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ORIGINAL ARTICLE

A meta-analysis of the efficacy and safety of iodine [^{131}I] metuximab infusion combined with TACE for treatment of hepatocellular carcinoma

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KEYWORDS
Hepatocellular carcinoma;
TACE;
Iodine [^{131}I] metuximab infusion;
Meta-analysis

Summary
Objectives: To compare the efficacy and safety of combination iodine [^{131}I] metuximab infusion and transcathether arterial chemoembolization (TACE) with those of TACE-alone for hepatocellular carcinoma (HCC).
Materials and methods: PubMed, Cochrane Library, Embase, Web of Science, China Biology Medicine, China Science and Technology Journal Database, Wan Fang Data, and Chinese knowledge resource integrated databases were used for the literature search regarding controlled clinical trials comparing combination TACE and iodine [^{131}I] metuximab infusion with TACE-alone for HCC treatment before February 1, 2016. The Jadad system evaluation method for research quality and RevMan 5.0 software were used for the meta-analysis.
Results: In total, 1302 patients from 10 studies were included. The meta-analysis showed that the combination TACE and iodine [^{131}I] metuximab infusion treatment for HCC was more effective than TACE alone, including 6-month survival (odds ratio [OR] = 2.05, 95% confidence interval [CI]: 1.41—2.98, $P = 0.0002$), 1-year survival (OR = 1.90, 95% CI: 1.41—2.55, $P < 0.00001$), and the total response rate (OR = 2.91, 95% CI: 2.08—4.07, $P < 0.00001$). Nine studies reported adverse reactions, mainly comprising poor appetite, nausea, vomiting, and abdominal discomfort. Fever, chills, and bone marrow suppression were more common in the combined treatment group, but abnormal liver function was not different between the two treatment groups. There was no report on serious complications or death directly related to either treatment.
Conclusions: Compared with TACE alone, the combination of TACE with iodine [^{131}I] metuximab infusion for treating unresectable HCC may improve local efficacy and overall survival in these types of patients.

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CBM	China Biology Medicine
CSTJ	China Science and Technology Journal Database
CNKI	Chinese knowledge resources integrated
Cr	complete response
Ct	computed tomography
Ci	confidence interval
HCC	hepatocellular carcinoma
MRI	magnetic resonance imaging
OR	odds ratio
Pr	partial response
RECIST	Response Evaluation Criteria in Solid Tumors
TACE	transcathether arterial chemoembolization
AFP	α-fetoprotein

Introduction

Primary hepatocellular carcinoma (HCC) is one of the most common malignant tumors. Its incidence accounts for over 1/3 of cancers worldwide, and ranks second among cancer-related deaths in China [1]. The onset of HCC is often undetected and most patients are diagnosed as late-stage, making them ineligible for surgery. Transcatheter arterial chemoembolization (TACE) is the first option for such patients with unresectable HCC, but TACE treatment alone is limited in its ability to eliminate tumor tissue and typically has a high recurrence rate [2]. With the rise of endo-radiological technology, radionuclide-labeled antibody-guided treatment is highly targeted and persistent, and has been widely used in treatment of HCC, thereby introducing a new field of clinical HCC treatment [3]. ^{131}I-metuximab is the first radioimmunotherapy used in China for the treatment of primary HCC. It is an antibody fragment with high specificity and affinity to HCC, and is considered the best carrier for targeted therapy of liver cancer [4]. The literature has shown that ^{131}I-metuximab can not only significantly decrease the recurrence rate of liver cancer after liver transplantation, but also has good efficacy for unresectable liver cancer when combined with TACE. However, because this treatment has only been recently implemented, there are few relevant clinical studies in the literature, with most involving a small number of subjects, or were not controlled studies, so its efficacy and safety still lacks high-level, evidence-based medical validation [5—8].

This study is an evidence-based evaluation of the performance of this integrated treatment regimen using overall survival, decrease in α-fetoprotein (AFP), tumor local control rate, and other measures of efficacy. After screening relevant research reports and evaluating their quality, a meta-analysis was performed in order to provide a more objective basis for reference of this clinical treatment.

Materials and methods

Search strategy

Computer searches of the PubMed, Cochrane Library, Embase, Web of Science, China Biology Medicine (CBM), China Science and Technology Journal Database (CSTJ), Wang Fang Data, Chinese knowledge resources integrated (CNKI), as well as other domestic and international databases, were performed for relevant journal articles, conference proceedings, and dissertations in the literature. The search was limited to literature in any language published before February 1, 2016. The Chinese search terms used were: liver cancer, TACE, Licartin, and ^{131}I-metuximab. The English search terms used were: hepatocellular carcinoma and transcatheter arterial chemoembolization. The logical operators, wildcards, and search range limits of each database were used in the search strategies. At the same time, keyword search strategies were used to find all controlled trials related to treatment of unresectable liver cancer treated using TACE combined with ^{131}I-metuximab infusion, after which manual filtering of the literature search results was performed. If a paper could not be downloaded, the corresponding author of the paper was contacted.

Inclusion criteria

The meta-analysis inclusion criteria included:

- retrospective and prospective controlled clinical trials;
- study subjects were patients with unresectable HCC;
- no fewer than 30 subjects in the study with complete medical data;
- two study groups, experimental group: TACE plus ^{131}I-metuximab treatment; control group: TACE treatment alone, completely identical TACE protocol and chemotherapy regimens between the two groups;
- endpoint indices:
  - short-term efficacy: complete response (CR), partial response (PR), response rate (RR = CR + PR),
  - long-term efficacy: survival rate and survival period.

Exclusion criteria

The meta-analysis exclusion criteria included:

- reviews, duplicate literature, theoretical essays, case reports, studies with inconsistent data before and after treatment, and studies in which survival analysis was missing;
- use of treatments other than TACE and ^{131}I-metuximab, such as systemic chemotherapy, alcohol septal ablation, external radiotherapy, surgical resection, liver transplantation, and so on;
- study only evaluated tumor local efficacy and not long-term overall survival.

Efficacy evaluation indices

For evaluation of efficacy, 6-month survival, 1-year survival, and response rate were selected. Of those, response rates were calculated according to the CR and PR criteria of the Response Evaluation Criteria in Solid Tumors (RECIST), developed by the WHO. These criteria includes shrinkage or necrosis of the tumor lesion by > 50% and maintenance for

4 weeks or more indicated treatment efficacy, which was specifically evaluated by enhanced computed tomography (CT) or magnetic resonance imaging (MRI) after treatment [9]. Safety was evaluated according to the complication and mortality rates reported in each randomized controlled trial.

Literature quality evaluation

Methodological quality evaluation, classification, and data extraction were performed on collected literature articles by two independent researchers according to the Jadad quality score [10], and results were cross-checked (any disagreement was resolved by discussion with a third researcher). Details of the scoring method are as follows:

- the subject-matching method assigned 0—2 points: 2 points = correct randomization and matching methods; 1 point = described as ''random'' by author, but specific methods were not explained; 0 points = no randomization method described in the paper;
- random-blinding method assigned 0—2 points: 2 points = correct blinding methods were used for both patients and experimenters; 1 point = described as ''double-blind'' by author, but specific methods were not explained; 0 points = not blinded;
- records of patients lost to follow-up during the follow-up period were assigned 0—1 points: 1 point = records number, time, and cause of patients lost to follow-up and patients that withdrew voluntarily were correctly recorded; 0 points = above records related to follow-up records were not kept. The total score was between 1 and 5 points, with 3 or more points indicating a high-quality study and 1—2 points indicating a low-quality study.

Statistical analysis

The RevMan 5.0 software provided by the Cochrane Community was used for statistical analysis. The odds ratio (OR) was used as a pooled statistic, with the 95% confidence intervals (CIs) being reported. The heterogeneity of each study was tested using the Chi^2 test. The significance level was $P < 0.05$. If the difference in heterogeneity was not statistically significant, the fixed effects model was used for the meta-analysis; otherwise, the random effects model was selected.

Results

Literature search results

Initially, 158 relevant studies were found, but after removal of duplicates and reading articles and abstracts, 21 studies were preliminarily included. Next, studies in which subjects were not matched and studies with inconsistent interventions and poor baseline comparability were excluded, leaving 10 clinical studies included in the final analysis. Five studies were randomized controlled trials and the other 5 were non-randomized controlled trials. A total of 1302 HCC patients were included; of which 639 patients underwent TACE plus ^{131}I-metuximab treatment, and 661 patients underwent TACE alone [5—8,11—16]. The patient characteristics, as well as the TACE and ^{131}I-metuximab hepatic artery infusion methods, in the included controlled trials all had a certain degree of comparability. The follow-up protocol in each study included AFP re-examination, liver function tests, conventional blood work, and other biochemical indices, as well as assessment with B-scan ultrasonography, CT, MRI, or other imaging modalities being conducted at 1—2 months post-treatment.

Characteristics and quality evaluation of the included studies

Differences in age, sex, clinical stage, and other characteristics between patients in the TACE plus ^{131}I-metuximab group and the TACE-alone group were not statistically significant and had good comparability. The Child—Pugh scale criteria were used for liver function scoring. Most patients in the included studies had liver function class of B or worse. None of the studies reported matching of hidden implementation and blinding. The protocol for patients lost to follow-up was not reported in 7 studies (Table 1).

Clinical efficacy and meta-analysis results

For comparison of survival between TACE plus ^{131}I-metuximab and the TACE-only groups, 3 of the 9 included controlled trials reported the median survival period, 4 studies reported the 6-month and 1-year survival rates, and 1 study reported the 2-year survival rate. Meta-analysis results showed that the difference in 6-month and 1-year survival between the two groups was statistically significant (6-month: OR = 2.05, 95% CI: 1.41—2.98, $P = 0.0002$; 1-year: OR = 1.90, 95% CI: 1.41—2.55, $P < 0.0001$ (Figs. 1 and 2). Statistical analysis showed that the 6-month and 1-year survival was better with ^{131}I-metuximab combined with TACE than with TACE alone.

Tumor response rate

There were 7 studies that used the RECIST criteria to evaluate post-treatment tumor response. The meta-analysis results showed that the difference was statistically significant (OR = 2.91, 95% CI: 2.08—4.07, $P < 0.00001$) (Fig. 3). Statistical analysis showed that relative to TACE alone, ^{131}I-metuximab combined with TACE had even higher efficacy and tumor response.

Publication bias

Six-month survival, 1-year survival, and tumor response rate were used as indices for the funnel plot analysis of the included studies. The funnel plots had good symmetry, indicating that the results were not affected by any significant publication bias (Figs. 4—6).

Table 1 Basic characteristics of included clinical studies related to HCC treatment with TACE combined with ^{131}I-metuximab infusion.

Author	Study type	Patients (T + I/T)	Tumor number	Tumor size (cm)	PVT (Yes/No)	Liver function class, A/B/C	^{131}I-metuximab dose (MBq/kg)	Follow-up period (months)	Grouping method	Number lost to follow-up	Quality score
Ma and Wang [5]	Randomized controlled trial	341 (167/174)	NA	NA	NA	298/43/0	27.75	24	Random	NA	4
He et al. [6]	Single-center clinical trial	185 (95/90)	NA	(≥ 5/< 5) T + I: 80/15; T: 81/9	None	179/6/0	27.75	12	Random	NA	2
Wu et al. [7]	Single-center non-randomized trial	133 (65/66)	(Solitary/multifocal) T + I: 3/65; T: 4/66	Largest tumor size: T + I: 4.1 (1.2—8.1); T: 3.8 (1—7.8)	None	111/27/0[a]	27.75	31	Non-random	8	1
Wu et al. [8]	Single-center non-randomized trial	242 (110/132)	NA	(≤ 5/> 5) T + I: 79/31 T: NA	NA	165/77/0	27.75	24	NA	NA	0
Li et al. [11]	Single-center randomized trial	47 (24/23)	NA	T + I: 6.60 ± 0.87; T: 6.51 ± 0.88	T + I: 9/15; T: 5/18	29/13/5	27.75	NA	Random	13	3
Yao et al. [12]	Prospective single-center trial	76 (38/38)	NA	NA	T + I: 18/20; T: 9/29	47/29/0	27.75	18	Non-random	3	1
Guo et al. [13]	Retrospective analysis	62 (31/31)	NA	NA	NA	NA	30.00	21	Random	NA	1
Guo et al. [14]	Retrospective analysis	63 (32/31)	NA	NA	NA	24/39/0	27.75	41	NA	NA	0
Dong et al. [15]	Retrospective analysis	78 (43/35)	NA	T + I: 9.65 ± 2.18; T: 9.66 ± 2.29	NA	NA	27.75	12	NA	NA	0
Wei et al. [16]	Retrospective analysis	75 (34/41)	NA	T + I: 9.62 ± 2.19; T: 9.67 ± 2.31	NA	NA	NA	12	NA	NA	0

T + I: TACE + ^{131}I-metuximab; T: TACE alone; NA: not applicable.
The Child—Pugh scale was used to determine liver function classes as A, B, or C.
[a] Includes 8 patients lost to follow-up.

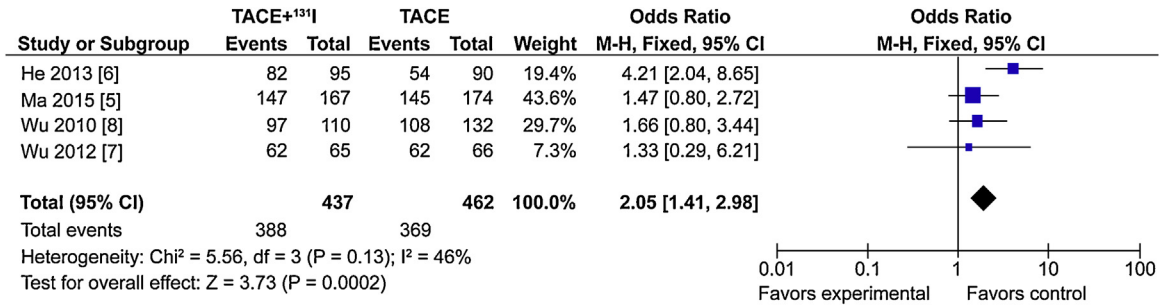

Figure 1 Forest plot analysis comparing the 6-month survival rate between TACE + ^{131}I-metuximab infusion and TACE-only treatment groups.

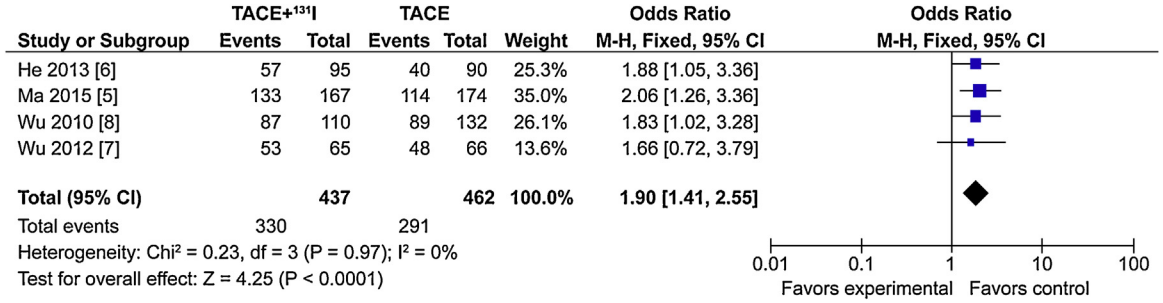

Figure 2 Forest plot analysis comparing the 1-year survival rate between TACE + ^{131}I-metuximab infusion and TACE-only treatment groups.

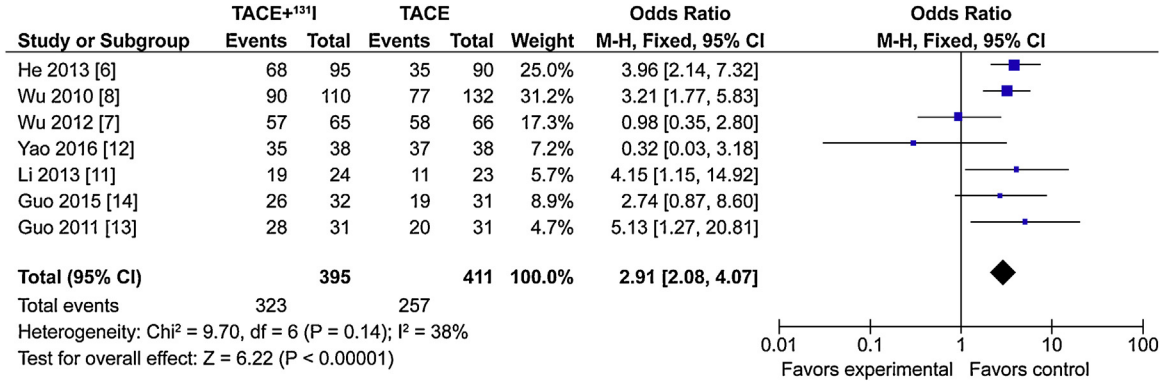

Figure 3 Forest plot analysis comparing the response rate between TACE + ^{131}I-metuximab infusion and TACE-only treatment groups.

Safety of iodine ^{131}I metuximab infusion combined with TACE

With the exception of 1 study, the 10 included studies all had reports of treatment-related adverse effects, which primarily included moderate fever, pain in the liver region, nausea, vomiting, and other digestive tract reactions; all were treated with short-term symptomatic treatment or resolved spontaneously. Some studies reported that the combination treatment had a greater suppressive effect on bone marrow than the TACE-only group, but the suppression was primarily of grade I/II [7,8] and the results of some studies did not support this conclusion [15]. No cases of liver failure, kidney failure, abdominal bleeding, stress ulcers, gallbladder perforation, or other serious adverse events or deaths were reported in any of the included studies.

Discussion

Necrosis of liver cancer tissue following TACE is directly correlated with iodized oil deposition. However, some embolism blind spots and sparse regions of cancer cells are not completely necrotic, which serve as the basis for tumor recurrence and metastasis [17]. The appearance of these blind spots occurs for the following two primary reasons:

- some liver cancer cells are supplied with blood from both the hepatic artery and the portal vein, and it is difficult for

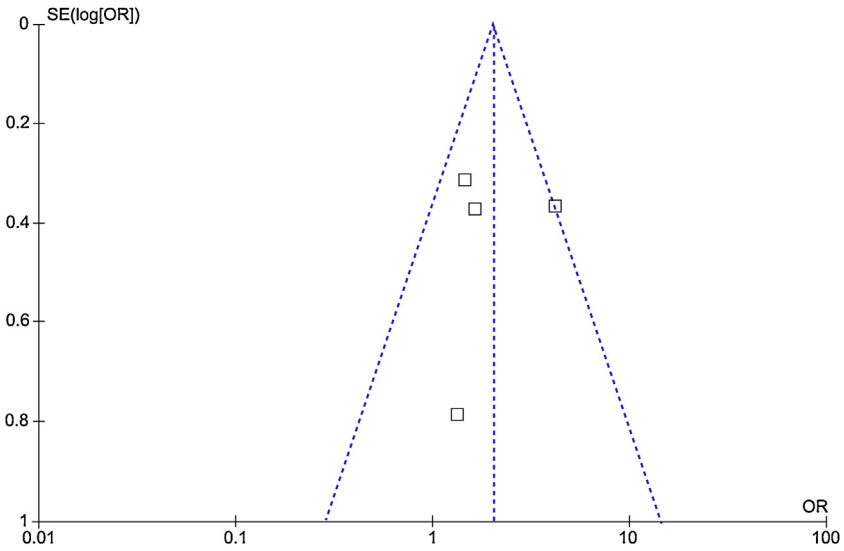

Figure 4 Funnel plot analysis comparing the 6-month survival rate between TACE + ^{131}I-metuximab infusion and TACE-only treatment groups.

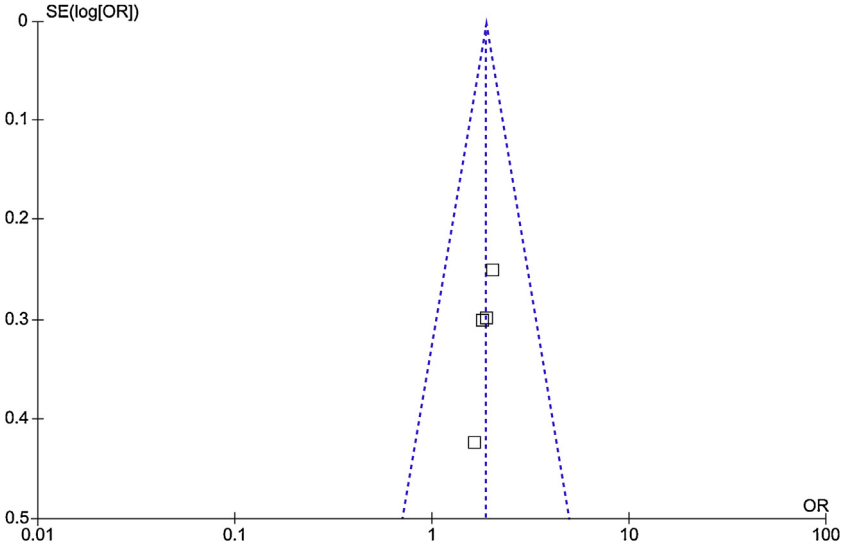

Figure 5 Funnel plot analysis comparing the 1-year survival rate between TACE + ^{131}I-metuximab infusion and TACE-only treatment groups.

the arterial embolic agent to deposit within the regions supplying blood to the tumor;
- tumor angiogenesis establishes collateral circulation after TACE, thereby providing blood to remaining tumor tissue [18].

The literature shows that the embolic necrosis rate of TACE in major liver cancer is < 50% [19]. Therefore, the long-term efficacy of TACE alone for the treatment of HCC is poor. HCC in patients with insufficient blood supply or HCC persisting after multiple TACE treatments, show reduced arterial blood supply to the tumor. When the blood-supplying arteries are narrow or few in number, iodized oil deposition with TACE alone shows both poor results and treatment efficacy. In addition, repeated TACE treatments may cause harm to the liver function of HCC patients and exacerbate liver dysfunction. These factors limit the application of TACE to the treatment of liver cancer to some extent, but the efficacy of traditional radiochemotherapy and other adjuvant treatments is even worse.

In recent years, the targeting of relevant antigens and the use of specific binding between antigens and antibodies allows HCC treatment by radioimmunotherapy to enter a new era using aggregation of radioisotopes at tumor sites. In [^{131}I-Hab18F(ab') 2], namely ^{131}I-metuximab, the HAbl8F(ab')2 fragment can specifically bind to the HAb18G antigen (CD147) distributed on the cell surface of cancer cells. In addition, the β-radiation released by ^{131}I can specifically kill cancer cells [20]. Studies have shown that ^{131}I-metuximab can aggregate more easily in the liver and exert its radioactive effects, whereas less of it stays in other organs or tissues. Thus, it is a good drug for the effective

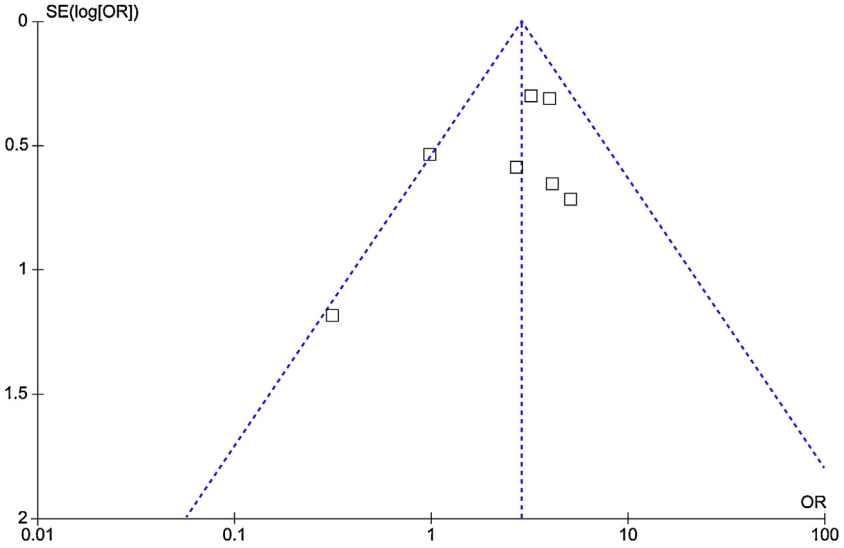

Figure 6 Funnel plot analysis comparing the response rate between TACE + ^{131}I-metuximab infusion and TACE-only treatment groups.

and highly targeted destruction of HCC [21]. Clinical trials and preliminary clinical application of ^{131}I-metuximab have already confirmed that it has efficacy and acceptable safety for the treatment of HCC, with the advantages of being highly targeted, low-dose, and highly destructive to tumors, which allows it to increase survival and decrease recurrence [21]. Increasing drug concentration through local arterial infusion is key to the interventional treatment of the tumor blood supply. Infusion of ^{131}I-metuximab through the hepatic artery further increases the targeting of the treatment and subsequently the efficacy of targeted tumor destruction. Li et al. performed whole-body dynamic SPECT acquisition on 24 liver cancer patients that underwent hepatic artery infusion of ^{131}I-metuximab and observed that ^{131}I-Hab18F(ab')2 was significantly elevated in liver cancer tissue compared to other organs [22]. The tumor/non-tumor (T/NT) ratio was greater than 1, and radioactivity in the cancerous liver tissue gradually become more concentrated with time, whereas radioactivity in normal liver tissue gradually decreased and the T/NT ratio gradually increased. This study showed that ^{131}I-metuximab not only significantly decreased the recurrence of liver cancer after liver transplantation but also had good efficacy for unresectable liver cancer when combined with TACE [5—8]. However, because this treatment has only been implemented recently, there are few relevant clinical studies, with these reports using numbers of subjects or were not controlled studies, so its efficacy and safety still lacks high-level, evidence-based medical validation.

Theoretically, treatment of HCC with ^{131}I-metuximab infusion combined with TACE has the advantage of overlapping effects. First, even more antigen is present upon tumor necrosis following TACE, which favors the binding of ^{131}I-metuximab with these antigens. Second, reduced tumor blood supply may also reduce ^{131}I-metuximab clearance from the tumor, increasing radioactivity intensity and extending the time of treatment. Third, ^{131}I-metuximab itself contains specific molecules for the diagnosis of tumor cell membrane expression and can play a role in specific targeting against tumors. Fourth, the short-range irradiation of cancer cells by ^{131}I radionuclides not only greatly reduces radiation injury to normal liver tissue but also greatly increases the radiation dose to the targeted tumor region [5,9—11]. Given that this study is a meta-analysis that searched for the short-term efficacy and safety of ^{131}I-metuximab infusion combined with TACE compared to those of TACE-only treatments among currently available studies of liver cancer treated with ^{131}I-metuximab, it provides a reliable basis for the clinical application of ^{131}I-metuximab combined with TACE. The characteristics of the patients in the included studies were mostly unresectable major liver cancer, multiple liver cancer, Child-Pugh liver function class of A or B (with some studies including small numbers of class C patients), and single doses of 27.75 MBq/kg (0.75 mCi/kg) of ^{131}I-metuximab. However, the treatment courses were not uniform, which confounded the study results to some degree. These included 2—30 mL of lipiodol emulsion used in TACE, with chemotherapy agents used, including doxorubicin-class agents, with solid embolic agents added in some cases, in order to completely occlude the arteries supplying blood to the tumor. The TACE courses (1 to 4) and lags (mostly 1—2 months) were similar in every randomized controlled trial.

The results showed that the 6-month and 1-year survival for femoral arterial infusion of ^{131}I-metuximab combined with TACE was superior to TACE alone. In addition, the ORs gradually increased over time, indicating that hepatic artery infusion of ^{131}I-metuximab combined with TACE was superior in increasing long-term survival. For response rate, the OR of response rate (CR + PR) was 2.91 (95% CI: 2.08—4.07), which shows that hepatic artery infusion of ^{131}I-metuximab combined with TACE was superior to TACE alone for local tumor control.

With respect to safety, the safety problems of ^{131}I-metuximab during the treatment process warrants further attention. On the one hand, ^{131}I-metuximab is an antibody drug, and allergic reactions can develop in many patients. In the present study, patients with allergic reactions were excluded. On the other hand, ^{131}I-metuximab

is highly radioactive, and the combination of TACE with chemotherapy agents increases the incidence of bone marrow suppression [13]. In the present study, the results of some of the included studies showed that the incidence of bone marrow suppression was higher in the combination treatment group relative to the TACE-only group [7,8], presenting primarily as grade I—II reduction in platelets and leukocytes. The main reason for this is that TACE chemotherapy uses a simultaneous combination of ^{131}I radiotherapy, but the above side effects can be controlled, and short-term recovery can be achieved by symptomatic treatment. Liver function transaminase examination of the two groups showed no statistically significant difference. No treatment-related serious adverse events or treatment-related deaths occurred in either the combination treatment or TACE-only groups.

Currently, there are few reports in the literature of randomized controlled trials reported HCC treatment with ^{131}I-metuximab combined with TACE, and their methodological quality is limited (only 1 high-quality paper with a quality score of 3 was found). Full text of some studies included in our meta-analysis could not be traced in English, but they were published in the Chinese core journals. In some of the included studies, the number of subjects was either insufficient or the randomization and grouping methods lacked blinding or were not completely explained, thereby generating some degree of bias. In order to minimize the bias, we rigorously conformed to the designated criteria when screening the literature. Our study was also limited by the high heterogeneity among the patients with different liver functions and tumor burdens, as some details were not applicable. Another limitation of our analysis was that response rates are difficult to interpret without a centralized review of radiological data. Finally, most studies majorly included Asian patients, who are different from the Western cohorts; thus, whether the data are completely applicable to non-Asian populations of patients remains to be clarified.

In summary, the present study used an evidence-based medical analysis to show that treating unresectable liver cancer with combined ^{131}I-metuximab arterial infusion and TACE was safe and could increase 6-month survival, 1-year overall survival, and the response rate, relative to TACE alone. However, more high-quality, randomized controlled studies are needed to further evaluate and confirm this treatment's efficacy.

Author contributions

Wenzhe Fan: the conception and design of the study.

Mingjian Lu, Wei Cui: acquisition of data.

Yanqin Wu, Wang Yao: analysis and interpretation of data.

Yue Zhao, Yu Wang: drafting the article or revising it critically for important intellectual content.

Jiaping Li: final approval of the version to be submitted.

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Disclosure of interest

The authors declare that they have no competing interest.

References

[1] Hussain K, El-Serag HB. Epidemiology, screening, diagnosis and treatment of hepatocellular carcinoma. Minerva Gastroenterol Dietol 2009;55:123—38.

[2] Zhou ZH, Liu LM, Chen WW, Men ZQ, Lin JH, Chen Z, et al. Combined therapy of transcatheter arterial chemoembolisation and three-dimensional conformal radiotherapy for hepatocellular carcinoma. Br J Radiol 2007;80:194—201.

[3] Bethge WA, Sandmaier BM. Targeted cancer therapy using radiolabeled monoclonal antibodies. Technol Cancer Res Treat 2005;4:393—405.

[4] Feng Q, Mi L, Yu XL, Huang Z, Chen Z. A study of anti-human liver cancer monoclonal antibody fragment HAb18(ab')2 lyophilization processes. Sheng Wu Ji Shu Tong Xin 2002;13:356—7.

[5] Ma J, Wang JH. ^{131}I-labeled-metuximab plus transarterial chemoembolization in combination therapy for unresectable hepatocellular carcinoma: results from a multicenter phase IV clinical study. Asian Pac J Cancer Prev 2015;16:7441—7.

[6] He Q, Lu WS, Liu Y, Guan YS, Kuang AR. ^{131}I-labeled metuximab combined with chemoembolization for unresectable hepatocellular carcinoma. World J Gastroenterol 2013;19:9104—10.

[7] Wu L, Yang YF, Ge NJ, Shen SQ, Liang J, Wang Y, et al. Hepatic artery injection of ^{131}I-labelled metuximab combined with chemoembolization for intermediate hepatocellular carcinoma: a prospective nonrandomized study. Eur J Nucl Med Mol Imaging 2012;39:1306—15.

[8] Wu L, Yang YF, Ge NJ, Shen SQ, Liang J, Wang Y, et al. Hepatic arterial iodine-131-labeled metuximab injection combined with chemoembolization for unresectable hepatocellular carcinoma: interim safety and survival data from 110 patients. Cancer Biother Radiopharm 2010;25:657—63.

[9] Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228—47.

[10] Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary. Control Clin Trials 1996;17:1—12.

[11] Li Z, Zhou J, Ren J, Zhang W, Han X. Clinical value of treatment of middle- and late-stage liver cancer and postoperative recurrence with ^{131}I metuximab infusion combined with transcatheter arterial chemoembolization. Zhong Hua Gan Zang Bing Za Zhi 2013;21:728—33.

[12] Yao Z, Chen Y, Luo J, Shao G, Zheng J, Zeng H, et al. A study of the efficacy and safety of 76 middle-to-late stage primary liver cancer patients with ^{131}I-metuximab infusion combined with TACE. Jie Ru Fang She Xue Za Zhi 2016;1:65—9.

[13] Guo X, Sun T, Li S. An analysis of outcomes of treatment of primary liver cancer with ^{131}I-metuximab infusion combined with TACE. Zhong Guo Xian Dai Yi Xue Za Zhi 2011;21:1026—8.

[14] Guo H, Zhu Y, Mao Y, Wang C, Fang Q, Han J, et al. A comparative study of treatment of primary liver cancer with ^{131}I-metuximab infusion combined with transcatheter arterial chemoembolization. Chengdu Yi Xue Yuan Xue Bao 2015;6:649—51.

[15] Dong L, Zhou W, Yu C, Hu W, Huang S. A clinical study of treatment of primary hepatocellular carcinoma with ^{131}I-metuximab infusion combined with TACE. Zhong Guo Xian Dai Yi Xue 2013;51:56—9.

[16] Wei C, Bian X, Wang Z, Wu G, Tao S, Song Z, et al. Short-term efficacy of treatment of primary hepatocellular carcinoma with ^{131}I-metuximab infusion combined with TACE. Wu Jing Yi Xue Yuan Xue Bao 2009;18:1068—70.

[17] Kume A, Nimura Y, Kamiya J, Nagino M, Kito Y. Percutaneous ethanol injection via an artificially induced right hydrothorax for hepatocellular carcinoma in the hepatic dome. Cardiovasc Intervent Radiol 2003;26:543—9.

[18] Wang B, Xu H, Cao G, Sun Y, Yu D, Ning H. Effect of transcatheter arterial chemoembolization on liver cancer angiogenesis and vascular endothelial growth factor expression. Zhong Hua Fang She Xue Za Zhi 2005;39:204—6.

[19] Nag S, DeHaan M, Scrnggs G, Mayr N, Martin EW. Long-term follow-up of patients of intrahepatic malignancies treated with iodine-125 brachytherapy. Int J Radiat Oncol Biol Phys 2006;64:736—44.

[20] Xu J, Xu HY, Zhang Q, Song F, Jiang JL, Yang XM, et al. HAb18G/CD147 functions in invasion and metastasis of hepatocellular carcinoma. Mol Cancer Res 2007;5:605—14.

[21] Chen ZN, Mi L, Xu J, Song F, Zhang Q, Zhang Z, et al. Targeting radioimmunotherapy of hepatocellular carcinoma with iodine (131I) metuximab injection: clinical phase I/II trials. Int J Radiat Oncol Biol Phys 2006;65:435—44.

[22] Li Y, Tan T, Mo Y, Lu W, Deng H, Yang X. A pharmacokinetic study of ^{131}I-metuximab infusion in the human body. Sheng Wu Yi Xue Gong Cheng Za Zhi 2007;24:857—61.