Ultrasonically Guided Percutaneous Microwave Coagulation Therapy for Small Hepatocellular Carcinoma

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Background. The authors have used percutaneous microwave coagulation therapy (PMCT) as a new percutaneous local treatment for single unresectable hepatocellular carcinoma (HCC) measuring 2 cm or less in greatest dimension (small HCC). PMCT was used to attempt a cure of the disease. In this study, the efficacy of this treatment was assessed.

Methods. PMCT was performed on 18 patients with single small HCC. A microwave electrode (custom-made, 30-cm long by 1.6-mm thick) was inserted percutaneously into the tumor area under ultrasonic guidance. Microwaves at 60 W for 120 seconds were used to irradiate the tumor and surrounding area.

Results. After PMCT was administered, various image findings were correlated with tissue necrosis. At the tumor and surrounding area, ultrasonography showed echogenic change, contrast enhancement disappeared on contrast enhanced computed tomography, and magnetic resonance imaging (T2-weighted image) showed decreased intensity in all cases after treatment. Complete necrosis of the tumor area in a specimen obtained from one patient who underwent hepatectomy after PMCT also was confirmed.

The treatment reduced levels of the tumor marker, alpha-fetoprotein, which had been high in some patients. Although the follow-up period was short (11–33 months), 17 patients remain alive. Local recurrence in the treated area has not been detected, and no serious side effects or complications have been encountered.

Conclusions. PMCT may be an effective and safe treatment for small HCCs. *Cancer* 1994; 74:817–25.

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Improvements in real-time ultrasonography have markedly increased the rate of detection of liver tumors, especially small nodular lesions. Similarly, precision in the pathologic diagnosis of small liver tumors has markedly improved because of advances in ultrasonography-guided fine needle biopsy.[1-3] In Japan, the incidence of small hepatocellular carcinoma (HCC) in patients with liver cirrhosis is high, and periodic ultrasonographic examination of patients with cirrhosis for detection of single HCC measuring 2 cm or less is considered an important procedure. To illustrate the accuracy of this procedure, the incidence of detecting these small HCCs has recently increased in Japan.[4,5]

As the initial treatment for small HCC, surgical resection, transcatheter arterial embolization,[6] and ultrasonography-guided local treatment have been performed alone or in combination. Surgical resection is not a viable option for all patients due to poor liver function induced by liver cirrhosis. Furthermore, transcatheter arterial embolization is sometimes ineffective because of inadequate angioneogenesis in small HCC.[7]

For these reasons, ultrasonography-guided percutaneous local treatment has been adopted independently or in combination with transcatheter arterial embolization. Percutaneous ethanol injection therapy (PEIT) is widely performed as a percutaneous local treatment because of its simplicity and low cost.[8-10] However, this modality is occasionally ineffective because of inhomogeneous distribution within the tumor.[8,11] There is therefore a need for more effective technique for destroying small HCC. We formulated ultrasonography-guided percutaneous microwave coagu-

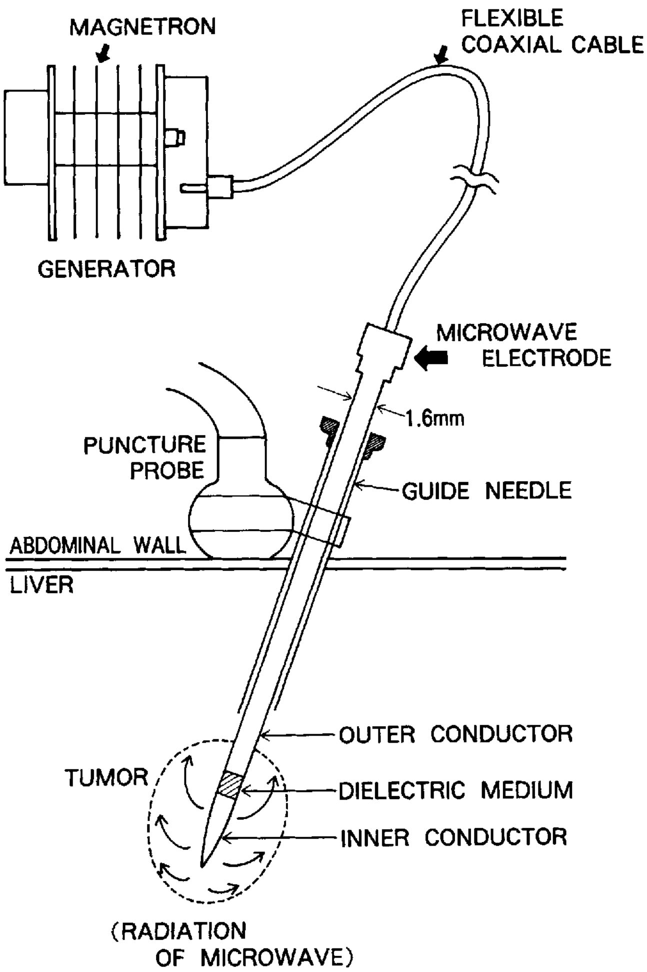

Figure 1. Illustration of the PMCT technique.

lation therapy (PMCT) as a new method of percutaneous local treatment to induce tumor necrosis.

In the current report, we present our clinical experience using PMCT alone for small HCCs.

Methods

Treatment Modalities

Microwave delivery system. The system consists of a magnetron, a flexible coaxial cable, and a microwave electrode. We used the microwave tissue coagulator (Microtaze HSE-8) designed by Heiwa Denshi Kogyo (Osaka, Japan) as a medical magnetron. Microwaves at a frequency of 2450 MHz can be generated by this medical magnetron (Fig. 1).

The high frequency energy, transmitted to the electrode through a coaxial cable, irradiates the target tissue. Tissue coagulation is induced by the heating effect of the microwaves.

Microwave electrode. The electrode is 1.6 mm thick and 30 cm long. At the electrode terminus, 1 cm of the inner conductor is exposed and is insulated from the circular outer conductor by silicone gum. The surface of the electrode is coated with polytetrafluorethylene (PTFE) to prevent the coagulated tissue from adhering to the electrode. For heat and electrical insulation, the space between the inner and outer conductors is filled with silicone gum and PTFE (Fig. 2).

Power Output Assessment

In vitro evaluation of heat dissipation was performed by assessing temperature changes in egg white heated by the microwave electrode. The extent of heating was measured using a thermographic camera (Infra-Eye180, Fujitu Limited, Tokyo). The results of such thermographic imaging are shown in Figure 3. This heating pattern did not change with change of insertion depth in egg white. Egg white in a glass chamber was heated by microwaves.

With irradiation at 60 W for 120 seconds, it was possible to raise the temperature over 56°C in an area 3.5 cm in maximal diameter and 2.5 cm in minimal diameter at the tip of the electrode. At this power and duration, the temperature of the shaft of the electrode did not exceed 50°C. If the power and duration of irradiation exceeded 60 W and 120 seconds, respectively, the temperature of the shaft exceeded 50°C. At this temperature, the skin may burn where the electrode has been inserted, even though the heat generated at the tip dissipates over a wider area. Therefore, we decided to

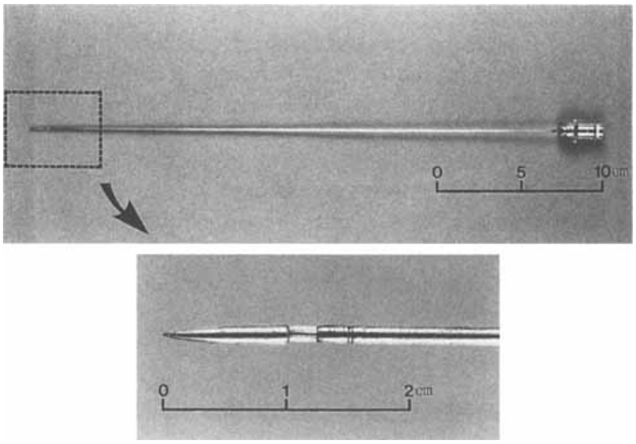

Figure 2. The custom-made microwave electrode. The conductor was stainless steel.

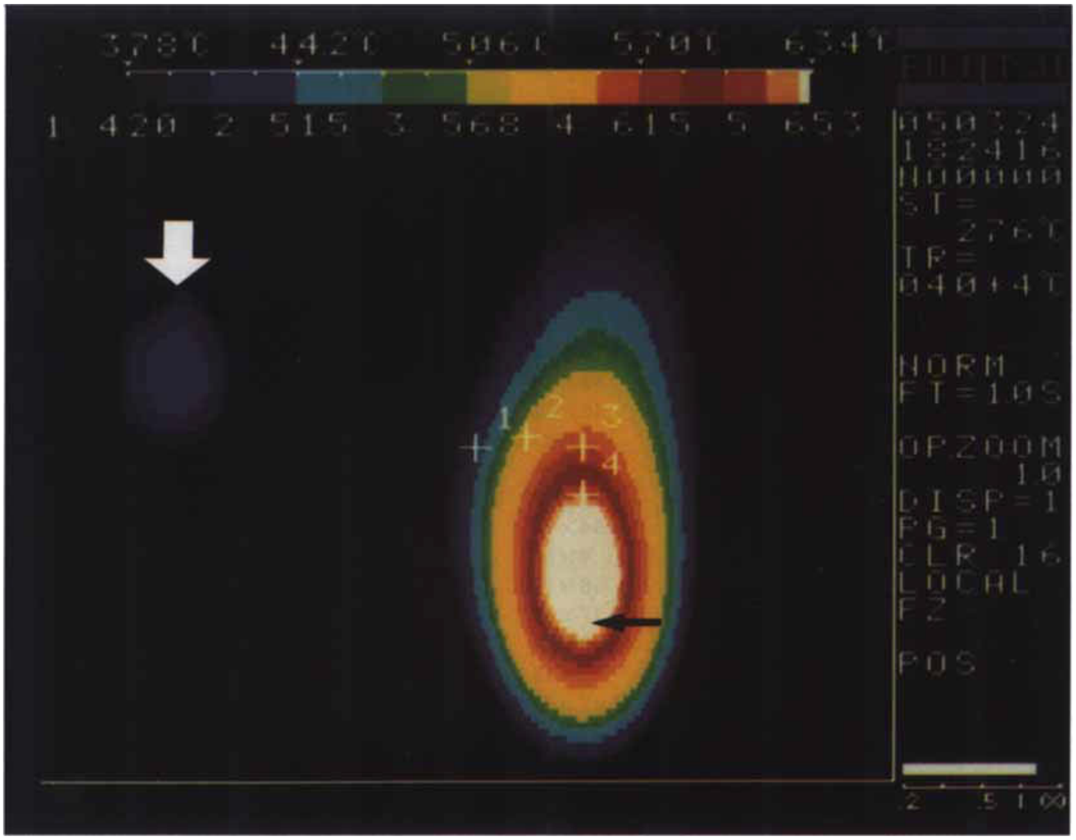

Figure 3. Thermographic appearance of microwave-irradiated (60 W, 120 seconds) egg white. (White arrow) A 10-yen coin (about 2.3 cm in diameter), used as a reference point. (Black arrow) The tip of microwave electrode. The temperature in the interior of the yellow area increased to more than 50°C; the orange area, to 56°C.

set the power and duration of microwaves at 60 W and 120 seconds, respectively, to prevent skin injury during clinical use.

Five healthy, fasting adult white rabbits (mean weight, 2.5 kg) were used. They were immobilized in the supine position and placed under ketamine hydrochloride anesthesia (1 mg/kg intramuscularly).

The right hepatic lobe was exposed through a median incision on the abdomen. The microwave electrode was inserted into the right lobe and the area was irradiated at 60 W for 120 seconds. The abdomen was then closed. The animals were killed 3 days later and the coagulated areas were observed.

The coagulated area was elliptic, with maximal and minimal diameters of 2.4 plus or minus 0.4 cm and 1.6 plus or minus 0.3 cm, respectively.

Clinical Subjects

The 18 patients who underwent PMCT (see Table 1) each had a single HCC measuring 2 cm or less in greatest dimension (small HCC: Stage I, according to the International Union Against Cancer[12]). In all cases, histologic diagnosis was confirmed by ultrasonography-guided fine needle biopsy performed at our hospital. Subjects were 16 men and 2 women ranging in age from 43 to 73 years (mean, 61 years). All were diagnosed with liver cirrhosis and were positive for hepatitis C virus antibody (c100-3). The site of the lesion was defined according to Couinaud's segmental model of the liver.[13]

In the current study, 17 patients were not surgical candidates for the following reasons:

1. Insufficient hepatic reserve for curative resection (Patients 3, 4, 6, 7, 10, 14, 15, 16, 17, and 18): These patients had deep-seated tumors despite the small size of HCC, thus wedge resection could not be performed.
2. Other high surgical risks, such as renal failure (Patient 5), pulmonary fibrosis (Patient 8), and ischemic heart disease (Patient 11)
3. Refusal by patients (Patients 1, 2, 9, and 13).

Table 1. Summary of 18 Patients With Small Hepatocellular Carcinoma Treated by Percutaneous Microwave Coagulation Therapy

Patient no.	Age (yr)	Sex	Child's class	Tumor size (mm)	Site	Serum AFP (ng/ml)	No. of times of PMCT	Prognosis (mo)
1	60	M	A	14 × 11	S8	19	2	33 alive
2	43	M	A	15 × 13	S8	39	2	33 alive
3	63	M	B	15 × 10	S8	12	2	32 alive
4	58	M	B	20 × 15	S4	148	4	22 died
5	66	M	A	20 × 19	S4	1190	4	26 alive
6	56	M	B	20 × 20	S5	89	4	25 alive
7	58	M	B	11 × 10	S8	61	1	24 alive
8	73	M	A	18 × 12	S5	33	3	21 alive
9	67	M	A	20 × 17	S8	35	4	19 alive
10	64	M	C	17 × 14	S4	147	3	17 alive
11	65	M	A	20 × 18	S5	5	4	15 alive
12	69	M	A	14 × 11	S8	33	2	Operation
13	46	F	A	9 × 8	S3	6	1	13 alive
14	57	M	C	18 × 17	S7	13	4	13 alive
15	60	M	B	17 × 14	S5	14	3	13 alive
16	59	M	C	20 × 19	S2	392	4	13 alive
17	70	F	B	15 × 15	S8	150	2	11 alive
18	60	M	B	17 × 14	S7	67	3	11 alive

AFP: alpha-fetoprotein; M: male; F: female; PMCT: percutaneous microwave coagulation therapy.

One patient (Patient 12) underwent elective hepatic resection 30 days after PMCT. To evaluate the efficacy of PMCT independently, transcatheter arterial embolization was not administered.

All procedures were thoroughly explained to the patients, and informed consent was obtained from each.

Clinical Method

An intravenous route was established, and 15 mg of pentazocine, an analgesic, were administered intravenously as a premedication. After the location of the tumor was confirmed using ultrasonography (RT-2800, 3.5 MHz Convex transducer, Yokogawa, Tokyo), the puncture line from the point of insertion of the electrode to the mass lesion was determined. Local anesthesia was induced along the puncture line by introducing 0.5% lidocaine from the insertion point at the skin to the peritoneum. Under ultrasonic guidance, a 14-gauge 15-cm guide needle was inserted in the vicinity of the tumor. After the inner needle of the guide was removed, the microwave electrode was inserted through the outer needle of the guide to place the electrode in the tumor area. The electrode was connected to the microwave generator through a flexible coaxial cable. The tumor area was then irradiated with microwaves at 60 W for 120 seconds. The electrode and the outer needle of the guide were then removed. The puncture line was irradiated with microwaves to prevent bleeding from the hepatic surface when the electrode was removed. This procedure constituted a single treatment.

The tumor and the surrounding parenchyma were treated several times (twice a week). The number of treatments was determined by findings on imaging studies. The interval between treatments was determined by the patient's compliance.

For imaging, ultrasonography, plain computed tomography ([P-CT] Xeed, TSX-001A, Toshiba, Tokyo), contrast-enhanced computed tomography ([CE-CT], TSX-001A, Toshiba) with drip infusion method, and magnetic resonance imaging (MRI, 1.5 T: superconducting unit, spin-echo sequence, repetition time/echo time = 2000/80 msec, T2-weighted image, MRT200-FXS, Toshiba) were used.

Ultrasonography was performed before, during, and after treatment in all patients. Follow-up ultrasonography was performed every month after completion of the treatment. P-CT, CE-CT, and MRI were performed in all patients before treatment. After treatment, P-CT, CE-CT, and MRI were performed only in patients in whom it had been possible to detect the tumor site by CT and/or MRI before treatment. Follow-up P-CT, CE-

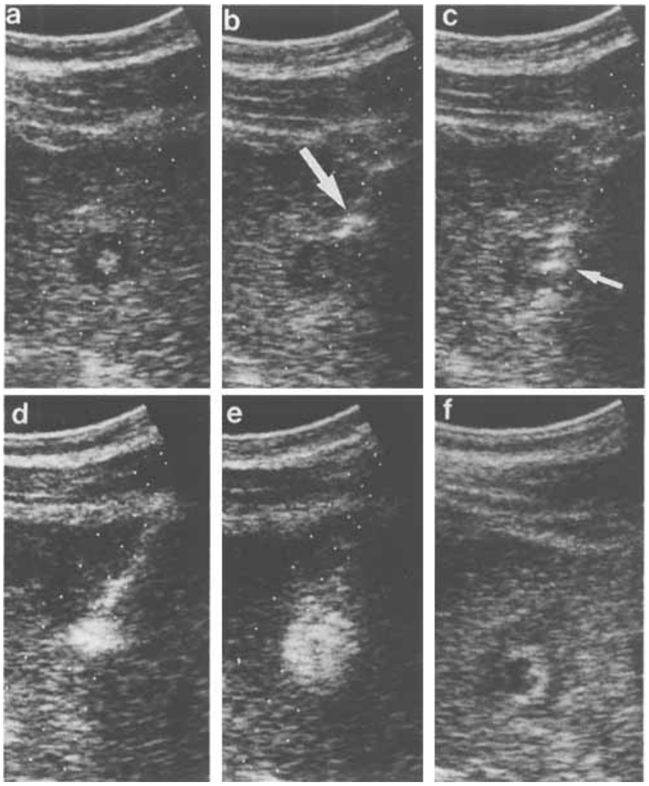

Figure 4. Patient 12: Ultrasonograms before, during, and after PMCT. (a) Before treatment. (b) The guide needle (white arrow) was inserted. (c) The microwave electrode (white arrow) was inserted into the interior of the tumor. (d) The tumor was irradiated. (e) Microwave irradiation was finished. (f) One week after PMCT. The image of the tumor changed from low echo with a high-echo spot to a mixed pattern after PMCT.

CT, and MRI were performed every 3 months after treatment.

Clinical observation periods after treatment ranged from 11 to 33 months.

Results

Change in Tumor Images After PMCT

Ultrasonography findings. Before treatment, the lesions were hypoechoic in 14 patients and hypoechoic with high echo spots in 4. After PMCT, the echogenicity of the tumor area increased and the lesions became hyperechoic in all cases. Within 2 weeks after PMCT, mosaic patterns (hypo-hyperechoic mixed pattern) were evident in all cases. The treated tumors maintained a mosaic pattern during the follow-up period. In two patients (Patients 7 and 13), it became impossible to detect the tumor site after 10 and 12 months, respectively, by monthly follow-up ultrasonography (Fig. 4).

CT findings. In 10 of 18 patients (Patients 3, 4, 5, 6, 8, 11, 14, 15, 16, and 18), the tumor was detected as a low-density area on P-CT before treatment. Of these, five lesions (Patients 4, 5, 6, 11, and 16) were enhanced by CE-CT. In 10 patients after treatment, the tumor and the surrounding area showed decreased density on P-CT and were not enhanced in CE-CT. In follow-up CT, the treated site maintained a low density and were no longer enhanced (Fig. 5).

MRI (T2-weighted) findings. In 8 of the 18 patients (Patients 4, 5, 6, 9, 11, 14, 16, and 18), tumors were identified as a high-intensity area before treatment. In these patients, the tumor area demonstrated a low-intensity area associated with a high-intensity ring surrounding the tumor after treatment. On follow-up MRI, the high-intensity ring gradually decreased in width and intensity and finally disappeared after 3–6 months. The treated low-intensity area remained during the follow-up period.

On CT and MRI during the follow-up period, a low-density and low-intensity treated area slightly decreased in size but did not disappear (Fig. 6).

Clinical Efficacy

Treatment was considered to have produced a sufficient effect and was therefore terminated when ultrasonography showed echogenic change and CE-CT confirmed the disappearance of contrast enhancement and/or MRI showed decreased intensity in the tumor and surrounding area. (Echogenic change, disappearance of enhancement, and change to low intensity after treatment have been correlated with tumor necrosis in other studies in which imaging findings have been correlated with histopathologic specimens.[8,14,15])

After PMCT was performed one to two times for a tumor of 1.5 cm or smaller and three to four times for a tumor greater than 1.5 cm in greatest dimension, various image findings correlated with tissue necrosis were observed at tumor and surrounding parenchyma.

Seventeen patients remain alive and consult our hospital periodically as outpatients. One patient (Patient 4) patient died of subarachnoidal hemorrhage 22 months after PMCT.

The serum alpha-fetoprotein levels decreased after treatment in those patients with a high serum alpha-fetoprotein level (Fig. 7).

Follow-up ultrasonography was conducted every month, and recurrences were detected in three patients (Patient 14 within 9 months, Patient 8 within 10 months, and Patient 6 within 18 months after PMCT). None of the patients with recurrence had shown an el-

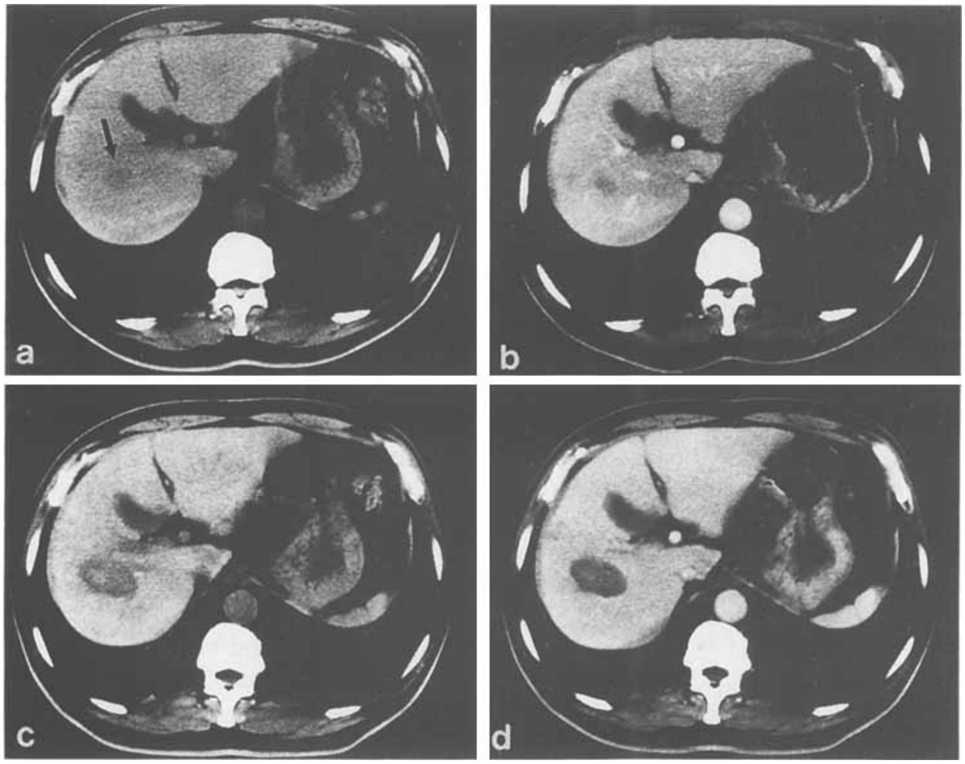

Figure 5. (Patient 14): Plain CT (a and c) and CE-CT (b and d). (a and b) Before treatment. The tumor site (black arrow) is S7. (c and d) One week after treatment. After treatment, the tumor and the surrounding area showed decreased density and were not enhanced.

evated serum alpha-fetoprotein level during the follow-up period. In these patients, recurrent nodules appeared in other subsegments but not at the original site treated by PMCT. These recurrent nodules were of the single nodular type with greatest dimension of 2 cm or smaller. The clinical course of these patients, after retreatment after PMCT, was uneventful, and there have been no further recurrences.

Adverse Effects and Complications of PMCT

All patients reported a slight heat sensation in the upper abdominal region during PMCT. Half of the patients felt some pain during treatment, but we neither discontinued treatment nor administered sedatives, because the pain was mild. After treatment, a transient fever developed in all patients but dissipated the following day.

Serum aminotransferase, alanine aminotransferase, and lactate dehydrogenase showed a transient rise after treatment in many patients but returned to pretreatment levels after approximately 1 week. Prothrombin time and 15-minute indocyanine green retention ratio remained unchanged after treatment. Local dissemination of the cancer cells along the puncture line was not encountered in any case. There were no other clinically relevant side effects or complications noted.

Histopathologic Findings in a Surgically Obtained Specimen

A surgical specimen was obtained from one patient (Patient 12) who had a small HCC measuring 1.4 cm in greatest dimension. This patient underwent elective hepatic subsegmentectomy 30 days after PMCT had been performed twice. Histopathologic findings revealed that thermal coagulation caused necrosis of the tumor and the surrounding parenchyma, leaving no viable cancer cells. A fibrous capsule had formed around the necrotic area (Fig. 8).

Discussion

PEIT is now often performed for patients with small HCCs when surgery is not indicated. Because PEIT is tolerated by most patients, it can be performed easily in those with liver cirrhosis. However, a number of reports in which the effects of PEIT were evaluated histopathologically and clinically have demonstrated that the injected ethanol did not always cause complete necrosis of the tumor.

It is more common in Japan to see HCCs surrounded by a fibrous capsule.[16] However, formation of fibrous capsules surrounding the tumor is often incom-

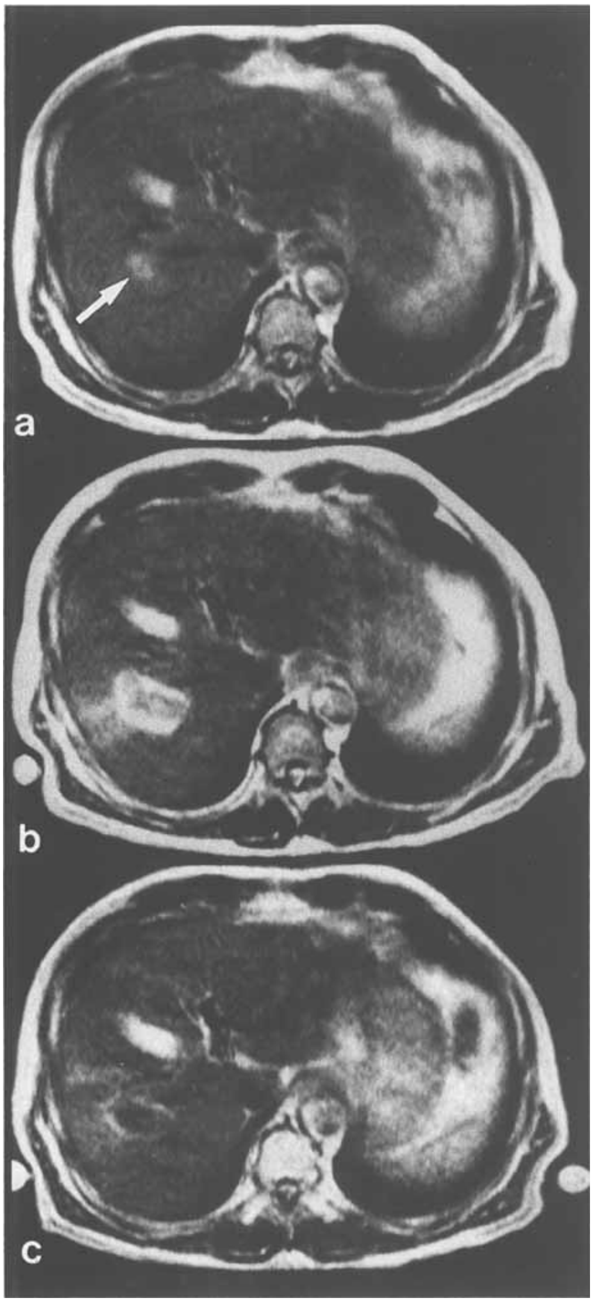

Figure 6. (Patient 14): MRI (T2-weighted images). (a) Before treatment. The tumor site (white arrow) was demonstrated as a high-intensity area. (b) One day after treatment. The tumor site became a low-intensity area, and a high-intensity ring appeared. (c) Two weeks after treatment. The change to low intensity was more marked, and the high-intensity ring was less marked.

plete in small HCCs. In such an instance, injected ethanol may spread to the noncancerous peripheral tissue or may flow into the large vessels around the tumors instead of remaining in the tumor, thus failing to cause tumor necrosis. Even when a fibrous capsule exists but the capsulated area or its periphery has been infiltrated by tumor cells, the injected ethanol may be blocked by the capsule and fail to reach tumor cells that have spread outside the capsule. Thus, the center of the encapsulated area may be effectively treated, whereas the effects of the ethanol on extracapsular spread may be somewhat limited. Therefore, we often observe viable cancer cells persisting in the extracapsular or intracapsular area in surgically resected or autopsy specimens after PEIT. These viable cells may cause local recurrences as well as intrahepatic and distant metastases.

When a drug is injected as a percutaneous local treatment for small HCCs, the problems cited above remain, regardless of the type of drug. To resolve these problems, a new therapeutic method must be based on concepts different from those of conventional drug injections. More recently, such local treatments as cryotherapy[17,18] and percutaneous laser photocoagulation[19] have been used to treat liver tumors. However, cryotherapy has the disadvantage of requiring laparotomy, and laser apparatus is very expensive. There is therefore a need for a simple, safe, inexpensive, and precise treatment for small HCC.

PMCT, which we formulated in the current study, heats tissue by molecular vibration of dipoles, particularly of water in tissue, and induces thermal coagulation in the target area. Regardless of the presence of a capsule, microwave irradiation is most reliable in inducing tissue coagulation across a designated area if the tip of the electrode is located in the target lesion. This sets PMCT apart from conventional types of percutaneous

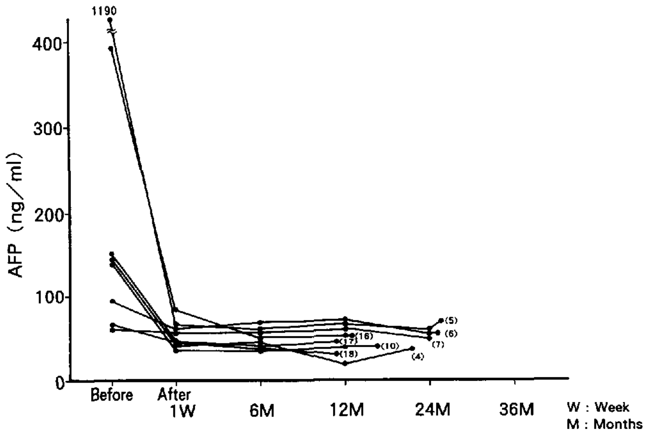

Figure 7. Sequential changes of serum alpha-fetoprotein level in patients who had elevated levels (≥50 ng/ml). Numbers in parentheses correspond to patient numbers as listed in Table 1. AFP: alpha-fetoprotein.

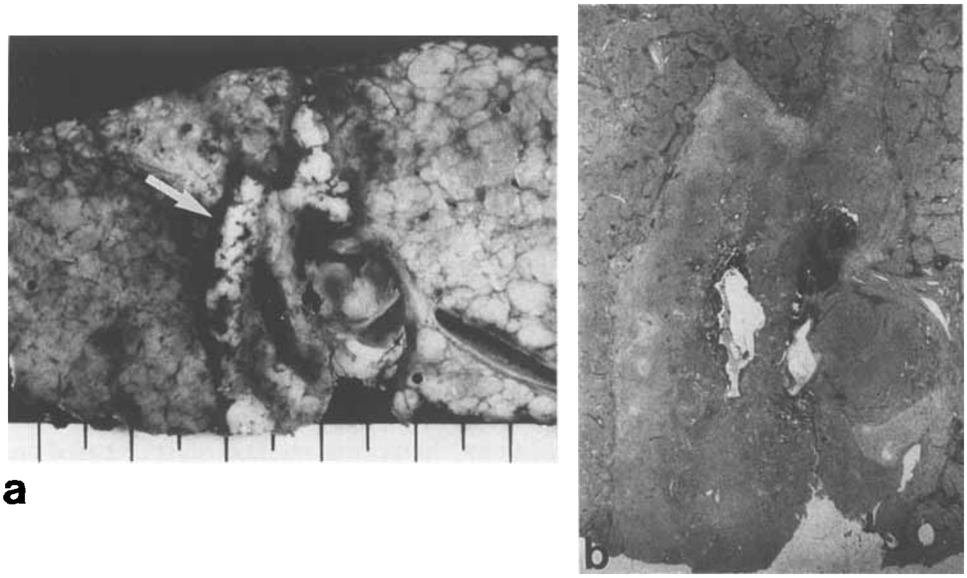

Figure 8. (Patient 12). (a) Macroscopic findings of the cut surface of the resected liver 30 days after PMCT. Whitish area shows the coagulation (white arrow). (b) The tumor area showed complete necrosis (H & E, original magnification ×1.4).

drug injection. This microwave coagulation system is simple and inexpensive (1/10th the cost of a laser apparatus).

Initially, in treating HCC, microwave coagulation was used in hepatic resection during open surgery for tissue coagulation and hemostasis. Some studies have reported excellent results.[20,21]

For percutaneous treatment, we could not use the electrode designed for hepatic resection, because the shaft of the electrode for surgical use is too thick (1 cm in diameter).

For percutaneous use of microwave coagulation, it was necessary to develop a thin electrode. Furthermore, it had to be designed so that this electrode would cause tissue coagulation at the tip of the electrode, but would not burn the skin. We succeeded in designing a thin electrode and decreased heat conduction through the electrode by filling the tubular space between inner and outer conductors with silicone gum and PTFE, leaving only the tip of the electrode exposed. With this new microwave electrode, which is 1.6 mm thick, it is possible to produce reliable percutaneous tissue coagulation of the liver in an elliptic shape by using microwaves at 60 W for 120 seconds without burning the skin. Microwave irradiation under conditions that exceed these values may enlarge the area of coagulation, but there is a high risk of burning the skin, subcutaneous tissue, and peritoneum.

This electrode is relatively thick (14-gauge, 1.6 mm) compared with the needle (21-gauge, 0.57 mm) normally used for PEIT. However, in the current study, we correctly targeted each tumor under ultrasonic guidance. Furthermore, it was possible to prevent hemorrhage and leakage of bile from the hepatic surface by irradiating along the puncture line as the guide and electrode were removed. We did not encounter any serious problems after PMCT.

After treatment, changes in various imaging studies (ultrasonography, CT, and MRI) reflected tissue necrosis. The high-intensity ring surrounding the tumor seen in MRI studies may indicate an inflammatory reaction, or it may represent local edema. This possibility requires further study.

We observed complete necrosis in a resected specimen and did not detect any local recurrences in the treated area after the initial treatment, although the follow-up period is still limited. In those patients with elevated levels of tumor marker (alpha-fetoprotein), we noted that the level fell after PMCT.

In assessing the therapeutic efficacy of PMCT, there is a great need for a controlled clinical trial compared with other treatments and long term observation after PMCT. Based on our experience, however, we think that PMCT shows good efficacy for small HCCs.

In the current study, PMCT was effective for small HCCs, but it cannot be applied as a single treatment to HCCs measuring more than 2 cm at greatest dimension, because the coagulated area induced by PMCT is small despite the reliability of coagulation capability. If PMCT alone were to be applied to large HCCs, the effect may be incomplete, and the stress on the patient may become unduly severe because of repetition of the treatment. Therefore, for large unresectable HCCs, PMCT is probably not adequate to use alone. Although we did not perform PMCT for multiple small lesions in the current study, we think that PMCT may be effective for multiple small HCCs and unresectable small metastatic liver tumors because of its reliable coagulation capability and mild invasiveness. Further study is required to evaluate the effectiveness of this treatment with longer follow-up and a larger series and to clarify the indications for this treatment.

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