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Optimizing the Indications for Local Ablation in the Treatment of Colorectal Liver Metastasis According to Recurrence at the Ablation Site

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Objective: Patients who underwent local ablation for colorectal liver metastasis (CRLM) were analyzed to identify those who would benefit most from local ablation (LA). **Materials and Methods:** A total of 55 CRLM lesions in 33 cases who underwent LA at our department from 1999 to 2004 were investigated. The local recurrence-free rate at the site of ablation (true recurrence-free rate) and the distance between the lesion and the major intrahepatic vessels (MIVs) were analyzed. **Results:** True recurrence occurred in 29 lesions (52.7%), and the 3-year true recurrence-free rate was 44.3%. The threshold of maximal tumor diameter for recurrence was 1.8 cm. There was no true local recurrence for the small group (lesions less than 1.8 cm), and that group's 3-year true recurrence-free rate was significantly better (small group vs large group (lesion≥1.8 cm): 100% vs 27.7%, $p<0.0001$). The 3-year true recurrence-free rate for lesions far from MIVs (distance>1 cm) was also significantly better than that for lesions close to MIVs (distance≤1 cm) (60.1% vs 33%, $p=0.0152$). **Conclusion:** In CRLM cases, lesions less than 1.8 cm and those further than 1 cm from MIVs are the most likely to benefit from LA.

Key Words: colorectal liver metastasis, local ablation, radiofrequency ablation, microwave coagulation

Introduction

According to the Japanese Society for Cancer of the Colon and Rectum (JSCCR) Guidelines for the Treatment of Colorectal Cancer[1] and guidelines prepared by the National Comprehensive Cancer Network[2], resection is recommended for colorectal liver metastasis (CRLM) in which curative resection can be carried out, and hepatic infusion chemotherapy, systemic chemotherapy, and local ablation (such as radiofrequency ablation (RFA), and microwave coagulation therapy (MCT)) are recommended for unresectable CRLM. Unlike chemotherapy, ablation is a local treatment modality, and it is less invasive in terms of larger remnant liver parenchyma than with resection[3]. It is currently used as an adjunct with hepatic resection or used for the treatment of unresectable CRLMs[4]. Local ablation is widely performed in the treatment of hepatocellular carcinoma (HCC)[5]. However, there is no satisfactory evidence that supports its use in terms of local control and for the best indications for the treatment of CRLMs[6]. Therefore, the efficacy of and best indications for local ablation in terms of the local recurrence-free rate at the site of local ablation were retrospectively investigated by analyzing clinicopathological background characteristics and treatment outcomes of CLRM cases that underwent local ablation at our department.

Materials and Methods

1. Patients

A total of 33 cases in 26 patients who were followed up after treatment of the 35 cases that underwent ablation therapy at the Department of Surgery 2, Tokyo Women's Medical University, from 1999 to 2004 were studied retrospectively. Of the 33 cases, 8 had been previously treated with local ablation more than twice, and 55 CRLMs had been treated. The reasons for selecting local ablation were difficulty of curative resection in 20 cases (61%), extrahepatic disease in 13 cases (39%), aging or comorbidity in 7 cases (20%), and concurrent hepatic resection in 7 cases (20%) (Overlapping rea-

Table 1 Patients' characteristics

Sex (number of patients)	
Male : Female	14 : 12
Synchronous : Metachronous (number of cases)	10 : 23
Age at ablation (±SD) (years)	63.6 (±10.8)
CRC factors T (number of patients)	
T1	0
T2	0
T3	26
T4	0
CRC factors N (number of patients)	
N0	6
N1	7
N2	8
N3	2
Unknown	3
Histological type of CRC (number of patients)	
Well differentiated adenocarcinoma	9
Moderately differentiated adenocarcinoma	14
Poorly differentiated adenocarcinoma	0
Unknown	3
Liver metastasis at ablation (number of cases)	
H0	0
H1	25
H2	6
H3	2
Grade classification of liver metastasis (number of cases)	
A	8
B	7
C	14
Unknown	4
Extrahepatic metastasis at ablation (number of cases)	
None	21
Distant lymph node metastasis	1
Peritoneum	1
Lung	8
Lung + lymph node metastases	1
Local recurrence	1
Change in the CEA level (number of cases)	
Decrease	28
Increase	3
Unknown	2

SD, standard deviation; CRC, colorectal cancer; CEA, carcinoembryonic antigen.

sons are included). Cases with inadequate ablation according to the operative findings were excluded.

The male to female ratio was 14 : 12. The T and N factors of the primary colorectal cancers (CRCs) are reported in Table 1. There were 10 cases of synchronous liver metastases, and 23 cases were metachronous. Synchronous metastases were defined as CRLMs identified at the time or within 6 months of the diagnosis of CRC. H classification and Grade classification are the classifications of liver metastases defined by the JSCCR. There were 25 cases with H1, 6 cases with H2, and 2 cases with H3. There were 8 cases with grade A, 7 cases with grade B, 14 cases with grade C, and 4 unknown cases.

Eleven cases underwent MCT, 14 cases underwent RFA, and 8 cases underwent combination MCT and RFA. Overall, 25 cases were performed under laparotomy, and 8 cases underwent percutaneous local ablation. The median follow-up period after treatment was 402 days. Postoperative complications included 2 cases of liver abscess in the MCT group, one case in the RFA group, and 1 case in the RFA and MCT group, with 1 case of pulmonary infarction in the MCT group.

2. Methods

Images obtained by enhanced computed tomography (equipment: Asteion and Aquilion, Toshiba, Tokyo, Japan; HiSpeed CT, Proseed SA, and LightSpeed Ultra 16, GE Healthcare UK, Ltd, Little Chalfont, Buckinghamshire, UK) were used for preoperative diagnosis and measurement of tumor diameter. Superparamagnetic iron oxide or gadolinium-enhanced magnetic resonance imaging was also used for preoperative diagnosis (equipment: Signa 1.5T, GE Healthcare UK, Ltd, Little Chalfont, Buckinghamshire, UK). Biopsies were not performed for preoperative diagnosis of lesions diagnosed clinically as CRLM.

The distance between the tumor and major hepatic vessels was defined as the shortest distance between the tumor margin and major hepatic vessels. Major hepatic vessels were defined as subsegmental and segmental portal vein branches, left, right, middle, and accessory right inferior hepatic veins, and inferior vena cava. The distance between the tumor and major hepatic vessels was defined as close when it was less than or equal to 1 cm, and as distant when greater than 1 cm.

As the general criteria for selecting MCT or RFA at laparotomy, MCT was used for tumors in which the deepest location of the tumor from the liver surface was within 2 cm, and RFA was used for deeper lesions. Percutaneous MCT was not performed after 2003. Percutaneous local ablation was per-

formed whenever the CRLM could be depicted by ultrasonography and no obstacle was found in the needle tract, in cases without concurrent hepatic resection. Pringle's maneuver was not performed during local ablation.

An OT-110M (Azwell, Osaka, Japan) was used for MCT, and an RITA500PA (RITA Medical Systems Inc, Mountain View, CA, USA) or Cool-tip RF System (Covidien, Dublin, Ireland) was used for RFA. MCT was performed for 40 seconds at an output of 70 Watts, and subsequent dissociation was carried out for 15 seconds. This procedure was repeated under ultrasonographic guidance by changing the placement of the puncture needle until complete ablation was achieved. The output setting of the RITA500PA was 50 Watts, and ablation was carried out for 10 minutes after the temperature reached 95-100℃. The output setting of the Cool-tip RF System was 80-140 Watts, and the ablation time was 12 minutes for one session. It was also done under ultrasonographic guidance. Repeated ablation was also performed until the whole tumor was ablated by changing the puncture positions. Written, informed consent for the local ablation was obtained from all patients prior to treatment.

After treatment, patients were followed up at the outpatient clinic once a month by checking blood tests including tumor markers, and recurrence was regularly checked by performing abdominal enhanced computed tomography or ultrasonography once within an interval of 3 to 6 months.

This study was approved by the Ethics Board of Tokyo Women's Medical University.

3. Analysis

1) Comparison between recurrent and non-recurrent lesions at the site of ablation

Maximal tumor diameter and positional relationships to the major vessels were compared according to recurrence at the site of ablation (true local recurrence). The 3-year local recurrence-free rates were also analyzed.

2) Identifying the best indications for local ablation

The threshold of tumor maximal diameter for recurrence at the site of ablation was calculated using the receiver operating characteristic (ROC) curve, and the group with tumors having a size less than the threshold was defined as the small group, and the group with tumors having a size greater than the threshold was defined as the large group. Furthermore, the tumor group was further divided into a close group and a distant group depending on the positional relationship with major vessels. In order to identify the best indications for local ablation, the indications were evaluated in terms of tumor maximal diameter and distance from major hepatic vessels.

4. Statistical analysis

Comparisons between the maximal tumor diameter of recurrent and non-recurrent lesions and the positional relationship of tumors with regard to recurrence at the sites of ablation were evaluated by Student's t-test. The ROC curve for the relationship between the maximal tumor diameter and the presence of true local recurrence was examined. The threshold was determined by finding the highest value obtained using the equation *sensitivity*—(*1-specificity*). The 3-year local recurrence-free rate was calculated using the Kaplan-Meier method, in which the difference between the two groups was evaluated by the log-rank test. JMP version 11.0 was used for the calculations, and differences with $p < 0.05$ were considered significant.

Results

1. Comparison between recurrent and non-recurrent lesions at the site of ablation

There were 29 recurrences (52.7%) in 55 lesions at the site of ablation, and the 3-year true local recurrence-free rate was 44.3% (Fig. 1). On analysis of the maximal tumor diameters of the recurrent and non-recurrent groups, the mean maximal tumor diameter was 20.2 mm for the non-recurrent group (26 lesions), while the mean maximal tumor diameter of the recurrent group was 36.4 mm; the difference was significant ($p < 0.0001$) (Fig. 2). There were 11 lesions that recurred (40.7%) in the distant group (27 lesions). The rate of true recurrence was higher in the close group (18 of 28 lesions: 64.3%), but the difference was not significant ($p = 0.108$) (Table 2).

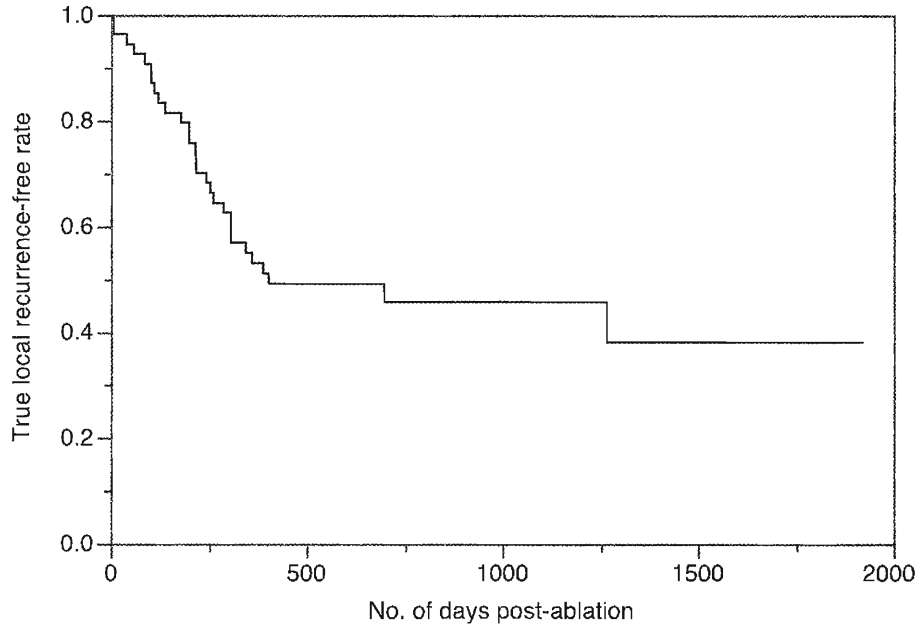

Fig. 1 Kaplan-Meier curve of the true local recurrence-free rate (overall)
The 3-year true local recurrence-free rate is 44.3%.

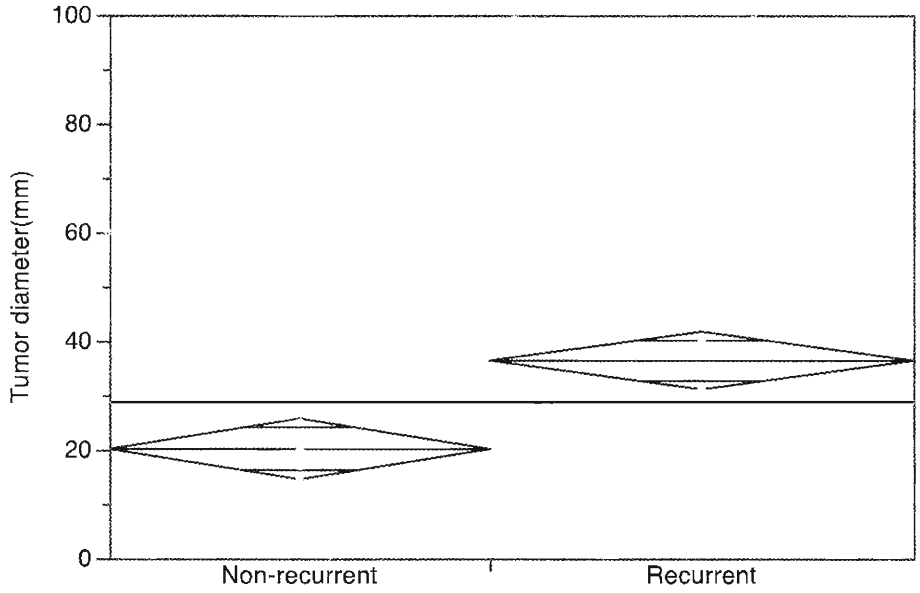

Fig. 2 Comparison of mean maximal tumor diameters between recurrent and non-recurrent lesions at the site of ablation
The mean maximal tumor diameter is 20.2 mm for the non-recurrent group (26 lesions), while the mean maximal tumor diameter of the recurrent group is 36.4 mm; the difference is significant ($p<0.0001$).

2. Analysis of the best indications for local ablation

The threshold of maximal tumor diameter for true recurrence according to the ROC curve analysis was 1.8 cm (area under the curve : AUC = 0.83) (Fig. 3). There was no true local recurrence for lesions of size less than 1.8 cm (small group: 14 lesions), and the 3-year true recurrence-free rate was significantly better than that of the large group (41 lesions) (small group vs large group: 100% vs 27.7%, $p<0.0001$).

Using the Kaplan-Meier method, the 3-year true

recurrence-free rate was significantly better for the distant group than for the close group (33% vs 60.1%, p = 0.0152) (Fig. 4). In the large group, the true local recurrence-free rate was also better for the distant group, but the difference was not significant (close 20.9% vs distant 37.7%, p = 0.0867) (Fig. 5).

Discussion

It has been reported that the 5-year survival rate of patients who underwent curative hepatic resection for CRLM ranged from 35% to 58%[4)7)8)], and this implies that patients could be cured of the disease if they underwent hepatic resection. However, CRLM with bilobar distribution is prone to be unresectable due to the limited volume of remnant hepatic parenchyma, and, therefore, the prognosis in such cases is unfavorable. Local ablation is now widely adopted for unresectable CRLMs to improve their clinical outcomes[9)~13)]. The consensus is that it is the treatment modality of choice for unresectable small HCCs[14)15)]. However, for CRLMs, there are possible drawbacks of local ablation. A higher local recurrence rate and a worse prognosis of patients who underwent local ablation and more extensive surgical resection for local recurrence after radiofrequency ablation than primary resection have been reported[4)16)17)]. On the other hand, the possibility of improving the prognosis of multiple CRLMs with local ablation has also been suggested by applying more suitable criteria[18)19)]. Even in the era of

Table 2 Recurrence in the close group and the distant group

	Non-recurrent	Recurrent	Total
Close group	10	18	28
Distant group	16	11	27
	26	29	55

The rate of true recurrence is higher in the close group (18 of 28 lesions: 64.3%), but the difference is not significant (p = 0.108) (two-sided test).

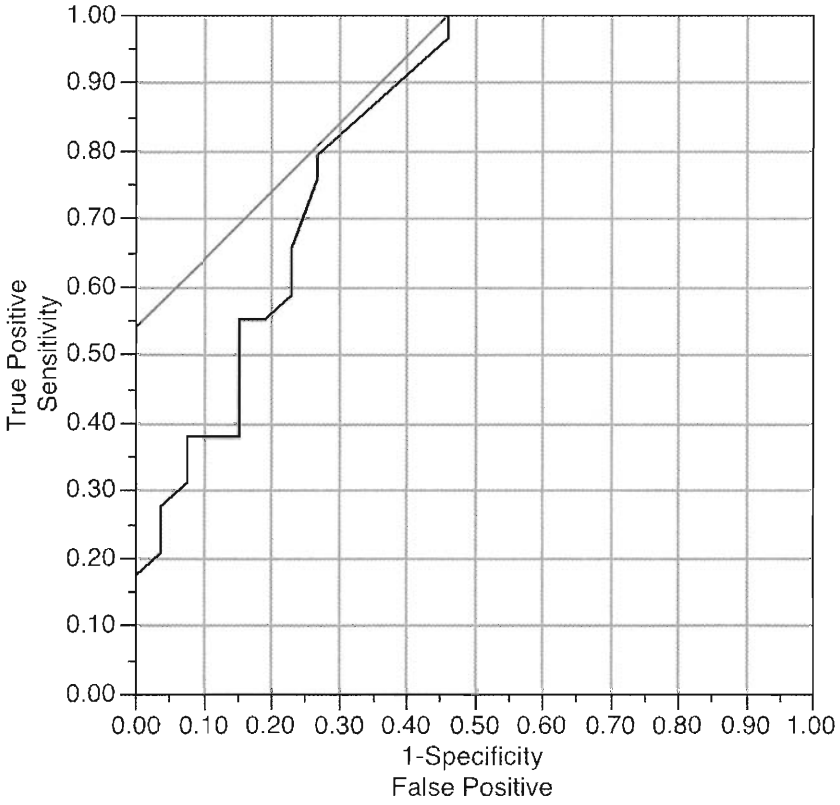

Fig. 3 Receiver operating characteristics (ROC) curve for the maximal tumor diameter and true local recurrence
The threshold of maximal tumor diameter for true recurrence according to the ROC curve analysis is 1.8 cm (area under the curve: AUC = 0.83)

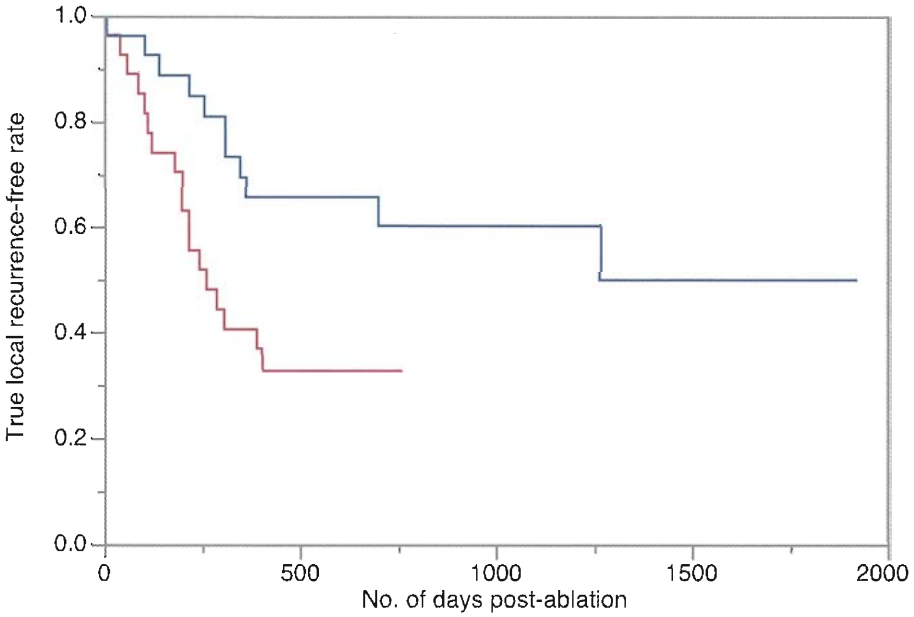

Fig. 4 Kaplan-Meier curves of the true local recurrence-free rate by the distance from major hepatic vessels (close and distant)
The 3-year true recurrence-free rate is significantly better for the distant group than for the close group (33.0% vs 60.1%, log-rank test p = 0.0152).
— Close group, — Distant group.

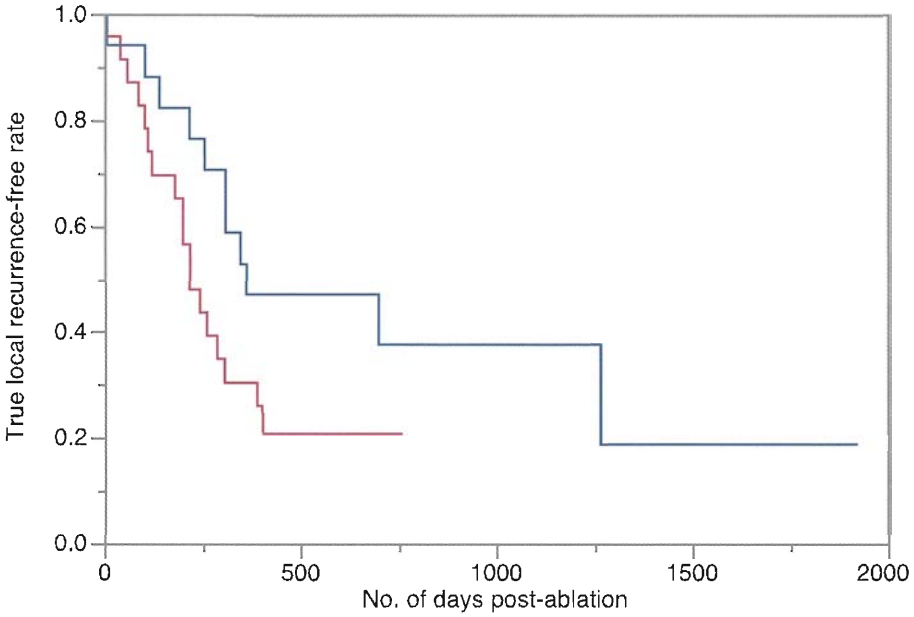

Fig. 5 Kaplan-Meier curve of the true local recurrence-free rates by distance from major hepatic vessels in the large tumor group
In the large group, the true local recurrence-free rate is also better for the distant subgroup, but the difference is not significant (close 20.9% vs distant 37.7%, log-rank test p = 0.0867).
— Close subgroup in the large group, — Distant subgroup in the large group.

advanced systemic chemotherapy, the prognosis of small CRLMs after local ablation is reported to be satisfactory[19][20]. With regard to the best indications for local ablation of CRLMs in terms of size, better

survival was reported by Gillams et al[20] for tumors less than 5 cm on multivariate analysis and by Veltri et al[19] especially for tumors less than 2.5 cm; thus smaller CRLMs would benefit from local ablation.

In the present study, true local recurrence was analyzed in order to evaluate the treatment outcome after local ablation. We believe that disease-free and overall survival may provide results that reflect by tumor biologic characteristics and other treatments such as chemotherapy. Gleisner et al[6] reported that the RFA-treated group had different baseline tumor and treatment-related factors affecting survival compared to the resection-alone group by propensity score methods, and warned that a retrospective analysis comparing survival to find the efficacy of a treatment modality such as local ablation may be confounded by different baseline characteristics affecting survival. In the present study, the larger tumor group had a higher true local recurrence rate, and lesions close to major hepatic vessels had a higher true local recurrence rate. Since the true local recurrence-free rate was 100% in the small group, it was analyzed for the distant subgroup of the large group in order to evaluate the effect on recurrence of positional relationships with major vessels. Although no significant difference was observed, a propensity for true local recurrence was evident. Therefore, local ablation should be restricted for the larger tumor group and lesions close to major hepatic vessels. As for the explanation for these results, inadequate ablation of large tumors and the heat sink effect[21], which impedes ablation near vessels, may be responsible. Since Welp et al[21] reported that there was significant temperature loss at an ablative electrode distance of 2 cm near a vessel, given that the 1 cm zone of surrounding liver parenchyma is ablated as the margin, we hypothesized that a tumor 1 cm from hepatic vessels is jeopardized by the heat sink effect. Since Elias et al[22] reported that a higher local recurrence rate after intraoperative radiofrequency ablation was correlated with liver metastases in direct contact with large vessels, we also believed that a tumor less than 1 cm from hepatic vessels would also be jeopardized by the heat sink effect. Therefore, we divided the treatment group into the close group, whose distance between the tumor and major hepatic vessels was less than or equal to 1 cm, and the distant group, whose distance between the tumor and major hepatic vessels was greater than 1 cm, in order to detect the influence of the heat sink effect. Limitations of local ablation are the range of ablation[23)~25)], worse staging compared to resection, and electrode track seeding[26]. However, in keeping with these facts, there is the possibility that smaller CRLMs and lesions far from major vessels do better with local ablation than larger and closer CRLMs. Although some authors who focused on the higher control rate for smaller lesions insisted on performing a randomized, controlled trial for resectable CRLMs by RFA and resection[26], in the present situation, we believe that local ablation would provide local control in terms of the therapeutic strategy for CLRMs by making use of its minimally invasive nature when it is applied to multiple CRLMSs, unresectable or resectable CRLMs of elderly patients, or patients with comorbidity. Although there were few cases of liver abscess and pulmonary infarction, local ablation is minimally invasive in terms of complications compared to hepatic resection[26].

It must be kept in mind that this study was retrospective and recruited patients from a single institution. Tumor diameter and distance between tumor and vessels were not measured by ultrasonography in this study. Whether providing good local control would permit good overall and disease-free survivals remains unknown. Therefore, to confirm these findings, a prospective study is necessary, and measurements of the distance between tumor and vessels by ultrasonography may clarify the heat sink effect.

Conclusion

Local ablation appears to provide comparatively good local control of CRLMs by selecting the appropriate size of lesions and tumor location relative to the major hepatic vessels, and a smaller lesion that is far from the major hepatic vessels appears to show comparatively good therapeutic effects.

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The authors reported no conflicts of interest.

References

1) **Watanabe T, Itabashi M, Shimada Y et al**: Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2010 for the treatment of colorectal cancer. Int J Clin Oncol **17**: 1–29, 2010
2) **National Comprehensive Cancer Network**: *In* Clinical practice guidelines in oncology (NCCN guidelines®) Colon cancer Version 3. 2014.
3) **Gold JS, Are C, Kornprat P et al**: Increased use of parenchymal-sparing surgery for bilateral liver metastases from colorectal cancer is associated with improved mortality without change in oncologic outcome: trends in treatment over time in 440 patients. Ann Surg **247**: 109–117, 2008
4) **Abdalla EK, Vauthey JN, Ellis LM et al**: Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. Ann Surg **239**: 818–825; discussion 825–827, 2004
5) **Shibata T, Isoda H, Hirokawa Y et al**: Small hepatocellular carcinoma: is radiofrequency ablation combined with transcatheter arterial chemoembolization more effective than radiofrequency ablation alone for treatment? Radiology **252**: 905–913, 2009
6) **Gleisner AL, Choti MA, Assumpcao L et al**: Colorectal liver metastases: recurrence and survival following hepatic resection, radiofrequency ablation, and combined resection-radiofrequency ablation. Arch Surg **143**: 1204–1212, 2008
7) **Martin LW, Warren RS**: Current management of colorectal liver metastases. Surg Oncol Clin N Am **9**: 853–876, 2000
8) **Penna C, Nordlinger B**: Colorectal metastasis (liver and lung). Surg Clin North Am **82**: 1075–1090, 2002
9) **Shibata T, Niinobu T, Ogata N et al**: Microwave coagulation therapy for multiple hepatic metastases from colorectal carcinoma. Cancer **89**: 276–284, 2000
10) **de Baere T, Elias D, Dromain C et al**: Radiofrequency ablation of 100 hepatic metastases with a mean follow-up of more than 1 year. AJR Am J Roentgenol **175**: 1619–1625, 2000
11) **Elias D, Goharin A, El Otmany A et al**: Usefulness of intraoperative radiofrequency thermoablation of liver tumours associated or not with hepatectomy. Eur J Surg Oncol **26**: 763–769, 2000
12) **Pawlik TM, Izzo F, Cohen DS et al**: Combined resection and radiofrequency ablation for advanced hepatic malignancies: results in 172 patients. Ann Surg Oncol **10**: 1059–1069, 2003
13) **Ogata Y, Uchida S, Hisaka T et al**: Intraoperative thermal ablation therapy for small colorectal metastases to the liver. Hepatogastroenterology **55**: 550–556, 2008
14) **Peng ZW, Lin XJ, Zhang YJ et al**: Radiofrequency ablation versus hepatic resection for the treatment of hepatocellular carcinomas 2 cm or smaller: a retrospective comparative study. Radiology **262**: 1022–1033, 2012
15) **Chen MS, Li JQ, Zheng Y et al**: A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. Ann Surg **243**: 321–328, 2006
16) **Reuter NP, Woodall CE, Scoggins CR et al**: Radiofrequency ablation vs. resection for hepatic colorectal metastasis: therapeutically equivalent? J Gastrointest Surg **13**: 486–491, 2009
17) **Kawaguchi Y, Hasegawa K, Saiura A et al**: Surgical resection for local recurrence after radiofrequency ablation for colorectal liver metastasis is more extensive than primary resection. Scand J Gastroenterol **49**: 569–575, 2014
18) **White RR, Avital I, Sofocleous CT et al**: Rates and patterns of recurrence for percutaneous radiofrequency ablation and open wedge resection for solitary colorectal liver metastasis. J Gastrointest Surg **11**: 256–263, 2007
19) **Veltri A, Guarnieri T, Gazzera C et al**: Long-term outcome of radiofrequency thermal ablation (RFA) of liver metastases from colorectal cancer (CRC): size as the leading prognostic factor for survival. Radiol Med **117**: 1139–1151, 2012
20) **Gillams AR, Lees WR**: Five-year survival in 309 patients with colorectal liver metastases treated with radiofrequency ablation. Eur Radiol **19**: 1206–1213, 2009
21) **Welp C, Siebers S, Ermert H et al**: Investigation of the influence of blood flow rate on large vessel cooling in hepatic radiofrequency ablation. Biomed Tech **51**: 337–346, 2006
22) **Elias D, Baton O, Sideris L et al**: Local recurrences after intraoperative radiofrequency ablation of liver metastases: A comparative study with anatomic and wedge resections. Ann Surg Oncol **11**: 500–505, 2004
23) **Curley SA, Izzo F, Delrio P et al**: Radiofrequency ablation of unresected primary and metastatic hepatic malignancies: results in 123 patients. Ann Surg **230**: 1–8, 1999
24) **Denys AL, De Baere T, Kuoch V et al**: Radiofrequency tissue ablation of the liver: in vivo and ex vivo experiments with four different systems. Eur Radiol **13**: 2346–2352, 2003
25) **Shibata T, Niinobu T, Ogata N**: Comparison of the effects of in-vivo thermal ablation of pig liver by microwave and radiofrequency coagulation. J Hepatobiliary Pancreat Surg **7**: 592–598, 2000
26) **Mulier S, Ruers T, Jamart J et al**: Radiofrequency ablation versus resection for resectable colorectal liver metastases: Time for a randomized trial? An Update. Dig Surg **25**: 445–460, 2008

局所制御能からみた大腸癌肝転移における熱凝固療法至適病変の検討

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〔目的〕大腸癌肝転移治療における熱凝固療法の至適病変について検討する.〔対象〕当科にて1999～2004年にMCT（マイクロ波凝固療法）あるいはRFA（ラジオ波焼灼療法）を施行した33症例，計55病変を対象とした.〔方法〕治療部位の局所無再発率，治療法別の再発率，再発腫瘍および非再発腫瘍の腫瘍最大径，主要脈管との位置関係などをretrospectiveに解析し，局所制御における至適病変について検討した.〔結果〕熱凝固療法が行われた55病変中29病変（52.7%）に治療部位再発が確認され，3年局所無再発率44.3%であった．ROC（受信者操作特性）曲線による解析にて，再発のcut off値は腫瘍径で1.8 cmであり（AUC＝0.83），cut off値未満の低値群（14病変）については治療部位再発を認めず，3年局所無再発率は有意に良好であった（低値群vs高値群：100% vs 27.7%，$p<0.0001$）．主要脈管との距離からみた3年局所無再発率は，＞1 cmである遠位群が有意に高かった（近位vs遠位：33.0% vs 60.1%，$p=0.0152$）.〔結論〕局所制御能からみた大腸癌肝転移に対する熱凝固療法の至適病変は直径1.8 cm未満で，主要脈管から1 cmより離れた遠位の病変である可能性が示唆された.