Lipiodol Transarterial Chemoembolization for Hepatocellular Carcinoma: A Systematic Review of Efficacy and Safety Data

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Transarterial chemoembolization (TACE) using lipiodol-based regimens, including the administration of an anticancer-in-oil emulsion followed by embolic agents, is widely used in the treatment of hepatocellular carcinoma (HCC). This approach has been supported by meta-analyses of randomized, controlled trials (RCTs) performed more than a decade ago. We performed a systematic review to understand current efficacy and safety data of lipiodol TACE in treatment of HCC. A search of the literature published between January 1, 1980 and June 30, 2013 was performed using MEDLINE and EMBASE databases. All potentially relevant publications were reviewed and articles were selected based on predefined inclusion and exclusion criteria. Of a total of 1,564 articles reviewed, 101 articles, including a total of 10,108 patients treated with lipiodol TACE, were selected for the efficacy analysis. Objective response rate was 52.5% (95% confidence interval [CI]: 43.6-61.5). Overall survival (OS) was 70.3% at 1 year, 51.8% at 2 years, 40.4% at 3 years, and 32.4% at 5 years. Median OS was 19.4 months (95% CI: 16.2-22.6). A total of 217 articles presenting precise description on numbers of adverse events (AEs) were selected for the safety review: In these studies, a total of 21,461 AEs were reported in 15,351 patients. Liver enzyme abnormalities were the most commonly observed AE, followed by the symptoms associated with postembolization syndrome. Overall mortality rate was 0.6% and the most common cause of death was related to acute liver insufficiency. Conclusions: In a systematic literature review, survival figures of HCC patients undergoing lipiodol TACE appear to be in line with those reported in previous RCTs, and no new or unexpected safety concerns were identified. (HEPATOLOGY 2016;64:106-116)

SEE EDITORIAL ON PAGE 23

Hepatocellular carcinoma (HCC) is the third-leading cause of cancer-related death worldwide.(1) Unlike most solid cancers, future incidence and mortality rates for HCC were projected to largely increase in several regions around the world over the next several years, mostly as a result of the dissemination of hepatitis C virus infection.(2,3) Despite the widespread implementation of surveillance programs of at-risk populations, the majority of patients with HCC are diagnosed late, when curative treatments—including liver transplantation, hepatic resection, and image-guided ablation—cannot be applied.(4) Transarterial chemoembolization (TACE) is widely used in treatment of HCC patients unsuitable for radical therapies. The data collected in the Global Investigation of therapeutic DEcisions in hepatocellular
carcinoma and of its treatment with sorafenib, the largest global observational study completed in the field of HCC so far, suggests that nearly half of all HCC patients receive TACE at some time point in the course of the disease. The most popular TACE technique has been the administration of an anti-cancer agent-in-oil emulsion followed by embolic agents. The key component of this procedure is lipiodol (Guerbet, Paris, France), which is used both as a vehicle to carry and localize the chemotherapeutic agent inside the tumor and as a microembolic agent for tiny tumor vessels.

The evidence supporting the use of lipiodol TACE in the treatment of HCC comes from two meta-analyses including randomized, controlled trials (RCTs) of arterial embolization or chemoembolization versus conservative management. These meta-analyses identified a distinct survival benefit for lipiodol TACE with cisplatin or doxorubicin compared to best supportive care. As a result, Lipiodol TACE has been recommended as the standard of care for the treatment of unresectable, large, or multinodular non-invasive tumors isolated to the liver in patients who have neither evidence of hepatic decompensation nor cancer-related symptoms, that is, those cases classified as intermediate stage according to the Barcelona Clinic for Liver Cancer (BCLC) staging system.

All RCTs comparing lipiodol TACE and best supportive care in the treatment of HCC were performed more than a decade ago. Distinct technical advances in the performance of TACE and improved patient selection and management took place since the completion of these studies. A comprehensive understanding of updated efficacy and safety data of lipiodol TACE in the treatment of HCC is important, especially considering that alternate options for regional hepatic tumor treatment—including arterial embolization with drug-eluting beads and internal radiation with yttrium-90 microspheres—have been proposed and are currently undergoing clinical investigation. Therefore, we performed a systematic literature review of the available evidence on the efficacy and safety of lipiodol TACE in treatment of HCC.

Materials and Methods

DATA SOURCES

A search of the published literature was performed using the MEDLINE and EMBASE databases. These databases were searched directly and indirectly through online search agents. Literature published between January 1, 1980 and June 30, 2013 was included in this search. All potentially relevant publications were reviewed, and articles were selected based on predefined inclusion and exclusion criteria. References within each study that met the stated selection criteria were manually searched for other potentially relevant studies. All abstracts and full-text articles published in English were collected for this analysis.

SEARCH TERMS

The following search terms were used to identify potential articles: hepatocellular carcinoma or HCC or liver cell carcinoma; trans-arterial chemoembolization or chemoembolization; intra-arterial injection or hepatic artery injection; randomized trials or random-ized studies; human trials; safety; and adults. All search terms were also combined with lipiodol, ethiodol, iodized oil, and poppy seed oil.

INCLUSION AND EXCLUSION CRITERIA

All studies with efficacy data relevant to evaluation of lipiodol TACE were selected based on the following
inclusion criteria: diagnosis of HCC is confirmed by histopathological examination or accepted noninvasive criteria; article is published in a peer-reviewed journal and reports efficacy or safety data of lipiodol TACE in adults patients with HCC; data come from the following organized solicited sources: clinical trials, observational studies, and registries; study provides detailed and precise descriptions of endpoints; and statistical methodology is available. Both prospective and retrospective studies and both single- and multiple-arm studies were included. All studies in which TACE was compared to either placebo, no treatment, best supportive care, or an active comparator were included. Exclusion criteria were the following: inadequate information about efficacy or safety of lipiodol TACE; dose or name of the chemotherapeutic agent is not available; the article is not written or published in English; the publication is a review, a letter to the editor, an editorial, a meta-analysis, a case report, or a chapter contained within a book; and the article has been withdrawn or citation information is incorrect.

LITERATURE REVIEW METHODOLOGY

A prospectively defined methodology was employed to reduce bias for selecting articles for this review. Two independent reviewers reviewed the first 10% of the articles to decide whether or not to include the article in the efficacy and/or the safety analysis. In case of conflict, an independent adjudicator provided the final decision on inclusion of the article. It was planned that in case interobserver variation for selection of articles was less than 5%, then further review will be performed by a single reviewer. Because the interobserver variation for qualification of the article in each analysis was less than 5% in the first 156 articles of a total of 1,564 articles, further review was completed by a single reviewer.

OBJECTIVES AND DATA EXTRACTION

The objectives of this systematic review were to assess efficacy and safety of lipiodol TACE. The primary efficacy endpoint was overall survival (OS); secondary efficacy endpoints included assessment of progression-free survival (PFS), time to progression (TTP), and objective tumor response. Standardized data extraction forms were used to collect and record the data. Articles were reviewed for general information (title, investigators, source, country, publication status, language, year of publication, and sponsoring of trial), trial characteristics (design, sample size, duration/follow-up, and quality assessment criteria and time and duration of data collection), participant-related data (diagnostic criteria, eligibility criteria, exclusion criteria, baseline characteristics, number of persons allocated to each group, and numbers at risk), intervention scheme (embolic materials, drug, dose, and route for experimental and control interventions), presentation of efficacy and safety results, completeness of the data, impact on patient management, if any, and risk-benefit assessment by author, conclusions, and authors’ recommendations.

STATISTICAL ANALYSIS

The methods described below combine the individual study summary statistics denoted generically by $\theta_j$, each with a given weight $w_j$. Both the fixed-effect approach and the random-effects approach to combining data are presented in the Supporting Information, because the notation and calculations from the fixed-effect approach are needed for the random-effects methodology used in this analysis. The methods described by Tierney et al. were used to guide in the collection and calculation of the necessary information. Because all the endpoints in this study are dichotomous in nature, the methods described are for a general parameter with the realization that it can be applied to all the endpoints in this study. Estimates calculated according to the nonhomogeneous model were used to test pair-wise hypotheses that different baseline variables had the same outcome by using meta-regression techniques.

Results

Of a total of 1,564 articles reviewed, 101 were selected for the efficacy analysis and 217 articles for the safety analysis (Fig. 1).

EFFICACY ANALYSIS

A total of 101 articles were selected for the efficacy review and 1,463 were disqualified. The reasons for exclusion of the studies from the efficacy analysis are summarized in Table 1. For the purpose of the efficacy review, only studies presenting TACE using lipiodol were selected. As a minimum requirement, patients underwent TACE using a mixture of
chemotherapeutic agent(s) and lipiodol followed by arterial embolization. Interventions comprising of chemotherapeutic agents emulsified with lipiodol, but without administration of embolizing agents ("chemolipiodolization"), were not regarded as lipiodol TACE. Other interventions, such as hepatic artery infusion of chemotherapeutic agents, bland embolization, or TACE, using devices such as drug-eluting beads without administration of lipiodol were excluded. Lipiodol TACE administered in combination with systemic agents such as sorafenib or procedures such as radiofrequency ablation or surgical resection, which could potentially influence the efficacy results, were also excluded.

Of the 101 studies evaluated, 52 were single-arm studies and 49 were multiple-arm studies. Of the 49 multiple-arm studies, 12 were randomized and 37 were nonrandomized (Supporting Table 1). A total of 12,372 patients were evaluated in the 101 selected studies. Efficacy data for lipiodol TACE were evaluated for a total of 10,108 patients. The remaining 2,264 patients in these studies underwent other anticancer treatments or received only supportive therapy. In 45 of 101 studies, patients with some grade of vascular invasion (mostly portal vein invasion) were included. Sixty-three studies enrolled only patients with either Child Pugh class A or B cirrhosis, whereas 25 included a minority of patients in Child Pugh class C. Thirteen studies did not provide information on liver function status by Child Pugh class.

We did not identify any RCT comparing lipiodol TACE versus best supportive care performed after 2002—and therefore not already included in the quoted previous meta-analysis. Three of the twelve RCTs were focused on the comparison of different doses of lipiodol, different classes of iodinated contrast material, or different types of embolic agents for the execution of TACE procedures. Two other RCTs compared lipiodol TACE versus either intravenous doxorubicin or transarterial chemotherapy with zinostatin stimalamer. Two additional RCTs compared lipiodol TACE with or without the addition of systemically active drugs (i.e., amiodarone in one study and bevacizumab in the other). Finally, a recent study compared different TACE single- and multiple-drug regimens. Given the

![FIG. 1. Algorithm of the systematic review of efficacy and safety data.](image)

**TABLE 1. Reasons for Exclusion of Articles From Efficacy Review**

| Reason for Exclusion                                                                 | No. of Articles |
|-------------------------------------------------------------------------------------|----------------|
| Review, letter to the editor, editorial, case report, or meta-analysis               | 522            |
| Article not published in peer-reviewed journals or lacking efficacy data of lipiodol TACE in patients with HCC | 374            |
| Article does not report data from the following organized solicited sources: clinical trials/noninterventional studies/registries | 211            |
| Insufficient information about efficacy of lipiodol TACE                             | 136            |
| Not written or published in English                                                  | 114            |
| Lack of precise descriptions of survival endpoints                                   | 55             |
| Diagnosis of HCC not confirmed by histopathological examination or established noninvasive methods | 29             |
| Dose or name of the chemotherapeutic agent not available                             | 20             |
| Details of statistical methodology not available                                     | 2              |
| Any                                                                                 | 1,463          |
different design and treatment arms of these studies, we were unable to perform specific meta-analyses.

The most commonly used chemotherapeutic agents, either as single agents or in combination regimens, were doxorubicin or epirubicin, cisplatin or miriplatin, and mitomycin (Table 2). Dose ranges of chemotherapeutic agents used were as follows: doxorubicin, 10-100 mg; epirubicin, 5-120 mg; cisplatin, 10-100 mg; miriplatin, 20-140 mg; and mitomycin, 2-30 mg. Three groups based on the highest dose of lipiodol used in the study for the TACE procedures were identified: dose group 1, highest dose of lipiodol ≤10 mL; dose group 2, highest dose of lipiodol >10-≤20 mL; and dose group 3, highest lipiodol dosage >20 mL. Accordingly, dose group 1 was noted in 53 studies, dose group 2 in 33, and dose group 3 in 18. The remaining studies did not have precise information about dosage or had different dose groups. The most commonly used embolic agent was gelatin sponge.

OS

The primary efficacy endpoint was overall survival (Table 3). Median OS was 19.4 months (95% confidence interval [CI]: 16.2-22.6). OS was 81.0% at 6 months post-TACE, 70.3% at 1 year, 51.8% at 2 years, 40.4% at 3 years, and 32.4% at 5 years (Fig. 2). Survival was evaluated according to year of publication. Studies were divided into two groups: those published until 2002 and those after 2002. Accordingly, group 1 comprised 1,808 patients and group 2 comprised 8,300. Median OS and 1-, 2-, and 3-year survival rates by year of publication are reported in Table 4. Available outcome data according to baseline patient characteristics were insufficient to perform a metaregression analysis for all variables except geographical region (Supporting Table 2). Median OS was significantly higher in Japan (31.3 months; 95% CI: 22.9-39.8) than in the West (18.3 months; 95% CI: 13.7-22.9) or the Asia-Pacific region (15.6 months, 95% CI: 13.7-22.9; Japan vs.

### Table 2. Chemotherapeutic Regimens Used for Lipiodol TACE of HCC

| Chemotherapeutic Regimen | No. of Studies |
|--------------------------|---------------|
| Single-drug regimens     |               |
| Doxorubicin or epirubicin| 38            |
| Cisplatin or miriplatin  | 23            |
| Mitomycin                | 4             |
| SMANC                    | 4             |
| Others                   | 12            |
| Multiple-drug regimens   |               |
| Doxorubicin + cisplatin  | 10            |
| + mitomycin              | 10            |
| Doxorubicin + cisplatin  | 7             |
| + mitomycin              | 7             |
| Others                   | 13            |

Data based on a systematic review of 101 clinical studies including 10,108 subjects. A few studies used more than one regimen. Abbreviation: SMANC, styrene maleic acid neocarzinostatin.

### Table 3. Analysis of OS After Lipiodol TACE for HCC

| OS      | No. of Studies | Estimate | Lower 95% CI | Upper 95% CI |
|---------|----------------|----------|--------------|--------------|
| Median, months | 63 | 19.4 | 16.2 | 22.6 |
| Percent |               |          |              |              |
| 6 months | 16 | 81.0 | 74.3 | 87.8 |
| 1 year  | 90 | 70.3 | 65.9 | 74.8 |
| 2 years | 71 | 51.8 | 44.6 | 59.0 |
| 3 years | 66 | 40.4 | 33.3 | 47.4 |
| 5 years | 26 | 32.4 | 24.5 | 40.3 |

Data based on a systematic review of 101 clinical studies including 10,108 subjects.

### Table 4. Analysis of OS After Lipiodol TACE for HCC by Year of Publication

| OS      | No. of Studies | Estimate | Lower 95% CI | Upper 95% CI |
|---------|----------------|----------|--------------|--------------|
| Median, months | <2002 | 19 | 18.5 | 14.6 | 22.4 |
|          | >2002        | 44       | 19.8 | 15.5 | 24.1 |
| 1-year, % | <2002        | 19       | 70.7 | 63.2 | 78.3 |
|          | >2002        | 71       | 70.4 | 65.2 | 75.5 |
| 2-year, % | <2002        | 21       | 51.1 | 37.1 | 65.1 |
|          | >2002        | 50       | 52.0 | 43.9 | 60.2 |
| 3-year, % | <2002        | 13       | 27.8 | 18.3 | 37.4 |
|          | >2002        | 53       | 43.4 | 34.9 | 51.8 |

FIG. 2. OS rates after lipiodol TACE for HCC. Data based on a systematic review of 101 clinical studies including 10,108 subjects. Bars show 95% CIs.
SECONDARY ENDPOINTS

A total of 11 studies presented data on progression-free survival at several time-points. PFS was 63.8% at 4 months, 57.2% at 6 months, 40.6% at 1 year, 24.0% at 2 years, and 15.6% at 3 years. Median PFS was evaluated in only six studies and ranged between 3 and 9 months. Eight studies presented data on TTP. Median TTP ranged from 3.1 to 13.5 months. Objective response rate, defined as sum of complete and partial response, was 52.5% (95% CI: 43.6-61.5). Criteria used for estimation of tumor response included Response Evaluation Criteria in Solid Tumors, modified Response Evaluation Criteria in Solid Tumors, European Association for the Study of the Liver, and Liver Cancer Study Group of Japan criteria.

SAFETY ANALYSIS

For the purpose of the safety analysis, studies presenting precise description on numbers of adverse events (AEs) were used. A total of 217 articles were selected for the safety review and 1,347 were excluded. The reasons for exclusion of the studies from the safety analysis are summarized in Table 5. Of note, the analysis of deaths included deaths reported in the 217 articles selected for the safety analysis and an additional 57 presenting information on safety of lipiodol TACE that were not included in the analysis because of the absence of precise description on type and number of AEs.

In the 217 selected studies, a total of 21,461 AEs were reported in 15,351 patients who underwent at least 27,497 treatment sessions.

For the purpose of the safety analysis, all events in the selected articles presented as AEs, complications, side effects, or toxicities were considered as AEs. Similar AEs were grouped into a common group based on the primary symptoms and most severe symptom. AEs were analyzed in two separate ways. A formal analysis was conducted as per statistical methodology described in the Materials and Methods. In addition, in order to estimate the percentages of most common AEs relative to total number of AEs observed, percentages of individual AEs were also computed relative to total number of AEs observed. This additional analysis was performed because, when reviewing each study, it was observed that some events were reported with a high proportion, owing to the small number of patients included in these individual studies.

Table 6 summarizes the most frequently observed AEs. In this table, percentage of individual AEs was estimated against the total number of AEs observed (n = 21,461). AEs that represented 0.5% or more of all AEs are listed in the table. Most common AEs were related to the occurrence of postembolization syndrome (PES). AEs related to PES include liver...
enzyme abnormalities, fever, abdominal pain, vomiting, and nausea. In this analysis, liver enzyme abnormalities represented 18.1% of all AEs, fever 17.2%, pain/abdominal pain 11.0%, vomiting 6.0%, and nausea 1.7%. The AE termed PES was identified only when a specific diagnosis of PES was mentioned in the article, which occurred in 4.8% of all AEs. Hematological/bone marrow toxicity was noted at 13.5%. Bilirubin-related abnormalities represented 4.6% of all AEs, hepatic decompensation/hepatic failure 2.9%, and ascites 0.5%. The percentage of hepatic arterial complications was 1.3% and the percentage of procedural complications was 1.0%.

The estimated rate of individual AEs as assessed in the safety review is presented in Table 7. Incidence of PES was 47.7% and liver enzyme abnormalities were noted in 52% of the patients. Fever occurred in 57.8% of the patients, abdominal pain in 42.5%, vomiting in 34.2%, and nausea in 32.4% (all of these individual symptoms possibly being part of the PES). Among the liver-related complications, bilirubin-related abnormalities were reported in 23.5% of the patients, hepatic decompensation/deterioration of hepatic function in 21.8%, ascites in 6.1%, and hepatic failure in 1.0%. Hematological/bone marrow toxicity occurred in 28.6% of the patients. Hepatic arterial complications were noted in 7.2% and procedural complications in 4.2% of the patients.

**Mortality**

A total of 214 deaths attributable to various causes were reported of a total of 34,137 patients undergoing 50,953 sessions. Hence, the overall mortality rate was 0.6%.

The most common cause of death was related to acute liver insufficiency and described as hepatic failure (n = 59) or hepatic encephalopathy/coma (n = 9). This was followed by infectious complications (n = 20), gastrointestinal bleeding resulting from varices or ulcer (n = 17), and intraperitoneal tumor rupture (n = 8). Abscess, pulmonary embolization, and pneumonia were noted in 4 patients each and dyspnea and infection in 3 each. Cause of death was not specified or

| AE Name                                      | No. of Studies | Total No. of Patients | No. of Patients With AE | AE Rate Estimate | Lower 95% CI | Upper 95% CI |
|----------------------------------------------|----------------|-----------------------|-------------------------|-----------------|-------------|-------------|
| Fever                                        | 91             | 7,028                 | 3,700                   | 57.8            | 50.2        | 65.4        |
| Liver enzyme abnormalities                   | 48             | 9,021                 | 3,892                   | 52.0            | 43.9        | 60.1        |
| PES                                          | 40             | 3,346                 | 1,032                   | 42.5            | 35.6        | 48.9        |
| Abdominal pain                               | 69             | 6,309                 | 1,781                   | 41.2            | 34.2        | 48.2        |
| Fatigue/malaise                              | 17             | 1,633                 | 457                     | 39.9            | 25.8        | 54.1        |
| Anorexia/loss of appetite                    | 16             | 1,867                 | 691                     | 38.0            | 28.5        | 47.6        |
| Vomiting                                     | 49             | 4,754                 | 1,297                   | 34.2            | 26.9        | 41.4        |
| Nausea                                       | 25             | 1,218                 | 361                     | 32.4            | 23.0        | 41.7        |
| Hematological/bone marrow toxicity           | 48             | 11,962                | 2,907                   | 28.6            | 25.0        | 32.1        |
| Bilirubin-related abnormalities              | 36             | 5,155                 | 985                     | 23.5            | 19.7        | 27.3        |
| Hepatic decompensation/deterioration of hepatic function | 23             | 3,287                 | 533                     | 21.8            | 14.3        | 29.2        |
| Elevated renal enzymes/renal dysfunction     | 23             | 2,446                 | 434                     | 15.1            | 10.4        | 19.9        |
| Alopecia                                     | 11             | 805                   | 113                     | 12.9            | 6.8         | 19.1        |
| Diarrhea                                     | 14             | 1,167                 | 113                     | 9.0             | 5.4         | 12.7        |
| Cholecystitis                                | 18             | 1,549                 | 47                      | 8.4             | 4.1         | 12.8        |
| Skin ulcer/rost/verythema                    | 12             | 1,390                 | 144                     | 8.2             | 5.1         | 11.3        |
| Hepatic arterial complications               | 20             | 3,061                 | 271                     | 7.2             | 5.0         | 9.5         |
| Ascites                                      | 22             | 1,805                 | 113                     | 6.1             | 4.0         | 8.1         |
| Pleural effusion                             | 12             | 2,056                 | 94                      | 4.2             | 2.2         | 6.2         |
| Procedural complications                     | 30             | 4,145                 | 212                     | 4.2             | 2.6         | 5.7         |
| Hepatic encephalopathy/coma                  | 14             | 1,346                 | 44                      | 2.0             | 0.9         | 3.2         |
| Gastrointestinal bleeding (varices or ulcer) | 44             | 5,721                 | 142                     | 1.9             | 1.3         | 2.4         |
| Hepatic failure                              | 31             | 5,837                 | 95                      | 1.0             | 0.6         | 1.4         |
| Bacteremia/septicemia                        | 17             | 2,301                 | 37                      | 1.0             | 0.5         | 1.4         |
| Abscess                                      | 30             | 5,138                 | 67                      | 0.9             | 0.6         | 1.2         |
| Renal failure                                | 15             | 1,488                 | 22                      | 0.6             | 0.2         | 1.0         |

AEs reported in 0.5% or more of all studies included in the review (i.e., more than 10 studies) are listed.
described as unknown in the remaining 83 patients. The relationship of AE’s relating to death with the intervention in the study was assessed as follows: related to procedure/treatment: 99 patients; possibly related: 1 patient; no clear relationship: 2 patients; and unrelated: 10 patients. One case of death was ascribed to possible allergic reaction to miriplatin and 3 to other comorbidities. No causality assessment was available in the remaining 98 patients.

Discussion

The rationale for lipiodol TACE is that the intra-arterial infusion of a water-in-oil emulsion of lipiodol and drugs such as doxorubicin or cisplatin, followed by embolization of the blood vessel with gelatine sponge particles or other embolic agents, will result in a strong and sustained cytotoxic effect combined with ischaemia. (31-35)

Use of lipiodol TACE in the treatment of HCC is based on meta-analyses of RCTs comparing embolization or chemoembolization versus conservative management. (14,15) A recent Cochrane meta-analysis (36) — whose methodology has been criticized by several experts (37,38) — questioned the evidence supporting the beneficial effect of TACE over no intervention on survival in patients with HCC. The authors of this Cochrane review advocated for more efforts to investigate the benefits of TACE through adequately powered, bias-protected trials. (39) However, it is highly unlikely that such RCTs will ever be performed. A few years ago, sorafenib, a multitargeted tyrosine kinase inhibitor, resulted in a survival benefit compared to placebo in two phase III RCTs, becoming the first systemic drug approved for the treatment of HCC. (40,41) Hence, having an untreated control arm would now be unethical. On the other hand, TACE and sorafenib are recommended for patients at different stages of the disease, and thus a direct comparison was not foreseen. (42,43)

With this in mind, and recognizing the importance of a comprehensive understanding of updated efficacy and safety data of lipiodol TACE, we performed a systematic review of available clinical studies selected according to predefined inclusion/exclusion criteria and assessed according to a standardized methodology. Separate analyses were performed for efficacy and safety data. Overall, a total of 101 studies were selected for the efficacy analysis, and a total of 217 were included in the safety analysis.

Efficacy data were collected for 10,108 patients treated by lipiodol TACE for HCC in 101 studies. The large majority of the studies were either single-arm studies (n = 52) or multiple-arm, nonrandomized studies (n = 37). Twelve studies were RCTs. As expected, we did not identify any RCT comparing lipiodol TACE versus best supportive care performed after 2002 and therefore not already included in the previous meta-analyses. (14,15) Hence, we were unable to update the results already presented concerning the survival benefit of TACE over no intervention. The other RCTs that were identified had different design and treatment arms and were focused on the comparison of different TACE techniques or protocols, (23-25,30) on the comparison of lipiodol TACE and either intravenous or transarterial chemotherapy, (26,27) and on the use of lipiodol TACE alone versus lipiodol TACE combined with amiodarone or bevacizumab. (28,29)

Median OS of HCC patients who received lipiodol TACE in this analysis—19.4 months—is consistent with the data reported in the previous meta-analyses. (14,15) Analysis of overall survival by year of publication showed that clinical studies published after 2002 reported longer median survival and higher 3-year survival rate than those published until 2002. OS figures suggest that different subgroups of patients can be identified according to their outcomes. In fact, the 1-year overall survival of around 70% indicates a poor prognosis for approximately one third of patients who received TACE. On the other hand, the data show that another one third of patients who receive TACE for HCC are alive after 5 years of follow-up. These long survivors suggest that TACE may be very efficacious for this subgroup of patients. Unfortunately, outcome data according to baseline variables were insufficient to perform a meta-regression analysis for most factors, including Child Pugh class, performance status, BCLC stage, presence of vascular invasion or extrahepatic spread, and alpha-fetoprotein value. However, survival analysis by geographical region showed that median survival was significantly longer in studies performed in Japan than in studies performed in the West or the Asia-Pacific region.

OS figures reported in the present meta-analysis should not be regarded as a benchmark for the best TACE candidates. Several recent investigations have suggested that proper patient selection and optimized treatment techniques and protocols may be associated with prolonged median survival. In a prospective Japan–Korea cooperative study including 99 patients (81% of whom in Child class A and 87% with Eastern
Cooperative Oncology Group performance status of 0), median OS was 37 months. A randomized study comparing lipiodol TACE and drug-eluting bead TACE reported median OS figures of 28 and 29 months, respectively. In the phase III trial that assessed the efficacy and safety of brivanib as adjuvant therapy to TACE in patients with unresectable HCC—a study that, despite earlier termination, included 502 patients and, as such, represents the largest TACE RCT ever performed—median OS in the placebo arm (receiving TACE as the only active treatment) was 26 months, far exceeding the expectations based on historical data, that had suggested to use a median survival of 18 months for the statistical assumptions.

In our safety review, the mortality rate was 0.6%, with 214 deaths registered of a total of 34,137 patients. The most common cause of death was liver insufficiency, leading to hepatic failure (n = 59) or encephalopathy and coma (n = 9). This was followed by infectious complications (n = 20), gastrointestinal bleeding attributable to varices or ulcer (n = 17), and intraperitoneal tumor rupture (n = 8). Liver enzyme abnormalities were the most commonly observed AE after lipiodol TACE, followed by the symptoms associated with PES (fever, abdominal pain, vomiting, and nausea). These AEs, that were typically self-limiting, occurred in around half of the patients. Some degree of hematological or bone marrow chemotherapy-related toxicity was observed in nearly 30% of the subjects and was mostly transient in nature. Among the liver-related complications, bilirubin-related abnormalities occurred in 23.5%, hepatic decompensation/deterioration of hepatic function in 21.8%, and ascites in 6.1%. These AEs were also transient in the majority of the subjects. However, hepatic failure was observed in 1% of the patients.

Although the data collected in the safety review confirm the well-established safety profile of lipiodol TACE, certain limitations inherent to literature review must be acknowledged. No standard definition of AEs was adopted. The AEs were reported with different terminologies as side effects, complications, toxicity, tolerance, or as events as such. Most of the articles do not describe clear onset, duration, severity, outcome, and relationship of AEs to the procedure. Percentage of AEs is affected by the size of the population and hence gives a large estimate of AEs if the study population is small. To address this limitation, AE percentage estimates based on total number of AEs were presented. Finally, the total number of patients not experiencing AEs in the selected studies could not be deduced because of limitations attributable to presentation of AEs data in these studies.

In conclusion, the results of our efficacy analysis, including a total of 10,108 HCC patients treated by lipiodol TACE, demonstrate a median OS of 19.4 months and a 5-year OS of 32.4%. These figures are in agreement with the data reported in adequately controlled RCTs of lipiodol TACE versus supportive therapy and thus confirm, in a large sample size, the conclusion of the previous meta-analysis. Based on the analysis of safety information available in literature, no new safety concerns were identified. Although the overall mortality rate was low—0.6% of a total of 34,137 patients undergoing 50,953 sessions—the most common cause of death was liver insufficiency leading to hepatic failure, which suggests that accurate patient selection, based on careful assessment of baseline liver function parameters, may be a key factor to minimize the risk of treatment-related death and reduce liver-related AEs.

Acknowledgment: Assistance with selection of articles and extraction of raw data was provided by RadMD.

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Supporting Information

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep.28453/suppinfo.