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A multi-technique hierarchical X-ray phase-based approach for the characterization and quantification of the effects of novel radiotherapies

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Cancer is the first or second leading cause of premature deaths worldwide with an overall rapidly growing burden [1]. Standard cancer therapies include surgery, chemotherapy and radiotherapy (RT) and often a combination of the three is applied to improve the probability of tumour control. Follow up techniques, able to monitor and investigate the effects of therapies, are important for surveying the efficacy of conventionally applied treatments. They are also key for evaluating the curing capabilities and the eventual onset of acute or late adverse effects of new therapies. In this framework, this research project proposed the X-ray Phase Contrast Imaging - Computed Tomography (XPCI-CT) technique [2] to study and quantify the effects of novel RTs, namely Microbeam and Minibeam Radiation therapy (MRT [3] and MB [4]), and to compare them to the standard Broad Beam (BB) induced effects on brain and lungs in pre-clinical settings. MRT and MB deliver an array of highly collimated micrometric spatially fractionated X-ray beamlets issued from a synchrotron radiation source. To visualize with high sensitivity the effects of the treatment along and outside their path, a high-resolution and a full-organ imaging approach is necessary. XPCI-CT was here suggested and proven as a powerful imaging technique able to determine and quantify the effects of the radiation on normal and tumour-bearing tissues [5-6]. Moreover, it is shown as an effective technique to complement, with 3D information, the histology findings in the follow-up of the RT treatments. Using a multi-scale and multi-technique X-ray-based approach, we analysed the effects of RT delivery on healthy and glioblastoma multiforme-bearing rat brains as well as on healthy rat lungs. Ex-vivo XPCI-CT datasets acquired with isotropic voxel sizes down to 0.65³ µm³ could distinguish, with high sensitivity, the idiopathic effects of MRT, MB and BB therapies. Histology, immunohistochemistry, synchrotron Small- and Wide-Angle X-ray Scattering and X-ray Fluorescence experiments were also carried out to accurately interpret and complement the XPCI-CT findings as well as to obtain a detailed structural and chemical characterization of the pathological and treatment-effect features. Overall, this multi-technique approach provided the recognition and differentiation of brain and lungs anatomical details down to the cellular level and identification of microscopic cancerous cell-clusters far from the main lesion. For brains, it was possible to discriminate tissue necrosis, tumour oedema, micrometric MRT-transections as well as high-density calcifications, identified, for the first time, as hydroxyapatite crystals with the coexistence of Fe deposits [5]. In lungs, radiation induced fibrosis and collagen noduli are visible. The former can be visualized as thickening of alveolar walls, expansion of alveolar spaces and destruction of their normal structures, which are replaced by irregular, abnormal air spaces and large areas of scarring [6]. The 3D nature of XPCI datasets was finally exploited to quantify the radio-induced pulmonary and brain lesions. This multi-technique approach appears to be well suited for investigating cancer development and radiotherapy effects on both the studied biological targets. In the future, other types of tumours and target organs will be considered and the method will be also tested for image-guidance during radiotherapy in preclinical research.

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