The point-by-point reply to the criticisms of the reviewers Manuscript ID WJG-10157
May 2, 2014

Dear, Sir:

We appreciate your valuable reviews entitled "**Optimal Duration of the Early and Late Recurrence of Hepatocellular carcinoma**" According to your considerable comments and suggestion, we thoroughly revised our manuscript.

We sincerely hope that our manuscript meets with your approval and thank you for taking the trouble to review it again.

Sincerely yours,

Yusuke Yamamoto, MD

Reviewer: 1

Comments to the Author

The paper "Optimal Duration of the Early and Late Recurrence of Hepatocellular carcinoma After Hepatectomy Based on the Difference in the Prognosis" shows that 17 months is the optimal cut-off value for differentiating early and late recurrence after hepatectomy for hepatocellular carcinoma based on the overall survival after initial recurrence. The approach to the problem that is the object of the study is quite original and the paper is well written; however, some questions should be answered:

Comments

1. Thirty two patients were resected after HCC recurrence; were there patients with early recurrence in this group? If the answer is yes, the hypothesis of the early recurrent tumor as metastasis of the first tumor could be reinforced if the initial and recurrent tumors show the same histological grading; the Authors should provide and comment this information.

Author's reply

According to the reviewer's suggestion, we examined the histological diagnosis of recurrent HCC. Nine patients underwent repeat hepatectomy for the recurrence of HCC within 17 months, and pathological data of recurrent HCC of 5 patients were available. All of them were same differentiation with primary tumor. Twenty-three patients underwent repeat hepatectomy for the recurrence of HCC after more than 17 months, and pathological data of recurrent HCC of 12 patients were available. Nine of them were same differentiation with primary tumor. On the other hand, 2 of them were well differentiated HCC, despite primary tumors were moderately differentiated HCC. We added the relevant sentences in the 'Result' section (page 9 line 26).

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differentiation with primary tumor.

We added the relevant sentences in the 'Result' section (page 10 line 10).

Twenty-three patients underwent repeat hepatectomy for the recurrence of HCC after more than 17 months, and pathological data of recurrent HCC of 12 patients were available. Nine of them were same differentiation with primary tumor. On the other hand, 2 of them were well differentiated HCC, despite primary tumors were moderately differentiated HCC.

2. Poor differentiation grading at histological examination, microvascular invasion, satellitosis and anatomical/non anatomical resection have all been identified as strong risk factors for early HCC recurrence in previous studies; why the Authors did not include these parameters in their analysis of risk factors for recurrence? It is not clear to me if the parameter portal invasion, identified as a significant risk factor for early recurrence, refers to macrovascular invasion or to microvascular invasion detected on the surgical specimen.

Author's reply

As reviewer's suggestion, poorly differentiated adenocarcinoma is a worse prognostic factor in univariate analysis. However, in the multivariate analysis, it is not an independent prognostic factor. We added the data in Table 1. "Portal vein invasion" means the "microvascular invasion" in this study. As reviewer's suggestion, we rewrote the "portal vein invasion" to "microvascular invasion". In this study, satellitois was included in the parameter of the multiple tumors.

	No	5-year OS after initial recurrence (%)	MST (months)	Univariate Analysis *P*	Multivariate Analysis	
					Hazard ratio (95% CI)	*P*
Type of resection				0.561		
Non-anatomical resection	52	17.5	33.4			
Anatomical resection	200	28.7	28.5			
Histological differentiation				0.001		
Others	225	28.7	35.7			
Poorly differentiated	27	10.6	11.1			
Microvascular invasion				0.012		
Absent	185	27.0	35.7			
Present	67	26.8	14.4			

3. Cirrhosis was detected as the only independent factor linked to late recurrence; it could be interesting to evaluate if the occurrence of late recurrence was significantly different according to the different etiologies of cirrhosis.

Author's reply

It is true that evaluating of the late recurrence according to the different etiologies of cirrhosis is very important, as reviewer suggested. However, hepatitis C virus antibody was routinely examined after 1990, so it is so sorry but we cannot examine the correct data about the occurrence of the late recurrence according to the different etiologies of cirrhosis.

4. There are some studies showing that interferon treatment after curative resection or ablation of HCC in HCV-related cirrhotics prevents HCC recurrence and improves survival (Singal AK, Aliment Pharmacol Ther 2010). In the Discussion session, when dealing about the secondary prevention of HCC recurrence after resection of the first tumor, the Author should cite and discuss these studies .

Author's reply

According to the reviewer's comment, we added the following sentence in the 'Discussion' section (page 13 line 6)

On the other hand, Singal et al. [32] reported that interferon treatment after curative resection or ablation of HCC in HCV-related cirrhotics prevents HCC recurrence and improves survival. To prevent late recurrence, the suppression of multicentric occurrence using polyprenoic acid or interferon treatment will be indicated in patients with cirrhotic livers.

According to the reviewer's suggestion, we added the following reference.

32. Singal AK, Freeman DH Jr, Anand BS. Meta-analysis: interferon improves outcomes following ablation or resection of hepatocellular carcinoma. Aliment Pharmacol Ther 2010; 32:851-858.

5. Child-Pugh C patients are not candidates to liver resection; however, in this series there are 2 Child Pugh C patients; the Authors should explain why these patients were resected.

Author's reply

According to the reviewer's comment, we checked again the all preoperative laboratory data. It is so sorry but we found the mistakes of those data of patients classified as Child Pugh C, and they are correctly classified as Child Pugh B. We rewrote the following sentences in the 'Patients and methods' section (page 6 line 7)

393 patients (97.2%) were grouped in class A and 11 (2.8%) in class B.