

SBRT) despite many differences to GN-RF: (1) safety margins are used in almost all SBRT indications; (2) in lung SBRT, the use of safety margins will result in inclusion of low density lung tissue into the target volume; (3) radiotherapy delivery is today performed using MLC and in many centers intensity-modulated techniques allowing more sophisticated dose shaping; (4) target and organs at risk motion will affect the delivered dose profile as compared the planned dose profile; (5) the composition of the target volumes in SBRT is very different to GN-RS - Organs-at-risk are not only close by but within the target volume; (6) in the RTOG protocols of SBRT for stage I NSCLC, dose prescription to a wide range of isodose lines is allowed.

Based on these differences between GN-RS and SBRT above, it is obvious that the concept of dose prescription to a fixed isodose line is not sufficient for SBRT practice. The dose profile within the target volume needs to be sufficiently prescribed and reported to achieve better standardization and comparability between institutions, studies and individual patients. Additionally, current SBRT technology allows to adapt the dose profile within the PTV to the patient-specific clinical requirements: homogeneous dose profiles or even cold spots might allow organ at risk sparing; in contrast, an escalation of the dose within the target center might be beneficial for targets without critical normal tissue within the PTV. Recommendations by the ICRU specific for the needs of SBRT are eagerly awaited and future studies will better define how to optimize SBRT dose planning.

SP-0413

To use or not to use the LQ model at "high" radiation doses
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In curative SBRT regimen, few large doses per fraction are applied in a highly conformal way. Such protocols, however, usually do not only differ from conventional protocols in the size of the dose per fraction, but also with regard to overall treatment time and total (equieffective) dose. Moreover, large doses per fraction are usually administered to (normal tissue) volumes that are clearly smaller compared to conventional protocols. Hence, all these parameters, i.e. recovery, repopulation, tumour reoxygenation and normal tissue volume effects, need to be included into considerations concerning the biological effect of SBRT protocols - independently for tumor, early and late responding tissues.

The effect of dose per fraction ("recovery") for tumors is - with few exceptions - considered as low, as expressed by a high a/b -value in the linear-quadratic (LQ) model. Recently, a high fractionation effect was shown for prostate and breast tumors, and is also discussed for others. For lung tumours, however, a small capacity for recovery can be assumed. Early responding normal tissues usually display a similarly low fractionation effect, while most late radiation effects have a high sensitivity with regard to changes in dose per fraction. Hence, doses per fraction must be adjusted to the respective tumor type and the expected (late) morbidity pattern in order to achieve the biologically equieffective doses that result in optimum dissociation between treatment efficacy and adverse events.

The linear-quadratic model has been shown to only inadequately describe the effect of large doses per fraction (>6-10 Gy) for cell survival endpoints in vitro (colony forming assay) and in vivo (e.g. intestinal crypt survival assay). Here, the LQ model overestimates the effects of exposure in the high-dose region. It needs to be emphasized, however, that in the vast majority of pre-clinical investigations and analyses of the fractionation effect for morphological and functional endpoints, large doses per fraction and/or single doses were regularly included. In clear contrast to the cell survival based analyses, these studies in general do not show any major difference of the fit of the LQ model for the in- or exclusion of large doses per fraction in the analyses. Moreover, no deviation of the resulting a/b -values from the respective estimates from clinical data was observed. This indicates the applicability of the LQ model also for the calculation of

equieffective doses at high doses per fraction, such as applied in SBRT protocols in the lung. Besides high dose per fraction,

SBRT protocols regularly include a shortening of the overall treatment time (OTT) compared to conventional or moderately hypofractionated protocols. This is associated with less tumour repopulation, which also contributes to the increased tumor effectiveness. With very few fractions in short time intervals, however, tumour reoxygenation may also be less effective, thus at least partly counteracting the benefit of the shorter OTT. It also needs to be noted that SBRT protocols with short OTT are less permissive for regenerative processes in early responding normal tissues. These protocols hence also bear a risk of increased early normal tissue reactions and thus, in certain tissues, of enhanced ("consequential") late effects.

The administration of large doses per fraction and large total doses is mainly facilitated by a strong conformation of the high-dose volume to the target, i. e. a minimization of the normal tissue volumes exposed to these doses, and is associated with very steep dose gradients within the adjacent normal tissues. However, it must be emphasized that in such scenarios, not only the amount of normal tissue effects may be changed, but also their quality, with altered tissue pathophysiology and morbidity endpoints that are usually not observed with conventional or moderately hypofractionated protocols. Prominent examples are the manifestation of atrophic rather than fibrotic processes, or pathologic rib fractures in SBRT of peripheral lung tumors.

In conclusion, administration of large doses per fraction in SBRT may be advantageous for biological reasons. Estimation of biologically equieffective doses may be based on the standard LQ model. However, such treatment strategies not only impact on tissue recovery, but can also affect other radiobiological parameters (radiopathology, repopulation, volume effects) in a complex manner. Therefore, the patients included in such therapeutic protocols need to be monitored carefully not only for treatment outcome, but also for treatment-related morbidity.

Proffered Papers: Physics 10: Functional Imaging I

OC-0414

Assessing 4DCT-ventilation as a functional imaging modality for thoracic radiation therapy

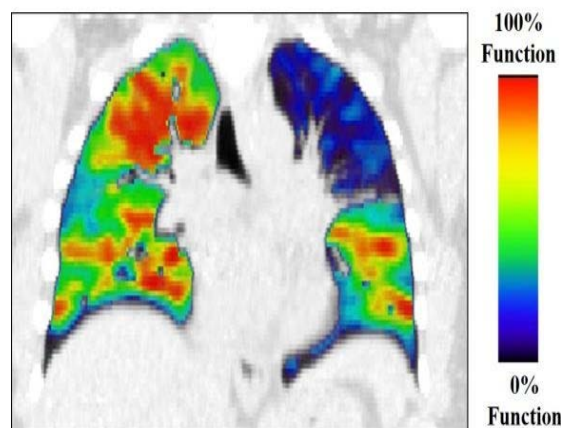
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Purpose or Objective: 4DCT-ventilation is an exciting new lung function imaging modality that uses 4DCT data to calculate lung function maps (Fig 1).



Because 4DCTs are acquired as part of routine clinical care, calculating ventilation from 4DCTs provides clinicians the ability to evaluate spatial lung function without added monetary or dosimetric cost to the patient. Development of clinical trials is underway to use 4DCT-ventilation for thoracic functional avoidance with the idea that preferential radiotherapy (RT) sparing of functional regions may decrease toxicity. Before 4DCT-ventilation is incorporated in a clinical trial; work is needed that assesses the clinical utility of 4DCT-ventilation imaging. The purpose of this study was to evaluate 4DCT-ventilation as a functional imaging tool for RT.

Material and Methods: The study assessed 118 stage III lung cancer patients. 4DCT images, spatial registration and a density-change based model were used to compute a 4DCT-ventilation map for each patient. Full 4DCT-ventilation assessment included: 1) comparison of 4DCT-ventilation against nuclear medicine ventilation (VQ) imaging and pulmonary function tests (PFT) 2) an analysis to determine whether dose to highly ventilated regions of the lung was a better predictor for toxicity than dose alone and 3) an evaluation of the percentage of lung cancer patients with significant ventilation defects. 4DCT-ventilation was compared to VQ imaging and PFTs using radiologist observations, sensitivity and specificity analysis, and correlation coefficients. Bootstrap methods were used to evaluate whether ventilation-based dose-function metrics were a better predictor for grade 3 radiation pneumonitis than dose metrics alone. Radiologists assessed the percentage of patients with significant ventilation defects with the idea that if patients had homogenous ventilation there would be no basis to preferentially spare any regions; conversely functional avoidance can be done for patients with ventilation defects.

Results: Comparing radiologist noted defects between 4DCT-ventilation and VQ imaging, we calculated a sensitivity, specificity, and accuracy of 90%, 64%, and 81% respectively. Correlation coefficients comparing 4DCT-ventilation to PFTs ranged from 0.63-0.72. Bootstrap results suggested an improvement in toxicity prediction using dose-function metrics compared to dose alone ($p=0.11$). Clinical ventilation defects were noted in 69% of our study cohort.

Conclusion: Our study demonstrates that 4DCT-ventilation provides clinically meaningful lung function information, is a better predictor of toxicity than dose alone, and that a significant portion of patients have substantial ventilation defects. Our work provides the largest and most comprehensive study to fully evaluate 4DCT-ventilation as a thoracic functional imaging tool and presents strong evidence for the incorporation of 4DCT-ventilation into prospective clinical trials.

OC-0415

The effect of breathing motion on CT radiomics feature extraction in oesophageal cancer

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Purpose or Objective: Medical imaging plays a crucial role in response evaluation due to its non-invasive character and wide applicability and availability. Next to the routinely used metrics (e.g. RECIST), extraction of a large number of quantitative radiomics features might unravel more information in these medical images. To quantify the reliability of these features across different phases in the breathing cycle, the stability of 59 radiomics features in respiratory-correlated 4D CT-scans of patients with oesophageal cancer was investigated. Since the tumour does not change during image acquisition, quantitative features derived from it should not change either. Hence, we

hypothesised that 4D-RCCT provides a valuable means to identify the most reliable features.

Material and Methods: Twenty-five oesophageal cancer patients (stage IB-IIIC) who received a 4D-RCCT scan for radiotherapy planning between October 2012 and March 2014 were included in this study. The gross tumour volume (GTV) of the primary tumour was delineated on the 50% exhale (50ex) CT phase using all available diagnostic information. The delineations were copied to the CT images of the other breathing phases: 0in, 25in, 50in, 75in, 100in, 25ex and 75ex. Next 15 first-order statistics and 44 textural radiomics features were calculated for the GTV. For each feature, the pairwise intra-class correlation coefficient (ICC) between all possible phase combinations was calculated. Features with a pairwise ICC-value of at least 0.85 between all phase combinations were considered to have an acceptable stability throughout all phases of the breathing cycle.

Results: Of the 44 textural features, 12 (27%) were not susceptible to breathing motion ($ICC > 0.85$). Also 9 out of the 15 (60%) first-order statistics features turned out to be stable. The statistics-energy and graylevel-nonuniformity (GLN) features, found to be prognostic in both head-and-neck and lung cancer [Aerts et al. Nat. Commun. 5 (2014)], were among the most stable features with minimum ICC-values of 0.98. In general, the highest ICC-values were observed when two adjacent phases (e.g. 50ex-75ex) were compared.

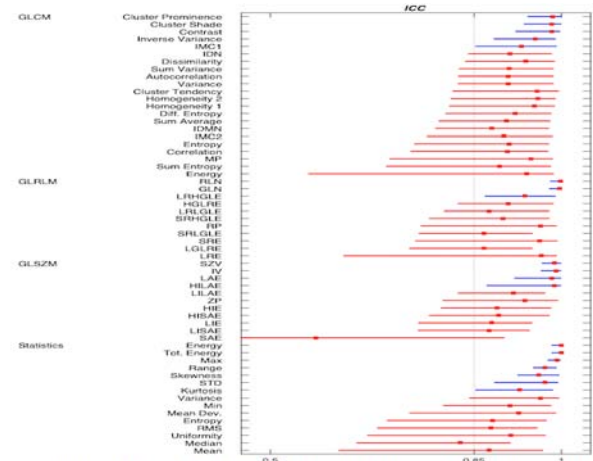


Figure 1. Graphical representations of the pairwise ICCs for all phases of the 4D-RCCT scan. The horizontal lines extend from the minimum to the maximum observed values per feature, and are blue when every ICC > 0.85. The red dots represent the median. Features are, for each feature group, ranked by their minimum ICC values. Abbreviations for the textural feature groups: gray-level co-occurrence (GLCM), gray-level run-length (GLRLM) and gray-level size-zone (GLSZM).

Conclusion: This study identified nineteen CT radiomics features that were not subject to breathing motion in patients with oesophageal cancer. The remaining features were affected by the differences in breathing phase. This emphasises the importance of tumour-site specific feature selection together with a strict imaging and delineation protocol before using them for further clinical applications.

OC-0416

FDG-PET can objectively quantify esophageal dose-response and toxicity during radiation therapy

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Purpose or Objective: To use FDG-PET uptake during treatment course to objectively quantify esophagitis severity, understand esophageal dose response, and examine the timing of increased PET uptake and esophagitis symptoms for possible early detection of eventual toxicity.