Intraoperative Microwave Tissue Coagulation as Treatment for Patients with Nonresectable Hepatocellular Carcinoma

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Background. The microwave tissue coagulator (2450 MHz) has been used clinically in the treatment of hepatocellular carcinoma (HCC) to transection of the liver parenchyma and has proven an excellent method for hemostasis. There are, however, few reports on the application of this coagulator to the induction of tumor necrosis.

Methods. Microwave tissue coagulation (MTC) was applied at laparotomy in eight patients with nonresectable multiple HCCs. All patients were treated with a combination of resection or intrahepato-arterial chemotherapy and MTC. A total of 222 bouts of MTC were applied to 21 tumors, the largest of which was 65 mm in largest dimension. The monopolar needle electrode was inserted directly into the tumor and the procedure was repeated at approximately 5 mm intervals.

Results. Levels of alpha-fetoprotein in serum were found to have decreased in all patients one month after surgery with MTC. Contrast-enhanced computerized tomography (CT) showed the complete absence of blood flow in all tumors subjected to MTC. Needle biopsy one month after MTC confirmed tumor necrosis in all cases. All patients are alive at the time of this report, with the longest survival period being 24 months. In three of eight patients, new tumors were confirmed by angiographic CT at sites separate from the treated tumors. MTC resulted in fewer adverse effects on liver function and less extensive inflammatory reactions than liver resection.

Conclusion. Intraoperative MTC appears to be an effective method for inducing local tumor necrosis, and may be of use in combination with palliative surgery for multiple HCC when radical liver resection is not feasible. Cancer 1995;75:794-800.

Key words: hepatocellular carcinoma, interstitial therapy, microwave tissue coagulation, multicentric carcinogenesis, multimodal treatment, intraoperative ultrasonography.

The marked improvement in the results of treatment of hepatocellular carcinoma (HCC) during the past 10 years is attributed primarily to progress in diagnostic imaging, the widespread use of screening of high risk groups, and advances in minimally invasive therapies devised for the treatment of HCC.1-5 Hepatectomy is the most effective radical approach because the tumor and surrounding liver tissue6,7 are completely removed. However, in cases involving a high probability of intrahepatic metastasis or multicentric carcinogenesis and deteriorated liver function caused by liver cirrhosis, liver resection often is not a possibility.6,8 Transarterial embolization9 and intrahepato-arterial chemotherapy10 have been used in patients with HCC, but results of single treatments are not always satisfactory. Recently, several interstitial techniques, such as ethanol-injection therapy,3,11,12 hepatic cryosurgery,13-15 and interstitial laser therapy,16 have been applied to induce tumor necrosis or to control the tumor growth in the treatment of HCC.

The microwave tissue coagulator developed in 1979 by Tabuse17 has been applied clinically to the transection of hepatic parenchyma with or without liver cirrhosis, and it has proven excellent for hemostasis.18,19 However, there are few reports of the application of this coagulator to induction of tumor necrosis.20 In this article, we report the therapeutic results of intra-
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Table 1. Characteristics of Patients With Hepatocellular Carcinoma Who Were Treated With MTC Therapy

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Cause of liver cirrhosis</th>
<th>75-g OGTT</th>
<th>Total bilirubin (mg/dl)</th>
<th>Albumin (g/dl)</th>
<th>ICG-R15 (%)</th>
<th>Prothrombin time (%)</th>
<th>Clinical stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>67</td>
<td>M</td>
<td>Alcohol</td>
<td>DP</td>
<td>1.0</td>
<td>3.8</td>
<td>28</td>
<td>59</td>
<td>II</td>
</tr>
<tr>
<td>2</td>
<td>64</td>
<td>M</td>
<td>HCV, HBV</td>
<td>DP</td>
<td>1.0</td>
<td>3.4</td>
<td>24</td>
<td>57</td>
<td>II</td>
</tr>
<tr>
<td>3</td>
<td>71</td>
<td>F</td>
<td>HCV</td>
<td>DP</td>
<td>0.5</td>
<td>2.8</td>
<td>35</td>
<td>57</td>
<td>II</td>
</tr>
<tr>
<td>4</td>
<td>75</td>
<td>M</td>
<td>HCV</td>
<td>DP</td>
<td>0.9</td>
<td>3.3</td>
<td>22</td>
<td>66</td>
<td>II</td>
</tr>
<tr>
<td>5</td>
<td>71</td>
<td>F</td>
<td>HCV</td>
<td>DP</td>
<td>0.7</td>
<td>3.9</td>
<td>9</td>
<td>90</td>
<td>I</td>
</tr>
<tr>
<td>6</td>
<td>68</td>
<td>M</td>
<td>HCV</td>
<td>NP</td>
<td>0.7</td>
<td>3.6</td>
<td>20</td>
<td>79</td>
<td>II</td>
</tr>
<tr>
<td>7</td>
<td>69</td>
<td>M</td>
<td>HCV</td>
<td>DP</td>
<td>1.1</td>
<td>3.4</td>
<td>33</td>
<td>78</td>
<td>II</td>
</tr>
<tr>
<td>8</td>
<td>64</td>
<td>M</td>
<td>HCV</td>
<td>DP</td>
<td>1.6</td>
<td>3.0</td>
<td>37</td>
<td>67</td>
<td>II</td>
</tr>
</tbody>
</table>

OGTT: oral glucose tolerance test; DP: diabetic pattern; NP: normal pattern; HCV: hepatitis C virus; HBV: hepatitis B virus; MTC: microwave tissue coagulation; ICG-R15: retention rate of indocyanine green dye at 15 minutes.

The clinical staging was based on material in reference 16.

 operative microwave tissue coagulation (MTC) therapy in patients with nonresectable HCC.

Patients and Methods

Patients

From April 1992 to March 1994 40 patients with HCC were treated at Tottori University Hospital; 8 of them, all of whom had multiple HCC and for whom radical surgery was impossible, received MTC therapy after laparotomy (Table 1). The patients (six men and two women) ranged in age from 64 to 75 years. All had liver cirrhosis. Seven tested positive for hepatitis C virus specific antibodies. The retention rate of indocyanine green dye at 15 minutes exceeded 20% in seven patients and 30% in three patients. Prothrombin time was less than 80% in seven patients and less than 60% in three. Seven patients were defined as having clinical stage I disease; one had clinical stage II disease; one had clinical stage I disease. In a 75-g oral glucose tolerance test, seven of the eight patients had a diabetic pattern. The number of tumors per patient ranged from one to seven in both lobes of the liver. Of the 28 tumors in the eight patients, 21 were confirmed histologically to be HCC. Seven superficially located tumors in three patients were excised surgically. MTC was administered to the remaining 21 deeply seated tumors in a total of 222 bouts, with an average of 10.6 bouts per tumor (Table 2). The maximum diameter of the tumors to which MTC was applied was 65 mm. In six of the eight patients, inthrahepato-arterial chemotherapy also was administered after surgery. Informed consent was obtained from all patients.

Microwave Coagulation of Tissue

The peritoneal cavity was entered through a bilateral subcostal incision. The liver was examined carefully by manual palpation and intraoperative ultrasonography (US) after mobilization of ligamentous detachment of the involved liver. The specific area of the liver to which MTC was administered was defined by the insertion of several guide needles around the targeted tumor under intraoperative US immediately before MTC. The needle electrode was inserted directly into the targeted tumor located in the specific area. MTC was administered for 20 seconds per bout and was repeated at approximately 5-mm intervals in the specific area to coagulate the whole tumor. A microwave tissue coagulator was operated at a frequency of 2450 MHz (Microtaze HSE-20M; Heiwa Electronic Ind., Ltd., Osaka, Japan).

The monopolar needle electrodes of two different lengths (HM-15 and HM-30, Heiwa Electronic Ind., Ltd.) were used properly, depending on the depth of the tumor. Microwaves are transmitted to a monopolar needle electrode via a coaxial cable. Microwave energy is generated between the tip and base of the electrode. Its maximum output of microwave energy is 150 watts. In this study, the output was 70 watts for 15-mm needle electrodes and 100 watts for 30-mm electrodes. These conditions have been applied in hepatectomy by means of microwave tissue coagulator, and no complications were caused by the maneuver. The coagulated tissue at the liver surface can be visually recognized as an approximately 10-mm round gray-yellow area around the needle electrode after one bout of MTC.

Antitumor effects were analyzed by serial computed tomography (CT) and by percutaneous needle biopsy of the tumors.
Table 2. Summary of MTC Therapy for the Eight Patients With Multiple Hepatocellular Carcinoma

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Total no. of tumors treated with MTC</th>
<th>No. of tumors</th>
<th>Maximum tumor dimension (mm)</th>
<th>Total no. of bouts of MTC</th>
<th>Combination with other treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4 (4)</td>
<td>3 (3)</td>
<td>S8, S5, S2</td>
<td>35</td>
<td>9 PH (S8) +</td>
</tr>
<tr>
<td>2</td>
<td>7 (3)</td>
<td>3 (1)</td>
<td>S8, S3, S2</td>
<td>20</td>
<td>12 PH (S6, S6, S3, S3) -</td>
</tr>
<tr>
<td>3</td>
<td>3 (3)</td>
<td>3 (3)</td>
<td>S8, S4, S4</td>
<td>14</td>
<td>11 - +</td>
</tr>
<tr>
<td>4</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>S8, S4</td>
<td>52</td>
<td>50 - +</td>
</tr>
<tr>
<td>5</td>
<td>2 (2)</td>
<td>1 (1)</td>
<td>S5</td>
<td>12</td>
<td>4 LS (S2-3) -</td>
</tr>
<tr>
<td>6</td>
<td>5 (3)</td>
<td>5 (3)</td>
<td>S8, S4, S4, S3, S3</td>
<td>22</td>
<td>21 - +</td>
</tr>
<tr>
<td>7</td>
<td>4 (3)</td>
<td>4 (3)</td>
<td>S5-6-7, S6, S6, S1</td>
<td>60</td>
<td>75 - +</td>
</tr>
<tr>
<td>8</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>S2-3</td>
<td>50</td>
<td>40 - -</td>
</tr>
</tbody>
</table>

PH: partial hepatectomy; LS: lateral segmentectomy; MTC: microwave tissue coagulation; IHAT: intrahepatic arterial chemotherapy.

All patients were given 400–600 mg of Tegafur orally per day.

Values in parentheses are the number of histologically confirmed hepatocellular carcinomas. Locations of tumors are based on the segmentation of Couinaud.

Results

There were no operative deaths and no severe complications, such as rupture of the tumor, delayed bleeding, bile leakage, or liver abscess.

Effects on Liver Function

The results of biochemical analysis of blood samples after MTC are shown in Figure 1. Serum levels of alanine aminotransferase and aspartate aminotransferase peaked on the first day after MTC, returning to pretreatment levels after 1 week. Total bilirubin levels in serum rose slightly after MTC, returning to pretreatment levels after 1 week in six of the eight patients. However, in one patient hyperbilirubinemia lasted for more than 1 month after surgery, with 6 weeks being required for recovery. No remarkable changes were observed in serum albumin levels or prothrombin times. Levels of C-reactive protein in serum increased temporarily after surgery but decreased on the seventh day.

Antitumor Effects

Levels of alpha-fetoprotein in serum were found to have decreased in all patients 1 month after MTC. In four patients with preoperative levels of alpha-fetoprotein greater than 50 ng/ml, the average extent of the decrease was 86%, as shown in Table 3. Contrast-enhanced CT showed the absence of blood flow in all tumors that had been treated by MTC (Fig. 2). Needle biopsy confirmed necrosis in all patients. All patients in the series are alive at the time of writing, with the longest survival being 24 months. In three of the patients,
Table 3. Therapeutic Results for the Eight Patients With Multiple Hepatocellular Carcinomas Who Were Treated With MTC

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Serum levels of AFP (ng/ml)</th>
<th>Tumor necrosis (needle biopsy 1 mo after MTC)</th>
<th>New tumors in residual liver</th>
<th>Survival after MTC (at time of writing) (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before MTC</td>
<td>One month after MTC</td>
<td>Extent of decrease (%)</td>
<td>Presence or absence (mo after MTC)</td>
</tr>
<tr>
<td>1</td>
<td>6.7</td>
<td>3.5</td>
<td>48</td>
<td>+ (10)</td>
</tr>
<tr>
<td>2</td>
<td>15.0</td>
<td>10.1</td>
<td>33</td>
<td>+ (2)</td>
</tr>
<tr>
<td>3</td>
<td>17.7</td>
<td>14.1</td>
<td>20</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>138.0</td>
<td>13.6</td>
<td>90</td>
<td>+ (6)</td>
</tr>
<tr>
<td>5</td>
<td>3550.0</td>
<td>52.6</td>
<td>85</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>6.3</td>
<td>4.6</td>
<td>27</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>235.0</td>
<td>19.9</td>
<td>92</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>50.0</td>
<td>11.0</td>
<td>78</td>
<td>–</td>
</tr>
</tbody>
</table>

MTC: microwave tissue coagulation; AFP: alpha-fetoprotein; PEIT: percutaneous ethanol-injection therapy; TCE: transcatheter arterial chemoembolization.

new tumors were confirmed within 10 months by CT during angiography that involved a tube inserted into the hepatic artery at sites separate from the sites of tumors to which MTC had been applied. These patients are being treated by percutaneous ethanol-injection therapy and transcatheter arterial chemoembolization.

Discussion

The life expectancy in patients with multiple HCC is notably lower than that in patients with single tumors, and approximately 80% of the former patients experience intrahepatic recurrence within 2 years of surgery.1 Okuda6 made a histopathologic comparison of liver biopsy samples in patients with recurrent residual HCC after surgery and the initially resected specimens. He concluded that, in 50% of the recurrent residual tumors, some evidence of multicentric development had been apparent in that report. In patients with HCC with evidence of multicentric development, even if tumors are radically resected, new tumors may redevelop within a short time after surgery. Thus, treatment modalities with minimal invasion are required for effective local control of tumor as a first choice.

Percutaneous ethanol-injection therapy is considered to be readily applicable to patients with liver cirrhosis because of the simplicity of the technique, the ease with which it can be applied, and the minimal involvement of organs.5,11,12 In patients with multiple or large tumors that require repeated punctures and large amounts of ethanol, serious complications can develop, such as damage to hepatic vessels and bile ducts,11,22,23 injury to abdominal organs,12 and subcutaneous seeding of cancer in the needle tract.24,25 However, Zhou et
al.\(^5\) indicated that cryosurgery was a promising, safe, and simple treatment for HCC because a patient with recurrent HCC had survived with no evidence of disease for more than 8 years after hepatic cryosurgery. In addition, Zhou et al.\(^5\) reported that the 5-year survival rate after cryosurgery was 37.5% for 21 patients with nonresectable small HCC. Similarly, Onik et al.\(^14\) and Ravikumar et al.\(^15\) proposed hepatic cryosurgery would offer long-term survival for patients with nonresectable metastatic tumors. Onik et al.\(^14\) reported that real-time US could assess the extent of the frozen area in hepatic cryosurgery. However, other interstitial techniques cannot be monitored in real time by US. Cryosurgery has been applied to superficially located tumors because of the inconvenience of its relatively large probe. The monopolar needle electrode used in MTC is a thin, 21-gauge needle. Thus, MTC potentially could be applied percutaneously because of its low risk of complications.\(^26\)

In MTC, the heat generated by microwave irradiation in tissues around the electrodes can be explained by Joule’s principle. The use of MTC to achieve tumor necrosis was first reported in 1981 by Tabuse and Katsumi.\(^20\) In intraoperative MTC, patients have to undergo laparotomy, with its relatively invasive stress. Reapplication of intraoperative MTC might be difficult in the treatment of recurrent disease because of adhesions around the initial treatment sites of the liver. However, a surgical approach provides the following possible advantages to MTC. First, there are fewer limits to the sites and angles for insertion of electrodes because the liver can be handled during intraoperative MTC. Thus, the surgical approach provides access to all parts of the liver for treatment. A percutaneous approach to MTC also has been attempted in Japan,\(^26\) but because electrode insertion sites are limited, it cannot be applied to multiple or large HCC in most patients. The second benefit is that multiple tumors can be simultaneously treated by MTC during one laparotomy. The third benefit is that intraoperative US provides more detailed diagnostic information than does ordinary US because the probe, which has higher frequency transducers, can be applied directly to the liver.\(^27\) However, MTC cannot be applied to tumors that are undetectable by intraoperative US, so we have used CO\(_2\) gas-enhanced angiography\(^28\) in patients with multiple HCC to maximize our intraoperative diagnostic capability. The last benefit is that the specific area undergoing MTC can be defined by insertion of guide needles around targeted tumors during laparotomy, because the extent of coagulation cannot be assessed in real time ultrasonically during MTC and for approximately 30 minutes afterward by microbubbles produced in liver tissue. We believe that complete thermal coagulation of targeted tumors can be achieved via MTC applied to the specific area defined by the insertion of guide needles around targeted tumors. Dynamic CT after MTC showed no blood flow within the coagulated areas, and tumor necrosis was confirmed by US-guided biopsy of tissue. In addition, no recurrence at the treatment sites was observed, although the results are short term. These findings may indicate that MTC has contributed to inducing tumor necrosis. However, in patients with multiple tumors, multimodal treatment with intrahepato-arterial chemotherapy and even MTC should be considered because of the strong possibility of the development of new tumors.

Most MTC has been administered within 30 seconds at a microwave output of less than 100 watts per
bouts. However, conduction for more than 30 seconds frequently carbonizes the tissue adjacent to the electrode. Carbonization might stop the stream of high frequency current from the electrode. In principle, we have applied 70 watts with a 20-second conduction time in transection of the liver and coagulation of the tumor. Under these conditions, resected specimen of hepatic nontumorous tissues, which were coagulated with one bout of MTC immediately before hepatic resection, showed an approximately 15-mm hemispheric discolored area around the electrode at the cut surface. At that discolored area, necrosis and severe degeneration were histologically proven (Fig. 3). MTC must be repeated with tumors of larger diameter, increasing the risk of injuring the functioning liver tissue. In our study, we encountered delayed recovery from hyperbilirubinemia after MTC in the patient with the largest tumor. This problem may have been attributable to thermal damage to major bile ducts adjacent to the tumor. Tumor adjacent to the hepatic hilum previously was thought to be a contraindication to MTC. We have found that tumors in close proximity to major vessels can be treated with relatively safety by MTC because the vessel wall may be cooled by rapid blood flow within major vessels. In patients with tumor near the major bile duct, we have performed biliary drainage through the cystic duct for approximately 5 days to prevent development of bile leak or liver abscess. We believe that repeated bouts of MTC of shorter duration allow easier adjustment of the coagulation area and provide a higher degree of safety. MTC resulted in fewer adverse effects on liver function and less extensive inflammatory reactions than did liver resection. Thus, intraoperative MTC is applicable to patients with poor liver function.

In conclusion, intraoperative MTC appears to be effective for inducing local tumor necrosis, and it should have a successful role in combination with palliative surgery for the treatment of multiple HCC when radical liver resection is not feasible.

References

23. Motoo Y, Okai T, Matsu O, Ohta H, Sawabu N. Liver atrophy
after transcatheter arterial embolization and percutaneous ethanol injection therapy for a minute hepatocellular carcinoma. 


