Late residual gamma-H2AX foci in murine spinal cord might facilitate development of response-modifying strategies: a research hypothesis.

Abstract: The central nervous system (CNS) is among the critical late-responding normal tissues which influence radiation treatment planning and dose prescription. Both mouse and rat spinal cord are established radiobiological models. As late reactions in rodents develop many months after irradiation, long-term follow-up is necessary. Development of radioprotective strategies and refinement of optimum dose and administration schedules are therefore quite complicated and time consuming. Obviously, surrogate endpoints that allow for screening of radioprotective agents and optimisation of dosing with shorter follow-up would speed up and facilitate this type of radiobiological research. Such surrogate endpoints should be analyzable during the clinically asymptomatic latent period, ideally as early as possible. As unrepaired cellular damage is a prerequisite for overt side-effects of radiotherapy, detection of residual damage might predict for radiation myelopathy. Immunohistochemical evaluation of irradiated mouse spinal cord with phosphorylated histone H2AX (\gamma\text{-H2AX}) was performed. Preliminary data suggest that residual damage can be detected in mouse spinal cord and that such foci continue to be detectable over a long time period, which clearly extends into the phase where development of late reactions starts. Our initial findings justify further research which attempts
to correlate γ-H2AX foci with the primary endpoint, i.e. radiation myelopathy. It can then be explored whether a given radioprotective agent reduces the number of foci and whether this translates into reduced incidence of radiation myelopathy. A rapid and reliable animal model would allow for screening of a large number of candidate drugs that might modify the radiation response of the spinal cord.