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Sexual Dysfunction and Other Distressful Symptoms in Cervical Cancer Survivors

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We live in the present, we dream of the future,
but we learn external truths from the past.

Song Meiling, ”Madame Chiang Kai-shek”

List of papers

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

I. Karin Bergmark, Elisabeth Åvall Lundqvist, Paul W Dickman, Lars Henningsohn, Gunnar Steineck
Vaginal changes and sexuality in women with a history of cervical cancer
The New England Journal of Medicine 1999;340:1383-1389

II. Karin Bergmark, Elisabeth Åvall Lundqvist, Paul W Dickman, Lars Henningsohn, Gunnar Steineck
Patient-rating of distressful symptoms after treatment for early cervical cancer
Acta Obstetricia et Gynecologica Scandinavica (Accepted)

III. Karin Bergmark, Elisabeth Åvall Lundqvist, Paul W Dickman, Lars Henningsohn, Gunnar Steineck
Long-term symptom prevalence after radical hysterectomy for early cervical cancer and among population controls
Submitted

IV. Karin Bergmark, Elisabeth Åvall Lundqvist, Paul W Dickman, Lars Henningsohn, Gunnar Steineck
Distressful symptoms in cervical cancer survivors after radical hysterectomy with or without preoperative brachytherapy
Submitted

V. Karin Bergmark, Elisabeth Åvall Lundqvist, Paul W Dickman, Lars Henningsohn, Gunnar Steineck
Sexual abuse: Long-term effect on sexuality and well-being, and relation to cervical cancer
Submitted

VI. Gunnar Steineck, Karin Bergmark, Lars Henningsohn, Massoud al-Abany, Paul W Dickman, Ásgeir Helgason
Symptom documentation in cancer survivors as a basis for therapy modifications
Acta Oncologica (Accepted)

Abstract

Background: The majority of cervical cancer survivors are young or middle-aged women who will live many years with their treatment-induced sequelae. The effects of preoperative brachytherapy are unclear and treatment traditions vary – in Sweden and internationally. The relative occurrence of long-term distressful symptoms related to different treatments and the extent to which the women want to trade off optimal survival chances are not known.
Methods: The effects of radical hysterectomy were studied in a comparison with population controls, and the effects of additional brachytherapy could be studied due to various treatment policies at different centres. We used an anonymous postal questionnaire, studying the nature, occurrence and intensity of the symptoms and, separately, the corresponding symptom-induced distress.
Results: We obtained information from 256 of 332 (77%) cervical cancer survivors and 350 of 495 (72%) population controls. Radical hysterectomy alone caused insufficient lubrication (relative risk [RR] 2.8 as compared to controls), reduced genital swelling at arousal (RR 1.5), reduced vaginal length (RR 6.1) and vaginal elasticity (RR 7.1), dyspareunia (RR 4.4), straining to void (RR 21.8), lymphoedema (RR 8.1) and distress from vaginal changes (RR 3.0). The addition of preoperative brachytherapy yielded RR 3.1 for defecation urgency, RR 8.5 for frequent nocturia and RR 1.6 for moderate and severe anxiety, but no excess risk concerning vaginal changes. The addition of external radiotherapy yielded, e.g., RR 13.1 for frequent nocturia and RR 4.8 for frequent defecation. A history of sexual abuse and cervical cancer gave RR 30.0 for superficial dyspareunia as compared to population controls with no history of sexual abuse. The majority of women were not prepared to forgo brachytherapy (even at a possible risk of 1% decreased survival) to avoid its long-term side effects.
Conclusion: Sexual dysfunction is the most distressful symptom in cervical cancer survivors, thus emphasising efforts to avoid it and interventions to relieve it. The excess risk of distressful treatment-induced symptoms from preoperative brachytherapy is low, if any, and the majority of women prioritise optimal survival over freedom from treatment-induced symptoms. To meet the needs of women with early cervical cancer, a valid (randomised) study of the effects of preoperative brachytherapy is warranted. The long-term situation for cervical cancer survivors can be improved by clinical application of the data from this and other studies, and a number of areas for future research that may better the situation even more have been specified.

Key words: cervical cancer, sexual dysfunction, distressful symptoms, lymphoedema, radical hysterectomy, brachytherapy, sexual abuse, trade-off, epidemiology

Abbreviations

AFUD	American Foundation of Urologic Disease
CES-D	Center for Epidemiological Studies self-report depression scale
FIGO	Federation Internationale de Gynecologie et d'Obstetrique
GQL	Göteborg Quality of Life instrument
Gy	Gray (SI-unit for absorbed energy per mass-unit)
ICD-10	International Statistical Classification of Diseases and Related Health Problems, tenth revision
HPV	Human Papilloma Virus
Pap-smear	Papanicolaou smear
Ref. No.	Reference Number
SOMA	Subjective Objective Management Analytic
STAI-T	Spielberger's State-Trait Anxiety Inventory (form Y)
WHO	World's Health Organisation

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Introduction

Today the majority of women with cervical cancer in developed countries survive. Women of all ages develop cervical cancer, but the majority are young or middle-aged. They will live many years with their long-term treatment-induced symptoms. The aim of cancer treatment is often maximal survival with minimal morbidity. Morbidity after treatment must be measured with the same care as tumour control. It is reasonable to make a concerted effort to minimise the side effects, prepare the women for unavoidable sequelae and treat these conditions with early intervention and rehabilitation.

Incidence

Cervical cancer is the third most prevalent cancer and one of the leading causes of death from cancer among women worldwide. Some 500,000 new cases are diagnosed and 200,000 deaths are registered every year.[1] In Sweden, the incidence rate has declined annually by 1.8% during the last 20 years as a result of organised Papanicolaou (Pap) smear screening, which was fully introduced in the mid-1970s. The age-adjusted incidence rate in Sweden is 8.9 per 100.000 (450 new cases 1999).[2] The incidence rate in 1965 was 25 per 100,000 and the majority of cases were diagnosed in advanced stages. Today the majority of new cervical cancer cases are diagnosed in middle-aged women with early-stage disease. The mean age at diagnosis is 50 years; the majority are in the age group 40-49 years, while 25% are younger than 40.[2,3]

Aetiology and Prevention

The development of cervical cancer is associated with persistent human papilloma virus (HPV)[4-6] and thus with sexual behaviour.[7,8] The HPV type among certain individuals might have a varying oncogenic potential for influencing carcinogenic development,[9] which might be modified by other factors, such as hostfactors[10] and sexual activity.[11,12] Most cases of cervical cancer are theoretically preventable with present-day knowledge. Organised Pap smear screening, efforts to avoid HPV infection and possibly other genital infections (by education in condom use) and the development of HPV vaccines[13] would reduce the cervical cancer incidence.

Clinical Signs, Diagnosis and Staging

The uterine cervix constitutes the distal portion of the uterus and projects through the vaginal vault. Women with early-stage cervical cancer often show no clinical signs and in these cases the disease is found at routine gynaecological examination or at Pap smear

screening. When present, the clinical signs are usually postcoital bleeding, intermenstrual bleeding or vaginal discharge. Cancer of the uterine cervix is generally manifested by superficial ulceration, an exophytic tumour or infiltration of the endocervix. The diagnosis is based on histological specimens (biopsy) and staging is based on a clinical evaluation (Table 1).[3]

Table 1 Clinical stages of cervical cancer, as defined by FIGO[3]

Stage	Definition
Stage I	Carcinoma strictly confined to the cervix (extension to the corpus should be disregarded).
Stage IA	Microinvasive carcinoma (early stromal invasion). Stage IA1: Measured invasion of the stroma no greater than 3 mm in depth and no wider than 7 mm in diameter. Stage IA2: Measured invasion of stroma greater than 3 mm but no greater than 5 mm in depth and no wider than 7 mm in diameter.
Stage IB	All other cases of stage I. Stage IB1: ≤4cm. Stage IB2: > 4cm.
Stage II	The carcinoma extends beyond the cervix, but has not extended to the pelvic wall. The carcinoma involves the vagina, but not the lower third.
Stage IIA	No obvious parametrial involvement.
Stage IIB	Obvious parametrial involvement.
Stage III	The carcinoma has extended on to the pelvic wall. On rectal examination, there is no cancer-free space between the tumour and the pelvic wall. The tumour involves the lower third of the vagina. Hydronephrosis or non-functioning kidney unless known other origin.
Stage IIIA	No extension on to the pelvic wall, but involvement of the lower third of the vagina.
Stage IIIB	Extension on to the pelvic wall or hydronephrosis.
Stage IV	The carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder or rectum.
Stage IVA	Spread of the growth to adjacent organs.
Stage IVB	Spread to distant organs.

The histological types are most frequently squamous cell carcinoma (80-90%), followed by adenocarcinoma (10-20%) and adenosquamous carcinoma (3-5%).[3]

Prognostic and Predictive Factors

The natural history of untreated cervical cancer is direct tumour growth, to loco-regional lymph nodes (first station nodes: parametrial, internal (obturator – hypogastric), external iliac, presacral and common iliac) and further to para-aortic nodes and distant spread (mediastinal nodes, lungs and skeleton).[3] In treated stage IB-IIA cervical cancer, metastases to

the lymph nodes[14,15] and a tumour size of over 4-6 cm are independent negative prognostic factors.[16,17] Lymph space involvement[18] and depth of invasion[18,19] are also candidate factors. It is unclear if the histology[20] and histological grade[15] influence the prognosis.

Treatment: History, Development and Rationale

Surgical treatment of cervical cancer was first introduced in the second half of the 19th century (Reis, Clark). Radical hysterectomy as the treatment for cervical cancer was developed by Ernst Wertheim who performed his first operation in 1898.[21] Surgery fell into disrepute because of a high operative mortality and radiotherapy was favoured instead. The development of radiotherapy as a treatment for cervical cancer started at the beginning of the 20th century after the discovery of radium by Marie Curie in 1898. With the evolution of anaesthesia, blood transfusions and antibiotics, surgery had a renaissance; Okabayashi in Japan in 1921, Bonney in England in 1935 and Meigs in USA in 1944 extended the radicality of the original Wertheim hysterectomy. Meigs also suggested that Taussig's technique of pelvic lymph node dissection should be performed.[22] In radical hysterectomy, the extensive dissection of the ureter, the bladder and rectum facilitates a more complete removal of the parametrium and of the paracervical tissue.[21-23] A varying portion of the upper vagina is also removed. Preoperative intracavitary radiotherapy (brachytherapy) was introduced in the 1930s[24] to shrink the tumour and to destroy subclinical disease.[25-28] The surgery performed on healthy tissue can then be more limited when removing residual disease. Radiotherapy, intracavitary[28,29] or external,[14,16,30,31] is sometimes added to surgery in conformity with the rationale that survival may be increased, although no distinct standards have been developed.[32-34] Local control is increased when external radiotherapy to a pelvic field is added when lymph node metastases are found at surgery.[19,35,36] However, survival has not been shown to be improved after adjuvant radiotherapy.[17,34,36] New – and rapidly adopted – schedules of neoadjuvant chemoradiotherapy[37] are being developed for high-risk disease. Radiotherapy alone, external, intracavitary, or a combination of both, is also curative in early cervical cancer.[38] Prospective randomised comparisons of radical surgery and radical irradiation[39-42] and preoperative radiation and surgery and radiotherapy alone[43] indicate that the modalities are quite comparable with respect to survival in earlystage cervical cancer.[44]

Treatment: Swedish Conditions

The standard treatment in Sweden for women with stage IB-IIA cervical cancer has previously been preoperative intracavitary brachytherapy followed by surgery.[27,45] However, various treatment policies have developed in the country during the last few decades, primarily because of concern that brachytherapy is associated with an excess risk of morbidity[46,47] and with ovarian failure.[48] Some of the centres have adhered to the traditional recommendations, while others have abandoned the preoperative treatment. This has produced a situation in which the geographical residence of the patient, rather than the individual judgement, determines the treatment.

Survival

Overall 5-year survival is 72% for cervical cancer.[3] The compiled reported 5-year survival is 82% for stage IB cervical cancer (node negative 91%, node positive 78%) and 71% for stage IIA (node negative 86%, node positive 64%).[3] The vast majority of survivors of cervical cancer are young or middle-aged women with a long life expectancy and, accordingly, will live many years with the sequelae of the disease and treatment.

SHORT-TERM MORTALITY AND MORBIDITY

The operative mortality in modern series is 0-1.4%.[49-51] In the immediate postoperative period, the mortality is 0-0.6%.[42] No reports on mortality after preoperative brachytherapy alone have been published, but the operative mortality after the addition of preoperative brachytherapy is 0-2.6%.[52-54] The acute mortality in association with external radiotherapy is 0-1.4% (severe radiation complications, e.g. intestinal perforation, ileus, necrotising enteritis).[55,56]

The most frequent acute morbidities after radical hysterectomy are (apart from acute operative morbidity, such as blood loss and infections) bladder insensitivity and voiding dysfunction, ileus, urinary fistulas (ureteral or bladder) and rectovaginal fistulas. Infections and fistulas have been reported after preoperative brachytherapy. In association with external radiotherapy, frequent defecations, acute enteritis and proctitis, frequent micturition, dysuria and fistulas have been reported.

LONG-TERM FUNCTION IN CERVICAL CANCER SURVIVORS

Chronic side effects may develop either directly out of acute toxicities, or independently, and may also develop years after the completion of cancer therapy. The reports on side effects consist either of specific symptom prevalences, side effect scales,[45,57-60] summary scores/modular questionnaires on the quality of life[61-63] or global measures.[57,64]

Sexual Function

Physiology: Sexual response as described by Kaplan[65] consists of three phases: desire, excitement and orgasm. Vasogenic, neurogenic, hormonal and psychogenic factors are involved in the sexual response.[66] Sexual desire is probably a combination of sexual drive (biology), motivation (psychology) and wish (social function), which influences the evaluation of the level of, and changes in, desire. Excitement and arousal are sometimes used synonymously. During female sexual arousal, stimulation leads to central nervous system activation, resulting in vaginal and clitoral smooth muscle relaxation and increased vaginal blood flow. The neural mechanisms regulating the genital functions depend on the integration of autonomic and somatic neural circuits. The spinal reflex phenomena involve stimulatory input through afferent fibres in the pudendal nerves and efferent stimuli through the sacral parasympathetic fibres. This culminates in a series of vasocongestive and neuromuscular events, which include increased clitoral and vaginal length and diameter, increased vaginal lubrication and vaginal wall engorgement.[66] Increased lubrication during sexual arousal is a direct result of increased blood flow. A transudate originating from the subepithelial vascular bed is passively transported onto the vaginal surface.[66] An elastic, mobile, and expandable vagina,[67] with a non-atrophic epithelium, a sufficiently lubricated mucosa and adequate innervation is beneficial for a satisfactory sexual act.

Pathophysiology: The pelvic parasympathetic nerves and the pelvic plexus lie mostly below the cardinal ligaments and in the (so-called) uterosacral ligaments, implying a risk of nerve damage after radical hysterectomy and excision of a vaginal cuff.[68] Vaginal stenosis after radiotherapy is reported to be caused by acute radiation reactions (erythema and oedema, leading to desquamation and ulceration, with haemorrhage and fibrin coating and, later, adhesions), which lead to chronic damage (fibrosis and vascular insufficiency). There may be a correlation between vaginal narrowing and the degree of pelvic fibrosis, which might possibly influence the elasticity of the vagina.[69] Radiotherapy-induced pelvic stenosis and fibrosis with a subsequently decreased blood flow and vaginal secretion has been suggested to

result in decreased vaginal sensation and dyspareunia.[70] Surgical or radiotherapeutical castration results in low levels of circulating oestrogens. In spontaneous menopause, oestrogen depletion results in vaginal atrophy and vaginal dryness.[71] Oestrogen depletion has been suggested to be of importance for the amount and rapidity of lubrication,[72] but this theory has been questioned. Reduced lubrication after radiotherapy may be mediated by the end-arterities of vaginal blood vessels and reduced vascularisation.[73] It has been suggested that radiotherapy-induced vaginal fibrosis may make the vagina non-responsive to oral and topical oestrogen.[74] The affected sexual desire among cancer survivors may be due to a treatment-induced decrease in sexual drive or may be a consequence of depression, sorrow, affected self-confidence, guilt (shame), fatigue or physical impairment of sexual motivation and wish.[75] Low sexual desire has been reported to be the main cause of reduced excitement in gynaecological cancer patients.[76] Another suggested reason for a reduced level of excitement is interferences during intercourse, specifically pain.[76,77]

Sexual dysfunction can be defined as the various ways in which an individual is unable to participate in a sexual relationship as he or she would wish (WHO ICD-10). According to AFUD's Consensus Panel classification and definition in 1999, female sexual dysfunction consists of four subgroups: hypoactive sexual desire disorder, sexual arousal disorder, orgasmic disorder and sexual pain disorder.[78] Sexual difficulties are reported often to appear together with the initial symptoms of disease and continue, although with different clinical scenarios, as attempts are made to resume sexual relations.[79] Sexual dysfunction develops early on after treatment and does not tend to resolve if left untreated.[79]

Previous reports: Andersen and van der Does have published a review[80] of sexual dysfunction after various treatments for gynaecological malignancies (Table 2).

Table 2 Compilation of sexual dysfunction after gynaecological cancer treatment[80]

	"Sexual inactivity"	Decline in frequency of intercourse	Sexual dysfunction	Dyspareunia
Surgery alone	20%	30%	25-40%	30%
Radiotherapy alone	20%	40%	40-50%	25%
Combination of surgery and radiotherapy	15%	40%	25-50%	35%

Disrupted sexual response cycle: The sexual response cycle[65] may be affected at any stage by cervical cancer or its treatments:

Desire (Table 3): The observed prevalence of low or decreased sexual desire among women with a history of gynaecological cancer (often mixed diagnoses in reports) after surgery is 5-34%,[81-84] 9-50% after preoperative brachytherapy and surgery,[85,86] 0-53% after surgery and external radiotherapy,[81,82,87] 10-65% after radiotherapy alone[82-84,86,88-90] and 8-54% after various treatments.[91-95] A low level of sexual desire is also common in the general female population (prevalence 15-43%).[96-98] Two studies compare female cancer patients (gynaecological or breast) and population controls and show equal levels of sexual desire.[76,99]

Excitement: There are some reports on reduced excitement, but only limited prevalence data on specific symptoms, e.g. no data on genital vasocongestion and two reports of reduced genital sensations (prevalence 16-18%).[92,93] The observed prevalence of reduced excitement is 12-29% after various treatments.[91] Studies reporting reduced excitement as affected arousability scores show a decline in arousability.[92,93,100]

Lubrication (Table 3): The prevalence of diminished lubrication in gynaecological cancer patients is reported in one study after surgery (prevalence 75%),[101] in one study after preoperative brachytherapy and surgery (17%),[86] in one study after surgery and external radiotherapy (prevalence 60%),[87] in three studies after radiotherapy alone (20-58%)[86,102,103] and in one study after various treatments (37%).[104] There are, however, more observations regarding reduced lubrication but, in these studies, scores are used and no prevalences are available. There is one published documentation regarding reduced lubrication related to oestrogen depletion among cervical cancer survivors: Pikin showed that 20% had reduced lubrication after radiotherapy alone and topical oestrogen, while 35% had this condition after radiotherapy alone and placebo cream (n=93).[103]

Orgasms (Table 3): Reduced frequencies of orgasms have been observed after preoperative brachytherapy and surgery in 5%;[85] after surgery and external radiotherapy in 44%,[87] after radiotherapy alone in 33-74%[84,88,105] and after various treatments in 3-29%.[91-93,104] There are no studies specifically reporting orgasm frequency after radical hysterectomy alone. Dysfunctional orgasms have been observed in 3-11% of patients after cervical cancer therapy.[104] There are more studies on affected orgasm (function and frequency), but they present scores without prevalences.

Dyspareunia (Table 3): The observed prevalence of dyspareunia is 10-53% after surgery alone,[81,82,101,104,106,107] 0-17% after preoperative brachytherapy and surgery,[52,85,86,107] 0-67% after surgery and external radiotherapy,[81,82,87] 2-54% after radiotherapy alone[82,86,88-

[90,102-104,108] and 4-40% after various treatments.[91-94] The comparable estimate for healthy women is 0-3%.[76,109] One author (Pitkin) has studied the effect of topical oestrogen therapy on cervical cancer survivors regarding its significance for dyspareunia: Of 31 patients treated with radiotherapy alone, 12 (39%) reported dyspareunia, and, among these, 10 reported varying degrees of relief following the use of topical oestrogen.[110] In his other study, 23% of the women treated with radiotherapy alone reported dyspareunia after treatment with topical oestrogen and 53% after a placebo cream.[103]

The ***frequency of intercourse*** is used as a measure of sexual dysfunction or negatively affected sexual adjustment. The intercourse frequency is generally reported to be decreased in gynaecological cancer survivors: in 6-50% after surgery,[82-84] in 16% after preoperative brachytherapy and surgery,[86] in 33% after surgery and external radiotherapy,[82] in 32-79% after radiotherapy alone[82-84,86,88,89,111] and in 6-57% after various treatments.[88,91-93,112] The percentage of patients "abandoning sexual activity" following cancer treatment is higher (mean 15-20%)[80] than the "normal" base rate for healthy counterparts (5-15%),[80] or, in longitudinal studies, starting at the diagnosis of cancer (1-5%).[91,100,104]

Vaginal stenosis and shortening: The terms stenosis, shortening and narrowing of the vagina (Table 3) are alternately used when pathophysiological or anatomical aspects of vaginal side effects are reported. For simplicity, previously published prevalences of the three terms are reported together here. The reported prevalence of the condition is 0-17% after radical hysterectomy,[74,81,82,107] 0-4% after preoperative brachytherapy and surgery,[52,86,107,113] 0-100% after surgery and external radiotherapy,[74,81,82,87,102,111] 0.2-100% after radiotherapy alone[74,82,86,88,89,102,103,108,114-117] and 13-50% after various treatments.[92,94,104] Topical oestrogen has been suggested to have a beneficial effect on preventing vaginal stenosis (and atrophy) after radiotherapy.[103] There are no published studies on patient's assessment of vaginal length.

Atrophy of the vaginal epithelium has been reported in 0% after radical hysterectomy,[74] in 4% after preoperative brachytherapy and surgery[86] and in 57-100% after external radiotherapy alone,[74,86,103] but there are no published data on the prevalence after surgery and external radiotherapy.

Postcoital vaginal bleeding: In review articles and clinical guidelines, vaginal bleeding at intercourse is mentioned as a possible reason for distress without presenting data on prevalences.[70,118] There is only limited information on the prevalence of vaginal bleeding in connection with intercourse (table 3) after treatment for cervical cancer, but the reported prevalence is 8% after radical hysterectomy,[101] 0% after preoperative brachytherapy and surgery[86] and 0.7-36% after radiotherapy alone.[86,90,102,108] Pitkin reported "a decline in

bleeding and/or discharge" after radiotherapy alone from 51% to 10% after topical oestrogen therapy.[110]

Table 3 Decreased sexual desire, decreased lubrication, dyspareunia, reduced orgasms, postcoital bleeding, vaginal stenosis and/or narrowing. Percentage of women with impaired function. For references see text.

Treatment	Desire	Lubrication	Orgasms	Dyspareunia	Bleeding	"Stenosis"
Surgery	5-34%	75%*	NR	10-53%	8%*	0-17%
Brachytherapy and radical hysterectomy	9-50%	17%*	5%*	0-17%	0%*	0-4%
Surgery and external radiotherapy	0-53%	60%*	44%*	0-67%	NR	0-100%
Radiotherapy (external +/- brachy)	10-65%	20-58%	33-74%	2-54%	0.7-36%	0.2-100%
Various treatments	8-54%	37%*	3-29%	4-40%	NR	13-50%

NR = no reports with prevalences available. ***SIC!*** Data in table without **range** is based on one report only.

Psychosocial, marital and fertility aspects of sexuality: A sense of decreased femininity[87,88,106] and negatively affected bodyimage[84,119-122] has been reported to influence sexual behaviour and satisfaction after cancer therapy in women.[92] Fear of injury, pain, recurrence or infection has also been reported to possibly affect sexual function in both the woman and her partner (prevalence 14-43%).[82,87,88,90,102] Also fear of the spouse contracting cancer from the patient has been reported in one study (prevalence 14%),[92] or suggested to be a possible problem.[88,123,124] Guilt (at a conscious or subconscious level regarding previous sexual experiences) has been reported to influence the course of adjustment.[92,95,123,124] Corney reported that 9 of 69 women (13%) felt some blame attributable to sexual relationships.[92] Poor communication and poor marital adjustment[83,125,126] have been reported to possibly have a major influence on sexual function after treatment of cervical cancer. In Adelusi's study, 21 of 78 women (36%) were divorced one year after treatment.[90] In Lalos' study of 47 partners of cervical or endometrial cancer patients, one third could not discuss the sexual and marital consequences of the cancer treatment.[126]

Infertility after cancer treatment is reported to be "a double burden" adversely affecting the life (prevalence 40-58% in women "of child-bearing age").[101,118,127] The treatment-induced infertility and sexual dysfunction have been reported to be an extra impediment to starting a new relationship (and to increase the risk of losing an existing dysfunctional one).[75]

Hormones: Surgical removal of the ovaries or radiotherapy leads to castration in all patients.[128] Even if the ovaries are left *in situ* after surgery, minor disturbances of the blood supply may lead to impaired function, which may compromise the production of hormones (prevalence 2-69%).[129-132] The ovarian stroma might, however, still produce androgens even after radiotherapy,[48] which complicates the evaluation. There is no available documentation on the significance of testosterone for the libido in cervical cancer survivors. Studies on the effects of surgery on hormonal levels and libido or the effects of testosterone replacement therapy generally cite malignancy as an exclusion criterion.

Urinary Function

Physiology: With filling of the bladder with urine from the ureters, the tension of the bladder wall increases and, at a certain point, a micturition reflex is initiated. Sensory fibres in the bladder wall are stimulated by a rise in tension and signals pass back to the central nervous system via the pelvic splanchnic nerves (S3-S4). Efferent parasympathetic fibres in the pelvic splanchnic nerves are stimulated and cause the bladder wall muscles to contract. A reciprocal relaxation of the vesical sphincter and a voluntary relaxation of the urethral sphincter (n. pudendus, S2-S4) allow urine to pass through the urethra. Relaxation of the pelvic floor musculature (S2) is also included.[133]

Pathophysiology: Voiding problems after radical hysterectomy have been attributed to detrusor instability,[134] denervation of the bladder and nerve lesions.[135] Various extents of resection of the cardinal ligament[135-137] and upper vagina[138] have an impact on voiding dysfunction. New data indicate that the extent of resection of the uterosacral ligament can also be of significance for the voiding function.[136] Urothelial damage (leading to irritative voiding symptoms or continence problems) and damaged vascular endothelial cells (leading to bladder fibrosis with subsequent reduced bladder capacity) have been suggested to constitute the pathophysiology behind radiation cystitis, but the exact mechanisms are not known.[139] Recurrent urinary tract infections may be the result of residual urine and atrophic urothelium.

Previous reports (Table 4): Historically, the incidence of urinary fistulas (vesico-vaginal, ureterovaginal) after radical hysterectomy was 10-20%.[49] In modern series (after 1990), the incidence is 0-4%.[14,49,51,139-141] The incidence of urinary fistulas is 0-4% after preoperative brachytherapy and surgery,[28,52,113,142-144] 0-3.5% after surgery and external radiotherapy[14,42,49,51,143,145] and 0-6% after radiotherapy alone.[114,115,140,145]

Table 4 Some urological disorders in cervical cancer survivors (for references, see text)

	Urinary fistulas	Impaired bladder sensitivity	Straining to void	Residual urine
Radical hysterectomy	0-6%	4-88%	13-36%	4-54%
Brachytherapy and surgery	0-4%	3-35%	50%*	9%*
Surgery and external radiotherapy	0-3.5%	0-73%	0-56%	19%*
Radiotherapy (external)	0-6%	3%*	6-11%	21%*

	Incontinence	Voiding frequency increased	Urgency	Nocturia
Radical hysterectomy	0-39%	9-37%	NR	11-67%
Brachytherapy and surgery	1-41%	NR	NR	NR
Surgery and external radiotherapy	0-63%	19-50%	NR	46-80%
Radiotherapy (external)	21-45%	14-36%	47%*	35%*

NR = no reports with prevalences available. * **SIC!** Data in table without **range** are based on one observation only.

Voiding difficulties: In modern series (after 1980), impaired bladder sensitivity has been observed after radical hysterectomy alone in 4-88%,[49,50,138,146-155] in 3-35% after preoperative brachytherapy and surgery,[152,156] in 0-73% after surgery and external radiotherapy and in 3% after radiotherapy alone.[149] A need to strain to void has been observed in 13-36% after radical hysterectomy alone,[42,101] in 50% after preoperative brachytherapy and surgery,[152] in 0-56% after surgery and external radiotherapy[42,149,155] and in 6-11% after radiotherapy alone.[149,157] Residual urine has been observed in 4-54% after radical hysterectomy alone,[101,148,153,158,159] in 9% after preoperative brachytherapy and surgery,[85] in 19% after surgery and external radiotherapy[153] and in 21% after radiotherapy alone.[157]

Continence difficulties: Frequency is observed after radical hysterectomy alone in 9-37%,[153] after surgery and external radiotherapy in 19-50%[153,155] and after radiotherapy alone in 14-36%.[157,160] There are no reports on the prevalence after preoperative brachytherapy and surgery. Urgency has been observed after radiotherapy alone in 47%,[157] but no reports on the prevalence after radical hysterectomy, after preoperative brachytherapy and surgery or after surgery and external radiotherapy. It is possible that some women having urgency are reported as having (urge) incontinence. Incontinence is observed in 0-39% after radical hysterectomy alone,[50,81,101,146,148,149,151,152,154,155,159] in 1-41% after preoperative brachytherapy

and surgery,[53,144,152,161,162] in 0-63% after surgery and external radiotherapy[81,146,149,151,155] and in 21-45% after radiotherapy alone.[149,157] Nocturia is observed after radical hysterectomy alone in 11-67%,[101,153,155] after surgery and external radiotherapy in 46-80%[153,155] and after radiotherapy alone in 35%.[157] There are no reports on the prevalence of nocturia after preoperative brachytherapy and surgery.

Bowel Function

Physiology: The innervation of the gastrointestinal tract relies largely on the vagus for its parasympathetic supply, but this ceases at the terminal part of the transverse colon. The remaining intestine is supplied by preganglionic fibres from the pelvic splanchnic nerves via the hypogastric plexuses (S2-S4) and visceral branches of the lumbar sympathetic trunk in company with the aortic plexus (Th11-L2). The filling of the rectum usually follows after the taking of food, which, through a gastrocolic reflex, sets off activity of the colon. Distension of the rectum initiates a defecation reflex. The contraction of the sphincter ani internus, which is maintained by its sympathetic nerve supply (sacral splanchnic nerves, S2-S4), is inhibited by its parasympathetic nerve supply (pelvic splanchnic nerves, S2-3). With the voluntary relaxation of the sphincter ani externus (S4) and muscles of the pelvic floor (S2), defecation occurs.[133] Gastrointestinal hormones are also involved in the regulation of bowel movements.

Pathophysiology: After radical hysterectomy, defecation may be compromised owing to damage to rectal nerve plexuses during the resection of the cardinal ligaments.[163] Proctitis is an inflammatory process affecting the rectal mucosa. The underlying pathology of submucosal injury is a combination of fibrosis, ischaemia (due to a compromise blood supply) and subsequent ulceration, which can be localised, diffuse, or full thickness, penetrating the wall of the rectum. The clinical signs are tenesmus, urgency, diarrhoea and/or constipation, anal sphincter dysfunction (affecting control of the bowels), mucoid or bloody discharge per rectum or bleeding with ulceration, which may perforate. The risk of severe proctitis is increased when the maximal rectal dose is more than 80 Gy.[164] Radiotherapy-induced chronic damage (fibrosis and vascular insufficiency) in the small intestine mucosa, submucosa, receptors and smooth muscles[165] and also secondary bile acid malabsorption, small intestine bacterial overgrowth and intestinal inflammation[166] have been suggested to be causes of small intestine enteritis with subsequent diarrhoea, frequency and urgency problems,[167-170] accompanied by varying periods of constipation. Probably the most significant non-radiation-related injury risk factor is a history of prior abdominal surgery or pelvic inflammatory disease.[115] A history of hypertension or diabetes mellitus may be associated with a greater risk

of late intestinal injury after radiotherapy.[171] Chronic radiation injury of the nerve function of the anal sphincter[172,173] or lumbosacral nerve plexus[174] has been reported after external radiotherapy with subsequent faecal leakage.

Previous reports: The incidence of observed rectovaginal fistulas is 0-0.6% after radical hysterectomy alone,[14,49,140] 0.4-1.7% after preoperative brachytherapy and surgery,[27,28,54,175-177] 0.6-2.3% after surgery and external radiotherapy[14,49,140,178] and 0.6-7.3% after radiotherapy alone.[27,42,55,108,114-116,140,175,179-182]

Table 5 Some bowel disorders in cervical cancer survivors. For references, see text.

	Rectal fistulas	Constipation	Frequent defecations/ diarrhoea	Proctitis	Enteritis
Radical hysterectomy	0-0.6%	5-80%	19%*	NR	NR
Brachytherapy and surgery	0.4-1.7%	1%*	1%*	1-8%	0.5-2.2
Surgery and external radiotherapy	0.6-2.3%	38%*	25%*	0.9%*	NR
Radiotherapy (external)	0.6-7.3%	NR	1.8-95%	1.3-47%	2.5-3.4%

NR = no reports with prevalences available. * **SIC!** Data in table without **range** are based on one observation only.

The prevalence of constipation after radical hysterectomy is 5-80%,[101,163,183,184] but bowel dysfunction after radical hysterectomy is only rarely reported in the literature.[101,163,183-187] There is one published report on constipation after preoperative brachytherapy and surgery (prevalence 1%),[144] one after surgery and external radiotherapy (prevalence 38%)[101] and none after radiotherapy alone.

In previous reports, frequent bowel movements and diarrhoea are often used as synonyms, although some reports distinguish between these two entities. For simplicity, previous prevalences of the two symptoms are reported together here. Increased stool frequency and/or diarrhoea has been observed in 19% after radical hysterectomy,[101] in 1% after preoperative brachytherapy and surgery,[144] in 25% after surgery and external radiotherapy[101] and in 1.8-95% after radiotherapy alone.[108,115,160,188,189] Many women with frequent bowel movements and/or diarrhoea are probably within the reports of proctitis; the observed prevalence is 1-8% after preoperative brachytherapy and surgery,[54,113,144,190] 0.9% after surgery and external radiotherapy[178] and 1.3-47% after radiotherapy alone.[42,54,55,108,114-116,145,181,189] They may also be within the reports of enteritis; prevalence 0.5-2.2% after preoperative brachytherapy and surgery[54,113] and 2.5-3.4% after radiotherapy alone.[54,181]

There are no reports on proctitis or enteritis after radical hysterectomy alone and no reports on enteritis after external radiotherapy and surgery. Faecal leakage is reported in one study[101] in 14% after radical hysterectomy alone and in 25% after the addition of external radiotherapy to surgery, and is mentioned as a potential problem after radiotherapy.[172,191]

Lymphoedema

Physiology: The lymphatic drainage of the cervix proceeds via preureteral, postureteral and uterosacral routes into the parametrial, internal iliac (obturator, hypogastric), external iliac, presacral and common iliac nodes (first station). Para-aortic nodes are the second station.[3] Pelvic lymphadenectomy performed during a Piver type III radical hysterectomy [193] usually includes excision of the external iliac, hypogastric, obturator and sacral nodes. Parametrial nodes are included in the hysterectomy specimen.

Pathophysiology: Secondary lymphoedema is the accumulation of lymph in the interstitial spaces, principally in the subcutaneous fat, caused by a defect in the lymphatic system, which leads to an abnormal collection of excessive tissue proteins, oedema, chronic inflammation and fibrosis.[194] Recurrent lymphangitis and cellulitis can lead further to gradual obliteration of lymphatic vessels.

Previous reports: The reported prevalence of lymphoedema grades 3-4 (elephantiasis, or defined as "severe") is 0.7-9% after radical hysterectomy alone,[14,42,49,51,81,147,183,195,196] 2-12% after preoperative brachytherapy and surgery,[29,144,162,197] 7-22% after surgery and radiotherapy[14,145,146,198,199] and 0.4-1.8% after radiotherapy alone.[42,56,108,145] Three reports exist were the women's assessments are included (Table 6).

Table 6 Lymphoedema, objective and/or subjective criteria (patient's assessment). Prevalence in percentage.

First author, year	Number	Prevalence	Treatment	Criteria
Martimbeau, 1978[200]	281 102 17	23% 30% 29%	IC + S S + RT +/- IC S	"Cosmetic nuisance", "pain or a feeling of distension", or "the need to wear larger shoes"
Høyer, 1990[81]	115	23%	S +/- RT	Complained about oedema of the legs
Werngren-Elgström, 1994[201]	44 6	36% 67%	IC + S IC + S + RT	Some subjective swelling

RT = External radiotherapy, S = Surgery, IC = Intracavitary brachytherapy

Women with breast cancer who develop lymphoedema exhibit higher levels of psychosocial, sexual and functional morbidity than women with breast cancer who do not

develop this complication.[202] No similar studies after cervical cancer therapy have been published.

Summary of Previous Reports on Morbidity Related to the Mode of Treatment

Radical hysterectomy alone results in voiding difficulties (prevalence 4-88% depending on outcome criteria and radicality of procedure), urinary continence difficulties (0-67%) constipation (5-80%), vaginal shortening (0-17%), sexual dysfunction (0-100%), lymphoedema (0.7-29%) and urinary (0-4%) and rectovaginal fistulas (0-0.6%).

Preoperative brachytherapy and radical hysterectomy result in voiding difficulties (prevalence 3-50%), urinary continence difficulties (1-41%), vaginal stenosis (0-4%), sexual dysfunction (0-50%), lymphoedema (2-36%) and urinary (0-4%) and rectovaginal fistulas (0.4-1.7%).

External radiotherapy and surgery result in voiding difficulties (prevalence 0-73%), urinary continence difficulties (0-80%), frequent defecation or diarrhoea (25%), vaginal stenosis (0-100%), sexual dysfunction (0-100%), lymphoedema (7-67%) and urinary (0-3.5%) and rectovaginal fistulas (0.6-2.3%).

Radiotherapy alone results in voiding difficulties (prevalence 3-12%), urinary continence difficulties (14-47%), frequent defecations or diarrhoea (1.8-95%), proctitis (1.3-47%), vaginal stenosis (0.2-100%), sexual dysfunction (0.7-100%), lymphoedema (0.4-1.8%) and urinary (0-6%) and rectovaginal fistulas (0.6-7.3%).

Sexual abuse

The incidence of sexual abuse among women with cervical cancer has not been defined. In Schover's study of 61 women, 8 reported "sexual trauma" (rape, incest victimisation, molestation as a child, molestation of own children, or multiple events) among the 31 women who were asked about "family violence".[104]

Patient Preferences

The issue of trading off quantity of life for quality of life has been examined in only one study of cervical cancer patients. In the study by Jim Wright and co-worker of patients treated with brachytherapy for cervical carcinoma (n=18) and newly diagnosed patients (n=20), the majority of patients preferred low-dose-rate (LDR) (56%) to high-dose-rate (HDR) (34%) brachytherapy if the methods were isoeffective.[203] Elderly gynaecological cancer patients have been reported to desire radical surgery and cure of the disease as strongly as young ones.[204]

GENERAL AIMS

To investigate the excess risk of long-term distressful symptoms after radical hysterectomy (as compared to no radical hysterectomy);

To investigate whether the addition of preoperative brachytherapy implies an excess risk of long-term distressful symptoms;

To determine whether sexual abuse modifies the risk of long-term distressful dysfunction in cervical cancer survivors after radical hysterectomy or brachytherapy;

To investigate patients' willingness to trade off optimal survival possibilities for a diminished therapy-induced symptom burden.

MATERIAL AND METHODS

The basic study design in papers I-V can be described as a follow-up of two cohorts.

Study Base

The patient population in papers I-V comprised all 332 women under the age of 80 registered at the seven departments of gynaecological oncology in Sweden in 1991-92 as having early (FIGO stage IB-IIA) cervical carcinoma and being alive at the start of the follow-up in November, 1996. The treatment of cervical cancer in Sweden is centralised in the seven regional departments of gynaecological oncology, i.e. all women with the diagnosis are referred to these centres for decisions about treatment at the discretion of the physician responsible, following specified regional treatment standards. The 489 women in the control group were randomly selected from the Swedish population register and were sampled to construct an age and geographic distribution similar to that of the cervical cancer patients. The study was conducted between November 1996 and May 1997.

Data Collection

Each woman was sent a letter of introduction between November, 1996, and May, 1997. The letters to the women with a history of cervical cancer were signed by Dr Bergmark and the head of the regional department of gynaecological oncology, explaining the aim of the study and containing an appeal to participate for their own benefit, but also to promote the understanding of all women with cervical cancer, current and future. The letters to the controls were signed by Dr Bergmark and Dr Steineck. The controls were informed in their introduction letter that they were randomly selected to study the prevalence of different symptoms in the general population, ranging over different ages, and that we were also studying a group of patients with gynaecological diseases. We particularly emphasized the importance of receiving information from all subjects, also those without symptoms, in order to get a true picture. Those who did not return an enclosed reply form, were telephoned two weeks later. If they were unreachable by telephone they were sent a second letter asking them to let us know whether they wanted to participate in the study or not. Everyone had the opportunity to refuse participation or obtain further information before deciding. We sent the questionnaire to all who answered favourably. The majority of women returned the questionnaires without further contact. Those who did not return the questionnaire within two or three weeks were contacted by telephone, if possible, or by letter. All received a letter of

thanks, which also served as a reminder. The study was anonymous in order to eliminate potential bias and the answers were recorded using a special reply form. The study was approved by the Regional Ethics Committee at the Karolinska Institute (Ref. No. 96-134).

Questionnaires, Outcome Measures

A questionnaire assessing urinary function, defecation and bowel problems, lymphoedema and problems concerning sexual function and the resulting distress from the symptoms was constructed. The questionnaire was initially developed during successive in-depth interviews with patients and clinicians to map the relevant symptoms and symptom-induced distress. A preliminary questionnaire was constructed, based on the interviews and previous questionnaires developed in our group.[205,206] It was tested at successive face-validity interviews and was adjusted progressively. Two pilot studies were conducted, each with 30 patients and 30 controls (approved by the Local Ethics Committee, Ref. No. 95-303) and the questionnaires and procedures for collecting the data were refined. The whole questionnaire consisted of 136 questions (293 variables) for the cases and 115 questions (265 variables) for the controls. The sections assessing sexual, urinary and bowel function and lymphoedema consisted of 77 questions. We wanted to use our data in direct conversations with our patients and colleagues and chose to focus on verbal categories as interpretable effect measures. The answers were generally given in four to seven verbal categories (Likert format) from no symptoms to severe symptoms – for example:

Have you noticed during the last 6 months that the moistness of your vagina (lubrication) would not be sufficient for sexual intercourse?

☐ Not relevant, I have not engaged in sexual intercourse (or similar activities) during the last 6 months

☐ Not at all
☐ I have noticed a little insufficient lubrication
☐ I have noticed moderate insufficient lubrication
☐ I have noticed very insufficient lubrication

To each question, the women had the option to answer that the symptom was not relevant. Different aspects of a symptom were assessed by separate questions measuring the nature, occurrence and/or intensity. The women were asked whether or not and to what extent the symptom distressed them – for example:

If you have had insufficient lubrication during the most recent 6 months and it were to persist, what do you think about it?

☐ Not relevant - I have not noticed any insufficient lubrication

☐ It does not distress me at all
☐ It distresses me a little
☐ It distresses me moderately
☐ It distresses me a lot

Regarding some comprehensive entities (overall sexual dysfunction, intercourse dysfunction, urinary dysfunction, bowel dysfunction and lymphoedema), the impact on their well-being was also included. The three-level approach (occurrence, symptom-induced distress, impact on well-being) was based on Ásgeir Helgason's work,[207] inspired in turn by the work of Portenoy and colleagues at the Memorial Sloan-Kettering Cancer Center in New York.[208,209] Furthermore, the questionnaire included some questions pertaining to sexuality in relation to marital satisfaction, body image, sense of femininity, attraction, sexual initiative, infertility and sense of loss of the uterus. Questions pertaining to sexual abuse included incidence figures (ever or never), grading of abuse (patient's subjective valuation: none, some degree, moderate degree, severe degree), frequency (repeated or not), incest (yes or no), age at first abuse, impact on present sexuality (none, little, moderate, much).

Psychological and quality-of-life factors were further examined with the following (validated) instruments: **STAI-T**, Spielberger's State-Trait Anxiety Inventory,[210] a self-explanatory instrument for the assessment of anxiety consisting of 20 statements related to symptoms of anxiety or composure; **CES-D**, Center for Epidemiological Studies Depression Scale,[211] a self-report for the assessment of depression-related symptoms developed by the National Institute of Mental Health, USA. It consists of 20 statements (items) related to such symptoms as dispiritedness, sense of guilt, helplessness, hopelessness, insomnia and lack of appetite during the last week. For both these scales (STAI-T and CES-D), each statement is rated on a 4-point Likert scale. A summary score is calculated with a maximum value of 80 and a minimum value of 20 and then divided by 20 (or the actual number of items answered in each scale), giving a possible maximum value of 4 (worst possible). We excluded responses with 18 or fewer ratings (of 20 possible). **GQL**, Göteborg Quality of Life,[212] is a Swedish instrument initially developed for the assessment of well-being and symptoms among men born in 1913 and 1923 in Gothenburg, which has been used in many population-based surveys of self-reported quality of life. The questions concern 15 areas of social,

physical and psychological well-being (e.g. home and family, residence, work, economy, mood, patience, appreciation inside and outside the home), each with a possible score of 1 to 7. A summary score was calculated and divided by 15 (or the actual number of items answered in each scale), producing a possible best score of 7 and a possible worst score of 1. We excluded responses with 13 or fewer ratings (of 15 possible). A 7-point **visual digital scale** [213,214] was used for the assessment of some general concepts (psychological well-being, anxiety, depression, level of energy, physical well-being).

In a series of trade-off questions, the women with a history of cancer were asked to consider hypothetically the possibility of risking a poorer prognosis if it had been possible for them to forgo the surgery, intracavitary radiotherapy or external radiotherapy, respectively. An alternative (hypothetical) treatment with fewer side effects was outlined, but with the risk of a diminished survival chance, specified as a percentage. The choice was marked on a vertical line specifying the risk of diminished survival (0%, 1%, 5%, 10%, 20%, 30%……90% and 100%).

Information was also collected on potential confounding and effect-modifying variables, including smoking, level of education, pre-treatment and current occupation and social status, age at first intercourse, religion, other operations and diseases (such as hypertension, diabetes mellitus, psychiatric disorders), including medication for pre-existing conditions and hormone replacement therapy and whether they had been treated for any recurrence. Information about the treatment was collected from the patients to safeguard anonymity.

Statistical Analysis

The responses to the questionnaire were dichotomised and the results were presented as ratios of proportions, i.e. "relative risks", RR, calculated as the proportion of cases reporting the outcome divided by the proportion of controls reporting the outcome. Estimated RR and associated 95% confidence intervals (CI) were calculated using the Mantel-Haenszel method.[215] Calculations were performed using the FREQ procedure of the SAS Sy[216]stem (Version 6.12 TS045). Results are presented in terms of the number and proportion of cases and controls reporting the outcome (from which the crude RR and CI can be estimated), along with the Mantel-Haenszel estimate of the age-adjusted RR and 95% CI.

RESULTS

Response Rates, Characteristics

Information was supplied by 256 (77%) of the 332 cases and 350 (72%) of the 489 controls. Their mean ages at the time of answering the questionnaire were 51 and 52 years, respectively, but the distribution between the groups varied (see also **Paper I**, Table 1). The mean age at the time of treatment was 45 years. The proportion of women living alone at the time of follow-up was higher among the cases than the controls. The treatment given is shown in Table 7. Moreover, adjuvant chemotherapy was given to 14%, distributed among the different groups. The majority of these women were also treated with adjuvant external radiotherapy (34/56).

Table 7 Treatment given.

Treatment	Number
Radical hysterectomy alone	93 (36%)
Radical hysterectomy and brachytherapy	57 (23%)
Radical hysterectomy and external radiotherapy (no brachytherapy)	24 (9%)
Radical hysterectomy, external radiotherapy and brachytherapy	55 (21%)
Radiotherapy alone	22 (9%)
Information missing	5 (2%)

At the time of the study, two centres (Stockholm, Uppsala) advised all women (without contraindications) with stage IB-IIA cervical cancer to undergo brachytherapy followed by radical hysterectomy. The preoperative brachytherapy was typically given as two medium-dose-rate applications (remote load cesium-137), three weeks apart, each application comprising 22.5-24 Gy to point A.[217] The surgery was generally performed four weeks after the second brachytherapy. Five centres (Göteborg, Linköping, Lund, Umeå, Örebro) advised these women to undergo primary radical hysterectomy. In Sweden, at the time (and today), pelvic lymphadenectomy performed during a radical hysterectomy usually includes excision of the external iliac, hypogastric, obturator and sacral nodes (Piver type III).[193] Few, if any, surgeons perform para-aortic lymphadenectomy. Patients with high-risk disease (lymph node metastasis, close or positive surgical margins) were offered postoperative radiotherapy. At all centres, standard postoperative external radiotherapy comprised 40-54.0 Gy to a pelvic field. In Stockholm, the field covered the para-aortic lymph nodes up to the renal artery level as well (40 Gy). In Göteborg, Umeå and Örebro, in high-risk disease, postoperative brachytherapy was given in addition to the external radiotherapy. Some patients received postoperative chemotherapy in Göteborg, Linköping and Lund. Patients deemed unsuitable

for surgery (advanced age, concomitant disease) were treated in all centres with radiotherapy alone, usually a combination of brachytherapy and external irradiation.

Fifty-seven per cent of the cases used oral or transdermal systemic oestrogen, as compared with 20% of the controls. Eleven per cent and 8%, respectively, regularly used topical oestrogen. Seventy-four per cent of the former patients, of all ages, stated that they welcomed information from their physician about sexuality. Less than 1% (n=2) of the former patients took a negative view of information on sexuality and the rest were neutral.

Reasons for Non-response

Cases (23%): No reason stated: 10%. Not returning the questionnaire: 6%. Unreachable by letter or telephone: 4%. Lack of time: 1%. Questionnaire too extensive: 0.3%. Other health problems: 2%. Emotional strain: 1%.

Controls (28%): No reason stated: 18%. Not returning the questionnaire: 1%. Unreachable by letter or telephone: 4%. Lack of time: 2%. Questionnaire too extensive: 1%. Other health problems: 1%. Emotional strain: 1%.

Results, Papers I-VI

Radical surgery alone (radical hysterectomy with pelvic lymphadenectomy) increased the prevalence of the following symptoms (compared with controls): lymphoedema (4–8-fold depending on definition), bladder-emptying difficulties (9-fold), straining during micturition (22-fold) and vaginal changes leading to dyspareunia (6–7-fold) (**III**). Symptom distress was considerable, but less than one fifth of the women were at all willing to trade off optimum long-term survival for freedom from treatment-induced symptoms and, of these, few were prepared to risk more than 1% decreased survival. In summary, radical surgery alone for cervical cancer adversely affects lymph drainage, micturition and sexual function.

The addition of preoperative brachytherapy to radical hysterectomy gave increased prevalences of defecation urgency; 10/57 (18%), frequent nocturia; 5/57 (9%) and a moderate to high degree of anxiety; 28/56 (50%), as compared to 5/89 (6%), 1/92 (1%) and 26/89 (29%), respectively, after radical hysterectomy (**IV**). No other statistically significant differences were found. The prevalence of distress from all bowel symptoms, as well as from all urinary symptoms, was somewhat higher in women who had undergone preoperative brachytherapy, but the relative risks covered 1.0. We found clear effects on the risk of long-term distressful bowel symptoms after external radiotherapy, illustrating the sensitivity of our

method (**II**, **IV**). Most women (47/54, 84%) gave higher priority to maximal survival than to freedom from long-term distressful symptoms of preoperative brachytherapy (**IV**). In summary, the addition of preoperative brachytherapy to radical hysterectomy probably results in defecation urgency, nocturia and anxiety in a few women.

Sexual dysfunction is a prime concern after all modes of treatment for cervical cancer (**I-V**). Women of all observed ages were sexually active and 167 (68%) of 247 cases and 236 (72%) of 330 controls reported regular vaginal intercourse. Among sexually active women, 26% of the cases and 11% of the controls reported that their vagina was not sufficiently lubricated for sex, 26% versus 3% reported a short vagina and 23% versus 4% an insufficiently elastic vagina. The type of treatment had little effect on the prevalence of specific vaginal changes, if any (**I**, **IV**). Dyspareunia was more common among the cases (mean 16%, range 9-29% for different treatments) than among the controls (2%) (**I**). There was a higher prevalence of superficial dyspareunia among women treated with radiotherapy (range 19-29% for different treatments) than radical hysterectomy alone (9%), but the relative risks covered 1.0 (**IV**). Twenty-six per cent of the cases and 8% of the controls reported moderate or much distress due to vaginal changes (**I**). The frequency of orgasms and orgasmic pleasure was similar in cases and controls.

Among women with a history of cervical cancer, 46 of 250 reported a history of sexual abuse (18%) (**V**). Among the controls, 50 of 332 women (15%) reported a history of sexual abuse. A history of sexual abuse results in a lifelong increased risk of sexual dysfunction and low level of well-being. We found that sexual abuse and cervical cancer were both independent risk factors for superficial dyspareunia. The relative risk was very high (30.0) when both factors were combined, illustrating a possible interaction between a history of sexual abuse and cervical cancer. The willingness to trade off optimal survival to avoid distressful symptoms did not vary with a history of sexual abuse. In summary, we found that both prior sexual abuse and a history of cervical cancer have certain long-term negative effects and that women with both factors are particularly at risk.

Lymphoedema was found to be more prevalent (**III-IV**) and more distressful (**II**) than in the majority of previous reports. We observed no major differences in prevalence according to the mode of treatment (range 14% to 20% when defined as constantly swollen legs).

When ranking distressful symptoms (**II**), signs of sexual dysfunction were the most prevalent among all women treated for early cervical cancer. Eight of the nine most distressful symptoms in the whole group of women with a history of cervical cancer were related to sexual dysfunction (much distress, 14-19%). When all distress of any degree was compiled

for the whole group of cervical cancer survivors, overall bowel dysfunction was the foremost condition leading to distress (48% of the women). Lymphoedema was also a symptom associated with much distress in all treatment groups with a mean of 41% (all degrees). The addition of external radiotherapy to surgery resulted in a mixture of sex-related and irritative bowel symptoms as the foremost distressful conditions.

Psychological and physical well-being, level of energy, anxiety and depression, are, on a group level among cervical cancer survivors, on a par with, or better than, the reports on population controls (**III-IV**). Women with a history of sexual abuse have a lower level of psychological well-being than women without such an experience (**V**). Women treated with preoperative brachytherapy and radical hysterectomy have somewhat higher levels of anxiety than women treated with radical hysterectomy alone (**IV**).

The majority of women were unwilling to trade off optimal survival chances for a diminished therapy-induced symptom burden (**III-V**). There were, however, a few women who took a different standpoint and were willing to risk a poorer prognosis.

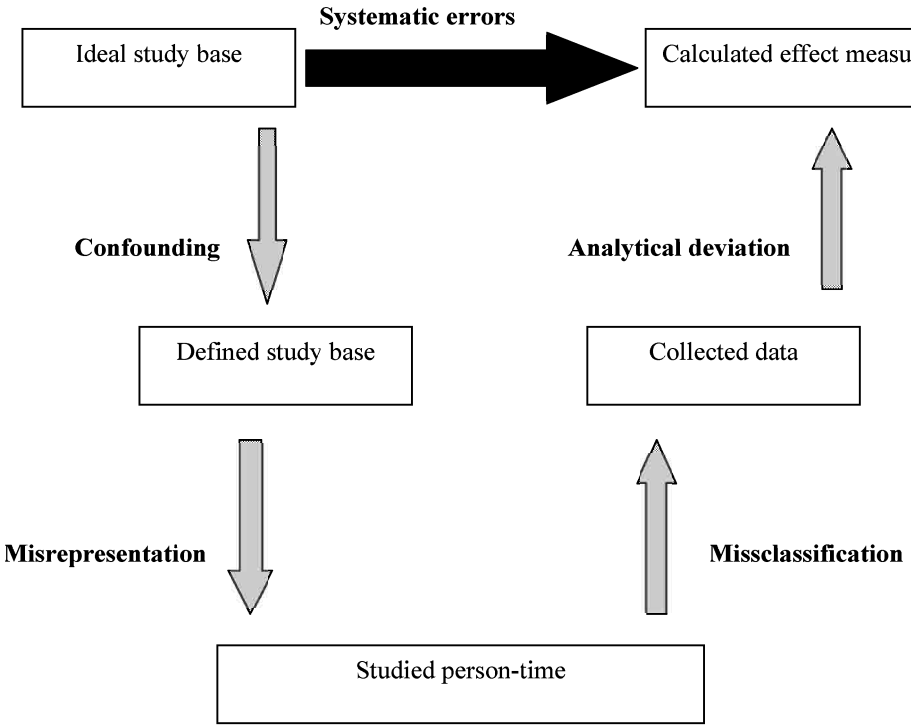
In order to suggest therapy modifications with the aim of diminishing the risk of long-term distressful symptoms in cancer survivors (**I-V**), we need data that relate details of therapy to the long-term symptom situation. In **VI**, we describe concepts and means we have used to assess distressful long-term symptoms. We focus on the subjective long-term situation and define symptoms as a perceived abnormality. For conceptual clarity, we consider one symptom at a time and do not include scales in which items are summarised. We translate (epidemiological) measures of disease occurrence in the population into measures of symptom occurrence in an individual. *Nature* separates specific symptom from one another. *Occurrence* describes how often the symptom appears, *intensity* its severity and *duration* how long it persists. The relevance of a symptom to emotions and social activities, e.g. cited as the associated symptom-induced *distress*, is a separate issue from symptom occurrence, intensity and duration.

DISCUSSION

Some Aspects on Design and Validity

A large, randomised, double-blinded and placebo-controlled study without loss of follow-up and with non-erroneous analyses provides valid data. All real-life studies deviate from this ideal setting and thereby involve validity problems to various extents. The validity problems can be discussed as systematic errors that cause the effect measure to deviate according to the rules of confounding, misrepresentation, misclassification, or analytical deviation (Figure 1) (Steineck, 1998).[218] In **VI**, we discuss how these errors are generally handled in our tradition. Some specific remarks are given below.

Figure 1. Validity model



Confounding

Survival and the risk of treatment-induced symptoms after preoperative brachytherapy would best be evaluated within a randomised trial in which women diagnosed with early-stage cervical cancer and scheduled for radical hysterectomy are included. The investigation reported here can be regarded as a "feasibility" study for such a randomised clinical trial determining, better than before, the "cost" (in terms of excess risk of distressful long-term symptoms) from the addition of preoperative brachytherapy and defining the women's view of the priority regarding the cost and optimal survival chances. The comparability in our non-randomised design is enhanced by the geographical variation in treatment policies around Sweden: in the studied population preoperative brachytherapy was offered to nearly all the women with early cervical cancer scheduled for radical hysterectomy in Stockholm and Uppsala, but not in the rest of the country. Still, it is reasonable to assume that patient selection (e.g., in distinguishing stage IIA from stage IIB) varies in different parts of the country, and a systematic error (confounding) resulting from this patient selection must be considered in interpreting our findings of an excess risk of defecation urgency, frequent nocturia and anxiety after the addition of preoperative brachytherapy. However, we find no reason to believe that the risk of defecation urgency, nocturia or anxiety in a cervical cancer survivor depends on the tumour being stage IIA or IIB. Another potential confounding factor is the extent of surgery and the skill of the surgeons, which may vary between centres and thereby vary with giving preoperative brachytherapy or not. To our knowledge, there is no indication of such a systematic variation or that any centre at the time had the ambition to save autonomic nerves (which may be responsible for compromised urinary or bowel function). Moreover, long-term anxiety may depend on the risk of psychological trauma in connection with the diagnosis and treatment, which, again, may vary around Sweden. We have no data on this matter.

The situation is more complex concerning radical hysterectomy (**VI**). A randomised study, comparing radical hysterectomy with no radical hysterectomy in women with cervical cancer certainly would determine differences in survival. However, concerning the question of to what extent the surgical trauma influences the risk of long-term distressful symptoms, any comparative data would be distorted by the symptoms induced by the growing tumour among women randomised to no radical hysterectomy. So, apart from being totally unethical (we cannot fail to treat these women), such a randomised study would not answer the question we asked. We contemplated a before-and-after study, but in this design (again) the tumour and the psychological burden of having a newly detected disease would compromise the

comparison, e.g., concerning symptom-induced distress. Also, in the after-situation, the women are older. So, the design we used can be considered the optimal one (**VI**) (besides randomising healthy women to radical hysterectomy or no radical hysterectomy, which would be unethical and impractical).

A large number of confounding factors must be considered, however, for the design we use, specific for every outcome studied (a confounder is related to both radical hysterectomy and the outcome, e.g., perceived vaginal shortness). Some potential confounders could be investigated statistically (directly or by "surrogate confounders"): we collected information on several demographic factors and adjusted the relative risk for them. Others could only be assessed; they include risk factors for cervical cancer, the history of contracting cervical cancer, the possibility of a "response shift",[219] tissue damage by the growing tumour before it was removed and all other aspects of the therapy besides the radical hysterectomy. For the findings we discuss as being real in **I**, **III-V** we have evaluated confounding, by measured and unmeasured confounders, and considered it unlikely that they explain the associations obtained.

A facilitating, if not necessary, condition for making a comparison between operated subjects and population controls (to evaluate the effect of the surgical trauma on the risk of long-term distressful symptoms) is the possibility of demarcating a study base without built-in confounding. Our registers in Sweden covering virtually the entire population, create good conditions for avoiding this error. Also, the organisation of health care, with most patients in a geographical region being treated at one centre of gynaecological oncology, promotes this kind of investigations. Thus, Sweden provides excellent circumstances to study the excess risk of long-term distressful symptoms after therapy.

Misrepresentation

We made a great effort to avoid validity problems introduced by non-participation. This included face validity to assess the respondents' motivation and aversion to different questions, efforts to make the layout of the questionnaire acceptable and to establish personal contact (by letter) with the woman before sending the questionnaire and a quick reminder by telephone if the questionnaire was not returned. Moreover, before the main study, we made two pilot studies and predicted that the non-participation rate in the main study would be acceptable. On comparing the figures we obtained (the non-participation rate in cervical cancer survivors was 76/332, 23%, and among controls 139/489, 28%) with those obtained in countries without population-based registers, one may consider that we have total control of

the denominator. Such is difficult to obtain without registers providing good coverage. We cannot exclude bias from non-participation, but do not consider it large enough to explain the associations we discuss as being real in **I-V**.

Misclassification

We could not "blind" our investigations. In **VI** we outline means employed in our studies to lessen the risk of measuring errors, including means to lessen the risk that measuring errors may vary between women having, or not having undergone preoperative brachytherapy, or between women having been subjected to radical hysterectomy and population controls. If the measuring errors of, e.g., symptom prevalence do not vary between the groups being compared, they tend not to affect (decreased sensitivity) the relative risks or dilute (decreased specificity) the relative risks obtained towards unity (1.0).[218,220]

One cornerstone in the efforts to resemble blinding was to collect the information by means of a self-administered questionnaire, which was anonymous also regarding those collecting the information. This method guards against an investigator influencing the answers, as well as a woman distorting the answers to please the physician who saved her life. Another cornerstone was the effort to make the questions conceptually and intuitively clear, that is, to make them understandable. This was done during in-depth interviews, face validity and in modifications after the pilot studies. Moreover, to be able to compare cervical cancer survivors with population controls, questions (with a few exceptions) were phrased identically to the respective groups.

To safeguard anonymity, information about the respective treatments was also obtained from the women themselves. It is possible that some answers are erroneous although, in a previous project (Helgason, unpublished data) we found 100% concordance between the information in hospital files and that obtained from questionnaires concerning antitumoural and hormonal therapy in prostate cancer patients. Again, such erroneous answers tend, on average, to dilute the relative risks we present towards unity and cannot explain, for instance, the excess risk of certain distressful symptoms we found after radical hysterectomy.

In many analyses, we dichotomised data and calculated relative risks. We believe these are more understandable to illustrate the clinical effect of, e.g., radical hysterectomy than, e.g., correlation or regression coefficients. Dichotomisation may lead to a loss of statistical power, which, however, cannot explain the associations obtained.

Analytical alterations

For some symptoms, not least those related to sexuality, symptom prevalence varies with age. We therefore regard age-adjusted relative risks as being potentially more valid than the crude relative risks, and such are presented in **I**, **III-V**. If one adjusts for a covariate that does not confound the association, the adjusted relative risk may be less valid than the unadjusted one. Thus we abstain from presenting multi-adjusted relative risks.

Generalisibility

Studies of long-term effects of surgery and radiotherapy are time-and-place-dependent since treatment techniques are refined over time. Thus, our results reflect cervical cancer therapy as given in Sweden in 1991-92 and may not be relevant to the situation in, e.g., Australia or the United States.

Radical Hysterectomy

Radical hysterectomy alone for cervical cancer adversely affects sexual function, micturition, lymph drainage and, possibly, defecation.

Reduced sexual desire after radical hysterectomy for cervical cancer has been reported in four previous studies,[81-84] which is consistent with our observation. There are also a number of studies in which women with several gynaecological malignancies treated in a variety of ways report reduced sexual desire after treatment. In the two studies in which population controls were included, there was a similar reduction in sexual desire among the controls and the women treated for cancer (gynaecological or breast).[76,99] Comparable results were observed in our study. We found, in addition, that cervical cancer survivors with a reduced sexual desire were more distressed by the change than controls with reduced desire.

Reduced intercourse frequency has previously been reported after radical hysterectomy. These findings are in accord with our results. However, we found a similar reduction in intercourse frequency among population controls. These findings contrast, in part, with the conclusions drawn in Andersen and van der Does's review of sexual dysfunction after gynaecological cancer therapy, in which the proportion of women "abandoning sexual activity" or having a decline in intercourse frequency, was higher in cancer patients than the "normal base rate" in the population. We found no such difference. We made a more direct comparison than Andersen and van der Does, and validity issues may account for the discrepant findings. Intercourse frequency is used in many previous studies as a measure of

sexual dysfunction or affected sexual adjustment after the treatment of cervical cancer. We did not determine the reasons for changes in intercourse frequency after treatment. It is quite possible that some women have intercourse despite, for instance, dyspareunia to satisfy their partner rather than themselves, or that the advantages outweigh the disadvantages of the treatment-induced sexual dysfunction.

Reduced sexual excitement and lubrication has previously been reported after radical hysterectomy for cervical cancer, which is in agreement with our findings. Prevalence-figures from previous reports vary with patient selection and the means of collecting information. Moreover, when summary scores are used to report a condition, prevalence figures cannot be retrieved. Furthermore, previous reports often include women with several gynaecological malignancies (along with cervical cancer, also vulvar, vaginal, ovarian and endometrial cancers), several stages and different modes of treatment, without separating one from the other. This compromises a comparison between studies. However, the reports give a clear picture that reduced excitement and lubrication is often reported after treatment of gynaecological cancer. Maas and co-workers, in their appeal, "A Plea for Preservation of the Pelvic Autonomic Nerves", suggest that part of the reduced lubrication might be attributable to autonomic nerve damage during radical hysterectomy, leading to reduced or inhibited genital vasocongestion and affected autonomic neural circuits.[221] The same group has recently published a feasibility study of nerve-sparing radical hysterectomy in which the authors anticipate a better long-term situation regarding vaginal, bladder and rectal function.[222]

Vaginal shortening after radical hysterectomy alone for cervical cancer has been documented in four previous studies. In these, the prevalences were 1%,[81] 3%,[107] 6%[82] and 17%.[74] The vaginal shortening was observed at gynaecological examination and described by the observer. The sensitivity of the method for clinically relevant information may be low. However, these objective findings are consistent with our figures concerning perceived shortness of the vagina after radical hysterectomy (reduced vaginal length, 19%, and reduced vaginal elasticity, 19%). The importance of assessing the perceived vaginal shortness at intercourse is highlighted by the symptom-induced distress we observed: Among the women reporting reduced vaginal length or elasticity, 47% reported moderate or much distress and 78% distress of any degree (a little, moderate or much) due to this symptom. Women with benign disease who have undergone simple hysterectomy may have less cushioning of the vaginal floor and additional shortening of the vagina, which has been suggested to influence the risk of dyspareunia.[223] This aspect has not been studied after radical hysterectomy, but the effects on the vagina after radical hysterectomy with resection of a vaginal cuff and

parametria are logically at least as significant as after simple hysterectomy. We found an association between reduced vaginal length and elasticity and dyspareunia after the treatment of cervical cancer. This is in accord with previous studies (prevalence of dyspareunia: 3–53% after radical hysterectomy for cervical cancer).[81,82,101,104,106,107] It is possible that a more considerate resection of the vagina (and its nerve supply), together with individualised intervention programmes (vaginal dilators, topical oestrogen, information on sexual techniques), would prevent or minimise the development of impaired vaginal function after radical hysterectomy.

Previous cystometric studies have demonstrated voiding dysfunction (impaired bladder sensitivity, the need to strain to void, poor flow, residual urine) after radical hysterectomy, which is consistent with our findings. On asking the women, we found an excess prevalence of these symptoms, but, unfortunately, we did not document symptom-induced distress directly. Butler-Manuel and co-workers have recently suggested[136,224] that bladder function may be preserved by a more considerate resection also of the uterosacral ligaments at radical hysterectomy, in addition to, and not only by, preservation of nerves in the cardinal ligaments.[135,137,146,225,226]

We found that constipation can be a clinically significant problem after radical hysterectomy alone. Case reports and three follow-up series[101,163,184] of women having undergone the operation all report an excess risk of constipation. Again, nerve-sparing techniques might improve the long-term situation. Dietary regimens to minimise constipation after radical hysterectomy may also be valuable in this regard.[184]

We found that lymphoedema after radical hysterectomy is prevalent and that this condition is highly distressful. There are three reports in which the women's assessments of the occurrence of lymphoedema after radical hysterectomy (with or without additional radiotherapy) are included,[81,200,201] and all three report an excess risk of lymphoedema. In our study, no additional risk of lymphoedema was noticed when radiotherapy (brachytherapy and/or external) was added to surgery. It is possible that some women in our study with constantly swollen or heavy legs do not strictly have lymphoedema by the established definitions, but we found no other explanations when we controlled for other medical conditions (e.g., a history of ischaemic heart disease or thrombosis) or medication. The high prevalence of lymphoedema after radical hysterectomy contrasts with our findings of lymphoedema after radical cystectomy and lymph node dissection for bladder cancer, where no excess risk for lymphoedema was found.[227] We used the same means for collecting information and identically phrased questions for these patients. This indicates that our

method has reasonable sensitivity for detecting the symptom. It is possible that the technique of lymph node dissection plays a role (e.g., lateral, caudal and proximal extent, or blunt versus sharp dissection) and could be modified at radical hysterectomy. Lymph node metastases in women with cervical cancer stage IB-IIA are found in 15-35% of the patients.[18,228] The development of sentinel node identification[229,230] and identification of risk factors other than tumour size for pelvic lymph node metastases (e.g., molecular markers for chromosomal alterations) may help to identify patients in whom lymph node dissection can be avoided, with a subsequent decrease in the prevalence of lymphoedema. If detected early, chronic lymphoedema might be preventable by compression and lymph drainage treatment.

Brachytherapy

The excess risk for treatment-induced symptoms after preoperative brachytherapy is low, if any. The addition of brachytherapy to radical hysterectomy probably results in frequent nocturia, defecation urgency and moderate and severe anxiety in some women. We could not document any certain effects on vaginal function.

The only previous studies that thoroughly report long-term morbidity after brachytherapy are Bertelsen's study of sexual dysfunction in 1983[86] and Kristensen and co-worker's study of urinary dysfunction in 1984.[152] Other studies of side effects after preoperative brachytherapy typically report grade 3-4 morbidity only, with one exception, Haie-Meder and co-workers.[52] In their prospective study comparing two different dose rates, the accumulative incidence of side effects is reported, using the French-Italian glossary, which compromises the comparison with our findings. However, previous studies are in conformity with our findings that there is no excess risk of severe morbidity and a limited risk of low-grade sequelae from the addition of preoperative brachytherapy to radical hysterectomy.

Our findings of sexual morbidity after preoperative brachytherapy differ from those of Bertelsen's.[86] In her study, none had "agglutination of the vagina" and 4% had a "tight" vagina. In our study, the prevalence of a moderate or substantial reduction in perceived vaginal length was 27% and a moderate or substantial reduction in perceived vaginal elasticity was 23%. The discrepant findings might possibly be explained by the differences in terminology and criteria at registration (at gynaecological examination versus the women's report of perceived symptoms at sexual intercourse). None of the women in Bertelsen's study reported dyspareunia after brachytherapy followed by radical hysterectomy, as opposed to

those in our study, in which 21% reported superficial dyspareunia and 17% deep dyspareunia. In Bertelsen's study, the women in the comparison group were treated with radiotherapy alone. Out of a total of 321 women, 22 treated with brachytherapy and radical hysterectomy and 45 treated with radiotherapy alone were selected. There is no information on whether or not, it was a random sample, nor on the criteria that determined the mode of treatment. It is possible that validity issues compromise the comparison with our findings.

With regard to urinary problems, Kristensen and co-worker's results correspond to our findings.[152] They did not find any statistically significant differences regarding voiding or continence disorders between women treated with radical hysterectomy as compared to preoperative brachytherapy and radical hysterectomy. However, they did not report any data on nocturia, as no other study on preoperative brachytherapy has done. We found an excess risk of frequent nocturia (three or more micturitions per night), but no excess risk of moderate nocturia (up to two micturitions per night) after preoperative brachytherapy, as compared to radical hysterectomy alone. If the radiation dose to the lower part of the bladder and urethra is minimised (by way of 3-dimensional radiotherapy planning), it is possible that the prevalence of nocturia and urgency problems could be reduced.

We observed an excess risk of defecation urgency after the addition of preoperative brachytherapy to radical hysterectomy. There are no previous reports on this symptom after brachytherapy. Enteritis (prevalence 0.5-2.2%),[54,113] proctitis (1-8%)[54,113,144,190] and diarrhoea (1%)[144] have been reported after preoperative brachytherapy in single series, and it is possible that some of these women also had defecation urgency, which would agree with our findings. We found that 18 of the 57 women (32%) treated with preoperative brachytherapy had some degree of distress (a little, moderate or much) from defecation urgency. In addition, 20% of the women reported loose or watery stools. On an analogy with urinary problems, if the radiation dose to the rectum and small intestine is minimised, it is possible that the prevalence of frequent loose stools and defecation urgency could be reduced.

Regarding our third finding of an excess risk of distressful symptoms after additional brachytherapy, as compared to radical hysterectomy alone, it should be noted that an increased risk of moderate or severe anxiety has not been reported in any other study. Long-term psychological morbidity has been studied in gynaecological cancer survivors,[120,231,232] but no report has been published with information on the situation for women after preoperative brachytherapy and radical hysterectomy. We do not know if our observation is directly related to the treatment, or if there might be other factors associated with the outcome.

Several of the validity problems in our study dilute the relative risks obtained. The relative risks near unity, obtained for many symptoms, contrast with those we found for external radiotherapy and radical hysterectomy, as well as those obtained in parallel studies using the same means of data collection.[227,233,234] Thus, there is good reason to interpret the relative risks near unity as an absence of effect from preoperative brachytherapy.

Sexual Abuse

Eighteen per cent of the women with a history of cervical cancer also had a history of sexual abuse. There has been no previous report on the incidence of sexual abuse in cervical cancer patients. Schover and co-workers reported that among the 31 women treated for cervical cancer whom they had asked about "family violence", 8 reported a history of "sexual trauma".[104]

In our study, a history of sexual abuse resulted in an excess risk of sexual dysfunction and decreased psychological well-being. There are signs of interaction between sexual abuse and cervical cancer and the risk of long-term sexual dysfunction, with a 29-fold excess risk of superficial dyspareunia, as compared to no history of sexual abuse or cervical cancer. In the diagnosis and treatment of cervical cancer, optimisation of patient management and minimisation of subsequent long-term psychological and somatic morbidity probably require special consideration of women with a history of sexual abuse. An open dialogue about the past trauma may be beneficial for the prevention of treatment-related symptoms in women with a history of sexual abuse and cervical cancer, but this needs further study.

One might hypothesise that women with a history of sexual abuse do not participate in screening programmes as often as other women, seek medical help later when symptoms occur, or have been exposed to different human papilloma virus (HPV) types of a higher malignancy potential. Incest and early sexual abuse predispose to having multiple sexual partners[235] and thus an accumulated increased risk of sexually transmitted HPV infection.[11] In women seeing gynaecologists for psychological symptoms or sexual dysfunction the identification of a history of sexual abuse may be an important factor in screening for and the early diagnosis of cervical neoplasia.

Women's Preferences

Generally speaking, procedures to prevent side effects should not compromise optimal survival chances as the majority of women were unwilling to decrease the symptom burden if

the process would compromise long-term survival. The only previous report on trade-off preferences among cervical cancer patients investigated whether patients preferred low dose rate (LDR) to high dose rate (HDR) brachytherapy if the methods were isoeffective.[203] A direct comparison with our information is compromised by the different outcome criteria. However, the report is consistent with our finding that it is possible to ask for patient preferences regarding the chances with, and risks from, different treatments. In our study, there are some women who declared themselves willing to trade off the chance of maximal survival for freedom from treatment-induced symptoms. The information must be interpreted cautiously, as the women are long-term survivors who may have changed their values since the original cancer diagnosis. However, to better meet individual preferences, we need to be attentive to patients who might reveal doubts about accepting the proposed treatment and respond to their uncertainty. Moreover, improved information would give the women further possibilities of making active decisions when faced with different treatment options.

Grading

To meet the women's needs, side-effect reporting should logically include meaningful end-points from the patient's point of view. The concordance between the patients' and the caregivers' ratings is often far from optimal.[236] The scarcity of reports on side effects other than for grades 3-4 may lead to an underestimation of long-term distressful symptoms and make light of the women's situation, with a possible risk of inadequate prevention and rehabilitation programmes. The majority of symptoms we have recorded would be classified as grade 0-1, using, for example, the SOMA scale[60] or French-Italian glossary.[58] Nevertheless, the cervical cancer survivors were highly distressed. Logically, the late effects are those that seriously influence the quality of life in cancer survivors. To avoid severe morbidity is, of course, imperative, but these events are few in numbers nowadays. We found that many cervical cancer survivors have some "low-grade" sequelae, which, on a group level, have a major practical relevance.

Ethical Considerations

To answer a questionnaire about adverse effects 5 years after the treatment of cervical cancer could result in the reopening of old wounds. We discussed this thoroughly within the research group and tried to emphasise our understanding of this possibility in our letters and other contacts with the patients. The study was preceded by several preparatory studies in which we tried to pay attention to signs of undue emotional strain because of our questions and we modulated the questionnaires and letters accordingly. The pilot studies and the main study were approved by the Local and Regional Ethics Committees at the Karolinska Institute, respectively. Answering the questions could also yield a deeper understanding of some of the reactions and help the woman formulate questions at future follow-up visits. The high response rate and positive comments in the questionnaires, separate letters and telephone calls indicate that we succeeded in our effort to approach this delicate subject respectfully. However, we are aware that some women wanted to contribute and share their experience but failed to complete the questionnaire because of the emotional strain. It is also possible that some women declined initial participation for the same reason.

The controls were informed that the aim of the study was to document different aspects of health in women and compare these with a group of women with gynaecological disease. However, we withheld the information that this gynaecological disease was cervical cancer. We feared that we might frighten off some women by using the word ”cancer”. This procedure too was approved by the Ethics Committees. Information about the controls has been reported separately in the papers and it is possible for, for instance, other health care providers to extract this information.

CONCLUSION

The majority of cervical cancer survivors are young and middle-aged women who will live many years with their treatment-induced sequelae. The findings from this and other studies could be used to better the long-term situation of the women by prevention, information, intervention and rehabilitation.

- Radical hysterectomy alone for cervical cancer adversely affects lymph drainage, micturition and sexual function. Vaginal changes compromising sexual function are the most prevalent distressful symptom after radical hysterectomy for cervical cancer. It is possible that part of the sexual dysfunction can be attributed to autonomic nerve damage during radical hysterectomy. Lymphoedema represents an important, previously partly unrecognised, cause of treatment-induced distress after therapy for early cervical cancer. Modifications of surgical techniques might possibly reduce the occurrence of treatment-induced symptoms and the subsequent distress.
- The excess risk of distressful symptoms from the addition of preoperative brachytherapy to radical hysterectomy is low, if any. Brachytherapy has little, if any, influence on vaginal function or lymphoedema, but probably results in defecation urgency, frequent nocturia and moderate and severe anxiety in some women.
- A history of sexual abuse is common in women with a history of cervical cancer. Women with a history of sexual abuse have an excess risk of decreased psychological well-being and sexual dysfunction. There are signs of interaction between sexual abuse and cervical cancer and the risk of long-term sexual dysfunction. Improved consideration of the care of these women is warranted.
- Generally speaking, procedures for the prevention of side effects should not compromise survival, as the majority of cervical cancer survivors prioritise survival over freedom from treatment-induced distressful symptoms.
- What is reported as “low-grade side effects” in clinical trials also result in considerable distress in cervical cancer survivors, indicating that the relevance of previous reports of long-term treatment-induced morbidity is uncertain.

FUTURE STUDIES

- Although preoperative brachytherapy has been used for over 60 years, its effect on survival has not been determined. There is a good rationale for a decreased local recurrence rate and survival gain with the addition of preoperative brachytherapy to radical hysterectomy. Given that women prioritise survival and the low risk of long-term distressful symptoms we documented, a sufficiently powered randomised study to evaluate the effect on survival of preoperative brachytherapy in a subgroup of cervical cancer patients (intermediate risk; tumour size 2-4 cm without known lymph node metastases) is suggested.
- Prevention, information and intervention studies regarding sexual dysfunction could possibly better the situation of cervical cancer survivors. Histological (nerve endings, blood vessels, oestrogen receptors, signs of fibrosis), physiological (vasocongestion, lubrication, propagation of nerve potentials) and pharmacological (oestrogen, topical and systemic) studies to learn the mechanisms of the specific effects on the vagina that we documented after radical hysterectomy and radiotherapy can be done. Further development of questionnaires could be used in a new data collection procedure, linked to histological, physiological and pharmacological studies. This information would facilitate appropriate modifications in therapy development (e.g., nerve-sparing surgery, 3-dimensional radiotherapy planning) and the development of information and intervention standards. The effects of early and intense post-therapy use of topical oestrogen (and debridement) and, possibly, topical anti-inflammatory drugs, e.g., benzydamine, and long-term vaginal function can be studied.
- Current information practice and rehabilitation programmes regarding lymphoedema can be analysed. The effects of modifications of lymph node dissection techniques and sentinel node identification can be studied, as well as the effects of intense rehabilitation programmes for lymphoedema.
- Studies on how to detect and support women with a history of sexual abuse at the initial diagnosis, treatment and follow-up of cervical cancer, but also for screening purposes and early diagnosis of cervical cancer, can be done. This could be studied by way of preparatory interviews and, possibly, in a questionnaire study.
- Determinants of anxiety after brachytherapy are not fully understood, but can be examined in a follow-up questionnaire study. We can document details regarding the application of intracavitary instruments and treatment and ask specific questions about the experience of the treatment period and follow-up.

- Therapy development (nerve-sparing surgery, 3-dimensional radiotherapy planning – also for brachytherapy and not only external radiotherapy) and its effects on long-term urinary function can be studied. The effects of oestrogen therapy, intravaginal and systemic, and the appropriate time to start therapy with regard to radiotherapy-induced urinary dysfunction can be studied. The effects of modern anticholinergic drugs (e.g., tolterodine) and beta2-agonists for prevention and relief of acute radiotherapy-induced cystitis and the subsequent long-term effect on urinary function can be studied.
- Therapy development (3-dimensional radiotherapy planning – also for brachytherapy, nerve-sparing surgery) and its effect on long-term bowel function can be studied.

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References

1. Pisani P, Parkin DM, Bray F, Ferlay J. Estimates of the worldwide mortality from 25 cancers in 1990. Int J Cancer 1999; 83:18-29.
2. Cancer Incidence in Sweden 1999. Centre for Epidemiology. 2001:4. Stockholm, Sweden, The National Board of Health and Welfare. 2001.
3. Benedet J, Odicino F, Maisonneuve P, Beller U, Creasman W, Heintz AP, Ngan HY, Sideri M, Pecorelli S. Annual Report on the Results of Treatment in Gynaecological Cancer. J Epidemiol Biostat 2001; 6:5-44.
4. McCance DJ, Singer A. The importance of HPV infections in the male and female genital tract and their relationship to cervical neoplasia. In Peto R, zur Hausen H (eds). Viral etiology of cervical cancer. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory; 1986:311-319.
5. Brisson J, Roy M, Fortier M, Bouchard C, Meisels A. Condyloma and intraepithelial neoplasia of the uterine cervix: a case-control study. Am J Epidemiol 1988; 128:337-342.
6. Franco EL, Rohan T, Villa LL. Epidemiologic evidence and human papillomavirus infection as a necessary cause of cervical cancer. J Natl Cancer Inst 1999; 91:506-511.
7. Brinton LA, Hamman RF, Huggins GR, Lehman HF, Levine RS, Mallin K, Fraumeni Jr JF. Sexual and reproductive risk factors for invasive squamous cell cervical cancer. J Natl Cancer Inst 1987; 79:23-30.
8. Kjellberg L, Wang Z, Wiklund F, Edlund K, Ångström T, Lenner P, Sjöberg I, Hallmans G, Wallin K-L, Sapp M, Schiller J, Wadell G, Mählck C-G, Dillner J. Sexual behaviour and papillomavirus exposure in cervical intraepithelial neoplasia: a population-based case-control study. J Gen Virol 1999; 80:391-398.
9. Franco EL, Villa LL, Ruiz A, Costa MC. Transmission of cervical human papillomavirus infection by sexual activity: differences between low and high oncogenic risk types. JID 1995; 172:756-763.
10. Nakagawa M, Stites DP, Patel S, Farhat S, Scott M, Hills NK, Palefsky JM, Moscicki AB. Persistence of human papillomavirus type 16 infection is associated with lack of cytotoxic response to the E6 antigens. JID 2000; 182:595-598.
11. Franceschi S, La Vecchia C, Decarli A. Relation of cervical neoplasia with sexual factors, including specific venereal diseases. In Peto R, zur Hausen H (eds). Viral etiology of cervical cancer. Cold Springs Harbor, NY: Cold Springs Harbor Laboratory; 1986:65-78.
12. Agarwal SS, Sehgal A, Sardana S, Kumar A, Luthra UK. Role of male behavior in cervical carcinogenesis among women with one lifetime sexual partner. Cancer 1993; 72:1666-1669.
13. Da Silva D, Eiben GL, Fausch SC, Wakabayashi MT, Rudolf MP, Velders MP, Kast WM. Cervical cancer vaccines: Emerging concepts and developments. J Cell Physiol 2001; 186:169-182.
14. Soisson AP, Soper JT, Clarke-Pearson DL, Berchuck A, Montana GS, Creasman WT. Adjuvant radiotherapy following radical hysterectomy for patients with stage IB and IIA cervical cancer. Gynecol Oncol 1990; 37:390-395.
15. Kamura T, Tsukamoto N, Tsuruchi N, Saito T, Matsuyama T, Akazawa K, Nakano H. Multivariate analysis of the histopathologic factors of cervical cancer in patients undergoing radical hysterectomy. Cancer 1992; 69:181-186.
16. Alvarez RD, Soong S-J, Kinney WK, Reid GC, Schray MF, Podratz KC, Morley GW, Shingleton HM. Identification of prognostic factors and risk groups in patients found

to have nodal metastasis at the time of radical hysterectomy for early-stage squamous carcinoma of the cervix. Gynecol Oncol 1989; 35:130-135.
17. Sedlis A, Bundy BN, Rotman M, Lentz SS, Muderspach LI, Zaino RJ. A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: A Gynecologic Oncology Group study. Gynecol Oncol 1999; 73:177-183.
18. Delgado G, Bundy BN, Zaino RJ, Sevin B-U, Creasman WT, Major F. Prospective surgical-pathological study of disease-free interval in patients with stage IB squamous cell carcinoma of the cervix: A Gynecologic Oncology Group study. Gynecol Oncol 1990; 38:352-357.
19. Hellebrekers BWJ, Zwinderman AH, Kenter GG, Peters AAW, Snijders-Keilholtz A, Graziosi GCM, Fleuren GJ, Trimbos JB. Surgically-treated early cervical cancer: Prognostic factors and the significance of depth of tumor invasion. Int J Gynecol Cancer 1999; 9:212-219.
20. Shingleton HM, Bell MC, Fremgen AM, Chmiel JS, Russel A, Jones WB, Winchester DP, Clive RE. Is there really a difference in survival of women with squamous cell carcinoma, adenocarcinoma, and adenosquamous cell carcinoma of the cervix? Cancer 1995; 76:1948-1955.
21. Wertheim E. The extended abdominal operation for carcinoma uteri. Am J Obstet 1912; 66:169-232.
22. Meigs JV. Radical hysterectomy with bilateral pelvic lymph node dissection. Am J Obstet Gynecol 1951; 62:854-870.
23. Carenza L, Villani C. Parametrial involvement and therapeutic programming in stage Ib cervical cancer. Ballière's Clin Obstet Gynecol 1988; 2:889-902.
24. Schlink H. Cancer of the cervix uteri: Australian results, 1930-1950. J Obstet Gynaecol Brit Empire 1960; 67:402-410.
25. Stallworthy J. Radical surgery following radiation treatment for cervical carcinoma. Ann Roy College Surg Engl 1964; 34:161-178.
26. Rampone JF, Klem V, Kolstad P. Combined treatment of stage IB carcinoma of the cervix. Obstet Gynecol 1973; 41:163-167.
27. Einhorn N, Bygdeman M, Sjöberg B. Combined radiation and surgical treatment for carcinoma of the uterine cervix. Cancer 1980; 45:720-723.
28. Gerbaulet A, Kunkler I, Kerr GR, Haie C, Michel G, Prade M, Lhomme C, Masselot M, Albano M, Dutreix A, Chassagne D. Combined radiotherapy and surgery: local control and complications in early carcinoma of the uterine cervix - the Villejuif experience 1975-1984. Radiother Oncol 1992; 23:66-73.
29. Calais G, Le Floch O, Chauvet B, Reynaud-Bougnoux A, Bougnoux P. Carcinoma of the uterine cervix stage IB and early stage II. Prognostic value of the histological tumor regression after initial brachytherapy. Int J Radiat Oncol Biol Phys 1989; 17:1231-1235.
30. Bloss JD, Berman ML, Mukhererjee J, Manetta A, Emma D, Ramsinghani NS, DiSaia PJ. Bulky stage IB cervical carcinoma managed by primary radical hysterectomy followed by tailored radiotherapy. Gynecol Oncol 1992; 47:21-27.
31. Stock RG, Chen ASJ, Flickinger JC, Kalnicki S, Seski J. Node-positive cervical cancer: Impact of pelvic irradiation and patterns of failure. Int J Radiat Oncol Biol Phys 1995; 31:31-36.
32. Zola P, Volpe T, Castelli G, Sismondi P, Nicolucci A, Parazzini F, Liberati A. Is the published literature a reliable guide for deciding between alternative treatments for patients with early cervical cancer? Int J Radiat Oncol Biol Phys 1989; 16:785-797.

33. Thomas GM, Dembo AJ. Is there a role for adjuvant pelvic radiotherapy after radical hysterectomy in early stage cervical cancer? Int J Gynecol Cancer 1991; 1:1-8.
34. Eifel PJ, Morris M. Irradiation alone or combined with surgery in carcinoma of the cervix: when will we know the answer? Int J Radiat Oncol Biol Phys 1995; 31:1007-1008.
35. Kinney WK, Alvarez RD, Reid GC, Schray MF, Soong S-J, Morley GW, Podratz KC, Shingleton HM. Value of adjuvant whole-pelvis irradiation after Wertheim hysterectomy for early-stage squamous carcinoma of the cervix with pelvic nodal metastasis: a matched-control study. Gynecol Oncol 1989; 34:258-262.
36. Snijders-Keilholtz A, Hellebrekers BWJ, Zwinderman AH, van der Vijver MJ, Trimbos JB. Adjuvant radiotherapy following radical hysterectomy for patients with early-stage cervical carcinoma (1984-1996). Radiother Oncol 1999; 51:161-167.
37. Green JA, Kirwan JM, Tierney JF, Symonds P, Fresco L, Collingwood M, Williams CJ. Survival and recurrence after concomitant chemotherapy and radiotherapy for cancer of the uterine cervix: a systematic review and meta-analysis. Lancet 2001; 358:781-786.
38. Marcial VA, Marcial LV. Radiation therapy of cervical cancer. Cancer 1993; 71:1438-1445.
39. Roddick JW, Greenslaw RH. Treatment of cervical cancer. A randomized study of operation and radiation. Am J Obstet Gynecol 1971; 109:754-764.
40. Newton M. Radical hysterectomy or radiotherapy for stage I cervical cancer. Am J Obstet Gynecol 1975; 123:535-542.
41. Morley GW, Seski JC. Radical pelvic surgery versus radiation therapy for stage I carcinoma of the cervix (exclusive of microinvation). Am J Obstet Gynecol 1976; 126:785-798.
42. Landoni F, Maneo A, Colombo A, Placa F, Milani R, Perego P, Favini G, Ferri L, Mangioni C. Randomised study of radical surgery versus radiotherapy for stage Ib-IIa cervical cancer. Lancet 1997; 350:535-540.
43. Perez CA, Camel HM, Kao MS, Hederman MA. Randomized study of preoperative radiation and surgery or irradiation alone in the treatment of stage IB and IIA carcinoma of the uterine cervix: Final report. Gynecol Oncol 1987; 27:129-140.
44. Einhorn N. Cervical cancer (cervix uteri). Acta Oncol 1996; 35:75-80.
45. Kottmeier HL. Complications following radiation therapy in carcinoma of the cervix and their treatment. Am J Obstet Gynecol 1964; 88:854-866.
46. Gusberg SB. Comment to JC Burch, Am J Obstet Gynecol 1970;106:1054-1060. Am J Obstet Gynecol 1970; 106:1061-1062.
47. Curtin JP. Radical hysterectomy - the treatment of choice for early-stage cervical carcinoma. Gynecol Oncol 2001; 62:137-138.
48. Janson PO, Jansson I, Skryten A, Damber JE, Lindstedt G. Ovarian endocrine function in young women undergoing radiotherapy for carcinoma of the cervix. Gynecol Oncol 1981; 11:218-223.
49. Averette HE, Nguyen HN, Donato DM, Penalver M, Sevin B-U, Estape R, Little WA. Radical hysterectomy for invasive cervical cancer. Cancer 1993; 71:1422-1437.
50. Zola P, Maggino T, Sacco M, Rumore A, Sinistrero G, Maggi R, Landoni F, Foglia G, Sartori E, de Taffoll J, Franchi M, Romagnolo C, Sismondi P. Prospective multicenter study on urologic complications after radical surgery with or without radiotherapy in the treatment of stage IB-IIA cervical cancer. Int J Gynecol Cancer 2000; 10:59-66.
51. Ayhan A, Tuncer ZS, Yarali H. Complications of radical hysterectomy in women with early stage cervical cancer: clinical analysis of 270 cases. Eur J Surg Oncol 1991; 17:492-494.

52. Haie-Meder C, Kramar A, Lambin P, Lancar R, Scalliet P, Bouzy J, Gerbaulet A. Analysis of complications in a prospective randomized trial comparing two brachytherapy low dose rates in cervical carcinoma. Int J Radiat Oncol Biol Phys 1994; 29:953-960.
53. Davidson NGP, LeVay JH, MacDonald H. Influence of microscopic residual disease on survival for stage IB and IIA carcinoma of the cervix following intracavitary irradiation. Clin Oncol 1990; 2:264-267.
54. Bachaud JM, Fu RC, Delannes M, Izar F, Martel P, David JM, Shubinski RE, Daly NJ, Montana GS. Non-randomized comparative study of irradiation alone or in combination with surgery in stage Ib, IIa and "proximal" IIb carcinoma of the cervix. Radiother Oncol 1991; 22:104-110.
55. Gallion HH, van Nagell JR, Donaldson EB, Hanson MB, Powell DE, Maruyama Y, Yoneda J. Combined radiation therapy and extrafascial hysterectomy in the treatment of stage IB barrel-shaped cervical cancer. Cancer 1985; 56:262-265.
56. Sundför K, Tropé CG, Kjorstad KE. Radical radiotherapy versus brachytherapy plus surgery in carcinoma of the cervix 2A and 2B. Acta Oncol 1996; 35:99-107.
57. World Health Organization. WHO Handbook for Reporting Results of Cancer Treatment. Geneva: World Health Organization; 1979.
58. Chassagne D, Sismondi P, Horiot JC, Sinistrero G, Bey P, Zola P, Pernot M, Gerbaulet A, Kunkler I, Michel G. A glossary for reporting complications of treatment in gynecological cancers. Radiother Oncol 1993; 26:195-202.
59. Pedersen DE, Bentzen SM, Overgaard J. Early and late radiotherapeutic morbidity in 442 consecutive patients with locally advanced carcinoma of the uterine cervix. Int J Radiat Oncol Biol Phys 1994; 29:941-952.
60. Pavy J-J, Denekamp J, Letschert J, Littbrand B, Mornex F, Bernier J, Gonzales-Gonzales D, Horiot JC, Bolla M, Bartelink H. Late effects toxicity scoring: the SOMA scale. Radiother Oncol 1995; 35:11-15.
61. Schag CAC, Ganz PA, Heinrich RL. CAncer Rehabilitation Evaluation System - Short Form (CARES-SF). Cancer 1991; 68:1406-1413.
62. Cella DF, Tulsky DS, Gray G, Sarafian B, Bonomi AE, Silberman M, Yellen SB, Winicour P, Brannon J, Eckberg K, Lloyd S, Purl S, Blendowski C, Goodman M, Barnicle M, Stewart I, McHale M, Bonomi P, Kaplan E, Taylor IV S, Thomas CR, Harris JR. The Functional Assessment of Cancer Therapy Scale: Development and validation of the general measure. J Clin Oncol 1993; 11:570-579.
63. Aaronson NK, Cull AM, Kaasa S, Sprangers MAG. The European Organization for Research and Treatment of Cancer (EORTC) modular approach to quality of life assessment in oncology: an update. In Spilker B (ed). Quality of Life and Pharmacoeconomics in Clinical Trials. Philadelphia: Lippincott-Raven Publishers; 1996:179-189.
64. Priestman TJ, Baum M. Evaluation of quality of life in patients receiving treatment for advanced breast cancer. Lancet 1976; i:901.
65. Kaplan HS. The new sex therapy. Active treatment of sexual dysfunction. London, England: Ballière Tindall; 1974.
66. Berman JR, Adhikari SP, Goldstein I. Anatomy and physiology of female sexual function and dysfunction. Eur Urol 2000; 38:20-29.
67. Masters WH, Johnson VE. Human Sexual Response. Boston: Little, Brown and Company; 1966.
68. Mundy AR. An anatomical explanation for bladder dysfunction following rectal and uterine surgery. Br J Urol 1982; 54:501-504.
69. Pitkin RM. Estrogen and the irradiated vagina. Obstet Gynecol 1975; 46:243-245.

70. Cartwright-Alcarese F. Addressing sexual dysfunction following radiation therapy for a gynecologic malignancy. Oncol Nurs Forum 1995; 22:1227-1232.
71. Heimer GM, Englund DE. Effects of vaginally-administered oestriol on post-menopausal urogenital disorders: a cytohormonal study. Maturitas 1992; 14:171-179.
72. Semmens JP, Tsai CC, Semmens EC, Loadholt CB. Effects of estrogen therapy on vaginal physiology during menopause. Obstet Gynecol 1985; 66:15-18.
73. Shield PW. Chronic radiation effects: A correlative study of smears and biopsis from the cervix and vagina. Diagn Cytopathol 1995; 13:107-119.
74. Abitol MM, Davenport JH. The irradiated vagina. Obstet Gynecol 1974; 44:249-256.
75. Auchincloss SS. After treatment. Cancer 1995; 76:2117-2124.
76. Andersen BL. Sexual functioning complications in women with gynecologic cancer: Outcomes and directions for prevention. Cancer 1987; 60:2123-2128.
77. Greenberg DB. The measurement of sexual dysfunction in cancer patients. Cancer 1984; 53:2281-2285.
78. Basson R, Berman JR, Burnett A, Derogatis LR, Ferguson D, Fourcroy J, Goldstein I, Graziottin A, Heiman JR, Laan E, Leiblum SR, Padma-Nathan H, Rosen RC, Segraves K, Segraves RT, Shabsigh R, Sipski M, Wagner G, Whipple B. Report of the international consensus development conference on female sexual dysfunction: definitions and classifications. J Urol 2000; 163:888-893.
79. Andersen BL, Lachenbruch PA, Anderson B, dePosse C. Sexual dysfunction and signs of gynecologic cancer. Cancer 1986; 57:1880-1886.
80. Andersen BL, van der Does J. Surviving gynecologic cancer and coping with sexual morbidity: an international problem. Int J Gynecol Cancer 1994; 4:225-240.
81. Høyer M, Ljungstroem B, Nyland M, Jakobsen A. Radical hysterectomy in cervical carcinoma stage Ib. Eur J Gynaec Oncol 1990; 11:13-17.
82. Abitol MM, Davenport JH. Sexual dysfunction after therapy for cervical carcinoma. Am J Obstet Gynecol 1974; 119:181-189.
83. Vincent CE, Vincent B, Greiss FC, Linton EB. Some martial-sexual concomitants of carcinoma of the cervix. Southern Med J 1975; 68:552-558.
84. Seibel MM, Freeman MG, Graves WL. Carcinoma of the cervix and sexual function. Obstet Gynecol 1980; 55:484-487.
85. Kern Hansen M. Surgical and combination therapy of cancer of the cervix uteri stage Ib and IIa. Gynecol Oncol 1981; 11:275-287.
86. Bertelsen K. Sexual dysfunction after treatment of cervical cancer. Dan Med Bull 1983; 30:31-34.
87. Jenkins B. Patients' reports of sexual changes after treatment for gynecological cancer. Oncol Nurs Forum 1988; 15:349-354.
88. Krumm S, Lamberti J. Changes in sexual behavior following radiation therapy for cervical carcinoma. J Psychosom Obst Gyn 1993; 14:51-63.
89. Vasicka A, Popovich NR, Brausch CC. Postradiation course of patients with cervical carcinoma. Obstet Gynecol 1958; 11:403-414.
90. Adelusi B. Coital function after radiotherapy for carcinoma of the cervix uteri. Br J Obstet Gynaecol 1980; 87:821-823.
91. Andersen BL, Anderson B, dePosse C. Controlled prospective longitudinal study of women with cancer: I. Sexual functioning outcomes. J Cons Clin Psychol 1989; 57:683-691.
92. Corney RH, Crowther ME, Everett H, Howells A, Shepard JH. Psychosexual dysfunction in women with gynaecological cancer following radical pelvic surgery. Br J Obstet Gynaecol 1993; 100:73-78.

93. Kylstra WA, Leenhouts GHMW, Everaerd W, Panneman MJM, Hahn DEE, Weijmar Schultz WCM, van de Wiel HBM, Heintz APM. Sexual outcomes following treatment for early stage gynecological cancer: a prospective multicenter study. Int J Gynecol Cancer 1999; 9:387-395.
94. Thranov I, Klee M. Sexuality of gynecologic cancer patients - a cross-sectional study. Gynecol Oncol 1994; 52:14-19.
95. Decker WH, Schwartzman E. Sexual function following treatment for carcinoma of the cervix. Am J Obstet Gynecol 1962; 83:401-405.
96. Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States. JAMA 1999; 281:537-544.
97. Stadberg E, Mattsson L-Å, Milsom I. Women's attitudes and knowledge about the climacteric period and its treatment. A Swedish population-based study. Maturitas 1997; 27:109-116.
98. Lewin B, Fugl-Meyer KS, Helmius G, Lalos A, Månsson S-A. Sex i Sverige. Lewin, B. Uppsala, Uppsala Universitets Förlag. 1997.
99. Ganz PA, Rowland JH, Desmond KA, Meyerowitz BE, Wyatt GE. Life after breast cancer: Understanding women's health-related quality of life and sexual functioning. J Clin Oncol 1998; 16:501-514.
100. Weijmar Schultz WCM, van de Wiel HBM, Bouma J. Psychosexual functioning after treatment for cancer of the cervix: a comparative and longitudinal study. Int J Gynecol Cancer 1991; 1:37-46.
101. Butler-Manuel SA, Summerville K, Ford A, Blake P, Riley AJ, Sultan AH, Monga AK, Stanton SL, Shepard JH, Barton DPJ. Self-assessment of morbidity following radical hysterectomy for cervical cancer. J Obstet Gynaecol 1999; 19:180-183.
102. Flay LD, Matthews JHL. The effects of radiotherapy and surgery on the sexual function of women treated for cervical cancer. Int J Radiat Oncol Biol Phys 1995; 31:399-404.
103. Pitkin RM, van Voorhis LW. Postirradiation vaginitis. Radiology 1971; 99:417-421.
104. Schover LR, Fife M, Gershenson DM. Sexual dysfunction and treatment for early stage cervical cancer. Cancer 1989; 63:204-212.
105. Seibel MM, Freeman MG, Graves WL. Sexual function after surgical and radiation therapy for cervical carcinoma. Southern Med J 1982; 75:1195-1197.
106. Filiberti A, Regazzoni M, Garavoglia M, Perilli C, Alpinelli P, Santoni G, Attili A, Stefanon B. Problems after hysterectomy: A comparative content analysis of 60 interviews with cancer and non-cancer hysterectomized women. Eur J Gynaec Oncol 1991; 12:445-449.
107. Pearcey RG, Peel KR, Thorogood J, Walker K. The value of pre-operative intracavitary radiotherapy in patients treated by radical hysterectomy and pelvic lymphadenectomy for invasive carcinoma of the cervix. Clinical Radiotherapy 1988; 39:95-98.
108. Eifel PJ, Levenback C, Wharton JT, Oswald MJ. Time course and incidence of late complications in patients treated with radiation therapy for FIGO stage IB carcinoma of the uterine cervix. Int J Radiat Oncol Biol Phys 1995; 32:1289-1300.
109. Glatt AE, Zinner SH, McCormack WM. The prevalence of dyspareunia. Obstet Gynecol 1990; 75:433-436.
110. Pitkin RM, Bradbury JT. The effect of topical estrogen on irradiated vaginal epithelium. Am J Obstet Gynecol 1965; 92:175-182.
111. Bruner DW, Lanciano RM, Keegan M, Corn B, Martin E, Hanks GE. Vaginal stenosis and sexual function following intracavitary radiation for the treatment of cervical and endometrial carcinoma. Int J Radiat Oncol Biol Phys 1993; 27:825-830.

112. Capone MA, Good RS, Westie KS, Jacobson AF. Psychosocial rehabilitation of gynecologic oncology patients. Arch Phys Med Rehabil 1980; 61:128-132.
113. Resbeut MR, Alzieu C, Gonzague-Casabianca L, Badinand D, Bardou VJ, Cravello L, Gamerre M, Houvenaeghel G, Cowen D. Combined brachytherapy and surgery for early carcinoma of the uterine cervix: Analysis of extent of surgery on outcome. Int J Radiat Oncol Biol Phys 2001; 50:873-881.
114. Kapp KS, Stuecklschweiger GF, Kapp DS, Poschauko J, Pickel H, Hackl A. Carcinoma of the cervix: analysis of complications after primary external beam radiotherapy and Ir-192 HDR brachytherapy. Radiother Oncol 1997; 42:143-153.
115. Lanciano RM, Martz K, Montana GS, Hanks GE. Influence of age, prior abdominal surgery, fraction size, and dose on complications after radiation therapy for squamos cell cancer of the uterine cervix. Cancer 1992; 69:2124-2130.
116. Perez CA, Grigsby PW, Lockett MA, Chao KSC, Williamson J. Radiation therapy morbidity in carcinoma of the uterine cervix: Dosimetric and clinical correlation. Int J Radiat Oncol Biol Phys 1999; 44:855-866.
117. Hartman P, Diddle AW. Vaginal stenosis following irradiation tharapy for carcinoma of the cervix uteri. Cancer 1972; 30:426-429.
118. Lamb MA. Psychosexual issues: The woman with gynecologic cancer. Semin Oncol Nurs 1990; 6:237-243.
119. Derogatis LR. Breast and gynecologic cancers: Their unique impact on body image and sexual identity in women. Vaeth, M., Blomberg, R., and Adler, L. Basel, New York, S. Kager. Frontiers of Radiation Therapy and Oncology. 1979: [14] 1-11.
120. Bos-Branolte G, Rijshouwer YM, Zielstra EM, Duivenvoorden HJ. Psychologic morbidity in survivors of gynecologic cancer. In Richter D, Bitzer J, Nijs P (eds). Advanced psychosomatic research in obstetrics and gynecology. Berlin: Springer-Verlag; 1991:3-15.
121. Sewell HH, Edwards DW. Pelvic genital cancer: Body image and sexuality. Veath, J. M., Blomberg, R., and Adler, L. Frontiers of Radiation Therapy & Oncology. Basel, New York, S. Karger AG. 1979: [14] 35-41.
122. Bellerose SB, Binik YM. Body image and sexuality in oophorectomized women. Arch Sex Behav 1993; 22:435-459.
123. Tamburini M, De Palo G, Filiberti A, Ventafridda V. Psychological and sexual dimensions of gynaecological cancer. Br J Sex Med 1987; 14:170-180.
124. Filiberti A, Tamburini M, Stefanon B, Merola M, Bandieramonte G, Vantafridda V, De Palo G. Psychological aspects of genital human papillomavirus infection: a preliminary report. J Psychosom Obst Gyn 1993; 14:145-152.
125. Bos-Branolte G, Rijshouwer YM, Zielstra EM, Duivenvoorden HJ. The partner relationship of patients in remission of gynecologic cancers; The woman's perspective. In van Hall E, Everaerd W (eds). The free woman. Women's health in the 1990's. Casterton Hall: The Parthenon Publishing Group; 1989:778-786.
126. Lalos A, Lalos O, Stendahl U. Experiences of the male partner in cervical and endometrial cancer - a prospective interview study. J Psychosom Obst Gyn 1995; 16:153-165.
127. Bos-Branolte G. Infertility: a price for cancer cure. In Dennerstein L, Fraser I (eds). Hormones and Behavior. Amsterdam, The Netherlands: Elsevier; 1986:575-584.
128. Hughes Jr CL, Wall LL, Creasman WT. Reproductive hormone levels in gynecologic oncology patients undergoing surgical castration after spontanous menopause. Gynecol Oncol 1991; 40:42-45.

129. Anderson B, LaPolla JP, Turner D, Chapman GB, Buller RE. Ovarian transposition in cervical cancer. Gynecol Oncol 1993; 49:206-214.
130. Feeney DD, Moore DH, Look KY, Stehman FB, Sutton GP. The fate of the ovaries after radical hysterectomy and ovarian transposition. Gynecol Oncol 1995; 56:3-7.
131. Chambers SK, Chambers JT, Kier R, Peschel RE. Sequelae of lateral ovarian transposition in irradiated cervical cancer patients. Int J Radiat Oncol Biol Phys 1991; 20:1305-1308.
132. Olejek A, Wala D, Chimiczewski P, Rzempoluch J. Hormonal activity of transposed ovaries in young women treated for cervical cancer. Gynecol Endocrinol 2001; 15:5-13.
133. Hall-Craggs ECB. Anatomy as a basis for clinical medicine. London: Williams & Wilkins; 1995.
134. Smith PH, Ballantyne B. The neuroanatomical basis for denervation of the urinary bladder following major pelvic surgery. Brit J Surg 1968; 66:929-933.
135. Photopulos GJ, Zwaag RV. Class II radical hysterectomy shows less morbidity and good treatment efficacy compared to class III. Gynecol Oncol 1991; 40:21-24.
136. Butler-Manuel SA, Buttery LDK, A'Hern RP, Polak JM, Barton DPJ. Pelvic nerve plexus trauma at radical hysterectomy and simple hysterectomy. Cancer 2000; 89:834-841.
137. Possover M, Stöber S, Plaul K, Schneider A. Identification and preservation of the motoric innervation of the bladder in radical hysterectomy type III. Gynecol Oncol 2000; 79:154-157.
138. Ralph G, Winter R, Michelitsch L, Tamussino K. Radicality of parametrial resection and dysfunction of the lower urinary tract after radical hysterectomy. Eur J Gynaec Oncol 1991; 12:27-30.
139. Marks LB, Carroll PR, Dugan TC, Anscher MS. The response of the urinary bladder, urethra, and ureter to radiation and chemotherapy. Int J Radiat Oncol Biol Phys 1995; 31:1257-1280.
140. Gaze MN, Kelly CG, Dunlop PRC, Redpath AT, Kerr GR, Cowie VJ. Stage IB cervical carcinoma: a clinical audit. Br J Radiol 1992; 65:1018-1024.
141. Ralph G, Tamussino K, Lichtenegger W. Urological complications after radical hysterectomy with or without radiotherapy for cervical cancer. Arch Gynecol Obstet 1990; 248:61-65.
142. Mundt AJ, Waggoner S, Herbst A, Rotmensch J. Preoperative intracavitary brachytherapy in early-stage cervical carcinoma. Am J Clin Oncol 1999; 22:73-77.
143. Morice P, Haie-Meder C, Rey A, Pautier P, Lhommé C, Gerbaulet A, Duvillard P, Castaigne D. Radiotherapy and radical surgery for treatment of patients with bulky stage IB and II cervical cancer. Int J Gynecol Cancer 2000; 10:239-246.
144. Gerdin E, Cnattingius S, Johnson P. Complications after radiotherapy and radical hysterectomy in early-stage cervical carcinoma. Acta Obstet Gynecol Scand 1995; 74:554-561.
145. Hopkins MP, Morley GW. Radical hysterectomy versus radiation therapy for stage IB squamous cell cancer of the cervix. Cancer 1991; 68:272-277.
146. Landoni F, Maneo A, Cormio G, Perego P, Milani R, Caruso O, Mangioni C. Class II versus class III radical hysterectomy in stage IB-IIA cervical cancer: A prospective randomized study. Gynecol Oncol 2001; 80:3-12.
147. Kinney WK, Egorshin EV, Podratz KC. Wertheim hysterectomy in the geriatric population. Gynecol Oncol 1988; 31:227-232.
148. Scotti RJ, Bergman A, Bhatia NN, Ostergard DR. Urodynamic changes in urethrovesical function after radical hysterectomy. Obstet Gynecol 1986; 68:111-120.

149. Farquharson DIM, Shingleton HM, Soong SJ, Sanford SP, Levy DS, Hatch KD. The adverse effects of cervical cancer treatment on bladder function. Gynecol Oncol 1987; 27:15-23.
150. Falk V, Lundgren N, Quarfordt L, Årström K. Primary surgical treatment of carcinoma stage I of the uterine cervix. Acta Obstet Gynecol Scand 1982; 61:481-486.
151. Kadar N, Saliba N, Nelson JH. The frequency, causes and prevention of severe urinary dysfunction after radical hysterectomy. Br J Obstet Gynaecol 1983; 90:858-863.
152. Kristensen GB, Frimodt-Möller PC, Poulsen HK, Ulbak S. Persistent bladder dysfunction after surgical and combination therapy of cancer of the cervix uteri stages Ib and IIa. Gynecol Oncol 1984; 18:38-42.
153. Ralph G, Tamussino K, Lichtenegger W. Urological complications after radical abdominal hysterectomy for cervical cancer. Ballière's Clin Obst Gyn 1988; 2:943-952.
154. Carenza L, Nobili F, Giacobini S. Voiding disorders after radical hysterectomy. Gynecol Oncol 1982; 13:213-219.
155. Bandy LC, Clarke-Pearson DL, Soper JT, Mutch DG, MacMillan J, Creasman WT. Long-term effects in bladder function following radical hysterectomy with and without postoperative radiation. Gynecol Oncol 1987; 26:160-168.
156. Marziale P, Atlante G, Le Pera V, Marino T, Pozzi M, Iacovelli A. Combined radiation and surgical treatment of stage IB and IIA and B carcinoma of the cervix. Gynecol Oncol 1981; 11:175-183.
157. Parkin DE, Davis JA, Symonds RP. Long-term bladder symptomatology following radiotherapy for cervical carcinoma. Radiother Oncol 1987; 9:195-199.
158. Sakamoto S, Takizawa K. An improved radical hysterectomy with fewer urological complications and with no loss of therapeutic results for invasive cervical cancer. Ballière's Clin Obst Gyn 1988; 2:953-962.
159. Kindermann G, Debus-Thiede G. Postoperative urological complications after radical surgery for cervical cancer. Ballière's Clin Obst Gyn 1988; 2:933-941.
160. Bye A, Tropé CG, Loge JH, Hjermstad M, Kaasa S. Health-related quality of life and occurrence of intestinal side effects after pelvic radiotherapy. Acta Oncol 2000; 39:173-180.
161. Cravello L, Gonzague-Casabianca L, Roger V, d'Ercole C, Smart C, Blanc B, Resbeut MR. Brachytherapy and vaginal hysterectomy for low-stage uterine cervix carcinoma. Gynecol Oncol 1999; 72:102-106.
162. Touboul E, Lefranc JP, Blondon J, Ozsahin M, Roche B, Mauban S, Batel-Copel L, Schwartz LH, Schlienger M, Laugier A, Guerin RA. Preoperative radiation therapy and surgery in the treatment of "bulky" squamous cell carcinoma of the uterine cervix (stage Ib,IIa,and IIb operable tumors). Radiother Oncol 1992; 24:32-40.
163. Barnes W, Waggoner S, Delgado G, Maher K, Potkul R, Barter J, Benjamin S. Manometric characterization of rectal dysfunction following radical hysterectomy. Gynecol Oncol 1991; 42:116-119.
164. Pourquier H, Dubois JB, Delard R. Cancer of the uterine cervix: Dosimetric guidelines for preservation of late rectal and rectosigmoid complications as a result of radiotherapeutic treatment. Int J Radiat Oncol Biol Phys 1982; 8:1887-1895.
165. Wellwood JM, Jackson BT. The intestinal complications of radiotherapy. Brit J Surg 1973; 60:814-818.
166. Yeoh EK, Horowitz M, Russo A, Muecke T, Ahmad A, Robb T, Chatterton B. A retrospective study of the effect of pelvic irradiation for carcinoma of the cervix on gastrointestinal function. Int J Radiat Oncol Biol Phys 1993; 26:229-237.

167. Pilepich MV, Asbell SO, Krall JM, Baerwald WH, Sause WT, Rubin P, Emami BN, Pidcock GM. Correlation of radiotherapeutic parameters and treatment related morbidity - analysis of RTOG study 77-06. Int J Radiat Oncol Biol Phys 1987; 13:1007-1012.
168. Pilepich MV, Krall JM, Sause WT, Johnson RJ, Russ HH, Hanks GE, Perez CA, Zinninger M, Martz K, Gardner P. Correlation of radiotherapeutic parameters and treatment related morbidity in carcinoma of the prostate - analysis of RTOG study 75-06. Int J Radiat Oncol Biol Phys 1987; 13:351-357.
169. Cox JD, Byhardt RW, Wilson JF, Haas JS, Komaki R, Olson LE. Complications of radiation therapy and factors in their prevention. World J Surg 1986; 10:171-188.
170. Yeoh EK, Horowitz M. Radiation enteritis. Surg Gynecol Obstet 1987; 165:373-379.
171. Potish RA. Surgical staging, extended field radiation, and enteric morbidity in the treatment of cervix cancer. Int J Radiat Oncol Biol Phys 1995; 31:1009-1010.
172. Varma JS, Smith AN, Busuttil A. Function of the anal sphincters after chronic radiation injury. Gut 1986; 27:528-533.
173. Birnbaum EH, Dreznik Z, Myerson RJ, Lacey DL, Fry RD, Kodner IJ, Fleshman JW. Early effect of external beam radiation therapy on the anal sphincter: A study using anal manometry and transrectal ultrasound. Dis Colon Rectum 1992; 35:757-761.
174. Iglicki F, Coffin B, Ille O, Flourié B, Amarenco G, Lémann M, Messing B. Fecal incontinence after pelvic radiotherapy: Evidence for a lumbosacral plexopathy. Dis Colon Rectum 1996; 39:465-467.
175. Einhorn N, Patek E, Sjöberg B. Outcome of different treatment modalities in cervix carcinoma stage IB and IIA. Cancer 1985; 55:949-955.
176. Kjorstad KE, Martimbeau PW, Iversen T. Stage IB carcinoma of the cervix, the Norwegian Radium Hospital results and complications. III. Urinary and gastrointestinal complications. Gynecol Oncol 1983; 15:42-47.
177. Csömör S, Vigváry Z, Szanyi L. Treatment experiences with intracavitary 137Cs after-loading in a five-year patient material with uterine-cervical carcinoma. Acta Chirurgica Hungarica 1991; 32:119-126.
178. Jacobs AJ, Perez CA, Camel HM, Kao MS. Complications in patients receiving both irradiation and radical hysterectomy for carcinoma of the uterine cervix. Gynecol Oncol 1985; 22:273-280.
179. Fujikawa K, Miyamoto T, Ihara Y, Matsui Y, Takeuchi H. High incidence of severe urologic complications following radiotherapy for cervical cancer in Japanese women. Gynecol Oncol 2001; 80:21-23.
180. Crook JM, Esche BA, Chaplain G, Isturiz J, Sentenac I, Horiot JC. Dose-volume analysis and the prevention of radiation sequelae in cervical cancer. Radiother Oncol 1987; 8:321-332.
181. Montana GS, Fowler Jr WC. Carcinoma of the cervix: Analysis of bladder and rectal radiation dose and complications. Int J Radiat Oncol Biol Phys 1989; 16:95-100.
182. Iversen T, Kjörstad KE, Martimbeau PW. Treatment results in carcinoma of the cervix stage IB in a total population. Gynecol Oncol 1982; 14:1-5.
183. Kenter GG, Ansink AC, Heintz APM, Aartsen EJ, Delemarre JFM, Hart AAM. Carcinoma of the uterine cervix stage I and IIA: Results of surgical treatments: complications, recurrence and survival. Eur J Surg Oncol 1989; 15:55-60.
184. Griffenberg L, Morris M, Atkinson N. The effect of dietary fiber on bowel function following radical hysterectomy: a randomized trial. Gynecol Oncol 1997; 66:417-424.
185. Stanhope CR. Editorial. Gynecol Oncol 1991; 42:114-115.
186. Vierhout ME, Schreuder HWB, Veen HF. Severe slow-transit constipation following radical hysterectomy. Gynecol Oncol 1993; 51:401-403.

187. Varma JS, Smith AN. Abnormalities of colorectal function in intractable constipation after hysterectomy. Gut 26, A581-A582. 1985.
Ref Type: Abstract
188. Danielsson Å, Nyhlin H, Persson H, Stendahl U, Stenling R, Suhr O. Chronic diarrhoea after radiotherapy for gynaecological cancer: occurrence and aetiology. Gut 1991; 32:1180-1187.
189. Wang CJ, Leung SW, Chen HC, Sun LM, Fang FM, Huang EY, Hsiung CY, Changchien CC. The correlation of acute toxicity and late rectal injury in radiotherapy for cervical carcinoma: evidence suggestive of consequential late effect (CQLE). Int J Radiat Oncol Biol Phys 1998; 40:85-91.
190. Bonar LD. Results of radical surgical procedures after radiation for treatment of invasive carcinoma of the uterine cervix in a private practice. Am J Obstet Gynecol 1980; 136:1006-1008.
191. Coia LR, Myerson RJ, Tepper JE. Late effects of radiation therapy on the gastrointestinal tract. Int J Radiat Oncol Biol Phys 1995; 31:1213-1236.
192. Benedet J, Odicino F, Maisonneuve P, Severi G, Creasman W, Shepherd J, Sideri M, Pecorelli S. FIGO Annual Report on the results of treatment in gynaecological cancer. Vol. 23. J Epidemiol Biostat 1998; 3:5-34.
193. Piver MS, Rutledge F, Smith JP. Five classes of extended hysterectomy for women with cervical cancer. Obstet Gynecol 1974; 44:265-272.
194. Mortimer PS. Therapy approaches for lymphedema. Angiology 1997; 48:87-91.
195. Kjorstad KE. Treatment complications in patients with earlystage cervical cancer. Ballière's Clin Obst Gyn 1988; 2:963-970.
196. Benedetti-Panici P, Scambia G, Baiocchi G, Maneschi F, Greggi S, Mancuso S. Radical hysterectomy: a randomized study comparing two techniques for resection of the cardinal ligament. Gynecol Oncol 1993; 50:226-231.
197. Timmer PR, Aalders JG, Bouma J. Radical surgery after preoperative intracavitary radiotherapy for stage IB and IIA carcinoma of the uterine cervix. Gynecol Oncol 1984; 18:206-212.
198. Fiorica JV, Roberts WS, Greenberg H, Hoffman MS, LaPolla JP, Cavanagh D. Morbidity and survival patterns in patients after radical hysterectomy and postoperative adjuvant pelvic radiotherapy. Gynecol Oncol 1990; 36:343-347.
199. Barter JF, Soong SJ, Shingleton HM, Hatch KD, Orr JW. Complications of combined radical hysterectomy - postoperative radiation therapy in women with early stage cervical cancer. Gynecol Oncol 1989; 32:292-296.
200. Martimbeau PW, Kjorstad KE, Kolstad P. Stage IB carcinoma of the cervix, the Norwegian Radium Hospital, 1968-1970: Results of treatment and major complications. I. Lymphedema. Am J Obstet Gynecol 1978; 131:389-394.
201. Werngren-Elgström M, Lidman D. Lymphoedema of the lower extremities after surgery and radiotherapy for cancer of the cervix. Scand J Plast Reconstr Hand Surg 1994; 28:289-293.
202. Passik SD, McDonald MV. Psychosocial aspects of upper extremity lymphedema in women treated for breast carcinoma. Cancer 1998; 83:2817-2820.
203. Wright J, Jones G, Whelan T, Lukka H. Patient preference for high or low dose rate brachytherapy in carcinoma of the cervix. Radiother Oncol 1994; 33:187-194.
204. Nordin AJ, Chinn DJ, Moloney I, Naik R, de Barros Lopes A, Monaghan JM. Do elderly cancer patients care about cure? Attitudes to radical gynecologic oncology surgery in the elderly. Gynecol Oncol 2001; 81:447-455.

205. Helgason ÁR, Adolfsson J, Dickman PW, Fredrikson M, Arver S, Steineck G. Waning sexual function - the most important disease-specific distress for patients with prostate cancer. Br J Cancer 1996; 73:1417-1421.
206. Helgason ÁR, Adolfsson J, Steineck G. Disease specific quality of life in men with prostate cancer - a three level epidemiological approach. J Epidemiol Biostat 1997; 4:213-218.
207. Helgason ÁR. Prostate cancer treatment and quality of life - a three level epidemiological approach. Thesis. Karolinska Institutet, Stockholm, Sweden. 1997.
208. Portenoy RK, Thaler HT, Kornblith AB, McCarthy Lepore J, Friedlander-Klar H, Kiyasu E, Sobel K, Coyle N, Kemeny N, Norton L, Scher H. The Memorial Symptom Assessment Scale: an instrument for the evaluation of symptom prevalence, characteristics and distress. Eur J Cancer 1994; 30A:1326-1336.
209. Steineck G, Bergmark K, Henningsohn L, al-Abany M, Dickman PW, Helgason ÁR. Symptom documentation in cancer survivors as a basis for therapy modifications. Acta Oncol 2002; Accepted.
210. Spielberger CD, Gorsuch RL, Lushene PR, Vagg PR, Jacobs GA. Manual for the state-trait anxiety inventory (form Y). Palo Alto, CA: Consulting Psychologists Press; 1983.
211. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. Appl Psychol Meas 1977; 1:385-401.
212. Tibblin G, Tibblin B, Peciva S, Kullman S, Svärdsudd K. "The Göteborg quality of life instrument" - an assessment of well-being and symptoms among men born 1913 and 1923. Scand J Prim Health Care 1990; 1:33-38.
213. Börjeson S, Hursti TJ, Peterson C, Fredrikson M, Fürst CJ, Åvall-Lundqvist E, Steineck G. Similarities and differences in assessing nausea on a verbal category scale and a visual analogue scale. Cancer Nurs 1997; 20:260-266.
214. Jaeschke R, Singer J, Guyatt GH. A comparison of seven-point and visual analogue scales. Controlled Clin Trials 1990; 11:43-51.
215. SAS Institute Inc. p. 350. In SAS Procedures Guide, Version 6. Cary, NC: SAS Institute Inc.; 1990.
216. Rothman KJ, Greenland S. p. 271. In Rothman KJ, Greenland S (eds). Modern Epidemiology. Philadelphia: Lippincott-Raven Publishers; 1998.
217. International Commission on Radiation Units and Measurements. ICRU report 38. Dose and volume specification for reporting intracavitary therapy in gynecology. International Commission on Radiation Units and Measurements. Bethesda, Maryland, USA. 1985; 38:1-22.
218. Steineck G, Kass PH, Ahlbom A. A comprehensive clinical epidemiological theory based on the concept of source person-time and four distinct study stages. Acta Oncol 1998; 37:15-23.
219. Sprangers MAG, Schwartz CE. Integrating response shift into health-related quality of life research: a theoretical model. Soc Sci Med 1999; 48:1507-1515.
220. Rothman KJ, Greenland S. Modern Epidemiology. Philadelphia, PA: Lippincott Williams & Wilkins; 1998.
221. Maas K, Moriya Y, Kenter G, Trimbos B, van de Velde C. A plea for preservation of the pelvic autonomic nerves. Lancet 1999; 354:772-773.
222. Trimbos B, Maas CP, Deruiter MC, Peters AAW, Kenter G. A nerve-sparing radical hysterectomy: Guidelines and feasibility in Western patients. Int J Gynecol Cancer 2001; 11:180-186.

223. Thakar R, Manyonda I, Stanton SL, Clarkson P, Robinson G. Bladder, bowel and sexual function after hysterectomy for benign conditions. Br J Obstet Gynaecol 1997; 104:983-987.
224. Barton DPJ, Butler-Manuel SA, Buttery LDK, A'Hern RP, Polak JM. Letter to the editor. Gynecol Oncol 2001; 82:410.
225. Yabuki Y, Asamoto A, Hoshiba T, Nishimoto H, Satou N. A new proposal for radical hysterectomy. Gynecol Oncol 1996; 62:370-378.
226. Höckel M, Konerding MA, Heussel CP. Liposuction-assisted nerve-sparing extended radical hysterectomy: Oncologic rationale, surgical anatomy, and feasibility study. Am J Obstet Gynecol 1998; 178:971-976.
227. Henningsohn L, Wijkstrom H, Dickman PW, Bergmark K, Steineck G. Distressful symptoms after radical cystectomy with urinary diversion for urinary bladder cancer: a Swedish population-based study. Eur Urol 2001; 40:151-162.
228. Magrina JF, Goodrich MA, Lidner TK, Weaver AL, Cornella JL, Podratz KC. Modified radical hysterectomy in the treatment of early squamous cervical cancer. Gynecol Oncol 1999; 72:183-186.
229. O'Boyle JD, Coleman RL, Bernstein SG, Lifshitz S, Muller CY, Miller DS. Intraoperative lymphatic mapping in cervix cancer patients undergoing radical hysterectomy: A pilot study. Gynecol Oncol 2000; 79:238-243.
230. Verheijen RHM, Pijpers R, van Diest PJ, Burger CW, Buist MR, Kenemans P. Sentinel node detection in cervical cancer. Obstet Gynecol 2000; 96:135-138.
231. Andersen BL. Predicting sexual and psycologic morbidity and improving the quality of life for women with gynecologic cancer. Cancer 1993; 71:1678-1690.
232. Chan YM, Ngan HYS, Yip PSF, Li BYG, Lau OWK, Tang GWK. Psychosocial adjustment in gynecologic cancer survivors: A longitudinal study on risk factors for maladjustment. Gynecol Oncol 2001; 80:387-394.
233. Henningsohn L, Wijkstrom H, Dickman PW, Bergmark K, Steineck G. Distressful symptoms after radical radiotherapy for urinary bladder cancer. Radiother Oncol 2002; In Press.
234. al-Abany M, Steineck G, Agren Cronqvist AK, Helgason ÁR. Improving the preservation of erictile function after external beam radiation therapy for prostate cancer. Radiother Oncol 2000; 57:201-206.
235. Riggs S, Alario AJ, McHorney C. Health risk behaviors and attempted suicide in adolescents who report prior maltreatment. J Pediatr 1990; 116:815-821.
236. Sprangers MAG, Aaronson NK. The role of health care providers and significant others in evaluating the quality of life of patients with chronic disease: a review. J Clin Epidemiol 1992; 45:743-760.