The Role of Thermal Ablation for Colorectal Liver Metastases in the Era of Effective Chemotherapy

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Abstract : After the introduction of new chemotherapeutic agents, including oxaliplatin and irinotecan, chemotherapy can induce tumor down-staging in patients with initially unresectable colorectal liver metastases (CRLM), which thus allows for hepatic resection. Recently, the application of thermal ablation, especially radiofrequency ablation (RFA), has been extended from hepatocellular carcinoma (HCC) to CRLM. However, randomized trials show little evidence to support the clinical efficacy of RFA for CRLM. We herein evaluate the clinical efficacy and the role of thermal ablation for CRLM in this era of effective chemotherapy. Non-randomized retrospective studies have demonstrated the effects of RFA alone for CRLM without new chemotherapeutic agents. The three- and five-year survival rates of RFA alone for CRLM ranged from 42% to 57%, and 21% to 37%, respectively. The local recurrence rate was between 9% and 15%. In contrast, the five-year survival rates after RFA with perioperative chemotherapy of irinotecan- or oxaliplatin-based regimens ranged from 34% to 54%. The local recurrence at the site of RFA ranged from 29.7% to 42.5%. After the introduction of new chemotherapeutic agents, RFA with perioperative chemotherapy of irinotecan- or oxaliplatin-based regimens may improve the survival in patients with CRLM compared to RFA alone. However, the rate of local recurrence of RFA with perioperative chemotherapy was similar to that after RFA alone. The three- and five-year survival rates of RFA in combination with hepatic resection for CRLM ranged from 38% to 47%, and 47% to 68%, respectively. The rate of local recurrence at the site of RFA was between 5 and 17.4%, respectively.

In our study, hepatic resection combined with RFA after the FOLFOX regimen resulted in excellent local control rates (2.5% recurrence per tumor).

In this era of new and more effective chemotherapy, combining RFA with chemotherapy or hepatic resection for CRLM can extend the indications of surgical resection and further improve patient survival.

Key Words : thermal ablation, colorectal liver metastases (CRLM), radiofrequency ablation (RFA),

perioperative chemotherapy, 5-FU/LV+oxaliplatin (FOLFOX)

Introduction

Colorectal cancer is the second leading cause of death due to cancer in the United States, and is the third leading cause in Japan¹⁾. Colorectal liver metastases (CRLM) are present in approximately 25% of patients at initial presentation²⁾ and 50% of patients develop liver metastases during the course of their disease³⁾. The management of patients with CRLM is a therapeutic challenge for both oncologists and surgeons. Surgical resection remains the golden standard for patients with resectable CRLM⁴⁾. Of patients with liver metastases, only 20% are initially considered resectable⁵⁾. Combination chemotherapy including modulated infusional 5-fluorouracil (5-FU) plus irinotecan or oxaliplatin can achieve a response rate of 50% and median survival of over 20 months⁶⁻⁹⁾. Oxaliplatin-based chemotherapy, including the FOLFOX regimen, can lead to tumor down-staging in patients with initially unresectable CRLM, and allowed hepatic resection in 16-38% of patients¹⁰⁻¹⁵⁾.

Currently, indications for thermal ablation including microwave coagulation therapy (MCT) and radiofrequency ablation (RFA) have been extended from hepatocellular carcinoma (HCC) to CRLM. However, there is little evidence supporting the routine use of RFA for patients with resectable CRLM because RFA is associated with high local recurrence and poor survival rates compared with conventional liver resection¹⁶⁾. However, some studies have reported that hepatic resection combined with local ablation therapy improved hepatic clearance and outcome in patients with CRLM^{17,18)}.

In this article, we reviewed the clinical efficacy and the role of RFA for CRLM in the era of new and more effective chemotherapy.

Survival of patients treated by RFA alone for CRLM

RFA for CRLM has shown various results in non-randomized retrospective studies. Table I showed the 5 independent studies including more than 40 patients treated by RFA alone for CRLM from 2000¹⁹⁻²³⁾. The three- and five-year survival from the time of diagnosis of liver metastases ranged from 42% to 57%, and 21% to 37%, respectively. The local recurrence rate was between 9% and 15%. Based on these studies, it cannot be concluded whether RFA is an acceptable alternative to resection for resectable CRLM.

Table I. Survival of RFA alone for CRLM

Author	year	No. of Patients with RFA	No. of tumors per patient	Diameter of tumors (cm)	Approach	Local recurrence rate per patient (%)	Overall survival rate (%)
Elias ¹⁹⁾	2002	47	1.4	2.1	P	11	NA
Abdalla ²⁰⁾	2004	57	1-8	2.5	O	9.0	21 (5 yr)
Machi ²¹⁾	2006	100	5.1	3.0	P, L, O	NA	42 (3 yr)
Abitabile ²²⁾	2007	47	3.1	2.4	P, O	NA	57 (3 yr)
Beppu ²³⁾	2008	40	2.5	2.7	P, L, O	15	37 (5 yr)

RFA, radiofrequency ablation ; CRLM, colorectal liver metastases ; NA, data not available ; P, percutaneous ;

L, laparoscopic ; O, open surgical approach ; yr, year

Only independent series with published data including more than 40 patients treated with RFA.

3-, 5-year overall survival was calculated from the time of diagnosis of liver metastases.

Survival of patients treated by RFA with perioperative chemotherapy for CRLM

The studies described the number of patients who received chemotherapy and the type of chemotherapeutic regimen were limited. The studies that used RFA with perioperative chemotherapy for CRLM were divided into two groups by the type of chemotherapeutic regimen. The studies that used RFA with perioperative chemotherapy of several regimens during the period of the study were listed in Table II, and the studies that only used perioperative chemotherapy of irinotecan- or oxaliplatin-based regimens were listed in Table III.

Table II showed the 8 studies that used RFA with perioperative chemotherapy of several regimens during the period of the study for CRLM^{24–31}. In these studies, the proportions of patients who received perioperative chemotherapy were between 25% and 88%. Based on the results of these studies, the three- and five-year survival rates ranged from 20% to 64%, and 15% to 30%, respectively. The rate of local recurrence at the site of RFA for CRLM was between 16 and 46%, respectively.

The five-year survival rates after RFA with perioperative chemotherapy of irinotecan- or oxaliplatin-based regimens are available from 4 studies (Table III)^{32–35}. In these studies, the proportions of patients who received perioperative chemotherapy of irinotecan- or oxaliplatin-based regimens were between 52.5% and 100%, and the five-year survival rates ranged from 34% to 54%. The local

Table II. Survival of RFA with perioperative chemotherapy for CRLM

Author	year	No. of Patients with RFA	No. of tumors per patient	Diameter of tumors (cm)	Rates of patients with chemotherapy (%)	Local recurrence rate per patient (%)	Overall survival rate (%) /MST
Livraghi ²⁴⁾	2003	88	1-3	2.1	88 (Pre RFA)	40	NA
Berber ²⁵⁾	2005	135	3.2	4.1	80 (Pre RFA)	46	44.6 months
Siperstein ²⁶⁾	2007	234	2.8	3.9	80 (Pre RFA)	NA	20 (3 yr)
Sorensen ²⁷⁾	2007	100	3.3	2.2	25 (Pre RFA)	NA	64 (3 yr)
Berber ²⁸⁾	2008	68	Solitary	3.7	82 (Pre RFA)	16	30 (5 yr)
Park ²⁹⁾	2008	30	1.2	≤3	73 (Post RFA)	23.3	15-20 (5 yr)
Veltri ³⁰⁾	2008	122	1.6	2.9	71 (Pre RFA)	26.3	54 (3 yr)
Reuter ³¹⁾	2009	66	2.8	3.2	67 (Pre RFA)	17	21 (5 yr)

RFA, radiofrequency ablation ; CRLM, colorectal liver metastases ; NA, data not available ; MST, median survival time ; yr, year

Pre RFA, chemotherapy was performed before RFA ; Post RFA, chemotherapy was performed after RFA

3-, 5-year overall survival and median survival time were calculated from the time of diagnosis of liver metastases.

Table III. Survival of RFA with perioperative chemotherapy of irinotecan- or oxaliplatin-based regimens for CRLM

Author	year	No. of Patients with RFA	No. of tumors per patient	Diameter of tumors (cm)	Rates of patients with chemotherapy (%)	No. of Patients received FOLFOX or FOLFIRI	Local recurrence rate per patient (%)	Overall survival rate (%)
Lee ³²⁾	2008	37	Solitary	≤3	89 (Post RFA)	18 (54.5%)	29.7	NA
Gillams ³³⁾	2008	40	Solitary	2.3	80 (Pre RFA)	21 (52.5%)	42.5	54 (5 yr)
Gillams ³⁴⁾	2009	309	4.0	3.7	72 (Pre RFA)	142 (59%)	NA	34 (5 yr)
Knudsen ³⁵⁾	2009	36	1-8	2.1	100 (Pre RFA)	36 (100%)	NA	34 (5 yr)

RFA, radiofrequency ablation ; CRLM, colorectal liver metastases ; NA, data not available ; yr, year ;

FOLFOX, chemotherapy with folinic acid, 5-fluorouracil, and oxaliplatin ; FOLFIRI, chemotherapy with folinic acid, 5-fluorouracil, and irinotecan,

Pre RFA, chemotherapy was performed before RFA ; Post RFA, chemotherapy was performed after RFA

3-, 5-year overall survival was calculated from the time of diagnosis of liver metastases.

recurrence at the site of RFA ranged from 29.7% to 42.5%. When new chemotherapeutic agents were used, it was possible for RFA with perioperative chemotherapy to improve survival. However, the rate of local recurrence at the site of RFA was similar to that of RFA alone, and larger studies are needed to determine whether there is a significant increase in survival sufficient to be worth the risks of chemotherapy. In a meta-analysis reported by Mulier *et al.*³⁶⁾, factors associated with significantly fewer local recurrences after RFA alone for CRLM included the following: small tumor size, the surgical (open or laparoscopic) approach, location away from large vessels, a 1 cm intentional margin, and greater physician experience. Berber *et al.*²⁵⁾ reported several predictors of survival in RFA-treated patients with CRLM. In their study, the patients were not candidates for resection, and 80% had intrahepatic tumor progression despite chemotherapy. The median survival was 28.9 months after RFA, and the local recurrence rate at the site of laparoscopic RFA was 46%. A poor response to chemotherapy prior to RFA may be one of the major risk factors for high local recurrence.

Chemotherapy plus RFA versus chemotherapy alone for CRLM

The chemotherapy plus local ablation versus chemotherapy (CLOCC) trial was a randomized phase II study conducted by the European Organization for Research and Treatment of Cancer (EORTC). The final results were reported at the American Society of Clinical Oncology 46th Annual Meeting in 2010³⁷⁾. In the study, 119 patients with unresectable CRLM were randomized to either chemotherapy alone (59 patients) or RFA followed by chemotherapy (60 patients) groups. In both arms, chemotherapy consisted of 6 months of FOLFOX with or without bevacizumab. The maximum tumor size was less than 4 cm, and the median tumor number was 4.0. At a median follow up of 4.4 years, the 30-month overall survival rates were 57.6% in the chemotherapy alone group and 61.7% in the RFA plus chemotherapy group, respectively. The median progression free survival was 9.9 months in the chemotherapy alone group and 16.8 months in the RFA plus chemotherapy group. The number of patients with first recurrence at the RFA site only was 5 (9%). The progression free survival therefore significantly improved in the RFA plus chemotherapy group compared to chemotherapy alone group.

Survival of patients treated by RFA in combination with hepatic resection for CRLM

Table IV showed the 5 studies that used RFA in combination with hepatic resection for CRLM^{17,18,20,38,39)}. Based on the results of these studies, the three- and five-year survival rates ranged from 38% to 47%, and 47% to 68%, respectively. The rate of local recurrence at the site of RFA for CRLM was between 5 and 17.4%, respectively.

Table IV. Survival of RFA in combination with hepatic resection for CRLM

Author	year	No. of Patients ith RFA+HR	No. of tumors per patient	Diameter of tumors (cm)	Local recurrence rate per patient (%)	Overall survival rate (%)
Abdalla ²⁰⁾	2004	101	NA	NA	5.0	43 (3 yr)
Elias ³⁸⁾	2005	63	5.6	NA	17.4	47 (3 yr)
De Jong ³⁹⁾	2009	134	5 (1-19)	3.4	NA	47.3 (5 yr)
Nikfarjam ¹⁷⁾	2009	23	2 (1-10)	3.0	NA	68 (5 yr)
Leung ¹⁸⁾	2010	16	3 (2-7)	2.9	NA	38 (3 yr)

RFA, radiofrequency ablation ; CRLM, colorectal liver metastases ; HR, hepatic resection ; NA, data not available ;
3-, 5-year overall survival and median survival time were calculated from the time of diagnosis of liver metastases.

Traditionally multiple bilobar CRLM were considered unresectable. However, RFA in combination with hepatic resection may be a potential treatment option for patients with multiple bilobar CRLM.

RFA in combination with hepatic resection for CRLM after chemotherapy of FOLFOX in our department

The determination of the initial resectability of CRLM is based on the possibility of safe and curative (R0) resection. When initially unresectable CRLM became resectable after several courses of FOLFOX, hepatic resection was immediately performed. The final decision to perform surgery after FOLFOX was based on the possibility of removing all metastases by hepatic resection with or without RFA¹⁵⁾. Between May 2005 and Dec 2009, 71 patients with initially unresectable CRLM were treated with FOLFOX. Of 71 patients, 26 (37%) of them were converted to be resectable after chemotherapy using the FOLFOX regimen in our department. Of 26 patients, 8 patients were treated with hepatic resection combined with RFA. Of 40 RFA sites in 8 patients, the median number of RFA sites was 4.5 (range 1-9) and their median diameter was 11 mm (range 3-25). All patients had bilobar disease. After chemotherapy using FOLFOX for 6 to 8 cycles, 6 patients (75%) had a partial response, and 2 patients (25%) had stable disease. Local recurrence at the site of RFA occurred in only one tumor (2.5% of tumors), as a 2.5 cm in diameter tumor, during the 30 months of mean observation.

The role of RFA for CRLM in the era of effective chemotherapy

In the NCCN (National Comprehensive Cancer Network) Clinical Practice Guidelines in Oncology and the guideline of Japanese Society for Cancer of the Colon and Rectum, hepatic resection is the standard of care for the local treatment of initially resectable CRLM⁴⁰⁾. For patients with initially unresectable CRLM, systemic chemotherapy is the preferred initial treatment. And hepatic resection is recommended for patients with initially unresectable CRLM converted to a potentially curable status following chemotherapy (Fig. 1). However, there is little evidence supporting the use of RFA for patients with CRLM. In the era of new and more effective chemotherapy, the role of RFA for CRLM has not yet been clearly defined.

Fig. 1. Therapeutic strategies for colorectal liver metastases

Conclusions

At present we cannot conclude whether RFA is an acceptable alternative to hepatic resection for resectable CRLM. Although RFA with perioperative chemotherapy can improve survival, the rate of local recurrence at the site of RFA was similar to that of RFA alone. However, RFA in combination with chemotherapy and hepatic resection for CRLM, especially multiple bilobar CRLM previously considered unresectable, can extend the indications for surgery and improve survival.

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