

ANSWERING REVIEWERS



October 27 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 13751-review.doc).

Title: Postsurgical radiation therapy for gastric carcinosarcoma with c-kit expression: a case report

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Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 13751

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

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

(1) We changed the title and provided running title based on the comments by Reviewer **00722674** as above.

(2) We added 2 more key words based on the comments by Reviewer **00722674**.

(3) We clarified when recurrence happened after surgery in the abstract based on the comments by Reviewer **00722674**. We added "Nine months after" in the text.

(4) We clarified the cause of death based on the findings of Autopsy by the suggestions of Reviewer **00722674**. We added "the patient died of respiratory failure due to bronchopneumonia with multiple lung metastases" in the text.

(5) We explained TKI therapy in the text based on the comments by Reviewer **00722674**. We added "Tyrosine kinase inhibitor" in the text.

(6) We changed expression regarding *Imanitib* as "Tyrosine kinase inhibitors (imatinib), which can selectively inhibit the enzymatic activity of several tyrosine kinase receptors including c-kit, are now considered adjuvant therapy for GISTs after complete resection in high-risk patients" based on the comments by Reviewer **00722674**.

(7) We clarified drinking and smoking habits of the patients in the text based on the comments by Reviewer **00030598**.

(8) We clarified the normal range of serum hemoglobin level (13.6-16.7 g/dl) in our laboratory based on the comments by Reviewer **00722674**.

(9) We changed the word gastro-endoscopy to gastroscopy and clarified the dosage of Cisplatin as (60mg/m² BSA: body surface area) into the text based on the comments by Reviewer **00722674**.

(10) We changed the sentence from “with no satisfied results on CT” to “CT scan showed no reduction of tumor size” in the text based on the comments by Reviewer **00722674**.

(11) We clarified the reason why we preformed surgical resection after one course of neoadjuvant chemotherapy based on the comments by Reviewer **00722674** and **00502831**. We added “We decided to perform surgical resection of the tumor, because the symptoms of appetite loss and malnutrition caused by the primary tumor were potential risks for discontinuation of treatment thereafter.” in the text.

(12) We clarified the histological findings of resected lymph nodes in the text based on the comments by Reviewer **00068559** and **00502831**. We added “Resected lymph nodes also contained biphasic structures consisting of carcinoma and sarcoma. The carcinomatous component was more prominent than the sarcoma component, and a few sarcoma cells were immunopositive for c-kit” in the text.

(13) We clarified post-operative TNM staging in the text based on the comments of Reviewer **00030598**. We added the sentence “The cancer was postoperatively determined as stage IV according to the TNM classification (pT2, N2, M1, P0)” in the text.

(14) Based on the comments of Reviewer **00030598** and **00502831**, we added “The primary tumor included a transitional mixed part of two pure areas of carcinoma and sarcoma components” in the text. And we added figure 2E in which transitional zone was shown.

(15) We clarified the reason why we did not choose *Imanitib* therapy after the failure of 1st line therapy using S1/CDDP therapy in the text based on the comments by Reviewer **02445518**, **00722674** and **00030598**. We added the sentence “Although imatinib is widely accepted for the treatment of GIST, its effect would have been limited in this case as the carcinomatous component did not show c-kit expression. There has been no study reported so far regarding imatinib mesylate for the treatment of gastric carcinosarcoma.”

(16) The relation between c-kit expression and good response to radiation therapy still remains unclear. We changed conclusion to a conservative inclusion based on the comments by Reviewer **00030598** and **02903404**. We added the text “Although evidence of a survival benefit from combined adjuvant chemotherapy has not been demonstrated, our case indicates a prolonged survival (22 months) with radiotherapy after tumor resection. Therefore, to improve survival and prognosis of gastric carcinosarcoma, intensive surgery and additional radiation therapy to metastatic foci should be considered, especially in cases of tumors with c-kit expression”

(17) We added COMMENTS in the text.

(18) We reduced references based on the comments by Reviewer **00722674**.

(19) We added arrows in the figures of CT scan to clarify the change of sizes of lymph nodes before and after radiation therapy based on the comments by Reviewer **00722674**.

(20) Based on the comments by Reviewer **00502831**, we performed immunohistochemistry of the tumor for E-Cadherin. Cell membrane of all carcinoma cells was positive for E-Cadherin immunostain. We added the result in Table1.

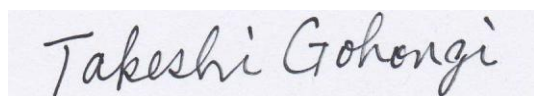
(21) Based on the comments by Reviewer **00502831** and **00030598**, we checked Her-2 expression in the tumor. The tumor showed no Her-2 expression in both sites. At the time of this case Herceptin was not approved in Japan for the treatment of gastric tumor by the Ministry of Health, Labor and Welfare. So we did not consider Herceptin for post-operative therapy. We did not include the result in the text.

(22) Based on the comments by Reviewer **00502831**, we studied Ki-67 index in the tumor. Ratio of Ki-67 was 71% positive in the carcinomatous site and 47% positive in sarcoma site, respectively. We did not include the result in the text.

3 References and typesetting were corrected

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

Sincerely yours,

A handwritten signature in black ink on a light blue background. The signature reads "Takeshi Gohongi" in a cursive, slightly slanted script.

Takeshi Gohongi, MD, PhD

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