

Peer Review File

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Reviewer A

Comment 1: The line of thought is difficult to follow. In their introduction, they write that the ideal treatment should comprise of a systemic agent with radiotherapy in introduce synergy. I presume from the introduction their pleas concern locally advanced disease.

Reply 1: We clarify in the text: Concurrent chemotherapy is advocated over radiotherapy alone for stage III NSCLC because of radiosensitizing effect and improved survival. However, grade 3-4 toxicity is also significantly increased and may not be suitable for frail patients (page 3-lines 8-11)

Comment 2: However, the paragraph concerning prevalence of PD-L1 is not. I think the authors want to point out that the prevalence in elder patients is not different from younger patients, but please rephrase this paragraph to this goal

Reply 2: We shorten the paragraph and summarize the prevalence of PD-L1 which is not different between older patients and younger patients (page 4, lines 21-23, page 5, lines 1-4.

Comment 3: Why use a confusing new term like HDP-L1 instead of TPS.

Reply 3: We agree and replace with TPS throughout the text.

Comment 4: Often the choice of reference seem doubtful. For example ref 13 is used to underwrite that CPI is a good radiosensitizer. Why not refer to the landmark papers itself or any original paper that really concern the radiosensitizing effect of RT+CPI.

Reply 4: We agree and replace ref 13 with another randomized study Rech et al which demonstrated that in patients with metastatic NSCLC and high TPS, CPI is superior to chemotherapy (page 4, lines 7-9).

Comment 5: Why dedicated another paragraph on all these details concerning all these papers of CPI including 2nd line papers in the following paragraph

Reply 5: We agree and shorten the paragraph.

Comment 6: Ref 54: Phase I trial are far from powered to make any claims on efficacy.

Reply 6: We agree and clarify: Even though this is a phase I study with its limitations, the study suggested that immunotherapy dose reduction may improve treatment tolerance and may serve as a template for future prospective studies (page 8, lines 22-24).

Comment 7: The authors mention several time that a dose reduction of nivolumab did lead to less toxicity or efficacy but also mention more toxicity with sarcopenia

Reply 7: We clarify. There is controversy about the role body mass index (BMI) in CPI's toxicity which needs to be investigated in the future for each individual agent

Reviewer B

Comment 1: Section: Prevalence of PD-L1 receptors in locally advanced NSCLC. We recommend reducing the content

Reply 1: We agree and reduce the content (page 4, lines 21-23, page 6, lines 1-4)

Comment 2: Page 6, paragraph 2

Abscopal effect is not a suitable example in this paper dealing with locally advanced NSCLC because it is term mainly used in metastatic disease. I would be better expressed in the following sentence. Chemoradiation induces tumor antigen release and an adaptive immune response.

Reply 2: We replace the sentence and shorten the paragraph as it is irrelevant (page 6, lines 1-4)

Comment 3: PET-CT is a diagnostic image and is not an IGRT technique:

Reply 3: We clarify: Advances in imaging such as positron emission tomography (PET) allows the clinician to outline the target more precisely for radiotherapy planning. Daily imaging prior to irradiation with cone beam CT scan for example also ensures accurate tumor targeting to minimize marginal miss and sparing of critical organs surrounding the target. Thus, radiation dose escalation to the tumor becomes feasible while minimizing radiation dose to the heart and lungs (page 6, lines 18-23).

Comment 4: Combining potential advantage of CPI and effectiveness of CPI.

Reply 4: We would like to elaborate for readers who may not be familiar with CPI since this review is intended for a large audience: thoracic surgeons, radiation oncologists, geriatricians, gerontologists, medical oncologists, nutritionists, medical oncologists, and scientists. In fact, this review may help us discuss on how to establish a protocol using hypofractionated radiotherapy and reduced dose of CPI among IGRG members

Comment 5: pharmacokinetics and toxicity. Combining those two sections.

Reply 5: We did with the same caveat as in 4.

Comment 6: It would be good if the studies related to hypofractionated RT in NSCLC could be summarized in a table.

Reply 6: We add 3 references 83-85 and summarize all the preliminary data of hypofractionated IGRT in Table 1. We all add comments on those studies to highlight the efficacy of IGRT (page 11, lines 18-23)

Comment 7: There are parts where PD-L1 is misspelled.

Reply 7: We correct it.

Comment 8: page 12, line 13. iGRG is an abbreviation.

Reply 8: We correct it.