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Percutaneous Radiofrequency Ablation versus Surgical Resection for the Treatment of Small Hepatic Carcinoma: A Meta-analysis

Li Xin[1], Yun-bing Wang[2], Jian-ping Gong[3,*]

[1]Department of surgery, Dadukou District People's Hospital, Chongqing, China
[2]Department of Hepatobiliary, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, China
*Corresponding author: gongjianping11@126.com

Abstract ***Aims:*** To evaluate the curative effect of percutaneous radiofrequency ablation (PRFA) versus surgical resection (SR) for the treatment of small hepatic carcinoma. ***Methods:*** Cochrane Library, Medline, Pubmed, CNKI, WanFang, VIP databases were searched from January 1990 to March 2013, then clinical control studies comparing curative effects of PRFA with SR in treatment of small hepatic carcinoma were acquired and reviewed. Qualities of these studies were evaluated. Publication bias was also assessed by using a funnel plot. Then primary outcomes, namely overall survival rates, disease-free survival rates and postoperative complication, were abstracted to conduct a combined analysis by using fixed or random effects model. ***Results:*** A total of eight studies involving 1287 patients were included in our study. The PRFA group has a lower overall survival rates over the SR group in 1 year (OR, 0.62; 95% confidence interval [CI], 0.43-0.89; P = 0.009), 3 years (OR, 0.44; 95% CI, 0.27-0.72; P=0.001), and 5 years (OR, 0.49; 95% CI, 0.35-0.68; P＜0.0001). The PRFA group has a lower disease-free survival rates over the SR group in 1 year (OR, 0.63; 95% CI, 0.49-0.82; P=0.0006), 3 years (OR, 0.45; 95% CI, 0.30-0.67; P=0.0001), and 5 years (OR, 0.46; 95% CI, 0.33-0.64; P＜0.00001). The postoperative complication of the PRFA group was lower than the SR group (OR, 0.21; 95% CI, 0.08-0.56; P＜0.00001). ***Conclusion****:* PRFA had lower overall survival rates after surgery and disease-free survival than SR, but it has a lower incidence of postoperative complications. Then PRFA, acted as an operation with smaller invasion and shorter hospitalization time, would be a good choice for the patients with hepatic carcinoma who is reluctant to be treated by SR.

Keywords: *percutaneous radiofrequency ablation, surgical resection, hepatic carcinoma, meta-analysis*

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1. Introduction

Hepatic carcinoma is one of the common malignant tumors, of which lots of patients died. More than 700,000 cases of hepatic carcinoma patients were diagnosed in 2008, with an age-adjusted worldwide incidence rate of 16 cases per 100,000 inhabitants [1,2,3]. The occurrence of this disease is prevalent both in Asia and Africa, with a rising trend in United States and Europe [4]. In the past several decades, with rapid developments of radiological technology and widespread application of screening programs, more potential patients were detected as hepatic carcinoma.

Theoretically, the best treatment of hepatic carcinoma is liver transplantation, which has possibilities of resecting the entire tumor-bearing liver, to eliminate the cirrhosis, and to achieve the best results [5,6]. However, liver transplantation can only benefit a minority of patients because of the shortage of donors and high cost of this surgery. As a result, surgical resection (SR) is still considered to be the first choice of method [7,8]. Nevertheless, only 9% to 29% of patients with hepatic carcinoma are candidates for surgery, just owing to either poor hepatic reserve resulting from underlying chronic liver disease or multifocal distribution of tumor nodules. Therefore, many non-surgical methods have been developed, such as percutaneous ethanol injection (PEI), percutaneous acetic acid injection (PAI), percutaneous radiofrequency ablation (PRFA), microwave coagulation (MWC), high intensity focused ultrasound (HIFU), cryoablation, and transcatheter arterial chemoembolization (TACE) [9-13].

At present, certain number of investigators [14,15,16] reported that SR had more advantages in aspects of survival rates and disease-free survival rates regardless of tumor size. However, some researchers [17,18,19,20] concluded that PRFA was as effective as SR in the treatment of solitary and small hepatic carcinoma. Additionally, one study [21] even considered PRFA as the first-line treatment for small resectable hepatic carcinomas. In total, which one is the better treatment of hepatic carcinoma is still a controversial problem. With the method of meta-analysis, the purpose of this study was to

evaluate the effects of PRFA compared with SR in the treatment of small hepatic carcinoma.

2. Materials and Methods

2.1. Study Search

Cochrane Library, Medline, Pubmed, CNKI, WanFang, VIP databases were searched from January 1990 to March 2013, then clinical control studies comparing curative effects of PRFA with SR in treatment of small hepatic carcinoma were acquired and reviewed. The key words we used included radiofrequency, radio-frequency, radio frequency, surgical resection, hepatectomy, liver cancer, hepatocellular carcinoma. In order to get potential studies, reference lists of previous papers were also reviewed.

2.2. Inclusion and Exclusion Criteria

One study would be included in our study when: (1) The diagnosis of patients were based on the Milan criteria. (2) The study aims to compare the effects of PRFA with HR for patients with small hepatic carcinoma. The diagnostic standard of hepatic carcinoma was the Milan criteria [22]: Diameter of solitary tumor is less than 5.0 cm. The number of multiple tumors do not surpass three, and diameter of the maximum one is less than 3.0 cm. All tumors have no sighs of vascular invasion or extrahepatic metastasis. (3) Primary outcomes were overall survival rates, disease-free survival rates in 1-year, 3-year, and 5-year respectively and postoperative complication. Included studies should evaluate at least one of the primary outcomes. (4) Clinical control studies including randomized controlled trials (RCT) and non-randomized controlled trials (NRCT, including cohort studies and case-control studies) would be appreciated. Besides, studies to be considered should clearly show indications for PRFA and HR. (5) If two or more studies were reported by the same authors in the same institution, either the study of higher quality or the most recent publication would be selected in our study. Criteria for exclusion: (1) Studies that did not clearly report the outcomes of interest would be excluded. (2) The study whose full text could not be acquired would be also excluded.

2.3. Data Extraction and Quality Assessment

Two reviewers (Li Xin and Yun-bing Wang) independently extracted the following parameters from original studies: first author, publication year, number of patients, characteristics of patients, study design, follow-up time, and clinical outcomes. Discrepancies between two reviewers were resolved by mutual discussion and consultation for associated experts. Qualities of these studies were evaluated with Jadad scale [23].

2.4. Statistical Analysis

Our meta-analysis was performed by the Review Manager version 5.3 (RevMan, Cochrane Collaboration, Oxford, England). A random effects model would be used in the process of data merge, if there was no statistical heterogeneity. Otherwise, a fixed effects model would be applied. Statistical heterogeneity was usually evaluated by the Cochran χ^2 test, and the statistical difference was considered significant when $P< 0.05$. The pooled odds ratios (ORs) in combination with 95% confidence interval (CI) was used to assess outcomes in our study. $P< 0.05$ was considered statistically significant. Publication bias was also assessed using a funnel plot when possible.

3. Results

3.1. Characteristics of Included Studies

According to the inclusion and exclusion criteria, in the end, a total of 8 studies (4 RCT and 4 NRCT; 1 in Chinese and 7 in English) involving 1278 patients which were published between 2004 and 2013 were included in our study. The mean age of these patients ranged from 47 years to 76.5 years. Most of these patients (61.8%, 790/1278) were in Child-Pugh class A. Most of them (61.0%, 779/1278) had only a single tumor in liver. The mean tumor size ranged from 1.9 cm to 3.8 cm. The mean follow-up time ranged from 3.9 months to 46.4 months. The characteristics of included studies are shown in Table 1. The Jadad scores of included RCT were all 5 cents, which indicates a good methodological quality for these studies. However, the NRCT acquired only one to three cents.

Table 1. Characteristics of included studies

First author, year	Study design	Treatment	Sample size	Mean age (years)	Sex (M/F)	Child-Pugh A/B	Mean follow-up (months)
Tohme S, 2013 [21]	NRCT	SR	50	66.3±1	31/19	44/6	29*
		PRFA	60	65.6±12	38/22	44/16	29*
Feng K, 2012 [19]	RCT	SR	84	47(18-76)	75/9	43/41	36*
		PRFA	84	51(24-83)	79/5	39/45	36*
Huang J, 2010 [14]	RCT	SR	115	55.91±12.68	85/30	106/9	46.4*
		PRFA	115	56.57±14.30	79/36	110/5	37.2*
Ueno S, 2009 [16]	NRCT	SR	123	67(28-85)	82/41	91/31/1	36.1*
		PRFA	155	66(40-79)	100/55	52/92/11	36.1*
Abu-Hilal M, 2008 [15]	NRCT	SR	34	67*	26/8	25/9	43*
		PRFA	34	65*	27/7	27/7	30*
Lu MD, 2006 [18]	RCT	SR	54	49±14	37/17	50/4	21±11
		PRFA	51	55±13	42/9	46/5	20±12
Chen MS, 2006 [17]	RCT	SR	90	49.4±10.9	75/15	ND	29.2±11.9
		PRFA	71	51.9±11.2	56/15	ND	27.9±10.6
Vivarelli M, 2004 [20]	NRCT	SR	79	65.2±8.2	57/22	70/9	28.9±17.9
		PRFA	79	67.8±8.7	67/12	43/36	15.6±11.7

Note: RCT: randomized controlled trials; NRCT: non-randomized controlled trials; PRFA: percutaneous radiofrequency ablation; SR: surgical resection. ND: Not described; *: median/mean.

3.2. Meta-analysis of Overall Survival Rates

3.2.1. One-year Overall Survival rate

The meta-analysis of 8 studies revealed that the 1-year overall survival rate in PRFA group (86.7%) was significantly lower than that in HR group (90.6%; OR, 0.62; 95% CI, 0.43–0.89; P = 0.009; Table 2), with no heterogeneity (P = 0.39; I2 = 5%).

Table 2. summary of meta-analysis results of primary outcomes

Variables	Number of studies [references]	Results		OR (95% CI)	Q test (P value)	I2(%)	Z test (P value)
		RFA	SR				
Overall survival rates							
1 year	8 [14-21]	86.70%	90.60%	0.62 [0.43, 0.89]	0.39	5%	0.009
3 years	7 [14,16-21]	63.70%	77.60%	0.44 [0.27, 0.72]	0.008	65%	0.001
5 years	4[14,15,16,21]	55.20%	70.80%	0.49 [0.35, 0.68]	0.008	4%	< 0.0001
Disease-free survival rates							
1 year	8[14-21]	71.20%	79.30%	0.63 [0.49, 0.82]	0.13	38%	0.0006
3 years	7[14,16-21]	36.40%	54.10%	0.45 [0.30, 0.67]	0.01	62%	0.0001
5 years	4[14,15,16,21]	24.20%	41.30%	0.46 [0.33, 0.64]	0.48	0%	< 0.00001
Complications	5[14,17,18,19,21]	7.60%	31.60%	0.21 [0.08, 0.56]	0.002	77%	0.002

3.2.2. Three-year Overall Survival rate

The meta-analysis of 7 studies revealed that the 3-year overall survival rate in PRFA group (63.7%) was significantly lower than that in HR group (77.6%; OR, 0.44; 95% CI, 0.27-0.72; P=0.001; Table 2), with no heterogeneity (P = 0.008; I2 = 65%).

3.2.3. Five-year Overall Survival rate

The meta-analysis of 4 studies revealed that the 5-year overall survival rate in PRFA group (55.2%) was significantly lower than that in HR group (70.8%; OR, 0.49; 95% CI, 0.35-0.68; P<0.0001; Table 2), with no heterogeneity (P = 0.37; I2 = 4%).

3.3. Meta-analysis of Disease-free Survival Rates

3.3.1. One-year Disease-free Survival Rate

The meta-analysis of 8 studies revealed that the 1-year overall survival rate in PRFA group (71.2%) was significantly lower than that in HR group (79.3%; OR, 0.63; 95% CI, 0.49-0.82; P=0.0006; Table 2), with no heterogeneity (P = 0.13; I2 = 38%).

3.3.2. Three-year Disease-free Survival Rate

The meta-analysis of 7 studies revealed that the 3-year overall survival rate in PRFA group (36.4%) was significantly lower than that in HR group (54.1%; OR, 0.45; 95% CI, 0.30-0.67; P=0.0001; Table 2), with no heterogeneity (P = 0.01; I2 = 62%).

3.3.3. Five-year Disease-free Survival Rate

The meta-analysis of 4 studies revealed that the 5-year overall survival rate in PRFA group (24.2%) was significantly lower than that in HR group (41.3%; OR, 0.46; 95% CI, 0.33-0.64; P<0.00001; Table 2), with no heterogeneity (P = 0.48; I2 = 0%).

3.4. Meta-analysis of Complications

The meta-analysis of 5 studies revealed that the postoperative complication in PRFA group (7.6%) was significantly lower than that in HR group (31.6%; OR, 0.21; 95% CI, 0.08-0.56; Table 2), with no heterogeneity (P = 0.002; I2 = 77%).

3.5. Sensitivity Analysis and Publication Bias

The primary outcomes were used to conduct sensitivity analysis. The results were similar, which means that combined results were highly reliable. Because the number of original studies was less than ten, the funnel plot is not suitable for assessing publication bias.

4. Discussion

Hepatic carcinoma was a common malignant tumor, which may lead to an inferior prognosis when diagnosis and treatment are not made in time. Until now, mechanisms about this cancer are still not presented clearly and thoroughly. Besides, available preventive methods about this disease were also not provided in detail. So, once it occurred, early treatment was a realistic and recognized strategy for it [24]. Small hepatic carcinoma was a special type of hepatic carcinoma, which was usually found in the early stage and considered to tend to own a relatively better prognosis. Lots of methods have come into being, surgery or not surgery, however the best one was still under consideration [25,26,27].

Until now, amounts of studies have explored and ensured the curative effects of both SR and PRFA in the treatment of small hepatic carcinoma. With the wide use of SR, the public commonly considered that the tumor could be eradicated because this operation can be conducted under direct vision. Compared with PRFA, however, SR has a larger trauma and a longer postoperative recovery time. Besides, SR may not be used for the patients with an inferior liver function or serious hepatic cirrhosis. In this way, PRFA may be an alterative in the treatment of small hepatic carcinoma. As thus, which one is better is really controversial. In order to solve this problem, we designed and conducted this meta-analysis. It could be indicated that surgical resection had significantly better survival rates in terms of overall survival rates in 1-year, 3-year, and 5-year, and disease-free survival rates in 1-year, 3-year, and 5-year. This could be partly explained by the increased understanding of liver segmental anatomy, perioperative care and the improvements

in surgical techniques. All these improvements have led to a dramatic decrease in operative mortality and an improvement in surgical outcome [28].

PRFA is a mini-invasive and target-selective technique, which can induce thermal lesions less than 2.5 to 3.5cm in diameter, using single or multiple expandable-tip electrodes [29]. RFA can be performed through percutaneous route, laparoscopic route or open approaches [30]. However, PRFA also has some limitations. If some tumors locate too close to other organs, like kidney, colon, or gallbladder, PRFA might not be recommended for fear of damages to important organs induced by heat. Besides, if the lesion is adjacent to big vessels, the tumor may also not be completely ablated because of heat-sink effect. The safety margin of PRFA is so narrower than that of SR, so PRFA is more prone to cause insufficient ablation of the primary tumor. SR could be used to efficiently excise the entire Couinaud segments containing tumors and possible venous tumor thrombus [31].

This meta-analysis suggested that the incidence of postoperative complications in PRFA group was less than that in SR group, which to some extent embodied mini-invasive characteristic of PRFA. PRFA has a smaller invasion and destroys tumors by heat energy. The patients could maintain conscious when this procedure was performed and only spend a shorter hospital stay after this operation [32].

There were also some limitations in our study. First, studies included in our meta analysis is so limited. This may lead to false positive or false negative conclusions (risk of random errors). Second, some data in the present study came from NRCT, which would partly have an effect on the overall level of clinical evidence. Third, there has been some statistical heterogeneity in our study, which may come from different demographics and tumor characteristics in each study. So, more studies should be designed with high methodological qualities to confirm the conclusion of our study.

5. Conclusions

This meta-analysis highly suggested that surgical resection was superior to PRFA in the treatment of patients with small hepatic carcinoma. But PRFA has characteristics of smaller invasion, shorter hospitalization time and lower incidence of postoperative complications. For patients who are unwilling to accept the method of surgical resection, PRFA may be an alterative.

Conflict of Interest Statement

None.

Author Contributions

Conceived and designed the experiments: Li Xin. Performed the experiments: Li Xin, Yun-bing Wang. Analyzed the data: Yun-bing Wang, Jian-ping Gong. Contributed reagents/materials/analysis tools: Yun-bing Wang, Jian-ping Gong. Wrote the paper: Yun-bing Wang. Modification of initial manuscript: Jian-ping Gong.

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