

P1.234: Excess Heart Base Dose Is Not Associated With Poorer overall survival (OS) in post-operative radiotherapy (PORT) - a Cox-Per-Voxel Analysis of the Lung ART Stage III Trial.

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Introduction

- When delivering a curative dose of radiation to a tumour, adjacent healthy tissues will also receive some radiation, potentially resulting in radiation-induced side-effects.
- Excess RT dose to the cardiac avoidance area (CAA) in the base of the heart - comprised of the right atrium, aorta base, superior vena cava, and left and right coronary arteries, has been associated with poorer OS in studies utilising VBA [1-6].
- Voxel-based analysis (VBA) aims to analyse how spatial dose distributions in a given patient cohort associate with treatment outcomes.
- The Lung ART phase III clinical trial [7] investigated post-operative radiotherapy (PORT) in 501 patients with NSCLC and proven N2 disease. Of these, 252 were randomised to receive 54 Gy in 27-30 fractions.
- PORT was not associated with increased disease-free survival at 3 years follow up, and the trial reported high rates of cardiopulmonary toxicity in the PORT arm, with 11% of deaths attributed to cardiac or cardiopulmonary disease [7].

Aim

To reanalyse data from the Lung ART trial for NSCLC [7] to investigate whether excess dose to the cardiac avoidance area (CAA) [8] is associated with mortality in patients receiving PORT.

Methods

- The template patient was chosen from a cohort of breast cancer patients [9] with intact lungs to improve registration outcomes.
- Dose distributions were non-rigidly registered to the template anatomy using NiftyReg [10].
- The contoured heart structure was used to limit the registration to this area to minimise the impact of varying post-surgical lung anatomy.
- Registration accuracy was visually verified prior to VBA.
- A univariable time-to-event Cox proportional hazards model was then fitted independently at each voxel.
- Permutation testing was used to account for multiplicity and to define the significance threshold as the 95th percentile of the distribution of the extreme (maximum and minimum) beta coefficient across all permutations.
- Dose density mapping was carried out on successfully registered patients by calculating mean and SD for each voxel.
- Voxel values were mapped onto the template patient CT.
- Dose summary statistics were calculated per-patient for the CAA volume.

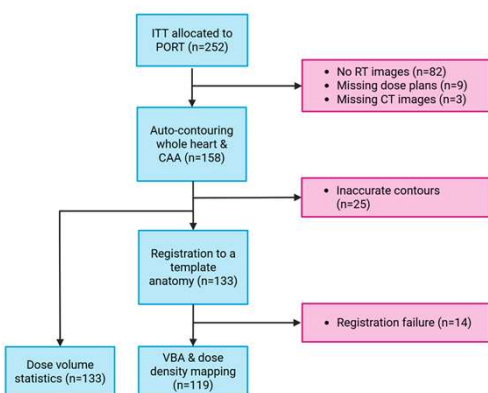


Figure 1: Flow diagram detailing why patients were excluded at each stage of analysis. ITT – intention to treat, PORT – post-operative radiotherapy, CAA – cardiac avoidance area, VBA – voxel-based analysis.

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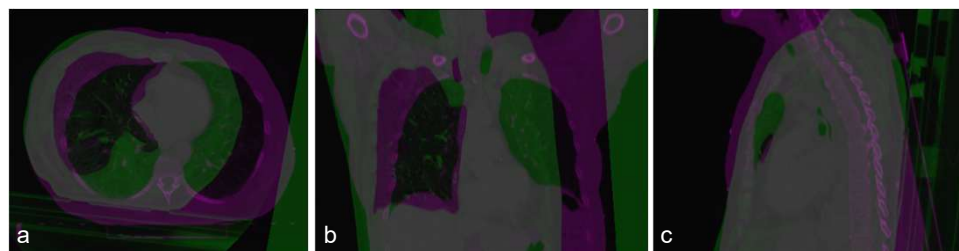


Figure 2: Axial (a), coronal (b), and sagittal (c) slices showing the registration outcome of a patient from the cohort who underwent a left sided pneumonectomy (green) with the template patient anatomy (purple). The absence of the left lung causes displacement of the mediastinum; this results in an inaccurate heart auto-contour due to the low contrast between the heart and surrounding tissue, and a failed registration of the heart.

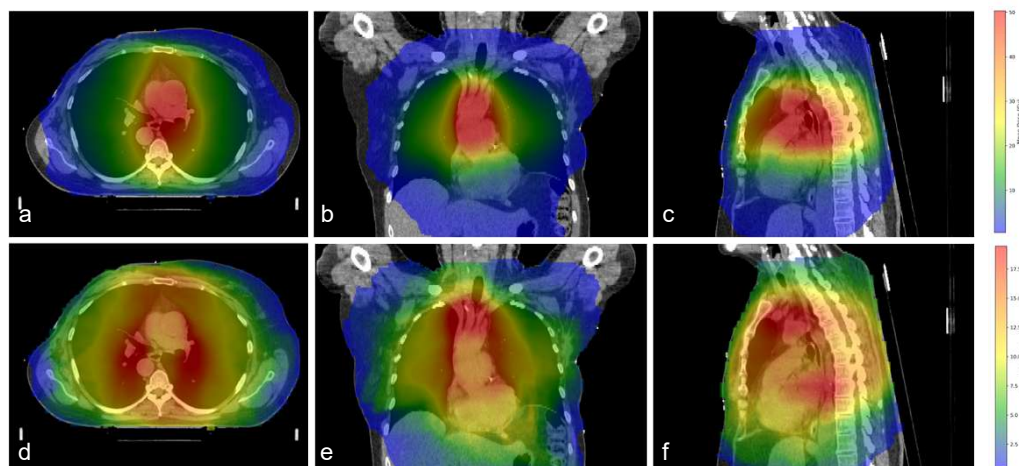


Figure 3: Dose density mapping of the 119 successfully registered patients, showing mean (a)(b)(c) and standard deviation (d)(e)(f) in Gy per voxel. Axial (a)(d), coronal (b)(e), and sagittal (c)(f) slices show the base of the heart. The highest mean dose is reported over the atria, aorta base, superior vena cava and the middle thoracic oesophagus.

Discussion and conclusions

- Significant dose–response regions were not found in the CAA in this Cox-per-voxel univariable analysis of NSCLC patients receiving PORT.
- The location of the few voxels with a significant dose–response relationship suggests the cause to be noise resulting from inaccuracy of the registration at the edge of the heart contour.
- High dose uniformity, caused by incorporation of paratracheal and subcarinal nodes to the CTV of all patients, limits the utility of VBA in determining association between excess dose to the CAA and OS.
- Max dose to the CAA far exceeded the limit of <21Gy described in prior literature; dose higher than this has been associated with excess cardiac adverse events and mortality [8].
- This aligns with the observed increase in cardiopulmonary adverse events and death in the PORT arm [7].
- Large interpatient anatomical variation caused by surgical resection presented challenges for both auto-contouring and registration, particularly for post-pneumonectomy patients who almost uniformly failed registration.
- The results of this analysis warrant cautious interpretation, due to the limited statistical power of the sample size from the exclusion of 133 patients.

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Results - VBA

- 119 patients were on the PORT arm were successfully registered to a common patient anatomy and included in VBA (figure 1).
- Failure of registration occurred primarily in patients who received a pneumonectomy and those with inaccurate heart contours (figure 2).
- Voxel-wise univariable Cox regression did not identify statistically significant dose–response regions of considerable size, with only 4 voxels located in the pericardium exceeding the threshold.
- Thresholds >1.5937 and <-1.7169 were established by permutation testing and β coefficients of these voxels were -3.5266, -3.0151, -2.0963 and -2.0033.
- Calculating the biologically effective dose (BED) per voxel using an α/β of 3 prior to analysis resulted in 5 voxels above the 95th percentile in the same location.
- The location of the voxels at the heart contour edge suggests the association is due to noise
- This was affirmed when no additional voxels were associated with the outcome when the threshold was lowered to the 90th percentile

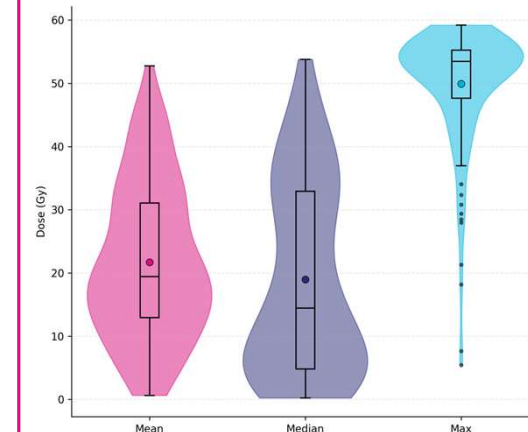


Figure 4: Violin plots showing dose summary statistics of the contoured CAA for 133 patients in the PORT arm. The central point represents the mean.

Results – dose density

- Dose density mapping showed a high mean and SD of dose to the atria and major vessels, where the CAA is located (figure 3).
- Mean doses in excess of 40Gy were delivered to this region across the registered cohort.
- This is due to the inclusion of the paratracheal and subcarinal nodes in the clinical target volume (CTV) for all patients [7].
- Dose summary statistics were calculated for the 133 contoured patients (figure 4).
- Mean and median dose were ~20Gy with a high SD – 21.69(12.14) and 18.97(15.18), respectively.
- Max dose to the CAA was high for the majority of patients, with a mean of 49.93(9.40).
- The high SD may be attributable to variation in the number and location of irradiated nodes in the CTV.

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