

Understanding normal-tissue late effects in the intestines after pelvic radiotherapy

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademien, Göteborgs universitet kommer att offentligen försvaras i Arvid Carlsson, Medicinaregatan 3, torsdagen den 23 april 2020, klockan 09:00

av

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Avhandlingen baseras på följande delarbeten

- I. Bull C, Malipatlolla D, Kalm M, Sjöberg F, Alevronta E, Grandér R, Sultanian P, Persson L, Boström M, Eriksson Y, Swanpalmer J, Wold AE, Blomgren K, Björk-Eriksson T, Steineck G. **A novel mouse model of radiation-induced cancer survivorship diseases of the gut.** Am J Physiol Gastrointest liver physiol. 2017 Nov 1; 313(5): G456-G466.
- II. Dilip K Malipatlolla, Piyush Patel, Fei Sjöberg, Sravani Devarakonda, Marie Kalm, Eva Angenete, Elinor Bexe Lindskog, Rita Grandér, Linda Persson, Andrea Stringer, Ulrica Wilderäng, John Swanpalmer, Hans Georg Kuhn, Gunnar Steineck, Cecilia Bull. **Long-term mucosal injury and repair in a murine model of pelvic radiotherapy.** Sci Rep. 2019; 9:13803.
- III. Malipatlolla DK, Piyush Patel, Sravani Devarakonda, Jolie Danial, Eva Mehdi, Henrietta Norling, Malin Warholm, Rita Grandér, Margareta Nyman, Ana Rascon, Andrea Stringer, Fei Sjöberg, Marie Kalm, Gunnar Steineck, Cecilia Bull. **A fiber-rich diet and persistent pathophysiological processes in the irradiated intestines.** (Manuscript).
- IV. Patel P, Malipatlolla DK, Devarakonda S, Bull C, Rascon A, Nyman M, Stringer A, Steineck G, Sjöberg F. **Oat bran fiber reduces systemic inflammation in mice subjected to pelvic irradiation.** (Manuscript).

**SAHLGRENKA AKADEMIN
INSTITUTIONEN FÖR KLINISKA VETENSKAPER**



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Abstract

Radiotherapy cures patients from deadly cancer, alone or in combination with other treatments. The photons must pass through normal tissue to converge on the tumor, and it is unavoidable that radiotherapy causes acute as well as late adverse effects. Roughly one million cancer survivors in Europe are suffering from radiation-induced intestinal symptoms, such as urgency to defecate, leakage of feces and mucus, bleeding, and excessive odorous gas discharge. The symptoms can appear weeks to years after the treatment and severely reduce the quality of life. Very little is known about how radiation-induced pathological processes progress over time and how various factors such as diet influence the disease course. To better understand the dynamics of intestinal injury after radiotherapy, we have developed a novel mouse model of pelvic radiotherapy and determined the injury and repair mechanisms over time. In the study for **Paper I**, we used the clinic's linear accelerator to irradiate a small field limited to the murine colorectum. The use of the clinic's linear accelerator protected overall animal health and ensured their long-term survival. We found that the pathophysiology after 4 fractions of 8 Gy was similar to what is seen in biopsies of pelvic-organ cancer survivors, and that crypt degeneration was fraction-dependent and still ongoing at six weeks post-irradiation. Moreover, there was an increased number of macrophages in the mucosa at six weeks, possibly reflecting a lasting inflammatory activity. In the study for **Paper II**, we characterized the mouse model over a period of 30 weeks. We observed that crypt degeneration was still present at 30 weeks post-irradiation, as well as an increased presence of macrophages, possibly reflecting a chronic, low-grade inflammation. We also found that crypt fission, not cell proliferation, was the main repair mechanism after one week post-irradiation and onwards. In **Papers III & IV**, we studied the effect of bioprocessed oat bran, rich in dietary fiber, on radiation-induced damage to the intestine. In **Paper III**, we observed that the intake of dietary fiber modified the onset, timing, and intensity of radiation-induced pathophysiological processes when compared to a fiber-free diet. In the study for **Paper IV**, we observed that irradiation resulted in a long-lasting increase of serum cytokines indicating a chronic low-grade inflammation and that a fiber-free diet worsened this pro-inflammatory serum profile. In convergence, pelvic irradiation results in long-lasting, possibly chronic, pathophysiological changes in the intestines that may be driven by underlying low-grade inflammation. Nevertheless, even long after irradiation, the intestine attempts to repair itself via crypt fission. This mechanism as well as dietary interventions has the potential to modify the progression of the disease and may be explored further.

Keywords: pelvic radiotherapy, intestinal inflammation, crypt fission, dietary fiber.

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