RESEARCH ARTICLE

Hepatic Re-resection Versus Transarterial Chemoembolization for the Treatment of Recurrent Hepatocellular Carcinoma after Initial Resection: a Systematic Review and Meta-analysis

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Abstract

Background: A systematic review and meta-analysis were performed to compare the post-recurrence survival with hepatic re-resection versus transarterial chemoembolization (TACE) for recurrent hepatocellular carcinoma (HCC) after initial resection. Materials and Methods: All relevant papers were searched via PubMed, EMBASE, and Cochrane Library databases. Hazard ratios (HRs) with 95% confidence intervals (CIs) were pooled using a random-effects model. Subgroup analysis was performed according to country. Sensitivity analysis was performed in studies which clearly reported the recurrent regions, in moderate/high-quality studies, in studies published in full-text form, and in studies published after 2005. Results: In total, twelve papers were included in our study. Five and seven of them were of moderate- and poor-quality, respectively. The overall meta-analysis demonstrated a statistically significantly higher post-recurrence survival in the hepatic re-resection group than in those undergoing TACE (HR=0.64, 95%CI=0.52-0.79, *P*<0.0001). Heterogeneity was statistically significant and statistical significance remained in the subgroup analysis. Sensitivity analyses were also consistent with the overall analysis. Conclusions: Hepatic re-resection might provide a better post-recurrence survival than TACE for recurrent HCC after initial resection. However, considering the low quality of published studies and the potential bias of treatment selection, further randomized trials should be warranted to confirm these findings.

Keywords: Hepatocellular carcinoma - resection - transarterial chemoembolization - recurrence - survival

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Introduction

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related death. Surgical resection is a curative treatment option of early HCC (Bruix and Sherman, 2011; 2012). However, the recurrence of HCC after surgical resection is very frequent with a 5-year incidence of >70% (Franco et al., 1990; Belghiti et al., 1991; Shirabe et al., 1991; Okada et al., 1994; Adachi et al., 1995; Balsells et al., 1996; Fong et al., 1999; Poon et al., 2001; Ercolani et al., 2003; Minagawa et al., 2003), which negatively influences the outcomes. Until now, there is no consensus regarding the management of recurrent HCC (Bruix and Sherman, 2011; 2012). Salvage liver transplantation is a promising treatment option of recurrent HCC (Majno et al., 2000; Poon et al., 2002; Sala et al., 2004; Hu et al., 2005; Hu et al., 2012; Wu et al., 2012; Liang et al., 2014). However, liver transplantation is largely restricted by the donor shortage. Re-resection and transarterial chemoembolization (TACE) represent two additional treatment options. Re-resection can provide a relatively good outcome of recurrent HCC in selected patients with solitary tumor, although it is compromised by reduced liver volume and presence of liver cirrhosis. By comparison, TACE is employed in patients with multiple tumors. Considering that the appropriate selection of treatment options is very important to improve the prognosis, we have conducted a systematic review and meta-analysis of observational studies to compare the post-recurrence survival of hepatic re-resection versus TACE for the treatment of recurrent HCC after initial resection.

Materials and Methods

This work was registered with PROSPERO (registration number: CRD42015017798).

Search strategy

The PubMed, EMBASE, and Cochrane Library databases were searched. Search items were as follows: ("hepatectomy" OR "liver resection" OR "hepatic

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resection" OR "liver surgery" OR "hepatic surgery") AND ("TACE" OR "transarterial chemoembolization") AND ("HCC" OR "hepatocellular carcinoma" OR "hepatic carcinoma") (Qi et al., 2015). The last search was performed on December 18, 2014.

Study selection

The inclusion criteria should be as follows.

Participants: patients with recurrent HCC.

Interventions: hepatic resection and TACE as re-treatment modalities.

Comparisons: hepatic re-resection versus TACE.

Outcomes: overall survival after HCC recurrence.

The exclusion criteria should be as follows.

1) Duplicate papers among databases and redundant publications.

2) Narrative or systematic reviews, study protocols, comments, experimental studies, and case reports (sample size <10).

3) Non-HCC.

4) Hepatic metastases.

5) Mixed malignancies.

6) Non-comparative studies.

7) No comparison between hepatic resection versus TACE.

8) TACE before and after hepatic resection.

9) Comparison between hepatic resection versus TACE for the initial treatment of HCC.

10) Comparison between hepatic resection versus TACE for the treatment of spontaneous rupture of HCC.

11) No separate data in the hepatic resection or TACE group.

12) No detailed data regarding the survival rate in the hepatic resection or TACE group.

13) No detailed data regarding the number of observed patients in the hepatic resection or TACE group.

If two or more papers by the same study team had the overlapping data, only one paper with more adequate data and/or a longer enrollment period would be included.

Data extraction

The following data were extracted: the first author, publication year, publication form, region, enrollment period, study design, study population, follow-up time, eligibility criteria, treatment selection criteria, number of cases with recurrent HCC in different groups, and post-recurrence survival rates. Post-recurrence survival was defined as the interval between tumor recurrence and death. If the post-recurrence survival was not reported, we attempted to extract the interval between re-treatment and death. However, we did not extract the interval between initial treatment and death. If only Kaplan-Meier curves were presented, we extracted the cumulative 1-, 2-, 3-, and/or 5-year survival rates by using the Distance Tool in the Measurements menu of Foxit PDF Reader software version 5.4.4.1023 (Foxit Cooperation, California, USA). This software was freely downloaded.

Study quality

The Newcastle-Ottawa Scale (NOS) is a well-known tool for assessing the quality of non-randomized studies. However, we should acknowledge that our study population and study objectives should be more specific (i.e., recurrent HCC and post-recurrence survival). According to the NOS, we developed the following questions that were more appropriate for the present systematic review.

1) Were the patients consecutively enrolled and prospectively followed?

2) Was the age at the time of HCC recurrence statistically similar between the two groups?

3) Was the gender at the time of HCC recurrence statistically similar between the two groups?

4) Was the Child-Pugh score/class or MELD score at the time of HCC recurrence statistically similar between the two groups?

5) Were the diameter and number of tumor at the time of HCC recurrence statistically similar between the two groups?

6) Was the recurrent region of HCC clearly reported?

7) Was the initial treatment modality of HCC clearly reported?

8) Were the criteria for treatment selection of recurrent HCC homogeneous between the two groups?

9) Was the follow-up time clearly reported?

If the answers to 7-9 questions were "Yes", the study would be considered to be of high quality. If the answers to 4-6 questions were "Yes", the study would be considered to be of moderate quality. Otherwise, it would be considered to be of poor quality.

Meta analysis

First, we calculated log(hazard ratio[HR]) with standard error by using a calculation sheet which was developed by Matthew Sydes and Jayne Tierney (Tierney et al., 2007). Then, HRs with 95% confidence intervals (CIs) were pooled by using a random-effects model. A P value of <0.05 was considered statistically significant. Heterogeneity between studies was assessed by using the I^2 statistic (I^2> 50% was considered as having substantial heterogeneity) and the Chi-square test (P<0.10 was considered to represent significant statistical heterogeneity). Funnel plots were performed to evaluate the publication bias. Subgroup analyses were performed according to the countries. Sensitivity analyses were performed in the following conditions: 1) the studies which clearly reported the recurrent regions of HCC; 2) the studies which were of moderate- or high-quality; 3) the studies which were published in the full-text form; and 4) the studies which were published after 2005. All meta-analyses were conducted by using the statistical package Review Manager version 5.1.6 (Copenhagen, The Nordic Cochrane Center, The Cochrane Collaboration, 2011).

Results

Study selection

Overall, 2028 papers were initially retrieved, including 1219 papers in PubMed, 758 in EMBASE, and 51 in Cochrane library databases. Finally, 12 papers were included in the present systematic review (Shimamura

et al., 1994; Imaoka et al., 1995; Lee et al., 1995; Ueno et al., 2009; Yang et al., 2009; Hirokawa et al., 2011; Umeda et al., 2011; Ho et al., 2012; Taniai et al., 2012; Yamamoto et al., 2013; Takemura et al., 2014; Wang et al., 2014) (Figure 1).

Study characteristics

Study characteristics were summarized in Table 1. Four and eight studies were performed in China and Japan, respectively. All of the included studies clearly reported that hepatic resection was the initial treatment option of HCC. Nine studies evaluated the outcomes of intrahepatic recurrent HCC, and another three studies did not report the recurrent regions of HCC. Eleven studies evaluated the interval between tumor recurrence and death, and another one study evaluated the interval between initial treatment and death. Criteria for patient selection and treatment selection were summarized in Supplementary Table 1 and 2, respectively.

Study quality

Five and seven studies were of moderate and poor quality, respectively (Supplementary Table 3). No study was of high quality.

Overall analysis

The overall meta-analysis demonstrated a statistically significantly higher post-recurrence survival in hepatic re- resection group than in TACE group (HR=0.64, 95%CI=0.52-0.79, P<0.0001) (Figure 2). The heterogeneity among studies was statistically significant (P=0.0003; I^2=68%). Funnel plot suggested the presence of publication bias (Figure 3).

Figure 1. Flowchart of Study Inclusion

Table 1. Study Characteristics: An Overview of Included Studies

First author, Journal (Year)	Publication forms	Regions	Study design	Period	Target population	Follow-up time
Hirokawa, J Gastrointest Surg (2011)	Full text	Japan	Retrospective cohort study	1998.10- 2008.10	Intrahepatic recurrence of HCC after initial hepatectomies; ≥2 recurrent tumors, each tumor ≤3cm	NA
Ho, Surgery (2012)	Full text	China Taiwan	Retrospective cohort study	2001- 2007	Intrahepatic recurrent HCC after primary hepatectomy	Mean (range) after recurrence: 32 (0-79) months in re-resection group; 22 (0-100) months in TACE group
Imaoka, Acta Hepatologica Japonica (1995)	Full text	Japan	Cohort study	1980- 1993	Intrahepatic recurrence after hepatectomy for HCC	NA
Lee, Ann Surg (1995)	Full text	China Taiwan	Cohort study	1986.1- 1992.12	Resectable recurrent HCC after hepatic resection (intrahepatic recurrent tumors and good liver function)	Mean (range) after recurrence: 49.8±26.2 (10-112) months in re-resection group; 41.0±21.6 (6-85) months in TACE group
Shimamura, Gan To Kagaku Ryoho (1994)	Full text	Japan	Retrospective cohort study	1987.1- 1992.12	Recurrences of HCC after hepatectomy	NA
Takemura, HPB (2014)	Abstract	Japan	Cohort study	1994- 2010	Recurrences of HCC after first time hepatectomy	NA
Taniai, Hepatol Int (2012)	Abstract	Japan	Cohort study	NA	Hepatic recurrent regions without other recurrent regions after initial hepatectomy	NA
Ueno, Surg Today (2009)	Full text	Japan	Retrospective cohort study	1992.1- 2005.12	Single nodular intrahepatic recurrence after curative primary resection of HCC	Mean (range) after recurrence: 34 (13-60) months in re-resection group; 29 (9-49) months in TACE group
Umeda, World J Surg (2011)	Full text	Japan	Retrospective cohort study	1998.8- 2007.8	Intrahepatic recurrence of HCC after curative resection	Median (range) after initial hepatic resection: 48 (8-128) months
Wang, Eur J Surg Oncol (2014)	Full text	China	Prospective cohort study	2004.11- 2010.5	Intrahepatic recurrent HCC within Milan criteria following hepatectomy	NA
Yamamoto, Anticancer Res (2013)	Full text	Japan	Cohort study	1980- 2009	Initial hepatic recurrence after a macroscopic curative hepatectomy for HCC	Median after recurrence: 50.3 months
Yang, Zhonghua Zhong Liu Za Zhi (2009)	Full text	China	Retrospective cohort study	2000.1- 2006.6	Intrahepatic solitary recurrence of HCC after hepatectomy	NA

*Abbreviations: HCC, hepatocellular carcinoma; NA, not available; TACE, transarterial chemoembolization

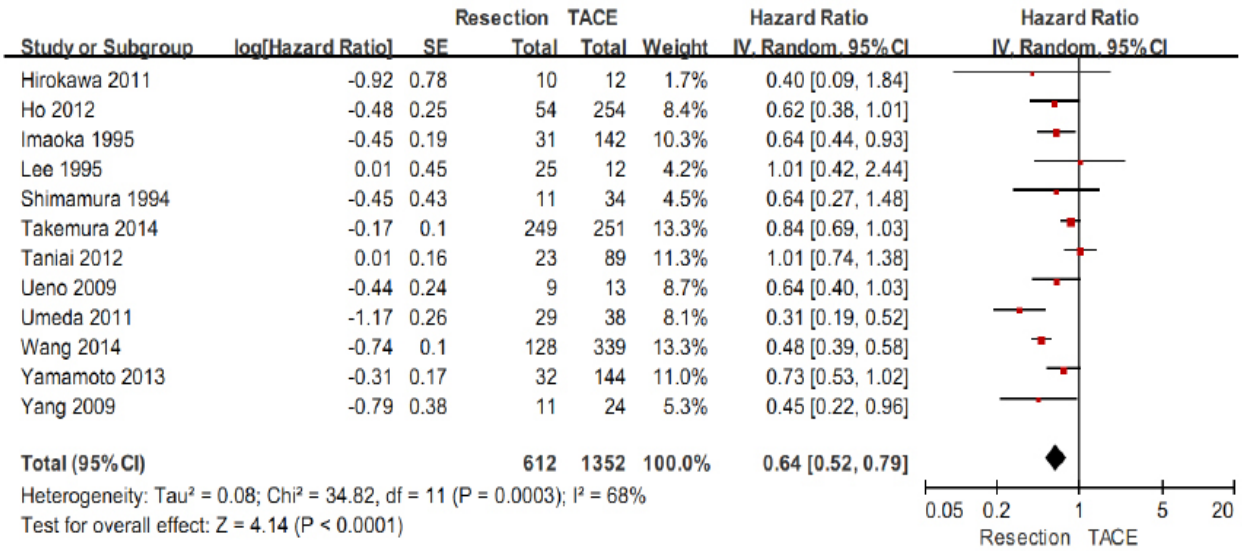

Figure 2. Overall Meta-analysis Comparing the Post-recurrence Survival between Patients with Recurrent HCC Undergoing Hepatic Re-resection and TACE

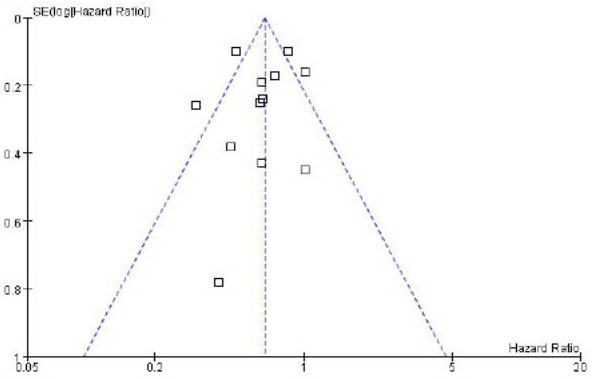

Figure 3. Funnel Plot to Explore the Publication Bias in the Overall Meta-analysis

Subgroup analysis

The subgroup meta-analysis of studies conducted in China demonstrated a statistically significantly higher post-recurrence survival in hepatic re-resection group than in TACE group (HR=0.52, 95%CI=0.42-0.65, *P*<0.00001) (Figure 4). The heterogeneity among studies was not statistically significant (*P*=0.33; I^2=13%).

The subgroup meta-analysis of studies conducted in Japan demonstrated a statistically significantly higher post-recurrence survival in hepatic re-resection group than in TACE group (HR=0.68, 95%CI=0.54-0.86, *P*=0.002) (Figure 4). The heterogeneity among studies was statistically significant (*P*=0.01; I^2=62%).

There was a statistically significant subgroup difference (*P*=0.11; I^2=61.3%).

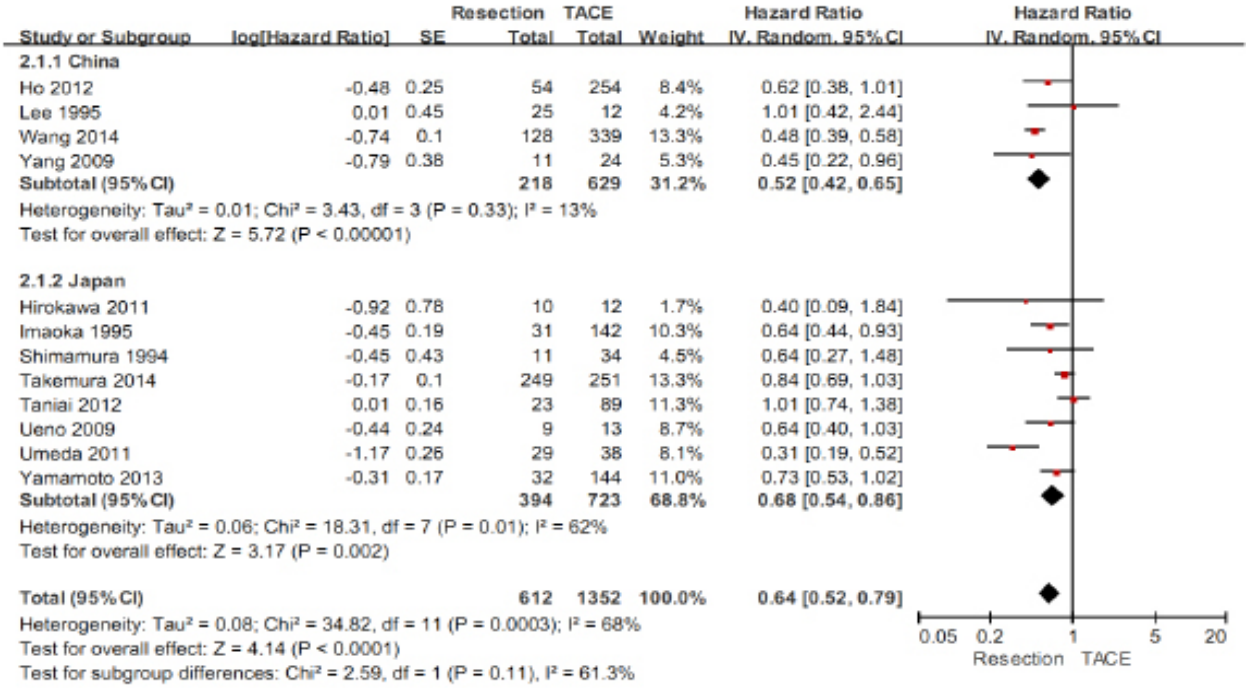

Figure 4. Subgroup Analysis Comparing the Post-recurrence Survival between Patients with Recurrent HCC Undergoing Hepatic Re-resection and TACE according to the Countries

Sensitivity analyses

In all sensitivity analyses, the post-recurrence survival remained statistically significantly higher in hepatic re-resection group than in TACE group (Supplementary Figures 1-4).

Discussion

To the best of our knowledge, this study might be the first systematic review and meta-analysis to compare the post-recurrence survival between patients undergoing hepatic re-resection and TACE. This study had several strengths. 1) The search strategy was extensive via the three major databases. 2) No publication language was restricted, because our review authors were skilled at Chinese, English, and Japanese languages. Two papers were published in Japanese. One paper was published in Chinese. 3) The study quality was strictly evaluated. We developed a total of nine questions to assess the study quality, which were more specific to the objectives of our study. They included four major categories, such as patient enrollment, comparability of patient characteristics, comparability of treatment selection, and follow-up work. 4) Subgroup and sensitivity analyses were performed to confirm the reliability of our findings.

The overall analysis suggested that hepatic re-resection had a significantly better post-recurrence survival than TACE. Notably, a relatively narrow CI might suggest a stable benefit of hepatic re-resection. The statistically significant heterogeneity should not be neglected. As we took a close look at the individual data, two included studies showed a very similar survival between the two groups (HR was equal to 1) (Lee et al., 1995; Taniai et al., 2012), but the remaining ten studies supported a better survival in hepatic re-resection group (HR was beyond 1) (Shimamura et al., 1994; Imaoka et al., 1995; Ueno et al., 2009; Yang et al., 2009; Hirokawa et al., 2011; Umeda et al., 2011; Ho et al., 2012; Yamamoto et al., 2013; Takemura et al., 2014; Wang et al., 2014). In addition, the subgroup analysis confirmed the statistically significance regardless of China or Japan. The sensitivity analyses were largely consistent with the overall analysis. These findings suggested that hepatic re-resection might be an optimal choice of therapy for recurrent HCC and that TACE might be an alternative treatment option if hepatic re-resection was unavailable or infeasible.

Patterns of tumor recurrence in HCC cases primarily include intrahepatic and extrahepatic regions. In a majority of included studies (75%, 9/12), only intrahepatic recurrence of HCC without extrahepatic involvement was considered as the target population. However, we had to acknowledge that the other patient characteristics were not well-matched between hepatic re-resection and TACE groups. Only two studies had statistically similar Child-Pugh score or class between the two groups (Ueno et al., 2009; Hirokawa et al., 2011). Only three studies had statistically similar tumor size and number between the two groups (Ueno et al., 2009; Hirokawa et al., 2011; Wang et al., 2014). In addition, none of included studies employed any random allocation methods. Only one retrospective study clearly reported that the treatment selection criteria were the same between the two groups (i.e., both resection and TACE were employed in patients with resectable HCC) (Lee et al., 1995). In the remaining studies, the patients with small and solitary HCC nodule are more likely to undergo surgical resection; by comparison, the patients with multiple HCC nodules are more likely to undergo TACE. Thus, we would like to emphasize that the potential bias in the selection of patients and treatment options might lead to an imbalance in the comparison of survival results between the two different treatment options. Therefore, our findings should be cautiously interpreted.

In conclusion, Generally, a systematic review of available data is helpful to clarify the current knowledge regarding the management of recurrent HCC and is necessary to guide the study design in future. Based on the present systematic review and meta-analysis, we found a statistically significant survival benefit of hepatic re-resection over TACE for recurrent HCC after initial resection. However, we could not draw any strong recommendations because these published data were of low quality. Further randomized controlled trials were warranted to avoid the potential bias of treatment selection and to achieve a definitive conclusion.

Acknowledgement

Author contributions: XQ: designed the study, performed the literature search and selection, data extraction, quality assessment, and statistical analysis, and drafted the manuscript. DW, LL, CS, XL, XC, and JC: participated in the literature search and selection, data extraction, and/or quality assessment. HL and XG: gave critical comments and revised the manuscript. All authors have made an intellectual contribution to the manuscript and approved the submission.

References

(2012). EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol*, **56**, 908-43.

Adachi E, Maeda T, Matsumata T, et al (1995). Risk factors for intrahepatic recurrence in human small hepatocellular carcinoma. *Gastroenterology*, **108**, 768-75.

Balsells J, Charco R, Lazaro JL, et al (1996). Resection of hepatocellular carcinoma in patients with cirrhosis. *Br J Surg*, **83**, 758-61.

Belghiti J, Panis Y, Farges O, et al (1991). Intrahepatic recurrence after resection of hepatocellular carcinoma complicating cirrhosis. *Ann Surg*, **214**, 114-7.

Bruix J, Sherman M (2011). Management of hepatocellular carcinoma: an update. *Hepatology*, **53**, 1020-2.

Ercolani G, Grazi GL, Ravaioli M, et al (2003). Liver resection for hepatocellular carcinoma on cirrhosis: univariate and multivariate analysis of risk factors for intrahepatic recurrence. *Ann Surg*, **237**, 536-43.

Fong Y, Sun RL, Jarnagin W, et al (1999). An analysis of 412 cases of hepatocellular carcinoma at a Western center. *Ann Surg*, **229**, 790-9.

Franco D, Capussotti L, Smadja C, et al (1990). Resection of hepatocellular carcinomas. Results in 72 European patients with cirrhosis. *Gastroenterology*, **98**, 733-8.

Hirokawa F, Hayashi M, Miyamoto Y, et al (2011). Appropriate treatment strategy for intrahepatic recurrence after curative

hepatectomy for hepatocellular carcinoma. *J Gastrointest Surg*, **15**, 1182-7.

Ho CM, Lee PH, Shau WY, et al (2012). Survival in patients with recurrent hepatocellular carcinoma after primary hepatectomy: comparative effectiveness of treatment modalities. *Surgery*, **151**, 700-9.

Hu RH, Ho MC, Wu YM, et al (2005). Feasibility of salvage liver transplantation for patients with recurrent hepatocellular carcinoma. *Clin Transplant*, **19**, 175-80.

Hu Z, Zhou J, Xu X, et al (2012). Salvage liver transplantation is a reasonable option for selected patients who have recurrent hepatocellular carcinoma after liver resection. *PLoS One*, **7**, 36587.

Imaoka S, Sasaki Y, Nakano H, et al (1995). The significance of re-hepatectomy for intrahepatic recurrence after hepatectomy for hepatocellular carcinoma. *Acta Hepatologica Japonica*, **36**, 664-8.

Lee PH, Lin WJ, Tsang YM, et al (1995). Clinical management of recurrent hepatocellular carcinoma. *Ann Surg*, **222**, 670-6.

Liang BY, Huang ZY, Zhou SJ, et al (2014). Primary results of salvage liver transplantation in the patients with unresectable recurrent hepatocellular carcinoma after initial liver resection. *Hepatogastroenterology*, **61**, 2014-20.

Majno PE, Sarasin FP, Mentha G, et al (2000). Primary liver resection and salvage transplantation or primary liver transplantation in patients with single, small hepatocellular carcinoma and preserved liver function: an outcome-oriented decision analysis. *Hepatology*, **31**, 899-906.

Minagawa M, Makuuchi M, Takayama T, et al (2003). Selection criteria for repeat hepatectomy in patients with recurrent hepatocellular carcinoma. *Ann Surg*, **238**, 703-10.

Okada S, Shimada K, Yamamoto J, et al (1994). Predictive factors for postoperative recurrence of hepatocellular carcinoma. *Gastroenterology*, **106**, 1618-24.

Poon RT, Fan ST, Lo CM, et al (2002). Long-term survival and pattern of recurrence after resection of small hepatocellular carcinoma in patients with preserved liver function: implications for a strategy of salvage transplantation. *Ann Surg*, **235**, 373-82.

Poon RT, Fan ST, Lo CM, et al (2001). Improving survival results after resection of hepatocellular carcinoma: a prospective study of 377 patients over 10 years. *Ann Surg*, **234**, 63-70.

Qi X, Wang D, Su C, et al (2015). Hepatic resection versus transarterial chemoembolization for the initial treatment of hepatocellular carcinoma: A systematic review and meta-analysis. 2015, In press.

Sala M, Fuster J, Llovet JM, et al (2004). High pathological risk of recurrence after surgical resection for hepatocellular carcinoma: an indication for salvage liver transplantation. *Liver Transpl*, **10**, 1294-300.

Shimamura T, Une Y, Nakajima Y, et al (1994). [Efficacy of transarterial embolization combined with percutaneous ethanol injection therapy for recurrent hepatocellular carcinoma]. *Gan To Kagaku Ryoho*, **21**, 2229-32.

Shirabe K, Kanematsu T, Matsumata T, et al (1991). Factors linked to early recurrence of small hepatocellular carcinoma after hepatectomy: univariate and multivariate analyses. *Hepatology*, **14**, 802-5.

Takemura N, Hasegawa K, Shindoh J, et al (2014). Significance of therapeutic options for recurrent hcc after liver resection. *HPB*, **16**, 452.

Taniai N, Yoshida H, Mamada Y, et al (2012). What is re-treatment for recurrent patients with hepatocellular carcinoma undergoing hepatectomy? *Hepatology International*, **6**, 241.

Tierney JF, Stewart LA, Ghersi D, et al (2007). Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials*, **8**, 16.

Ueno M, Uchiyama K, Ozawa S, et al (2009). Prognostic impact of treatment modalities on patients with single nodular recurrence of hepatocellular carcinoma. *Surg Today*, **39**, 675-81.

Umeda Y, Matsuda H, Sadamori H, et al (2011). A prognostic model and treatment strategy for intrahepatic recurrence of hepatocellular carcinoma after curative resection. *World J Surg*, **35**, 170-7.

Wang K, Liu G, Li J, et al (2014). Early intrahepatic recurrence of hepatocellular carcinoma after hepatectomy treated with re-hepatectomy, ablation or chemoembolization: A prospective cohort study. *Eur J Surg Oncol*.

Wu L, Hu A, Tam N, et al (2012). Salvage liver transplantation for patients with recurrent hepatocellular carcinoma after curative resection. *PLoS One*, **7**, 41820.

Yamamoto Y, Ikoma H, Morimura R, et al (2013). Changing trends in long-term outcomes after hepatic resection for hepatocellular carcinoma: A 30-year, single-center experience. *Anticancer Res*, **33**, 5097-105.

Yang LT, Cheng XD, Du YA, et al (2009). [Prognostic factors and outcome in patients with intrahepatic recurrence after hepatectomy for hepatocellular carcinoma]. *Zhonghua Zhong Liu Za Zh*i, **31**, 612-6.