Pelvic floor function after gynaecological cancer treatment

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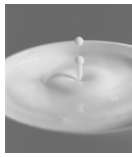
Chapter 1

General Introduction



General Introduction

Malignancies of the female genital tract are in general treated with surgery, radiation or chemotherapy, sometimes with additional hyperthermia. Treatment of gynaecological malignancies influences sexual functioning, as well as bladder and bowel function due to the anatomical vicinity of the urinary and digestive tract. Specific locations of disease and the various modes of treatment could result in different types of adverse effects on bladder, bowel and sexual function. Qualitative and quantitative aspects of the contribution of gynaecological cancer and its treatment modalities on bladder, bowel and sexual functioning are insufficiently known. Knowledge about relations between type of treatment and specific pelvic floor symptoms is important to inform patients and to prevent and reduce these symptoms.

For this thesis we studied women who had been treated for cervical, endometrial or vulvar cancer. As ovarian cancer is predominantly an intra-abdominal disease with a low overall survival rate, patients with this disease have not been included in our studies.

Treatment of gynaecological malignancies

Cervical cancer

In the Netherlands the incidence of cervical cancer was 7 per 100,000 women between 1997 and 2007, i.e. around 680 new patients per year. (1) Around 230 women died each year from cervical cancer in the same decade. (1) Approximately 7000 women who have been treated for cervical cancer live in the Netherlands. (2) Progression of disease occurs primarily via local invasion of adjacent structures, and via lymphatic spread, affecting first the pelvic lymph nodes and second the para-aortic lymph nodes. (3) For International Federation of Obstetrics and Gynaecology (FIGO) stage IA and IB and stage IIA tumours, five-year survival rates vary from 70% to up to 100%. (4) Five-year survival rates of more advanced stage tumours, i.e. FIGO stage IIB to IV, range from 5 to 70%. (4)

Mode of treatment of cervical cancer depends on the stage of disease and the condition of the patient. In summary, when the tumour is of limited size and restricted to the cervix and without known lymphatic spread (i.e. FIGO stages IA2 – IIA), women are primarily treated with a radical hysterectomy with pelvic lymph node dissection. Several types of radical hysterectomy have been developed during the last decades. In the Academic Medical Center (AMC), Amsterdam, the Netherlands, gynaecologic oncologists have been applying radical hysterectomy with pelvic lymph node dissection according to Wertheim and Okabayashi. (5;6)

When histopathologically prognostic unfavourable factors are present in the excised tissue, patients are offered adjuvant chemo-radiotherapy. Radiotherapy is primarily administered, with or without chemotherapy, when the tumour is large or local or regional spread is present. (2;7)

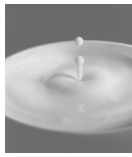
The radiation dosages are similar for adjuvant and primary chemo-radiotherapy. During five weeks, patients are treated five days per week with external beam radiotherapy and once a week with chemotherapy. The total amount of Grays is 45 to 50 with external beam radiotherapy. Sometimes patients are treated additionally with brachytherapy up to 70 grays in total. Additionally, weekly cisplatin-containing chemotherapy can increase the five-year survival with 15% in patients primarily treated with radiotherapy. (2)

Endometrial cancer

Annually, around 1600 women were diagnosed with endometrial cancer in the Netherlands from 1997 to 2007 and around 350 women died annually from this disease. (1) An estimate of 14000 women live in the Netherlands who have been treated for uterine malignancies. (2) Endometrial cancer has the lowest mortality rate of all malignant gynaecological diseases, which can be explained by the notable and early symptom of postmenopausal bleeding and the biological properties of the majority of the tumours. Progression of disease occurs via the pelvic and para-aortic lymphatic system. Metastases usually develop in the vagina and lungs. Overall five year survival rates for FIGO stage I and II are 79 to 92% and for higher stages these rates decrease to 43 to 18%. (8)
When the tumour is restricted to the corpus uteri, treatment can be limited to a hysterectomy with bilateral salpingo-oophorectomy. In case of stromal endocervical involvement additional pelvic lymph node dissection is performed, with or without para-aortal sampling of lymph nodes according to local protocol. When the tumour is surgically irresectable primary radiation therapy is administered. In FIGO stage I and II adjuvant radiotherapy, i.e. external beam radiation or vaginal brachy therapy, is administered when patients have an intermediate to high risk profile based on their age and the histopathology of the tumour. (2;9)

Vulvar carcinoma

Vulvar carcinoma is a rare gynaecological malignancy with an annual incidence of 2 per 100.000 women. (10) In the Netherlands, around 250 women were diagnosed every year with vulva carcinoma between 1997 and 2007 and around 70 women deceased yearly from this malignancy. (1) About 1400 women live in the Netherlands who have been treated for malignancies of the vulva. (2)
Treatment either consists of primary surgery with or without adjuvant radiotherapy or of primary radiotherapy, depending on size and localization of the tumour, suspicion of lymph node metastases, and the general condition of the patient. (11) Before the year 2000, a radical vulvectomy with ‘en bloc’ resection of the bilateral inguinal lymph nodes was performed. Since 2000 the sentinel node procedure has been introduced enabling a more precise indication for an inguinal lymph node dissection. Nowadays, radical local excision of the lesion with a sentinel node procedure is the preferred surgical procedure. These adjustments to the surgical treatment of vulvar cancer and individualisation of the performed procedure reduce morbidity in these patients without a negative effect on survival rates. (2;12)



Bladder, bowel and sexual symptoms and their influence on quality of life

Gynaecological malignancies in early stages, i.e. cervical, endometrial and vulvar cancer, have overall good prognosis. Therefore improvement of quality of life has become an important treatment outcome. (13-15) Complications and treatment-related morbidity are likely to occur due to the proximity of the pelvic organs and structures and the extensively treated sites. Particularly, bladder, bowel and sexual symptoms result from these treatments. (16-26) In women who do not have gynaecological cancer and thus have not undergone the before mentioned treatments bladder, bowel and sexual symptoms adversely affect quality of life. (27-31) However, studies with gynaecological cancer patients have only rarely employed disease specific quality-of-life questionnaires to quantify distress experienced from bladder, bowel or sexual side-effects. (17;25;32;33)

The collective term for symptoms related to bladder and bowel function, such as the involuntary loss of urine or faeces, is “pelvic floor symptoms”. Officially sexual symptoms or dysfunction are included in this term, but in the studies described in this thesis, we will mention sexual function or symptoms separately from the pelvic floor symptoms related to the bladder and bowel. (34)

Quality of life is a term which stands for to the subjective well-being of a person, including physical, mental and social functioning. In cancer clinical trials quality of life is often a secondary outcome. (35) Pelvic floor symptoms are usually not life-threatening, but may exert a negative impact on social, physical and emotional functioning. The distress patients experience by these symptoms, an important sign of impaired quality of life, is the main indicator for treatment in women who attend a pelvic floor specialist, whether they will be treated medically, surgically or with behavioural or biofeedback therapy.

Pelvic floor specialists include uro-gynaecologists, urologists, gastro-enterologists, pelvic physiotherapists, colo-rectal surgeons, continence nurses and (psycho-) sexologists.

Questions arise about the prevalence and extent of distress from pelvic floor symptoms patients experience after different treatment modalities. Moreover, a pertinent question is related to the associations between patient and clinical characteristics and the distress from pelvic floor and sexual symptoms gynaecological cancer treatment. To date, only in women from the general population, risk factors for distressing pelvic floor symptoms were studied. Familial, obstetric and medical factors, such as assisted childbirth by forceps and chronic coughing, were found to be negatively related to pelvic floor function. (36-39) We do not know the prevalence of and amount of distress from specific pelvic floor and sexual symptoms after gynaecological cancer treatment. Physicians are therefore not able to provide accurate counselling and follow up concerning these symptoms after the different treatment modalities. Moreover, we do not know how patient, disease and treatment factors affect pelvic floor related quality of life after these treatments. Such insights are needed not only to recognize symptoms but also to inform and support gynaecological cancer patients.

Hydronephrosis after radical hysterectomy with pelvic lymph node dissection

As mentioned before, early stage cervical cancer is usually treated with radical hysterectomy with pelvic lymph node dissection, with or without adjuvant chemo-radiotherapy. One of the side effects of this treatment is hydronephrosis. The reported incidence is 21% two weeks after radical hysterectomy and lymph node dissection (RH+LND) and 15% three months after this procedure. (40;41) Two mechanisms could explain the dilatation of renal pelvis with or without hydro-ureter after RH+LND: [1] surgical denervation of ureters resulting in reduction of the peristaltic movements, and [2] obstruction of the ureter due to a surgical lesion or scar tissue formation, possibly increased by adjuvant radiotherapy. (40;42)

Hydronephrosis after RH+LND resolves in most patients spontaneously within six months after surgery. (40) Because severe hydronephrosis might impair renal function and could ultimately result in renal failure, routine imaging of the kidneys during the post-operative phase has been proposed to diagnose this surgery related complication. Less than two decades ago intravenous pyelogram (IVP) was abandoned as a routine check after radical hysterectomy. (43) Following the cessation of the postoperative IVP, routine renal ultrasound at four weeks after RH+LND was introduced in the AMC to detect asymptomatic hydronephrosis at an early stage. (44)

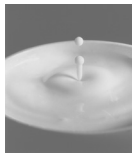
Even though this is a routine postoperative procedure in our center, we do not know how many patients are diagnosed and treated for clinically relevant hydronephrosis and whether they benefit from early detection of hydronephrosis. If such routine ultrasound is not beneficiary, stopping it would save medical costs and additional hospital visits for the patients.

Help-seeking behaviour for pelvic floor symptoms

Our clinical impression is that gynaecological cancer survivors do not often seek medical help for distressing pelvic floor and sexual symptoms. From empirical studies we know that not all women with pelvic floor symptoms visit a doctor for medical help. For instance, less than half of the amount of women with stress urinary incontinence seek help. (45-47) Embarrassment, lack of knowledge about its causes and solutions, unfamiliarity with treatment options and presence of concomitant symptoms were found to be reasons for not seeking medical treatment. (48-50) Embarrassment is also the most frequent reason for not seeking help or consulting a physician for distressing sexual problems. (51)

Whether help seeking behaviour of gynaecological cancer survivors differs from that of the general female population is unknown. Gynaecological cancer patients routinely visit their gynaecologist and radiotherapist and consequently could easily be referred to a pelvic floor specialist. Recent studies showed that oncologic specialists identified pelvic floor symptoms in 5 to 15% of gynaecological cancer survivors. This percentage is surprisingly low if one

considers that 23 to 58% of these women reported to have severe pelvic floor symptoms. (32;52) It could be that gynaecological cancer survivors are also embarrassed or reluctant to bring up these symptoms. As pelvic floor and sexual symptoms negatively affect quality of life and might be alleviated by treatment, insight into the personal factors that impede help seeking behaviour in gynaecological cancer patients is therefore needed. (53)



Prevention and treatment of pelvic floor symptoms

Pelvic floor symptoms in women who do not have a gynaecological malignancy and thus have not undergone cancer treatments may have multiple causes. Genetic factors and trauma related to childbirth play a large role. (54-57) The amount of distress women experience may be caused by the severity of symptoms and also by characteristics of the patient (e.g. age), disease (e.g. stage), treatment (e.g. adjuvant radiotherapy) and psychological make-up (e.g. optimism). (56;58;59).

Prevention of bladder, bowel and sexual symptoms is attempted in some oncological treatments, such as nerve-sparing radical hysterectomy in early stage cervical cancer. (60) In endometrial cancer the more selective use of radiation therapy reduces the severity of radiation related pelvic floor symptoms. (9;61) In vulvar cancer patients surgical treatment has become less extensive in comparison to types of treatment in the past, reducing morbidity related to this surgical procedure. (12)

Treatment of pelvic floor symptoms has changed rapidly over the course of the last two decades, since the introduction of the tension-free vaginal tape for stress urinary incontinence. (62) Also other therapies, such as bulking agents for stress urinary incontinence, medication, neuro-stimulation and intra-vesical botox application for overactive bladder symptoms have been introduced, and pelvic floor muscle training and biofeedback have been shown effective for various pelvic floor symptoms. (63-68) To date, in gynaecological cancer survivors, the effect of such treatment options have only been evaluated at an individual level. (69)

Objectives of the thesis

Part I

1. To assess the prevalence of and distress from bladder, bowel and sexual symptoms and level of pelvic floor-related quality of life in patients after gynaecological cancer treatment
2. To explore associations between patient, disease, treatment, and psychological variables and pelvic floor symptoms and sexual function in patients after gynaecological cancer treatment
3. To examine the prevalence of hydronephrosis after early stage cervical cancer treatment and the diagnostic value of postoperative routine renal ultrasound
4. To study help-seeking behaviour for severe pelvic floor symptoms of gynaecological cancer patients after treatment

Part II

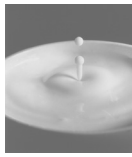
5. To evaluate strategies intended to reduce gynaecological cancer treatment related-pelvic floor morbidity

Outline of the thesis

In **Part one** of this thesis we investigate the pelvic organ and sexual function, pelvic floor related quality of life and help-seeking behaviour in gynaecological cancer patients after treatment.
In Chapter 2 we examine the prevalence of and distress from pelvic floor symptoms in patients treated for cervical cancer by different treatment modalities.
In Chapter 3 the associations are studied between demographic, disease-related and psychological variables and severe pelvic floor symptoms in patients treated for cervical cancer.
In Chapter 4 we assess the sexual function of women who have undergone extensive and less extensive treatment for vulvar cancer, and we investigate the associations between sexual function and patient, disease, treatment, and psychological characteristics.
In Chapter 5 a retrospective study is presented evaluating the prevalence of hydronephrosis after radical hysterectomy and pelvic lymph node dissection for early stage cervical cancer and the usefulness of routine renal ultrasound.
Chapter 6 presents the results of a qualitative study about patients' personal reasons for not seeking medical help for bothersome pelvic floor symptoms after treatment for gynaecological malignancy. Furthermore we explore the willingness to undergo treatment for these symptoms and invite suggestions to improve post-operative out-patient care.

In **Part two** of this thesis we study preventive and therapeutic measures for pelvic floor symptoms during and after gynaecological cancer treatment.
In Chapter 7 we present the results of a randomised clinical trial about the effect of pelvic physiotherapy on pelvic floor symptoms after treatment for early stage cervical cancer.
In Chapter 8 a pilot study is presented, evaluating the feasibility and the effect of intravesical instillations with chondroitin sulphate 0.2% solution in gynaecological cancer patients treated with pelvic radiotherapy.
Chapter 9 presents the results of the surgical treatment of stress urinary incontinence in two cervical cancer survivors.

Chapter 10 contains the summary of the results and conclusions presented in this thesis, clinical implications and implications for future studies about prevention and treatment of pelvic floor symptoms in gynaecological cancer patients.



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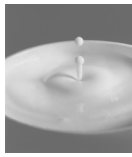

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