Author's response to reviews

Title: Application of tumor-node-metastasis staging 2002 version in locally advanced hepatocellular carcinoma: is it predictive of surgical outcome?

Authors:

Binkui Li (libinkui@mail.sysu.edu.cn)
Yunfei Yuan (yuanyf@mail.sysu.edu.cn)
Guihua Chen (chenquihua2@126.com)
Liru He (helirujasmine@163.com)
Yaqi Zhang (zhangyaqi_1950@163.com)
Jinqing Li (lijing@mail.sysu.edu.cn)
Guohui Li (liguohui2@126.com)
Wan Yee Lau (josephlau@cuhk.edu.hk)

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Author's response to reviews: see over
Prof. Melissa Norton,                                           July 9, 2010  
Editor-in-Chief,  
BMC Cancer Office,  
Floor 6, 236 Gray's Inn Road,  
London, United, WC1X 8HL,  
Kingdom  
TEL: +44 (0) 20 3192 2013;  
FAX: +44 (0)20 3192 2010

RE: Ms No.: 8862523003647808

Title: Application of tumor-node-metastasis staging 2002 version in locally advanced hepatocellular carcinoma: is it predictive of surgical outcome?

Dear Prof. Melissa Norton,

Thank you for reviewing the above-referenced manuscript submitted earlier to your office. We would like to take this chance to express our appreciation to you and colleagues.

In accord with the Reviewers’ comments and suggestions, the manuscript has been revised accordingly. All the changes have been highlighted with red ink. We feel that the revised manuscript has been strengthened by both the Reviewer’s comments and suggestions and we are very appreciated of their time and effort. A point-by-point response to the Reviewers’ comments and suggestions has been prepared and follows this cover letter.

If there are any questions or problems for our re-submission, please feel free to contact me.

Sincerely yours,

Yunfei Yuan,  
Professor of Surgical Oncology,  
State Key Laboratory of Oncology in South China,  
Department of Hepatobiliary Oncology,  
Sun Yat-sen University Cancer Center,  
651 Dongfeng Road East,  
Guangzhou 510060,  
PR China,  
Tel/Fax: (86 20)8734 3118,  
E-mail: yuanyf@mail.sysu.edu.cn
Response to comments of the Reviewers

Reviewer #1: Professor Oliver Stoeltzing

Response to Major Comments:

1. The Reviewer is right that, the four groups of locally advanced HCC investigated should be clarified in the Abstract. The four groups include HCC with “Multiple tumors more than 5 cm”, “Major vascular invasion”, “Invasion of adjacent organs” and “Perforation of visceral peritoneum”. We have described these in the revised abstract of the manuscript (See the 9th to 12th line of page 2 in the revised manuscript).

2. It is true that resection margin is a critical issue that often is being discussed. Actually, we have also attempted to investigate the prognostic value of resection margin in our present study. All patients enrolled had received R0 resection, and all the tumors had been completely resected with an obvious margin (margin > 0mm) or at least along with the edge of the tumors (margin = 0mm) (See the 18th to 20th line of page 5 in the revised manuscript). Totally, about 110 (36.9%) of the 298 HCC patients with resection margin > 0mm (See Table 1). However, resection margin was not found to be a significant prognostic factor in locally advanced HCC (See Table 2). The possible reason might be that resection margin does not play an important role in the tumor recurrence in such advanced HCC patients.

3. In Table 1, “resection margin > 0mm” means the tumor was macroscopically completely resected, and with an obvious margin. We have described this definition in the revised manuscript (See the 18th to 20th line of page 5 in the revised manuscript) and revised Table 1 (See the last 1st to 2nd line of footnotes in the revised Table 1).
4. We agree that the description "Multiple tumors, any >5 cm" was not clear enough. We have changed the description into "Multiple tumors more than 5 cm" according to the AJCC/UICC definition (See the revised manuscript). Thanks for the Reviewer’s good suggestion.

5. It is true that the use of "G" for groups (1-4) is mis-understandable since Tumor Grading is also usually defined by "G". We have changed "G" into "Gp" for the abbreviation of group to avoid misunderstanding (See the revised manuscript). Many thanks for the correction!

6. We agree that MELD scores should be investigated and reported to define the "illness" of patients. We have provided these data in the “Results” section of the revised manuscript (See the revised Table 1 and Table 2). We think the MELD score is a good supplementary approach used to assess liver functional reserve and to determine the severity of cirrhotic patients, in addition to Child–Pugh grading and indocyanine green retention rate at 15 minutes (ICGR15) which were also available in the manuscript.
Reviewer #2: Professor Matthias M Dollinger

Response to Major Comments:

1. Many thanks for the Reviewer’s comments and good suggestions. The Reviewer is right that median overall survival of all groups should be provided. Actually, the median survivals of Group 1(Gp1), Gp2, Gp3 and Gp4 were 5.8, 21.7, 17.3 and 19.5 months, respectively. These data have been presented in the “Results” section (See the 1st to 3rd line of page 10 in the revised manuscript). In addition, the median survivals of Gp5, Gp6 and Gp7 were 7.6, 5.7 and 4.3 months, respectively. We have added these data in the revised manuscript (See the 14th to 16th line of page 10 in the revised manuscript).

2. We agree that the baseline characteristics of the patients should also be provided. The demographic and clinicopathological characteristics of the 298 patients with locally advanced HCC in this study have already been listed in Table 1 (See the revised Table 1), from which, we think, the baseline characteristics of the patients can be reached.

3. The Reviewer is right that a fundamental problem was also implicated in the present study: whether surgical resection should be indicated for HCC patients with major vascular invasion who had a median survival of only 5.8 months? To date, the choice of the best treatment for these patients is still under debate. To answer this question, we totally agree that it is important to evaluate the role of surgical resection compared to the natural history of HCC and other therapeutic modalities in HCC patients with major vascular invasion. However, because the objective of this study was to compare the prognosis of four categories of locally advanced HCC patients treated with hepatic resection and as a retrospective review, we did not include patients treated with other therapies (such as TACE or sorafenib or supportive treatment) but not surgery. So we could not do the direct
comparison of surgery and other therapies in the present study. Some information from a literature review may be helpful for this problem. The reported natural history of the median survival is about 10 weeks (Am J Clin Oncol 1998;21(4): 386–391; Hepatology 1999;29(1):62–67). In a recent study, Ruzzenente A et al. reported that survival for patients with macroscopic vascular involvement submitted to hepatic resection or local ablative treatment was significantly longer than supportive treatment, but no significant difference was observed between resection and local ablative treatment (J Gastrointest Surg 2009;13(7):1313-20). The authors concluded that, even if the prognosis of patients with macroscopic vascular involvement is very poor, the presence of macroscopic vascular invasion should not considered an absolute contraindication to surgery because hepatic resection in selected cases can improve survival compared to supportive treatment. To the best of our knowledge, there are no head-to-head studies that compared hepatic resection with sorafenib in these patients at present. Thus, further prospective randomized control trials are required to clarify these issues.

4. We agree that impact of the combination of TACE and surgery should be analyzed. Actually, in our univariate survival analysis, we analyzed 24 clinicopathological factors that might influence patient survival, including the combination of TACE and surgery. The results showed that neither preoperative TACE nor postoperative TACE showed an impact on patient survival (See Table 2). However, as a retrospective study, many factors can cause bias in the selection for TACE, e.g., patients’ choice of treatment, liver function stages, and tumor location. Thus, we think randomized control study is needed to clarify whether combination of TACE can bring survival benefits to locally advanced HCC patients treated with hepatic resection.

Response to Minor Comments:
1. We have consulted a statistician (Professor Qing Liu, Dept. of GCP, Sun Yat-sen University Cancer Center) about the question—“24 variables are probably statistically too many for 298 patients with random effects being possible”. The reply is that the possible random effects are not caused by the number of variables but by the sample size. When the sample size is large enough, there is no obvious limit that how many variables can be analyzed in survival analysis. He thought the case number in this study is enough and agreed with the statistical analysis. We have appreciated his contribution in the “Acknowledgement” of the revised manuscript. Many thanks for the reviewer’s suggestion!