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Review Article

Treatment and outcomes of multinodular hepatocellular carcinoma: a systematic review and meta-analysis

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ABSTRACT

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide. Recent advances in surgical techniques and perioperative management have been suggested to have improved survival. However, full agreement about the overall survival ofpatient with multinodular HCC is still not reached yet. The aim of this meta-analysis is to evaluate the survival of patients with multinodular HCC undergoing recent treatment modalities.Weperformed the systematic computerized search for eligible articles fromfour databases (PubMed, Embase, Google Scholar and Web of Science) published before February 2018. Summary effect size (ES) and 95% confidence interval (CI) were calculated with the random-effects model and fixed-effects model. A total of 25 studies with 18954 multinodular hepatocellular carcinoma patients were included. Overall survival was shorter inpatient having multinodular carcinoma undergoing different treatment modalities (ES 1.12, 95 % CI 1.02 to 1.21; p=0.000) which was statistically significant. Those undergoing hepatectomy was shorter (ES 1.49, 95% CI 1.33 to 1.64; p=0.304) which was not statistically significantand patients undergoing RFA was shorter (ES 1.61, 95% CI 1.28 to 1.94; p=0.020) which was statistically significant. Begg's funnel plot showed no publication bias exists.Our meta-analysis result showed that the overall survival of patients with multinodular carcinoma is shorter.

Keywords: Hepatocellular carcinoma, HCC, Multinodular carcinoma, Prognosis, Meta-analysis

INTRODUCTION

Hepatocellular carcinoma (HCC) is the 5th most common malignancy worldwide and 3rd- leading cause of cancer-related death worldwide and one of the most commonmalignancies and a major cause of death among both sexes, anddespite diagnostic and therapeutic improvements, its incidenceand mortality rates have obviously increased in recent years, especially in Asian countries.[1] Although the survival of HCC patients has been improved by advances in surgical techniques and perioperative management, such as Liver resection, Liver transplantation, radiofrequency ablation (RFA) and transcatheter arterial chemoembolization (TACE), long-term survival remains unsatisfactory owing to the high rate of recurrence and metastasis.[2] Firstly, huge HCC is the absolute contraindication of the livertransplantation. Secondly, radiofrequency ablation (RFA) and trans-arterial chemoembolization (TACE) has been proved to be of little efficacy. Moreover, Sorafenib, as the only therapeutic targeted drug approved by the FDA, could not achieve tumor regression.[3,4] Hence; surgical resection is the only option for huge HCC. Hepatic resection (HR) offers the best survival benefit forpatients in early stages of HCC.[5] As one of the most aggressive cancers, hepatocellular carcinoma (HCC) occupies 85%-90% of

primary liver cancer and it is responsible for significant morbidity and mortality in cirrhosis.[6] The major risk factors for HCC are hepatitis B or hepatitis C infection, cirrhosis and aflatoxin contamination, other factors such as alcohol drinking, obesity, smoking, and diabetes were also found to be associated with increased risk of HCC.[7]

Prognosis for patients with HCC depends on tumor stage, with curative therapies only available for patients detected at an early stage. Patients detected at an early stage can achieve 5 year survival rates of 70% with transplant or resection, whereas those with advanced HCC are only eligible for palliative treatments and have a median survival of less than one year.[8] According to Barcelona Clinic Liver Cancer staging strategy and The American Association for the Study of Liver Disease guidelines, surgical resection is not advocated in the treatment of multinodular HCC. Despite this, many recent clinical studies show that resection can achieve good results in patients with multinodular HCC. If resection or transplantation is not performed, these patients are usually managed with palliative procedures such as trans-arterial chemoembolization, radioembolization, and cytotoxic chemotherapy. The definition of multinodular HCC in the Milan criteria consists of HCC nodules more than 3 is known as multinodular HCC. For those patients with large HCC who can be respected, the overall survival has been shown to be better than the nonsurgicaltreatment.[9] Although partial hepatectomy is considered as one of the first line treatments for patients with early stage

HCC, the outcome is far from satisfactory due to a high recurrence rate in five years.[10-12] Spontaneous rupture is one of the most fatal complications of hepatocellular carcinoma (HCC) and possesses a geographically variable incidence. In Western countries, the incidence of ruptured HCC is less than 3%.[13] In this study, we performed a systematic review and meta-analysis of Retrospective and prospective to conform the treatment and outcomes of multinodular HCC patients.

METHODS

Search strategy

This systematic review and meta-analysis are conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement.[14] In 2018 February, authors RA independently carried out comprehensive literature searches in following online electronic databases: PubMed, Web of Science, Google Scholar, EMBASE and the CENTRAL database of the Cochrane Library using the predefined keywords. The search strategy was as follows: (HCC OR Hepatocellular carcinoma OR liver cancer OR hepatic tumor OR hepatic malignancy) AND (multifocal OR multinodular OR multiple nodules) AND (survival OR prognostic OR prognosis OR outcome OR prediction) AND (Hepatic resection ORhepatectomy). Besides, the references of retrieved articles and reviews were manually checked to identify additional articles meeting the inclusion in this meta-analysis for the inclusion of potential complements. The language of the paper was restricted to English, however, no restrictions on publication year, geographical location, and the age of the participants. In addition, we augmented the searches with the subject heading terms option as much as possible. A list of titles and abstracts of potentially relevant studies were generated and imported into managerial software (EndNote®) X8.2.

Selection criteria and quality evaluation

In order to qualify for meta-analysis, the studies needed to meet the following specific conditions: (1) patients with HCC, despite the difference in treatment they received (2) proper reporting and adequate data on multinodular HCC, (3) hazard ratio (HR) of multinodular HCC and 95% confidence interval (CI) were allowed or could be calculated by other data, (4) prognostic factors for long-term survival evaluated by multivariate analyses.

Studies which did not meet the above criteria were excluded from selection. Animal studies, letter to theeditor, reviews, editorials, abstracts, and unpublished results were excluded from this meta-analysis. If reports pertained to overlapping populations, only the study with the largest sample size was retained authors RA prudentially filtered the retrieved citations, and selected potential researches according to titles, abstracts, and full-texts.

Quality assessment of each study was independently performed in accordance with the Newcastle-Ottawa Quality Assessment Scale (NOS). The highest total scores were 9. NOS scores of $\geq$6 were considered as high -studies. If disagreements or discrepancies existed, the third reviewer was shouted to reach the consensus.

Data extraction and outcomes

The predefined substantial contents of each selected articles were extracted by independent investigators RA reported all outcome measures for quality assurance purpos[15] and cross-checked and to reach the consensus. Any disagreement was resolved by open discussion along with the third reviewer. From each study, the first author's name, publication year, country, study design, enrollment period, number of participants, study population and participants interventionwere extracted and inserted into Excel database.

Ethical Statement

All results and analyses were based on previous ethically approved studies thus no further ethical approval and patient consent are required for this meta-analysis.

Statistical analysis

All analyses were performed using Statistics/Data Analysis (Stata®) software version 12.0 (Stata Corp LP, College Station, Texas 77845 USA) and Microsoft Excel 2016.The hazard ratio (HRs) and 95% confidence intervals (95% CIs) for the available data were calculated to identify potential associations with overall survivalthe multivariate analysis and univariate analysis were reported in the same study, we chose the multivariate analysis to generate the pooled estimates Statistical heterogeneity of the studies was assessed using I^2 test and $p<0.001$ was set to determine significance. Heterogeneity was defined as low, moderate or high, based on the I^2 value of less than 25%, between 25% and 75% and over 75% respectively. When heterogeneity was significant a random effect model (Inverse Variance method) was used for analysis.[16] For outcomes with moderate-to-high heterogeneity, were performed a sensitivity analysis, in which the pooled estimates were recalculated by omitting one study at a time to detect which study is the main source of heterogeneity. Publication bias was accessed by using Begg's tests.[17]

RESULTS

Identification of the studies

The comprehensive electronic data search yielded 835 articles and 6 articles were retrieved from other sources. After removal of duplicates, 610 unique articles were accessed and 516 irrelevant articles were excluded. Remaining 94 articles were screened for full-text articles and 54 full-text articles were identified. From 54 full-text articles 20 articles were excluded on the basis of their title and abstract, 1 review and 9 articles without proper outcome were excluded. 25 clinical study comprising 18,954 patients were included for qualitative synthesis. Finally, total twenty-five studies comprising 18,954 patients were used in quantitative data synthesis. PRISMA flow diagram is shown in Figure 1.

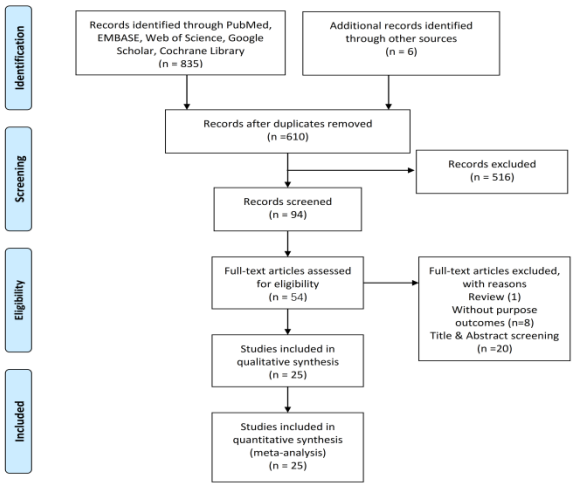

Figure 1: PRISMA flow chart of literature search and selection of studies.

Study characteristics

Following comprehensive literature search twenty-five, full-text articles were included in this meta-analysis.[18-42] The four prospective and twenty-one retrospective clinical study were conducted between 1981 and 2015.[18-42] Of these, the sixteen studies were conducted in China, two in Japan two in Taiwan two in multiple countries conducted at same time, one in Germany one in Singapore and one in Korea.[18-42] Among 25 studies; treatment modality of three studies was RFA, one study was PEI+TACE[18] 1 study was TACE+RFA[23]1 study was PEI+RFA+TACE+RT+BSC[24]1 study was Hepatic resection+TACE+PHT[36]1 study was TACE+HR[38]1 study was TACE+MWA, one study was TAE+Hepatectomy, one study was liver transplantation and 14 studies were hepatectomy.[18-42] The number of patients ranging from 82 to 3933. There was 100% agreement between two reviewers on a review of the extracted data. Table 1 summarizes the baseline characteristics and main evaluation indices of the included studies.

Table 1: Baseline characteristics of included studies.

Study	Year	Country	Study design	No of patients	Enrollment period	Study population	Treatment
Chang et al.	2013	Taiwan	Prospective	108	1991-1999	HCC	PEI+TACE
Dan et al.	2013	China	Retrospective	178	2005-2008	HCC	RFA
Fan et al.	2011	China	Prospective	82	2005-2009	HCC	Hepatectomy
Goh et al.	2014	Singapore	Retrospective	110	2000-2011	HCC	Hepatectomy
Hoffmann et al.	2014	Germany	Retrospective	95	2001-2011	HCC	Hepatectomy
Jinyong et al	2017	China	Retrospective	1560	2000-2008	HCC	TACE+RFA
Jun et al.	2013	Korea	Retrospective	743	2005-2012	HCC	PEI+RFA+TACE+ HAIC+RT+BSC
Li et al.(A)	2016	China	Retrospective	3388	1999-2009	HCC	Curative resection
Li et al.	2016	China	Retrospective	3933	1999-2009	HCC	Curative resection
Liu et al.(A)	2014	China	Retrospective	153	2003-2012	HCC	Liver resection
Liu et al.	2015	China	Retrospective	206	1997-2002	HCC	Hepatectomy

Continued.

Study	Year	Country	Study design	No of patients	Enrollment period	Study population	Treatment
Ng et al.	2005	Multi-national	Prospective	404	1982-2002	HCC	Hepatic resection
Ochiai et al.	2012	Japan	Retrospective	483	1987-2005	HCC	Hepatectomy
Pawlik et al.	2005	Multi-national	Retrospective	300	1981-2000	HCC	Hepatic resection
Shiina et al.	2012	Japan	Prospective	2825	1999-2009	HCC	RFA
Su et al.	2014	Taiwan	Retrospective	188	1991-2006	HCC	Hepatic resection
Wang et al.	2014	China	Retrospective	505	2003-2011	HCC	Curative hepatectomy
Xiao et al	2013	China	Retrospective	280	2000-2011	HCC	Liver transplantation
Xiao et al.	2015	China	Retrospective	167	2001-2008	HCC	Hepatic resection +TACE+PHT
Yang et al.	2013	China	Retrospective	258	2002-2011	HCC	Hepatic resection
Yuan et al.	2016	China	Retrospective	444	2005-2013	HCC	TACE+HR
Zhang et al.	2015	China	Retrospective	837	2001-2012	HCC	RFA
Zheng et al.	2018	China	Retrospective	258	2011-2015	HCC	TACE+MWA
Zhong et al.(A)	2015	China	Retrospective	927	2000-2013	HCC	Hepatic resection
Zhong et al.	2016	China	Retrospective	162	2004-2014	HCC	TAE+ Hepatectomy
Total				18,954			

Abbreviations: PEI; TACE; RFA; HAIC; RT; BSC; PHT; HR; MWA; TAE.

Table 2: Summary of outcome measures.

Study	OR	LCI	UCI
Chang et al.	2.53	1.26	5.08
Dan et al.	5.52	3.41	8.93
Fan et al.	2.631	1.066	6.492
Goh et al.	1.94	1.04	3.63
Hoffmann et al.	1.92	1.04	3.53
Jinyong et al	1.328	1.011	1.542
Jun et al.	0.248	0.08	3.07
Li et al.	1.351	1.191	1.532
Li et al.	1.61	0.84	3.07
Liu et al.	2.161	1.262	3.703
Liu et al.	1.683	0.46	2.732
Ng et al.	1.69	1.23	2.33
Ochiai et al.	0.57	0.03	9.4
Pawlik et al.	2.25	1.17	4.3
Shiina et al.	1.58	1.13	2.21
Su et al.	2.389	1.319	4.367
Wang et al.	2.431	1.596	3.702
Xiao et al	1.301	0.848	1.997
Xiao et al.	1.805	1.059	3.087
Yang et al.	2.454	1.061	5.696
Yuan et al.	2.416	1.582	3.693
Zhang et al.	1.53	1.158	2.004
Zheng et al.	0.748	0.579	0.966
Zhong et al.	2.416	1.582	3.693
Zhong et al.	0.25	0.09	0.73

Table 3: Meta-analysis of multinodular HCC and overall survival.

Author	Fixed		Random	
	ES (95%CI)	% Weight	ES (95%CI)	% Weight
Chang et al. (2013)	2.530 (1.260-5.080)	0.23	2.530 (1.260-5.080)	1.75
Dan et al. (2013)	5.520 (3.410-8.930)	0.11	5.520 (3.410-8.930)	0.96
Fan et al. (2011)	2.631 (1.066-6.492)	0.11	2.631 (1.066-6.492)	0.99
Goh et al. (2014)	1.940 (1.040-3.630)	0.50	1.940 (1.040-3.630)	2.98
Hoffman et al. (2014)	1.920 (1.040-3.530)	0.54	1.920 (1.040-3.530)	3.12
Jinyong et al. (2016)	1.328 (1.011-1.542)	11.95	1.328 (1.011-1.542)	6.94
Jun et al. (2013)	0.248 (0.084-0.731)	8.05	0.248 (0.084-0.731)	6.75
Li et al. (2015)	1.351 (91.191-1.532)	28.97	1.351 (1.191-1.532)	7.18
Li et al. (2016)	1.610 (0.840-3.070)	0.68	1.610 (0.840-3.070)	3.52
Liu et al. (2015)	2.161 (1.262-3.703)	0.57	2.161 (1.262-3.703)	3.19
Liu et al. (2014)	1.683 (0.460-2.732)	0.65	1.683 (0.460-2.732)	3.46
Ng et al. (2005)	1.690 (1.230-2.330)	2.78	1.690 (1.230-2.330)	5.82
Ochiai et al. (2012)	0.570 (0.030-9.400)	0.04	0.570 (0.030-9.400)	0.36
Pawlik et al. (2005)	2.250 (1.170-4.300)	0.34	2.250 (1.170-4.300)	2.34
Shiina et al. (2011)	1.580 (1.130-2.210)	2.89	1.580 (1.130-2.210)	5.87
Su et al. (2014)	2.389 (1.319-4.367)	0.36	2.389 (1.319-4.367)	2.43
Wang et al. (2914)	2.431 (1.596-3.702)	0.76	2.431 (1.596-3.702)	3.73
Xiao et al. (2013)	1.301 (0.848-1.997)	2.55	1.301 (0.848-1.997)	5.71
Xiao et al. (2014)	1.805 (1.059-3.078)	0.83	1.805 (1.059-3.078)	3.89
Yang et al. (2013)	2.454 (1.061-5.696)	0.16	2.454 (1.061-5.696)	1.29
Yuan et al. (2015)	2.416 (1.582-3.693)	0.76	2.416 (1.582-3.693)	3.73
Zhang et al. (2015)	1.530 (1.158-2.004)	4.71	1.530 (1.158-2.004)	6.37
Zheng et al. (2018)	0.748 (0.579-0.966)	22.49	0.748 (0.579-0.966)	7.13
Zhong et al. (2015)	2.416 (1.582-3.693)	0.76	2.416 (1.582-3.693)	3.73
Zhong et al. (2016)	0.250 (0.090-0.730)	8.22	0.250 (0.090-0.730)	6.76
Dan et al. (2013)	5.520 (3.410-8.930)	1.43	5.520 (3.410-8.930)	7.98
Shiina et al. (2011)	1.580 (1.130-2.210)	37.48	1.580 (1.130-2.210)	44.34
Zhang et al. (2015)	1.530 (1.158-2.004)	61.08	1.530 (1.158-2.004)	47.68

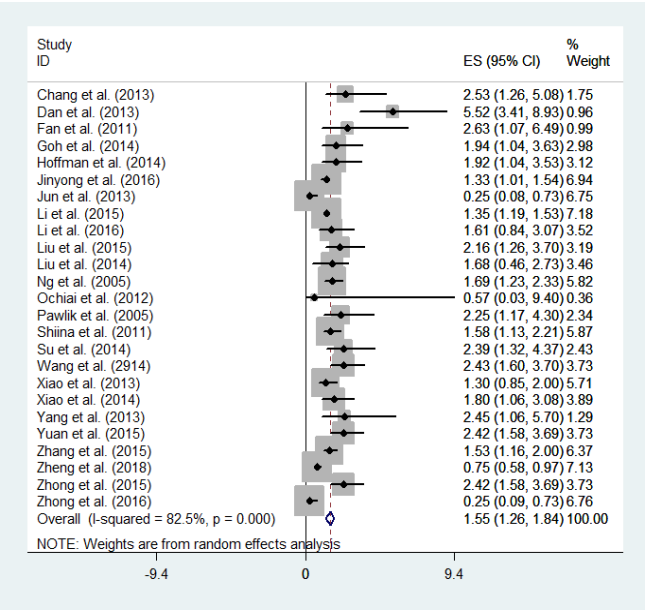

Figure 2: Forest plot of meta-analysis results of the relationship between multinodular hepatocellular carcinoma and overall survival.

Quantitative data synthesis

Overall survival of multinodular hepatocellular carcinoma

Twenty-five studies reported data for overall survival on multinodular hepatocellular carcinoma (Table 2).[18-42] Overall survival was shorter in a patient having multinodular carcinoma undergoing different treatment modalities (ES 1.12, 95% CI 1.02 to 1.21; p=0.000) which was statistically significant with high heterogeneity (I^2 =82.5) (Table 3). The results suggest no publication bias, with p=0.45 for Begg's test.

Survival of a patient with multinodular hepatocellular carcinoma undergoing RFA

Three studies reported data for the survival of a patient with multinodular hepatocellular carcinoma undergoing RFA.[19,32,39] Survival of patients with multinodular carcinoma undergoing RFA was shorter (ES 1.61, 95% CI 1.28 to 1.94; p=0.020) which was statistically significant with moderate heterogeneity (I^2=74.5). The

results suggest no publication bias, with P = 0.602 for Begg's Test.

Survival of a patient with multinodular hepatocellular carcinoma undergoing hepatectomy

Fourteen studies reported data on survival of a patient with multinodular hepatocellular carcinoma undergoing hepatectomy.[20-22,25-31,33,34,37,42] Survival of patients with multinodular carcinoma undergoing hepatectomy was shorter (ES 1.49, 95% CI 1.33 to 1.64; p=0.304) which was not statistically significant with mild heterogeneity (I^2=13.7). The results suggest no publication bias, with p=0.511 for Begg's Test.

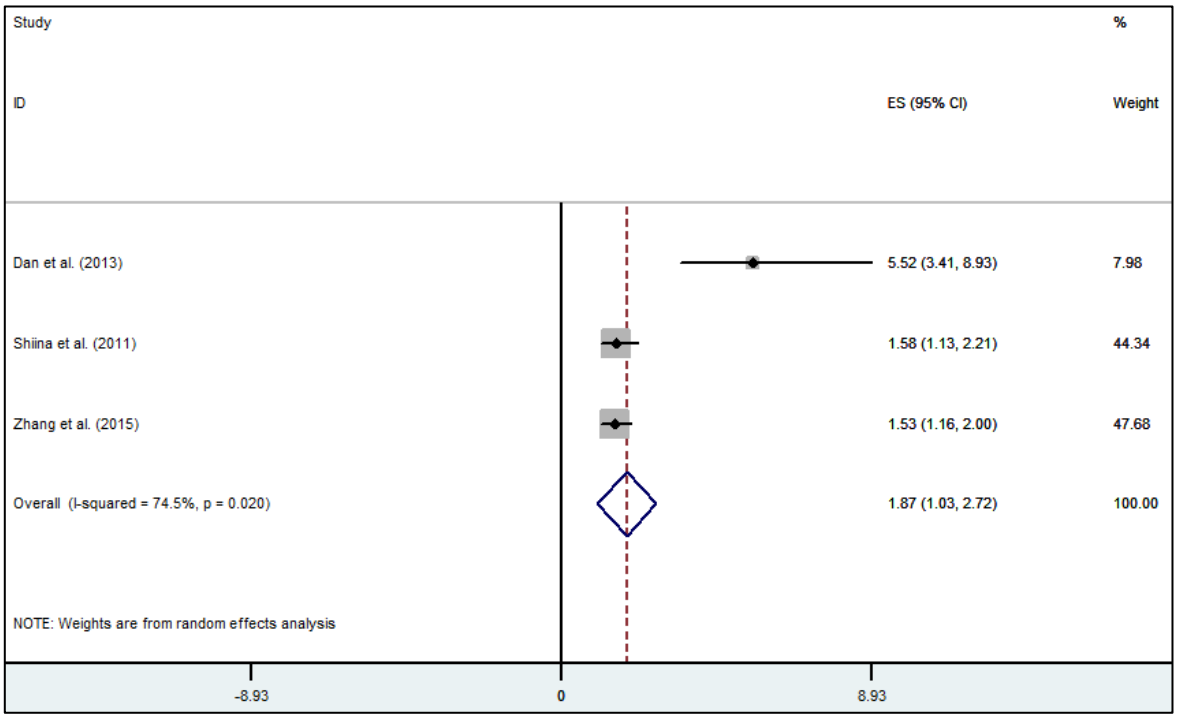

Figure 3: Forest plot of meta-analysis results of the relationship between multinodular hepatocellular carcinoma and survival of patient undergoing RFA.

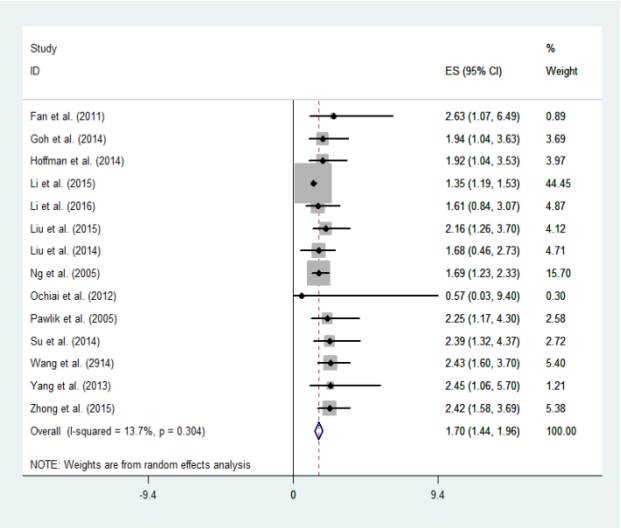

Figure 4: Forest plot of meta-analysis results of the relationship between multinodular hepatocellular carcinoma and survival of patient undergoing Hepatectomy.

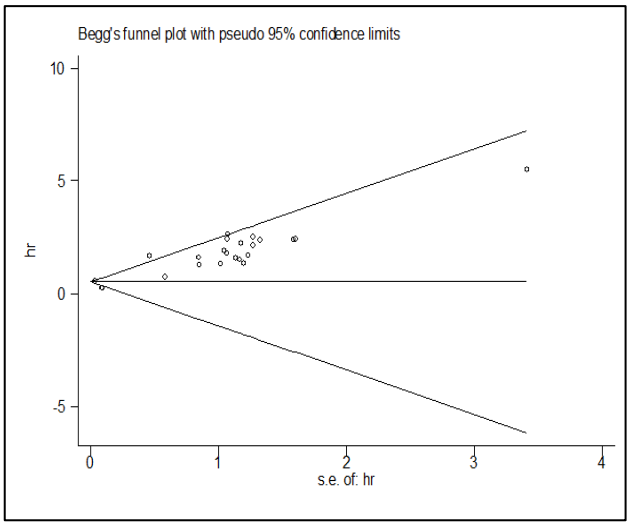

Figure 5: Funnel plot of the publication bias of overall survival (Begg′s test).

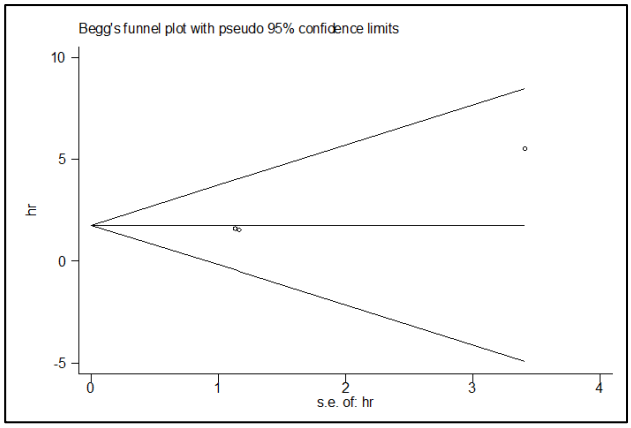

Figure 6: Funnel plot of the publication bias of survival of patient undergoing RFA (Begg′s test).

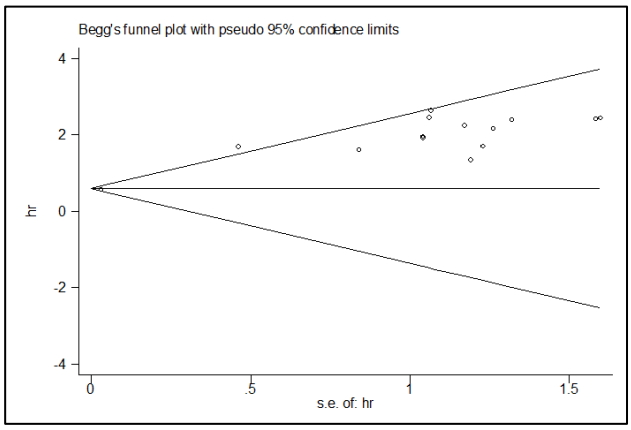

Figure 7: Funnel plot of the publication bias of survival of patient undergoing hepatectomy (Begg′s test).

DISCUSSION

This systematic review aimed to evaluate the survival of patients with multinodular HCC undergoing recent treatment modalities. Our result suggested that overall survival is shorter in a patient with multinodular hepatocellular carcinoma.

The prognosis of HCC is generally poor. Partial hepatectomy remains the best hope for a cure but is suitable for only 9–27% of patients.[43] One of the major causes of such a low resectability rate is the presence of significant background cirrhosis. The other possible cause is the high incidence of tumor multiplicity because patients with multiple tumors have a poorer outcome compared with those with a solitary tumor.[44-46] This has also been demonstrated in the present study, which shows that survival of patients with MNHCC is significantly shorter than the survival of patients with single HCC. However, some still perform an aggressive surgical intervention and try to establish selection criteria for those patients who would benefit from hepatectomy.[44,45]The main nonsurgical therapies included were RFA, PEI,and TACE. The principle of RFA is that heat generated by high radiofrequency waves inactivates local tumor cells quickly and effectively. In PEI, anhydrous alcohol dehydrates cancer cells, which degenerates and necrotizes them directly, and thus promotes tumor intravascular thrombosis. For TACE, a designated amount of embolization agents is injected into the target artery to produce ischemic necrosis of the tumor tissue. Based on various international treatment guidelines, few of these patients are eligible for percutaneous ethanol injection, RFA, or liver transplantation because of the strict indications for these procedures.[47] HCC is the high incidence of HCC recurrence. In reports from centers around the world, the 5-year recurrence rates after radical therapies for HCC and efforts to prevent and effectively manage the recurrence of HCC are undoubtedly the most important strategies for improving the overall survival with radical treatment for HCC. Although HCC is highly malignant, it usually remains undiagnosed until it progresses to multifocal or large intrahepatic lesions, at which point the patient is ineligible for surgical resection.[48]

Thus, TACE is the standard treatment for large or multinodular HCC. About 30% of patients with early-stage may benefit from curative therapies, such as surgical resection, liver transplantation.[49] Moreover, for patients with large lesions or live dysfunction, surgical resection is not recommended as the first-treatment choice, whereas the palliative care, including transcatheter arterial chemoembolization (TACE) and percutaneous ethanol injection (PEI), are widely used for HCC patients to relieve suffering and improve quality of life. TACE has been proved to prolong the survival in intermediate-stage HCC patients, especially for those with large and multiple lesions.[50] Some suggestions should be considered in future research

Some limitation of our study should of concern. First, this meta-analysis included studies conducted on different treatment modalities, demographic baseline, pathological stage, perioperative management and median follow up which could have led to high heterogeneity, this was why we used the random effect model for the purpose to merging and reducing the impact of heterogeneity. Secondly, we chose only English literature which could lead to selection bias and measurement bias, although we did not find publication bias using Begg's test. Thirdly, the geographical restriction is present in this meta-analysis, as all of the original studies were from China and European countries. Therefore, geographicalof our findings to other ethnic groups should be considered with caution. finally, the survival analysis was calculated by ES value that might lead to an unauthentic conclusion.

In conclusion, based on current evidence, present meta-analysis reveals that despite the advancement in different surgical modalities and perioperative management the overall survival of patients with multinodular hepatocellular carcinoma was shorter.

Considering the shortcomings of our research, our conclusion should be carefully considered. However, considerably larger sample size, careful patient selection, especially in the case of patients with >3 tumors, for whom HR is associated with high risk of hospital mortality multicenter, and tightly controlled studies with longer follow up time are warranted.

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Conflict of interest: None declared
Ethical approval: Not required

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