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Combined Anti-Connective Tissue Growth Factor and Radiotherapy with Carbon ion in Experimental Tumor- and Normal Tissue Response Models

Promotionsfach: Radiologie

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This dissertation explored the potential to combine CTGF inhibition with radiotherapy for the treatment of pancreatic cancer. Carbon radiotherapy was compared with photon radiotherapy alone and in combination with human FG-3019 and murine FG-3149 antibodies against CTGF using *in-vitro* and *in-vivo* assays.

Inhibition of CTGF in combination with radiotherapy, and particularly carbon radiotherapy, offer a promising approach in PDAC treatment. Treatment with anti-CTGF in combination with radiation therapy delayed the tumor growth, which was triggered by reduced tumor cell proliferation, impaired DNA damage repair, increased tumor cell apoptosis, reduced collagen accumulation in tumor stroma, and reduced tumor vasculature.

A new method to quantify the lung parenchyma density (HU) and volume (cm³), the two key quantitation readouts for longitudinal monitoring based on an objective 3D segmentation algorithm using clinical-CT was employed. In the radiation-induced lung fibrosis model, the morphologic results in histopathology were also in alignment with the results of quantitative clinical-CT and qualitative micro- μ CT used for assessment of lung fibrosis in the experimental mouse model.

Presence of anti-CTGF Ab (FG-3149) during carbon ion irradiation resulted in enhanced acute lung injury with increased apoptosis and impaired DNA damage repair capacity which ultimately resulted into augmented radiation induced pulmonary fibrosis at the late stage. In contrast, late onset of anti-CTGF therapy 16 weeks post carbon irradiation

injury attenuated the radiation-induced lung fibrosis. Improved respiratory function was seen in mice treated with FG-3019 including normal pH, BE, low PCO₂, low TCO₂, increased sO₂% and decreased HCO₃ concentration in the blood.

Further mechanistic studies are required and initiated to characterize the detailed functions of pathways modulated by CTGF inhibition and ionizing radiation.