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Long-term outcomes after hepatic resection combined with radiofrequency ablation for initially unresectable multiple and bilobar liver malignancies

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ABSTRACT

Background: Hepatic resection (HRE) combined with radiofrequency ablation (RFA) offers a surgical option to a group of patients with multiple and bilobar liver malignancies who are traditionally unresectable for inadequate functional hepatic reserve. The aims of the present study were to assess the perioperative outcomes, recurrence, and long-term survival rates for patients treated with HRE plus RFA in the management of primary hepatocellular carcinoma (HCC) and metastatic liver cancer (MLC).

Methods: Data from all consecutive patients with primary and secondary hepatic malignancies who were treated with HRE combined with RFA between 2007 and 2013 were prospectively collected and retrospectively reviewed.

Results: A total of 112 patients, with 368 hepatic tumors underwent HRE combined with ultrasound-guided RFA, were included in the present study. There were 40 cases of HCC with 117 tumors and 72 cases of MLC with 251 metastases. Most cases of liver metastases originated from the gastrointestinal tract (44, 61.1%). Other uncommon lesions included breast cancer (5, 6.9%), pancreatic cancer (3, 4.2%), lung cancer (4, 5.6%), cholangiocarcinoma (4, 5.6%), and so on. The ablation success rates were 93.3% for HCC and 96.7% for MLC. The 1-, 2-, 3-, 4-, and 5-y overall recurrence rates were 52.5%, 59.5%, 72.3%, 75%, and 80% for the HCC group and 44.4%, 52.7%, 56.1%, 69.4%, and 77.8% for the MLC group, respectively. The 1-, 2-, 3-, 4-, and 5-y overall survival rates for the HCC patients were 67.5%, 50%, 32.5%, 22.5%, and 12.5% and for the MLC patients were 66.5%, 55.5%, 50%, 30.5%, and 19.4%, respectively. The corresponding recurrence-free survival rates for the HCC patients were 52.5%, 35%, 22.5%, 15%, and 10% and for the MLC patients were 58.3%, 41.6%, 23.6%, 16.9%, and 12.5%, respectively.

Conclusions: HRE combined with RFA provides an effective treatment approach for patients with primary and secondary liver malignancies who are initially unsuitable for radical resection, with high local tumor control rates and promising survival data.

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1. Introduction

Hepatic resection (HRE) has been recognized as the sole curative treatment of choice for patients with primary hepatocellular carcinoma (HCC) and metastatic liver cancer (MLC), offering long-term survival between 20% and 30% at 5 y [1,2]. However, hepatectomy can be performed only in approximately 10%–20% of such patients [3–5]. The primary obstacles to complete resection in most patients who present with multiple or bilobar diseases are the need to leave sufficient residual functional hepatic parenchyma to support posthepatectomy hepatic function after surgical curative resection [6,7].

A large volume of the literature on radiofrequency ablation (RFA) for primary and metastatic liver tumor is available, and its safety, efficacy, repeatability, acceptable local control recurrence, and long-term survival rates have been well demonstrated [8–10]. Although traditional limits to liver resection have been exceeded as advancements in hepatic surgery and postoperative patient management in the last two decades, patients with multiple or bilobar liver tumors are often still considered for palliative chemotherapy only, because of too small future liver remnant volume.

Strategies designed to increase the proportion of patients who are candidates for complete surgical treatment of liver metastases are emerging. Hepatectomy with simultaneous intraoperative RFA has been reported with a curative intent. However, the clinical outcomes after this procedure are still lacking and confusing. Our surgical group has rich experience with liver resection and RFA [11–13]. Therefore, we use RFA either as an adjunct to resection or as the primary modality of treatment for patients who were not candidates for curative resection. The safety in terms of complications and the efficacy in terms of local control or local recurrence, and long-term survival after HRE plus RFA are also described.

2. Materials and methods

2.1. Patient population

The protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in *a priori* approval by the Clinical Trial Ethics Committee of West China Hospital, Sichuan University. The ethics committee also approved the retrospective analysis of patient data without the informed consent because of the low risk for breaching confidentiality. A retrospective analysis of prospectively collected data of patients with HCC and MLC who had undergone elective liver resection or RFA at our hospital was performed. Only patients who underwent combined HRE and RFA between Jan 2007 and May 2013 were included in this analysis. Demographic, perioperative outcomes, and long-term survival data were retrospectively collected and analyzed. All patients were histologically confirmed primary or metastatic hepatic malignancies.

2.2. Inclusion and exclusion criteria

The preoperative assessments included liver function evaluation based on liver biochemistry, serum tumor marker test, coagulation profiles, Child–Pugh classification, ultrasonography, colonoscopy, computed tomography (CT) scan, magnetic resonance imaging (MRI), and hepatic digital subtraction angiography. Liver volumetric CT had been done to estimate the future liver remnant volume for all the patients with complicated multiple or bilateral tumors.

Inclusion criteria were as follows: (1) patients with liver function of Child–Pugh class A or B; (2) patients who were deemed initially unresectable because of the number or bilobar location of tumors, tumor proximity to major vascular structures, and the presence of cirrhosis with a functional hepatic reserve inadequate to tolerate HRE or RFA; (3) patients with the absence of extrahepatic diseases; and (4) patients were considered for RFA even if they had tumor close to a major portal or hepatic vein branch or the inferior vena cava, but they were excluded if tumor involved the main right or/and left bile duct [14]. Patients with refractory ascites, patients with platelet count $<15 \times 10^9$/L, patients whose prothrombin time was prolonged more than 3.0 times above normal, patients with poor general condition who could not tolerate surgery or were unwilling to receive surgical intervention, and patients treated with HRE or RFA alone were excluded from the present study.

2.3. HRE combined with RFA

In the present study, all patients were treated surgically with both resection and RFA during one surgical procedure. Routinely, the HRE was performed first. Surgical resection was carried out under general anesthesia. The right subcostal incision with a midline extension was chosen. On entering the abdomen, an initial exploration was performed to preclude the presence of extrahepatic disease. Liver resections were defined according to the Couinaud classification of liver segments. HRE was considered anatomic when at least one segment was removed entirely; all other resections were defined as nonanatomic or atypical. Major hepatectomy was defined as resection of more than three Couinaud segments, whereas "minor" hepatectomy was defined as resection involving one or two segments. Portal triad clamping was prepared in all patients; however, only 45 patients required intermittent portal triad clamping (15-min clamping and 5-min release periods) to control intraoperative blood loss.

Intraoperative ultrasonography (IOUS) was routinely performed to estimate the number, size, location, and vascular proximity of the hepatic lesions, and to give an accurate vascular map of liver anatomy. After removal of the large lesion, the remaining unresectable lesions were treated with RFA by using a commercially available system (Cool-Tip System; Radionics, Burlington, MA) and a needle electrode with a 2- or 3-cm exposed tip and with ultrasound guidance (Vivid4; GE Healthcare). The comprehensive approaches used for RFA have been detailed by our group previously [11–13]. Treatment continued until complete ablation features were achieved by ultrasonography.

2.4. Definition

Bilobar tumor involvement was defined as tumor(s) involving any segments of the left and right hemihepatic. Failure of ablative treatment was defined as incomplete ablation as judged by IOUS. Local recurrence was diagnosed when CT scans demonstrated an increase in size or the change in CT contrast-enhanced appearance characteristics of original malignant tumors. Synchronous disease was defined as the identification of liver metastases within 6 mo from the date of resection of the primary cancer. The Clavien–Dindo classification of surgical complications was applied to the existing research as previously described [15]. Postoperative mortality was defined as any patient who died within 90 d postoperatively. Hepatic failure was defined as the bilirubin level >7 mg/dL [16]. Ascites was defined as postoperative daily ascitic fluid drainage from abdominal drains exceeding 10 mL/kg of preoperative body weight [17]. The primary outcomes for this study were tumor recurrence and long-term survival. The secondary outcomes were blood loss, hospital stay, and complications. *In situ* recurrence was defined as radiologic (CT or MRI) and/or histologic (needle biopsy) detection of recurrent tumor at the original ablation site during postoperative follow-up. Overall survival (OS) was defined from the date of HRE plus RFA until the date of last follow-up or death occurred from any reasons. Disease-free survival was defined from the date of surgery until the date of disease recurrence identified by radiology or biopsy during follow-up.

2.5. Follow-up

All the included patients were enrolled in our strict follow-up system, except those who expired, lost contact, or quit. At least two phone numbers for each patient (or relatives) were required to be given to us. We scheduled visits through them. After discharge, serum tumor markers (e.g, carcinoembryonic antigen and α-fetoprotein) and a liver ultrasonography and/or contrast-enhanced CT scan were performed approximately 3 mo for the initial 1 y after operation. Thereafter, we screened patients by tumor marker measurement and helical CT every 6 mo and MRI when recurrence was suspected. All MLC patients had a colonoscopy within 1 y after liver resection. Follow-up was considered closed at the time of death or the last follow-up visit.

2.6. Statistical analysis

OS and disease-free survival were estimated using the Kaplan–Meier method. Comparisons of RFS and OS between patient subgroups were performed using the log-rank test. A Cox proportional hazards model was used to estimate the relative risk and 95% confidence interval. Multivariable Cox models that adjusted for the high-risk factors were used for exploratory analyses to identify additional variables that might potentially be prognostic. All statistical analysis was performed using SPSS (version 13.0; SPSS Inc, Chicago, IL). A value of $P < 0.05$ was considered statistically significant.

3. Results

3.1. Patient and tumor characteristics

From January 2007 to May 2013, HCC and MLC were diagnosed in 3005 patients in our hospital, of which 1875 patients received surgical intervention. Of these, 1347 patients treated with HRS or RFA alone were excluded and 112 patients treated surgically with both resection and RFA during one operation were included in the present study. The baseline characteristics of all patients are presented in Table 1. There were 65 men and 47 women with the median age 50 y (range, 17–80 y). Of these 112 patients, 40 were HCC patients with 117 tumors. All 40 patients with HCC were cirrhotic; 36 were Child class A and four were class B. Seventy-two patients had metastatic liver carcinomas with 251 metastases: from gastric and colorectal tract in 44 patients (61.1%), from gallbladder carcinoma in seven patients (9.7%), from primary breast cancer in five patients (6.9%), from lung cancer in four patients (5.6%), from pancreatic cancer in three patients (4.2%), and from various primary malignancies in nine other patients (renal cancer, $n = 3$; sarcoma, $n = 2$; cholangiocarcinoma, $n = 4$;), respectively.

A total of 154 tumors were treated with HRE, whereas 214 tumors underwent RFA. Surgical resection was used to treat a single tumor in 31 patients (25.4%), two tumors in 24 patients (21.4%), three tumors in 20 patients (17.8%), four tumors in 22 patients (19.6%), and more than four in 15 patients (13.4%). RFA of one single lesion in 25 patients (22.3%), two tumors in 24 patients (21.4%), three tumors in 30 patients (26.7%), four tumors in 17 patients (15.2%), and more than four in 16 patients (14.3%). The ablation success rates, which were measured by IOUS, were 93.2% for HCC and 96.8% for MLC.

Table 1 – The baseline characteristics of all included patients.

Candidates and tumor characteristics	*n* (%)
HCC	40 (35.7%)
MLC	72 (64.3%)
Colorectal metastases	34 (47.2%)
Gastric metastases	10 (13.9%)
Renal carcinoma metastases	3 (4.2%)
Pulmonary cancer metastases	4 (5.6%)
Breast cancer metastases	5 (6.9%)
Gallbladder carcinoma	7 (9.7%)
Pancreas metastasis	3 (4.2%)
Sarcoma metastasis	2 (2.8%)
Cholangiocarcinoma	4 (5.6%)
Total no. of tumors treated	
HRE	154
RFA	214
Median diameter of tumor treated with HRE (cm)	5.3 (range, 3.5–8.5)
Median diameter of tumor treated with RFA (cm)	3.0 (range, 2.2–11.4)

HCC = primary hepatocelluar carcinoma; HRE = hepatic resection; MLC = metastatic liver cancer; RFA = radiofrequency ablation.

3.2. *Perioperative parameters*

The types of liver resection are detailed in Table 2. In total, 63 patients (56.2%) underwent major hepatectomy and 49 patients (43.8%) underwent minor hepatectomy. There was no difference in the rate of major hepatectomy between the HCC and MLC groups ($P = 0.62$). The median operative time was 307 min (range, 0–770 min). The median intraoperative estimated blood loss was 300 mL (range, 100–800 mL). The median number units of packed red blood cell and fresh frozen plasma transfused per patient was 2 U (range, 0–77 U). Overall, 16 patients (14.2%) received a perioperative blood transfusion. The median duration of hospital stay was 7 d (range, 4–25 d).

3.3. *Morbidity and mortality*

There were two patients who died of postoperative acute liver failure and bleeding for an overall mortality rate of 1.8%. The particular number and types of complications for all patients are listed in Table 3. Thirteen patients suffered a single complication, and 11 patients had more than one complication. The most common complications were bile leakage and intra-abdominal ascities in 10 patients (8.9%) and 13 patients (11.6%), respectively. Liver failure was not a common complication in our series, occurring only in two patients (1.8%). The postoperative morbidity rates were 22.3%, respectively. However, there was no correlation between the extent of the liver resection or number of tumors treated with RFA and the development of postoperative complications. However, patients with advanced age, large incisional surface areas, and long operation time were associated with the development of bile leakage and ascites.

Table 2 – The types of liver resection according to the Couinaud classification of liver segments.

Types of surgical procedures	*n* (%)
Major resections (≥3 segmentectomy)	63 (56.2%)
Right hepatectomy (segments V, VI, VII, and VIII)	17 (15.2%)
Left hepatectomy (segments II, II, and IV)	12 (10.7%)
Extended left hepatectomy (segments II, II, IV, and V)	10 (8.9%)
Left lateral lobectomy (segments II, II, and VII)	11 (9.1%)
Central hepatectomy (segments IV, V, and VIII)	13 (11.6%)
Minor resections (one or two segments, nonanatomic resections)	49 (43.8%)
Left lateral lobectomy (segments II and III)	7 (6.3%)
Bisegmentectomy	19 (17.1%)
Segments IV and V	7 (6.3%)
Segments III and IV	8 (7.1%)
Segments V and VI	4 (3.6%)
Segmentectomy	23 (20.5%)
Segment III	3 (2.7%)
Segment IV	4 (3.8%)
Segment V	6 (4.9%)
Segment VI	5 (4.5%)
Segment VII	5 (4.5%)

Major hepatectomy: more than three Couinaud segments were resected; minor hepatectomy: one or two segments were resected.

Table 3 – Postoperative morbidity according to the Dindo distinction of operative complications.

Variants	*n* (%)
Bile leak (grade IIIa)	10 (8.9%)
Ascities (grade I)	13 (11.6%)
Acute hepatic failure (grade IV)	2 (1.8%)
Adhesional obstruction/ileus (grade II)	1 (0.9%)
Pulmonary inflammation (grade II)	4 (3.6%)
Wound infection (grade I)	3 (2.7%)
Diarrhea (grade II)	2 (1.8%)
Perihepatic abscess (grade IIIa)	2 (1.8%)
Postoperative bleed (grade IV)	1 (0.9%)
Urinary tract complication (grade II)	2 (1.8%)
Reoperation (grade IIIb)	1 (0.9%)
Adult respiratory distress syndrome (grade IIIb)	1 (0.9%)
Grade I total	16 (14.2%)
Grade II total	9 (8.4%)
Grade III total	14 (11.5%)
Grade IV total	3 (2.5%)
Major complication	17 (15.2%)
No. of patients with complications	25 (22.3%)
Mortality	2 (1.8%)

Grade I complications require variation without necessitating operative or medicinal treatment. Grade 2 complications need medicinal therapy. Grade 3 complications need operative, endoscopic, or radiologic assistance. Grade 4 complications are life-threatening additional complications which include central nerves system, solitary body organ malfunction, and multiorgan malfunction necessitating intensive care unit administration. Grade 5 complications are demise of the affected individual. In existing analysis, grades 1 and 2 are categorized as minor and grades 3–5 are considered to be major complications.

3.4. *Recurrence*

Recurrence was found in 73 patients during the follow-up period. Overall recurrence rate was significantly higher in the HCC group than in the MLC group by intention-to-treat analysis at 3 y (72.3% *versus* 56.1%, $P = 0.03$). No statistical differences of recurrence were found in RFA site, non-RFA site, and distant organ. The 1-, 2-, 3-, 4-, and 5-y overall recurrence rates were 52.5%, 59.5%, 72.3%, 75%, and 80% for the HCC group and 44.4%, 52.7%, 56.1%, 69.4%, and 77.8% for the MLC group, respectively.

Local recurrence or persistence of metastatic tumors at the site of the RFA occurred in 32 operations in 23 patients. Of these 32 lesions, 28 had repeat RFA and 16 (57.1%) achieved local control. A significant difference in local recurrence rates was observed in the comparison of lesions less than 4 cm (15.2%) and those more than 4 cm (57.2%) in diameter. Tumor size and major vessel invasion appeared to be the main risk factors for local recurrence because of treatment failure.

3.5. *Long-term survival*

The median length of follow-up was 37 mo. At the time of last follow-up (May 2013), 22 patients had no evidence of disease, 32 patients were alive with disease, 64 patients were dead of disease, and 16 had died of other causes. The 1-, 2-, 3-, 4-, and 5-y OS rates for the HCC patients were 67.5%, 50%, 32.5%, 22.5%, and 12.5% and for the MLC group were 66.5%, 55.5%, 50%, 30.5%, and 19.4%, respectively (Fig. 1). The corresponding recurrence-free survival rates were 52.5%, 35%, 22.5%, 15%, and 10% for the HCC group and 58.3%, 41.6%, 23.6%, 16.9%, and 12.5% for the MLC group, respectively (Fig. 2).

3.6. *Risk factors for OS and recurrence rates*

The following clinicopathologic variables that might correlate with OS and recurrence rates were evaluated by univariable and multivariable analyses (Table 4). Results demonstrated that patients with HCC, the presence of ascites, the largest tumor size more than 5 cm, and the tumor number more than three were associated with lower survival and higher tumor recurrence rates.

4. Discussion

Liver resection is still the management of choice with the best chance for long-term cure in patients with primary and metastatic hepatic tumors. However, only a small percentage of these patients are candidates for curative surgical resection, because of the tumor size, location near major intrahepatic vessels, multifocality, or inadequate hepatic function related to coexistent cirrhosis [3–5]. Traditionally, for a tumor to be considered appropriate for curative resection, there must not be any extrahepatic disease or severe hepatic dysfunction, the tumor or tumors must not be so extensive that too little functioning liver remains after the resection, and at least a 1-cm tumor-free resection margin should be attained and there should not be any involvement of the confluence of the portal vein [14]. Recent advances in the surgical technique, anesthesia, and perioperative care have led to the development of several additional alternative treatment methods designed to provide therapy for most patients diagnosed with liver cancer who are not candidates for surgical curative resection. These additional treatment methods include neoadjuvant chemotherapy [17], transarterial chemoembolization [18], preoperative portal vein embolization, two-stage hepatectomy [19,20], and RFA [21,22].

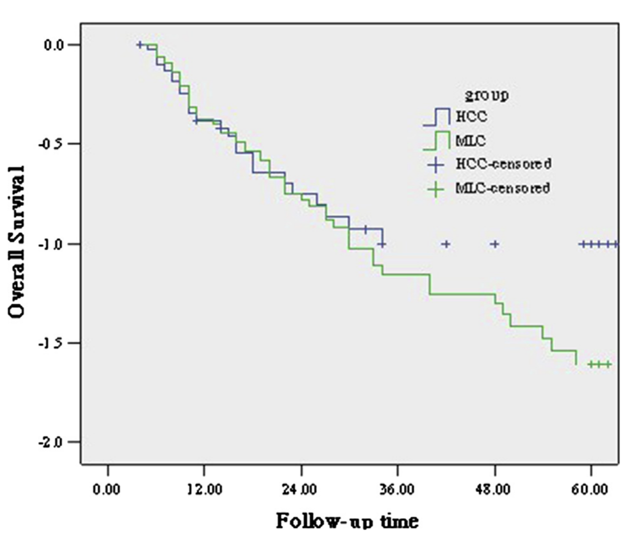

Fig. 1 – The Kaplan–Meier OS curve for the 40 HCC patients and 72 MLC patients demonstrates that there is no statistically significant difference between the two groups ($P = 0.83$, the log-rank test). (Color version of figure is available online.)

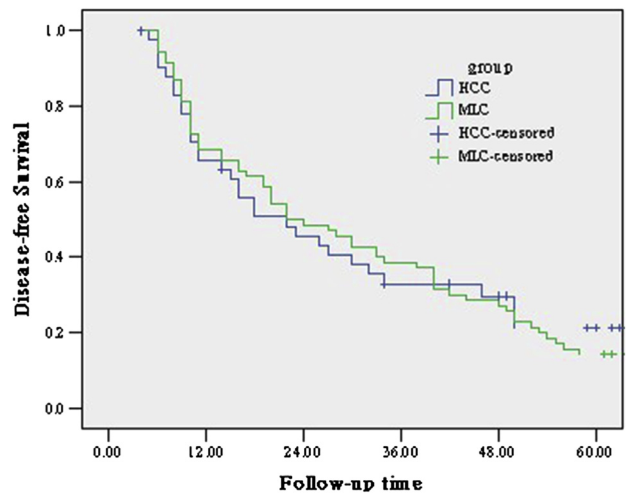

Fig. 2 – The Kaplan–Meier disease-free survival curve for the 40 HCC patients compared with 72 MLC patients. There was no statistically significant difference between the two groups ($P = 0.88$, the log-rank test). (Color version of figure is available online.)

RFA has become a widely used ablative technique for primary and secondary liver tumors and its safety, efficacy, and acceptable local recurrence and short-term survival rates had been well demonstrated in the literature. However, most studies have investigated RFA as an isolated, alternative therapy for unresectable hepatic disease. HRE combined with RFA is playing an increasingly important role in treating patients with extensive disease; however, to our knowledge, HRE combined with simultaneous intraoperative RFA of initially unresectable hepatic tumors has been less reported [8,14] and its benefit is still unknown. For this purpose, we hypothesize that HRE combined with RFA may have a better impact on both operative outcomes and survival time in patients with initially unresectable MLC and HCC. In the present study, we sought to determine the impact of HRE plus RFA on perioperative outcomes for patients with primary and secondary liver malignancies. This study provides further evidence that HRE combined with RFA for initially unresectable HCC and MLC can be performed safely in selected patients, with low morbidity rate, high local tumor control rates, and promising long-term survival.

RFA is a technique based on the conversion of electromagnetic energy into heat to destruct tumors in various organs. It is either a useful adjunct therapy to partial liver resection or the primary modality of treatment for patients who were not candidates for curative resection [21–24]. The application of RFA expanded the armamentarium of intentionally curative treatment modalities. For instance, when a patient has bilobar or multiple liver cancers, two choices exist: to combine liver resection with local RFA and to perform a two-stage resection. Although evidence to make a rational decision is still lacking, we advocate the policy to try to make the patient tumor free in one operation procedure consisting of curative resection and ablation.

Table 4 – Univariate and multivariate analyses of the relative risk for OS and recurrence rates.

Characteristics	Univariate analysis (P)	Multivariable	
		Relative risk (95% CI)	P value
Survival models			
Age (y) (≤60 *versus* >60)	χ^2 = 6.567, P = 0.345	2.342 (0.564–4.651)	0.124
Gender (male/female)	χ^2 = 5.673, P = 0.256	1.832 (1.003–5.623)	0.326
Underlying liver disease			
Hepatitis *versus* non-hepatitis	χ^2 = 10.230, P = 0.354	4.321 (1.436–6.573)	0.452
Cirrhosis *versus* non-cirrhosis	χ^2 = 8.654, P = 0.673	3.985 (0.985–5.887)	0.123
HCC *versus* MLC	χ^2 = 3.675, P = 0.001	1.769 (0.007–3.786)	0.031
Albumin (g/L) (≤35 *versus* >35)	χ^2 = 5.412, P = 0.874	5.895 (1.223–7.455)	0.412
Ascites (present *versus* absent)	χ^2 = 3.632, P = 0.001	2.366 (1.464–3.874)	0.089
Child–Pugh (B *versus* A)	χ^2 = 5.971, P = 0.357	1.385 (0.227–4.652)	0.116
Largest tumor size (cm) (≤5 *versus* >5)	χ^2 = 6.784, P = 0.004	5.274 (1.339–7.285)	0.017
Tumor number (≤3 *versus* >3)	χ^2 = 5.321, P = 0.002	4.113 (2.271–8.337)	0.024
Hepatectomy (major *versus* minor)	χ^2 = 11.648, P = 0.494	3.339 (0.451–5.646)	0.367
Recurrence models			
Age (y) (≤60 *versus* >60)	χ^2 = 7.332, P = 0.486	2.896 (0.877–5.019)	0.334
Gender (male/female)	χ^2 = 6.783, P = 0.521	6.775 (3.393–8.442)	0.358
Underlying liver disease			
Hepatitis *versus* non-hepatitis	χ^2 = 8.953, P = 0.451	2.561 (0.124–4.873)	0.235
Cirrhosis *versus* non-cirrhosis	χ^2 = 7.743, P = 0.368	1.836 (0.238–3.679)	0.117
HCC *versus* MLC	χ^2 = 3.585, P = 0.001	1.678 (0.112–4.351)	0.002
Albumin (g/L) (≤35 *versus* >35)	χ^2 = 0.236, P = 0.752	3.765 (1.801–7.227)	0.326
Ascites (present *versus* absent)	χ^2 = 9.663, P = 0.659	3.286 (1.747–4.951)	0.412
Child–Pugh (B *versus* A)	χ^2 = 8.331, P = 0.225	1.765 (0.985–2.784)	0.117
Largest tumor size (cm) (≤5 *versus* >5)	χ^2 = 0.674, P = 0.001	3.331 (0.656–7.853)	0.005
Tumor number (≤3 *versus* >3)	χ^2 = 2.669, P = 0.001	2.345 (1.020–4.865)	0.012
Hepatectomy (major *versus* minor)	χ^2 = 11.347, P = 0.382	1.876 (0.009–3.338)	0.159

CI = confidence interval; HCC = hepatocelluar carcinoma; MLC = metastatic liver cancer.

In 2010, our group performed a randomized controlled trial to compare the long-term outcomes of surgical resection and RFA for patients with HCC to the Milan criteria. Results demonstrated that RFA provides a similar short and promising long-term outcome when compared with patients with initial surgical resection [13]. Similar findings were found in other series [23,25,26]. In this study, our data approach these figures with 1-, 2-, 3-, 4-, and 5-y OS rates as 67.5%, 50%, 32.5%, 22.5%, and 12.5%, respectively, for HCC patients and 66.5%, 55.5%, 50%, 30.5%, and 19.4%, respectively, for MLC patients. The corresponding recurrence-free survival rates were 52.5%, 35%, 22.5%, 15%, and 10% for the HCC patients and 58.3%, 41.6%, 23.6%, 16.9%, and 12.5% for the MLC patients, respectively.

When considering patients for a combined approach of liver resection of large tumors and RFA of smaller lesions in the same or opposite lobe, standard surgical considerations apply. Thus, an adequate volume of perfused, functional hepatic parenchyma must remain to avoid postoperative liver failure. The volume of liver that must remain varies from patient to patient, depending on the presence of normal liver *versus* diseased liver related to chronic hepatitis virus infection, ethanol abuse, or some other cause of chronic hepatic inflammation leading to cirrhosis. RFA does not replace standard HRE in patients with resectable disease. Rather, RFA expands the population of patients who may be treated with aggressive liver-directed therapy in attempts to improve survival, quality of life, and/or palliation. Some patients heretofore are not candidates for surgical therapy because of bilobar liver tumors that can be treated with a combination of liver resection and RFA [27].

Previous publications have shown that RFA does not increase the perioperative morbidity significantly when added to HRE. However, the current RFA has certain limitations or disadvantages. First, serious adverse events after RFA have been reported, including the cryoshock syndrome, hemorrhage after ice ball cracking, acute renal failure, fever, and hepatic abscess. Second major disadvantage of RFA is the incidence of ablation site recurrences. Although the reported incidence is highly variable, up to 60% can be found in the literature [28]. Finally, although the RFA procedure is best guided by real-time ultrasound, immediate intraoperative assessment of the completeness of RFA can be difficult, unlike surgical resection in which the margin of resection can be examined intraoperatively.

5. Conclusions

This retrospective study reflects a single-center experience of HRE combined with RFA in the management of patients who are initially unsuitable for radical resection for metastases liver diseases and primary liver cancers. Our study is one of the few studies with a large number of patients and long-term follow-up, which demonstrates that HRE combined with RFA offers a promising future in the treatment of hepatic malignancies. It also increases the number of patients who may be candidates for curative surgical resection, although our study could be criticized for its patient and treatment selection, lack of tumor stage, and the retrospective nature of the assessment of outcomes.

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Wu H. designed the study; Qiu J.G. and Wu H. conducted most of the study and wrote the manuscript; Chen S.T. and Pankaj P. edited the manuscript.

The authors have no conflicts of interest to disclose.

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