

**Towards eliminating pelvic bone pain after radiation therapy
among long-term gynecological cancer survivors**

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*Den mätta dagen, den är aldrig störst.
Den bästa dagen är en dag av törst.
Nog finns det mål och mening i vår färd
- men det är vägen, som är mödan värd.*

Karin Boye

ABSTRACT

Aim: To investigate the prevalence of self-reported symptoms after pelvic radiation therapy among long-term gynecological cancer survivors, with special focus on pelvic bone pain, how it affects the daily life of the women and the relationship to absorbed doses.

Methods: In an unselected, population-based study, gynecological cancer survivors from the Gothenburg and Stockholm regions, treated with pelvic radiation therapy between 1991 and 2003, were compared with a non-radiation-treated control population. Data were collected by means of a study-specific, validated, postal questionnaire with 351 questions reflecting symptoms from the pelvic organs including demographics, co-morbidities, psychological and quality-of-life issues. Treatment details were retrieved from medical records, organs at risk delineated on pretreatment scans, and dose-volume histograms exported. We used epidemiological methods for study design and data interpretation.

Results: Among cancer survivors 78 % (616/789) returned a completed questionnaire, among control women 72 % (344/478). Median follow-up was 74 months (26-179 months). Cancer survivors reported a higher occurrence of symptoms from all organ systems studied; the anal sphincter, the bowels, the urinary tract, the pelvic bones, symptoms related to sexuality, and symptoms from lower abdomen and legs. The highest age-adjusted relative risks among all survivors were found for emptying of all stools into clothing without forewarning, relative risk 12.7, and for defecation urgency with an immediate need for a toilet, relative risk 5.7, compared to controls.

Pubic bone pain was reported by 11% (73/637) of all survivors and by 4% (12/339) of the controls. Hip pain was reported by 36% (225/632) of the survivors and sacral pain by 39% (249/633). Hip and sacral pain were common among controls, 33% (113/343) and 52% (179/344), respectively.

Pubic bone pain showed a six-fold increase among survivors who had received radiotherapy as only treatment, a ten-fold increase for pubic bone pain walking indoors and a six-fold increase walking 500 m, compared with controls. Survivors treated with radiotherapy in combination with surgery showed a three-fold increase in pubic bone pain, and a four-fold increase both in pain walking indoors and in pain walking 500 m.

Daily pain from the hips when walking 500 m showed a four-fold increase among survivors treated with radiotherapy as only treatment, and a three-fold increase for daily pain both in hips and sacrum when walking indoors, compared with controls.

Mean absorbed dose to the pubic bone was a significant predictor of pain. The frequency of pubic bone pain among survivors exceeded that of controls for mean absorbed doses at 30 Gy and for hip pain at 37.5 Gy.

Conclusions: Our data suggest that radiation-induced pubic bone pain dominates pelvic bone pain among gynecological cancer survivors treated with radiation therapy. Hip and sacral pain being common among controls illustrates the importance of specifically asking about walking difficulties to single out treatment-related symptoms. Keeping the mean absorbed pubic bone dose below 30 Gy and the hip dose below 37.5 Gy may keep the occurrence of long-lasting pelvic pain among survivors of gynecological cancer at the level of the occurrence reported by non-irradiated women.

Keywords: Pelvic radiotherapy, Gynecological cancer, Pelvic bone pain, Dose-volume response

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SAMMANFATTNING PÅ SVENSKA

Syfte: Att undersöka förekomsten av besvärande symtom efter strålbehandling mot bäcken hos långtidsöverlevare efter gynekologisk cancer, med särskilt fokus på smärta från bäckenbenen, hur det dagliga livet påverkas för kvinnorna samt förhållandet mellan smärta och absorberad stråldos.

Metod: I en oselekterad, populationsbaserad studie identifierades långtidsöverlevande kvinnor som erhållit strålbehandling mot bäcken för gynekologisk cancer mellan 1991 och 2003 i Göteborgs- och Stockholmsregionerna. En kontrollgrupp av kvinnor som inte strålbehandlats rekryterades från det svenska befolkningsregistret. Ett studiespecifikt frågeformulär med 351 frågor utvecklades och validerades. Symtom som rör tarmarnas funktion med fokus på avföringsläckage, urinblåsans funktion, skelettsmärter i rygg och bäcken, lymfödem samt sexuell funktion efterfrågades liksom förekomst av övriga sjukdomar, psykiska besvär, livskvalitet och levnadsförhållanden. Behandlingsinformation hämtades från patientjournaler. Symtomförekomst, frekvens, duration och intensitet rapporterades av den enskilda kvinnan genom att besvara det hemskickade frågeformuläret. För de kvinnor som överlevt sin cancersjukdom och där det var möjligt har vi återskapat behandlingsplanerna och ritat in riskorgan (normalvävnad) i bäckenet; analsfinkter, ändtarm, sigmoideum, tunntarm, urinblåsa, vagina, symfys, höfter och korsben. Information om absorberad stråldos har sammanförts med information från frågeformuläret. Analyser och tolkning har skett med epidemiologisk metodik.

Resultat: Sammanlagt 78% (616/789) bland canceröverlevarna och 72% (344/478) bland kontrollerna skickade tillbaka ett ifyllt frågeformulär. Median uppföljningstid var 74 månader (26-179 månader). Canceröverlevare rapporterade en högre förekomst av symtom från alla studerade organsystem. Den högsta relativa risken bland alla överlevare visade ”tömning av all avföring i kläderna utan förvarning”, 12.7 gånger högre förekomst, samt ”plötsligt påkomna avföringsträngningar som krävt omedelbart toalettbesök”, 5.7 gånger högre förekomst, jämfört med kontroller som inte erhållit strålbehandling. För kvinnor som erhållit enbart strålbehandling var förekomsten av symtom ofta dubbelt så hög som för dem som erhållit strålbehandling som tillägg till kirurgi.

Smärta från symfyssen rapporterades av 11% (73/637) bland de kvinnor som fått strålbehandling jämfört med endast 4% (12/339) bland kontrollerna. Smärta från höften rapporterades av 36% (225/632) och smärta från korsryggen av 39% (249/633) bland överlevarna medan smärta från höfter och korsrygg var vanligt bland kontrollerna, 33% (113/343) respektive 52% (179/344).

Smärta från symfyssen visade en sexfaldig ökning bland överlevare som erhållit enbart strålbehandling och en trefaldig ökning bland dem som erhållit strålbehandling i kombination med kirurgi jämfört med kontroller. Smärta från symfyssen vid gång inomhus var tio gånger vanligare och smärta vid gång 500 m fyra gånger vanligare efter enbart strålbehandling

jämfört med kontroller. Efter strålbehandling i kombination med kirurgi var förekomsten av smärta fyra gånger ökad både vid gång inomhus och vid gång 500 m.

Daglig smärta från höfterna vid gång 500 m visade en fyrfaldig ökning samt daglig smärta från både höfter och korsrygg vid gång inomhus visade en trefaldig ökning för de som erhållit enbart strålbehandling jämfört med icke strålbehandlade kontroller.

Absorberad stråldos mätt som medeldos var en signifikant orsaksfaktor till smärta från symfyssen. Medeldosen där frekvensen smärta bland överlevarna skiljer sig från kontrollerna var 30 Gy för symfyssen och 37.5 Gy för höfterna. För korsbenet fann vi inte någon motsvarande dosnivå.

Slutsats: Våra data tyder på att vid smärta från symfyssen efter strålbehandling för gynekologisk cancer är strålning den dominerande orsaken till långvariga besvär. Eftersom smärtor från höfter och korsrygg är vanligt bland kvinnor i normalbefolkningen som inte erhållit strålbehandling måste man här fråga specifikt efter gångsvårigheter på grund av smärta från höfter eller korsrygg för att identifiera strålbehandlingsrelaterade symtom. Genom att hålla medeldosen till symfyssen under 30 Gy och till höfterna under 37.5 Gy kan man sannolikt begränsa förekomsten av långvarig smärta hos canceröverlevare till samma nivå som för normalbefolkningen.

LIST OF PUBLICATIONS

This thesis is based on the following papers, referred to in the text by their Roman numerals:

- (1) **Waldenström AC***, Alsadius D*, Pettersson N, Johansson KA, Holmberg E, Steineck G, Müller M. Variation in position and volume of organs at risk in the small pelvis. *Acta Oncol.* 2010;49(4):491-9.
*contributed equally
- (2) Lind H, **Waldenström AC**, Dunberger G, al-Abany M, Alevronta E, Johansson KA, Olsson C, Nyberg T, Wilderäng U, Steineck G, Åvall-Lundqvist E. Late symptoms in long-term gynecological cancer survivors after radiation therapy: a population-based cohort study. *Br J Cancer.* 2011;105(6):737-45.
- (3) **Waldenström AC***, Olsson C*, Wilderäng U, Dunberger G, Lind H, al-Abany M, Palm Å, Åvall-Lundqvist E, Johansson KA, Steineck G. Pain and Mean Absorbed Dose to the Pubic Bone After Radiotherapy Among Gynecological Cancer Survivors. *Int J Radiat Oncol Biol Phys.* 2011;80(4):1171-80.
*contributed equally
- (4) **Waldenström AC**, Olsson C, Wilderäng U, Dunberger G, Lind H, Alevronta E, al-Abany M, Tucker S, Åvall-Lundqvist E, Johansson KA, Steineck G. Relative Importance of Hip and Sacral Pain Among Long-term Gynecological Cancer Survivors Treated with Pelvic Radiotherapy and their relationships to Mean Absorbed Doses. *Int J Radiat Oncol Biol Phys.* 2012;84(2):428-36.

ABBREVIATIONS

2D	Two-dimensional
3D	Three-dimensional
3D-CRT	Three-dimensional conformal radiotherapy
CI	Confidence interval
CT	Computed tomography
DVH	Dose volume histogram
EBRT	External beam radiation therapy
Gy	Gray, the SI-unit for absorbed radiation dose (1 Gy = 1 Joule/kg)
HDR	High dose rate
IMRT	Intensity-modulated radiation therapy
Ir	Iridium
ICRU	International Commission on Radiation Units
LQ	Linear quadratic
MRI	Magnetic resonance tomography
MLC	Multi leaf collimator
MV	Megavolt
OAR	Organ at risk
RR	Relative risk
RT	Radiotherapy
TPS	Treatment planning system
VMAT	Volumetric Modulated Arc Therapy

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1. INTRODUCTION

Pelvic pain after treatment for a gynecological malignancy will always bring up the ghost of recurrence. The access to diagnostic tools like CT and MRI will help to ease the mind although the pain remains. In my clinical work I have been struck by the number of patients diagnosed with pelvic insufficiency fractures after treatment with pelvic radiation. Going through the clinical charts there was a period of pain preceding the diagnosis of fracture and the pain was not always restricted to the areas visually affected on the diagnostic images.

The reported percentage of pelvic insufficiency fractures among gynecological cancer survivors varies between 0.5% and 89%, depending on the diagnostic methods available, the follow-up time, and whether the study was performed retrospectively or prospectively [1-11]. Pain often precedes the radiological findings of pelvic insufficiency fractures and radiologically documented healing has been found to correlate with disappearance of pain [4, 8, 12]. The pain may present within one year after completion of radiotherapy [3, 5, 6, 12] and can be severe enough to impair walking ability [9]. Pain duration up to three years has been reported [9]. The extent to which pain affects other aspects of daily life has been little described.

Several investigators have documented a relationship between pain and pelvic insufficiency fractures [1, 3-7, 10, 12, 13]. Absorbed doses around 50 Gy to the sacrum and sacroiliac joints, estimated from prescribed doses to the tumor, have been associated with the development of pelvic insufficiency fractures [1, 5, 10, 13]. However, there have been no studies of the relationship between absorbed doses to the pelvic bones, estimated from more detailed dose data, and pain among long-term survivors.

Acknowledging the association between pelvic bone pain after radiation treatment and the presence of pelvic insufficiency fractures, we looked under the tip of the iceberg (Figure 1).

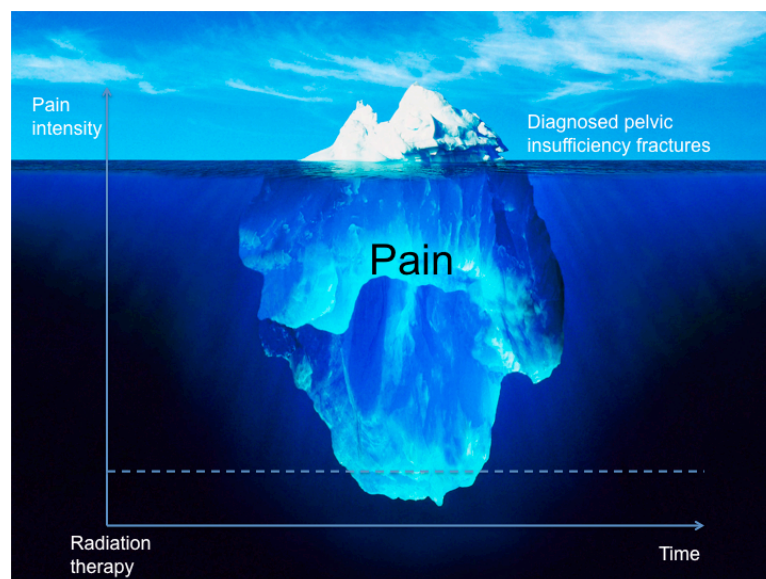


Figure 1. Iceberg: roughly 1/9 above water - small manifestation of a larger problem.

2. AIM

This work is part of a larger study where the overall aim was to investigate the prevalence of self-reported symptoms from normal tissues in the pelvic region after radiation therapy for gynecological cancer among long-term survivors. A second aim was to study relationships between pelvic bone doses and the occurrence of pain and specific symptoms affecting daily life of the surviving women. Here pelvic bones refer to the pubic bone, the hip bones and the sacrum.

My specific aims are:

- I** To provide a framework for the delineation procedure of normal tissues in the pelvis before undertaking the more extensive task of delineating organs at risk in two large cancer survivor cohorts, and also in this setting to obtain some information about the movements of the pelvic organs based on both men and women. *Paper I*

- II** To collect information on self-reported symptoms, clinical characteristics and treatment details for long-term gynecological cancer survivors previously treated with pelvic radiation and compare the occurrence of pelvic bone symptoms among survivors with non-radiation treated control women from the general population. *Paper II*

- III** To explore the occurrence of pain from the pelvic bones among long-term survivors treated with radiation therapy for gynecological cancer, the effect of pain on daily life, and how it relates to the absorbed doses in these organs. *Paper III+IV*

3. BACKGROUND

3.1 Gynecological Cancer

Gynecological cancer constitutes 10 percent of all female cancers in Sweden, with an incidence of approximately 2850 cases per year [14]. In 2011 endometrial cancer was the most common diagnosis (1431) followed by ovarian cancer (626), cervical cancer (421), vulvar cancer (146), uterine sarcoma (102), fallopian tube cancer (50) and vaginal cancer (36) (Figure 2). Gynecological cancers are staged according to the International Federation of Gynecology and Obstetrics (FIGO) [15-17].

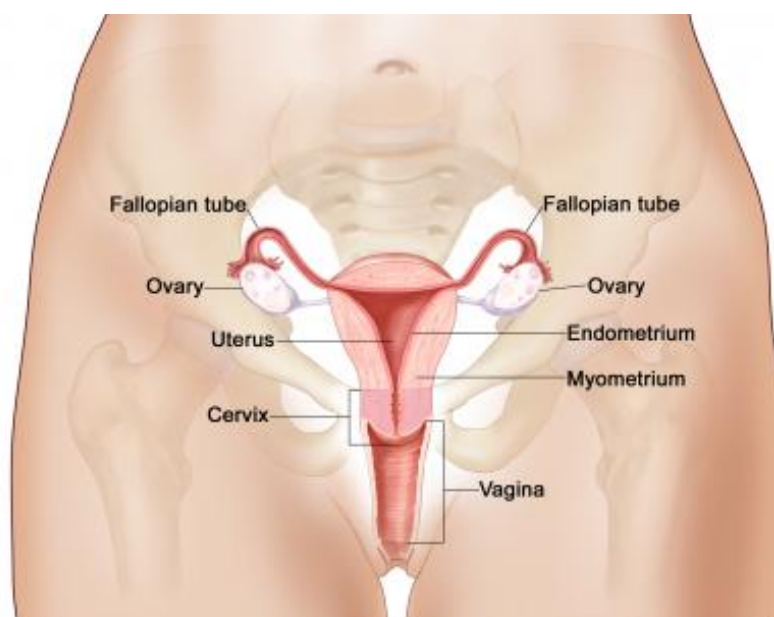


Figure 2. Female pelvic organs.

Endometrial cancer

Endometrial cancer is the most common gynecological cancer in Europe [18]. In Sweden it is the sixth most common cancer among women with an incidence of approximately 1400 new cases per year [14]. Endometrial cancer often presents with a vaginal bleeding and is usually diagnosed at an early stage when the tumor is still limited to the uterus. The 5-year age-standardized relative survival was 83 percent for women diagnosed between 1999 and 2003 in Sweden [19].

The standard treatment has been primary surgery with hysterectomy and bilateral salpingo-oophorectomy. Lymphadenectomy has not been performed routinely until recently. Adjuvant radiotherapy in the form of external beam radiation therapy combined with brachytherapy has been widely used in Sweden for patients with stage I. Patients with a more advanced stage of disease have often received a combination of surgery, chemotherapy and radiotherapy.

According to a new Swedish national treatment program for endometrial cancer lymphadenectomy will be performed on early stage endometrial cancer in patients with a preoperative high-risk profile, followed by adjuvant chemotherapy. Radiotherapy will be added for certain risk groups.

Ovarian cancer and fallopian tube cancer

Ovarian cancer is the second most common gynecological cancer in Europe [18]. In Sweden the incidence in 2011 was 625 ovarian and 50 fallopian tube cancers. The symptoms of ovarian cancer are non-specific and most patients with early stage of disease are asymptomatic resulting in more advanced disease at diagnosis.

Ovarian and fallopian tube cancers are surgically staged according to the FIGO classification. Primary treatment consists of cytoreductive surgery including hysterectomy, bilateral salpingo-oophorectomy and omentectomy aiming at macroscopic complete resection [20]. Postoperative chemotherapy with paclitaxel and carboplatin is given as standard treatment [21]. Difficulties due to a late diagnosis and the frequent development of chemoresistance make the prognosis poor, with a relative survival of 44 per cent for women diagnosed between 2005 and 2009 in Sweden [14]. Whole abdominal radiation is rarely used nowadays due to severe late side effects [22] but consolidation treatment for local tumors may benefit the patient.

Cervical cancer and vaginal cancer

Globally cervical cancer is the most common gynecological cancer and the second main cause of cancer death among women in the developing countries [23]. In Sweden, the incidence of cervical cancer has decreased by more than fifty per cent after organized screening programs was introduced in the 1960's, resulting in 421 new cases registered in 2011. For patients diagnosed with cervical cancer between 1999 and 2003 the 5-year age-standardized relative survival for all stages was 65 percent [19].

The FIGO-staging of cervical cancer is based on clinical evaluation [15, 17]. Lymph node status is not taken into account for staging but is a strong prognostic factor considered in the treatment planning.

Microinvasive cervical cancer is usually cured by cone biopsy, trachelectomy, or simple hysterectomy. Early stage cervical cancer has been treated with radical hysterectomy and pelvic lymph node dissection or radiotherapy, depending on local tradition and size of the tumor. For locally advanced cervical cancer radiotherapy with concomitant chemotherapy in the form of weekly cisplatin infusions is the standard treatment.

The main etiological factor for cervical cancer is a persistent infection with high-risk human papilloma virus (HPV). New available vaccines against 70 percent of the viruses have the

potential to reduce the number of cervical cancers and together with a well-functioning screening activity the incidence of cervical cancer can be minimized or detected at an early stage.

Vaginal cancer is closely linked to cervical cancer and HPV-infections. The incidence in Sweden was 36 in 2011. The 5-year overall survival in vaginal cancer is 54 per cent [24]. Radiotherapy is the primary treatment, either as single treatment or in combination with surgery or chemotherapy.

Vulvar cancer

The incidence of vulvar cancer in Sweden was 146 in 2011 [14]. This disease develops along two separate pathways. The first is associated with a high-risk HPV infection and usually occurs in younger women. The second is associated with lichen sclerosus or squamous cell hyperplasia. The five-year overall survival in stage I is close to 80 percent but poor for advanced and recurrent disease [25].

Treatment has moved from radical vulvectomy with bilateral inguino-femoral lymphadenectomy to a more individualized approach taking the size and position of the tumor into account. Early-stage vulvar cancer can be treated using the sentinel node technique and local excision [26]. For patients with advanced stages definitive radiotherapy is preferred, if possible together with concurrent chemotherapy.

Uterine sarcoma

Uterine sarcoma is a rare but an aggressive form of uterine malignancy and approximately 100 cases per year are diagnosed in Sweden. The diagnosis is often made after surgery with hysterectomy and bilateral salpingo-oophorectomy. The role of adjuvant pelvic radiotherapy is unclear although studies suggest improved local control but no improvement in disease-free or overall survival [27]. The disease-specific 5-year survival varies between 49 and 56 percent depending on histological type and stage [28].

3.2 Radiation therapy

Radiation therapy has been used for more than a hundred years in the treatment of gynecological cancer. Ionizing radiation can damage the DNA of the cells directly, and also by the creation of free radicals within the cells that in turn damage the DNA. There are two major types of treatment, external beam radiation therapy (EBRT) and brachytherapy (BT). The response to different fractionation schemes for both normal and tumor tissues can be mathematically described by the linear-quadratic (LQ) model [29, 30].



Figure 3. Linear accelerator used in external beam radiation therapy.

External beam radiation therapy

External beam radiation therapy is widely used, either as only treatment (definitive radiotherapy) or after surgery (adjuvant), and sometimes before surgery (neoadjuvant, in order to increase operability). Chemotherapy may be added concomitantly or after radiotherapy, chemotherapy before radiotherapy is not commonly used today. Linear accelerators (Figure 3), usually with photon energy of 6 to 20 MV, are used for delivering the radiation dose, which is prescribed, recorded and reported according to recommendations by International Commission on Radiation Units and Measurements [31]. The total dose is divided into fractions, usually given once a day for five days a week. The total treatment time varies between five to seven weeks depending on diagnosis and treatment intention. Absorbed radiation dose is expressed in Gy and daily fractions around 2 Gy are common. In clinical practice the three-dimensional (3D) dose distribution from the treatment planning system is viewed by using a 2D dose-volume histogram (DVH).

Imaging techniques like Computerized Tomography (CT), Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET) facilitate the identification of the clinical target volume (CTV) and the critical normal tissues surrounding the tumor, the organs at risk (OARs) [32]. Pre-treatment CT-scans are incorporated into computerized treatment-planning systems to enable the definition of 3D-volumes of interest and the calculation of absorbed doses in these volumes. Delineations of tumor volumes (targets) include extra margins to compensate for subclinical tumor extension, organ movements and uncertainties in positioning of the patient (set-up). The treatment plan is then transferred to the linear accelerator where the multi leaf collimator (MLC) (Figure 4) is used to shape the treatment fields according to the treatment plan. MLCs have replaced the manually placed customized lead blocks used earlier (Figure 5).

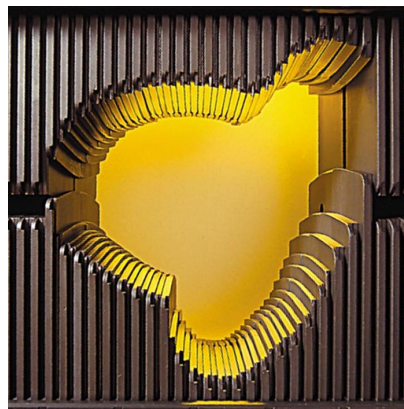


Figure 4. Shaping of treatment field using multi leaf collimator.

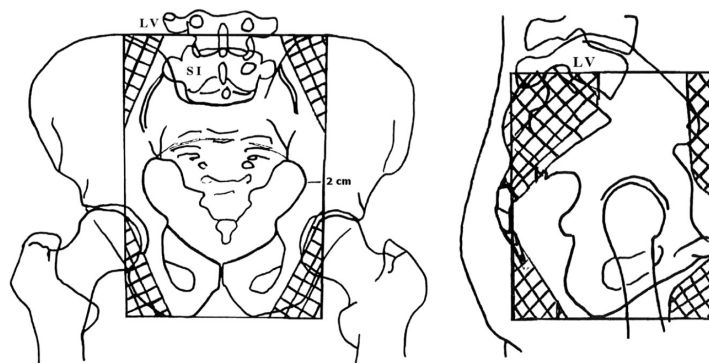


Figure 5. Shaping of treatment fields using lead blocks.

For the pelvic area a four-field box technique has commonly been used (Figure 6). Today the dose distribution can be further improved by IMRT (Intensity Modulated Radiation Therapy) or VMAT (Volumetric Modulated Arc Therapy) which use non-uniform beam intensities to enable the shaping of more conformal isodose distributions (Figure 7) [33]. Accurate immobilization of the patient and repeated image-guided controls of the patient positioning during the whole treatment are necessary to ensure good treatment quality.

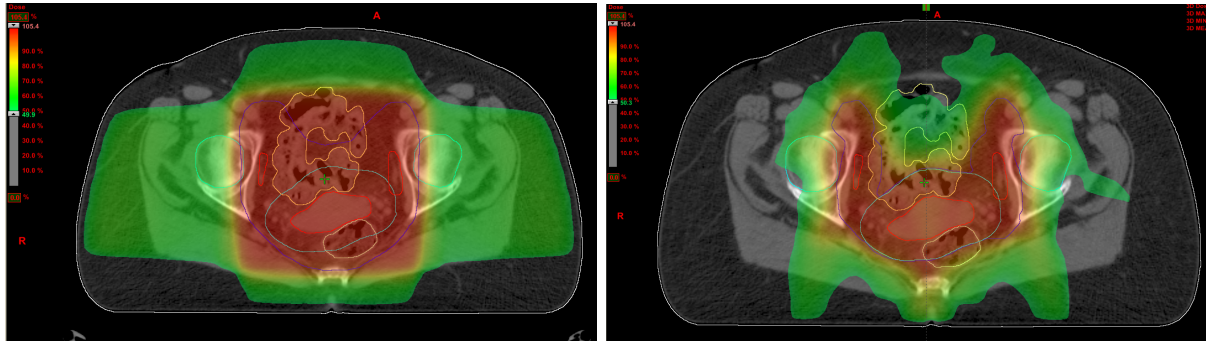


Figure 6 (left). Dose distribution using a “four-field box technique” in the treatment of gynecological cancer. **Figure 7** (right). Dose distribution using IMRT-technique for the same patient as in figure 6.

Brachytherapy

In brachytherapy (brachy = Greek for short distance) the radioactive source is placed inside a hollow organ (intracavitary) or directly in the tumor (interstitially). The primary advantage is the rapid dose fall-off outside the high-dose region resulting in less volume of normal tissue being irradiated. One commonly used radionuclide today is Iridium¹⁹². For the treatment of gynecological malignancies, brachytherapy can be delivered both at a high dose rate (HDR) and at a low dose rate (LDR) and the treatment times may vary from minutes to hours. An applicator is placed in the patient and a remote afterloading system is used to place the source at different positions in the applicator. The optimal dose distribution is created by optimizing the dwell times in the different positions (Figure 8).

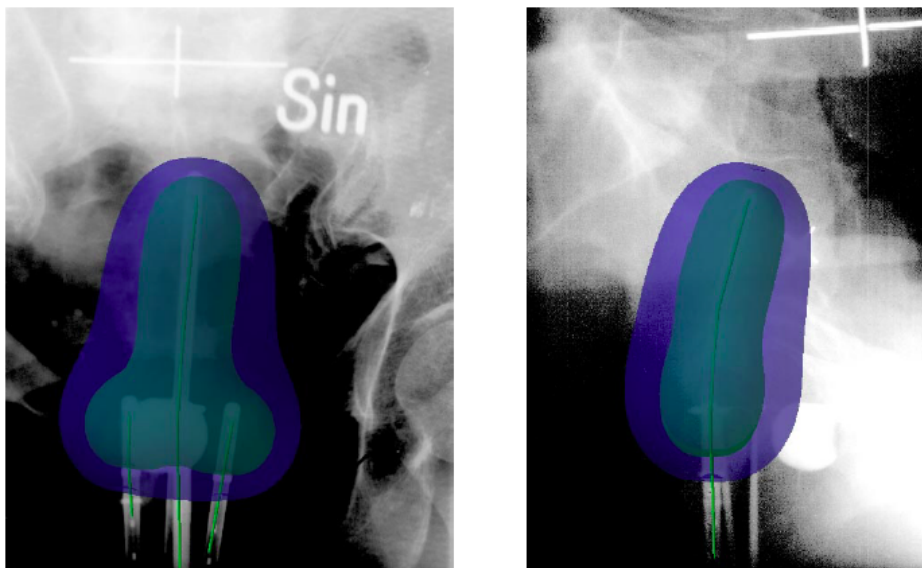


Figure 8. Brachytherapy applicators in place showing the 100% (green) and 50% (purple) isodoses, frontal and lateral views.

3.3 Organs at risk

The female reproductive organs are surrounded by the urinary bladder, the anal sphincter, the rectum, the colon, the small intestines, and the pelvic bones (Figure 9, Figure 10). They form organs at risk and should receive as little unwanted radiation dose as possible.



Figure 9. Organs at risk: anal sphincter (green), rectum (light green), sigmoid (orange), small intestines (yellow), bladder (blue), vagina (pink), pubic bone, femoral heads and sacrum (white). Frontal and lateral views are shown.

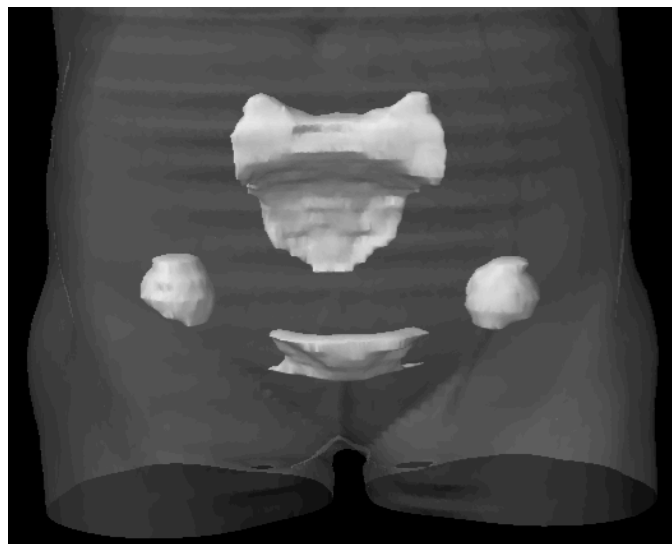


Figure 10. The pelvic bones: The pubic bone, the femoral heads and the sacrum.

3.4.1 Radiation-induced side effects in normal tissues

The degree and extent of symptoms reflecting radiation-induced side effects depend on treatment-related factors such as total dose, dose per fraction, fractionation schedule, total treatment time, irradiated volume and type of radiation. Patient-related factors like age, comorbidity, and genetic radiation susceptibility as well as additional treatment modalities like surgery or chemotherapy given sequentially or concomitantly may worsen the normal tissue injury [34-36]. Also the functional reserve and the structural organization of an irradiated organ are important [37]. In an organ with serial organization, e.g. the spinal cord, a high dose to a very small volume can result in tissue injury. In this case the maximum organ dose is the critical parameter. In an organ with parallel organization, e.g. the kidneys, the averaged dose to the whole volume of the organ is related to tissue injury. Tumor factors like histology, size, stage, and grade influence the treatment related factors.

Acute side effects emerge during or shortly after radiation treatment and are most pronounced in tissues with high cell turnover like the gastrointestinal tract or the skin [38, 39]. They are expected to subside within three months. Symptoms still persisting or appearing more than three months after completing radiation treatment many cite as late side effects [38, 40]. While early radiation effects may be transient, late effects tend to be irreversible and may even be progressive [41]. Association between late radiation effects and the severity of the acute reaction in the same tissue, even after a symptom-free period, have been described. There are both experimental and clinical evidence for a consequential component of chronic radiation effects in tissues like the gut, urinary bladder and oral mucosa where the acute mucosal radiation response is associated with a breakdown of a superficial protective barrier [42, 43].

In the soft tissue, irradiation leads to acute vascular changes within 24 hours. Reactive oxygen species (ROS) acts directly on DNA, resulting in tissue injury including endothelial cell damage, increased permeability, edema, and fibrin accumulation [44, 45]. An inflammatory response including macrophage activation, release of cytokines, and increased oxygen consumption leads to vascular injury and hypoxia. Activation of cytokines like transforming growth factor β (TGF β) leads to fibrosis and impaired function in blood and lymph vessels. Additional hypoxia leads to chronic radiation-induced injury. Abnormal microenvironmental conditions exist long after radiation treatment is over and will perpetuate the tissue damage [34].

Radiation-induced “osteitis” was first described by Ewing 1926 as a reduction in bone vasculature after endarteritis and periarteritis [46]. Swelling and vacuolization of the endothelial cells lead to loss of vascularization resulting in sclerotic connective tissue and development of fibrosis. Besides damaged vasculature, radiation increases osteoclast activity within bones alongside with reduction in osteoblast numbers and function which result in bone resorption and atrophy [47]. This lowers both the generation of mature bone and impairs

bone mineralization. A reduced turnover rate also enhances the risk of osteoporosis (Figure 11).

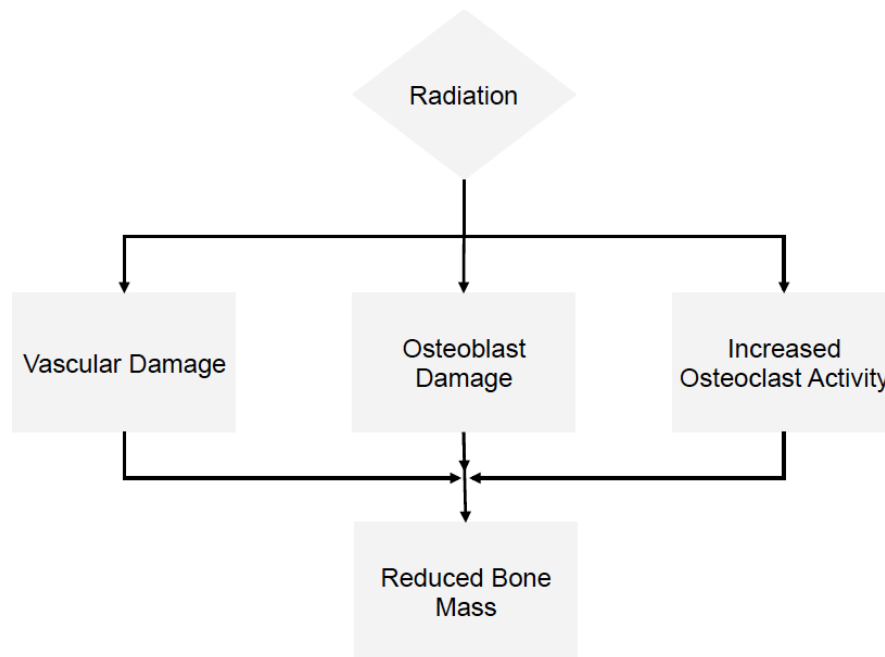


Figure 11. Suggested causes for reduction in bone mass following irradiation.

Demineralization of bone and loss of trabecular number have been described earlier [48, 49]. Reduction in bone mass is dependent on several factors, including treatment-related factors like irradiated volume, dose per fraction [50], total dose [51], and age of the patient [49, 52]. Recovery may occur from repopulation of inhabitant mesenchymal stem cells or repopulation from the systemic circulation [53]. Other factors affecting the vascular supply to the bone, e.g. hypertension, diabetes mellitus, and arteriosclerosis, will increase the risk of fractures after radiotherapy [54].

With an increasing number of younger women surviving after radiation treatment there is an increased cumulative risk for late side effects [55-57]. Also the risk of radiation-induced secondary malignancies motivates long-term follow up. Radiation has been described as a “two-edged sword”, being a major modality for the treatment of cancer but at the same time it can be the cause of cancer. It takes large studies to show a statistically significant, though very small, increase in the risk for second malignancies, especially in long term survivors. The increased risk becomes greater with time [58].

Moving from 3D-conformal radiotherapy to intensity-modulated radiation therapy (IMRT) involves a larger volume of normal tissue being exposed to lower doses. Increase in monitor units for IMRT will increase the dose outside the boundary of the primary collimator due to both leakage and scattered radiation. Compared with 3D-CRT an additional 0.75 percent of the surviving population has been estimated to develop a second malignancy due to the change to IMRT [59].

3.4.2 Pelvic bone pain

Hip, back or groin pain, or sciatica following radiation treatment have usually been attributed to conditions such as arthritis or disc disease which might have underestimated the incidence of radiation-induced pelvic bone complications significantly [60]. MRI has a higher sensitivity in detecting ischemic damage and subsequent pelvic insufficiency fractures compared to plain radiographs and CT. Pelvic insufficiency fractures (PIF) have the same location as traumatic fractures - in the major weight-bearing structures of the pelvic girdle [3].

In a retrospective study of 510 cervical cancer patients treated with radiotherapy the cumulative 5 -year incidence of PIF diagnosed using MRI was 45%. The median time for diagnosis was 17 months (range 1-87 months) after radiotherapy [7]. Pelvic pain had developed in 43% of the patients and lasted from 1 to 32 months. Multiple fractures were diagnosed in 61%, and 85% had sacral involvement. In another retrospective study among 300 American women treated with definitive radiotherapy for cervical cancer the pelvic fracture rate was 10%, the median time to fracture was 14 months (range 2-63 months) [11]. (2010). Nearly half of the patients were symptomatic and pain was in all but one the presenting symptom. The most common fracture site was the sacrum. The fractures were diagnosed within two years for 83% of the patients. However, the imaging was not performed consistently and the follow-up was limited, making the true complication rate uncertain.

Pain often precedes fractures and healing correlates with disappearance of pain [4, 12]. Latency from onset of pain to fracture of 2.5 months (range 1-10) has been reported [12]. This is consistent with older findings of symptoms generally developing before the appearance of roentgenographic evidence of necrosis or fracture [61].

The prognosis is good but the insufficiency fractures will heal more slowly than fractures involving normal bone. Pain-free independent walking at an average of 11 months (range 4-24) has been reported [62]. Different sites of fracture may have a different healing time, sacral fractures heal fairly quickly while pubic fractures may have a protracted course [63].

4. MATERIAL AND METHODS

4.1 Study population

Paper I

We identified 17 patients, ten men treated for prostate cancer and seven women treated for gynecological malignancies, who had received pelvic radiotherapy as primary treatment and who, in addition to the pre-treatment CT scan, CT 1, had a second CT scan, CT 2. The second CT-scan was made due to dose-escalation to a smaller target volume in the male patients and for the women the reasons differed; addition of a para-aortic field (2), the first CT did not cover the planned target volume (3) or dose-escalation to a smaller target (2). All patients were scanned in the supine position and a knee-cushion was used for immobilization of the pelvis. Intravenous contrast was administered to visualize the posterior bladder wall. No standardized instruction regarding bladder filling was given over the studied time period, nor was there any specific routine regarding emptying of the rectum. The radiotherapy was given between 1997 and 2005 at Sahlgrenska University Hospital in Gothenburg, Sweden.

Paper II, III and IV

A cohort of 1800 women treated with external pelvic radiation therapy alone or in combination with surgery for a gynecological malignancy was identified. The women were consecutively treated between February 1991 and December 2003 at Radiumhemmet, Karolinska University Hospital in Stockholm or at Jubileumskliniken, Sahlgrenska University Hospital in Gothenburg. At follow-up in January 2006, 789 survivors (Stockholm n=595 and Gothenburg n=194) met the eligibility criteria, i.e. born 1927 or later, being able to read and understand Swedish and not having or having had recurrent disease. Medical records were reviewed to confirm the cancer diagnosis, stage of disease and treatment techniques regarding surgery, radiation therapy and chemotherapy. The eligible survivors were invited to take part in a study investigating symptoms after pelvic radiation therapy for gynecological cancer using a study-specific questionnaire (section 4.2). Of these, 616 (78 %) returned a completed questionnaire and participated in **Paper II**.

In **Paper III and IV** different eligibility criteria were used. Survivors who had had a recurrence after primary surgery for early-stage disease and successfully had been treated with radiation therapy and thereafter followed for a minimum of three years, and were without a new recurrence, were included. This added 34 to the 616 survivors in paper II, giving 650 survivors who returned a completed questionnaire. For these survivors, 538 dose-volume histograms over the pubic bone could be retrieved and were used for the analyses in paper III. For the analyses in paper IV, we were able to retrieve 358 dose-volume histograms over the sacrum, right hip and left hip.

We also recruited 478 women from the Swedish Population Registry, matched for age and residency, in order to provide corresponding symptom rates among non-radiation-treated

individuals (background rates). An error in the matching procedure led to a younger control population (median age 57.5) compared to the cancer survivors (median age 66.0) and this was adjusted for in the statistical analyses.

4.2 Questionnaire

The study-specific questionnaire used in papers II-IV was developed to investigate symptoms among long-term gynecological cancer survivors after pelvic radiotherapy. The qualitative phase was based on semi-structured in-depth interviews with 26 gynecological cancer survivors previously treated with pelvic radiotherapy. When no further information could be extracted a questionnaire was constructed consisting of 351 questions covering symptoms from the gastrointestinal tract, urinary bladder, genitals, pelvic bones, abdomen and legs. The women were asked to assess the occurrence of symptoms during the previous six months using a person-prevalence or a person-incidence scale. Besides questions relating to symptoms from the different organ systems they were asked about demographic characteristics, information concerning disease and treatment, quality of life, and physical health. The final version was validated face-to-face using women within the study population to ensure that the questions were correctly understood. Participation rate and rate of missing values were tested in a pilot study. The questionnaire was also validated face-to-face with non-radiation-treated women.

For information about pain from the pelvic bones, 39 questions dealt with information about intensity, quality, frequency, and duration of pain, along with other physical symptoms originating from the pelvic bones. Nine questions were specifically related to the pubic bone and the anatomical region was illustrated by a picture. Nine questions accompanied by a picture of the hip bone regions were specifically related to symptoms from the hips. Similarly, nine questions accompanied by a picture of the sacral region were related to symptoms from the sacrum (Figure 12).

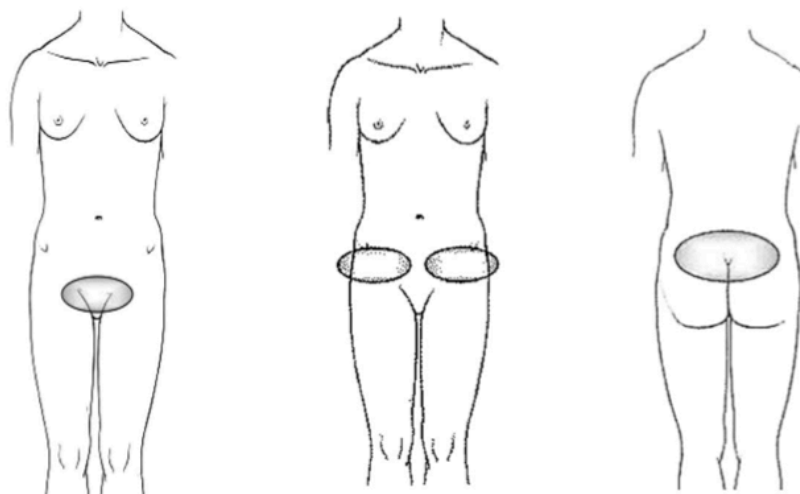


Figure 12. Illustrations of the anatomical regions accompanying the questions about pain from the pubic bone, the hips and the sacrum.

Pain from the pubic bone was assessed by asking “Have you had pain in your pubic bone after completion of radiotherapy?” Women answering “Yes, I have had pain in my pubic bone, but I am free of pain today” or “Yes, I still have pain in my pubic bone” were defined as having or having had pubic bone pain. Impact on daily life was measured by asking how the pain in their pubic bone had affected sleep, ability to walk indoors or to walk 500 m. The response alternatives were “No”, “Yes, occasionally”, “Yes, at least monthly”, “Yes, at least weekly”, “Yes, at least three times a week” or “Yes, at least once a day”. Pain from the hips and pain from the sacrum were assessed similarly.

The women in the control population were asked about the same symptoms but were defined as affected if having pain, or having had pain during the past six months since they had not been exposed to radiation therapy.

4.3 Contouring of organs at risk

Paper I

The seven organs at risk investigated were the sigmoid, the distal 4 cm of the sigmoid, the rectum, the anal sphincter, the urinary bladder, the penile bulb, and the cavernous bodies (intracorporeal parts). The distance between adjacent CT-slices was 5 mm for 15 of the patients and 7 mm for two of the women.

When delineating the organs we followed the outer border of the structure where this was possible. Where the CT scan was suboptimal for proper visualization of the structures, interpolation between adjacent slices was made. In the CT slices where it was difficult to differ between the sigmoid colon and the small intestine, we were helped by the second scan, and also by clinical experience. The organs at risk were delineated by two oncologists, myself and David Alsadius, reaching consensus on the outlining in all cases to keep variations of delineation due to interpersonal bias to a minimum. The two CT scans of the same patient were not blinded. The organ delineations were confirmed by a senior radiologist (Marcus Müller).

Paper II, III and IV

Ten organs at risk were identified; the anal sphincter, the rectum, the sigmoid, the small intestines, the urinary bladder, the vagina, the pubic bone, the right and left femoral heads, and the sacrum. Available treatment plans were retrieved in the treatment planning systems and the organs at risk were contoured on pre-treatment CT scans taken with 5-20 mm slice thickness. The dose distributions in these ten organs were then calculated. Consistent contouring was assured by using written guidelines including pictures (Table 1). Only two persons at each clinic performed the contouring under the supervision of myself in Gothenburg and Helena Lind in Stockholm.

Anal sphincter	inner muscle layer of the sphincter up to the anal verge
Rectum	outer contour (including filling) - lower limit: the anal verge - upper limit: the recto-sigmoid junction
Sigmoid	outer contour (including filling) - lower limit: where the rectum deviates from its mid-position - upper limit: transition into colon descendens in the left iliac fossa (the same position in two consecutive CT-slices)
Small intestines	outer contour, delineated as continuous islands when appropriate - upper limit: level of caudal part of left and right SI-joints - lower limit: as far as there is visible small intestines
Urinary bladder	outer wall (including filling) - make sure to include the lower part
Pubic bone	delineate the symphysis and reach laterally including the anterior parts of the superior and inferior rami (see pictures) - upper limit: 1 cm above visible symphysis - lower limit: 1 cm below visible symphysis
Vagina	an approximation (impossible to visualize vagina on CT) - "an oval" is delineated, 3 cm wide and 1 cm deep, between the rectum and bladder - upper limit: if visible or metal marker in the vaginal vault - if not at the level of the pelvic cavity or the upper pubic symphysis - lower limit: the vulva
Right + Left femoral heads	delineate the head, make sure the whole volume is included (exclude the neck)
Sacrum	the body of the sacrum (exclude the dorsal spinal processes and the coccyx)

Table 1. Definitions for delineation of pelvic organs at risk in paper II-IV.

4.4 Radiotherapy

Paper II-IV

Cancer treatment was administered according to local treatment programs and applied study protocols that were in use at the time of treatment.

External beam radiation therapy was usually delivered with a four-field box technique according to a template or individually CT-planned using 15-18 MV to 39.6-65.0 Gy at 1.5-2.0 Gy per fraction to the ICRU prescription point. Absorbed doses to the pubic bone, sacrum, right hip and left hip for each patient were calculated and exported as dose-volume histograms using the Cadplan, Eclipse (VARIAN, Palo Alto, California, USA) or TMS (Nucletron, Veenendaal, The Netherlands) treatment planning systems. The DVH was normalized to the total volume of each OAR (relative volume) except for the small intestines which were measured by the absolute volume. The mean and maximum absorbed doses for external beam

radiation to each organ at risk were calculated. For analyses regarding the hips, we used the dose-volume histogram pertaining to the one hip with the highest mean dose.

Brachytherapy was prescribed and delivered according to local practice and did not include complete 3D-brachytherapy dose information. We therefore estimated the brachytherapy dose distribution to the pubic bone, hips and sacrum for five randomly selected cervical cancer patients treated to a total BT dose of 12 Gy at 4 Gy per fraction. The orthogonal radiographs were matched with the patients' external beam CT planning scans according to the bony structures of the pubic bone and the sacrum using the Eclipse treatment planning system. The dose contribution from the brachytherapy to the pelvic bones was then calculated. Total mean and maximum doses to the pubic bone for all fractions were 1.4 ± 0.4 Gy and 2.4 ± 0.9 Gy, respectively. Corresponding doses for both hips were 0.8 ± 0.2 Gy and 1.5 ± 0.4 Gy; for sacrum 0.9 ± 0.2 Gy and 1.8 ± 0.6 Gy, respectively. We excluded the brachytherapy dose contribution in our analyses.

4.5 Statistical analyses

In **paper I** the variation in position was measured as the absolute difference of extreme points compared to a reference point of each organ at risk in two consecutive CT-scans (Figure 13).

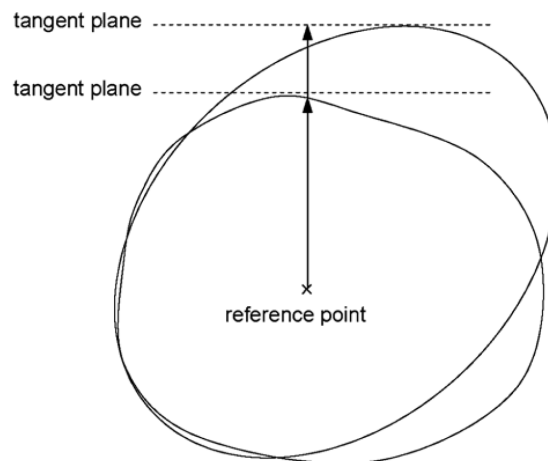


Figure 13. The variation in position measured as the absolute difference of extreme points.

The volume of each organ was calculated by the radiotherapy planning system. The relative overlap was calculated by dividing the overlap volume by the smaller volume (Figure 14).

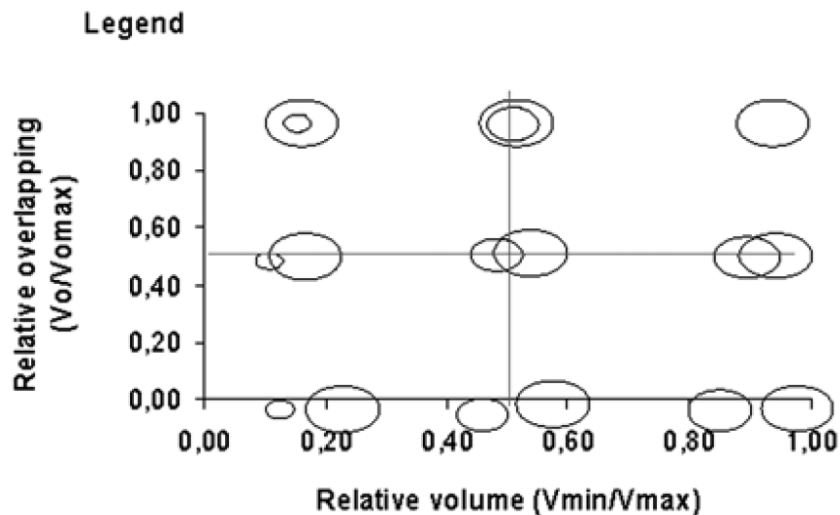


Figure 14. Diagram displaying the relative volume and the overlapping of two volumes.

In **paper II-IV** the answers from the questionnaire and data from the medical records were coded and transferred to the freeware data entry program Epi-data (www.epidata.dk). To describe the frequency of symptom occurrence data were dichotomized as a binary endpoint. The alternatives were “No”(not having the symptom), “Yes, occasionally”, “Yes, at least once a month”, “Yes, at least once a week”, “Yes, at least three times a week” and “Yes, at least once a day”. Cut-off level for each question was chosen to balance clinical relevance and background noise.

Generally the time frame was “during the past six months” for all questions both to survivors and control women. An exception was made for the questions concerning pain from the pubic bone, hips or sacrum in the questionnaire sent to the survivors. Here we asked for pain after completion of radiotherapy. We calculated the proportions having each outcome (symptom) among cancer survivors and control women, and used the relative risk (RR) defined as the ratio between these proportions as outcome measure. Using relative risk as an effect measure is a more intuitive and understandable way of illustrating the clinical effect of a certain treatment for a clinician. Variables reflecting potential confounders that could affect the occurrence of a studied symptom, e.g. age, Body Mass Index (BMI) or co-morbidities, were included in the statistical models to produce adjusted prevalence ratios. For this we used log-binomial regression models with 95 percent confidence levels.

As descriptive statistics we report mean values and standard deviations but also medians and ranges when suitable. Potential differences between two groups were considered using a two-sided P value, and a P value <0.05 was considered to indicate a statistically significant difference. For this we used *t*-test or Fisher’s exact test when appropriate.

5. RESULTS

5.1 Paper I – preparatory study

Comparing the variation in position and volume for the seven delineated organs in the small pelvis for seventeen patients, we found that the sigmoid varied considerably both in position and volume between the two different CT-scans (Figure 15). The largest deviation was anteriorly in the distal 4 cm of the sigmoid. For rectum the anterior wall was increasingly mobile in cranial direction (Figure 16). The urinary bladder changed in volume with the extension mainly located cranially. The cavernous bodies, the penile bulb and the anal sphincter showed little variation in position and volume.

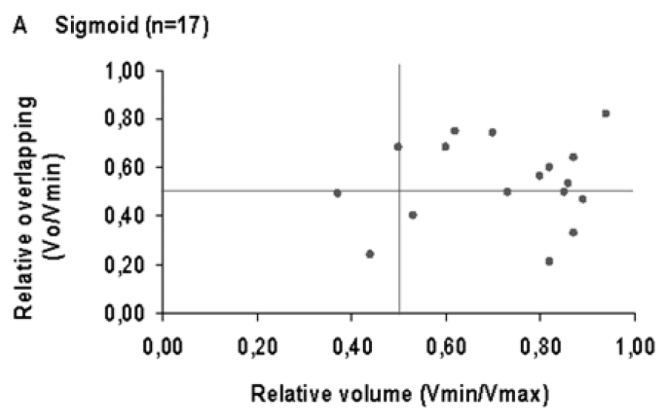


Figure 15. Relative volume (smallest volume/largest volume) in relation to relative overlapping (overlap volume/smallest volume) for the sigmoid in 17 patients.

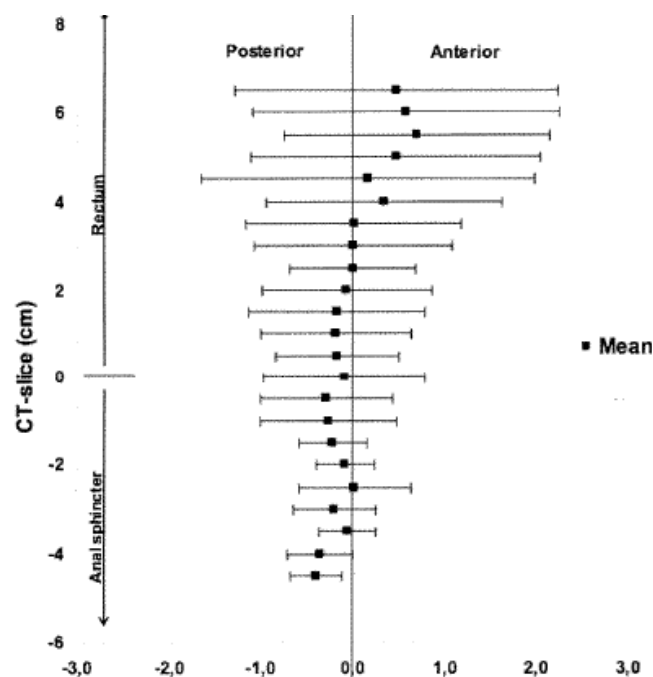


Figure 16. Variation in position of the anterior wall of rectum and anal sphincter in two consecutive CT scans in 17 patients, ten males and seven females.

5.2 Paper II

Of the 1800 identified gynecological cancer survivors treated with external radiation therapy, between 1991 and 2003, at Sahlgrenska University Hospital and Karolinska University Hospital, 1011 did not meet the eligibility criteria and were excluded from the study population; approximately 550 women had died before follow-up or had had a recurrence, 436 were born before 1927 and thus 80 years of age or older and 23 did not speak or understand Swedish. Eight control women did not meet the eligibility criteria and were excluded; they were born before 1927, did not speak Swedish or had been treated with pelvic radiation therapy.

Out of the 789 cancer survivors identified, 92 did not participate; 46 gave a reason for their non-participation, 29 women did not give any reason for their non-participation and 17 of the women could not be reached by telephone. Among the 478 eligible control women, 58 did not participate; 16 gave a reason for their non-participation, 37 women did not give any reason, and five of the women were not reached by telephone.

For the survivors the median follow up after radiation therapy was 74 months with a range of 26-179 months. The median age for cancer survivors was 66 years and the median age for control women 58 years. Endometrial cancer was the most common diagnosis (60 percent) followed by cervical cancer (23 percent). In all, 84 percent of the survivors were treated for stage I-II disease. The majority, 90 percent of the gynecological cancer survivors, was treated with surgery followed by external beam radiation therapy. Most of the remaining 10 percent were cervical cancer survivors with radiotherapy as their only treatment. Comorbidities that differed significantly between groups were hypertension, congestive heart failure, and diabetes mellitus (Table 2).

Comorbidity	Cancer survivors		Control women	
	N = 616	n/N (%)	N = 344	n/N (%)
Angina pectoris		32/600 (5)		11/341 (3)
Arthritis		170/599 (28)		95/340 (28)
Congestive heart failure		33/600 (6)		8/341 (2)
Diabetes mellitus		58/611 (9)		17/338 (5)
Hypertension		227/600 (38)		91/341 (27)
Lung disease		40/600 (7)		12/341 (4)
Mental problems		78/600 (13)		43/341 (13)
Myocardial infarction		18/600 (3)		5/341 (1)
Osteoporosis		58/600 (10)		25/341 (7)
Rheumatism		37/600 (6)		19/341 (6)
Thrombosis		47/600 (8)		16/341 (5)

Table 2. Self-reported comorbidities among survivors and control women.

Compared to non-irradiated control women cancer survivors reported a higher occurrence of symptoms from all organ systems studied; the anal sphincter, the bowels, the urinary tract, the pelvic bones, symptoms related to sexuality, and symptoms from lower abdomen and legs. The highest age-adjusted relative risks among all survivors were found for emptying of all stools into clothing without forewarning and defecation urgency with an immediate need for a toilet. Survivors treated with only radiation therapy reported higher occurrences of symptoms (Table 3).

Symptom	Controls N=344 n/N %	All survivors N=616 n/N %	Age-adjusted relative risk (95% CI)	RT with surgery, N = 549 n/N %	Age-adjusted relative risk (95% CI)	Only RT N = 67 n/N %	Age-adjusted relative risk (95% CI)
Anal sfincter	3/344	70/606	12.7	55/546	8.8	15/60	30.3
Emptying of all stools into clothing without forewarning, at least occasionally	1%	12%	(4.0-40.3)	10%	(2.8-28.3)	25%	(9.1-101.1)
Bowel	19/341	175/602	5.7	157/542	5.7	18/60	6.0
Defecation urgency, at least once a week	6%	29%	(3.5-9.1)	29%	(3.5-9.1)	30%	(3.3-10.8)
Urinary tract	11/343	56/604	2.8	46/544	2.5	10/60	5.1
Difficulty feeling the need to empty the bladder, at least occasionally	3%	9%	(1.5-5.4)	8%	(1.3-5.0)	17%	(2.3-11.3)
Sexuality	4/339	28/593	5.0	21/532	4.3	7/61	9.6
Protracted genital pain lasting for more than one year	1%	5%	(1.7-14.5)	4%	(1.4-13.0)	11%	(2.9-31.8)
Pelvic bones	6/343	46/603	4.9	35/542	4.1	11/61	10.3
Pubic pain when walking indoors, at least occasionally*	2%	8%	(2.1-11.6)	6%	(1.7-10-2)	18%	(4.0-26.7)
Lower abdomen and legs	3/336	17/597	3.6	14/537	4.0	3/60	5.2
Erysipelas on abdomen or legs	1%	3%	(1.0-12.8)	3%	(1.1-14.5)	5%	(1.1-25.1)

* after completed radiotherapy

Table 3. Symptoms with the highest relative risk from each studied organ system.

The intestinal symptoms have been described in more detail by Dunberger *et al.* [64-66].

The highest relative risks among all survivors reporting pain from the pelvic bones were for “pubic pain when walking indoors at least occasionally” and “pubic pain when walking outdoors 500 m, at least occasionally” compared to controls. Looking at the survivors who had been treated with only radiotherapy the relative risks were ten and seven times higher, respectively.

5.3 Paper III and IV

Among 650 gynecological cancer survivors who had completed the questionnaire (participation rate 79 percent) 538 dose-volume histograms for the pubic bone and 358 dose-volume histograms for the hips and the sacrum could be retrieved.

Looking at pain from the different anatomical sites among the survivors in our study, 11 percent (73/637) suffered or had suffered pain from the pubic bone after completed radiotherapy, 36 percent (225/632) from the hips and 39 percent (249/633) from the sacrum.

Among the 358 women with complete treatment records for hips and sacrum, pain from the hips was reported by 37 percent compared to 36 percent reported by all survivors answering the questionnaire. Corresponding figures for pain from the sacrum were 40 percent compared to 39 percent, as stated above.

Of 67 survivors reporting pubic bone pain, seven women also reported pain from the hips and eight women from the sacrum. Of 215 women reporting pain from the hips, 113 women reported pain also from the sacrum and seven women from the pubic bone. Of 242 women reporting pain from the sacrum, 113 women also reported pain from the hips and eight from the pubic bone. Forty-two women (63 percent) reported pain from all three sites. (Figure 17).

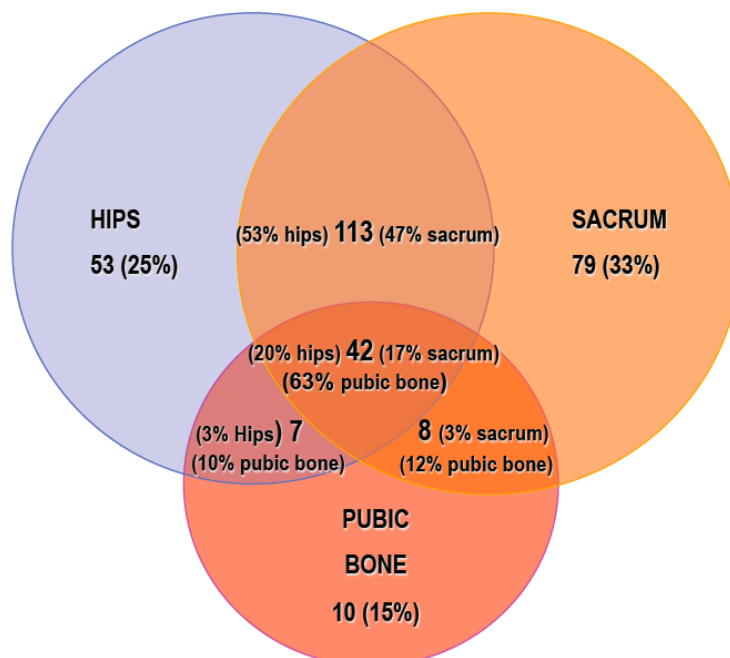


Figure 17. Multiple sites of pain in the pelvic bones for survivors.

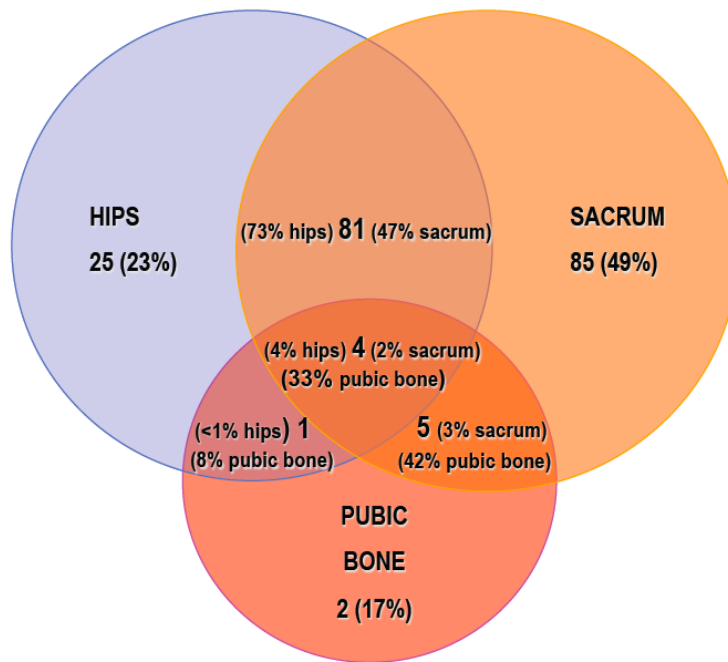


Figure 18. Multiple sites of pain in the pelvic bones for controls

The prevalence among non-irradiated control women from the general population for pain from the pubic bone was 4 percent (12/339), for pain from the hips 33 percent (113/343) and for pain from the sacrum 52 percent (179/344). Contrary to the occurrence among survivors, pubic bone pain is rare among non-irradiated control women from the general population (Figure 18).

Pain characteristics

The pain from the sacrum and the pubic bone was characterized as aching or pressing whereas pain from the hips was described as stabbing or cutting besides aching [67]. The onset of pain from hips and sacrum was generally later than from the pubic bone. The duration of pain was the same for all three pelvic bone sites, lasting more than 24 months for approximately two thirds of the survivors (Table 4).

	Onset of pain			Duration of pain		
	1-3 months	3-24 months	> 24 months	< 3 months	3-24 months	> 24 months
Pubic bone	49%	27%	24%	18%	33%	49%
Hips	26%	40%	34%	8%	24%	68%
Sacrum	33%	36%	31%	14%	22%	64%

Table 4. Onset and duration of pain from the different pelvic bones.

Physical symptoms

Pubic bone

Compared with the control population, the prevalence of developing pubic bone pain showed a six-fold increase among survivors who had received radiotherapy as their only treatment and a three-fold increase among survivors who had been treated with radiotherapy in combination with surgery. Sleeping difficulties due to pubic bone pain showed a thirteen-fold increased prevalence among the survivors in the first group and a six-fold increase among the survivors in the second group. In addition, the survivors treated with radiotherapy only showed a ten-fold increased prevalence for pubic bone pain when walking indoors, and six-fold when walking 500 m. The corresponding prevalence for the survivors treated with radiotherapy in combination with surgery was a four-fold increase for both symptoms (Table 5). In all, 23 of the survivors with pain (32%) reported difficulties both sleeping, walking indoors and walking 500 m, 20 survivors (27%) reported two of these symptoms and 16 (22%) reported one symptom.

Symptom	Controls	Surgery + Radiotherapy		Definitive radiotherapy	
	n/N %	n/N %	Age-adjusted relative risk (95% CI)	n/N %	Age-adjusted relative risk (95% CI)
Pain in the pubic bone	12/339 4%	59/575 10%	3.3 (1.7-6.1)	14/62 23%	6.4 (3.1-13.1)
Pain walking indoors	6/343 2%	38/574 7%	4.4 (1.8-10.5)	11/63 17%	9.9 (3.8-25.9)
Pain walking 500 m	7/343 2%	38/566 7%	3.8 (1.7-8.6)	8/62 13%	6.3 (2.4-16.8)
Pain affecting sleep	3/342 1%	26/547 5%	5.9 (1.8-19.7)	7/62 11%	12.8 (3.4-48.4)

Table 5. Prevalence and age-adjusted relative risk of pubic bone pain and physical symptoms.

Hips

In the group of long-term survivors treated with radiotherapy as their only treatment, there was a four-fold increase in daily pain from the hips walking 500 m compared to controls. Daily pain walking indoors showed a three-fold increase. Women treated with radiotherapy in combination with surgery showed a two-fold increase for daily pain both for walking indoors and for walking 500 m compared to controls. Adjusting for age affected the prevalence ratio only slightly.

Sacrum

Among long-term survivors treated with radiotherapy only, daily pain from sacrum walking indoors and daily pain walking 500 m showed a three-fold increase compared to controls.

Pain and mean absorbed dose

Pubic bone

For the pubic bone mean absorbed dose was a statistically significant predictor of pain ($P=0.035$). The average of all mean absorbed doses among the survivors was 41.2 ± 6.2 Gy (range 10.4 to 66.2 Gy). It was higher among the survivors who reported pain than among those who did not report pain (42.6 ± 6.8 Gy vs. 41.0 ± 6.0 Gy; $P=0.047$). The doses varied with diagnosis, cervical and vaginal cancers showed the highest average mean absorbed doses (45.2 ± 8.6 Gy) and ovarian and tubal cancer the lowest (38.5 ± 6.0 Gy). Pain from the pubic bone was reported more often as the mean absorbed dose to the pubic bone became higher and for mean absorbed dose of ≥ 52.5 Gy, 5 of 12 women (42%) reported pain.

Other factors than mean absorbed dose ≥ 52.5 Gy that occurred more frequently among the survivors reporting pain were age <55 years at time of treatment, arthritis and rheumatism. Adjusting for these factors or other factors reported to influence the occurrence of pelvic insufficiency fractures and potentially also the occurrence of pain did not affect the prevalence ratios substantially.

Hips

Mean absorbed dose was a significant predictor of pain from the hips ($P=0.023$). The average of all mean absorbed hip doses was 32.4 ± 6.1 Gy. It was higher among the survivors reporting pain (33.1 ± 6.7 Gy) compared to those who did not report pain (32.0 ± 5.7 Gy). The corresponding figures for average maximum doses for all survivors were 44.8 Gy ± 6.2 Gy, 45.3 ± 7.1 Gy for survivors with pain and 44.5 ± 5.6 Gy for survivors without pain. Comparisons of mean and maximum doses between groups showed no statistically significant difference.

Sacrum

Mean absorbed dose as a predictor of pain from the sacrum was not statistically significant ($P=0.0502$). The average of all mean absorbed doses in the sacrum was 37.9 ± 4.8 Gy (range 1.5 to 58.5 Gy). It was also higher among the survivors reporting pain (38.7 ± 4.5 Gy) compared to those who did not report pain (37.4 ± 4.9 Gy). The corresponding figures for average maximum doses for all survivors were 44.8 Gy ± 5.1 Gy, 45.7 ± 4.7 Gy for survivors with pain and 44.3 ± 5.3 Gy for survivors without pain. Comparisons of mean and maximum doses between groups resulted in P values of 0.013 and 0.059, respectively.

The mean volume to the pubic bone was 61 ± 13 cm³ (range 25 to 100 cm³) and for the hips 44 ± 8 cm³ (range 25 to 72 cm³) and for sacrum 250 ± 42 cm³ (range 166 to 373 cm³).

For the pubic bone the mean dose where the frequency of pain among survivors exceeded that of the control population occurred at 30 Gy and for pain from the hips at 37.5 Gy. For sacral pain a relation between mean absorbed dose and pain was not obtained in this cohort (Figure 19).

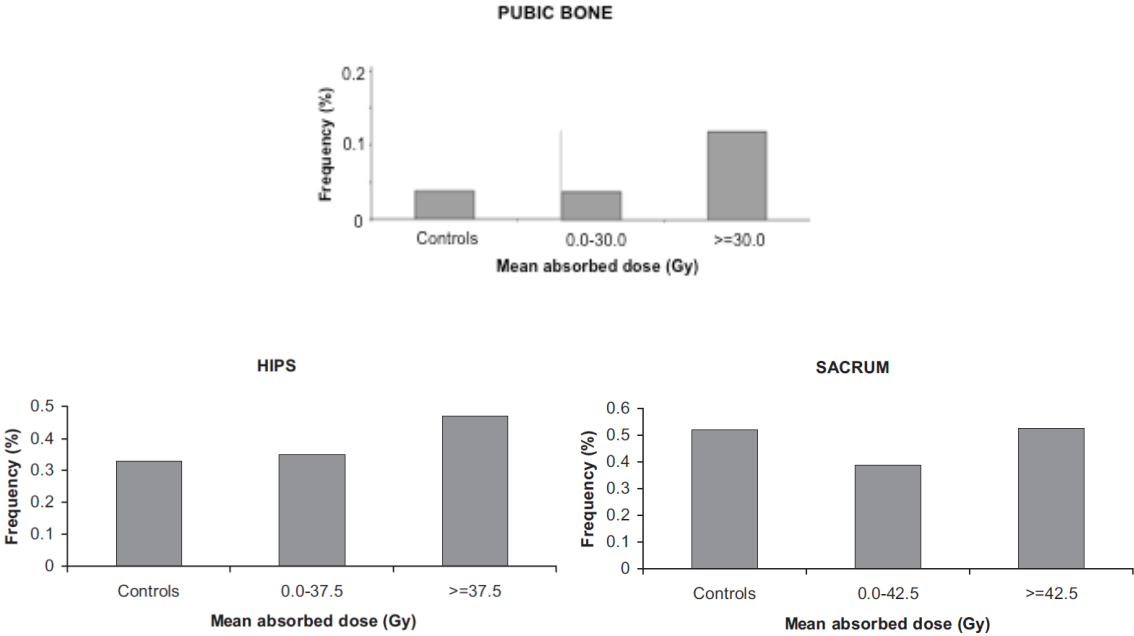


Figure 19. Comparing the frequency of pain from the pubic bone, hips and the sacrum among controls and survivors in relation to mean absorbed dose.

6. DISCUSSION

6.1 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. Systematic errors may introduce bias to a study while random errors relate to precision. Confounding, misrepresentation and misclassification are all threats to the validity of a study. We have used epidemiological methods for study design and data interpretation as adapted to the cancer survivorship field according to the hierarchical step-model for causation of bias [68]. In this model the studied person time is the total time during which a person has been studied (Figure 20).

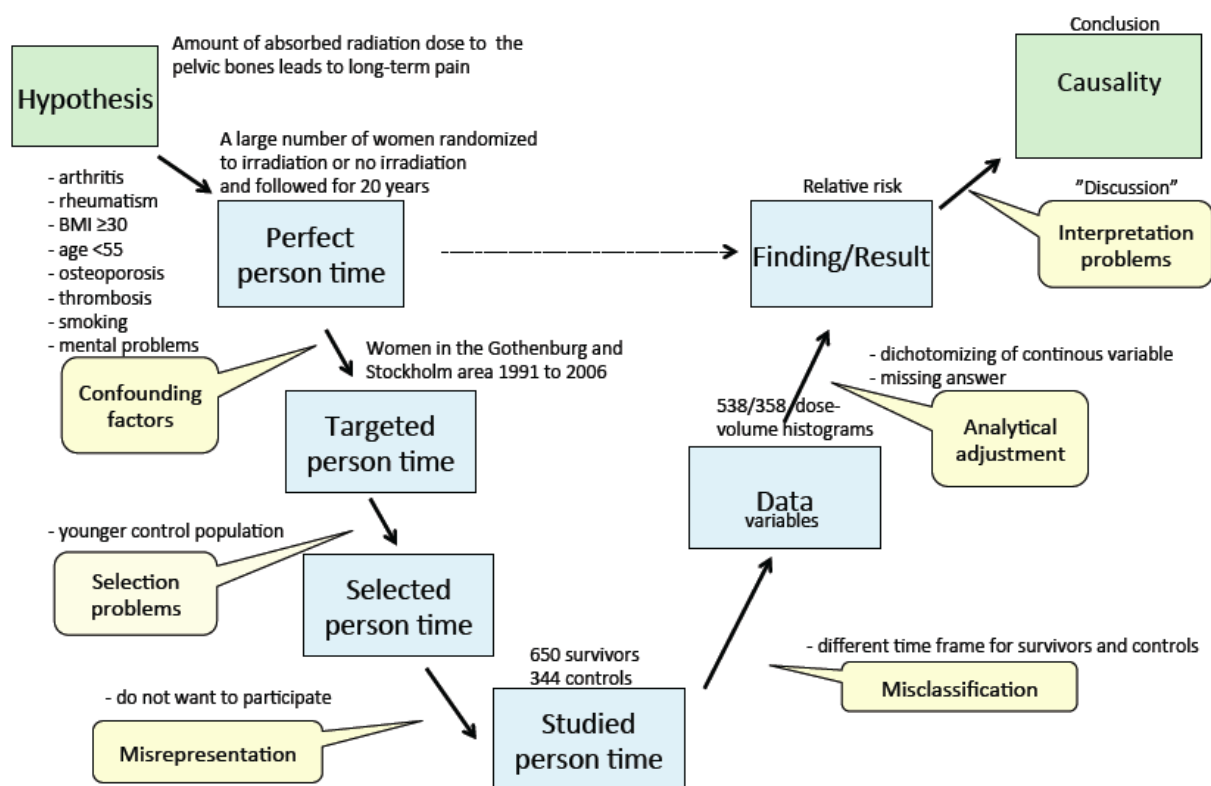


Figure 20. The hierarchical step-model for causation of bias used in paper III and IV.

Confounding

Confounding factors are associated both with the exposure (absorbed radiation dose) and the outcome (long-term symptom) and are true causes of the outcome but not considered to be part of the causal chain (Figure 21). Not considering confounding factors may lead to an over- or underestimation of the true association between exposure and outcome.

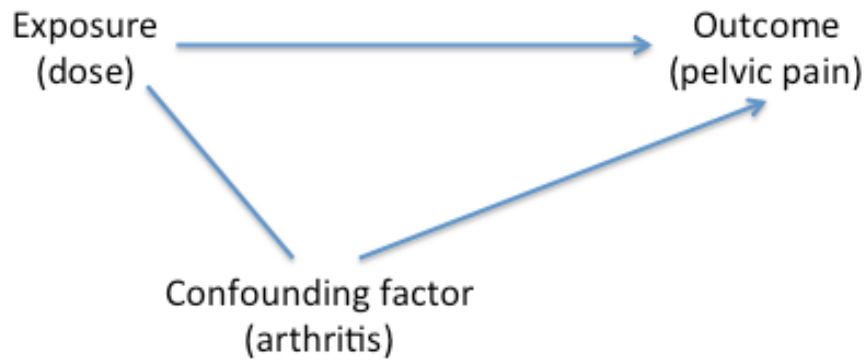


Figure 21. Example of a confounding factor that may affect the outcome of pain after radiotherapy.

Other possible causes for differences between survivors with and without a studied symptom can be collected through additional information from the questionnaire and medical records e.g. comorbidities and demographics. They can be adjusted for in the analyses in order to diminish the confounding effect or the effect measures (Figure 22).

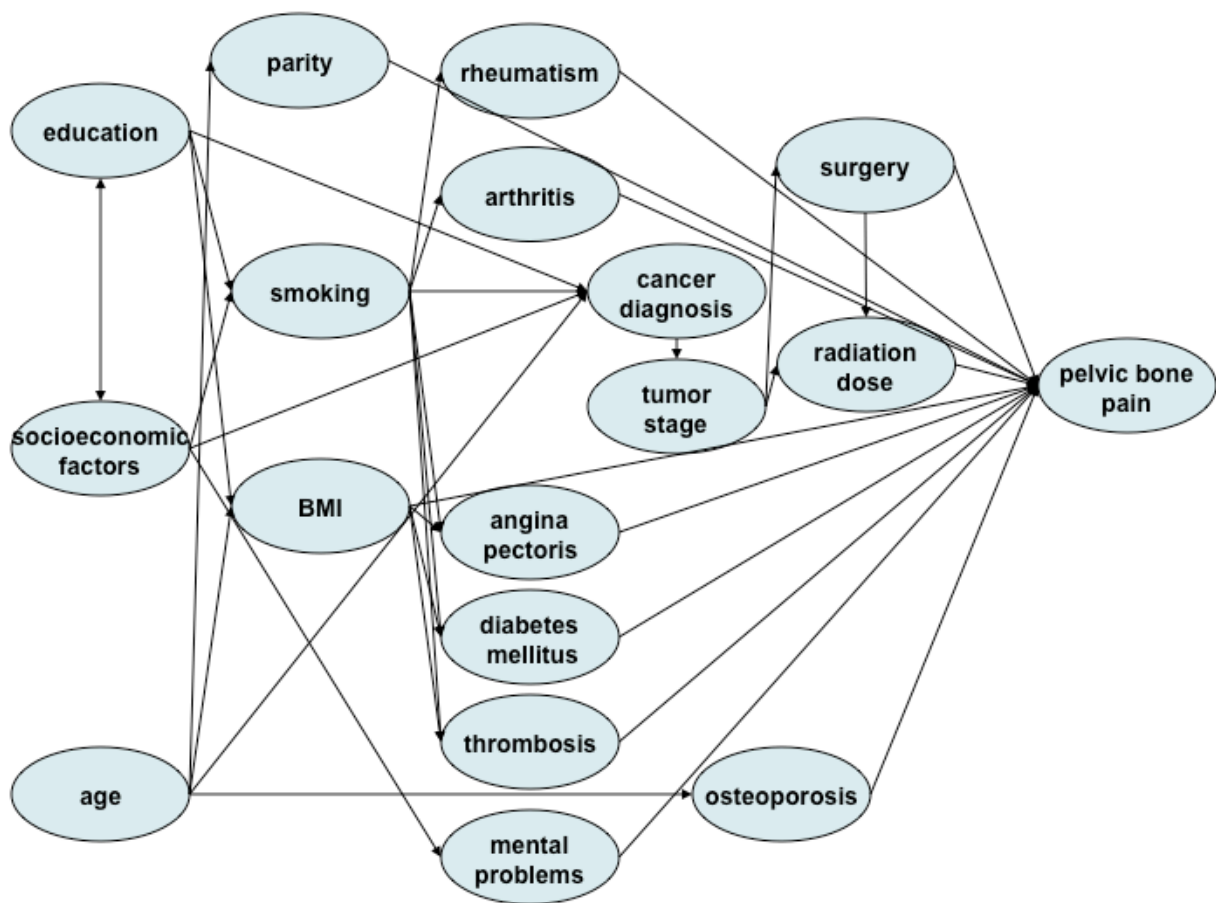


Figure 22. Directed Acyclic Graph showing potential confounding factors for pelvic bone pain.

In paper III, other factors that occurred more frequently among the survivors reporting pubic pain were age, arthritis, rheumatism, and to some extent BMI. The unadjusted prevalence ratio for pain associated with mean absorbed dose ≥ 52.5 Gy was 3.7. When adjusting for a single factor at a time or for multiple factors, the prevalence ratio was within the range of 2.8-4.1. However, we did not look at the prevalence ratios for pain associated with mean dose ≥ 30 Gy.

In paper IV the survivors reporting pain from the hips more frequently suffered from arthritis, osteoporosis and thrombosis. Rheumatism, smoking and BMI were also slightly overrepresented. When adjusting for a single variable at a time the prevalence ratio of 1.5 for pain associated with mean absorbed dose ≥ 37.5 Gy stayed at 1.4 to 1.5. Besides the comorbidities just mentioned, the survivors reporting pain from the sacrum more frequently suffered from mental problems.

For pain from the pubic bone we looked for a dose level clearly demonstrating an increased risk, the background noise among control women being very low. For pain from the hips and the sacrum where the background noise was large, we focused on the difference in symptom occurrence that separated the survivors from the non-irradiated control women.

Misrepresentation

Systematic errors may be introduced due to sampling from the targeted person-time, non-participation or loss to follow-up.

Efforts to minimize non-participation were carried out through the whole procedure; the study was well grounded in the initial qualitative phase with validation of the questionnaire and the method tested in a pilot study within the study-population before entering the quantitative phase and data collection. An attractive layout of the questionnaire, a personal contact (letter) before sending the questionnaire to the willing and a reminder (telephone) to the forgetful increased the number of women participating in the study. Also approaching survivors from an unselected patient cohort and randomly sampled controls from the Swedish Population Registry with a relatively high participation rate in both groups, 79 percent and 72 percent respectively, helped to minimize misrepresentation.

Information on the excluded women's health, wellbeing or cause of death is unknown. We can only hypothesize that women with recurrent disease and those who had died prior to follow-up belonged to a less healthy group. Whether non-participants belonged to a healthier or a less healthy part of the population is not known.

In paper IV we could retrieve 358 complete treatment records among the 650 survivors answering the questionnaire. The loss was due to technical problems when changing treatment planning systems. The missing data were concentrated to some of the oldest cases but also data from more recent treatments were missing. We have no reason to believe that

missing data should cause a selection-induced bias of our effect measures. Diagnoses and doses among the missing dose plans were randomly distributed. Pain from the hips was reported by 37 percent of the 358 survivors compared with 36 percent for the whole group of 650 survivors. The corresponding figures for pain from the sacrum were 40 percent and 39 percent, respectively.

Misclassification

Incorrect information due to measurement errors can cause systematic errors that wrongly may influence the calculated effect measure. Measurement errors can be differential, i.e. dependent on and varying with either the exposure or the outcome. Or they can be non-differential and independent of the exposure or outcome.

When using a questionnaire the questions should ideally be phrased identically for survivors and controls. Here we experienced a problem with the women in the control population. Since they had not been exposed to radiation therapy they could not relate to the time “after completed radiotherapy”. We asked them for the same symptoms as we did for survivors - if they had pain or had had pain - but the time frame was during the past six months. Six months was chosen as a reasonable time to balance symptom capture and the risk of information loss. The longer period for recall in assessing pain among the survivors compared with that of controls may have led to a greater prevalence in the survivor group and thus a differential measurement error. On the other hand, memory abates with time and could lead to a lower prevalence. Had we asked the survivors about pain during the previous six months, we would not have found many survivors in whom we could analyze how pain affected their daily lives since their period of pain might have occurred years ago.

Errors in the contouring of the organs at risk, set-up uncertainty, and organ motion contribute to an uncertainty in the estimated absorbed dose, which we expect to dilute the association between absorbed dose and occurrence of long-term symptoms.

Another possible source of inaccuracy is the estimated volumes of the pubic bone, hip and sacral bone due to varying CT slice thickness and uncertainties in the algorithms to estimate volumes in the treatment planning systems used over the studied time period.

Analytical adjustment

When dichotomizing a variable it is critical that the cut-off level is wisely chosen. Using a more specific cut-off will result in a more clear effect but due to few events a statistical difference might be difficult to prove. Looking at different dose intervals you can see where the occurrence of pain increases. Dichotomizing continuous variables may lead to a loss of statistical power, but will in this case not change the obtained associations.

6.2 GENERAL DISCUSSION

Pain

Pain from the pubic bone after completion of radiotherapy was reported by 11 percent of the long-term survivors, showing a six-fold increased prevalence among survivors who had received radiotherapy as their only treatment compared with the non-radiation-treated control population and a three-fold increased prevalence among the survivors who had been treated with radiotherapy in combination with surgery. Sleeping difficulties due to pubic bone pain showed a thirteen-fold increased prevalence among the survivors after radiotherapy only and a six-fold increase among the survivors being treated with radiotherapy in combination with surgery. In addition, the survivors treated with radiotherapy only showed a ten-fold increased prevalence for pubic bone pain when walking indoors, and a six-fold increase when walking 500 m. The corresponding prevalence among the survivors treated with radiotherapy in combination with surgery was a four-fold increased prevalence for both symptoms.

Hip pain after completed radiotherapy was reported by 36 percent of the survivors. Daily pain when walking 500 m was nearly four times as common among survivors treated with only radiotherapy compared with controls.

Sacral pain was reported by 39 percent of the survivors. Daily pain from sacrum walking indoors and daily pain walking 500 m showed a three-fold increase among survivors who had been treated with only radiotherapy compared to controls.

The most common sites for radiation-induced pelvic bone complications for gynecological malignancies, including pelvic insufficiency fractures (PIF), are the sacrum (52-93 percent) [6, 11, 60, 69] followed by the pubic bone (20-64 percent) [6, 11, 69] and acetabulum (3-11 percent) [6, 11]. Multiple sites are common and 50 percent or more of the patients with PIF also report pain [1, 6, 10, 11].

Pain from the hips and the sacrum are common symptoms in the general population. The occurrence of pain from the hips and the sacrum in our control population were higher than what has recently been reported by Vistad *et al.* who asked 91 long-term (≥ 5 years) survivors treated with radiotherapy for cervical cancer about pelvic pain the previous month [70]. They found 45 percent hip pain and 55 percent lower back pain among survivors. Corresponding figures among controls were 22 percent and 27 percent respectively. The definition of pain, its reference to location and time frame as well as means for data collection differs in these studies make a comparison difficult.

Dose

Comparing averaged absorbed doses and volumes for the pelvic bones we found that the frequency of pubic bone pain among survivors exceeded that of controls for mean absorbed doses of 30 Gy. The corresponding dose for hip pain is 37.5 Gy. For sacral pain we did not find a relationship between mean absorbed dose and pain in this cohort.

The majority of the survivors had been treated for endometrial cancer with prescribed doses to the tumor target of approximately 45 Gy, making the variations in the absorbed doses in the pelvic bones around this value small (Figure 23). Women with cervical cancer are generally treated with definitive radiotherapy to higher total doses and thus exposed to a higher risk of developing pain.

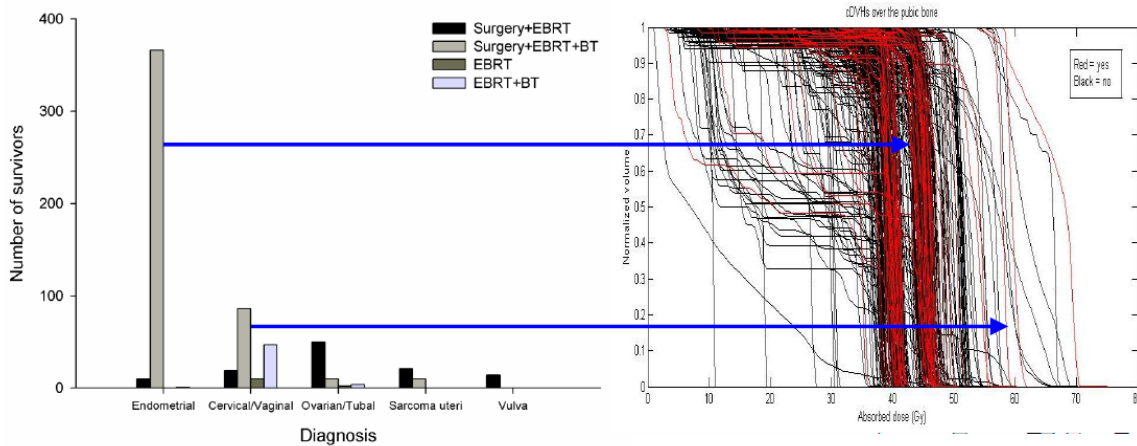


Figure 23. Cancer diagnosis and DVHs for corresponding mean doses for the pubic bone, pain in red.

In the analyses for the pubic bone, we found that mean absorbed external beam dose ≥ 52.5 Gy was a contributing factor to pain after radiotherapy. Absorbed doses of >50 Gy have previously been associated with pelvic insufficiency fractures [1, 10]. TD 5/5 and TD 50/5 (the five percent risk and fifty percent risk in five years) to develop radio-osteonecrosis and insufficiency fractures for the pelvic bones are not yet conclusively determined. For the femoral head and necrosis Emami *et al.* have estimated TD 5/5 as 52 Gy and TD 50/5 as 65 Gy [71].

From a pathophysiological point of view, we cannot be sure which part of the pelvic bones that is most critical for the development of pain. We therefore chose to delineate the whole pubic bone, only the femoral head and the whole sacrum. We considered delineating the acetabulum but found it too difficult to do in a standardized way. If the volumes had been defined alternatively, the results might have differed.

Expressing the dose to a volume in terms of the average dose may not be very representative when the dose distribution over the volume is highly inhomogeneous (Figure 24 a-c). For the hips and the sacrum the mean doses differ from the maximum doses, indicating an inhomogeneous dose distribution, while for the pubic bone the mean and maximum doses are quite close, indicating a more homogeneous dose distribution (Table 6). One may debate if mean dose is the most representative measure for the relationship between dose and complications in different normal tissues.

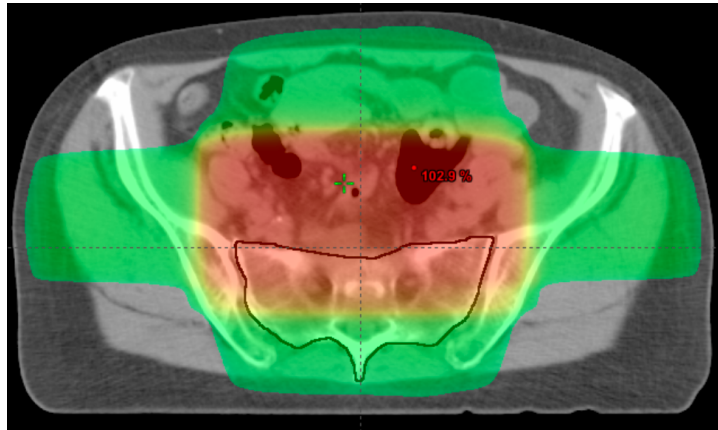


Figure 24 a.

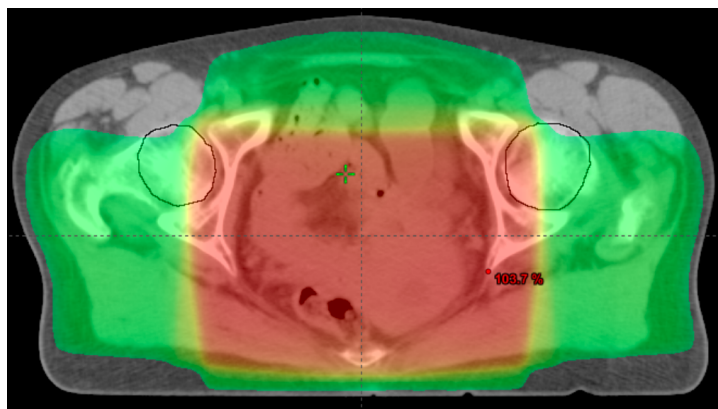


Figure 24 b.

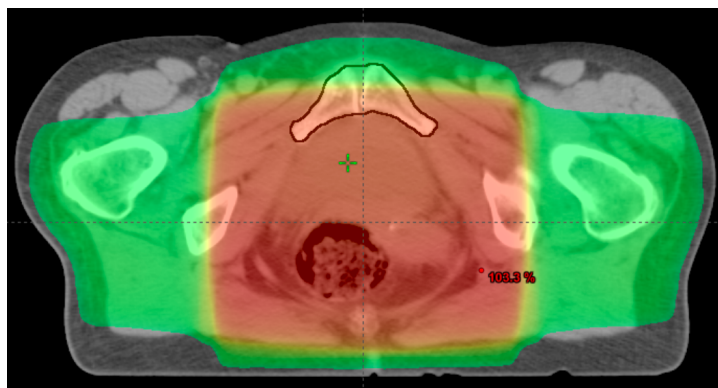


Figure 24 c.

Figures 24 a-c. Dose distributions over the sacrum, the femoral heads (hip bones) and the pubic bone in the treatment of gynecological cancer - red/brown color shows >90% of the prescribed dose, yellow 75-90% and green 50-75%, respectively.

Pelvic bone site	Hip N=358 (95% CI)	Sacrum N=358 (95% CI)	Pubic bone N=538 (95% CI)
Mean absorbed dose \pm SD (Gy)	32.4 \pm 6.1	37.9 \pm 4.8	41.2 \pm 6.2
Maximum absorbed dose \pm SD (Gy)	44.8 \pm 6.2	44.8 \pm 5.1	44.4 \pm 5.9
Volume \pm SD (cm ³)	44 \pm 8	250 \pm 42	61 \pm 13

Table 6. Mean and maximum absorbed doses and volumes for the pelvic bones.

Strengths

This study includes information from a large group of unselected, long-term survivors and also from non-irradiated women in the general population. We used epidemiological methods adapted to the survivorship field [68]. High participation and response rates for both groups reduced the risk of selection-induced problems. A validated, study-specific, postal questionnaire was used, minimizing the risk of interviewer-related problems.

The use of a relevant and conceptually clear questionnaire, where symptoms are “atomized” [72] (i.e. broken down to reflect specific radiation pathophysiology) and developed with guidance from survivors that explore the impact of a specific symptom on daily activities will further aid us in extracting information [73, 74].

Other tools used today for evaluation of adverse events are the RTOG-EORTC toxicity criteria [75] and CTCAE version 3 [76]. Since patient-reported outcomes have become more important the SF-36 [77] questionnaire is often used as well as the FACT-C [78] or the EORTC QLQ-C30 [79]. The latter is used together with disease-specific modules e.g. for endometrial, cervical and ovarian cancer. Many of the questionnaires above combine multiple signs and symptoms into a single grade leading to loss of specificity.

Limitations

When looking at pain from the pubic bone and different cut-offs for mean absorbed doses, there were very few survivors in the higher dose ranges. Two-dimensional DVHs are not ideal representations of the three-dimensional dose-volume information. Other limitations are a single pre-treatment CT, different fractionation schedules, the impact of combined treatment modalities, and host factors (comorbidities, risk factors like smoking, and individual radiosensitivity).

This study is based on a population cohort of women treated with external radiation therapy and who have survived longer than three years without recurrence. It is important to keep in mind that all patients don't live long enough to develop pain or fractures [3] or long enough to be followed up in a study, e.g. cervical cancers that are irradiated to a higher dose because of more advanced disease. This might underestimate the long-term morbidity.

Although gynecological cancer patients in Sweden are treated at a few large centers; in this study the Stockholm/Gotland area and Gothenburg area cover 40 percent of the Swedish

population, our data were based on a Swedish female population with limited geographical spread and our results may not be directly generalized to other populations.

7. CONCLUSION

The focus of this work has been to explore the occurrence of pain from the pelvic bones after radiation therapy, the effect of pain on daily life, and how it relates to the absorbed doses in these organs. The main conclusions are:

Paper I

- When the sigmoid, the rectum and the urinary bladder are situated in an area with a sharp dose gradient the absorbed dose may be affected due to set-up uncertainty and organ motion. This is of importance when describing the relationship between doses and patient-reported outcomes, especially for organs that move during the course of treatment.

Paper II

- Gynecological cancer survivors treated with pelvic radiation reported a higher occurrence of symptoms from all pelvic normal tissue organs studied; the anal sphincter, the bowels, the urinary tract, the pelvic bones, symptoms related to sexuality and symptoms from lower abdomen and legs, compared with non-radiation-treated women from the general population. For survivors treated with radiation as their only treatment the occurrence of symptoms was often twice as high compared with women treated with radiation in combination with surgery.

Paper III and IV

- One out of ten long-term survivors suffered pain from the pubic bone, more than one third from the hips and two fifths from the sacrum, after completed radiation therapy. The pain lasted longer than two years for half of the survivors. Pain in the pubic bone was rare among non-radiation-treated women from the general population while pain from the hips and the sacrum were common in the general population.
- Compared with non-radiation-treated women from the general population, there was a six-fold increase in pubic bone pain among survivors who had received radiotherapy as their only treatment and three-fold among survivors who had been treated with radiotherapy in combination with surgery.
- Physical symptoms affecting daily life were common among all survivors. Survivors treated with only radiotherapy showed a ten-fold increased prevalence for pubic bone pain when walking indoors, and six-fold when walking 500 m. For survivors who had been treated with radiotherapy in combination with surgery the corresponding prevalence was a four-fold increased prevalence for both symptoms.
- Daily pain from the hips when walking 500 m showed a four-fold increased prevalence for survivors treated with radiotherapy only and for daily pain when

walking indoors a three-fold increased prevalence both from the hips and from the sacrum was found.

- The mean absorbed dose where the frequency of pain among survivors exceeded that of the control population was 30 Gy for the pubic bone and 37.5 Gy for the hips. For sacral pain no such relation could be obtained in this cohort.
- Pubic bone pain being rare among controls, only four percent, means that if you suffer from pain in your pubic bone after radiation therapy for gynecological cancer, the association to the treatment is high.
- Hip and sacral pain being common among population controls illustrates the importance of specifically asking about walking difficulties weekly or more often, in order to single out treatment-related symptoms that affect the daily lives of the survivors.

8. FUTURE PERSPECTIVES

A therapeutic gain cannot be achieved without carefully balancing tumor cure and survival rates against morbidity and quality of life, as has been concluded by Sören Bentzen [39]. To achieve this we need:

Development of more precise dose planning and dose delivery

- For radiotherapy of gynecological cancer, the delineation of the pelvic bones and other organs at risk on CT-scans for treatment planning will help to minimize the volume receiving unwanted radiation without jeopardizing tumor coverage. Also access to MRI and PET makes the tumor target definition more precise. The use of intensity-modulated radiotherapy (IMRT) and volumetric modulated arc radiotherapy (VMAT) may further aid to lower the absorbed dose to the normal tissues.

Careful recording of patient-related factors

- Patient-related factors e.g. arthritis and other co-morbidities together with life-style factors e.g. smoking increase the risk of developing both acute and chronic side effects.

Standardized scoring systems for specific normal-tissue endpoints

- An internationally applicable scoring system that can be recorded at every follow-up and then automatically saved in a data base together with patient characteristics and treatment information.

Long-term follow-up after radiation therapy

- It is important to inform and motivate patients undergoing radiation therapy what they can do themselves to optimize their future quality-of life. Information about the nature of radiation-induced symptoms will increase the chance of early diagnosis and spare the survivors much worry. Offering optimal management of the side effects can be coordinated in special follow-up programs.

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before the story takes a further pace
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