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Tumour anti-vascular effects of radiotherapy (RT) in lung cancer measured using quantitative whole tumour perfusion CT (p-CT)

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Objective: Functional imaging with p-CT provides a non-invasive method of quantifying tumour vascular function. To date, p-CT measurement is limited to a single axial level, with potential for measurement error in heterogeneous tumours. We describe a novel dynamic helical technique allowing whole tumour analysis, and measured tumour vascular changes seen after radiotherapy.
Materials/Methods: Following local research ethics committee approval and written informed consent, twelve patients with advanced non-small cell lung cancer who were due to receive palliative RT (27 Gy in 6 fractions over 3 weeks) were scanned using 16-detector row CT. All patients were scanned before treatment and after the second fraction (9 Gy) of RT. Four patients were also scanned after the fourth (18 Gy) and sixth (27 Gy) fractions of RT. The perfusion studies, consisting of multiple sequential volumetric acquisitions encompassing the entire tumour, were acquired following IV contrast injection. Using Patlak analysis, median values of permeability and blood volume were determined for the whole tumour. Coloured parametric maps of tumour perfusion were also generated allowing visual inspection of whole tumour vasculature.
Results: Mean baseline tumour blood volume and permeability were 5.78 (SD 2.2) ml/100ml and 10.7 (SD 4.2) ml/100ml/min respectively. After the second, fourth, and sixth fractions of RT, blood volume increased from baseline by 37.3% (paired t-test, $p = 0.02$), 57.8% ($p = 0.06$) and 17.1% ($p = 0.01$) respectively. Increases in permeability were also seen after RT but failed to reach significance. Visual inspection of perfusion parametric maps suggest that increases in tumour perfusion after RT were most apparent at the rim of the tumour.
Conclusion: Tumour vascular changes after RT can be measured using whole tumour p-CT. We have demonstrated an acute hyperaemic response to RT in lung cancer.

Poster presentations (Mon, 31 Oct)
Imaging

1107 POSTER

Dynamic contrast enhanced MRI (DCE-MRI) implementation and reproducibility for quantitative analysis in a multi-center trial of an anti-angiogenic agent

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Background: Dynamic Contrast Enhanced MRI (DCE-MRI) provides biomarkers which change rapidly in response to pharmacologic activity of anti-angiogenic compounds in tumours, and are readily translatable from animal models into clinical trials. A considerable body of data has been published demonstrating the ability of quantitative DCE-MRI to detect response to anti-angiogenic and antivascular drug treatment in single center trials[1]. In contrast, there is limited evidence to date to show that DCE-MRI can be implemented in a multi-center setting. Since most oncology drug trials are performed in multiple centers, in order to expedite patient recruitment, particularly in later phases of development, limitation of DCE-MRI to single centre studies would be a severe limitation. The purpose of this work was to develop, evaluate and implement rigorous standardization and quality control methods to support this technology in a multi-center setting.
Methods: A comprehensive site training, cross-calibration and quality control process was prospectively implemented for a multi-center trial of an anti-angiogenic compound, ZD6474, using DCE-MRI. 2 sites were included in the study, with 2 different scanner models from 2 different manufacturers. Collected data underwent rigorous centralized quality checks for readability, completeness, compliance with the MRI protocol, lack of significant misregistration, uniformity of signal intensities across series within dataset, adequacy of lesion identification and coverage, and consistency in the application of the technique across visits. A software package was developed and validated in compliance with Good Clinical Practices [GCP] and 21 CFR Part 11, Electronic Records and Signatures, so as to derive reliable analyses of data from the various centers. The analysis software underwent exhaustive testing to ensure accurate replication of two voxelwise DCE-MRI analysis methods previously performed at academic research centers: IAUC (the initial area under the time-concentration curve[3]) and K^{trans} (transfer constant between blood plasma and extravascular extracellular space[5]). The software was tested using a simulated data set and live subject data. The reproducibility of the DCE-MRI process was assessed using repeat datasets without intervening changes in treatment.
Results: of 19 patients enrolled, 17 underwent DCE-MRI studies after study treatment. All were metastatic liver studies of a range of tumor cell types. 42 DCE-MRI timepoints were acquired and centrally collected for quantitative analysis. 11 patients (27 timepoints) were deemed fully analyzable (a data loss of 36%). The issues identified for the remaining patients encompassed anomalous signal intensity differences between the precontrast and early dynamic series, misregistration between the precontrast and the dynamic series and poor dynamic range of signal intensities. The software package was tested and validated by comparison with an independently derived analysis, implemented at an academic centre lacking validation in compliance with GCP and 21 CRF Part 11. Control for differences in user-defined parameters including: integration start time; lower and upper bounds of T1, S0, and contrast concentration; and tumor and muscle region of interest selection, was essential. In addition, during the comparison it was noted that small differences in the details of the implementation of the IAUC and K^{trans} analyses could lead to significant differences in measurements obtained on the same data, in particular: baseline T1 estimates computed using iterative or analystic approaches; Tofts' model concentration vs. time estimates computed using the sum of exponentials verses definite integral form of the model with numerical integration (trapezoidal approximation); estimates fitted using a conjugate gradient method versus a (derivative free) simplex method. After eliminating these points of divergence, the results from the two implementations were essentially identical. The reproducibility of the DCE-MRI method was assessed and the results found to be in general agreement with previously reported values in the literature[2,4]. The coefficient of variation (CoV) for IAUC60 was 0.19 and mean % absolute change of median parameter value, 23%. The results for K^{trans} were CoV 0.18 and mean % absolute change of median parameter value, 17%. It is worth noting that the previous reports are from single centre studies. This is, to the best of our knowledge, the first demonstration of comparable reproducibility in a multi-centre trial.
Conclusions: DCE-MRI represents an important tool for the clinical development of anti-angiogenic compounds for the treatment of cancer. The utility of such physiologic imaging for quantitative analysis in multi-center clinical trials is demonstrated through the implementation of careful standardization and quality control measures as well as centralized data analysis by means of validated software. Despite the undoubted utility of the method, considerable loss of data may occur in this form of trial, which should be taken into consideration for trial design.

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