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Reviewer A

The authors described that heat-shock protein 70, glutamine synthetase and glypican-3 serves as an independent prognostic factor for sarcomatoid hepatocellular carcinoma.

Criticism

1. The authors should comment the reason to select c-Met, heat-shock protein 70, glutamine synthetase and glypican-3 for staining by IHC.

Reply: Since biomarkers for SHC is lacked, a serious of tumor markers were accessed in SHC. Heat-shock protein 70, glutamine synthetase and glypican-3 are applied for diagnosis in hepatocarcinoma in our clinic. CK7 and CK19 are applied for diagnosis in intrahepatic cholangiocarcinoma. We measured all these markers in SHC.
Therapy strategy of SHC is the same as hepatocarcinoma. MET is associated with resistance to sorafenib, which is the first-line treatment strategy in HCC. More importantly, high-level of MET indicated the significant antitumor activities of the second-line medicine cabozantinib. The activation of MET in SHC may be a promising efficacy-predicting biomarker.
We highlighted the reason of the selection of c-Met in line 221-223 and line 329-332.

2. The status of IHC staining of c-Met, HSP70, GPC3, and GS should be described in Table, according to All cases, training group and variation group. Moreover, the status of two positive markers out of HSP70, GP3, GS) should be shown in Tables.

Reply: These data has been added in the table 1 (line 499).

3. In result of histological and pathological findings, references were described. This meaning of references could not be understood.

Reply: We have revised the context and these references were moved to the discussion part for detailed description (line 294-298).

4. In abstract, abbreviation of HSP70, GP3, GS should be fully spelled in first describe.

Reply: We have made revision.

Reviewer B

The contents of this manuscript were interesting. However, the following comments should be clarified before being considered for publication.

The abbreviations (IHC, HSP70, GPC3, GS, HepPar1, AFP, CK7, CK19) should be spelled in full in their first appearances in the text unless the abbreviation is world-wide accepted.

Reply: We have made corresponding revision in the manuscript.

Methods

1. Regardless of the cause of death was defined as an item in the calculation of overall survival (OS) and recurrence-free survival (RFS). Since the number of the included patients was not very large, death caused by reason not related to sarcomatoid hepatocellular carcinoma (SHC) can be a significant confounding factor for the results. The authors should exclude patients died from causes not related to SHC.

Reply: We further checked all causes of death. Patients living for less than 5 years were all died of SHC or associated complications. The others were died of chronic organ failure but none of patients were died of unexcepted reasons such as car accident.

Results

1. The sex ratio (male: female) described in Clinical characteristics was 2.3:1.0 (44: 19) which was completely reversed the data shown in Table 1. Which description was correct?

Reply: We made a mistake in the table 1 and have corrected it (line 499).

2. The total number of patients in Table 1 item “Maximal Tumor Size” was not correct (61 rather than 64).

Reply: We feel sorry that maximal tumor size ≥10cm should be 6 but not 4. We have corrected the mistake.

3. The authors should explain why the total number of CK7 staining was only 59 patients (positive in 61.7%, 34/59) rather than 63 patients.

Reply: The pathological sections of some patients were lost and we have completely all results (line219-221).

4. Table 1 showed that all patients were classified as <= AJCC IIIA. However, Table

2-4 had item of extrahepatic metastasis which is belonged to AJCC IVA or IVB.

Reply: The classification should be Ia/Ib/II/III-IV. We have made a revision in table 1.

Discussion

1. There was no data described in section of results to support the description "In this study, high c-Met expression levels were associated with larger tumour size (P = 0.050) (line 321-322). Moreover, patients with high levels of c-Met showed significant difference only at univariate analysis of RFS rather than OS in all patients. There was also no significant difference at multivariate analysis of either OS or RFS in all patients, and either OS or RFS in training cohort. Therefore, the sentence "Patients with high levels of c-Met also had poorer RFS compared to patients with low c-Met levels (P < 0.050)" (line 323-324) need to be revised. This manuscript had no confident data to support c-Met expression as a potential promising treatment target for patients with SHC as described in abstract and conclusion of the text.

Reply: The association between c-Met and tumor size has been added in the results (line 224). The sentence "Patients with high levels of c-Met also had poorer RFS compared to patients with low c-Met levels (P < 0.050)" has been amended as "High levels of c-Met indicated poorer RFS in univariate analysis (P < .05)." for accurate description. In the conclusion and abstract, context about c-Met has been deleted (line 335).

2. The sentence "The prognosis for patients with SHC differs from conventional SHC(13)." need to be corrected (line 333).

Reply: The mistake has been corrected (line 342).

Reference

1. Reference 33 was not suitable to be cited in the following sentence "The previous study reported that selective c-Met inhibitors have antitumour activity in HCC and a favourable safety profile (32, 33)."

Reply: Reference 33 was deleted.

Supplementary Table1

item Ki-67 rather than KI67

Reply: The mistake has been corrected.