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Original Research

Radiation dose to heart base linked with poorer survival in lung cancer patients

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Abstract ***Background:*** Advances in radiotherapy (RT) have allowed an increased proportion of lung cancer patients to be treated curatively. High doses delivered to critical thoracic organs can result in excess mortality with tolerance doses poorly defined. This work presents a novel method of identifying anatomical dose-sensitive regions within the thorax.
Methods: A high-resolution, normal-tissue dosimetric analysis was performed to identify regions in the heart that correlate with poorer survival. A total of 1101 patients treated with curative-intent RT were selected and all computed tomography imaging and dose distributions were deformed to a reference. Mean dose distributions were created for patients who survived versus those who did not at a set time point. Statistical significance of dose differences was investigated with permutation testing. The dose received by the most statistically significant region of the thorax was collected in all patients and included in a multivariate survival analysis.
Results: The permutation testing showed a highly significant region across the base of the heart, where higher doses were associated with worse patient survival ($p < 0.001$). Cox-regression multivariate analysis showed region dose, tumour volume, performance status and nodal stage were significant factors associated with survival, whereas cardiac mean dose, V5 and V30 showed no significance. Survival curves, controlling for these factors, were plotted with patients receiving doses greater than 8.5 Gy to the identified region showing worse survival (log-rank $p < 0.001$, hazard ratio 1.2).

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Conclusion: The application of this novel methodology in lung cancer patients identifies the base of the heart as a dose-sensitive region for the first time.

1. Introduction

Radiotherapy (RT) plays a major role in curative-intent treatment of lung cancer. Advances in radiation technology have enabled curative-intent doses to be delivered to a larger proportion of locally advanced patients while keeping doses to normal tissues within accepted safety limits. This increase in the proportion of patients treated with curative intent is expected to improve local control, which is known to be associated with better survival [1,2].

However, over the last 2 years, evidence relating irradiation of the heart to excess mortality has emerged. Bradley *et al.* [3] reported the outcomes from RTOG 0617, a multicentre phase III study comparing 60 Gy versus 74 Gy delivered in 2 Gy fractions. They showed that a higher treatment dose was associated with increased mortality and multivariate analysis of survival identified heart doses, volume receiving 5 Gy (V5) and volume receiving 30 Gy (V30), as associated with patient survival. Subsequently, a study showed that higher mean heart dose was significantly associated with higher cardiac event rates [4]. There is now great interest in investigating how dose-to-anatomical sub-structures of the heart links to survival. Despite this emerging evidence, in current practice, heart dose constraints remain poorly defined, generic and date back to articles published over 25 years ago [5,6]. One of the major limitations of previous studies is the evaluation of dose to the whole heart as one structure or divided into a small number of pre-defined sub-structures.

There is, therefore, a clear unmet need to define heart sub-structures at risk and heart dose constraints for this group of patients. The analysis of large population-based cohorts of lung cancer patients treated with curative RT is an attractive strategy to identify dose-sensitive heart structures. However, this approach is limited by the fact that heart sub-structures are not delineated routinely as part of the RT planning process. The methodology in this article, applied to lung cancer patients for the first time, does not require any delineation structures. Instead, performs a high-resolution, voxel-by-voxel dosimetric analysis, identifying regions correlated with patient survival.

2. Methods

A total of 1163 lung cancer patients treated between 2010 and 2013 at a single academic cancer centre, with routine curative-intent RT (55 Gy in 20 fractions), with or without induction chemotherapy, were randomly selected for analysis. Institutional approval had been gained to use these patients. Three-dimensional conformal and intensity-modulated radiation therapy (IMRT) plans were both used in this work. Patient images were deformable registered to a reference patient using the Nifty Registration package, (NiftyReg, UCL, UK [7]). To avoid potential effects from sliding tissue between the ribs and the lung, bone was excluded from the registration process by truncating Hounsfield Units at 100. The deformable registration is based on a B-spline parameterisation approach. The planned dose distribution was normalised to the reference by directly applying the derived deformable vector field. A visual validation of the registration was performed to ensure that all patients were successfully normalised into the same spatial reference. This approach allows large numbers of patients to be included in the analysis without the requirement for additional contouring.

A sub-set of 386 patients, in whom the heart had been contoured by a clinical oncologist, were used to evaluate the accuracy of deformable registration. The uncertainty was estimated using the standard deviation of the centre of mass coordinates of deformed heart contours. To assess the influence of this uncertainty on the data mining results, dose distributions for each patient were blurred by a Gaussian filter with corresponding width. Results using original dose distributions and blurred distributions were compared.

The difference in mean dose distributions for patients who survived versus those who did not survive at a given time point from end of treatment (3–36 months) was calculated, with patients censored for follow-up. To test if the dose difference between the two groups was statistically significant, permutation testing was used, with 1000 permutations performed. The maximum t-value was used over the average dose distribution to test for significance [8]. The test statistic, maximum t-value, is calculated from the difference in mean dose in a voxel between the two groups divided by the standard deviation of the voxels, with the maximum t-value selected. Permutations then generate random samples to determine the distribution of maximum t-values, this tests the null hypothesis that there is no difference between the two groups. This approach indicates areas of the anatomy, where the observed dose difference is related to a statistically significant difference in patient survival. To