Author’s response to reviews

Title: Respiratory-gated (4D) contrast-enhanced FDG PET-CT for radiotherapy planning of lower oesophageal carcinoma: feasibility and impact on planning target volume

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Version: 1 Date: 21 Jun 2017

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Response to Reviewer reports:

Reviewer 1: In this study, the Authors have evaluated the feasibility and potential impact on target delineation of respiratory-gated (4D) contrast-enhanced 18Fluorine Fluorodeoxyglucose positron emission tomography - computed tomography, in the treatment planning position, for a prospective cohort of patients with lower third oesophageal cancer.

Major comments:

1. Background section, page 5, lines 110-111. "However, motion artefacts with 3D PET-CT can reduce target contrast and overestimate lesion size." Moreover, un-gated imaging of moving lesions can decrease Standardized Uptake Values. 4D PET scanning is able to recover SUV. Please rephrase considering this comment.

This sentence has been amended to include a comment regarding inaccuracy of SUV measurements and a new reference has been added to support this.

Thank you for highlighting these studies. The 1st study by Guo et al evaluated 3D PET with 4D CT rather than integrated 4D PET-CT. We have referenced this work as suggested in both the background and discussion sections. The 2nd study by Figura et al is a published abstract from a poster presentation rather than a full manuscript detailing a small \( n = 4 \) retrospective study of 4D PET-CT in oesophageal cancer which we have also referenced and added to the discussion as suggested.

3. **Results section**. Can the Authors evaluate the centre of mass coordinates and assess differences between 4D PET-CT, 3D PET-CT and 4D CT?

Centre of gravity distance (CGD) data which is equivalent to centre of mass co-ordinates was obtained at the time of data analysis but not presented. This metric has now been incorporated into the results section as suggested and the relevant tables have been updated with comparison between the different imaging techniques.

4. **Results section**. Have the Authors data to evaluate the degree of association between PTV values and tumour motion vectors?

We do not have this data and would not easily be able to analyse this aspect. We believe this relates to when ITV was calculated based on manually working out tumour motion on a 3D axis i.e. anterior-posterior motion = 5mm, superior-inferior = 10mm etc. We routinely use 4D CT for radiotherapy planning of oesophageal carcinoma patients at our institution and do not use tumour motion vectors in the planning process because there are likely to be tumour deformation and non-respiratory dependant motion effects which will not be captured accurately using tumour vectors alone. The rationale for our approach is supported by previous work by Guerrero et al (Intrathoracic tumour motion estimation from CT imaging using the 3D optical flow method.
Phys Med Biol 2004; 49(17): 4147-4161). We mitigate against these effects by individually producing and reviewing clinical target volumes on each dataset. The resulting volumes would therefore most likely account for all the effects of physiological motion and produce an accurate treatment volume. This treatment volume shape would therefore enable the optimisation of the plan to be carried out precisely and be reproducible during treatment.

5. Results section, "Positional Analysis" paragraph. Please improve statistical analysis evaluating if presented data reach statistical significance.

Detailed statistical analysis was not performed due to concerns over the validity of results due to the small sample size, however as advised additional statistical analysis has now been performed using non-parametric analysis of variance (ANOVA, Friedman test) which confirms no statistically significant difference in any of the positional metrics across PTVs delineated on the different imaging combinations. The p-values have been added as a new table (Table 6) and commentary on these results has been added to the discussion.

Minor comments:

1. Please, revise English and punctuation throughout the manuscript.

This aspect has been carefully checked and a few minor typographic/grammatical errors have been corrected – see tracked changes in revised manuscript.

2. References' style is not homogeneous. Please refer to the instructions for Authors provided by the Journal.

This aspect has been carefully checked and amendments made to conform with Journal style – see tracked changes in revised manuscript.


The typographic error in this reference has been corrected.
Reviewer 2: This study analyzed the feasibility and potential impact on target delineation of respiratory-gated (4D) PET-CT by comparing the PTVs of lower oesophageal carcinoma derived from 4D CT, 4D CT with co-registered 3D PET and 4D PET-CT. Overall, the design and method is well, there are few reports on 4D PET-CT for oesophageal carcinoma. However, I still have some comments that I like to address see below:

1. The study only included complete datasets of 7 patients. Whether the results of 7 patients could reflect a reliable phenomenon?

We agree with this comment and have not over-reached in our conclusions; the purpose of the study was primarily to assess feasibility and secondly to compare target volume delineation. We have clearly documented the study limitations and made recommendations for further required research in this area. We have stated that our study is too small to draw any conclusions about clinical benefit. Despite the small cohort size, we feel our manuscript adds novel data to the currently limited evidence in this setting.

2. The study used the paired T-test for analyzing the variations of different of target volumes. However, non-parametric test should be used for the study due to few cases.

As suggested, statistical analysis of target volumes and tumour length have been re-analysed using a non-parametric test (Mann-Whitney) and the relevant sections of the manuscript have been amended accordingly (Statistical Methods, Results, Table 2).

3. The authors should elaborate the contouring standard and how to determine the upper and lower bound of oesophageal carcinoma on 4DCT, and PET-CT, it is crucial to the study.

The tumour length and outlines were derived from diagnostic imaging which included an Endoscopic Ultrasound, contrast-enhanced CT and 3D PET-CT. The longest tumour dimension was used for outlining. All imaging measured the maximal length of the tumour with specific reference to an anatomical structure e.g. carina or superior aortic arch. This enabled the oncologist and radiologist to identify the superior and inferior extent of the diseased oesophagus in relation to these structures; thereby allowing them to outline this segment of the entire circumference of oesophagus to be outlined. All 4D CT and PET-CT scans included at least one of the reference structures (e.g. superior aortic arch or carina) and therefore the target volumes were produced consistently on each of these datasets with reference to these structures. This additional information and a reference to the SCOPE1 trial which first described using this method of GTV delineation in oesophageal cancer has been added to the Contouring section of the Methods. This approach to contouring has subsequently been adopted in the NeoSCOPE clinical trial which is also referenced in this section.
4. Comparison of different target volumes is based on registration of 4DCT and PET (or 4D PET-CT). The authors should state the registration method and whether the method would affect the results.

The 4D CT and PET data acquisitions were acquired at the same attendance with the patient immobilized in the radiotherapy treatment position to ensure inherent registration. Post-processing was used to generate an averaged 3D PET from the 4D PET scan. No supplemental (de-formable) co-registration was necessary as the PET and CT components were inherently registered. We have clearly documented this in the PET-CT Technique section of the Methods. Given that PET and CT imaging data was acquired concurrently with the patient immobilised the results should not have been adversely affected – a couple of sentences to clarify this have been added to the Discussion.