Late effect of radiation therapy on normal tissue.

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Body of Abstract: The prime goal of radiation therapy is the delivery of lethal doses of radiation to cancer cells with the least toxicity to adjacent normal tissues. Late normal tissue toxicity may, however, occur several months to several years after radiation therapy, depending on various factors, such as the total dose administered, radiation quality, treated volume, fractionation schedule, and individual sensitivity. The simple classification of radiation injury as early and late effect depending on the timing of clinical symptoms is now replaced by a “continuum concept” based on the fact that there is a link between initiation, development and persistence of radiation injury.

The response of normal tissue to radiation injury is caused by complex multicellular alterations that might be partially compared to a post-traumatic wound healing process. However, the initial free radical burst caused by tissue exposure to ionizing radiation lead to radiation specific DNA damage, protein and lipid alterations. Furthermore, repetitive radiation exposure caused by the fractionation of radiation therapy may alter the ongoing repair processes and might thus contribute to inflammatory cells recruitment and to sustained inflammatory response. After a latency phase, late effects comparable to a chronic wound healing process may develop in susceptible patients.

Different mechanistic models have been proposed to account for late normal tissue damage. The “consequential late effect” model proposes that radiation-induced fibrosis might result from the initial mucosal injury. According to the “target cell” model, fibrosis occurs in the connective tissue, where cell turnover and proliferation rates are slow. The “indirect effect” model involves cell response to vascular damage and paracrine mediators.

However, no treatment is today available for patients. Thus, an important issue for the future is to improve the knowledge of the mechanisms involved in the development and persistence of late tissue damage, in order to develop new preventive and curative strategies, and improve the quality of life of cancer survivors.