Intestinal health after pelvic radiotherapy - towards understanding persisting pathophysiological mechanisms

Akademisk avhandling

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av

Sravani Devarakonda

Fakultetsopponent:

Johan D. Söderholm, Professor

Linköpings Universitet, Sverige

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Intestinal health after pelvic radiotherapy - towards understanding persisting pathophysiological mechanisms

Sravani Devarakonda
Department of Oncology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Sweden

Abstract
Pelvic cancer survivors struggle with life-long symptoms caused by radiotherapy. Many pelvic cancer survivors live with a constant fear of leaking faeces and the need to always have a toilet within reach. Some of these survivors are forced to retire early and live in social isolation. Radiotherapy saves lives, but radiation-induced damage to intestinal tissue close to, or within, the radiation field causes permanent changes in the cancer survivor’s bowel habits. Our goal was to understand the pathogenic mechanisms that continue to cause symptoms even decades after the treatment.

By irradiating the mouse colorectum using the clinic’s linear accelerator for radiotherapy, we have developed a novel model that mimics the human pathophysiological condition in the irradiated colorectal mucosa. The model was used to investigate whether the intake of dietary fiber, known to promote intestinal health, could modulate radiation-induced normal-tissue damage (Paper I). Our findings revealed that dietary fiber modified several intestinal pathophysiological processes and repair mechanisms following irradiation, most notably preventing a late, possibly chronic, bacterial invasion and reducing signs of inflammation. Dietary fiber appeared to also modulate parameters of neurogenesis in the brain following radiotherapy-induced injury to the colorectum, suggesting a connection between intestinal health after radiotherapy and brain health (Paper II). To translate the preclinical findings on inflammation to clinic, a biopsy-study was performed in cancer survivors up to 20 years after pelvic radiotherapy (Paper III). A low-grade chronic intestinal inflammation was observed after pelvic radiotherapy, as evidenced by an elevated neutrophil presence and activity. Inadequate mucus protection was also found, possibly leading to increased pathogen infiltration. These results challenge the notion that pelvic radiotherapy causes acute intestinal inflammation that either heals, or causes tissue to become fibrotic without further inflammation.

In conclusion, this thesis demonstrates that the mucosal resilience to radiotherapy may be modulated by quite simple means, such as dietary approaches. Moreover, protecting intestinal health after radiotherapy may also protect brain health. The thesis also demonstrates the presence of a chronic, low-grade inflammation in the intestinal mucosa after pelvic radiotherapy, possibly driven by infiltrating bacteria due to a poor mucus protection. The findings can have implications for future approaches to safeguarding intestinal health while providing effective pelvic cancer therapy. Keywords: pelvic radiotherapy, dietary fiber, intestinal inflammation, neurogenesis.