



**Karolinska  
Institutet**

**Department of Oncology and Pathology**

# **Towards prevention of Pelvic Radiation Disease in Gynecological Cancer Survivors**

**AKADEMISK AVHANDLING**

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av

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## ABSTRACT

**Background:** To improve the therapeutic ratio of radiation therapy, an increased knowledge of how dose distributions affect normal tissue outcomes is critically needed; however normal tissue outcomes in terms of self-reported atomized symptoms among gynecological cancer survivors are rare in the literature.

**Aims:** To investigate the prevalence of self-reported symptoms and their impact on daily life among long-term gynecological cancer survivors previously treated with pelvic radiation therapy. In addition, we wanted to study how the dose-volume distribution of ionizing radiation delivered to organs at risk contributes to the occurrence of a specific late symptom affecting quality of life, and how the relationship may best be described by radiobiological modeling.

**Methods:** We identified 789 eligible gynecological cancer survivors from the Stockholm and Gothenburg regions, treated with pelvic radiation therapy alone or as part of combined therapy in 1991 to 2003. A control group of 478 women matched for age and residence was selected randomly from the Swedish Population Registry. In 2006 data was collected by means of a study-specific, validated postal questionnaire including 351 questions on symptoms from the pelvic region, demographics, co-morbidities, psychological and quality of life issues. Details about treatment techniques were retrieved from medical records. Participation rate was 78 percent (N=616) for cancer survivors and 72 percent (N= 344) for control women. Electronically stored treatment plans were reactivated for 519 survivors (84 percent), and organs at risk were contoured for calculation of dose distribution. Dose-volume data were used for fitting different radiobiological models.

**Results:** The median age for cancer survivors was 66.0 years and the median follow-up time after ending radiation therapy was 74 months (range 26 to 179 months). The most common diagnosis was endometrial cancer (59 percent) followed by cervical cancer (23 percent). Surgery was part of treatment in 90 percent of the survivors. Cancer survivors reported a higher occurrence of symptoms from all studied normal tissues (i.e., symptoms from the anal-sphincter region, bowel, urinary tract, pelvic bones, lower abdomen and legs as well as symptoms related to sexuality) compared to controls. The highest age-adjusted relative risk (RR) 12.7 (95% CI: 4.0-40.3) was found for the symptom 'emptying of all stools into clothing without forewarning' with a prevalence of 12 percent among survivors and 0.9 percent among control women.

Among the 70 cancer survivors reporting 'emptying of all stools into clothing without forewarning' the symptom negatively affected quality of life in 51 of the survivors (74 percent). This symptom kept the survivors from going to parties (RR 11.8; 95% CI 6.6-21.1), from traveling (RR 9.3; 95% CI 5.3-16.5), affected their ability to work (RR 7.9; 95% CI 3.8-16.4) and hindered their sexual activity (RR 9.2; 95% CI, 4.8-17.6).

Mean absorbed doses exceeding 50 Gy to the anal-sphincter region, the rectum, the sigmoid and the small intestines were related to the occurrence of 'emptying of all stools into clothing without forewarning'. When adjusting for risk factors such as birth weight over four kg, heart failure and gluten and or lactose intolerance, mean absorbed doses over 45 Gy to the anal-sphincter region and over 50 Gy to the sigmoid were related to the symptom.

The dose-volume-effect relationships for the organs at risk related to 'emptying of all stools into clothing without forewarning' were further explored and the dose-response parameters for the Relative Seriality, the Lyman model were estimated. The best fit was for the sigmoid, with the highest AUC and  $\gamma_{50}$ . The volume parameters indicate that the anal sphincter and small intestines behave serially while the rectum behaves parallel. The sigmoid has a mixed serial and parallel behavior.

**Findings:** Gynecological cancer survivors are at increased risk of 'emptying of all stools into clothing without forewarning' after pelvic radiation therapy. This symptom which affects social functioning is related to mean absorbed external doses to bowel organs and the anal sphincter region, of which the dose to the sigmoid is the best predictor of the occurrence of the symptom 'emptying of all stools into clothing without forewarning'.

**Implication:** Based on our findings dose-restriction to the involved organs at risk may in the future prevent this severe socially disabling symptom which today affect one out of ten gynecological cancer survivors.