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**Three-dimensional conformal radiotherapy combined with transcatheter arterial chemoembolization for hepatocellular carcinoma: a meta-analysis**

Zou LQ *et al*. HCC Treated with 3D-CRT and TACE

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**Abstract**

**Aim:** To compare transcatheter arterial chemoembolization (TACE) and three-dimensional conformal radiotherapy (3D-CRT) with TACE monotherapy in hepatocellular carcinoma (HCC).

**Methods:** We searched all the eligible studies from the Cochrane Library, PubMed, Medline, Embase, and CNKI. The meta-analysis was performed to assess the survival beneﬁt, tumor response, and the decline rates of  fetal protein (AFP) level. According to the heterogeneity of the studies, pooled odds ratios (ORs) with 95% conﬁdence interval (CI) were calculated using the fixed-effects or random-effects model. An observed OR > 1 indicated that the addition of 3D-CRT to TACE could offer survival beneﬁts to patients and would be considered statistically significant. Statistical analyses were performed using Review Manager Software.

**Results:**Ten studies met the criteria to perform a meta-analysis including 908 HCC participants, in which 400 patients in the combination of TACE and 3D-CRT group while 508 patients in the group of TACE alone. TACE combining 3D-CRT signiﬁcantly improved 1-, 2-, and 3-year overall survival compared with TACE monotherapy [OR = 1.87, 95%CI: 1.37–2.55, *P <* 0.0001], (OR = 2.38, 95%CI: 1.78–3.17, *P <* 0.00001) and (OR = 2.97, 95%CI: 2.10–4.21, *P <* 0.00001). In addition, TACE plus 3D-CRT was associated with a higher tumor response (complete remission and partial remission) (OR = 3.81; 95%CI: 2.70–5.37; *P <* 0.00001), and decline rates of AFP level (OR = 3.24, 95%CI: 2.09–5.02, *P <* 0.00001).

**Conclusion:** This meta-analysis demonstrated that TACE combining 3D-CRT was better than TACE monotherapy for patients with HCC, which needs to be conﬁrmed by large multicenter trials．

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**Key words:** Hepatocellular carcinoma; Chemoembolization; Three-dimensional conformal radiotherapy; Meta-analysis

**Core tip**: Transcatheter arterial chemoembolization (TACE) is the most commonly used for patients with unresectable hepatocellular carcinoma (HCC) as a palliative therapy that could prolong survival with unsatisfactory long-term effect. Three-dimensional conformal radiotherapy (3D-CRT) has been utilized for HCC in a series of trials resulting in promising results. This meta-analysis demonstrated that TACE combining 3D-CRT was better than TACE monotherapy in the treatment of HCC, which still needs to be confirmed by large prospectively randomized, controlled, multicenter trials.

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**Introduction**

Liver cancer in human is the ﬁfth most frequently diagnosed cancer worldwide and the second most frequent cause of cancer death[[1](#_ENREF_1)]. The highest liver cancer rates are found in East and South-East Asia, especially in China. It is recognized that only a small proportion of patients with early-stage hepatocellular carcinoma (HCC) may beneﬁt from surgical resection. Transcatheter arterial chemoembolization (TACE) is the most commonly used for patients with unresectable HCC as a palliative therapy that could prolong survival[[2-5](#_ENREF_2)]. However, the long-term curative effect is unsatisfactory for TACE alone, because of tumor relapse from intracapsular or extracapsular invasion by HCC and remaining tumor cells after the treatment[[6](#_ENREF_6)]. In addition, severe side effects were observed with the use of repeated rigorous TACE, including liver and renal failure, bone marrow depression, postembolization syndrome, and liver abscess[[7](#_ENREF_7)].

Traditionally, radiation therapy (RT) has played a minor role in the treatment of hepatic cancers because of the low tolerance of the whole-organ to irradiation, with a limit of approximately 30–35 Gy[[8](#_ENREF_8)]. With the advent of new elegant three-dimensional conformal radiotherapy (3D-CRT), it allows the tumor to receive a higher dose and the surrounding normal liver tissue to receive lower doses[[9](#_ENREF_9),[10](#_ENREF_10)]. Currently, 3D-CRT has been utilized for HCC in a series of trials resulting in promising results in asian countries, including improvements in response rate, disease control and overall survival.

Therefore, we did this meta-analysis to evaluate whether the addition of 3D-CRT to TACE could offer any survival beneﬁts to asian patients with advanced HCC.

**Materials and methods**

***Literature search***

PubMed, Medline, Embase, Chinese BioMedical Literature Database (CBM), and the Cochrane Library were searched for studies published from October 2000 to October 2013. The following medical subject heading (MeSH) terms were used: (“hepatocellular carcinoma” or “HCC”) AND (“transcatheter arterial chemoembolization” or “TACE”) AND (“three-dimensional conformal radiotherapy” or “3D-CRT”).

**Selection criteria**

 Studies were considered eligible if they met the following inclusion criteria: (1) study designs were prospective cohort studies or case-control studies; (2) patients in the treatment group received combination therapy consisting of 3D-CRT and TACE with TACE alone in the control group; (3) participants had unresectableHCC; (4) data were reported on outcomes of overall survival (OS). Studies were excluded in the analysis if: (1) reviews, commentaries, editorials, case reports, and letters; (2) patients included received surgery; (3) lacked of key information for calculation with methods developed by Parmar*et al*[[11](#_ENREF_11)], Williamson *et al*[[12](#_ENREF_12)], and Tierney *et al*[[13](#_ENREF_13)]; and (4) duplicated or redundant publications.

***Data extraction***

Each study was evaluated and classified by two independent investigators (Liqun Zou and Binglan Zhang). Disagreements were resolved in consultation with a third investigator. The extracted items comprised: first author, publication year, country, study design, number of patients, number of combination group and sole TACE group, tumor size and stage, survival rates.

***Statistical analysis***

Statistical analyses were performed using Review Manager Software (RevMan 5.2; Cochrane Collaboration, Oxford, United Kingdom). Odds ratios (OR) with 95% confidence intervals (CIs) was calculated for the quantitative aggregation of survival result. An observed OR > 1 indicated that the addition of 3D-CRT to TACE could offer survival beneﬁts to patients and would be considered statistically significant.

Forrest plots were used to estimate the therapeutic effect on survival. Heterogeneity was defined as *p* < 0.10 or *I*2 > 50%[[14](#_ENREF_14)]. Data that were not significantly heterogeneous (*p* ≥ 0.10, *I*2 ≤ 50%) were calculated using a fixed effects model. If not, a random effect model was used. The Begg’s test was used to assess potential publication bias, *p* > 0.05 was considered that there was no potential publication bias[[15](#_ENREF_15)].

**Results**

***Selection of studies***

This meta-analysis yielded a total of 653 trials. After reviewing the titles and abstracts, 598 studies were excluded and 55 left for further evaluation. Of the 55 trials, 22 were excluded for inadequate control group, 15 for reviews or case reports, 5 for surgical intervention, and 3 for interventions other than TACE alone in the control group. Finally, there were 10 studies[[16-25](#_ENREF_16)] fulfilling the inclusion criteria and being sent for review in our meta-analysis (Figure 1).

The main characteristics of included studies are listed in Table 1. Among these included studies published between 2001 and 2010, two were randomized clinical trials and 8 were nonrandomized observational studies. All the trials originated from Asia because of the high incidence of hepatitis B infection here. In addition to two articles that did not report liver function of the patients, all the other 8 studies included patients with liver function of Child–Pugh class A or B. The Karnofsky score of most patients is equal or greater than 70. There were 400 patients in the combination of TACE and 3D-CRT group, and 508 patients in the group of TACE alone. Among the 10 studies, there were eight, nine, and eight studies that reported comparative data for overall survival rate at 1, 2, and 3 years, respectively (Table 2); seven and four studies that reported comparative data for tumor response and the decline rates of the  fetal protein (AFP) level, respectively.

***Survival rates***

**One-year survival:** Eight trials (802 patients) were identiﬁed with the outcome measurements of 1-year survival rates. Meta-analysis showed a signiﬁcant improvement in the 1-year survival favoring combination therapy (OR = 1.87, 95%CI: 1.37–2.55, *P <* 0.0001) (Figure 2). There is no heterogeneity among the trials included, using ﬁxed-effects model (heterogeneity **2 = 9.02, *P* = 0.25; *I*2 = 22%).

**Two-year survival:** Data of 2-year survival rate were reported in nine studies (860 patients) and there was also no heterogeneity among these studies (heterogeneity **2 = 7.10, *P* = 0.53; *I*2 = 0%), thus the fixed-effects model was used to pool the results. Meta-analysis showed the combination of 3D-CRT and TACE was also associated with a higher 2-year survival rate compared with the TACE alone group (OR = 2.38, 95%CI: 1.78–3.17, *P <* 0.00001) (Figure 2).

**Three-year survival:** Eight trials (802 patients) were identiﬁed with the outcome measurements of 3-year survival rates. Analysis of the 3-year survival (425 participants) also showed a significant benefit with the combination therapy method (OR = 2.97, 95%CI: 2.10–4.21, *P <* 0.00001)(Figure 2). In the chi-square and I-square tests, there were no heterogeneous findings (heterogeneity **2 = 3.02, *P* = 0.88; *I*2 = 0%).

***Tumor response***

Seven trials (698 patients) were identiﬁed with outcome measurements of complete response (CR) and partial response (PR). There is no heterogeneity among the trials included, using ﬁxed-effects model (heterogeneity **2 = 5.90, *P* = 0.43; *I*2 = 0%).The pooled analysis showed that compared with TACE alone, the combination method signiﬁcantly improved CR+PR (OR = 3.81; 95%CI: 2.70–5.37; *P <* 0.00001) (Figure 3).

***decline rates of AFP level***

Four trials (391 participants) were identified with the outcome measurements of the decline rates of AFP level. There was no evidence of heterogeneity among the trials included, using ﬁxed-effects model (heterogeneity **2 = 2.47, *P* = 0.48; *I*2 = 0%). Meta-analysis showed the combination of 3D-CRT and TACE was associated with a higher decline rate of AFP level compared with the TACE monotherapy (OR = 3.24, 95%CI: 2.09–5.02, *P <* 0.00001), and the results are shown in Figure 3.

***Publication bias***

Begg’s funnel plot was performed to assess the publication bias in all included studies for evaluation of survival rates, tumor response and the decline rates of AFP level separately. Begg’s funnel plot did not reveal any evidence of significant asymmetry in the 1-year OS (*p* = 0.621), 2-year OS (*p* = 0.835), and 3-year OS (*p* = 0.138) (Figure 4). There was also no indication of publication bias in Begg’s test of tumor response (*p* = 0.652) and the decline rates of AFP level (*p* = 0.497) (Figure 5).

**Discussion**

Since the hepatic artery provides at least 80% of the blood supply to HCC, TACE has been suggested as a standard therapeutic method for patients who are unsuitable for surgical management[[2](#_ENREF_2),[26](#_ENREF_26)]. However, TACE alone frequently results in incomplete tumor necrosis[[27](#_ENREF_27)]. Previous meta-analysis has shown that the efficacy of TACE combined with radiofrequency ablation (RFA), high-intensity focused ultrasound (HIFU), or percutaneous ethanol injection (PEI) was significantly better than that of TACE alone in patients with HCC[[3](#_ENREF_3),[28-](#_ENREF_28)[35](#_ENREF_35)]. PEI has been widely used in treating HCC, but the effectiveness is limited to the diameter of HCC lesions[[36](#_ENREF_36)]. RFA monotherapy was found to be associated with a higher tumor progression rate, and the main cause is the residual tumor tissue after RFA. Additionally, RFA cannot be a suitable treatment for tumors with multiple nodules. Consequently, the combination of TACE and other local therapies may have several theoretical advantages. So far, there is no meta-analysis performed to assess the efficacy of the combination of TACE and 3D-CRT compared with TACE alone for treatment of HCC, and we performed this meta-analysis in which 10 studies were included eventually. However, incidence of complication in CRT with TACE might be higher than TACE alone.

The result of our meta-analysis demonstrated that the combination of 3D-CRT and TACE was associated with higher survival rates (OR 1-year = 1.87, 95%CI: 1.37–2.55, *P <* 0.0001; OR 2-year = 2.38, 95%CI: 1.78–3.17, *P <* 0.00001; OR 3-year = 2.97, 95%CI: 2.10–4.21, *P <* 0.00001). In addition, the combination of TACE and 3d-CRT had a significantly better tumor response (OR = 3.81; 95%CI: 2.70–5.37; *P <* 0.00001) and higher decline rate of AFP level (OR = 3.24, 95%CI: 2.09–5.02, *P <* 0.00001). Thus, the method with TACE plus 3D-CRT was a better choice than the method with only TACE for treatment of patients with HCC.

In the past, there was the concern that the normal liver tissue is sensitive and of poor tolerance to radiation, so radiotherapy was limited in the treatment of HCC. Fortunately, with the advent of 3-dimensional planning systems, 3D-CRT can minimize the irradiation of normal tissue and improve the distribution of target irradiation dose to tumors. Numerous clinical studies of TACE in combination with 3D-CRT for treatment of patients with HCC have emerged in recent years. In our meta-analysis, all the included trials adopted 3D-CRT technique. About 20% of the blood supply of HCC comes from the portal vein, resulting in that a small number of tumor cells remain viable and the tumor may recur after TACE. And 3D-CRT can make as a consolidation planned procedure to target residual hepatic tumor. Furthermore, Seong *et al* has reported that the anticancer drugs applied in the procedure of TACE will retain in the tumor and may have a radiosensitizing effect[[37](#_ENREF_37)].

In addition, we evaluated the adverse effects of TACE and 3D-CRT in the included studies. Five trials reported the development of radiation-induced liver disease (RILD), but no difference in results of liver function test was found between the combination and control groups. Other common adverse effects were the postembolization syndrome including leukocyte count decline, fever, mild nausea, abdominal pain, and elevation of serum aminotransferase level or total bilirubin, which were transient and the patients often recovered in a short time.

Although there was no heterogeneity and publication bias in our meta-analysis, this study may have several possible limitations. Firstly, the number of RCT was very limited, and only two RCTs were included. Secondly, the basic characteristics of included cases are not all the same, including clinical stage, the microvascular infiltration, tumor number and size, and different stage of liver function. In addition, the interventional measures used (anticancer drugs of TACE, TACE course, radiation dose and methods) were different. Future studies need better design and more strict management of conduction. More patients’ information should be collected in the trials, including status of infection by hepatitis virus and degree of tumor cell differentiation. Last but not the least, a major limitation is that the studies included in our meta-analysis are all come from Asia countries, owing to no articles published comparing the efficacy of TACE plus 3D-CRT versus TACE alone in non-asian areas.

In conclusion, this meta-analysis based on 10 included studies indicates that TACE combined with 3D-CRT is a promising treatment for HCC. Importantly, these results need to be validated in further prospectively randomized, controlled multi-center clinical trials.

**comments**

***Background***

transcatheter arterial chemoembolization (TACE) has been recognized as a standard treatment for unresectable hepatocellular carcinoma(HCC), but TACE alone has achieved very limited success. With the advent of three-dimensional conformal radiotherapy (3D-CRT), it has been utilized for HCC in a series of trials resulting in promising results. However, the role of TACE combined with 3D-CRT remains unclear.

***Research frontiers***

Three-dimensional conformal radiotherapy (3D-CRT) allows higher RT doses HCC and minimizes liver injury, which can result in promising outcomes, including increases in response rate, tumor control and overall survival. In the current study, the authors did a meta-analysis to assess the efficacy of 3D-CRT plus TACE compared with TACE alone for HCC, and our meta-analysis was the first to do so.

***Innovations and breakthroughs***

Previous studies assessing the effectiveness of 3D-CRT plus TACE compared with TACE alone reported conflicting results. Consequently, the authors did a meta-analysis to evaluate whether the addition of 3D-CRT to TACE could offer any survival beneﬁts for hepatocellular carcinoma. The result indicated that 1-, 2-, and 3-year overall survival, tumor response, and decline rates of AFP level treated with 3D-CRT plus TACE were significantly higher than those with TACE alone.

***Applications***

This current limited evidence demonstrated that TACE plus 3D-CRT was better than TACE monotherapy in the treatment of hepatocellular carcinoma, which can improve the overall survival rate and provides better prognosis for patients with HCC.

***Terminology***

TACE is performed with the infusion of a mixture of chemotherapy drugs and has been widely used to treat HCC. 3D-CRT is operated by three-dimensional conformal RT treatment planning system and would be possible to minimize liver injury and increase irradiation dose to HCC.

***Peer review***

This manuscript presents a meta-analysis of ten studies (two of them were randomized trials) comparing TACE alone to its combination with 3D-CRT in the treatment of hcc**.** Although, as stated by the authors at the end of the discussion, there is a variety of drugs and techniques used and more studies will be required, this paper provides an important overview on this subject.

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**Table 1 Clinical characteristics of 10 included trials**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Author** | **Year** | **Study design** | ***n* (CMT/TACE)** | **Tumor stage** | **KPS** | **Child-Pugh Class (A/B/C)** | **Anticancer drug of TACE** |
| Chia-Hsien Cheng *et al*[25] | 2001 | Nonrandomized | 33 (17/16) | II, IIIA, IVA | ≥ 70 | 33/0/0 | doxorubicin, cisplatin, MMC |
| Lan *et al*[24] | 2005 | Nonrandomized | 102 (42/60) | II, III |  |  | 10-Hydroxycamptothecine, DDP, 5-FU |
| Li *et al*[23] | 2003 | Nonrandomized | 82 (41/41) |  |  | 50/32/0 | 10-Hydroxycamptothecine, 5-FU, MMC or ADM |
| Liao *et al*[22] | 2010 | Randomized | 48 (24/24) | III, IV |  | 34/14/0 | 5-FU, DDP, ADM |
| Liu *et al*[21] | 2005 | Nonrandomized | 114 (54/60) |  | ≥ 70 | 83/31/0 | MMC, ADM, CBP |
| Shang *et al*[20] | 2007 | Nonrandomized | 76 (40/36) | T1-2N0M0 | ≥ 70 |  | 5-FU, DDP, ADM or MMC |
| Shim *et al*[19] | 2005 | Nonrandomized | 73 (38/35) | III, IVa |  | 65/8/0 | doxorubicin |
| Wu *et al*[18] | 2004 | Nonrandomized | 81 (41/40) | I, II | ≥ 70 | 55/26/0 | MMC, ADM, CBP or DDP |
| Zeng *et al*[17] | 2004 | Nonrandomized | 203 (54/149) |  |  | 158/45/0 | 5-FU, DDP, MMC |
| Zhao *et al*[16] | 2006 | Randomized | 96 (49/47) | T1N0M0, T2N0M0 | ≥ 70 | 96/0/0 | 10-Hydroxycamptothecine, DDP, 5-FU |

TACE: transcatheter arterial chemoembolization; CMT: Combination therapy; KPS: Karnofsky score; ADM: Doxorubicin; CBP: Carboplatin; 5-FU: 5-fluorouracil; MMC: Mitomycin C.

**Table 2 Outcomes of the combination therapy groups and the sole transcatheter arterial chemoembolization groups**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | **1-year survival** | **2-year survival** | **3-year survival** |
| **Ref.** | **Year** | **TACE + 3D-CRT** | **TACE alone** | **TACE + 3D-CRT** | **TACE alone** | **TACE + 3D-CRT** | **TACE alone** |
| Chia-Hsien Cheng *et al*[25] | 2001 |  |  | 58% | 56% |  |  |
| Lan *et al*[24] | 2005 | 57.10% | 61.70% | 40.50% | 30.00% | 26.20% | 16.70% |
| Li *et al*[23] | 2003 | 73. 2 % | 54. 8 % | 58. 7 % | 27. 3 % | 41. 9 % | 12. 8 % |
| Liao *et al*[22] | 2010 | 74.00% | 50% |  |  | 30.00% | 14% |
| Liu *et al*[21] | 2005 | 66.50% | 53.90% | 48.40% | 37.20% | 37.40% | 17.80% |
| Shang *et al*[20] | 2007 | 78% | 50% | 60% | 32% | 34% | 18% |
| Shim *et al*[19] | 2005 |  |  | 36.80% | 14.30% |  |  |
| Wu *et al*[18] | 2004 | 90. 2% | 89. 7% | 75. 6% | 58. 7% | 44. 6% | 24. 0% |
| Zeng *et al*[17] | 2004 | 71.50% | 59.60% | 42.30% | 26.50% | 24.00% | 11.10% |
| Zhao *et al*[16] | 2006 | 82% | 55% | 63% | 28% | 43% | 15% |

TACE: transcatheter arterial chemoembolization; 3D-CRT: Three-dimensional conformal radiotherapy.

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**Figure 1 Route and results of including trials of the meta-analysis.**

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**Figure 2 Outcomes of overall survival of combination therapy compared with sole transcatheter arterial chemoembolization therapy.**

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**Figure 3 Better tumor response and higher decline in  fetal protein level were shown in patients treated with combination therapy.**

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**Figure 4 No significant asymmetry was revealed in 1-year (A), 2-year (B) and 3-year (C) overall survival.**

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**Figure 5 No publication bias was found in tumor response (A) and reduction in  fetal protein level (B).**