Peer Review File

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Reviewers: Accept pending minor revision

Comments:

This article review the question related to the dose/fractionation issue of NSCLC and how to increase the therapeutic ratio of radiotherapy.
The article was well written and easy to understand. The subject is interesting, as a major question arising from the application of the linear–quadratic (LQ) model and the validity of this model.

Specific comments:

1-To add more details about the advantages and limits of the linear–quadratic (LQ) model of cell killing and its application in radiotherapy to model radiotherapy outcomes. As we know the LQ model is reasonably predictive of dose response relation in vitro and in vivo and for the dose per fraction ranged 2 -15 Gy. In addition, it is important to distinguish between the validity of the LQ model and the appropriate parameters. There are different issues (e.g, the alpha/beta ratio in vitro vs. vivo, fractionation, etc) and what is the dose per fraction for which the LQ model should be used?

REPLY 1:
We added the following statements that probably will express our opinions on this issue more explicitly:

"(…) The published clinical local control data is consistent with this model being reasonably predictive of in vitro and in vivo normal tissue dose-response relations in the dose per fraction range from small (<2 Gy) to very large (18-20 Gy) fraction sizes (25, 29). However, both preclinical data and modeling studies show that tumor hypoxia is more of a detrimental factor for single-dose treatments than for fractionated irradiation, which was confirmed for NSCLC, where SBRT-like 3- to 5-fractions hypofractionated schedules were suggested to be optimal for hypoxic tumors, despite the increased risk of intra-fraction

repair due to a synergistic effect with inter-fraction reoxygenation (30). For the same BED, tumor control was significantly less for single doses than fractionated irradiation consistently with the predicted loss of tumor response because of tumor hypoxia of single doses compared with fractionated RT for the same BED (25).”

2-I recommend to add the references:

REPLY 2:
Michael C. Roach, Jeffrey D. Bradley, and Cliff G. Robinson. Optimizing radiation dose and fractionation for the definitive treatment of locally advanced non-small cell lung cancer. J Thorac Dis. 2018 Aug; 10(Suppl 21): S2465–S2473.

Was added: ref. 98

Lindblom E, Dasu A, Toma-Dasu I. Optimal fractionation in radiotherapy for non-small cell lung cancer--a modelling approach. Acta Oncol. 2015;54(9):1592-1598.

Was added: ref. 30

Stephen D. Robinson, Bilal A. Tahir, Katherine A.R. Absalom et al. Radical accelerated radiotherapy for non-small cell lung cancer (NSCLC): A 5-year retrospective review of two dose fractionation schedules. Radiotherapy and Oncology; Volume 143, February 2020, Pages 37-43.

Has already been cited: ref. 16

Parisi E, Genestreti G, Sarnelli A, et al. Accelerated hypofractionated radiotherapy plus chemotherapy for inoperable locally advanced non-small-cell lung cancer: final results of a prospective phase-II trial with a long-term follow-up. Radiat Oncol 14, 112 (2019).

Was added to the Table 1: ref. 71