Author's response to reviews

Title: Toxic risk for stereotactic body radiotherapy with helical tomotherapy concurrent and following with erlotinib for non-small cell lung cancer patient - case report

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Author's response to reviews: see over
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Editor-in-Chief,

BMC Cancer

Dear Professor Norton:

On behalf of all authors, I appreciate the time and effort of the editor and reviewers in critiquing our work (MS: 3100979884018932). Attached is a point-by-point response to the Reviewers’ comments. We submit this manuscript for reconsideration for publication in BMC Cancer. Thank you for your great effort on our work.

Yours sincerely,

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Reviewer 1

Comment 1: This is a potentially important case report, illustrating a possible radiosensitization by erlotinib in a patient who received thoracic radiotherapy and died as a result of radiation pneumonitis. However, the authors do not provide the V20 and mean lung doses for both lungs, only for each lung separately, so it is difficult to judge if the radiation plan was appropriate (i.e. if the V20 for both lungs was too high). Besides, for the hypofractionated regimens, the V20 (both lungs) values are lower than for standard fractionated regimens. For example, the V20 in the RTOG 0236 study (20 Gy x 3 fractions to 60 Gy) was required to be <10%, and not the customary <35%, as when using a 2 Gy daily fraction size.

Response: Thank you for your comments. The details for V20 and mean lung doses were revised as follows: Page 5 line 10 - The whole-course V20 and mean lung dose for total lung were 10% and 10.24 Gy, respectively. Page 6 line 16 –The mean lung dose (≥ 21 Gy), V20 (> 31%) [10], and ipsilateral V20 Gy [5] correlates with radiation pneumonitis. Nonetheless, the Radiation Therapy Oncology Group 0236 protocol using SBRT via HT for NSCLC provided safe and effective treatment when the V20 was restricted to less than 10% to 15% [11]. The V15 and V20 and the mean lung dose for each separate lung in the divided courses are shown in the Table. Moreover, the whole-course V20 and mean lung dose for the total lungs were 10%
and 10.24 Gy, respectively. According to previous reports [5, 10, 11], this plan was safe and no symptomatic radiation pneumonitis occurred among the NSCLC patients.

**Comment 2:** Besides, the paper requires to be rewritten by the native English speaker to be fully understandable to the audience.

**Response:** The paper was revised by a native English speaker.

**Reviewer 2**

**Comment 1:** It is a good article for case report, but it needs a carefully rewording with grammar checking.

**Response:** Thank you for your recommendation. We will search help for English review and has been revised as new manuscript.

**Comment 2:** P3 ln 1 add Helical Tomo before HT because it the first time mentioned.

**Response:** Helical tomotherapy was inserted before HT at the first mention in the article. In page 3 line 2 – Stereotactic body radiation therapy (SBRT) using the helical tomotherapy (HT)…

**Comment 3:** P3 ln 4 does not be studied?? re-sentencing
Response: The sentence was revised: Page 3 line 3 – Using SBRT concurrently with erlotinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), for non-small cell lung cancer (NSCLC) is not previously reported.

Comment 4: P4 ln 4 what does it mean for “extreme”?
Response: The inappropriate word was deleted.

Comment 5: P5 lns 7-12 please reword
Response: The sentences were revised on Page 5 line 2 – Then, erlotinib was added concurrently to the radiotherapy regimen. This regimen comprised 54 Gy given in nine fractions delivered with SBRT using HT, at 95% of the prescribed isodose for the planned target volume. The split courses with 3 fractions per week were prescribed. (Fig 1A and 1B) Targeting was based on new, separate CT scans for each split course.

Comment 6: P5 ln 8 hypofractionated “scheme”; ln 10 Two separate CT scans were; ln 15 Two and half; ln 16 for volume it should be 3 dimensions; ln 18, delete later
Response: The sentences were revised accordingly on page 5 line 2 – Then, erlotinib was added concurrently to the radiotherapy regimen. This regimen comprised 54 Gy given in nine fractions delivered with SBRT using HT, at 95% of the prescribed
isodose for the planned target volume. The split courses with 3 fractions per week were prescribed. (Fig 1A and 1B) Targeting was based on new, separate CT scans for each split course.

Page 5 line 12 – By 2.5 months after the combination therapy, the tumor shrank from 4 x 3.9 x 4.5 cm to 2.4 x 2.9 x 2.1 cm and erlotinib 150 mg/day was prescribed as maintenance therapy.

Page 5 line 14 – Unfortunately, the patient developed dyspnea three months after the combination therapy.

Comment 7: P5 ln 11, you have separated CT sets, but do you do the re-plan with new CT set?

Response: Yes! We do the re-plan with new CT sets. The sentences have been reworded as below: In page 5 line 2 – Then, erlotinib was added concurrently to the radiotherapy regimen. This regimen comprised 54 Gy given in nine fractions delivered with SBRT using HT, at 95% of the prescribed isodose for the planned target volume. The split courses with 3 fractions per week were prescribed. (Fig 1A and 1B) Targeting was based on new, separate CT scans for each split course.

Comment 8: P6 ln 2, equals?, ln 3 than?, ln 5 is it 7 fractions/week?, ln 7, in to
(into?), of 6 Gy (per fraction?).

**Response:** The sentences were revised accordingly on *page 6 line 6* – The hypofractionated scheme yields equivalent survival rates, without fatal, symptomatic pneumonitis for patients with stage III NSCLC when compared with conventional radiotherapy [3]. Belderbos et al. [8] reported that radiation dose escalation was safe up to 94.5 Gy in 42 fractions with a mean lung dose 13.6 Gy or less in 6 weeks in NSCLC patients. The patients underwent irradiation 5 days per week, and twice daily when more than 30 fractions were prescribed, with at least a 6-h interval in between each fraction. According to linear-quadratic (LQ) modeling [9], the biologic effect of 94.5 Gy/42 fractions converted to a hypofractional dose of 6 Gy per fraction (EQD6), for which the acute effects and late normal tissue effects would be equivalent to 72 and 54 Gy, respectively.

**Comment 9:** Rewording for Ins 5-18, p6

**Response:** The sentences were revised accordingly on *page 6 line 8* – Belderbos et al. [8] reported that radiation dose escalation was safe up to 94.5 Gy in 42 fractions with a mean lung dose 13.6 Gy or less in 6 weeks in NSCLC patients. The patients underwent irradiation 5 days per week, and twice daily when more than 30 fractions were prescribed, with at least a 6-h interval in between each fraction. According to
linear-quadratic (LQ) modeling [9], the biologic effect of 94.5 Gy/42 fractions converted to a hypofractional dose of 6 Gy per fraction (EQD6), for which the acute effects and late normal tissue effects would be equivalent to 72 and 54 Gy, respectively. The mean lung dose (≥ 21 Gy), V20 (> 31%) [10], and ipsilateral V20 Gy [5] correlates with radiation pneumonitis. Nonetheless, the Radiation Therapy Oncology Group 0236 protocol using SBRT via HT for NSCLC provided safe and effective treatment when the V20 was restricted to less than 10% to 15% [11]. The V15, V20, and mean lung dose for each separate lung by divided course are shown in the Table. Moreover, the whole-course V20 and mean total lung dose were 10% and 10.24 Gy, respectively. According to previous reports [5, 10, 11], this plan was safe and no symptomatic radiation pneumonitis occurred among the NSCLC patients.

Comment 10: Rewording Ins 1-4 and Ins 10-19 p7

Response: The sentences were revised accordingly on page 7 line 8 – Moreover, addition of standard-dose erlotinib to chemoradiotherapy was feasible and without evidence of increased toxicities [4]. However, prior tissue injury from radiation therapy could lead to cells with altered responses when the drug is subsequently applied [15]. Erlotinib enhanced radiation responses including cell cycle arrest, apoptosis induction, accelerated cellular repopulation, and DNA damage repair [14].
Therefore, it is possible for erlotinib to induce an altered response in cells when erlotinib is applied after irradiation.

**Page 8 line 2** – Irradiation modulates the anticancer drug’s pharmacokinetics even under low doses and in off-target areas [19]. Additionally, combined low-dose radiation and erlotinib induced symptomatic pneumonitis in one NSCLC patient [20]. Another NSCLC patient developed radiation recall dermatitis induced by erlotinib [21]. According to these reports, we believe EGFR inhibitor might not only enhance the effects of radiation, but also might enhance the adverse effects of radiation, especially when prescribed following previous concurrent treatment with radition. Furthermore, radiation modulates the systemic effects of drugs regardless of the treatment effects or side effects. Erlotinib appears to modulate the effects of irradiation, both good and bad.

**Comment 11**: P7 ln 4 “mentioned”??

**Response**: The mistyped word was corrected.

**Comment 12**: Rewording Ins 1-4 p15

**Response**: Page 15 Ins 1-4 were revised accordingly on page 15 line 2 – Figure 1.

Tomotherapy treatment planning with high conformity (conformal index, CI = 1.03).
Red, green, and blue areas are 100%, 90%, and 50% of the prescribed radiation dose, respectively. Dose distribution in the first treatment course (A) and in the second treatment course (B). The blue dots outline the lung structure and the sky-blue dots indicate the radiation target.

Comment 13: P15 ln 3, what are area within the blue dots, 50% or structure? Where is the target in fig. 1?

Response: Page 15 line 2 – Figure 1. Tomotherapy treatment planning with high conformity (conformal index, CI = 1.03). Red, green, and blue areas are 100%, 90%, and 50% of the prescribed radiation dose, respectively. Dose distribution in the first treatment course (A) and in the second treatment course (B). The blue dots outline the lung structure and the sky-blue dots indicate the radiation target.

Comment 14: P16, mean lung dose …5.3 Gy is for total lung or Rt lung or Lt lung?

Response: The unclear sentence was revised and the mean lung dose “…5.3 Gy” was deleted to avoid reader confusion on page 5 line 10 – The whole-course V20 and mean lung dose for the total lung were 10% and 10.24 Gy, respectively. In page 6 line 16 - The mean lung dose (≥ 21 Gy), V20 (> 31%) [10], and ipsilateral V20 Gy [5] correlates with radiation pneumonitis. Nonetheless, the Radiation Therapy Oncology
Group 0236 protocol using SBRT via HT for NSCLC provided safe and effective treatment when the V20 was restricted to less than 10% to 15% [11]. The V15, V20, and mean lung dose for each separate lung by divided course are shown in the Table. Moreover, the whole-course V20 and mean total lung dose were 10% and 10.24 Gy, respectively. According to previous reports [5, 10, 11], this plan was safe and no symptomatic radiation pneumonitis occurred among the NSCLC patients.

Comment 15: P16, V15 and v20 is the ….and (or??) contralateral…

Response: The sentence was revised accordingly on page 14 line 1 – Table 1. Mean lung volume, dose, V15, and V20 for each lung in the first and second radiotherapy courses, with 2 weeks interval between radiotherapy courses.