Management of hepatocellular carcinoma: an overview of major findings from meta-analyses

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ABSTRACT

This paper aims to systematically review the major findings from meta-analyses comparing different treatment options for hepatocellular carcinoma (HCC). A total of 153 relevant papers were searched via the PubMed, EMBASE, and Cochrane library databases. They were classified according to the mainstay treatment modalities (i.e., liver transplantation, surgical resection, radiofrequency ablation, transarterial embolization or chemoembolization, sorafenib, and others). The primary outcome data, such as overall survival, diseases-free survival or recurrence-free survival, progression-free survival, and safety, were summarized. The recommendations and uncertainties regarding the treatment of HCC were also proposed.

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common causes of cancer-related death [1–3]. Currently, the most widely accepted therapeutic algorithm is derived from BCLC staging system [4–5], in which the mainstay treatment options for HCC include liver transplantation (LT), surgical resection, radiofrequency ablation (RFA), percutaneous ethanol injection (PEI), transarterial embolization (TAE) or chemoembolization (TACE), and sorafenib. Several novel therapeutic modalities have been also explored, such as percutaneous acetic acid injection (PAI), three-dimensional conformal radiation therapy (3D-CRT), argon-helium cryotheraphy system (AHCS), traditional Chinese medicine (TCMs), cytokine-induced killer (CIK) cell therapy, and portal vein embolization (PVE), etc. It remains unclear about whether or such novel therapeutic modalities could be applied to the clinical practice. Meta-analysis can provide the highest level of evidence for our clinical decisions by combining all scattered data [6–7]. Herein, we systematically reviewed the major findings from all meta-analyses regarding the treatment of HCC and attempted to propose the evidence-based recommendations and uncertainties.

RESULTS

Overall, 2039 papers were identified. Among them, 153 meta-analysis papers were finally included [8–160] (Figure 1). The number of relevant papers was gradually increased over years (Supplementary Figure S1). The characteristics of these included papers were shown in Table 1. Their major findings were summarized according to the treatment modalities (Tables 2–5 and Supplementary Tables S1–S8).

LT

Living donor LT (LDLT) versus deceased donor LT (DDLT)

Three meta-analyses compared the outcomes of LDLT versus DDLT [8, 41, 67]. All of them demonstrated that the OS was statistically similar between the two groups [8, 41, 67]. Two of them showed that the 1-, 3-, and 5-year DFS were statistically similar between the two groups [8, 67], but another one favored DDLT in term of DFS [41]. One of them found...
that the recurrence was statistically similar between the two groups [67]; by comparison, another one favored LDLT in term of 5-year recurrence, but not 1- or 3-year recurrence [8].

Only non-RCT studies, rather than RCTs, were included in the three meta-analyses.

The meta-analysis by Grant had a larger number of included studies than those by Al Hasan and Liang (16 versus 7 and 7) (Supplementary Table S9). Notably, there was an overlap of included studies between the two meta-analyses by Liang and Grant. All studies which were included in the meta-analysis by Liang were also covered by the meta-analysis by Grant. The meta-analysis by Al Hasan did not show the included studies.

Given its superiority in the quantity of non-RCT studies, the results of the meta-analysis by Grant might be more reliable. In details, LDLT has lower DFS than DDLT.

**Primary versus salvage LT**

Two meta-analyses compared the outcomes of primary versus salvage LT [59, 157]. Both of them demonstrated that the OS and 1- and 3-year DFS were statistically similar between the two groups [59, 157]. One of them favored primary LT in term of 5-year DFS [157]; by comparison, another one showed that the 5-year DFS was statistically similar between the two groups [59]. In addition, salvage LT had significantly longer operative time, increased intra-operative blood loss, and larger number of transfused units of packed red blood cells than primary LT [157]. But the length of hospital and ICU stay was statistically similar between the two groups [157].

Only non-RCT studies, rather than RCTs, were included in the two meta-analyses.

The meta-analysis by Zhu had a larger number of included studies than that by Li (14 versus 11) (Supplementary Table S10). Notably, there was an overlap of included studies between them. All studies which were included in the meta-analysis by Li were also included in the meta-analysis by Zhu.

Given its superiority in the quantity of non-RCT studies, the results of the meta-analysis by Zhu might be more reliable. In details, salvage LT achieves the same short- and long-term survival as primary LT. However, primary LT was significantly superior to salvage LT in terms of operative time, blood loss, and blood transfusion.

**Sirolimus-based immunosuppression after LT**

Two meta-analyses compared the outcomes of sirolimus-based immunosuppression versus no sirolimus after LT [66, 83]. Both of them favored the use of sirolimus after LT in terms of OS, DFS/RFS, and recurrence [66, 83].

Only non-RCT studies, rather than RCTs, were included in the two meta-analyses.

Both of them had a similar number of included studies (5 versus 5) (Supplementary Table S11). But not all included studies were the same between them.

The results were completely consistent between the two meta-analyses. In details, the use of sirolimus after LT should be favored.

**LT versus surgical resection**

Seven meta-analyses compared the outcomes of LT versus surgical resection [25, 46, 96, 98, 129, 131, 146]. There were 4, 4, 6, and 1 meta-analyses to compare the 1-, 3-, 5-, and 10-year survival, respectively. As for the 1-year survival, three of them demonstrated that the survival was statistically similar between the two groups [129, 131, 146], but another one favored surgical resection [98]. As for the 3-year survival, two of them found that the survival was statistically similar between the two groups [46, 131], but another two favored LT [129, 146]. As for the 5-year survival, two of them showed that the survival was statistically similar between the two groups [96, 98], but another four favored LT [25, 129, 131, 146]. As for the 10-year survival, the only one meta-analysis favored LT [98]. There were 3, 3, 4, and 1 meta-analyses to compare the 1-, 3-, 5-, and 10-year DFS, respectively. As for the 1-year DFS, two of them favored LT [131, 146], but another one found that the 1-year DFS was statistically similar between the two groups [98]. As for the 3-year DFS, all of them favored LT [46, 131, 146]. As for the 5-year DFS, all of them favored LT [98, 129, 131, 146]. As for the 10-year DFS, the only one meta-analysis favored LT [98]. Two meta-analyses compared the recurrence. Both of them favored LT in term of recurrence [129, 146].

Only non-RCT studies, rather than RCTs, were included in these meta-analyses.

The meta-analysis by Zhang had the largest number of included studies (n = 62) (Supplementary Table S12). By comparison, the number of included studies was less than 20 in 6 other meta-analyses.

Given its superiority in the quantity of non-RCT studies, the results of the meta-analysis by Zhang might be more reliable. In details, LT provides a significantly better survival and a lower recurrence.

**Surgical resection**

**Surgical resection margin 1 cm versus 2 cm**

Only one meta-analysis compared the outcomes of hepatectomy with a margin aiming at 2 cm versus those with a margin aiming at 1 cm [109]. Regardless of study design, the 1-year survival was statistically similar between the two groups [109]. In the subgroup analysis of randomized studies, the 3- and 5-year survival and DFS were better in patients undergoing hepatectomy with a margin aiming at 2 cm than in those with a margin aiming at 1 cm [109]. Contrarily, in the subgroup
analysis of non-randomized studies, the 3- and 5-year survival and DFS were statistically similar between the two groups [109].

One RCT and 4 non-RCT studies were included in this meta-analysis.

**Laparoscopic versus open resection**

Nine meta-analyses compared the outcomes of laparoscopic versus open resection [30, 62, 94–95, 111, 126, 135, 137, 156]. All of them demonstrated that the OS and DFS/RFS at any time points were statistically similar between the two groups [30, 62, 94–95, 111, 126, 135, 137, 156]. Two of them also found that the recurrence was statistically similar between the two groups [62, 126]. Eight of them demonstrated statistically similar operative time between the two groups [30, 62, 95, 111, 126, 135, 137, 156], but one demonstrated significantly longer operative time in laparoscopic resection group [94]. All of them demonstrated that blood loss or intraoperative bleeding was significantly less in laparoscopic resection group [30, 62, 94–95, 111, 126, 135, 137, 156]. Among the 7 meta-analyses evaluating the blood transfusion, 6 demonstrated significantly less blood transfusion in laparoscopic resection group [30, 62, 111, 126, 137, 156], and one demonstrated statistically similar blood transfusion between the two groups [94]. Among the 6 meta-analyses evaluating the overall complications, 5 demonstrated significantly less complications in laparoscopic resection group [30, 62, 94, 111, 135], and one demonstrated statistically similar complications between the two groups [126]. Among the 8 meta-analyses evaluating the hospital length, all demonstrated significantly shorter hospital study in laparoscopic resection group [30, 62, 94, 111, 126, 135, 137, 156].

Only non-RCT studies, rather than RCTs, were included in these meta-analyses.

The meta-analyses by Park, Xiong, and Yin had the largest number of included studies (n = 15) followed by the meta-analyses by Yao (n = 13), Zhou (n = 10), Li (n = 10), Fancellu (n = 9), Pang (n = 7), and Twaij (n = 4) (Supplementary Table S13). The included studies were completely same between the two meta-analyses by Xiong and Yin. However, the studies included in the meta-analysis by Park were different from those included in the meta-analyses by Xiong and Yin.

Given its superiority in the quantity of non-RCT studies, the results of the meta-analyses by Park, Xiong, and Yin might be more reliable. In details, they suggested that the operative time was statistically similar between the two groups and that laparoscopic resection was superior to open resection in terms of blood loss, blood transfusion, complications, and hospital stay.

![Figure 1: Flowchart of study inclusion.](image-url)
### Table 1: Study characteristics: An overview of included studies

| First author | Journal (Year) | Country          | Type of participants | No. included studies/pts. | Comparisons                                      | Type of studies |
|--------------|----------------|------------------|----------------------|---------------------------|--------------------------------------------------|----------------|
| Al Hasan     | Liver Transpl (2014) | Saudi Arabia     | Unselected HCC       | 7/1388                    | Living donor LT vs deceased donor LT              | 0; 7           |
| Bouza        | BMC Gastroenterol (2009) | Spain           | Early, small HCC     | 6/787                     | RFA vs PEI                                       | 6; 0           |
| Breitenstein | Br J Surg (2009) | Switzerland      | Unselected HCC       | 7/620                     | Interferon after resection or ablation            | 7; 0           |
| Cai          | HPB (2013) | China            | HCC ≤ 5 cm           | 5/NA                      | RFA vs surgical resection                        | NA; NA         |
| Camma        | Radiology (2002) | Italy            | Unresectable HCC     | 18/2466                   | TACE vs non-active treatment; different transarterial modalities of therapy (TACE, TCE, TAE) | 5; 13; 0       |
| Cao          | Ultrasound Med Biol (2011) | China           | Unselected HCC       | 9/736                     | TACE plus HIFU vs TACE alone                     | 0; 9           |
| Chen         | Dig Dis Sci (2011) | China            | Unselected HCC       | 9/1503                    | Anatomic vs nonanatomic resection                | 0; 9           |
| Chen         | Zhonghua Wai Ke Za Zhi (2008) | China           | HCC ≤ 5 cm, number of lesions ≤ 3 | 6/697                    | RFA vs surgical resection                        | 1; 5           |
| Chen         | Chinese-German Journal of Clinical Oncology (2013) | China           | Unresectable HCC     | 9/870                     | CIK cell + TACE                                  | 9; 0           |
| Cheng        | J Cancer Res Clin Oncol (2014) | China           | Resectable HCC       | 10/909                    | Preoperative TACE vs control; postoperative TACE vs control | 4; 6; 0; 0     |
| Cheung       | Evid Based Complement Alternat Med (2013) | China           | Unresectable HCC     | 67/5211                   | TACE + Chinese medicines vs TACE alone           | 67; 0          |
| Cho          | Hepatology (2009) | Korea            | Unselected HCC       | 4/652                     | RFA vs PEI                                       | 4; 0           |
| Cho          | Expert Opin Investig Drugs (2009) | China           | HCC patients receiving TACE | 30/2428                  | TACE + Chinese herbal therapy vs TACE alone      | 30; 0          |
| Chu          | Asian J Surg (2010) | China            | Post-operative HCC   | 5/206                     | Vitamin analogues (vitamin A and K2) after hepatic resection or local ablative therapy | 5; 0           |
| Cinco        | Hepatology International (2011) | Philippines     | Advanced HCC         | 2/828                     | Sorafenib vs placebo                            | 9; 0           |
| Cucchetti    | Ann Surg Oncol (2012) | Italy           | Unselected HCC       | 18/9036                   | Anatomic vs nonanatomic resection                | 0; 18          |
| Cucchetti    | J Hepatol (2013) | Italy            | Early HCC ≤ 5 cm     | 17/8420                   | RFA vs surgical resection                        | NA; NA         |
| Dhir         | HPB (2012) | USA              | Early HCC within Milan Criteria | 10/1763                  | LT vs resection                                  | 0; 10          |
| Dong         | World J Gastroenterol (2014) | China           | Unselected HCC       | 22/NA                     | Surgical resection vs nonsurgical-resection ablation therapies; RFA vs PEI; RFA vs RFA+TACE | 2; 5; 0; 10; 5 |
| Duan         | World J Surg Oncol (2013) | China           | Unselected HCC       | 12/8612                   | RFA vs surgical resection                        | 2; 12          |
| Duffy   | Hepatology (2013) | USA | Unselected HCC | 6/2464 | Antiangiogenic agents vs placebo | 6 | 21 |
|---------|-------------------|-----|----------------|--------|----------------------------------|----|----|
| Estanisla | J Gastroenterol Hepatol (2009) | Philippine | Advanced HCC | NA/NA | Octreotide vs no octreotide | NA | NA |
| Fancellu | J Surg Res (2011) | Italy | Resectable HCC | 9/590 | Minimally-invasive vs open hepatectomy | 0 | 9 |
| Feng    | J Cancer Res Clin Oncol (2014) | China | Small HCC (1 lesion < 6.5 cm; no more than 3 lesions < 4.5 cm) | 23/15482 | RFA vs surgical resection | 3 | 20 |
| Flores  | J Gastroenterol Hepatol (2009) | Philippines | Post-operative HCC | 2/236 | Adjuvant immunotherapy in combination with surgical resection | 2 | 0 |
| Fu      | Hepato-gastroenterology (2014) | China | Small HCC (single < 6.5 cm, or ≤ 3 lesions, ≤ 4.5 cm) | 5/776 | RFA vs surgical resection | 5 | 0 |
| Fu      | J Cancer Res Clin Oncol (2014) | China | Unselected HCC | 9/900 | TACE + sorafenib vs TACE alone | 5 | 4 |
| Fu      | J Cancer Res Ther (2014) | China | Unresectable HCC | 9/608 | Kanglaite injection plus hepatic arterial intervention vs hepatic arterial intervention alone | 0 | 9 |
| Furtado | Ann Surg Oncol (2014) | Australia | Unselected HCC | 5/334 | Surgery + Adjuvant I(131) lipiodol vs surgery alone | 2 | 3 |
| Gao     | Hepato-gastroenterology (2013) | China | Unresectable HCC | 7/693 | DEB-TACE vs conventional TACE | 0 | 7 |
| Germani | J Hepatol (2010) | UK | Unselected HCC | 8/1035 | RFA vs PEI; Percutaneous acetic acid injection vs PEI | 5; 2 | 0; 0 |
| Geschwind | Am J Clin Oncol (2003) | USA | Unselected HCC | 4/268 | Therapeutic embolization vs supportive care alone | 4 | 0 |
| Gong    | Nucl Med Commun (2014) | China | Unselected HCC | 6/466 | Adjuvant therapy with intra-arterial iodine-131-labeled lipiodol ([131]I-lipiodol) to hepatic resection | 2 | 8 |
| Grant   | Clin Transplant (2013) | Canada | Unselected HCC | 16/2202 | Living donor LT vs deceased donor LT | 0 | 16 |
| Gu      | J Cancer Res Clin Oncol (2014) | China | Unselected HCC | 18/2120 | TACE + local ablative therapy vs monotherapy | 7 | 11 |
| Guo     | J Cancer Res Clin Oncol (2009) | China | Advanced HCC | 6/352 | Octreotide vs placebo or best supportive care | 6 | 0 |
| Han     | Journal of Interventional Radiology (China) (2013) | China | Unselected HCC | 8/698 | RFA + TACE vs TACE | 0 | 8 |
| Han     | PLoS One (2014) | China | Unresectable HCC | 5/454 | DEB-TACE vs conventional TACE | 3 | 2 |
| Hoshida | Hepatology (2000) | Japan | Non-advanced HCC | 17/NA | Surgical resection vs PEI; Surgical resection vs LT | 0; 0 | 5; 12 |
| Hu      | HPB (2013) | China | Unselected HCC | 18/NA | RFA vs surgical resection | 4 | 14 |
| Huang   | Hepato-gastroenterology (2013) | China | Unselected HCC | 4/433 | RFA vs cryosurgery ablation | 0 | 4 |
| Huang   | J Gastroenterol Hepatol (2014) | China | Unresectable HCC | 7/700 | DEB-TACE vs conventional TACE | 2 | 5 |
| Author       | Journal/Conference                                      | Country   | Group                  | Number of Patients | Intervention/Comparison                                                                 |
|--------------|----------------------------------------------------------|-----------|------------------------|--------------------|-----------------------------------------------------------------------------------------|
| Huang        | J Viral Hepat (2013)                                     | China     | Unselected HCC         | 22/3156            | Adjuvant interferon therapy after curative treatment                                    |
| Huang        | Zhonghua Nei Ke Za Zhi (2008)                            | China     | Early HCC within Milan Criteria | 6/862              | RFA vs other therapeutic methods                                                      |
| Ji           | Med Sci Monit (2011)                                     | China     | Advanced HCC           | 9/759              | Octreotide vs placebo or no treatment                                                  |
| Jiang        | Tumour Biol (2014)                                       | China     | Unselected HCC         | 19/1728            | RFA + TACE vs RFA alone                                                                |
| Jiang        | World J Surg Oncol (2013)                                | China     | Unselected HCC         | 10/1029            | Adjuvant interferon therapy after treatment with surgical resection or TACE            |
| Kong         | Tumour Biol (2014)                                       | China     | Unselected HCC         | 19/1728            | RFA + TACE vs RFA alone                                                                |
| Lan          | Journal of Gastroenterology and Hepatology Research (Hong Kong) (2013) | China     | Unselected HCC         | 10/701             | Lamivudine treatment vs no antiviral therapy after liver resection or RFA              |
| Leng         | ANZ J Surg (2014)                                        | China     | HCC patients with PVTT | 5/600              | TACE vs control treatment                                                              |
| Li           | World J Gastroenterol (2012)                             | China     | Unselected HCC         | 11/1013            | Primary LT vs salvage LT                                                               |
| Li           | Hepatol Res (2012)                                       | China     | Unselected HCC         | 10/627             | Laparoscopic vs open liver resection                                                   |
| Li           | Hepato-gastroenterology (2011)                           | China     | Unselected HCC         | 4/776              | Anatomic vs nonanatomic resection                                                      |
| Li           | J Gastroenterol Hepatol (2012)                           | China     | Unselected HCC         | 6/877              | RFA vs surgical resection                                                              |
| Li           | Chinese Journal of Evidence-Based Medicine (2012)        | China     | Intermediate-advanced stage | 17/907            | TACE + thermotherapy vs TACE alone                                                    |
| Li           | Chinese Journal of Evidence-Based Medicine (2013)        | China     | Intermediate-advanced stage | 16/1467           | TACE + argon-helium cryotherapy system (AHCS) vs TACE alone; TACE + argon-helium cryotherapy system vs AHCS |
| Li           | Chinese Journal of Cancer Prevention and Treatment (2013) | China     | Unselected HCC         | 8/818              | Adjuvant IFN vs without IFN after curative treatment                                   |
| Li           | Clin Res Hepatol Gastroenterol (2014)                   | China     | Unresectable HCC       | 11/936             | CIK+TACE+RFA vs TACE+RFA; CIK+TACE vs TACE                                           |
| Liang        | Liver Transpl (2012)                                     | China     | Unselected HCC         | 7/1310             | Living donor LT vs deceased donor LT                                                   |
| Liang        | Liver Transpl (2012)                                     | China     | Unselected HCC         | 5/2950             | Sirolimus-based immunosuppression (SRL) after LT vs SRL-free                         |
| Author | Journal | Country | Study Type | Patients | Comparator 1 | Comparator 2 | Results |
|-------|---------|---------|------------|----------|--------------|--------------|---------|
| Liao | PLoS One (2013) | China | Unselected HCC | 28/2497 | TACE+PEI vs TACE; TACE+RT vs TACE; TACE+ three-dimensional conformal radiation therapy (3D-CRT) vs TACE; TACE+RFA vs TACE; TACE+HIFU vs TACE | 4; 3; 1; 1; 1 | 5; 4; 5; 0; 4 |
| Liu | World J Gastroenterol (2010) | China | Unselected HCC | 10/1522 | RFA vs surgical resection | 0 | 10 |
| Liu | Surg Laparosc Endosc Percutan Tech (2010) | China | Unselected HCC | 8/1188 | RFA vs surgical resection | 8 | 0 |
| Liu | Tumour Biol (2014) | China | Unselected HCC | 7/571 | RFA + TACE vs RFA alone | 7 | 0 |
| Liu | PLoS One (2014) | China | Unresectable HCC | 17/676 | TACE + sorafenib vs monotherapy | 3 | 14 |
| Llovet | Hepatology (2003) | Spain | Unresectable HCC | 14/1443 | TACE vs control treatment; Tamoxifen vs control treatment | 7; 7 | 0; 0 |
| Lu | Eur J Gastroenterol Hepatol (2013) | China | Unselected HCC | 7/574 | RFA + TACE vs RFA alone | 7 | 0 |
| Ma | Experimental Hematology and Oncology (2012) | China | Unresectable HCC | 13/1212 | CIK cell therapy vs non- CIK therapy | 13 | 0 |
| Ma | Chinese Journal of Cancer Prevention and Treatment (2011) | China | Post-operative HCC | 4/423 | Hepatic resection or RFA alone vs surgery + adoptive immunotherapy | 4 | 0 |
| Marelli | Cardiovasc Intervent Radiol (2007) | UK | Unselected HCC | 12/NA | TACE vs control treatment; TACE vs TAE alone | 9; 3 | 0 |
| Mathurin | Aliment Pharmacol Ther (2003) | France | Post-operative HCC | 21/NA | Adjuvant therapy after curative liver resection | 10 | 11 |
| Meng | Radiother Oncol (2009) | China | Unselected HCC | 17/1476 | TACE + radiotherapy vs TACE alone | 5 | 12 |
| Meng | Hepatology International (2011) | China | Post-operative HCC | 4/209 | Vitamin K2 vs placebo after curative treatment | 4 | 0 |
| Meng | J Altern Complement Med (2008) | China | Unresectable HCC | 37/2653 | TACE + Traditional Chinese Medicine vs TACE alone | NA | NA |
| Meng | Explore (NY) (2011) | China | Unresectable HCC | 12/1008 | TACE + Traditional Chinese Medicine vs TACE alone | 11 | 0 |
| Menon | Aliment Pharmacol Ther (2013) | UK | Unselected HCC | 5/474 | Sirolimus-based immunosuppression (SRL) after LT vs SRL-free | 0 | 5 |
| Miao | World J Gastroenterol (2010) | China | Unselected HCC | 16/1224 | Adjuvant antiviral therapy after curative therapy | 5 | 8 |
| Miyake | J Viral Hepat (2010) | Japan | Unselected HCC | 5/355 | Interferon-alpha after curative therapy | 3 | 2 |
| Moriguchi | Hepatology (2006) | Japan | Unselected HCC | 4/604 | Tumor ablation plus interferon therapy | 4 | 0 |
| Author | Journal/Conference | Country | Group | Methods | Surgical Resection | RFA/PEI (PAT) vs RFA alone | RFA + TACE vs RFA or TACE alone | TACE or TAE vs placebo, sham, or no intervention | Adjuvant chemotherapy after resection | Vitamin K2 or its analogues vs placebo or No vitamin K | PEI vs percutaneous acetic acid injection; PEI vs surgery | Adjuvant interferon therapy after curative therapy | Interferon after resection or ablation | Nucleot(s)ide analogues vs placebo or no treatment after curative treatment |
|--------|-------------------|---------|-------|---------|--------------------|----------------------------|--------------------------------|-------------------------------------|----------------------------------------|-----------------------------------------------|------------------------------------------------|---------------------------------------------|---------------------------------------------|---------------------------------------------|------------------------------------------------------------------|
| Ni     | J Cancer Res Clin Oncol (2013) | China | Unselected HCC | 10/21494 | RFA/PEI (PAT) vs surgical resection | 6 | 4 |
| Ni     | World J Gastroenterol (2013) | China | Unselected HCC | 8/598 | RFA + TACE vs RFA alone | 8 | 0 |
| Ni     | J Cancer Res Clin Oncol (2013) | China | Unselected HCC | 6/376 | RFA + TACE vs RFA or TACE alone | 6 | 0 |
| Nowak | Cochrane Database Syst Rev (2004); Cancer (2005) | Australia | Unresectable HCC | 10/1709 | Tamoxifen vs placebo/no intervention | 10 | 0 |
| Oliveri | Cochrane Database Syst Rev (2011) | Denmark | Unresectable HCC | 9/645 | TACE or TAE vs placebo, sham, or no intervention | 9 | 0 |
| Ono | Cancer (2001) | Japan | Post-operative HCC | 3/108 | Adjuvant chemotherapy after resection | 3 | 0 |
| Orlando | Am J Gastroenterol (2009) | Italy | Small HCC | 5/701 | RFA vs PEI | 5 | 0 |
| Pang | Chinese Journal of Evidence-Based Medicine (2010) | China | Unselected HCC | 7/309 | Laparoscopic vs conventional open hepatectomy | 0 | 7 |
| Parks | HPB (Oxford) (2014) | USA | Unselected HCC | 15/1002 | Laparoscopic vs open liver resection | 0 | 15 |
| Proneth | Ann Surg Oncol (2014) | Germany | Unselected HCC | 9/1572 | LT vs resection | 0 | 7 |
| Qi | J Clin Gastroenterol (2014) | China | Early-stage HCC | 3/559 | RFA vs surgical resection | 3 | 0 |
| Rahman | J Gastrointest Surg (2012) | USA | Unselected HCC | 9/2279 | LT vs resection | 0 | 9 |
| Riaz | BMC Gastroenterol (2012) | Pakistan | Post-operative HCC | 5/754 | Vitamin K2 or its analogues vs placebo or No vitamin K | 5 | 0 |
| Schoppmeyer | Cochrane Database Syst Rev (2009) | Germany | Early HCC | 3/261 | PEI vs percutaneous acetic acid injection; PEI vs surgery | 2; 1 | 0; 0 |
| Shen | J Gastroenterol Hepatol (2013) | China | Small HCC < 3 cm | 4/766 | RFA vs PEI | 4 | 0 |
| Shen | J Clin Gastroenterol (2013) | China | Unresectable HCC | 5/1462 | Sorafenib vs placebo | 5 | 0 |
| Shen | J Hepatol (2010) | China | Unselected HCC | 13/1180 | Adjuvant interferon therapy after curative therapy | 9 | 4 |
| Shu | Integr Cancer Ther (2005) | USA | Unresectable HCC | 26/2079 | Chinese herbal medicine + chemotherapy vs chemotherapy alone | 24 | 2 |
| Singal | Aliment Pharmacol Ther (2010) | USA | Unselected HCC | 10/645 | Interferon after resection or ablation | 5 | 5 |
| Sun | World Chinese Journal of Digestology (2011) | China | Small HCC | 11/2965 | RFA vs surgical resection | 2 | 9 |
| Sun | PLoS One (2014) | China | Unselected HCC | 13/6350 | Nucleot(s)ide analogues vs placebo or no treatment after curative treatment | 1 | 12 |
| Author | Journal/Conference | Country | Clinic Type | Study Details | TACE + Compound vs TACE alone | Hepatectomy with a margin aiming at 2 cm vs a margin aiming at 1 cm | Anatomic vs nonanatomic resection | Laparoscopic vs open liver resection | Preoperative TACE vs control | Prophylactic antibiotic treatment vs no prophylactic antibiotic treatment after transarterial therapy | Different adjuvant therapy after potentially curative treatment | Antiviral treatment vs no anti-viral treatment | Traditional Chinese Medicines vs other treatment | TACE + Cinobufacini vs TACE only | Adoptive immunotherapy vs non-immunotherapy after surgery | Laparoscopic vs open liver resection |
|--------|-------------------|---------|-------------|---------------|-------------------------------|-------------------------------------------------|---------------------------------------------------|---------------------------------|----------------------------------|----------------------------------------------------------|----------------------------------|---------------------------------------------|----------------------------------|---------------------------------|-------------------------------------------------|----------------------------------|
| Sun    | Afr J Tradit Complement Altern Med (2012) | China   | Unresectable HCC | 10/726 | TACE + Compound Kushen Injection vs TACE alone | 0 | 10 |
| Tang   | Hepato-gastroenterology (2012) | China   | Unselected HCC | 5/799 | Hepatectomy with a margin aiming at 2 cm vs a margin aiming at 1 cm | 1 | 4 |
| Tang   | Hepato-gastroenterology (2013) | China   | Resectable HCC | 12/1829 | Anatomic vs nonanatomic resection | 0 | 12 |
| Twaij  | World J Gastroenterol (2014) | United Kingdom | Unselected HCC | 4/420 | Laparoscopic vs open liver resection | 0 | 4 |
| Wang   | Hepato-gastroenterology (2011) | China   | Unselected HCC | 3/257 | Preoperative TACE vs control | 3 | 0 |
| Wang   | PLoS One (2014) | China   | Early HCC | 28/11873 | RFA vs surgical resection | 3 | 25 |
| Wang N | Med Oncol (2011) | China   | Unselected HCC | 7/623 | TACE + PEI vs TACE alone | 7 | 0 |
| Wang W | Liver Int (2010) | China   | Unselected HCC | 10/595 | TACE + percutaneous ablation therapy (RFA or PEI) vs TACE or percutaneous ablation therapy alone | 10 | 0 |
| Wang   | Asian Pac J Cancer Prev (2013) | China   | Unselected HCC | 4/1382 | Sorafenib with or without chemotherapy vs placebo with or without chemotherapy | 4 | 0 |
| Wang   | Can J Gastroenterol (2012) | China   | Unresectable HCC | 4/210 | Prophylactic antibiotic treatment vs no prophylactic antibiotic treatment after transarterial therapy | 3 | 1 |
| Wang   | Can J Gastroenterol (2013) | China   | Post-operative HCC | 27/2614 | Different adjuvant therapy after potentially curative treatment | 27 | 0 |
| Weis   | Cochrane Database Syst Rev (2013) | Germany | Unselected HCC | 11/NA | RFA vs surgical resection; RFA vs PEI or RFA vs acetic acid injection; RFA vs microwave ablation; RFA vs laser ablation | 3; 6; 1; 1 | 0; 0; 0 |
| Wong   | Aliment Pharmacol Ther (2011) | China   | Unselected HCC | 9/551 | Antiviral treatment vs no anti-viral treatment | 0 | 9 |
| Wu     | J Exp Clin Cancer Res (2009) | China   | Unresectable HCC | 45/3236 | Traditional Chinese Medicines vs other treatment | 45 | 0 |
| Wu     | J Cancer Res Ther (2014) | China   | Unresectable HCC | 9/659 | TACE + Cinobufacini vs TACE only | 0 | 9 |
| Xie    | Tumour Biol (2014) | China   | Advanced HCC | 5/582 | TACE vs TAE | 5 | 0 |
| Xie    | J Cancer Res Clin Oncol (2012) | China   | Unresectable HCC | 13/1840 | TACE vs microsphere embolization | 7 | 6 |
| Xie    | PLoS One (2012) | China   | Post-operative HCC | 6/494 | Adoptive immunotherapy vs non-immunotherapy after surgery | 6 | 0 |
| Xiong  | World J Gastroenterol (2012) | China   | Unselected HCC | 9/550 | Laparoscopic vs open liver resection | 0 | 15 |
| Xu       | Journal of Xi’an Jiaotong University (Medical Sciences) (2012) | China | Unselected HCC | 9/2145 | LT vs resection | 0 | 9 |
| Xu       | Hepatobiliary Pancreat Dis Int (2014) | China | Unselected HCC | 17/4238 | LT vs resection | 0 | 17 |
| Xu       | World J Surg Oncol (2012) | China | Early HCC | 13/2535 | RFA vs surgical resection | 2 | 11 |
| Xu       | Eur J Med Res (2014) | China | Small HCC < 5 cm | 6/983 | RFA vs PEI | 6 | 0 |
| Xu       | Hepatol Res (2014) | China | Unselected HCC | 9/1565 | Adjuvant interferon therapy after surgical treatment | 5 | 4 |
| Xue      | BMC Gastroenterol (2013) | China | Advanced HCC with PVTT | 8/1601 | TACE vs conservative treatment | 0 | 8 |
| Yan      | Dig Dis Sci (2012); Dig Dis Sci (2013) | China | Unselected HCC | 19/1728 | RFA + TACE vs RFA alone | 8 | 11 |
| Yang     | Mol Biol Rep (2014) | China | Unresectable HCC | 6/1181 | TACE + sorafenib vs TACE alone | 3 | 3 |
| Yao      | Chinese Journal of Evidence-Based Medicine (2013) | China | Unselected HCC | 13/701 | Laparoscopic vs open hepatectomy | 0 | 13 |
| Ye       | Asian Pac J Cancer Prev (2012) | China | Unselected HCC | 11/1576 | Anatomic vs nonanatomic resection | 0 | 11 |
| Yin      | Ann Surg Oncol (2013) | China | Unselected HCC | 15/1238 | Laparoscopic vs open hepatectomy | 0 | 15 |
| Yu       | Chinese-German Journal of Clinical Oncology (2013) | China | Unselected HCC | 7/1347 | Preoperative TACE vs control | 0 | 7 |
| Zhang    | PLoS One (2014) | China | Unresectable/advanced HCC | 6/1254 | TACE + sorafenib vs TACE alone | 2 | 4 |
| Zhang    | Anticancer Drugs (2010) | China | Advanced HCC | 3/924 | Sorafenib-based therapy with other agent-based therapy | 3 | 0 |
| Zhang    | Hepatobiliary Pancreat Dis Int (2012) | China | Advanced HCC | 6/1164 | Sorafenib vs placebo | 3 | 3 |
| Zhang    | Molecular and Clinical Oncology (2014) | China | Unselected HCC | 14/1385 | Adjuvant interferon after curative surgery or ablation therapy | 9 | 5 |
| Zhang    | Int J Cancer (2009) | China | Post-surgical or ablative HCC | 6/600 | IFN-alpha with placebo or no treatment after tumor resection or ablation | 6 | 0 |
| Zhao     | Journal of Interventional Radiology (China) (2013) | China | Unselected HCC | 21/2339 | RFA + TACE vs RFA or TACE alone | 21 | 0 |
| Zhao     | Zhonghua Wai Ke Za Zhi (2008) | China | Unselected HCC | 9/494 | Preoperative portal vein embolization (PVE) vs no PVE for extended hepatectomy | 0 | 9 |
Anatomic resection versus non-anatomic resection

Six meta-analyses compared the outcomes of anatomic versus non-anatomic resection [15, 23, 60, 110, 136, 152]. Four of them demonstrated that the OS was statistically similar between the two groups [15, 60, 110, 136], but another two favored anatomic resection in term of 5-year survival [23, 152]. One of them found that the DFS was statistically similar between the two groups [60], but another four favored anatomic resection in term of DFS [15, 23, 136, 152]. Two of them showed that the recurrence was statistically similar between the two groups [15, 110], but another two favored anatomic resection in term of local intrahepatic recurrence [136, 152]. Post-operative complications were statistically similar between the two groups [23, 110, 136, 152].

Only non-RCT studies, rather than RCTs, were included in these meta-analyses. The meta-analysis by Cucchetti had the largest number of included studies (n = 18) followed by the meta-analyses by Zhou (n = 16), Tang (n = 12), Ye (n = 11), Chen (n = 9), and Li (n = 4) (Supplementary Table S14).

Given its superiority in the quantity of non-RCT studies, the results of the meta-analysis by Zhang might be more reliable. In details, anatomic resection was superior to non-anatomic resection in terms of OS and DFS.
| First author | Journal (Year) | Comparisons | OS | DFS, RFS, TTP, PFS | Recurrence, time to recurrence | Other endpoints | Major comments |
|--------------|----------------|--------------|----|-------------------|-------------------------------|----------------|----------------|
| Living donor LT (LDLT) versus deceased donor LT (DDLT) | | | | | | |
| Al Hasan | Liver Transpl (2014) | LDLT vs DDLT | OS: 1-, 3-, 5-year: statistically similar. | DFS: 1-, 3-, 5-year: statistically similar. | Recurrence: 1-, 3-year: statistically similar. 5-year: favor DDLT. | NA. | OS and DFS are comparable, but long-term recurrence is higher in LDLT. |
| Grant | Clin Transplant (2013) | LDLT vs DDLT | OS: statistically similar. | DFS: favor DDLT. | NA. | NA. | LDLT has lower DFS than DDLT. |
| Liang | Liver Transpl (2012) | LDLT vs DDLT | OS: 1-, 3-, 5-year: statistically similar. | RFS: 1-, 3-, 5-year: statistically similar. | Recurrence: statistically similar. | NA. | LDLT is an acceptable option especially for patients within Milan criteria. |
| Primary LT versus salvage LT | | | | | | |
| Li | World J Gastroenterol (2012) | Primary LT vs salvage LT | OS: 1-, 3-, 5-year: statistically similar. | DFS: 1-, 3-, 5-year: statistically similar. | NA. | NA. | OS and DFS were not significantly different. |
| Zhu | Transplant Proc (2013) | Primary LT vs salvage LT | OS: 1-, 3-, 5-year: statistically similar. | DFS: 1-, 3-year: statistically similar. 5-year: favor primary LT. | NA. | | Operative time: longer in salvage LT. Intraoperative blood loss: increased in salvage LT. Number of transfused units of packed red blood cells: larger in salvage LT. Length of hospital stay and ICU stay: statistically similar. Peri-operative mortality: statistically similar. Salve LT achieves the same short- and long-term outcomes as primary LT. |
| Sirolimus-based immunosuppression (SRL) after LT | | | | | | |
| Liang | Liver Transpl (2012) | SRL after LT vs SRL-free | OS: 1-, 3-, 5-year: favor SRL. | DFS: 1-year: favor SRL. | Recurrence: 1-year: favor SRL. | | Major SRL-related post-transplant complications: statistically similar. | SRL is safe and prolongs survival and decrease tumor recurrence. |
| Menon | Aliment Pharmacol Ther (2013) | SRL after LT vs SRL-free | Overall mortality: favor SRL. | RFS: better in SRL (no statistical comparison). Recurrence-related mortality: low in SRL. | Recurrence: favor SRL. | NA. | SRL has lower recurrence rate, lower overall mortality and longer RFS and OS. |
| Author   | Journal/Year | Study Design | OS:                                                | DFS:                           | 1-year:                                  | 5-year:                                  | 10-year:                                 | Conclusion |
|----------|--------------|--------------|----------------------------------------------------|-------------------------------|------------------------------------------|------------------------------------------|------------------------------------------|------------|
| Dhir     | HPB (2012)   | LT vs resection | 5-year: early HCC: favor LT. early HCC with well compensated cirrhosis: favor LT. early HCC using ITT strategy: statistically similar. early HCC with well compensated cirrhosis using ITT strategy: favor LT. | NA.                           | NA.                                      | NA.                                      | LT has favorable survival advantage in some settings. |
| Hoshida  | Hepatology (2000) | Surgical resection vs PEI and LT (including LT vs surgical resection) | OS: Surgical resection vs LT: 3-year: statistically similar. | DFS: Surgical resection vs LT: 3-year: favor LT. | NA.                                      | NA.                                      | LT improved 3-year DFS for HCC patients. |
| Proneth  | Ann Surg Oncol (2014) | LT vs resection | OS: 5-year: statistically similar. | NA.                           | NA.                                      | NA.                                      | LR is a good alternative to LT in patients with resectable HCC in whom both seem feasible. |
| Rahman   | J Gastrointest Surg (2012) | LT vs resection | OS: 1-year: all studies: favor resection. non-ITT analysis: statistically similar. ITT analysis: favor resection. 5-year: all studies: statistically similar. non-ITT analysis: statistically similar. ITT analysis: favor LT. | DFS: 1-year: all studies: statistically similar. non-ITT analysis: statistically similar. ITT analysis: statistically similar. 5-year survival: all studies: favor LT. | NA.                                      | NA.                                      | LT results in increased DFS and OS. |
Surgical resection + $^{131}$I lipiodol versus surgical resection alone

Two meta-analyses compared the outcomes of surgical resection in combination with $^{131}$I lipiodol versus surgical resection alone [36, 40]. Both of them favored the combination therapy in terms of OS, DFS, and recurrence [36, 40].

Only non-RCT studies, rather than RCTs, were included in these meta-analyses.

The meta-analysis by Gong had a larger number of included studies than that by Furtado (10 versus 5) (Supplementary Table S15). Notably, there was an overlap of included studies between them. All studies which were included in the meta-analysis by Furtado were also included in the meta-analysis by Gong.

The results were completely consistent between the two meta-analyses. In details, surgical resection in combination with $^{131}$I lipiodol should be favored.

Surgical resection + TACE versus surgical resection alone

Pre-operative TACE

Four meta-analyses compared the outcomes of surgical resection in combination with pre-operative TACE versus surgical resection alone [17, 116, 138, 153]. All of them found that the OS, DFS, and recurrence were statistically similar between the two groups [17, 116, 138, 153].

RCT studies were included in the meta-analyses by Cheng (n = 4), Wang (n = 3), and Zhou (n = 4), but not in the meta-analysis by Yu (n = 0).

The meta-analysis by Zhou had the largest number of included studies (n = 21) followed by the meta-analyses by Yu (n = 7), Cheng (n = 4), and Wang (n = 3) (Supplementary Table S16). All studies which were included in the two meta-analyses by Cheng and Wang were also included in the meta-analysis by Zhou.

The results were completely consistent between the two meta-analyses. In details, pre-operative TACE did not improve the OS or DFS.

Post-operative TACE

Two meta-analyses compared the outcomes of surgical resection in combination with post-operative TACE versus surgical resection alone [17, 149]. Both of them favored post-operative TACE in terms of OS, DFS, and recurrence [17, 149].

Only RCT studies were included in the two meta-analyses.

Although the number of included studies was the same between the two meta-analysis by Cheng and Zhong (n = 6) (Supplementary Table S17), not all included studies were the same between them.

The results were completely consistent between the two meta-analyses. In details, post-operative TACE should be favored.

Surgical resection + adjuvant chemotherapy versus surgical resection alone

Five meta-analyses compared the outcomes of surgical resection in combination with adjuvant chemotherapy versus surgical resection alone [78, 92, 112, 147–148].
Table 3: Findings of meta-analyses: An overview of included studies regarding surgical resection

| First author | Journal (Year)               | Comparisons                                      | OS                                           | DFS, RFS, TTP, PFS | Recurrence, time to recurrence | Other endpoints                          | Major comments                                                                 |
|--------------|------------------------------|--------------------------------------------------|---------------------------------------------|--------------------|---------------------------------|------------------------------------------|--------------------------------------------------------------------------------|
| **Surgical resection margin**                                                                 |                                                  |                                                |                          |                                  |                                              |                                                                                  |
| Tang         | Hepato-gastroenterology (2012) | Hepatectomy with a margin aiming at 2 cm vs a margin aiming at 1 cm | OS: RCT: 1-year: statistically similar; 3-, 5-year: favor hepatectomy with a margin aiming at 2 cm. Non-RCT: 1-, 3-, 5-year: statistically similar. | DFS: RCT: favor hepatectomy with a margin aiming at 2 cm. Non-RCT: statistically similar. | NA.                             | Post-operative morbidity: statistically similar. Post-operative mortality: statistically similar. Blood loss: statistically similar. | Survival was similar between resection aiming at 2 cm and 1 cm. |
| **Laparoscopic resection (LR) versus open liver resection (OR)**                                |                                                  |                                                |                          |                                  |                                              |                                                                                  |
| Fancellu     | J Surg Res (2011)             | Minimally-invasive vs open hepatectomy           | OS: 1-, 2-, 3-, 5-year: statistically similar. | DFS: 1-, 2-, 3-, 5-year: statistically similar. | NA.                             | Operative time: statistically similar. Blood loss: less in minimally-invasive hepatectomy. Transfusion: lower in minimally-invasive hepatectomy. Peri-operative complications: lower in minimally-invasive hepatectomy. Postoperative stay: shorter in minimally-invasive hepatectomy. Positive margin: lower in minimally-invasive hepatectomy. | Minimally-invasive hepatectomy was associated with adverse events after procedure. |
| Li           | Hepatol Res (2012)            | LR vs OR                                         | NA.                                         | NA.                              | Tumor recurrence: statistically similar. | Operative time: statistically similar. Blood loss: less in LR. Need for blood transfusion: fewer in LR. Postoperative complications: fewer in LR. Hospital stay: shorter in LR. | LR is a safe and feasible choice for selected HCC.                                   |
| Pang         | Chinese Journal of Evidence-Based Medicine (2010) | LR vs OR                                       | In-hospital mortality: statistically similar. | NA.                              | NA.                             | Operation time: longer in LR. Blood loss: less in LR. Blood transfusion: statistically similar. Postoperative complications: less in LR. Length of stay: shorter in LR. | LR is associated with less complications.                                          |
| Parks        | HPB (Oxford) (2014)           | LR vs OR                                         | OS: 1-, 3-, 5-year: statistically similar. | NA.                              | NA.                             | Operative time: statistically similar. Blood loss: lower in LR. | LR should be an acceptable alternative treatment.                                 |
| Author   | Journal                          | Study Type | Results                                                                                   | Conclusion                                                                 |
|----------|----------------------------------|------------|-------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|
| Twaij    | World J Gastroenterol (2014)     | LR vs OR   | NA.                                                                                       | LR is safe and may provide improved patient outcomes when compared to the open technique. |
| Xiong    | World J Gastroenterol (2012)     | LR vs OR   | NA.                                                                                       | LR appears to be a safe and feasible option for resection of HCC in selected patients. |
| Yao      | Chinese Journal of Evidence-Based Medicine (2013) | LR vs OR   | OS: 3-, 5-year: statistically similar. Peri-operative mortality: statistically similar. Tumor-free survival: 3-, 5-year: statistically similar. | LR is safe and feasible for treating HCC. |
| Yin      | Ann Surg Oncol (2013)            | LR vs OR   | OS: 1-, 3-, 5-year: statistically similar. RFS: 1-, 3-, 5-year: statistically similar.     | LR may have short-term advantages in terms of blood loss and postoperative morbidity for HCC. Both procedures have similar long-term outcomes. |
| Author   | Journal                      | Study Type | Endpoint | Result | Complication | Details |
|----------|------------------------------|------------|----------|--------|--------------|---------|
| Zhou     | Dig Dis Sci (2011)           | LR vs OR   | OS: statistically similar | DFS: statistically similar | NA | Operative time: statistically similar. Blood loss: less in LR. Blood transfusion: less in LR. Cirrhotic decompensation/ascites: lower in LR. Liver failure: lower in LR. Bile leakage and bleeding: statistically similar. Pulmonary complications: less in LR. Hospital stay: shorter in LR. LR may be an alternative choice for treatment of HCC. |
| Chen     | Dig Dis Sci (2011)           | AR vs NAR  | OS: 5-year: statistically similar | DFS: 5-year: favor AR | 5-year: favor AR | NA | AR is associated with better DFS than NAR. |
| Cucchetti | Ann Surg Oncol (2012)         | AR vs NAR  | OS: 5-year: favor AR | DFS: 5-year: favor AR | NA | Postoperative morbidity: statistically similar. Patient survival and DFS after AR seem to be superior to NAR. |
| Li       | Hepato-Gastroenterology (2011) | AR vs NAR  | OS: 1-, 3-, 5-year: statistically similar | DFS: 1-, 3-, 5-year: statistically similar | NA | NA. AR can extend 3-year DFS of patients with small HCC in the sensitivity analysis. |
| Tang     | Hepato-gastroenterology (2013) | AR vs NAR  | OS: 1-, 3-, 5-year: statistically similar | DFS: favor AR | Recurrence: statistically similar | Postoperative complications and blood loss: statistically similar. AR does not provide significant benefit in the survival, recurrence and morbidity. |
| Ye       | Asian Pac J Cancer Prev (2012) | AR vs NAR  | OS: statistically similar | DFS: favor AR | Local intrahepatic recurrence: lower in AR. Overall intrahepatic recurrence: lower in AR. Early intrahepatic recurrence: lower in AR. Late intrahepatic recurrence: statistically similar. Safety: Postoperative mortality: statistically similar. Postoperative morbidity: statistically similar. AR was superior to NAR in terms of local recurrence and 5-year DFS. |
| Study | Journal | Treatment | OS | DFS | Recurrence | Morbidity | Mortality | Length of stay | Conclusion |
|-------|---------|------------|----|-----|------------|-----------|-----------|---------------|------------|
| Zhou  | Langenbecks Arch Surg (2011) | AR vs NAR | OS: 3-year: statistically similar. 5-year: favor AR. | DFS: 3-, 5-year: favor AR. | Local intrahepatic recurrence: lower in AR. Early recurrence: lower in AR. | Postoperative morbidity (liver failure, bile leakage, intra-abdominal bleeding, ascites, intra-abdominal abscess, upper gastrointestinal bleeding, pulmonary problem, pleural effusion, and wound problem): statistically similar. Postoperative mortality: statistically similar. Length of hospital stay: statistically similar. | AR was superior to NAR in terms of better survival and preventing local recurrence. |
| Furtado | Ann Surg Oncol (2014) | Surgery + adjuvant \(^ {131}\)I lipiodol vs surgery alone | OS: 1-, 2-, 3-, 5-year: favor surgery + adjuvant \(^ {131}\)I lipiodol. | DFS: 1-, 2-, 3-, 5-year: favor surgery + adjuvant \(^ {131}\)I lipiodol. | NA. | NA. | There is strong evidence for the use of adjuvant \(^ {131}\)I lipiodol to prolong DFS and OS, up to 5 years after resection. |
| Gong | Nucl Med Commun (2014) | Adjuvant therapy with \(^ {131}\)I lipiodol to hepatic resection | OS: 3-, 5-year: favor surgery + adjuvant \(^ {131}\)I lipiodol. | DFS: NA. | Recurrence: 2-, 5-year: lower in surgery + adjuvant \(^ {131}\)I lipiodol. | NA. | Postoperative adjuvant therapy with intra-arterial \(^ {131}\)I lipiodol to hepatic resection of HCC significantly improves OS and DFS rates and reduces recurrence rates. |
| Cheng | J Cancer Res Clin Oncol (2014) | Preoperative and postoperative TACE vs control | Preoperative TACE - OS: statistically similar. Mean tumor size ≥ 5 cm: statistically similar. Mean tumor size < 5 cm: statistically similar. Postoperative TACE - OS: favor postoperative TACE. Mean tumor size ≥ 5 cm: favor postoperative TACE. Mean tumor size < 5 cm: NA. | Preoperative TACE - DFS: statistically similar. Mean tumor size ≥ 5 cm: statistically similar. Mean tumor size < 5 cm: statistically similar. Postoperative TACE - DFS: favor postoperative TACE. Mean tumor size ≥ 5 cm: favor postoperative TACE. Mean tumor size < 5 cm: statistically similar. | NA. | NA. | Preoperative TACE did not improve DFS and OS for curative resection of HCC. Postoperative TACE offers potential benefits for curative HCC (tumor size > 5 cm). |
| Wang | Hepato-gastroenterology (2011) | Preoperative TACE vs control | OS: statistically similar. | DFS: statistically similar. | NA. | NA. | There are no significant benefits for 5-year OS and DFS. |
| Yu | Chinese-German J Clinical Oncology (2013) | Preoperative TACE vs control | OS: 5-year: favor preoperative TACE. | DFS: 3-year: statistically similar. 5-year: favor preoperative TACE. | NA. | NA. | Preoperative TACE can improve the 5-year DFS and OS rate. |
| Authors | Journal | Postoperative adjuvant TACE | Mortality: 1-, 3-year: favor postoperative TACE. 5-year: statistically similar. | Tumor recurrence: less in postoperative TACE. | NA. | NA. | Postoperative adjuvant TACE seems promising for HCC with risk factors (multiple nodules of > 5 cm or vascular invasion). |
|---------|---------|-----------------------------|--------------------------------------------------------------------------------|------------------------------------------------|------|------|---------------------------------------------------|
| Zhong   | Hepatol Res (2010) | Postoperative TACE | OS: 5-year: statistically similar. | DFS: 5-year: statistically similar. | Total recurrence: statistically similar. Intrahepatic recurrence: statistically similar. Extrahepatic recurrence: statistically similar. | Overall morbidity and in-hospital mortality: statistically similar. | Preoperative TACE does not seem to improve prognosis for resectable HCC. |
| Zhou    | BMC Gastroenterol (2013) | Preoperative TACE vs no preoperative TACE | OS: 5-year: statistically similar. | DFS: 5-year: statistically similar. | Total recurrence: statistically similar. Intrahepatic recurrence: statistically similar. Extrahepatic recurrence: statistically similar. | Overall morbidity and in-hospital mortality: statistically similar. | Preoperative TACE does not seem to improve prognosis for resectable HCC. |

**Surgical resection + adjuvant chemotherapy versus resection**

| Authors | Journal | Adjuvant therapy + curative liver resection | OS: Pre-operative transarterial chemotherapy: RCTs: 1-, 2-, 3-year: statistically similar. Both RCTs and Non-RCTs: 1-, 2-, 3-year: statistically similar. Post-operative transarterial chemotherapy: RCTs: 1-year: statistically similar. 2-, 3-year: favor post-operative transarterial chemotherapy. Both RCTs and Non-RCTs: 1-, 2-, 3-year: favor post-operative transarterial chemotherapy. Oral 5-fluorouracil: Both RCTs and Non-RCTs: 1-, 2-, 3-year: statistically similar. Combination of systemic and transarterial chemotherapy: 1-, 2-, 3-year: statistically similar. | Cumulative probability of no recurrence: Pre-operative transarterial chemotherapy: RCTs: 1-, 2-, 3-year: statistically similar. Both RCTs and Non-RCTs: 2-year: favor pre-operative transarterial chemotherapy. 1-, 3-year: statistically similar. Post-operative transarterial chemotherapy: RCTs: 1-year: statistically similar. 2-, 3-year: favor post-operative transarterial chemotherapy. Both RCTs and Non-RCTs: 1-, 2-, 3-year: favor post-operative transarterial chemotherapy. Oral 5-fluorouracil: Both RCTs and Non-RCTs: 1-, 3-year: statistically similar. Combination of systemic and transarterial chemotherapy: 1-, 2-, 3-year: statistically similar. | NA. | NA. | Post-operative transarterial chemotherapy improved survival and decreased the cumulative probability of no recurrence. |
|---------|---------|---------------------------------------|--------------------------------------------------------------------------------|------------------------------------------------|------|------|---------------------------------------------------|
| Mathurin| Aliment Pharmacol Ther (2003) | Adjuvant therapy + curative liver resection | NA. | | | | |
| Name       | Journal                  | Study  | Treatment                                      | OS:                              | DFS:                              | Mortality:                      | NA:                           | Notes                                                                                                                                 |
|------------|--------------------------|--------|-----------------------------------------------|----------------------------------|----------------------------------|--------------------------------|-------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|
| Ono        | Cancer (2001)            | Adjuvant chemotherapy after resection | worse in adjuvant chemotherapy after resection. | statistically similar.           | NA.                             | NA.                           | NA.                          | Cancer recurrence in the remnant liver is enhanced and the long-term outcome is deteriorated by postoperative chemotherapy after resection of HCC in cirrhotic patients. |
| Wang       | Can J Gastroenterol (2013)| Different adjuvant therapy after potentially curative treatment (including chemotherapy) | OS: Chemotherapy; statistics similar. | RFS: Chemotherapy; statistically similar. | NA.                             | NA.                           | NA.                          | Combination of systemic and transhepatic arterial chemotherapy is not recommended for HCC after potentially curative treatment. |
| Zheng      | Int J Cancer (2014)      | Hepatectomy + adjuvant chemotherapy vs hepatectomy alone | OS: 1-, 2-, 3-year: favor hepatectomy + adjuvant chemotherapy. | DFS: 1-, 2-, 3-year: favor hepatectomy + adjuvant chemotherapy. | NA.                             | NA.                           | NA.                          | Adjuvant chemotherapy is an effective treatment to improve the prognosis of primary HCC patients who underwent hepatectomy. |
| Zhong      | Mol Clin Oncol (2014)    | Adjuvant conventional oral systemic chemotherapy after curative hepatic resection | OS: 1-, 3-, 5-year: statistically similar. | DFS: 1-, 3-, 5-year: statistically similar. | NA.                             | NA.                           | NA.                          | Adjuvant conventional oral systemic chemotherapy provides only marginal benefits for HCC patients undergoing curative hepatic resection. |

**Surgical resection + immunotherapy versus resection**

| Name       | Journal                  | Study  | Treatment                                      | OS:                              | Mortality:                      | Recurrence:                      | NA:                           | Notes                                                                                                                                 |
|------------|--------------------------|--------|-----------------------------------------------|----------------------------------|--------------------------------|--------------------------------|-------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|
| Flores     | J Gastroenterol Hepatol (2009) | Adjuvant immunotherapy in combination with surgical resection | statistically similar. | NA.                             | Recurrence: statistically similar. | NA.                           | NA.                          | Adjuvant immunotherapy only shows a trend towards a benefit in improving survival and decreasing risk of tumor recurrence among patients with HCC after hepatic resection. |
| Ma         | Chinese J Cancer Prevention and Treatment (2011) | Hepatic resection or RFA alone vs surgery + adoptive immunotherapy | Mortality: 1-, 3-year: statistically similar. | NA.                             | Recurrence: 1-year: favor surgery + adoptive immunotherapy. | 3-year: statistically similar. | NA.                          | Adjuvant immunotherapy seems promising for patients with HCC after hepatic resection or radiofrequency ablation. |

DFS: Disease-free survival. OS: Overall survival. RFS: Relapse-free survival.
Different adjuvant therapy after potentially curative treatment (including adoptive immunotherapy)

OS: Adoptive immunotherapy: statistically similar.
RFS: Adoptive immunotherapy: favor adoptive immunotherapy.
NA.

Adjuvant immunotherapy produce limited success for survival.

Adoptive immunotherapy: statistically similar.

Adoptive immunotherapy: favor adoptive immunotherapy.

Adjuvant immunotherapy with cytokine induced killer cells or lymphokine activated killer cells may reduce recurrence in postoperative HCC, but may not improve survival.

OS: 1-, 3-year: statistically similar.

Recurrence: 1-, 3-year: favor adoptive immunotherapy.

Side effects: Only systematic reviews, but not meta-analyses.

NA.

For solitary HCC ≤ 5 cm, RFA can achieve comparable OS as resection, but higher recurrence rate and lower DFS.

For very early HCC with 2–3 nodules < 3 cm, RFA is more cost-effective than resection. For single larger early stage HCCs, surgical resection remains the best strategy.
| Author | Journal | Study Design | OS: 1-, 3-, 5-year | DFS: 1-, 3-, 5-year | Complications | Notes |
|--------|---------|--------------|---------------------|----------------------|--------------|-------|
| Duan   | World J Surg Oncol (2013) | RFA vs surgical resection | favor resection. | favor resection. | NA. | The long-term efficacy of resection is better than that of RFA, but with more complications and a longer hospital stay. |
| Feng   | J Cancer Res Clin Oncol (2014) | RFA vs surgical resection | OS: 1-, 3-, 5-year | favor resection. | NA. | Surgical resection leads to a higher OS and RFS rate in treating small HCC. |
| Fu     | Hepato-gastroenterology (2014) | RFA vs surgical resection | OS: 1-, 3-year | statistically similar. 5-year: favor resection. | RFS: 1-year: statistically similar. 3-, 5-year: favor resection. | Recurrence: 1-year: statistically similar. 2-, 3-year: favor resection. | |
| Hu     | HPB (2013) | RFA vs surgical resection | OS: 3-, 5-year | favor resection. | NA. | Local recurrence: favor resection. | |
| Li     | J Gastroenterol Hepatol (2012) | RFA vs surgical resection | OS: 1-, 3-, 5-year | favor resection. HCC ≤ 3 cm: 1-, 5-year: statistically similar. 3-year: favor resection. | RFS: favor resection. | Recurrence: 1-year: statistically similar. 2-, 3-year: favor resection. | |
| Liu    | World J Gastroenterol (2010) | RFA vs surgical resection | OS: 1-year, 3-year, end of follow-up: statistically similar. | | NA. | Recurrence: 1-, 3-year: statistically similar. end of follow-up: favor RFA. | RFA did not decrease the number of overall recurrences, and had no effect on survival when compared with surgical resection in a selected group of patients. |
| Liu    | Surg Laparosc Endos Percutan Tech (2010) | RFA vs surgical resection | OS: 1-, 2-year: statistically similar. 3-, 5-year: favor resection. | RFS: 1-, 3-, 5-year: favor resection. | Recurrence in previous sites: favor resection. Recurrence in new areas: favor RFA. Recurrence of extrahepatic areas: statistically similar. | NA. | RFA may have comparable results with surgical resection. |
| Ni     | J Cancer Res Clin Oncol (2013) | RFA/PEI (PAT) vs surgical resection | OS: 1-year: statistically similar. 2-, 3-, 5-year: favor resection. Small HCC ≤ 3 cm: 2-, 3-, 5-year: favor resection. | RFS: 1-, 2-, 3-, 5-year: favor resection. | NA. | Resection was superior to RFA and PEI for treatment of patients with early-stage HCC, but with more complications. |
| Qi     | J Clin Gastroenterol (2014) | RFA vs surgical resection | OS: Favor resection. | RFS: Favor resection. | NA. | Resection might improve the OS and RFS in small HCC patients, but with more complications and longer hospital stay. |
| Study | Journal | RFA vs | OS | DFS | Recurrence | Complications | Findings |
|-------|---------|--------|----|-----|-------------|---------------|----------|
| Sun   | World Chinese J Digestology (2011) | surgical resection | 1-, 3-, 5-year: favor resection | Tumor-free survival: 1-, 3-, 5-year: favor resection | NA | Complications: less in RFA | Resection has more complications, but a better overall efficacy. |
| Wang  | PLoS One (2014) | surgical resection | OS: RCT: 1-, 3-year: statistically similar. 5-year: favor resection. NRCT: 1-, 3-, 5-year: favor resection. | DFS: RCT: statistically similar. NRCT: 1-, 3-, 5-year: favor resection. RFS: RCT: 1- and 3-year: statistically similar. 5-year: favor resection. NRCT: 1-, 3-, 5-year: favor resection. | Recurrence: RCT: 1-year: statistically similar. 3-, 5-year: favor resection. NRCT: favor resection. | In-hospital mortality: statistically similar. Complications: less in RFA. Hospital stay: longer in resection. | The effectiveness of RFA is comparable to resection with fewer complications but higher recurrence, especially for very early HCC. |
| Weis  | Cochrane Database Syst Rev (2013) | other therapeutic methods (including RFA vs surgical resection) | OS: RFA vs surgical resection: statistically similar (random effect model); favor resection (fixed effect model). | NA | NA | Duration of admission: RFA vs surgical resection: shorter in RFA. | Hepatic resection is superior to RFA regarding survival. However, RFA might be associated with fewer complications and a shorter hospital stay than hepatic resection. |
| Xu    | World J Surg Oncol (2012) | surgical resection | OS: 1-, 3-, 5-year: favor resection. HCC < 3 cm: 1-, 3-, 5-year: favor resection. | DFS: 1-year: statistically similar. 2-, 3-, 4-year: favor resection. | Recurrence: favor RFA. | Complications: less in RFA. | Resection had significantly improved survival benefits and lower complications for early HCC, especially for HCC ≤ 3 cm in diameter. |
| Zhou  | Zhonghua Wai Ke Za Zhi (2011) | surgical resection | OS: 1-, 2-, 3-year: statistically similar. | DFS: 1-, 2-, 5-year: statistically similar. 3-year: favor resection. | Local intrahepatic recurrence: favor resection. Distant intrahepatic recurrence: statistically similar. | Postoperative morbidity: less in RFA. Postoperative mortality: statistically similar. | For small HCC within the Milan criteria, RFA had a similar OS to resection. RFA was less invasive with a lower postoperative morbidity. |
| Zhou  | BMC Gastroenterol (2010) | surgical resection | OS: 1-, 2-, 5-year: statistically similar. 3-year: favor resection. | DFS: 1-, 2-, 5-year: statistically similar. 3-year: favor resection. | Local intrahepatic recurrence: favor resection. Distant intrahepatic recurrence: statistically similar. | Postoperative morbidity: less in RFA. Postoperative mortality: statistically similar. | Resection was superior to RFA in the treatment of patients with small HCC eligible for surgical treatments, particularly for tumors > 3 cm. |
| PEI vs resection | | | | | | |
| Hoshida | Hepatology (2000) | Surgical resection vs PEI and LT (including PEI vs resection) | Surgical resection vs PEI: 3-year: statistically similar. | DFS: Surgical resection vs PEI: 3-year: statistically similar. | NA | NA | OS and DFS were comparable between PEI and resection. |
| Schoppmeyer | Cochrane Database Syst Rev (2009) | PEI vs PAI or surgery (including PEI vs surgery) | PEI vs surgery: statistically similar. | RFS: PEI vs surgery: statistically similar. | NA | NA | Insufficient evidence for firm conclusions regarding comparison between PEI vs surgery. |
### Non-surgical-resection ablation vs resection

**Dong**  
*World J Gastroenterol* (2014)  
Non-surgical-resection ablation vs surgical resection  
- **OS:** Non-surgical-resection ablation vs surgical resection: 1-, 3-year: statistically similar.  
- **DFS:** Non-surgical-resection ablation vs surgical resection: 1-, 3-year: statistically similar.  
- **Local recurrence:** Non-surgical-resection ablation vs surgical resection: At the end of follow-up: favor surgical resection.  
- **Adverse events:** Non-surgical-resection ablation vs surgical resection: Lower in surgical resection.  
- **Surgical resection is superior to non-surgical ablation for the treatment of small HCC.**

### RFA versus percutaneous ethanol injection (PEI) or percutaneous acetic acid injection (PAI)

**Bouza**  
*BMC Gastroenterol* (2009)  
RFA vs PEI  
- **OS:** 1-, 2-, 3-, 4-year: favor RFA.  
- **DFS:** 1-, 2-, 3-year: favor RFA.  
- **Local recurrence:** less in RFA.  
- **Tumor complete response:** favor RFA.  
- **Total complications:** less in PEI.  
- **Major complications:** statistically similar.  
- **The superiority of RFA versus PEI was supported, in terms of better survival and local control of the disease, for the treatment of patients with relatively preserved liver function and early-stage non-surgical HCC.**

**Cho**  
*Hepatology* (2009)  
RFA vs PEI  
- **OS:** 3-year: favor RFA.  
- **Local recurrence:** less in RFA.  
- **RFA demonstrated significantly improved 3-year survival status for patients with HCC, when compared to PEI.**

**Dong**  
*World J Gastroenterol* (2014)  
Surgical resection and non-surgical-resection ablation therapies (including RFA vs PEI)  
- **OS:** RFA vs PEI: 1-year: statistically similar. 2-, 3-year: favor RFA.  
- **Local recurrence:** RFA vs PEI: less in RFA.  
- **Complete necrosis:** RFA vs PEI: better in RFA.  
- **Complete tumor necrosis:** better in RFA.  
- **RFA is superior to PEI in term of 2- and 3-year OS.**

**Germani**  
*J Hepatol* (2010)  
RFA, PEI, PAI (including RFA vs PEI and PAI)  
- **OS:** RFA vs PEI: favor RFA. RFA vs PAI: statistically similar.  
- **Local recurrence:** RFA vs PEI: less in RFA. RFA vs PAI: statistically similar. de novo tumours: RFA vs PEI: statistically similar. RFA vs PAI: statistically similar.  
- **Complete necrosis:** RFA vs PEI: less in RFA. RFA vs PAI: statistically similar. RFA vs PEI: statistically similar. Major complications: RFA vs PEI: statistically similar.  
- **RFA seems to be a superior ablative therapy than PEI for HCC, particularly for tumours > 2 cm. RFA and PAI have similar survival rates.**

**Orlando**  
*Am J Gastroenterol* (2009)  
RFA vs PEI  
- **OS:** 1-, 2-, 3-year: favor RFA.  
- **Local recurrence:** less in RFA.  
- **Complete tumor necrosis:** better in RFA.  
- **RFA is superior to PEI in the treatment of small HCC with respect to OS and DFS. RFA shows a significantly smaller risk of local recurrence.**
| Author      | Journal                           | Comparison                          | OS: (survival)                                                                 | Local recurrence: | Complications: | Remarks                                                                 |
|-------------|-----------------------------------|-------------------------------------|--------------------------------------------------------------------------------|-------------------|----------------|-------------------------------------------------------------------------|
| Shen        | J Gastroenterol Hepatol (2013)    | RFA vs PEI                          | 3-year: favor RFA                                                             | NA.               | NA.            | RFA appears superior to PEI with respect to 3-year survival for small HCCs < 3 cm. RFA was more feasible in patients with HCCs > 2 cm or Child–Pugh A liver function. |
| Weis        | Cochrane Database Syst Rev (2013) | RFA vs other therapeutic methods (including RFA vs PEI or PAI) | RFA vs PEI or PAI: favor RFA.                                                | NA.               | NA.            | RFA seems superior to PEI regarding survival.                            |
| Xu          | Eur J Med Res (2014)              | RFA vs PEI                          | 1-, 2-, 3-year: favor RFA.                                                    | NA.               | NA.            | RFA is superior to PEI in better survival and local disease control for small HCCs < 5 cm in diameter. |

**RFA versus cryosurgery ablation (CSA)**

| Author      | Journal                                      | Comparison                          | OS: (survival)                                                                 | Local recurrence: | Complications: | Remarks                                                                 |
|-------------|----------------------------------------------|-------------------------------------|--------------------------------------------------------------------------------|-------------------|----------------|-------------------------------------------------------------------------|
| Huang       | Hepato-gastroenterology (2013)               | RFA vs CSA                          | statistically similar.                                                         | NA.               | NA.            | RFA is significantly superior to CSA.                                    |

**RFA versus laser ablation**

| Author      | Journal                                      | Comparison                          | OS: (survival)                                                                 | Local recurrence: | Complications: | Remarks                                                                 |
|-------------|----------------------------------------------|-------------------------------------|--------------------------------------------------------------------------------|-------------------|----------------|-------------------------------------------------------------------------|
| Weis        | Cochrane Database Syst Rev (2013)            | RFA vs other therapeutic methods (including RFA vs laser ablation) | RFA vs laser ablation: statistically similar.                                 | NA.               | NA.            | RFA seems to be similar to laser ablation. (Only one trial was identified.) |

**RFA vs microwave ablation**

| Author      | Journal                                      | Comparison                          | OS: (survival)                                                                 | Local recurrence: | Complications: | Remarks                                                                 |
|-------------|----------------------------------------------|-------------------------------------|--------------------------------------------------------------------------------|-------------------|----------------|-------------------------------------------------------------------------|
| Weis        | Cochrane Database Syst Rev (2013)            | RFA vs other therapeutic methods (including RFA vs microwave ablation) | NA.                                                                            | Local progression: RFA vs microwave ablation: statistically similar. | NA.   | RFA seems to be similar to microwave ablation. (Only one trial was identified.) |

**RFA vs any other therapeutic methods**

| Author      | Journal                                      | Comparison                          | OS: (survival)                                                                 | Local recurrence: | Complications: | Remarks                                                                 |
|-------------|----------------------------------------------|-------------------------------------|--------------------------------------------------------------------------------|-------------------|----------------|-------------------------------------------------------------------------|
| Huang       | Zhonghua Nei Ke Za Zhi (2008)                 | RFA vs other therapeutic methods    | 3-year: favor RFA                                                             | NA.               | Local recurrence: favor RFA.                                           | RFA is superior to other treatment methods with respect to local recurrence and 3-year overall survival in early HCC and is the preferred therapeutic methods for small HCC. |

**PEI versus PAI**

| Author      | Journal                                      | Comparison                          | OS: (survival)                                                                 | Local recurrence: | Complications: | Remarks                                                                 |
|-------------|----------------------------------------------|-------------------------------------|--------------------------------------------------------------------------------|-------------------|----------------|-------------------------------------------------------------------------|
| Germani     | J Hepatol (2010)                             | RFA, PEI, PAI (including PAI vs PEI)| PAI vs PEI: statistically similar.                                           | Local recurrence: | Complete necrosis: PAI vs PEI: statistically similar.                  | PAI did not differ significantly from PEI for all the outcomes evaluated. |
| Author     | Journal/Journal Name       | Study Design                          | OS: PEI vs PAI | RFS: PEI vs PAI | Hospital stay | Major complications | Major Adverse events | Major Complications |
|------------|----------------------------|---------------------------------------|----------------|----------------|---------------|----------------------|---------------------|---------------------|
| Schoppmeyer | Cochrane Database Syst Rev (2009) | PEI vs PAI or surgery (including PEI vs PAI) | OS: statistically similar. | RFS: statistically similar. | NA. | PEI and PAI do not differ significantly regarding benefits and harms in patients with early HCC. |
| Dong       | World J Gastroenterol (2014) | Surgical resection and non-surgical resection therapies (including RFA vs RFA+TACE) | OS: RFA vs RFA+TACE: 1-, 3-year: statistically similar. 5-year: favor RFA+TACE. | NA. | NA. | RFA in combination with TACE can improve the 5-year OS. |
| Han        | J Intervent Radiol (China) (2013) | RFA + TACE vs TACE | OS: 1-, 2-, 3-year: favor RFA+TACE. | NA. | NA. | RFA plus TACE can significantly improve the long-term survival rate. |
| Jiang      | Tumour Biol (2014) | RFA + TACE vs RFA alone | OS: 1-, 3-year: favor RFA+TACE. | NA. | NA. | RFA plus TACE improve the survival rates compared with RFA alone for patients with HCC. |
| Kong       | Tumour Biol (2014) | RFA + TACE vs RFA alone | OS: 1-, 3-, 5-year: favor RFA+TACE. | NA. | NA. | The combination of RFA with TACE has advantages in improving OS. |
| Liao       | PLoS One (2013) | TACE + 3D-CRT, HIFU, PEI, RFA, or RT vs TACE alone (including TACE+RFA vs TACE) | OS: RCT: 1-year: TACE+RFA vs TACE: statistically similar. | NA. | NA. | TACE combined with RFA could not improve the OS status, as compared with TACE alone. |
| Liu        | Tumour Biol (2014) | RFA + TACE vs RFA alone | OS: 1-, 3-year: favor RFA+TACE. | RFS: 1-, 3-year: favor RFA+TACE. | NA. | Major complications: statistically similar. | Adverse events: NA. (systematic reviews, but not meta-analyses). |
| Lu         | Eur J Gastroenterol Hepatol (2013) | RFA + TACE vs RFA alone | OS: 1-, 3-year: favor RFA+TACE. 5-year: statistically similar. > 3 cm: 1-, 3-, 5-year: favor RFA+TACE. < 3 cm: statistically similar. | NA. | NA. | Major complications: statistically similar. | RFA plus TACE improve the survival rates compared with RFA alone for patients with HCC > 3 cm. |
| Ni         | World J Gastroenterol (2013) | RFA + TACE vs RFA alone | OS: 1-, 2-, 3-year: favor RFA+TACE. 5-year: statistically similar. < 3 cm: 1-, 3-year: statistically similar. 3–5 cm: 1-, 3-, 5-year: favor RFA+TACE. > 5 cm: 1-, 3-year: favor RFA+TACE. | RFS: 3-, 5-year: favor RFA+TACE. 1-year: statistically similar. Progression rate: less in RFA + TACE. | NA. | Major complications: statistically similar. | |
| Author | Journal | Treatment | OS: 1-, 3-year | RFS: 1-year | Local recurrence | Tumor response | Notes |
|--------|---------|-----------|----------------|-------------|-----------------|--------------|-------|
| Ni     | J Cancer Res Clin Oncol (2013) | RFA + TACE vs RFA or TACE alone | favor RFA+TACE | statistically similar | favor RFA+TACE | | The combination of TACE and RFA has better effectiveness than that of TACE and RFA monotherapy in the treatment for patients with HCC. |
| Yan    | Dig Dis Sci (2012); Dig Dis Sci (2013) duplicates | RFA + TACE vs RFA alone | favor RFA+TACE | | | | The combination of TACE with RFA can improve the OS and provides better prognosis for patients with HCC. |
| Zhao   | J Intervent Radiol (China) (2013) | RFA + TACE vs RFA or TACE alone | favor RFA+TACE | | | | RFA plus TACE is superior to TACE or RFA monotherapy. |
| Liao   | PLoS One (2013) | TACE + 3D-CRT, HIFU, PEI, RFA, or RT vs TACE alone (TACE + PEI vs TACE) | | | | | TACE combined with PEI could improve the OS status than performing TACE alone. |
| Wang   | Med Oncol (2011) | TACE + PEI vs TACE alone | favor TACE + PEI | | | | The efficacy of TACE combined with PEI is significantly better than that of TACE alone. |
| Wang   | Liver Int (2010) | TACE + percutaneous ablation therapy (RFA or PEI) vs TACE or percutaneous ablation therapy alone (TACE + PEI vs PEI) | favor TACE + PEI | | | | TACE combined with PEI improved the OS status for large HCCs. |
| Gu     | J Cancer Res Clin Oncol (2014) | TACE + local ablative therapy vs monotherapy | favor TACE + local ablative therapy | | | | The combination of TACE with local ablative therapy was superior to monotherapy in the treatment for patients with HCC. |

**PEI + TACE versus monotherapy**

| Author | Journal | Treatment | OS: 1-, 2-, 3-year | Local recurrence | Tumor response | OS: Decline rates of the AFP level: favor TACE + PEI | Adverse events: (systematic reviews, but not meta-analyses). | Notes |
|--------|---------|-----------|----------------|-----------------|--------------|----------------------------------------|-------------------------------------------------|-------|
| Liao   | PLoS One (2013) | TACE + 3D-CRT, HIFU, PEI, RFA, or RT vs TACE alone (TACE + PEI vs TACE) | | | | | | |
| Wang   | Med Oncol (2011) | TACE + PEI vs TACE alone | | | | | | |
| Wang   | Liver Int (2010) | TACE + percutaneous ablation therapy (RFA or PEI) vs TACE or percutaneous ablation therapy alone (TACE + PEI vs PEI) | | | | | | |

**Any local ablative therapy + TACE versus monotherapy**

| Author | Journal | Treatment | OS: 1-, 2-, 3-, 5-year: favor TACE + local ablative therapy | Tumor response: favor TACE + local ablative therapy. | Notes |
|--------|---------|-----------|----------------------------------------|-------------------------------------------------|-------|
| Gu     | J Cancer Res Clin Oncol (2014) | TACE + local ablative therapy vs monotherapy | | | The combination of TACE with local ablative therapy was superior to monotherapy in the treatment for patients with HCC. |
| First author | Journal (Year) | Comparisons | OS | DFS, RFS, TTP, PFS | Recurrence, time to recurrence | Other endpoints | Major comments |
|--------------|----------------|-------------|----|------------------|-------------------------------|----------------|---------------|
| Camma        | Radiology (2002) | TACE or TAE vs non-active treatment; different transarterial modalities of therapy | TACE or TAE vs non-active treatment: 2-year mortality: lower in TACE or TAE. TAE vs transarterial chemotherapy: overall mortality: lower in TAE. | NA. | NA. | NA. | In patients with unresectable HCC, chemoembolization significantly improved the overall 2-year OS compared with nonactive treatment, but the magnitude of the benefits was relatively small. |
| Geschwind    | Am J Clin Oncol (2003) | Therapeutic embolization vs supportive care alone | OS: 3-, 6-month: statistically similar. | NA. | NA. | NA. | The data fail to show a survival advantage associated with therapeutic embolization versus supportive care alone in patients with unresectable HCC. |
| Leng         | ANZ J Surg (2014) | TACE vs control treatment | OS: 1-year: better in TACE. | NA. | NA. | NA. | TACE improves the 1-year survival of patients with HCC and PVTT. |
| Llovet       | Hepatology (2003) | TACE or tamoxifen vs control treatment (including TACE versus no treatment) | OS: TACE vs control treatment: 2-year: favor TACE. | NA. | NA. | NA. | Chemoembolization improves survival of patients with unresectable HCC and may become the standard treatment. |
| Marelli      | Cardiovasc Intervent Radiol (2007) | Transarterial therapy vs conservative management | TACE, TAE, or transarterial oily chemoembolization versus conservative treatment: mortality: lower in TACE, TAE, or transarterial oily chemoembolization. | NA. | NA. | NA. | TACE improves survival. |
| Oliveri      | Cochrane Database Syst Rev (2011) | TACE or TAE vs placebo, sham, or no intervention | OS: statistically similar. | NA. | NA. | NA. | No firm evidence to support or refute TACE or TAE for patients with unresectable HCC. |
| Author | Journal | Methodology | TACE vs TAE | OS | Complications | Notes |
|--------|---------|-------------|-------------|----|---------------|-------|
| Xue | BMC Gastroenterol (2013) | TACE vs conservative treatment | 6-month, 1-year: favor TACE. | NA | NA | TACE, as a safe treatment, has potential for incurring a survival benefit for advanced HCC with PVTT, even with MPV obstruction. |
| Camma | Radiology (2002) | TACE or TAE vs non-active treatment; different transarterial modalities of therapy (including TAE vs TACE) | TAE vs TACE: overall mortality: statistically similar. | NA | NA | The addition of an anticancer drug did not improve the therapeutic benefit of TAE. |
| Marelli | Cardiovasc Intervent Radiol (2007) | Transarterial therapy vs conservative management; different transarterial modalities of therapy (including TACE vs TAE) | TACE vs TAE: statistically similar. | NA | NA | TAE appears as effective as TACE. |
| Xie | Tumour Biol (2014) | TACE vs TAE | OS: statistically similar. | NA | NA | Adverse events: higher in TACE (no statistical comparison). |
| Gao | Hepato-gastroenterology (2013) | DEB-TACE vs cTACE | NA | NA | Complete or partial response, stable or progressive disease, disease control: statistically similar. DEB-TACE is able to accomplish the same tumor response as conventional TACE. |
| Han | PLoS One (2014) | DEB-TACE vs cTACE | NA | NA | Disease control: statistically similar. Complications: statistically similar. Severe complications: statistically similar. DEB-TACE has the same disease control rate without an increase in complications and severe complications. |
| Huang | J Gastroenterol Hepatol (2014) | DEB-TACE vs cTACE | OS: 1-, 2-year: better in DEB-TACE. 6-month, 3-year: statistically similar. | NA | NA | Objective tumor response: better in DEB-TACE. Adverse side effect: similar (no statistical comparison). DEB-TACE provides significantly better tumor response compared with cTACE; DEB-TACE is as safe as cTACE. |
| Study | Year | TACE vs microsphere embolization | OS: favor microsphere embolization. 1-year: Total analysis: favor microsphere embolization. Yttrium 90 (90Y) microspheres: statistically similar. 32P glass microspheres: favor 32P glass microspheres. | TTP: longer in microsphere embolization. | Tumor response: Total analysis: better in microsphere embolization. Yttrium 90 (90Y) microspheres: statistically similar. 32P glass microspheres: favor 32P glass microspheres. Microsphere embolization treatment of patients with surgically unresectable HCC provided much better survival and treatment response than that of TACE. |
|-------|------|---------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|------------------------------------------------------------------------------------------------|
| Xie   | J Cancer Res Clin Oncol (2012) | TACE vs microsphere embolization |                                                                                                                                                 | NA.                             |                                                                                                 |

| Study | Year | TACE + sorafenib vs TACE alone | OS: 6-month, 1-year: favor TACE+sorafenib. 2-year: statistically similar. 3-, 6-month progression free rate: Lower in TACE+sorafenib. | TTP: Longer in TACE+sorafenib. | Objective response ratio & clinical benefit ratio: better in TACE+sorafenib. Complications: higher in TACE+sorafenib. Combination of sorafenib and TACE showed survival and clinical benefits in patients with HCC, though enhanced morbidity. |
|-------|------|---------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|NA.                             | NA.                                                                                              |
| Fu    | J Cancer Res Clin Oncol (2014) | TACE + sorafenib vs TACE alone |                                                                                                                                                 | NA.                             | Combination therapy may bring benefits for unresectable HCC patients in terms of TTP but not OS. |
| Liu   | PLoS One (2014) | TACE + sorafenib vs monotherapy | OS: statistically similar.                                                                                                                     | NA.                             |                                                                                                 |
| Yang  | Mol Biol Rep (2014) | TACE + sorafenib vs TACE alone | All studies: favor TACE+sorafenib. RCTs: statistically similar. Retrospective studies: favor TACE+sorafenib.                                                                 | NA.                             | Response to treatment: All studies: favor TACE+sorafenib. RCTs: favor TACE+sorafenib. Retrospective studies: favor TACE+sorafenib. When compared with TACE monotherapy, the combination of TACE and sorafenib is likely to improve OS, TTP and response to treatment, but with more sorafenib-related adverse events. |
| Zhang | PLoS One (2014) | TACE + sorafenib vs TACE alone | OS: favor TACE+sorafenib.                                                                                                                     | TTP: longer in TACE+sorafenib.  | Objective response ratio: better in TACE+sorafenib. Complications: higher in TACE+sorafenib. The combination therapy of TACE plus sorafenib in patients with intermediate or advanced stage of HCC, can improve the OS, TTP, and objective tumor response, but with a significantly increased risk of adverse reactions. |

All studies: favor TACE+sorafenib. RCTs: statistically similar. Retrospective studies: favor TACE+sorafenib.
### TACE + HIFU versus TACE

| Author | Journal | Study Details | OS: | Adverse Events: | Combined Therapy |
|--------|---------|---------------|-----|----------------|-----------------|
| Cao    | Ultrasound Med Biol (2011) | TACE + HIFU vs TACE alone | favor TACE + HIFU | NA | Tumor response: better in TACE + HIFU. Combined therapy was more therapeutically beneficial. |
| Liao   | PLoS One (2013) | TACE + 3D-CRT, HIFU, PEI, RFA, or RT vs TACE alone (including TACE+HIFU vs TACE) | OS: RCT: 1-year: TACE+HIFU vs TACE: favor TACE+HIFU. 3-year: TACE+HIFU vs TACE: statistically similar. Observational studies: 1-year: TACE+HIFU vs TACE: favor TACE+HIFU. 3-year: TACE+HIFU vs TACE: favor TACE+HIFU. | NA | Adverse events: NA. (systematic reviews, but not meta-analyses). TACE combined with HIFU could improve the OS status than TACE alone. |

### TACE + thermotherapy versus TACE

| Author | Journal | Study Details | OS: | Adverse Events: | Combination Therapy |
|--------|---------|---------------|-----|----------------|------------------|
| Li     | Chinese Journal of Evidence-Based Medicine (2012) | TACE + thermotherapy vs TACE alone | 1-, 2-year: favor TACE + thermotherapy. 0.5-, 1.5-, 3-year: statistically similar. | NA | Overall effective rate: better in TACE + HIFU. Quality of life: better in TACE + HIFU. |

### TACE + argon-helium cryotherapy system (AHCS) versus TACE

| Author | Journal | Study Details | OS: | Adverse Events: | Compared with the TACE or AHCS alone, TACE combined with AHCS can improve long-term survival rate and short-term curative effect, and improve the patients’ immunity. |
|--------|---------|---------------|-----|----------------|-------------------------------------------------|
| Li     | Chinese Journal of Evidence-Based Medicine (2013) | TACE + AHCS vs TACE alone; TACE + AHCS vs AHCS | TACE + AHCS vs TACE alone: Total effective rate, complete necrosis rate, recurrence: favor TACE + AHCS. AFP reduction and CD4 improvement: Favor TACE + AHCS. Adverse events: statistically similar. TACE + AHCS vs AHCS alone: AFP reduction and CD4 improvement: favor TACE + AHCS. | NA | Compared with the TACE or AHCS alone, TACE combined with AHCS can improve long-term survival rate and short-term curative effect, and improve the patients’ immunity. |
| Author       | Journal               | Intervention                                                                 | OS: RCT:                                                                 | Adverse events: | Tumor response: |
|--------------|-----------------------|------------------------------------------------------------------------------|--------------------------------------------------------------------------|----------------|----------------|
| Liao         | PLoS One (2013)       | TACE + radiotherapy vs TACE alone (including TACE+radiotherapy vs TACE)      | 1-year: TACE+radiotherapy vs TACE: favor TACE+radiotherapy.              | NA             | NA             |
|              |                       |                                                                               | 3-year: TACE+radiotherapy vs TACE: favor TACE+radiotherapy.               |                |                |
|              |                       |                                                                               | Observational studies:                                                  |                |                |
|              |                       |                                                                               | 1-year: TACE+radiotherapy vs TACE: favor TACE+radiotherapy.               |                |                |
|              |                       |                                                                               | 3-year: TACE+radiotherapy vs TACE: favor TACE+radiotherapy.               |                |                |
|              |                       |                                                                               | 5-year: TACE+radiotherapy vs TACE: favor TACE+radiotherapy.               |                |                |
| Meng        | Radiother Oncol (2009)| TACE + radiotherapy vs TACE alone                                           | OS: 1-, 2-, 3-, 5-year: favor TACE + radiotherapy.                       | NA             | NA             |
|              |                       |                                                                               | Tumor response: favor TACE + radiotherapy.                               |                |                |
|              |                       |                                                                               | Nausea/vomit: statistically similar.                                     |                |                |
|              |                       |                                                                               | Leukocyte count declined: statistically similar.                         |                |                |
|              |                       |                                                                               | Alanine aminotransferase level increased: statistically similar.         |                |                |
|              |                       |                                                                               | Total bilirubin level increased: higher in TACE + radiotherapy.          |                |                |

TACE combined with radiotherapy could improve the OS status than TACE alone.

| Author       | Journal               | Intervention                                                                 | OS: RCT:                                                                 | Adverse events: | Tumor response: |
|--------------|-----------------------|------------------------------------------------------------------------------|--------------------------------------------------------------------------|----------------|----------------|
| Liao         | PLoS One (2013)       | TACE + three-dimensional conformal radiation therapy (3D-CRT) vs TACE alone | 1-year: TACE+3D-CRT vs TACE: favor TACE+3D-CRT.                           | NA             | NA             |
|              |                       |                                                                               | 3-year: TACE+3D-CRT vs TACE: favor TACE+3D-CRT.                           |                |                |
|              |                       |                                                                               | Observational studies:                                                  |                |                |
|              |                       |                                                                               | 1-year: TACE+3D-CRT vs TACE: favor TACE+3D-CRT.                           |                |                |
|              |                       |                                                                               | 3-year: TACE+3D-CRT vs TACE: favor TACE+3D-CRT.                           |                |                |

TACE combined with 3D-CRT could improve the OS status than TACE alone.
| Author | Journal | Study Design | Outcomes |
|--------|---------|--------------|----------|
| Cheung | Evid Based Complement Alternat Med (2013) | TACE + TCM vs TACE alone | OS: 6-, 12-, 18-, 24-, 36-month: favor TCM. NA. NA. Tumor response: favor TCM. Quality of life using KPS: favor TCM. TACE toxicity: favor TCM. The use of TCM may increase the efficacy and reduce the toxicity of TACE in treating patients with unresectable HCC. TCM could be considered as an adjuvant therapy for unresectable HCC patients during TACE. |
| Cho    | Expert Opin Investig Drugs (2009) | TACE + Chinese herbal therapy vs TACE alone | OS: 1-, 2-, 3-year: favor TCM. 6-month: statistically similar. NA. NA. Tumor response: favor TCM. Quality of life: favor TCM. Immunolisation: favor TCM. Recovery of liver function: favor TCM. AFP concentration: lower in TCM. Reduction in chemotherapy toxicities: favor TCM. The use of TCM to enhance the efficacy of TACE in HCC patients. |
| Meng   | J Altern Complement Med (2008) | TACE + TCM vs TACE alone | OS: 6-, 12-, 24-, 36-month: favor TACE+TCM NA. NA. Tumor response: favor TACE+TCM. Symptom alleviation: favor TACE+TCM. Quality of life by Karnofsky performance score: favor TACE+TCM. Bone toxicity rate: favor TCM. TCM plus TACE, compared with TACE alone, was more therapeutically beneficial. |
| Meng   | Explore (NY) (2011) | TACE + TCM vs TACE alone | NA. NA. NA. Proportion of CD3+ T cells: favor TACE + TCM. Proportion of CD4+ T cells: favor TACE + TCM. Proportion of CD8+ T cells: statistically similar. Ratio of CD4 / CD8: favor TACE + TCM. Proportion of NK cells: favor TACE + TCM. Adverse events: decreased in TACE + TCM. TCM in combination with TACE improves the immune response of patients with unresectable HCC. |
### Oral systemic chemotherapy

Oral systemic chemotherapy was evaluated in two meta-analyses [78, 148]. The OS, RFS, and recurrence were statistically similar between patients with and without chemotherapy [78, 148].

RCT studies were included in the meta-analyses by Zhong \((n = 3)\) and Mathurin \((n = 1)\).

The meta-analysis by Zhong had a larger number of included studies than that by Mathurin \((3 \text{ versus } 2)\) (Supplementary Table S18). Not all included studies were the same between them.

The results were completely consistent between the two meta-analyses. In details, the adjunctive use of oral systemic chemotherapy should not be favored in patients undergoing surgical resection.

### Transarterial chemotherapy

Transarterial chemotherapy was evaluated in one meta-analysis [78]. As for the pre-operative transarterial chemotherapy, the overall analysis of both RCTs and non-RCTs demonstrated that chemotherapy improved the 2-year survival, but not the 1- or 3-year survival. The subgroup analysis of RCTs showed that the 1-, 2-, and 3-year recurrence were statistically similar between the two groups. As for the post-operative transarterial chemotherapy, the overall analysis of both RCTs and non-RCTs demonstrated that chemotherapy improved the 1-, 2-, and 3-year survival. The subgroup analysis of RCTs showed that chemotherapy improved the 2- and 3-year survival, but not the 1-year survival.

Approaches of chemotherapy were mixed in three meta-analyses [92, 112, 147]. The statistical results were largely inconsistent among them. One of them favored the chemotherapy in term of OS [147]; one showed that

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**Table**

| Authors | Reference | Group 1 | Group 2 | OS | TTP | KPS | Liver function | Immune function | Notes |
|---------|-----------|---------|---------|----|-----|-----|---------------|---------------|-------|
| Sun     | Afr J Tradit Complement Altern Med (2012) | TACE + Compound Kushen Injection vs TACE alone | 1-year OS: favor TACE + Compound Kushen Injection. | NA | NA | NA | NA | Compound Kushen Injection plus TACE is superior to TACE alone for unresectable HCC. |
| Wu      | J Cancer Res Ther (2014) | TACE + Cinobufacini vs TACE only | OS: 1-year: statistically similar. 2-year: favor TACE + Cinobufacini. | NA | NA | NA | NA | Cinobufacini combined with TACE can significantly increase the objective response rate and 2-year survival rate compared with TACE only in patients with advanced HCC. |
| Chen    | Chinese-German J Clin Oncol (2013) | TACE + CIK cell therapy vs TACE alone | OS: favor CIK cell + TACE. 0.5-, 1-, 2-year: favor CIK cell + TACE. | TTP: favor CIK cell + TACE. | NA | NA | NA | CIK cells combined with TACE therapy demonstrated a significant superiority in improving recent and forward curative effects, immunity function, quality of life and liver function of HCC patients. |
| Li      | Clin Res Hepatol Gastroenterol (2014) | CIK cell therapy+TACE+RFA vs TACE+RFA; CIK cell therapy+TACE vs TACE | OS: CIK+TACE+RFA vs TACE+RFA: 1-, 2-, 3-year: favor CIK+TACE+RFA. CIK+TACE vs TACE: 0.5-, 1-, 2-year: favor CIK+TACE. | RFS: CIK+TACE+RFA vs TACE+RFA: 1-year: favor CIK+TACE+RFA. | NA | NA | NA | CIK cells transfusion therapy truly showed a synergistic effect for HCC patients after minimally invasive treatment especially for a long-term survival. |
the OS was statistically similar between the two groups [112]; one demonstrated that the OS was decreased by chemotherapy [92].

RCT studies were included in the meta-analyses by Zheng (n = 13), Wang (n = 8), and Ono (n = 3).

The meta-analysis by Zheng had a larger number of included studies than those by Wang and Ono (48 versus 8 and 3) (Supplementary Table S19).

Given its superiority in the quantity of RCT studies, the results of the meta-analysis by Zheng might be more reliable.

**Surgical resection + immunotherapy versus surgical resection alone**

Four meta-analyses compared the outcomes of surgical resection in combination with immunotherapy versus surgical resection alone [32, 75, 112, 124]. All of them demonstrated that the OS was statistically similar between the two groups [32, 75, 112, 124]. One of them favored the combination therapy in terms of DFS/RFS. One of them favored the combination therapy in terms of 1- and 3-year recurrence [124]; one favored the combination therapy in term of recurrence at the previous sites, but favored RFA in terms of recurrence at new sites [69]; one demonstrated that the OS was statistically similar between the two groups, but the 3-year survival was better in surgical resection group [33, 72, 89, 117]; one found that the 1- and 5-year survival were statistically similar between the two groups, but the 3-year survival was better in surgical resection group [155]; one reported that surgical resection had better OS than RFA in the subgroup analyses of a single nodule 3–5 cm and ≤ 3 cm, but the OS was statistically similar between the two groups in the subgroup analyses of a single nodule < 2 cm and 2–3 nodules < 3 cm [24].

As for the DFS, nine of them favored surgical resection in terms of DFS/RFS at any time points [11, 27, 31, 61, 72, 89, 97, 106, 155]; three showed that the 1-year DFS was statistically similar between the two groups, but the 3- and/or 5-year DFS were better in surgical resection group than in RFA group [16, 33, 151]; one reported that surgical resection had better DFS than RFA in the subgroup analyses of a single nodule 3–5 cm and ≤ 3 cm, but the DFS was statistically similar between the two groups in the subgroup analyses of a single nodule < 2 cm and 2–3 nodules < 3 cm [24].

As for the recurrence, three of them favored surgical resection [11, 47, 61]; two favored RFA [127, 151]; one found that the recurrence was statistically similar between the two groups [24]; three showed that the 1-year recurrence was statistically similar between the two groups, but the 3-year recurrence was less in surgical resection group than in RFA group [31, 33, 117]; one reported that the 1- and 3-year recurrence were statistically similar between the two groups, but the recurrence at the end of follow-up was less in RFA group than in surgical resection group [69]; one demonstrated that the distant intrahepatic recurrence was statistically similar between the two groups, but the local intrahepatic recurrence was less in surgical resection group than in RFA group [153]; one favored surgical resection in term of recurrence at previous sites, but favored RFA in term of recurrence at new sites [72].

According to the description of each meta-analysis, RCT studies were included the meta-analyses by Liu (Surg Endosc, 2010) (n = 8), Ni (n = 6), Fu (n = 5), Zhou (Zhonghua Wai Ke Za Zhi, 2011) (n = 4), Hu (n = 4), Feng (n = 3), Qi (n = 3), Wang (n = 3), Weis (n = 3), Duan (n = 2), Li (n = 2),

**Ablation therapy**

**RFA versus surgical resection**

Eighteen meta-analyses compared the outcomes of RFA versus surgical resection [11, 16, 24, 27, 31, 33, 47, 61, 69, 72, 89, 97, 106, 117, 119, 127, 151, 153]. As for the OS, seven of them favored surgical resection [27, 31, 47, 61, 97, 106, 127]; four demonstrated that the OS was statistically similar between the two groups [11, 16, 119, 151]; four showed that the 1-year survival was statistically similar between the two groups, but the 5-year survival was better in surgical resection group [33, 72, 89, 117]; one found that the 1- and 5-year survival were statistically similar between the two groups, but the 3-year survival was better in surgical resection group [155]; one reported that surgical resection had better OS than RFA in the subgroup analyses of a single nodule 3–5 cm and ≤ 3 cm, but the OS was statistically similar between the two groups in the subgroup analyses of a single nodule < 2 cm and 2–3 nodules < 3 cm [24].

As for the DFS, nine of them favored surgical resection in terms of DFS/RFS at any time points [11, 27, 31, 61, 72, 89, 97, 106, 155]; three showed that the 1-year DFS was statistically similar between the two groups, but the 3- and/or 5-year DFS were better in surgical resection group than in RFA group [16, 33, 151]; one reported that surgical resection had better DFS than RFA in the subgroup analyses of a single nodule 3–5 cm and ≤ 3 cm, but the DFS was statistically similar between the two groups in the subgroup analyses of a single nodule < 2 cm and 2–3 nodules < 3 cm [24].

As for the recurrence, three of them favored surgical resection [11, 47, 61]; two favored RFA [127, 151]; one found that the recurrence was statistically similar between the two groups [24]; three showed that the 1-year recurrence was statistically similar between the two groups, but the 3-year recurrence was less in surgical resection group than in RFA group [31, 33, 117]; one reported that the 1- and 3-year recurrence were statistically similar between the two groups, but the recurrence at the end of follow-up was less in RFA group than in surgical resection group [69]; one demonstrated that the distant intrahepatic recurrence was statistically similar between the two groups, but the local intrahepatic recurrence was less in surgical resection group than in RFA group [153]; one favored surgical resection in term of recurrence at previous sites, but favored RFA in term of recurrence at new sites [72].
Sun \((n = 2)\), Xu \((n = 2)\), Chen \((n = 1)\), and Zhou (BMC Gastroenterol, 2010) \((n = 1)\). The information regarding the inclusion of RCT studies was not available in the meta-analyses by Cai and Cucchetti. After checking the relevant information, we confirmed the following: 1) in the meta-analysis by Liu (Surg Endosc, 2010), all included studies were non-RCTs; 2) in the meta-analysis by Ni, there were one RCT regarding resection v.s. PEI, one RCT regarding resection v.s. PEI or ablation, and two RCTs with overlapped data; 3) in the meta-analysis by Fu, there were one RCT regarding comparison of resection v.s. PEI or ablation and two RCTs with overlapped data; 4) in the meta-analysis by Zhou (Zhonghua Wai Ke Za Zhi, 2011), one included study was non-RCT; and 5) because no included studies were listed in the meta-analysis by Hu, we could not check the accuracy. Thus, the largest number of RCT studies included in the meta-analyses should be 3.

The meta-analysis by Wang had the largest number of included studies \((n = 28)\) followed by the meta-analyses by Feng \((n = 23)\), Hu \((n = 18)\), Cucchetti \((n = 17)\), Xu \((n = 13)\), Duan \((n = 12)\), Sun \((n = 11)\), Zhou (BMC Gastroenterol, 2010) \((n = 10)\), Ni \((n = 10)\), Liu (World J Gastroenterol, 2010) \((n = 10)\), Liu (Surg Laparosc Endosc Percutan Tech, 2010) \((n = 8)\), Li \((n = 6)\), Chen \((n = 6)\), Fu \((n = 5)\), Cai \((n = 5)\), Zhou (Zhonghua Wai Ke Za Zhi, 2011) \((n = 4)\), Weis \((n = 3)\), and Qi \((n = 3)\) (Supplementary Table S21).

Given the superiority in the quantity of RCT studies, the meta-analyses by Feng, Qi, Wang, and Weis might be more reliable. In details, surgical resection should be superior to RFA for the improvement of OS.

**PEI versus surgical resection**

Two meta-analyses compared the outcomes of PEI versus surgical resection [46, 100]. Both of them demonstrated that OS and DFS were statistically similar between the two groups [46, 100].

Only one RCT study was included in the meta-analysis by Schoppmeyer.

The meta-analysis by Hoshida had a larger number of included studies than that by Schoppmeyer (5 versus 1) (Supplementary Table S22). However, no included studies were overlapped between them.

The results were completely consistent between the two meta-analyses. In details, PEI was similar to surgical resection in terms of OS and DFS.

**Non-surgical-resection ablation versus surgical resection**

One meta-analysis compared the outcomes of non-surgical-resection ablation versus surgical resection [26]. The 1- and 3-year survival and DFS were statistically similar between the two groups [26].

**RFA versus PEI or PAI**

Eight meta-analyses compared the outcomes of RFA versus PEI or PAI [9, 20, 26, 38, 93, 102, 119, 130]. All of them favored RFA over PEI in terms of OS, DFS, and/or recurrence [9, 20, 26, 38, 93, 102, 119, 130]. Additionally, one of them found that the OS, local recurrence, de novo tumor, and adverse event were statistically similar between RFA and PAI groups [38].

RCT studies were included in the meta-analyses by Bouza \((n = 6)\), Weis \((n = 6)\), Xu \((n = 6)\), Dong \((n = 5)\), Germani \((n = 5)\), Orlando \((n = 5)\), Cho \((n = 4)\), and Shen \((n = 4)\).

The meta-analyses by Bouza, Weis, and Xu had the largest number of included studies \((n = 6)\) followed by the meta-analyses by Dong \((n = 5)\), Germani \((n = 5)\), Orlando \((n = 5)\), Shen \((n = 5)\), and Cho \((n = 4)\) (Supplementary Table S23).

The results regarding the comparison between RFA v.s. PEI were completely consistent among meta-analyses. In details, RFA should be superior to PEI for the improvement of OS and DFS.

**RFA versus cryosurgery ablation**

One meta-analysis compared the outcomes of RFA versus cryosurgery ablation [51]. Although the OS was statistically similar between the two groups, RFA had less recurrence and complications than cryosurgery ablation [51].

**RFA versus other therapeutic methods**

One meta-analysis compared the outcomes of RFA versus any other therapeutic methods [50]. RFA was superior to other treatment methods for early HCC in terms of local recurrence and 3-year survival [50]. However, no subgroup analysis was performed according to the different treatment modalities.

Additionally, one meta-analysis compared the outcomes of RFA versus microwave or laser ablation [119]. However, only one trial was identified for each comparison.

**PEI versus PAI**

Two meta-analyses compared the outcomes of PEI versus PAI [38, 100]. Both of them showed that the OS, RFS, and recurrence were statistically similar between the two groups [38, 100].

RCT studies were included in the meta-analyses by Germani \((n = 2)\) and Schoppmeyer \((n = 2)\).

Both of them had a similar number of included studies \((n = 2)\) (Supplementary Table S24). However, not all of the included studies were identical.

The results were completely consistent between the two meta-analyses. In details, PEI was similar to PAI in terms of OS and RFS.
RFA + TACE versus mono-therapy

Eleven meta-analyses compared the outcomes of RFA in combination with TACE versus RFA or TACE alone [26, 45, 53, 55, 68, 71, 74, 87–88, 133, 144]. Seven of them favored the combination therapy in terms of OS [45, 53, 55, 71, 88, 133, 144]; two favored the combination therapy in terms of 1- and 3-year survival, but not 5-year survival [74, 87]; one favored the combination therapy in term of 5-year survival, but not 1- or 3-year survival [26]; one found that the 1-year survival was statistically similar between the two groups [68].

Three meta-analyses compared the RFS of RFA in combination with TACE versus RFA or TACE alone [71, 87–88]. As for the 1-year RFS, one meta-analysis favored the combination therapy [71], but another two showed that the 1-year RFS was statistically similar between the two groups [87–88]. By comparison, all of them favored the combination therapy in term of 3-year RFS [71, 87–88].

RCT studies were included in the meta-analyses by Zhao (n = 21), Jiang (n = 8), Kong (n = 8), Ni (World J Gastroenterol, 2013) (n = 8), Yan (n = 8), Liu (n = 7), Lu (n = 7), Ni (J Cancer Res Clin Oncol, 2013) (n = 6), and Liao (n = 1), but not in the meta-analyses of Dong and Han.

The meta-analysis by Zhao had the largest number of included studies (n = 21), followed by those by Jiang (n = 19), Kong (n = 19), Yan (n = 19), Yan (n = 18), Han (n = 8), Ni (World J Gastroenterol, 2013) (n = 8), Liu (n = 7), Lu (n = 7), Ni (J Cancer Res Clin Oncol, 2013) (n = 6), Dong (n = 5), and Liao (n = 1) (Supplementary Table S25). Notably, all of the 19 included studies were completely identical among the three meta-analyses by Jiang, Kong, and Yan.

Given the superiority in the number of RCTs, the meta-analyses by Zhao, Jiang, Kong, Ni, and Yan should be more reliable. In details, RFA in combination with TACE should be favored in term of OS.

PEI + TACE versus mono-therapy

Three meta-analyses compared the outcomes of PEI in combination with TACE versus PEI or TACE alone [68, 114–115]. Two of them favored the combination therapy in term of OS [114–115]. Another one meta-analysis was performed according to the study design. In the subgroup analysis of RCTs, the combination therapy significantly improved the 3-year survival, rather than 1-year survival. By contrast, in the subgroup analysis of observational studies, the combination therapy significantly improved the 1-year survival, rather than 3-year survival [68].

RCT studies were included in all of the 3 meta-analyses by Wang N (Med Oncol, 2011) (n = 7), Wang W (Liver Int, 2010) (n = 6), and Liao (PLoS One, 2013) (n = 4).

The meta-analysis by Wang N (Med Oncol, 2011) had a larger number of included studies than those by Wang W (Liver Int, 2010) and Liao (7 versus 6 and 4) (Supplementary Table S26). However, not all studies included by Wang W and Liao were included by Wang N.

Given the superiority in the number of RCTs, the meta-analysis by Wang N (Med Oncol, 2011) might be more reliable. In details, PEI in combination with TACE should be favored in term of OS.

Any ablation therapy + TACE versus mono-therapy

Two meta-analyses compared the outcomes of unclassified ablation therapies in combination with TACE versus mono-therapy [42, 115]. Both of them favored the combination therapy in terms of OS, recurrence, and tumor response [42, 115].

RCT studies were included in the meta-analyses by Wang (n = 10) and Gu (n = 7).

The meta-analysis by Gu had a larger number of included studies than that by Wang (18 versus 10) (Supplementary Table S27). However, not all studies included by Wang were included by Gu.

The results were completely consistent between the two meta-analyses. In details, TACE in combination with ablation therapy was favored.

TACE

TACE/TAE versus no active treatment

Seven meta-analyses compared the outcomes of TACE/TAE versus no active treatment or supportive care [12, 39, 57, 73, 77, 91, 132]. Two of them showed that the OS was statistically similar between the two groups [39, 91]; another five favored TACE/TAE in term of OS [12, 57, 73, 77, 132].

RCT studies were included in the meta-analyses by Marelli (n = 9), Oliveri (n = 8), Llovet (n = 7), Camma (n = 5), Geschwind (n = 4), and Leng (n = 2), but not in the meta-analysis by Xue.

The meta-analysis by Marelli had the largest number of included studies (n = 9) followed by those by Oliveri (n = 8), Xue (n = 8), Llovet (n = 7), Camma (n = 5), Geschwind (n = 4), and Leng (n = 3) (Supplementary Table S28). However, not all included studies were completely overlapped among them.

Given the superiority in the number of RCTs, the meta-analysis by Marelli might be more reliable. In details, TACE/TAE should be favored.

TACE versus TAE

Three meta-analyses compared the outcomes of TACE versus TAE [12, 77, 125]. All of them showed that the OS was statistically similar between the two groups [12, 77, 125].
Only RCT studies were included in the meta-analyses by Xie \((n = 5)\), Marelli \((n = 3)\), and Camma \((n = 2)\).

The meta-analysis by Xie had a larger number of included studies than those by Marelli and Camma \((5 \text{ versus } 3 \text{ and } 2)\) (Supplementary Table S29). However, not all included studies were completely overlapped among them.

The results were completely consistent among them. In details, TACE was similar to TAE in term of OS.

**Drug-eluting head (DEB)-TACE versus conventional TACE (cTACE)**

Three meta-analyses compared the outcomes of DEB-TACE versus cTACE \([37, 44, 48]\). One of them evaluated the OS \([48]\). DEB-TACE was significantly better than cTACE in terms of 1- and 2-year survival. But the 6-month and 3-year survival were statistically similar between the two groups.

Two of them demonstrated that tumor response or disease control rate was statistically similar between them. Another one meta-analysis demonstrated that tumor response rate was significantly higher in DEB-TACE group than in cTACE group.

Two of them evaluated the complications \([37, 44]\). The incidence of complications was statistically similar between the two groups.

RCT studies were included in the meta-analyses by Han \((n = 3)\) and Huang \((n = 2)\), but not in the meta-analysis by Gao.

The meta-analysis by Huang had a larger number of included studies than those by Han and Gao \((7 \text{ versus } 5 \text{ and } 2)\) (Supplementary Table S30). However, not all included studies were completely overlapped among them.

Given the superiority in the number of RCTs, the meta-analysis by Han might be more reliable. In details, DEB-TACE was similar to cTACE in the term of tumor response.

**TACE versus microsphere embolization**

One meta-analysis compared the outcomes of TACE versus microsphere embolization \([123]\). Microsphere embolization was superior to TACE in terms of OS, TTP, and tumor response \([123]\). In the subgroup analyses, the benefit was statistically significant in patients undergoing \(^{32}\)P glass microspheres, but not in those undergoing \(^{90}\)Y microspheres.

RCT studies were included in the meta-analysis by Xie \((n = 7)\).

**TACE + sorafenib versus TACE**

Four meta-analyses compared the outcomes of TACE in combination with sorafenib versus TACE alone \([35, 70, 134, 140]\). Three of them favored the combination therapy in term of OS \([35, 134, 140]\), but another one found that the OS was statistically similar between the two groups \([70]\). The survival benefit of the combination therapy was statistically significant in the subgroup analysis of retrospective studies, but not in that of RCTs \([134]\).

RCT studies were included in the meta-analyses by Liu \((n = 3)\), Yang \((n = 3)\), and Zhang \((n = 2)\), but not in the meta-analysis by Fu.

The meta-analysis by Fu had the largest number of included studies \((n = 9)\), followed by those by Liu \((n = 7)\), Yang \((n = 6)\), and Zhang \((n = 6)\) (Supplementary Table S31). However, not all included studies were completely overlapped among the 4 meta-analyses.

Given the superiority in the number of RCTs, the meta-analysis by Liu and Yang might be more reliable. In details, TACE plus sorafenib was not favored in term of OS.

**TACE + high-intensity focused ultrasound (HIFU) versus TACE**

Two meta-analyses compared the outcomes of TACE in combination with HIFU versus TACE alone \([13, 68]\). One of them demonstrated that both OS and tumor response were improved by the combination therapy \([13]\). Another one meta-analysis was performed according to the study design \([68]\). In the subgroup analysis of observational studies, both 1- and 3-year survival were significantly improved by the combination therapy \([68]\). By comparison, in the subgroup analysis of RCTs, only 1-year survival, rather than 3-year survival, was significantly improved by the combination therapy \([68]\).

RCT study was included in the meta-analysis by Liao \((n = 1)\), but not in the meta-analysis by Cao.

The meta-analysis by Cao had a larger number of included studies than that by Liao \((9 \text{ versus } 5)\) (Supplementary Table S32). All studies which were included in the meta-analysis by Liao were also included in the meta-analysis by Cao.

Given the superiority in the number of RCTs, the meta-analysis by Liao might be more reliable. In details, TACE plus HIFU should be favored in term of 1-year survival, but not 3-year survival.

**TACE + thermotherapy versus TACE**

Only one meta-analysis compared the outcomes of TACE in combination with thermotherapy versus TACE alone \([64]\). Both 1- and 2-year survival were significantly improved by the combination therapy, but the 0.5-, 1.5-, and 3-year survival were statistically similar between the two groups \([64]\). Additionally, the overall effective rate and quality of life were improved by the combination therapy \([64]\).

**TACE + AHCS versus TACE or AHCS**

Only one meta-analysis compared the outcomes of TACE in combination with AHCS versus TACE or AHCS alone \([65]\). Compared with TACE alone, the combination
therapy had significantly better 0.5-, 1-, 1.5-, 2-, and 2.5-year survival, but the 3-year survival was statistically similar between the two groups [65]. Compared with AHCS alone, the combination therapy had significantly better 0.5-, 1.5-, 2-, and 2.5-year survival, but similar 1- and 3-year survival [65]. Additionally, the combination therapy was superior to the mono-therapy in terms of total effective rate, complete necrosis rate, recurrence, AFP reduction, and CD4 improvement.

**TACE + radiotherapy versus TACE alone**

Two meta-analyses compared the outcomes of TACE in combination with radiotherapy versus TACE alone [68, 80]. Both of them demonstrated that the combination therapy had significantly better 1-, 2-, 3-, and 5-year survival than TACE alone [68, 80]. Additionally, one of them showed that the combination therapy significantly increased the tumor response, but did not influence the development of adverse events, such as nausea/vomit, leukocyte count declined, alanine aminotransferase level increased, and total bilirubin level increased [80].

RCT studies were included in the meta-analyses by Meng (n = 5) and Liao (n = 3).

The meta-analysis by Meng had a larger number of included studies than that by Liao (17 versus 7) (Supplementary Table S33). All studies which were included in the meta-analysis by Liao were also included in the meta-analysis by Meng.

The results regarding the OS were completely consistent among them. In details, TACE plus radiotherapy should be favored in term of OS.

**TACE + 3D-CRT versus TACE alone**

Only one meta-analysis compared the outcomes of TACE in combination with 3D-CRT versus TACE alone [68]. Regardless of study design, the combination therapy was superior to TACE alone in terms of 1- and 3-year survival [68].

Only one RCT study was included in the meta-analysis by Liao.

**TACE + TCMs versus TACE alone**

Six meta-analyses compared the outcomes of TACE in combination with TCMs versus TACE alone [18–19, 79, 81, 108, 122]. Three of them favored the combination therapy in term of OS [18, 79, 108]; one favored the combination therapy in terms of 1-, 2-, and 3-year survival, but not 6-month survival [19]; one favored the combination therapy in term of 2-year survival, but not 1-year survival [122]; one did not report the survival data [81].

Five of them favored the combination therapy in term of tumor response [18–19, 79, 81, 122]. Another one did not report the relevant data [108].

Four of them favored the combination therapy in term of quality of life [18–19, 79, 108]. Another two did not report the relevant data [81, 122].

RCT studies were included in the meta-analyses by Cheung (n = 67), Cho (n = 30), and Meng (Explore (NY), 2011) (n = 11), but not in the meta-analyses by Sun and Wu. The information regarding the inclusion of RCTs was not reported in the meta-analysis by Meng (J Altern Complement Med, 2008).

The meta-analysis by Cheung had the largest number of included studies (n = 67), followed by those by Meng (n = 37), Cho (n = 30), Meng (n = 12), Sun (n = 10), and Wu (n = 9) (Supplementary Table S34). However, not all included studies were completely overlapped among the 6 meta-analyses.

Given the superiority in the number of RCTs, the meta-analysis by Cheung might be more reliable. In details, TACE plus TCMs should be favored in terms of OS, tumor response, and quality of life.

**TACE + CIK cell therapy versus TACE alone**

Two meta-analyses compared the outcomes of TACE in combination with CIK cell therapy versus TACE alone [14, 63]. The combination therapy was beneficial in terms of OS, RFS, TTP, quality of life, and liver and immune function [14, 63]. Additionally, one of them evaluated whether or not adjunctive CIK cell therapy could improve the outcomes of TACE in combination with RFA [63]. Adjunctive CIK cell therapy was beneficial in terms of OS and RFS [63].

RCT studies were included in the meta-analyses by Chen (n = 9) and Li (n = 6).

The meta-analysis by Li had a larger number of included studies than that by Chen (11 versus 9) (Supplementary Table S35). However, not all included studies were completely overlapped between them.

The results regarding the OS were completely consistent among them. In details, TACE in combination with CIK cell therapy should be favored.

**Sorafenib**

Seven meta-analyses compared the outcomes of sorafenib versus placebo (Supplementary Table S1) [22, 28, 101, 118, 141, 143, 160]. The use of sorafenib was beneficial in terms of OS, TTP, and disease control rate [22, 101, 118, 141, 143, 160]. However, the time to symptomatic progression was statistically similar between the two groups [22, 118, 160]. The incidence of adverse events was significantly increased by the use of sorafenib [28, 101, 118, 141, 143, 160].

RCT studies were included in the meta-analyses by Shen (n = 5), Duffy (n = 4), Wang (n = 4), Zhang T (Anticancer Drugs, 2010) (n = 3), Zhang X (Hepatobiliary Pancreat Dis Int, 2012) (n = 3), Cinco (n = 2), and Zou (n = 2).

The meta-analysis by Shen had a larger number of included studies than those by Wang, Duffy, Zhang T (Anticancer Drugs, 2010), Zhang X (Hepatobiliary Pancreat Dis Int, 2012), Zou, and Cinco (5 versus 4, 4, 3, 3, 2, and 2) (Supplementary Table S36). All studies
which were included in the meta-analysis by Wang, Duffy, Zhang T (Anticancer Drugs, 2010), Zhang X (Hepatobiliary Pancreat Dis Int, 2012), and Zou were also included by Shen. In the meta-analysis by Cinco, the included studies were not reported.

The results were completely consistent among them. In details, sorafenib should be favored.

**Antiviral therapy**

Nineteen meta-analyses compared the outcomes of antiviral therapy versus no antiviral therapy (Supplementary Table S2) [10, 49, 54, 56, 58, 84–86, 103, 105, 107, 112, 120, 128, 139, 142, 154, 158–159]. Thirteen of them favored the use of antiviral therapy in term of OS [10, 49, 54, 84, 105, 107, 112, 120, 128, 139, 142, 154]; one found that the use of antiviral therapy significantly improved the 5-year survival in HCV patients, but not HBV patients [58]; one demonstrated that the 1-year survival was statistically similar between the two groups [56]; one showed that 1-, 2-, 3-, 4-, and 5-year survival were statistically similar between the two groups [159]; another three did not report the survival data [85, 103, 158].

Five meta-analyses evaluated the DFS/RFS [49, 56, 103, 112, 154]. Four of them favored the use of antiviral therapy in term of DFS/RFS [56, 103, 112, 154]. Another one meta-analysis was performed according to the study design and type of viral hepatitis. In the subgroup analysis of RCTs, the DFS/RFS was statistically similar between the two groups regardless of HCV or HBV [49]. In the subgroup analysis of non-RCTs, antiviral therapy improved the DFS/RFS by in HCV patients, but not HBV patients [49].

Fifteen meta-analyses evaluated the recurrence [10, 54, 56, 58, 84–85, 105, 107, 120, 128, 139, 142, 154, 158–159]. Ten of them favored the use of antiviral therapy in term of recurrence [10, 56, 84–85, 105, 107, 120, 139, 154, 158]; one favored the use of antiviral therapy after TACE, but not surgical resection [54]; two favored the use of antiviral therapy in HCV patients, but not HBV patients [58, 128]; one favored the use of antiviral therapy in terms of 1-, 3-, and 4-year recurrence, but not 2- or 5-year recurrence [159]; another three did not report the survival data [85, 103, 158].

RCT studies were included in the meta-analyses by Zhuang (PLoS One, 2013) (n = 13), Huang (n = 10), Shen (n = 9), Wang (n = 9), Zhang (Mol Clin Oncol, 2014) (n = 9), Jiang (n = 8), Li (n = 8), Zou (Zhonghua Gan Zang Bing Za Zhi, 2012) (n = 8), Breitenstein (n = 7), Zhang (Int J Cancer, 2009) (n = 6), Miao (n = 5), Singal (n = 5), Xu (n = 5), Moriguchi (n = 4), Miyake (n = 3), Sun (n = 1), and Zhou (n = 1), rather than those by Lan and Wong.

The meta-analysis by Huang had a larger number of included studies than those by Zhang, Zhou, Miao, Shen, Sun, Zhuang (PLoS One, 2013), Jiang, Lan, Miyake, Sunal, Wang, Wong, Xu, Li, Zhang, Zhuang (Zhonghua Gan Zang Bing Za Zhi, 2012), Breitenstein, and Moriguchi (23 versus 19, 14, 13, 13, 13, 10, 10, 10, 10, 9, 9, 9, 8, 8, 8, 7, and 4) (Supplementary Table S37). In the meta-analysis by Moriguchi, the included studies were not reported. However, not all included studies were completely overlapped between them.

Given the superiority in the number of RCTs, the meta-analysis by Zhuang (PLoS One, 2013) and Huang might be more reliable. In details, interferon therapy after curative treatment should be favored.

**Vitamin**

Five meta-analyses compared the outcomes of vitamin versus placebo (Supplementary Table S3) [21, 82, 99, 112, 150]. Two of them favored the use of vitamin in term of OS [112, 150]; two favored the use of vitamin in term of 2-year survival, but not 3-year survival [21, 82]; one showed that the 1- and 2-year survival were statistically similar between the two groups [99].

One meta-analysis favored the use of vitamin in term of RFS [112].

Two meta-analyses favored the use of vitamin in term of 1-year recurrence, but another two did not [21, 82]. Four meta-analyses favored the use of vitamin in terms of 2- and 3-year recurrence [21, 82].

RCT studies were included in the meta-analyses by Wang (n = 6), Zhong (n = 6), Chu (n = 5), Riaz (n = 5), and Meng (n = 4).

The meta-analysis by Zhong had a larger number of included studies than those by Chu, Wang, Riaz, and Meng (7 versus 6, 6, 5, and 4) (Supplementary Table S38). In the meta-analysis by Meng, the included studies were not reported. However, not all included studies were completely overlapped between them.

Given the superiority in the number of RCTs, the meta-analyses by Wang and Zhong should be more reliable. In details, the use of vitamin should be favored in term of OS. However, its benefit was weak.

**Octreotide**

Three meta-analyses compared the outcomes of octreotide versus placebo (Supplementary Table S4) [29, 43, 52]. As for the 6- and 12-month survival, one of them favored the use of octreotide [52], but another two did not show any significant difference between the two groups [29, 43]. As for the 24-month survival, two of them showed that the survival was statistically similar between the two groups [29, 43], but another one did not report the relevant data [52].

RCT studies were included in the meta-analyses by Ji (n = 9) and Guo (n = 6).

The meta-analysis by Ji had a larger number of included studies than those by Guo and Estanislao (11 versus 6 and 3) (Supplementary Table S39). In the meta-
Given the superiority in the number of RCTs, the meta-analyses by Ji and Guo might be more reliable. In details, the benefit of octreotide remains uncertain.

One meta-analysis compared the outcomes of kanglaite injection plus hepatic arterial intervention versus hepatic arterial intervention alone (Supplementary Table S5) [34]. The combination therapy was beneficial in terms of tumor response, Karnofsky score improvement, and pain relief [34]. But neither OS nor DFS/RFS was evaluated [34].

One meta-analysis compared the outcomes of Chinese herbal medicine plus chemotherapy versus chemotherapy alone [104]. The combination therapy was beneficial in terms of OS and tumor response [104].

One meta-analysis compared the outcomes of TCM versus other treatment [121]. TCM was superior to other treatments in terms of OS and tumor response [121].

CIK cell therapy

One meta-analysis compared the outcomes of CIK cell therapy versus other treatment (Supplementary Table S6) [76]. CIK cell therapy was superior to other treatments in terms of OS, PFS, disease control rate, tumor response, and quality of life [76].

Tamoxifen

Two meta-analyses compared the outcomes of tamoxifen versus placebo or no treatment (Supplementary Table S7) [73, 90]. Both of them demonstrated that the OS was statistically similar between the two groups [73, 90].

RCT studies were included in the meta-analyses by Nowak (n = 10) and Llovet (n = 7).

Although the meta-analysis by Nowak had a larger number of included studies than that by Llovet (10 versus 7) (Supplementary Table S40), the included studies were not similar between them.

The results were completely consistent among them. In details, tamoxifen should not be favored.

Antibiotics

One meta-analysis compared the outcomes of antibiotics versus no antibiotics after hepatic transarterial therapy [113]. The incidence of fever, bacteremia, septicemia, and sepsis were not significantly improved by antibiotics [113].

DISCUSSION

AASLD and EASL guidelines recommend BCLC staging algorithm for the management of HCC. Only 5 treatment modalities have been considered in the current guidelines. In details, the therapeutic modalities of HCC include the LT, surgical resection, and RFA for HCC in the stage 0 and A, TACE for HCC in the stage B, sorafenib for HCC in the stage C, and supportive treatment for HCC in the stage D. However, the BCLC staging algorithm is not flawless and needs to be persistently updated. Nowadays, more and more novel treatment modalities have been widely produced and adopted. Their efficacy and safety have been gradually established. In this circumstance, our study was worthwhile, because it attempted to collect the relevant evidence as many as possible and to provide an overview of outcomes of novel and well-established treatment modalities for HCC based on the results of meta-analyses. More notably, we found that lots of combination therapy might be more effective and safe. For example, the meta-analyses of RCTs demonstrated that RFA plus TACE was superior to mono-therapy, and that surgical resection plus post-operative therapy was superior to surgical resection alone. Given the quality of such meta-analyses, the guidelines should be updated regarding the use of combination therapy.

Limitations

This was a time-consuming work, because a large number of relevant meta-analyses were included. Several limitations should be acknowledged. First, we must clarify that only the results of meta-analyses, but not the accuracy of meta-analyses, were systematically reviewed. Because we cannot repeat every meta-analysis, we cannot guarantee that their findings were accurate. Second, we did not consider the heterogeneity among included studies in every meta-analysis. A significant heterogeneity could affect the stability of a meta-analysis. Third, we arbitrarily evaluated the reliability of meta-analyses according to the number of RCTs and non-RCTs.

Recommendations

LT

1. LDLT has lower DFS than DDLT (grade of recommendation: low).
2. Short- and long-term outcomes may be comparable between primary and salvage LT (grade of recommendation: low).
3. Sirolimus-based immunosuppression should be recommended after LT (grade of recommendation: low).

Surgical resection

1. Surgical resection margin aiming at 2 cm may be superior to 1 cm for the improvement of long-term outcomes (grade of recommendation: moderate).
2. Survival benefit may be comparable between laparoscopic and open resection. Additionally, laparoscopic resection had less blood loss, blood
transfusion, and complications and shorter hospital stay (grade of recommendation: low).

3. Anatomic resection, but not non-anatomic resection, should be recommended (grade of recommendation: low).

4. Adjunctive I\(^{131}\) lipiodol therapy may be considered in patients undergoing surgical resection (grade of recommendation: low).

5. Post-operative TACE, but not pre-operative TACE, may be considered in patients undergoing surgical resection (grade of recommendation: low).

6. Immunotherapy may not be considered in patients undergoing surgical resection (grade of recommendation: low).

7. PVE may not be considered in patients undergoing surgical resection (grade of recommendation: low).

Ablation

1. Surgical resection should be superior to RFA in term of OS (grade of recommendation: high).

2. RFA, but not PEI or cryosurgery ablation, should be recommended (grade of recommendation: high).

3. RFA in combination with TACE may be superior to TACE or RFA mono-therapy (grade of recommendation: high).

4. PEI in combination with TACE may be superior to TACE or PEI mono-therapy (grade of recommendation: high).

TAE/TACE

1. TACE/TAE should be superior to placebo (grade of recommendation: high).

2. Survival benefit may be comparable between TACE and TAE (grade of recommendation: high).

3. DEB-TACE was comparable to conventional TACE (grade of recommendation: high).

4. \(^{32}\)P glass microspheres embolization may be superior to TACE for the improvement of OS (grade of recommendation: high).

5. Adjunctive HIFU therapy may further improve the outcomes of TACE (grade of recommendation: moderate).

6. Adjunctive radiotherapy therapy may further improve the outcomes of TACE (grade of recommendation: high).

7. Adjunctive 3D-CRT therapy may further improve the outcomes of TACE (grade of recommendation: moderate).

8. Adjunctive TCMs therapy may further improve the outcomes of TACE (grade of recommendation: high).

9. Adjunctive CIK cell therapy may further improve the outcomes of TACE (grade of recommendation: high).

Sorafenib

1. Sorafenib is superior to placebo for the improvement of OS (grade of recommendation: high).

Other treatments

1. Antiviral therapy should be recommended for the improvement of recurrence (grade of recommendation: high).

2. Vitamin should be recommended for the improvement of OS (grade of recommendation: high).

3. Tamoxifen should not be recommended (grade of recommendation: high).

Uncertainties

1. The superiority of LT to surgical resection for the improvement of OS remains inconclusive. The accurate candidates for LT and surgical resection need to be clearly established.

2. The superiority of surgical resection to RFA for the improvement of OS remains under debate. The indications of RFA should be refined.

3. Although transarterial radioembolization appears to be more advantageous than TACE, their cost-effectiveness should be further explored.

4. Although TACE appears to be more effective than no treatment, the survival benefit of TAE/TACE versus other active treatments should be confirmed.

5. The benefits of combination therapy may be confirmed in the future guidelines.

MATERIALS AND METHODS

Search strategy and study selection

We searched all meta-analysis papers regarding the treatment of HCC via the PubMed, EMBASE, and Cochrane library databases. Search items were as follows: (hepatocellular carcinoma) AND (meta-analysis). The last search was performed on October 1, 2014.

Eligibility criteria were as follows. 1) All meta-analyses regarding the treatment of HCC were included. 2) Duplicate publications were excluded. 3) Narrative reviews were excluded. 4) Only systematic reviews without meta-analyses were excluded. 5) Only systematic review protocols were excluded. 6) Patients without HCC were excluded. 7) Other topics, but not treatment modalities, were excluded.

Primary outcomes were overall survival (OS), diseases-free survival (DFS) or recurrence-free survival (RFS), progression or time-to-progression (TTP), progression-free survival (PFS), recurrence or time-to-recurrence, safety, and other endpoints.
Reliability of meta-analyses

As the results were different among the meta-analyses, the reliability was evaluated according to the quality and quantity of original studies included in every meta-analysis. First, we evaluated the quality of original studies. If a larger number of randomized controlled trials (RCTs) were included, the results of a meta-analysis would be more reliable. Second, if the number of randomized controlled trials was similar, we further evaluated the number of non-RCT studies. If a larger number of non-RCT studies were included, the results of a meta-analysis would be more reliable. Third, if the number of RCT and non-RCT studies included was similar but the results were different among meta-analyses, we further evaluated the statistical methods. Hazard ratio could reflect a general effect over time; by comparison, odds ratio or risk ratio reflected an individual effect at a fixed time point. Thus, if the hazard ratio was calculated, the results of a meta-analysis would be more reliable.

Grade of recommendations

High grade recommendation was considered, if the results of meta-analyses were based on more than 3 single-center RCTs or 1 multi-center RCT. Low grade recommendation was considered, if the results of meta-analyses were based on the non-RCT studies alone. As for something in between, moderate grade recommendation was considered.

Abbreviations

3D-CRT, three-dimensional conformal radiation therapy; AHCS, argon-helium cryotherapy system; CIK, cytokine-induced killer; DDLT, deceased donor liver transplantation; DEB, drug-eluting bead; DFS, disease-free survival; HCC, hepatocellular carcinoma; HIFU, high-intensity focused ultrasound; LDLT, living donor liver transplantation; LT, liver transplantation; OS, overall survival; PEI, percutaneous ethanol injection; PAI, percutaneous acetic acid injection; PFS, progression-free survival; PVE, portal vein embolization; RCT, randomized controlled trials; RFA, radiofrequency ablation; RFS, recurrence-free survival; TACE, transarterial chemoembolization; TAE, transarterial embolization; TCMs, traditional Chinese medicine; TTP, time-to-progression.

CONFLICTS OF INTEREST

None.

Authors’ contributions

XQ: designed the study, performed the literature search and selection, data extraction, and drafted the manuscript; YZ and HL: performed the literature selection and data extraction; XG and GH: gave critical comments and revised the manuscript. All authors have made an intellectual contribution to the manuscript and approved the submission.

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