



統合分析研究計畫申請書

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一、計畫名稱	中文：Bayesian 網狀統合分析再發性肝細胞癌治療策略之預後研究 英文：Bayesian Network Meta-analysis on the Prognosis of Treatment Strategies for Intra-hepatic Recurrent Hepatocellular Carcinoma	
二、研究問題	<p>Precise treatment strategies for recurrent hepatocellular carcinoma (rHCC) still remains controversy despite new development of therapeutic methods nowadays. Hence, liver surgeons have more attention to apply an effective treatment method for our patients without delay when recurrent lesion appeared in the imaging study. The early detection of rHCC had commonly used by imaging or circulating tumor cell.(2, 3) Therefore we try to conduct the network meta-analysis to search the best treatment method for the most difficult part of rHCC patients. After this network meta-analysis, we do expect to obtain a best suitable treatment method for our rHCC patients</p>	
三、研究背景其重要性描述	<p>1. 研究目的。</p> <p>Hepatocellular carcinoma was well common disease and had ranked the first killer in man and the third in women in Taiwan for several years(1). Recurrent HCC patients have a high frequency to occur in most patients and reflex a life threatening status, Precise treatment strategies for rHCC still remains controversy despite new development of therapeutic methods nowadays. Hence, liver surgeons have more attention to apply an effective treatment method for our patients without delay when recurrent lesion appeared in the imaging study. The early detection of rHCC had commonly used by imaging or circulating tumor cell.(2, 3) Therefore we try to conduct the network meta-analysis to search the best treatment method for the most difficult part of rHCC patients based on their status.</p> <p>2. 過去相關研究文獻回顧。</p> <p>Over the last decade, many studies have published comparisons of different treatment options on rHCC. To achieve higher-grade evidence in this field, several previous meta-analyses reviewed these observational studies(13, 14). However, all of these studies were traditional two-arm</p>	

meta-analyses, which omitted important information obtained from the indirect comparisons. Network meta-analysis is a novel methodology, which is capable of integrating all of the direct or indirect comparisons that we could reach, and provide a useful ranking of the included intervention arms (15). Zheng J et al.(9) had the first study is the first network meta-analysis comparing the oncological prognosis of different strategies in the treatment of rHCC in 2020. High rates of recurrence and metastasis have consistently undermined the patients' survival, leading rHCC to become a major global health problem. Many treatments have been utilized for rHCC including HR, RFA, TACE, LT, RT. Without a standard practice guideline, the management strategies of rHCC were various in each hospital. Facing so many treatment options, clinicians usually determine the final treatment by experience or patients' preference. Because of a shortage of high-grade evidence to guide clinical practice, the current Bayesian network meta-analysis was conducted to clarify which treatment is the most optimal strategy for rHCC. In the study of Zheng's study resulted that, LT has the best effect on achieving a better OS, followed by RH and RT, while TACE was the most inferior therapy which was significantly worse than LT, RH, and RFA(9). Meanwhile, for the endpoint of RFS, the results indicated that SLT was superior to other interventions, while TACE showed the worst performance. tumor size is one of the significant prognostic factors associated with survival(16-18). Currently, surgical resection is still the most frequent option in both primary and recurrent HCC. And, we could observe from the network meta-analysis that RH is the most involved intervention in the rHCC and was widely used to compare with other treatments(9). A review including 22 studies and 1125 patients resulted that RH approach for rHCC was safe and achieved 0–6% perioperative mortality and 22–83% of 5-year survival rate(19, 20).

At the time of recurrence, a part of patients was assessed as multiple nodular, large tumor size, difficult tumor locations (such as adjacent large blood vessels or bile ducts), or insufficient residual liver volume or liver function, unable to receive curative treatment. For these patients, TACE and SBRT were effective treatments. As a non-radical treatment, TACE can hardly achieve a similar effect as radical treatments. However, it has been found in clinical practice that TACE significantly improves the survival in patients with rHCC, especially for unresectable patients

3.研究重要性。

	<p>At present, many institutions have issued guidelines for the primary HCC, and many consensuses have been established(4). However, for rHCC, there is still debate on the selection of treatment strategies, despite its relatively similar nature with primary HCC. There are accounts of salvage treatment options to be considered for rHCC, such as repeat hepatic resection (RHR), radiofrequency ablation (RFA), trans-arterial chemoembolization (TACE), liver transplantation (LT), radiation therapy (RT), and systemic treatment, etc.(5-8) Toward different advantages of those therapeutic options, clinicians often feel confused about which one is the best and how to make the most suitable strategy. Most previous meta-analyses have directly compared the therapeutic effect of only two of these treatments. The propose of this study was to conduct a comparison of the most common treatments for rHCC, including RHR, RFA, TACE, LT, and RT with network meta-analysis (9, 10). In addition, we try to add target therapy(TT) and immunotherapy(IMT) present the result with a Bayesian network meta-analysis which will be the first study for rHCC from Taiwan</p>
<p>四、研究假說</p>	<p>Previous traditional meta-analyses have directly compared the therapeutic effect of only two of these treatments(5, 11). The propose of this study was to conduct a systemic comparison of the most common treatments for rHCC, including RH, RFA, TACE, SLT and SBRT, and present the result with a Bayesian network meta-analysis. In addition, systemic chemotherapy(SC), target therapy(TT) and immunotherapy(IT) will be enrolled in treatment option for comparative analysis.</p>
<p>五、統合分析方法</p>	<p>說明應包含</p> <ol style="list-style-type: none"> 1. 使用資料庫名稱。 <p>We will perform a systematic literature search of PubMed, EMBASE, and Cochrane Library databases, published from January 2010 to Dec.2021, to identify all of the relevant randomized controlled trials and observational studies. The included search terms were as follows: HCC, recurrent hepatocellular carcinoma, liver cancer, recurrence, recurrent hepatocellular carcinoma, resection, hepatectomy, RFA, TACE, chemotherapy, chemoembolization, transplantation, radiotherapy.</p> <p>Comprehensive meta-analysis software include Bayesian network meta-analysis comparative effects model/random effective s/fixed effects model(12). The current network meta-analysis has not been registered in the PROSPERO international database.</p> 2. 所使用關鍵字。 <p>HCC, recurrent hepatocellular carcinoma, liver cancer, recurrence, recurrent, repeated hepatic resection, local ablation, RFA, TACE, systemic chemotherapy, chemoembolization, liver transplantation,</p>

radiotherapy.

3. 排除及納入條件。

Clinical trials included in this meta-analysis meet the following criteria: 1) *study design*: randomized controlled trials or observational studies; 2) *patients*: patients developed an intrahepatic recurrent HCC after initial curative treatments; 3) *intervention*: the included studies must compare at least two of the most common treatments for rHCC, including RH (laparoscopy or open), RFA (transcutaneous or laparoscopic), TACE, SLT, SBRT; 4) *outcomes measure*: at least one endpoint should be measured, including OS and RFS. The excluded studies met the following criteria: 1) the forms of published studies were conference abstracts, commentary articles, case reports, non-comparative studies, or reviews; 2) the participants of the studies suffered from extrahepatic metastasis of HCC or portal venous thrombosis; 3) the information of the main outcomes was insufficient. If there were more than two studies from the same cohort, we only extracted the data from the most recent publication.

4. 初估使用資料及預估納入篇數。

Following the primitive search strategy, a total of about 800 citations published from January 1, 2010, to the end of 2019 were retrieved for the treatment of rHCC. After removal of duplicates and initial screening, about 200 relevant articles were full-text reviewed based on the selection criteria. Finally, prospective more than 40 studies and more than thousand patients with intrahepatic HCC recurrence were enrolled for further data extraction and pooled analysis. The PRISMA flow diagram and the basic characteristics of the included studies will be formatted in table. All of the included studies are retrospectively cohort studies without any RCTs. The study period will range from 2000, and the median follow-up time was more than 20 months. The majority of studies may be performed in Asia-Pacific region (China, Japan, and Korea), where is also the region of the highest incidence of HCC all over the world. For these articles implementing multivariable regression analysis of the survival, the reported independently prognostic factors will be summarized as well.

5. 特殊族群分層。

We will conduct a subgroup analysis specific tumor size, and divided them into two groups. In the subgroup of tumor size ≤ 3 cm, containing 4 interventions (RHR, RFA, TACE, LT) will be included to analyze. In addition, other sub-group is recurrence after surgical resection to compare other non-surgical treatment as a primary treatment option.

	<p>6. 品質分析。</p> <p>We will conduct a subgroup analysis specific tumor size, and divided them into two groups. In the subgroup of tumor size ≤ 3 cm, containing 4 interventions (RHR, RFA, TACE, LT) will be included to analyze. In addition, other sub-group is recurrence after surgical resection to compare other non-surgical treatment as a primary treatment option.</p>
<p>六、統計方法</p>	<p>The consistency analysis of direct and indirect comparisons was conducted by the method of node splitting test. If P-value ≥ 0.05, it suggested that the consistency of the model is satisfying. To evaluate the overall heterogeneity of the model to calculate the deviation of the size of the heterogeneity variance parameter. The probability ranking diagrams of therapeutic effect were established by the rank probability function.</p>
<p>七、登錄 PROSPERO</p>	<p><input type="checkbox"/> 已完成登錄，Registration number :</p> <p><input checked="" type="checkbox"/> 未登錄，原因: prepare to register before journal submission.</p> <p>References:</p> <ol style="list-style-type: none"> 1. MOHW. Taiwan's Leading Causes of Death in 2016. https://www.moh.gov.tw/cp-115-33347-2.html. 2017. 2. Liao X, Wei J, Li Y, Zhong J, Liu Z, Liao S, et al. 18F-FDG PET with or without CT in the diagnosis of extrahepatic metastases or local residual/recurrent hepatocellular carcinoma. <i>Medicine</i>. 2018;97(34):e11970. Epub 2018/08/26. doi: 10.1097/md.00000000000011970. PubMed PMID: 30142825; PubMed Central PMCID: PMC6112887. 3. Cui K, Ou Y, Shen Y, Li S, Sun Z. Clinical value of circulating tumor cells for the diagnosis and prognosis of hepatocellular carcinoma (HCC): A systematic review and meta-analysis. <i>Medicine</i>. 2020;99(40):e22242. Epub 2020/10/07. doi: 10.1097/md.00000000000022242. PubMed PMID: 33019399; PubMed Central PMCID: PMC7535562. 4. EASL. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. <i>J Hepatol</i>. 2018;69(1):182-236. Epub 2018/04/10. doi: 10.1016/j.jhep.2018.03.019. PubMed PMID: 29628281. 5. Eisele RM, Chopra SS, Lock JF, Glanemann M. Treatment of recurrent hepatocellular carcinoma confined to the liver with repeated resection and radiofrequency ablation: a single center experience. <i>Technology and health care : official journal of the European Society for Engineering and Medicine</i>. 2013;21(1):9-18. Epub 2013/01/30. doi: 10.3233/thc-120705. PubMed PMID:

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2021 統合分析研究計畫審查結果

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申請人	陳仁隆	申請編號	EDAH_MA_1100102
計畫名稱	Bayesian 網狀統合分析再發性肝細胞癌治療策略之預後研究		
審查結果	通過		
回覆單 (請擇一勾選)	<p>研究計畫編號 = EDAH5110012</p> <p><input checked="" type="checkbox"/> 同意執行本計畫。 請填妥下列文件並簽名後繳回。 【統合分析研究計畫執行同意書】(一式兩份)。</p> <p><input checked="" type="checkbox"/> 放棄執行本計畫。 請於勾選後，回擲至醫研部。</p> <p>計畫主持人: <u>陳仁隆</u> (請簽名)</p>		