PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A Single Arm Prospective Interventional Study assessing feasibility of using Gallium-68 ventilation and perfusion PET/CT to avoid functional lung in patients with stage III non-small cell lung cancer
AUTHORS	Bucknell, Nicholas; Hardcastle, Nicholas; Jackson, Price; Hofman, Michael; Callahan, Jason; Eu, Peter; Iravani, Amir; Lawrence, Rhonda; Martin, Olga; Bressel, Mathias; Woon, Beverley; Blyth, Benjamin; MacManus, Michael; Byrne, Keelan; Steinfort, Daniel; Kron, Tomas; Hanna, Gerard; Ball, David; Siva, Shankar

VERSION 1 – REVIEW

REVIEWER	Matthew Hatton Weston Park Hospital, Whitham Rd., Sheffield, S10 2SJ
REVIEW RETURNED	10-Aug-2020

GENERAL COMMENTS	This manuscript is a summary of protocol for a feasibility study of the application of functional imaging in radiotherapy planning aiming at functional lung avoidance during in radical radiotherapy treatment for NSCLC. The manuscript represents a well written summary of the protocol and I assume the study in in set up phase. The imaging and radiotherapy protocol are well described, statistics are descriptive and functional lung imaging will be used to offer patients a dose escalated concurrent radiotherapy treatment. Therefore, with the results of RTOG 0617 in mind I feel - Systemic treatment has the ability to affect a number of the secondary outcomes so details of acceptable chemotherapy schedules should be listed A respiratory function cut off is required in the inclusion criteria Details of monitoring programs that confirm QA, compliance with protocol, treatment toxicity etc. are required

REVIEWER	Yaacov Lawrence Sheba Medical Center, Israel
REVIEW RETURNED	09-Sep-2020

GENERAL COMMENTS	This is a well written and important protocol written by investigators with expertise in the field. The question (using VMAT to optimise dose to tumor and avoid functional lung tissue) is appropriate and relevant. My only one comment, a minor one, is the dependence on technology that is not I believe widespread (V/Q PET), hence if the study is positive it is not clear how it could be widely im

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

This manuscript is a summary of protocol for a feasibility study of the application of functional imaging in radiotherapy planning aiming at functional lung avoidance during in radical radiotherapy treatment for NSCLC. The manuscript represents a well written summary of the protocol and I assume the study in in set up phase.
Response: Thank you for your comments. The study is currently active and enrolling trial participants.

The imaging and radiotherapy protocol are well described, statistics are descriptive and functional lung imaging will be used to offer patients a dose escalated concurrent radiotherapy treatment. Therefore, with the results of RTOG 0617 in mind I feel -
Systemic treatment has the ability to affect a number of the secondary outcomes so details of acceptable chemotherapy schedules should be listed
Response: We agree this is important to describe and have provided the two chemotherapy schedules anticipated to be used in concurrent treatment of patients receiving chemoradiation. We envisage, based on local practices majority of patients will receive weekly carboplatin and paclitaxel.

A respiratory function cut off is required in the inclusion criteria
Response: Our local practice is to not routinely exclude patients from radical treatment based on respiratory function cut offs but rather based on performance status with additional consideration being given to patients with known interstitial lung disease. For this reason we have chosen to exclude patients with known interstitial lung disease and limit trial participation to those who are ECOG 0-2.

Details of monitoring programs that confirm QA, compliance with protocol, treatment toxicity etc. are required.
Response: Thank you for your recommendation, we agree this should be included in the manuscript. This has now been included on page 13, lines. 21-43.

Reviewer: 2

This is a well written and important protocol written by investigators with expertise in the field. The question (using VMAT to optimise dose to tumor and avoid functional lung tissue) is appropriate and relevant.
My only one comment, a minor one, is the dependence on technology that is not I believe widespread (V/Q PET), hence if the study is positive it is not clear how it could be widely implemented.

Response: Thank you for your comments. We agree that a significant limitation of the study is the current availability of V/Q PET worldwide. The technical capacity to do these investigations is expected to improve with the availability of Gallium 68 generators (used for PSMA PET/CT imaging) however licencing issues will make this investigation difficult to obtain in certain jurisdictions. For this reason we have secondary objectives to compare the V/Q PET/CT with inhale/exhale CT ventilation and dual energy CT iodine mapping (which provides a surrogate for pulmonary perfusion). We are performing this planned secondary analysis as CT ventilation and dual energy CT are both technologies that already have widespread availability. If the outcomes are comparable between V/Q PET/CT, CT ventilation and/or dual energy CT iodine mapping, then we expect that the alternative technologies will be good choices to use in future studies. However comparison between ‘ground truth’ V/Q PET and alternative modalities has not been prospective performed to date.