyperthermia. The average diastolic blood pressure was 77.0 ± 0.8 mm Hg before hyperther-

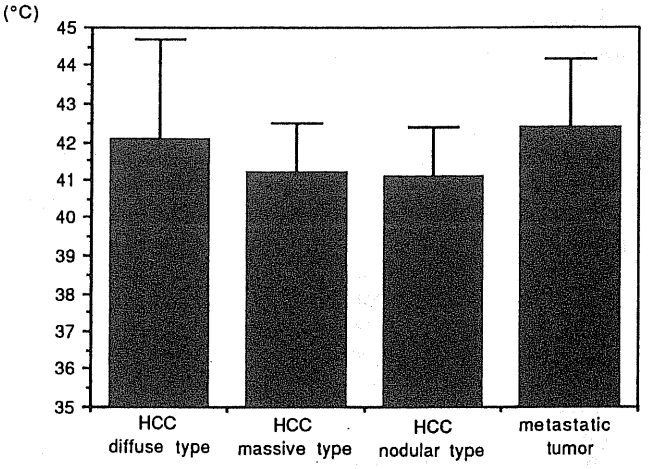

Fig. 1. Tumor maximum temperature was compared among various tumor types. Diffuse-type HCC and metastatic liver tumor showed higher temperatures than the others.

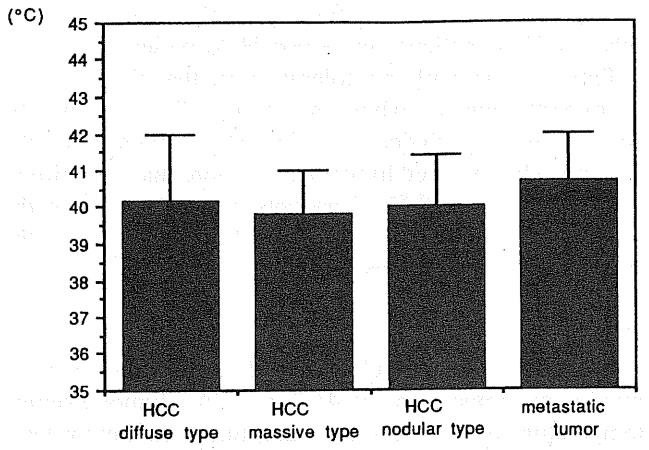

Fig. 2. The minimum temperature was compared among various tumor types. Metastatic tumors showed higher temperatures than the others.

mia, and 75.1 ± 0.8 mm Hg after hyperthermia. The pressure gap before hyperthermia was 49.8 ± 0.7 mm Hg, and 49.3 ± 0.9 mm Hg after hyperthermia. As mentioned in our previous paper (8), patients' blood pressure responses differed. Blood pressure increased after hyperthermia in 50% of the patients and decreased in the other 50%. However, in a single patient the blood pressure response to each hyperthermia session was usually the same.

In the present series, the pulse rate markedly increased after hyperthermia in most of the patients, from 82.8 ± 1.1 beats/min before hyperthermia to 96.5 ± 1.3 beats/min afterward. The pulse rate of only 21 patients (11%) decreased after hyperthermia.

Body temperature was also measured in 54 patients before and after hyperthermia. The body temperature before hyperthermia was 36.3 ± 0.1°C, and 37.4 ± 0.2°C after hyperthermia. In almost all patients, body temperature increased after hyperthermia.

The sequelae of the hyperthermia were not too severe. Heat burn of the subcutaneous fat tissue occurred in 20 of 173 cases (12%). Gastric ulceration occurred in 4 of 173 cases (2%). Liver function as measured by glutamate oxaloacetate transaminase (GOT), glutamate pyruvate transaminase (GPT), and alkaline phosphatase (ALP) was slightly elevated after hyperthermia, which did not markedly change the patients' condition. In one case, widespread liver necrosis developed in the left lobe of the liver, where the tumor was located. Thereafter, the tumor was controlled after hyperthermia.

Sequelae of thermometry occurred in 9 of 77 cases (11%). Intraabdominal hematoma and pneumothorax developed in one patient. Continuous severe peritoneal pain occurred in seven cases, which spontaneously disappeared within a day.

Local tumor control

As shown in Table 1, of the 73 HCC cases evaluated by CT, 7 (10%) had a CR, 15 (21%) had a PR, 37 (51%) had a NR, and 14 (19%) developed a PD.

According to the various combination therapy, the CR, PR, NR, and PD rates in the HCC group were 1 of 11 (9%), 5 of 11 (45%), 3 of 11 (27%), and 2 of 11 (18%) with TAE; 0, 0, 14 of 18 (78%), and 4 of 18 (22%) with chemotherapy; 6 of 14 (43%), 3 of 14 (21%), 5 of 14 (36%), and 0 with immunotherapy; 0, 7 of 14 (50%), 6 of 14 (43%), and 1 of 14 (7%) with radiotherapy; and 0, 0, 9 of 16 (56%), and 7 of 16 (44%) with no other combination therapy, respectively.

Of the 45 non-HCC cases who were evaluated by CT, CR was obtained 3 (7%), PR in 17 (38%), NR in 12 (27%), and PD in 13 (29%).

According to combination therapy, the CR, PR, NR, and PD rates in the non-HCC group were 3 of 15 (20%), 6 of 15 (40%), 3 of 15 (20%), and 3 of 15 (20%) with TAE, 0, 5 of 9 (56%), 0, and 4 of 9 (44%) with chemotherapy; 0, 1 of 5 (20%), 4 of 5 (80%), and 0 with immunotherapy; 0, 5 of 8 (63%), 2 of 8 (25%), and 1 of 8 (12%) with radiotherapy; and 0, 0, 3 of 8 (37%), and 5 of 8 (63%) with no other combination therapy, respectively.

Tumor temperature and local control

The relationship between tumor temperature and local response rate was evaluated in patients with HCC (Figs. 3a,b).

Table 1. Local response of tumor in each combination therapy

	TAE	Radiation	Immunotherapy	Chemotherapy	None	Total
HCC						
CR	1/11 (9%)	0	6/14 (43%)	0	0	7/73 (10%)
PR	5/11 (45%)	7/14 (50%)	3/14 (21%)	0	0	15/73 (21%)
NC	3/11 (27%)	6/14 (43%)	5/14 (36%)	14/18 (78%)	9/16 (56%)	37/73 (51%)
PD	2/11 (18%)	1/14 (7%)	0	4/18 (22%)	7/16 (44%)	14/73 (19%)
Total	11	14	14	18	16	73
Non-HCC						
CR	3/15 (20%)	0	0	0	0	3/45 (7%)
PR	6/15 (40%)	1/5 (20%)	5/8 (63%)	5/9 (56%)	0	17/45 (38%)
NC	3/15 (20%)	4/5 (80%)	2/8 (25%)	0	3/8 (37%)	12/45 (27%)
PD	3/15 (20%)	0	1/8 (12%)	4/9 (44%)	5/8 (63%)	13/45 (29%)
Total	15	5	8	9	8	45

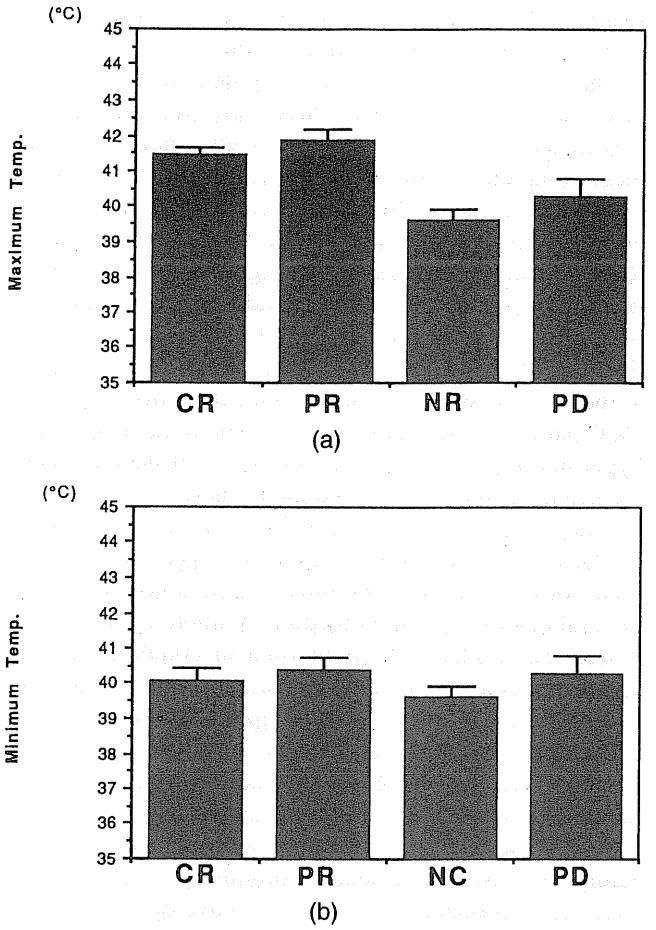

Fig. 3. The relationship between maximum tumor temperature (a) and minimum tumor temperature (b). The CR and PR groups showed higher tumor temperature than the NR and PD groups. CR = complete response; PR = partial response; NR = no response; PD = progressive disease.

The average maximum temperatures of the patients with CR, PR, NR, and PD were 41.5 ± 0.2°C, 41.9 ± 0.3°C, 41.1 ± 0.4°C, and 41.5 ± 0.7°C, respectively. The average minimum temperatures of the patients were 40.1 ± 0.4°C, 40.4 ± 0.4°C, 39.6 ± 0.3°C, and 40.2 ± 0.5°C, respectively. The maximum and minimum temperatures of the patients with CR and PR (41.8 ± 0.2°C and 40.3 ± 0.4°C) were higher than in the patients with NR and PD (41.3 ± 0.5°C and 39.8 ± 0.4°C), but not significantly.

Survival

The cumulative survival rate of the HCC and non-HCC patients are shown in Fig. 4.

The 1-year cumulative survival rate of the HCC patients was 30.0%, and the 5-year survival rate was 17.5%. The median survival was 5 months, and the longest survival was 144 months. The number of patients who survived >3 years was 10, of whom 5 were complete responders and had no further recurrence.

Significant differences between the therapy regimens were found only between immunotherapy and hyperthermia alone ($p < 0.01$) and between immunotherapy and chemotherapy ($p < 0.01$).

The 1-year cumulative survival rate of the non-HCC patients was 32.5%, and the 5-year survival rate was 0%. The median survival was 5 months, and the longest survival was 30 months.

DISCUSSION

The treatment results showed us that 33 (19%) of the patients could not be administered hyperthermia more than four times. However, only nine (5%) of the patients could not tolerate hyperthermia because of focal heat pain. Twenty-four (14%) of the other patients had poor liver function and could not tolerate the hyperthermia. They had massive ascites, jaundice, or ruptured esophageal varices. Therefore, four sessions of radiofrequency hyperthermia were tolerable in patients with advanced liver tumors when their general condition was not bad and the thickness of subcutaneous fat tissue was < 20 mm.

The toxicity results were informative. Eight-megahertz RF hyperthermia was performed 1154 times on 173 patients, and no serious systemic effect was encountered. Of course, patients with a pacemaker were not given hyperthermia treatment. In the patients treated, no serious general or cardiac complication was evoked. In general, pulse rates increased after hyperthermia, and body temperature also increased after hyperthermia. These two systemic factors apparently reflect the systemic hyperthermic effect on the patients. The systolic and diastolic blood pressures changed individually, probably caused by the balance between cardiac output and peripheral vascular vasodilatation.

The most frequent complication was mild subcutaneous fat necrosis, which occurred in 12%. It sometimes appeared a day after hyperthermia, and disappeared within a month. Gastric ulceration occurred in four patients because of excess heating of the stomach. Although the gastric ulceration rate was low, the ulcerations continued for a few months. There-

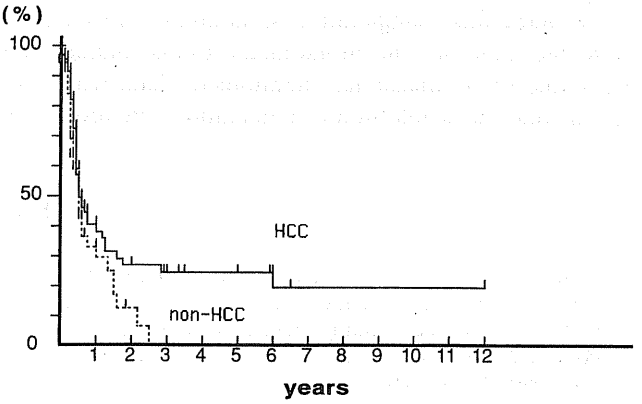

Fig. 4. Cumulative survival rates of HCC and non-HCC.

fore, antiulcerative treatment should be carefully combined before and after hyperthermia. In contrast, liver function did not change markedly after hyperthermia.

Thermometry was performed in 77 (55%) of the 140 patients who received four or more hyperthermia sessions. In the other 45% of those 140 patients, the accompanied bleeding tendency with poor liver function, the tumor location, or massive ascites made it very hard to measure the intratumor temperatures. Sequelae caused by thermometry were noted in only nine patients (11%). Two of them were serious, with intraperitoneal hematoma or pneumothorax. Therefore, noninvasive thermometry using MRI (6) is strongly expected for thermometry of the liver tumors.

Our limited thermometry results showed us the intratumor temperature of different tumor types. Among diffuse, nodular, and massive types of HCC, the diffuse type could be heated to a higher temperature than the nodular and massive types. This may be attributable to the tumor vascularity. The diffuse-type tumor is less vascular than the massive-type and nodular-type tumor. Non-HCC tumors could be heated to a higher temperature than HCC, which also could be caused by their poor vascularity.

The local tumor control rate was evaluated for each combination therapy. The patient's liver function was better when combined with TAE, radiation, immunotherapy, or chemotherapy, respectively in that order. The local tumor control rate of the patients with HCC was best by hyperthermia treatment combined with immunotherapy. Because most of the liver tumors could not be heated to more than 42.0°C, another adjuvant therapy to increase intratumor temperature is necessary. The systemic hyperthermic effect using picibanyl as an immunotherapy was helpful to the hyperthermia treatment. Therefore, hyperthermia for HCC should be combined with immunotherapy to increase the intratumor temperature. For patients with non-HCC, TAE was as effective as immunotherapy. TAE was also helpful for local hyperthermia. For non-HCC, TAE is recommended as the best adjuvant therapy for hyperthermia.

A relationship between tumor temperature and local control was demonstrated. Patients with CR and PR had a higher intratumor temperature. However, patients with a low intratumor temperature sometimes showed a remarkable response. The thermometry results obtained here are single two-dimensional thermometry data which did not include the whole tumor temperature. Therefore, the relationship between intratumor temperature and local tumor control should be carefully evaluated.

The survival of the patients with HCC was 30.0% at 1 year and 17.5% at 5 years. There were five patients with a complete response. Compared with other modalities, these complete responders suggested a dramatic response of the tumor caused by hyperthermia. Hyperthermia-induced protein denaturation in the liver is being studied. Ritchie *et al.* demonstrated that significant protein denaturation occurs in liver during mild hyperthermia at 40–45°C (10). Further biological and immunological investigations of this phenomenon are forthcoming. In contrast to the present HCC results, the clinical results of the non-HCC patients were relatively poor. The initial response to hyperthermia was favorable; however, all patients had a recurrence within 3 years and died. Therefore, further experimental investigations and clinical trials are needed.

There are several clinical reports on hyperthermia treatment for liver tumors. The most common protocols were in combination with embolization. Yumoto *et al.* (14) reported the results of hyperthermia in combination with styrene maleic anhydride neocarzinostatin (SMANCS) and doxorubicin suspension in lipiodol. Their local response rate was 40% in 10 cases with hyperthermia and embolization, and 20% in 10 cases with embolization alone. The former group had a significantly better survival rate than the latter. Temperature-sensitive liposomal adriamycin is also experimentally promising (15, 16). However, no established clinical reports have been published. Combination therapy of chemohyperthermia was reported by Maeta *et al.* (5). They reported that the local control rate of HCC was 2 of 8 (25%) and that of liver metastases was 9 of 24 (38%). Thermoradiotherapy was reported by Kim *et al.* (4) and Seong *et al.* (11). Their local response rate was 27 of 67 (40%), the 1 year survival was 44.8%, and the 3-year survival was 15.6%.

The present series is the largest treated by 8-MHz RF capacitive heating equipment. The sequelae of hyperthermia were not severe. Therefore, RF hyperthermia could be considered a safe treatment modality even for patients with advanced liver tumors.

In conclusion, hyperthermia can be considered an effective treatment modality for advanced diffuse-type HCC, especially combined with immunotherapy. Hyperthermia should be considered an adjuvant treatment method for non-HCC in combination with TAE, chemotherapy, or radiotherapy.

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