Clinical outcome of small hepatocellular carcinoma after different treatments: A meta-analysis

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Abstract

AIM: To compare clinical outcomes between surgical resection (RES) and nonsurgical-RES (nRES) ablation therapies for small hepatocellular carcinoma (HCC).

METHODS: MEDLINE, Embase and Cochrane Library databases were systematically searched for studies of RES and nRES treatments for small HCC between January 2003 and October 2013. The clinical outcome measures evaluated included overall survival rate, disease-free survival rate, adverse events, and local recurrence rate. Odds ratios (ORs) with 95% CIs were calculated using either the fixed effects model or random effects model. The $\chi^2$ and $I^2$ tests were calculated to assess the heterogeneity of the data. Funnel plots were used to assess the risk of publication bias.

RESULTS: Our analysis included 12 studies that consisted of a total of 1952 patients (RES vs nRES), five studies that consisted of 701 patients [radiofrequency ablation (RFA) vs percutaneous ethanol injection (PEI)], and five additional studies [RFA vs RFA + transcatheter arterial chemoembolization (TACE)] that all addressed the treatment of small HCC. For cases of RES vs nRES, there was no significant difference in the 1-year (OR = 0.99, 95% CI: 0.87-1.12, $P = 0.85$) or 3-year (OR = 0.97, 95% CI: 0.84-1.11, $P = 0.98$) overall survival rate; however, there was a significant increase in the RES group in the 5-year overall survival rate (OR = 0.81, 95% CI: 0.68-0.95, $P = 0.01$). The 1-year (OR = 0.94, 95% CI: 0.82-1.08, $P = 0.37$) and 5-year (OR = 0.99, 95% CI: 0.85-1.14, $P = 0.85$) disease-free survival rates showed no significant differences between the two groups. The 3-year disease-free survival rate (OR = 0.81, 95% CI: 0.69-0.96, $P = 0.02$) was higher in the RES group. For cases of RFA vs PEI, our data analysis indicated that RFA treatment was associated with significantly higher 2-year (OR = 0.76, 95% CI: 0.58-0.99, $P = 0.043$) and 3-year (OR = 0.73, 95% CI: 0.54-0.98, $P = 0.039$) overall survival rates; however, there were no significant differences in the 1-year (OR = 0.92, 95% CI: 0.72-1.17, $P = 0.0502$) overall survival rate or incidence of adverse events (OR = 1.84, 95% CI: 0.76-4.45, $P = 0.173$). For cases of RFA vs RFA+TACE, there were no significant differences in the 1-year (OR = 1.17, 95% CI: 0.88-1.56, $P = 0.27$) or 3-year (OR = 1.25, 95% CI: 0.90-1.73, $P = 0.183$) overall survival rate; however, the 5-year overall survival rate (OR = 3.19, 95% CI: 1.51-6.74, $P = 0.002$) in patients treated by RFA+TACE was higher than that treated by RFA alone.

CONCLUSION: Surgical resection is superior to nonsurgical ablation for the treatment of small HCC. Among the studies analyzed, RFA is the most efficacious single nonsurgical ablation treatment.
INTRODUCTION

Hepatocellular carcinoma (HCC) is a common malignancy, its incidence is increasing worldwide, and it is responsible for thousands of deaths every year[1]. The definition of small HCC in the Milan criteria consists of a single HCC nodule < 5 cm or up to 3 nodules and a maximum diameter of each nodule < 3 cm. As a result of technological improvements, the number of therapeutic modalities available for HCC has increased dramatically. In addition to the traditional surgical resection and liver transplantation, other surgical therapies, such as transcatheter arterial chemoembolization (TACE), radiofrequency ablation (RFA), percutaneous ethanol injection (PEI), and percutaneous microwave coagulation therapy (MCT), have also been used[2]. Theoretically, the best treatment for small HCC is liver transplantation, but the scarcity of donor organs and high costs constrain the use of this treatment[3,4]. Therefore, the demand for novel treatment strategies for small HCC has been raised in both surgical resection (RES) and non-surgical RES (nRES) cases. Both RES and nRES treatments are recommended, and the recommendations range from an evidence-based guideline in Japan to guidelines established by the American Association for the Study of Liver Disease[5,6]. RES has been used as the standard treatment for small HCC for a long period, and in clinical studies, Takayama et al[3] reported that RES had more advantages over other treatments (i.e., survival and recurrence rate) regardless of the tumor size. However, other clinical outcomes showed that some non-surgical ablation methods, such as RFA, could achieve a similar therapeutic effect while significantly avoiding postoperative complications[5]. Thus, alternative therapies for small HCC are controversial. In previous studies, a meta-analysis was conducted on cases of RES vs RFA or RES vs other single non-surgical ablation methods. Our meta-analysis was designed to determine the superior choice of treatment for small hepatocellular carcinoma from among surgical resection and non-surgical ablation methods.

MATERIALS AND METHODS

Study selection

A search was performed using MEDLINE, Embase, and Cochrane Library databases for publications dated from January 2003 to October 2013 by two investigators separately. The corresponding author was consulted when the criteria for inclusion or exclusion of a study were controversial. The following MeSH search headings in English were used: hepatocellular carcinoma, HCC, liver cancer, hepatic tumor, liver resection, surgical resection, hepatectomy, radiofrequency ablation, microwave, high-intensity focused ultrasound, cryoablation, ethanol, and acetic acid.

Criteria for inclusion

To be eligible for the meta-analysis, a study had to fulfill the following criteria: (1) treatment of HCC by RES vs nRES or nRES vs nRES; (2) tumor size meeting the Milan criteria; (3) no antitumor treatment before the intervention; (4) no previous or simultaneous malignancies; and (5) description of the details of overall survival rate, recurrence-free survival rate, tumor progression rate, and major complications.

Criteria for exclusion

The study was excluded if it (1) dealt with recurrent HCC or metastatic carcinoma; (2) did not have appropriate data or could not allow to extract available data from the published results; or (3) was an abstract or review without original data. If two or more similar studies were reported by the same author in one institution, the one with higher quality was included or the largest one was included if they were of same quality.

Statistical analysis

The meta-analysis was performed using State Software (State 12). The odds ratios (OR) with 95%CI were calculated using either the fixed-effect or random-effect model depending on the absence or presence of significant heterogeneity. The $\chi^2$ and I$^2$ tests were calculated to assess heterogeneity. We considered an $I^2 > 50\%$ as significant heterogeneity, and a P-value < 0.05 was considered statistically significant. If $P < 0.05$ and $I^2 > 50\%$, the random-effect model was used; otherwise, the fixed effects model was used. Funnel plots were used to assess the risk of publication bias.

RESULTS

Included studies

MEDLINE, Embase, and Cochrane Library databases
Table 1 Characteristics of cases using surgical resection vs nonsurgical ablations

| Ref.       | Treatment | M/F | Mean tumor size (cm) | Mean age (yr) | Mean AFP (ng/mL) | Child-Pugh A/B | Mean follow-up (mo) |
|------------|-----------|-----|----------------------|---------------|------------------|----------------|---------------------|
| Huang et al\(^{[9]}\) | PEI       | 19/19 | 2.0 (n = 21)         | 63 ± 10.9     | > 200 (n = 7)     | 29/3           | 37.7 ± 14.5         |
|            | RES       | 27/11 | 2.0 (n = 24)         | 59 ± 11.4     | > 200 (n = 8)     | 28/0           | 38.4 ± 16.4         |
| Chen et al\(^{[9]}\) | RFA       | 56/15 | 3.0 (n = 37)         | 51.9 ± 11.2   | > 200 (n = 31)    | 71/0           | 27.9 ± 10.6         |
|            | RES       | 75/15 | 3.0 (n = 42)         | 49.4 ± 10.9   | > 200 (n = 30)    | 90/0           | 29.2 ± 11.9         |
| Huang et al\(^{[9]}\) | RFA       | 85/30 | 3.0 (n = 45)         | 55.9 ± 12.68  | > 400 (n = 32)    | 106/9          | 37.2 (6-60)         |
|            | RES       | 79/36 | 3.0 (n = 57)         | 56.57 ± 14.30 | > 400 (n = 21)    | 110/5          | 46.4 (1-260)        |
| Feng et al\(^{[9]}\) | RFA       | 79/5  | 2.0 (n = 31)         | 51 (24-83)    | 215.5 (0.5-8530)  | 39/45          | 56               |
| Cho et al\(^{[9]}\) | PEI       | 86/30 | 2.0 (n = 43)         | 58.0 ± 9.7    | > 20 (n = 47)     | 92/24          | 68                |
| Chen et al\(^{[9]}\) | RFA       | 91/25 | 2.0 (n = 43)         | 56.0 ± 8.9    | > 20 (n = 47)     | 92/24          | 68                |
| Abe-Hilal et al\(^{[9]}\) | RFA    | 27/7  | 3.8 (1.3-5)          | 65            | -                | 27/7           | 30 (6-60)          |
| Ueno et al\(^{[9]}\) | RFA       | 100/55| 2.7 ± 0.1            | 66 (40-79)    | 131 ± 33          | -              | 36.8 ± 1.5         |
| Kazawa et al\(^{[9]}\) | RFA + TACE| 82/41 | 2.0 ± 0.1            | 67 (28-85)    | 382 ± 108         | -              | 35.0 ± 1.7         |
| Nishikawa et al\(^{[7]}\) | RFA      | 40/15 | 2.0 (n = 19)         | 67.5 ± 8.4    | > 400 (n = 5)     | -              | 49 (1-102)         |
| Guo et al\(^{[9]}\) | RFA       | 95/67 | 1.99 ± 0.62          | 68.4 ± 8.7    | 74.7 ± 181.1      | 102/22         | 37.2 (2-484)        |
| Guo et al\(^{[9]}\) | RES       | 50/19 | 2.68 ± 0.49          | 67.4 ± 9.7    | 376 ± 1989.8      | 45/5           | 39.6 (8-84)         |
| Kim et al\(^{[9]}\) | RFA + TACE| 31/6 | 3.46 ± 0.75          | 61.7 ± 11.1   | > 100 (n = 7)     | 37/0           | 29.9 ± 7.8         |
| Lai et al\(^{[9]}\) | RFA       | 36/11 | 3.66 ± 0.76          | 58.8 ± 10.7   | > 100 (n = 14)    | 45/2           | 31.7 ± 10          |
| Lai et al\(^{[9]}\) | RFA       | 19/12 | 1.8 ± 0.6            | 63.1 ± 12.8   | 201.3 (2-2221.9)  | -              | 35.1 ± 17.4        |
| RFA       | 55/25     | 2.9 ± 1.1            | 60.8 ± 9.9    | 256.5 (91.5-5193) | -              | 29.7 ± 19.9       |

RES: Resection; RFA: Radiofrequency ablation; PEI: Percutaneous ethanol injection; TACE: Transcatheter arterial chemoembolization; M: Male; F: Female; AFP: Alpha-fetoprotein.

Table 2 Characteristics of cases involving percutaneous ethanol injection vs radiofrequency ablation

| Ref.       | Treatment | M/F | Mean tumor size (cm) | Mean age (yr) | Mean AFP (ng/mL) | Child-Pugh A/B | Mean follow-up (mo) |
|------------|-----------|-----|----------------------|---------------|------------------|----------------|---------------------|
| Brunello et al\(^{[29]}\) | PEI       | 49/30 | 2.25 ± 0.54          | 70.3 ± 8.1    | 16.5 (MD)        | 39/30          | 25.3 (MD)          |
| Lin et al\(^{[9]}\) | RFA       | 43/27 | 2.42 ± 0.49          | 69.0 ± 7.7    | 22.0 (MD)        | 39/31          | 26.1 (MD)          |
| Shinya et al\(^{[9]}\) | PEI       | 34/18 | 2.8 ± 0.93           | 67 ± 6.0     | > 400 (n = 8)    | 39/12          | 23.8 ± 10.4        |
| Lin et al\(^{[9]}\) | RFA       | 35/17 | 2.9 ± 0.8            | 59 ± 10.0    | > 400 (n = 7)    | 41/11          | 24.5 ± 11.3        |
| Shi et al\(^{[9]}\) | RFA       | 36/17 | 2.0 (n = 57)         | 65 (n = 41)  | > 400 (n = 7)    | 85/29          | 2.9 (MD)           |
| Lin et al\(^{[9]}\) | RFA       | 39/23 | 2.3 ± 0.8            | 60.8 ± 4.0   | 400 (n = 9)      | 47/15          | 26 ± 12            |
| Lencioni et al\(^{[9]}\) | RFA | 30/22 | 2.5 ± 1.0            | 65 ± 10.0    | 400 (n = 10)     | 46/46          | 28 ± 12            |
| RFA       | 30/20     | 2.8 ± 0.8            | 69 ± 7.4     | 54 (MD)         | 35/15          | 22.4 ± 8.6         |
| RFA       | 36/16     | 2.8 ± 0.6            | 67 ± 6.0     | 54 (MD)         | 45/7           | 22.9 ± 9.4         |

PEI: Percutaneous ethanol injection; RFA: Radiofrequency ablation; M: Male; F: Female; AFP: Alpha-fetoprotein; MD: Median; RES: Resection.

were systematically searched for studies on RES vs nRES or nRES vs nRES treatments for small HCC published between January 2003 and October 2013. The identification of studies for inclusion was shown in Figure 1. Twelve studies of RES vs RFA \(^{[21-25]}\) (2 RCTs, Huang et al\(^{[9]}\) and Chen et al\(^{[9]}\), five studies of PEI vs PEI \(^{[5-9]}\), and five studies of RFA vs RFA + TACE \(^{[11,15,19,27,29]}\) were included.

Out of a total of 1952 patients, 953 were allocated to the RES group and 999 to the nRES group to evaluate the treatment options used for HCC. The age, mean tumor size, and mean AFP were well controlled by the study authors when patients were enrolled. Dynamic CT was performed in follow-up, and the follow-up time was considered to be sufficient. Main serious complications included liver failure, biliary fistula, abdominal bleeding, wound infection or dehiscence in the surgical group and pleural effusion, liver abscess, and abdominal bleeding in the RFA group. The demographic and clinical characteristics of the patients are shown in Table 1.

A total of 701 patients in five RCT studies were analyzed to compare PEI and RFA methods for the treatment of small HCC. Dynamic CT was performed in follow-up, and the clinical characteristics of the patients are shown in Table 2.

Five studies were used to compare TACE and radiofrequency ablation with radiofrequency ablation alone for small HCC; however, only Shibata et al\(^{[20]}\) and Zhao et al\(^{[21]}\) were specialized in the treatment of small HCC. We extracted data from Peng et al\(^{[22]}\), Morimoto et al\(^{[23]}\), and Cheng et al\(^{[24]}\) because the tumor sizes met the Milan criteria; however, there were limited patient descriptions.
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| Study ID | OR (95%CI) | weight |
|----------|------------|--------|
| Huang (2005) | 0.55 (0.26, 1.15) | 5.89 |
| Cho (2007) | 0.75 (0.49, 1.15) | 14.97 |
| Abu-Hilal (2008) | 1.05 (0.48, 2.31) | 3.74 |
| Ueno (2009) | 0.79 (0.55, 1.14) | 19.86 |
| Kagawa (2010) | 0.84 (0.48, 1.49) | 8.11 |
| Huang (2010) | 0.72 (0.46, 1.10) | 16.32 |
| Nishikawa (2011) | 0.85 (0.55, 1.32) | 13.33 |
| Guo (2013) | 0.80 (0.50, 1.27) | 12.14 |
| Lai (2013) | 1.18 (0.63, 2.19) | 5.64 |
| Overall (I² = 0.0%, P = 0.910) | 0.80 (0.68, 0.95) | 100.00 |

**RES vs nRES**

**Overall survival rate:** The meta-analysis shows that there was no significant difference between the two groups in the 1-year (all trials reported these data, OR = 0.99, 95%CI: 0.87-1.12, P = 0.85) or 3-year (11 trials reported these data, OR = 0.97, 95%CI: 0.84-1.11, P = 0.98) overall survival rate. However, there was a significant improvement in the 5-year overall survival rate in the RES group (nine trials reported these data, OR = 0.81, 95%CI: 0.68-0.95, P = 0.01) (Figure 2A).

**Disease-free survival rate:** The meta-analysis shows that there was no significant difference in the 1-year (all trials reported these data, OR = 0.94, 95%CI: 0.82-1.08, P = 0.37) or 5-year (nine trials reported these data, OR = 0.99, 95%CI: 0.85-1.14, P = 0.85) disease-free survival rate between the two groups. The 3-year disease-free survival rate (11 trials reported these data OR = 0.81, 95%CI: 0.69-0.96, P = 0.02) was better in the RES group (Figure 2B).

**Adverse events:** The meta-analysis (six trials reported these data) showed that there was a significant decrease in the incidence of adverse events in the RES group (OR = 0.22, 95%CI: 0.15-0.34, P < 0.01).

**Local recurrence rate:** The local recurrence rate until the end of the follow-up period (four trials reported these data) was significantly higher in the nRES group when compared with the RES group (OR = 1.83, 95%CI: 1.07-3.13, P = 0.03).

**RFA vs PEI**

**Survival rate:** Our meta-analysis indicated that there was no significant difference in the 1-year (OR = 0.92, 95%CI: 0.72-1.17, P = 0.0502) overall survival rate between the two groups; however, RFA treatment re-
sulted in significantly higher 2-year (OR = 0.76, 95%CI: 0.58-0.99, \( P = 0.043 \)) and 3-year (OR = 0.73, 95%CI: 0.54-0.98, \( P = 0.039 \)) overall survival rates (Figure 3A-C).

Adverse events: No significant differences in adverse events were found between the two groups (OR = 1.84, 95%CI: 0.76-4.45, \( P = 0.173 \)) (Figure 3D).

**RFA vs RFA + TACE**

Survival rate: There was no significant difference in the 1-year (OR = 1.17, 95%CI: 0.88-1.56, \( P = 0.27 \)) and 3-year (OR = 1.25, 95%CI: 0.90-1.73, \( P = 0.183 \)) survival rates. The 5-year survival rate (OR = 3.19, 95%CI: 1.51-6.74, \( P = 0.002 \)) in patients treated by RFA+TACE was higher than that by RFA alone (Figure 4A-C).

**Sensitivity analysis**
The test for heterogeneity showed that there was no significant heterogeneity by incorporating multiple studies. The fixed-effect model was used to calculate the survival rate and recurrence rate. The results were similar, and the combined results were highly reliable.

**Publication bias**
The publication bias in this study was detected using a funnel plot of 1-year overall survival rate and 5-year overall survival rate data (Figure 5). The basic symmetry
of the funnel plot suggested that there was no publication bias in these studies.

**DISCUSSION**

Small HCC is a common malignant disease, especially in Asian regions\(^{(31)}\). Because of the limitations of donor scarcity and high costs, surgical resection and certain nonsurgical ablation methods were frequently used for the treatment of small HCC. According to a search of the literature, radiofrequency ablation was the most common method used among various nonsurgical ablation techniques. Few clinical trials have emphasized the therapeutic effects of surgical resection vs other nonsur-
Hepatocellular carcinoma (HCC) is a common malignancy, its incidence is increasing worldwide, and it is responsible for thousands of deaths every year. Theoretically, the best treatment for small HCC is liver transplantation, but the scarcity of donor organs and high costs constrain the use of this treatment. Therefore, the demand for novel treatment strategies for small HCC has been raised for both surgical resection (RES) and nonsurgical-RES (nRES) cases. However, alternative therapies for small HCC are controversial. Hence, it is necessary to compare all the treatment options for small HCC, including surgical resection and nonsurgical ablation methods.

**Innovations and breakthroughs**

The current analysis comprehensively compared the effectiveness and safety of surgical resection and common nonsurgical ablation methods for the treatment of HCC. Meanwhile, it also provided evidence for the superior choice among nonsurgical ablation methods for treatment of small HCC. The analysis indicated that the overall and recurrence-free survival rates of patients in the resection group were significantly higher than those in patients who underwent radiofrequency ablation (RFA).

**Applications**

Surgical resection was superior to nonsurgical ablation methods in the treatment of small HCC in terms of longer survival; however, the incidence of adverse events after RES was higher than that after nRES. Among the studies analyzed, RFA is the best nonsurgical ablation method; and the combination of transcatheter arterial chemoembolization (TACE) and RFA was more efficacious than RFA alone.

**Terminology**

The principle of RFA is that heat generated by high radiofrequency waves inactivates local tumor cells quickly and effectively. Anhydrous alcohol dehydrates cancer cells, which degenerates and necrotizes them directly, and thus promotes tumor intravascular thrombosis. For TACE, a designated amount of embolization agents is injected into the target artery to produce ischemic necrosis of the tumor tissue. When compared with RES, these methods significantly reduce the physical injury and liver dysfunction that may lead to increased hospitalization.

In conclusion, surgical resection was superior to nonsurgical ablation methods for the treatment of small HCC in terms of a longer survival rate. However, the incidence of adverse events after RES was higher than that after nRES. We acknowledge that the number of cases undergoing PEI and TACE was insufficient, but the studies that we assessed suggest that RFA is the best single nonsurgical ablation method. However, RFA plus TACE was better than RFA alone for the treatment of small HCC.
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