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Flat C, 23/F., Lucky Plaza,  
315-321 Lockhart Road,  
Wan Chai, Hong Kong, China

## ESPS Peer-review Report

**Name of Journal:** World Journal of Gastroenterology

**ESPS Manuscript NO:** 2979

**Title:** Hepatic arterial infusion chemotherapy in hepatocellular carcinoma with portal vein tumor thrombosis

**Reviewer code:** 02462197

**Science editor:** Wen, Ling-Ling

**Date sent for review:** 2013-03-29 15:23

**Date reviewed:** 2013-03-30 18:41

| CLASSIFICATION                                     | LANGUAGE EVALUATION   | RECOMMENDATION                      | CONCLUSION   |
|--|---|-------------------------------------|--|
| <input type="checkbox"/> Grade A (Excellent)       | <input type="checkbox"/> Grade A: Priority Publishing                 | Google Search:                      | <input type="checkbox"/> Accept                        |
| <input type="checkbox"/> Grade B (Very good)       | <input checked="" type="checkbox"/> Grade B: minor language polishing | <input type="checkbox"/> Existed    | <input type="checkbox"/> High priority for publication |
| <input checked="" type="checkbox"/> Grade C (Good) | <input type="checkbox"/> Grade C: a great deal of language polishing  | <input type="checkbox"/> No records | <input type="checkbox"/> Rejection                     |
| <input type="checkbox"/> Grade D (Fair)            | <input type="checkbox"/> Grade D: rejected                            | <input type="checkbox"/> Existed    | <input type="checkbox"/> Minor revision                |
| <input type="checkbox"/> Grade E (Poor)            |   | <input type="checkbox"/> No records | <input checked="" type="checkbox"/> Major revision     |

## COMMENTS TO AUTHORS

March 30, 2013 World Journal of Gastroenterology ESPS Manuscript NO: 2979 Title: Hepatic arterial infusion chemotherapy in hepatocellular carcinoma with portal vein tumor thrombosis This is a retrospective monocentre study aimed to evaluate the prognostic factors and anti-tumor effects of hepatic arterial infusion chemotherapy in patients with large hepatocellular cancers and portal vein tumor thrombosis. GENERAL COMMENTS The results of the present manuscript are interesting, due to the potential alternative role of locoregional chemotherapy vs. use of sorafenib in HCC patients, even in the presence of distant metastases and/or vascular invasion; Despite the present study is not innovative, and several recent studies have been published on the same argument (Miyaki D, et al. J Gastroenterol Hepatol 2012; Baek YH, et al. World J Gastroenterol 2012), it is interesting to underline that the current research is focalized also on patients with distant metastases and/or vascular invasion. SPECIFIC COMMENTS 1 - In Abstract, the Authors need to explain some of the abbreviations (i.e., HAIC, HCC, PVTT, ECF); 2 - In Material and methods, it is not completely clear how many patients were finally enrolled for the study. Probably, it is better to anticipate the part dedicated to the selection criteria with respect to the sentence: "Fifty of these 68 patients had PVTT, received more than two cycles of HAIC and were enrolled in this study." 3 - Moreover, in some parts in the abstract it is reported that only patients with HCC  $\geq 10$  cm were enrolled for the study. It is not clear for me why this statement is not reported in the selection criteria: moreover, the 400 cm<sup>3</sup> proposed cut-off corresponds to a single lesion of 9 cm of diameter, inferior to the so-cited 10 cm. Finally, in table 1 the inferior range of tumor volume corresponds to a single lesion of less than 4 cm of diameter. Authors need to better clarify this aspect, eventually removing



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from the abstract the sentences regarding the selection of patients with lesions bigger than 10 cm. 4 - The meaning of ECF must be explained in the text when it is reported the first time. 5 - The main problem of the present paper is in Results section: firstly, construction of multivariate analyses on a population of only 50 patients looks to me not completely correct from the methodological point of view. Elevated risks of colinearity and singularity phenomena are expected in this case. An accurate analysis of goodness of covariates fitting must be performed using specific tests. Authors must underline the limit of the numerosity of the sample size in Discussion. 6 - Moreover, and it the real problem of the paper, it is completely unclear for me in which way disease control and PIVKA reduction are risk factors. However, looking at the results of the multivariate models, hazard ratios (no the odds ratios, you used a Cox regression model!) are  $> 1$ . Authors must reevaluate their analyses, eventually selecting no more than 2-3 covariates in each case, and carefully looking at the way in which they doomed their variables and in which way they inserted them in the statistical software.



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### ESPS Peer-review Report

**Name of Journal:** World Journal of Gastroenterology

**ESPS Manuscript NO:** 2979

**Title:** Hepatic arterial infusion chemotherapy in hepatocellular carcinoma with portal vein tumor thrombosis

**Reviewer code:** 02519881

**Science editor:** Wen, Ling-Ling

**Date sent for review:** 2013-03-29 15:23

**Date reviewed:** 2013-03-31 17:25

| CLASSIFICATION                                     | LANGUAGE EVALUATION   | RECOMMENDATION                      | CONCLUSION   |
|--|---|-------------------------------------|--|
| <input type="checkbox"/> Grade A (Excellent)       | <input type="checkbox"/> Grade A: Priority Publishing                 | Google Search:                      | <input checked="" type="checkbox"/> Accept             |
| <input type="checkbox"/> Grade B (Very good)       | <input checked="" type="checkbox"/> Grade B: minor language polishing | <input type="checkbox"/> Existed    | <input type="checkbox"/> High priority for publication |
| <input checked="" type="checkbox"/> Grade C (Good) | <input type="checkbox"/> Grade C: a great deal of language polishing  | <input type="checkbox"/> No records | <input type="checkbox"/> Rejection                     |
| <input type="checkbox"/> Grade D (Fair)            |   | BPG Search:                         | <input type="checkbox"/> Minor revision                |
| <input type="checkbox"/> Grade E (Poor)            | <input type="checkbox"/> Grade D: rejected                            | <input type="checkbox"/> Existed    | <input type="checkbox"/> Major revision                |
|  |   | <input type="checkbox"/> No records |  |

### COMMENTS TO AUTHORS

I congratulate the authors for the attempt of this rather novel approach but I would like to ask how this approach is different from TACE without the embolisation part and did the authors experience any problems with hepatic artery thrombosis. Furthermore, did the authors had experience in patients with less advanced disease?



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## ESPS Peer-review Report

**Name of Journal:** World Journal of Gastroenterology

**ESPS Manuscript NO:** 2979

**Title:** Hepatic arterial infusion chemotherapy in hepatocellular carcinoma with portal vein tumor thrombosis

**Reviewer code:** 02444769

**Science editor:** Wen, Ling-Ling

**Date sent for review:** 2013-03-29 15:23

**Date reviewed:** 2013-04-06 19:47

| CLASSIFICATION                                     | LANGUAGE EVALUATION   | RECOMMENDATION                      | CONCLUSION   |
|--|---|-------------------------------------|--|
| <input type="checkbox"/> Grade A (Excellent)       | <input type="checkbox"/> Grade A: Priority Publishing                 | Google Search:                      | <input type="checkbox"/> Accept                        |
| <input type="checkbox"/> Grade B (Very good)       | <input checked="" type="checkbox"/> Grade B: minor language polishing | <input type="checkbox"/> Existed    | <input type="checkbox"/> High priority for publication |
| <input type="checkbox"/> Grade C (Good)            | <input type="checkbox"/> Grade C: a great deal of language polishing  | <input type="checkbox"/> No records | <input checked="" type="checkbox"/> Rejection          |
| <input type="checkbox"/> Grade D (Fair)            | <input type="checkbox"/> Grade D: rejected                            | <input type="checkbox"/> Existed    | <input type="checkbox"/> Minor revision                |
| <input checked="" type="checkbox"/> Grade E (Poor) |   | <input type="checkbox"/> No records | <input type="checkbox"/> Major revision                |

## COMMENTS TO AUTHORS

This is a case-only clinical trial that evaluated the prognostic factors and anti-tumor effects of HAIC in patients with HCC tumors  $\geq 10$  cm and PVTT. They concluded that HAIC may be considered as an effective treatment modality for advanced HCC with PVTT in patients with tumors  $\geq 10$  cm. In general the authors provided new but weak information that might help clinical decision of advanced HCC. But the design of this study is questionable therefore the information authors try to convey to our society might be misleading. Major points: Major concerns come from the heterogeneity of the patients. Materials & Methods, last paragraph: "During or after the HAIC treatment, additional therapies were performed as necessary, depending on the tumor responses to HAIC, performance status, and hepatic function. Additional treatment included targeted therapy with sorafenib, external radiation therapy, transarterial chemolipiodolization (TACL), systemic chemotherapy, local therapies, such as radiofrequency ablation (RFA) or percutaneous ethanol injection (PEI), or surgical treatment". And worse, RESULTS, Patients Characteristics, "Twenty-four patients (48%) received previous treatment, and the most common previous treatment was TACL." When you apply so many modalities to the 50 patients, how could you justify the real effect of HAIC? Why a control group was absent (either TACE, radiology, Sorafenib or placebo)? For example, Sorafenib is the standard care of BCLC-C patients. And as claimed by the authors, all patients were Child-A/B thus these patients are amenable to TACE. By doing so, at least we would know the HAIC modality is superior or not. It is possible to achieve these data from the institute. Minor points: Why these patients were not amenable to TACE but good for HAIC? The target of HAIC is liver mass, why extrahepatic metastasis did not influence survival?



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### ESPS Peer-review Report

**Name of Journal:** World Journal of Gastroenterology

**ESPS Manuscript NO:** 2979

**Title:** Hepatic arterial infusion chemotherapy in hepatocellular carcinoma with portal vein tumor thrombosis

**Reviewer code:** 02441335

**Science editor:** Wen, Ling-Ling

**Date sent for review:** 2013-03-29 15:23

**Date reviewed:** 2013-04-07 10:24

| CLASSIFICATION                                     | LANGUAGE EVALUATION   | RECOMMENDATION                      | CONCLUSION  |
|--|---|-------------------------------------|---|
| <input type="checkbox"/> Grade A (Excellent)       | <input type="checkbox"/> Grade A: Priority Publishing                 | Google Search:                      | <input type="checkbox"/> Accept                                   |
| <input type="checkbox"/> Grade B (Very good)       | <input checked="" type="checkbox"/> Grade B: minor language polishing | <input type="checkbox"/> Existed    | <input checked="" type="checkbox"/> High priority for publication |
| <input checked="" type="checkbox"/> Grade C (Good) | <input type="checkbox"/> Grade C: a great deal of language polishing  | <input type="checkbox"/> No records | <input type="checkbox"/> Rejection                                |
| <input type="checkbox"/> Grade D (Fair)            |   | BPG Search:                         | <input type="checkbox"/> Minor revision                           |
| <input type="checkbox"/> Grade E (Poor)            | <input type="checkbox"/> Grade D: rejected                            | <input type="checkbox"/> Existed    | <input type="checkbox"/> Major revision                           |
|  |   | <input type="checkbox"/> No records |   |

### COMMENTS TO AUTHORS

This is a good article about the treatment modality for advanced HCC with PVTT in patients with tumors  $\geq 10$  cm by using HAIC, which shows HAIC is an effective treatment modality. I have several questions for the authors: 1. Please mention in the text how many cases were histologically diagnosed? 2. Why the removal of thrombus was not performed in your patients? 3. In Table 1 of baseline patient characteristics, we know the types of portal vein thrombosis(Vp2/Vp3/Vp4) and tumor volume (cm<sup>3</sup>), but we also hope to see the changes of these parameters after HAIC, in order to evaluate the treatment efficacy.



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### ESPS Peer-review Report

**Name of Journal:** World Journal of Gastroenterology

**ESPS Manuscript NO:** 2979

**Title:** Hepatic arterial infusion chemotherapy in hepatocellular carcinoma with portal vein tumor thrombosis

**Reviewer code:** 02461636

**Science editor:** Wen, Ling-Ling

**Date sent for review:** 2013-03-29 15:23

**Date reviewed:** 2013-04-12 06:30

| CLASSIFICATION                                     | LANGUAGE EVALUATION  | RECOMMENDATION                      | CONCLUSION   |
|--|--|-------------------------------------|--|
| <input type="checkbox"/> Grade A (Excellent)       | <input checked="" type="checkbox"/> Grade A: Priority Publishing     | Google Search:                      | <input type="checkbox"/> Accept                        |
| <input type="checkbox"/> Grade B (Very good)       | <input type="checkbox"/> Grade B: minor language polishing           | <input type="checkbox"/> Existed    | <input type="checkbox"/> High priority for publication |
| <input checked="" type="checkbox"/> Grade C (Good) | <input type="checkbox"/> Grade C: a great deal of language polishing | <input type="checkbox"/> No records | <input type="checkbox"/> Rejection                     |
| <input type="checkbox"/> Grade D (Fair)            |  | BPG Search:                         | <input checked="" type="checkbox"/> Minor revision     |
| <input type="checkbox"/> Grade E (Poor)            | <input type="checkbox"/> Grade D: rejected                           | <input type="checkbox"/> Existed    | <input type="checkbox"/> Major revision                |
|  |  | <input type="checkbox"/> No records |  |

### COMMENTS TO AUTHORS

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## ESPS Peer-review Report

**Name of Journal:** World Journal of Gastroenterology

**ESPS Manuscript NO:** 2979

**Title:** Hepatic arterial infusion chemotherapy in hepatocellular carcinoma with portal vein tumor thrombosis

**Reviewer code:** 02519060

**Science editor:** Wen, Ling-Ling

**Date sent for review:** 2013-03-29 15:23

**Date reviewed:** 2013-04-15 06:24

| CLASSIFICATION                               | LANGUAGE EVALUATION  | RECOMMENDATION                      | CONCLUSION   |
|--|--|-------------------------------------|--|
| <input type="checkbox"/> Grade A (Excellent) | <input type="checkbox"/> Grade A: Priority Publishing                | Google Search:                      | <input type="checkbox"/> Accept                        |
| <input type="checkbox"/> Grade B (Very good) | <input type="checkbox"/> Grade B: minor language polishing           | <input type="checkbox"/> Existed    | <input type="checkbox"/> High priority for publication |
| <input type="checkbox"/> Grade C (Good)      | <input type="checkbox"/> Grade C: a great deal of language polishing | <input type="checkbox"/> No records | <input type="checkbox"/> Rejection                     |
| <input type="checkbox"/> Grade D (Fair)      | <input type="checkbox"/> Grade D: rejected                           | BPG Search:                         | <input type="checkbox"/> Minor revision                |
| <input type="checkbox"/> Grade E (Poor)      |  | <input type="checkbox"/> Existed    | <input type="checkbox"/> Major revision                |
|  |  | <input type="checkbox"/> No records |  |

## COMMENTS TO AUTHORS

The authors performed hepatic arterial infusion chemotherapy (HAIC) in 50 patients with large HCC with portal vein tumor thrombus (PVTT), resulting in 6% complete response (CR), 26% partial response (PR), and 44% stable disease (SD), and found that a tumor volume less than 400 cm<sup>3</sup> and normal PIVKA-II were the significant pretreatment prognostic factors. This paper is potentially interesting because HAIC is expected to be an alternative therapy for advanced HCC patients. However, there are critical flaws that preclude recommendation for acceptance. Enrollment criteria are not clearly determined in the study. This will prevent journal's readers to interpret the results properly. (1) The authors described that patients with HCC  $\geq 10$  cm were treated in the abstract, however, they did not mention it in the materials and methods. (2) Approximately half of the patients received previous treatments such as radiation, radiofrequency ablation, or transarterial chemolipiodolization. Therefore, the cohort of this study is quite heterogenous, which makes interpretation of the results difficult. The authors should enroll the patients who had HAIC as an initial treatment, or analyze separately. (3) The authors analyzed only the patients who received more than 2 cycles of HAIC. 18 patients are anticipated to have received only 1 cycle of HAIC for some reasons such as disease progression and adverse effects. The authors should analyze all of the patients who received HAIC at least once. (4) Did the authors enroll the patients with renal insufficiency, cardiovascular or pulmonary diseases, etc? (5) The authors should define PVTT response clearly.