

## **Point-by-point responses**

Manuscript NO. 72377: Rare case of hepatocellular carcinoma metastasis to urinary bladder: A case report and review of the literature

### REVIEWER'S COMMENTS

Reviewer #1:

1. Language revision

Answer 1: Thank you for your delicate comments. We improved the unnatural expressions and sentence structure through additional language correction.

Reviewer #2:

1. The authors need to show the chemotherapy drug of TACE and the time of therapy interval.

Answer 1: Thank you for your detailed comments. In our hospital, TACE is performed by infusion of Adriamycin (50 mg) and lipiodol (10 cc) mixture and then embolization through gelfoam. The patient underwent the second TACE approximately 5 months (140 days) after the first TACE performed immediately after HCC was diagnosed. The additional TACE after bladder metastasis was confirmed was about 5 months (163 days) after the second TACE. We added in the case summary part of Abstract and history of present illness part of Case presentation as follows:

Case summary

Afterwards, she underwent two transcatheter arterial chemoembolization (TACE)s within five months for HCC.

#### History of present illness

For multiple intrahepatic masses, we performed TACE immediately after diagnosis and at 5 months after the 1<sup>st</sup> TACE on the main mass. TACE was performed by infusion of Adriamycin (50 mg) and lipiodol (10 cc) mixture, followed by embolization with gelfoam.

2. The authors don't tell us the evidence of treatment options. Why choose TACE alone for the patient?

Answer 2: Thank you for your valuable comments. The patient had multinodular HCC and the main mass was greater than 5 cm, and there was no evidence of portal vein invasion, lymph node metastasis and distant metastasis. Her Child-Pugh score was A and her Eastern Cooperative Oncology Group (ECOG) performance status was 0. Accordingly, the stage was T3N0M0 in TNM staging of American Joint Committee on Cancer (AJCC) 8th edition, and stage III when referring to modified Union for International Cancer Control (UICC) staging, and Barcelona Clinic Liver Center (BCLC) staging was conceived as stage B.

According to the EASL clinical practice guideline of HCC 2018, TACE can be tried first for intermediate HCC, so TACE was first tried on the patient, and systemic chemotherapy was additionally considered based on a recent journal (Kudo M. et al. Gut. 2020 Aug;69(8):1492-1501). However, the patient's condition deteriorated due to hepatitis and post-embolization syndrome occurring immediately after two TACEs. On the other hand, the response of TACE to the mass was good, so chemotherapy was delayed. We modified history of present

illness part of the Case presentation and Treatment part, Outcome and follow-up part as follows:

#### History of present illness

As a result, HCC was diagnosed without evidence of portal vein invasion, lymph node metastasis, or distant metastasis (Figure 2).

#### Treatment

Because her Eastern Cooperative Oncology Group (ECOG) performance status was 0-1 and her Child-Pugh score was A, local treatment through TACE was first attempted on the main mass. Systemic chemotherapy was then planned.

#### Outcome and follow-up

After TUR-BT, TACE, to which the mass had previously responded well, was performed again. Lenvatinib was then added as a systemic chemotherapy.

3. The part of treatment is very simple, such as, it is should be list the change of AFP in the course of treatment.

Answer 3: Thank you for your careful comments. The patient's alpha-fetoprotein (AFP) was 3.9 ng/mL at the time of initial diagnosis and remained as low as 3.5 ng/mL after treatment. Protein induced by vitamin K absence or antagonist-II (PIVKA-II) was also 24.0 mAU/mL at the time of diagnosis and remained low at 23.4 mAU/mL after treatment. We added in the Treatment part as follows:

#### Treatment

TACE was performed twice. Her AFP level was 3.5 ng/mL and her PIVKA-II level was 23.4 mAU/mL, which did not rise during the treatment period.