

Aug 25, 2016

Dear Editor
World Journal of Gastroenterology

Name of Journal: *World Journal of Gastroenterology*.

Manuscript NO: 28748

Column : Editorial

Title:

Transarterial chemoembolization with drug-eluting beads in hepatocellular carcinoma

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Correspondence to: Myeong Jun Song, MD, PhD

We have carefully considered the suggestions by the reviewers. We fully agree with the opinions of the reviewers.

Point-by-Point Response to Reviewer I

Reviewer 1

Nam and colleagues aim to provide a comprehensive overview on DEB-TACE in HCC patients. The topic has been already deeply explored and I am not sure authors add something relevant to the debate on the effectiveness of drug-eluting beads in hepato-oncology. Moreover, authors should improve their manuscript based on the following points:

1) Authors seem to ignore the recently developed smaller beads, such as Tandem Embozene (Malagari K, CVIR 2016) and M1 DC Beads (Spreafico, CVIR 2015). Please complete the Editorial with the findings of these two preliminary studies. Add also a small comment on HepaSpheres 30-60 μ m (Malagari K, CVIR 2014).

→ We totally agree with your comment. As you comment, we revised and added the manuscript as follows : the paragraph of **Clinical impact of microspheres with smaller diameters** (See page 8-9, line11-3 in revision)

2) Authors cite their study (Song M, J Hepatol 2012) but do not comment that their results (clearly in favor of DEB-TACE over cTACE) have not been confirmed in several other papers either retrospective (Recchia, Oncol Rep 2012, Facciorusso, J Gastroenterol Hepatol 2016) and RCTs (Golfieri R, British J Cancer 2015; Sacco R, JVIR 2012). Again on the comparison between DEB-TACE and cTACE, cite the last meta-analysis on this topic (Facciorusso A, Dig Liver Dis. 2016 Jun;48(6):571-7. doi: 10.1016/j.dld.2016.02.005. Epub 2016 Feb 21. PMID: 26965785) and the last retrospective study (Facciorusso A, J Gastroenterol Hepatol 2016).

→ We agree with your recommendation. We revised our manuscript according to treatment response and survival of your mentioned studies.

→ First, we added the paragraph in **response to DC Beads TACE** as follows; “However, these significant improvements in treatment responses of DC Beads TACE as compared to those of cTACE were not proven in other studies. In two randomized controlled trials (RCTs), Golfieri *et al.*^[30] reported treatment response of 177 HCC patients involving 89 in DC Beads TACE and 88 in cTACE. OR rates at 3 months showed 74.7% and 74.1% for DC Beads TACE and cTACE, respectively ($P > 0.999$). Also, Sacco *et al.*^[31] showed statistically insignificant differences in CR and PR rates at 1 month between DC Beads TACE and cTACE (51.5 % and 48.5% vs. 70.6% and 29.4%, respectively, $P=0.1$). Facciorusso *et al.*^[32]

reported single center study with early/intermediate HCC patients (n=249). In this study, cTACE showed better tumor response and time to progression (TTP). OR rates were 85.3% in cTACE and 74.8% in DC Beads TACE (P=0.039), and median TTP were 17 months in cTACE and 11 months in DC Beads TACE, respectively (P<0.001)." (See page 7, line 13-24 in revision)

→ Second, we also added the paragraph in **survival** as follows; "However, the survival benefits of DC Beads TACE over cTACE remain controversial. Recchia *et al.* reported retrospective study that included 35 patients of DEB-TACE and 70 patients of cTACE.^[41] There was no statistically significant difference in median OS between cTACE and DEB-TACE (11.4 months vs. 18.4 months, respectively). Facciorusso *et al.*^[32] also reported that median survival of early/intermediate stage HCC patients (n=249) between cTACE and DC Beads TACE showed insignificant differences (39 months vs. 32 months, respectively, P=0.1).

In two RCTs, Golfieri *et al.*^[30] reported the 2 year survival rates between DC Beads TACE and cTACE (56.8% vs. 55.4%, respectively, P=0.949) of 117 HCC patients. Sacco *et al.*^[31] also showed that estimated 2-year cumulative survival rates were statistically insignificant between DC Beads TACE and cTACE (86.8% vs. 83.6%, respectively, P=0.96). Furthermore, Facciorusso *et al.* reported meta-analysis consisted of four RCTs and 8 observational studies with 1,449 patients who underwent 689 DC Beads TACE and 760 cTACE.^[42] In this study, statistically insignificant trends in favor of DC Beads TACE were observed for 3-year survival rates.(See page 10-11, line 16-2 in revision)

3) Another aspect that should be at least briefly commented is the health-economy evaluation of DEB-TACE. Please read, comment, and cite the recent paper by Cucchetti A (Cucchetti A, Dig Liver Dis 2016) and the relevant editorial by Angelico (Angelico M, TACE vs DEB-TACE: who wins? Dig Liver Dis 2016).

→ We fully agree with the reviewer's comment. We revised to add the new paragraph (assessment of cost effectiveness) as follows; "Cucchetti *et al.* investigated the cost effectiveness of DC Beads TACE.^[47] In meta-analysis, patients with cTACE experienced significantly frequent post-TACE syndrome ($P=0.018$) and longer hospitalization ($P=0.01$). DC Beads TACE earned 4.0 quality-adjusted life-years (QALYs) while cTACE earned 3.3 QALYs. Total costs of DC Beads TACE were € 11,656 and those of cTACE were € 10,389. DC Beads TACE spent higher costs than cTACE, but, higher QALYs were achieved from the treatment. Expected cost-effectiveness for DC Beads TACE was € 3,089/QALY and that of cTACE was € 3,246/QALY. Improvement of quality of life could be attained by DC Beads TACE with modest increment of costs."(See page 11-12 line 27-6 in revision).

→ We also revised to add the new paragraph in discussion as follows; "DC Beads TACE may provide improved survival rates and quality of life to some extent as compared to cTACE.^[32,41,47,49] However, several RCTs and meta-analysis do not demonstrate significant survival advantages of DC Beads TACE.^[30,31,42] Because of relatively small numbers of prospective randomized trials, further investigations with well designed, large scaled, comparative studies searching for the long-term survival are necessary. DC Beads TACE seemed to afford better cost-effectiveness than cTACE.^[47] However, previous studies were based on various conditions involving different countries and institutes in terms of costs, clinical circumstances, and technical procedures. Study with standardized technical protocols and performances will be needed to validate the cost-effectiveness of DC Beads TACE.

Indeed, it remains inconclusive as to the superiority of DC Beads TACE over cTACE. Decision to performing DC Beads TACE or cTACE needs to be tailored in each individual patient depending on his or her economic status, physician's experiences, and expertise of institute. Future studies are warranted to determine the appropriate indications of DC Beads TACE."(See page 13 line 1-15 in revision).

Point-by-Point Response to Reviewer II

To the Author: Congratulations for this review, very well presented and very useful

Thank you again for publishing our manuscript in the World Journal of Gastroenterology.

Sincerely yours,

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