Review

Thermal Ablation for Colorectal Liver Metastases

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Abstract: Hepatic resection in combination with systemic chemotherapy is a standard treatment modality for colorectal liver metastases (CRLM). Recently, thermal ablation, including microwave coagulation therapy (MCT) and radiofrequency ablation (RFA), has been utilized in the treatment of unresectable and partially resectable CRLM. A review of the English language literature and a summary of our experiences in applying thermal ablation in the treatment of CRLM are described here. RFA is used worldwide, and MCT is primarily utilized in eastern countries. In using percutaneous and laparoscopic/open surgical RFA, local recurrence rates were 16% and 4% for tumors < 3 cm, 26% and 22% for tumors between 3-5 cm, and 60% and 50% for tumors > 5 cm. In a large series of treatments which utilized RFA for liver tumors, the mortality and morbidity rates were only 0.3 and 7.2%, respectively. The incidence of tumor seeding after the use of RFA for the treatment of CRLM is as high as 1.4%. Cumulative 5-year survival rates were 29%-36% using MCT and 14%-35% using RFA for unresectable CRLM. Long-term survival data for resectable CRLM are unclear. In our experience, local recurrence rates were undetectable in following the treatment of 30 cases of CRLM (average tumor diameter: 1.7 cm, average observation period: 26 months) which were treated with surgical RFA combined with hepatic resection after efficacious systemic chemotherapy. In conclusion: 1) thermal ablation can be applied to unresectable CRLM without perivascular invasion, and for tumors < 3 cm with a percutaneous or surgical approach, and for tumors < 5 cm with a surgical approach; 2) RFA after effective chemotherapy can provide an extremely high local control rate; and 3) the application of thermal ablation for resectable CRLM is still controversial due to the lack of sufficient evidence obtained from a randomized trial.

Key Words: thermal ablation, colorectal liver metastases, radiofrequency ablation, microwave coagulation therapy

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Introduction

Hepatic resection is the only curative option available for patients with colorectal liver metastases (CRLM), and systemic chemotherapy using new agents such as oxaliplatin, irinotecan, and bevacizumab, has contributed to the prolongation of the survival and to the increase of hepatic resection rates in patients with CRLM\(^1\)\(^-\)\(^5\). Thermal ablation, including microwave coagulation therapy (MCT) and radiofrequency ablation (RFA) was initially developed as a curative treatment for small hepatocellular carcinomas (HCC)\(^6\)\(^-\)\(^9\). MCT acts chiefly on the water or aqueous components of tissues, producing dielectric heat and tissue coagulation. A cylinder shaped coagulated area with a 1 cm diameter and of the same length of the needle used for applying MCT is usually produced. In contrast, RFA can produce thermal injury in liver tissue via an alternating electric current in the tissue radiofrequency range (460-500 kHz). RFA can produce a larger bulbar coagulative area up to 3 cm in diameter. Currently, indications for thermal ablation have been extended to large HCC or CRLM\(^10\)\(^-\)\(^20\). In this department, the use of MCT and RFA for unresectable CRLM were initially developed in 1992 and in 1999, respectively\(^8\)\(^,\)\(^10\). In this article, a survey of recent trends and the therapeutic efficacy of thermal ablation for the treatment CRLM is discussed.

Local recurrence after thermal ablation for CRLM

In surveying the literature, the local recurrence rate at therapeutic sites after the application of RFA for CRLM varies between 2 and 40\%\(^{14\)\(^-\)\(^17\),\(^20\)\(^-\)\(^22\)}\). In a recent meta-analysis of 763 RFA-treated CRLM with a minimum follow-up of 6 months, the mean local recurrence rate was 14.7\%\(^{20}\). The local recurrence rate in 88 resectable patients who were observed for a median follow-up of 33 months after treatment with percutaneous RFA for CRLM was 40\%, which was relatively high\(^{23}\).

RFA was used for the treatment of liver tumors, and the treatment approach was designed with consideration of tumor size, location, and surgical margin\(^{21}\). The local recurrence rate was 3.5\% after a surgical approach compared to 26.4\% after a percutaneous approach (\(P < 0.0001\)). In the percutaneous and laparoscopy/laparotomy approach, the rates were 16\% and 4\% for tumors with a diameter of less than 3 cm, 26\% and 22\% for tumors between 3 to 5 cm, and 60\% and 50\% for tumors with a diameter of over 5 cm\(^{21}\). Tumors with a diameter of 3 to 5 cm must be treated with surgical RFA, and tumors larger than 5 cm might not be suitable candidates for RFA. The local recurrence rate after RFA for tumors located less than 5 mm from a blood vessel (which is at least 3 mm in diameter) is 36.5\%, compared to 6.3\% for tumors which were located at greater distances from these vessels\(^{23\)\(^,\)\(^24}\). The local recurrence rates after RFA for tumors with a surgical margin of 0 cm, 0.5 cm, and 1 cm are 14.5\%, 16.4\%, and 6.5\%, respectively\(^{23}\).

Recurrence patterns after percutaneous RFA and surgical wedge resection for solitary CRLM were evaluated\(^{25}\). Surgical wedge resection means a partial hepatic resection with a suitable margin. The two year local tumor progression-free survival rate was 88\% in the wedge resection group and 41\% in the RFA group. Approximately 30\% of the patients in each group presented distant metastases. The median overall survival rate from the time of resection was 80 months in the wedge resection group versus 31 months in the RFA group. For high-risk candidates for resection, RFA may help to manage liver metastases, but a careful follow-up and additional therapy is necessary to achieve long-term survival.
Side effects and complications after thermal ablation for CRLM

A multicenter study confirmed that RFA is a relatively low-risk procedure for the treatment of liver tumors. Of 3554 lesions (1610 HCCs and 693 liver metastases) treated, the mortality and morbidity rates were only 0.3% and 7.2%, respectively. In another study evaluating the early and late complications following RFA in 608 patients, the mortality rate was 0.5%. Early complications were more likely to occur in patients treated with surgical open RFA (8.6%) compared with percutaneous RFA (4.4%). Late complications developed in 2.4% of the patients. The combined early and late complication rate was 9.5%. Major complications included liver abscesses, subcutaneous abscesses, damage or perforation of the gastrointestinal tract and the diaphragm, pseudoaneurysm formation, thrombosis of inferior caval vein, pneumothorax requiring drainage, and subcutaneous metastases in the RFA tract, etc. The incidence of seeding after RFA treatment for CRLM was 0%-1.4% in a large series of patients. Risk factors for the development of track seeding include preoperative biopsies, multiple electrode placements and sessions, a direct approach to subcapsular tumors, no cauterization of the electrode track, and poor differentiation of the tumor. Seeding after RFA is a serious complication which can reduce a patient’s chances for a cure.

Long-term survival of thermal ablation for CRLM

Hepatic resection has been the gold standard in the treatment of CRLM and provides an excellent prognosis; the 5-year survival rate is 23%-58%, and the 10-year survival rate is 17%-28% (1-5,23). Thermal ablation was initially developed as a palliative treatment for unresectable liver tumors. When applied to unresectable CRLM, the 5-year survival rates were 29-36% with MCT (10-12) and 14-35% with RFA (13,15,17,18,26,21) (Table I). Systemic chemotherapy with infusional 5-FU and leucovorin in combination with oxaliplatin (FOLFOX) and/or irinotecan (FOLFIRI) has been widely applied for the treatment of unresectable CRLM, and has significantly improved response rates and overall survival. Nevertheless the 5-year survival rates are still low at 0% to 20%, including the patients who needed secondary surgeries to remove metastases (2-4,28). Thermal ablation, indeed, has a positive impact on the survival of unresectable CRLM. However, the survival rate after RFA for unresectable CRLM versus the survival rate after resection for resectable CRLM showed a much better survival rate after resection (14,16,17). In the treatment of solitary CRLM, the 5 year survival rates were 71% and 27% with resection or RFA, respectively (17).

Table I. Therapeutic effects of RFA for unresectable CRLM

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients</th>
<th>No. of tumors per patient</th>
<th>Diameter of tumors (cm)</th>
<th>Approach</th>
<th>Mortality (%)</th>
<th>5-Year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15)</td>
<td>167</td>
<td>4.1</td>
<td>3.9 (1-12)</td>
<td>P</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>13)</td>
<td>121</td>
<td>2.6</td>
<td>2.1 ± 0.9 (0.9-4)</td>
<td>P</td>
<td>0</td>
<td>35</td>
</tr>
<tr>
<td>18)</td>
<td>100</td>
<td>5.1</td>
<td>3 ± 1.6 (0.3-17)</td>
<td>P, L, O</td>
<td>1</td>
<td>31</td>
</tr>
<tr>
<td>20)</td>
<td>47</td>
<td>3.1</td>
<td>2.4 ± 1.6</td>
<td>P, L, O</td>
<td>0</td>
<td>21</td>
</tr>
<tr>
<td>17)</td>
<td>30</td>
<td>1.0</td>
<td>3 (1-7)</td>
<td>P, O</td>
<td>0</td>
<td>27</td>
</tr>
<tr>
<td>Our series</td>
<td>40</td>
<td>2.5</td>
<td>2.7 (0.5-60)</td>
<td>P, L, O</td>
<td>0</td>
<td>41</td>
</tr>
</tbody>
</table>

RFA, radiofrequency ablation; CRLM, colorectal liver metastases; NA, data not available; P, percutaneous; L, laparoscopic; O, open surgical approach.

Only independent series with published data on 5 year survival rates calculated from the time of RFA application were retained (21).
There are no long-term survival data available to compare RFA versus hepatic resection for resectable CRLM. Therefore, a randomized trial of RFA versus hepatic resection was proposed for completely resectable CRLM; this was to involve only small tumors (< 3 cm), more than 5 mm away from vessels (perivascular invasion negative), with an intentional margin of 1 cm, and no contraindication for RFA\textsuperscript{21}. Today, more than 80\% of patients treated with RFA, have concomitant systemic chemotherapy\textsuperscript{17,22} The ongoing CLOCC trial (a Phase III study of the local treatment of colorectal liver metastases with radiofrequency ablation and chemotherapy versus chemotherapy alone) from the EORTC (European Organization for Research and Treatment of Cancer) probably will answer the question of whether or not systemic chemotherapy plus thermal ablation is superior to chemotherapy alone.

\textit{Clinical evaluation of thermal ablation for CRLM in this department\textsuperscript{19}}

Between 1992 and 2002, 40 patients with unresectable CRLM were treated with thermal ablation at the Department of Gastroenterological Surgery, Graduate School of Medical Sciences, Kumamoto University and its affiliated hospitals. Twenty-two percent of 182 patients with CRLM in the same period were treated with thermal ablation. According to the treatment strategy for CRLM during that period, thermal ablation was applied to initially unresectable tumors equal to or smaller than 5 cm without prior chemotherapy. Percutaneous, endoscopic and open surgical approaches were individually selected according to tumor size, number, and location. It is quite important to select an appropriate approach for the treatment of tumors with a sufficient surgical margin. The mean tumor size and tumor number was 27 mm (range 5-60 mm) and 2.5 (range 1-9), respectively. The local recurrence rate was 15\% at the therapeutic site and 10\% in the adjacent area over an average 2.5-year observation period. The five year overall survival rate was 37\%, and was 41\% in patients with hepatic resection (Fig. 1).

![Graph](image)

\textbf{Fig. 1.} Cumulative survival curves for CRLM based on therapeutic modality. This figure includes data from 45 patients with hepatic resection, 40 with thermal ablation, and 97 with hepatic arterial chemotherapy. Five-year survival rates were 41\%, 37\%, and 5\% respectively for the three groups. Survival rates following hepatic resection and thermal ablation were significantly better than survival following hepatic arterial chemotherapy ($P < 0.001$).
After the introduction of FOLFOX in 2005, a new treatment strategy for CRLM was developed. Thermal ablation was applied primarily to patients treated with FOLFOX, in combination with hepatic resection. FOLFOX was administered for initially unresectable CRLM. In 31 patients with initially unresectable CRLM, it was possible to treat 11 patients with hepatic resection only, and 6 patients were treated using hepatic resection in combination with RFA. In total, 30 tumors in 6 patients were treated with RFA, and hepatic resection was used for the remnant tumors. The average tumor diameter was 16.5 mm (range 12 mm to 25 mm). Local recurrence was never observed in the 30 tumors treated with surgical RFA during an average follow up period of 26 months. Such good local control may have resulted from the reduced tumor size and low viability of the tumors after an effective FOLFOX therapy. The CLOCC trial was undertaken to determine whether RFA in combination with chemotherapy leads to a superior overall survival rates when compared to chemotherapy alone for the treatment of colorectal liver metastases. Although, in the CLOCC trial, RFA was used and followed up by chemotherapy, RFA was recommended after effective chemotherapy. The reason was that RFA induced obstruction of key arteries, liver metastasis, or arterio-portal shunt formation might lead to an insufficient drug delivery to the targeted tumor.

Conclusions

At the present, thermal ablation can be applied in the treatment of unresectable CRLM without perivascular invasion, and for tumors smaller than 3 cm with a percutaneous or surgical approach, and for tumors smaller than 5 cm with a combined surgical approach. RFA after effective chemotherapy can provide ideal local control. A randomized control trial of RFA versus hepatic resection for resectable CRLM is needed to clarify the long-term clinical effects of RFA.

References

