Comparative analysis of radiofrequency ablation and resection for resectable colorectal liver metastases

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Abstract

AIM: To evaluate the therapeutic efficacy of radiofrequency ablation (RFA) for resectable colorectal liver metastases (CRLM) compared with that of resection.

METHODS: Between June 2004 and June 2009, we retrospectively analyzed 29 patients with resectable CRLMs; 17 patients underwent RFA, and 12 underwent hepatic resection. All of the patients were informed about the treatment modalities and were allowed to choose either of them. RFA including an intraoperative approach was performed by a radiologist; otherwise, hepatic resection was performed by a surgeon. Comparative analysis of the two groups was performed, including comparisons of gender, age, and clinical outcomes, such as primary tumor stage and survival rates.

RESULTS: The mean tumor size was significantly larger in the resection group (3.59 cm vs 2.02 cm, P < 0.01), and the 5-year overall survival (OS) rate for all patients was 44.7%. There was no difference in the 5-year OS rates between the RFA and resection groups (37.8% vs 66.7%). Univariate analysis indicated significantly lower 5-year OS rates for patients with a tumor size > 3 cm. The 5-year disease-free survival (DFS) rates were 17.6% and 22.2% in the RFA and resection groups, respectively (P = 0.119). Univariate analysis revealed that in cases of male gender, age > 65 years, T stage < IV, absence of lymphatic metastasis, and tumor size > 3 cm, RFA resulted in significantly inferior 5-year DFS rates compared with surgical resection.

CONCLUSION: Surgical resection revealed superior outcomes in the treatment of resectable CRLMs, particularly in cases with a hepatic tumor size > 3 cm.

Key words: Colorectal neoplasm; Metastasis; Radiofrequency; Hepatectomy; Survival

Core tip: Colorectal liver metastasis is diagnosed in approximately 50% of patients with colorectal cancer. Surgical resection is the optimal treatment strategy. Alternative local treatment modalities can be adapted, and radiofrequency ablation (RFA) is widely accepted. We examined whether RFA is an appropriate alternative method to surgery for resectable colorectal liver metastases. This study retrospectively compared the therapeutic efficacy of RFA and compared it with that of surgical resection in a single institute.

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INTRODUCTION
A 2005 annual report of cancer incidence indicated that colorectal cancer (CRC) is the third most common malignancy worldwide and the second most common (12.5%) in Korea, following gastric cancer. The 5-year survival rate of CRC is reportedly 61%[6-8], and hepatic metastasis develops in approximately 40%-50% of patients with CRC; approximately 50% of diagnosed patients present the synchronous type[3,9]. Although surgical resection is the most effective current treatment for resectable colorectal cancer liver metastases (CRLMs)[6,10], only 10%-15% of such cases are suitable for the procedure[8,9]. Several alternative treatment modalities for unresectable CRLMs have been developed, of which radiofrequency ablation (RFA) is widely accepted as an effective alternative local treatment modality[10].

Surgical hepatic resection is the treatment of choice for resectable CRLMs. Although RFA is an alternative to resection in hepatocellular carcinoma[11-13], there is little information regarding indications for RFA in resectable CRLMs. RFA is performed within a limited number of clinical settings for resectable CRLMs[11,14]. The purpose of the present study was to compare the therapeutic efficacies of RFA and hepatic resection for resectable CRLMs within a single institution.

MATERIALS AND METHODS
In this study, we compared the treatment outcomes of 12 patients who underwent hepatic resection with 17 who underwent RFA for synchronous or metachronous resectable CRLMs between June 2004 and June 2009 at the Department of Surgery, Pusan National University Hospital (Busan, South Korea). The inclusion criteria for this study were as follows: (1) no signs of preoperative extrahepatic metastases; (2) tumor size < 5 cm; and (3) a single metastatic tumor. The exclusion criteria were as follows: (1) no signs of preoperative extrahepatic metastases; (2) tumor size < 5 cm; and (3) a single metastatic tumor. The exclusion criteria were as follows: (1) no signs of preoperative extrahepatic metastases; (2) tumor size < 5 cm; and (3) a single metastatic tumor. The exclusion criteria were as follows: (1) no signs of preoperative extrahepatic metastases; (2) tumor size < 5 cm; and (3) a single metastatic tumor. The purpose of the present study was to compare the therapeutic efficacies of RFA and hepatic resection for resectable CRLMs within a single institution.

Diagnosis of CRLM
The diagnosis of hepatic or extrahepatic metastasis was confirmed on the basis of the findings of serum carcinoembryonic antigen (CEA), contrast-enhanced computed tomography (CT) of the abdomen and chest, magnetic resonance imaging (MRI), and 18F-2-fluoro-2-deoxyglucose positron emission tomography (FDG-PET). Hepatic metastasis was defined as any newly developed hepatic tumors detected during patient follow-up after curative resection of CRC. A needle biopsy was not routinely performed before RFA but was performed in patients with atypical hepatic mass enhancement.

RFA
RFA for hepatic metastases was performed when patients refused surgical hepatic resection after being informed of the treatment method, complications, and survival rates. RFA was performed percutaneously under local anesthesia or during and simultaneously with CRC resection. RFA was performed using a 200-W generator in the impedance control mode and a monopolar single or clustered internally cooled electrode (Covidien, Boulder, CO, United States). Written informed consent was obtained from all patients before initiating treatment.

Surgical resection
A major resection was defined as resection of more than three hepatic segments and minor resection as two segments or less. Major and minor resections were performed in five and seven patients, respectively (Table 1). None of the patients received perioperative transfusion, and there was no incidence of postoperative mortality.

Follow-up protocol
Seven days after resection or RFA, contrast-enhanced CT of the abdomen was performed, and serum CEA levels were measured to determine the baseline values. The same evaluations were repeated every four months during the initial two years and every six months thereafter. Endoscopic analysis and FDG-PET were performed annually, and chest CT or MRI was added when tumor recurrence was suspected.

Statistical analysis
Overall survival (OS) and disease-free survival (DFS) rates were analyzed using the Kaplan-Meier method, and the statistical significance of differences in the survival rates was evaluated using the log-rank test. A two-tailed P-value < 0.05 was considered statistically significant. The statistical analysis was performed using SPSS statistical software (ver. 12.0; SPSS Inc., Chicago, IL, United States).

RESULTS
Clinicopathological data
Information regarding the patients and pathological results is provided in Tables 2 and 3. The mean tumor diameter in the RFA group (2.02 cm; range, 0.8-4.6 cm) was significantly smaller than that in the resection group (3.59 cm; range, 1.6-4.9 cm). There were no other significant differences between the two groups. Four of the 17 patients in the RFA group and 7 of the 12 in the resection group presented a hepatic tumor > 3 cm in size; no significant difference was evident between the two
The 5-year OS rate was 44.7% among all patients with CRLMs, 37.8% in the RFA group, and 66.7% in the resection group ($P = 0.29$; Figure 1). The 5-year OS rate was lower in patients with a hepatic tumor size > 3 cm than in those with a tumor size < 3 cm (Table 5). Moreover, the 5-year DFS rates were 17.6% and 22.2% in the RFA and resection groups, respectively ($P = 0.119$; Figure 2). The variables associated with lower DFS rates included male gender, age > 65 years, CRC T stage < IV, absence of lymphatic invasion, and tumor size > 3 cm (Table 6).

**DISCUSSION**

Surgical resection is the treatment of choice for resectable CRLMs, whereas RFA has been used for unresectable CRLMs as an alternative treatment to improve patient survival\(^{[13,14]}\). While some series have reported RFA equivalent to resection, others have shown RFA to be inferior to resection based on overall survival\(^{[15-17]}\). However, the efficacy of RFA for resectable CRLMs remains controversial. Reuter et al\(^{[18]}\) reported superior DFS rates in patients with resectable CRLMs following surgical resection than follow-

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**Table 2  Summary of patient information**

| No. | Age (yr) | Sex | Comorbidity | Treatment modality | Location | Timing of metastasis | Recurrence | Results |
|-----|----------|-----|-------------|--------------------|----------|----------------------|------------|---------|
| 1   | 51       | M   |             | RFA                | Colon    | Meta                 | Yes        | S       |
| 2   | 60       | M   |             | RFA                | Colon    | Meta                 | Yes        | D       |
| 3   | 69       | M   | DM, HT      | Resection          | Rectum   | Meta                 | Yes        | D       |
| 4   | 76       | M   |             | Resection          | Rectum   | Meta                 | Yes        | D       |
| 5   | 62       | M   |             | RFA                | Colon    | Syn                  | No         | S       |
| 6   | 61       | M   | DM          | RFA                | Rectum   | Meta                 | Yes        | D       |
| 7   | 70       | F   |             | Resection          | Colon    | Meta                 | Yes        | S       |
| 8   | 70       | M   |             | Resection          | Rectum   | Meta                 | No         | S       |
| 9   | 71       | F   |             | Resection          | Rectum   | Meta                 | Yes        | S       |
| 10  | 69       | F   | DM, HT      | Resection          | Colon    | Syn                  | Yes        | S       |
| 11  | 74       | F   |             | Resection          | Colon    | Syn                  | No         | S       |
| 12  | 71       | M   |             | Resection          | Colon    | Meta                 | Yes        | S       |
| 13  | 82       | M   |             | Resection          | Rectum   | Meta                 | Yes        | D       |
| 14  | 58       | F   |             | RFA                | Colon    | Meta                 | No         | S       |
| 15  | 60       | M   | RFA         | Colon              | Syn      | Meta                 | Yes        | D       |
| 16  | 56       | F   |            | RFA                | Colon    | Meta                 | Yes        | S       |
| 17  | 56       | M   |            | RFA                | Colon    | Meta                 | Yes        | S       |
| 18  | 54       | F   |            | RFA                | Colon    | Meta                 | Yes        | D       |
| 19  | 52       | F   |            | RFA                | Rectum   | Meta                 | No         | S       |
| 20  | 60       | M   | RFA         | Colon              | Meta     | Yes                  | D          |     |
| 21  | 55       | M   | RFA         | Rectum             | Meta     | Yes                  | D          |     |
| 22  | 75       | M   | Resection   | Colon              | Syn      | Meta                 | Yes        | D       |
| 23  | 54       | F   | RFA         | Rectum             | Meta     | Yes                  | D          |     |
| 24  | 63       | F   | RFA         | Colon              | Syn      | Yes                  | D          |     |
| 25  | 66       | M   | Resection   | Rectum             | Syn      | Yes                  | S          |     |
| 26  | 56       | F   | RFA         | Rectum             | Meta     | Yes                  | D          |     |
| 27  | 67       | M   | Resection   | Colon              | Meta     | Yes                  | D          |     |
| 28  | 58       | M   | RFA         | Rectum             | Syn      | No                   | S          |     |
| 29  | 71       | M   | Resection   | Colon              | Meta     | Yes                  | S          |     |

DM: Diabetes mellitus; HT: Hypertension; RFA: Radiofrequency ablation; Meta: Metachronous; Syn: Synchronous; S: Survival; D: Death; M: Male; F: Female.

**Figure 1** The 5-year overall survival rate. A: For all patients (44.7%); B: In the surgical resection (66.7%) and radiofrequency ablation (RFA) groups (37.8%).
ing RFA. By contrast, Mulier et al\(^{[19]}\) reported no significant difference in OS between RFA and surgical resection for local control of CRLMs. Furthermore, in a recent study, Kanas et al\(^{[20]}\) reported a 5-year OS rate of 30%-40% in

### Table 3  Summary of pathological findings

| No. | Metastatic tumor size (cm) | Diff | T  | N  | M  | LNR | LV | PN |
|-----|--------------------------|-----|----|----|----|-----|----|----|
| 1   | 2.5                      | Mod | 3  | 2  | 0  | 0.23 | Pos| Pos|
| 2   | 1.6                      | Mod | 3  | 2  | 0  | 0.17 | Pos| Pos|
| 3   | 4                        | Mod | 4  | 2  | 0  | 0.37 | Pos| Pos|
| 4   | 4.2                      | Mod | 4  | 1  | 0  | 0.43 | Pos| Pos|
| 5   | 3.2                      | Mod | 3  | 1  | 1  | 0.07 | Pos| Neg|
| 6   | 4.2                      | Mod | 2  | 2  | 0  | 0.25 | Pos| Pos|
| 7   | 4                        | Mod | 3  | 0  | 1  | 0   | Pos| Pos|
| 8   | 2.8                      | Mod | 4  | 0  | 0  | 0   | Pos| Pos|
| 9   | 4.4                      | Mod | 1  | 2  | 0  | 0.06 | Neg| Neg|
| 10  | 4.9                      | Well| 3  | 1  | 1  | 0.03 | Pos| Neg|
| 11  | 2.8                      | Mod | 3  | 0  | 0  | 0   | Neg| Pos|
| 12  | 2.3                      | Mod | 4  | 1  | 0  | 0.08 | Neg| Neg|
| 13  | 3.2                      | Mod | 4  | 2  | 1  | 0.33 | Neg| Pos|
| 14  | 1.2                      | Mod | 3  | 2  | 0  | 0.14 | Pos| Pos|
| 15  | 0.9                      | Poor| 3  | 2  | 0  | 0.12 | Pos| Pos|
| 16  | 1.7                      | Poor| 3  | 1  | 0  | 0.04 | Pos| Pos|
| 17  | 2                        | Mod | 3  | 1  | 0  | 0.03 | Neg| Neg|
| 18  | 1                        | Mod | 3  | 2  | 0  | 0.34 | Pos| Pos|
| 19  | 2.5                      | Mod | 4  | 0  | 0  | 0   | Neg| Neg|
| 20  | 2                        | Mod | 3  | 1  | 0  | 0.14 | Pos| Pos|
| 21  | 1.6                      | Mod | 3  | 1  | 0  | 0.08 | Pos| Pos|
| 22  | 1                        | Mod | 3  | 1  | 0  | 0.04 | Pos| Pos|
| 23  | 3.8                      | Mod | 2  | 0  | 0  | 0   | Neg| Neg|
| 24  | 3.7                      | Mod | 3  | 0  | 1  | 0   | Neg| Neg|
| 25  | 1                        | Mod | 3  | 0  | 0  | 0   | Neg| Neg|
| 26  | 3.6                      | Mod | 4  | 2  | 1  | 0.58 | Neg| Pos|
| 27  | 1.2                      | Mod | 3  | 0  | 0  | 0   | Pos| Pos|
| 28  | 0.8                      | Mod | 4  | 1  | 1  | 0.03 | Neg| Neg|
| 29  | 1.3                      | Mod | 3  | 0  | 0  | 0   | Neg| Neg|

Diff: Differentiation of primary tumor; T: T stage; N: N stage; M: M stage; LNR: Lymph node ratio; LN: Lymphovascular invasion; PN: Perineural invasion; Mod: Moderate; Poor: Poorly; Pos: Positive; Neg: Negative.

### Table 4  Clinicopathological data of colorectal liver metastases \(n\) (%)

|                | RFA \((n = 17)\) | Resection \((n = 12)\) | \(P\)-value |
|----------------|------------------|------------------------|-------------|
| Sex            |                  |                        |             |
| Male           | 7 (41)           | 4 (33)                 | 0.49        |
| Female         | 10 (59)          | 8 (67)                 |             |
| Age (yr)       |                  |                        |             |
| ≤ 65           | 12 (71)          | 4 (33)                 | 0.07        |
| > 65           | 5 (29)           | 8 (67)                 |             |
| Timing of metastasis |      |                        |             |
| Synchronous    | 5 (29)           | 3 (25)                 | 1.00        |
| Metachronous   | 12 (71)          | 9 (75)                 |             |
| Primary site   |                  |                        |             |
| Colon          | 10 (59)          | 8 (67)                 | 0.72        |
| Rectum         | 7 (41)           | 4 (33)                 |             |
| T stage        |                  |                        |             |
| I - III        | 13 (76)          | 8 (67)                 | 0.68        |
| IV             | 4 (24)           | 4 (33)                 |             |
| Lymphovascular |                  |                        |             |
| Positive       | 8 (47)           | 8 (67)                 | 0.45        |
| Negative       | 9 (53)           | 4 (33)                 |             |
| Perineural invasion |        |                        |             |
| Positive       | 10 (59)          | 7 (58)                 | 1.00        |
| Negative       | 7 (41)           | 5 (42)                 |             |
| Lymph node metastasis |      |                        |             |
| Positive       | 11 (65)          | 9 (75)                 | 0.69        |
| Negative       | 6 (35)           | 3 (25)                 |             |
| Size of metastasis (cm) |      |                        |             |
| ≤ 3 cm         | 13 (76)          | 5 (42)                 | 0.07        |
| > 3 cm         | 4 (24)           | 7 (58)                 |             |
| Recurrence     |                  |                        |             |
| Yes            | 14 (82)          | 9 (75)                 | 0.67        |
| No             | 3 (18)           | 3 (25)                 |             |

RFA: Radiofrequency ablation.
patients with resectable CRLMs. Moreover, they observed that the survival rate in the resection group was favorable and reported that statistical significance could be expected using a larger patient population, even in the actual 5-year OS rate in the RFA group and in the nonactual survival in the resection group. Our 5-year OS rates were 66.7% in the resection group and 37.8% in the RFA group (actuarial 5-year survival rates), which is comparable to those reported in other published studies. In patients with hepatic tumors < 3 cm, the 5-year OS rate was 80.0% in the RFA group and 49.5% in the resection group \( (P = 0.46) \). In patients with a hepatic tumor size > 3 cm, the 5-year OS rates were 0% in the RFA group and 57.1% in the resection group \( (P = 0.005) \). In addition, the DFS rate in the resection group was superior to that in the RFA group.

To date, there exist some controversies regarding the
contribution of clinicopathological factors to survival following surgery for resectable CRLMs\(^2(3)\). Surgical resection in CRLM is considered the treatment of choice for local tumor control rather than systemic therapy. RFA, which has the advantages of minimal invasiveness and sparing the liver parenchyma, might be favorable for the local control of CRLMs, which requires adjuvant chemotherapy as well\(^2(3)\). However, less definitive evidence exists regarding the risk of intrahepatic or hematogenous metastases after RFA for patients with CRLMs. Fourteen patients who underwent RFA in our study experienced recurrences of multiple liver metastases and peritoneal carcinomatosis, and two patients developed metastases in the lung and spleen. The local recurrence rates after RFA are reportedly 2%-40%\(^2(3,22-25)\), and Ahtisaari et al\(^2(6)\) reported that local recurrence rates reached 8.8% overall and 1.6% for CRLMs < 3 cm in diameter. In the present study, one patient developed tumor recurrence following RFA and was excluded; the patient was followed up for 37 mo without recurrence after consecutive hepatic resection.

The statistical analysis in the present study identified the following risk factors for poor DFS in the RFA group compared with the resection group: male gender, age > 65 years, lower T stage, colon cancer, and absence of lymph node metastasis. These findings might be the result of the omission of intensive adjuvant chemotherapy in patients with less-advanced CRC stages.

Some limitations to the present study include its retrospective design and the small number of included cases. However, to our knowledge, this is the first report regarding the actuarial 5-year survival rate after RFA, which was 37.8% in patients with resectable CRLMs. Surgical resection is believed to be superior to RFA for resectable CRLMs; nevertheless, RFA displayed some interesting advantages to justify its adoption in patients with resectable CRLMs. Although a randomized controlled study of RFA is warranted, more strict indication criteria are needed before adopting RFA as a replacement for surgical resection in resectable CRLMs.

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