Retrospective Clinical Research Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
48(7) 1–12

DOI: 10.1177/0300060520940509
journals.sagepub.com/home/imr
SAGE

Radiofrequency ablation versus traditional liver resection and chemotherapy for liver metastases from gastric cancer

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Abstract

Objective: To compare the short- and long-term outcomes of radiofrequency ablation (RFA) versus liver resection and chemotherapy for liver metastases from gastric cancer.

Methods: We retrospectively evaluated 50 patients who underwent curative gastrectomy and local treatments for liver metastases (RFA, n = 20; liver resection, n = 20; and chemotherapy, n = 10) from 2008 to 2018.

Results: The short- and long-term outcomes of each local treatment were evaluated. The median overall survival (OS) after RFA was similar to that after liver resection (20 vs. 20 months, respectively) and longer than that after chemotherapy (20 vs. 10 months, respectively). The 3-year OS and progression-free survival (PFS) rates after RFA were 20% and 10%, respectively, while those in the liver resection group were 23.5% and 23.5%, respectively. The 3-year OS rate after chemotherapy was 10%. The size and number of metastases were prognostic factors for patients with gastric cancer with liver metastasis without statistical significance.

Conclusions: Among patients with liver metastasis from gastric cancer, OS and PFS were satisfactory and comparable between RFA and liver resection but better than those of chemotherapy. RFA is an appropriate option for patients with gastric cancer who have a solitary liver metastasis measuring $\leq$3.0 cm.

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Keywords
Gastric cancer, liver metastasis, radiofrequency ablation, liver resection, chemotherapy, overall survival, progression-free survival

Date received: 23 March 2020; accepted: 15 June 2020

Introduction

Gastric cancer (GC) is one of the most common malignant tumors worldwide. It is the fourth most common incident cancer and the second most common cause of cancer-related death.[1] Patients with advanced disease generally show a poor prognosis because of distant metastases and recurrence, even after multimodality treatment, as a result of the aggressive oncological behavior of GC and poor response to chemotherapy.[2,3] The liver is the organ most frequently involved in GC, and liver metastasis develops in 5% to 14% of all patients with GC.[4,5] Metastasis to the liver is the most common cause of death in patients with GC.

Liver resection, ablation techniques, and systemic chemotherapy are options for patients with GC with liver metastases (GLM). Liver resection provides local disease control, improved progression-free survival (PFS), and better 5-year overall survival (OS) than chemotherapy alone.[6] However, not all patients with GLM benefit from liver resection because of the aggressive oncological behavior of GC, limited surgical indications, post-hepatectomy liver failure, and frequent occurrence of peritoneal dissemination. To improve the outcomes of GLM, various treatments such as systemic chemotherapy, radiotherapy, hepatic arterial infusion chemotherapy, and radiofrequency ablation (RFA) have been proposed in the clinical setting.[7–9]

In recent years, ablative therapies have been developed for the treatment of primary and metastatic liver cancer with curative intent.[10,11] RFA has been demonstrated to be a safe and effective alternative for unresectable liver metastases, especially those from colorectal cancer.[12] Some retrospective studies have demonstrated that the effect of RFA is comparable with that of liver resection in the treatment of GLM.[13,14] However, because of the low number of patients with GLM, clinical studies evaluating the short- and long-term outcomes of RFA for GLM are still lacking, and predicting which patients will benefit from RFA is difficult.

This retrospective study was performed to evaluate the feasibility and safety of RFA as an alternative treatment for patients with GLM. We compared the short- and long-term results of RFA, liver resection, and chemotherapy in patients with GLM.

Patients and methods

Patients

The study was approved by the institutional review board of the Second Affiliated Hospital of Zhejiang University, which waived the requirement for written informed consent because of the retrospective nature of the study. All methods were performed in accordance with the relevant guidelines and regulations. Patients with GLM treated with RFA, liver resection, or chemotherapy from January 2008 to November 2018 were retrospectively enrolled.

The histological types of GLM at the time of the operations were categorized as well-differentiated, moderately and poorly differentiated, neuroendocrine carcinoma, hepatoid adenocarcinoma, and others (signet ring cell carcinoma, poorly differentiated, or mucinous). The TNM staging of GC was evaluated according to the American Joint Committee on Cancer TNM classification (8th edition). Patients were considered to have synchronous hepatic metastasis when the hepatic metastasis was present at the time of presentation with GC or when the liver metastasis appeared within 6 months after gastrectomy. Patients with metachronous metastases were considered to be clear of hepatic metastases 6 months after surgery with R0 resection. The OS and PFS described in this report were mainly calculated from liver-directed treatment to eliminate the influence of survival time before liver metastasis.

Process of RFA

All RFA operations were performed by the same surgeon using a commercially available RFA therapeutic instrument (Cool-tip system; Medtronic, Minneapolis, MN, USA). Multiple- or single-needle electrodes with a 2- or 3-cm tip were used in the operations depending on the size and site of the tumor. Every ablation cycle lasted 6 to 12 minutes depending on the size of the tumor. Overlapping ablation was performed if any residual tumor tissue was found during the operation.

For the patients with synchronous metastasis, RFA was carried out under general anesthesia during gastrectomy. For the patients with metachronous metastasis, RFA was carried out under B-type ultrasonic guidance. Intraoperative ultrasound and postoperative magnetic resonance imaging were used to check for complete necrosis of the liver metastases. Any patients with a residual tumor 1 month after the operation underwent another RFA procedure to confirm complete destruction of the metastases. Most patients with liver metastasis of <3 cm achieved a complete response after the first RFA treatment. Two or more RFA treatments were needed for the other patients. All patients were followed up with a repeated magnetic resonance imaging scan every 3 months in the first year and every 6 months after the first year according to the latest guidelines of the Chinese Society of Clinical Oncology and National Comprehensive Cancer Network.[15]

Statistical analysis

Several statistical analysis methods, including t tests and Fisher's exact test, were used to analyze the continuous variables and categorical variables. Whether the variables were parametric or non-parametric was carefully evaluated. The patients' OS was calculated from liver-directed treatment to death or the date of the last or most recent follow-up visit. The patients' PFS was calculated from liver-directed treatment to the date on which recurrence was detected by radiological examination. The statistical analysis software program SPSS, version 15.0 for Windows (SPSS Inc., Chicago, IL, USA) was used to analyze the obtained information. The Kaplan–Meier method was used to obtain the survival rates for GLM. Univariate and multivariate analyses were conducted using a Cox proportional hazard model to compare the differences between prognostic factors. Statistical significance was defined as $p < 0.05$. All data included in this study are available upon request by contact with the corresponding author.

Results

Patient characteristics

Fifty patients with GLM treated with RFA, liver resection, or chemotherapy were retrospectively enrolled in this study.

The clinicopathologic characteristics of all treated patients are shown in Table 1. Thirty-five patients (70%) were diagnosed with synchronous metastasis, and 15 patients (30%) had metachronous metastasis. In the RFA group, 11 of 20 patients (55%) presented with synchronous metastasis compared with 19 (95%) in the liver resection group and 5 (50%) in the chemotherapy group. In the RFA group, the pathological stage was III and IV in 11 (55%) and 7 (35%) of 20 patients compared with 1 (5%) and 19 (95%) in the liver resection group and 4 (40%) and 5 (50%) in the chemotherapy group, respectively. Patients with GLM treated with RFA had a shorter hospital stay (7.2 ± 5.0 days) than those treated with liver resection (17.4 ± 8.0 days) and chemotherapy (15.3 ± 5.7 days) ($p = 0.00$ for both). There was no difference in age or sex among the three groups. The clinicopathologic characteristics of the liver metastatic lesions, including number, size, and lobar distribution, were also similar among the three groups. Chemotherapy was allowed before or after RFA and liver resection. A three-drug or two-drug cytotoxic regimen was administered depending on the Karnofsky performance scores of patients who were subject to frequent toxicity evaluations. The most commonly used drugs were those in 5-fluorouracil-based regimens, and the next most frequently used drugs were platinum compounds, docetaxel, and epirubicin. Postoperative chemotherapy was recommended in all patients treated with RFA and liver resection because of the possibility of metastasis. Two patients in the RFA group and three patients in the liver resection group refused chemotherapy because they were unable to tolerate the treatment.

Morbidity and mortality

The morbidity and mortality rates in the RFA and liver resection groups are shown in Table 2. In the RFA group, three patients (15%) had complications, including one (5%) severe complication (Clavien–Dindo grade $\geq$III) with no treatment-related mortality. In the liver resection group, five patients (25%) had complications, including three (15%) severe complications. Three (15%) cases of treatment-related mortality were noted. The subsequent treatments involved necessary interventions such as abdominal puncture and a surgical operation to stop bleeding and repair anastomosis leakage. There was no statistically significant difference in morbidity between the two groups. The mortality rate was higher in the liver resection group than in the RFA group, but without statistical significance.

Survival, recurrence, and prognostic factors

The median OS was 32 months [95% confidence interval (CI), 14.6–49.4 months] in the RFA group, 21 months (95% CI, 14.1–27.9 months) in the liver resection group, and 17 months (95% CI, 10.8–23.2 months) in the chemotherapy group. After the liver-directed treatments, the median OS after RFA was 20 months, with 3-year OS and PFS rates of 20% and 10%, respectively. The median OS after liver resection was 20 months, with 3-year OS and PFS rates of 23.5% and 23.5%, respectively. The median OS after chemotherapy was 10 months, with a 3-year OS rate of 10% (Figure 1).

In the univariate analysis of OS, the patients' age showed significant prognostic value ($p = 0.015$). The size of the metastasis showed a tendency to be a prognostic factor, although with no statistical significance. A solitary metastasis and unilobar distribution showed significant prognostic value in the metachronous group ($p = 0.021$ and $p = 0.029$, respectively). In the univariate analysis of PFS, a solitary

Table 1. Clinicopathologic characteristics of all treated patients.

	Liver resection (n = 20)	p value	RFA (n = 20)	p value	Chemotherapy (n = 10)
Age, years	61.0 ± 12.6	0.57	63.0 ± 8.5	0.81	62.2 ± 7.3
Sex					
Male	16 (80)	0.68	17 (85)	0.20	10 (100)
Female	4 (20)		3 (15)		0 (0)
T classification					
T2	2 (10)	0.55	1 (5)	0.60	1 (10)
T3	6 (30)	0.20	10 (50)	0.03	1 (10)
T4a	12 (60)	0.34	9 (45)	0.07	8 (80)
N classification					
N0	5 (25)	0.49	7 (35)	0.14	1 (10)
N1	5 (25)	0.08	1 (5)	0.06	3 (30)
N2	3 (15)	0.43	5 (25)	0.76	2 (20)
N3	7 (35)	1	7 (35)	0.79	4 (40)
Number of metastatic lymph nodes	5.4 ± 6.2	0.97	5.4 ± 6.4	0.52	7.0 ± 6.0
Pathological stage					
Stage I	0 (0)	0.31	1 (5)	0.60	1 (10)
Stage II	0 (0)	0.31	1 (5)	0.47	0 (0)
Stage III	1 (5)	0.00	11 (55)	0.44	4 (40)
Stage IV	19 (95)	0.00	7 (35)	0.43	5 (50)
Histology					
Well-differentiated	0 (0)	0.15	2 (10)	0.30	0 (0)
Moderately and poorly differentiated	12 (60)	0.75	11 (55)	0.01	10 (100)
Neuroendocrine carcinoma	2 (10)	0.63	3 (15)	0.20	0 (0)
Hepatoid adenocarcinoma	2 (10)	0.55	1 (5)	0.47	0 (0)
Others	4 (20)	0.68	3 (15)	0.20	0 (0)
Extrahepatic lymph node metastasis					
Yes	10 (50)	0.53	8 (40)	0.04	8 (80)
No	10 (50)		12 (60)		2 (20)
Timing of metastasis					
Synchronous	19 (95)	0.00	11 (55)	0.80	5 (50)
Metachronous	1 (5)		9 (45)		5 (50)
Number of metastases					
1	16 (80)	0.29	13 (65)	0.02	2 (20)
2	3 (15)	0.68	4 (20)	0.13	0 (0)
≥3	1 (5)	0.29	3 (15)	0.00	8 (80)
Lobar distribution					
Unilobar	17 (85)	0.68	16 (80)	0.00	3 (30)
Bilobar	3 (15)		4 (20)		7 (70)
Diameter of liver metastasis, cm	2.9 ± 1.6	0.89	2.8 ± 1.7	0.28	2.1 ± 2.0
CEA, ng/mL	6.3 ± 7.7	0.87	5.1 ± 5.4	0.13	8.6 ± 6.5
Hospital stay, days	17.4 ± 8.0	0.00	7.2 ± 5.0	0.00	15.3 ± 5.7

Data are presented as mean ± standard deviation or n (%).
RFA, radiofrequency ablation; CEA, carcinoembryonic antigen.

Table 2. Comparison of complications of liver-directed treatments by Clavien–Dindo classification.

	RFA (n = 20)	Liver resection (n = 20)	p value
Overall complications	3 (15)	5 (25)	0.429
Severe complications	1 (5)	3 (15)	0.292
Biliary fistula (IIIa)	-	1 (5)	
Intra-abdominal bleeding (IV)	1 (5)	1 (5)	
Anastomosis leakage (IV)	-	1 (5)	
Mortality	-	3 (15)	0.072

RFA, radiofrequency ablation.

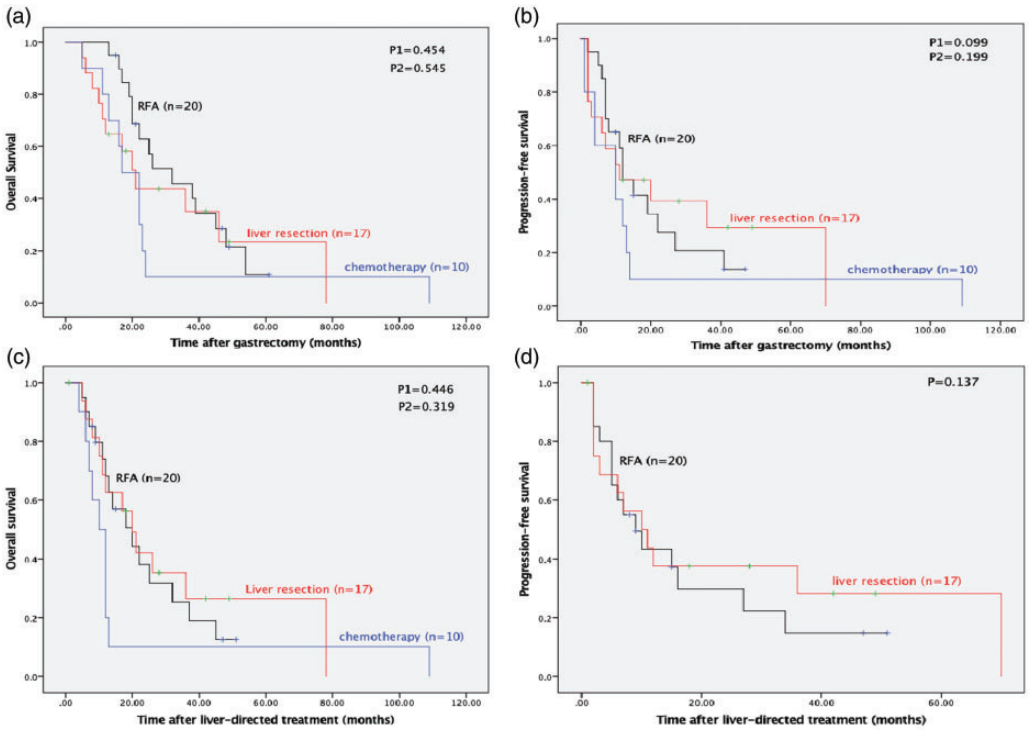

Figure 1. Kaplan–Meier plots of estimated overall survival and progression-free survival from the date of gastrectomy and liver-directed treatment. (a) Overall survival curves for all patients after gastrectomy. (b) Progression-free survival curves for all patients after gastrectomy. (c) Overall survival curves for all patients after liver-directed treatments. (d) Progression-free survival curves for liver-directed treatments. RFA, radiofrequency ablation.

metastasis showed significant prognostic value in the metachronous group ($p = 0.045$). The size of the metastasis showed a tendency to be a prognostic factor in the metachronous group, although with no statistical significance.

In the multivariate analysis, the number of metastases showed significant prognostic

Table 3. Multivariate analysis of overall survival and progression-free survival after liver-directed treatment.

		Overall survival		Progression-free survival	
	RFA	HR reference	p value	HR reference	p value
Treatment	Liver resection	0.953 (0.453, 2.003)	0.953	0.730 (0.329, 1.621)	0.439
	Chemotherapy	1.310 (0.452, 3.793)	0.619		
Age ($\leq$60 vs. >60 years)		0.426 (0.217, 0.834)	0.013	0.449 (0.214, 0.942)	0.034
Sex (male vs. female)		1.160 (0.464, 2.902)	0.750	1.044 (0.407, 2.680)	0.929
Extrahepatic lymph node metastasis (yes vs. no)		1.181 (0.579, 2.409)	0.647	1.443 (0.645, 3.228)	0.372
Number of metastases (single vs. multiple)		0.348 (0.138, 0.878)	0.025	0.254 (0.087, 0.739)	0.012
Lobar distribution (unilobar vs. bilobar)		2.774 (0.883, 8.712)	0.081	3.149 (0.780, 12.707)	0.107
Size of metastasis ($<$3 vs. $\geq$3 cm)		0.554 (0.281, 1.095)	0.089	0.586 (0.270, 1.273)	0.107
Timing (synchronous vs. metachronous)		0.808 (0.403, 1.621)	0.548	1.355 (0.561, 3.269)	0.499

RFA, radiofrequency ablation; HR, hazard ratio.

value for OS ($p = 0.025$) and PFS ($p = 0.012$) (Table 3). The size of the metastasis and the lobar distribution showed a tendency to be prognostic factors, although with no statistical significance.

Although no significant difference in the OS or PFS rate was found in patients with different sizes of metastases, the trend suggested that patients with smaller metastases had longer OS and PFS. Comparisons were carried out to identify the relationships among the size of the metastasis, number of metastases, and liver-directed treatments. Kaplan–Meier survival analyses (Figure 2) were performed based on the tumor size ($\leq$3.0 vs. >3 cm) and liver-directed treatments within each group. The median OS and PFS for patients with liver metastases of $\leq$3.0 cm who underwent RFA were 25 and 16 months, respectively, compared with 21 and 11 months in the liver resection group. The median OS and PFS for patients with liver metastases of >3.0 cm who underwent RFA were 13 and 5 months, respectively, compared with 17 and 6 months in the liver resection group. A similar Kaplan–Meier survival analysis (Figure 3) was performed based on the number of liver metastases and liver-directed treatments.

Discussion

The liver is second only to the lymph nodes as the most frequent site of metastasis from other solid cancers.[16] It is the main target organ of hematogenous spread of GC.[4,17] Conventional systemic chemotherapy is still the standard therapy recommended for stage IV and metastatic GC according to both the National Comprehensive Cancer Network Guidelines[18] and the Japanese Guidelines.[19] However, the use of systemic chemotherapy alone makes long-term survival difficult to achieve because the median survival is $\leq$13 months.[20–22] Liver resection and RFA have been recommended as alternative treatment options for GC with liver-only metastasis.[6,23,24] The optimal clinical approach for GLM is still controversial.

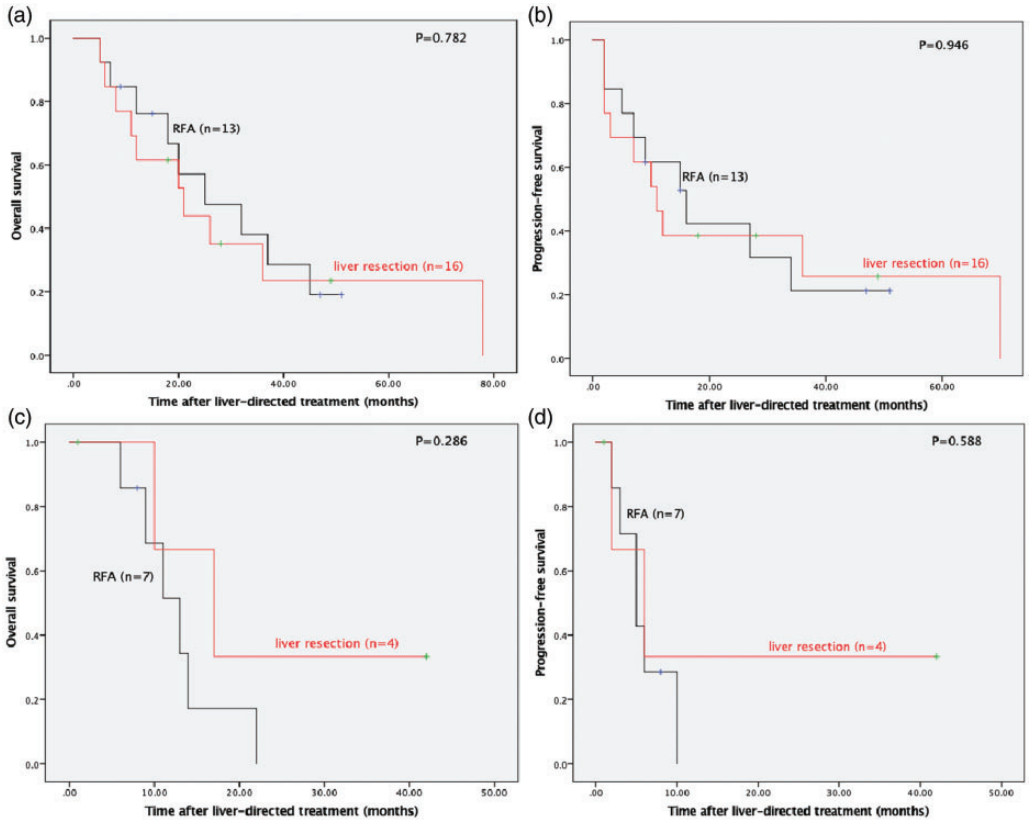

Figure 2. Kaplan–Meier plots of estimated overall survival and progression-free survival by liver metastasis size and liver-directed treatments. (a) Overall survival curves for liver metastasis measuring $\leq$3.0 cm. (b) Progression-free survival curves for liver metastasis measuring $\leq$3.0 cm. (c) Overall survival curves for liver metastasis measuring $>$3.0 cm. (d) Progression-free survival curves for liver metastasis measuring $>$3.0 cm. RFA, radiofrequency ablation.

Liver resection has been considered the standard treatment option in patients with colorectal cancer with liver metastasis, with 5-year survival rates of 37% to 58%.[25] However, the same excellent results have not been obtained in GC because of the biological aggressiveness of the disease. Furthermore, not all patients with GLM can benefit from liver resection because of the limited surgical indications, risk of post-hepatectomy liver failure, and frequent occurrence of peritoneal dissemination. As a minimally invasive technique, RFA has been regarded as an alternative to liver resection for primary or metastatic liver tumors, especially for hepatic carcinoma and liver metastasis from colorectal cancer. Several research groups have reported the benefit of RFA in treating GLM.[13,14,26] Lee et al.[27] showed that the median OS after RFA for GLM was 20.3 months. RFA is a safe and feasible treatment option for GLM. Guner et al.[28] showed that the outcomes of RFA were satisfactory and comparable with those of liver resection in select patients with GLM.

The median OS was better in the RFA group than in the liver resection and

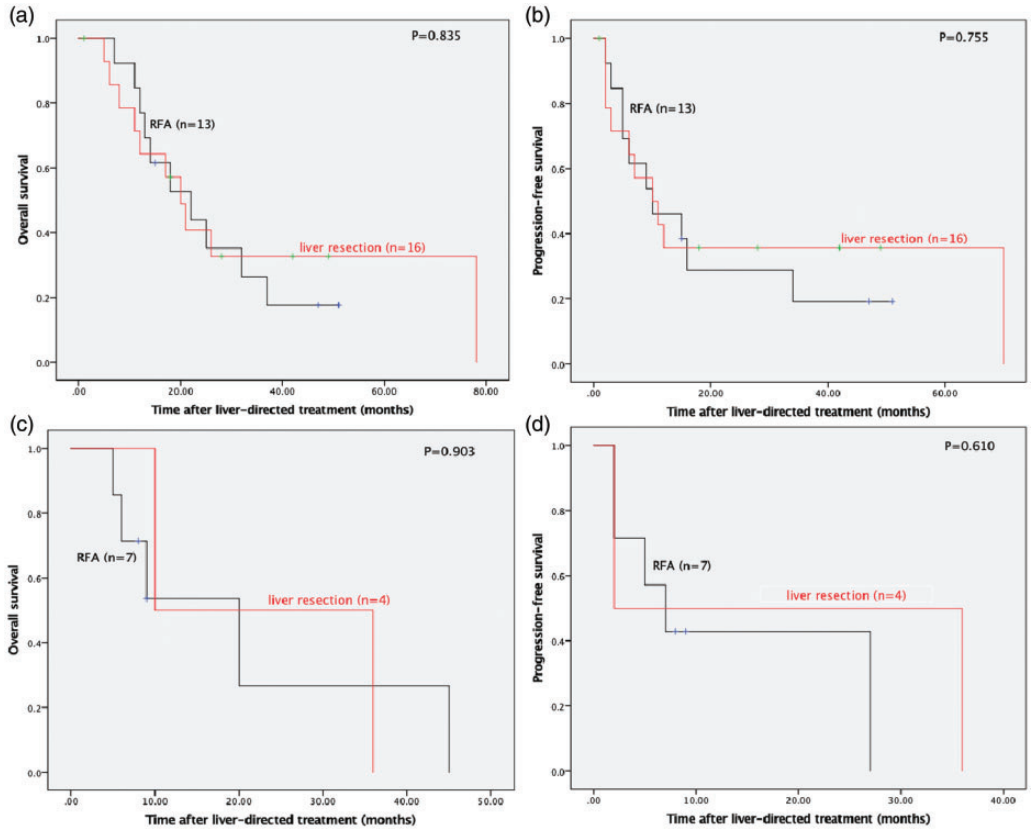

Figure 3. Kaplan–Meier plots of estimated overall survival and progression-free survival by liver metastasis number and liver-directed treatments. (a) Overall survival curves for solitary liver metastasis. (b) Progression-free survival curves for solitary liver metastasis. (c) Overall survival curves for two or more liver metastases. (d) Progression-free survival curves for two or more liver metastases. RFA, radiofrequency ablation.

chemotherapy groups (32 months vs. 21 and 17 months, respectively). Most patients in the liver resection group had synchronous metastasis; only 1 of 20 patients in this group had metachronous metastasis. In the RFA group, however, 9 of 20 patients had metachronous metastasis, which may have influenced the result of the comparison between RFA and liver resection if only OS after gastrectomy is compared. To eliminate this influence, OS and PFS after the liver-directed treatments were calculated. The median OS after RFA were both 20 months, with 3-year OS and PFS rates of 20% and 10%, respectively. The median OS after liver resection was 20 months, with 3-year OS and PFS rates of 23.5% and 23.5%, respectively. The median OS after chemotherapy was 10 months, with a 3-year overall survival rate of 10% (Figure 1). The OS provided by RFA was comparable with that provided by liver resection for patients with GLM and was better than that provided by chemotherapy alone. With respect to morbidity and mortality, patients in the RFA group

had a lower morbidity rate (1%) and mortality rate (0%) than those in the liver resection group.

The maximum liver metastatic tumor size for which RFA is safe and effective remains highly controversial.[29] To achieve a 1-cm ablative margin, the maximum tumor size under optimal conditions (based on the 5-cm standard kill zone from RFA) is 3 cm. In this study, the univariate and multivariate analyses showed that a metastasis size of $\leq$3.0 cm may be a prognostic factor for OS and PFS, although without statistical significance. Furthermore, Kaplan–Meier survival analyses (Figure 2) were performed based on tumor size ($\leq$3.0 vs. >3 cm) and liver-directed treatments within each group. The median OS and PFS for patients with liver metastasis of $\leq$3.0 cm in the RFA group were better than those in the liver resection group, although without statistical significance.

A higher number of liver metastases always indicates more aggressive oncological behavior and a higher recurrence risk.[30] In this study, the univariate and multivariate analyses indicated that the number of metastases had significant prognostic value for OS ($p = 0.025$) and PFS ($p = 0.012$). Similar Kaplan–Meier survival analyses (Figure 3) were performed based on the number of liver metastases and liver-directed treatments, and OS and PFS were comparable between the RFA group and liver resection group.

The median OS in the RFA group was better than that in the chemotherapy group (20 vs. 10 months, respectively). However, the mean OS was comparable between the two groups (23.3 vs. 19.3 months, respectively) because 1 of 10 patients in the chemotherapy group survived as long as 106 months because of a good response to chemotherapy. Patients with metachronous metastasis had better OS in the RFA group than in the chemotherapy group (hazard ratio, 1.468; 95% CI, 0.481–4.479). As mentioned above, nine patients with metachronous metastasis received RFA, while only one patient with metachronous metastasis underwent liver resection. Peritoneal adhesions readily form after the first operation, making it difficult for patients with metachronous metastasis to undergo hepatectomy. The risk of post-hepatectomy liver failure and frequent peritoneal dissemination also prevent patients from undergoing repeated hepatectomy. Thus, RFA is a better choice for these patients with GLM.

This study has several limitations. Its retrospective nature makes selection bias unavoidable. The number of patients included in the study was small. There were significant differences in the clinicopathological characteristics among the groups: the existence of lymph node metastasis, the number of metastases, and the lobar distribution of liver metastases. The proportion of patients with these adverse prognostic factors was higher in the chemotherapy group than in the other groups. If possible, a larger number of patients will be included in a subsequent study to allow for matching and therefore more definitive conclusions.

Conclusion

RFA and liver resection showed satisfactory and comparable OS and PFS results for patients with liver metastasis, and they showed better OS and PFS than did the chemotherapy group. Additionally, RFA showed lower morbidity and mortality rates than liver resection. RFA is an appropriate option for patients with GC with a solitary liver metastasis measuring $\leq$3.0 cm. RFA is also better for both patients and surgeons in the treatment of GC with metachronous liver metastasis.

Author contributions

Kezhong Tang and Zhe Tang designed the study. Linping Dong collected and summarized the patients' information. Bo Zhang and Lantian Wang analyzed the results. Kezhong Tang and Zhe Tang wrote the manuscript.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This work was supported by the Natural Science Foundation of Zhejiang Province [grant number LQ19H160021].

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