Int J Clin Exp Med 2020;13(10):7349-7356
www.ijcem.com /ISSN:1940-5901/IJCEM0112285

Review Article

Clinical efficacy and long-term prognosis of laparoscopic liver resection and radiofrequency ablation for small hepatocellular carcinoma

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Received April 10, 2020; Accepted June 13, 2020; Epub October 15, 2020; Published October 30, 2020

Abstract: This study aimed to explore the clinical efficacy and long-term prognosis of laparoscopic liver resection (LLR) and radiofrequency ablation (FRA) in small hepatocellular carcinoma (sHCC) with a diameter ≤5 cm. Altogether 160 sHCC patients were selected, including 70 patients treated with LLR and 90 patients treated with FRA. The two groups were compared in terms of the operation, intraoperative blood loss, postoperative liver function index, complications, pain score, quality of life (QLQ), 5-year overall survival (OS) and 5-year disease-free survival (DFS), and prognostic factors, were all analyzed. The FRA group was superior to the LLR group in operation time, length of stay, intraoperative blood loss, postoperative liver function index, pain score and QLQ score. There was no statistical difference in the complications and OS for 5 years between the LLR group and the FRA group (P=0.569, log-rank test). The 5-year DFS in the LLR group was higher than that in the FRA group (P=0.027, log-rank test). Child-Pugh classification, tumor size, liver cirrhosis and portal vein tumor thrombus were independent risk factors affecting the prognosis of sHCC patients. LLR is the first clinical treatment for sHCC. RFA can be selected for patients who cannot undergo surgery.

Keywords: Laparoscopic hepatectomy, radiofrequency ablation, small hepatocellular carcinoma, efficacy, prognosis

Introduction

Liver carcinoma is the fifth most common carcinoma and the second most common cause of carcinoma-related death in the world. Hepatocellular carcinoma (HCC) accounts for about 90% of primary liver carcinoma and is a major health problem worldwide [1]. At present, HCC can be treated by various methods, such as liver transplantation, surgical resection, thermal ablation, transcatheter arterial chemoembolization, sorafenib and other targeted drugs [2]. Among them, the first three methods have the potential to cure HCC, so they are often used to treat patients with small HCC (sHCC) with a diameter ≤5 cm. At present, there is still controversy over the best treatment for sHCC. Although liver transplantation is the most effective, the controversy still exists, which mainly focuses on the choice between liver resection and thermal ablation due to the lack of liver transplantation donors and excellent results obtained by resection or ablation [3].

With the development of medical equipment and technology, many non-surgical ablation methods have been developed clinically, of which radio frequency ablation (RFA) is a new ablation technology with great prospects in recent years. It has the beneficial characteristics of a small wound, easy operation, few complications, and little influence on liver function. In addition, for three or fewer nodules with diameter ≤3 cm, reliable local tumor control can be accomplished in most cases in a single application, so it is often applied to treat patients with sHCC [4, 5]. Laparoscopic liver resection (LLR), one of the operative methods for liver diseases introduced in the 1990s, has proven to be safe and feasible for hepatectomy in the past 20 years [6]. Compared with traditional open hepatectomy, LLR has the advan-

tages of less intraoperative bleeding, less complications and short length of stay; it is the standard method for sHCC, but it is still in the exploratory stages [7].

At present, there are many studies related to hepatectomy and RFA for treatment of sHCC, but not many on comparing LLR and RFA for long-term prognosis of sHCC, and there are great differences in conclusions. Therefore, this study aimed to provide more effective and reliable treatment methods for patients with sHCC by using these two methods, and observing their curative effects and influence on long-term prognosis of patients.

Method

General data

Altogether 160 patients with sHCC from December 2011 to December 2013 were collected, and they were grouped into the LLR group (70 cases) and FRA group (90 cases) according to the treatment plan. Inclusion criteria: All of them had primary HCC and met the diagnostic criteria [8]; the maximum diameter of multiple tumors was ≤3 cm, or the maximum diameter of single tumors was ≤5 cm; no vascular invasion and extrahepatic metastasis were found by imaging; all patients were treated for the first time; patients were grade A or B of Child-Pugh [9]. Exclusion criteria: patients with coagulation insufficiency; patients with physical condition assessment that could not tolerate surgery; patients without complete clinical information or who were lost in follow-up; patients accompanied by serious systemic diseases and other tumor diseases. This study was approved by the Ethics Committee of Jiuquan city people's hospital of Gansu Province and was in accordance with Helsinki Declaration. The subjects and their families signed an informed consent form.

Treatment methods

The LLR group received laparoscopic resection. After general anesthesia was performed on the patient, the patient's body position was adjusted according to the location and size of the tumor, and the CO_2 pneumoperitoneum pressure was maintained at 12 mmHg. According to the preoperative CT, MRI and other imaging studies of the patient, the incision line was determined and marked with the aid of B-ultrasound during the operation. For tumors that could not use anatomical liver resection, the gap between the incision edge and the tumor edge was more than 1 cm. The liver parenchyma was cut off with ultrasonic scalpel, and the section pipe (diameter >3 mm) was clamped with titanium clip and then severed. The obtained cancer tissue was placed in a specimen bag, the liver section was washed repeatedly and the wound surface was treated to stop bleeding, then a peritoneal cavity drainage tube was placed, and the specimen was completely taken out for later use.

The FRA group received radiofrequency ablation. Under the guidance of CT, the electrode needle was inserted into the tumor center through percutaneous transhepatic puncture. According to the patient's tumor size and physical condition, the ablation times were determined. The ablation range exceeded the tumor edge by 1 cm for 8-15 min. The electrode temperature was 105-110°C, and the ablation effect was observed by CT after surgery. After ablation, needle ablation was performed.

Follow-up after operation

The two groups were followed up for 5 years after operation by outpatient service, telephone, visits and other methods, once every month. The 5-year survival curve and recurrence curve were established for patients. The criteria for judging recurrence were as follows: local recurrence was found if new tumor or lesion enlargement occurred at the edge of surgery and ablation of the patient through ultrasound, CT or MRI examination, and distant recurrence was found if new tumors occurred at other parts of the liver.

Outcome measures

The operation time, hospitalization time, intraoperative blood loss, postoperative liver function index changes and complications of the two groups were compared.

Visual analogue scale (VAS) [10] was applied to test the pain degree of the patient one day after operation; with no pain scored as 0 points. The tolerable and slight pain was scored with 1-3 points. Pain affecting a person's rest was scored with 4-6 points. Pain that was intolerable and affected sleep and appetite was scored with 7-10 points.

According to QLQ-C30 [11], the QLQ of patients who survived for 1 year after treatment was evaluated, including 4 items of disease control, life behavior, exercise and psychological emotional changes. Each item had a full score of 100 points, and the higher score indicated better QLQ.

Statistical analysis

SPSS 21.0 (from EASYBIO) was applied for statistical analysis, and GraphPad Prism 7 to illustrate the data. In this study, the comparison of the counting data was represented by chi-square test, the comparison of the measurement data was explored by t-test. Kaplan-Meier was applied to establish survival curves for the two groups of patients, Log-rank to explore the difference of survival curves. When $P<0.05$, the difference was statistically significant.

Results

Comparison of general data

There was no evident difference in general data such as gender, age, weight, educational level, diet preference, residence, exercise, marital status, smoking history, Child-Pugh classification, tumor diameter, and liver cirrhosis ($P>0.05$). See **Table 1**.

Comparison of operation

There was no death in either group before discharge. The operation time and hospitalization time of the FRA group were shorter than that of the LLR group, and the intraoperative blood loss in the FRA group was less than that of the LLR group ($P<0.05$). See **Table 2**.

Comparison of liver function indexes

There was no statistical difference in ALT and AST levels before treatment ($P>0.05$). After treatment, ALT and AST levels were increased, but in the FRA group they were lower than in the LLR group ($P<0.05$). See **Table 3**.

Comparison of postoperative short-term complications

There was no evident difference in the postoperative short-term complications between the two groups ($P>0.05$). See **Table 4**.

Postoperative pain

VAS score of the LLR group (3.67±1.56) was higher than that of the RFA group (1.67±0.66) ($P<0.05$). See **Figure 1**.

Comparison of 5-year OS and DFS

The 1-, 3-, and 5-year OS in the LLR group were 95.71%, 81.38%, and 61.42%, respectively; while those in the FRA group were 94.44%, 77.14%, and 57.78%, respectively. Log-rank test revealed no statistically evident difference ($P=0.569$, log-rank test). The 1-, 3-, and 5-year DFS in the LLR group were 85.71%, 64.29%, and 44.29%, respectively; while those in the FRA group were 71.11%, 51.11%, and 28.89%, respectively ($P=0.027$, log-rank test). See **Figure 2**.

Comparison of QLQ

The QLQ of the patients who survived 12 months after treatment was evaluated. QLQ-C30 score in the FRA group was higher than in the LLR group, including disease control, life behavior, exercise and psychological emotion ($P<0.05$). See **Table 5**.

Univariate analysis of factors affecting the OS of sHCC after treatment

Univariate analysis was carried out on the general factors and clinical pathological factors of the two groups of patients. The results showed that sex, AFP level, tumor number, capsule integrity and treatment methods were not prognostic factors affecting the 5-year OS of patients with sHCC ($P>0.05$). Child-Pugh classification, tumor size, vascular tumor thrombus and liver cirrhosis may be prognostic factors affecting the 5-year OS rate of patients with sHCC ($P>0.05$). See **Table 6** for details.

Multivariate analysis of factors affecting the OS of sHCC after treatment

Cox proportional hazards model analysis revealed that Child-Pugh classification, liver cirrhosis, tumor size and vascular tumor thrombus were independent death factors for sHCC. See **Table 7** for details.

Discussion

With the improvement of disease and medical knowledge, more patients with sHCC have been

Table 1. Comparison of general data ([n (%)], x ± sd)

Group	LLR group (n=70)	FRA group (n=90)	χ^2/F	P
Gender			0.299	0.585
Male	51 (72.86)	62 (68.89)		
Female	19 (27.14)	28 (31.11)		
Average age (years)	58.34±7.98	59.23±9.24	0.641	0.522
Average body weight (KG)	64.24±9.78	65.56±8.88	0.892	0.374
Education level			2.078	0.149
<high school	43 (61.43)	45 (50.00)		
≥ high school	27 (38.57)	45 (50.00)		
Diet preference			3.478	0.062
Light	46 (65.71)	71 (78.89)		
Oily	24 (34.29)	19 (21.11)		
Residence			0.819	0.366
Urban	37 (52.86)	54 (60.00)		
Rural	33 (47.14)	36 (40.00)		
Exercise			0.297	0.586
Yes	31 (44.29)	36 (40.00)		
No	39 (55.71)	54 (60.00)		
Marital status			0.715	0.670
Married	57 (81.43)	69 (76.67)		
Unmarried	4 (5.71)	8 (8.89)		
Divorced	9 (12.86)	13 (14.44)		
Smoking history			1.154	0.283
Yes	45 (64.29)	65 (72.22)		
No	25 (35.71)	25 (27.78)		
Drinking history			2.753	0.097
Yes	36 (51.43)	58 (64.44)		
No	34 (48.57)	32 (35.56)		
Child-Pugh classification			1.022	0.312
A	54 (77.14)	63 (70.00)		
B	16 (22.86)	27 (30.00)		
Tumor diameter (cm)			0.558	0.455
≥ 3	27 (38.57)	40 (44.44)		
<3	43 (61.43)	50 (55.56)		
Cirrhosis			0.641	0.424
Yes	44 (62.86)	62 (68.89)		
No	26 (37.14)	28 (31.11)		

Table 2. Comparison of operation (x ± sd)

Group	n	Operation time (min)	Hospitalization time (d)	Intraoperative blood loss (ml)
LLR group	70	132.24±31.56	16.13±2.65	357.23±138.11
FRA group	90	40.24±12.67	8.71±1.73	24.35±10.67
t		25.186	21.357	22.799
P		<0.001	<0.001	<0.001

treated. For sHCC patients, most have the possibility of radical surgery. However, there is still great controversy about the best choice to treat sHCC. Surgical resection is generally considered to be the first choice for the treatment of sHCC patients, which has the characteristics of high prevalence rate, long tumor-free survival period, and low recurrence rate [12]. With the continuous updating and progress of medical technology, RFA, a minimally invasive treatment method, was developed. Its main principle is to generate heat through the use of high-frequency electromagnetic wave ions to make the temperature of the center of the patient's tumor reach above 60C, thus causing coagulation necrosis of tumor tissue and achieving the goal of killing tumor cells [13]. The results reveal that RFA can achieve a complete ablation rate of over 90% for sHCC patients with a diameter ≤3 cm [14]. In recent years, with the increasing application of RFA with good clinical results, more and more evidence support RFA as the first choice for sHCC [15-17]. Therefore, we applied in this study the comparison of the therapeutic effects of two treatment methods on patients with small liver cancer.

Our results showed that the operation time, hospitalization time, intraoperative blood loss, liver function index, pain score, QLQ score and other indexes of the FRA group were all better than those of the LLR group. However, the 5-year OS of the FRA group was not evidently different from that of the LLR group, and the DFS was evidently lower than that of the

Table 3. Comparison of liver function indexes before and after treatment (x ± sd)

Group	Alanine aminotransferase ALT (U/L)		Aspartate aminotransferase AST (U/L)	
	Before treatment	After treatment	Before treatment	After treatment
LLR group (n=70)	31.58±8.67	385.14±127.12*	27.89±7.11	212.17±51.36*
FRA group (n=90)	29.54±9.44	192.72±49.84*	29.44±10.38	113.44±30.75*
t	1.405	13.130	1.069	15.094
P	0.162	<0.001	0.287	<0.001

Note: * indicates compared with before treatment, P<0.05.

Table 4. Comparison of postoperative short-term complications [n (%)]

Group	LLR group (n=70)	FRA group (n=90)	χ^2	P
Ascites	1 (1.43)	4 (4.44)	-	-
Jaundice	0	3 (3.33)	-	-
Pulmonary infection	0	1 (1.11)	-	-
Pleural effusion	0	1 (1.11)	-	-
Hypoproteinemia	2 (2.86)	4 (4.44)	-	-
Abdominal bleeding	2 (2.86)	3 (3.33)	-	-
Incision infection	0	2 (2.22)	-	-
Incidence of complications	5 (7.14)	18 (20.00)	5.288	0.215

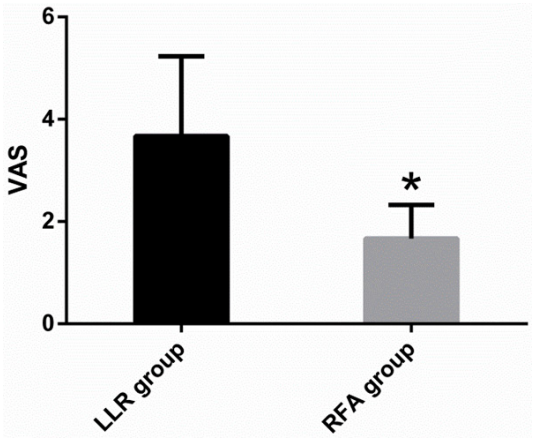

Figure 1. Comparison of postoperative VAS scores. Note: * indicates compared with LLR group, P<0.05.

LLR group. The results might be related to incomplete RFA ablation. LLR can remove more intrahepatic micrometastases while completely removing the primary tumor body. Recently, many investigations have generated similar conclusions to our research results. For example, two groups of sHCC patients (single cancer nodule diameter <4 cm) who received LLR therapy (LH group, n=78) and RFA therapy (RFA group, n=78) were selected retrospectively for research, and the OS and recurrence-free survival were mainly compared. The results revealed that the OS was not evidently different in 3 years, but the recurrence-free survival of the RFA group was lower than the LH group; and the operation time, intraoperative blood loss and blood transfusion, hospitalization time, total parenteral nutrition and other indicators of the RFA group were better than the LH group [18]. There were also studies comparing the long-term effects of RFA and LLR in patients with sHCC. The results showed that compared with RFA, LLR had no significant difference in the 5-year OS, while the 5-year relapse-free survival was evidently higher, and there was no obvious difference in the complications. Therefore, they pointed out that LLR should be considered as the first-line method for treating single sHCC [19]. It further showed that LLR had better long-term effects on patients with sHCC, so we recommend LLR as the first clinical treatment for sHCC, and RFA treatment could be selected for patients who could not use surgery.

As there are many choices for sHCC, it is very important to understand the prognostic factors affecting the survival after treatment, so as to formulate the best treatment plan. There are many factors affecting the survival of patients with sHCC after treatment. In this study, the general factors and pathological factors were explored by single factor analysis. The results revealed that Child-Pugh classification, tumor size, cirrhosis, and vascular tumor thrombus might be prognostic factors that affect the OS of PLC patients. Cox proportional hazards model analysis revealed that Child-Pugh classification, tumor size, cirrhosis and portal vein tumor thrombus were independent risk factors affecting the OS of patients with sHCC. Tumor size was recognized as a risk factor affecting

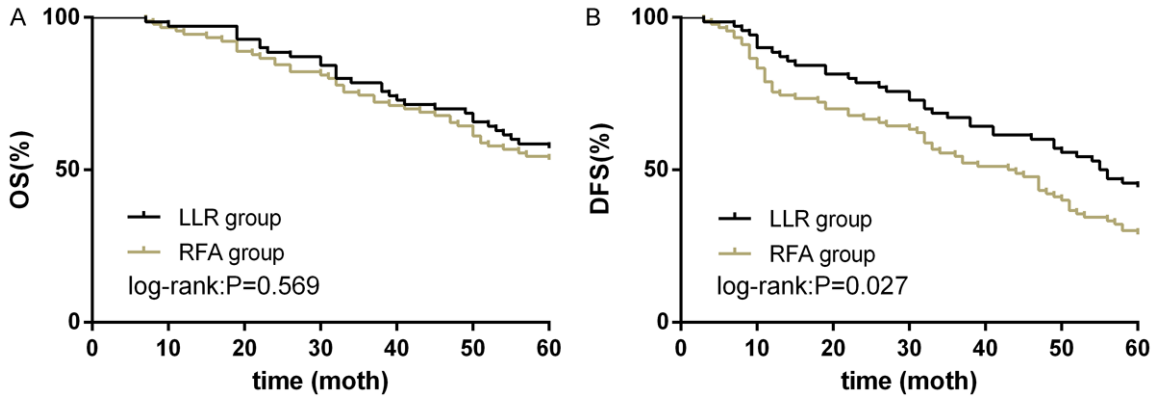

Figure 2. Comparison of 5-year OS and DFS. Comparison of 5-year OS between the two groups (A); Comparison of 5-year DFS between the two groups (B).

Table 5. Comparison of QLQ (Points, x ± sd)

Group	Number of cases	Disease control	Life behavior	Physical activities	Psychological emotion
LLR group	67	78.44±5.56	80.54±6.42	74.62±5.63	79.54±5.45
FRA group	85	84.24±5.12	86.54±5.85	70.54±5.66	83.57±5.66
t		6.676	6.0134	4.426	4.430
P		<0.001	<0.001	<0.001	<0.001

Table 6. Univariate analysis of influence on OS of sHCC after treatment

Group	Number of investigation cases (Cases)	Number of 5-year survival cases (cases)	χ^2	P
Gender			0.502	0.579
Male	113	71		
Female	47	24		
Age (years)			0.974	0.324
<60	69	35		
≥ 60 years old	91	60		
Child-Pugh classification			5.060	0.025
A	117	81		
B	43	14		
Tumor diameter (cm)			6.257	0.014
≥ 3	67	25		
<3	93	70		
AFP (μg/L)			2.546	0.111
<400	97	67		
≥ 400	63	28		
Cirrhosis			6.040	0.014
Yes	101	74		
No	59	21		
Portal vein tumor thrombus			5.490	0.019
Yes	112	79		
No	48	16		
Number of tumors			1.524	0.217
Single	105	55		

Multiple	55	40		
Tumor envelope			0.681	0.409
Complete	123	78		
Incomplete	37	18		
Treatment methods			0.055	0.814
LH	70	43		
RFA	90	52		

Table 7. Multivariate analysis of factors affecting the OS of sHCC after treatment

Group	β	SE	Wald	P	OR (95% CI)
Child-Pugh classification	0.556	0.184	9.234	0.002	4.785 (1.244~7.665)
Cirrhosis	0.612	0.173	11.345	<0.001	3.956 (1.424~5.655)
Tumor size	0.321	0.117	7.057	0.009	3.265 (1.183~4.897)
Portal vein tumor thrombus	0.121	0.061	4.767	0.034	4.112 (1.411~6.252)

survival rate of patients with HCC [20]. Some studies found that the OS of patients with liver tumor <2 cm was higher than that of patients with liver tumor 2~5 cm [21]. Portal vein tumor thrombus was a common complication in patients with HCC, which seriously affected the prognosis [22]. Child-Pugh grade could reflect the liver function of patients. Some studies indicated that the 5-year OS of grade A patients after RFA treatment was higher than that of grade B patients [23]. Other studies pointed out that Child-Pugh classification was a related factor affecting the OS of patients with HCC after hepatectomy [24]. Liver cirrhosis was a well-known risk factor for primary HCC, that is, HCC patients with liver cirrhosis have poor prognosis [25]. Therefore, the occurrence of cirrhosis and portal vein tumor thrombus should be mainly prevented after operation.

There are some deficiencies in this study. For example, the number of samples is relatively small and we failed to explore the pain and QLQ of patients before treatment, which lead to certain limitations in the results. The prognostic factors affecting the DFS after surgery were not explored. These deficiencies will be continuously improved in the following research.

To sum up, the short-term and long-term effects of RFA and LLR on sHCC are similar, but the long-term recurrence rate of LLR is significantly lower than that of RFA. RFA has the advantages of less trauma, less influence on liver function and low incidence of postoperative complications. Therefore, RFA can be selected for patients who cannot undergo surgery or do not accept surgery, and LLR is better for patients who can accept surgery.

Disclosure of conflict of interest

None.

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