Author’s response to reviews

Title: Abscopal effect of radiation on multiple lung metastases of lung adenocarcinoma: a case report

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Author’s response to reviews:

Feb 7th, 2019

Dr. Maurizio Martini, MD, Ph.D.
Associate Editor
BMC Cancer

Dear Dr. Maurizio Martini:
Along with my coauthors, I would like to resubmit the attached manuscript, titled “Abscopal effect of radiation on multiple lung metastases of lung adenocarcinoma: a case report” as a “Case Report” for publication in BMC Cancer. The manuscript ID is: BCAN-D-18-03040.

We wish to thank the reviewers for their valuable and constructive advice regarding our manuscript. We believe that their insightful suggestions have enriched our manuscript and allowed us to produce a better and more balanced account of our research.

We have carefully rechecked our manuscript and made the necessary revisions (highlighted in red font in the revised file) in accordance with the reviewers’ suggestions. Please find enclosed our point-by-point responses to the comments and concerns raised. The manuscript has been edited and proofread by Editage (www.editage.jp).

We believe that the quality of our manuscript has been substantially improved and hope that the revised version is now suitable for publication in your esteemed journal.

Thank you for your continued consideration.

We look forward to hearing from you at your earliest convenience.

Sincerely,

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RESPONSES TO THE REVIEWERS’ COMMENTS

Reviewer #1

We wish to thank the reviewer for their thoughtful comments.

Comment 1: The clinical history of the case is not completely clear, especially regarding the use of anti-EGFR therapy. The patient presented lymph node mediastinal metastases after two years from surgery. Since the patient had an activating mutation of the EGFR in the excised tumor, it was presumable to think that the same molecular alteration was present in the metastases. Therefore, it seems strange that the patient has undergone radiation therapy rather than a treatment with specific inhibitors of EGFR. Why this therapeutic choose?

Response: Thank you for this inquiry. We have added the following sentence to the case presentation: “Radiation therapy alone was selected because the recurrence of the diseases was limited to the local region and the patient was 79 years old at the time of recurrence.” (page 7, lines 86–88).

Comment 2: In the text it is not clear if the radiotherapy was performed concurrently with the anti-EGFR therapy. It seems concurrently. In fact, the author mentioned the anti-EGFR therapy with the phrase "EGFR tyrosine kinase inhibitor (TKI) treatment was planned as a start" then the treatment was from the beginning so that they reported the absence of cytotoxic effect of EGFR-TKI. The abscopal effect of irradiation is described as the out-of-field response to localized irradiation therapy that results in systemic antitumorogenic effects such as the regression of a tumor distant from the target site. The effect is probably mediated by immune-response to the radiotherapy "alteration" of the tumor. In this case the dramatic complete disappearance of the tumor was probably due to the concomitant EGFR-TKI treatment and radiotherapy. The abscopal effect of irradiation does not make sense to exist in this case report. Only a clear explanation of the history of the clinical case could resolve doubts.

Response: Thank you for your valuable comments. In order to make it clear that the patient did not receive EGFR-TKI treatment, we have added the following sentence to the case presentation:
“The patient was therefore under watchful observation, without receiving EGFR-TKI treatment.” (page 8, lines 110–111).

Reviewer #2

We wish to thank the reviewer for their thoughtful comments.

Major points

The authors should consult with the radiation oncologist who treated this patient about the detail of radiotherapy. Needless to say, radiation field and dose is very important. However I can't imagine how this patient was treated. Was a total of 60 Gy delivered to the mediastinum and right hilum through two opposed lateral fields? The radiation fields as a figure should be added.

Response: Thank you for this inquiry. We have added the following sentences to the case presentation: “Radiation therapy amounting to a total dose of 60.0 Gy, distributed in 30 fractions, was performed over a period of 6 weeks. The 3D radiotherapy-planning technique was used. In the first 4 weeks, 40.0 Gy was distributed in 20 fractions using two opposed lateral fields (Fig. 1a, b). In the subsequent 2 weeks, an additional 20.0 Gy was distributed in 10 fractions using multiple beams (Fig. 1c, d) for covering multiple mediastinal lymph node metastases but sparing the spinal cord and hilum of the left lung. The planning target volume included multiple mediastinal and right hilar lymph nodes, with a 10 mm margin to account for microscopic disease, internal moving, and setup errors. The percentage volume of lung receiving a dose of more than 20 Gy (V20) was 29.3%. Treatment was delivered using a 10 MV X-ray and five fractions per week.” (page 7, line 88, to page 8, line 99). We have added figure 1, which shows the radiation field.

Minor points

Reviewer: Ln #5 There seems to be a typo in one of the author name "Yuki Tsutusmi".

Response: We apologize for the error. We have replaced “Tsutusmi” with “Tsutsumi”.

Reviewer: Ln #12 The staging system and its edition should be added. If UICC(8Th) is applied, cT1cN0M0 is appropriate.

Response: Thank you for this suggestion. We have added the following sentences to the case presentation: “The computed tomography (CT) scan of the chest revealed a 2.3 × 1.6 cm nodule, and the patient was diagnosed with pulmonary adenocarcinoma (cT1bN0M0, stage IA, according to the TNM classification of the Union for International Cancer Control (UICC), 7th edition; cT1cN0M0, stage 1A3, according to the UICC, 8th edition).” (page 6, line 75, to page 7, line 78).

Reviewer: Ln #89 The term "The planning volume" is wrong, it should be replaced by "The planning target volume"

Response: We apologized for the error. We have replaced “the planning volume” with “the planning target volume”.

Reviewer: Ln #99-#101 It is desirable to show PET/CT images.

Response: Thank you for this suggestion. We have added PET/CT images (Fig. 3a, b).

Reviewer: Ln #103 The pulmonary metastatic state at 6 months should be described. The authors should add the images of complete disappearance of pulmonary mets.

Response: Thank you for this suggestion. We have added CT images of the state at 6 months (Fig. 4).

Reviewer: Fig. #2 60.0Gy/30 fraction → 60.0 Gy/30 fractions

Response: Thank you for this suggestion. We have replaced “fraction” with “fractions” in the figure.