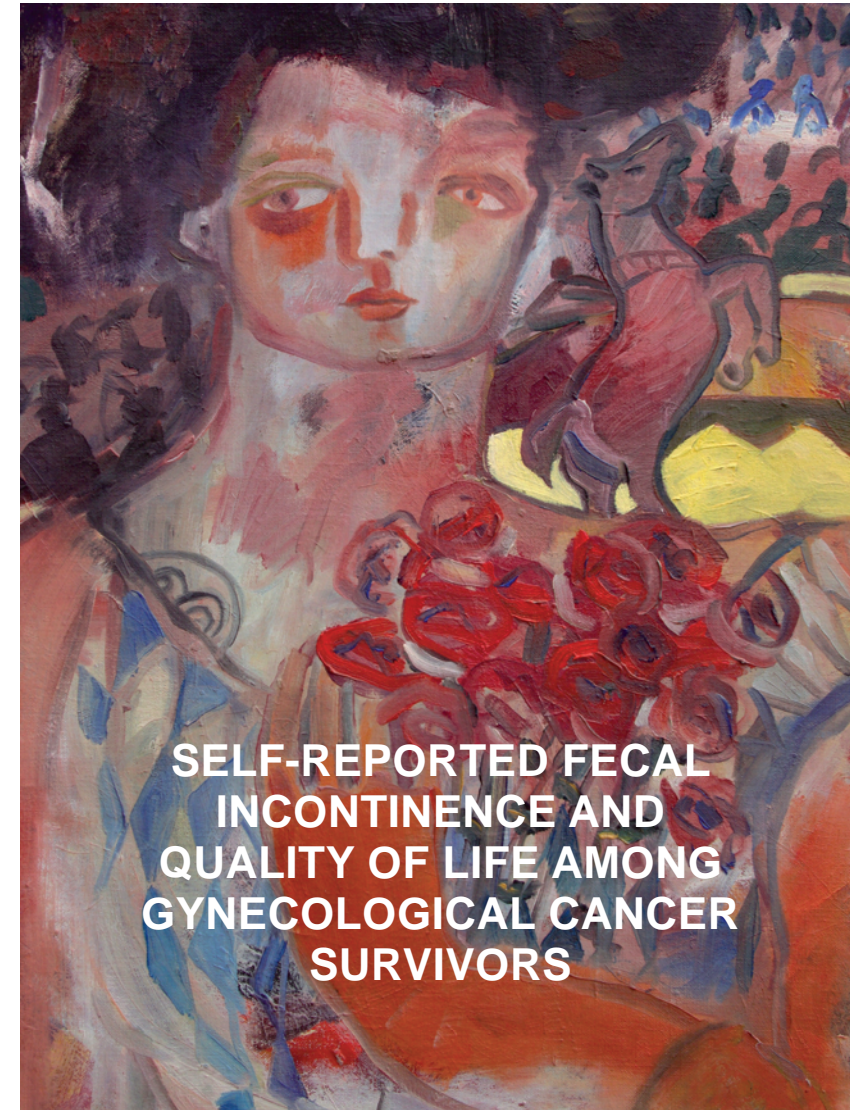


Thesis for doctoral degree (Ph.D.)
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Self-reported fecal incontinence and quality of life among gynecological cancer survivors

Gail Dunberger



SELF-REPORTED FECAL
INCONTINENCE AND
QUALITY OF LIFE AMONG
GYNECOLOGICAL CANCER
SURVIVORS

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Gail Dunberger



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Stockholm 2010

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***“Everyone wants it to be like normal...
For me it is not and it will never be,
Since most people believe normal is
the way it was before and it can’t be...”***

ABSTRACT

Gastrointestinal symptoms following pelvic radiotherapy are common; however, self-reported descriptions of gastrointestinal symptoms and their impact on daily life among gynecological cancer survivors are rare in the literature. The aim of this thesis was to investigate the prevalence of long-lasting gastrointestinal symptoms after pelvic radiotherapy among gynecological cancer survivors and to explore its impact on quality of life. In addition, we wanted to study the perception of being part of a study encompassing an extensive study-specific questionnaire.

We identified 789 eligible women in the Stockholm and Gothenburg areas, treated with pelvic radiotherapy during the period 1991–2003, alone or as part of combined treatment, for gynecological cancer. As controls, we randomly recruited 478 women, frequency-matched by age and residence from the Swedish Population Registry. We collected data in 2006 by means of a study-specific, validated, postal questionnaire including 351 questions covering symptoms from the pelvic region. We asked about demographics, psychological and quality of life issues as well as social functioning. Participation rate was 78 percent for cancer survivors and 72 percent for controls.

To obtain links between long-lasting symptoms and quality of life, we provided detailed characteristics of the gynecological cancer survivors. The mean age was 64.4 years (range 28 to 79 years) and the average follow-up period after completion of radiotherapy was 86.1 months (range 30 to 183 months). The most common diagnosis was endometrial cancer (59 percent) followed by cervical cancer (23 percent). Treatment included surgery in 90 percent of the survivors.

In 26 of 32 self-reported gastrointestinal symptoms we found a statistically significant increased age-adjusted relative risk (RR) for the cancer survivors, when compared to control women. The greatest age-adjusted absolute risk difference between cancer survivors and control women was observed for the symptom “defecation urgency with fecal leakage” with a prevalence of 49 percent among cancer survivors and 12 percent among controls. The highest age-adjusted RR 11.9 (95% CI: 3.8–37.8), was for the symptom “emptying of all stools into clothing without forewarning”.

The symptom “emptying of all stools into clothing without forewarning” was reported by 70 cancer survivors (12 percent), with lowered quality of life in 74 percent of the 70 cancer survivors. This symptom kept the survivors from going to parties (RR 11.8; 95% CI 6.6-21.1), travelling (RR 9.3; 95% CI 5.3-16.5), affected work ability (RR 7.9; 95% CI 3.8-16.4), hindered their sexual life (RR 9.2; 95% CI 4.8-17.6), and changed them as persons (RR 4.9; 95% CI 2.9-8.1).

To assess the perception of participation in a study-specific questionnaire survey we also included a cohort of 491 cystectomized urinary bladder cancer survivors. Among the total cohort (N=1068), 95 percent reported that the study was valuable and 54 percent felt they had been positively affected by their participation.

This thesis shows quality of life would drastically improve if gynecological cancer survivors could get rid of their gastrointestinal symptoms. For future survivors, we can learn about threshold dose of ionizing radiation with relevant risk-organs, to avoid inducing the gastrointestinal symptoms. For today's survivors, we can learn to design effective interventions.

LIST OF PUBLICATIONS

This thesis is based on the following papers:

- I. Helena Lind, Ann-Charlotte Waldenström, **Gail Dunberger**, Massoud al-Abany, Eleftheria Alevronta, Karl-Axel Johansson, Caroline Olsson, Tommy Nyberg, Gunnar Steineck, Elisabeth Åvall-Lundqvist. Gynecological Cancer Survivors Treated with Pelvic Radiotherapy in Stockholm and Gothenburg, Sweden 1991-2003. Manuscript.
- II. **Gail Dunberger**, Helena Lind, Gunnar Steineck, Ann-Charlotte Waldenström, Tommy Nyberg, Massoud al-Abany, Ullakarin Nyberg, Elisabeth Åvall-Lundqvist. Self-reported Symptoms of Faecal Incontinence among Long-term Gynaecological Cancer Survivors and Population-based Controls. *Eur J Cancer*. 2010;46:606-615
- III. **Gail Dunberger**, Helena Lind, Gunnar Steineck, Ann-Charlotte Waldenström, Tommy Nyberg, Massoud al-Abany, Ullakarin Nyberg, Elisabeth Åvall-Lundqvist. Fecal Incontinence Affecting Quality of Life and Social Functioning Among Long-Term Gynecological Cancer Survivors. *International Journal of Gynecological Cancer*. 2010;20:449-460
- IV. Helena Thulin*, **Gail Dunberger***, Helena Lind, Erik Onelöv, Lars Henningsohn, Elisabeth Åvall-Lundqvist, Gunnar Steineck, Ulrika Kreicbergs. Cancer survivors are positively affected by their participation using a study designed questionnaire. Submitted.

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LIST OF ABBREVIATIONS

BMI	Body Mass Index
CI	Confidence Interval
EORTC	European Organization for Research and Treatment of Cancer
FACT-G	The Functional Assessment of Cancer Therapy General
FI	Fecal incontinence
FIG	French-Italian Glossary
FIGO	International Federation of Gynecology and Obstetrics
Gy	Gray
HRQoL	Health-related quality of life
HPV	Human Papilloma Virus
IBS	Irritable Bowel Syndrome
LENT	Late Effects of Normal Tissue
PORTEC	Post Operative Radiation Therapy in Endometrial Cancer
RR	Relative Risk
RTOG	Radiation Therapy Oncology Group
SF-36	Study Short Form
SOMA	Subjective, Objective, Management, Analytic Scale
TAME	Toxicity, Adverse long-term effects, Mortality risk, End results

INTRODUCTION

Advances in gynecological cancer treatment have resulted in improved survival and increased numbers of cancer survivors. Approximately 25 000 women living in Sweden today are cured from gynecological cancer and many of them have received pelvic radiotherapy as part of their treatment. Symptoms related to treatment can last or occur years after completion of radiotherapy and therefore be mistaken for other conditions when seeking help outside the oncology centres. It is essential to increase our knowledge of long-lasting symptoms after cancer treatment in order to provide today's cancer survivor's adequate management and help. Studies of long-term gynecological cancer survivors may also lead to refinement of treatment so that future patients can be spared from symptoms affecting their quality of life.

Gastrointestinal symptoms are common after pelvic radiotherapy and have previously been reported but detailed self-assessed and self-reported reports of gastrointestinal symptoms, and their impact on quality of life, are thus far lacking. This knowledge is needed to improve interventions, treatment and rehabilitation of cancer patients and we need to share this information with a wider range of health-care professionals.

After many years as an oncology nurse in the radiotherapy department, in psycho-social oncology and rehabilitation of cancer patients a growing curiosity of existing long-lasting symptoms after gynecological cancer treatment and how symptoms impact on daily life and well-being eventually became a starting point of this thesis.

BACKGROUND

GYNECOLOGICAL CANCER

Gynecological cancer can arise in the vulva, vagina, cervix and corpus uteri, the fallopian tubes and the ovaries. Cancer of the female organs constitutes more than 12 percent of all female cancers in the Nordic countries¹ and approximately 2 700 new cases of gynecological cancer are annually diagnosed in Sweden². The risk of gynecological cancer increases with age and the majority of women are diagnosed when they are 60 years of age or older. However, it is important to note that the desire to live is strong regardless of age³. Gynecologic cancer does not only affect a bodily organ: it affects life, sexuality, intimacy and the ability to give life. Thus, it affects the very core of being a woman.

Endometrial cancer

Endometrial cancer is the most common gynecological cancer in North America and Europe⁴. In Sweden it is the 5th most common cancer among women, with an incidence of approximately 1 400 women diagnosed annually². The incidence of endometrial cancer has steadily increased during the past 40 years, but stabilization has been noted in the past 10 years¹. Due to demographic changes and with increasing life expectancy it is predicted that the number of new cases of endometrial cancer will dramatically increase unless effective preventive strategies are implemented⁵. Among Nordic patients diagnosed in 1999–2003 the five year relative survival was in the range 75 to 83 percent and Sweden had the highest survival throughout the period⁶. In 2007, the number of women living (prevalence) in Sweden with diagnosed endometrial cancer was 18 689¹.

Most cases of endometrial cancer develop in postmenopausal women and often present with vaginal bleeding. The most widely accepted hypothesis for the etiology of endometrial cancer is unopposed estrogens not counterbalanced by the presence of progestogens⁷. Worldwide obesity is the most important risk factor estimated to account for 40 percent of the incidence⁸.

The extent of disease at presentation, i.e. stage of disease is the most important prognostic factor. Endometrial cancer is staged surgically according to the International Federation of Gynecology and Obstetrics (FIGO) classification, which recently has been revised⁹. A majority of patients with endometrial cancer (75-80 percent) are diagnosed at an early stage of the disease, FIGO stage I, where the disease is limited to the corpus uteri¹⁰. However, around 10 percent of patients diagnosed with a presumably stage I disease have lymph node metastases i.e. a stage III. Although lymphadenectomy is part of the staging procedure according to FIGO and the presence of lymph node metastases is a strong prognostic factor lymphadenectomy has not been routinely performed in Sweden. This is possibly due to the wide indications of adjuvant pelvic radiotherapy and the risk for increased morbidity from lymphadenectomy.

The standard treatment for endometrial cancer is primary surgery, typically consisting of hysterectomy and bilateral salpingo-oophorectomy. The potential therapeutic effect of lymphadenectomy has been controversial. In a recent Cochrane metanalysis including 1 945 women and based on two randomized studies no significant difference was found in overall and recurrence-free survival between women undergoing lymphadenectomy and those not undergoing lymphadenectomy. However, women who received lymphadenectomy had a significantly higher risk of surgically related systemic morbidity and lymphedema or lymphocyst formation than those who had no lymphadenectomy (RR = 3.72, 95% CI:1.04-13.27 and RR = 8.39, 95% CI: 4.06-17.33 for risk of surgically related systemic morbidity and lymphedema or lymphocyst formation respectively)¹¹. Hence, available data suggest that lymphadenectomy provides prognostic information, but at the price of increased morbidity and without therapeutic effect.

Adjuvant pelvic radiotherapy has until recently been widely used in Sweden and elsewhere for patients with stage I. Recently several randomised studies have shown a risk reduction of locoregional recurrence of about 70 percent but without survival benefit. For patients with stage I and high risk of recurrence (deep myometrial invasion and grade 3) a trend for improved survival was reported in a Cochrane metanalysis which may support the use of adjuvant pelvic radiotherapy for these patients¹². It has also been suggested that adjuvant chemotherapy may be beneficial either combined with adjuvant radiotherapy or alone^{13, 14}. Patients with a more advanced stage of disease often receive a combined treatment modality of surgery, radiotherapy and chemotherapy. The treatment for endometrial cancer stage IV is individualized.

Gynecological surgery may cause gastrointestinal side-effects such as constipation¹⁵. Constipation may be due to a combination of slow gut transit and disturbance in the coordinated muscle movement required for evacuation¹⁶, due to injury of the parasympathetic nerves which may occur during pelvic surgery¹⁷. Reported occurrence in previously asymptomatic patients is approximately 10 percent^{15, 17}.

Uterine sarcoma

Uterine sarcoma is a rare but aggressive form of gynecological malignancy accounting for approximately five percent of all uterine malignancies. The malignant cells form in the muscles of the uterus or in other tissues supporting the uterus. In Sweden, approximately 100 new cases of uterine sarcomas are diagnosed annually².

Uterine sarcoma is classified into three different types according to the origin of the tissue they arise from i.e. carcinosarcoma, leiomyosarcoma, endometrial stromal sarcoma and undifferentiated sarcomas. Carcinosarcoma (mixed mesodermal sarcomas or mullerian tumors) is the most common type accounting for up to 50 percent of the uterine sarcoma and arise from the endometrium and other organs of mullerian origin. Although controversy exists whether carcinosarcomas are true sarcomas or derived

from an epithelial precursor, carcinosarcoma has recently been reclassified as a dedifferentiated form of endometrial carcinoma¹⁸. Hence, staging and treatment are in accordance with endometrial cancer.

Leiomyosarcoma arises from the myometrial muscle and account for one third of the sarcomas. Endometrial stromal sarcoma is divided into two types, i.e. low-grade endometrial stromal sarcoma and high-grade endometrial stromal sarcoma (or high-grade undifferentiated sarcomas).

Previously, staging of uterine sarcoma has been in accordance with staging of endometrial cancer but in 2009 a new FIGO staging classification specifically designed for uterine sarcoma was adopted¹⁸. The majority of women have an early stage of disease at presentation.

The rarity of sarcoma and the diverse histology have contributed to the lack of consensus of optimal treatment and risk factors. The prognosis of patients with uterine sarcomas has not improved in recent decades. Overall five year survival rate varies between 17.5 percent and 54.7 percent in different studies¹⁹. In a recently reported series of 100 cases, the two, five, and 10-year overall survival rates were 62 percent, 51 percent, and 38 percent respectively. In multivariate analysis, stage, age, tumour size, and parity have been shown to independently influence overall survival¹⁹. Another study of 208 patients with leiomyosarcoma of the uterus showed that high grade, advanced stage, and oophorectomy were associated with significantly worse disease-specific survival²⁰. Additional risk factors are tumour size, age, and menopausal status^{20, 21}.

Preoperative diagnosis of uterine sarcoma is difficult and the diagnosis is often made when surgery, the primary treatment for uterine sarcoma is being carried out. Typically, surgery consists of hysterectomy and bilateral salpingo-oophorectomy. The use of adjuvant radiotherapy for uterine sarcoma is controversial. Most studies are retrospective although one randomized trial has recently been published suggesting improved local pelvic control but no improvement in overall survival^{22, 23}. For inoperable sarcomas treatment options include pelvic radiotherapy and chemotherapy, chemotherapy and for low-grade endometrial stromal sarcoma hormonal therapy.

Ovarian cancer and cancer of the fallopian tube

Ovarian cancer consists of several histopathological entities of which epithelial ovarian cancer comprises about 80 percent of malignant ovarian neoplasms²⁴. Worldwide approximately 240 000 women are diagnosed annually with epithelial ovarian cancer²⁵ and the incidence is highest in Northern America and Europe. Epithelial ovarian cancer is the leading cause of death from gynecological cancer in the US and Europe reflecting the difficulties of early diagnosis and the development of chemoresistant disease.

In Sweden 735 women were diagnosed with epithelial ovarian cancer in 2008². In 2007, 8 446 women diagnosed with epithelial ovarian or fallopian tube cancer lived in Sweden¹. The incidence rate increases with age and the median age at diagnosis is 64 years. In the Nordic countries ovarian cancer trends are encouraging with overall declines in incidence and mortality as well as increasing survival. Nevertheless the prognosis is poor with five year relative survival below 50 percent⁶.

Fallopian tube cancer is a rare disease with an incidence rate in Sweden of around 50 cases annually². The disease is managed in a similar manner to epithelial ovarian cancer. It has recently been suggested that the fallopian tube may be the origin of some ovarian cancer²⁶. Epidemiological studies have identified several risk factors for epithelial ovarian cancer. A decreased risk is associated with younger age at pregnancy, the use of oral contraceptives and or breast feeding. Conversely nulliparity and older age at birth is associated with an increased risk of epithelial ovarian cancer. Family history accounts for about 5 percent of women with epithelial ovarian cancer and is associated with an earlier onset²⁷. The symptoms of ovarian cancer are nonspecific and patients may report abdominal fullness, dyspepsia or bloating although most patients with early-stage disease are asymptomatic²⁷.

Ovarian and fallopian tube cancer are surgically staged according to the FIGO classification²⁸. The majority of patients have advanced stage of disease at diagnosis. Primary treatment for a presumed epithelial ovarian and fallopian tube cancer is cytoreductive surgery followed in most cases by systemic chemotherapy²⁷. Surgery includes a total hysterectomy, bilateral salpingo-oophorectomy and omentectomy with the goal to achieve macroscopic complete resection²⁹. Based on several randomized studies the standard postoperative chemotherapy consists of paclitaxel and carboplatin³⁰. In Sweden, intravenous chemotherapy is used. The use of intraperitoneal chemotherapy is still controversial³¹.

Whole abdominal radiotherapy may be an option as consolidation treatment for advanced epithelial ovarian and fallopian tube cancer based on the results from a Swedish-Norwegian study³². In this randomised study including 172 patients with stage III epithelial ovarian cancer who were in complete surgical remission after primary surgery progression-free survival was significantly longer for the radiotherapy group than in the chemotherapy group and the untreated control group. However, treatment-related toxicity was more frequent in the radiotherapy group with severe late gastrointestinal radiation reaction observed in 10 percent.

Cervical and vaginal cancer

Worldwide cervical cancer is the most common gynecological cancer, and the second main cause of death among women in the developing countries⁴. The incidence of cervical cancer in Sweden has decreased by more than 50 percent since the introduction of organized screening programmes in the 1960s¹. In Sweden 461 women were diagnosed in 2008². The five year overall age-standardized survival rate

in Sweden for cervical patients, diagnosed during 1999–2003, is 65 percent⁶. Cervical cancer affects younger women to a greater extent than most other gynecological malignancies. The majority of women diagnosed with cervical cancer are younger than 50 years of age at the time of diagnosis³³. Age at diagnosis is a major determinant of cancer survival, with five year relative survival among patients younger than 50 years at around 85 to 90 percent in past years, with survival steadily decreasing as age increased⁶.

The main etiological factor for cervical cancer is persistent infection with sexually transmittable high-risk human papillomaviruses³⁴. New prophylactic vaccines against human papillomavirus (HPV) infection are currently available and have the potential to reduce the burden of cervical and other HPV-associated cancers, including vulvar and vaginal cancers. Smoking is another potential risk factor³⁵.

Cervical cancer staging is the oldest staging in the literature, dating back in 1928³⁶. Although the FIGO staging has recently been revised it is still based on clinical evaluation³⁷. Lymph node status is not taken into account despite its importance as a prognostic factor. However, lymph node assessment in the workup is an important factor for treatment planning³⁸.

Surgery and radiotherapy seems to produce similar therapeutical outcomes for the treatment of early cervical cancer (FIGO stage IA2-IIA)³⁹. However, radical surgery remains the preferred treatment, especially in younger women due to the negative effect of radiotherapy on ovarian function and other long-term effects^{40, 41}. The five year survival rate after radical hysterectomy among node-negative patients with early stages of cervical cancer has been reported to be over 85 percent⁴².

Cervical cancer is an excellent example of how studies on treatment related side-effects and quality of life have resulted in individualized treatment reducing morbidity without compromising disease control. Standard radical hysterectomy with pelvic lymphadenectomy is associated with damage to the pelvic autonomic nerves⁴³, which is believed to lead to impaired bladder function, defecation problems and sexual dysfunction^{15, 40, 44}. The beneficial effects of nerve-sparing surgery have been reported^{45, 46} and recently reviewed by Rob and co-workers⁴². If preservation of fertility is important, radical trachelectomy after pelvic lymphadenectomy can be considered among patients with early stage, IA2-I, of disease⁴⁷.

The current standard treatment for patients with locally advanced disease (FIGO stages IB2-IVA) is chemoradiotherapy⁴⁸. The Cochrane meta-analysis demonstrated a reduction of local and distant recurrence and progression, and improved disease-free survival but at the price of increased acute hematologic and gastrointestinal toxicity and data were too sparse for an analysis of late toxicity⁴⁸. Neoadjuvant chemotherapy followed by surgery may also be a treatment option for patients with locally advanced cervical cancer, especially those with early stages of disease but it has not yet been proven to offer a greater benefit compared to surgery alone⁴⁹. Currently there are two

ongoing randomized phase III trials (EORTC 55994, NTC 00193739) comparing neoadjuvant chemotherapy followed by surgery with concomitant chemoradiotherapy.

In Sweden, 83 women were diagnosed with a *vaginal* cancer in 2008². Vaginal cancer usually affects women between 60 to 64 years of age. The cause of vaginal cancer is closely linked to cervical cancer and HPV infections seem to be a necessary co-factor⁵⁰. The overall survival in vaginal cancer is 50 percent⁵¹. The surgical staging classification is according to FIGO⁵¹. Radiotherapy is the primary treatment option for patients beyond stage I – alone or in combination with surgery or chemotherapy⁵¹.

Vulvar cancer

Vulvar cancer is a relatively rare disease comprising about five percent of gynecological cancers. In Sweden 193 women were diagnosed with vulvar cancer in 2008². The five year survival in stage I is near 80 percent⁵² but poor for advanced and recurrent diseases⁵³. A majority of patients are elderly with a peak observed in the 70th age group⁵². Vulvar cancer is surgically staged according to FIGO⁵².

The disease develops along two separate pathways. The first is associated with high-risk HPV infection, usually occurs in younger women and the second is associated with lichen sclerosis or squamous cell hyperplasia and is HPV independent⁵³⁻⁵⁵.

Traditionally radical vulvectomy with bilateral inguino-femoral lymphadenectomy has been the cornerstone of treatment for most patients. However, due to significant morbidity⁵⁶ treatment is moving towards an individualized approach taking the size and position of the tumor into account^{52, 57}.

Due to the treatment-related side-effects associated with inguino-femoral lymphadenectomy the sentinel node biopsy technique could be offered in early-stage vulvar cancer as a treatment option although not evaluated in prospective trials. More long-term follow-up data are needed. The role of sentinel node biopsy in gynecological cancer has recently been reviewed⁵⁸.

For patients with advanced stage of vulvar cancer treatment is tailored to individual patient needs and usually includes combined treatment modalities using chemotherapy, surgery and radiotherapy. The efficiency and safety of neoadjuvant modalities using chemotherapy followed by surgery has recently been reported in a Cochrane review⁵⁹. No randomized controlled trials were identified. Based on five included studies the results showed that preoperative chemoradiotherapy reduces tumor size and improves operability. However, the treatment was associated with skin toxicity in nearly all patients and wound breakdown, infection, lymphedema, lymphorrhea, lymphoceles were also common.

TREATMENT-RELATED SIDE-EFFECTS AFTER PELVIC RADIOTHERAPY

Radiotherapy induces acute and late side effects. The degree and extent of an injury is based on the physical characteristics of radiation exposure including dose rate, fractionation, total dose, field size and type of radiation⁶⁰. Symptoms occurring after radiotherapy are local or loco-regional but could affect tissue or organs beyond irradiated area. Effected organs-at-risk after pelvic radiotherapy, includes the bowels and anal sphincter (gastrointestinal), the urinary bladder, the genitals, lymph-nodes, the pelvic bones and the bone marrow.

Acute symptoms may start within hours of the exposure⁶¹ and occur during or up to 90 days after radiotherapy⁶². Examples of early gastrointestinal symptoms after pelvic radiotherapy are nausea and vomiting causing anorexia, inflammation of the intestines, mucositis, abdominal cramping and loose stools^{61, 63}. Symptoms from the urinary bladder include painful urination and infections and from the genitals vaginal inflammation, infections or dryness as well as painful sexual intercourse, dyspareunia⁶⁴.

Late effects of radiotherapy are considered as late if they developed more than three months after treatment or persist for more than three months after completion of treatment⁶⁵. Chronic symptoms develop in most patients in one to two years⁶⁶ but they can occur as late as 20 years after treatment⁶⁷ and the functional expression depends on the tissue or organ affected⁶⁶. The incidence, severity or grade of a specific side-effect depends on how therapy is delivered, but shows a great individual variability among patients, even after identical treatment⁶⁶. Risk factors are high age as well as co-morbidity factors, involving impaired vascularity seen in hypertension or diabetes mellitus⁶⁸⁻⁶⁹.

Late effects include fibrosis, atrophy, vascular and neural damage and a range of endocrine and growth-related effects⁶⁶. The development of radiotherapy-induced fibrosis is characterized by a gradual aggravation over several years or even decades, culminating in an irreversible side effect. It starts with the initial pre-fibrotic phase lasting for a few months after radiotherapy, often asymptomatic but may be marked by signs of non-specific chronic local inflammation. Then follows a constitutive phase of organized fibrotic sequelae during the first few years after radiotherapy, in which the local inflammation signs have disappeared, and the tissues have thickened and hardened, with irregular widened capillaries such as telangiectasia⁷⁰.

Instruments for recording radiation effects

There are a variety of systems for the recording of late effects of radiotherapy treatment. In 1987 a French-Italian working group developed the French-Italian Glossary (FIG)⁷¹. In this scoring system the maximal damage after treatment is divided into four grades for each affected organ. Each grade is further subdivided into a maximum of six subgroups. A subgroup includes several signs and symptoms⁷¹.

The FIG has been criticized for mixing various end-points for the same organ. Furthermore, early and late morbidity are not separated and complications are graded by combining subjective symptoms and objective findings in each specific grade⁷².

The LENT SOMA system is one of the most common systems for recording late effects. In 1995 the international collaboration between the RTOG and the EORTC resulted in the recommendation of the SOMA/LENT toxicity score. The Late Effects of Normal Tissue (LENT) toxicity includes five grades, with grade 1 for minor symptoms to grade 5 for loss of organ or fatal outcome⁷³. The RTOG/EORTC is a scoring system for all major organs that may be injured by radiotherapy⁷⁴.

The LENT SOMA system is a comprehensive system and provides much information, but it has been found to be time consuming and difficult to implement in routine practice outside of clinical studies^{75, 76}. Furthermore it has been criticized for not assessing development of anorectal symptoms such as fecal incontinence or tenesmus and because it does not allow for reflecting on patients' experience when scoring 1 or 2⁷⁷. Other self-assessments have been used to evaluate anorectal symptoms after pelvic radiotherapy, e.g. Proctitis Symptom Score⁷⁸, and the Vaizey modification of Wexner Incontinence Score⁷⁹.

In recent years a third system, TAME, has been developed for summarizing the toxicity burden of cancer treatment. TAME consolidates traditional adverse-event data into three risk domains: short-term (acute) Toxicity (T), Adverse long-term (late) effects (A), and Mortality risk (M) generated by a treatment programme (E=End results)⁸⁰.

Gastrointestinal side-effects

The reported incidence of late anorectal adverse side-effects after pelvic radiotherapy varies from five to 10 percent⁸¹ to 80 percent⁸². Different methods of evaluation complicate the comparison between studies. Most frequently reported gastrointestinal symptoms are loose stools (diarrhea), defecation urgency, flatulence, fecal leakage, abdominal pain and bloating⁸²⁻⁸⁸. Smoking has been found to be strongly correlated with small bowel complications⁸⁹.

Loose stools or diarrhea after pelvic radiotherapy are commonly reported with the incidence varying between 14 and 52 percent^{63, 82, 87, 90-92}. The mechanisms causing loose stools are incompletely understood⁹³. The small intestine has the highest cell turnover rate and is vulnerable⁹⁴. Loose stools can result from multiple causes such as bile salt mal-absorption, carbohydrate mal-absorption and small intestine strictures or altered motility or both, giving rise to a functional stagnant loop and bacterial overgrowth⁹⁴⁻⁹⁷. Microvascular change from smoking and diabetes mellitus are potential risk factors for greater morbidity^{89, 98}.

Defecation urgency is another common symptom reported after pelvic radiotherapy with a reported incidence of 45 to 53 percent^{63, 85, 99-101}. Patients with defecation

urgency often have a feeling of incomplete defecation, tenesmus⁹⁵. One factor which increases defecation urgency is stool consistency. Decrease in rectal compliance may reduce the ability of the rectum to act as a reservoir to store stool and may lead to urgency as well as inflammation, psychological issues and malignancy in lower gastrointestinal tract^{95, 102}.

Flatulence is produced by colonic bacterial fermentation of ingested nutrients and endogenous glycoprotein's. Gas transit studies have shown that patients complaining of gas symptoms have impaired handling of intestinal contents, related to abnormal gut reflexes, which may result in segmental pooling and focal gut distension. Daily flatus numbers up to 25 are considered to be normal¹⁰³.

Disruption of gas transit produces bloating. Four factors are involved in the pathophysiology of bloating: a subjective sensation of abdominal bloating, objective abdominal distention, volume of intra-abdominal contents, and muscular activity of the abdominal wall¹⁰⁴.

Abdominal pain affects up to 30 percent of all patients after pelvic radiotherapy⁹². The causal pathway for this symptom may be partial small bowel obstruction caused by localized stricture or a result of impaired mobility in the small intestines with interruption of normal peristalsis by fibrosis⁶¹. Other reported explanations for abdominal pain are bowel spasm or fecal loading⁹³. Severe complication, reported as Grade 3 or 4, are reported after pelvic radiotherapy and includes symptoms as bowel obstruction, subileus, sigmoid stenosis, fistulation, bleeding or secondary cancers^{76, 85}.

Anal incontinence

Leakage of fecal material is generally termed fecal incontinence (FI). Anal incontinence is a definition used to also include the loss of flatus¹⁰⁵. A wide range of symptoms are included in the definition such as: elimination of flatus, staining, soiling, seepage as well as leakage to complete emptying of bowel content^{106, 107}. However, the involuntary passage of flatus alone should probably not be categorized as fecal incontinence as it is difficult to define when passage of flatus is abnormal¹⁰⁷.

Many definitions of fecal incontinence exist and in 2009 the Fourth International Consultation on Incontinence proposed to adopt the definition of fecal incontinence as "the involuntary loss of liquid or solid stool that is a social or hygienic problem"¹⁰⁸. Fecal incontinence may be categorized into *passive* fecal incontinence, being the involuntary discharge of stool without awareness, *urge* fecal incontinence, the discharge of fecal material in spite of active attempts to retain bowel contents, or a combination of both passive and urge fecal incontinence^{106, 107, 109, 110}.

The reported incidence of FI among people living in the community ranges from two to 24 percent^{111, 112}. The incidence is similar among women and men, but increases

strongly with age¹¹³. Fecal incontinence of loose stools is more common than incontinence of solid stool¹¹³.

Continence relies on the appropriate functioning of the pelvic barrier, rectal curvatures and transverse rectal folds¹⁰⁷. Factors such as rectal and colonic storage capacity, perception of rectal sensation, stool consistency and cognitive and behavior functioning also play important roles^{107,114}. An abnormality in any of these factors may result in fecal incontinence. These factors may have their origin in local, anatomical, or systemic disorders and incontinence is often multifactorial¹⁰⁶. Conditions that are associated with fecal incontinence are:

- increasing age
- obesity
- injuries (obstetric trauma, anorectal surgical procedures)
- neuropathy (stretch injury, obstetric trauma, diabetes)
- anatomical disturbances of pelvic floor (fistula, rectal prolapse, descending perineum syndrome)
- inflammatory conditions (IBS, Crohn's disease, ulcerative colitis)
- central nervous system diseases (dementia, stroke, spinal cord lesions, multiple sclerosis, brain tumor)
- bowel habits (diarrhea, urgency, constipation)
- side effects of treatment^{106, 107, 113, 114}

Fecal incontinence is reported after pelvic radiotherapy^{82, 88, 100, 101}, usually appearing years after radiotherapy¹¹⁵. In studies of late fecal incontinence after pelvic radiotherapy the incidence varies between 3 and 53 percent^{82, 88, 100, 101}. Patients treated for prostate cancer, may have a lower rate compared with those treated for gynecological, bladder or anal cancer, and rectal cancer patients seem to have the highest rate of fecal incontinence¹⁰².

The pathogenesis of radiation-induced injury of the anorectal organ of continence is incompletely understood¹¹⁵. The core aspects for continence mentioned earlier are anal resting tone, squeeze pressure and rectal volume or rectal compliance^{88, 115}. After pelvic radiotherapy associated aspects for incontinence include disorders as: proctitis, colitis and other disturbances in the lower digestive tract. The consistency of the stool is an important factor in maintenance of continence^{102, 115}. Proctitis contributes to an aggravation by associated symptoms as tenesmus and defecation urgency.

Radiotherapy to the rectum can lead to fibrosis of the rectal wall with a reduction in rectal volume or compliance. Radiotherapy-induced stenosis may cause over-flow and make incontinence worse¹¹⁵. Finally impairment of the innervations also contributes to incontinence. One theory is that efferent nerves are compressed by fibrotic tissue and atrophy occurs as a result¹¹⁶.

Different entities of fecal leakage as well as the pathophysiology of fecal leakage after pelvic radiotherapy have not been studied comprehensively. There are hardly any occurrences or intensities of fecal leakage nor any comparisons with the general population. Furthermore, studies evaluating social functioning, well-being and quality of life in connection to fecal incontinence are lacking.

Other side-effects

The lower urinary tract is less radiosensitive than the small bowel and generally a lower rate of complications induced by radiotherapy is seen in the lower urinary tract¹¹⁷. Late complication from the bladder may be the result of damage to the vascular endothelial cells¹¹⁷. Known complications in the urinary bladder after radiotherapy are radiation cystitis, fibrotic bladder with low-compliance, neurogenic voiding dysfunction, uretal stenosis and fistula formation^{117, 118}.

Lymphedema of the legs, lower abdomen and genitals may result after cancer treatment; these symptoms are all due to failure of adequate lymph drainage¹¹⁹. Lymphedema after cancer treatment occurs due to a disruption or compression of the lymph transport system and may be categorized as chronic or acute¹²⁰. The condition is a rather neglected subject in gynecological cancer survivors and attracts little attention or research interest but nevertheless could be associated with deformity of the body¹²⁰.

Pelvic fractures as a result of radiation therapy are seldom taken into account when assessing side-effects after radiotherapy and they are easily mistaken for metastatic lesions¹²¹. The reported incidence of fractures in the literature varies depending on follow-up strategies. Ikushima and coworkers investigated 158 gynecological cancer patients treated with pelvic radiotherapy. They found that most patients with pelvic fractures have pain but some could be asymptomatic¹²². Risk factors for pelvic fractures are age, osteoporosis, low body weight, current smoking and history of low-trauma fractures^{123, 124}. One of the main factors responsible for the late effects on irradiated bone is injury of the microvasculature of mature bone¹²².

It has recently been reported that pelvic radiotherapy is associated with an increased risk of secondary leukemia¹²⁵.

QUALITY OF LIFE AND WELLBEING

Quality of life is a subjective, multidimensional concept reflecting the patient's perception of all aspects of her health experience¹²⁶. Different definitions of quality of life exist but so far no standard definition has been agreed upon. According to the World Health Organization quality of life is the "individuals' perception of their position in life in the context of the culture and value system in which they live and in relation to their goals, expectations, standards, and concerns"¹²⁷. Quality of life has also been defined as "the difference or the gap, at a particular period of time between the hopes and expectations of the person and one's present life experiences"¹²⁸. The

same objective health status may be found in two individuals but the perception of their quality of life may be completely different from each other.

In a systematic review, Jones and co-workers reported the impact of different treatment regimes for gynecological cancer on health-related quality of life (HRQoL). They conclude that more research is needed on HRQoL of long-term survivors of gynecological cancer¹²⁹. In studies after radiotherapy, most data are collected prospectively at the end of radiotherapy and with the time interval ranging from one to 24 months post-treatment^{90, 130}. Few studies report quality of life in long-term gynecological cancer survivors treated with pelvic radiotherapy. Five years after diagnosis is considered a useful starting-point in long-term survivorship studies as most recurrence occurs within five years¹³¹. In another review, Vistad and co-workers summarized patient-rated quality of life-studies on long-term survivors of cervical cancer¹³². They conclude that future research should pay more attention to fatigue, anxiety and depression as well as to physical problems such as lymphedema and disturbed bowel function¹³². Existing studies on gynecological cancer patients have shown that decreased health-related quality of life is more often associated with radiotherapy than with surgery or chemotherapy^{132, 133}. Additional risk factors for maladjustment are multimodal treatment, increased length of treatment, younger age and even lower levels of education and poor social support¹³⁴.

A quality of life-questionnaire tailored to the needs of gynecological cancer survivors would include questions about urinary, bowel and sexual function¹³⁵. Fecal incontinence is recognized as one of the most troubling symptom-induced sources of distress to cancer patients^{84, 100}. This is confirmed by Gami and co-workers who found one year post radiotherapy that gastrointestinal symptoms had an adverse effect on quality of life among survivors after pelvic radiotherapy⁸². The presence of diarrhea after radiotherapy four years post treatment affected quality of life among gynecological cancer survivors⁹⁰ and urgency, diarrhea and flatulence were particularly troublesome among survivors after pelvic cancers¹³⁶. In the Post Operative Radiation Therapy in Endometrial Cancer (PORTEC-2) trial Nout and co-workers investigated the short-term HRQoL of patients with high-intermediate risk of endometrial carcinoma⁸⁷. They reported higher levels of diarrhea and bowel symptoms with limitations and toilet dependency among endometrial cancer survivors treated with pelvic radiotherapy compared to women treated with brachy therapy only⁸⁷. However, the impact of FI on working ability, social functioning, sexual life and activities outside the home has only been sparsely reported among long-term gynecological cancer survivors treated with pelvic radiotherapy.

Sexuality and intimacy after gynecological cancer

Sexual functioning can be affected by illness, treatment, pain, anxiety, anger, stressful circumstances and medication¹³⁷. Gynecological cancer treatment impacts sexual functioning, sexuality and intimacy, both during and after cancer treatment and sexual health has been increasingly recognized as an essential aspect of quality of life^{40, 137, 138}.

There is a growing acknowledgement that these needs are not being addressed by providers¹³⁹.

Genital symptoms and sexual dysfunction after cancer treatment, include overall menopausal symptoms, with hot flashes, vaginal dryness, urinary complaints and sleeping difficulties which has been reported to be significantly more bothersome among women who have received pelvic radiotherapy^{137, 138}. Other dysfunctions and difficulties after gynecological cancer treatment includes reproductive inability, becoming sexually aroused, attaining sufficient vaginal lubrication, vaginal stenosis and a persistent pain with attempted vaginal entry, or penile vaginal intercourse, dyspareunia^{84, 138}. Pain may lead to avoidance of intimacy, and fear of intercourse. Irradiated women report having significantly more pain with intercourse than cancer survivors who had radical hysterectomy alone^{40, 138}. Pain may be caused by vaginal dryness due to lack of estrogen, fibrosis due to cancer treatment or by psychological reasons^{40, 137, 138, 140}. Acute disruption of estrogen production will produce significant menopausal symptomatology. Premenopausal women who undergo surgical menopause often have severe symptoms; in general, the younger a woman undergoes menopause, the more likely she is to experience severe symptoms¹³⁷. The use of hormone replacement therapy in endometrial and ovarian cancer survivors is a topic a debate⁷. Limited studies are available to date. Since safety of using hormone replacements remains controversial and prospective studies are lacking, providers need to be able to provide alternatives to hormone replacement.

Instruments measuring quality of life

The assessment of quality of life is becoming an important issue in gynecological oncology, and there is growing interest in including quality of life measurements in clinical trials. Still, far from all clinical trials include health-related quality of life as one of the main end points¹⁴¹. Quality of life measurements can provide important information but the challenge is to translate this guidance to health-care practice. The concept of quality of life includes multidimensional factors, although there is no standardized definition. The most common domains include aspects of physical, functional, demographical, psychological and social wellbeing^{142, 143}.

Several standardized quality of life measurements have been developed for clinical trials to evaluate cancer treatment and how it affects quality of life. The Medical Outcomes Study Short Form-36 Health Survey (SF-36) is a generic health-related quality of life questionnaire. SF-36 measures eight important health concepts and is widely used in health surveys¹⁴⁴.

Two major instruments have emerged in cooperative group studies of treatment effects on quality of life; In Europe the European Organization for Research in the Treatment of Cancer questionnaire (EORTC QLQ-C30, QLQ-C36) is commonly used¹⁴⁵. It measures physical, role, emotional, and social functioning along with disease-specific symptoms, financial impact and global Quality of life. The EORTC QLQ-C30 general

core questionnaire is supplemented by a variety of modules to assess disease-specific symptoms. In gynecological cancer there are modules for ovarian, endometrial and cervical cancer.

The Functional Assessment of Cancer Therapy General questionnaire (FACT-G) is more frequently used in the USA¹⁴⁶. The FACT-G is a 27-item self-report measure of general questions divided into four HRQoL domains: Physical well-being, Social and Family well-being, Emotional well-being and Functional well-being. There are two subscales specific to gynecological cancer; cervical and ovarian cancer.

Other assessments have been used to capture gastrointestinal symptoms and disability experienced after pelvic radiotherapy^{83, 92}. The modified Inflammatory Bowel Disease Questionnaire includes questions about bowel symptoms, systemic symptoms and emotional and social function⁹².

Detailed inventories of treatment-related symptoms, reported by the gynecological cancer survivors themselves as well as evaluation on how these symptoms impact daily life of cancer survivors are needed. We believe a scoring system; commonly used in clinical trials to score toxicity during and after treatment, do not fulfill these criteria.

AIM

The overall aim of this thesis is to study the prevalence of long-lasting gastrointestinal symptoms among long-term gynecological cancer survivors compared to women from the general population as well as to study how gastrointestinal symptoms impact on quality of life and social functioning among gynecological cancer survivors after pelvic radiotherapy.

Specific aims of this thesis were:

- To give a detailed description of demographics and clinical characteristics as well as treatment given to the included gynecological cancer survivors
- To make a comprehensive, detailed inventory of gastrointestinal symptoms reported by long-term gynecological cancer survivors treated with pelvic radiation therapy and control women from the general population
- To investigate how the fecal leakage symptom, patient-reported as emptying of all stools into clothing without forewarning, impact self-assessed quality of life from a social, psychological, sexual, and functional aspect among gynecological cancer survivors treated with pelvic radiotherapy
- To assess the perception of participation in a study-specific questionnaire survey among cancer survivors treated for a gynecological or a urinary bladder cancer

MATERIAL AND METHODS

STUDY POPULATION

Paper I-III

Through medical records we identified 1 800 women who had been treated between 1991 to 2003 with external pelvic radiotherapy for a gynecological malignancy at Radiumhemmet, Karolinska University Hospital in Stockholm, or at Jubileumskliniken, Sahlgrenska University Hospital in Gothenburg of whom 1 303 were alive in 2004. At follow-up in January 2006, the total was decreased for the following reasons: 497 patients had died, 436 patients were too old (born before 1927), 53 had had a recurrence, 23 did not understand or were not able to read Swedish and two had not received pelvic radiotherapy. In total 789 patients remained and were eligible for the main study.

The number of controls that were to be included in the study was estimated from power calculations. The Swedish Population Registry delivered names and addresses of 366 control women, matched for residential area and age. An error in the matching procedure led to a younger control population and an additional 120 women, age 70-79 were added to provide a better match of the mean age of cancer survivors and control women. Eight of the total number of 486 control women did not meet the eligibility criteria: born 1927 or later, understand Swedish and no prior pelvic radiotherapy. In total 478 women remained and were eligible for the study. Age was adjusted for in all calculations when controls were compared to cancer survivors.

Paper IV

The study comprised individuals from two different cohorts of cancer survivors; gynecological cancer survivors, described above under Paper I-III, and urinary bladder cancer survivors.

The urinary bladder cancer survivor cohort included 491 men and women. Eligibility criteria were: cystectomized for a urinary bladder cancer, alive at the start of follow up, younger than 80 years of age and an ability to understand Swedish. In total the study population in Paper IV consisted of 1280 gynecological and urinary bladder cancer survivors.

QUALITATIVE PHASE - DEVELOPMENT OF QUESTIONNAIRE

Interviews

The qualitative phase lasted 18 months and was the foundation of the study. The gynecological cancer survivors were contacted by mail and asked if they were willing to participate in an interview in connection with a doctor's follow-up at the Department of Gynecological Oncology at Radiumhemmet, Karolinska University Hospital. The cancer survivors had all undergone pelvic radiotherapy one to five years earlier. A few days after the first contact, each cancer survivor was contacted again by phone and asked if she would be willing to participate. Those who volunteered were interviewed at the research unit, at the hospital or in their home. The interviews were performed in a semi-structured way and many topics were raised; a common starting-point was to ask how they perceived the radiotherapy treatment. After a couple of minutes the interviewer focused on the informant's present situation, current symptoms, quality of life, social functioning and coping strategies.

After interviewing 12 survivors the decision was made to continue with the interviews and to include cancer survivors who had undergone radiotherapy treatment 10 years earlier. Two survivors with this experience were added. The goal was to continue interviewing until no new information was identified and in total 26 women shared their experiences. A secretary continuously prepared word-by-word transcripts from the interview recordings.

Subsequent to the interviews the reported symptoms were sorted into different anatomical parts of the pelvic area; the gastrointestinal tract, the bladder, genitals, pelvic bones and the legs. Sexual dysfunction and eating habits formed other themes along with psychological symptoms affecting quality of life and social functioning. Most women addressed symptoms from the gastrointestinal area, with changed bowel habits having loose stools, flatulence and leakage of gas and fecal materials.

Study-specific questionnaire

Based on the interviews, our clinical knowledge, previous knowledge within the research unit and the literature, a study-specific questionnaire was constructed. The different themes, sorted into specific areas, were formulated into questions and divided into sections.

The final questionnaire consisting of 351 questions was created by arranging the questions in sequence, as follows:

1. Demographic data, including parity and delivery, information about the disease and it's treatment: questions 1-22
2. Psychological issues, quality of life and social functioning: questions 23-35

3. Gastrointestinal questions, including questions about coping with gastrointestinal conditions: questions 36-150
4. Urinary tract questions including questions about coping with urinary tract conditions: questions 151-197
5. Lymphedema, including question on treatment for this condition: questions 198-217
6. Bone pain including questions on treatment for pain: questions 218-247
7. Food and eating habits: questions 248-256
8. Sexuality including questions in relation to partner: questions 257-315
9. Physical health, concurrent diseases, medication, BMI, smoking: questions 316-340
10. Questions regarding participation in the study: questions 341-351

In each part of the constructed questionnaire we asked about the incidence, prevalence, intensity and duration of the symptoms when appropriate. For example:

- *“Have you emptied all stools into your clothes without forewarning during the past six months?”* with the possible answers: *“No”, “Yes, occasionally”, “Yes, at least once a month”, “Yes, at least once a week”, “Yes, at least three times a week”, “Yes, at least once a day”*.

One hundred and fifteen questions addressed bowel habits, such as anal incontinence, leakage severity (soiling to all stool), forewarning or not, frequency, prevalence and duration as well as coping strategies and quality of life conditions.

For quality of life and social functioning we used a seven-point Visual Digital Scale. For example:

- *“How would you evaluate your quality of life during the past six months?”* with answers ranging from *“No quality of life”* to *“Best possible quality of life”* as end points.

Responses ranging from 1 to 5 on the scale were defined as low to moderate quality of life.

For evaluating the perception of participation nine questions were included. For example:

- *“Do you believe it is valuable to conduct a study like this?”* with the possible answers: *“No, not at all”, “Yes, somewhat”, “Yes, moderate”, “Yes, much”*.

In addition, there were place for supplementary comments.

The final version was tested for face validity on 20 individuals, where a majority was cancer survivors from the study-population. This led to the formulation of new versions and the process continued until no changes were suggested by the participants.

Pilot study

Paper I-III

The questionnaire was tested in a pilot study with 20 gynecological cancer survivors within the study population. The questions' conceivability, the answering rate on each question and the logistics were tested. This method was then used in the main study. A response rate of 80 percent was regarded as sufficient to continue with the main study. The study was approved by the Regional Ethic Committee of Karolinska Institutet in Stockholm.

Paper IV

The urinary bladder cancer questionnaire used in Paper IV was developed using the same method as described above.

QUANTITATIVE PHASE - MAIN STUDY

Data collection

From January to October 2006, an introductory letter was sent to 789 survivors and 478 controls explaining the objectives of the study emphasizing that participation in the study was voluntary. One week later an interviewer phoned each informant. Those giving informed oral consent to participate received a postal questionnaire along with a letter and additional information. To maintain anonymity, each questionnaire contained a number for identification. Three weeks later, a thank-you-card was sent to show appreciation or to serve as a reminder. A week later the interviewer phoned those who had not returned their questionnaire. The method for data collection has been used and described in more than 70 publications^{40, 147, 148}.

All medical records were reviewed to confirm diagnosis, stage of disease, treatment modality and recurrence among cancer survivors. The intention to treat the patients was in accordance with the local treatment program and applied study protocols which have changed over the study period.

Data entry

Transfer of all data from the questionnaires answered by cancer survivors was performed using the freeware data and validation program Epi-Data 3.02 (www.epidata.dk).

Statistical analyses

In Paper I statistical analyses were performed with IBM SPSS Statistics 17.0 (IBM, Armonk, New York, United States). In Paper II-IV calculations were performed using the SAS statistical software package (version 9).

In Paper IV content analysis of the open ended questions was facilitated by the Open Code 2.1 (www.phmed.umu.se/enheter/epidemiologi/forskning/open-code). Hand-written comments were thematically coded into broad analytic categories and classified into content areas.

RESULTS

RESULTS PAPER I-III

Participation rate

Six hundred and sixteen (78 percent) cancer survivors returned a completed questionnaire and participated in the study. Among 478 eligible control women, 344 (72 percent) returned the questionnaire.

Reasons for non-participation

Ninety-two cancer survivors did not participate and the following reasons were given for their nonparticipation:

- 29 no reason given
- 21 due to poor physical health
- 17 not reachable
- 14 due to poor psycho-social health
- 9 due to psychological reasons
- 2 family member said no on behalf of the cancer survivor

Six hundred and ninety-seven (88 percent) gave informed oral consent and were sent a questionnaire. Fifty-two cancer survivors did not return the questionnaire and 29 sent back a blank questionnaire.

Among control women 58 did not participate and the following reasons were given:

- 37 no reason given
- 13 due to poor physical health
- 5 not reachable
- 3 due to poor psycho-social health

Four hundred and twenty (88 percent) gave informed oral consent and were sent a questionnaire but 66 did not return the questionnaire and 10 sent back a blank.

Overall characteristics of cancer survivors and control women

At the time of the study the mean age was 64.4 years among cancer survivors and 58.0 among the population based-controls. More cancer survivors than control women were single or widows and they also had a lower level of education. As to employment status more cancer survivors than control women were retired.

No large differences were seen for smoking or Body Mass Index (BMI). Twice as many survivors compared to control women neither exercised nor had given birth.

Control women reported more injury to the vagina and or perineum than cancer survivors, no difference was seen concerning anal sphincter injury. Cardiovascular diseases were more common among cancer survivors but no differences were found for diabetes mellitus, intercurrent bowel or neurological diseases.

The following gynecological cancer diagnosis were represented in the study; endometrial cancer (59 percent), cervical cancer (23 percent), ovarian cancer (7 percent), uterus sarcoma (5 percent), vaginal cancer (2 percent), fallopian tube cancer (2 percent) and vulvar cancer (1 percent).

Paper I:

Characteristics of endometrial cancer patients

Three hundred and sixty-six cancer survivors were treated for an *endometrial* cancer. Mean age was 68.0, ranging from 38 to 79 years. Overweight or obesity was reported in 54 percent of the endometrial cancer survivors and 45 percent had hypertension and all reported cases of neurological disorders (15 patients) were found among the endometrial cancer survivors. FIGO stages at diagnoses among endometrial cancer patients were for stage I: 70 percent, stage II: 17 percent and stage III: 13 percent.

All endometrial cancer patients underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy, with or without omentectomy. Eight percent had additional lymph-node sampling. Chemotherapy (a combination of cyclofosfamide, antracyclins and cisplatinum) was given to 21 percent high-risk patients and brachytherapy to 98 percent of the endometrial cancer patients.

Mean total dose of external beam irradiation given was 42 Gy (range 10.8 to 46.8Gy). Ninety-two percent were treated towards a pelvic field and 81 percent with a four-field technique. Mean time since external radiotherapy was 86 months (range 30 to 183 months).

Characteristics of cervical cancer patients

One hundred and forty-two cancer survivors were treated for a *cervical* cancer. Cervical cancer survivors had the lowest mean age, 56.3 years, ranging from 30 to 79 years. Thirty-six percent of them were current smokers and 17 percent had given births to more than three children. FIGO stages at diagnoses among cervical cancer patients were for stage I: 50 percent, stage II: 34 percent and stage III: 20 percent.

Sixty-one percent underwent surgery. Radical hysterectomy with bilateral salpingo-oophorectomy and pelvic lymphadenectomy was performed in 83 percent whereas 15 percent underwent total hysterectomy and bilateral salpingo-oophorectomy, of which an occult cervical cancer was found in the majority of cases. Eighty-seven percent of the

cervical cancer patients had brachytherapy, 43 percent had chemotherapy, whereas 52 percent concomitant chemoradiotherapy with weekly cisplatin.

Among cervical patients treated with radiotherapy alone the mean total dose of external radiotherapy was 54.6 Gy (range 39.6 to 70 Gy) compared to a total mean dose of 44.1 Gy (range 14.4 to 67 Gy) among patients who had surgery. A vast majority had a four-field box technique. Seventy-two percent had a pelvic field and 24 percent an extended pelvic field covering the paraaortic lymph nodes. Mean follow-up since radiotherapy was 77 months (range 30 to 168 months) in patients who did not have surgery and 86 months (range 30 to 180 months) in patients who had surgery.

Characteristics of ovarian and fallopian tube cancer patients

Fifty-eight cancer survivors were treated for either an *ovarian* or *fallopian tube cancer*. Mean age among the cancer survivors was 62.8 years, ranging from 33 to 79 years. FIGO stages at diagnoses among ovarian and fallopian tube cancer patients were for stage I: 42 percent, stage II: 40 percent and stage III: 18 percent.

All ovarian and fallopian tube cancer patients underwent primary cytoreductive surgery. Total abdominal hysterectomy with bilateral salpingo-oophorectomy and omentectomy was performed in 57 of 58 patients. Eighty-eight percent had chemotherapy and two percent had brachy- and chemotherapy. Ninety percent were treated with platinum-based chemotherapy before or after surgery. One patient received brachytherapy.

Mean total dose of radiotherapy given was 39.8 Gy (range 30.0 to 60.0 Gy). The external radiotherapy was typically given with parallel opposed technique to 20 Gy to the whole abdomen with an additional 20 Gy to an abdominal volume with lowered cranial margins. Ovarian- and fallopian tube cancer survivors had the longest follow-up time with a mean of 120 months (range 33 to 183 months).

Characteristics of uterine sarcoma cancer patients

Thirty cancer survivors were treated for a *uterine sarcoma*. Mean age was 63.7 years, ranging from 28 to 77 years. Uterine sarcoma survivors reported most cases of vaginal or perineum injuries (30 percent) and diabetes mellitus (21 percent). FIGO stages at diagnoses among uterine sarcoma cancer patients were for stage I: 67 percent, stage II: 13 percent and stage III: 10 percent.

All patients underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy; five patients (17 percent) were given chemotherapy (a combination of cyclofosfamide, anthracyclins and cisplatin) before or after external radiotherapy and nine patients (30 percent) had brachytherapy. The external radiotherapy was delivered in daily fraction of 1.8 Gy to a pelvic volume and the prescribed total dose was 50.4 Gy, resulting in a mean dose of 47.6 Gy (range 39.6 to 52.2 Gy). Mean time since external radiotherapy was 91 months (range 32 to 157 months).

Characteristics of vaginal cancer patients

Fourteen survivors were treated for a *vaginal cancer*. Mean age was 58.5 years, ranging from 42 to 78 years. FIGO stages at diagnoses among vaginal cancer patients were for stage I: 71 percent and stage II: 29 percent. Seven vaginal cancer patients underwent local resection and seven did not have surgery, eleven (79 percent) patients had brachytherapy and none had chemotherapy.

The external radiotherapy resulted in a mean total dose of 48.5 Gy (range 39.6 to 59.4 Gy) for patients who did not have surgery and 43.2 Gy (range 39.6 to 46.0 Gy) for patients who had surgery. Mean follow-up since external radiotherapy was 75 months (range 30 to 130 months).

Characteristics of vulvar cancer patients

Only six cancer survivors were treated for a *vulvar cancer*. Mean age was 65.5 years, ranging from 61 to 73 years. FIGO stages at diagnoses among vaginal cancer patients were for stage I: 17 percent and stage II: 83 percent.

All patients underwent vulvar resection and bilateral inguinal lymph-adenectomy followed by external radiotherapy with a prescribed dose of 40-45 Gy. No brachy- or chemotherapy was given.

Total mean total dose of external radiotherapy delivered was 43.6 Gy (range 35.2 to 48.6 Gy). Mean time since external radiotherapy was 94 months (range 55 to 119 months).

Paper II

The largest risk difference between cancer survivors and control women were seen for the following symptoms:

Symptoms	Cancer survivors No/total (%)	Controls No/total (%)	Age-adjusted Risk Difference
Defecation urgency with fecal leakage occasionally	298/603 (49)	42/343 (12)	+37
Loose stools at least once a week	234/602 (39)	48/344 (14)	+28
Leakage of loose stools while awake occasionally	199/608 (33)	18/344 (5)	+27

The highest relative risks, RR, were for the following symptoms:

Symptoms	Cancer survivors No/total (%)	Controls No/total (%)	Age-adjusted Relative Risk (95% CI)
Emptying of all stools into clothing without forewarning occasionally	70/606 (12)	3/344 (1)	11.9 (3.8-37.8)
Leakage of loose stools while awake occasionally	199/608 (33)	18/344 (5)	6.1 (3.8-9.7)
Defecation urgency at least once a week	175/602 (29)	19/341 (6)	5.9 (3.7-9.4)

The survivors described 18 symptoms of fecal leakage of which a vast majority of the symptoms were statistically significant in comparison with control women. When comparing cancer survivors treated with radiotherapy but without surgery with cancer survivors who had surgery, the largest age adjusted risk differences were seen for the following symptoms:

Symptoms	Pelvic radiotherapy – No surgery	Pelvic radiotherapy and surgery	Age-adjusted Risk Difference
Emptying of all stools into clothing without forewarning occasionally	15/59 (25)	55/547 (10)	+18
Abdominal pain with vomiting occasionally	11/35 (31)	46/272 (17)	+16
Leakage of loose stools while awake occasionally	27/61 (44)	172/547 (31)	+13

Paper III

Among survivors, 70 (12 percent) reported that they at least occasionally had the symptom emptying of all stools into clothing without forewarning, compared to three out of 344 (<1 percent) controls, age-adjusted RR 11.9 (95% CI 3.8-37.8). Adjustment for known risk factors for FI such as obesity, diabetes mellitus, neurological diseases, increased parity, inflammatory bowel diseases and operative vaginal delivery did not alter the result. We compared quality of life and social functioning among cancer survivors with the symptom emptying of all stools into clothing without forewarning with cancer survivors without the symptom.

The mean age was slightly higher among cancer survivors with emptying of stools without forewarning compared to women without the symptom. Affected survivors were less often living with a partner, had lower levels of education, exercised less frequently and had more often a disability pension. Vacuum delivery, episiotomy and injury of vagina, perineum and the anal sphincter as well as intercurrent diseases were more prevalent among survivors with emptying all stools into clothing without forewarning compared to survivors without the symptom. Cervical cancer and

uterine sarcoma were proportionally more frequent among cancer survivors with the symptom, although the most common diagnosis was endometrial cancer.

Seventy-four percent of the survivors with emptying of stools without forewarning considered their overall quality of life as low to moderate compared to 51 percent among survivors without the symptom. The symptom emptying of all stools into clothing without forewarning affected self-assessed quality of life from a social, psychological, sexual and functional aspect.

The highest age-adjusted risk differences were seen for the following variables:

Quality of life variables	Cancer survivors with emptying of all stools without forewarning No/total (%)	Cancer survivors without emptying of all stools without forewarning No/total (%)	Age-adjusted Risk Difference
Affected by sudden emptying of the bowel	58/67 (87)	102/535 (19)	+67
Defecation urgency bothers	59/70 (84)	163/532 (31)	+56
Have not felt clean due to fecal leakage	50/70 (71)	105/533 (20)	+52
Loose stools bothers	49/67 (73)	139/527 (26)	+48

The highest relative risks were seen for the following variables:

Quality of Life variables	Cancer survivors with Emptying of all stools without forewarning No/total (%)	Cancer survivors without Emptying of all stools without forewarning No/total (%)	Age-adjusted Relative Risk (95% CI)
Located toilets in advance at least once a week	32/68 (47)	21/530 (4)	11.9 (7.3-19.4)
Fecal leakage have kept me from going to parties	24/69 (35)	16/531 (3)	11.8 (6.6-21.1)
Fecal leakage affected my ability to do housework	16/68 (24)	13/530 (2)	10.0 (5.0-19.7)
Fecal leakage has kept me from travelling	22/70 (31)	18/534 (3)	9.3 (5.3-16.5)

Approximately 50 percent needed to locate toilets in advance and 60 percent stayed close to toilet facilities at all times. Incontinence devices and diapers were used by almost half of the affected women and thoughts and practical arrangements about bowel movements occupied them several hours daily.

Adjustment for potential confounding factors (age, level of education, marital status, employment status, exercise, smoking and BMI) for quality of life changed the ration of proportions with at most 2.1 (adjusting “fecal leakage has kept me from going to parties” for employment status from 11.5 to 9.4).

Eighty-three percent of the cancer survivors with emptying of stools without forewarning were able to defer feces for less than five minutes compared to 38 percent among cancer survivors and 11 percent among controls. Fifty-one percent of the affected survivors compared to 35 percent without the symptom had talked to a medical professional about FI.

RESULT PAPER IV

Participation rate

One thousand and sixty-eight (83 percent) eligible cancer survivors participated in the study.

Characteristics of cancer survivors

The study population comprised 67 percent women and 33 percent men with a mean age of 65.5 years, ranging from 28 to 80. Fifty-seven percent were retired and 30 percent were still working.

Reasons for non-participation

One hundred and thirty-one cancer survivors in the total study population did not participate. Reasons for non-participation for the gynecological cancer survivors are given under Paper I-III. The urinary bladder cancer survivors reported the following reasons for nonparticipation:

- 5 deaths after start of follow-up
- 6 not reachable
- 7 due to poor physical health
- 1 mental retardation
- 7 refusal

Four hundred and sixty five (95 percent) urinary bladder cancer survivors gave informed oral consent and were sent a questionnaire but 13 sent back a blank questionnaire.

Results

Each questionnaire included a section that assessed the perception of participation, with each section consisting of either nine or six questions, with an answering rate of 96 to 98 percent among cancer survivors. In addition a voluntary supplementary comment about being part of the study was written by 166 (16 percent) participants. One thousand and three (95 percent) participants reported they felt that the study was valuable, 559 (54 percent) felt they had been positively affected by their participation and 39 (four percent) expressed having been negatively affected. Among the 39 negatively affected participants, 22 (56 percent) participants reported anxiety and depression, at follow-up. No statistically significant difference could be seen due to age among the negatively affected.

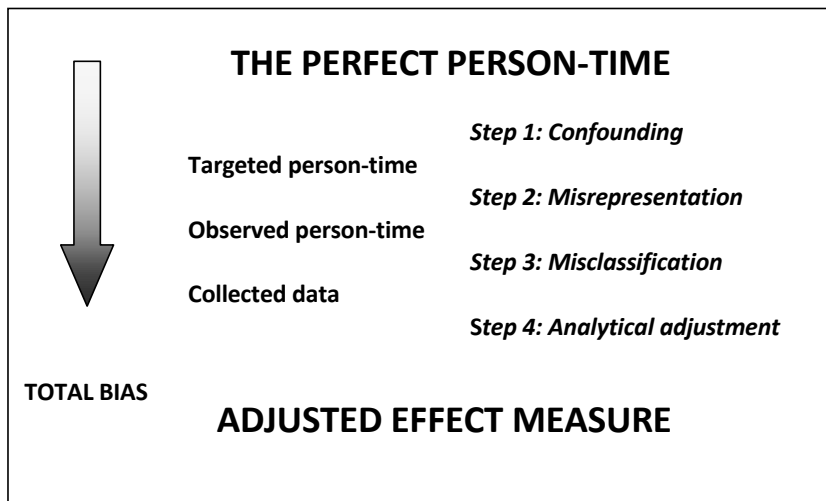
DISCUSSION

METHODOLOGICAL CONSIDERATIONS

The validity of an effect-measure in a study refers to measuring what is supposed to be measured, or the accuracy of the measurement. Optimizing the validity of an effect-measure must always be an ambition.

In the perfect study our aim would have been to study all individuals in a perfect study-time, however, in real life this is not doable. In our study, we have therefore chosen to study the experience of 789 gynecological cancer survivors during six months (3 to 15 years after their treatment), which generated 394.5 person-years.

The validity of an effect-measure depends on the degree of absence of errors in the assessment of the effect. In our research group, we have a tradition of using the hierarchical step-model¹⁴⁹ as a navigator for causation of bias in order to avoid the reefs of systematic errors. According to the step-model illustrated in the figure below, there are four main steps towards the adjusted effect measure.



Step 1: Confounding

A confounding factor may hide an actual association between the studied variables where no real association between them exists. If confounding factors are neither measured nor considered, results may be biased¹⁵⁰. To be defined as a confounding factor, the factor must both be associated with the exposure (in our study, radiotherapy) and be an independent risk factor for the outcome (in our study, leakage of feces)¹⁵¹.

When confounding factors are not taken into account, this may lead to an over- or underestimation of the true association between exposure and outcome¹⁵¹.

In our study, great preventative measures were taken in the preparatory phase to avoid systematic errors due to confounding factors. As gynecological cancer only affects women we did not have to take gender into account as a possible confounder. However, we collected as much information as possible on other potential confounding factors, either through the questionnaires or through medical records. Information drawn from cancer survivors included; age, education, residential area, smoking, BMI, medications, type of delivery, co-morbidities such as diabetes mellitus, neurological diseases, heart conditions (i.e. hypertension, heart-failure, ischemic heart disease). From medical records we collected data on diagnosis, stage of disease, treatment modality, recurrence and radiotherapy doses. Known or suspected causal factors for the outcomes we studied were taken into account in our analyses.

Step 2: Misrepresentation

The second step in the hierarchical step-model, misrepresentation, may introduce bias due to non-participation and selection-induced problems may therefore occur. The study is well grounded in the initial qualitative phase with validation of the instrument and the method being tested in a pilot study within the study-population to make sure that we could continue to the quantitative phase and collect the data.

All women in the Stockholm or Gothenburg region diagnosed with a gynecological malignancy are referred to either Karolinska University Hospital in Stockholm or Sahlgrenska University Hospital in Gothenburg, having a catchment area of 3 500 000 individuals. The cohort consisted of unselected patients arriving consecutively to these two clinics and a control group that was randomly selected from the Swedish population Registry.

Non-participants induce loss of information from the targeted person-time and therefore it is crucial to avoid non-participation. The participation rate in the pilot and main studies was high, 80 and 78 percent respectively for the gynecological cancer survivors and 72 percent for the control women in the main study. A detailed description of our method of collecting data, including an informative introduction letter sent to all participants and a following introductory telephone call, has already been described (see chapter on Method). We believe that working intensely in the initial phase of data collection can partly explain our reasonably high participation rate, thereby minimizing risk of selection-induced problems.

Out of 789 cancer survivors 92 did not participate; 46 gave a reason for their non-participation (Paper I-III, Figure I), 29 women did not give any reason for their non-participation and we never reached telephone contact with 17 of the women. Among 478 control women 58 did not participate; 16 gave a reason for their non-participation

(Paper I-III, Figure I), 37 women did not give any reason for their non-participation and we never reached telephone contact with five of the women.

We can only speculate if non-participants of whom we have no information belong to the healthier part of the population or the less healthy. We cannot overrule the possibility that those who did not participate were somehow different than participants which might influence our results.

A large number of cancer survivors, 1 011, did not meet the eligibility criteria and were therefore excluded from the study population: approximately 550 women had died before follow-up or had a recurrence, 436 were born before 1927 and 23 did not speak Swedish. Eight control women did not meet the eligibility criteria; born before 1927, did not speak Swedish or had pelvic radiotherapy, and were excluded. Information on the excluded women's health, well-being and reason for their death is also unknown to us and we can only hypothesize that the older women, women with recurrence and those who had died prior to follow-up belonged to the less healthy.

Step 3: Misclassification

According to the hierarchical step-model for causation of bias, the third step of a study may introduce bias when the information collected is incorrect for some reason. Therefore, a fundamental and a crucial part of each study is the instrument. In developing our instrument, we began by performing semi-structured interviews with the target population (women with gynecological cancer). During the interviews they were all given the chance to talk about their personal experience and the challenge that can arise in their new life situation after a cancer treatment. The interviews proceeded with additional cancer survivors until we did not gain any new information. The development of the study-specific questionnaire was therefore founded in the interviews, our clinical knowledge and a bank of knowledge within our research-team.

An important task was to make all questions clear and understandable. Face validation within the study-population led to modifications, new drafts were developed and validated. We believe that by intensively preparing the questionnaire and developing questions with the studied population in a face-to-face situation we increase the likelihood of the respondents acknowledging the questions and answering them as intended, thereby decreasing the risk of misclassification.

The questionnaire was mailed to the participants. They had several weeks to complete the questionnaire in the privacy and security of their own home. We believe that this lowers the risk of potential interviewer-induced bias¹¹². The researchers were also independent from a clinical setting, which decreases the risk of "I-want-to-please-my-surgeon" bias¹⁵².

Step 4: Analytical adjustment

Statistics are used to estimate effects of an association. Errors may occur due to confounders and other biases. In the ideal study the two categories of exposure (cancer survivors versus control women) are supposed to resemble each other as much as possible (for example age and place of residency). In order to imitate the role model of studies – randomization - and to make the comparison between cancer survivors and control women as perfect as possible we adjusted for age as we had a younger control population.

FINDINGS AND INTERPRETATIONS

Paper I

Although tumour outcome and acute toxicity reporting is fairly standardized, there is no consensus as to how best quantify late normal-tissue effects after radiotherapy. The RTOG/EORTC LATE Radiation Morbidity System⁷⁴ scores between 0 (no symptom) to 5 (death directly related to radiation effects) and is not patient-reported. A certain toxicity grade may include several symptoms and information on symptom intensity, duration and distress is lacking. For instance, toxicity for small and large intestines grade 2 includes moderate diarrhea and colic; bowel movement > five times daily; excessive rectal mucus or intermittent bleeding. Patient questionnaires have been developed for cervical cancer from the LENT SOMA scales but they do not assess specific symptoms, such as fecal incontinence¹⁰², and does not reflect on patients experience when scoring 1 or 2⁷⁷. Furthermore, comparison with other assessments without a scoring system is not always compatible and both under- or overestimations may have to be considered.

Attempts to find new ways to assess gastrointestinal side-effects after pelvic radiotherapy have been evaluated in order to develop a feasible tool that could easily be completed by the patients in the clinic. Olopade and co-workers modified an instrument otherwise used in the general population and assessed whether outcome measures used for non-malignant gastrointestinal disease were useful to detect gastrointestinal morbidity after radiotherapy⁹². The instrument, a modified Inflammatory Bowel Disease and Vaizey Incontinence Questionnaire has been compared with the SOMA/LENT questionnaire. The authors found that the modified Inflammatory Bowel Disease and Vaizey Incontinence Questionnaire was reliable in assessing new gastrointestinal symptoms as well as overall QoL and it was much easier to use than the SOMA/LENT instrument⁹². Abayomi and co-workers also explored late effects of pelvic radiotherapy, chronic radiation enteritis⁸³. The instrument¹⁵³ used in their study was previously used among women with anal incontinence, not caused by cancer treatment.

We have gained a comprehensive knowledge of existing symptoms occurring after pelvic radiotherapy for gynecological cancer treatment. We believe the use of a

validated instrument, grounded in the experiences of the cancer survivors, made this possible. Despite a lengthy questionnaire, where many questions might be considered as exhaustive and intimate, the participation rate was high. With access to medical records we could also retrieve all pieces of necessary information. Such a comprehensive and detailed study has to our knowledge not been performed previously.

The study cohort is highly heterogeneous encompassing all gynecological cancer cases treated consecutively and treatment recommendations have changed over time. These circumstances contributed to a variability of the absorbed dose of ionizing radiation to the organs-at-risk, which will enable us to study the dose-volume effects of radiotherapy to normal-tissue in correlation to self-assessed symptoms.

Paper II

The gynecological cancer survivors we studied reported over 30 long-term gastrointestinal symptoms, of which 18 are anal incontinence symptoms. Frequent symptoms were loose stools, defecation urgency and almost 50 percent reported leakage of feces. The cancer survivors reported a higher prevalence of gastrointestinal symptoms than did women from the general population. We believe it is important to evaluate, intervene and treat gastrointestinal symptoms after cancer treatment in order to improve or restore quality of life in gynecological cancer survivors.

Loose stools, defecation urgency and fecal leakage are reported gastrointestinal symptoms after pelvic radiotherapy^{83, 86-88, 93, 99, 100, 102} but comparison between studies is often compromised by different assessments used as well as the time between treatment and follow-up. As pointed out in a recent review by Andreyev, gastrointestinal symptoms after pelvic radiotherapy are even more common than generally recognized and they are frequently poorly managed⁹⁵. Specific therapeutic interventions before and after radiotherapy may help reduce, relieve or eliminate chronic, undesirable changes in bowel habits once they have occurred¹⁵⁴.

In an effort to decrease the acute bowel toxicity and to study the long-term effects of pelvic radiotherapy on bowel function Haddock and co-workers investigated the effect of sucralfate. At follow-up one year after pelvic radiotherapy they found an even higher prevalence of urgency than in our study but a lower prevalence of loose stools⁶³. The cancer survivors in the study by Haddock and co-workers were treated not only for gynecological cancer but for other cancers in the pelvic region and we know from other studies that gynecological cancer survivors generally have more gastrointestinal symptoms than prostate cancer survivors⁸².

We also aimed to elucidate different types of fecal leakage and several questions were asked in connection with this condition. The most frequent leakage symptom, occurring among almost half of all cancer survivors, was “defecation urgency with fecal leakage”.

Olopade and co-workers also investigated different types of fecal incontinence using a modified questionnaire developed for a population with inflammatory bowel diseases. By adding the Vaizey Incontinence questionnaire they studied the prevalence of fecal incontinence among cancer survivors after treatment⁹². They captured several different entities of fecal incontinence in a cohort of 62 gynecological cancer patients and found that 31 percent were incontinent for solid stools, 47 percent incontinent for liquid stools, and 58 percent incontinent for gas⁹². A comparison between the measured prevalence of solid, liquid and gas incontinence in our study and in the study that Olopade and co-workers conducted is also compromised by different methods used to assess fecal incontinence and time since treatment. In the study by Olopade and co-workers the follow-up after radiotherapy was a mean of 27 months compared with 86.1 months in our study.

The increased occurrence of the self-assessed and self-reported fecal leakage symptom “emptying of all stools into clothing without forewarning” was reported by 70 (12 percent) cancer survivors. This symptom did almost not exist among control women (0.9 percent), which indicate that treatment caused this symptom. Due to the reported lack of forewarning one may hypothesize that the symptom “emptying of all stools into clothing without forewarning” is a passive fecal incontinence symptom, being the discharge of stool without forewarning^{109, 155}. However, a vast majority could not defer feces when feeling the need to defecate for longer than a maximum of five minutes. Almost 35 percent of the women could defer feces for a maximum of one minute and one may therefore speculate that this symptom, reported after pelvic radiotherapy, may consists of both a sensory and irritable component. In addition, we found the symptom to be intermittent (unpublished data). Hence, 50 survivors reported that they had “emptying of all stools into clothing without forewarning” at least occasionally, 11 at least every month, five at least every week and four survivors had the symptom at least three times a week. Further preliminary results among affected women have shown co-existing symptoms such as: fecal leakage without forewarning despite previous defecation in 84 percent, occasionally leakage of solid stools in 27 percent, leakage of loose stools in 79 percent and defecation urgency with fecal leakage in 97 percent of affected cancer survivors (unpublished data). In addition 71 and 70 percent have defecation urgency and loose stools, at least once a week respectively. This indicates a relationship with bowel habits. One may therefore interpret that survivors with the symptom “emptying of all stools into clothing without forewarning” may intermittently experience triggers, which sometimes results in unpreventable fecal incontinence but also, at least occasionally, discharge of stools without awareness.

“Emptying of all stools into clothing without forewarning” and other types of fecal leakage among gynecological cancer survivors have not been thoroughly studied previously. We have only found two papers addressing this symptom in cancer survivors previously^{83, 156}. Abayomi and co-workers studied 95 women treated with pelvic radiotherapy for endometrial and cervical cancer⁸³. The cancer survivors were asked to complete a questionnaire exploring bowel problems and quality of life.

They used a validated questionnaire previously utilized in studies to identify patients with fecal incontinence¹⁵³. Half of the studied women reported bowel symptoms with a wide variation in severity. Younger women and women with cervical cancer were more likely to have symptoms. Twenty-six percent reported leakage of loose stools, 16.5 percent leakage of solid stools and 41.5 percent had to rush to the toilet. In free-hand comments women reported lack of warning for fecal incontinence⁸³. In the other study, Andreyev and co-workers investigated 265 patients referred to a gastroenterologist for gastrointestinal symptoms. All patients had previously undergone radiotherapy for a pelvic cancer. A total of 79 patients had fecal incontinence, whereas 65 patients were reported to have active FI, 10 passive FI and four a combination of both¹⁵⁶.

Paper III

Seventy-four percent of the survivors with the symptom “emptying of all stools into clothing without forewarning” reported a low to moderate quality of life and that this also kept the gynecological cancer survivors from social activities and hindered their sexual lives. A majority of the women located accessible toilets in advance and one third stated that having fecal leakage had changed them as persons. Gastrointestinal symptoms have more effect on quality of life than generally reported⁸² and previous studies also conclude that when having a symptom after pelvic radiotherapy, fecal leakage is one of the most distressful⁸⁴.

The following quotation from a young cancer survivor gives, perhaps, a greater insight on the impact of fecal incontinence on wellbeing:

“I must always think about staying near a toilet or holding myself in order to avoid defecating in my clothes. Even experiencing loose stools is a pain. My thoughts revolve around trips to the restroom and I always have extra panties and sanitary napkins with me. As a 39 year old, I experience these emotions with humiliation.”

If fecal incontinence occurs without forewarning before the defecation event, we can assume that the condition is not only unpredictable but disabling and very embarrassing, as confirmed by Abayomi and co-workers⁸³. The studied gynecological cancer survivors reported that chronic radiation enteritis, with urgency, loose stools and fecal incontinence, had an impact on work, activity outside the house, ability to travel and social life⁸³. The comparison with our study is not totally feasible as we used different definitions of the symptoms and different way of measuring daily life activities. But the conclusion is definitely the same; fecal incontinence has an impact on social life and functioning. Abayomi and co-worker also confirm that the lack of warning or triggers for FI makes coping strategies more necessary⁸³. The women in our study took precautions before leaving home, located toilets in advance or stayed near a toilet at all times. They spent several hours every day on practical arrangements concerning defecation and bowel movements. Toilet dependency has also been reported by Nout and co-workers⁸⁷ who studied 348

gynecological cancer survivors, treated either with vaginal brachytherapy or radiotherapy for an endometrial cancer. Patients who received pelvic radiotherapy reported significantly higher levels of diarrhoea and fecal leakage and reported a significantly higher need to remain close to a toilet⁸⁷. They also reported lowered social functioning in the women treated with radiotherapy⁸⁷. Gami and co-workers also concluded in their study of 107 cancer survivors treated with pelvic radiotherapy that quality of life is affected in every second patient with diarrhoea and every fifth patient with fecal incontinence⁸².

The chronic effects of pelvic radiotherapy have also been evaluated by Yeoh and co-workers¹⁵⁷. They studied 35 prostate cancer patients one year after completion of treatment and 17 men had defecation urgency, fecal incontinence was reported in nine men. Half of the patients had to make changes in their daily activities¹⁵⁷.

Years may have passed since cancer treatment and an association between symptoms and treatment is no longer obvious. Some survivors may believe that symptoms are an inevitable part of being old¹⁵⁸, others find it too embarrassing to talk about. We need to ask the patients if they have leakage of feces. Leigh and co-workers reported already in 1982 that almost one in two will not disclose the fecal incontinence symptom unless specifically asked¹⁵⁹. In our study, only fifty one percent of the women with the severe FI symptoms “emptying of all stools into clothing without forewarning” had talked to a health care professional about having FI, 16 percent had not talked to anyone. Leakage of feces is still surrounded by taboos and maybe more difficult to talk about than sexual dysfunction.

Paper IV

Gynecological and urinary bladder cancer survivors found the study-specific designed long-term follow-up studies valuable and were positively affected by their participation. The following quotation captures the essence of our conclusion:

“I want to thank you so much! After reading through and responding to this I feel so much better! Received an explanation for all of my aches and pains. I wish that I didn’t have to return this book!”

We believe a study-specific questionnaire, developed in close cooperation with the cancer survivors, can be supportive and promote reflection upon one’s own situation, needs and concerns.

Researchers all over the world take interest in finding new treatment strategies to improve survival and reduce cancer toxicity and cancer patients are often approached. Surveys are performed with vulnerable individuals; yet very few explore and publish papers describing how participants perceive their participation. Existing literature exploring participation in research studies most often focuses on ethical considerations or methodological issues. We also aimed to increase our knowledge and gather information about cancer survivors to improve health-care for

present and future cancers patients. The gynecological cancer survivors shared many very intimate parts of their lives when answering questions about leakage of feces and sexual habits in a very comprehensive questionnaire. We believe when cancer survivors participate and share their experience we are obliged to make sure that the findings are useful and generalisable. Although the gynecological questionnaire included in total 351 questions and many questions were considered as exhaustive, private and intimate by some, the participation-rate was high (78 percent). Still, we have no answers from 22 percent. Asch and co-workers¹⁶⁰ characterized the typical participation rate for mailed surveys, published in medical journals. The average participation rate for these mailed surveys was approximately 60 percent, meaning that another 40 percent of invited participants do not respond, and problems arise when we do not know anything about the non-participants.

Very few participants were negatively affected and stated that the survey had reminded them of things they had forgotten. However, a greater part found the long-term follow-up valuable and a majority were positively affected. By answering the questionnaire they got the chance to reflect on their illness, treatment and survivorship and gained new knowledge. This result is not surprising since the study-specific questionnaire is developed in close cooperation with the cancer survivors. Great precautions were also taken in validating the instrument. This is in agreement with Charlton and co-workers who also point out the importance of a questionnaire being carefully designed, pre-tested and pilot-tested, with consequential modifications to increase validity, reliability and responsiveness¹⁶¹.

It is a win-win concept where both cancer survivors and researchers gain valuable insight. This knowledge will help and guide when planning studies on future cancer survivors.

THE FUTURE

Valuable research concerning long-term side effects after radiotherapy of the pelvic region has been gathered and in this thesis gastrointestinal symptoms - especially fecal incontinence, are reported. A more detailed analysis will be performed to investigate the relationship between different gastrointestinal symptoms and fecal leakage, as well as symptoms from other normal-tissues in the pelvic area.

Knowledge of which dose levels of the ionizing radiation for a specific volume of a pelvic organ-at-risk that may develop symptoms, can lead to suggestions of dose constraints to avoid that particular symptom. Recommendations based on both dose levels and irradiated organ-volume will guide the radiotherapists in their decisions. Further knowledge in how to contour the tumor target area and organs-at-risk along with the technical development in treatment planning systems and treatment delivery systems, will in turn make it possible for a more precise administration of ionizing radiation. The optimal result would be to provide a customized and risk-adapted therapy based on current knowledge of the effect of each cancer therapy on normal tissue depending on pre-existing risk factors in the individual patient.

Severe symptoms such as fecal incontinence and loose stools affect daily life and well-being negatively. The symptoms are difficult to speak about and routines for identifying symptoms, risk factors and patients at risk should be implemented in care and after-care. We want to strive to find new ways to treat side effects that have arisen and establish and facilitate contacts with other specialist groups outside of oncology. We also want to design intervention programs and evaluate treatment for further development of care and treatment. The information to patients and survivors of cancer before, during and after treatment can be developed further.

Many women have long since finished treatment and follow-up and may seek care for symptoms at their general practitioner, a private practice or another health care-giver. To increase knowledge regarding late side effects, with the intention of decreasing suffering, information should be spread to a larger audience in the health care system, since this should lead to better care and treatment. An increasing number of patients and patient's close family also seek and spread information using the internet and blogs. The internet, blogs and patient organizations are valuable information channels where important evidence-based information can be spread.

Rehabilitation of cancer patients needs to be strengthened and organized multi-professionally and multi-disciplinary. Rehabilitation should be a natural part of oncological treatment and should begin in connection with the diagnosis of a cancer disease. A rehabilitation plan should contribute to a positive development and a hope that there is a way back into a normal everyday daily life during and after disease and treatment. It should be a living document formulated in close collaboration with patient and family or other closest to the patient.

GENERAL CONCLUSIONS

Cancer survivors having undergone pelvic radiotherapy alone or as part of combined treatment between the period 1991-2003 for a gynecological malignancy had a higher occurrence of long-lasting gastrointestinal symptoms as compared to population controls.

An increased occurrence of self-reported fecal incontinence was observed. A majority of all women with a history of gynecological cancer treated with pelvic radiotherapy reported leakage of feces at the time of defecation urgency. Loose stool is another common symptom affecting the cancer survivors. Almost 40 percent reported occurrence of loose stool at least once a week.

Twelve percent also reported “emptying of all stools into clothing without forewarning” and 74 percent of them reported low to moderate quality of life. This symptom kept the gynecological cancer survivors from social activities and hindered their sexual lives. A greater part of these women located accessible toilets in advance and one third stated that having fecal leakage had changed them as persons. The cancer survivors also spent several hours every day on practical arrangements concerning defecation.

By using a study-specific questionnaire, cancer survivors’ found the long-term follow-up valuable and more than half of them reported they were positively affected by their participation. Such an approach may improve each cancer survivor’s opportunity to reflect on their illness, treatment and survivorship and provide valuable insight to researchers.

SWEDISH SUMMARY

LÄCKAGE AV AVFÖRING LEDER TILL NEDSATT LIVSKVALITET

Årligen insjuknar cirka 2 700 svenska kvinnor i en gynekologisk cancersjukdom. Tumörsjukdomen kan ha sitt ursprung i livmodern, livmoderhalsen, äggstockar, äggledare, vagina och i de yttre könsdelarna, vulva. Gynekologisk cancer drabbar oftast kvinnor över 60 år, med undantag av cancer i livmoderhalsen som är vanligast bland kvinnor under 50 år. Behandlingen är operation, strålbehandling, kemoterapi och hormonell behandling, ofta i olika kombinationer. Den vanligaste cancerformen är livmoderkroppscancer och 1 200 kvinnor diagnostiseras årligen. Sjukdomen brukar upptäckas i ett tidigt stadium och majoriteten av alla patienter botas efter kirurgi som ibland följs av strålbehandling.

Men gynekologisk cancer är inte bara en sjukdom som angriper ett kroppsligt organ. Sjukdomen påverkar på flera plan och kan även innebära en psykosocial påfrestning. Det drabbar kvinnans inre rum, hennes sexualitet, intimitet, självkänsla och förmågan att ge liv.

Nästan 1 000 kvinnor deltog i en stor epidemiologisk studie som undersökt förekomsten av fysiska symtom och självskattad livskvalitet efter behandling vid en gynekologisk cancersjukdom. Kvinnorna som deltog i studien hade strålbehandlats över bäckenområdet. Vi tillfrågade också kvinnor ur normalbefolkningen, som canceröverlevarna jämfördes med. Canceröverlevarna rapporterade många kvarvarande fysiska symtom som lös avföring, plötsliga avföringsträngningar och läckage av avföring jämfört med de kvinnor som inte behandlats för en gynekologisk cancersjukdom. Läckage av avföring sätter ner den självskattade livskvaliteten och påverkar canceröverlevarnas sociala liv. Kvinnorna har också delgivit värdefull information om sin bakgrund, om fysiska symptom, livskvalitet och påverkan på det dagliga livet efter en behandling vid en gynekologisk cancersjukdom.

Det övergripande målet med studien var att finna bakomliggande orsaker till symtom som kan uppstå efter strålbehandling mot bäckenområdet. Denna kunskap vill vi använda till att förbättra vården för dagens och framtidens gynekologiska cancerpatienter. Vi vill också att vår ökade kunskap ska leda till en förbättring av vård, eftervård och rehabilitering av de kvinnor som diagnostiserats med en gynekologisk cancersjukdom.

Som grund för studien låg en lång inledande och förberedande, kvalitativ, fas. Vi startade med att genomföra 26 intervjuer med kvinnor som diagnostiserats med en gynekologisk cancersjukdom och som fått strålbehandling mot bäckenområdet. I ett samtal berättade kvinnorna om vilka symtom de hade efter sjukdom och behandling och hur de påverkade det dagliga livet. Inte alltid förknippade kvinnorna fysiska symtom de uppgav med cancerbehandlingen. Samtalet pågick så länge som kvinnorna

ville, oftast 60 till 90 minuter. Samtalet spelades in och skrevs därefter ut ordagrant av en sekreterare för att bearbetas och tematiseras.

Dessa långa samtal varvade med litteraturstudier och våra samlade kliniska erfarenheter av gynekologisk cancer och strålbehandling låg till grund för det fortsatta arbetet att utveckla ett studiespecifikt frågeformulär. Frågeformuläret blev mycket omfattande och på 351 frågor ville vi veta så mycket som möjligt om fysiska symtom från tarm, blåsa och smärtor från skelettet. Frågor om lymfsvullnad, sexualliv, livskvalitet, kost och kvinnans sociodemografiska förhållanden ingick även.

När frågeformuläret började närma sig en slutgiltig version testade vi frågor och svarsalternativ i en så kallad ansiktsvalidering. Det innebar att 20 personer fick fylla i formuläret och berätta om det fanns några oklarheter i hur frågor eller svarsalternativ var formulerade. Detta genererade ett antal ändringar av formuläret och denna process pågick tills dess att deltagarna uppgav att de förstod alla frågor och svarsalternativ.

Vi genomförde därefter en förstudie med 20 kvinnor ur studiepopulationen för att undersöka om metoden fungerade och om svarsfrekvensen var acceptabel. Arton av tjugo kvinnor fyllde i formuläret och 80 procents svarsfrekvens gav oss klarsignal att gå vidare till huvudstudien.

Studien hade därmed efter 18 månader nått fram till andra fasen – den kvantitativa delen och huvudstudien. Vi skickade en förfrågan om deltagande i studien till närmare 870 gynekologiska canceröverlevare, strålbehandlade mellan åren 1991 och 2003 vid Karolinska Universitetssjukhuset i Stockholm respektive Sahlgrenska Universitetssjukhuset i Göteborg. Samma förfrågan skickades även till närmare 500 kvinnor framtagna ur det svenska befolkningsregistret, som representerade jämförelsegruppen. För att få ingå i studien hade vi beslutat att kvinnorna skulle vara födda 1927 eller senare, kunna förstå och läsa svenska språket och de fick inte ha haft återfall i sin cancersjukdom. De kvinnor som ingick i kontrollgruppen uteslöts om de hade diagnostiserats med en gynekologisk sjukdom eller fått strålbehandling mot bäckenområdet. De var också födda efter 1927 och vår ambition var att fördelningen på ålder och bostadsort (postnummer) skulle vara så lika som möjligt.

Samtliga kvinnor i studien, över 1 000, blev uppringda och tillfrågade om de ville medverka och de som gav sitt tillstånd och tackade ja fick ett frågeformulär på posten och deltog därmed i studien. Ett par veckor efter det att formuläret skickats ut skickade vi ett tackkort till kvinnorna som samtidigt var en påminnelse till dem som ännu inte skickat tillbaka formuläret. De som därefter ändå inte hade skickat tillbaka formuläret blev uppringda och påmindas om att vi önskade få in formuläret. Sammanlagt ringde vi över 2 000 samtal.

Efter sju månaders datainsamling hade 616 (78 procent) canceröverlevare och 344 (72 procent) kontrollkvinnor skickat tillbaka ett ifyllt formulär och deltog i den slutliga

analysen. Samtliga formulär matades in i en databas och informationen kunde därmed bearbetas statistiskt.

Våra resultat visade att hälften av de 616 canceröverlevare i studien läckte avföring i samband med avföringsträngningar, jämfört med 12 procent av kontrollkvinnorna. Den högsta relativa risken fann vi för en annan form av avföringsläckage, nämligen ofrivillig total tarmtömning i kläderna utan förvarning, motsvarande 70 kvinnor (12 procent) av canceröverlevare. Detta var ett mycket ovanligt symtom bland kontrollerna, där under en procent uppgav en förekomst av symtomet. Vi hade funnit ett symtom som inte tidigare beskrivits närmare bland denna grupp av canceröverlevare. De canceröverlevare som rapporterade symtomet ofrivillig total tarmtömning i kläderna utan förvarning, uppgav även nedsatt livskvalitet. Sjuttiofyra procent rapporterade låg till måttlig livskvalitet jämfört med 51 procent bland övriga canceröverlevare, utan ofrivillig tarmtömning i kläderna. Bland kontrollerna uppgav 57 procent låg till måttlig livskvalitet.

Av canceröverlevare med ofrivillig total tarmtömning i kläderna utan förvarning, uppgav 80 procent att när de kände avföringsträngningar kunde de hålla avföringen 0 till max 5 minuter, jämfört med 38 procent av övriga canceröverlevare utan symtomet och 11 procent bland kontrollerna. Kvinnorna med ofrivillig total tarmtömning uppgav även att de hade andra samtida symtom från tarmarna.

Att läcka avföring är förenat med tabun och stigma och vi vet att canceröverlevare inte gärna talar med någon om att de läcker avföring. I vår undersökning hade 33 procent av canceröverlevare talat med en läkare eller sjuksköterska medan 16 procent inte hade talat med någon alls om att de läcker avföring.

De sista nio frågorna i formuläret handlade om upplevelsen av att delta i en studie och om kvinnorna påverkats av deltagandet. Nästan alla, 95 procent av canceröverlevare, tyckte att det var värdefullt att en studie som denna genomfördes. En majoritet var också positivt påverkade. Endast ett fåtal kvinnor tyckte att studien hade påverkat dem negativt. Många upplevde också att de genom att delta i studien hade fått mer kunskap om de kvarvarande symtom de hade samt om sjukdom och behandling.

Avslutningsvis några fria kommentarer som kvinnorna har skrivit i anslutning till frågorna i formuläret:

”Det känns som man hela tiden måste tänka på att ha nära till toalett eller att man måste hålla sig för att det inte ska komma i kläderna vid tarmträngningar och gaser. Även den lösa avföringen känns jobbig. Tankar kretsar mycket runt toalettbestyr och jag bär alltid med mig extra trosor och bindor. Som en 39-årig kvinna upplever jag det känslomässigt förnedrande.”

”Att vara inlåst under ett berg, ensam på Jubileumskliniken för inre strålning var det mest skrämmande jag varit med om i mitt liv! ”

”Ordet cancer är för alla skrämmande. Men jag är ett levande bevis på att det går att bota. Trots ensamhet eller tröst från nära och kära, då alla har gått ifrån mig. Jag är tacksam för att jag idag lever...”

”Gaser, avföring etc. har inte hindrat mig från att göra det jag vill, däremot har det lagt sordin på glädjen. Känt oro – ska jag fjärta mitt i presentationen eller i trappan...”

”Frågor om sexuallivet berörde mig mycket, då jag med mina skador ej kan ha något sexliv. Min man sedan 53 år och jag trodde vi hade accepterat det.”

”Jag saknar barn och barnbarn...”

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