

We thank you for your interest in this research and for your reviews of our manuscript "Concurrent hepatocellular carcinoma metastasis to stomach, colon, and brain: a case report." We have provided point-by-point responses to your comments below.

Major points: 1. This case had a short survival comparing reported cases (Jiang XB et al. BMC cancer 2012). The reason may depend on the aggressive phenotype of HCC, with cancer stems cell marker. Other markers (e.g. CK7, CK19, or vimentin) should be checked in both primary and metastatic HCC.

**Response:** Immunohistochemical tests were additionally conducted for hepatocyte paraffin 1 (HepPar1), glypican-3 (GPC3), p53, Ki-67, and vimentin for the primary tumor and metastatic lesions. These are described in Figures 4 and 5 and Table 1.

2. Clinical course should be clearly showed. The latest HCC was intrahepatic metastasis or metachronous HCC? Was primary HCC controlled clinically by the hepatectomy? Why metastatic HCCs were disseminated from the primary HCC that was surgically resected three years before an admission?

**Response:** He had multiple intrahepatic recurrences 5 month after the pulmonary operation. He received a transarterial chemoembolization (TACE). One month after the TACE, the metastatic lesions increased noticeably on CT. In addition, he had a history of past illness. We have included this information into the revised manuscript Case Presentation section.

3. Please discuss other treatment options. The author has mentioned "the optimal treatment was sorafenib". The aggressive surgery does not seem expand the patient's survival. The recent progress of the multi-kinase inhibitors should be discussed.

**Response:** Recently, a study was published that lenvatinib is not inferior to sorafenib as a treatment for unresectable HCC<sup>1</sup> and was approved by the Ministry of Food and Drug Safety in Korea. Post-sorafenib treatment, such as regorafenib, pembrolizumab, etc.<sup>2</sup>, was eligible for classification under the national insurance benefit of Korea. However, these drugs, as post-lenvatinib treatment, are not suitable today. We could not use lenvatinib for the 1st-line therapy for the patients with unresectable or metastatic HCC.

The cause of the patient's death was due to the rapid deterioration of liver function. We anticipated being able to gain more survival time through the use of sorafenib after surgery. In

addition, surgical treatment is more effective in improving patients' symptoms than other treatments. There is no study as yet that compares the differences between surgical treatment and other treatments. This statement has been explained in the revised Discussion section.

Minor points: 1. Laboratory data should be noted, including coagulation and liver function tests.

**Response:** Thank you for your suggestion. These results were added to the revised manuscript [page 5, lines 5–9].

2. Was autopsy or autopsy-imaging conducted for assessment?

**Response:** Autopsy or autopsy imaging was not conducted, but the patient had an abdominal CT scan 10 days after brain surgery. The CT scan showed slightly increasing intrahepatic tumors and a large number of ascites.

3. Did the patient himself provide a written informed consent for the publication?

**Response:** He did not agree to publication of his cause of death. We received approval from the Institutional Review Board (IRB) in our institution (IRB No. D-2005-003-002)

## References

- (1) Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, Blanc JF. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *The Lancet* 2018; 391: 1163-1173 [PMID: 29433850 DOI: 10.1016/S0140-6736(18)30207-1]
- (2) NCCN clinical practice guidelines in oncology (NCCN guidelines). Hepatobiliary cancers. Version 2. 2020. NCCN.org. [http://www.nccn.org/professionals/physician\\_gls/pdf/hepatobiliary.pdf](http://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf) (Available: May 8, 2020).