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Psychological Impact On Long-Term Gynaecological Cancer Survivors due to Radiation-induced Survivorship Syndromes

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Table of Contents

List of Abbreviations	3
Abstract.....	4
Background	5
Aim	10
Material and Methods	10
Study population.....	10
Development of questionnaire	11
Validation	11
Data collection procedures.....	11
Selection of questions	12
Statistical methods	13
Ethics.....	13
Results	13
Demography	13
Association between radiation-induced survivorship syndromes and QOL outcomes.....	17
Discussion	19
Strengths and limitations	23
Conclusions and Implications	23
Non-pharmacological interventions.....	8
Pharmacological interventions	9
Future research.....	23
Populärvetenskaplig sammanfattning	24
Acknowledgements	26
References	26
Appendix.....	29
Supplementary table.....	30

List of Abbreviations

BMI	Body Mass Index
CI	Confidence Interval
CRF	Cancer-Related Fatigue
EBRT	External Beam Radiotherapy
IBD	Inflammatory Bowel Disease
IL	Interleukin
NCCN	National Comprehensive Center Network
PROMs	Patient-Reported Outcome Measures
QOL	Quality of Life
RCT	Randomised Control Trial
RR	Relative Risk
TGF	Transforming Growth Factor
TNF	Tumor Necrosis Factor

Abstract

Background: We know from previous studies that faecal incontinence (leakage syndrome) has a negative effect on self-assessed quality of life (QOL) and social functioning among gynaecological cancer survivors treated with external pelvic radiotherapy. There is, however, a lack of knowledge regarding how other radiation-induced bowel syndromes affect QOL in these survivors.

Aim: To investigate the association between the adverse effects of radiation therapy experienced by gynaecological cancer survivors and their QOL.

Methods: Previous studies identified 28 gastrointestinal symptoms that reflect decreasing health among gynaecological cancer survivors after external pelvic radiotherapy measured two to 15 years after treatment. The 28 symptoms were grouped by the original researchers into five radiation-induced survivorship syndromes (*urgency syndrome, leakage syndrome, excessive gas discharge, excessive mucus discharge and blood discharge*) by using factor analysis. A patient-reported outcome measures (PROMs) questionnaire was sent to 623 survivors and 344 matched population-based controls. Based on six questions chosen from the questionnaire, different QOL outcomes were measured: *Self-assessed QOL, feeling sad or depressed, worry or anxiety, psychological well-being, self-assessed physical health and self-esteem*.

Results: The participation rate for cancer survivors was 76% and for the control group 72%. Data show that all five radiation-induced survivorship syndromes contribute to lower self-assessed QOL, lower psychological well-being, and have negative effects on physical health and self-esteem compared to the control group. No significant elevated risk for depression or anxiety was seen.

Conclusion: Gynaecological cancer survivors with radiation-induced survivorship syndrome have a lower self-assessed QOL. Living with urgency, leakage, excessive gas, excessive mucus or blood in faeces is associated with greater occurrence of adverse psychological consequences in survivors than women in the control group.

Keywords: Gynaecological cancer; Psychological well-being; Quality of life; Radiation-Induced Survivorship Syndromes; Bowel toxicity

Background

Cancer is one of the leading causes of morbidity and mortality worldwide. In Sweden, approximately 2800 women develop gynaecological cancer every year and approximately 30,000 women are gynecological cancer survivors (1, 2). There are five main types of cancer that occur in the female reproductive system: cervical, ovarian, endometrial, vaginal, and vulvar cancer (3). The most common gynaecological cancer type is endometrial cancer. In addition, there are types that are much less common such as uterine sarcoma and fallopian tube cancer. Surgery, radiotherapy and chemotherapy are different methods used for treatment. The choice of treatment depends mainly on the type and stage of cancer. Most women with gynaecological cancer receive pelvic radiotherapy, and it is estimated that across the developed world, between 150 000 to 300 000 people undergo pelvic radiotherapy yearly and that 80% of these will develop gastrointestinal symptoms during treatment (4). The first use of radiotherapy in cancer treatment occurred in 1896, and only one year later damaging effects to the intestine caused by radiation were described (5). Since radiation is used as treatment for patients with pelvic cancer more often than any other tumor site, understanding the effects of radiation in the pelvis is of great importance (6).

Pelvic radiation disease is defined as changes that arise in healthy tissues as a result of radiation delivered to a tumour in the pelvis (6). Gastrointestinal symptoms can vary from mild to very severe. These symptoms have been divided into two groups, acute and late onset. Acute changes are seen until 90 days after last treatment and late changes occurring thereafter (7). Acute changes in the gastrointestinal tract are mediated by cytotoxic effect of radiation on fast growing epithelium, and this effect is amplified by inflammatory processes (7). These two mechanisms increase the concentration of free radicals and cause damage to DNA (8). As concerns late-onset symptoms, reactions that began in the acute phase are amplified leading to

loss of stem cells, incomplete healing, and ischemia. All of these may cause intestinal fibrosis (5).

Chronic radiation enteritis typically develops between 18 months and 6 years following radiotherapy, although it has been reported as appearing as late as 15 years after treatment (9). Up to one-fifth of patients receiving pelvic radiotherapy develop chronic radiation enteritis, which is associated with increased morbidity and mortality (9).

Radiation enteritis has multifactorial causes, including the method and dose of radiation delivered, genetic background, and environmental factors such as smoking and diet. However, the extent to which each risk factor contributes to toxicity is unknown (5).

Mechanisms involved in radiation-induced gastrointestinal toxicity are similar to mechanisms involved in Inflammatory Bowel Disease (IBD), the two main forms of which are Crohn's disease and ulcerative colitis (5). Clinically, both are often characterised by symptoms such as diarrhoea, rectal bleeding and malabsorption. Histologically, both display pronounced infiltration of innate and adaptive immune cells into the lamina propria, and this is associated with epithelial destruction and mucosal ulceration (5). Ulcerative colitis tend to be limited to the mucosa while Crohn's disease and radiation-induced gastrointestinal toxicity tend to be transmural (5). Radiation-induced gastrointestinal toxicity and IBD share some inflammatory mechanisms. Both have upregulated gene expression and secretion of pro-inflammatory cytokines IL-1 β , TNF α and TGF- β (7, 10). Inflammation seen in intestinal toxicity is induced by ionizing radiation; the cause for IBD is less well established (11). Cancer survivors treated by radiotherapy have a reduced diversity of the Firmicutes and Bacteroidetes, two bacteria phyla that have an important role in controlling intestinal inflammation. The same kind of

depletion has been seen among patients with IBD (7, 12). These patients also have an increased number of pathogenic bacteria such as *enterobacteriaceae* (13, 14). An imbalance between the bacteria phyla involved in intestinal homeostasis and an increase in pathogens is the cause of dysbiosis. Even though both diseases share many similarities, radiation-induced gastrointestinal toxicity receive less attention from healthcare and fundings spent on research (15).

In a study conducted by Steineck et al. (16), gynaecological cancer survivors were given a questionnaire two to 15 years after they had undergone pelvic radiotherapy. A total of 28 gastrointestinal symptoms were reported by survivors; these symptoms may be grouped into five syndromes through factor analysis (Figure 1). These symptoms are manifestations of five different radiation-induced survivorship syndromes: Urgency syndrome, leakage syndrome, excessive gas discharge, excessive mucus discharge, and blood discharge (16). In each syndrome, one symptom predominates but can be accompanied by other less prevalent symptoms. For example, patients with urgency syndrome mainly have trouble with defecation urgency but may also complain of stool leakage, gas, mucus or blood discharge in feces. Seventy-four percent of survivors affected with faecal incontinence (leakage syndrome) reported low to moderate QOL and one third of them reported that they would have refrained from radiation treatment if they had been fully aware of the negative consequences (17).

Up to 90% of cervical cancer survivors who had pelvic radiotherapy may have permanent changes in their bowel habits and up to 50% state that these symptoms negatively impact their QOL (18). Fecal urgency, tenesmus, and fecal incontinence have the largest negative impact on QOL (18). The specific symptoms that are most bothersome vary by disease site;

symptoms related to bowel problems are most important for endometrial cancer patients while body image is more important for cervical cancer patients (19).

Available treatment methods are either non-pharmacological or pharmacological interventions.

Non-pharmacological interventions

Cancer rehabilitation aims to improve quality of life following cancer. The World Health Organisation recommends that rehabilitation includes: “Identification of a person’s problems and needs, relating the problems to relevant factors of the person and the environment, defining rehabilitation goals, planning and implementing the measures, and assessing the effects” (20).

A systematic review summarised the effects of psychosocial interventions in women with gynaecological cancers on their QOL outcomes (21). Twenty-two studies with 1926 participants were included. Eighteen were RCTs, two cohort studies and one intervention. Education about symptom distress, information provided about cancer, and coping training showed benefits for reducing psychological distress. Individual and group counselling interventions reduced symptoms of depression and anxiety and improved patient’s attitudes toward their health care. Cognitive-behavioural therapy improved self-esteem and body image. Relaxation techniques and guided imagery led to reductions in symptom-related body discomfort (21).

Reviews of exercise studies in patients with cancer have concluded that exercise reduces fatigue and improves QOL (22). Studies have led to a hypothesis that endometrial cancer

survivors who are able to perform 150 min/week of physical activity may be protected from negative effects of higher BMI on QOL (23).

Pharmacological interventions

Cancer survivors with gastrointestinal symptoms are recommended to treat symptoms by using bulk-forming agents or anti-diarrheal agent and incontinence products. In more severe cases pancreatic enzymes supplements, bile acid sequestrant or antibiotics might be required (24). Erythropoietin treatment used for CRF caused by anaemia can improve a patient's fatigue level and QOL (25).

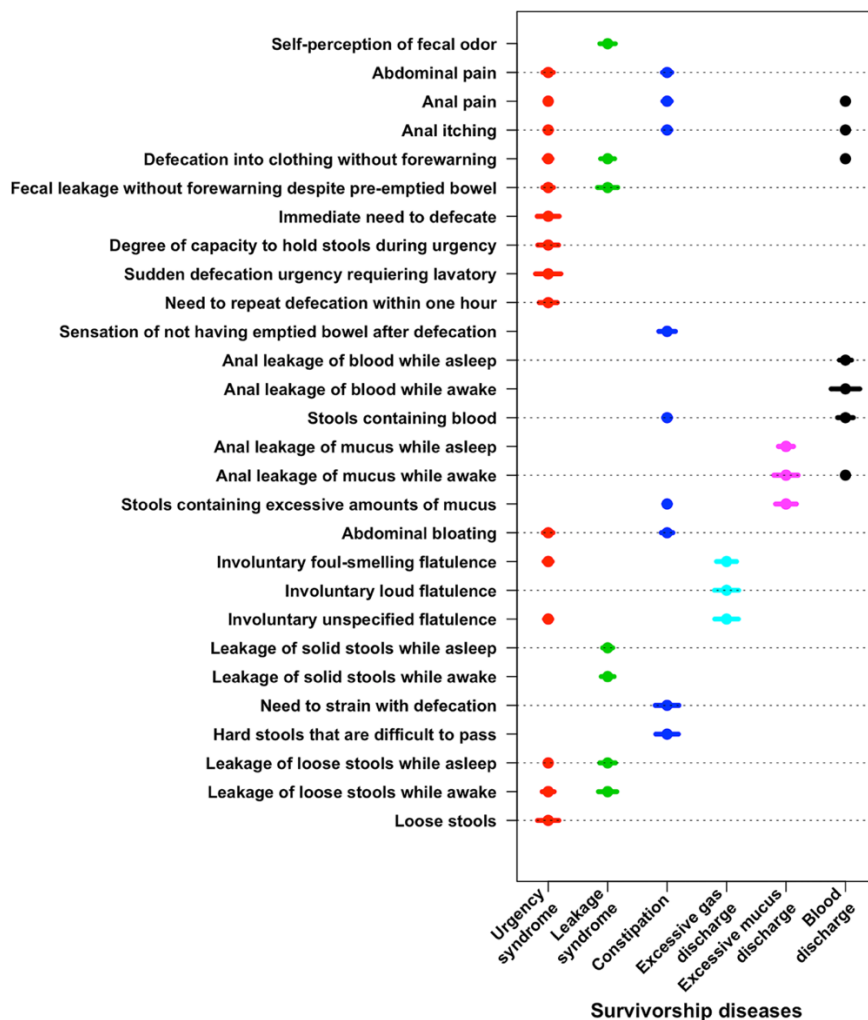


Figure 1 Results from a modified factor analysis showed that 28 frequent gastrointestinal symptoms reported could be grouped into five syndromes that can be manifestations of five different radiation-induced survivorship syndromes; Urgency syndrome (red), leakage syndrome (green), excessive gas discharge (light blue), excessive mucus discharge (purple) and blood discharge (black). Constipation (blue) was not statistically significant ($P > 0.001$).

Mann-Whitney test) and was thus not included as a radiation-induced survivorship syndrome. Reproduced from Steineck et al. (9).

Aims

- To investigate the association between five radiation-induced survivorship syndromes and six different QOL outcomes among gynaecological cancer survivors.
- Compare physical and mental health among cancer survivors and women in the control group.
- Identify specific symptoms resulting from late treatment toxicity that have the greatest effect on QOL.

Material and Methods

Study population

The study carried out by Dunberger and co-workers began by selecting a cohort of 1800 women with gynecological malignancy were treated with external pelvic radiotherapy between 1991 and 2003 at Radiumhemmet, Karolinska University Hospital in Stockholm and at Jubileumskliniken, Sahlgrenska University Hospital in Gothenburg (Figure 2). An introduction letter was sent to 823 eligible survivors after excluding patients who did not meet one or more of the following eligibility criteria: deceased at follow up, born before 1927, could not understand or read Swedish, had recurrence of disease and did not receive pelvic radiotherapy. In the end, 623 (76%) survivors were included in the study (17).

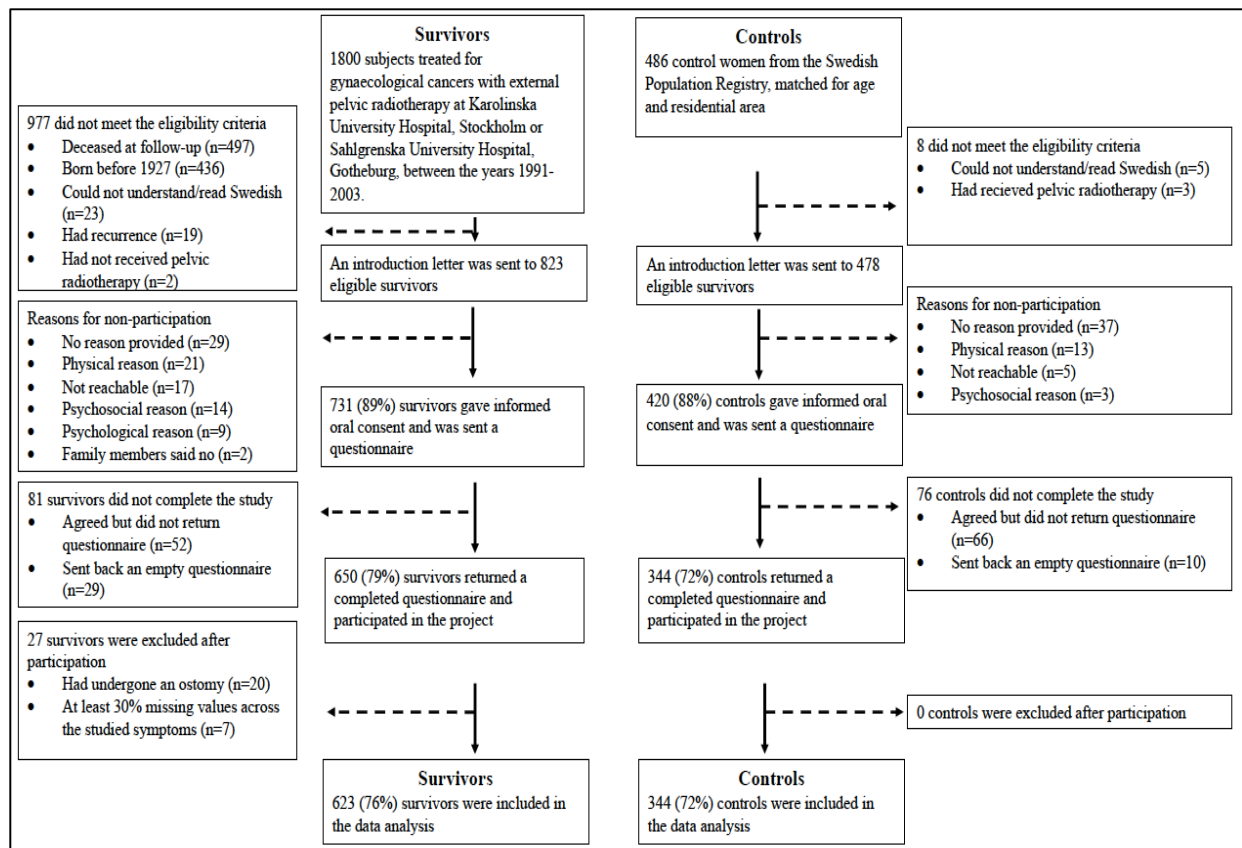


Figure 2 Flowchart of study population: Cancer survivors and control group with inclusion and exclusion criteria.

A control group was created consisting of 486 women randomly recruited from Swedish Population Registry matched by age and place of residence to the survivor group. An error in the matching procedure led to an age difference between control and cancer survivors, this was adjusted for in all analyses. Exclusion criteria were previous pelvic radiotherapy and that they could not understand or read Swedish. In the end, 344 (72%) controls were included in the study (17).

Data collection procedures

Between January and October 2006 all gynecological cancer survivors and population based controls received an introductory letter and a phone call. All who confirmed that they were willing to participate by giving oral consent received the questionnaire. The longest interval between 2006 and the time of treatment was 15 years, and the shortest two years. Each questionnaire contained a number to enable identification while maintaining anonymity. All

actions were taken by a neutral third-party secretariat (26); none of the health-care professionals involved had access to the data. The results from the questionnaire were coded and transferred to data entry and validation using program Epi-Data (www.epidata.dk).

Selection of questions

The questionnaire consisted of 351 questions and contained eight parts: Part 1 covered demographic data, information about disease and its treatment. Part 2 dealt with self-assessed depression and anxiety, QOL, physical health and social functioning. Parts 3 to 8 covered physical symptoms, intercurrent diseases and sexual health (17).

Based on six questions chosen from the questionnaire, different QOL outcomes were measured. All six questions had answering categories using a Visual-analogue scale ranging from 1-7. The measurement of QOL was based on answers to the question “*How would you evaluate your quality of life during the past six months?*” where 1 signified no QOL and 7 best QOL with a cutoff point of 1-3 classified as low self-assessed QOL. (Appendix)

The questions “*How would you evaluate your mental health during the past six months?*” and “*How would you evaluate your physical health during the past six months?*” were used in determining the survivor’s mental and physical health. The question “*How would you evaluate your self-esteem during the past six months?*” was used to obtain information about the subjective emotional evaluation of the subjects. Low psychological well-being, low self-assessed poor physical health and low self-esteem were denoted by answers in the interval 1-3 (Appendix).

The following two questions were used to determine the survivors’ mood: “*Have you felt sad or depressed during the past six months?*” and “*Have you felt worry or anxiety during the*

past six months?” The end points of the scales for these questions were 1 for ”Never” and 7 for ”All the time”. Feeling sad or depressed or experiencing worry or anxiety were denoted by answers in the interval 5-7 (Appendix).

Statistical methods

To assess bivariate relationships between QOL outcomes including self-assessed QOL, feeling sad or depressed, worry or anxiety, psychological well-being, self-assessed physical health, self-esteem and radiation-induced survivorship syndromes, we used log-binomial regression analysis. Relative risk is used as a measure of the strength of the link between QOL outcome and radiation-induced survivorship syndrome with 95% confidence interval (CI). Results were age-adjusted using log-binomial regression analysis. Statistical analyses were performed using SAS 9.4 for Windows (SAS Institute Inc., Cary, NC, USA). The relative risk was considered statistically significant when 95% confidence interval did not contain the reference value, 1.00.

Ethics

Informed consent was obtained from the study participants. Each questionnaire are coded and not possible to trace. The Regional Ethical Review Board approved of the study protocol (2005/1425-31/4), Stockholm, Sweden (16).

Results

Demography

Clinical characteristics of cancer survivors and controls are presented in table 1. Mean age among survivors are 67 years and among control women 58.5 years. In the survivor group most women are between 70-80 years old, in a marriage or living with a partner. 243 survivors with cardiovascular co-morbidities in comparison to 96 women in control group.

The most common gynaecological cancer was endometrial cancer (58%) followed by cervical cancer and ovarian cancer. Most survivors received both surgery and radiotherapy treatment 564 of 623 (91%). A total of 340 women received additional brachytherapy, 114 women additional brachytherapy and chemotherapy, and 63 women additional chemotherapy. Surgical procedures consisted of total hysterectomy, bilateral salpingoophorectomy with or without omentectomy.

In the group treated with radiotherapy alone, 26 of 59 women received external beam radiotherapy (EBRT) and brachytherapy, 23 women received EBRT, brachytherapy and chemotherapy, 8 women received EBRT and chemotherapy, and 2 women only EBRT.

All cancer survivors received EBRT using a linear accelerator delivering an energy varying between 6 and 50 megavoltage (MV) photons. The dose of radiotherapy used as adjuvant therapy was between 40 and 50 Gy (1,6-2,0 Gy per fraction, 5d a week). The mean dose given to the women who had only radiotherapy was 54 Gy (39,6-70 Gy).

Before 1996, a two-field technique was used and from 1996 a four-field box technique became the standard technique. In total, 503 (81%) survivors had brachytherapy and 208 (33%) received chemotherapy as an adjuvant treatment.

A total of 421 of these 623 (68%) of cancer survivors live with radiation-induced survivorship syndrome. Among the control women 128 of 344 (37%) experienced symptoms resembling radiation-induced survivorship syndrome (unpublished data).

Table 1 Demographics and clinical characteristics of cancer survivors and control group
Percentage may not total 100 because of rounding.

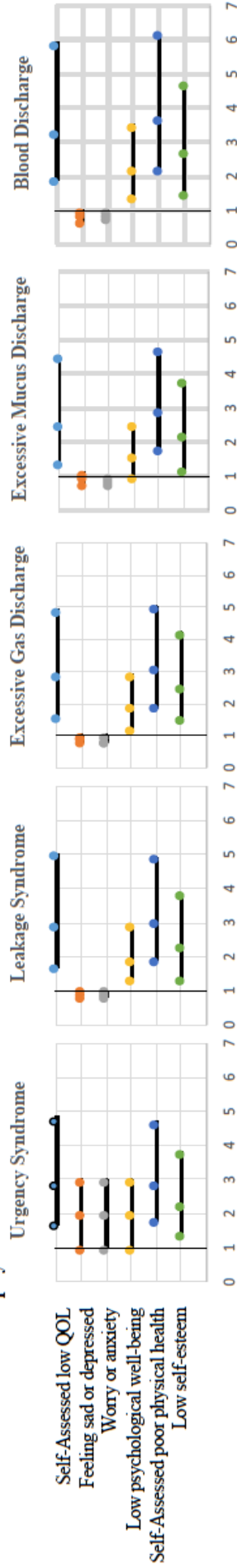
Characteristics	Cancer survivors <i>n</i> = 623 (%)	Control group <i>n</i> = 344 (%)
Age		
29–39	15 (2)	23 (7)
40–49	49 (8)	72 (21)
50–69	94 (15)	80 (23)
60–69	223 (36)	75 (22)
70–80	242 (39)	92 (27)
Mean age (range)	67	58.5
Not stated	-	2 (<1)
Marital status		
Married or living with a partner	355 (57)	220 (64)
Has a partner but lives alone	36 (6)	22 (6)
Widow	81 (13)	37 (11)
Single	149 (24)	65 (19)
Not stated	2 (<1)	-
Level of education		
Elementary school	194 (31)	69 (20)
Secondary school	238 (38)	146 (42)
Collage/university	190 (30)	127 (37)
Not stated	1 (<1)	2 (<1)
Employment status		
Student	6 (1)	2 (1)
Unemployed	14 (2)	6 (2)
Employed	204 (33)	188 (55)
Housewife, other	12 (2)	5 (1)
On sick leave	11 (2)	10 (3)
Disability pension	55 (9)	15 (4)
Retired	318 (51)	117 (34)
Not stated	3 (<1)	1 (<1)
Smoking		
Current smoker	141 (23)	88 (26)
Former smoker	190 (31)	108 (32)
Never smoked	278 (46)	146 (43)
Not stated	14 (2)	2 (<1)
Exercise		
Never	72 (12)	20 (6)

Characteristics	Cancer survivors <i>n</i> = 623 (%)	Control group <i>n</i> = 344 (%)
At least once a month	84 (13)	59 (17)
At least once a week	450 (72)	262 (76)
Not stated	17 (3)	3 (1)
Body Mass Index		
<18.5 (underweight)	17 (3)	5 (2)
18.5–24.9 (normal weight)	268 (46)	163 (50)
25.0–29.9 (overweight)	201 (34)	116 (35)
>30.0 (obese)	99 (17)	43 (13)
Not stated	38 (6)	17 (5)
Intercurrent diseases		
Cardiovascular disease	243 (40)	96 (28)
Diabetes mellitus	54 (9)	17 (5)
Lung disease	37 (6)	12 (3)
Diagnosis (ICD 10)		
Endometrial cancer (C54)	363 (58)	Not applicable
Cervical cancer (C53)	147 (24)	
Ovarian cancer (C56)	49 (8)	
Uterine sarcoma (C49)	30 (5)	
Vaginal cancer (C52)	14 (2)	
Fallopian tube cancer (C57)	14 (2)	
Vulvar cancer (C51)	6 (1)	
Treatment modality		
Surgery and EBRT, total	564 (91)	Not applicable
+ Brachytherapy	340 (55)	
+ Brachy- and chemotherapy	114 (18)	
+ Chemotherapy	63 (10)	
Surgery and radiotherapy alone	47 (8)	
EBRT alone, total	59 (10)	
+ Brachytherapy	26 (4)	
+ Brachy- and chemotherapy	23 (4)	
+ Chemotherapy	8 (1)	
Radiotherapy alone	2 (<1)	

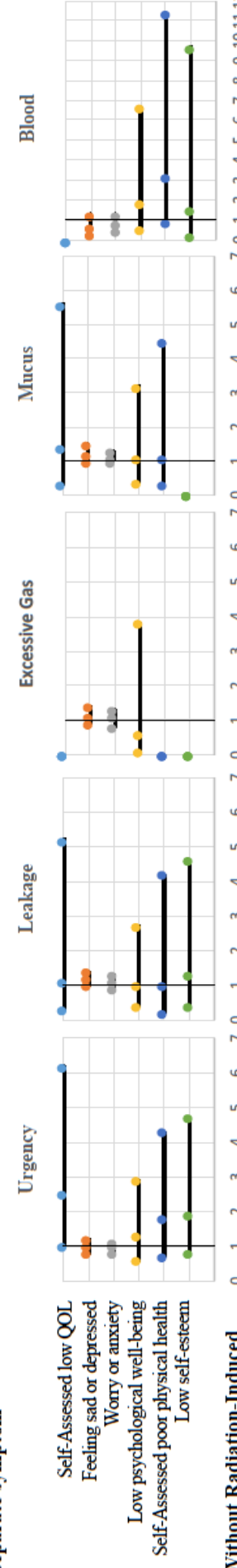
Association between radiation-induced survivorship syndromes and QOL outcomes

The data show that all five radiation-induced survivorship syndromes are associated with lower self-assessed QOL, lower psychological well-being, and that all have a more negative effect on physical health and self-esteem than seen in the control group (Figure 3A, for more detailed information see the supplementary table). All radiation-induced survivorship syndrome increases risk for having lower QOL and poor physical health about three times greater than in control women. All radiation-induced survivorship syndromes except excess mucus discharge (RR 1.6) result in a two times higher risk for the survivors to have reduced psychological well-being. About two to three times increased risk for having low self-esteem. No significant elevation in risk for being depressed or having anxiety was observed.

A: Radiation-Induced Survivorship syndrome



B: Separate symptom



C: Without Radiation-Induced Survivorship syndrome



Figure 3 Presenting different clinical manifestations of bowel toxicity after radiotherapy among gynaecological cancer survivors compared with control women. Age-adjusted relative risk with 95% CI are shown on X-axis. QOL outcomes are presented on Y-axis. Diagrams describes association between radiation-induced survivorship syndrome/separate symptom/without syndrome and QOL outcomes.

3A) Gynaecological cancer survivors living with radiation-induced survivorship syndrome (urgency syndrome, leakage syndrome, excessive gas discharge, excessive mucus discharge or blood discharge)

3B) Gynaecological cancer survivors living with only one symptom eg. urgency without any component of leakage, gas, mucus or blood.

3C) Gynaecological cancer survivors living without radiation-induced survivorship syndrome

The highest relative risks for adverse change among survivors with blood discharge were for self-assessed poor physical health, RR 3.7 (95% CI: 2.2-6.2).

The greatest effect on self-assessed low QOL, RR 3.3 (95% CI: 1.9-5.9) is seen among survivors with blood discharge. Highest relative risks for adverse change among survivors with blood discharge were for self-assessed poor physical health, RR 3.7 (95% CI: 2.2-6.2).

A separate analysis intended to elucidate the relationships between survivors and controls complaining mainly of one dominant symptom (Figure 3B). Living with one dominant symptom such as urgency without also experiencing any other component of leakage syndrome, blood discharge, excessive mucus discharge or excessive gas discharge is rather rare. No statistical significance is seen between the two groups. Group size varying from around 10 women with excessive gas discharge, excessive mucus discharge, leakage or blood discharge to 40 women with urgency.

There are about 200 women in the group who did not report experiencing radiation-induced survivorship syndromes. Relative risks for each QOL outcome overlaps 1.00 and thus these women do not show any difference in QOL outcomes compared to the control women (Figure 3C).

Discussion

All five radiation-induced survivorship syndromes are associated with lower self-assessed QOL, lower psychological well-being, and each syndrome have a negative effect on physical health and self-esteem compared to population based control group. Each radiation-induced survivorship syndrome increases the risk for having lower QOL and physical health by a factor of three compared to the control women. The highest relative risks among survivors

with blood discharge for experiencing radiation-induced survivorship syndrome concern self-assessed poor physical health and self-assessed low QOL. No significant elevation in risk is seen for depression or anxiety.

Treatment modality affects long-term QOL in gynaecological cancer patients. Those patients who undergo relatively more radical surgery and those patients receiving radiotherapy have the most persistent bowel dysfunction many years after treatment of any of the survivors (18). In a study that focused on psychosocial problems among women with cervical cancer receiving EBRT with or without brachytherapy, depression and worry were initially high but decreased to the level of controls after six months. Psychosocial problems affecting QOL in cervical cancer survivors include mood and stress disorders, body image and fear of recurrence (18). In comparison with results found in this report the level of depression or anxiety is not affected by the intensity of the radiation-induced survivorship syndrome. Gynaecological cancer survivors were followed two-15 years after treatment, if they felt depressed or worry initially were not documented and thus difficult to evaluate.

A literature review by Nout et al. summarized studies about patient-reported outcome measures (PROMs) and QOL in women with gynecologic malignancies who were treated with pelvic radiotherapy and found that endometrial cancer survivors had statistically significant higher rates of diarrhea and fecal leakage than any of the others (20). This limited the daily activities of this group and they thus had lower physical and role-physical functioning even 15 years after treatment (20). Role-physical functioning was concerned with job-related limitations and limitations on the ability of the women to do housework (27). Van de poll-Franse and colleagues conducted the largest retrospective health-related QOL study yet made among patients with endometrial cancer. Irradiated patients scored lower on all QOL scales compared

to normal population (28). Pelvic radiotherapy was independently linked with negative vitality and physical and social well-being (28). Park et al. reported in their case-control study including 860 cervical cancer survivors in Korea that cervical cancer survivors had significantly worse social functioning and bowel symptoms than seen in the national population. Anxiety about sexual performance was also seen among survivors (29).

In a cross-sectional study with 235 patients, Carlsson et al. found that gynaecological cancer survivors previously treated with chemotherapy had more problems with fatigue and constipation than did those who did not receive chemotherapy. Patients treated with external radiotherapy and/or brachytherapy had significantly more problems with flatulence and diarrhoea than those who did not have such treatment (30).

A population-based study from the Netherlands evaluated 666 endometrial cancer survivors and found a correlation between increased BMI and decreased physical function, decreased vitality, gastrointestinal problems and more fatigue symptoms (31). In the present study, 300 (48%) of the total of 623 had a BMI above 25 and 285 of 623 (46%) had BMI under 25. Since there was no big difference between these two groups no conclusion can be drawn about the possible importance of BMI.

In this study cardiovascular co-morbidities are more common among survivors. We know from before that cardiovascular disease and stroke have negative impacts on mental and physical health (32). Cardiovascular co-morbidities may be a contributing reason for decreased QOL seen among survivors, another difference between the two groups are survivors receiving a though cancer diagnosis which also can affect their QOL (33).

Cancer-related fatigue (CRF) is defined by the National Comprehensive Center Network (NCCN) as a persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning. In contrast to the tiredness that might be felt by a healthy individual, CRF is a sensation of greater magnitude, disproportionate to activity and not relieved by rest. Fatigue is the most prevalent symptom of individuals with cancer who receive radiotherapy and cytotoxic chemotherapy (34). Jakobsson, Ahlberg, Taft et al. prospectively followed twenty-nine women undergoing pelvic radiotherapy for anal or uterine cancer (35). They examined if CRF is associated with radiation-induced intestinal injury, as assessed by both plasma citrulline and diarrhea. Fatigue and diarrhea were assessed using PROMs questionnaire. Plasma citrulline is a biomarker of epithelial cell mass in the small bowel and has been shown to decrease during pelvic radiotherapy (36). The study indicates a link between CRF and intestinal injury during pelvic radiotherapy, CRF increased significantly ($p < .001$) and citrulline decreased significantly ($p < .001$). The study included a small sample size and thus should be considered as a preliminary finding (35).

CRF can help to explain why cancer survivors have lower QOL, reduced capacity of mental and physical health, low self-esteem and feelings of anxiety and depression. It is unknown whether fatigue is the cause of these symptoms or if fatigue is an effect of these factors (25). The pathophysiology of fatigue is not fully known (35). Many factors are thought to contribute to the development of CRF for example anemia, circadian rhythm disruption and an inflammatory reaction caused by the release of inflammatory mediators (37). One possible mechanism to the development of CRF during pelvic radiotherapy could be translocation of bacteria and other proinflammatory components into the systemic circulation, resulting in a cytokine-induced inflammatory reaction which in turn may elicit fatigue (35).

Strengths and limitations

Strengths of the study on which this report is based on include large sample size and high participation rate. Returning filled-in questionnaires to a trial secretariat probably minimized risk of measurement errors and avoided interviewer-related bias.

In the study the control group was younger on average than patients so statistical methods were used to adjust for this difference. The results are based on place and time specific and may not be able to apply for other settings. The upper age limit was 80 years and whether the results differ among the elderly is unknown. Some statistical analysis performed included small group sizes which resulted in a non-significant result, but it is important to remember the possibility that a non-significant result may actually be a real difference with a larger sample (38).

Conclusions and Implications

Gynaecological cancer survivors with radiation-induced survivorship syndrome have a lower self-assessed QOL. Living with urgency, leakage, excessive gas, excessive mucus or blood in faeces is associated with greater occurrence of adverse physical and psychological consequences in survivors than women in the control group.

Future research

New knowledge and skills learnt from clinical research and experience improve treatment methods for curing patients. Even though the treatment is much better today, we still lack much of the knowledge we need, to be able to prevent all side-effects. We need in the future to develop more advanced prevention, alleviation, and treatment methods for our present cancer survivors who suffer from radiation-induced survivorship syndromes.

Populärvetenskaplig sammanfattning

Att överleva cancer men att leva med följsjukdomar En studie om livskvalitet och psykisk hälsa hos gynekologiska canceröverlevare efter strålbehandling

I Sverige drabbas ca 2800 kvinnor av gynekologisk cancer varje år. Det finns fem olika typer av cancer som drabbar kvinnans könsorgan: blygdläppar, slida, livmoder, äggledare och äggstockar. De tre vanligaste formerna är livmodercancer, äggstockscancer och livmoderhalscancer. Sjukdomsbilden varierar beroende på vilken typ av cancerform. Livmodercancer som ofta upptäcks tidigt är chansen till överlevnad stor medan äggstockscancer som är den mest aggressiva formen är svår att upptäcka i tidigt skede.

Behandlingen innefattar nästan alltid kirurgi eller strålbehandling. Cellgifter och biologiska läkemedel har fått en mer och mer betydande roll. Antalet canceröverlevare har ökat i samhället tack vare ökad medelålder hos befolkning tillsammans med modern teknik, nya läkemedel och optimerade behandlingsregimer. Det innebär också att canceröverlevare lever längre cancerfria men tvingas samtidigt handskas med följsjukdomar efter strålbehandling. En vanligt förekommande biverkning på strålbehandling är påverkan på tarmhälsan.

Vår studie handlar om en grupp kvinnor med gynekologisk cancer som blivit strålbehandlade mellan år 1991 och 2003. De har följts upp 2-15 år efter strålbehandling med ett frågeformulär rörande deras hälsa. Frågeformuläret besvarades även av en kontrollgrupp bestående av friska kvinnor med samma profil såsom ålder och boendeort. 28 symptom som nedsätter tarmhälsan efter strålbehandling har identifierats efter en sammanställning av formulären. Dessa 28 symptom kan grupperas in i fem distinkta syndrom som kallas för *radiation-induced survivorship syndrome*: läckagesyndrom, trängningssyndrom, svår slemutsöndring, okontrollerad flatulens samt anal blödning.

Syftet med denna studie är att förstå hur radiation-induced survivorship syndrom till följd av strålbehandling påverkar livskvalitet samt psykiska och kroppsliga hälsan hos canceröverlevare i jämförelse med friska populationen.

Resultatet pekar på att samtliga fem radiation-induced survivorship syndrom; läckagesyndrom, trängningssyndrom, svår slemutsöndring, okontrollerad flatulens samt anal blödning är associerade med sämre självskattad livskvalitet, lägre psykiskt välbefinnande, sämre kroppslig hälsa och självkänsla jämfört med den friska populationen. Att leva med något av syndromen leder till en tredubblad ökad risk för sämre livskvalitet och fysisk hälsa. I undersökningen fann vi ingen skillnad i humöret, depression eller ångest är inte vanligare hos cancer överlevare i jämförelse med kontrollgruppen.

Det finns många omdiskuterade teorier till varför tarmbesvär uppkommer efter strålning, men än idag råder det fortfarande oklarhet. Mängden stråldos, metod av strålbehandling, genetiska orsaker samt miljöfaktorer som t.ex. rökning och födoämnen tros vara bidragande orsaker.

I dagsläget saknas effektiv behandling mot besvären som canceröverlevarna lider av. Det finns förslag i olika studier som visar behov av cancerrehabilitering i form av psykoterapi eller själasörjande samtal. Det finns även symptomlindrande behandling i form av inkontinensskydd vid läckage, volymökande medel och stoppande medel för normalisering av avföring samt specifika behandlingar som gallsyrhämmare. Trots den intensiva forskning som pågår idag, finns det fortfarande många kunskapsluckor och mycket kvar att lära för våra framtida canceröverlevare.

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Appendix Six questions selected from the questionnaire ”En undersökning om kvinnors hälsa efter strålbehandling vid en gynekologisk cancersjukdom”. Reproduced from Gail Dunberger et al.

1. Hur har Din livskvalitet varit, det senaste halvåret?

– Sätt en ring runt den siffra som bäst stämmer in på Dig –

1-----2-----3-----4-----5-----6-----7

Ingen livskvalitet alls

Bästa möjliga livskvalitet

2. Har Du känt Dig nedstämd eller deprimerad, det senaste halvåret?

– Sätt en ring runt den siffra som bäst stämmer in på Dig –

1-----2-----3-----4-----5-----6-----7

Aldrig

Hela tiden

3. Har Du känt oro eller ångest, det senaste halvåret?

– Sätt en ring runt den siffra som bäst stämmer in på Dig –

1-----2-----3-----4-----5-----6-----7

Aldrig

Hela tiden

4. Hur har Ditt psykiska välbefinnande varit, det senaste halvåret?

– Sätt en ring runt den siffra som bäst stämmer in på Dig –

1-----2-----3-----4-----5-----6-----7

Inget välbefinnande

Bästa tänkbara välbefinnande

5. Hur har Din kroppsliga hälsa varit, det senaste halvåret?

– Sätt en ring runt den siffra som bäst stämmer in på Dig –

1-----2-----3-----4-----5-----6-----7

Sämsta tänkbara hälsa

Bästa tänkbara hälsa

6. Hur har Din självkänsla varit, det senaste halvåret?

– Sätt en ring runt den siffra som bäst stämmer in på Dig –

1-----2-----3-----4-----5-----6-----7

Ingen självkänsla

Bästa tänkbara självkänsla

Supplementary table Presenting association between radiation-induced survivorship syndrome/without syndrome and QOL outcome among cancer survivors and control women. Bold indicates significant value.

QOL outcome for each syndrome	Control No./total no. (%)	Cancer Survivors No./total no. (%)	Survivors vs controls Age-Adjusted Relative risk (95% CI)	Survivors vs controls Unadjusted Relative risk (95%CI)
Without syndrome				
Self-Assessed low QOL	16/213 (8)	16/200 (8)	1.4 (0.7-2.9)	1.1 (0.5-2.1)
Feeling sad or depressed	51/214 (24)	40/201 (20)	1.1 (1.0-1.2)	0.8 (0.6-1.2)
Worry or anxiety	41/215 (19)	27/201 (13)	1.1 (1.0-1.2)	0.7 (0.5-1.1)
Low psychological well-being	28/213 (13)	21/200 (11)	0.7 (0.4-1.3)	0.8 (0.5-1.4)
Self-Assessed poor physical health	19/213 (9)	23/201 (11)	1.3 (0.7-2.4)	1.3 (0.7-2.3)
Low self-esteem	18/210 (9)	18/201 (9)	1.2 (0.6-2.3)	1.0 (0.6-2.0)
Urgency syndrome				
Self-Assessed low QOL	16/213 (8)	67/323 (21)	2.9 (1.7-4.8)	2.8 (1.6-4.6)
Feeling sad or depressed	51/214 (24)	99/323 (31)	0.9 (0.8-1.0)	1.3 (1.0-1.7)
Worry or anxiety	41/215 (19)	95/324 (29)	0.9 (0.8-1.0)	1.5 (1.1-2.1)
Low psychological well-being	28/213 (13)	79/324 (24)	1.9 (1.2-2.8)	1.9 (1.2-2.8)
Self-Assessed poor physical health	19/213 (9)	85/324 (26)	2.9 (1.8-4.7)	2.9 (1.8-4.7)
Low self-esteem	18/210 (9)	61/324 (19)	2.3 (1.4-3.8)	2.2 (1.3-3.6)
Leakage syndrome				
Self-Assessed low QOL	16/213 (8)	58/265 (22)	2.9 (1.7-5.0)	2.9 (1.7-4.9)
Feeling sad or depressed	51/214 (24)	78/263 (30)	0.9 (0.8-1.0)	1.2 (0.9-1.7)
Worry or anxiety	41/215 (19)	72/264 (27)	0.9 (0.8-1.0)	1.4 (1.0-2.0)
Low psychological well-being	28/213 (13)	69/264 (26)	1.9 (1.3-2.9)	2.0 (1.3-3.0)
Self-Assessed poor physical health	19/213 (9)	72/265 (27)	3.0 (1.9-4.9)	3.0 (1.9-4.9)
Low self-esteem	18/210 (9)	51/265 (19)	2.3 (1.3-3.8)	2.2 (1.4-3.7)
Excessive gas discharge				
Self-Assessed low QOL	16/213 (8)	40/193 (21)	2.9 (1.6-4.9)	2.8 (1.6-4.8)
Feeling sad or depressed	51/214 (24)	61/192 (32)	0.9 (0.8-1.0)	1.3 (1.0-1.8)
Worry or anxiety	41/215 (19)	61/193 (32)	0.8 (0.8-1.0)	1.7 (1.2-2.3)

Low psychological well-being	28/213 (13)	47/192 (25)	1.9 (1.2-2.9)	1.9 (1.2-2.8)
Self-Assessed poor physical health	19/213 (9)	53/194 (27)	3.1 (1.9-5.0)	3.1 (1.9-5.0)
Low self-esteem	18/210 (9)	39/194 (20)	2.5 (1.5-4.2)	2.3 (1.4-4.0)
Excessive mucus discharge				
Self-Assessed low QOL	16/213 (8)	30/167 (18)	2.5 (1.4-4.5)	2.4 (1.3-4.2)
Feeling sad or depressed	51/214 (24)	46/167 (28)	1.0 (0.8-1.1)	1.2 (0.8-1.6)
Worry or anxiety	41/215 (19)	41/167 (25)	0.9 (0.8-1.0)	1.3 (0.9-1.9)
Low psychological well-being	28/213 (13)	35/167 (21)	1.6 (1.0-2.5)	1.6 (1.0-2.5)
Self-Assessed poor physical health	19/213 (9)	41/167 (25)	2.8 (1.7-4.6)	2.8 (1.7-4.6)
Low self-esteem	18/210 (9)	29/167 (17)	2.2 (1.2-3.8)	2.0 (1.2-3.5)
Blood discharge				
Self-Assessed low QOL	16/213 (8)	28/113 (25)	3.3 (1.9-5.9)	3.3 (1.9-5.8)
Feeling sad or depressed	51/214 (24)	39/113 (35)	0.9 (0.7-1.0)	1.4 (1.0-2.1)
Worry or anxiety	41/215 (19)	34/114 (30)	0.9 (0.8-1.0)	1.6 (1.1-2.3)
Low psychological well-being	28/213 (13)	34/114 (30)	2.2 (1.4-3.5)	2.3 (1.5-3.5)
Self-Assessed poor physical health	19/213 (9)	38/114 (33)	3.7 (2.2-6.2)	3.7 (2.3-6.2)
Low self-esteem	18/210 (9)	26/114 (23)	2.7 (1.5-4.7)	2.7 (1.5-4.6)