Format for ANSWERING REVIEWERS

April 5th, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: AMEpc3117_final with highlights.doc).

Title: Downstaging and Resection after Neoadjuvant Therapy for Fibrolamellar Hepatocellular Carcinoma

Author: Gilton Marques Fonseca, Antonio Drauzio Varella, Fabricio Ferreira Coelho, Emerson Shigueaki Abe, Rodrigo Blanco Dumarco, Paulo Herman.

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The manuscript has been improved according to the suggestions of reviewers:

Major comments:

A. Introduction:
None

B. Case Report

1.) Alpha-Feto Protein in this patient is reported to be highly elevated (44.395 ng/ml) which is uncommon for FLHCC. This fact should at least be discussed.
A: Probably this patient belongs a peculiar group of 7-11% that has high levels of alpha-fetoprotein. We discussed this aspect.

2.) Which stainings were used to confirm histopathological diagnosis of FLHCC? (please also provide a reference for the staining used). Where were the specimens evaluated? (reference center?)
A: The patient was initially evaluated in another hospital and referred for our service with the histopathological summary. Our specialized pathologist reviewed the biopsy and, using hematoxylin and eosin (H&E) stains, diagnosed FLHCC through classical histology (tumor comprised of large polygonal cells with nuclear atipia, arranged in lamellar bands of collagen fibers).

3.) The authors report that "33 cycles" of GemOx were applied over a period of 11 months. No dosage or chemotherapy scheme is provided. In Hepatocellular carcinoma (HCC) two slightly different dosages of GemOx have been evaluated, however for both regimens the cycles were repeated after 2 weeks, which is not consistent with 33 cycles in 11 months. The authors should specify dosage and schedule of the regimen used here.
A: The patient received Oxaliplatin 100mg plus Gemcitabine 1.400mg every 2 weeks during 11 months. We changed this information in Case Report text.

4.) How was the patient classified as non-resectable? Why was liver transplantation not an option?
A: The patient was considered as unresectable because extensive vascular involvement, especially hepatic veins, as described: "A computed tomography scan (CT) (Figure 1) showed a suggestive FLHCC mass with 17x15cm affecting the right lobe of liver and segment 4b with obstruction of the right portal branch, invasion of the right and middle hepatic vein, circumferential wrapping of the left hepatic vein and compression of the inferior vena cava."
Transplant was not considered due to the presence of hilar lymph nodes (extra hepatic disease). We explained these informations.

5.) What were the staging intervals? How was staging done (MRI or CT?)? How was follow up done? How was absence of recurrence of disease 10 months after surgery evaluated?
A: The staging intervals were every 4 months with CT scan or MRI. Follow up was done with CT scan every 4 months. Absence of recurrence of disease was evaluated by CT scan, without any sign of disease. Indeed, two weeks ago, 14 months after the procedure, the patient performed a new CT scan without any sign of recurrence. Image was included on Figure 1.

6.) The authors state that "histological examination confirmed fibrolamellar hepatocellular with free margins". Please specify if margins were microscopically or marcoscopically tumor free i.e. R0 or R1.
A: Margins were microscopically free (R0 resection).

C. Discussion

1.) Although the discussion section provides interesting information, several statements here are unspecific and at least partly not accurate. The discussion section should therefore be thoroughly rewritten giving accurate and clear information. Examples are as follows:

1.1) The authors state that for unresectable FLHCC "all known options did not show effectiveness". This is a very broad and unspecific statement that the authors do not support by a reference. (For example in Kaseb et al. Prognostic Indicators and Treatment Outcome in 94 Cases of Fibrolamellar Hepatocellular Carcinoma, Oncology 2013 Kaplan-Meier Curves for advanced FLHCC receiving chemotherapy are provided). Further the authors claim that no data on responses to different chemotherapy regimens was given in Reference 1 (Ang et al. 2013). However Ang et al. give detailed information in the text on responses to several chemotherapy regimes. This statement should therefore be corrected and information from other sources (e.g. Kaseb et al.) should be included.
A: We performed suggested changes.

1.2) It is unclear what "and evaluation of new drugs or combination treatments in clinical trials were tested" means.
A: Drugs or combination treatments, from ref. 12:
- Doxorrubicin alone and plus gemcitabine:
Lai CL, Wu PC, Chan GC, Lok AS, Lin HJ. Doxorubicin versus no antitumor therapy in inoperable hepatocellular carcinoma. A prospective randomized trial. Cancer 1988;62:479–483.
Lombardi G, Zustovich F, Farinati F, Cillo U, Vitale A, Zanus G, et al. Pegylated liposomal doxorubicin and gemcitabine in patients with advanced hepatocellular carcinoma: results of a phase 2 study. Cancer 2011;117:125–133.
- Combination of cisplatin, doxorubicin, 5-fluorouracil, and alpha-IFN:
Leung TW, Patt YZ, Lau WY, Ho SK, Yu SC, Chan AT, et al. Complete pathological remission is

possible with systemic combination chemotherapy for inoperable hepatocellular carcinoma. Clin Cancer Res 1999;5:1676–1681.
Yeo W, Mok TS, Zee B, Leung TW, Lai PB, Lau WY, et al. A randomized phase III study of doxorubicin versus cisplatin/interferon alpha-2b/doxorubicin/fluorouracil (PIAF) combination chemotherapy for unresectable hepatocellular carcinoma. J Natl Cancer Inst 2005;97:1532–1538.
- irinotecan
Boige V, Taieb J, Hebbar M, Malka D, Debaere T, Hannoun L, et al. Irinotecan as first-line chemotherapy in patients with advanced hepatocellular carcinoma: a multicenter phase II study with dose adjustment according to baseline serum bilirubin level. Eur J Cancer 2006;42:456–459.
- taxanes
Hebbar M, Ernst O, Cattan S, Dominguez S, Oprea C, Mathurin P, et al. Phase II trial of docetaxel therapy in patients with advanced hepatocellular carcinoma. Oncology 2006;70:154–158.
- gemcitabine
Guan Z, Wang Y, Maoleekoonpairoj S, Chen Z, Kim WS, Ratanatharathorn V, et al. Prospective randomised phase II study of gemcitabine at standard or fixed dose rate schedule in unresectable hepatocellular carcinoma. Br J Cancer 2003;89:1865–1869.
- topotecan
Alexandre J, Tigaud JM, Gross-Goupil M, Gornet JM, Romain D, Azoulay D, et al. Combination of topotecan and oxaliplatin in inoperable hepatocellular cancer patients. Am J Clin Oncol 2002;25:198–203.
- thymidilate synthase inhibitors
Stuart K, Tessitore J, Rudy J, Clendennin N, Johnston A. A Phase II trial of nolatrexed dihydrochloride in patients with advanced hepatocellular carcinoma. Cancer 1999;86:410–414.

1.3) The authors state that "The gemcitabine plus oxaliplatin regimen appeared to be the most promising, based on its lack of renal and hepatic toxicity in cirrhotic patients". It is unclear whether this refers to HCC treatment in general or treatment of this specific patient. It should be discussed why GemOx was used in this non-cirrhotic patient.
A: This phrase refers to HCC treatment. We opted to discuss the HCC treatment for HCC with GemOx, because there are not many studies showing its benefits for FLHCC. The reasons we have chosen GEMOX were good tolerance, and based on the report of Gras and colleagues (ref. 15) of good results in patients with FLHCC.

1.4) It is unclear why the authors report in detail about smaller studies with surgery after downstaging with GemOx in HCC, while the largest study cited here (Zaanan et al.) 204 pts of whom 10 received surgery after downstaging with GemOx is not mentioned.
A: We mentioned this multicenter study.

2.) Possible similarities between the reports of downstaging with GemOx in patients with HCC and the previous report in a patient FLHCC with this patient should be discussed.
A: We discussed possible similarities between the reports of downstaging with GemOx in patients with HCC and the previous report in a patient FLHCC with this patient.

Minor comments:

General: there are several grammatical and spelling mistakes, please correct thoroughly.
A: AmEditor performed a revision for correct grammatical and spelling mistakes. The certificate

follows with submission.

A. Introduction

1.) Possible conflicts of interest should be revealed
A: No conflict of interest. We explained this topic.

B. Case Report

1.) Ethnicity of the patient should be specified.
A: The patient is Caucasian. We specified this in text.

C. Discussion

None

Thank you again for publishing our manuscript in the *World Journal of Gastrointestinal Surgery*.

Sincerely yours,

Gilton Marques FONSECA, MD
Digestive Surgery Division, Department of Gastroenterology
University of São Paulo School of Medicine.
Avenida Doutor Enéas de Carvalho Aguiar, 255, Instituto Central, 9° andar, Sala 9074, CEP: 05403-900, Cerqueira Cesar – São Paulo, SP, Brazil.
Telephone: +55 11 26617560 Fax: +55 11 26617560
E-mail: medgilton@yahoo.com.br