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

Dong W *et al*. Clinical Outcome of small hepatocellular carcinoma with different treatments

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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 (OR) with 95%CI were calculated using either the fixed effects model or random effects model. The *χ*2 and I2 tests were calculated to assess the heterogeneity of the data. Funnel plots were used to access the risk of publication bias.

**RESULTS:**Our analysis included twelve studies that consisted of a total of 1952 patients (RES *vs* nRES), five studies that consisted of 701 patients [radiofrequency ablation (RFA) *vs* PEI], and five additional studies (RFA *vs* RFA+TACE) that all addressed the treatment of small HCC and were published between January 2003 and October 2013. For cases of RES *vs* nRES, there was no significant difference between these two groups in the 1-year (OR = 0.99, 95%CI: 0.87-1.12, *P* = 0.85) and 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 for 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 difference 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 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) and 3-year (OR = 1.25, 95%CI: 0.90-1.73, *P* = 0.183) overall survival rates; however, the 5-year overall survival rate (OR = 3.19, 95%CI: 1.51-6.74, *P* = 0.002) in patients treated with RFA + TACE was higher than for RFA treatment 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.

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**Key words:** Hepatocellular carcinoma; Meta-analysis; Surgical resection; Nonsurgical ablation; Radiofrequency ablation; Percutaneous ethanol injection; Recurrence; Survival

**Core tip:** The efficacy of surgical resection over nonsurgical ablation for the treatment of small hepatocellular carcinoma has long been debated. In previous studies, a meta-analysis was conducted on cases of resection (RES) *vs* radiofrequency ablation or RES *vs* other single nonsurgical ablation methods. Our meta-analysis was designed to determine the superior choice of treatment for small hepatocellular carcinoma from among surgical resection and nonsurgical ablation methods.

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**INTRODUCTION**

Hepatocellular carcinoma is a common malignancy, its incidence is increasing worldwide, and it is responsible for thousands of deaths every year[[1](#_ENREF_1)]. The definition of small hepatocellular carcinoma in the Milan criteria consists of a single hepatocellular carcinoma (HCC) < 5 cm or up to 3 nodules and a maximum diameter of each nodule < 3 cm. As a result of technological improvements, the therapeutic modalities for HCC have 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](#_ENREF_2)]. Theoretically, the best treatment for small HCC is liver transplantation, but the scarcity of donor organs and high costs constrain this treatment[[3](#_ENREF_3), [4](#_ENREF_4)]. Therefore, the demand for novel treatment strategies of small HCC have been raised in both surgical resection (RES) and 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](#_ENREF_5),[6](#_ENREF_6)]. RES has been used as the standard treatment of small HCC for a long period, and in clinical studies, Takayama and colleagues reported that RES had more advantages over other treatments (*i.e.,* survival and recurrence rate) regardless of the tumor size[[7](#_ENREF_7)]. However, other clinical outcomes showed that some nonsurgical ablation methods, such as RFA, could achieve a similar therapeutic effect while significantly avoiding postoperative complications[[8](#_ENREF_8)]. Thus, alternative therapies for small HCC are controversial. In previous studies, a meta-analysis was conducted on cases of RES versus RFA or RES versus other single nonsurgical ablation methods. Our meta-analysis was designed to determine the superior choice for treatment of small HCC out of surgical resection and nonsurgical 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, acetic acid.

***Criteria for inclusion***

To be eligible for the meta-analysis, a study had to fulfill the following criteria: (1) the treatment of HCC in RES versus nRES or nRES versus nRES; (2) the size of the tumor met 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 was present.

***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 extract available data from the published results; (3) 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; or (4) was an abstract or review without original data.

***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 *χ*2 and *I*2 tests were calculated to assess heterogeneity. We considered an *I*2 > 50% as significant heterogeneity, and a *P* < 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 access the risk of publication bias.

**RESULTS**

***Included studies***

MEDLINE, Embase, and Cochrane Library databases were systematically searched for studies that published on RES *vs* nRES treatments or nRES *vs* nRES methods for small HCC between January 2003 and October 2013. Twelve studies of RES *vs* RES[9-20] (2 RCT, Huang *et al*[9] and Chen *et al*[10]), five studies[21-25] of RFA *vs* PEI (5 RCT), and five studies[26-30] of RFA vs RFA+TACE (1 nRCT, Zhao *et al*[27]) were included.

Out of a total of 1952 patients, 953 were allocated to the RES group and 999 were allocated 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. The 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 patients are shown in Table 1.

A total of 701 patients in five RCT studies were analyzed to compare percutaneous ethanol injection (PEI) and radiofrequency ablation (RFA) methods for the treatment of small hepatocellular carcinoma. Dynamic CT was performed in follow-up, and the clinical characteristics of patients are shown in Table 2.

Five studies were used to compare transcatheter arterial chemoembolization (TACE) and radiofrequency ablation with radiofrequency ablation alone for small hepatocellular carcinoma; however, only Shibata *et al*[26] and Zhao *et al*[27] were specialized in the treatment of small HCC. We extracted data from Peng *et al*[28], Morimoto *et al*[29], and Cheng *et al*[30] because the patients’ tumor sizes met the Milan criteria; however, there were limited patient descriptions.

***RES vs nRES***

**Overall survival rate:** The meta-analysis shows that there was no significant difference between the two groups for the 1-year (all trials reported these data, OR = 0.99, 95%CI: 0.87-1.12, *P* = 0.85) and 3-year (eleven 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 RES group for the 5-year overall survival rate (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) and 5-year (nine trials reported these data, OR = 0.99, 95%CI: 0.85-1.14, *P* = 0.85) rates between the two groups. The 3-year disease-free survival rate (eleven 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 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 up 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 two groups; however, RFA treatment resulted in a 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 rate (Figure 3 A, B and 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 3 D).

***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 with RFA + TACE was higher than that of RFA alone (Figure 4 A, B and 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 recurrences for the treatment of small HCC. 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 other 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 the various nonsurgical ablation techniques. Few clinical trials have emphasized the therapeutic effects of surgical resection versus other nonsurgical methods, and a very limited number of high quality RCTs were available.

Our meta-analysis suggested that the incidence of adverse events after nRES for the treatment of HCC was lower than the RES group, which might be explained by the specific characteristics of these therapies. The main nonsurgical therapies included were RFA, PEI and TACE. The principle of RFA is that heat generated by high radio frequency waves inactivates local tumor cells quickly and effectively. In PEI, 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 function damage that lead to increased hospitalization.

In our meta-analysis, we showed that the local recurrence rate was higher after RFA than RES, which can be potentially accounted for in two ways. First, the safety margin of RFA was narrower than that of RES[32]. Second, the nRES methods were not able to find the potential sites of microscopic diseases; therefore, the clearance of tumors is more complete in RES because the method usually involves the removal of the entire tumor-containing segment[33].

Although RFA has been suggested to cause more complications than nRES, patients treated by RFA had a longer overall survival rate and disease-free survival rate. This may be due to low local recurrences and improvements in surgical techniques, including surgical maneuvers and technical innovations. Many studies have suggested that anatomic resection seems to be superior to nonanatomic resection because of poorer liver function reserve in the nonanatomic resection group[34]. Additionally, the use of a laparoscope and the da Vinci Surgical System may also reduce prognostic risk factors, leading to a long survival[35].

Our analysis of RFA and PEI treatments for small HCC indicated that RFA was associated with a significantly longer overall survival rate. This maybe be due to a lower recurrence in the RFA group[22]. The reported major complications vary from study to study. Livraghi *et al*[36] and Lencioni *et al*[25] concluded that the risk of adverse events was significantly higher after PEI treatments. These results were similar to those reported by Shiina *et al*[23]. However, there was no significant difference between these two groups in our meta-analysis. A few studies have assessed RFA versus RFA plus TACE treatments for small HCC; however, there was limited useful data that could be extracted. Our study showed that the overall survival rate of patients who were treated with RFA plus TACE was higher than that of RFA treatment alone. The efficacy of RFA can be enhanced by occlusion of the hepatic artery because the blood supply to a classical HCC is primarily provided by the hepatic artery. In the TACE plus RFA group, a larger area that included regions of the surrounding nontumorous liver parenchyma was coagulated[29].

For our meta-analysis, we searched through the relatively recent literature for multiple nRES trials to complete a comprehensive analysis of indicators. RCT and NRCT trials were both included in this study because very few quality RCT trials were available. We also acknowledge that the trials for nonsurgical ablation were insufficient, which might be due to the primary selection of RFA among nRES methods in clinical work. Thus, additional data are needed to obtain a more accurate conclusion.

In conclusion, surgical resection was superior to nonsurgical ablation methods for the treatment of small HCC based on a longer survival rate. However, the adverse events after RES were higher than that of nRES cases. We acknowledge that the cases using PEI and TACE were 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.

**COMMENTS**

***Background***

Hepatocellular carcinoma 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 hepatocellular carcinoma (HCC) is liver transplantation, but the scarcity of donor organs and high costs constrain the use this treatment. Therefore, the demand for novel treatment strategies of small HCC has been raised for both surgical resection (RES) and 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.

***Research frontiers***

Meta-analysis, a quantitative technique for therapeutic evaluation, may be used when controversy persists after several studies. Our meta-analysis was designed to determine the superior treatment for small HCC from among surgical resection and common nonsurgical ablation methods.

***Innovations and breakthroughs***

Our 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. Our analysis indicated that the overall and recurrence-free survival rates of patients in the resection group were significantly higher than those that underwent radiofrequency ablation (RFA).

***Applications***

Surgical resection was superior to nonsurgical ablation methods in the treatment of small HCC for long survival rates; however, the adverse events after RES were higher than that of nRES cases. Among the studies analyzed, RFA is the best nonsurgical ablation method, and the combination of TACE and RFA was more efficacious than RFA alone.

***Terminology***

The principle of RFA is that heat generated by high radio frequency waves inactivates the local tumor cells quickly and effectively. Anhydrous alcohol dehydrates cancer cells, which degenerates and necrotizes the cells directly and promotes tumor intravascular thrombosis. For TACE, a designated amount of embolization agents are injected into the target artery to produce ischemic necrosis of the tumor tissue. All of these methods are common ablation methods for small HCC.

***Peer review***

This is an important subject. Meta-analysis, a quantitative technique for therapeutic evaluation, may be used when controversy persists after several studies.

**REFERENCES**

1 **Llovet JM**, Burroughs A, Bruix J. Hepatocellular carcinoma. *Lancet* 2003; **362**: 1907-1917 [PMID: 14667750 DOI: 10.1016/S0140-6736(03)14964-1]

2 **Li L**, Zhang J, Liu X, Li X, Jiao B, Kang T. Clinical outcomes of radiofrequency ablation and surgical resection for small hepatocellular carcinoma: a meta-analysis. *J Gastroenterol Hepatol* 2012; **27**: 51-58 [PMID: 22004366 DOI: 10.1111/j.1440-1746.2011.06947.x]

3 **Duan C**, Liu M, Zhang Z, Ma K, Bie P. Radiofrequency ablation versus hepatic resection for the treatment of early-stage hepatocellular carcinoma meeting Milan criteria: a systematic review and meta-analysis. *World J Surg Oncol* 2013; **11**: 190 [PMID: 23941614 DOI: 10.1186/1477-7819-11-190]

4 **Merchant N**, David CS, Cunningham SC. Early Hepatocellular Carcinoma: Transplantation versus Resection: The Case for Liver Resection. *Int J Hepatol* 2011; **2011**: 142085 [PMID: 21994848 DOI: 10.4061/2011/142085]

5 **Makuuchi M**, Kokudo N, Arii S, Futagawa S, Kaneko S, Kawasaki S, Matsuyama Y, Okazaki M, Okita K, Omata M, Saida Y, Takayama T, Yamaoka Y. Development of evidence-based clinical guidelines for the diagnosis and treatment of hepatocellular carcinoma in Japan. *Hepatol Res* 2008; **38**: 37-51 [PMID: 18039202 DOI: 10.1111/j.1872-034X.2007.00216.x]

6 **Bruix J**, Sherman M. Management of hepatocellular carcinoma. *Hepatology* 2005; **42**: 1208-1236 [PMID: 16250051 DOI: 10.1002/hep.20933]

7 **Takayama T**, Makuuchi M, Hasegawa K. Single HCC smaller than 2 cm: surgery or ablation?: surgeon's perspective. *J Hepatobiliary Pancreat Sci* 2010; **17**: 422-424 [PMID: 19936598 DOI: 10.1007/s00534-009-0239-7]

8 **Livraghi T**, Meloni F, Di Stasi M, Rolle E, Solbiati L, Tinelli C, Rossi S. Sustained complete response and complications rates after radiofrequency ablation of very early hepatocellular carcinoma in cirrhosis: Is resection still the treatment of choice? *Hepatology* 2008; **47**: 82-89 [PMID: 18008357 DOI: 10.1002/hep.21933]

9 **Huang GT**, Lee PH, Tsang YM, Lai MY, Yang PM, Hu RH, Chen PJ, Kao JH, Sheu JC, Lee CZ, Chen DS. Percutaneous ethanol injection versus surgical resection for the treatment of small hepatocellular carcinoma: a prospective study. *Ann Surg* 2005; **242**: 36-42 [PMID: 15973099 DOI: 10.1097/01.sla.0000167925.90380.fe]

10 **Chen MS**, Li JQ, Zheng Y, Guo RP, Liang HH, Zhang YQ, Lin XJ, Lau WY. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. *Ann Surg* 2006; **243**: 321-328 [PMID: 16495695 DOI: 10.1097/01.sla.0000201480.65519.b8]

11 **Huang J**, Yan L, Cheng Z, Wu H, Du L, Wang J, Xu Y, Zeng Y. A randomized trial comparing radiofrequency ablation and surgical resection for HCC conforming to the Milan criteria. *Ann Surg* 2010; **252**: 903-912 [PMID: 21107100 DOI: 10.1097/SLA.0b013e3181efc656]

12 **Feng K**, Yan J, Li X, Xia F, Ma K, Wang S, Bie P, Dong J. A randomized controlled trial of radiofrequency ablation and surgical resection in the treatment of small hepatocellular carcinoma. *J Hepatol* 2012; **57**: 794-802 [PMID: 22634125 DOI: 10.1016/j.jhep.2012.07.022]

13 **Cho YB**, Lee KU, Suh KS, Kim YJ, Yoon JH, Lee HS, Hahn S, Park BJ. Hepatic resection compared to percutaneous ethanol injection for small hepatocellular carcinoma using propensity score matching. *J Gastroenterol Hepatol* 2007; **22**: 1643-1649 [PMID: 17845692 DOI: 10.1111/j.1440-1746.2007.04902.x]

14 **Abu-Hilal M**, Primrose JN, Casaril A, McPhail MJ, Pearce NW, Nicoli N. Surgical resection versus radiofrequency ablation in the treatment of small unifocal hepatocellular carcinoma. *J Gastrointest Surg* 2008; **12**: 1521-1526 [PMID: 18592325 DOI: 10.1007/s11605-008-0553-4]

15 **Ueno S**, Sakoda M, Kubo F, Hiwatashi K, Tateno T, Baba Y, Hasegawa S, Tsubouchi H. Surgical resection versus radiofrequency ablation for small hepatocellular carcinomas within the Milan criteria. *J Hepatobiliary Pancreat Surg* 2009; **16**: 359-366 [PMID: 19300896 DOI: 10.1007/s00534-009-0069-7]

16 **Kagawa T**, Koizumi J, Kojima S, Nagata N, Numata M, Watanabe N, Watanabe T, Mine T. Transcatheter arterial chemoembolization plus radiofrequency ablation therapy for early stage hepatocellular carcinoma: comparison with surgical resection. *Cancer* 2010; **116**: 3638-3644 [PMID: 20564097 DOI: 10.1002/cncr.25142]

17 **Nishikawa H**, Inuzuka T, Takeda H, Nakajima J, Matsuda F, Sakamoto A, Henmi S, Hatamaru K, Ishikawa T, Saito S, Nasu A, Kita R, Kimura T, Arimoto A, Osaki Y. Comparison of percutaneous radiofrequency thermal ablation and surgical resection for small hepatocellular carcinoma. *BMC Gastroenterol* 2011; **11**: 143 [PMID: 22204311 DOI: 10.1186/1471-230x-11-143]

18 **Guo WX**, Sun JX, Cheng YQ, Shi J, Li N, Xue J, Wu MC, Chen Y, Cheng SQ. Percutaneous radiofrequency ablation versus partial hepatectomy for small centrally located hepatocellular carcinoma. *World J Surg* 2013; **37**: 602-607 [PMID: 23212793 DOI: 10.1007/s00268-012-1870-z]

19 **Kim JW**, Shin SS, Kim JK, Choi SK, Heo SH, Lim HS, Hur YH, Cho CK, Jeong YY, Kang HK. Radiofrequency ablation combined with transcatheter arterial chemoembolization for the treatment of single hepatocellular carcinoma of 2 to 5 cm in diameter: comparison with surgical resection. *Korean J Radiol* ; **14**: 626-635 [PMID: 23901320 DOI: 10.3348/kjr.2013.14.4.626]

20 **Lai EC**, Tang CN. Radiofrequency ablation versus hepatic resection for hepatocellular carcinoma within the Milan criteria--a comparative study. *Int J Surg* 2013; **11**: 77-80 [PMID: 23220487 DOI: 10.1016/j.ijsu.2012.11.019]

21 **Brunello F**, Veltri A, Carucci P, Pagano E, Ciccone G, Moretto P, Sacchetto P, Gandini G, Rizzetto M. Radiofrequency ablation versus ethanol injection for early hepatocellular carcinoma: A randomized controlled trial. *Scand J Gastroenterol* 2008; **43**: 727-735 [PMID: 18569991 DOI: 10.1080/00365520701885481]

22 **Lin SM**, Lin CJ, Lin CC, Hsu CW, Chen YC. Randomised controlled trial comparing percutaneous radiofrequency thermal ablation, percutaneous ethanol injection, and percutaneous acetic acid injection to treat hepatocellular carcinoma of 3 cm or less. *Gut* 2005; **54**: 1151-1156 [PMID: 16009687 DOI: 10.1136/gut.2004.045203]

23 **Shiina S**, Teratani T, Obi S, Sato S, Tateishi R, Fujishima T, Ishikawa T, Koike Y, Yoshida H, Kawabe T, Omata M. A randomized controlled trial of radiofrequency ablation with ethanol injection for small hepatocellular carcinoma. *Gastroenterology* 2005; **129**: 122-130 [PMID: 16012942 DOI: 10.1053/j.gastro.2005.04.009]

24 **Lin SM**, Lin CJ, Lin CC, Hsu CW, Chen YC. Radiofrequency ablation improves prognosis compared with ethanol injection for hepatocellular carcinoma lt; or =4 cm. *Gastroenterology* 2004; **127**: 1714-1723 [PMID: 15578509]

25 **Lencioni RA**, Allgaier HP, Cioni D, Olschewski M, Deibert P, Crocetti L, Frings H, Laubenberger J, Zuber I, Blum HE, Bartolozzi C. Small hepatocellular carcinoma in cirrhosis: randomized comparison of radio-frequency thermal ablation versus percutaneous ethanol injection. *Radiology* 2003; **228**: 235-240 [PMID: 12759473 DOI: 10.1148/radiol.2281020718]

26 **Shibata T**, Isoda H, Hirokawa Y, Arizono S, Shimada K, Togashi K. Small hepatocellular carcinoma: is radiofrequency ablation combined with transcatheter arterial chemoembolization more effective than radiofrequency ablation alone for treatment? *Radiology* 2009; **252**: 905-913 [PMID: 19567647 DOI: 10.1148/radiol.2523081676]

27 **Zhao M**, Wang JP, Li W, Huang ZL, Zhang FJ, Fan WJ, Zhang L, Li XS, Pan CC, Wu PH. [Comparison of safety and efficacy for transcatheter arterial chemoembolization alone and plus radiofrequency ablation in the treatment of single branch portal vein tumor thrombus of hepatocellular carcinoma and their prognosis factors]. *Zhonghua Yi Xue Za Zhi* 2011; **91**: 1167-1172 [PMID: 21756768]

28 **Peng ZW**, Zhang YJ, Chen MS, Xu L, Liang HH, Lin XJ, Guo RP, Zhang YQ, Lau WY. Radiofrequency ablation with or without transcatheter arterial chemoembolization in the treatment of hepatocellular carcinoma: a prospective randomized trial. *J Clin Oncol* 2013; **31**: 426-432 [PMID: 23269991 DOI: 10.1200/jco.2012.42.9936]

29 **Morimoto M**, Numata K, Kondou M, Nozaki A, Morita S, Tanaka K. Midterm outcomes in patients with intermediate-sized hepatocellular carcinoma: a randomized controlled trial for determining the efficacy of radiofrequency ablation combined with transcatheter arterial chemoembolization. *Cancer* 2010; **116**: 5452-5460 [PMID: 20672352 DOI: 10.1002/cncr.25314]

30 **Cheng BQ**, Jia CQ, Liu CT, Fan W, Wang QL, Zhang ZL, Yi CH. Chemoembolization combined with radiofrequency ablation for patients with hepatocellular carcinoma larger than 3 cm: a randomized controlled trial. *JAMA* 2008; **299**: 1669-1677 [PMID: 18398079 DOI: 10.1001/jama.299.14.1669]

31 **Teo EK**, Fock KM. Hepatocellular carcinoma: an Asian perspective. *Dig Dis* 2001; **19**: 263-268 [PMID: 11935085 DOI: 10.1159/000050692]

32 **Makuuchi M**, Hasegawa H, Yamazaki S. Ultrasonically guided subsegmentectomy. *Surg Gynecol Obstet* 1985; **161**: 346-350 [PMID: 2996162]

33 **Makuuchi M**, Hasegawa H, Yamazaki S, Takayasu K, Moriyama N. The use of operative ultrasound as an aid to liver resection in patients with hepatocellular carcinoma. *World J Surg* 1987; **11**: 615-621 [PMID: 2823489]

34 **Cucchetti A**, Cescon M, Ercolani G, Bigonzi E, Torzilli G, Pinna AD. A comprehensive meta-regression analysis on outcome of anatomic resection versus nonanatomic resection for hepatocellular carcinoma. *Ann Surg Oncol* 2012; **19**: 3697-3705 [PMID: 22722807 DOI: 10.1245/s10434-012-2450-z]

35 **Bentas W**, Wolfram M, Jones J, Bräutigam R, Kramer W, Binder J. Robotic technology and the translation of open radical prostatectomy to laparoscopy: the early Frankfurt experience with robotic radical prostatectomy and one year follow-up. *Eur Urol* 2003; **44**: 175-181 [PMID: 12875935 DOI: 10.1016/s0302-2838(03)00256-2]

36 **Livraghi T**, Goldberg SN, Lazzaroni S, Meloni F, Solbiati L, Gazelle GS. Small hepatocellular carcinoma: treatment with radio-frequency ablation versus ethanol injection. *Radiology* 1999; **210**: 655-661 [PMID: 10207464 DOI: 10.1148/radiology.210.3.r99fe40655]

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**Figure 1 Identification of studies for inclusion in the meta-analysis.**

**Figure 2 Comparison of methods for surgical resection and nonsurgical ablation for small hepatocellular carcinoma based on the overall survival rate and disease-free survival rate.** A: 5-year overall survival rate, B: 3-year disease-free survival rate.

**Figure 3 Comparison of adverse events with 1-, 2-, and 3-year overall survival rates between** **a percutaneous ethanol injection and radiofrequency ablation for treatment of small hepatocellular carcinoma.** A: Adverse events, B: 1-year overall survival rate, C: 2-year overall survival rate, D: 3-year overall survival rate. All analyses used the Mantel-Haenszel method.

**Figure 4 Comparison** **between transcatheter arterial chemoembolization plus radiofrequency ablation and radiofrequency ablation alone as a treatment for small hepatocellular carcinoma based on overall survival rate.** A: 1-year overall survival rate, B: 3-year overall survival rate, C: 5-year overall survival rate. All analyses used the Mantel-Haenszel method.

**Figure 5 Funnel plot of surgical resection versus nonsurgical ablations.** A: 1-year overall survival rate, B: 5-year disease-free survival rate.

**Table 1 Characteristics of cases using surgical resection versus 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](#_ENREF_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*[[10](#_ENREF_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*[[11](#_ENREF_9)] | RFA | 85/30 | ≤ 3.0 (*n* = 45) | 55.91 ± 12.68 | > 400 (*n* = 32) | 106/9 | 37.2 (6.0-60) |
|  | RES | 79/36 | ≤ 3.0 (*n* = 57) | 56.57 ± 14.30 | > 400 (*n* = 21) | 110/5 | 46.4 (1.2-60) |
| Feng *et al*[[12](#_ENREF_9)] | RFA | 79/5 | ≤ 2.0 (*n* = 31) | 51 (24-83) | 215.5 (0.5-8530) | 39/45 | 36 |
|  | RES | 75/9 | ≤ 2.0 (*n* = 25) | 47 (18-76) | 262.8(1.7-10,220) | 43/41 | 36 |
| Cho *et al*[[13](#_ENREF_9)] | PEI | 86/30 | ≤ 2.0 (*n* = 43) | 58.0 ± 9.7 | > 20 (*n* = 47) | 92/24 | 68 |
|  | RES | 91/25 | ≤ 2.0 (*n* = 43) | 56.0 ± 8.9 | > 20 (*n* = 47) | 92/24 | 68 |
| Abu-Hilal *et al*[[14](#_ENREF_9)] | RFA | 27/7 | 3.8 (1.3-5) | 65 | - | 27/7 | 30 (0-60) |
|  | RES | 26/8 | 3.0 (2-5) | 67 | - | 25/9 | 43 (2-129) |
| Ueno *et al*[[15](#_ENREF_9)] | RFA | 100/55 | 2.7 ± 0.1 | 66 (40-79) | 131 ± 33 | - | 36.8 ± 1.5 |
|  | RES | 82/41 | 2.0 ± 0.1 | 67 (28-85) | 382 ± 108 | - | 35.0 ± 1.7 |
| Kagawa *et al*[[16](#_ENREF_9)] | RFA+TACE | 39/23 | ≤ 2.0 (*n* = 19) | 67.5 ± 8.4 | > 400 (*n* = 5) | - | 49 (1-102) |
|  | RES | 40/15 | ≤ 2.0 (*n* = 9) | 66.1 ± 8.4 | > 400 (*n* = 10) | - | 50 (9-95) |
| Nishikawa *et al*[[17](#_ENREF_9)] | RFA | 95/67 | 1.99 ± 0.62 | 68.4 ± 8.7 | 74.7 ± 181.1 | 102/22 | 37.2 (2.4-84) |
|  | RES | 50/19 | 2.68 ± 0.49 | 67.4 ± 9.7 | 376 ± 1989.8 | 45/5 | 39.6 (8.4-84) |
| Guo *et al*[[18](#_ENREF_9)] | RFA | 78/16 | ≤ 3.0 (*n* = 62) | 56 (19-75) | > 200 (*n* = 34) | 63/31 | 28 (7-75) |
|  | RES | 94/8 | ≤ 3.0 (*n* = 75) | 51.5 (18-75) | > 200 (*n* = 34) | 95/7 | 32 (6-86) |
| Kim *et al*[[19](#_ENREF_9)] | RFA+TACE | 31/6 | 3.46 ± 0.75 | 61.7 ± 11.1 | ≥ 100 (*n* = 7) | 37/0 | 29.9 ± 7.8 |
|  | RES | 36/11 | 3.66 ± 0.76 | 58.8 ± 10.7 | ≥ 100 (*n* = 14) | 45/2 | 31.7 ± 10 |
| Lai *et al*[[20](#_ENREF_9)] | RFA | 19/12 | 1.8 ± 0.6 | 63.1 ± 12.8 | 201.3 (2-2221.9) | - | 35.1 ± 17.4 |
|  | RES | 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: A-fetoprotein.

**Table 2 Characteristics of cases involving percutaneous ethanol injection versus radiofrequency ablation**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Author** | **Treatment** | **M/F** | **Mean tumor size (cm)** | **Mean age （yr）** | **Mean AFP****(ng/mL)** | **Child–Pugh****A/B** | **Mean follow-up****(months)** |
| Brunello *et al*[[21](#_ENREF_9)] | PEI | 49/30 | 2.25 ± 0.54 | 70.3 ± 8.1 | 16.5 (MD) | 39/30 | 25.3 (MD) |
|  | RFA | 43/27 | 2.42 ± 0.49 | 69.0 ± 7.7 | 22.0 (MD) | 39/31 | 26.1 (MD) |
| Lin *et al*[[22](#_ENREF_9)] | PEI | 34/18 | 2.8 ± 0.9 | 67 ± 6.0 | > 400 (*n* = 8) | 39/12 | 23.8 ± 10.4 |
|  | RFA | 35/17 | 2.9 ± 0.8 | 59 ± 10 | > 400 (*n* = 7) | 41/11 | 24.5 ± 11.3 |
| Shiina *et al*[[23](#_ENREF_9)] | PEI | 87/27 | ≤ 2.0 (*n* = 57) | ≤65 (*n* = 41) | > 400 (*n* = 7) | 85/29 | 2.9 (MD) |
|  | RFA | 79/39 | ≤ 2.0 (*n* = 45) | ≤65 (*n* = 45) | > 400 (*n* = 6) | 85/33 | 3.1 (MD) |
| Lin *et al*[[24](#_ENREF_9)] | PEI | 39/23 | 2.3 ± 0.8 | 60 ± 8 | 400 (*n* = 9) | 47/15 | 26 ± 12 |
|  | RES | 30/22 | 2.5 ± 1.0 | 61 ± 10 | 400 (*n* = 10) | 46/46 | 28 ± 12 |
| Lencioni *et al*[[25](#_ENREF_9)] | PEI | 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 | 57 (MD) | 45/7 | 22.9 ± 9.4 |

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