Efficacy of combining temperature- and power-controlled radiofrequency ablation for malignant liver tumors

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[Abstract] Background and Objective: Single mode of radiofrequency ablation (RFA) often leads to limited ablation in the zone of necrosis. This study clarifies the efficacy of combining temperature- and power-controlled RFA for malignant liver tumors.

Methods: Between April 2008 and August 2008, 58 patients with malignant liver tumors received RFA at Sun Yat-sen University Cancer Center. The patients were divided into 2 groups using a random number table: one group received combined temperature- and power-controlled RFA (the combination group), and the other group received power-controlled RFA alone (the control group).

Results: Three patients were lost to follow-up and 55 patients were included for evaluation. Twenty-five patients with 29 tumors were treated by the combination RFA, and 27 tumors (93.1%) achieved either complete response (CR) or partial response (PR). One patient had a seriously decreased heart rate. In the control group, 30 patients with 32 tumors received power-controlled RFA, and 29 tumors (90.6%) achieved CR or PR. There were no serious complications. There was no difference between the combination and control groups in treatment time ((13.3 ± 1.3) min vs. (10.2 ± 2.3) min, P = 0.459). The number of sessions of RFA for the combination group was less than that of control group (1.3 sessions vs. 2.4 sessions), but the difference was not significant (P = 0.579).

Conclusion: RFA controlling both temperature and power is effective and safe for patients with malignant liver tumors, and the number of sessions of RFA for the combination group was less than that of the control group.

Key words: Malignant liver tumors, radiofrequency ablation, efficacy
suboptimal[10]. Considering these intrinsic shortcomings of the two approaches, both single modes of RFA share the disadvantage of a limited scope of ablation. The present study aimed to treat patients with malignant liver tumors by using the combination of temperature- and power-controlled RFA. We presumed that these two methods were complementary and the combination could expand the scope of ablation, so the operator could better judge the completeness of the treatment. And we aimed to clarify the efficacy and safety of the combination of temperature- and power-controlled RFA compared with the power-controlled method alone.

Data and Methods

Selection of subjects

Between April 2008 and August 2008, 58 patients with malignant tumors in the liver received RFA at the Department of Hepatobiliary Surgery, Sun Yat-sen University Cancer Center. The inclusion criteria were as follows: (1) the diameter was less than 5 cm for solitary tumor, and the largest tumor less than 3 cm in diameter for multiple tumors (the number of tumors is less than 3); (2) liver function was Child-Pugh Grade A or B; (3) there was a safe puncture path from the skin to the tumor mass as determined by ultrasonography; (4) there was no distal metastasis or tumor thrombus in the portal vein and its branches; (v) the patient had no hepatoencephalopathy, refractory ascites, or upper gastrointestinal tract bleeding in the past; (vi) no severe coagulopathy; and (vii) indocyanine green retention rate at 15 minutes (ICGR15) < 30%.

Primary liver cancer was diagnosed according to guidelines of the American Association for the Study of Liver Diseases (AASLD) or confirmed by pathology. Metastatic tumors were confirmed by the pathology of the primary tumor.

Methods

The included patients were randomly assigned to two groups using a random numbers table: a group receiving the combined methods (the combination group) and a control group. The combination group received RFA with combined temperature- and power-controlled methods, and the control group received power-controlled RFA alone. An S-1500 radiofrequency instrument (including the radiofrequency generator and surgical electrodes, there were 10 electrodes at most, the extending diameter was 5 cm at most, and the electrode rod had a maximum length of 15 cm) was used in the combination group, which had both temperature- and power-controlled mode. The RF2000 radiofrequency system (a multiple warhead therapeutic system; Radiotherapeutics) was used in the control group, which had single power-controlled mode. Baseline characteristics of patients in both groups are shown in Table 1.

Table 1  Demographic data of patients included for evaluation

<table>
<thead>
<tr>
<th>Item</th>
<th>Combination group</th>
<th>Control group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>20</td>
<td>24</td>
<td>0.999</td>
</tr>
<tr>
<td>Women</td>
<td>5</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>53.7 ± 13.1</td>
<td>54.3 ± 10.2</td>
<td>0.622</td>
</tr>
<tr>
<td>Tumor size (cm)</td>
<td>2.78 ± 1.27</td>
<td>2.45 ± 1.47</td>
<td>0.657</td>
</tr>
<tr>
<td>Number of tumors</td>
<td>1.20 ± 0.40</td>
<td>1.15 ± 0.25</td>
<td>0.999</td>
</tr>
<tr>
<td>Gamma-glutamyltranspeptidase (U/L)</td>
<td>90.32 ± 103.2</td>
<td>103.45 ± 95.36</td>
<td>0.999</td>
</tr>
<tr>
<td>Alanine aminotransferase (U/L)</td>
<td>30.78 ± 12.33</td>
<td>36 ± 12.25</td>
<td>0.999</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>38.43 ± 5.02</td>
<td>39.85 ± 4.34</td>
<td>0.728</td>
</tr>
<tr>
<td>Total bilirubin (μmol/L)</td>
<td>16.00 ± 5.31</td>
<td>17.81 ± 10.25</td>
<td>0.999</td>
</tr>
<tr>
<td>Tumor type</td>
<td></td>
<td></td>
<td>0.487</td>
</tr>
<tr>
<td>Primary liver cancer</td>
<td>18</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Liver metastasis</td>
<td>7</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Alpha-fetoprotein (ng/mL)</td>
<td></td>
<td></td>
<td>0.491</td>
</tr>
<tr>
<td>≤ 400</td>
<td>14</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>&gt; 400</td>
<td>11</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Indocyanine green retention rate in 15 minutes</td>
<td>0.493</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 10%</td>
<td>22</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>10%-15%</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

a. Continuous variables are presented as mean ± SD, and compared by Student t test; otherwise, values represented number of patients are compared using χ2 test.

Puncture was performed for all patients under the guidance of Hitachi EUB-2000 ultrasound instrument. Local anesthesia combined with intravenous injection of Diprivan were performed. After inducing the anesthesia, under the guidance of ultrasound, the electrode needle was inserted into the liver tumor and the inner hook-shape expandable electrode tines were deployed. For the combination mode, the temperature control was set for 15 min followed by the power control. In the temperature-controlled mode, the temperature was set at 90–95°C and the ablation duration was 15 min for each time. The power control mode began at 10 W, followed by stepwise increments of 10 W each minute until electrical impedance increased abruptly. The needle
was extracted 1 cm and rotated 180°, and another period of ablation was performed. Single-mode ablation was based on power-controlled mode. For patients with large tumors, the needles were deployed in a multidirectional pattern and ablation was conducted multiple times from multiple angles to ensure complete tumor ablation and ablation to potential malignant tissue in the 5–10 mm zone surrounding the tumor. Of the 58 patients, 56 received single ablation and 2 patients (in the single-mode [control] group) received ablations twice.

Follow-up

General conditions, routine blood tests, and liver function of these patients were examined 1 week (± 3 days) after the procedure. Imaging studies (contrast-enhanced computed tomography (CT), magnetic resonance imaging (MRI), or ultrasonography), liver function, alpha-fetoprotein (AFP) or carcinoembryonic antigen (CEA) (for patients whose preoperative levels were abnormal), and routine laboratory examinations were performed 1 month (± 7 days) and 3 months (± 21 days) after the procedure.

Assessment of clinical response

Clinical response was assessed according to the WHO response criteria for solid tumors. Complete remission (CR) was defined as the complete disappearance of the lesion for more than 1 month. Partial response (PR) was the reduction of tumor size by 50% for more than 4 weeks. No change (NC) was a less than 50% reduction in tumor size or tumor enlargement less than 25%. Progressive disease (PD) was the enlargement of the tumor by more than 25% or the occurrence of new lesions. The rate of effectiveness was calculated by CR + PR (lesions that could not be ablated at one time should receive another ablation, and the later result was used as evaluating index).

Adverse reactions were described using the number of adverse events and the incidence. The severity of the adverse events and their association with the treatment are described in the results section.

Results

Follow-up

Of the 58 patients in our study, 3 patients failed to follow up in 1 month after the procedure (2 from the combination group and 1 from the control group), but they completed the examination at 3 months after the procedure and were thus included in the analysis. Another 3 patients were lost to follow-up at 3 months after the procedure (noncompliance with the examination) with 2 in the combination group and 1 in the control group. The missing rate was 5.2%.

Short-term efficacy in the combination group

Twenty-seven patients were included in the combination group, of whom 2 were lost to follow-up, and thus 25 were involved in the final analysis (29 tumor masses). There were 20 men and 5 women with a median age of 51 years (range, 39–69 years). There were 18 patients with primary liver cancer and 7 with metastatic tumors (4 patients with colon cancer, 1 with gastric cancer, 1 with nasopharyngeal carcinoma, and 1 with cancer of the pancreatic head). A total of 21 patients had single tumors and 4 patients had two tumors. In total, there were 29 tumors in the 25 patients, of which, there were 18 tumors with diameters < 3 cm, 11 tumors 3–5 cm, and the mean diameter of the tumors was (2.78 ± 1.27) cm. After ablation, the rate of CR was 82.8% (24/29), PR was 10.3% (3/29), and PD was 6.9% (2/29).

Of the 25 patients, 18 had primary liver cancer, and 11 had positive AFP preoperatively. Three months after ablation, the AFP returned to normal level in 3 patients (27.3%), 3 patients (27.3%) showed significantly reduced AFP, and 5 patients (45.4%) showed an unremarkable decrease or an increase.

In the 27 patients that underwent RFA (including the missing patients), 1 patient showed a reduced heart rate during the procedure. The lowest rate was 40 bpm and sustained for 10 s, and the heart rate returned to normal after discontinuing the ablation. No severe adverse events or complications, such as needle path burn, burn at the site of the circuit electrode plate, needle path metastasis, tumor rupture after the procedure, gastrointestinal (or peritoneal) hemorrhage, liver abscesses or death, were reported.

Short-term efficacy in the control group

Of the 31 enrolled patients, 1 was lost to follow up, and 30 patients were included in the analysis (32 tumors). There were 24 men and 6 women with a median age of 53 years (42–66 years). A total of 24 patients had primary carcinoma and 67 patients had metastatic liver tumors (3 patients with colon cancer; 1 with gastric cancer, 1 with nasopharyngeal carcinoma, and 1 with breast cancer). There were 28 patients with single tumors and 2 patients with 2 tumors. There were 32 lesions in the 30 patients, including 22 with diameters < 3 cm, 10 with diameter 3–5 cm, and the mean diameter of the tumors was (2.45 ± 1.47) cm. Of the 32 lesions, there were 28 CR (87.5%), 1 PR (3.1%), and 3 PD (9.4%).

Of the 30 patients, 24 had primary liver cancer, and 16 of them had positive AFP preoperatively. At 3 months after ablation, the AFP returned normal in 4 patients (25%), 8 patients (50%) showed significantly reduced AFP, and 4 patients (25%) showed an unremarkable decrease or an increase. No severe adverse events or complications were reported.

Comparisons of efficacy and safety between the two groups

The effectiveness rates of the combination and control groups were 93.1% and 90.6%, respectively. There was no significant difference between the two groups in the effectiveness of tumor control (P = 0.999). The incidence rates of severe complications for the combination and control groups were 4% (125) and 0% (0/30), respectively, which was not statistically significant (P = 0.464). The mean lengths of treatment of the combination and control groups were similar ((13.3 ± 1.3) min vs. (10.2 ± 2.3) min; P = 0.459). The number of needle insertion events in the combination group was slightly less than in the control group (1.3 vs. 2.4, P = 0.579).
Discussion

Our study demonstrated that the combination of temperature- and power-controlled modes of RFA for malignant tumors in the liver was effective. Besides its high efficacy, its length of treatment was similar to that of the single-mode group. However, in terms of the number of needle insertion events, the combination mode required fewer insertions. Although it is not statistically significant, the trend also informed us that the combination mode might reduce the potential complications of hemorrhage and needle path seeding brought by repeated needle insertions. Because the present study is in nature clinical validation and the sample size is small, it does not have enough statistical power to detect the difference between the conventional mode and the combination mode. Theoretically, the single power-controlled or temperature-controlled modes have their own instinct shortcomings, and the combination is expected to expand the ablation scope, thereby improving RFA effectiveness.

Controlling temperature and power are the two major monitoring modalities in RFA. The power-controlled method judges the completeness of ablation by detecting circuit impedance. However, due to the differences in chemical and physical properties, the same parameter set may result in premature dehydration and carbonization in some tissues, so the radiofrequency power cannot be output and spread adequately. Currently, the international standard to solve this problem is to improve the design of RFA needles and adjust the ablation parameters. The former includes the use of a cold water RFA needle or to combine with intratumor normal saline injection\(^1\).\(^2\)\(^,\)\(^3\)\(^,\)\(^4\). The principle is to cool the RFA needle or inject normal saline to delay the dehydration and carbonization of ablated tissues, thereby increasing the output of RFA power and expanding the ablation scope. The latter method is to balance the power output and increase the ablation scope by emitting RFA power in pulses\(^5\)\(^,\)\(^6\) or using lower initial power and slower incremental power\(^7\). The temperature control mode can compensate for the shortcomings of power control mode. With the preset of a target temperature, the ablation system can adjust the output power automatically to maintain a certain temperature, and thereby the energy output can be balanced. For tumors at some particular sites, including those beside major vessels, the blood flow may take away some energy, resulting in incomplete ablation\(^8\).\(^9\). Clinicians both home and abroad prefer to temporarily interrupt the afferent flow of blood to the liver to expand the ablation scope, which has been validated in some studies\(^10\).\(^11\)\(^,\)\(^12\)\(^,\)\(^13\). Some clinical investigations also reported that the RFA after chemotherapy for vascular interventional embolisms could benefit patient survival\(^14\). Because vascular embolism agents are injected into the tumor vessels and the blood flow in the tumor declines, the ablation energy can be more effectively focused to produce a larger ablation scope.

Reports on the combination of temperature- and power-controlled RFA for malignant tumors in the liver are rare both at home and abroad, so no experiences of this combination can be referenced. The combination mode designed in our study began with the first session of temperature control for 15 min and was followed by the power control mode to finish the ablation. There are two principles for this design. First, the determination of endpoints with altered resistance in the power control mode is more reliable than that determined by temperature for judging the completeness of the ablation. Thus, we control the temperature to achieve a certain ablation scope and then control the power to validate the completeness of the ablation. Second, the authors use power-controlled RFA in their daily clinical practice and have accumulated a large amount of experience. Thus, this clinical trial combines temperature-controlled RFA with the guarantee that patients have received effective treatment. As a matter of fact, the combination of the two modalities should be balanced to ensure that the power output can be maximized, the output power is focused on the target tumor tissues, and the power loss can be minimized. A balance between power output and effective temperature should be reached, which cannot only prevent premature carbonization and dehydration, but also reach effective temperatures to maximize the ablation scope. The S-1500 RFA instrument combined temperature and power controls and can combine the two modes in different proportions. As compared with conventional RFA instruments, the power output in the S-1500 RFA instrument is more flexible and the assessment of response is more reliable.

However, the present study failed to demonstrate a statistically significant preference for the combination modality. The reasons may be either the small sample size or the way the two modes were combined. The present study only explored the effectiveness of the combination pattern of temperature and power, when in fact, the combination patterns are varied, including the specific means of the combination, the setting of temperature and time, as well as the setting of the initial and step-up power. In conclusion, our study showed that the combination of temperature- and power-controlled RFA was effective in treating malignant tumors in the liver, and the desired ablation scope can be achieved by fewer needle punctures. Consequently, the combination treatment may reduce complications and improve efficacy. Nevertheless, to verify the relationship between the combined method and its actual effectiveness requires larger scale, prospective, and controlled trials.

References


