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Status, limitations, and perspectives of current applications of pre-treatment computed tomography in radiation oncology

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Computed tomography (CT) images from fan-beam medical grade scanners are the current gold standard for treatment planning in radiation oncology: they provide geometrically correct, reliable, and quantitative measures of photon attenuation in the patient. However, this information is not fully identical with the physical quantities needed for dose calculation and optimization and additional uncertainty is introduced by inferring them from the kV images. Also, the low soft tissue contrast in CT impacts delineation accuracy. While additional imaging modalities are advocated as complementary – sometimes alternative – techniques to CT imaging, uncertainties in image registration can even deteriorate the quality of treatment planning.
Dual-energy CT – i.e. using scans from two X-ray spectra or detection in two separate energy ranges – retains the virtues of computed tomography while it opens at the same time the possibility to overcome the restrictions mentioned. It can improve the accuracy of dose calculation and delineation and enables to abandon the use of a general translation rule ("Hounsfield look-up table") for the photon attenuation (CT numbers) - replacing it by a patient-specific determination of radiological tissue quantities. DECT-derived quantities might additionally provide opportunities in advanced image analysis methods such as radiomics, i.e. the machine-learning-based approach for the prediction of patient outcome and treatment personalization. CT-based radiomics analyses might even be able to uncover information that can so far only be derived from additional multi-modal imaging.
Currently, many applications based on innovations in pre-treatment CT imaging and image analysis are investigated that could have the potential to change clinical practice in future. This presentation is intended to set the stage for the focus session which tries to look into the question, which of these applications can find its way into routine clinical application.

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Dual-energy CT for photon therapy – benefits and limitations

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In current treatment planning for both photon and particle therapy, a heuristic Hounsfield look-up table (HLUT) is used for the conversion of CT numbers to electron density or particle stopping-power ratios, respectively. However, this conversion is ambiguous and cannot account for patient-specific tissue variability or non-tissue materials (e.g., implants, contrast agent). This can lead to substantial difference in dose distributions. In contrast, dual-energy computed tomography (DECT) allows for direct patient- and tissue-specific determination of radiological quantities. Therefore, DECT is currently being investigated by many groups as an alternative imaging modality.
While the benefit of DECT is rather pertinent in particle therapy, where an accurate range prediction is crucial, we suggest that it might also improve conventional photon treatment planning, especially in the presence of non-tissue materials such as implants. In this context, DECT-based material characterization can help to identify implants of unkown composition. Moreover, their electron density can automatically be correctly assigned, as the DECT algorithm does not require tissue equivalency. This might provide more accurate dose distributions in cases, where the beam traverses a non-tissue material that would deviate considerably from the HLUT.
Furthermore, the acquisition of a DECT scan of patients with administered contrast agent enables the calculation of an image, where the influence of the contrast agent can effectively be removed. This would render the additional native CT scan obsolete, reducing overall CT dose to the patient. Finally, DECT also allows for a certain tuning of contrast by an overlay of the two images, which might be exploited for diagnostic or delineation purposes.

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Dual-energy CT for particle therapy – benefits and limitations

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Due to the physical advantages of particles in energy deposition compared to photons, a high-conformal tumor coverage can be reached while sparing healthy tissue more effectively. However, particle treatment planning is currently associated with large uncertainties related to a CT-based stopping-power and eventually particle range prediction. To fully exploit the physical benefit of particles, this substantial part of the overall range uncertainty of approximately 3.5 % of total range should be reduced.
Dual-energy CT (DECT) imaging is a promising technique to increase the accuracy of CT-based range predictions as already shown by many research groups. The effective benefit of DECT for particle treatment planning of cancer patients is currently proven using a comprehensive validation scheme to quantify the potential reduction of range uncertainties in daily clinical practise. In the framework of a joint project between DKFZ and OncoRay, extensive investigations on different levels (inhomogenous phantoms, biological tissue, clinical patient scans) have been performed. Here, a considerably improved accuracy of DECT compared to the current state-of-the-art, single-energy CT (SECT), could be shown in an anthropomorphic ground-truth phantom and biological tissues. Moreover, relative comparisons of predicted particle ranges in more than 100 proton treatment fields of patients reveal median range deviations of 1.5 – 2.0 % of total range between DECT and SECT. Based on these results, the clinical use of DECT-based range prediction would clearly improve the accuracy and robustness of particle treatment planning and is thus highly recommended to be the new standard imaging modality for treatment planning in particle therapy.

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Radiomics-prediction of patient-specific outcome using pre-treatment CT imaging

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Radiomics is the high-throughput analysis of medical images for treatment personalisation. It is hypothesised that medical images contain information related to both cancer treatment success and toxicity probabilities, allowing for the stratification of cancer patients using radiomics signatures prior to treatment. Models including radiomics features based on pre-treatment imaging are commonly reported to outperform models based on clinical parameters alone. Features extracted from medical images are the linchpin around which radiomics revolves. Generalisable radiomics models consist of a small signature set of highly reproducible image features and are trained on a large heterogeneous multi-centre patient dataset. Developments in radiomics are expected to follow two non-exclusive paths. The first path is the development of radiomics models using large multi-centre data sets of hundreds or thousands of patients. These data sets are heterogeneous, with varying imaging protocols, varying treatment and varying volume delineations. The size and heterogeneity of the available data will allow selection of a small set of reproducible features. However, such a feature set may not capture all the complexities and produce a sub-optimal model for treatment individualisation. The second path therefore focusses on increasing the size of the set of relevant, non-redundant and robust features. Standardisation of methodology and protocols, combined with an increase in quality and specificity of pre-treatment imaging enlarges the set of relevant features. Dual energy CT (DECT) is interesting in this respect. DECT is highly quantitative, offers noise reduction compared to conventional single-energy CT, and also allows for voxelwise determination of tissue-specific aspects such as electron density, effective atomic number, and tissue composition. Evaluations of DECT-based radiomics are ongoing, and first results will be presented at the meeting. In conclusion, high quality, standardised imaging and the willingness to share and collaborate are crucial for translation of radiomics from a promising technique into clinical application.

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CT-radiomics to assess biological and functional tumor properties

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Recently, the use of Computed Tomography (CT) image data for *Radiomics* has been proposed, which is the high-throughput extraction of a large amount of quantitative, mathematical features from imaging data to predict radiotherapy (RT) outcome. The aim of this study was to investigate the correlation of a prognostic CT-radiomics signature with hypoxia PET information, which has been shown earlier to be prognostic for therapy outcome in head and neck cancer (HNC).
For this study, planning CT data including contoured tumor volumes were available for n=149 HNC patients. The validation data set consisted of additional n=23 HNC patients where a planning CT and a hypoxia PET scan acquired with [^{18}F]-FMISO was available. For radiomics analysis, a total of 1141 radiomics features including intensity, shape, texture and wavelet features were calculated for each CT. In a first step, a prognosis model was trained using the data of the initial 149 HNC patients to derive a prognostic CT-radiomics signature. Then, the accuracy of this CT-radiomics signature was validated and compared to the prognosis score of FMISO PET (tumor to background > 1.4) in the validation cohort.
For the training cohort, a CT-radiomics signature was developed using Neural Networks which consisted of five radiomics features. The area under the curve (AUC) of this model was 0.79 ± 0.14. Applying this signature to the validation cohort yielded a residual AUC of 0.68, whereas patient stratification according to FMISO PET led to AUC_{FMISO}=0.67.
The results of this study show the great potential of CT-radiomics in terms of prognosis modeling and patient stratification. However, this study demonstrates that identification of patients with radiation resistant tumors using CT-radiomics performs comparable to FMISO PET imaging. Hence, CT-radiomics may have a role in the selection of hypoxic patients and thus in the planning of biologically adapted, personalized RT approaches.

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Do we need improved (dual-energy) CT imaging?

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In the era of image-guided high-precision radiotherapy, all clinically used imaging modalities need to benefit the individual patient's treatment outcome in order to be reimbursed. From a radiation oncologist's point of view dual-energy CT (DECT) ought to (1) improve target volume delineation, (2) decrease proton range uncertainty and (3) guide patient stratification using advanced image analysis methods, i.e., Radiomics.
(1) With the acquisition of DECT scans more information on the tissue composition and its contrast can be gathered. This may potentially air delineation of the primary tumor and surrounding organs at risk. Possibly, even the inter-observer variability may be reduced. In order to assess whether this is a measurable effect, we are currently conducting a delineation study. However, can this potential benefit also be transferred into clinical routine?
(2) Using DECT, the prediction of electron density (for photon therapy) and stopping-power ratio (for proton therapy) can be improved. Consequently, DECT would increase overall accuracy due to a patient-specific calculation without neglecting the intra- and inter-patient tissue diversity and variability. In particle therapy, CT-related range uncertainties may be reduced and the full potential of the beam modality subsequently exploited. Do we, however, dare to directly apply this in our clinics?
(3) Apart from improved treatment planning and delivery, DECT may also further characterize the primary target volume and possibly metastatically affected lymph nodes to predict outcome and enable patient stratification. This approach has been shown beneficial on non-contrast enhanced CT scans in non-small cell lung and head and neck cancer patients. Thus far, there are no data on the value of DECT. Thus, we need to ask: Are our current imaging protocols good enough to be quantitative? Do we need standardized imaging protocols in our own institution and different institutions? What does it take to make clinical decisions based on Radiomics?