Radiation-induced changes in microcirculation and interstitial fluid pressure affecting the delivery of macromolecules and nanotherapeutics to tumors.

Abstract:
The immature, chaotic microvasculature of most solid tumors can present a significant impediment to blood-borne delivery, uneven distribution, and compromised penetration of macromolecular anticancer drugs and diagnostic agents from tumor microvessels across the interstitial space to cancer cells. To reach viable tumor cells in relevant concentrations, macromolecular agents are confronted with several barriers to vascular, transvascular, and interstitial transport. Amongst those (1) heterogeneous and poor blood supply, (2) distinctly reduced or even abolished hydrostatic and oncotic pressure gradients across the microvessel wall abrogating the convective transport from the vessel lumen into the interstitial space (impairment of transvascular transport), and (3) impediment of convective transport within the interstitial compartment due to elevated interstitial fluid pressure (IFP) (resulting from hyperpermeable blood vessels coupled with non-functional lymphatics) and a dense structure of the interstitial matrix are the major mechanisms hindering drug delivery. Upon irradiation, changes in these barrier functions are inconclusive so far. Alterations in vascular transport properties following fractionated radiation up to 40 Gy are quite inconsistent in terms of direction, extent, and time course. Total doses above 45 Gy can damage tumor...
microvessels, additionally impeding vascular delivery. Vascular permeability for macromolecules might be enhanced up to a total dose of 45 Gy. However, this effect is counteracted/abolished by the elevated IFP in solid tumors. When assessing IFP during fractionated radiotherapy in patient tumors, inconsistent alterations have been observed, both in direction and extent. From these data it is concluded that modulations in vascular, transvascular, and interstitial transport by irradiation of solid tumors are rather unclear so far. Translation of experimental data into the clinical setting thus needs to be undertaken with especial care.