Dear editors and reviewers

First of all, thank you very much for spending your time reviewing this case report. I profoundly appreciate your comments and tried to absorb your valuable opinions to make this case report more precise and professional.

The sentences and words that I rewrote or added are all marked with red. The explanations are as follows:

Page 5: "Surgical resection and liver transplantation are the first-line curative treatments for large HCC, while small HCC (preferably < 2cm in diameter) in an accessible location, away from critical structures, can be cured by local ablative techniques."

➔ This sentence was adapted due to the comment of reviewer #2.

Page 5: "Based on the physical property of Bragg peak, proton beams deposit the dose maximum at a predefined depth in the tumor. Behind the maximal deposit, the dose drops rapidly, having no exit dose."

➔ Our physicist advised me to use the term „dose" rather than „energy".

Page 5: "The additional esophagogastroduodenoscopy and colonoscopy demonstrated chronic gastritis with helicobacter pylori infection and sigmoid diverticulosis, but no evidence of other gastrointestinal malignancy."

➔ Answer to reviewer #1: The patient received both upper and lower gastrointestinal endoscopy at the time of tumor diagnosis in January 2014 and immediately got an eradication of helicobacter pylori infection. In the colonoscopy there was no evidence of colorectal polyps. Although he had complained of diarrhea since the treatment with Sorafenib, his oncologist attributed it to the typical side effect of Sorafenib and did not recommend a renewed colonoscopy.

Page 7: "From this time forward, the patient also commenced with targeted therapy, i. e. tyrosine kinase inhibitor (sorafenib) and continued in his normal occupational activities (working as a driver)."

➔ The opinion of reviewer #2 was accepted.

Page 7: "The thoracic CT scan at 19 mo after the PBT also did not reveal any suspicious metastasis."

➔ The last CT scan of thorax was done in October 2015 (19 months after PBT) and did not show any metastasis. According to the German guidelines program for hepatocellular carcinoma, the follow-up should be taken every 3-6 months for 2 years using multi-phase sectional imaging (preferably MRI). After completing the follow-up, patients should be included in the screening program again with sonography of liver and control of AFP every 6 months (that is what his oncologist has prescribed). Extrahepatic diagnostics in the follow-up should be symptom-oriented. Because AFP was significantly increased at the time of tumor diagnosis and has fallen to normal range since 20th month after the proton beam therapy to date, both his oncologist in Dresden and I do not see the necessity to refer him to additional examinations, such as thoracic CT scan and upper and lower gastrointestinal endoscopy again. But if you are insisting on it, I can arrange a thoracic CT scan in this August, as the patient is planning to visit our center concerning the annual MRI liver.

Page 8: "Choi *et al*[12] reviewed the different radiotherapy techniques and summarized the results of radiotherapy, partially combined with liver transplantation, TACE and concomitant chemotherapy, for HCC in each tumor stage. Radiotherapy can amend the total therapeutic assortments and outcomes of HCC by improving local control, enabling downstaging and treating unresectable HCC with vascular invasion or multiple intrahepatic metastases. The latest National Comprehensive Cancer Network (NCCN) guidelines[22] consider external-beam radiation therapy as a category 2B option for patients with unresectable HCC or those with contraindication for operation due to comorbidity. Besides, stereotactic

body radiation therapy can be recommended as alternative to ablation and embolization techniques, particularly after their failure or in case of their contraindication. Because prospective randomized controlled trials evaluating the outcome of various techniques of external-beam radiation therapy versus ablation and arterially directed therapies are still pending or ongoing, clear guidelines of treatment recommendations for large unresectable HCC, specifically with vascular invasion and intrahepatic metastasis, are still missing."

➔ The advice of reviwer #2 was taken into account. I added the conclusion of Choi et al. and the newest NCCN guidelines for HCC to point out the problem of finding the most appropriate therapeutic method for large unresectable HCC.

Page 10: "To assess whether the patient can withstand apneic oxygenation, besides general preanesthesia evaluation, additional tests, such as arterial blood gas test, body plethysmography and echocardiography, can be required in case of relevant cardiopulmonary comorbidity."

➔ According to the recommendation of reviewer #1, I added a statement about the special tests concerning the suitability for apenic oxygenation. In routine, there is no request for any special tests. Following the guidelines for preanesthesia evaluation, our department of anesthesiology only needs common examinations like recent electrocardiography, laboratory test and spirometry test. In certain circumstances, body plethysmography, echocardiography and arterial blood gas test can be required.

Page 10: "Although the patient presented in our case report had several adverse prognostic factors, his case demonstrates that large unresectable HCC with vascular invasion and intrahepatic metastases can be treated excellently with PBT."

➔ Somehow I cannot find the spelling error which the reviewer #2 meant.

Page 15: "22. **Benson AB III**, D'Angelica MI, Abbott DE, Abrams TA, Alberts SR, Saenz DA, Are C, Brown DB, Chang DT, Covey AM, Hawkins W, Iyer R, Jacob R, Karachristos A, Kelley RK, Kim R, Palta M, Park JO, Sahai V, Schefter T, Schmidt C,

Sicklick JK, Singh G, Sohal D, Stein S, Tian GG, Vauthey JN, Venook AP, Zhu AX, Hoffmann KG, Darlow S. NCCN Guidelines Insights: Hepatobiliary Cancers, Version 1.2017. J Natl Compr Canc Netw 2017 May; **15:** 563–573. [PMID: 28476736 PMCID: PMC5557008 DOI: 10.6004/jnccn.2017.0059]"

➔ The reference of NCCN guidelines was added.

Page 17-19: "D - G: The HCC involved all three hepatic veins as well as the portal vein. The inferior vena cava was also compressed."

➔ On the advice of reviewer #2, I provided 4 additional images to show more clearly that all three main hepatic vein and portal vein were invaded by the HCC.

Sincerely,

Yi-Lan Lin