

Peer Review File

Article Information: <https://dx.doi.org/10.21037/tcr-22-232>

Reviewer Comments

This is a study protocol paper entitled "Evaluating the Histologic Effects of Neoadjuvant Stereotactic Body Radiation Therapy (SBRT) followed by Pulmonary Metastasectomy— Rationale and Protocol Design for the Post SBRT Pulmonary Metastasectomy (PSPM) Trial". In this paper, the authors described a very interesting and well-designed study protocol and their comment. This is a very important topic that contributed to literature, however, some points should be corrected before acceptance of this paper.

Comment 1:

line 62: "secondary lung cancer" is confusing. Please avoid using it and I would replace it with pulmonary metastases.

Reply 1: We made the suggested change.

Changes in the text: We changes in the text: "secondary lung cancer" replaced with "pulmonary metastases" (pages 4, 5 lines 65, 74 and 83)

Comment 2:

line 69: We agree with the authors in that there have been few efforts assessing the effectiveness of SBRT in tumor eradication at a histological level. However, there were a few cases undergoing salvage surgery after SBRT for pulmonary metastases and viable cells were confirmed. Please cite the following article.

Salvage pulmonary resection after stereotactic body radiotherapy: A feasible and safe option for local failure in selected patients.

Antonoff MB, Correa AM, Sepesi B, Nguyen QN, Walsh GL, Swisher SG, Vaporciyan AA, Mehran RJ, Hofstetter WL, Rice DC.

J Thorac Cardiovasc Surg. 2017 Aug;154(2):689-699.

Salvage Pulmonary Metastasectomy for Local Relapse After Stereotactic Body Radiotherapy. Hamaji M, Mitsuyoshi T, Yoshizawa A, Sato T, Matsuo Y, Chen-Yoshikawa TF, Sonobe M, Mizowaki T, Date H. Ann Thorac Surg. 2018 Apr;105(4):e165-e168.

Reply 2: " As suggested, we added both the references

Changes in the text: page 5, lines 75, 76. Accordingly fixed the reference list and numbers in the manuscript.

Comment 3:

line 96: Did the authors consider any set number of pulmonary metastases for SBRT or this study ? The number of pulmonary metastasis lesions is associated with survival outcomes and treatment strategy. The authors should comment on whether they should set a number of lesions in eligible patients.

Reply 3: "we added text as "We set a number of no more than 5 metastases per lung based on restrictions from an SBRT standpoint. While it is true that number of mets is a prognostic indicator, data supports being able to completely resect these lesions as a more telling prognostic factor—hence our rational. (see Pages 6-7, lines 115-117)".

line 101: The authors are encouraged to make comments on the size criteria. How is the effect of SBRT different, depending on the size of lesions ?

Reply 4: In consultation with our lung SBRT expert, we restricted treatment to lesions less than 5cm in size—lesions with greater size would not be candidate for this trial and have traditionally been the upper limit for SBRT in other trials of oligometastatic disease. (see Pages 6-7, lines 117-120)".

Comment 5:

line 110: The dose is one of the most important elements in the study protocol. Are those doses considered as neoadjuvant or definitive (curative) ?

Reply 5: "we added as "These doses are based on previously published data in the context of lung malignancies and are considered definitive SBRT doses given that we are evaluating the pCR of SBRT from a curative perspective. (see Page 7, lines 131-133)".

Comment 6:

line 262: In addition to colorectal cancer pulmonary metastasis, please discuss pulmonary metastasis from sarcoma, which is more complex. Please cite the following article.

Surgical and non-surgical management of repeat pulmonary metastasis from sarcoma following first pulmonary metastasectomy. Hamaji M, Chen F, Miyamoto E, Kondo T, Ohata K, Motoyama H, Hijiya K, Menju T, Aoyama A, Sato T, Sonobe M, Date H.

Surg Today. 2016 Nov;46(11):1296-300.

Reply 6: "we added some the reference as suggested by reviewer.

Changes in the text: we added "the surgical and non-surgical management

of sarcoma pulmonary metastases can be more complex particularly with repeat thoracotomy¹⁸, however given the relative lower incidence of sarcoma compared to other cancer subtypes, the effect of this on a Phase II trial is unlikely to be significant." (see Page 15, line 300-302)"

Comment 7:

Please discuss the extent of resection. Very few surgeons have experience in surgery after SBRT in pulmonary metastases. The extent of resection after SBRT would be more extensive than upfront resection. This is also a very important point.

Reply 7: Our experience does not demonstrate a change in surgical planning post SBRT. Surgeons (based on guidelines) are recommended to perform sublobar resections as indicated. The benefit of SBRT is that it does not appear to change surgical planning or extent of resection given that it is focal radiation with less tissue spread.
