Improved radiotherapy for locally advanced Non-Small Cell Lung Carcinoma (NSCLC) patients - DTU Orbit (15/03/2019)

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Lung cancer is worldwide one of the most common cancer diseases with a high mortality rate. There is thus an urgent need for improving radiotherapy for these patients. Radiotherapy for lung cancer patients is challenging because the tumor and organs at risk (OARs) move with the breathing motion. Deep-Inspiration-Breath-Hold (DIBH) is a technique that potentially can improve the treatment for these patients. DIBH is frequently and routinely used for breast cancer treatments. However, it is still an experimental method for lung cancer patients e.g. due to preconceptions about their incapability to comply with the DIBH technique. For DIBH, the patients are guided to hold their breath almost at their maximum inspiration level during imaging and treatment. This leads to reduction of the breathing motion which decreases the movement of the tumor and OARs. It also expands the lung tissue which is beneficial with respect to sparing the healthy lung from radiation. In order to ensure that the tumor is receiving the prescribed dose, safety margins are added to the gross tumor volume (GTV). The size of the margins depends on the uncertainties related to the patient setup, target delineation, respiration, other internal motion, etc. These extra margins result in larger irradiated volumes, increasing the risk of radiation-induced side effects. By reducing the uncertainties and thereby the margins, the healthy tissue can be spared from unnecessary radiation. The respiratory uncertainties can potentially be reduced by the DIBH method for the lung cancer patients.

The overall aim of the clinical part of this thesis was to clarify the potential benefit of offering DIBH gating, compared to free-breathing (FB), for lung cancer patients. Particularly, the benefits for locally advanced non-small cell lung cancer (NSCLC) patients were explored. For the dosimetric part of the thesis, the dosimetric aspects of correct dose calculations in heterogeneous patient-like geometries were studied. The clinical aspects of DIBH were evaluated in three different studies, where planning and setup verification images acquired in both FB and DIBH were evaluated.

In adaptive radiotherapy (ART) the treatment plan is adapted to geometrical changes of the patient over the course of treatment. However, defining anatomical structures for treatment planning is a time consuming process prone to large uncertainties. In order to save time and to reduce the uncertainties during ART, image registrations between the planning computed tomography (CT) and the subsequently acquired images may facilitate the delineation process. Study I investigated the uncertainties related to automatic deform image registrations between the planning CT and the setup images acquired at the accelerator, and the extra CTs acquired over the course of treatment. The studied algorithm was found not to be adequate enough to correct for image artifacts and large anatomical deformations present in the images. Furthermore, no difference between DIBH and FB was observed.

Study II investigated different image based setup verification protocols. The goal was to minimize the applied setup margins. It was found that soft-tissue registration on the tumor volume resulted in the smallest planning target volume (PTV), irrespectively of FB and DIBH. Setup uncertainties were however introduced during DIBH, but the resulting PTV in DIBH was nevertheless smaller compared to FB. We speculate the increased uncertainty was due to some patients tended to arch with their back to compensate for their insufficient compliance to reach the breath-hold amplitude level.

Study III investigated the clinical dosimetric benefit of DIBH treatments, planned using a commercial Anisotropic-Analytical-Algorithm (AAA) dose calculation algorithm. Detailed Monte Carlo (MC) simulations were carried out for this purpose. DIBH resulted in better dose sparing of the OARs, compared to FB. However, the MC simulations revealed similar inferior target dose coverage between MC and AAA irrespectively of FB and DIBH treatment plans. This observation is therefore related to the treatment planning dose calculation algorithm rather than the breathing adapted treatment technique.

The dosimetric aspects of complex dosimetry in heterogeneous patient-like geometries were explored in two different studies in the thesis. In order to investigate known calculation issues in the thorax region, a thoracic-like phantom was designed and constructed to obtain detailed dosimetry information in heterogeneous clinically relevant geometries. The lungs of the phantom were constructed in low-density balsa wood, the body in Poly(methyl methacrylate) (PMMA), and the bone in high-density delrin.

Study IV investigated the performance of AAA, using a plastic scintillator detector system and the well-defined heterogeneous phantom. The treatment planning system (TPS) calculated doses agreed for the least complex cases, while for the more complex cases dose deviations ≥ 4% were observed. The dosimetric challenges in TPS calculations for clinically relevant geometries were underpinned.

For lung cancer treatments, tumor volume changes during radiotherapy are well known. Due to incorrect scatter calculations by the TPS, the dosimetric challenges increase when tumor and field sizes decrease. The philosophy of radiotherapy is to deliver the same prescribed dose to the tumor volume, irrespective of the size of the tumor. Study V investigated the dosimetric challenges for the TPS in the heterogeneous thoracic-like geometry and its dependence on tumor size. Thus, a change of tumor size and resulting plan adaption over the course of a treatment was simulated. For this purpose, tumor inserts of different sizes (ranging from 1-8 cm in diameter) was used in the phantom. Severe dose deviations were observed, especially for small tumor sizes ≤ 2 cm in diameter. Our results imply that there exist severe tumor-size dependency, which potentially could have implications on the radiotherapy treatment planning of lung cancer.

This thesis concludes that the clinical gain of DIBH is not always beneficial over FB treatments. There were additionally identified severe tumor-size dependent dose deviations that were large enough to potentially have implications for lung cancer radiotherapy treatment planning. The scintillator system and the heterogeneous phantom provide a promising tool for critical evaluation of complex radiotherapy calculations and dose delivery.

**General information**