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# Towards Prevention of Pelvic Radiation Disease in Gynecological Cancer Survivors

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*"Det är skönare lyss till en sträng, som brast, än att  
aldrig spänna en bäge"*

Verner von Heidenstam

## ABSTRACT

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

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

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

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

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

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

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

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

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

# LIST OF PUBLICATIONS

This thesis is based on the following papers, referenced to by their Roman numerals:

- I. **Helena Lind**, Ann-Charlotte Waldenström, Gail Dunberger, Massoud al-Abany, Eleftheria Alevronta, Karl-Axel Johansson, Caroline Olsson, Tommy Nyberg, Ulrica Wilderäng, Gunnar Steineck, Elisabeth Åvall-Lundqvist. Late Symptoms in Long-term Gynaecological Cancer Survivors after Radiation Therapy. A population-based cohort study. *Br J Cancer*. 2011;105:737-45
- II. 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. *Int J Gynecol Cancer*. 2010;20:449-60
- III. **Helena Lind**, Eleftheria Alevronta, Gunnar Steineck, Ann-Charlotte Waldenström, Tommy Nyberg, Caroline Olsson, Ulrica Wilderäng, Gail Dunberger, Massoud al-Abany, Elisabeth Åvall-Lundqvist. Emptying of All Stools into Clothing Without Forewarning and Mean Dose to Bowel and Anal-Sphincter Region. Submitted.
- IV. Eleftheria Alevronta, **Helena Lind**, Massoud al-Abany, Ann-Charlotte Waldenström, Caroline Olsson, Gail Dunberger, Panayotis Mavroidis, Tommy Nyberg, Karl-Axel Johansson, Elisabeth Åvall-Lundqvist, Gunnar Steineck, Bengt K Lind. Dose-Volume-Effect Relationships for Organs at Risk Related to Emptying of All Stools into Clothing Without Forewarning. Manuscript.

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## LIST OF ABBREVIATIONS

AUC	Area under the curve
BMI	Body mass index
BT	Brachytherapy
CI	Confidence interval
CT	Computerized tomography
DVH	Dose-volume histogram
EBRT	External beam radiation therapy
EORTC	European Organization for Research and Treatment of Cancer
FACT-G	Functional Assessment of Cancer Therapy General
FI	Fecal incontinence
FIG	Franco-Italian Glossary
FIGO	Federation Internationale de Gynecologie et d'Obstetrique
Gy	Gray
HPV	Human papilloma virus
LENT	Late effects on normal tissue
LKB	Lyman Kutcher Burman
MLC	Multi leaf collimator
MRI	Magnetic resonance imaging
NTCP	Normal tissue complication probability
OR	Odds ratio
OAR	Organs at risk
PET	Positron emission tomography
PLND	Pelvic Lymph Node Dissection
PORTEC	Postoperative radiation therapy in endometrial cancer
QoL	Quality of life
RCT	Randomized controlled trial
RR	Relative risk
RT	Radiation therapy
RTOG	Radiation Therapy Oncology Group
SOMA	Subjective, objective, management, analytic scale
TAME	Toxicity, adverse long-terms effect, mortality risk, end results
TCP	Tumor complication probability
TD	Tolerance dose



# 1. INTRODUCTION

The prevalence of long-term gynecological cancer survivors is rapidly increasing thanks to early detection and advances in treatment. A significant number of these women have received radiation therapy (RT) and will seek help for transient or permanent, mild to severe, radiation-induced symptoms, i.e., *pelvic radiation disease*. These symptoms can be mistaken for other conditions or simply neglected and it is therefore essential to increase our knowledge and awareness of late side-effects after RT in order to provide today's cancer survivors adequate management and help.

Modern RT techniques such as intensity modulated radiation therapy (IMRT) allow the radiation dose to conform more precisely to the three-dimensional shape of the tumor. Higher radiation doses can be focused on the tumor while minimizing the dose to the surrounding normal tissue. In order to take advantage of the new planning and delivery techniques, we need to learn more about dose-response and dose-volume relationships for clinically relevant normal-tissue endpoints.

This study of long-term gynecological cancer survivors treated with conventional pelvic RT can add to knowledge and contribute to refinement of future treatments thus sparing patients from symptoms affecting quality of life (QoL).

## 2. BACKGROUND

### Gynecological cancer

The gynecological organs consist of the ovaries, the fallopian tubes, the corpus and cervix uteri, the vagina and the vulva. The female reproductive organs are in close proximity of the urinary bladder, bowel, anal sphincter and pelvic bones (Figure 1). In Sweden, gynecological cancer constitutes 12 percent of all female cancer and approximately 2900 new cases are diagnosed annually<sup>1</sup>. In 2009 1422 cases of endometrial cancer, 740 ovarian, 437 of cervical, 127 vulvar, 91 uterine sarcomas, 40 fallopian tube and 31 cases of vaginal cancer were diagnosed.

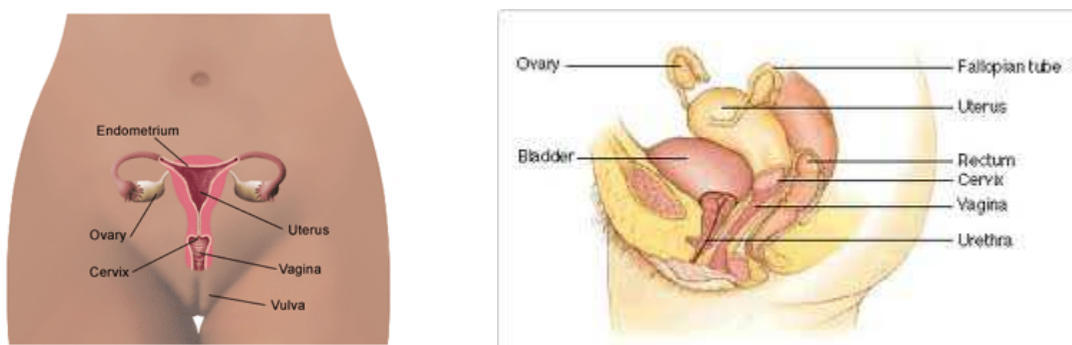


Figure 1. Female reproductive organs

#### *Endometrial cancer*

Endometrial cancer is the most common gynecological cancer disease in developed countries, with the highest incidences in North America and in Western Europe. In Sweden it is the 5<sup>th</sup> most common cancer among women<sup>1</sup>. The incidence of endometrial cancer is steadily rising as life expectancy is increasing, and the disease mostly affects postmenopausal women. The median age at diagnosis is 63 years, rarely affecting women under the age of 40.

Long-term exposure of estrogens not counterbalanced by the presence of progesterone is the most widely accepted hypothesis on the etiology of the majority of endometrial cancers, the type-I endometrial carcinoma<sup>2</sup>. The 'unopposed estrogen hypothesis' can explain most of the identified risk factors including obesity, early menarche and late menopause, nulliparity and hormone replacement therapy<sup>3</sup>. The use of Tamoxifen also carries an increased risk<sup>4</sup>. The less common type-2 endometrial carcinomas (high grade, non-endometrioid cell type) seem to be unrelated to estrogens and carry a worse prognosis. About five percent of endometrial cancer is considered to be hereditary and linked to hereditary nonpolyposis colorectal cancer<sup>5</sup>

Endometrial cancer is usually diagnosed at an early stage when still limited to the uterus, since it most often presents with vaginal bleeding. Survival rates are therefore generally high. Sweden had the highest 5-year survival rate among Nordic patients diagnosed in 1999 to 2003, 89 percent<sup>6</sup>.

In Sweden, gynecological cancer is staged according to the International Federation of Gynecology and Obstetrics (FIGO)<sup>7</sup>. The FIGO staging for carcinoma of the endometrium, cervix and vulva has recently been revised<sup>8</sup>. Endometrial cancer is staged surgically and lymphadenectomy is part of the staging procedure. Around 10 percent of women with presumably stage I disease have lymph node metastases, i.e. a stage III. No therapeutic benefit of lymphadenectomy has been proven according to a meta-analysis by Cochrane<sup>9</sup> including 1945 patients. Lymphadenectomy was associated with increased risk of surgically-related systemic morbidity and lymph edema or lymphocyst development. Against this background and the wide use of adjuvant RT, lymphadenectomy has not been routinely performed in Sweden.

The standard treatment for endometrial cancer includes primary surgery, typically consisting of hysterectomy and bilateral salpingo-oophorectomy. Adjuvant EBRT combined with vaginal brachytherapy (BT) has until recently been widely used in Sweden for alleged stage I patients.

Preoperative intrauterine BT was previously frequently used in stage I cancer<sup>10</sup>. The rationale for using preoperative BT was to reduce the risk of tumor spread during surgery. Initially a low dose-rate packing method with <sup>226</sup>Radium was used. The preoperative BT was gradually replaced with primary surgery during the 1990s in order to be able to allocate women to different prognostic groups and thereby avoid overtreatment. The method is still an effective curative treatment in women unfit for surgery.

Several randomized controlled trials (RCTs) have addressed the benefit of adjuvant RT in early stages of endometrial cancer. A systematic review by Cochrane including four trials with 1779 patients compared adjuvant RT versus no RT in stage I endometrial cancer following surgery<sup>11</sup>. The analysis showed a tendency toward improved survival in women with stage I and high risk of recurrence, i.e., stage IC and grade 3 who received adjuvant pelvic EBRT. This may support the use of adjuvant EBRT in this setting.

Women with low risk of recurrence, grade 1-2 endometrioid cancer stage IA-IB, is treated with surgery alone<sup>12</sup>. For women with intermediate risk of recurrence either observation or vaginal BT is warranted<sup>13, 14</sup>.

The effect on survival of postoperative adjuvant chemotherapy has recently been assessed by Cochrane<sup>15</sup>. Pooling of survival data from 2197 women showed a significant overall and progression-free survival benefit for postoperative platinum-based chemotherapy. The data suggests an additive value in combination with RT, but may also be an alternative to RT. Concurrent chemoradiotherapy<sup>16</sup> is currently being explored in an RCT (PORTEC 3). Patients with advanced stages of endometrial cancer often receive a combination of surgery, RT and chemotherapy.

## *Cervical cancer*

The organized population-based screening in Sweden, introduced in the 1960s, leading to early detection of precancerous lesions and their treatment, has greatly reduced the incidence and mortality of cervical cancer, the second most common cancer among women in the world. Median age at diagnosis is 59 years and one quarter is younger than 40 years of age<sup>1</sup>. The majority of women are diagnosed with an early stage of disease. The 5-year survival rates for Nordic patients diagnosed in 1999 to 2003 are quite comparable across the populations, with ratios varying between 64 and 68 percent<sup>17</sup>. The survival rate exceeds 85 percent among patients younger than 50 years of age, with survival steadily decreasing as age increases.

A persistent infection with high risk HPV is the most important etiological factor<sup>18</sup>. HPV vaccines offer a promising option for preventing cervical cancer, including other HPV-related tumors such as vaginal and vulvar cancers<sup>19</sup>. Smoking and other genital infections are also considered to be risk factors<sup>20</sup>.

The treatment of cervical cancer is determined by the stage of disease. The FIGO staging for cervical cancer is based on clinical evaluation<sup>8</sup>.

Microinvasive cervical cancer (FIGO stage IA1 and IA2) is usually cured by cone biopsy, trachelectomy or simple hysterectomy. Surgery and RT seem to be equally effective in FIGO stage IB or IIA cervical cancer<sup>21</sup>. Radical hysterectomy and pelvic lymph node dissection (PLND) is usually the treatment of choice due to the risk of side effects by RT<sup>22, 23</sup>. Beneficial effects of nerve-sparing surgery on bladder, gastrointestinal and sexual function have been reported<sup>24-26</sup>. Radical trachelectomy after PLND can be considered in women wishing to preserve fertility<sup>27</sup>.

Preoperative intrauterine BT was previously frequently used in Sweden for early stages (stage IB-IIA) of cervical cancer. Initially a manual technique with <sup>226</sup>Radium applicators was used and patients were treated according to the individualized Stockholm method described by Kottmeier in 1964<sup>28</sup>. The manual technique included a combination of an intrauterine tube (43-70 mg Radium) and a vaginal applicator (50-70 mg Radium). In Stockholm, an after-loading technique with <sup>137</sup>Cesium gradually replaced the manual technique in the early 1990s, using a circular-shaped vaginal applicator and a uterine applicator in the Selectron System<sup>29</sup>. Patients were treated with two uterovaginal intracavitary treatments with a three-week interval, followed by surgery (or in surgically unfit patients with EBRT four weeks later). The total dose to Point A<sup>30</sup> was 45 Gy for squamous cell carcinoma and 48 Gy for adenocarcinomas. Patients treated with intracavitary BT and receiving EBRT had a central shield with a width of four cm. The prescribed dose to the shielded volume was adjusted in order not to exceed a total dose of 50 Gy to the rectum and 60 Gy to the urinary bladder. An additional prophylactic

para-aortic field with total dose of 40 Gy (1.6 Gy per fraction) was prescribed to patients with pelvic lymph node metastasis until 2000. The Stockholm treatment results of preoperative EBRT in FIGO stage IB-IIA cervical cancer have been published by Beskow *et al*<sup>31</sup>. Pathologic complete remission after preoperative intracavitary BT of cervical cancer stage IB and IIA is a strong prognostic factor for long-term survival. Similar favorable results after preoperative EBRT have recently been published by a French group<sup>32</sup>.

Women with high-risk for recurrence such as lymph node metastasis, parametrial invasion and positive resection margins have a recurrence rate of nearly 40 percent after surgery<sup>33</sup>. These women are treated with concomitant chemoradiation which has been shown to increase progression-free survival from 63 to 80 percent and overall survival from 71 to 81 percent<sup>34</sup>.

The role of adjuvant treatment for women with stage IB with intermediate risk of recurrence following surgery is debated, due to the risk of overtreatment and the lack of proven survival benefit. The risk of recurrence among patients with intermediate risk factors, such as deep stromal invasion, large tumor size and lymph-vascular space invasion varies between 2 to 31 percent at three years<sup>35, 36</sup>. In all, 277 stage IB cervical patients with two or more intermediate risk factor cervical patients were randomized to observation after surgery or adjuvant EBRT. A long-term follow-up showed a statistically detectable reduction in risk of recurrence and prolongation of progression-free survival, but improvement in overall survival did not reach statistical significance<sup>36</sup>.

For locally advanced (FIGO stage IB2-IVA) weekly intravenous cisplatin 40 mg/m<sup>2</sup> combined with concomitant EBRT is established a standard treatment. The latest published meta analysis based on 13 RCTs comparing concomitant chemoradiation versus the same RT demonstrated a six percent improvement in 5-year survival ( $p < 0.01$ ) but at the price of increased acute hematologic and gastrointestinal toxicity. Data were too sparse for an analysis of late toxicity<sup>37</sup>. The role of neoadjuvant chemotherapy has yet to be determined and currently two ongoing RCTs are comparing neoadjuvant chemotherapy following surgery versus concomitant chemoradiation.

### *Ovarian and Fallopian tube cancer*

Around 90 percent of malignant ovarian tumors originate from the coelomic epithelium<sup>38</sup>. The estimated number of new cases worldwide is 225 000 annually and the highest incidence of ovarian cancer is found in North America and Northern and Western Europe<sup>39</sup>. Epithelial ovarian cancer is the leading cause of death from gynecological cancer in these continents reflecting the difficulties of detecting the disease in early stage and the development of

chemoresistant disease. Population-based relative 5-year survival is below 50 percent<sup>17</sup>. The median age at diagnosis is 65 years<sup>1</sup>.

Etiology is multifactorial reflecting the heterogeneity of epithelial ovarian cancer. Increasing age, early menarche, late menopause, nulliparity and endometriosis are associated with an increased risk of epithelial ovarian cancer. A decreased risk is associated with the use of oral contraceptives and breast feeding. A hereditary component is found in at least ten percent of the cases, most commonly *BRCA1* or *BRCA 2* mutations<sup>40</sup>.

Fallopian tube cancer is a rare disease. Studies indicate that the fallopian tubes may be the origin of some epithelial ovarian cancer<sup>41</sup>. Fallopian tube cancer is managed in a similar manner as epithelial ovarian cancer.

Both ovarian and fallopian tube cancer is surgically staged according to the FIGO classification<sup>42</sup>. Primary cytoreductive surgery followed by postoperative chemotherapy with paclitaxel and carboplatin is the standard treatment for ovarian cancer<sup>43</sup>. Whole abdominal radiation therapy is rarely used due to severe late gastrointestinal side-effects, but can be used in the palliative setting<sup>44</sup>.

### *Uterine sarcoma*

Uterine sarcomas are rare and highly malignant gynecological diseases that account for three percent of uterine cancers. It affects around 100 Swedish women annually with a median age of 55 years<sup>1</sup>. Their rarity and histological diversity contributes to the lack of consensus on prognostic risk factors and optimal treatment<sup>45</sup>. The disease originates from the muscle cells in the uterus or from supporting tissues surrounding the uterus. The prognosis varies and depends on the type of mesenchymal tumor and stage of disease. The 5-year survival rate is reported to be between 17 and 55 percent<sup>46-48</sup>.

Until recently the FIGO classification for endometrial carcinoma has been used to stage uterine sarcomas but in 2009 a new FIGO classification has been specifically designed for uterine sarcomas, due to their divergent biologic behavior. *Carcinosarcomas* has recently been reclassified as dedifferentiated form of endometrial carcinoma and should be staged as endometrial cancer. Treatment is similar to high-risk endometrial cancer. *Leiomyosarcomas* composed of malignant uterine smooth-muscle cells is the most common subtype of uterine sarcoma, after excluding carcinosarcomas. They are associated with poor prognosis even when diagnosed at an early stage. Treatment includes hysterectomy and the ovaries can often be preserved. The role of adjuvant RT is not fully established<sup>49</sup>. Endometrial stromal tumors are divided into *low-grade endometrial stromal sarcomas* and *undifferentiated sarcomas*<sup>50</sup>. Low-grade endometrial stromal sarcomas have a favorable

prognosis and are often sensitive to progestational treatment. In contrast, undifferentiated sarcomas are highly aggressive and have a poor prognosis. Treatment for endometrial stromal tumors consists of primary surgery including hysterectomy and bilateral salpingo-oophorectomy. The benefit of adjuvant pelvic EBRT is unclear although studies suggest improved local control without improvement of disease free survival<sup>49, 51</sup>. For patients with advanced disease treatment options include surgery in combination with chemotherapy and pelvic EBRT.

### *Vaginal cancer*

Primary vaginal cancer, with no involvement of the cervix or the vulva, is a rare disease and most published results are based on small studies retrospectively collected. Vaginal cancer occurs most often among women older than 60 years of age. The etiology of vaginal cancer is, like cervical cancer, linked to persistent infection with high-risk HPV<sup>18</sup>. Overall survival is approximately 50 percent<sup>52</sup>. Vaginal cancer is usually treated with a combination of EBRT and vaginal BT, with or without chemotherapy<sup>52</sup>. Surgery is an option for small lesions in stage I.

### *Vulvar cancer*

Vulvar cancer accounts for five percent of gynecological cancers with less than 100 new cases every year in Sweden<sup>1</sup>. A majority of women are at least 70 years of age at diagnosis<sup>53</sup>. The FIGO staging classification is surgical. The 5-year survival rate is favorable in Stage I, near 80 percent, but poor for more advanced disease<sup>54</sup>.

Two separate pathways of disease development have been found; the first is associated with high-risk HPV and affects younger women and the second is associated with lichen sclerosis or squamous cell hyperplasia and is independent of HPV<sup>55</sup>.

Radical vulvectomy with bilateral inguinal lymphadenectomy has so far been the predominant way of treating vulvar cancer, but due to significant morbidity a more individualized approach has developed<sup>56</sup>. Treatment for more advanced stages of disease is individualized and usually involves a combination of surgery, RT and chemotherapy. A systematic review by Cochrane evaluated the efficiency and safety of neoadjuvant chemoradiation and the results, based on five non-randomized trials, showed an improvement in operability at the expense of increased severe toxicity<sup>57</sup>.

## Radiation therapy

Radiation therapy (RT) has been used for many years in the treatment of gynecological cancer diseases. Shortly after the discovery of Radium in 1898, treatment for gynecological cancers was introduced<sup>58</sup>. There are two major ways of delivering ionizing radiation therapy; EBRT and BT.

### *External beam radiation therapy*

External beam radiation therapy (EBRT) was initially given by using X-ray devices or Cobalt-60 machines. Due to poor penetration, a wide penumbra and risk of skin reactions, most clinics have replaced these devices with linear accelerators which produce electrons between 4 and 20 MeV and photons with energy of 6 to 20 MV. A few clinics have been equipped with racetrack accelerators that can deliver photons of 50 MV. Particles such as protons and light ions are also used to irradiate cancer cells. The radiation dose produced by these particles is very precisely disposed due to low lateral scatter and the sharply defined dose maximum, the Bragg peak (Figure 2).

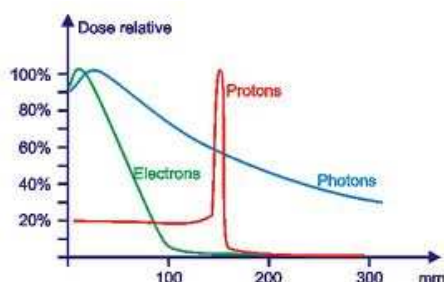


Figure 2. Proton Bragg peak

Treatment volumes and organs at risk need to be carefully defined. Prescribing, recording and reporting of photon beam therapy is performed according to recommendations by International Commission on Radiation Units and Measurements<sup>59</sup>. Pretreatment Computerized Tomography (CT), Magnetic resonance imaging (MRI) and Positron emission tomography (PET) can be used to identify tumour target volume and surrounding normal tissues. By contouring target areas in consecutive slices, three-dimensional volumes were constructed, and the absorbed doses were calculated. The treatment fields used to be shaped by manually placed customized lead blocks, as illustrated in Figure 3.

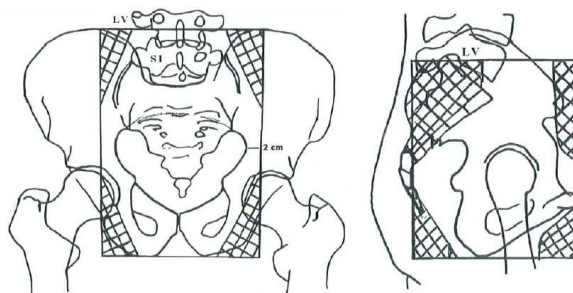


Figure 3. Pelvic fields with lead blocks

Modern treatment machines are equipped with integrated computerized Multi Leaf Collimators (MLC) that forms the treatment fields according to the treatment plan (Figure 4).

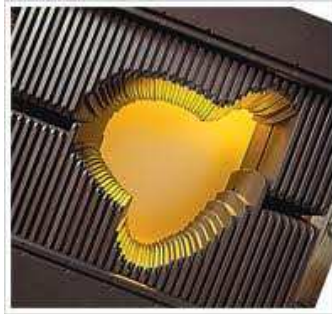


Figure 4. Multi Leaf Collimator

The dose distribution can be further improved by IMRT or RapidArc, which uses non-uniform beam intensity patterns. IMRT can produce concave shaped isodose distributions and it has a sharp fall off near the edge of the treatment volumes. (Figure 5).

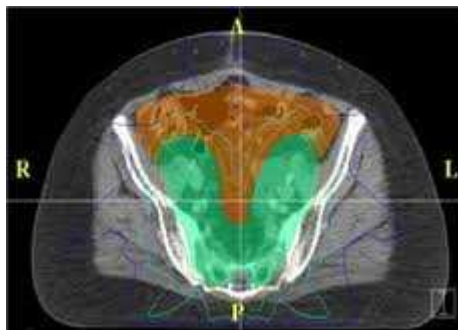


Figure 5. IMRT dose plan

Proper immobilization and repeated image guidance during treatment course is necessary to ensure good quality of the EBRT.

### *Brachytherapy*

Brachytherapy (*brachy*, Greek for short distance).is RT with short range where the radioactive source is put directly in the tumour (interstitially) or inside a hollow organ (intracavitary). The first treatments with BT were performed already during the first decades of the 20<sup>th</sup> century. The Stockholm method for BT was developed at Radiumhemmet and the first treatment results on cervical cancer were published in 1929<sup>60</sup>. The discovery of artificial radioactivity shortly

before World War II paved the way for the use of radionuclides such as Iridium and Cesium. Remote afterloading devices were developed to overcome radiation protection problems in the handling of the radioactive substances.

The dose is prescribed to an isodose encircling a small target volume and the dose distribution is very heterogeneous, being minimal at distance from the radioactive source and much higher at its center. The dose is delivered continuously with a short total treatment time ranging from minutes to hours. Low dose rate BT (LDR BT) Cesium delivers 0.4-2 Gy/hour and high dose rate BT (HDR BT) Iridium delivers 12 Gy/hour or more. A three-dimensional image-based approach for delineation of gross tumor volume and clinical tumor volume and organs at risk provides optimization and tailored BT dose planning<sup>61</sup>.

## Radiobiology

The Linear-Quadratic (LQ) model, which was first proposed by Douglas and Fowler in 1976<sup>62</sup>, considers radiation damage as a result of one of two separate, but concurrent processes. First, the amount of damage varies linearly with dose in the single-hit process in the  $\alpha$ -component. Secondly, the amount of damage varies with the square of the dose in the  $\beta$ -component<sup>63</sup>. The total damage created by the dose  $d$ , is given as;

$$\alpha d + \beta d^2$$

In terms of clinically observable effect it is more convenient to describe the effect as the surviving fraction ( $S$ ) of cells, which decreases as an exponential function of the total damage;

$$S = \exp (-\alpha d - \beta d^2)$$

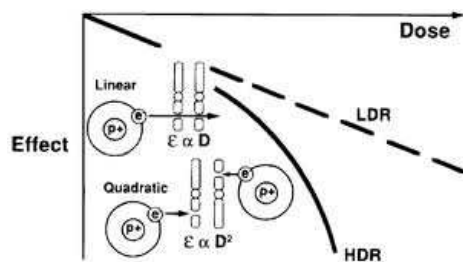


Figure 6. Effect of high dose rate and low dose rate on cell survival curve

$$\ln(S) = -\alpha d - \beta d^2$$

Introduction of the number of fractions,  $N$ ;

$$-\ln(S_N) = N\alpha d + N\beta d^2$$

Biological effective dose (BED) is derived by dividing both sides with  $\alpha$ ;

$$BED = Nd [1 + d/(\alpha/\beta)]^{64}$$

This equation applies well in the case of N well-spaced fractions delivered to tissues with no or little growth (most normal tissues) during the time it takes to deliver all N fractions. For rapidly growing normal tissues and tumors one has to take the repopulation into account.

Tissue-specific  $\alpha/\beta$ -ratio reflects the shape of the dose-response curve. Normal tissues are considered to have  $\alpha/\beta$ -ratios around 3 Gy. Rapidly growing normal tissues and tumors are considered to have values around 10 Gy (Figure 7).

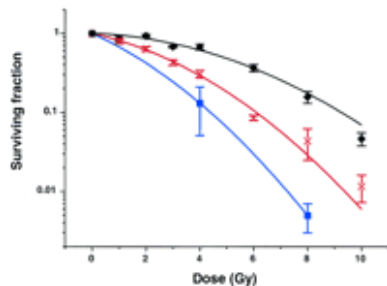


Figure 7. Cell survival curves for  $\alpha/\beta$  ● = 3, ● = 4, ● = 10

Lower dose per fraction and an increased number of fractions lead to a sparing effect which is most pronounced in tissues with slow proliferation. Time between two fractions must be at least six hours in order to allow sublethal damages to repair. Continuous LDR BT can show a similar sparing effect as seen with hyperfractionation. This is the rationale for giving pelvic EBRT in several fractions of 1.6-2.0 Gy.

The effects on cells are described by the 4 R's of radiobiology:

*Repair* of sublethal DNA damage. This is thought to be more effective in normal cells as opposed to cancer cells. *Redistribution* into phases in which cells are more radiosensitive. *Repopulation* through an increase in cell division that is seen at some point in time after radiation is delivered. *Deoxygenating* of hypoxic regions where cells are thought to be resistant to radiation (Figure 8). Presence of oxygen is an essential component in cell killing<sup>65</sup>.

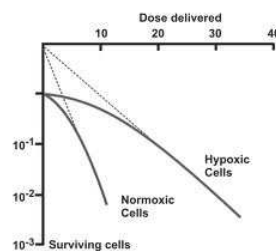


Figure 8. Cell survival curves for hypoxic and normoxic cells

## Development of radiotherapy-induced side effects

The process of acute radiation damage starts immediately after exposure. Unrepaired or misrepaired DNA damage usually leads to cell death within the first or subsequent cell divisions. Cell death may also occur through apoptosis. Activation of different cellular signaling cytokines leads to inflammatory responses. The acute effects are most pronounced in tissues with high cell turnover such as cells outlining the gastrointestinal tract and the skin. Symptoms develop when these cells no longer can be replaced by the action of stem-cells and therefore most symptoms do not show immediately<sup>66</sup>.

Acute side-effects are considered to be symptoms that develop during the course of the treatment or shortly afterwards and remain for a maximum of three months and then subside. The symptoms can remain beyond three months with unchanged strength or even progress. Symptoms present at three months after completed RT are considered to be late side effects. Severe acute side effects are considered to be predictive of the risk of having late side effects; consequential late effects<sup>67</sup>.

The degree and extent of the radiotherapy-induced toxicity depends on type of radiation, dose per fraction<sup>68</sup>, total dose, dose rate, total treatment time<sup>69</sup> and irradiated volume. The mechanism leading to the side-effects is multifactorial, including patient characteristics<sup>70, 71</sup> and radiogenomics. Ionizing radiation not only induces a direct cell killing but also induces activation of cytokines and growth factors, which could be potential targets for preventing or treating late side-effects<sup>64, 66, 72-74</sup>.

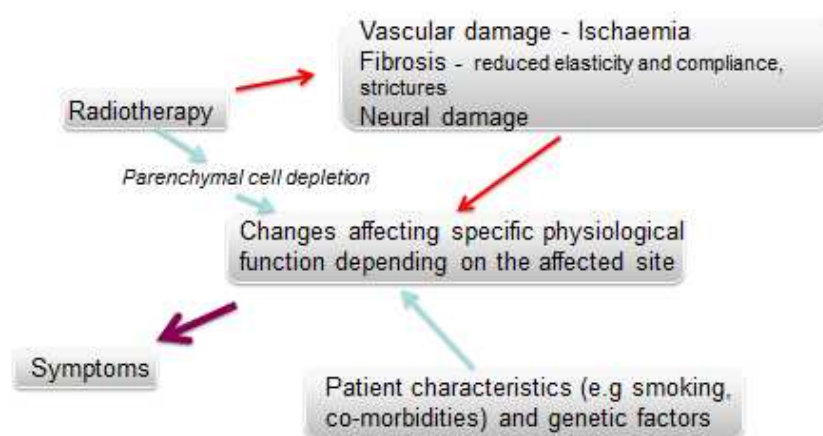


Figure 9. Mechanisms for developing long-term symptoms

### *Risk factors for developing radiotherapy-induced toxicity*

The development of radiotherapy-induced toxicity can be influenced by many factors. Radiation treatment related factors such as the total dose and dose per

fraction; fractionation schedule, decides the amount of damage but also the capacity for repair of sublethal DNA-damage<sup>63</sup>. Irradiation with protons will create more extensive damage compared to electrons due to the larger biological effect<sup>75</sup>. Factors involving the tumor and normal tissue in close proximity to the tumor are of the utmost importance as are additional treatment modalities.

#### Radiation treatment related factors

- Total dose
- Dose per fraction
- Fractionation schedule
- Total treatment time
- Irradiated volume
- Type of radiation

#### Tumour related factors and factors involving irradiated normal tissue

- Size
- Grade
- Stage
- Histology
- Location
- Functional reserve in irradiated organ
- Structural organization of irradiated organ<sup>76</sup>

#### Other treatments administered in sequence or concomitantly

- Surgery
- Chemotherapy
- Biological treatment

#### Patient related factors

- Age
- Smoking
- Diabetes mellitus
- Cardiovascular disease
- Inflammatory bowel disease
- Connective tissue disorder
- Injuries affecting pelvic floor
- Other co-morbidities
- Genetic susceptibility towards radiation induced injury

Several studies show different aspects of late side effects; Cozzarini *et al* retrospectively scored late genitourinary toxicity according to CTCAE v3 in 742 prostate cancer survivors after pelvic EBRT<sup>77</sup>. Acute Grade 2 or more was found to be predictive for the development of late Grade 3 toxicity with a prevalence of 16 percent compared to 10 percent, supporting the theory of consequential late effects<sup>67</sup>. Conventional EBRT in the Cozzarini study carried a risk of 21 percent compared to conformal EBRT; 11 percent, illustrating the effect of treatment technique. Survivors with hypertension had an 8-year risk of Grade 3 sequelae of 18 percent compared to normotensive survivors with a risk of 10 percent. These results support the idea of negative impact of co-morbidities<sup>64, 78</sup>.

In a retrospective analysis of 806 women treated with adjuvant postoperative pelvic EBRT for endometrial or cervical cancer, Huscher *et al* assessed the rate of late small bowel toxicity<sup>79</sup>. The 5- and 10-year toxicity rates were four and seven percent. Survivors older than 60 years of age had a doubled risk of developing severe late small bowel toxicity with a Hazards Rate of 2.2. Daily fractions of 1.8 Gy or less led to significantly lowered risk of bowel damage risk. Again severe acute toxicity was predictive of late toxicity, supporting the idea of consequential late effects<sup>67</sup>.

Eifel *et al* retrospectively reviewed actuarial risk of complications in 1784 irradiated stage IB (FIGO) cervical cancer survivors over a period of 20 years<sup>80</sup>. Complication rate at 3 years was 7.7 percent and at 5 years 9.3 percent with symptoms progressing with time. Risk of fistula formation and bowel obstruction was doubled in survivors who had prior abdominal surgery. An increased cumulative risk was seen for women who were young at the time of treatment and may be a result of long survival and prolonged time under risk.

## Instruments for recording late side effects and quality of life

There is a wide variety of instruments for the recording of late side effects after radiotherapy. Many of them combine multiple signs and symptoms into a single grade leading to a loss of specificity.

*The French Italian Glossary (FIG)*<sup>81</sup> was developed in the 80s to record radiation side effects regardless of treatment strategy. The complications after treatment are described in terms of five degrees of increasing severity from 0 to 4 for 14 organs and/or normal tissues contained in the female pelvis. Each grade is further subdivided into subgroups, each of which describes different symptoms and signs. As a result the FIG mixes various endpoints for the same organ, early and late morbidity are not separated and both subjective and objective effects are combined.

In 1995 the RTOG and the EORTC organizations agreed on a common system for toxicity criteria<sup>82</sup>. The system included five degrees of injury within 17 organ categories, with the Grade 0 indicating no injury and Grade 5 meaning that the effect was lethal.

The *LENT (Late Effects of Normal Tissue) SOMA (Subjective, Objective, Management, Analysis)*<sup>83</sup> grading system is more detailed than the RTOG/EORTC toxicity criteria. Grade 0 indicates no toxicity. Grade 1 includes symptoms normally reported by the patients (subjective category); Grade 2 includes what is reported by a physician or by clinical examination (objective category); Grade 3 includes steps to alleviate symptoms (management category); Grade 4 includes items given by more advanced diagnostics (analytic category). Although providing much information, it has been found to be time consuming and difficult to use routinely outside controlled studies.

By incorporating LENT SOMA items the *CTCAE v3 (Common Terminology Criteria for Adverse Events version 3)*<sup>84</sup> of 2003 was developed. Among the newly adopted principles is the merging of acute and late effect criteria which will be used without predetermined time-base designation and the fact that it is applicable to all treatment modalities.

*TAME*<sup>85</sup> which was introduced in 2007 is the most recently developed system made for summarizing the total toxicity caused by cancer treatment. Short-term, acute, Toxicity, Adverse long-term, late, effects, and Mortality risk are summarized into End results<sup>85</sup>.

The use of multiple scoring systems for adverse events has created difficulties when trying to compare results between studies and institutions.

Traditionally, the primary endpoints of an evaluation of medical treatment have only included improvement in clinical outcome, cure and survival, and not the QoL. However, the assessment of patient-related outcomes has become a more essential part of the evaluation in gynecological oncology.

The *Medical Outcomes Study Short Form-36 (SF-36)*<sup>86</sup> is a questionnaire that measures eight health domains and is often used in health surveys.

The European Organization for Research in the Treatment of Cancer has developed the *EORTC QLQ-30*<sup>87</sup>, which measures physical, emotional and social functioning, disease-specific symptoms, economic impact and global QoL. This questionnaire can be combined with disease-specific modules for endometrial, cervical and ovarian cancer.

The Functional Assessment of Cancer Therapy questionnaire (FACT-C)<sup>88</sup> contains questions covering four areas of well-being; Physical, Social and Family, Emotional and Functional. Two subscales are specific to cervical and ovarian cancer.

## Radiation induced symptoms and quality of life

General side-effects of RT include fatigue, nausea, nutritional problems, skin reaction and susceptibility to infections.

Recent studies have demonstrated that gastrointestinal symptoms after curative pelvic are far more common than generally believed<sup>89-92</sup>. Symptom occurrence and intensity can differ depending on if and how survivors are asked. Many of the symptoms are thought to be embarrassing and therefore questions may not be asked about them and the symptoms may not even be mentioned<sup>93</sup>. Permanently changed bowel functioning is found in up to 80 percent of cancer survivors following pelvic RT.

One of the most common symptoms is *loose stools* with an incidence from around 15 to 50 percent<sup>94, 95</sup>. The underlying mechanism includes disturbed small bowel function, accelerated bowel transit, altered bile contents, pancreatic malfunction and aggravation of existing inflammatory bowel disease<sup>96</sup>. Overgrowth of bacteria may enhance the problem with bloating and foul smelling flatulence<sup>97, 98</sup>.

*Defecation urgency* has been reported in between 45 and 55 percent of survivors after pelvic RT<sup>99-103</sup>. The urgency can be a result of decreased rectal compliance which reduces the ability to store the fecal content. Urgency can also be caused by local inflammatory processes and additional malignancies such as rectal cancer.

*Fecal incontinence* defined as 'involuntary loss of liquid or solid stool that is a social or hygienic problem'<sup>104</sup> is said to affect from 20 to 50 percent of survivors<sup>102, 103, 105-107</sup>. The mechanism leading to fecal incontinence includes changes in anal resting tone, squeeze pressure and rectal compliance<sup>93, 108</sup> and also decreased perception of rectal sensation due to impaired efferent innervations<sup>109</sup>. The consistency of the stool is important for preservation of continence with loose stools leading to higher risk for incontinence<sup>106, 108</sup>.

Flatulence is produced by bacterial fermentation of food and glycoproteins in the colon. Patients complaining of gas symptoms have an impaired handling of the intestinal contents with segmental pooling and focal gut distension. Disrupted gas transit can result in bloating<sup>110, 111</sup>.

*Abdominal pain* has been reported in up to 30 percent of all survivors after pelvic RT<sup>112</sup>. Several different mechanisms can contribute to the development of pain such as bowel obstruction due to impaired motility and strictures and by bowel spasms<sup>100, 113, 114</sup>.

The urinary tract has been regarded as less radiosensitive compared to the bowel<sup>115</sup> and reports on prevalence of specific *urinary symptoms* among gynecological cancer survivors are scarce. Most studies show that late post-radiation urinary morbidity continues to progress decades after RT<sup>116</sup>.

A prevalence of 8 to 25 percent of genitourinary toxicity including urinary urgency, recurrent episodes of urinary infections and minor incontinence has been reported in survivors after adjuvant RT in endometrial cancer survivors<sup>92, 13</sup>. Higher risk of late urinary side effects has been reported among cervical cancer survivors which is probably attributable to higher doses of radiation<sup>117</sup>.

The vascular endothelial cells are damaged which leads to perivascular fibrosis, vascular occlusion and focal bladder ischemia by six to twelve

months. The smooth muscle is replaced by fibroblasts and collagen resulting in decreased bladder compliance and decreased volume. Long-term toxicity includes cystitis with pain, urinary urgency and haematuria, urinary incontinence, decreased storage capacity, voiding dysfunction, urethral stenosis and fistula formation<sup>115</sup>.

Feltl *et al* reported that 0.44 percent of gynecological cancer survivors developed painful micro fractures in the pelvic bones caused by *osteoradionecrosis* at a median follow-up time of seven years after pelvic RT<sup>118</sup>. In the study by Ikushima 11.4 percent of the survivors developed painful insufficiency fractures in the pelvic bones. Risk factors were preexisting osteoporosis, age, smoking and low body weight<sup>119</sup>

Resection of pelvic lymph nodes and vessels together with gravitational influence on lymphatic flow can lead to lymphatic congestion – *lymph edema*. Secondary toxicity can result in skin breakdown, erysipelas, pain, neuropathy and myopathy. Survivors frequently describe the lymph edema symptoms as heaviness, and swelling<sup>120</sup>.

*Post-treatment leukemia* has been found to be increased in survivors treated with pelvic RT. The risk peaked at five to ten years and remained elevated for ten to fifteen years after completed treatment. No increase in myeloma has been reported<sup>121</sup>.

In recent years there has been an increasing interest in measuring QoL as part of clinical trials<sup>122</sup> also in long-term cancer survivors<sup>123</sup>. QoL is said to be a subjective perception which embraces all dimensions of the health experience<sup>124</sup>. The World Health Organization states that QoL is the individuals' perception of that person's position in life in the context of the culture and value system in which he or she lives and in relation to the individual's goals, expectations, standards and concerns<sup>125</sup>.

Available studies on QoL in long-term gynecological cancer survivors lead to the conclusion that more research is needed<sup>126</sup>. Studies have shown that QoL is decreased more often in survivors treated with RT than in those treated with surgery or Chemotherapy. More than one treatment modality, long treatment duration and low socioeconomic status enhance the risk of decreased QoL<sup>127</sup>.

## Radiobiological modeling and normal tissue complications

The principal aim of radical RT is to achieve the highest tumor control probability (TCP) and at the same time to minimize the normal tissues complication probability (NTCP) in order to have the lowest complication rate.

Dose-volume response models or NTCP models can be used as tools for the optimization of RT treatment plans in order to minimize toxicity<sup>128</sup>. The probability curve has an S-shape as illustrated in Figure 10. The models aim to reduce complicated dosimetric and anatomical information to a single risk measure.

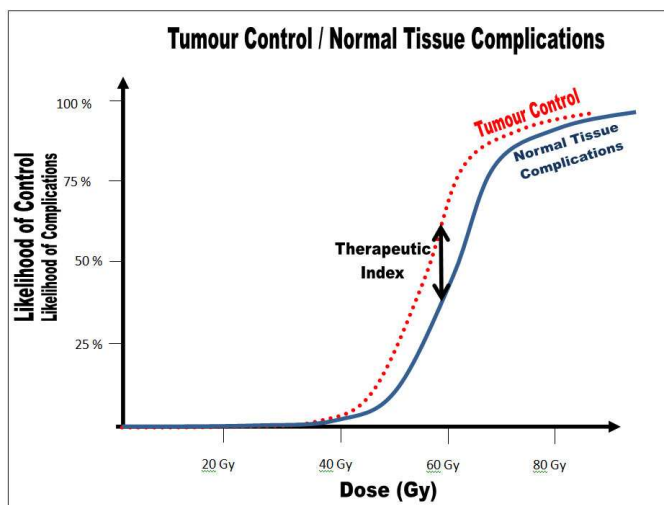


Figure 10. Normal Tissue Complication Probability, NTCP

Commonly accepted tolerable doses to normal tissues have mostly been derived empirically and can only serve as estimates of radiation tolerance. The paper by Emami *et al*<sup>129</sup> is still considered to contain the standard recommendations for normal tissue tolerance in RT. Some of the presented tolerance doses were based on experimental and clinical investigational data. Others were based on less solid data, but are still considered to be relatively reliable. A few dose data were based on individual clinicians' experience and can be a result of extrapolating existing data. These doses have provided assistance for estimating complication probabilities in tissues that receive a uniform dose to a part of the tissue and no dose to the remainder. Emami *et al* presented tolerance doses (TD) for increasing parts of each assessed organ with a five (TD 5/5) and 50 (TD 50/5) percent risk of developing specified clinical end-points within five years after treatment.

The Emami data for gastrointestinal organ including the small bowel, the colon and the rectum was hard to find due to lack of sufficient dose information or problems to estimate organ volume. TD 5/5 for the whole small bowel has been estimated to 40 Gy and for one-third of the organ volume to 45-50 Gy for development of obstruction, perforation and fistula. TD 5/5 for whole colon has been estimated to 45 Gy and TD 5/5 for one-third of the volume to 55 Gy. For the rectum no volume effect was seen and the TD 5/5 was estimated to 60 Gy. The estimated TD 5/5 data for the whole urinary bladder was 65 Gy compared to one-third of the volume; which was 80 Gy. The TD 50/5 data for the urinary bladder has been assumed to be in the order of 80 Gy. Whole femoral head had a TD 5/5 of 52 Gy and 50/5 of 65 Gy.

A limited number of available organ specific dose-volume and outcome data are presented in the paper by Marks *et al*<sup>128</sup> although they are accompanied by multiple caveats.

Two-dimensional dose-volume histograms (DVH) from specific organs at risk can be extracted from the treatment planning system. Information including the maximum, the minimum and the mean dose, the standard deviation of dose, and the volume of studied organs can also be extracted.

In 1985 Lyman *et al* suggested an empirical mode, which used available tolerance dose data to estimate the complication probability. The relation between a dose of uniform radiation and the probability of the effect formed a probit function, an S-shaped curve characterized by the dose that corresponds to 50 percent complication probability after uniform irradiation of the reference volume, TD 50, and the slope of the curve<sup>130</sup>. The Lyman model also describes the volume effect.

In 1991 Kutcher *et al* combined the probit function with the DVH reduction method for transforming non uniform DVHs into equivalent uniform DVHs to account for the inhomogeneously irradiation of the organ<sup>131</sup>. The Emami tolerance data in combination with Lyman's model resulted in the *LKB (Lyman Kutcher Burman) model* in 1991 which provided estimated normal tissue complication probabilities for any combination of dose and irradiated volume for the normal tissues and end points considered<sup>132</sup>.

In 1997 Niemierko defined the generalized Equivalent Uniform Dose (gEUD) concept. The gEUD is a way of 'summarizing' the whole dose distribution in a volume of interest to a single figure and is the most common expression for OAR. The gEUD is the dose that supposedly, if given uniformly to the entire organ, will cause the same complication rate as the true dose distribution<sup>133</sup>.

The *RS (Relative Seriality) model* presented by Källman *et al* in 1992<sup>76</sup>, assumes that organs have combinations of serial and parallel functional subunits. One of the model parameters describes the ratio of serial subunits to all subunits of the organ; the endpoints relative seriality, hence the name. In an organ with serial organization (the spinal cord), a high dose to a very small volume can result in serious toxicity, which is an effect of maximum dose. In an organ with parallel organization (the lung), a low dose to a large part of the organ volume can cause side effects, which is an effect of mean dose.

New RT techniques allow the treatment planners to decide which regions of the normal tissues that could be spared. The QUANTEC (Quantitative Analyses of Normal Tissue Effects in the Clinic) project<sup>134</sup> aims to collect all available three-dimensional dose/volume and outcome data and to summarize them in a clinically useful manner. One of the new concepts is to atomize symptoms in an attempt to find specific pathophysiological processes that explain the outcome.

The NTCP models have some limitations. They are based on two-dimensional DVHs which are not ideal representations of the three-dimensional dose-volume information since they discard the organ-specific spatial information. Other limitations are a single pre-treatment CT, differences

in fractionation schedules and variance in treatment routines within and between clinics.

Additional difficulties to be overcome in NTCP modeling are the effects of different fractionation schemes, the impact of combined treatment modalities as chemoradiation, host factors as smoking, co-morbidities and radiogenomics, trading of risk between organs. An increased understanding of expected toxicity produced by different competing treatment plans may guide the radiotherapist in choosing the most optimal one.

### 3. AIM

The overall aim of this study was to investigate the prevalence of late self-reported symptoms from normal tissues in the pelvic region among long-term gynecological cancer survivors as well as to study how the dose-volume distribution of ionizing radiation delivered to organs at risk contributes to the occurrence of a late specific symptom affecting QoL

#### Specific aims

To survey the occurrence of physical symptoms among long-term gynecological cancer survivors previously treated with pelvic RT and compare with control women from the general population.

To investigate how the patient-reported symptom 'emptying of all stools into clothing without forewarning', impacts self-assessed QoL from a social, psychological, sexual, and functional perspectives among gynecological cancer survivors treated with pelvic radiotherapy

To investigate the association between mean absorbed dose to the bowel and anal-sphincter region after pelvic RT and the occurrence of the symptom 'emptying of all stools into clothing without forewarning'.

To assess the dose-volume response relationships between 'emptying of all stools into clothing without forewarning' and pelvic organs at risk using different radiobiological models.

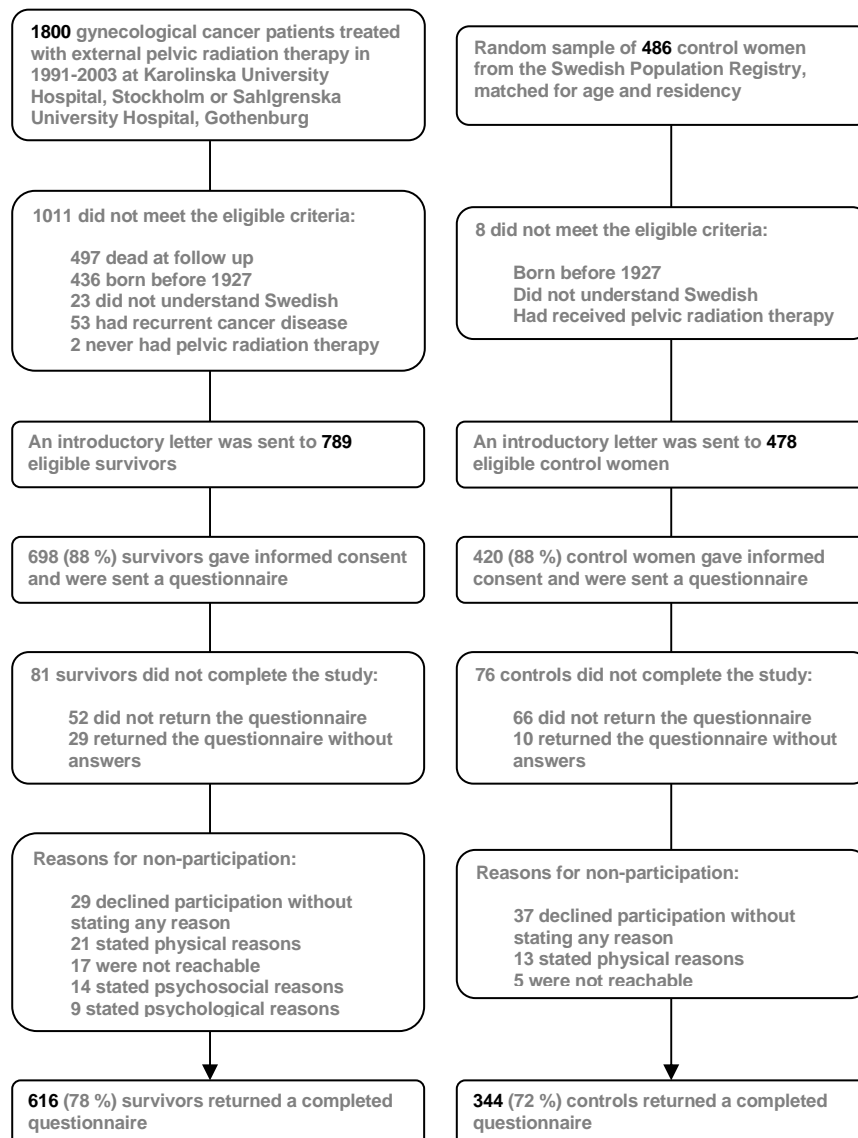
## 4. MATERIAL AND METHODS

### Study population

In 2005 we identified 1800 women consecutively treated between March 1991 and December 2003 with curative EBRT for a gynecological malignancy at Radiumhemmet, Karolinska University Hospital in Stockholm or at Jubileumskliniken, Sahlgrenska University Hospital in Gothenburg.

The chosen time frame represented the initiation of three-dimensional treatment planning with access to electronically stored data, which was a prerequisite for the study. The method was introduced in 1991 in Stockholm and in 1994 in Gothenburg. The year 2003 was chosen to allow development of treatment-related long-term side effects and at the same time to exclude the majority of patients who had recurrent disease shortly after treatment. The flow chart for inclusion is illustrated in Figure 11.

Figure 11. Flow chart for inclusion.



Inclusion criteria were prior pelvic EBRT, younger than 80 years of age, no recurrence and able to read and write Swedish. At follow-up in January 2006 789 survivors (Stockholm n=595 and Gothenburg n=194) were eligible for the study. In total 497 women had died, 436 were born before 1927, 53 had had a recurrence, 23 were not able to read Swedish and two did in fact never receive any pelvic RT and were not included. Women with prior abdominal surgery and malignancy other than a gynecological cancer were allowed to participate.

Power calculations were performed to estimate the sufficient number of control women. In a random sample from The Swedish Population Registry we received 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, aged 70 to 79 were added to provide a better match of age of cancer survivors and control women. Eight out of the 486 control women were not included because they were born before 1927, did not understand Swedish or were previously treated with pelvic RT. In total 478 control women remained and were eligible for the study.

*The study population in Paper I* consists of the 616 out of 789 (78 percent) survivors and the 344 out of 478 (72 percent) control women who participated in the study.

*The study population in Paper II* comprised the 606 out of 616 (98 percent) cancer survivors and 344 (100%) control women who answered the question 'Have you had emptying of all stools into clothing without forewarning, the past six months?'

*The study population in Paper III* consists of the 519 survivors for whom it was possible to recover electronically stored radiation treatment dose data for organs at risk.

*The study population in Paper IV* consists of a subset of the survivors described in Paper III and included the 83 survivors who were treated with EBRT without EBRT.

## Questionnaire

The development of the questionnaire started with a qualitative preparatory phase lasting for 18 months. Twenty-six gynecological cancer survivors treated with EBRT one to ten years earlier agreed to be interviewed. The semi-structured interviews were tape recorded and lasted on average one hour each. The questions focused on the informants' present situation, the current symptoms, QoL and social functioning. Verbatim transcripts were made by a secretary. The self-reported symptoms were sorted into areas of supposed anatomical origin. The symptoms and themes that were captured in the interviews were reformulated as questions. In addition we added questions based on our clinical experience, previous questionnaires from our research unit and through studying available literature.

Face-to-face validation was performed in women within the study population making sure the questions were conceptually clear and correctly understood. The questionnaire was also validated face-to-face with non-irradiated persons. Participation rate, rate of missing values and logistics were tested in a pilot study.

The final questionnaire consisted of ten chapters with a total of 351 questions, as follows:

**Demographic characteristics, obstetric data, cancer disease and cancer treatment: Q 1-22**

**Psychological issues, QoL-measures and social functioning: Q 23-35**

**Gastrointestinal symptoms and coping strategies: Q 36-150**

**Urinary tract symptoms and coping strategies: Q 151-197**

**Lymph edema in abdomen and legs: Q 198-217**

**Pelvic bone pain: Q 218-247**

**Eating habits: Q 248-256**

**Sexuality and body image: Q 257-315**

**Physical health, co-morbidities, medication, Body mass index (BMI), smoking and smoking: Q316-340**

**Questions on study participation: Q 341-351**

In each part of the questionnaire we asked about the incidence, prevalence, intensity and duration of the symptoms when appropriate. One hundred and fifteen questions addressed bowel habits such as anal incontinence, leakage severity (soiling to all stools), forewarning or not, frequency, prevalence and duration as well as coping strategies and QoL conditions.

For QoL and social functioning we used a seven-point Visual Digital scale. Responses ranging from 1 to 5 on the scale were defined as low to moderate QoL<sup>135</sup>.



**Strålbehandling  
vid en gynekologisk cancersjukdom**

Figure 12. Questionnaire

The main data collection was carried out in January to October 2006. We sent an introductory letter to 789 patients and 478 controls explaining the objectives of the study emphasizing that their participation in the study was voluntary. One week later an interviewer called each informant. Those giving informed oral consent to participate received a postal questionnaire along with a letter again explaining our objectives for conducting the study. The cancer survivors were informed that data also were collected from their medical records. Three weeks later after the initial contact a thank-you card was sent to show appreciation for the subject's participation or serve as a reminder. Yet a week later the interviewer called those who had not returned the questionnaire. Each questionnaire contained a number for identification to maintain confidentiality. Information collected from medical record included cancer diagnosis, treatment techniques and dose-distribution data.

The results from the questionnaire and the data from the medical records were coded and transferred to the freeware data entry program Epi-Data ([www.epidata.dk](http://www.epidata.dk)). Statistical analyses were performed using IBM SPSS Statistics 17.0 (IBM, Armonk, New York, United States).

The Regional Ethics Committee has approved of the study.

## Contouring of organs at risk

Ten organs at risk were identified; the anal-sphincter region, rectum, the sigmoid, the small intestines, the urinary bladder, the vagina, the pubic bone, the sacrum and finally the left and right femoral heads. Available treatment plans with CT slices were retrieved in the treatment planning systems and the organs at risk were contoured in order to calculate the dose distribution in these ten organs. Consistent contouring was assured by using written guidelines including pictures. Two persons at each clinic performed the contouring under the supervision of a Senior Oncologist (H.L. in Stockholm and A-C.W. in Gothenburg) during 2006 and 2007.

The *anal-sphincter* region was represented by the inner muscle layer of the sphincter up to the anal verge. The *rectum* was depicted by its outer contour with filling extending from the anal verge to the recto sigmoid junction. The *sigmoid* was outlined from where the rectum deviated from its mid-position to where it could be located in the left part of the abdomen in at least two consecutive slices and connecting to the colon descendens. The *small intestines* were defined as all visible small bowels in the pelvic region up to the caudal part of the sacroiliac joints. The *urinary bladder* was represented by its outer contour including filling (Figure 13). The *pubic bone* was contoured using the symphysis as a starting-point reaching laterally including the anterior parts of the superior and inferior rami. The *sacrum* was defined by the body of the sacrum, excluding the dorsal spinal processes and the coccyx. The left and the right *femoral heads* were outlined separately covering the head but excluding the femoral neck (Figure 14). The *vagina* was defined as an elliptical area measuring one by three cm located between the urethra/urinary bladder and the rectum to cervix portio or if not present to

the lower border of the pelvic cavity. Some of the cervical cancer patients had two or three silver seed markers of the cervix.

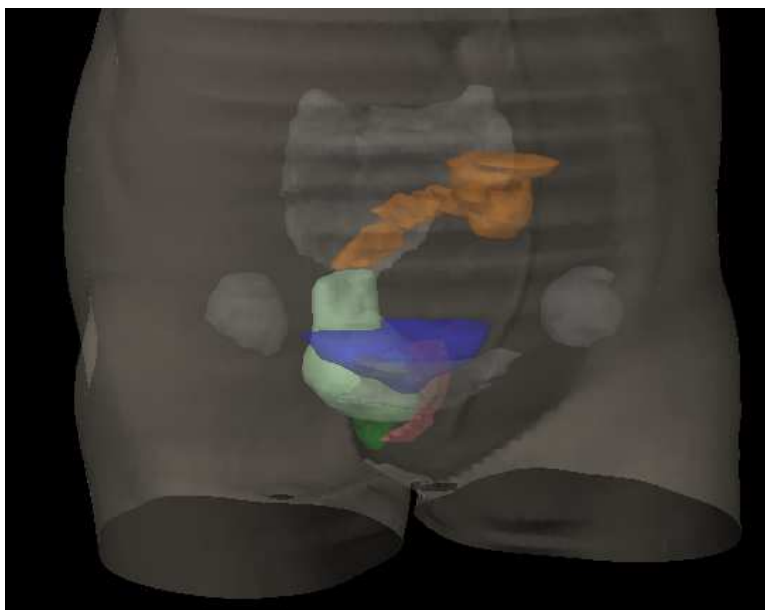


Figure 13. Frontal view of organs at risk.

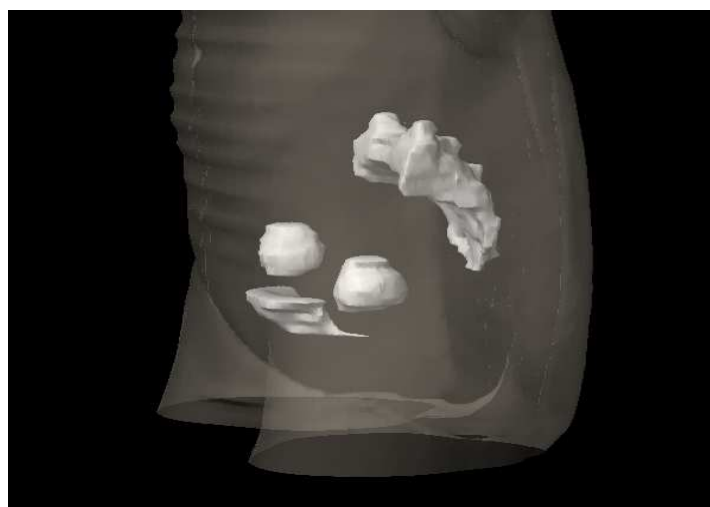


Figure 14. Lateral view of pelvic bones

Outlining in contiguous CT slices resulted in a three-dimensional volume where the dose of ionizing radiation could be calculated in each volume element; i.e. voxel. DVHs of the ten OARs were produced for each individual patient and exported from the treatment planning system. The DVH was normalized to the total volume of each OAR (percentage of volume) except for the small intestines which were measured by the actual volume. The mean absorbed doses for EBRT for all OARs were calculated for each group of the tumor diagnoses.

## Radiation therapy equipment and techniques

Cancer treatment was administered according to local treatment programs and applied study protocols that were in use at the time of treatment. The protocols have been revised and updated gradually in accordance to new medical evidence.

Three-dimensional treatment planning systems were used for the construction of EBRT dose plans; *TMS* (Nucletron, Veenendaal, the Netherlands) in Stockholm and *Cadplan* and *Eclipse* (Varian Medical Systems, Palo Alto, United States) in Gothenburg.

The planning was based on designated CT scans performed prior to radiotherapy with a *Siemens Somatom HiQ single slice* (Siemens AG, München, Germany) in Stockholm and a *General Electric High Speed Fx* (Fairfield, Connecticut, United States) in Gothenburg. Scans were made in treatment position on a flat table top, using laser markers and conversion factors to electron density and with tissue heterogeneity correction applied. The CT slices ranged from 5 to 20 mm. The EBRT dose was prescribed either at isocenter or as mean dose to the target covering at least 95 percent of the planning target volume. Patients were treated in supine position, using megavoltage linear accelerators; *Brown Boveri Company* (now: Asea Brown Boveri, Zürich, Switzerland), *Elekta* (Elekta AB, Stockholm, Sweden), *Philips* (Koninklijke Philips Electronics, Amsterdam, the Netherlands), *Siemens* and *Varian* or with a racetrack accelerator; *Scanditronix* (Scanditronix Medical AB, Uppsala, Sweden) with two opposing fields or a four-field box technique. Daily dose per fraction varied between 1.6 and 2.0 Gy. EBRT RT was verified by portal image films and with check-and-confirm systems.

BT was applied using standardized techniques and applicator templates. The BT dose was prescribed according to local practice; to Point A in Stockholm and 2 mm outside the applicator surface in Gothenburg. In 1991-1994 the BT treatment in Stockholm, was administered by manually deposited intrauterine insertions of low dose rate  $^{226}\text{Radium}$  implants according to the packing method of Heyman<sup>136</sup> and by intravaginal BT treatment with low dose rate  $^{137}\text{Cesium}$ . A Selectron (Nucletron) remote afterloading equipment was used to operate the  $^{137}\text{Cesium}$ . Around 1994 the treatments including  $^{226}\text{Radium}$  were replaced by high dose rate  $^{192}\text{Iridium}$  using an afterloading device; *Microselectron* (Nucletron) in Stockholm. In Gothenburg only high dose rate BT treatment technique was applied by using a *GammaMed 12i HDR*, (Varian Medical System). Pre-treatment orthogonal x-ray images verified the position of the BT applicator.

# 5. RESULTS

## Paper I

In all, 616 of 789 (78 percent) cancer survivors and 344 of 478 (72 percent) control women participated in the study. The median follow-up time was 74 months (range 26 to 179 months). The median age for cancer survivors was 66.0 years and for controls 57.5 years. The most common diagnose was endometrial cancer followed by cervical cancer as illustrated by Figure 15.

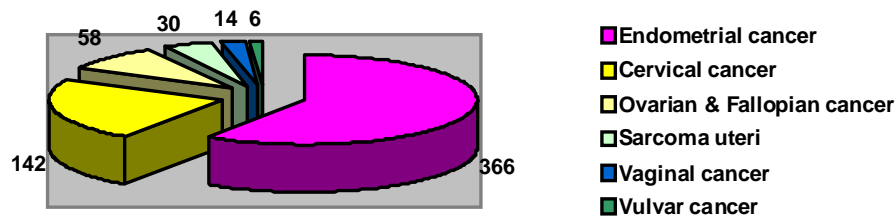


Figure 15. Diagnoses in Paper I

More than 90 percent of the survivors had surgery in addition to EBRT. The remaining 10 percent consisted of a subset of cervical and vaginal cancer patients who were treated without surgery. Treatment in each diagnosis is illustrated in Figure 16.

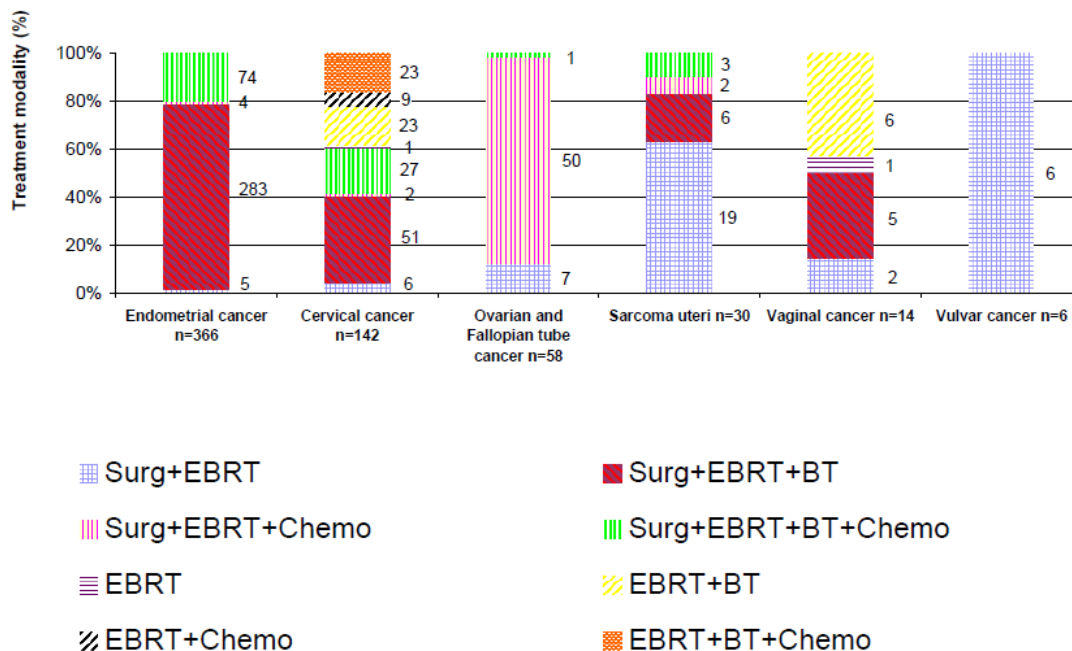


Figure 16. Diagnosis and treatment

Nulliparity, hypertension, diabetes mellitus and heart failure were more prevalent in cancer survivors. Operational procedures at delivery and perineal injuries were more common among controls.

With a median follow-up time of 6.2 years from completed EBRT, cancer survivors reported a higher occurrence of symptoms from all the studied organs compared to matched control women.

The highest RRs for 'Anal-sphincter region' were 'emptying of all stools into clothing without forewarning at least occasionally' RR = 12.7 (95% CI 4.0-40.3) and 'leakage of loose stools while awake at least occasionally' RR = 6.0 (95% CI 3.7-9.6).

The highest RRs for 'Bowel' were 'defecation urgency at least once a week' RR = 5.7 (95% CI 3.5-9.1) and 'protracted abdominal pain lasting more than a year' RR = 3.2 (95% CI 1.9-5.6).

The highest RRs for 'Urinary tract' were 'difficulties to feel the need to empty bladder' RR = 2.8 (95% CI 1.5-5.4) and 'difficulty emptying bladder at least occasionally' RR = 2.7 (95% CI 1.4-5.2).

The highest RRs for 'Sexuality' were 'protracted genital pain lasting more than a year' RR = 5.0 (95% CI 1.7-14.5) and 'genital bleeding during or after intercourse at least once' RR = 3.7 (95% CI 2.1-6.7).

The highest RRs for 'Pelvic bones' were 'pubic pain when walking indoors at least occasionally' RR = 4.9 (95% CI 2.1-11.6) and 'pubic pain when walking outdoors 500 m at least occasionally' RR = 3.7 (95% CI 1.7-8.4).

The highest RRs for 'Lower abdomen and legs' were 'erysipelas on abdomen or legs' RR = 3.6 (95% CI 1.0-12.8) and 'lower abdomen heaviness at least occasionally' RR = 2.1 (95% CI 1.5-3.0).

All RRs were increased when survivors with surgery were excluded.

## Paper II

In all, 606 of 616 cancer survivors (98 percent) and 344 of 344 control woman (100 percent) that were participating in the study had answered the question 'Have you had emptying of all stools into clothing without forewarning, the past six months?'.

Seventy out of 606 (12 percent) survivors reported having the symptom 'emptying of all stools into clothing without forewarning' at least occasionally the previous six months before answering the questionnaire. Three out of 344 (less than one percent) of control women had had a similar experience. The RR between survivors and controls was 11.9 (95% CI 3.8-37.8).

The symptom was relatively more common in cervical cancer and uterine sarcoma survivors as seen in Figure 17.

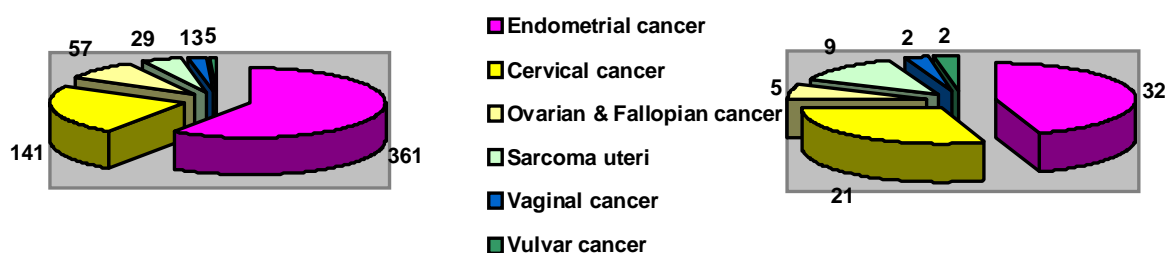


Figure 17. Diagnoses in Paper II; all survivors and survivors with the symptom

It was relatively less common with BT in survivors experiencing 'emptying of all stools into clothing' as seen in Figure 18 below.

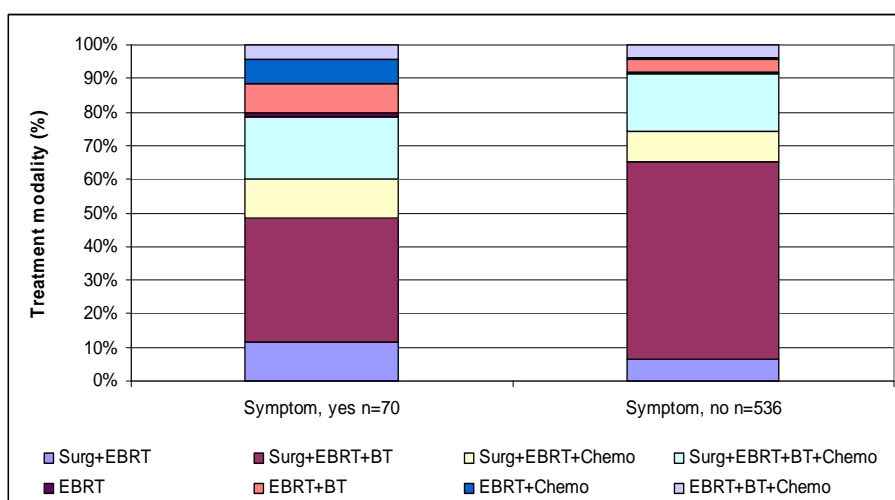


Figure 18. Treatment modalities for survivors with and without 'emptying of all stools'

Adjustment for known risk factors for fecal incontinence such as BMI >25, diabetes mellitus, neurological diseases, Crohn's disease, ulcerative colitis, episiotomy and caesarean did not alter the result.

Seventy four percent of the survivors with the symptom had a low to moderate QoL compared with 51 percent of survivors without the symptom. In addition

the survivors with the symptom were bothered by a number of other physical issues to a greater extent than survivors that without 'emptying of all stools' (Figure 19).

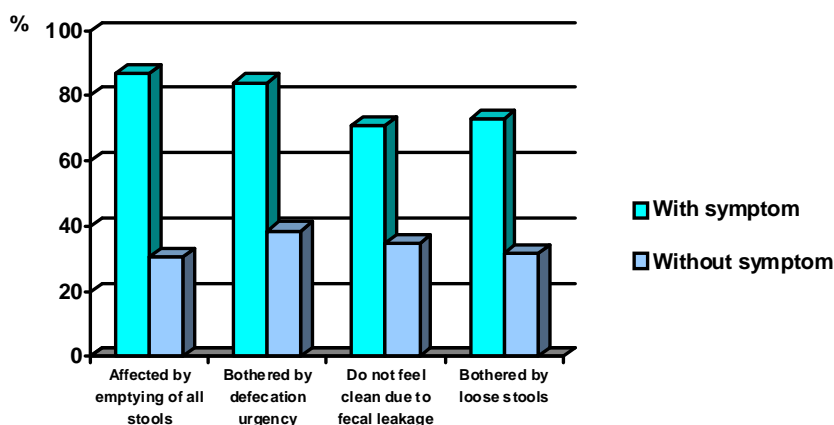


Figure 19. Symptoms leading to bother in survivors with and without 'emptying all stools'

'Emptying of all stools kept the survivors from going to parties RR= 11.8 (95% CI 6.6-21.1), kept the survivors from traveling RR = 9.3 (95% CI 5.3-16.5), affected their work ability RR = 7.9 (95% CI, 3.8-16.4) and hindered their sexual life RR = 9.2; (95% CI 4.8-17.6).

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

### Paper III

In all, we had access to electronically stored treatment plans for 519 of 616 cancer survivors (84 percent). Proportions of diagnoses were more or less unchanged from the comparison with the original 616 survivors as seen in Figure 15 and 20.

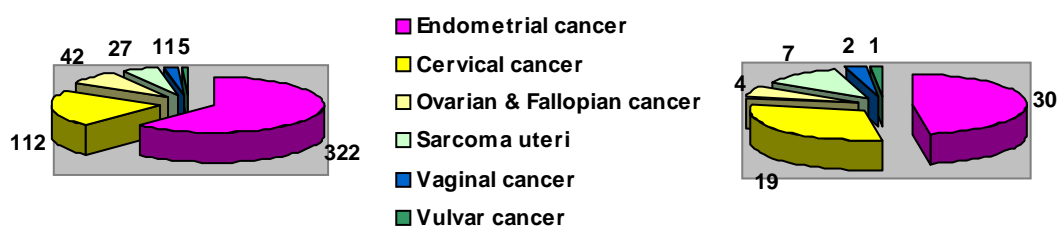


Figure 20. Diagnoses in Paper III; all survivors and survivors with the symptom, respectively

Mean absorbed dose was 46.3 Gy ( $\pm$ SD 8.2) in survivors with 'emptying of all stools into clothing without forewarning' compared to 43.3 Gy ( $\pm$ SD 5.5) in survivors without the symptom. Proportions of treatment modalities are presented in Figure 21.

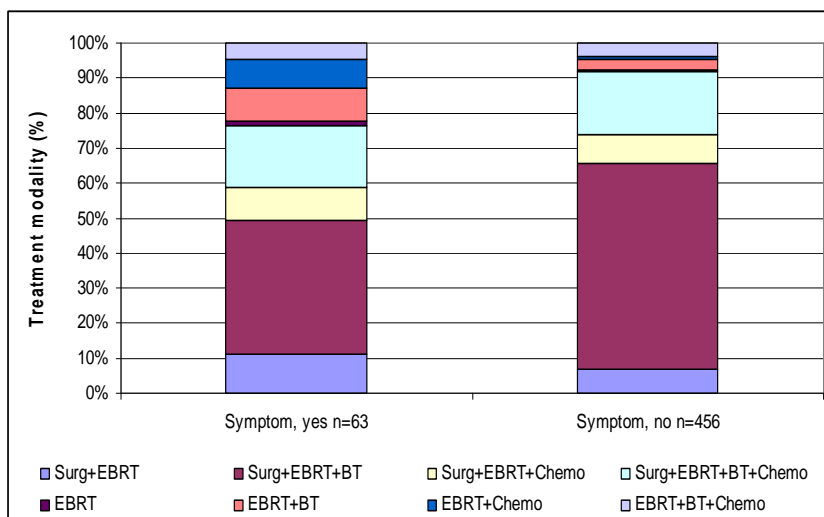


Figure 21. Treatment modalities in survivors with or without 'emptying of all stools'

Unadjusted RRs and odds ratios (ORs) for having 'emptying of all stools into clothing without forewarning' for all organs at risk were significantly increased for mean doses over 50 Gy.

Regression analysis included the risk factors 'At least two deliveries of birth weight exceeding 4 kg', 'Anal-sphincter injury', 'Heart failure', 'Lactose and/or gluten intolerance' and 'BT dose' in the model used for adjusting ORs for the mean absorbed dose levels. Adjustment led to significantly increased OR also for mean dose over 45 Gy to the anal-sphincter region: OR = 3.3 (95% CI 1.0-10.5) and when excluding 'high-dose' BT we found OR = 4.5 (95% CI 1.2-17.2).

For doses over 50 Gy to the anal-sphincter region OR = 17.1 (95% CI 4.0-73.0) and when excluding 'high-dose' BT we found OR = 22.4 (95% CI 3.3-152.4), for the rectum OR = 4.2 (95% CI 1.0-18.2) and OR = 3.4 (95% CI 0.3-32.6), for the sigmoid OR = 5.6 (95% CI 1.1-26.3) and OR = 5.0 (95% CI 0.9-26.8) and for the small intestines OR = 3.7 (95% CI 0.8-16.4) and OR = 4.0 (95% CI 0.8-20.2).

The DVHs for survivors with and without the symptom were most widely separated for the sigmoid as seen in Figure 22.

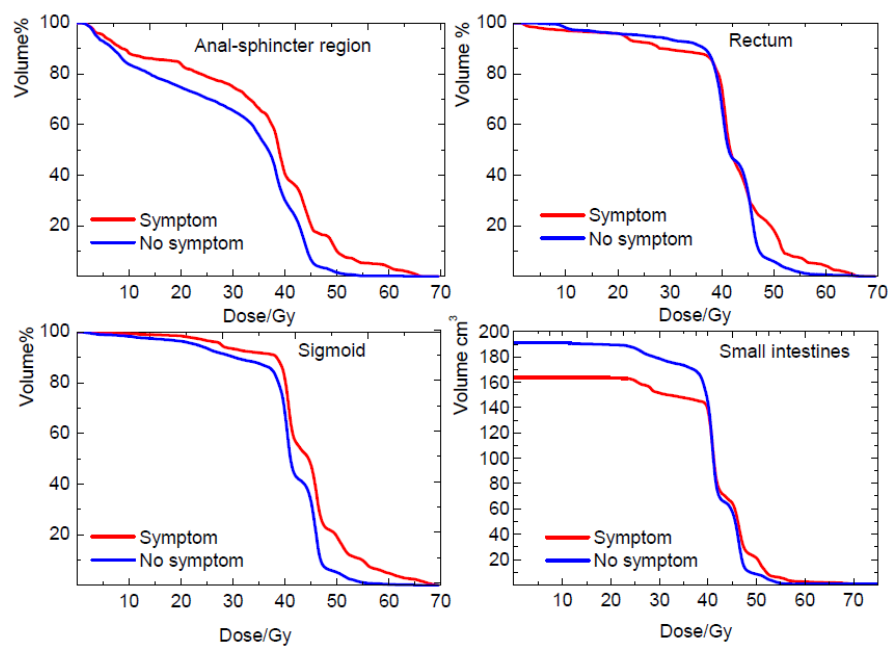


Figure 22. Dose-volume histogram for organs at risk

## Paper IV

This paper included 83 gynecological cancer survivors who did not receive BT as part of their treatment survivors for whom we had access to electronically stored treatment plans. By using these inclusion criteria most endometrial cancer survivors were excluded as seen in Figure 23.

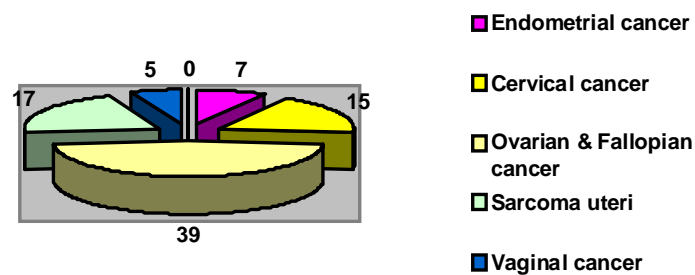


Figure 23. Diagnoses in Paper IV

Survivors with 'emptying of all stools into clothing without forewarning' were slightly younger and had more often been treated for cervical cancer or sarcoma uteri. Proportions of treatment modalities are shown in Figure 24.

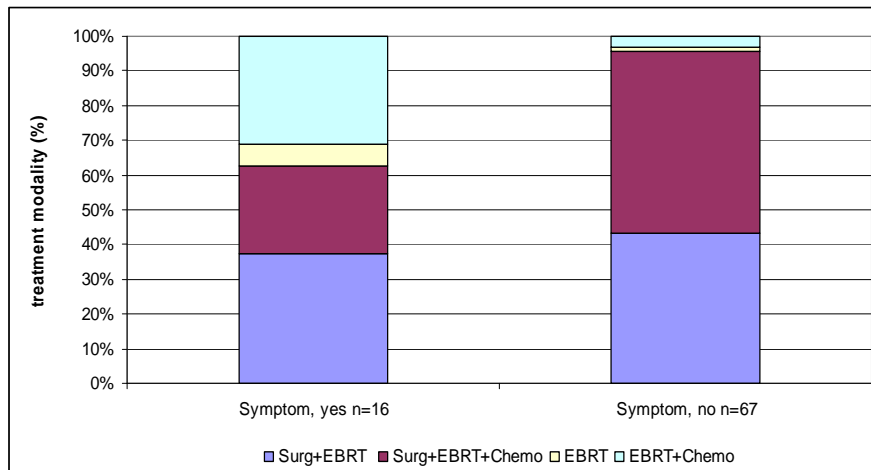


Figure 24. Treatment modalities in survivors with and without 'emptying of all stools'

The absorbed mean dose to survivors with 'emptying of all stools into clothing without forewarning' was 52.1 Gy ( $\pm$ SD 11.8) compared to survivors without the symptom; 43.0 Gy ( $\pm$ SD 8.7). Among the studies organs at risk, the dose to the sigmoid was the best predictor of the symptom with the best AUC value and highest  $\gamma_{50}$ -value.

The response probability for developing the symptom 'emptying of all stools into clothing without forewarning' for 50 Gy to the sigmoid was 25 percent according to the RS model and 27 percent according to the Lyman model (Figure 25).

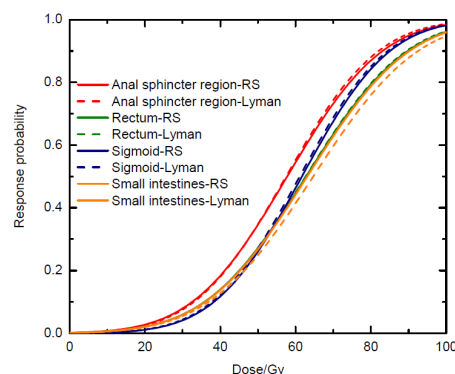


Figure 25. Dose response probabilities using Relative Seriality or Lyman model

The volume parameters for the anal-sphincter region and the small intestines for the three models indicate a serial behavior of the organs for this endpoint. It means in practice that the maximum dose would describe the dose-effect

relationship for the anal-sphincter region and the small intestines best. The rectum and to a lesser extent the sigmoid were found to have a parallel behavior structure, which indicate that the mean dose would be more appropriate for rectum and sigmoid dose-effect relationships (Figure 26).

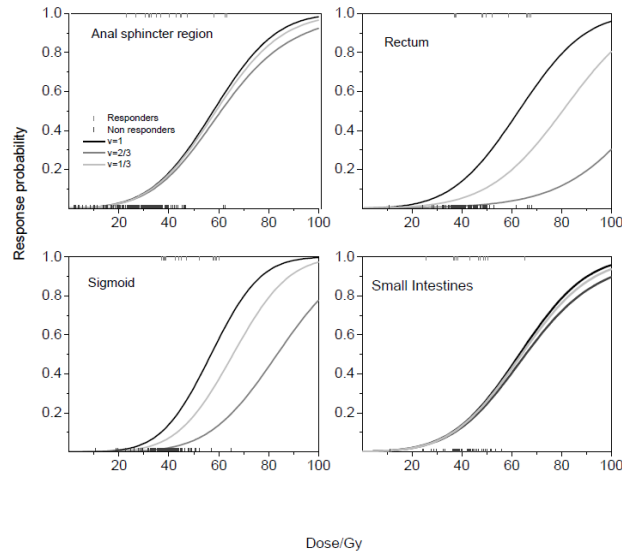


Figure 26. Dose-response probabilities using Relative Seriality and Lyman models for OARs

## 6. DISCUSSION

### Methodological considerations

Validation is the process of assessing whether or not the scientific conclusions presented in a study are reliable and supported by the corresponding data. The validity of a study is primarily dependent on presence of bias.

In order to evaluate the quality of our study data, all possible sources of bias must be identified and categorized step-wise. Finally the combined effect of all bias was used to estimate the quality of the used effect-measures.

As guidance we have used the *Hierarchical step-model*<sup>137</sup>.

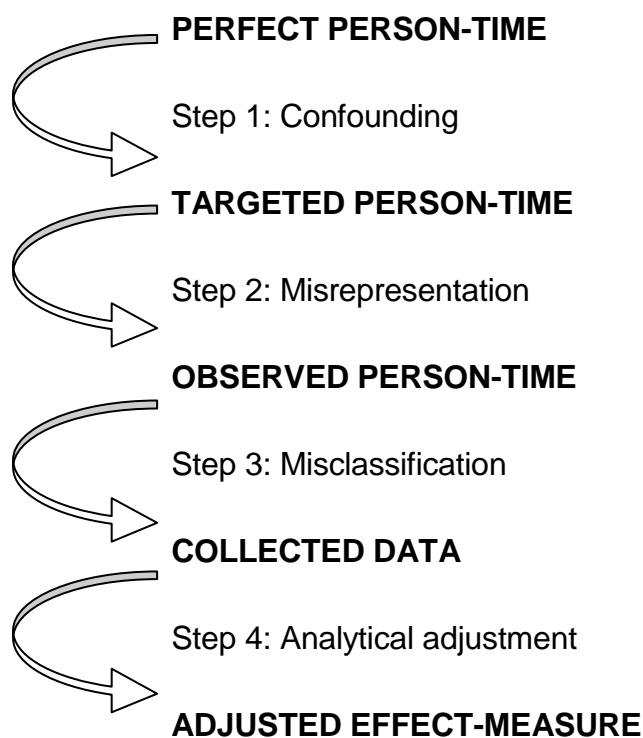


Figure 27. Hierarchical step-model

**Confounding factors**<sup>138</sup> are associated both with the exposure (absorbed radiation dose) and the outcome (long-term symptom) and are considered true causes of the outcome but are not a part of the causal chain.

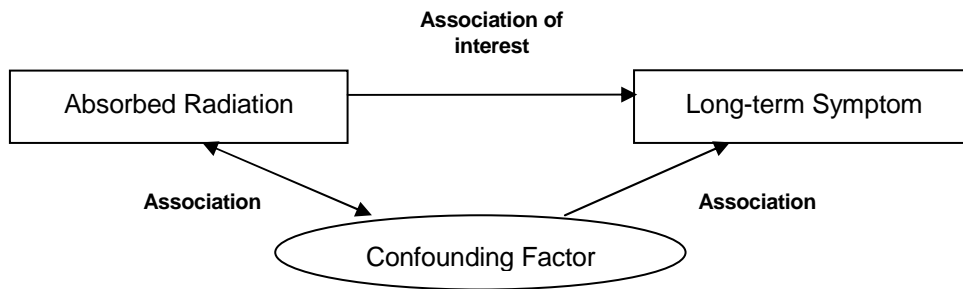


Figure 28. Confounding

If confounding factors are not considered this may lead to an over- or underestimation of the true association between exposure and outcome. A positive confounding factor will strengthen the association, whereas a negative confounding factor will decrease the strength of the association; 'bias toward the null hypothesis'.

In order to minimize systematic errors due to confounding, which may decrease the validity, i.e., the quality of outcome measure; we have matched control women and survivors by age and residence. In addition we have collected information on potential confounding factors through the questionnaire and medical records. The self-reported information included among others age, marital status, education, employment, residency, smoking, BMI, exercise, obstetric data, pelvic floor injuries, intercurrent diseases and medication. We also collected data on diagnosis, stage of disease, Chemotherapy, and EBRT. Known or suspected causal factors for the outcome were studied and adjusted for in the analyses.

Non-participation, survivors lost to follow-up and sampling from the targeted person-time resulting in a partial loss of the targeted person-time may lead to ***misrepresentation***. It is crucial to avoid this missing piece of information since the lack of knowledge results in an effect-measure that can be changed in any unpredictable direction. An estimation of the maximum and minimum effect of the non-participation can be made.

Extensive measures have been carried out to minimize non-participation. The initial qualitative in-depth interviews captured new topics and revealed areas that were perceived as important and relevant for the survivors, leading to an increased incentive to participate. All women in Stockholm and Gothenburg diagnosed with a gynecological cancer disease are treated at the regional oncology centre at each respective University Hospital. The cohort consisted of unselected patients arriving consecutively to these two clinics. Control women matched for age and residency were recruited through random sampling from the Swedish Population Registry.

In all 1011 of the cancer survivors did not meet the eligibility criteria and were not included in the study-base. They were either dead, had recurrent disease, were too old, did not understand Swedish or had never had pelvic RT. Among controls 8 women were not included because of being too old, did not understand Swedish and had had previous pelvic RT.

All the 789 eligible survivors and 478 controls were contacted on several occasions, by mail and by phone contributing to a high participation rate of 78 percent for the survivors and 72 percent for the control women. The participation rate was assessed in the pilot study before moving on to the main study. The women who did not participate, either stated physical illness as the main reason for their decision or gave no reason at all. We lack information regarding health among these which results in a decrease of the quality of the outcome measure.

Electronically stored treatment plans were reactivated for 519 of the survivors, in total 84 percent. Some of the tapes were broken and yet others simply missing. The missing data were concentrated to some of the oldest cases, but affected in some instances also more recent treatments. Diagnoses and doses among the missing dose plans were randomly distributed.

**Misclassification** may introduce bias when the collected information is not true. Measuring errors that do not vary between the groups that are being compared, *non-differential misclassification*, do not typically affect the relative risks in case of decreased sensitivity, but in measurement with decreased specificity, the relative risk will approach 1.0. If misclassification is different between the groups, *differential misclassification*, the relative risk can be changed in any direction.

To mimic the technique of “blinding”, we collected symptom information by means of a self-administered questionnaire answered in privacy at home without survivors being aware of our research hypotheses. This method decreased the risk of inducing interviewer-related problems due to a possible wish to please the care giver. The method of asking for symptom occurrence during the previous six months decreased the risk of recall-induced problems and also helped to avoid capturing temporary symptoms. The qualitative in-depth interviews, face-to-face validation, modification of questions when necessary and a pilot study all aimed to construct a relevant and conceptually clear questionnaire. Questions for survivors and controls were identical except for those specifically concerning cancer disease and its treatment. The questionnaires were numbered to maintain confidentiality. Treatment data were collected from medical records to ensure correct information. Measuring errors due to organ movements, set-up errors and errors in the contouring of pelvic organs at risk may dilute the association between the dose to the organs at risk

and occurrence of long-term symptoms. The organs were contoured without previous knowledge of the survivors' symptoms or questionnaire answers, also having the effect of "blinding".

**Analytical considerations:** Relative risks were used as an effect measure in many of the analyses<sup>139</sup>. Dichotomizing continuous predictors may lead to a loss of statistical power, but will in this case not change the obtained associations. A relative risk is a more intuitive and understandable way of illustrating the clinical effect of a certain treatment for a clinician.

## Findings

### Paper I

Gynecological cancer survivors treated with pelvic RT alone or as part of combined treatment reported higher occurrence of late specific symptoms from all normal organs addressed in the study; the anal-sphincter region, the bowel, the urinary tract, the pelvic bones and lymph system compared to matched control women. In addition there was higher occurrence of symptoms related to sexuality among survivors. *Atomized* symptoms originating from the anal sphincter and the bowel have been less well studied and their occurrences among gynecological cancer survivors are not fully elucidated<sup>89, 107</sup>. The gastrointestinal symptom with the highest relative risk was 'emptying of all stools into clothing without forewarning' with a 12-fold increase in risk in survivors compared to controls. In a previous study from our group 65 prostate cancer survivors were assessed by a postal questionnaire and dosimetric data including DVHs two to four years after curative EBRT. Fecal leakage was found to correlate to anal-sphincter dose of 45-55 Gy. There was also a correlation between defecation urgency and loose stools and rectal dose of 25-42 Gy<sup>140</sup>.

Late urinary side-effects appear to be less common but there are on the other hand few published reports on the prevalence of specific urinary symptoms among long-term gynecological cancer survivors. The urinary bladder has been regarded as less sensitive to radiation compared to the gastrointestinal organs<sup>115</sup>. Genitourinary complication rates following postoperative adjuvant EBRT in early stages of endometrial cancer have been assessed in the PORTEC-1 trial and the GOG99 trial. The PORTEC-1 trial reported a prevalence of eight percent of urinary urgency, recurrent infections and minor incontinence (measured by FIG glossary) compared to a prevalence of 25 percent of unspecified urinary toxicity (measured by 1985 GOG Adverse Events Criteria Scale) in the GOG99 trial. Higher risks of late urinary side-effects are reported in cervical cancer survivors, which can possibly be an effect of higher radiation doses<sup>117</sup>. Most studies show that the urinary morbidity continues to progress decades after RT. This statement is contradicted by the study by Pieterse *et al*<sup>141</sup>, where no increase in bladder dysfunction was found two years after postoperative EBRT of 94 early stage cervical cancer patients. The short follow-up time and the fact that there were only two questions

concerning bladder function may have contributed to this result. In a survey of 291 cervical cancer survivors 6.6 years after treatment Korfage *et al* assessed late symptoms and health-related QoL<sup>142</sup>. They compared self-reported symptoms after RT alone and postoperative EBRT. Frequent micturition was found in 42 percent versus 45 percent, urinary leakage in 19 percent versus 26 percent and difficulties emptying the bladder in 6 percent versus 11 percent. Our results indicate that late side effects from the urinary tract following RT are underestimated and underreported.

In a population-based cohort study of long-term early stage cervical cancer, the survivors reported more sexual dysfunction compared to control women<sup>143</sup>. This study has included all gynecological cancer disease. The impact of RT on sexual function has since then been confirmed in several publications<sup>142, 144-146</sup>. Currently there are only a few evidence based actions that deal with physical symptoms as reviewed by Cochrane Collaboration<sup>147</sup>.

Symptomatic bone fracture caused by osteradionecrosis is a very rare but disabling condition with an overall incidence less than one percent as reported by Feltl *et al*<sup>118</sup>. At a median time of 44 months (range 6-197 months) after pelvic EBRT with or without BT for a gynecological malignancy 0.44 percent of survivors had verified insufficiency fracture and pain. The main risk factor for developing pelvic bone pain was osteoporosis<sup>119</sup>. The condition seems to be underreported compared to our data, especially in survivors previously treated with RT only. In a previous paper from our research group we reported on pubic bone pain and increased frequency of pain with mean absorbed dose exceeding 52.5 Gy to the pubic bone<sup>148</sup>.

Lymph edema in the lower abdomen and the legs is late symptom affecting gynecological cancer survivors<sup>149</sup>. In a population-based postal survey of 802 gynecological cancer survivors 25 percent reported lymph edema or had symptomatic lower limb swelling. The symptoms were most pronounced in vulvar cancer survivors<sup>150</sup>. These results are in accordance with our result where survivors in general reported swollen lower abdomen and sense of heaviness and in 20 percent, and in addition swollen legs and sense of heavy legs in 35 percent.

## Paper II

Seventy-four percent of the survivors with the symptom 'emptying of all stools into clothing without forewarning' reported a low to moderate QoL. This symptom stopped the gynecological cancer survivors from participating in social activities and made it difficult to have a sex life. Many of the women stated that they located accessible toilets before they left home. One out of three said that having fecal leakage had changed their personality. Gastrointestinal symptoms after pelvic RT have more impact on QoL than previously reported<sup>105</sup> and in particular fecal leakage, which is one of the most stressful symptoms<sup>143</sup>.

Fecal incontinence occurring suddenly, unpredictably and with no time to react is disabling and very embarrassing. Similar results are reported in studies by Abayomi *et al*<sup>91, 151</sup>. The gynecological cancer survivors reported that chronic radiation enteritis with loose stools, fecal incontinence and fecal urgency had an impact on work, ability to perform in activities outside the house and social life. The lack of warning before defecation made coping strategies essential. Need of immediate access to a toilet has also been reported by Nout *et al* who studied 348 gynecological cancer survivors treated with either vaginal EBRT or EBRT for an endometrial cancer. Survivors treated with EBRT reported significantly higher levels of loose stools and fecal leakage and a significantly higher need to remain closer to a toilet which resulted in lowered social functioning<sup>152</sup>. In a study by Gami *et al* 107 cancer survivors treated with pelvic RT the QoL was affected in 50 percent of patients with diarrhea and in 20 percent of patients with fecal incontinence<sup>105</sup>.

Many cancer survivors associate current symptoms with normal ageing, not realizing that previously administered treatment can be the main cause. They may hesitate to talk about embarrassing symptoms such as fecal incontinence<sup>93</sup>. An important task for the health care providers is to actively ask for symptoms that are surrounded by taboos.

### Paper III

Not many studies have reported on the relationship between anorectal dose parameters and the risk of late fecal incontinence in gynecological cancer survivors as opposed to prostate and rectal cancer survivors. In a study of Fiorino *et al* dosimetric rectal data from 506 prostate cancer patients were analyzed. Rectal volume receiving 40 Gy or more ( $V_{40}$ ) and surgery were the strongest predictors of fecal incontinence defined as 'use of pads'<sup>153, 154</sup>. In 641 prospectively scored (RTOG/EORTC scale) prostate cancer survivors Peeters *et al* found fecal incontinence requiring pads to be associated with anal wall parameters<sup>155</sup>. Similar results were reported by our own group showing a significant correlation between mean absorbed dose of 45 to 55 Gy to the anal sphincter and the risk of fecal incontinence in prostate cancer survivors<sup>156</sup>. These results are in accordance with the present study that showed a dose-effect relationship between mean absorbed doses over 50 Gy to the anal-sphincter region, the rectum, the sigmoid and the small intestines.

Several reports support the hypothesis that specific symptoms originate from specific anatomic regions. Smeenk *et al* reported on fecal urgency and incontinence origin from both the anal and rectal wall, while fecal frequency mostly originated from the rectal wall<sup>157</sup>. In addition they found that dose-effect relations differed between the described symptoms. The importance of discriminating between different symptoms and their origin to increase specificity is supported by Heemsbergen *et al* who found a dose-effect relation for fecal incontinence in the anal region and lower rectum<sup>158</sup>. The sigmoid colon

has been suggested by Fonteyn *et al* as being co-responsible for the development of lower intestinal toxicity besides the anal sphincter and the rectum<sup>159</sup>. In addition was the small bowel volume receiving 50 to 60 Gy predictive for the development of late side effects, which is in line with our results.

The dose contribution from BT is difficult to estimate because of the use of different techniques regarding isotopes, applicators, anatomical arrangements and doses in the absence of three-dimensional treatment planning. We have made the assumption that <sup>192</sup>Iridium BT used postoperatively in endometrial cancer patients with a prescribed total dose of at most 11.25 Gy did not substantially affect the studied OARs. In an effort to investigate the effect of 'high' doses of BT we excluded survivors that were treated with <sup>192</sup>Iridium exceeding 11.25 Gy or <sup>226</sup>Radium with or without <sup>137</sup>Cesium. The resulting prevalence ratios were even higher which indicate that EBRT to the four OARs is related to 'emptying of all stools into clothing without forewarning'.

Normal-tissue injury induced by ionizing radiation is thought to be a progressive process. Still, there are reports showing both increase and decrease of rectal symptoms with time in prostate cancer survivors<sup>160</sup>. In the present study there was a tendency towards an increase of symptom occurrence with time, but it was not statistically significant during follow-up from 28 to 120 months after completing pelvic radiation therapy.

#### Paper IV

Among the four studied organs at risk, the dose to the sigmoid was found to be the best predictor of the symptom 'emptying of all stools without forewarning', having the best Area Under the Curve-value (AUC-value) and the highest normalized dose response gradient ( $\gamma_{50}$ -value). It is still import to mention the fact that the figures do not differ very much. The response probability for 50 Gy was 25 percent according to the relative seriality and 27 percent according to the Lyman model, which indicates that either model can be used. The volume parameters obtained for the anal-sphincter region and the small intestines indicate a serial behavior of the organs for this endpoint. The rectum and to a lesser extent the sigmoid were found to have a parallel structure. The values from the maximum likelihood estimates of the used models and the Log Likelihood (LL) values showed no significant difference between the Relative Seriality and the Lyman models, and either method could be used in order to predict the probability of the symptom and dose to the OARs.

Although the sigmoid is highly mobile and the exact location is difficult to estimate, the dose distribution in its anterior wall appears almost uniform as reported by Waldenström *et al*<sup>161</sup> and thus the exact location at contouring may become less critical.

Fonteyn *et al* reported late radiation therapy induced lower intestinal toxicity following IMRT in 241 prostate cancer patients<sup>159</sup>. The late side-effects included five symptoms from the RTOG toxicity score supplemented with urgency, fecal incontinence and anal pain. Grade 2 symptoms were found in 13 percent of the survivors. There was a correlation between sigmoid volume parameters and grade 1-2 symptoms suggesting that the sigmoid should be considered as an organ at risk, which is in accordance with our results.

Studies concerning gynecological cancer survivors and dose-volume response parameters for the anal sphincter and bowel for fecal incontinence symptoms are scarce. In a radiobiological study of 65 prostate cancer survivors assessed with a study-specific questionnaire and access to three-dimensional dose distributions, Mavroidis *et al*<sup>162</sup> found a parallel behavior of the anal sphincter with fecal incontinence as end point. These results were confirmed in a study by Peeters *et al*<sup>163</sup> including 468 prostate cancer survivors evaluated after RT.

A statistically significant correlation was found between radiation to the anal-sphincter region and the risk of fecal leakage in the interval of 45 to 55 Gy in a study including 72 prostate cancer survivors assessed with a questionnaire two to four years after RT by al-Abany *et al*<sup>140</sup>.

Other factors have been found to influence the development of 'emptying of all stools without forewarning'. Alsadius *et al* reported that current smokers among prostate cancer survivors had an increased risk of having the symptoms with a prevalence ratio of 4.7 (95% CI 2.3-9.7)<sup>164</sup>. Corresponding data for the gynecological cancer survivors did not show any significant difference among survivors with or without the symptom who were current smokers. The only factor that was significantly associated with having this specific fecal incontinence was heart failure.

The mean absorbed to anal-sphincter region and bowel organs is related to the late fecal incontinence symptom 'emptying of all stools into clothing without forewarning'. Besides the anal-sphincter region and the rectum also the sigmoid and small intestines should be contoured and saved separately in RT.

## 7. GENERAL CONCLUSIONS

Gynecological cancer survivors having undergone pelvic radiation therapy alone or as part of combined treatment between 1991 and 2003 report a higher occurrence of symptoms from the gastrointestinal and urinary tract as well as lymph edema, sexual dysfunction and pelvic pain compared with non-irradiated control women.

Twelve percent of women with a history of gynecological cancer treated with pelvic radiation therapy reported 'emptying of all stools without forewarning' and 74 percent of them reported low to moderate quality of life. This symptom kept the cancer survivors from social activities and hindered their sexual lives. A majority of these women located accessible toilets in advance and spent several hours every day on practical arrangements around defecation.

Mean absorbed external doses to the anal-sphincter region, the rectum, the sigmoid and the small intestines are related to the risk of 'emptying of all stools into clothing without forewarning' in long-term gynecological cancer survivors.

Radiobiological modeling indicates that the dose to the sigmoid is the best predictor of the occurrence of 'emptying of all stools into clothing without forewarning'. The volume parameters indicate that the anal sphincter and small intestines behave serially while the rectum behaves parallel. The sigmoid has a mixed serial and parallel behavior. Other factors in addition to external beam radiation therapy dose and heart failure may be related with the development of the symptom.

The implications of our study are that;

Health-care providers need to actively ask patients about specific symptoms in order to provide proper diagnostic investigations and management.

Not only the rectum and anal sphincter should be contoured and spared separately in radiation therapy planning but also the sigmoid and the small intestines.

Dose-restriction to the involved organs at risk may in the future prevent 'emptying of all stools into clothing without forewarning', a severe socially disabling symptom which today affects one out of ten gynecological cancer survivors.

## 8. SWEDISH SUMMARY/SVENSK SAMMANFATTNING

### Gynekologisk cancer och strålbehandlingsrelaterade symtom

I Sverige insjuknar årligen cirka 2 900 kvinnor i en gynekologisk cancersjukdom. Livmoderkroppscancer, den vanligaste cancersjukdomen, drabbar cirka 1 400 kvinnor, cancer i äggstockar och äggledare knappt 800, livmoderhalscancer drygt 400, cancer i de yttre könsdelarna 127 kvinnor och de mer sällsynta livmodersarkomen och slidcancer drabbar tillsammans drygt 100 kvinnor årligen. Antalet kvinnor som överlevt en gynekologisk cancersjukdom blir allt fler och många av dessa kvinnor har erhållit strålbehandling mot bäckenområdet som enda behandling, eller som del av behandling i kombination med operation och eller kemoterapi.

Strålbehandling riktas mot det sjuka området men drabbar även omkringliggande normal vävnad, så kallade riskorgan vilket är bakgrunden till att biverkningar kan uppkomma. Hur stor stråldos och volym som olika riskorgan kan erhålla innan kvinnan drabbas av livskvalitetsnedsättande symtom är ofullständigt klarlagt. Kunskap om dessa faktorer kan bidra till en förbättrad strålbehandling i framtiden och möjliggöra att canceröverlevare kan besparas från symtom som inverkar på deras livskvalitet.

Det övergripande målet med denna avhandling var att kartlägga förekomsten av sent uppträdande symtom från bestrålade riskorgan i bäckenområdet bland gynekologiska canceröverlevare. Vi ville också studera hur dos av joniserande strålning och volym av bestrålade bäckenorgan bidrar till utvecklandet av ett specifikt livskvalitetsnedsättande symtom. Detta är kunskap vill vi använda till att förbättra vården för dagens och morgondagens gynekologiska cancerpatienter.

I denna epidemiologiska studie deltog 789 gynekologiska canceröverlevare från Stockholm och Göteborg som genomgått strålbehandling mot bäckenområdet, som enda behandling eller som del av kombinationsbehandling, under åren 1991-2003. Som kontrollgrupp tillfrågades 478 slumpvis utvalda kvinnor, matchade för ålder och bostadsort, från befolkningsregistret.

En 18 månader lång förberedande kvalitativ fas utgjorde grunden för studien. Vi inledde med att intervju 26 kvinnor som tidigare fått yttre strålbehandling mot bäckenområdet i botande syfte för gynekologisk cancer. I ett icke tidsbegränsat samtal, oftast timslångt, berättade kvinnorna om de symtom och besvär de hade, många utan att själva relatera detta till genomgången behandling. Samtalet spelades in och skrevs därefter ut ordagrant av en sekreterare. Materialet sorterades och delades in efter teman.

Dessa intervjuer varvade med litteraturstudier och våra samlade kliniska erfarenheter av gynekologisk cancer och strålbehandling låg till grund för vårt fortsatta arbete med att utveckla ett studiespecifikt frågeformulär. När frågeformuläret började närma sig en slutgiltig version testade vi frågor och svarsalternativ i en ansiktsvalidering med 20 personer. Testpersonerna uppmanades att resonera högt kring frågornas begriplighet och om svarsalternativen var klara och rimliga. Detta genererade ett antal

förändringar, varefter formuläret åter testades tills dess alla deltagare uppgav att de förstod alla frågor och svarsalternativ. Det slutgiltiga frågeformuläret bestod av 351 frågor och omfattade frågor om symtom från tarm, urinvägar, skelettsmärter, lymfsvullnad och sexualitet. Frågor om livskvalitet, kost, andra sjukdomar och sociodemografiska frågor ingick också.

Därefter genomförde vi en förstudie med 20 kvinnor ur studiepopulationen för att undersöka logistiken kring utskick och svar samt om svarsfrekvensen var acceptabel. Arton av 20 kvinnor besvarade formuläret och en svarsfrekvens överstigande 80 procent gav oss klarsignal att gå vidare med huvudstudien.

Huvudstudien, den *kvantitativa fasen*, startade genom att vi skickade ut en inbjudan till de 789 gynekologiska canceröverlevare som uppfyllde våra inklusionskriterier för deltagande i studien; födda 1927 eller senare, kunna läsa och skriva svenska, och inte ha haft återfall i sin cancersjukdom. Samma förfrågan skickades till de 478 kvinnor som slumpmässigt tagits fram ur det svenska befolkningsregistret och som utgjorde jämförelsegruppen. Exklusionskriterier för kontrollgruppen var; om de hade haft en gynekologisk cancersjukdom eller fått strålbehandling mot bäckenområdet. De skulle också var födda 1927 eller senare och ambitionen var att få en likartad fördelning av ålder och bostadsort.

Alla dessa kvinnor, över 1 000 stycken, blev uppringda och tillfrågade om de ville delta. De som gav sitt informerade samtycke fick ett frågeformulär per post. Ett par veckor efter det att formuläret skickats ut, skickade vi ett tackkort som samtidigt fungerade som en påminnelse för dem som ännu inte skickat tillbaka formuläret. De som därefter fortfarande inte skickat tillbaka formuläret blev uppringda på nytt och sammanlagt genomfördes över 2 000 telefonsamtal. Efter sju månaders datainsamling hade 616 (78 procent) canceröverlevare och 344 (72 procent) kontroller skickat tillbaka ett ifyllt formulär. Data från formulären matades in i en databas varefter informationen kunde bearbetas statistiskt. Information om behandlingstekniker inhämtades från den medicinska journalen.

Vi kunde lokalisera och återaktivera tidigare strålplaner från 519 (84 procent) canceröverlevare. Genom att markera varje riskorgans anatomiska gränser på de skiktröntgenbilder som togs inför behandlingen, kunde vi mäta bäckenorganens volym och stråldos. Med hjälp av en skriftlig manual som vi gemensamt kommit överens om och i samarbete med röntgenläkare, ritade vi på ett enhetligt sätt ut konturerna av tio riskorgan; ändtarmens slutmuskel, ändtarmen, den S-formade delen av tjocktarmen (sigmoideum), den del av tunntarmen som var belägen i lilla bäckenet, slidan, urinblåsan, korsbenet, blygdbenet samt höger och vänster höftkula. Arbetet med inritningarna var omfattande och tog mer än ett år att slutföra.

Våra resultat visade en medianuppföljningstid på 74 månader (spridning 26 till 179 månader) efter avslutad strålbehandling. Den vanligaste diagnosen var livmoderkroppscancer (59 procent) följt av livmoderhalscancer (23 procent). Majoriteten (90 procent) av canceröverlevarna hade förutom yttre strålbehandling även genomgått operation. De gynekologiska canceröverlevarna rapporterade en högre förekomst av symtom från alla de

normala vävnader som studerats (d v s symtom från ändtarmens slutmuskel, tarmkanalen, urinvägar, bäcken skelettet, nedre delen av buken och ben samt sexuellt relaterade symtom) jämfört med kvinnor från normalbefolkningen. Hälften av canceröverlevarna i studien läckte avföring i samband med avföringsträngningar, jämfört med 12 procent av kvinnorna i jämförelsegruppen. Den högsta relativa risken, 12.7, fann vi för symtomet 'ofrivillig total tarmtömning i kläderna utan förvarning', vilket drabbade 70 av 616 (12 procent) canceröverlevare jämfört med 1 kvinna i kontrollgruppen (0.9 procent). Av de canceröverlevare som rapporterade 'ofrivillig total tarmtömning i kläderna utan förvarning' hade 74 procent nedsatt livskvalitet. Detta symtom hindrade de drabbade kvinnorna att delta i sociala aktiviteter och inverkade på deras sexualliv.

En medelstråldos överstigande 50 Gy till ändtarmens slutmuskel, ändtarmen, sigmoideum och tunntarmen var associerad med symtomet 'ofrivillig total tarmtömning i kläderna utan förvarning'. Om man dessutom tog hänsyn till riskfaktorer för avföringsläckage så var en medelstråldos överstigande 45 Gy till ändtarmens slutmuskel associerad med symtomet. Matematiska beräkningar talar för att dosen till sigmoideum bäst kan förutsäga risken att drabbas av 'ofrivillig total tarmtömning i kläderna utan förvarning'.

Sammanfattningsvis har gynekologiska canceröverlevare en ökad risk att få 'ofrivillig total tarmtömning i kläderna utan förvarning' efter strålbehandling mot bäckenområdet. Detta symtom som inverkar på sexualitet och hindrar sociala aktiviteter är relaterat till medel dosen av yttre strålbehandling till tarmkanalen och ändtarmens slutmuskel. Dosen till sigmoideum kan bäst förutsäga denna risk. Genom att begränsa stråldosen till dessa riskorgan kan detta gravt handikappande symtom förebyggas i framtiden.

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