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Comparison of laparoscopic hepatectomy, percutaneous radiofrequency ablation and open hepatectomy in the treatment of small hepatocellular carcinoma

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Abstract: Objective: Three mainstream techniques—laparoscopic hepatectomy (LH), percutaneous radiofrequency ablation (pRFA), and open hepatectomy (OH)—were compared in this study, in terms of their efficacies in the treatment of small hepatocellular carcinoma (HCC). Methods: A comparative study was performed within a total of 94 patients diagnosed with small HCC in our hospital from 2005 to 2010, who underwent LH (28), RFA (33), or OH (33). They had either a single tumor lesion of less than 5 cm or up to three nodules with diameters of less than 3 cm each. Outcomes were carefully evaluated throughout a 3-year follow-up interval and statistically interpreted. Results: The pRFA group had a significantly lower disease-free survival rate compared with the two surgical groups (P=0.001) and significantly shorter overall survival (P=0.005), while the LH group and the OH group had no difference in survival results. For patients younger than 60 years old, surgical approaches offered a better long-term overall survival prognosis (P=0.008). There were no statistically significant differences among the three groups in overall survival for elderly patients (P=0.104). Conclusions: Among patients with small HCC, LH may provide better curative effects than pRFA without increasing complication rates. pRFA leads to faster recurrence than surgical resections. LH has similar therapeutic effects to OH and causes less trauma. For patients younger than 60 years old, LH may be the best curative treatment. Elderly patients may choose either surgery or pRFA.

Key words: Hepatocellular carcinoma, Laparoscopic hepatectomy, Minimally invasive techniques, Open hepatectomy, Percutaneous radiofrequency ablation
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1 Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide and has long been a major public health problem in the Asia-Pacific region, where the incidences of viral hepatitis and liver cirrhosis are relatively high. The incidence of HCC in China alone accounts for 57% of all cases worldwide (Tanaka *et al.*, 2011). Two surgical approaches, the traditional open hepatectomy (OH) and the laparoscopic hepatectomy (LH), are widely used in health care centers to treat resectable HCC. While the open approach is associated with more blood loss and longer recovery time, LH allows for the perception of finer detail which leads to less invasiveness. Moreover, numerous randomized controlled trial (RCT) reports and meta-analyses have demonstrated that laparoscopic liver surgery for patients with HCC could achieve short-term and long-term outcomes comparable to case-matched open

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liver surgery (Koffron *et al.*, 2007; Pearce *et al.*, 2011; Rao *et al.*, 2012). In all LH techniques, total LH provides better cosmetic results, less blood loss, and fewer hospitalization days in comparison.

Although surgery provides the best chance of a cure in patients with resectable tumors, less than 30% of patients with small HCC are eligible for surgery (Verslype *et al.*, 2009; Zhu, 2012). Local ablative therapy, especially radiofrequency ablation (RFA), has been established as the primary local ablative modality at most institutions. Moreover, recent research has suggested that RFA for HCCs with maximal diameters of 3–5 cm may achieve comparable long-term overall survival and disease-free survival with surgery (Kim *et al.*, 2010; Asham *et al.*, 2013; Lai and Tang, 2013; Fang *et al.*, 2014). Furthermore, percutaneous RFA (pRFA) has distinct advantages over hepatectomy by being minimally invasive, having a lower risk of hemorrhage, and having considerable repeatability. Thus, pRFA may play a dual role as a curative choice for small HCCs and as an effective alleviative treatment for large or metastasized cancer lesions.

During the past two decades, along with technical progress and people's increased desire for good quality of life, minimally invasive techniques have gained great popularity in the treatment of small solid tumors. To date, some articles concerning the treatment of small HCC have reported the comparison between OH and LH, while some have reported the efficacy of RFA. Few reports exist on the comparison between LH and RFA, and no comparative study between the three techniques is available. For this article, we conducted a retrospective study on the basis of prospectively collected data to provide a more comprehensive understanding of these three techniques, and to compare their long-term outcomes in the treatment of small HCC patients.

2 Materials and methods

2.1 Patients and parameters

Between January 2006 and December 2011, more than 3000 patients in Sir Run Run Shaw Hospital (SRRSH), Zhejiang University, China, had the diagnosis of HCC confirmed by cytohistological evidence from liver biopsy specimens, or, in the absence of biopsy evidence, on the diagnostic criteria for HCC used by the American Association for the Study of Liver Diseases (AASLD) and the 2011 Chinese guidelines for HCC management in our hospital. A total of 2913 of these patients underwent LH (n=585) or RFA therapy (n=508) or OH (n=1820) in our liver disease center. In general, patients were offered the option to choose any of these treatments. Potential advantages and disadvantages of each treatment were fully explained to patients. For patients whose tumors were at certain locations or with particularly large sizes, suggestions and treatment protocols were rendered by the surgeon or physician in charge. No procedure was performed until consent was obtained from the patient and his/her family. Among these enrolled patients, we used the following inclusion criteria: (1) patients were first diagnosed with HCC and completed all treatments for HCC in our hospital; (2) they had a maximum tumor diameter of less than 3 cm and number of intrahepatic tumors no greater than 3, or a single intrahepatic lesion with a diameter of less than 5 cm; (3) Child-Pugh class A or B; (4) Barcelona Clinic Liver Cancer (BCLC) level 0 or A; (5) no intrahepatic and distant metastases; (6) no invasion of the portal vein, the hepatic vein trunk or secondary braches; (7) indocyanine green retention rates of less than 30% at 15 min; (8) all included patients suitable for LH, RFA, or OH according to the guidelines.

The following patients were excluded: (1) patients met the inclusion criteria but declined to participate, or refused to provide a personal medical record; (2) patients whose permanent pathology after the procedure suggested benign focal nodular hyperplasia (FNH), inflammatory nodules, metastatic liver cancer, or primary liver cancer of other pathological types (e.g. cholangiocarcinoma); (3) patients whose first therapeutic result was not satisfactory (tumor with indistinct border, location near the blood vessels, or poor differentiation) added anti-tumor treatments (e.g. transcatheter arterial chemoembolization (TACE), percutaneous ethanol injection (PEI), or chemotherapy) immediately after surgery or pRFA; (4) self-discharged patients, or patients who met the inclusion criteria but failed to complete the treatment course for socioeconomic reasons.

Restrained by the above criteria, 110 patients remained as proper subjects: 35 for the LH group, 35 for the RFA group, and 40 for the OH group. The clinical data of final recruited patients were carefully collected and interpreted by dependable statistical software. Pathological results, a chest X-ray and a contrast computed tomography (CT) scan of abdomen, were examined for information regarding tumor location, size, and recurrence. Magnetic resonance imaging (MRI) and positron emission tomography (PET)-CT were also referred in selected patients. Laboratory blood tests included hepatitis B surface antigen, antibodies to hepatitis C, serum α-fetoprotein (AFP), albumin, and total bilirubin. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and prothrombin time (PT) were obtained both before and after the target procedure. Pugh's modification of Child's criteria (Child-Pugh class) and the BCLC level were deliberated through a therapeutic flow-chart. Adjuvant therapies received before and after the treatment were recorded.

2.2 Study design

Our null hypothesis was that LH, OH, and pRFA provided similar prognostic outcomes and survival rates for patients with small HCC. The primary end points of the trial were the 36-month disease-free survival rate and the overall survival rate. The secondary end points were the overall recurrence rate. Overall survival and disease-free survival were measured from the date of the procedure to the time of death and to the time when a recurrent tumor was first detected, respectively. Operating time, blood loss, need for blood transfusions, postoperative complication rates, mortality, and the length of hospitalization were also compared. Collection and processing of data were permitted and approved by patients. The clinical study was supervised by the Research Ethics Committee of the SRRSH, which is affiliated with School of Medicine, Zhejiang University, China.

2.3 Procedure

Patients in the surgical resection groups underwent a partial hepatectomy. All surgeries were carried out under general anesthesia. Each procedure was hosted and performed by experienced general surgeons in the Department of Surgery in SRRSH, who have performed both OH and LH for 15 years or more. In the LH group, subjects underwent the total laparoscopic approach. Patients underwent the classic open approach in the OH group.

For the RFA group, all procedures were performed by a dedicated team from the Department of Medical Oncology in SRRSH, after a multidisciplinary meeting, with a standard protocol of either a Tyco RFA device (Valley Lab, Tyco Health Care Group, Boulder, CO, USA) or a Rita RFA device (Oncology Products Group Angio Dynamics, Latham, NY, USA). Patients underwent pRFA under the guidance of real-time bedside ultrasonography (BUS) or CT in an operative room setting under local anesthesia by 2 ml 2% lidocaine. Each tumor was treated with a single electrode placement and ablation. During the ablation process, the patient was given an intravenous injection of 3 ml midazolam to relieve pain.

2.4 Follow-up

After any procedure, liver function of the patient was re-examined before discharge. A multidetector abdominal contrast CT scan was given four weeks after the treatment and was highly recommended for every 6 months in the following 3 years. B-ultrasonography of the abdomen served as an acceptable substitution to CT for patients who were at risk of injury caused by an overdose of radiation. Dynamic contrast MRI was performed when intrahepatic recurrence was difficult to ascertain. When extrahepatic metastasis symptoms were expected (cough, bloody phlegm, or bone pain), a chest CT and a bone emission computed tomography (ECT) scan were performed. At each of the follow-up visits, blood tests including the routine count of blood cells (CBC), liver function, and serum AFP were monitored. The follow-up visits were spaced out to 6–12 months after 3 years depending on the wishes of the patient. During follow-up, we continuously contacted patients at 3–6 month intervals by telephone to ensure their periodic review of liver disease, and helped them to schedule clinic appointments and to investigate the condition of their disease.

Complete surgical removal was approved by the pathological results, which showed negative resection margins. Complete pRFA was defined as the absence of any peripheral enhancement in the contrast-enhanced phase at the first CT scan after treatment. When patients were found to have a recurrence, they were readmitted into the hospital to receive the next episode of treatment.

2.5 Statistical analysis

We used the SPSS 19.0 statistical software package (SPSS Inc., Chicago, Illinois, USA) to run statistical tests. For quantitative data, the Gaussianity test was performed to test for homogeneity of variables. Homogeneous variances were expressed as mean±standard deviation (SD) and were compared thereafter by one-way analysis of variance (ANOVA). Multiple comparisons between the three groups within ANOVA were simultaneously analyzed by a least significant difference (LSD) or Bonferroni test. A Pearson Chi-square test was applied to analyze categorical data. All curves were generated by the Kaplan-Meier method and the differences between the groups were compared using the log-rank test. *P*-values of less than 0.05 were considered statistically significant.

3 Results

3.1 Patients

Of the 110 patients categorized into the three analytical groups, 16 of them either refused to participate during intervention (5 of 16) or were lost in the follow-up (11 of 16), which left 94 as proper subjects (Fig. 1). Remaining patients were matched by age, sex, Child-Pugh class, hepatitis B and hepatitis C virus infection, cirrhosis status, and preoperative laboratory results (Table 1). Patient demographics were not significantly different between the three groups, except for the fact that the pRFA patients were older than those in the surgical groups (F=5.934, P=0.004). This is quite understandable because older patients usually tend to choose more conservative and less invasive therapeutic methods considering their state of health. On the other hand, the average tumor size of the RFA group was found to be smaller than those of the two surgical groups (F=5.692, P=0.005). In general, the majority of subjects suggested impaired liver function reserved with active viral infection, and were characterized as male, hepatitis B virus (HBV)-antigen positive, cirrhosis, increased AFP, Child-Pugh A classification, and BCLC 0 level.

In the LH group, complete surgical resection was achieved in all 28 patients, which was pathologically demonstrated by the negative circumferential resection margin. Fourteen patients underwent LH combined with cholecystectomy, 4 LHs were combined with intraoperative chemotherapy (intraperitoneal chemotherapy), and the others went through hepatectomy alone. Among the 33 patients treated with hepatectomy in the OH group, 2 were transferred from the laparoscopic exploration group. Thirty-two of 33 patients (97.0%) achieved radical resection, with one male patient revealed to have a residual tumor adjacent to the surgical zone at his one-month follow-up. He was given local ablation therapy during the follow-up period and survived for 36 months. In the RFA group, 8 ablations were guided by CT while

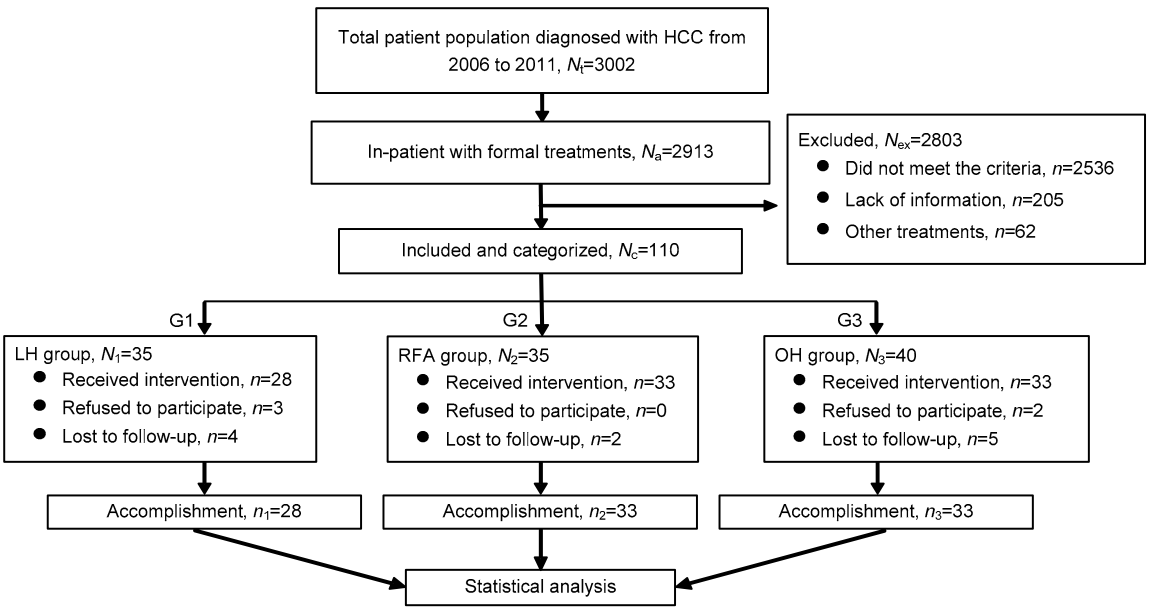

Fig. 1 Patient assignment for each study group

Table 1 Demographics and baseline characteristics of the study population

Characteristics	LH group (n_1=28)	RFA group (n_2=33)	OH group (n_3=33)	F or χ^2 value	P-value
Age (year)	56.5±12.6	62.8±11.3	52.8±11.8	6.001	b, c
Male gender	24 (86%)	29 (88%)	28 (85%)	0.220	
BMI (kg/m^2)	22.6±3.0	22.7±3.4	23.9±2.9	1.887	
Type-II diabetes	4 (14%)	9 (27%)	5 (15%)	2.682	
Lineal descent cancer history	7 (25%)	6 (18%)	9 (27%)	1.084	
Alcohol use	12 (43%)	9 (27%)	12 (36%)	2.115	
Cigarette smoking	12 (43%)	12 (36%)	17 (51%)	2.061	
Child-Pugh classification ratio (A/(A+B)×100%)	28 (100%)	29 (88%)	31 (94%)	3.471	
BCLC level (0/(0+A)×100%)	6 (21%)	10 (30%)	5 (15%)	1.795	
HBsAg (+)	23 (82%)	25 (76%)	29 (88%)	1.344	
Hepatitis C antibody (+)	1 (4%)	1 (3%)	0 (0%)	1.109	
Liver cirrhosis	18 (64%)	26 (79%)	22 (67%)	2.282	
Portal hypertension	1 (4%)	6 (18%)	5 (15%)	2.943	
Tumor number					
One	26	30	31		
Two	2	3	2		
Mean tumor size (cm)	3.0±1.1	2.4±0.9	3.3±1.1	4.535	b, c
Preoperative lab results					
ALT (IU/L)	30.7±19.4	47.5±52.6	34.3±22.3	1.885	
AST (IU/L)	32.8±17.0	35.9±16.3	31.3±13.2	0.755	
Total bilirubin (μmol/L)	14.5±5.8	18.2±11.4	13.5±5.3	2.848	b
Albumin (g/L)	38.6±3.9	38.1±5.1	39.8±3.9	1.375	
Prothrombin time delay (s)	0.87±1.0	1.31±1.3	0.90±1.2	1.550	
Platelet count (10^9 L^{-1})	142.2±51.6	110.8±46.5	126.3±61.5	2.917	c
AFP (ng/ml)*	15.5 (1.7–16932.7)	21.7 (1.9–4097.0)	15.0 (2.1–19643.7)	0.081	

Data are expressed as mean±SD, number (percentage), number, or median (range). * Non-normal distribution data analyzed with the Kruskal-Wallis test. a: P<0.05, LH vs. OH; b: P<0.05, RFA vs. OH; c: P<0.05, LH vs. RFA. BMI: body mass index; BCLC: Barcelona Clinic Liver Cancer; HBsAg: hepatitis B surface antigen; ALT: alanine aminotransferase; AST: aspartate aminotransferase; AFP: α-fetoprotein

the rest of the cases were guided by BUS. Complete necrosis at the first postoperative imaging was present in 90.9% of patients (30 of 33). Three patients received repeated RFA after the one-month follow-up imaging, as they were believed to have had inadequate ablation during the first treatment. One patient in the OH group had a liver transplantation 37 months after surgery and one patient had a transplantation 48 months after RFA. All patients mentioned above presented no protocol switch and were kept in their respective groups for survival and recurrence analysis.

3.2 Treatment morbidity and mortality

Table 2 presents the postoperative outcomes. The RFA group had significantly shorter procedure duration (F=5.597, P=0.006) and less blood loss compared with the resection groups (F=56.353, P=0.000). Hospitalization was significantly shorter in the RFA group than in the resection groups (F=10.867, P=0.000). Results from the paired comparison revealed that operating time and intraoperative blood loss were significantly less in the LH group than in the OH group. The only treatment-related hospital mortality of all patients was in the OH group. A 69-year-old male patient died because of postoperative refractory hemorrhage and disseminated intravascular coagulopathy (DIC); he was automatically discharged according to his family's will after half an hour's resuscitation. Adverse events in the LH group were as follows: biliary fistula (3), pleural effusion (1), pneumonia (1), liver section effusion (1), and intra-abdominal infection (1). Complications related with

Table 2 Postoperative endpoints

Group	Operating time (min)	Blood loss (ml)	Need for blood transfusion	Morbidity	Mortality	Hospital stay (d)
LH (n_1=28)	120.5±33.2 (70–200)	340.0±295.2 (20–1200)	7 (25.0%)	7 (25.0%)	0 (0%)	10.4±4.5
RFA (n_2=33)	43.7±8.5 (32–70)	14.9±10.7 (5–45)	1 (3.0%)	8 (24.2%)	0 (0%)	6.30±6.9
OH (n_3=33)	160.1±69.3 (75–355)	850.0±1716.3 (50–10000)	17 (51.5%)	12 (36.4%)	1 (3.0%)	12.9±5.6
F or χ^2 value	56.353	5.497	19.920	1.454	1.868	10.867
P-value	a, b, c	a, b	a, b, c			b, c

Data are expressed as mean±SD (range), number (percentage), or mean±SD. a: P<0.05, LH vs. OH; b: P<0.05, RFA vs. OH; c: P<0.05, LH vs. RFA

the OH groups were: pleural effusion (4), intra-abdominal infection (3), hemorrhage (2), biliary fistula (1), liver section effusion (1), and pneumonia (1). Adverse effects in the RFA group included fever (3), abdominal pain (2), scald of the skin (1), hemoptysis (1), and agranulocytosis (1). The overall complication rate was 25% in the LH group, 36.4% in the OH group, and 24.2% in the RFA group. Biliary fistula and right-sided reactive pleural effusion were the most common complications in operating patients. Adequate percutaneous drainage helped the fistula heal itself, and pleural effusion could be resolved with thoracentesis or conservative management, such as albumin supplement. The complications of the RFA group, although with no significantly less incidence rate, were less severe or fatal than those of the resection groups. Expectant and supportive treatment was successful for the most febrile and in-pain patients.

3.3 Other outcomes

As has also been shown in Table 2, the perioperative need for transfusion (red blood cells (RBC) or fresh frozen plasma (FFP) or platelets (PLT)) was much lower in the RFA group (1 of 35) than in the resection groups. Between the two resection groups, however, the LH group presented with less blood loss and thus less need for blood transfusion than the OH group (25.0% vs. 51.5%). The mean operation time and length of hospitalization were also significantly shorter in the RFA group.

3.4 Disease-free survival and recurrence

In the LH group, recurrence occurred in 10 patients (7 local recurrences and 3 distant metastases). Eight patients had tumor reconstruction in the OH group (7 local recurrences and 1 distant metastasis). Twenty-four patients in the RFA group experienced recurrence within 3 years after the procedure (21 local recurrences and 3 distant metastases). The 3-year disease-free survival rates for the three groups were 64.3%, 27.3%, and 75.7%, respectively. Accordingly, the disease-free survival rate was significantly lower in the RFA group than in either the LH group or the OH group (χ^2=13.810, P=0.001; Fig. 2a). Taking it one step further, we conducted pair-wise comparison between each of the two methods and found the significance showed only between the RFA group and two resection groups. The LH group and the OH group shared similar disease-free survival rates, which was confirmed when we pooled the two groups as one resection group and compared again with the RFA group (Fig. 2b).

Once the recurrence was confirmed by follow-up imaging, patients were readmitted into the hospital where a multidisciplinary team (MDT) proposed a treatment plan for them. The further treatment plan was based on liver function, tumor growth pattern, patients' systemic status, and their personal will. The optional modalities included TACE, local ablation, secondary hepatectomy, chemotherapy, radiotherapy, systemic target therapy (basically, sorafenib injection), traditional Chinese herbs or palliative therapy (Table 3). Nine patients utilized more than one method to treat the tumor recidivism. TACE and local ablations were the most commonly used strategies after recurrence.

3.5 Overall survival

Twenty-five patients died during the study period. Two deaths in the LH group were not referable to liver conditions: one patient died in a motor vehicle accident, and the other died of a cardiovascular event. The causes of death of all OH and RFA patients were HCC-related. The 3-year overall survival rates were

Table 3 Number of modalities for treating recurrence

Group	TACE	Local ablative therapy	Secondary surgical resection	Chemotherapy	Systemic targeted therapy	Radiotherapy	Traditional Chinese herbs	Palliative therapy
LH	13	4	0	1	2	1	2	1
RFA	6	9	2	4	2	1	1	2
OH	9	3	0	0	0	0	1	3

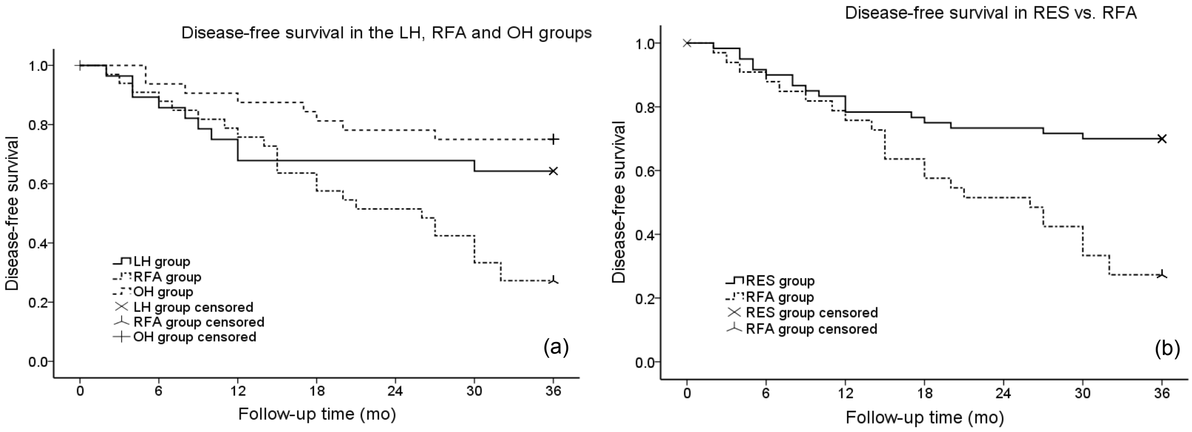

Fig. 2 Disease-free survival analysis

(a) Probability of disease-free survival in patients treated with LH, OH, or RFA (log-rank test, χ^2=13.810, P=0.001). (b) Probability of disease-free survival in patients treated with surgical resection (RES) vs. RFA (log-rank test, χ^2=13.101, P=0.001). mo: month

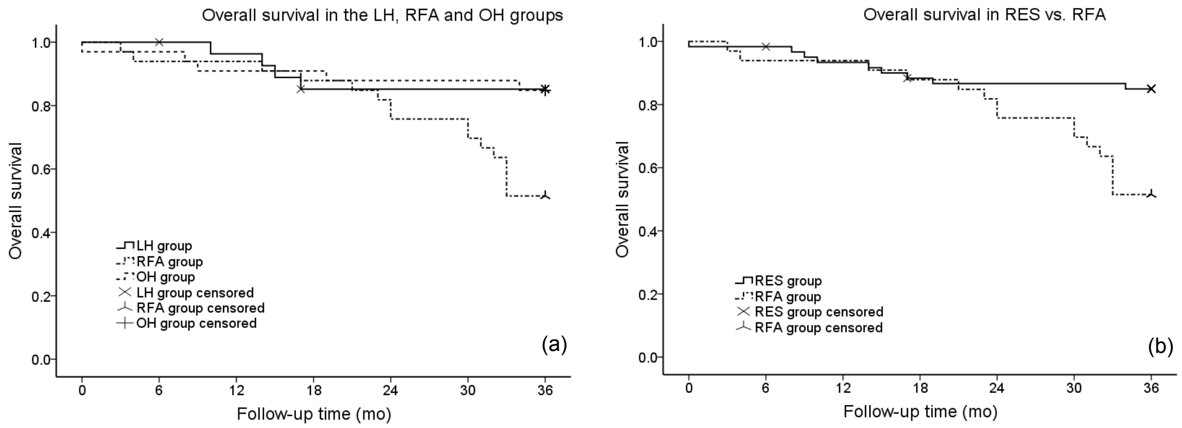

Fig. 3 Three-year overall survival analysis

(a) Probability of overall survival in patients treated with LH, OH, or RFA (log-rank test, χ^2=10.736, P=0.005). (b) Probability of overall survival in patients treated with surgical resection (RES) vs. RFA (log-rank test, χ^2=10.736, P=0.001). mo: month

85.7%, 51.5%, and 84.8% for the LH group, the RFA group, and the OH group, respectively. The log-rank test indicated significant diversity among the three groups, and the main difference was between the RFA group and the LH or OH group (χ^2=10.736, P=0.005; Fig. 3a). Thus, we amalgamated the LH group with the OH group as a resection group. The comparison between the surgical resection group with the RFA group drew the same conclusion (χ^2=10.736, P=0.001; Fig. 3b). The Cox regression analysis revealed that age, number of tumors, and tumor size were not significant covariates affecting the influence of treatment. In 88 patients with only one tumor discovered, the 3-year overall survival was also significantly lower in the RFA group than in the RES group (χ^2=6.838, P=0.009; Fig. 4).

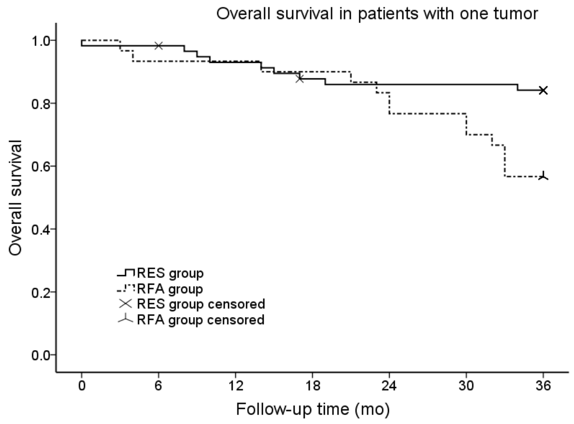

Fig. 4 Overall survival in 88 patients with only one tumor, according to resection status

The 3-year overall survival rate was 84.5% for patients who underwent surgical resection and 56.7% for patients treated with RFA (log-rank test, χ^2=6.838, P=0.009). mo: month

3.6 Analysis of patients with different age zones

Because the average diagnostic age of HCC was 57.8 years from 2005 to 2013 and the mean age of RFA patients was 62.60 years in our study, we set a cut-off line of 60 years old to explore whether there were any survival differences between the older and the younger population. There were 57 patients under 60 years of age and 39 patients aged 60 years or more. The survival function test showed that, among those who were younger than 60 years old, treatment significantly influenced 3-year disease-free survival (χ^2=10.092, P=0.006; Fig. 5a). Among the elderly patients, however, there were no significant differences found among the three study groups (χ^2=5.473, P=0.065; Fig. 5b). In the meantime, the overall survival was only influenced by treatments in the group of younger patients (χ^2=9.685, P=0.008; Fig. 6a).

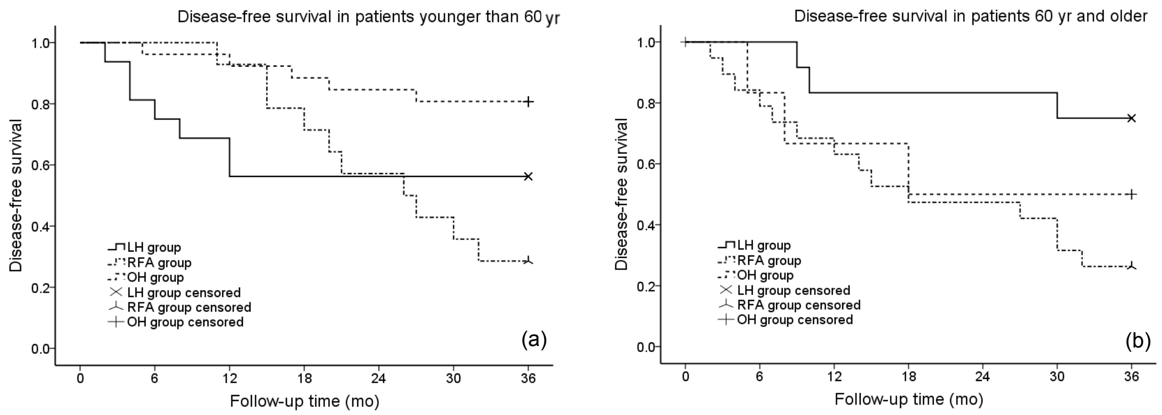

Fig. 5 Disease-free survival in patients within different age ranges

(a) The 3-year disease-free survival rate among those younger than 60 years old was 56.3% for LH patients, 28.6% for RFA patients, and 80.8% for OH patients (log-rank test, χ^2=10.092, P=0.006). (b) The 3-year disease-free survival rate among those 60 years and older was 75.0% for LH patients, 26.3% for RFA patients, and 57.1% for OH patients (log-rank test, χ^2=5.473, P=0.065). mo: month; yr: years

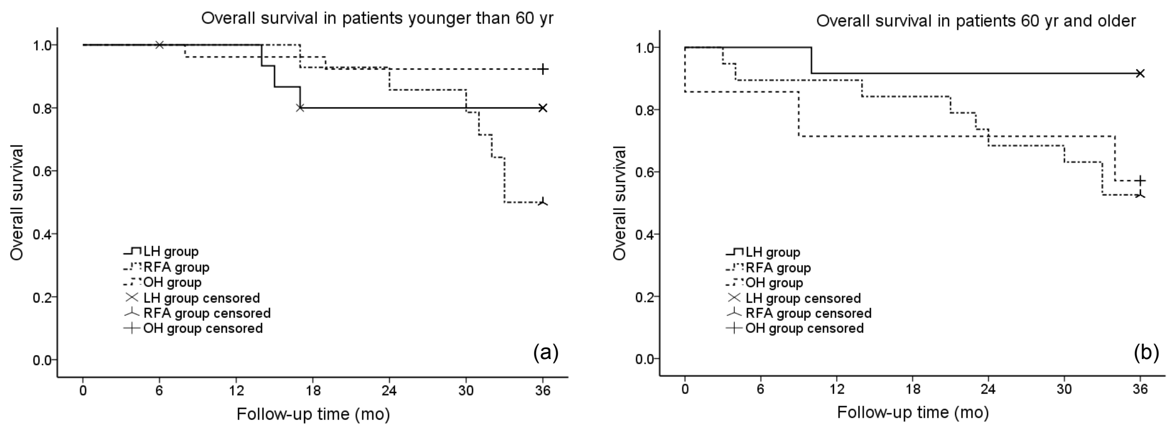

Fig. 6 Overall survival in patients within different age ranges

(a) The 3-year overall survival rate among those younger than 60 years was 81.3% for LH patients, 50.0% for RFA patients, and 92.3% for OH patients (log-rank test, χ^2=9.685, P=0.008). (b) The 3-year overall survival rate among those 60 years and older was 91.7% for LH patients, 52.6% for RFA patients, and 57.1% for OH patients (log-rank test, χ^2=4.532, P=0.104). mo: month; yr: years

4 Discussion

The three techniques discussed above were all successfully used for the treatment of selected HCC patients. Due to the differences in inclusion criteria and applied technology, the conclusions from previous clinical trials and meta-analysis on the treatment of HCC with surgical resections and RFA were contradictory (Fang *et al.*, 2014; Feng *et al.*, 2015; Song *et al.*, 2015). Based on the follow-up after three years, our study showed that for HCC patients who had no more than 3 intrahepatic nodules with diameters of less than 3 cm, or a single lesion with a diameter of less than 5 cm, surgical removal offered a better outcome than pRFA in terms of both disease-free survival and 3-year overall survival. Although complete resection for small tumors may offer curative effects at the expense of a large volume of functional liver parenchyma (Benvegnù *et al.*, 2004; Fattovich *et al.*, 2004), it was still the first-line choice for patients with small HCC. Between the two surgical options, OH and LH showed no difference in survival. Nevertheless, LH had the lead over OH because it gave less trauma and its operation time was shorter. Song *et al.* (2015) conducted a retrospective study to compare LH and RFA in treating single small HCC. They reported no survival differences between the LH and RFA groups, while the LH group was associated with increased morbidity complications. However, based on our data, we came to the conclusion that LH offered better curative effects than pRFA without increasing complication rates.

Compared with surgical resections, pRFA seemed to be associated with faster recurrence and shorter survival. Previous literature suggested that laparoscopic and open RFA might achieve better tumor control than pRFA (Santambrogio *et al.*, 2003; Mulier *et al.*, 2005). The open approaches allowed ablation by means of multiple needle electrode punctures at different angles, which prevented dead ends inside tumors as much as possible. Ayav *et al.* (2010) reported that the rate of incomplete ablation by the percutaneous approach was as high as 18% compared with 13.8% for the open approach. Contradictorily, a lower recurrence rate was at the expense of greater trauma. Moreover, these patients with tumor recurrence could be suitable for a second or third pRFA procedure. These two invasive RFA techniques were not fully investigated and assessed in our study because HCC patients in China hardly ever chose ablation after an open procedure. It was observed in our study that pRFA was characterized with much less intraoperative blood loss, shorter hospitalization, and minor perioperative complications. These perspectives, although not directly related with survival, might interact with the socioeconomic status and psychological conditions of cancer patients, which would further influence their quality of life. Therefore, it was one of the most important treatment options to consider for small HCC.

According to our analysis within different age zones, younger patients benefited more from hepatectomy. They should be recommended to have minimal invasive surgery if the criteria are met. When designing a treatment plan for elderly patients, however, clinicians may encourage them to choose either surgery or pRFA to cure small HCC. For patients with early or intermediate stages of HCC, survival is more related to the functional reserve of the liver than to the tumor itself. Local ablative therapies are repeatable and thus can be used as an effective supplementary therapy without causing massive injury to the sick liver.

This study could be criticized for the following limitations. First, this was not an RCT, although data were collected prospectively. Patients were divided into three groups according to the decisions of both the doctor and the patient's family. Bias may exist in the treatment selection based on the patient's age, their intension-to-treat wishes, and the tumor status. And from past experience, for example, patients with a tumor in the posterior-superior lobe were often not considered for LH. Besides this, the sample population may not be fully extrapolated to the whole HCC population worldwide. Numerous literatures have shown that the occurrence and progression of HCC are quite different between east and west populations (Lai *et al.*, 2012). Our study cohort reflected more the conditions of HCC patients in the East Asian area. Secondly, we were not able to analyze the influences of post-procedure methods on survival. On the one hand, there was a greater variation in palliative methods, chemotherapy or Chinese traditional medicine for patients to choose from, which made it difficult to collect accurate data. On the other hand, our sample population was not statistically powerful enough for analysis if it was divided into different post-procedure groups. Researchers have reported that the combination of TACE with surgery or RFA would greatly improve the curative effects of HCC (Feng, 2013; Gu *et al.*, 2014; Liu *et al.*, 2014). Further exploration is in urgent need to throw light upon this issue. Last but not least, when discussing the survival conditions within different age zones, we artificially drew a line at 60 years of age, based on the average age of the HCC patients. The boundary of division should be carefully argued for larger HCC populations.

In conclusion, for small HCC patients, radical resections including OH and LH offer better survival results than pRFA. Laparoscopic surgery shared similar curative effects with OH in terms of both disease-free survival and 3-year overall survival. Minimally invasive surgery should be recommended in younger patients with small HCC, while elderly patients may choose either liver resection or RFA. Compared to surgery, pRFA is less invasive and more repeatable. Because of the heterogeneity of patients and the disease itself, puzzles remain which could be resolved through well-designed, adequately powered and bias-free RCTs. To provide effective control of HCC, public health workers need to conduct rigorous screening for high-risk groups, while physicians and surgeons must work out a therapy that is most appropriate and personalized for HCC patients at certain stages of the disease.

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Compliance with ethics guidelines

Chong LAI, Ren-an JIN, Xiao LIANG, and Xiu-jun CAI declare that they have no conflict of interest.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from all patients for being included in the study. Additional informed consent was obtained from all patients for whom identifying information is included in this article.

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中文概要

题　目：腹腔镜肝切除术、经皮射频消融术及传统开放手术对小肝癌的治疗比较

目　的：评估比较目前三种主流技术对小肝癌的治疗作用及对患者预后的影响。

创新点：首次同时比较两种手术技术和一种微创射频技术对小肝癌患者的治疗效果，并且将小肝癌患者通过年龄分层，获得最优的治疗选择，以期指导临床上更个性化及精准化的治疗方案。

方　法：选取 2005 年至 2010 年间 94 例符合单个肿瘤直径小于 5 cm 或不超过 3 个肿瘤且每个肿瘤直径小于 3 cm 的小肝癌患者，分至 3 个治疗组，分别为腹腔镜肝切除组（28 例）、经皮射频消融组（33 例）和开放肝切除组（33 例）。经过 3 年的跟踪随访，统计比较 3 组患者的疾病预后及相关指标。

结　论：本研究中统计结果显示，经皮射频消融组的无瘤生存率和总生存率明显比两个手术组低（图 2 和 3）。腹腔镜手术组和开放手术组的生存及预后情况无明显差异，而腹腔镜手术组的创伤和术后并发症率要低于开放手术组（表 2）。本研究根据中心经验将全部患者以 60 岁进行年龄划分（图 5 和 6）。对于 60 岁以下的小肝癌患者来说，手术的效果明显优于射频消融术，故应优先选择微创的腹腔镜肝切除术；60 岁以上的小肝癌患者经射频治疗获得的生存结果与手术无显著差异，同时射频治疗具有创伤轻微、可重复、并发症少等优势，故可以酌情选择手术或射频治疗。

关键词：肝细胞性肝癌；腹腔镜肝切除术；经皮射频消融术；微创技术；开放肝切除术