# Early stage cervical cancer; Quality of cancer care and Quality of life

Leiden, 2007
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ISBN: 978-90-8559-300-3

Cover photography: Carla van de Puttelaar, Amsterdam

Lay-out and print: Optima Grafische Communicatie B.V.

Financial support for printing of this thesis was provided by:

Stichting Nationaal Fonds tegen Kanker-voor onderzoek naar reguliere en alternatieve therapieën.
J.E. Jurriaanse Stichting
Sanofi Pasteur MSD N.V.
Ortho-Biotec, divisie van Janssen-Cilaq B.V.
Medical Dynamics
Smiths medical Nederland B.V.
Amgen B.V.
Nycomed Nederland B.V.

# Early stage cervical cancer; Quality of cancer care and Quality of life

## Proefschrift

ter verkrijging van

de graad van Doctor aan de Universiteit Leiden,

op gezag van de Rector Magnificus prof.mr. P.F. van der Heijden,

volgens besluit van het College voor Promoties

te verdedigen op donderdag 13 september 2007

klokke 13:45 uur

door

**Quirine Dionne Pieterse**

geboren te Dordrecht in 1975

Promotiecommissie

| | |
|---|---|
| Promotores: | Prof. Dr. G.G. Kenter<br>Prof. Dr. J.B.M.Z. Trimbos |
| Co-promotor: | Dr. M.M. ter Kuile |
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# Contents

Chapter 1

# General introduction

## Introduction

The incidence of carcinoma of the uterine cervix in The Netherlands is 9/100.000 which means that every year 650 women are treated for the disease (1). World-wide, cervical cancer is the second most common type of female cancer, accounting for 10% of all newly diagnosed cancers in women (1;2). The treatment of choice depends on the stage of the disease and can either be surgery or radiotherapy. Especially in young women the surgical approach has the great advantage over radiotherapy of preserving the ovaries, keeping a more functional vagina and obtains more detailed information about the nature and pattern of spread of the tumour at hand. The state of the art treatment for women with early stage cervical cancer (I-IIa) is a radical hysterectomy with pelvic lymphadenectomy (RHL) with or without adjuvant (chemo) radiation (3;4). Operation consists of extirpation of the uterus, the paracervical and paravaginal tissue, plus a portion of the upper vagina and the perivascular fatty and connective lymph-bearing tissues on the lateral pelvic wall. Patients with unfavourable prognostic factors, such as lymph node metastases, tumour growth into the parametria or irradical surgical resection margins and tumours with a combination of large diameter, deep infiltration or vaso-invasion may receive postoperative radiotherapy.

The results of treatment for low stage carcinoma of the uterine cervix have improved tremendously over the past century. Today, the prognosis of early stage cervical carcinoma after RHL is good in most cases, with 5-year survival rates of 80-90% (5-11). Furthermore, the mortality rates of surgical treatment have dropped from 50% to almost zero and the morbidity figures are acceptably low. However, cervical cancer still afflicts a lot of women and, therefore, improvement of the quality of treatment procedures remains an important issue. The good results of the treatment for early stage cervical cancer in terms of survival, have their price: loss of fertility, bladder dysfunction, colorectal motility disorders and sexual dysfunction (12-20). A better control of the quality of surgical procedures in oncology, for example, is possible and may have a major impact on outcomes of cancer patients (21).

It is time to improve the balance between cure and quality of life. This thesis describes the results of studies concerning the sequelae of the treatment and the treatment-related information acquired by registries of women with early stage cervical cancer in order to improve the quality of treatment procedures and the quality of life.

## Quality control of treatment procedure

In recent years increasing attention has been paid to the quality of cancer care. In surgery, little or no quality assurance guidelines are yet available. One of the reasons for this is the scarcity of quantifiable parameters in surgery. Moreover, the impact of primary surgical treatment is often underestimated especially when postoperative adjuvant treatments are evaluated (22).

For many years, most treatment failures were considered to be caused by the biological behaviour of the tumour rather than by inadequate local therapy (22). However, several studies have shown that an improvement in surgical procedures had much more influence on local recurrence rates than the use of adjuvant radiotherapy (23-27). In order to monitor the quality of treatment the registration of all aspects of cancer care is essential. Concerning surgery, the most important items should be the operation-related morbidity, mortality, adequacy of resection or radicality, local recurrences and overall survival. Registries would probably be the most relevant means to acquire all this information. A regular audit of the data could achieve more awareness of existing differences in outcome, gain more insight into the existence of other risk factors or morbidity and could lead to other treatment modalities. This would probably have a major impact on the quality of treatment and quality of life.

## Quality of life

Treatment for cervical cancer by RHL has an adverse effect on bladder, colorectal and sexual functioning (12-20). When diagnosing a woman with a life-threatening disease and treating her with a RHL or with radiotherapy, it may not seem a priority to discuss micturial, colorectal and especially not sexual issues. However, urinary incontinence restricts patients' activity, affects the quality of her live and is a cause of patient discomfort. Furthermore, sexual function is an essential component of many people's lives and the diagnosis of a gynaecological cancer can affect many aspects of sexual function and satisfaction, and therefore is an issue that should not be ignored. It has been shown that for women with gynaecological cancer, the maintance of a positive self-image and feelings of sexuality is an issue of central importance in the provision of quality of their daily living (28). Moreover, sexuality is important during illness and in particular following a diagnosis of gynaecological cancer. Intimate contact can be a form of support during the distressing time after the diagnosis. Because sexual function and satisfaction are based on both physical and psychological components, the treatment for gynaecological cancer can affect both of these aspects, particularly because of the anatomical nature of the cancer (29). The impact of morbidity after the treatment for gynaecological cancer should therefore never be underestimated.

Research has shown that in gynaecological cancer, levels of communication between doctors and the women with cancer are still low (30). In a study of Stead et al. it was shown that reasons for not discussing sexual issues included 'it is not my responsibility', 'embarrassment', 'lack of knowledge and experience' and 'lack of resources to provide support if needed'. While some of these reasons were also viewed as barriers by the women involved in the study, the results showed that there is a need from the women's perspective to improve communication about sexual issues (30).

A further reason for lack of communication about sexual issues is a lack of research evidence to support the discussions. Fortunately, this evidence is gradually building, with a range of research being carried out in the different types of gynaecological cancer (31).

## Postoperative morbidity following radical hysterectomy

*Urologic dysfunction*

It is well known that RHL can lead to postoperative urinary dysfunction such as urinary retention and straining or inability to void, and, to a lesser extent, urge and stress incontinence (14;15;17;20;32). Results of urodynamic studies evaluating urinary dysfunction in patients after RHL are suggestive for disruption of the autonomic nerve supply to the bladder and urethra: the rest-tone and the filling pressure of the bladder increase, whereas pressure in and along the length of the urethra decreases (17;20;33). Loss of compliance of the bladder is thought to be caused by neural denervation of the bladder and urethra in combination with direct surgical injury to the bladder wall, lymph stasis, interruption of the blood supply, and fibrosis of the urethra (17;33;34). Furthermore, a substantial number of patients appear to suffer from impaired bladder sensation, which is an additional indication for disruption of the nerve supply (35;36). The inferior hypogastric plexus is the pathway for the autonomic nerve supply of the internal genitals and the lower urinary tract, and is topographically closely related to its target organs. It is therefore conceivable that damage to this plexus during surgery plays an important role in the etiology of the observed urologic morbidity. This theory is further strengthened by the observation of various authors that the extent of dysfunction is related to the radicality of the surgical procedure in the pelvis (14;34-38). The precise effect of disruption of the autonomic nerve system in the function of the pelvic muscles is not known.

Long-term bladder dysfunctions after RHL occur in about 8-80% of patients (14;37;39;40). This discrepancy reflects the varying degrees of surgical radicality, the diverse follow-up intervals and the various instrumental methods used in literature. However, up to one half of patients undergoing RHL experience at least one lower urinary tract symptom that develops after surgery and at a variable period of time (14;32;34;36;41-43).

Radiotherapy is described as a cause of hydronephrosis due to distal ureteric stricture, urge and stress incontinence and changes observed in the bladder such as mural thickening, mucosal irregularity, focal ulceration, reduction in size, and vesicovaginal fistula. Furthermore, some authors have reported that about 10% of patients treated with radiotherapy experience radiation-induced urologic complications (44-50). Unfortunately, most of these studies offer retrospective data collected from the medical files and lack detailed information.

## Colorectal dysfunction

Colorectal dysfunction after RHL has been described in 5-58% (51-55) and in the form of severe constipation in 5-10% (14;19;32). The pelvic autonomic nerves play an equally important role in colorectal motility as in bladder function. The neural control of the coordinated contractions of the smooth muscle of the bowel as well as the sensory innervation of the bowel runs through the inferior hypogastric plexus. Several studies have shown colorectal motility disorders after hysterectomy for benign as well as for malignant conditions (19;54;55). Anorectal manometry revealed significant changes in colorectal function after RHL, showing a pattern which correlates to a partial denervation of the bowel (55-57).

Radiotherapy causes strictures of the recto-sigmoid which showed a smooth mucosa, fine surface ulceration, focal ulceration or a 'cobble-stone' appearance. Furthermore, patients who receive radiation may also experience early or late large bowel complications such as bleeding, fistulae and perforations. Lesions observed in the small bowel included fixity of bowel loops, thickening of the wall, coarsening of the mucosal pattern and strictures. All these changes could also cause colorectal dysfunction (44;47;50;58). The incidence of colorectal complications of postoperative radiotherapy varies in the literature from 3% to 30% (59-61). The reasons for such a disparity are multiple and include different systems to classify the late radiation side-effects and differences in the reporting of complications.

*Lymphedema*

RHL results in long-term lymphedema that gives rize to moderate or much symptom induced distress in about half of the affected women (32). During the past decade lymphedema has been reported to occur in 3-23% after RHL (14;32;40;62). However, the assessed prevalence of the disorder varies with the definition. Bergmark et al. found that 19% of the women reported constantly swollen legs or lower abdomen, while 12% reported constantly heavy legs or lower abdomen. Furthermore, there are limited data on long-term lymphedema in women treated for cervical cancer, and most studies only report the physician's documentation of grade 3-4 edema (63) in the medical records, with prevalence ranging from 0-5% (11;40;64).

It is reasonable to assume that the incidence of lymphedema will depend on the surgical technique used during the RHL and the extent of the lympadenectomy (65). However, the mechanism behind lymphedema and the prevention of it needs further research. Modifications of surgical techniques and intense rehabilitation programs for lymphedema might reduce the occurrence of this treatment-induced symptom and the subsequent distress.

## Sexual dysfunction

Women who have been treated for cervical cancer by RHL have persistent vaginal changes that compromise sexual activity and result in considerable distress. Changes or problems that have been described are diminished lubrication, a narrow and short vagina, dyspareunia and sexual dissatisfaction. Sexual dysfunction after RHL occurs in about 25% of the patients (12;13;18;66-71). Radiotherapy also causes sexual dysfunction and vaginal changes by chronic fibrotic changes in pelvic tissue (44;72;73). After surgery, alone or in combination with radiotherapy, several symptoms related to sexual dysfunction appeared to be the primary sources of symptom-induced distress. It is concluded that sexual function is important to women with a history of cervical cancer (66).
The autonomic nerves are essential for a normal sexual function. They supply the blood vessels of the internal genitalia and are involved in the neural control of vasocongestion and, consequently, the lubrication-swelling response (74;75). It is assumed that orgasm is the sensory consequence of the contraction of the internal genitalia, mediated by sympathetic fibres of the autonomic nervous system of which the superior and inferior hypogastric plexus are the pathway from the spinal cord (76).

## Measuring instruments of morbidity

*The Gynaecologic Leiden Questionnaire; a subjective measuring instrument of urological, colorectal and sexual morbidity.*

To obtain an impression of the impact of a given treatment on a patient's quality of life and to understand the patient's perception of symptom severity, self-report questionnaires may give more informative answers (77;78). Over the last decades several questionnaires have been developed to diagnose dimensions of female sexual dysfunction (79;80). Lately, Jensen et al. showed the results of the validation of the Sexual function-Vaginal changes Questionnaire (SVQ), that was to investigate sexual and vaginal problems in gynaecological cancer patients (81).
For the Dutch language area however, until recently (82) no questionnaire was available that focuses on sexual and vaginal problems due to disease and treatment specific for gynaecological cancer patients. We developed a Dutch self-report questionnaire, the Gynaecologic Leiden Questionnaire (LQ), which is the first Dutch questionnaire that includes items for sexual function, voiding- and bowel problems for women with cancer. The Gynaecologic LQ has 1 item for weariness, 1 item for lymphedema, 11 items for sexual functioning, 6 items for voiding and 2 items for bowel problems.

*Vaginal photoplethysmography; an objective measuring instrument of sexual morbidity.*

Sexual arousal in women is characterized by the appearance of vaginal lubrication, which is produced by an increase of the arterial flow to the vaginal wall, leading to the transudation of fluid (83). This vaginal response to erotic stimulation in women is the most comparable response to erection in men.

The most reliable method of measuring vaginal blood flow is vaginal photoplethysmography (84;85). The vaginal photoplethysmograph is a menstrual tampon-sized device, easy to insert and sterilize, containing an infrared light-emitting diode as a light source and a photo transistor as a light detector. The light source illuminates the vaginal tissues, and the phototransistor responds to the incident light that is backscattered from the vaginal wall and the blood circulating within it. Because the opacity of the tissue, and hence the amount of light backscattered, is largely dependent upon the volume of blood within it, the vaginal photoplethysmograph provides a measure of vasocongestion. The increased vaginal blood flow during sexual arousal reflects a highly automated genital response mechanism, occurring irrespectively of subjective appreciation of the sexual stimulus (86;87). The genital physiological response is an involuntary reflex mediated by the (unconscious) autonomic nervous system (88). Assessment of vaginal vasocongestion through vaginal photoplethysmography during visual sexual stimulation can be an important tool in the attempt to measure physiological aspects of sexual arousal in women after hysterectomy. Pras et al. determined the feasibility of vaginal photoplethysmography in order to measure physical late effects of radiotherapy on sexual function. Patients (n=9) treated with radiotherapy for cervical, endometrial or ovarian cancer, who were in complete remission for over 1 year, underwent vaginal photoplethysmography to measure changes in vaginal vasocongestion, while watching erotic video fragments. The results were compared with those of healthy women (n=8). No significant difference was seen in vaginal vasocongestion during the various video fragments between the two groups, probably because the group of patients was small and heterogeneous. The authors concluded that vaginal photoplethysmography can be used to measure vaginal vasocongestion in patients treated with radiotherapy to the proximal vagina (89).

Theoretically, one would expect disruption of the inferior hypogastric plexus to result in decreased vaginal vasocongestion at vaginal photoplethysmography after RHL. At the Leiden University Medical Centre we performed a study on the changes in vaginal blood flow in women with a history of RHL. Vaginal pulse amplitude during sexual stimulation by erotic films was assessed in twelve women with a history of RHL, in twelve women with a history of simple abdominal hysterectomy and in seventeen age-matched controls. Self-reported ratings of subjective sexual arousal were collected after each erotic stimulus condition. The maximum vaginal pulse amplitude differed between the three groups ($p=0.043$) (90). Women with a history of RHL had a significantly lower maximum response than controls ($p=0.015$). Women in the RHL group and controls reported an equally strong subjective arousal after the erotic stimulus condition. Women with a history of simple hysterectomy showed an intermediate maximum vaginal pulse amplitude, but differences with the other two groups were not significant. Despite the limits of the study design and its size, the study indicates that RHL seems to be associated with a disturbed vaginal blood flow response during sexual arousal. The disturbed response could not be explained solely by uterine extirpation, since it was not observed to the same extent after simple hysterectomy. The difference in outcome might be related to a more extended denervation of the vagina with increasing radicality of surgery (91-97).

## The pelvic autonomic nerves in radical hysterectomy

Radical hysterectomies on the pelvis of female cadavers have been performed, the course of the sympathetic and parasympathetic nerves in the small pelvis have been studied and the autonomic nerves have been found to be closely related to tissues that are routinely damaged during RHL (97-99). By performing RHL on cadaver pelves first and dissecting the nerves later, it became evident that the hypogastric nerves and the proximal and distal part of the inferior hypogastric plexus are routinely damaged during this surgical procedure. Therfore, it is conceivable that surgical damage to the pelvic autonomic nerves is responsible for a considerable part of postoperative morbidity following RHL (93). Others have quantified nerve disruption after RHL. Immunohistochemical staining of nerve tissue in biopsies from surgical margins after simple hysterectomy and RHL has shown that both hysterectomies are associated with disruption of nerves. Quantitative analysis of these biopsies showed that the nerve disruption was significantly greater in RHL than in simple hysterectomy (94).
A study from our institution showed that preservation of the autonomic nerves in rectal cancer surgery was feasible, and yielded very good functional results concerning micturition and sexual function (100). Preservation of the autonomic nerves during RHL would be expected to result in comparable improvements in voiding and bowel function and sexuality for cervical cancer patients.

## Outline of this thesis

Since January 1984, the Leiden University Medical Centre (LUMC) prospectively collects more than 200 relevant clinical and pathological parameters of women with cervical cancer treated in the LUMC. From January 1984 untill April 2005 this database consists of 985 patients. Of these 985 patients, 643 underwent a RHL. The purpose of this thesis was to use the treatment-related information of this database to get inside information and to become aware of the possibilities for improvement in the current treatment procedures, in order to monitor the quality of treatment.
Furthermore, when the results of cancer treatment in terms of survival are good it is also important to focus on the sequelae of the treatment. The incidence of lymphedema, urinary and colorectal dysfunction has been reported with variable rates (14;19;32;34;36;37;41;54;55) and sexual dysfunction after RHL has been shown to occur in about 25% of the patients (12;13;18;66-71). Furthermore, a study assessed by vaginal plethysmography, showed that RHL seems to be associated with a disturbed vaginal blood flow response during sexual arousal (90). The second purpose of this thesis was to monitor the sequelae of the treatment of women with a history of early stage cervical cancer in order to have measures in attempts to improve the quality of life.
The aim of the studies, described in detail in the following chapters, is summarised in short.

*Chapter 2*

This study was designed to evaluate the role of postoperative radiotherapy for patients with early stage cervical carcinoma with tumour related risk factors, other than positive nodes, parametrial invasion or non-radical margins. Furthermore, the prognosis of patients using the criteria of the LUMC for giving adjuvant radiotherapy was compared with that of the Gynecologic Oncology Group.

*Chapter 3*

A systemic lymphadenectomy can reliably establish the presence or absence of lymph node involvement, with the attendant consequences for prognosis and treatment. Yet, it has never been proven that the removal of nodes itself leads to better survival figures (101). This is the first study that has evaluated the number of removed lymph nodes in the quality control of the surgical treatment of early stage cervical cancer and the possible association of patient, tumour and treatment factors with the number of lymph nodes examined in node-negative early stage cervical cancer patients.

*Chapter 4*

The possibility to give an accurate individual prediction of the future (disease free) survival of patients with a history of early stage cervical cancer was evaluated, given the fact that a patient has been disease free for a specific period after treatment. Statistical analysis was done on the existing database with multi-state risk models specifically designed for this purpose.

*Chapter 5*

The LUMC developed a Dutch self-report questionnaire, the Gynaecologic Leiden Questionnaire (LQ), which is the first Dutch list consisting of the items for sexual function, voiding- and bowel problems for women with cancer. In this study, we investigated the psychometric properties of the items concerning sexual functioning of the Gynaecologic LQ.

*Chapter 6*

The prevalence of lymphedema, bladder dysfunction, colorectal motility disorders and sexual dysfunction among women who had been treated for cervical cancer by a RHL was determined in this study. We provide the results of the first longitudinal study of self-reported bladder, defecation, sexual and vaginal problems with a baseline score before the RHL. We compared this group of patients with a group of age-matched controlled women from the general population. Because the effect of adjuvant radiotherapy on late side effects is still unclear, we also compared patients who underwent adjuvant radiotherapy to those who did not.

*Chapter 7*

RHL for cervical cancer causes surgical damage to the autonomic nerves which are responsible for the increased vaginal blood flow during sexual arousal. The aim of the current study, of which we report preliminary data in this thesis, was to determine whether the nerve-sparing technique indeed leads to an objectively less disturbed vaginal blood flow response during sexual stimulation. The mean vaginal pulse amplitude during sexual stimulation by erotic film was assessed in women with a history of a conventional RHL, in women with a history of a nerve-sparing RHL and in healthy controls.

*Chapter 8*

The results of the studies presented in this thesis and the future perspectives are discussed in this chapter.

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Chapter 2

# Postoperative radiation therapy improves prognosis in patients with adverse risk factors in localized, early stage cervical cancer; a retrospective comparative study.

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*Int J Gynecol Cancer 2006; 16:1112-1118*

## Abstract

**Objective:** To assess the role of postoperative radiotherapy for early stage cervical carcinoma with risk factors other than positive nodes, parametrial invasion or positive margins, and to compare outcomes using the Leiden University Medical Centre (LUMC) modification of the Gynecologic Oncology Group (GOG) system with the GOG prognostic scoring system itself.

**Methods:** Between January 1984 and April 2005, 402 patients with early stage cervical cancer underwent radical hysterectomy. Fifty-one patients (13%) had 2 of the 3 risk factors; pathological tumour size (≥40mm), invasion (≥ 15 mm) and capillary lymphatic space involvement and were identified as the so-called High Risk group (HR group).We compared 34 patients who received radiotherapy based on the LUMC risk profile (67%) with 17 who did not (33%). The GOG score was calculated as well. We compared the GOG scores within the LUMC risk groups: HR+ (2 out of 3 risk-factors) and HR- (less than 2 out of 3 risk-factors).

**Results:** Differences in 5- year Cancer Specific Survival (CSS) and 5-year Disease Free Survival (DFS) between the HR group treated with (86%; 85%) and without radiotherapy (57%; 43%) were statistically significant. The LUMC criteria did not significantly differ from the GOG risk profile, concerning recurrence, CSS and DFS.

**Conclusions:** High-risk patients benefit from adjuvant radiotherapy. The LUMC modification of the GOG system seems to be simpler, has a slightly higher threshold for the indication for radiotherapy, but without a difference in outcome.

## Introduction

The treatment for women with early stage cervical cancer (FIGO I-IIa) (1) can either be a radical hysterectomy with pelvic lymphadenectomy (RHL) or radiotherapy. When RHL is performed and adverse risk factors are present, such as lymph node involvement, parametrial invasion and positive surgical margins, postoperative radiotherapy is indicated (2-12). However, within the group of recurrences, 50% of these patients are without these risk factors (13-16). Several studies have suggested that patients with disease confined to the cervix but with certain other primary tumour related risk factors might also benefit from postoperative radiotherapy (3;17-20). In a study performed by the Gynecologic Oncology Group (GOG), Delgado et al. identified capillary lymphatic space involvement (CLS), clinical tumour size and depth of tumour invasion into the cervical stroma (DI) as independent prognostic variables. A GOG score >120 was correlated with a 41% recurrence rate (3). In a randomised GOG trial, Sedlis et al. used the GOG scoring system and combined the risk factors large tumour size, deep (greater than one third) stromal invasion and the presence of CLS. The authors reported a 44% reduction of the risk of recurrence after adjuvant radiotherapy when a combination of these risk factors was present compared without radiotherapy (12).

Before 1997, patients in our centre received adjuvant radiotherapy if lymph node involvement, parametrial invasion or positive surgical margins were found. In 1997 we extended the indication for postoperative radiotherapy, using a modification of the GOG scoring system. Patients with at least 2 of the following 3 risk factors received postoperative radiotherapy: pathological tumour size (≥40mm), depth of invasion (≥ 15 mm) and CLS. The choice for the definition of these risk factors was based on the results from the literature (3;21;22) and on a retrospective analysis of our own treatment results, indicating that depth of invasion ≥ 15mm was an independent prognostic risk factor (23). The aim of the present study was to assess treatment outcome of patients with early stage cervical carcinoma (FIGO I-IIa) (1) without lymph node involvement, parametrial invasion or positive surgical margins, but with the presence of these adverse risk factors. We compared the outcome of patients who received adjuvant radiotherapy on the basis of adverse tumour factors mentioned above with patients with a similar risk profile treated before 1997 who did not receive radiotherapy. Finally, we compared prognosis of patients using our criteria for giving adjuvant radiotherapy (Leiden University Medical Centre (LUMC) risk profile) with those of the GOG prognostic scoring system (GOG risk score (RS)) (3).

## Material and Methods

*Study group*

Between January 1984 and April 2005, 643 patients with stage I-IIa cervical carcinoma were treated in our centre (LUMC) with a RHL. Relevant clinical and pathological parameters of this group of pa-

tients were prospectively collected in a database. Patients with lymph node involvement, parametrial invasion or positive surgical margins were excluded from this study (n=232). One patient received preoperative radiotherapy, 5 patients received preoperative chemotherapy and 3 patients postoperative chemotherapy; they were also excluded from the study.

*LUMC risk profile*

For the first analysis we selected from the remaining 402 patients the women with at least 2 of the 3 following risk factors; pathological tumour size ≥40mm, depth of invasion ≥ 15 mm and CLS. Fifty-one (13%) patients met these criteria and were identified as the so-called High Risk group (HR group). Among these 51 patients we compared the prognosis of those patients who received adjuvant radiotherapy (after 1997) with those who did not (before 1997 or protocol violation after 1997). Reasons for protocol violation for not receiving radiotherapy after 1997 were refusal of the patient (n=3) or complicating comorbidity (n=3).

*GOG risk score*

For the second analysis we used the GOG risk score (RS) (3). A GOG score was calculated for each of the 402 patients by multiplying the 3 relative risk scores (RR) associated with clinical tumour size, depth of tumour penetration and presence or absence of CLS. The GOG used the cervical tumour regression coefficient for the superficial, middle and deep penetration of the tumour (3). Because we used the infiltration depth in millimetres, we took the mean RR of the superficial, middle and deep penetration to calculate the RR for depth of tumour penetration. Furthermore we used the pathological tumour size instead of the clinical tumour size. We could not calculate the RS for 41(10%) patients because of missing data such as exact depth of invasion or tumour size or information from referring hospitals (conisation and colposcopy). Fourteen patients would receive radiotherapy according to the LUMC RS as well as according to the GOG score, but did not. Nine patients would not receive radiotherapy according to both scorings systems, but they did. These 23 patients were excluded from the analysis, because we were interested in the differences between the 2 scorings systems. A total of 338 patients was left. We divided the patients into 2 groups: RS≤120 and RS>120 and compared the prognosis of these patients with the prognosis of the patients stratified according to our own risk system (LUMC risk profile): the group with 2 out of 3 risk factors present who received adjuvant radiotherapy (HR+) and the group without 2 out of 3 risk factors present who did not receive adjuvant radiotherapy (HR-).

*Staging and pathology*

Preoperative staging was performed according to the guidelines of the International Federation of Gynaecology and Obstetrics (FIGO) (1). The following characteristics from the pathology slides were documented: tumour size, histologic tumour type and depth of invasion. When no residual tumour was found in the radical hysterectomy specimen, presurgical data from conization or biopsies were

used. The depth of invasion was measured from the most superficial epithelial-stromal interface of the adjacent intra-epithelial process to the lower limits of invasion (24). Capillary lymphatic space involvement (CLS) was considered positive when neoplastic cells were seen within endothelium-lined spaces. Central recurrences were defined as those involving vagina, bladder or rectum. Regional recurrences were those involving the pelvic sidewall but remained confined to the pelvis and distant recurrences were those with disease outside the pelvis with or without pelvic involvement.

*Radiotherapy*

External beam radiotherapy was administered to the pelvis using a four-field box technique. Patients were treated with 10 MV photons from a linear accelerator to a total dose of 46 Gy in 2 Gy fractions, specified at the isocentre. A brachytherapy boost was given to the vaginal vault in case of extensive CLS (68% of the patients), using vaginal colpostats, 15 Gy low dose rate or equivalent dose, prescribed at 5 mm from the vaginal mucosa.

*Survival analysis*

The follow-up was closed on April 2005 and ranged for the 402 patients from 0 to 223 months. The mean duration of follow-up was 60 months. The mean and median duration of follow-up for the 51 HR patients was 54 and 40 months, respectively; with adjuvant radiotherapy 50 and 38 months and without radiotherapy 59 and 58 months, respectively. The disease free survival (DFS) was defined as the time from RHL to cytologically or histologically proven evidence of recurrent disease or date last seen. Cancer specific survival (CSS) was defined as the time from date of operation to death by tumour or date last seen. Survival curves were made using the Kaplan-Meier method (25). The difference in DFS and CSS by treatment regimen was evaluated using the log-rank test (25;26). The chi-square test was used to calculate the relative risk and a p-value <0.05 was considered as statistically significant.

## Results

*High-risk patients according to LUMC risk profile*

Fifty-one (13%) patients met the LUMC criteria for postoperative radiotherapy. The clinical and histological characteristics of the HR patients who were treated with (n=34, 67%; after 1997) and without postoperative radiotherapy (n=17, 33%; before 1997 or protocol violation after 1997) are listed in Table 1. Median age was 44 and 42 years for the patients with and without radiotherapy respectively. Apart from the number of deep infiltrating tumours (more frequent in the irradiated group), the various characteristics of the 2 groups were similar.

Recurrence of disease was diagnosed in 11 of these 51 (22%) patients. Of these 11 patients, 8 died of disease (Table 2 and 3). A significantly larger percentage of the HR patients who did not receive

| Characteristics of the HR patients | Patients treated with RT n (34) n (%) | Patients treated without RT n (17) n (%) |
|---|---|---|
| **Age** | | |
| 21-30 | 2(6) | 1(6) |
| 31-60 | 29(85) | 12(71) |
| 61≥ | 3(9) | 4(24) |
| Median | 44 | 42 |
| Minimum | 29 | 30 |
| Maximum | 74 | 88 |
| Sd | 11 | 17 |
| **Histology** | | |
| Squamous cell | 28(82) | 15(88) |
| Adenocarcinoma | 5(15) | 1(6) |
| Adenosquameus | 1(3) | 1(6) |
| **FIGO** | | |
| Ib | 28(82) | 12(71) |
| IIa | 6(18) | 5(29) |
| **Tumour size** | | |
| ≥40mm | 27(79) | 13(77) |
| <40mm | 7(21) | 4(24) |
| Unknown | 0(0) | 0(0) |
| Maximum | 90 | 55 |
| Minimum | 20 | 23 |
| Mean | 47 | 43 |
| **Depth of invasion** | | |
| ≥15mm | 29(85) | 11(65) |
| <15mm | 5(15) | 4(24) |
| Unknown | 0(0) | 2(12) |
| Maximum | 47 | 30 |
| Minimum | 11 | 10 |
| Mean | 22 | 17 |
| **CLS** | | |
| Positive | 26(77) | 13(77) |
| Negative | 7(21) | 3(18) |
| Unknown | 1(3) | 1(6) |

Table 1. Clinical and histological characteristics of the HR patients who were treated with (n=34) and without (n=17) postoperative radiotherapy (RT).

adjuvant radiotherapy had recurrence of disease, with a RR of 0.29 (95% confidence interval 0.1-0.8, p=0.02) (Table 2). Central recurrences were only diagnosed in patients who did not receive adjuvant radiotherapy (Table 3). The median time from surgery to recurrence and from recurrence to death was 15 and 12 months respectively for the total group. Two of the 51 patients died because of other reasons: one because of a psoasabces and diverticulitis and the other because of cardiac failure. The 5-year CSS and DFS of the entire HR group of 51 patients was 74 % and 69%, respectively. The 5-year CSS and DFS were 86% and 85% respectively, among the patients treated with adjuvant radiotherapy (n=34) in contrast to the patients without adjuvant radiotherapy (n=17), who had a 5-year CSS and DFS

| Recurrence HR group | Radiotherapy n(%) | No radiotherapy n(%) | Total |
|---|---|---|---|
| Yes | 4(12) | 7(41) | 11(22) |
| No | 30(88) | 10(59) | 40(78) |
| Total | 34(67) | 17(33) | 51(100) |

Table 2. Number and percentage of recurrence of disease in the HR group with and without radiotherapy.

| Radiotherapy | Months to recurrence | Site of recurrence | Survival after recurrence (months) | Status |
|---|---|---|---|---|
| Yes | 5 | distant | 7 | DOD |
| Yes | 14 | regional | 14 | NED |
| Yes | 20 | regional | 0 | ALD |
| Yes | 31 | distant | 34 | DOD |
| No | 7 | central | 8 | DOD |
| No | 7 | central+regional | 213 | NED |
| No | 10 | central | 10 | DOD |
| No | 15 | regional | 14 | DOD |
| No | 25 | central+regional | 32 | DOD |
| No | 37 | central+regional | 32 | DOD |
| No | 51 | distant | 9 | DOD |

Table 3. HR patients with recurrent cervical carcinoma. DOD, dead of disease; NED, no evidence of disease; ALD, alive with disease.

of 57% and 43%, respectively (Fig.1 A, B). The differences in CSS and DFS between the 2 groups were statistically significant (p=0.013 and p=0.006, respectively).

*Comparison of the GOG risk score and LUMC risk profile*

Table 4 shows the comparison of the GOG and LUMC risk assessment in the total of 338 patients. In 322 of 338 patients (95%) there was agreement in allocated high-risk profile in the LUMC and the GOG system. In 16 patients (5%) there was no agreement and in all these cases the patients had a high RS according to the GOG system, but not according to the LUMC assessment. Because the threshold to give

| | HR- (LUMC) (n) | HR+ (LUMC) (n) | Total (n) |
|---|---|---|---|
| RS<120 (GOG) (n) | 288 | 0 | 0 |
| RS>120 (GOG) (n) | 16 | 34 | 50 |
| Total (n) | 304 | 34 | 338 |

Table 4. Table of the number of patients; GOG prognostic scoring system versus LUMC system. HR: high risk group, RS: GOG risk score.

adjuvant radiotherapy was lower using the GOG prognostic scoring system, we determined if there would be a difference in CCS and DFS when the GOG RS was used instead of the LUMC risk profile. To answer this question the HR + group (high risk group, n=34) was compared with the HR- group (no high risk group, n=16). The 2 groups were treated according to the LUMC system; the HR+ group did receive radiotherapy and the HR- group did not. Both groups had a RS>120 (GOG system).
Eight of the 50 patients (16%) had recurrence of the disease, four patients in each group (HR+: 12%, HR-: 25%). There was no statistically significant difference in recurrence between these 2 groups (RR 0.5, 95% confidence interval 0.13-1.7, p=0.23).
For the 34 high-risk patients (HR+; RS>120) who received radiotherapy the median time from therapy to recurrence was 18 months, from recurrence to death 20 months. For the 16 patients (HR-; RS>120) treated without radiotherapy time to recurrence was 20 months, from recurrence to death 39 months. One of the 50 patients died because of a psoasabces and diverticulitis.
The 5-year CSS and DFS of the entire group of 50 patients (HR+ and HR- groups with a RS>120) were 88 and 79%, respectively. The 5-year CSS and DFS were 86% and 85% among the HR + group (n=34), in contrast to 92% and 62% for the HR- group (n=16) (Fig. 2 A, B). These differences were however, not statistically significant (p=0.444 and p=0.212, respectively).

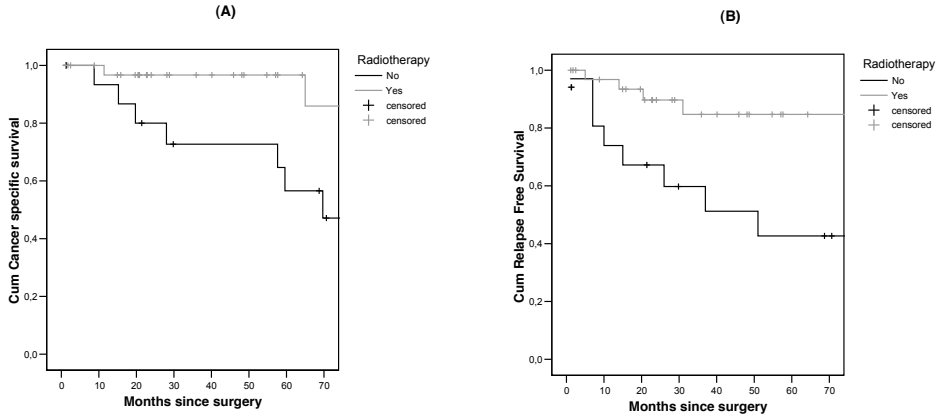


Figure 1. Survival (A) and disease free survival (B) of the HR group with adjuvant radiotherapy (n=34) and the HR group without radiotherapy (n=17).

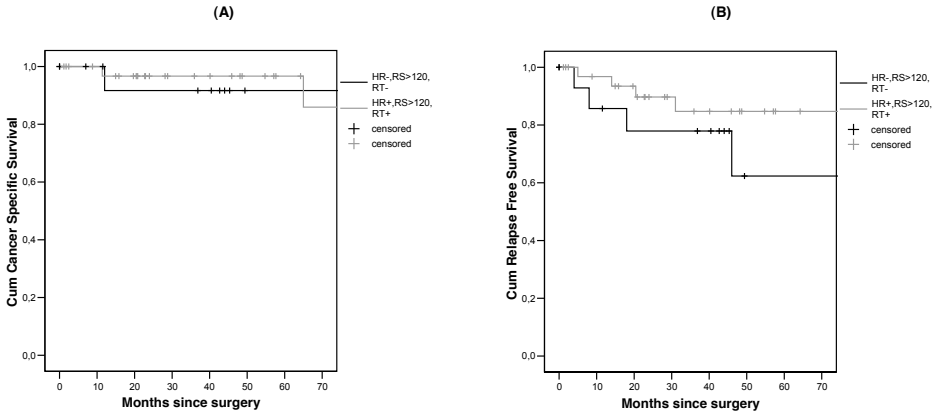


Figure 2. Survival (A) and disease free survival (B) of the HR+ and HR- group and both with a RS>120.
(HR-, RS>120, RT-: Less than 2 of the 3 risk factors positive, a GOG risk score>120 and no adjuvant radiotherapy (RT))
(HR+, RS>120, RT+: At least 2 of the 3 risk factors positive, GOG risk score >120 and adjuvant radiotherapy (RT))

## Discussion

The role of postoperative radiotherapy was evaluated for patients with early stage cervical carcinoma with tumour related risk factors, other than positive nodes, parametrial invasion or positive margins. The current study indicated that the high risk group according to the LUMC risk profile, characterized by at least 2 of the 3 risk factors, significantly benefited from postoperative radiotherapy. We found that a significantly larger percentage (41 vs 12%, p=0.02) of the HR group who did not receive radiotherapy, had recurrence of disease. Central recurrence only appeared in the latter group. The differences in CSS and DFS between the HR group with adjuvant radiotherapy (86%; 85%) and HR group without adjuvant radiotherapy (57%; 43%) were statistically significant. The fact that the patients who did receive postoperative radiotherapy might represent a higher risk group as far as the percentage of deep infiltrating tumours is concerned, underlines this conclusion. Furthermore, this study showed that the LUMC modification of the GOG prognostic scoring system did not significantly differ from the GOG prognostic scoring system itself, with regard to risk of recurrence, CSS and DFS.
The strength of the current study is the fact that a prospective database and a consecutive series of patients were used. However, the observations are based on limited numbers of patients.
Our results concerning the benefit of radiotherapy for the HR group are according to the literature. Delgado et al. found CLS, clinical tumour size and DI to be the parameters best predicting prognosis in patients with early stage cervical cancer with negative lymph nodes. Using the GOG prognostic scoring system, they found that in patients with a combination of these risk factors, but with negative nodes, the 3-year risk of recurrence could be as high as 41% (3). In a randomised study, Sedlis et al. used

a modification of the GOG scoring system and included 277 patients with stage Ib cervical carcinoma with at least 2 out of 3 risk factors: CLS, large tumour size and DI (greater than one third). The results of this study showed that the risk of recurrence was significantly reduced by 44% (p=0.02) in patients treated with postoperative radiotherapy (12). Furthermore, a recent study by Rushdan et al. reported that postoperative radiotherapy given in patients with a high risk score, significantly improved their 5-year recurrence rate and disease-free survival (27). Similar results were also reported by other investigators (7;13).

However, in the retrospective analysis by Van der Velden et al. no survival benefit was found using adjuvant radiotherapy for risk factors other than positive nodes, parametrial extension and positive margins. They reported that the variant of RHL could be an explanation for the observed difference between this study and literature data. Van der Velden et al. used the Wertheim/Okabayashi variant of the RHL, with a more radical removal especially of the lower parametrial and paracolpal tissues compared to Wertheim/Meigs procedure (28). Because of the expected higher morbidity rate of the Wertheim/Okabayashi procedure, we perform the Wertheim/Meigs variant (29).

The cited studies used the GOG prognostic scoring system or a modification of it to decide on the indication for radiotherapy. To calculate a GOG score for an individual patient, one has to multiply 3 relative risk scores associated with exact tumour size, DI related to the specific part of the uterine wall, and the presence or absence of CLS. This requires various pathology details. All 3 details were not always available in our group of patients and therefore we could not calculate the GOG risk score in 10% of the cases. Furthermore, the LUMC risk profile is simpler and more straightforward than the GOG prognostic scoring system and even simpler than the modification of Sedlis et al.(12). In the current study, there was 95% (n=322) agreement in allocation of a high-risk profile to the patients for the LUMC and the GOG system. According to the GOG system, 5% (n=16) of the LUMC low risk patients would have had an indication for radiotherapy. This difference did not affect the prognosis of these patients in any detectable way; there was no significant difference in recurrence of disease, CSS and DFS, although statistical significance might not have been reached because of the small number of patients.

The risk of late side effects after adjuvant radiotherapy could be an argument against adjuvant radiotherapy in absence of the major risk factors lymph node metastases, positive margins or parametrial involvement. However, in a recent study of our own data we found that adjuvant radiotherapy did not significantly increase the risk of bladder dysfunction, bowel symptoms, lymphedema and sexual function after 2 years follow-up (30).

It is concluded that, despite the relatively limited numbers of patients analyzed, the current study confirms that high-risk patients significantly benefit from adjuvant radiotherapy. Moreover, this study compared in a prospective way a modification of the GOG RS to the GOG prognostic scoring system itself. Furthermore, we found that the LUMC risk profile is simpler and more straightforward in use, has a slightly higher threshold to define patients as high risk who need adjuvant radiotherapy as compared to the GOG prognostic scoring system, but without compromising their prognosis.

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Chapter 3

# The number of pelvic lymph nodes in the quality control and prognosis of radical hysterectomy for the treatment of cervical cancer.

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*Eur J Surg Oncol 2007; 33:216-221*

## Abstract

**Objective:** To determine if the number of removed lymph nodes in radical hysterectomy with lymphadenectomy (RHL) influences survival of patients with early stage cervical cancer and to analyze the relation of different factors like patient age, tumour size and infiltration depth with the number of nodes examined in node-negative early stage cervical cancer patients.

**Methods:** Of consecutive patients, who underwent RHL between January 1984 and April 2005, 331 had negative nodes (group A) without adjuvant therapy and 136 had positive nodes (group B). The Kaplan-Meier method and Cox regression model were used to detect statistical significance. Factors associated with excision of nodes were confirmed with linear regression models.

**Results:** The median number of removed nodes was 19 and 18 for group A and group B, respectively. There was no significant relationship between the number of removed nodes and the cancer specific survival (CSS) or disease free survival (DFS) for patients of group A (p=0.625 and p=0.877, respectively). The number of removed nodes in group B was not significantly associated with the CSS (p=0.084) but it was for the DFS (p=0.014). Factors like patient age, tumour size and infiltration depth were not associated with the number of nodes.

**Conclusions:** No relation was found between the number of negative nodes examined after RHL for the treatment of early stage cervical cancer and CSS or DFS. However, a higher amount of removed lymph nodes leaded to a better DFS for patients with positive nodes. It is suggested that patients with positive nodes benefit from a complete pelvic lymphadenectomy and a sufficient yield of removed nodes.

## Introduction

Pelvic lymphadenectomy is widely performed as part of the treatment of patients with cervical cancer stage I-IIa (1-6). Spread of the disease outside the cervix, especially in the pelvic nodes, has the strongest effect on prognosis (5-8). The goal of lymphadenectomy is to remove and diagnose cancer cells that have been transported to the lymphatic tissue draining the uterine cervix and the upper vagina. A systemic lymphadenectomy can reliably establish the presence or absence of lymph node involvement, with the attendant consequences for prognosis and treatment (5).

In other cancers such as breast cancer, it has been suggested that removal of the axillary regional nodes in patients with breast cancer is important for long-term survival, even when such nodes are interpreted as pathologically negative (9-15).

In endometrial carcinoma the role of lymphadenectomy remains a topic of continuing debate. Literature data document the possible therapeutic benefit of selective lymphadenectomy in the management of patients with early stage endometrial cancer. However, it remains an unresolved issue whether a minimum number of nodes should be required to consider the lymphadenectomy as adequate, since data from randomized studies are lacking (16-19). Benedetti-Panici et al. reported in their randomized clinical trial that systematic lymphadenectomy improves the progression-free survival in women with optimally debulked advanced ovarian carcinoma (20). They supported the concept of therapeutic lymphadenectomy.

For the treatment of early stage cervical cancer, the therapeutic value of lymphadenectomy is also still a matter of debate. Other authors emphasized the possible beneficial effect of removing metastatic lymph nodes, especially when they are bulky (21-27). The aim to remove all accessible lymphatic tissue in the pelvis might also include micrometastases which have a high rate by false-negatives on CT and MRI, and the inaccuracy of intraoperative lymph node palpation (34). Furthermore, the number of removed nodes is underlined by some authors as a matter of quality of the surgery (5;21). Yet, it has never been proven that the removal of nodes itself leads to better survival figures (26).

The aim of the present study is to determine if the number of removed pelvic lymph nodes in radical hysterectomy with pelvic lymphadenectomy (RHL) influences survival of patients with early stage cervical cancer. As it is a clinical impression that the number of reported lymph nodes can depend on several factors, including anatomic differences between patients, variations in local inflammatory parameters, variations in surgical techniques, processing of the specimen and its examination by the pathologist, the second purpose of this study is to examine the association of patient, tumour and treatment characteristics with the number of lymph nodes examined in early stage cervical cancer patients.

## Material and Methods

*Patient characteristics and study design*

Between January 1984 and April 2005, 643 patients with stage I-IIa cervical carcinoma were treated in our centre with RHL. Relevant clinical and pathological parameters of this group were prospectively collected in a database. For the first purpose of this study we used 2 groups: a group with negative nodes (n=503) and a group with positive nodes (n=140).

Patients in our centre received adjuvant radiotherapy if lymph node involvement, parametrial invasion or positive surgical margins were found. Since 1997, patients with at least 2 of the following 3 risk factors also received postoperative radiotherapy: pathological tumour size (≥40mm), depth of invasion (≥ 15 mm) and capillary lymphatic space involvement.

From the group with negative nodes, 143 patients received adjuvant radiotherapy and 5 patients received chemotherapy. These 148 patients were excluded. Twenty patients were excluded because data of the total number of examined lymph nodes were missing, and 4 patients were excluded because an incomplete lymphadenectomy was performed due to various reasons. For the further analysis 331 patients remained (group A).

Para aortic lymph nodes were removed in 4 patients with positive nodes. These patients were excluded from the study, because it has been reported that para aortic node dissection could influence the survival (27;28). For the further analysis 136 patients with positive nodes remained (group B). Hundred thirty one patients received adjuvant radiotherapy and 14 received chemotherapy. In this group 10 patients did not have a complete lymphadenectomy.

To investigate the relationship between patient, tumour and treatment characteristics and the number of removed nodes, we only studied the group of patients with negative lymph nodes (group A), since it has been a former policy to abandon a complete lymphadenectomy when lymph node metastases were found during surgery.

All patients in the study were treated by the same four gynaecologic oncologists (GGK, AAWP, JBT, KNG) during this period. Fifteen percent of the patients in group A and 24% of the patients in group B were referred from Suriname (South America) for their treatment. In all cases a RHL type III was performed (29).

Lymphadenectomy consisted of removal of all the fatty tissue from 6 different stations: along the common iliac vessels until halfway the aortic bifurcation, the external and internal iliac vessels, and the obturator fossa, at both sides. Parametrial nodes were not included in the counting of number of nodes. Para aortic nodes were only removed in case of palpable enlarged nodes or confirmed positive common iliac nodes at frozen section. In the current study there were no para aortic lymph nodes removed in patients of group A and B. The follow-up was closed on April 2005 and ranged from 0 to 223 months for the group with negative nodes and 0 to 220 months for the group with positive nodes. The mean and median duration of follow-up for the group with negative nodes was 57 months and 53

months, respectively; for the group with positive nodes 37 months and 18 months, respectively. The disease free survival (DFS) was defined as the time from RHL to cytologically or histologically proven evidence of recurrent disease or date last seen. Cancer specific survival (CSS) was defined as the time from date of operation to death by tumour or date last seen.

*Pathologic examination*

Radical hysterectomy specimens were routinely examined. Four µm thick tumour sections of formalin-fixed, paraffin embedded material were stained with haematoxylin and eosin (H&E). The following tumour characteristics were documented: tumour size, histological tumour type, capillary lymphatic space involvement (CLS) and depth of invasion. CLS was considered positive when neoplastic cells were seen within endothelium-lined spaces. The depth of invasion was measured from the most superficial epithelial-stromal interface of the adjacent intra-epithelial process to the lower limits of invasion (30).

At pelvic lymph node dissection the lymph nodes were labeled according to site. After arriving at the department of pathology, the specimens were formalin fixed. The next day, conventional lymph node retrieval technique was performed for each specimen separately, i.e. inspection, palpation, and/or serial sectioning of the resected tissue. Certain (often larger) lymph nodes were measured and sectioned in multiple slides of 2 to 3 mm after which representative samples were embedded. Smaller (possible) lymph nodes were totally embedded. The 4 µm thick sections of formalin-fixed, paraffin embedded material were stained with haematoxylin and eosin (H&E).

*Data analysis*

The relationship between the number of removed nodes and the survival of patients was examined graphically with the Kaplan-Meier method. The number of nodes was categorized as <10, 10-15, 16-20, 21-25, 26-30 and >30 nodes. We also analyzed the number of lymph nodes examined with a cut-off based on the median number of nodes in the cohort. The Cox regression model was used to determine statistical significance (31;32). Furthermore, the relationship between the following variables; patient age, referral from Surinam, postmenopausal status, conisation before surgery, tumour size, infiltration depth, CLS and the number of removed lymph nodes was investigated by using univariate and multivariate linear regression models. The parameter of Surinam origin of the patients was included because historically patients with cervical cancer from Surinam (SA) are referred to the Leiden University Medical Centre for treatment. These patients have a different ethical origin as compared to the Dutch patients. The number of removed nodes was regarded as a normally distributed continuous variable in the linear regression models, because a histogram showed an almost normal distribution. Statistical significance was assigned at a level of $p<0.05$.

# Results

*Number of lymph nodes*

The mean age at the time of the operation among the patients with negative lymph nodes (group A) was 43.3 years (SD 11.5) (Range 21-82 years) in contrast to the patients with positive lymph nodes (group B) who had a mean age of 47.0 years (SD 13.6) (Range 25-80 years). The clinical and histological characteristics of the 2 groups of patients with early stage cervical cancer are listed in Table 1. In group A the median number of lymph nodes examined was 19 (mean, 19.90; SD, 8.16) with a range of

| Characteristics | Group A (n=331) n | Group B (n=136) n |
|---|---|---|
| **Age** | | |
| <40 | 148 | 51 |
| ≥40 | 183 | 85 |
| Mean | 43.3 | 47.0 |
| Minimum | 21 | 25 |
| Maximum | 82 | 80 |
| SD | 11.5 | 13.6 |
| **Tumour size** | | |
| ≥40mm | 35 | 63 |
| <40mm | 233 | 61 |
| Unknown | 63 | 12 |
| Maximum | 70 | 110 |
| Minimum | 0 | 0 |
| Mean | 19.2 | 42 |
| **Depth of invasion** | | |
| ≥15mm | 44 | 76 |
| <15mm | 27 | 55 |
| Unknown | 13 | 5 |
| Maximum | 25 | 65 |
| Minimum | 0 | 0 |
| Mean | 6.4 | 16 |
| **CLS** | | |
| Positive | 52 | 95 |
| Negative | 25 | 31 |
| Unknown | 29 | 10 |
| **Referred from Surinam** | | |
| Yes | 48 | 32 |
| No | 283 | 104 |
| **Postmenopausal** | | |
| Yes | 65 | 42 |
| No | 266 | 94 |
| **Conisation** | | |
| Yes | 109 | 11 |
| No | 222 | 125 |

Table 1. Clinical and histological characteristics of the patients with early stage cervical cancer, node negative (group A) and node positive (group B).

4-53. The median number of lymph nodes examined in group B was 18 (mean, 17.47; SD, 7.91) with a range of 1-38. The number of examined lymph nodes in both groups followed a normal distribution. Table 2 shows the number of examined nodes in both groups categorized into 6 groups.

| **Number of removed lymph nodes (analysis groups)** | **Group A (n=331) n** | **Group B (n=136) n** |
|---|---|---|
| <10 | 22 | 23 |
| 10-15 | 85 | 35 |
| 16-20 | 83 | 30 |
| 21-25 | 73 | 26 |
| 26-30 | 33 | 17 |
| >30 | 35 | 5 |

Table 2. Number of removed nodes in patients with negative lymph nodes (group A) and positive lymph nodes (group B), categorized into 6 analysis groups.

*Negative lymph nodes and prognosis*

Overall, the CSS and DFS of the patients with negative nodes did not differ between the 6 analysis groups. Also there was no difference in the CSS and the DFS between the group with less than 19 removed lymph nodes and the group with 19 or more removed lymph nodes. The Cox regression model did not show a significant relationship between the number of removed lymph nodes and the CSS or DFS (p=0.625 and p=0.877, respectively).

*Positive lymph nodes and prognosis*

The number of removed lymph nodes in patients with positive nodes was positively correlated with a better DFS (p=0.014). Figure 1 shows the DFS curves for the 6 analysis groups of patients with positive nodes. The DFS curves of the group less than 18 removed lymph nodes and the group with 18 or more removed lymph nodes are shown in Figure 2. The Cox regression model did not show a significant relationship between the number of examined lymph nodes and CSS (p=0.084). The number of removed positive nodes for these patients is listed in Table 3. The number of positive nodes was positively correlated with a better CSS (p=0.017) and DFS (p=0.048).

| **Number of removed positive lymph nodes** | **Group B n** |
|---|---|
| 1 | 65 |
| 2 | 30 |
| 3 | 21 |
| 4-14 | 20 |

Table 3. Number of removed positive nodes in patients with positive lymph nodes (group B).

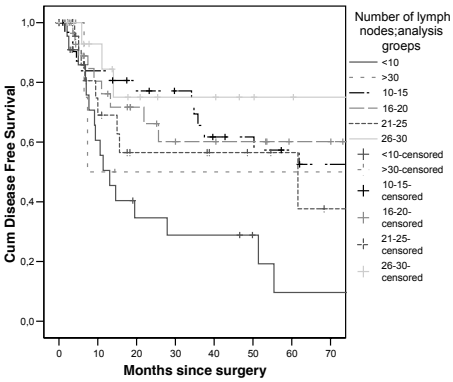


Figure 1. Disease free survival of the categorized 6 analysis groups, of patients with positive lymph nodes (Group B).

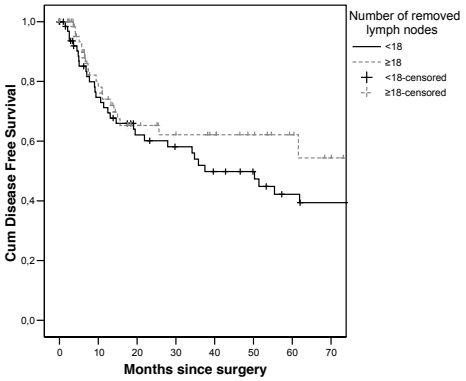


Figure 2. Disease free survival of the 2 groups with a cut-off based on the median number of removed nodes, in patients with positive lymph nodes (Group B).

*Relationship between several factors and the number of lymph nodes examined*

To evaluate a possible relationship between several patient and tumour characteristics and the number of examined lymph nodes, we used the patients of group A, with negative lymph nodes (n=331). The univariate and multivariate linear regression models using the variables patient age, referral from Surinam, postmenopausal status, conisation before surgery, tumour size, infiltration depth and CLS, did not show that any of these factors were associated with the number of examined lymph nodes.

## Discussion

The role of the number of removed pelvic lymph nodes after RHL for the treatment of early stage cervical cancer was evaluated for patients with negative and positive lymph nodes. Furthermore, the association of different factors with the number of lymph nodes was examined.

The strength of the current study is the fact that a prospective database and a consecutive series of patients were used. Furthermore, all patients were treated by the same group of gynaecologic oncologists.

The therapeutic value of removing lymph nodes, especially when they are bulky, has been reported by different authors (21-27;33). However, the number of removed lymph nodes in the quality control of the surgical treatment of early stage cervical cancer has never been evaluated before. The hypothesis that removal of a larger number of regional nodes in patients with breast cancer improves survival is nowadays strongly supported by both prospective randomized trials and multiple retrospective stud-

ies of large groups of women (9-15). This may be explained as being due to understaging caused by examination of too few lymph nodes (more likely for node-negative patients) or as a real association between the extent of the dissection and improved disease control (more likely for node-positive patients) (34).

From the present study of patients with negative as well as positive nodes, it can be concluded that a large variability in the number of lymph nodes exists. Despite this finding, there was no evidence that a higher number of examined lymph nodes lead to better survival figures for patients with negative lymph nodes. Thus the explanation of a possible relation between the number of examined nodes and survival caused by examination of too few lymph nodes (understaging) could not be confirmed for these patients. In contrast, the current study did show an association between the extent of the dissection and a better disease control, as a larger number of removed lymph nodes prolonged the DFS for patients with positive lymph nodes. However, the improvement in DFS was not translated into an improvement in CSS. One possible explanation for this might be that the follow-up has been too short and a longer period might be needed before long-term survival values are definitive.

The large variability in the number of examined lymph nodes is difficult to explain. The stable group of surgeons does not seem to have impact on the extent of the surgery, which might lead to variable numbers of removed nodes. One explanation could be the fact that the number of reported nodes may not reflect the number of removed nodes. Total node count is not only a reflection of completeness of lymphadenectomy, but is also dependent on the pathologist's evaluation of the surgical specimen. Total node count and thorough evaluation of all lymph nodes in the specimen are depending on the pathologist's macroscopic evaluation, and are therefore subject to bias. In our centre, the conventional lymph node retrieval technique was used embedding all large and easily recognized lymph nodes. If a structure was not a lymph node by inspection or palpation, it was embedded completely, reducing the risk to leave any lymph node in the fatty tissue. Hereby the pathologist's bias was reduced to a minimal. Compared with other studies, the median number of removed nodes in the current study is somewhat lower (1;2;28;35;36). The reason for this difference might be that in our study parametrial nodes were not included in the number of nodes and para aortic nodes were not removed in the patients of this study. Furthermore, 10 patients of the group with positive nodes did not undergo a complete lymphadenectomy, as the procedure was aborted in view of subsequent radiation.

Surgery is still the most important treatment variable in most solid cancers and its impact has been emphasized in past decades. A better control of the quality of surgical procedures in oncology is possible and may have a major impact on outcomes of cancer patients (37).

This is the first study that has evaluated the number of removed lymph nodes in the quality control of the surgical treatment of early stage cervical cancer and the possible association of different factors with the number of lymph nodes examined. In a previous analysis we reported on the effect on survival of pelvic lymphadenectomy of 294 patients with early stage cervical cancer treated by RHL (26). Patients with positive nodes and with complete lymphadenectomy (n=23) had significantly less

recurrences compared to patients with positive nodes with incomplete lymphadenectomy (n=40). The complete lymphadenectomy showed an independent beneficial effect on the DFS. The findings of the current study are in line with the results of this previous analysis (26).
Until the results of other trials are known, the outcome of the present study suggests that there is no relation between the number of tumour negative nodes examined after a RHL for the treatment of early stage cervical cancer and CSS or DFS. However, the number of examined lymph nodes leads to better DFS figures for patients with positive lymph nodes. This suggests that patients with early stage cervical cancer with positive lymph nodes benefit from a sufficient number of removed lymph nodes. And because on forehand, one does not know whether the removed pelvic lymph nodes will be positive or negative, the most important clinical consequence of the present study is that one should complete the lymphadenectomy when frozen section reveals lymph node involvement during RHL.

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Chapter 4

# An individual prediction of the future (disease free) survival of patients with a history of early stage cervical cancer; multi-state model.

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*Int J Gynecol Cancer 2007; in press*

## Abstract

**Objective:** To evaluate the possibility to give a prediction of the future (disease free) survival, given the fact that a patient with a history of early stage cervical cancer has been disease free for a specific period after treatment.

**Methods:** Between January 1984 and April 2005, 615 patients with cervical cancer stage I-IIa underwent radical hysterectomy with or without adjuvant radiotherapy. The Kaplan-Meier method was used to detect statistical significance and multi-state risk models to estimate the influence of covariates and to generate predicted survival curves by simulation. Simulations were done for patients with positive lymph nodes (n=123), patients with negative lymph nodes (n=492) and four hypothetical patients.

**Results:** The 5-year cancer specific survival and disease free survival of the entire group was 84% and 76%, respectively. The probability of death of the two lymph node groups and the four hypothetical patients were demonstrated in predicted cumulative probability plots.

**Conclusions:** It is possible with multi-state risk models to give a detailed prediction of the future (disease free) survival, given the fact that a patient has been disease free for a specific period after treatment. This possibility is an important step forward to improve the quality of cancer care.

## Introduction

The prognosis of early stage cervical carcinoma after radical hysterectomy is excellent in most cases, with 5-year survival rates of 80-90% (1-4). However, recurrences confront the physician and the patient with a rather dismal prognosis, leading to the death in more than 85% of cases (5;6) and this 'sword of Damocles' is often present in the patient's mind. When a patient confronts the physician with questions about the exact risk of recurrence or death in their individual case by time, it can be difficult and sometimes even impossible to answer this adequately. An adequate answer could also provide information to individualise the treatment management and the (length of) programs of surveillance. Furthermore, it could provide psychological support.

Standard survival data measure the time span from some time origin until the occurrence of one type of event. If several types of events (like recurrence or death) occur, a model describing progression to each of these competing risks is needed. For a cervical cancer patient, if the event of interest is death, then recurrence becomes an intermediate event worth modelling. These intermediate event types provide more detailed information on the disease/recovery process and allow for more precision in predicting the prognosis of patients.

Multi-state models may be considered as a generalization of the basic framework for dealing with survival data to the case where several (possibly competing) events occur successively over time. The occurrence of successive events constitutes the transitions from an initial state to a final state. Here, the states of these cervical cancer patients are recurrence and death. Furthermore, these models allow the incorporation of prognostic factors in order to study the influence of these factors on each of the transition rates. Multi-state models can be used to predict the likelihood to reach a specific future state (e.g. recurrence) on the basis of their present state at various time intervals following initial treatment.

The aim of this study is to give a prediction of the future (disease free) survival, given the fact that a patient has been disease free for a specific period after treatment. For this means a database was used in which all clinical and pathological parameters of patients with cervical cancer treated in our institute were prospectively collected since January 1984. Statistical analysis was done with multi-state risk models specifically designed for this purpose.

## Patients and Methods

### *Study group*

Between January 1984 and April 2005, 643 patients with stage I-IIa cervical carcinoma were treated at the department of gynaecology of the Leiden University Medical Centre (LUMC) with a radical hysterectomy and pelvic lymphadenectomy (RHL) with or without adjuvant radiotherapy. All patients in the

study were treated by the same four gynaecologic oncologists. Clinical and pathological parameters were prospectively collected in a database. Two patients were excluded from this analysis because they received both pre- and postoperative radiotherapy, nine because of preoperative chemotherapy and 17 because they received postoperative chemotherapy. Of the remaining 615 patients, 536 (87%) underwent a radical hysterectomy according to Rutledge type III (7) and pelvic lymphadenectomy, and 79 (13%) patients a class II (Te Linde) extended hysterectomy, all in combination with pelvic lymphadenectomy.

*Staging and pathology*

Preoperative staging was performed according to the guidelines of the International Federation of Gynaecology and Obstetrics (FIGO) (8). The following characteristics from the pathology slides were documented: tumour size, histologic tumour type, depth of invasion, parametrial involvement and capillary lymphatic space status (CLS). When no tumour was found in the material from the radical hysterectomy specimen, presurgical data from conisation or biopsies were used. The depth of invasion was measured from the most superficial epithelial-stromal interface of the adjacent intra-epithelial process to the lower limits of invasion (9). CLS was regarded positive when neoplastic cells were seen within endothelium lined spaces.

*Radiotherapy*

The indications for postoperative radiotherapy were (1) node positivity, (2) parametrial infiltration, (3) positive or non radically free (less than 5 mm) surgical margins, (4) the combination of at least 2 of the following 3 risk factors: pathological tumour size (≥4omm), depth of invasion (≥ 15 mm) and CLS involvement. Seven patients had individual reasons for postoperative radiation, such as surgical or medical difficulties to complete the operation as planned or tumour spill during surgery. External beam radiotherapy was administered to the pelvis using a four-field box technique. Patients were treated with 10 MV photons from a linear accelerator to a total dose of 46 Gy in 2 Gy fractions, specified at the isocentre. A brachytherapy boost was given to the vaginal vault in case of extensive CLS (68% of the patients), using vaginal colpostats, 15 Gy low dose rate or equivalent dose, prescribed at 5 mm from the vaginal mucosa.

*Data analysis*

The follow-up was closed on April 2005 and ranged from 0 to 223 months with a mean duration of 53 months. The disease free survival (DFS) was defined as the time from RHL to cytologically or histologically proven evidence of recurrent disease or date last seen. Cancer specific survival (CSS) was defined as the time from date of operation to death by tumour or date last seen. Survival after recurrence was defined as the time from cytologically or histologically proven evidence of recurrent disease to death by tumour or date last seen. Survival curves were made using the Kaplan-Meier method (10). The dif-

ference in DFS and CSS by treatment regimen was evaluated using the log-rank test (10;11). A p-value <0.05 was considered statistically significant. The variables that have been taken into consideration in the analysis of individual patient survival are; lymph nodes involvement, tumour size, depth of invasion, CLS, parametrial invasion, adenosquamous carcinoma and positive surgical margins.

*Multi-state modeling*

After therapy, only a fraction of patients encounters a relapse. After relapse, the probability of dying (within five years) is high. So we are dealing with a survival process with three states: the initial state directly after therapy, the relapse state and death. Every patient starts in the initial state and may undergo a transition to the second state (relapse) or (from the second state) to the third state (death). The proper way to model such a process, on the basis of observed data, is multi-state survival analysis. The dependence of the hazard of each possible transition as a function of time and covariates (like for example lymph node status and tumour size) is modelled by the proportional hazard approach, commonly known as the Cox model.

The first phase of multi-state modelling is the estimation of coefficient values for the covariates and the baseline hazard curves. In a second stage these results are used to predict individual survival curves, given the values of the covariates for a (virtual or real) patient.

The occurrence of relapse strongly increases the probability of a fatal outcome. Conversely, the longer a patient stays relapse-free, the better her chances for survival. The methodology allows the computation of conditional survival curves, given the length of the relapse-free period. Such curves allow doctors and patients to get a better estimate of future prospects.

The multi-state analysis was performed with a library of statistical functions for the R system, an open-source statistical system (12). The library was developed at the Department of Medical Statistics and Bioinformatics of the LUMC (13). It uses established routines for estimation of the proportional hazards sub-models. To construct compound survival curves (in the present case for the path from disease-free to recurrence to death), a simulation approach is used, generating event histories for a large number of pseudo-patients with given values of their covariates (14).

The multi-state model makes the usual assumptions of the Cox model: the effect of covariates can be modelled as a change in hazards of events (recurrence or death) which is constant over time. Another important assumption that we make is that of "clock reset": at the moment of relapse, time starts running in this state, independent of the length of the spell in the disease-free state. Thus, the clock is reset every time the patient enters a new state.

The predicted (conditional) survival functions are based on the non-parametric estimate of baseline hazard that results from the Cox model. This means that the simulation uses the observed time points in the data, because the Cox model by construction "knows nothing" about intervals between events. As a result a simulated survival curve looks like a staircase with unequal steps. We apply P-splines to produce smooth curves which allow easy interpolation (15).

| Characteristics | Patients (n=615) | |
|---|---|---|
| | n | % |
| **Age** | | |
| ≤30 | 47 | 8 |
| 31-60 | 479 | 78 |
| 61-90 | 89 | 15 |
| **FIGO** | | |
| Ia | 21 | 3 |
| Ib | 510 | 83 |
| IIa | 84 | 14 |
| **Cell type** | | |
| Squamous cell | 443 | 72 |
| Adenocarcinoma | 125 | 20 |
| Adenosquamous | 34 | 6 |
| Double tumor | 4 | 1 |
| Others | 9 | 2 |
| **Lymphnode metastases** | | |
| Yes | 123 | 20 |
| No | 488 | 79 |
| Not done | 4 | 1 |
| **Parametrial infiltration** | | |
| Yes | 58 | 9 |
| No | 541 | 88 |
| Unknown | 16 | 3 |
| **Non-radical surgical margins** | | |
| Yes | 94 | 15 |
| No | 505 | 82 |
| Unknown | 16 | 3 |
| **Tumour size** | | |
| ≥ 40mm | 167 | 27 |
| <40mm | 345 | 56 |
| Unknown | 103 | 17 |
| **CLS*** | | |
| Positive | 218 | 35 |
| Negative | 349 | 57 |
| Unknown | 48 | 8 |
| **Depth of invasion** | | |
| ≥15mm | 189 | 31 |
| <15mm | 405 | 66 |
| Unknown | 21 | 3 |
| **Adjuvant radiotherapy** | | |
| Yes | 254 | 41 |
| No | 361 | 59 |

Table 1. The clinical and histological characteristics of the 615 patients.

* Capillary lymphatic space involvement.

## Results

The age of the patients ranged from 21 to 88 years, with a mean of 45. Forty one percent received adjuvant radiotherapy. The clinical and histological characteristics of the patients are listed in Table 1. Of the 615 patients in the study population, 116 (19%) developed recurrence of disease and 80 (13%) died of the disease. The interval from RHL to recurrence ranged from 2-134 months, with a median of 26. The interval from recurrence to death ranged from 1-47 months with a median of 15. Sixty-three percent of the recurrences occurred in the first 2 years after the therapy. Only 8 % of the relapses occurred after 5 years. The 5-year CSS (Fig. 1) and DFS of the entire group was 84% and 76%, respectively.

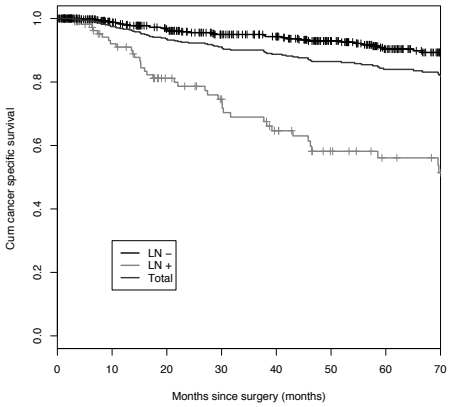


Figure 1. Cancer specific survival of the entire group (n=615), the patients with positive lymph nodes (n=123) and the patients with negative lymph nodes (n=492). Legend: Total, entire group; LN+, positive lymph nodes; LN-, negative lymph nodes. See colour figure page 151.

The 5-year CSS (Fig.1) and DFS were 56% and 43% respectively, among the patients with positive lymph nodes (n=123) in contrast to the patients with negative lymph nodes (n=492), who had a 5-year CSS (Fig.1) and DFS of 90% and 84%, respectively. The differences in CSS and DFS between the 2 groups were statistically significant (p<0.001 and p<0.001, respectively). Table 2 shows the risk factors and their estimator of coefficient in the two stages.

| **Risk factors** | **Disease free-recurrence** | | **Recurrence-death** | |
|---|---|---|---|---|
| | **Coefficient** | **SE** | **Coefficient** | **SE** |
| Lymph node involvement | 0.737 | 0.270 | 0.891 | 0.345 |
| Tumour size | 0.032 | 0.007 | 0.013 | 0.010 |
| Depth of invasion | -0.003 | 0.017 | 0.000 | 0.025 |
| CLS* | 0.648 | 0.278 | -0.828 | 0.389 |
| Parametrial invasion | 0.761 | 0.281 | -0.486 | 0.427 |
| Adenosquamous carcinoma | 0.907 | 0.353 | 0.011 | 0.454 |
| Non-radical surgical margins | 0.391 | 0.286 | 0.851 | 0.383 |

Table 2. Risk factors and their estimator of coefficient and Standard error (SE) in the two stages, disease free to recurrence and recurrence to death. * Capillary lymphatic space involvement.

The predicted probability of death of patients with and without positive lymph nodes is shown in Figure 2. If a patient with negative nodes survives 60 months since therapy without recurrence (T60), she will have a probability of only 1.4% (0.014) that she will be death after another 100 months (160 months since therapy). On the other hand, if a patient with positive lymph nodes has no recurrence at 60 months since therapy (T60), she will have a probability of 73.3% (probability of death 0.267) that she is still alive after another 100 months.

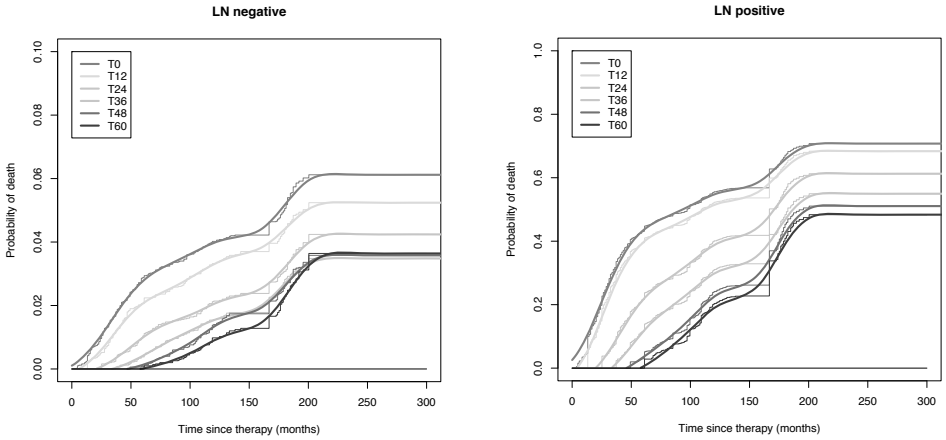


Figure 2. Predicted cumulative probability plots of patients with early stage cervical cancer with negative lymph nodes (LN negative) and with positive lymph nodes (LN positive).
Legend: T0=0 months, T12= 12 months, T24=24 months, T36=36 months, T48=48 months and T60=60 months. See colour figure page 151.

To demonstrate the results of an individual prediction of the future survival we defined four hypothetical patients (A, B, C and D) for simulation. The different risk factors that were used for simulation in these four hypothetical patients are shown in Table 3. Figure 3 shows the predicted cumulative probability plots

| Risk factors | Patient A | Patient B | Patient C | Patient D |
|---|---|---|---|---|
| Lymph node involvement | + | - | - | + |
| Tumour size | 45 mm | 18 mm | 50 mm | 30 mm |
| Depth of invasion | 18 mm | 7 mm | 20 mm | 10 mm |
| CLS* | + | - | + | - |
| Parametrial invasion | + | - | - | - |
| Adenosquamous carcinoma | + | - | - | - |
| Non-radical surgical margins | + | - | - | - |

Table 3. The values of the different risk factors of four hypothetical patients used for simulation. * Capillary lymphatic space involvement.

of patient A, B, C and D. When patient C survives 12 months without recurrence (T12) she has a probability of 21.5 % to be death after 60 months since surgery. But when there is still no sign of the disease after 24 months (T24) the probability that she will be death after 60 months since surgery will be reduced to 12.7 % (Fig.3). When patient A, B, C and D all experience no recurrence after 12 months, the probability to death after 24 months since treatment is 95.9%, 1.9%, 9.2% and 25.1%, respectively (Fig.3).

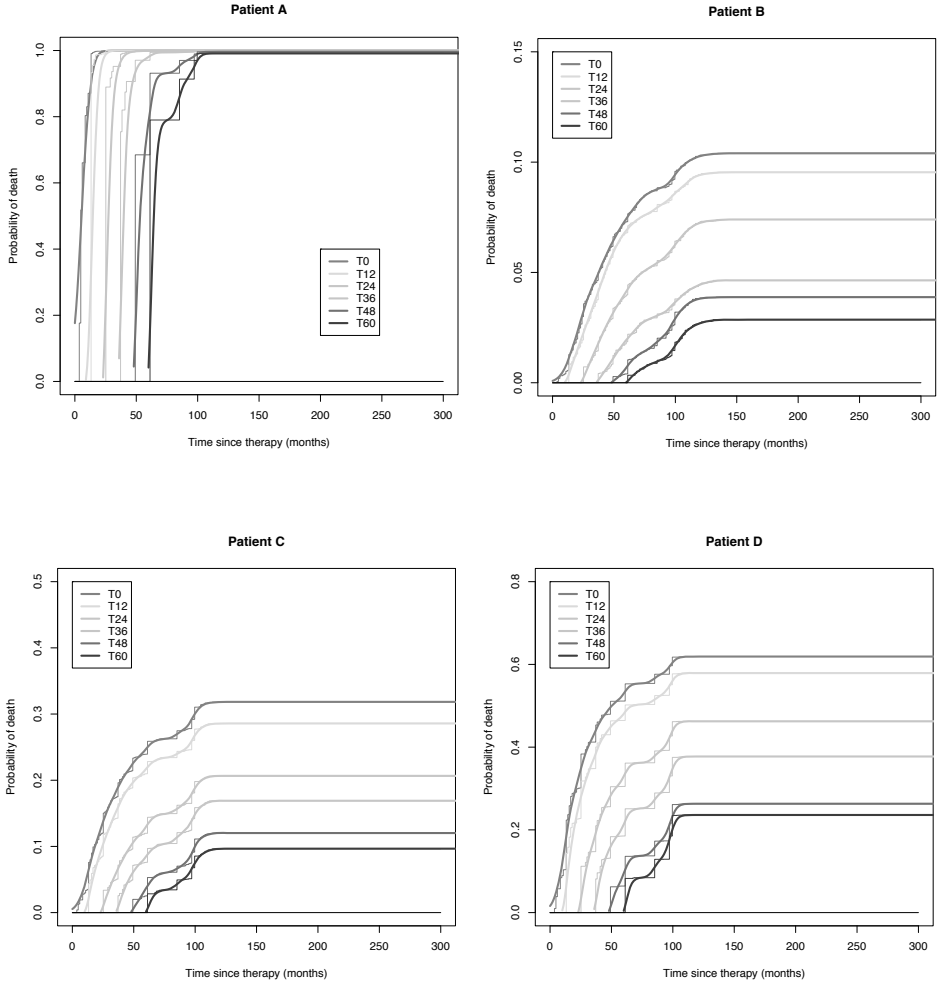


Figure 3. Predicted cumulative probability plots of patient A, B, C and D (Table 3). Legend: T0=0 months, T12= 12 months, T24=24 months, T36=36 months, T48=48 months and T60=60 months. See colour figure page 152.

## Discussion

The possibility to give a detailed prediction of the future (disease free) survival was evaluated, given the fact that a patient has been disease free for a specific period after treatment. The characteristics of our patients in terms of CSS, DFS and the time of recurrence are in accordance with the literature (1-6;16-20), defining our study group as a standard population of patients with early stage cervical cancer. Finally, the current study indicated that with the use of multi-state risk models a prediction of the future (disease free) survival could be calculated.

The strength of the current study is the fact that a prospective database and a consecutive series of patients were used. Besides, all patients were treated by the same group of gynaecologic oncologists. Furthermore, multi-state risk models were used. In complex survival data such as data of patients after a RHL for the treatment of early stage cervical cancer, a number of important (time-) dependent variables (positive lymph nodes, metastases, recurrence) must be taken into consideration in the analysis of patient survival. Multi-state modelling is proposed, analyzing each state separately using e.g. Cox regression models. This enabled us to evaluate which risk factors influence the prognosis of a patient and the complete model could hereafter be used to synthesize patient survival. On the other hand, uncertainties can occur at several levels. Given the model output, there is simulation uncertainty, which can be reduced by simulating enough pseudo-patients. Because the model is based on limited data (615 patients), there are uncertainties in the parameter estimates; no amount of simulation can reduce these. Next, there is a third source of uncertainty. While the moment of death is known with great precision, the relapse state of a patient is often determined at follow-up visits. So the exact date of transition—if such a concept is meaningful at all—cannot be known. In survival analysis parlance this is known as interval censoring. Commonly the date of the follow-up visit at which relapse is ascertained is taken as the moment of its occurrence. We have followed that convention too. Finally, since multi-state survival analysis is a recently developed analysis method it is yet not easy to provide confidence intervals for the probabilities. This will be a future development.

Various types of multi-state models have previously analysed other types of treatment and disorders, including bone marrow transplantations (21), liver transplantations (22), diabetes (23), quality of life in cancer (24), malaria (25) and nosocomial infections in intensive care unit patients (26). The current study is the first study that used multi-state risk models to evaluate the future (disease free) survival of patients treated for cervical cancer stage I-IIa.

Almost all studies evaluating the follow-up, use a minimum follow-up period of 5 years (1-4). However, the majority (70-90%) of recurrences are diagnosed within the first 2 years of initial treatment (5;6;18-20). Besides, there seems to be no consensus in policy as post treatment surveillance programs differ widely among institutions (27) and numerous reports in the literature have shown that routine clinical follow-up surveillance is ineffective in detecting recurrent disease or in achieving a more favourable outcome (20;28-31). When a prediction of the future (disease free) survival could be calculated for

an individual patient, it could provide information to individualise the treatment management and the (length of) programs of surveillance and this obviously will benefit cost and time implications. Furthermore, improving the quality of cancer care will undoubtedly lead to a better quality of life for cancer patients.

As the experience with this new statistical approach will increase, it can only be a matter of time before gynaecologic oncologists will have a program, based on multi-state modelling, on their computer. By this program they will be able to fill in all the individual adverse risk factors, which will lead to the prediction of the future (disease free) survival for that individual patient.

Until the results of other trials are known, the outcome of the present study shows the possibility to give a prediction of the future (disease free) survival, given the fact that a patient has been disease free for a specific period after treatment. It can be concluded that this possibility is an important step forward to improve the quality of cancer care.

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Chapter 5

# The Gynaecologic Leiden Questionnaire: psychometric properties of a self-report questionnaire of sexual function and vaginal changes for gynaecological cancer patients.

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## Abstract

**Objective:** The aim of this study was to investigate the psychometric properties of the items concerning sexual functioning of the Gynaecologic Leiden Questionnaire (LQ), which consists of items for postoperative morbidity for women with cancer.

**Methods:** The total study sample consisted of 198 subjects: 66 patients treated for cervical cancer, 66 patients with sexual complaints and 66 subjects from the general population.

**Results:** By means of factor analysis three subscales were derived: Female Sexual Complaints (FSC), Female Sexual Function (FSF) and Female Orgasm (FO). The reliability of the subscales appeared to be satisfactory. The scores on the three subscales differentiated well between the patients treated for cervical cancer, patients with sexual complaints and the subjects from the general population. Furthermore, the subscales were sensitive to change within the patients treated for cervical cancer. The convergent and divergent construct validity of the Gynaecologic LQ was investigated using other validated instruments measuring sexual functioning, sexual dissatisfaction, marital distress, general life distress and psychological distress. The Gynaecologic LQ subscales were found to represent relatively independent constructs.

**Conclusions:** The results support the reliability and psychometric validity of the Gynaecologic LQ in the assessment of sexual functioning and vaginal changes in gynaecological cancer patients.

## Introduction

Diagnosis and treatment of gynaecological cancer are very likely to have a negative impact on the sexual function of the patient (1-6). It is known that women who have been treated for cervical cancer by radical hysterectomy with pelvic lymphadenectomy (RHL) have persistent vaginal changes that compromise sexual activity and result in considerable distress. Changes or problems that have been described are diminished lubrication, a narrow and short vagina, dyspareunia and sexual dissatisfaction (1-7). Therefore, the treatment of cancer should not only be evaluated with regard to survival. The complications and personal implications of the disease and treatment should also be assessed. To obtain an impression of the impact of a given treatment on a patient's quality of life and to understand the patient's perception of symptom severity, self-report questionnaires may give more informative answers (8). Over the last decades several questionnaires have been developed to diagnose dimensions of female sexual dysfunction (9;10). Lately, Jensen et al. showed the results of the validation of the Sexual function-Vaginal changes Questionnaire (SVQ), that was developed to investigate sexual and vaginal problems in gynaecological cancer patients (11).
For the Dutch language area however, until recently (12) no questionnaire was available that focuses on sexual and vaginal problems due to disease and treatment specific for gynaecological cancer patients. We developed a 21-items Dutch self-report questionnaire, the Gynaecologic Leiden Questionnaire (LQ), which is the first Dutch list consisting of items for sexual function, voiding- and bowel problems for women with gynaecological cancer. The items of the Gynaecologic LQ were based on the items to assess sexual function, voiding- and bowel problems of a non-validated questionnaire which has been successfully used in rectal cancer studies (13). Clarity of formulation was assessed by presenting the scale items to patients treated for early stage cervical cancer. The final version of the Gynaecologic LQ consists of one item for weariness, one item for lymph edema, 11 items for sexual functioning, 6 items for voiding and 2 items for bowel problems. The aim of this study is to investigate the psychometric properties of the items concerning sexual functioning of the Gynaecologic LQ.

## Methods

### *Study population*

The study involved three subject groups: 1) patients with a history of a RHL for the treatment of cervical cancer stage I-IIa, (*oncology group (ONCO)*); 2) patients of an out-patient clinic of sexology (*female sexual dysfunction group (FSD)*); 3) subjects from the general population (*control group (CONTROL)*).
The data from the prospective study of Pieterse et al.(7) were used for the ONCO group. This group consisted of consecutive patients who stayed at the department of gynaecology to undergo a RHL for early stage cervical cancer at the Leiden University Medical Centre (LUMC). They were asked to

complete the Gynaecologic LQ before, 3, 12 and 24 months after the operation (7). For the validation of the Gynaecologic LQ we used the Gynaecologic LQ that was completed 12 months after the operation. Sixty-six women who completed the Gynaecologic LQ after 12 months of follow-up were included.
The FSD group consisted of women with a sexual problem who solicited for therapy at an out-patient clinic for sexology of a university medical hospital. The women completed the questionnaires at the end of the first visit. Sixty-six consecutive women with sexual complaints, matched for age with the ONCO group, were included. All the women had a heterosexual relationship.
For the CONTROL group the data from the prospective study of Pieterse et al. (7) were used. This group consisted of employees from the hospitals and relatives and friends of these employees. Sixty-six women were selected. The CONTROL group was matched for age and marital status with the ONCO group ($\chi^2$=0.04, p=.849). Demographic data of the three groups are given in Table 1.

*The Gynaecologic LQ*

| **Characteristics** | **ONCO (n=66)** | **FSD (n=66)** | **CONTROL (n=66)** | **Chi-square**[1] | **p-value** |
|---|---|---|---|---|---|
| **Age** n,(%) | | | | $\chi^2$=7.97 | 0.436 |
| 21-30 | 8(12) | 11(17) | 9(14) | | |
| 31-40 | 26(39) | 29(44) | 26(39) | | |
| 41-50 | 25(28) | 15(23) | 25(38) | | |
| 51-60 | 6(9) | 11(17) | 6(9) | | |
| >60 | 1(2) | 0 | 0 | | |
| **Living together** n,(%) | | | | $\chi^2$=24.33 | 0.000 |
| With a partner | 46(70) | 66(100) | 47(71) | | |
| Without partner | 20(30) | 0 | 19(29) | | |

Table 1. Demographic characteristics of ONCO group (patients treated for cervical cancer), FSD group (out-patients with sexual complaints) and CONTROL group (subjects from the general population). [1]Observed two-tailed significance. Statistical significance at a level of p<0.05.

The current study investigated only the psychometric properties of the items concerning sexual functioning of the Gynaecologic LQ. The 11 items cover aspects of sexual satisfaction, sexual desire, orgasm, lubrication and pain (see attachment). Items covering treatment specific problems e.g. short or narrow vagina and dry vagina were also included. An inherent problem in the development of questionnaires on sexuality is that not all participants had a partner and that not all the participants were sexually active. For the analysis two questions were excluded because they were not answered on a 5 point Likert scale (item 1 “sexual active lately?”, yes/no and item 10 “numbness labia or thigh?”, yes/no). A higher score on a particular item indicates higher endorsement of the dysfunction or problem measured. Therefore, items 2, 3, 4, 5 and 6 were recoded.

The Dutch version of the Gynaecologic LQ was translated into English by three independent persons. A consensus translation of each was translated into Dutch by a native Dutch speaker. On the basis of differences between the original and retranslated versions of the questionnaires, some additional changes were made in the English translation (see attachment).

*Measures used for construct for validation*

Only in the FSD group, data for the divergent and convergent construct validity were collected. The following measures were used:

*The Female Sexual Function Index (FSFI)* (10). The FSFI is a multidimensional self-report questionnaire for assessing sexual function in women (10). The FSFI consists of 19 items that assess sexual desire, arousal, lubrication, orgasm, satisfaction and pain. The psychometric qualities of original FSFI (10;14;15) and the Dutch FSFI translation (16) were found satisfactory to good. A higher score means a better sexual function.

*The Female Sexual Distress Scale (FSDS)* (17). The FSDS is a 12-items self-report questionnaire that is developed to assess sexuality related personal distress. Overall the FSDS seems a valid and reliable measure for assessing sexuality related personal distress in women (17). The reliabilility and psychometric validity of the Dutch FSDS is excellent (16). Higher scores indicate more sexual dissatisfaction.

*The Golombok Rust Inventory of Sexual Satisfaction (GRISS)* contains 28 items and covers the most frequently occurring sexual complaints of heterosexual persons with a steady partner. Seven subscale scores can be derived: anorgasmia, vaginismus, (in)frequency of sexual contact, sexual non-communication, dissatisfaction, non-sensuality, and avoidance of sex. For the current study we only used the anorgasmia and vaginismus subscales of the GRISS. The psychometric qualities of original GRISS (18;19) and the Dutch version were found to be satisfactory (20;21). Higher scores indicate more problems.

*The Maudsley Marital Questionnaire (MMQ)* is a 20-items self-report instrument measuring dissatisfaction with the general relationship, with the sexual relationship, and dissatisfaction with life in general. For the current study we only used the subscales general relationship and dissatisfaction with life in general. The MMQ has shown good reliability and validity (22). The psychometric qualities of the Dutch version of the MMQ were also found to be satisfactory (23). Higher scores represent larger dissatisfaction.

To measure psychological distress, *the Symptom Checklist-90 (SCL-90)* (24) was used. The Dutch version of the SCL-90 (25;26) was used as an index of psychological distress. The psychometric qualities of the Dutch version were found to be satisfactory. Higher scores represent greater psychological distress.

*Statistical analysis*

Exploratory principle component analysis was conducted on the items of the Gynaecologic LQ in the ONCO and FSD groups. The Kaiser criterion (27) was used to determine the number of components. According to the Kaiser criterion, only components whose eigenvalues are larger than 1 are considered

as being of interest. Where a multi-componential solution resulted, simultaneous components analysis (28) was used to identify the optimal dimensional structure in the different subgroups. This analysis tries to establish component weights such that the components optimally summarize the variables in each group. Based on the components, subscales were constructed[1]. The internal consistency was calculated using Cronbach's alpha in the ONCO group, the FSD group and the CONTROL group. The stability of the Gynaecologic LQ was assessed by calculating the test-retest reliability in CONTROL group. To test the discriminant validity of the Gynaecologic LQ-subscales between the three subject groups, univariate comparisons were made by means of one-way analysis. The sensitivity to change was assessed by a repeated analysis of variance in the ONCO group.
The divergent and convergent construct validity were studied using a higher order principal components analysis with varimax rotation of the scores on the Gynaecologic LQ subscales together with the scores on (subscales of) standardized psychometric instruments measuring theoretically related constructs (complaints): sexual functioning (FSFI), sexual dissatisfaction (FSDS), marital and general life maladjustment (MMQ), and psychological distress (SCL-90).

## Results

*Preliminary analysis*

Prior to analysis, all variables were examined for missing values and fit between their distributions and the assumptions of multivariate analyses. The majority of the item score of the Gynaecologic LQ in the CONTROL group was very low, resulting in positively skewed distributions. For seven out of 9 items the median was category one, indicating that on these seven items at least 50% of the subjects in the CONTROL group only used the first of the five available response categories. This can be explained by the fact that these subjects in the CONTROL group did not have any complaints. Therefore, we decided to exclude the CONTROL group from the factor structure analysis.
Since item 4 (orgasm during masturbation) did not correlate with any of the other Gynaecologic LQ items (<.35) (29), item 4 was also excluded from the further analysis.

1 The original version of the Dutch Gynaecologic LQ consisted of one item with a 6-point Likert scale (item 5) and one item with a 4-point Likert scale (item 2). To obtain uniform weights of the individual items on a subscale, we recoded the answering formats of item 2 and 5. For item 5, two answer formats "Less than once a month" and "Approximately once a month" were added together and the score of item 2 was multiplied with 5/4. In the final version of the Gynaecologic LQ, the answer format "always" was added to item 2.

*Factor structure*

Explorative principal component analysis was conducted on the 8 items of the Gynaecologic LQ in the ONCO and FSD groups. On the basis of the Kaiser criterion (30), a three-component solution was obtained in both groups. A three-component simultaneous components analysis (28) was conducted to find the components weights with which the components optimally summarized the variables in the two subject groups. The total amount of variance explained by component 1 was 43% in the ONCO group and 30% in the FSD group. For component 2 the total amount of variance was 17% in the ONCO group and 23 % in the FSD group. The total amount of variance explained by the third component was in both subject groups 13%. The total amount of variance explained by the components resulting from the simultaneous components analysis was 71% for the ONCO group and 65% for the FSD group. These percentages differed not more than 1.0 % from the variance accounted for by the separate principal component analyses in the two subject groups. Thus it may be concluded that the same combinations of variables can be used in both subject groups to describe the data adequately. The loading of the individual items on the three common components in the ONCO and FSD group are shown in Table 2. Items with a loading on one component exceeding 0.55 and a difference between loadings on the three components of at least >0.10 in the two subject groups were considered to belong to a subscale. The first subscale consisted of item 7 (Do you experience vaginal dryness during sexual intercourse?), 8 (Do you experience your vagina as too tight or too short during sexual intercourse?) and 9 (Is sexual intercourse painful to you?). This was interpreted as reflecting Female Sexual Complaints (FSC). The

| **Gynaecologic Leiden Questionnaire( LQ) items** | **ONCO** | **FSD** |
|---|---|---|
| Component 1: Female Sexual Complaints (FSC) | | |
| 7 Do you experience vaginal dryness during sexual intercourse? | 0.739 | 0.578 |
| 8 Do you experience your vagina as too tight or too short during sexual intercourse? | 0.884 | 0.825 |
| 9 Is sexual intercourse painful to you? | 0.890 | 0.850 |
| Component 2: Female Sexual Function (FSF) | | |
| 2 Do you feel sexual desire? | 0.693 | 0.766 |
| 3 Do you notice that your vagina becomes lubricated ("wet") during sexual arousal? | 0.717 | 0.754 |
| 5 Do you have sexual contact with a partner? | 0.754 | 0.692 |
| 11 How satisfied are you with your present sexual life? | 0.785 | 0.706 |
| Component 3: Female Orgasm (FO) | | |
| 6 Do you reach orgasm during sexual intercourse? | 0.703 | 0.720 |

Table 2. Component loadings of the individual items of the Gynaecologic Leiden Questionnaire on the three components resulting from the simultaneous components analysis in the ONCO group (patients treated for cervical cancer) and FSD group (out-patients with sexual complaints).

second subscale included item 2 (Do you feel sexual desire?), 3 (Do you notice that your vagina becomes lubricated ("wet") during sexual arousal?), 5 (Do you have sexual contact with a partner?) and 11 (How satisfied are you with your present sexual life?), and was considered to represent Female Sexual Function (FSF). The third subscale only consisted of item 6 (Do you reach orgasm during sexual intercourse?) and represent Female Orgasm (FO).

*Reliability*

For the internal consistency the ONCO group, the FSD group and the CONTROL group were used. Since subscale FO consists of only one item, only the consistency of subscales FSC and FSF were assessed. The Cronbach's alpha values (Table 3) of the subscales FSC and FSF were sufficient in our ONCO group (>0.70) (31). The correlation-coefficients between test and re-test, ranging from 0.78 to 0.93, were never more than 0.20 lower than Cronbach's Alpha of a subscale (31). These results indicate that the Gynaecologic LQ subscales have appropriate levels of stability over a period of 2.8 weeks of

| Subscale | ONCO | FSD | CONTROL |
|---|---|---|---|
| FSC | | | |
| Chronbach's alpha | 0.80 | 0.65 | 0.68 |
| FSF | | | |
| Chronbach's alpha | 0.73 | 0.72 | 0.68 |

Table 3. Crohnbach's alpha of the subscale Female Sexual Complaints (FSC) and the subscale Female Sexual Function (FSF) of the Gynaecologic Leiden Questionnaire of ONCO group(patients treated for cervical cancer), FSD group (outpatients with sexual complaints) and CONTROL group (subjects from the general population).

time (SD= 1.7; range: 1 - 8 weeks).

As an internal criterion for the validity of the three subscales, interscale correlations were computed in the three groups and ranged from 0-0.53. For the purpose of interpretation$|0.10| < r < |0.30|$ is considered as small, $|0.30| < r < |0.50|$ as medium and $r > |0.50|$ as large (32) . These results indicate that the Gynaecologic LQ subscales do not measure totally independent constructs.

No significant associations were found between the Gynaecologic LQ subscales on the one hand and age or 'living with a partner' on the other. Therefore, it can be concluded that the Gynaecologic LQ subscales scores are independent of biographic variables.

*Discriminant validity*

The power of the Gynaecologic LQ subscales to discriminate between different groups of subjects was investigated within the three study groups. As can be seen in Table 4, the Gynaecologic LQ subscales proved to differentiate between the three groups. The women treated for cervical cancer (ONCO) scored significantly higher on the FSF, FSC and FO subscales than women from the general population

| Subscale | ONCO Mean (SD) | FSD Mean (SD) | CONTROL Mean (SD) | F-ratio | Post-hoc-tests |
|---|---|---|---|---|---|
| FSC(n=58) | 2.2(1.1) | 2.9(1.1) | 1.4(0.5) | 38.59* | CONTROL<ONCO<FSD |
| FSF(n=58) | 2.6(0.8) | 3.5(0.7) | 1.9(0.6) | 73.77* | CONTROL<ONCO<FSD |
| FO(n=58) | 2.9(1.3) | 3.9(1.3) | 1.7(0.9) | 48.80* | CONTROL<ONCO<FSD |

Table 4. Untransformed mean, standard deviation (SD) and transformed F ratios for the scores on the Female Sexual complaints (FSC), the Female Sexual Function (FSF) and Female Orgasm (FO) in ONCO group (patients treated for cervical cancer), FSD group (out-patients with sexual complaints) and CONTROL group (subjectsfrom the general population).* All p-values were <0.01, statistical significance at a level of p<0.05.

(CONTROL) and significantly lower on FSF, FSC and FO subscales than women who request therapeutic assistance for sexual problems (FSD).

*Sensitivity to change*

To test if the Gynaecologic LQ subscales change in the theoretically proposed direction following an intervention the data from the prospective study of Pieterse et al. (7) were used. Sixty-two of the 66 patients of the ONCO group completed the 24 months follow-up and were included in the analysis. The differences in the subscale scores were analysed at three time moments: before the RHL and 12 months and 24 months after the RHL.

Before the RHL all three subscales score significantly lower than 12 months ($p<0.01$) and 24 months after the treatment (FSC, $p<0.01$; FSF, $p<0.01$; FO, $p=0.037$). The scores of the three subscales did not significantly differ 12 and 24 months after the treatment ($p>0.5$). These findings are in line with the results of the prospective study of Pieterse et al. (7) in which the patients reported significantly less sexual complaints before than after the RHL. Moreover, sexual dysfunction was reported up to 24 months of follow-up. Only item 'orgasm during sexual intercourse' that formed the subscale FO, never reached significantly difference over time in that study (7).[2]

*Construct validity*

A principal components analysis suggested a four-component solution that accounted for 72% of the total variance (Table 5). We found that the first component accounted for 31% of the variance and interpreted it as *sexual dysfunction*. High loadings were found on this component for the FSF and the five FSFI subscales arousal, desire, satisfaction, lubrication and orgasm. The second component, accounting for 18% of the total variance, is interpreted as *sexual pain disorder*. High loadings on this component were found for the FSC, the GRISS subscale vaginismus and the FSFI subscale pain. The third component, accounting for 13% of the total variance, is interpreted as *psychological distress*. High

2 Sensitivity to change was also tested for all the 72 patients of the prospective study of Pieterse et al. (7) who completed the 24 months follow-up. The results were comparable with the results reported.

| Rotated factor matrix | I | II | III | IV |
|---|---|---|---|---|
| FSFI-Arousal | 0.901 | | | |
| **FSF** | -0.860 | | | |
| FSFI-Desire | 0.850 | | | |
| FSFI-Satisfaction | 0.845 | | | |
| FSFI-Lubrication | 0.827 | | | |
| **FSC** | | 0.872 | | |
| GRISS-Vaginismus | | 0.840 | | |
| FSFI-Pain | | -0.708 | | |
| SCL-90-Psychological distress | | | 0.893 | |
| MMQ-General life maladjustment | | | 0.769 | |
| FSDS-Sexual dissatisfaction | | | 0.711 | |
| MMQ-Marital maladjustment | | | 0.412 | |
| GRISS-Anorgasmia | | | | 0.821 |
| **FO** | | | | 0.820 |
| FSFI-Orgasm | 0.487 | | | -0.661 |

Table 5. Principal component analysis with varimax rotation of the Gynaecologic LQ subscales and other scales for women with sexual complaints (n=66). Rotated factor loadings of >0.35 are reported. FSFI=Female Sexual Function Index; FSDS= Female Sexual Distress Scale; GRISS= Golombok Rust Inventory of Sexual Satisfaction; MMQ= Maudsley Marital Questionnaire ; SCL-90= Symptom Checklist-90.

loadings on this component were observed for the SCL-90 total score, the MMQ subscale scores for general life maladjustment and relationship maladjustment and the FSDS. The fourth component, accounting for 11% of the total variance, is interpreted as *orgasm disorder*. High loadings were found on this component for the FO, the FSFI subscale orgasm and the GRISS subscale anorgasmia. These results indicate that the Gynaecologic LQ subscales represent relatively independent constructs.

## Discussion

The aim of the present study was to investigate the psychometric properties of the items concerning sexual functioning of the Gynaecologic LQ.

Component analysis of the Gynaecologic LQ in patients treated for cervical cancer and patients with sexual complaints yielded a three-component solution. Three items appeared to contribute to component 1, the subscale Female Sexual Complaints (FSC). Four items contribute to component 2, the subscale Female Sexual Function (FSF) and only one item formed component 3, the subscale Female Orgasm (FO) (Table 2).

The internal consistency was sufficient. The stability was good for all three subscales. The scores on the three subscales were overall not associated with age or 'living with a partner'. The convergent and divergent validity of the Gynaecologic LQ was good, since the 3 subscales corresponded with subscales measuring similar complaints and discriminated from subscales measuring other (psychological)

problems. The scores from the three subscales appeared to differentiate between patients treated for cervical cancer, patients with sexual complaints and subjects from the general population. Furthermore, the subscales were sensitive to change within the patients treated for cervical cancer.

To get insight in the morbidity after RHL in our own population, the Gynaecologic LQ was developed since no other validated Dutch list existed. We already used the Gynaecologic LQ in a prospective study (7) in which it was concluded that women after RHL for early stage cervical carcinoma were associated with adverse effects mainly on sexual functioning. The findings were in line with the literature (2-4;33;34). It is expected that our new developed nerve-sparing modification of the RHL (35) will lead to less postoperative morbidity. The validated LQ will be used as a tool to compare the nerve-sparing RHL with the conventional RHL.

Since the Gynaecologic LQ is a Dutch self-report questionnaire, an English version would need to be tested in English speaking populations to check the reliability and validity.

However, the scoring system of the Gynaecologic LQ is not very easy in use. Our suggestion would be to simplify the scoring system of the Gynaecologic LQ by using a uniform Likert scale and that a higher score on all items indicates higher endorsement of the dysfunction or problem measured. In this way the Gynaecologic LQ will be more comfortable to do measurements with.

In conclusion, the results of the current study support the reliability and psychometric validity of the Gynaecologic LQ in the assessment of sexual functioning and vaginal changes in gynaecological cancer patients. The validated Gynaecologic LQ is the first developed Dutch questionnaire which can be used to assess sexual function for women with gynaecological cancer. In an era where quality of life is considered of major importance in the evaluation of cancer treatment, instruments like these are essential tools to improve our treatment modalities for cancer patients.

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# Attachment

**The Gynaecologic Leiden Questionnaire**

Sexual activity can include masturbation or sexual contact with a partner. When thinking of sexual contact with a partner, please do not only think of sexual intercourse, but also consider other ways of making love that you or your partner experience as sexually arousing.

1. Have you been sexually active lately?
   1.Yes
   2.No

2. Do you feel sexual desire?
   1. Never
   2. Seldom
   3. Sometimes
   4. Often
   5. Always

3. Do you notice that your vagina becomes lubricated ("wet") during sexual arousal?
   0. No sexual activity
   1. Never
   2. Seldom
   3. Sometimes
   4. Often
   5. Always

4. Are you able to reach an orgasm during masturbation?
   0. No masturbation
   1. Never
   2. Seldom
   3. Sometimes
   4. Often
   5. Always

5. Do you have sexual contact with a partner?
   1. No
   2. Approximately once a month
   3. A few times a month
   4. Approximately once a week
   5. A few times a week

The following questions ask about sexual intercourse. If you never engage in sexual intercourse, please continue with question number 10.

6. Do you reach orgasm during sexual intercourse?
   1. Never
   2. Seldom
   3. Sometimes
   4. Often
   5. Always

7. Do you experience vaginal dryness during sexual intercourse?
   1. Never
   2. Seldom
   3. Sometimes
   4. Often
   5. Always

8. Do you experience your vagina as too tight or too short during sexual intercourse?
   1. Never
   2. Seldom
   3. Sometimes
   4. Often
   5. Always

9. Is sexual intercourse painful to you?
   1. Never
   2. Seldom
   3. Sometimes
   4. Often
   5. Always

10. Do you experience numbness of your labia and/or the inner sides of your tights?
    1. Never
    2. Seldom
    3. Sometimes
    4. Often
    5. Always

11. How satisfied are you with your present sexual life?
    1. Very satisfied
    2. Satisfied
    3. Not satisfied/ not dissatisfied
    4. Dissatisfied
    5. Very dissatisfied.

Chapter 6

# An observational longitudinal study to evaluate miction, defecation and sexual function after radical hysterectomy with pelvic lymphadenectomy for early stage cervical cancer.

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*Based on: Int J Gynecol Cancer 2006; 16:1119-1129*

## Abstract

**Objective:** To evaluate the problems with voiding, defecation and sexuality after a radical hysterectomy with or without adjuvant radiotherapy for the treatment of cervical cancer stage I-IIa.

**Methods:** An observational longitudinal study of self-reported bladder, defecation, sexual problems with a baseline score.

**Results:** Ninety-four women were included in the study. An age matched control group existed of 224 women. The patients showed significant more negative effects on sexual function compared both with the controls as well as compared with their situation before the treatment throughout 24 months of follow-up. The problems included less lubrication, a narrow and short vagina, numb areas around the labia, dyspareunia, and sexual dissatisfaction. Up to 12 months after the treatment the patients complained significantly more of little or no urge to urinate and diarrhoea as compared with the controls. Adjuvant radiotherapy did not increase the risk of bladder dysfunction, colorectal motility disorders and sexual functions.

**Conclusions:** We conclude that a radical hysterectomy for the treatment of early stage cervical carcinoma is associated with adverse effects mainly on sexual functioning.

## Introduction

State of the art treatment for women with early stage cervical cancer (I-IIa) is a radical hysterectomy with pelvic lymphadenectomy (RHL) with or without adjuvant (chemo) radiation (1). Although RHL has good result in terms of survival, it also has its price: loss of fertility, bladder dysfunction, colorectal motility disorders, lymphedema and sexual dysfunction (2-10).

Autonomic nerve damage during surgery plays a crucial role in the aetiology of this morbidity (11). The effects of the treatment for cervical carcinoma on the women's sexuality and the resulting distress, have recently received some attention (4;12-19). In 1999 Bergmark et al. contacted 256 women with a history of early-stage cervical cancer who had been treated 5 years before and asked them to answer a questionnaire about vaginal changes and sexual function. In this retrospective study they reported vaginal changes, like decreased lubrication and a short vagina, after RHL in 25% of cases (3). Weimar Schultz et al. showed in a comparative and longitudinal study that the sexual response of women treated for cervical carcinoma, was significantly disturbed although current sexual behaviour and motivation for sexual interaction were within the normal range (4). Recently, Jensen et al. published the first longitudinal study, which was partly prospective. It comprised 173 patients with early-stage cervical cancer after RHL, who received questionnaires up to 2 years after the operation. Information about the sexual function before the diagnosis of cancer was obtained retrospectively, one year after the operation. The authors reported that RHL had a persistent and negative impact on patients' sexual interest and vaginal lubrication and that the majority of other sexual and vaginal problems disappeared over a two years period (5).

Furthermore, it is well known that RHL can lead to postoperative urinary dysfunction such as urinary retention, straining or inability to void, and, to a lesser extent, to urge and stress incontinence (6;8). Severe constipation has also been described in 5-10% (6;10).

Finally, it remains controversial whether RHL with or without adjuvant radiotherapy or radiation alone has a more adverse impact on the sexual function of patients (3;20-25). Jensen et al., reported persistent and severe sexual problems throughout the 2 years after radiotherapy with only small changes over time (20). On the other hand the results of Bergmark et al. showed that surgery alone had more adverse effects on sexual function than combined treatment modalities, including surgery and radiotherapy or radiotherapy alone (3). The authors did not comment on this.

To evaluate the symptoms that arise following RHL with or without adjuvant radiotherapy for the treatment of cervical cancer, we performed a prospective study in 2 Dutch university centres. The aim of this study was to determine the prevalence of lymphedema, bladder dysfunction, colorectal motility disorders and sexual dysfunction among women who had been treated for cervical cancer by a RHL.

We compared this group of patients with a group of age-matched controlled women from the general population. Because the effect of adjuvant radiotherapy on late side effects is still unclear, we also compared patients who underwent adjuvant radiotherapy to those who did not.

## Patients and Methods

*Patients and controls*

From May 1998 until January 2003 women with early stage cervical cancer who had to undergo RHL were enrolled in the study. These women were treated in the Leiden University Medical Centre or the University Medical Centre Utrecht. In all cases, a RHL type III was performed through a midline incision. Nerve-sparing surgery was not yet routine practice during the time of the study. Patients with lymph node metastasis, parametrial infiltration, tumour growth in the vaginal surgical margins or a combination of unfavourable tumour size, deep infiltration and lympho-vascular space involvement received adjuvant radiotherapy. Radiotherapy included external pelvic irradiation, brachytherapy or both. Ovaries were not routinely transposed before potential radiotherapy. Data on the treatment results were obtained from the prospective databank. Exclusion criteria were: unable to understand the Dutch language and no follow-up due to living outside the Netherlands. The Medical Ethics Committee of both centres approved the study and all women gave their written informed consent.
The control group consisted of women without cervical cancer and who had not undergone a hysterectomy in the past and were matched for age. They were employees from the hospitals and relatives and friends of these employees. The control group was asked to complete the questionnaire once.

*Questionnaire*

For this study 14 items of the 21 items self-report Gynaecologic Leiden questionnaire (LQ) were used[31]. The 14 items used in the current study were related to lymphedema (1), sexual function (9), voiding (2) and bowel problems (2). The Gynaecologic LQ was completed before the operation and at 3, 12, and 24 months after the operation. Eight questions (sexual function (7), bowel problems (1)) were answered on a 4 or 5-point Likert-scale ranging from 'never' to 'always'. Four questions (bowel problems (1), voiding problems (2), lymphedema (1)) were answered on a 3-point ordinal scale (yes/sometimes/no). Two questions (sexual function) were answered on a dichotome scale (yes/no). In order to obtain an uniform answering format for all the 14 items, the 3, 4 and 5-point scales were dichotomized. Dichotome answer categories were obtained by adding up the answer categories. Since the score on each item did not indicate that a higher score means more endorsement it depends on the score how the dichotome answer categories were computed: 3-point scale: 'yes and sometimes' versus 'no' *or* 'no and sometimes' versus 'yes'; 4/5-point scale: 'sometimes, often and always' versus 'seldom and never' *or* 'often and always' versus 'sometimes, seldom and never'.

[1] At the time of the current study the Gynaecologic LQ was not yet validated. Recently, the validation of the psychometric properties of the items concerning sexual functioning of the Gynaecologic LQ was performed (Chapter 5). The results of that study support the reliability and psychometric validity of the Gynaecologic LQ in the assessment of sexual functioning and vaginal changes in gynaecological cancer patients (Chapter 5).

*Data analyses*

Sexual function, voiding and bowel dysfunction were analyzed in four ways: before versus after the operation, changes since the operation, premenopausal versus postmenopausal, patient versus control, and radiotherapy versus no radiotherapy.

The responses to the questionnaires were dichotomized and the results are presented as relative risks (RR) and corresponding 95% confidence intervals (CI). RR was calculated as the proportion of women with cervical cancer before the treatment reporting the particular problem divided by the proportion of these women after the surgery. The same was done for the patients versus the controls, radiotherapy versus no radiotherapy and pre menopausal versus postmenopausal. In some cases, the relative risk could not be computed, because of zero counts. When this occurred, we added 1 to each cell of the two by two table (an application of Laplace's rule of succession).

We used the scores from all the sexual function items in the 24 months questionnaire to compare the sexual situation at 24 months after the surgery with the situation before treatment. The possible options were better, no change or worse. The Chi square test was used to test whether the score distributions differed from no change. The analyses were performed using SPSS statistical package 11.0 for windows.

## Results

*Patients and controls*

A total of 94 consecutive women were included in the study. Analysis was performed 2 years after involvement of the last patient. Seventy-three women filled in all the questionnaires, in 21 cases data were not available. Nine women did not return all the questionnaires for unknown reasons, they all had a complete remission and are still alive. Two women moved to another city or country. Ten women died. Of these last women, 9 died as a result of the cervical carcinoma and 1 woman due to a cerebral tumour. The mean age at the time of the operation was 43.3 years (SD 11.0) (Range 21-72 years). The characteristics and distribution of treatment of the patients are shown in Tables 1 and 2. The control group consisted of 224 women. All characteristics of the control group are shown in Table 1. Thirty-one women became postmenopausal because they received radiotherapy or their ovaries were removed. Eleven of them used hormonal replacement therapy (HRT) after the treatment.

| Characteristics before operation | Women with Cancer n (%) | Controls n (%) |
|---|---|---|
| Total patients | 94 | 224 |
| Total complete questionnaires | 73(78) | 224(100) |
| **Age** | | |
| 21-30 | 9(10) | 22(10) |
| 31-40 | 36(39) | 77(35) |
| 41-50 | 27(29) | 67(30) |
| 51-60 | 11(12) | 40(18) |
| 61-70 | 9(10) | 16(7) |
| 71-80 | 1(1) | 0(0) |
| **Marital status** | | |
| Married or living with a partner | 65(70) | 173(77) |
| Single | 13(14) | 30(13) |
| Divorced | 12(12) | 14(6) |
| Widow | 4 (4) | 7(3) |

Table 1. Characteristics of patients and controls.

| Characteristics | Women with Cancer n* (%) |
|---|---|
| **Hormonal status pre-surgery** | |
| Premenopausal | 77(83) |
| Postmenopausal | 16(17) |
| **Hormonal status post-surgery** | |
| Premenopausal | 46(50) |
| Became postmenopausal | 31(33) |
| Postmenopausal | 16(17) |
| **FIGO** | |
| Ia | 5(6) |
| Ib | 79(87) |
| IIa | 5(6) |
| IIb | 2(2) |
| **Ovaries** | |
| Left in situ | 67(72) |
| Removed | 26(28) |
| **Adjuvant radiotherapy** | |
| No | 58(62) |
| Yes | 36(38) |
| External | 12(13) |
| Brachytherapy | 1(1) |
| External & brachytherapy | 23(25) |
| **HRT** | 11(12) |

Table 2. Treatment characteristics of the cervical cancer patients. * Total number varies between 91-94, because of missing data.

*Patient before surgery versus patient after surgery*

The absolute numbers, RR and corresponding 95% CI for all items are shown in Table 3.
Patients had significantly more lymphedema 3 months after the treatment up to 24 months follow-up. At the 3 months follow-up, a significantly larger percentage of the patients complained of little or no urge to urinate. After 12 months follow-up a significantly larger percentage of the patients reported moderate urine incontinence. Only after 24 months follow-up a significantly larger percentage of the patients complained of "little or no lubrication" during sexual arousal compared to the pre-surgery levels. Compared to the situation before the operation, throughout the first 24 months a significantly larger percentage of the patients reported complaints of pain during coitus, a short vagina, numb areas around the labia, dry vagina during coitus and dissatisfaction with sexual relationship.

**No/total no.responding (%)**

| | Before surgery | 3 Months | | 12 Months | | 24 Months | |
|---|---|---|---|---|---|---|---|
| **Characteristics** | **Patient** | **Patient** | **RR(95%CI)** | **Patient** | **RR(95%CI)** | **Patient** | **RR(95%CI)** |
| Often diarrhoea | 1/94(1) | 5/93(5) | 5.1(0.6-42) | 4/77(5) | 4.9(0.6-43) | 2/73(3) | 2.6(0.2-28) |
| Often constipation | 3/94(3) | 3/93(3) | 1.0(0.2-4.9) | 4/77(5) | 1.6(0.4-7.1) | 3/73(4) | 1.3(0.3-6.2) |
| Little/no urge | 0/93(0) | 10/93(11) | **11(1.5-84)*** | 5/77(7) | 7.2(0.9-59)* | 4/73(6) | 6.4(0.8-53)* |
| Severe incontinence | 0/94(0) | 1/93(1) | 2.0(0.2-22)* | 1/76(1) | 2.5(0.2-27)* | 1/73(1) | 2.6(0.2-28)* |
| Moderate incontinence | 24/94(26) | 30/93(32) | 1.3(0.8-2.0) | 34/76(45) | **1.7(1.1-2.6)** | 30/73(41) | 1.5(0.97-2.3) |
| Lymphedema | 0/94(0) | 8/92(9) | **9.2(1.2-71)*** | 11/78(14) | **14(1.9-109)*** | 14/73(19) | **19(2.6-142)*** |
| Numbness thigh/labia | 3/90(3) | 69/90(77) | **23(7.5-70)** | 59/78(76) | **25(8.1-76)** | 52/73(71) | **22(7.0-66)** |
| Not sexual active lately | 41/91(45) | 37/89(42) | 0.9(0.7-1.3) | 21/78(27) | 0.6(0.4-0.9) | 21/73(29) | 0.6(0.4-1.0) |
| Little or no interest in sex | 16/90(18) | 25/90(28) | 1.6(0.9-2.7) | 20/78(26) | 1.3(0.8-2.4) | 18/73(25) | 1.4(0.8-2.5) |
| Little or no lubrication during sexual arousal | 3/80(4) | 7/69(10) | 2.7(0.7-10) | 4/65(6) | 2.0(0.5-8.2) | 9/64(14) | **3.8(1.1-13)** |
| Dry vagina during coitus[a] | 5/78(6) | 9/55(16) | 2.6(0.9-7.2) | 10/60(17) | **3.1(1.1-8.2)** | 13/55(24) | **4.6(1.7-12)** |
| Narrow or short vagina[a] | 2/77(3) | 10/55(18) | **7.0(1.6-31)** | 9/59(15) | **5.9(1.3-26)** | 14/55(25) | **9.9(2.4-42)** |
| Pain during coitus[a] | 5/78(6) | 8/55(15) | 2.3(0.8-6.6) | 11/59(19) | **3.1(1.2-8.4)** | 10/55(18) | **2.9(1.0-9.7)** |
| No orgasm during coitus[a] | 16/79(20) | 18/58(31) | 1.5(0.9-2.7) | 18/60(30) | 1.4(0.8-2.5) | 18/55(33) | 1.6(0.9-2.9) |
| No satisfaction with sex life | 4/76(5) | 8/66(12) | 2.3(0.7-7.3) | 11/62(18) | **3.3(1.1-10)** | 13/58(22) | **4.3(1.5-12)** |

Table 3. Prevalence and relative risk of micturation, defecation, lymphedema and sexual complaints after a radical hysterectomy with or without radiotherapy in a group of patients (n=94) before surgery compared to 3, 12 and 24 months after surgery. RR: relative risk; 95% CI:95% confidence interval. Bold numbers indicate significance at the 5% level. * Laplace succession rule. [a] This question was not answered when the women never had coitus.

*Changes since the operation*

We also calculated the change of all the sexual function items 24 months after the treatment (Table 4). Only the sexual activity had increased two years after the operation. All the other items deteriorated within 24 months of follow-up.

| **Change since operation (24 month) n 73** | **Better %** | **No change %** | **Worse %** |
|---|---|---|---|
| Not sexually active | 19 | 74 | 7 |
| Little or no interest | 12 | 62 | 26 |
| Little or no lubrication | 4 | 69 | 27 |
| Dry vagina during coitus | 4 | 66 | 30 |
| Narrow/short vagina | 4 | 64 | 32 |
| Pain during coitus | 8 | 66 | 26 |
| No orgasm during coitus | 11 | 63 | 26 |
| Satisfaction sex life | 8 | 55 | 37 |

Table 4. Change of all the sexual function items 24 months after the treatment (n=73).

*Premenopausal versus postmenopausal*

The ovaries were removed in 26 patients and 36 received radiotherapy. Analysis comparing premenopausal (i.e. women who stayed premenopausal and women who received HRT) versus postmenopausal women or women who became postmenopausal after the treatment, did show some differences. The absolute numbers, RR and corresponding 95% CI for all items are shown in Table 5. A significantly larger percentage of the patients who were postmenopausal before the treatment reported to be less sexually active lately and were less interested in sex compared to the women who were premenopausal. After the treatment a significantly larger percentage of the patients who were already postmenopausal before the treatment and the patients who became postmenopausal after the treatment, complained of no or less sexual activity and no or less interest in sex, up to 24 months follow-up. After 2 years follow-up only a significantly larger percentage of the patients who were postmenopausal after the treatment complained of a narrow or short vagina compared to the women who were premenopausal after the treatment. No other differences after 2 years follow-up were found.

*Patient versus control*

The absolute numbers, RR and corresponding 95% CI for all items are shown in Table 6.
After 3 and 12 months follow-up, a significantly larger percentage of patients reported diarrhoea and more problems with urge to urinate compared to women in the control group. After 2 years, the differences between the patients and controls concerning bladder dysfunction and colorectal motility disorders, were no longer statistically significant. Up to 2 years follow-up a significantly larger percentage of the patient group reported lymphedema than the control group.

| | Before surgery | | 3 Months | | 12 Months | | 24 Months | |
|---|---|---|---|---|---|---|---|---|
| **Characteristics** | **pre** | **post** | **pre** | **post** | **pre** | **post** | **pre** | **post** |
| **Often diarrhoea** | | | | | | | | |
| no./total no.(%) | 1/77(1) | 0/16(0) | 1/57(2) | 4/35(11) | 2/49(4) | 2/27(7) | 1/47(2) | 1/25(4) |
| RR pre- vs postmenopausal(95%CI) | 1.0 | 2.3(0.2-24)* | 1.0 | 6.5(0.8-56) | 1.0 | 1.8(0.3-12) | 1.0 | 1.9(0.1-29) |
| **Often constipation** | | | | | | | | |
| no./total no.(%) | 2/77(3) | 1/16(6) | 2/57(4) | 1/35(3) | 2/49(4) | 1/27(4) | 1/47(2) | 1/25(4) |
| RR pre- vs postmenopausal(95%CI) | 1.0 | 2.4(0.2-25) | 1.0 | 0.8(0.1-8.7) | 1.0 | 0.9(0.1-9.6) | 1.0 | 1.9(0.1-29) |
| **Little/no urge** | | | | | | | | |
| no./total no.(%) | 0/77(0) | 0/16(0) | 6/57(11) | 4/35(11) | 3/49(6) | 2/27(7) | 3/47(6) | 1/25(4) |
| RR pre- vs postmenopausal(95%CI) | 1.0 | 4.6(0.3-70)* | 1.0 | 1.1(0.3-3.6) | 1.0 | 1.2(0.2-6.8) | 1.0 | 0.6(0.1-5.7) |
| **Severe incontinence** | | | | | | | | |
| no./total no.(%) | 0/77(0) | 0/16(0) | 0/57(0) | 1/35(3) | 0/48(0) | 1/27(4) | 1/47(2) | 0/25(0) |
| RR pre- vs postmenopausal(95%CI) | 1.0 | 4.6(0.3-70)* | 1.0 | 3.2(0.3-34)* | 1.0 | 3.5(0.3-37)* | 1.0 | 0.9(0.1-9.7)* |
| **Moderate incontinence** | | | | | | | | |
| no./total no.(%) | 18/77(23) | 5/16(31) | 20/57(35) | 9/35(26) | 20/48(42) | 13/27(48) | 18/47(38) | 12/25(48) |
| RR pre- vs postmenopausal(95%CI) | 1.0 | 1.3(0.6-3.1) | 1.0 | 0.7(0.4-1.4) | 1.0 | 1.2(0.7-1.9) | 1.0 | 1.3(0.7-2.2) |
| **Lymphedema** | | | | | | | | |
| no./total no.(%) | 0/77(0) | 0/16(0) | 5/56(9) | 3/35(9) | 6/49(12) | 5/28(18) | 11/47(23) | 3/25(12) |
| RR pre- vs postmenopausal(95%CI) | 1.0 | 4.6(0.3-70)* | 1.0 | 1.0(0.2-3.8) | 1.0 | 1.5(0.5-4.4) | 1.0 | 0.5(0.2-1.7) |
| **Numbness thigh/labia** | | | | | | | | |
| no./total no.(%) | 2/75(3) | 1/14(7) | 43/56(77) | 26/33(79) | 39/49(80) | 20/28(71) | 33/47(70) | 18/25(72) |
| RR pre- vs postmenopausal(95%CI) | 1.0 | 2.7(0.3-28) | 1.0 | 1.0(0.8-1.3) | 1.0 | 0.9(0.7-1.2) | 1.0 | 1.0(0.8-1.4) |
| **Not sexual active lately** | | | | | | | | |
| no./total no.(%) | 29/74(40) | 12/16(75) | 14/56(25) | 23/32(72) | 7/49(14) | 14/28(50) | 8/47(17) | 12/25(48) |
| RR pre- vs postmenopausal(95%CI) | 1.0 | **1.9(1.3-2.9)** | 1.0 | **2.9(1.7-4.8)** | 1.0 | **3.5(1.6-7.6)** | 1.0 | **2.8(1.3-6.0)** |
| **Little or no interest in sex** | | | | | | | | |
| no./total no.(%) | 7/74(10) | 9/15(20) | 10/56(18) | 15/33(45) | 5/49(10) | 15/29(54) | 7/47(15) | 11/25(44) |
| RR pre- vs postmenopausal(95%CI) | 1.0 | **6.3(2.8-14)** | 1.0 | **2.6(1.3-5.0)** | 1.0 | **5.3(2.1-13)** | 1.0 | **3.0(1.3-6.7)** |
| **Little or no lubriaction during sexual arousal** | | | | | | | | |
| no./total no.(%) | 1/68(2) | 2/11(2) | 5/51(10) | 2/17(12) | 2/47(4) | 2/17(12) | 6/46(13) | 3/17(18) |
| RR pre- vs postmenopausal(95%CI) | 1.0 | **12(1.2-125)** | 1.0 | 1.2(0.3-5.6) | 1.0 | 2.8(0.4-18) | 1.0 | 1.4(0.4-4.8) |
| **Dry vagina during coitus[a]** | | | | | | | | |
| no./total no.(%) | 2/68(3) | 3/9(33) | 8/43(19) | 1/11(9) | 8/43(19) | 2/16(13) | 11/41(27) | 2/13(8) |
| RR pre- vs postmenopausal(95%CI) | 1.0 | **11(2.2-59)** | 1.0 | 0.5(0.1-3.5) | 1.0 | 0.7(0.2-2.8) | 1.0 | 0.6(0.2-2.3) |
| **Narrow or short vagina[a]** | | | | | | | | |
| no./total no.(%) | 1/68(2) | 1/8(13) | 7/43(16) | 3/11(27) | 6/43(14) | 3/15(20) | 6/41(15) | 7/13(54) |
| RR pre- vs postmenopausal(95%CI) | 1.0 | 8.5(0.6-123) | 1.0 | 1.7(0.5-5.5) | 1.0 | 1.4(0.4-5.0) | 1.0 | **3.4(1.4-8.5)** |
| **Pain during coitus[a]** | | | | | | | | |
| no./total no.(%) | 4/68(6) | 1/9(11) | 6/43(14) | 2/11(18) | 7/43(16) | 4/15(27) | 7/41(17) | 3/13(23) |
| RR pre- vs postmenopausal(95%CI) | 1.0 | 1.9(0.2-15) | 1.0 | 1.3(0.3-5.6) | 1.0 | 1.6(0.6-4.8) | 1.0 | 1.4(0.4-4.5) |
| **No orgasm during coitus[a]** | | | | | | | | |
| no./total no.(%) | 11/68(16) | 5/10(50) | 13/44(30) | 5/13(39) | 9/43(21) | 8/16(50) | 11/41(27) | 6/13(46) |
| RR pre- vs postmenopausal(95%CI) | 1.0 | **3.1(1.4-7.0)** | 1.0 | 1.3(0.6-3.0) | 1.0 | 2.4(1.1-5.1) | 1.0 | 1.7(0.8-3.7) |
| **Not content with sex life** | | | | | | | | |
| no./total no.(%) | 2/68(3) | 2/7(29) | 3/48(6) | 5/17(29) | 7/46(15) | 4/15(27) | 10/43(23) | 3/14(21) |
| RR pre- vs postmenopausal(95%CI) | 1.0 | **9.7(1.6-58)** | 1.0 | **4.7(1.3-18)** | 1.0 | 1.8(0.6-5.2) | 1.0 | 0.9(0.3-2.9) |

Table 5. Age adjusted relative risks of colorectal motility disorders, bladder dysfunction, lymphedema and sexual dysfunction. Premenopausal (n=77) versus postmenopausal (n=16). RR: relative risk; 95% CI:95% confidence interval. Bold numbers indicate significance at the 5% level. * Laplace succession rule. [a] This question was not answered when the women never had coitus. Pre, premenopausal; post, postmenopausal.

| No/total no.responding (%) | | Before surgery | | 3 Months | | 12 Months | | 24 Months | |
|---|---|---|---|---|---|---|---|---|---|
| **Characteristics** | **Control** | **Patient** | **RR(95%CI)** | **Patient** | **RR(95%CI)** | **Patient** | **RR(95%CI)** | **Patient** | **RR(95%CI)** |
| Often diarrhoea | 2/223(1) | 1/94(1) | 1.2(0.1-13) | 5/93(5) | **6.0(1.2-30)** | 4/77(5) | **5.8(1.1-31)** | 2/73(3) | 3.1(0.4-21) |
| Often constipation | 5/223(2) | 3/94(3) | 1.4(0.4-5.8) | 3/93(3) | 1.4(0.4-5.9) | 4/77(5) | 2.3(0.6-84) | 3/73(4) | 1.8(0.5-7.5) |
| Little/no urge | 4/223(2) | 0/93(0) | 0.5(0.1-4.0)* | 10/93(11) | **6.0(1.9-19)** | 5/77(7) | **3.6(1.0-13)** | 4/73(6) | 3.1(0.8-12) |
| Severe incontinence | 0/224(0) | 0/94(0) | 2.4(0.2-37)* | 1/93(1) | 4.8(0.4-52)* | 1/76(1) | 5.8(0.5-64)* | 1/73(1) | 6.2(0.6-67)* |
| Moderate incontinence | 75/224(33) | 24/94(26) | 0.8(0.5-1.1) | 30/93(32) | 1.0(0.7-1.4) | 34/76(45) | 1.3(0.98-1.8) | 30/73(41) | 1.2(0.9-1.7) |
| Lymphedema | 7/224(3) | 0/94(0) | 0.3(0.0-2.3)* | 8/92(9) | **2.8(1.0-7.5)** | 11/78(14) | **4.5(1.8-11)** | 14/73(19) | **6.1(2.6-15)** |
| Numbness thigh/labia | 2/223(1) | 3/90(3) | 3.7(0.6-22) | 69/90(77) | **86(21-341)** | 59/78(76) | **84(21-337)** | 52/73(71) | **79(20-318)** |
| Not sexual active lately | 37/224(17) | 41/91(45) | **2.7(1.9-4.0)** | 37/89(42) | **2.5(1.7-3.7)** | 21/78(27) | **1.6(1.0-2.6)** | 21/73(29) | **1.7(1.1-2.8)** |
| Little or no interest in sex | 16/222(7) | 16/90(18) | **2.5(1.3-4.7)** | 25/90(28) | **3.9(2.2-6.9)** | 20/78(26) | **3.6(1.9-6.5)** | 18/73(25) | **3.4(1.8-6.4)** |
| Little or no lubrication during sexual arousal | 6/213(3) | 3/80(4) | 1.3(0.3-5.2) | 7/69(10) | **3.6(1.3-10)** | 4/65(6) | 2.2(0.6-7.5) | 9/64(14) | **5.0(1.9-14)** |
| Dry vagina during coitus[a] | 8/195(4) | 5/78(6) | 1.6(0.5-4.6) | 9/55(16) | **4.0(1.6-10)** | 10/60(17) | **4.1(1.7-9.8)** | 13/55(24) | **5.8(2.5-13)** |
| Narrow or short vagina[a] | 4/196(2) | 2/77(3) | 1.3(0.2-6.8) | 10/55(18) | **8.9(2.9-27)** | 9/59(15) | **7.5(2.4-23)** | 14/55(25) | **13(4.3-36)** |
| Pain during coitus[a] | 3/196(2) | 5/78(6) | **4.2(1.0-17)** | 8/55(15) | **9.5(2.6-35)** | 11/59(19) | **12(3.5-42)** | 10/55(18) | **12(3.4-42)** |
| No orgasm during coitus[a] | 41/196(21) | 16/79(20) | 1.0(0.6-1.6) | 18/58(31) | 1.5(0.9-2.4) | 18/60(30) | 1.4(0.9-2.3) | 18/55(33) | 1.6(0.98-2.5) |
| No satisfaction with sex life | 6/202(3) | 4/76(5) | 1.8(0.5-6.1) | 8/66(12) | **4.1(1.5-11)** | 11/62(18) | **6.0(2.3-15)** | 13/58(22) | **7.6(3.0-19)** |

Table 6. Prevalence and relative risk of micturation, defecation, lymphedema and sexual complaints after a RHL with or without radiotherapy in a group of patients (n=94) compared to age matched control women from the general population (=224), 3, 12 and 24 months after surgery. RR: relative risk; 95% CI:95% confidence interval. Bold numbers indicate significance at the 5% level. * Laplace succession rule. [a] This question was not answered when the women never had coitus.

Before the operation, a significantly larger percentage of the patients reported to be not sexually active lately, to have little or no interest in sex, and having more pain during coitus compared to the control group. Throughout the 2 years follow-up, this statistical significance persisted. Little or no lubrication during sexual arousal was reported by a significantly larger percentage of the patients after 3 and 24 months. A dry vagina during coitus, a narrow or short vagina and numb areas around the labia all significantly increased throughout the first 2 years after the treatment. The percentage of patients who complained of no orgasm during coitus was never statistically significant. A significantly larger percentage of the patients reported dissatisfaction with their sex life compared to the controls up to 2 years of follow-up.

*Radiotherapy versus no radiotherapy*

We compared the patients with adjuvant pelvic radiotherapy to the patients without adjuvant pelvic radiotherapy. Thirty-six of the 94 patients received adjuvant radiotherapy after surgery. The absolute numbers, RR and corresponding 95% CI for all items are shown in Table 7.

When compared to surgery alone, the patients with adjuvant pelvic radiotherapy were not more often significantly associated with bladder dysfunction, colorectal motility dysfunction or lymphedema. Only

| | Before surgery | | 3 Months | | 12 Months | | 24 Months | |
|---|---|---|---|---|---|---|---|---|
| **Characteristics** | **no RT** | **RT** | **no RT** | **RT** | **no RT** | **RT** | **no RT** | **RT** |
| **Often diarrhoea** | | | | | | | | |
| no./total no.(%) | 1/58(2) | 0/36(0) | 0/58(0) | 5/35(14) | 1/48(2) | 3/29(10) | 0/47(0) | 2/26(8) |
| RR RT vs surgery alone(95%CI) | 1.0 | 0.8(0.1-8.5)* | 1.0 | **10(1.3-80)*** | 1.0 | 5.0(0.5-46) | 1.0 | 5.3(0.6-49)* |
| **Often constipation** | | | | | | | | |
| no./total no.(%) | 0/58(0) | 3/36(8) | 2/58(3) | 1/35(3) | 2/48(4) | 2/29(7) | 3/47(6) | 0/26(0) |
| RR RT vs surgery alone(95%CI) | 1.0 | 6.4(0.7-55)* | 1.0 | 0.8(0.1-8.8) | 1.0 | 1.7(0.3-11) | 1.0 | 0.4(0.1-3.8)* |
| **Little/no urge** | | | | | | | | |
| no./total no.(%) | 0/57(0) | 0/36(0) | 5/58(9) | 5/35(14) | 1/49(2) | 4/28(14) | 1/47(2) | 3/26(12) |
| RR RT vs surgery alone(95%CI) | 1.0 | 1.6(0.1-24)* | 1.0 | 1.7(0.5-5.3) | 1.0 | 7.0(0.8-60) | 1.0 | 5.4(0.6-50) |
| **Severe incontinence** | | | | | | | | |
| no./total no.(%) | 0/58(0) | 0/36(0) | 0/58(0) | 1/35(3) | 0/49(0) | 1/27(4) | 0/47(0) | 1/26(4) |
| RR RT vs surgery alone(95%CI) | 1.0 | 1.6(0.1-25)* | 1.0 | 2.3(0.3-35)* | 1.0 | 3.6(0.3-38)* | 1.0 | 3.6(0.3-37)* |
| **Moderate incontinence** | | | | | | | | |
| no./total no.(%) | 11/58(19) | 13/36(36) | 20/58(35) | 10/35(29) | 18/49(37) | 16/27(59) | 18/47(38) | 12/26(46) |
| RR RT vs surgery alone(95%CI) | 1.0 | 1.9(0.96-3.8) | 1.0 | 0.8(0.4-1.6) | 1.0 | **1.6(1.0-2.6)** | 1.0 | 1.2(0.7-2.1) |
| **Lymphedema** | | | | | | | | |
| no./total no.(%) | 0/58(0) | 0/36(0) | 4/57(7) | 4/35(11) | 4/49(8) | 7/29(24) | 8/47(17) | 6/26(23) |
| RR RT vs surgery alone(95%CI) | 1.0 | 1.6(0.1-25)* | 1.0 | 1.6(0.4-6.1) | 1.0 | 3.0(0.95-9.2) | 1.0 | 1.4(0.5-3.5) |
| **Numbness thigh/labia** | | | | | | | | |
| no./total no.(%) | 1/56(2) | 2/34(6) | 48/57(84) | 21/33(64) | 39/49(80) | 20/29(69) | 36/47(77) | 16/26(62) |
| RR RT vs surgery alone(95%CI) | 1.0 | 3.2(0.3-35) | 1.0 | 0.8(0.6-1.0) | 1.0 | 0.9(0.7-1.2) | 1.0 | 0.8(0.6-1.1) |
| **Not sexual active lately** | | | | | | | | |
| no./total no.(%) | 25/56(45) | 16/35(46) | 18/57(32) | 19/32(59) | 11/49(22) | 10/29(35) | 10/47(21) | 11/26(42) |
| RR RT vs surgery alone(95%CI) | 1.0 | 1.0(0.6-1.6) | 1.0 | **1.9(1.2-3.0)** | 1.0 | 1.5(0.8-3.2) | 1.0 | 2.0(0.98-4.0) |
| **Little or no interest in sex** | | | | | | | | |
| no./total no.(%) | 7/56(13) | 9/34(27) | 14/57(25) | 11/33(33) | 10/49(20) | 10/29(35) | 9/47(19) | 9/26(35) |
| RR RT vs surgery alone(95%CI) | 1.0 | 2.1(0.9-5.2) | 1.0 | 1.4(0.7-2.6) | 1.0 | 1.7(0.8-3.6) | 1.0 | 1.8(0.8-4.0) |
| **Little or no lubriaction during sexual arousal** | | | | | | | | |
| no./total no.(%) | 1/51(2) | 2/29(7) | 4/48(8) | 3/21(14) | 2/44(5) | 2/21(10) | 6/43(14) | 3/21(14) |
| RR RT vs surgery alone(95%CI) | 1.0 | 3.5(0.3-37) | 1.0 | 1.7(0.4-7.0) | 1.0 | 2.1(0.3-14) | 1.0 | 1.0(0.3-3.7) |
| **Dry vagina during coitus[a]** | | | | | | | | |
| no./total no.(%) | 3/50(6) | 2/28(7) | 7/41(17) | 2/14(14) | 5/40(13) | 5/20(25) | 9/38(24) | 4/17(24) |
| RR RT vs surgery alone(95%CI) | 1.0 | 1.2(0.2-6.7) | 1.0 | 0.8(0.2-3.6) | 1.0 | 2.0(0.7-6.1) | 1.0 | 0.1(0.4-2.8) |
| **Narrow or short vagina[a]** | | | | | | | | |
| no./total no.(%) | 2/49(4) | 0/28(0) | 5/41(12) | 5/14(36) | 5/40(13) | 4/19(21) | 7/38(18) | 7/17(41) |
| RR RT vs surgery alone(95%CI) | 1.0 | 0.6(0.1-5.3)* | 1.0 | 2.9(0.99-8.6) | 1.0 | 1.7(0.5-5.6) | 1.0 | 2.2(0.93-5.4) |
| **Pain during coitus[a]** | | | | | | | | |
| no./total no.(%) | 4/50(8) | 1/28(4) | 6/41(15) | 2/14(14) | 6/40(15) | 5/19(26) | 6/38(16) | 4/17(24) |
| RR RT vs surgery alone(95%CI) | 1.0 | 0.5(0.1-3.8) | 1.0 | 1.0(0.2-4.3) | 1.0 | 1.8(0.7-5.0) | 1.0 | 1.5(0.5-4.6) |
| **No orgasm during coitus[a]** | | | | | | | | |
| no./total no.(%) | 8/50(16) | 8/29(28) | 12/42(29) | 6/16(38) | 11/40(28) | 7/20(35) | 12/38(32) | 6/17(35) |
| RR RT vs surgery alone(95%CI) | 1.0 | 1.7(0.7-4.1) | 1.0 | 1.3(0.6-2.9) | 1.0 | 1.3(0.6-2.8) | 1.0 | 1.1(0.5-2.5) |
| **Not content with sex life** | | | | | | | | |
| no./total no.(%) | 3/51(6) | 1/25(4) | 3/44(7) | 5/22(23) | 8/42(19) | 3/20(15) | 11/41(27) | 2/17(12) |
| RR RT vs surgery alone(95%CI) | 1.0 | 0.7(0.1-6.2) | 1.0 | 3.3(0.9-13) | 1.0 | 0.8(0.2-2.7) | 1.0 | 0.4(0.1-1.8) |

Table 7. Age adjusted relative risks of colorectal motility disorders, bladder dysfunction, lymphedema and sexual dysfunction. Radiotherapy (n=36) versus no radiotherapy (n=58). RR: relative risk; 95% CI:95% confidence interval. Bold numbers indicate significance at the 5% level. *Laplace succession rule. [a] This question was not answered when the women never had coitus. RT, radiotherapy.

at 3 months follow-up, a significantly larger percentage of patients with adjuvant pelvic radiotherapy experienced more often diarrhoea and at 12 months follow-up moderate urine incontinence (Table 7).

After 3 months a significantly larger percentage of patients with adjuvant pelvic radiotherapy were less sexually active lately compared to the patients without adjuvant radiotherapy. No significant differences in the percentages were found between the two patient groups for numb areas around the labia, dry vagina, pain during coitus, narrow vagina, little or no lubrication, sexual activity, interest in sex, satisfaction with sex life, and orgasm (Table 7).

## Discussion

The current study shows that treatment for cervical cancer stage I-IIa by RHL with or without adjuvant pelvic radiotherapy has a negative effect on sexual function. The difference in sexual function was not only significant compared to the controls but also compared to the sexual situation before the treatment. The changes or problems included less lubrication, a narrow and short vagina, numb areas around the labia, dyspareunia and sexual dissatisfaction. Furthermore, in the long term no differences were observed for bladder and colorectal dysfunction.

Retrospective studies of frequency of late postoperative micturition and colorectal problems show various figures: incontinence in 10-12%, urinary retention or inability to void in 2-4% and severe constipation in 5-10% (6;10;26;27). After 2 years follow-up, we found no significant difference anymore concerning bladder dysfunction and colorectal dysfunction compared to the control group and compared to the situation before surgery. Contrary to these findings, Sood et al.(31), for example, have shown that anorectal manometry revealed significant changes in colorectal function after RHL, showing a pattern which correlates to a partial denervation of the bowel (31). Furthermore, results of urodynamic studies evaluating urinary dysfunction in patients after RHL are suggestive for disruption of the autonomic nerve supply to the bladder and urethra (8;9). The fact that the patients in our study did not report a significant difference in bladder and colorectal functions 24 months after the operation compared with the situation before the operation might be a reflection of post-surgical recovery or an indication that the perception of quality of life may be independent of there objective measures. The relief resulting from the completion of this potentially curative treatment may also have contributed to the subjective improvement despite changes in bowel and bladder function. And finally, most studies of colorectal and micturial dysfunction offer data collected from the medical files (6;10;26;27). This study used questionnaires and has a longitudinal design what makes it more difficult to compare with the literature.

In the literature, secondary lymphedema after RHL is reported up to 23% (28;29). We found percentages of up to 19%. As well as compared to the control group as compared to the situation before the operation, a significantly larger percentage of the patients complained of lymphedema up to 24 months of follow-up.

As to the short-term effects of RHL on sexual function, Grumann et al. (21) assessed in a study of 20 women with early stage cervical carcinoma the effects of RHL on the sexual function up to 8 months. They found that women with cancer had vaginal dryness 4 and 8 months after the operation and reduced sexual activity. Modest but consistent downward trends regarding sexual activity, sexual desire, excitement, orgasm, and resolution were found 4 and 8 months after surgery, although these last items were not statistically significant (21). Jensen et al. also found short-term adverse effects on sexual function: dyspareunia, short vagina and sexual dissatisfaction (5). In line with these results, we also found that during the first months after the operation women with early stage cervical cancer have sexual dysfunction.

Concerning the long-term effects, Butler-Manual found in a retrospective survey of women who had undergone RHL with or without radiotherapy a significant increase of vaginal dryness during sexual activity and dissatisfaction with their sexlife (16). In their cross-sectional study, Bergmark et al. compared 256 women with a history of early stage cervical cancer with 350 controls using validated questionnaires. They found that the patients had decreased lubrication, genital swelling during arousal, and a short vagina during intercourse (3). The long-term effects that Jensen et al. reported were complaints that persisted after 2 years and included less vaginal lubrication and sexual interest (5). We also find these long-term effects on sexual function. The short term effects described above by Jensen et al., still persisted after 2 years follow-up in the current study. In agreement with these authors it can be concluded that up to 2 years after the RHL, women with early stage cervical cancer experience negative effects on sexual function.

In the current study, 38% received radiotherapy after the operation. A significantly larger percentage of patients with adjuvant radiotherapy were less sexually active and had more diarrhoea after 3 months follow-up. At 12 months follow-up, a significantly larger percentage of patients with adjuvant radiotherapy had moderate incontinence. But adjuvant radiotherapy did not increase the risk of bladder dysfunction, colorectal motility disorders, lymphedema and other sexual functions after 2 years follow-up.

One would expect that hormonal status particularly influences the sexual functioning, because castration lowers serum testosterone and estrogens concentrations (3). In line with this, the current study showed that up to 2 years follow-up women who were postmenopausal or became postmenopausal had less libido and were less sexually active compared to the women who were premenopausal. However, Bergmark et al. suggested that ovarian hormones have minor effects on libido or the frequencies of sexual intercourse (3). In the current study, a significantly larger percentage of the patients who were postmenopausal after the treatment reported a narrow or short vagina after 2 years follow-up. Most patients who became postmenopausal after the treatment had received adjuvant radiotherapy. Although adjuvant radiotherapy did not show an increase risk on sexual function, a short or narrow vagina is an effect of the adjuvant radiotherapy and not due to hormonal changes directly (20). This could explain the difference that a significantly larger percentage of the patients who were postmeno-

pausal after the treatment reported a narrow or short vagina compared to the premenopausal patients. Other significant differences were not found. We suggest that the hormonal status has less effect on complaints as pain during coitus, less lubrication and orgasm.

Autonomic nerve damage during surgery is thought to play a crucial role in the aetiology of bladder dysfunction, colorectal motility disorders and sexual dysfunction that can be seen after RHL. The autonomic nerves are essential for a normal physiologic function and neurogenic control of the pelvic organs (11;22;26;27;30-32). The autonomic nerves for example, supply the blood vessels of the internal genitalia and are involved in the neural control of vasocongestion and, consequently, lubrication swelling response (32). Evidence from surgical practice has shown that a lesser extent of surgically inflicted autonomic nerve injury lowers the incidence of morbidity (33-36).

In our centre, we used photoplethysmographic assessment of vaginal pulse amplitude to measure objectively the vaginal blood flow during sexual arousal (30;37). Increased vaginal blood flow during sexual arousal reflects a highly automatized genital response mechanism, occurring irrespectively of subjective appreciation of the sexual stimulus (38;39). From this study, it was concluded that a RHL seems to be associated with a disturbed vaginal blood flow response during sexual arousal caused by denervation of the vagina (40).

The surgical concept of the identification and preservation of the pelvic autonomic nerves was introduced by Japanese gynaecologists in the sixties (36). Recently, the Leiden Medical Centre developed a nerve-sparing technique that is described elsewhere (11). This technique was not yet utilized in the present study and the benefit of this procedure will be studied in a multicentre prospective trial in order to establish the results of nerve-sparing surgery and the effects on sexual functioning.

The current study did show sexual dysfunction after treatment for low stage cervical carcinoma. It is the first longitudinal study of self-reported bladder, defecation, sexual and vaginal problems with a baseline score before the RHL. We compared the morbidity after treatment with the situation before treatment and the normal population. As could be expected, before the operation a significantly larger percentage of the patients reported not to be sexually active, have little or no interest in sex and have more pain during coitus, compared to the healthy controls. Probably this has to do with their disease status itself or with the psychological impact of the illness. Psychological function and quality of life status effect sexual function in women (41). Future research on the effect of RHL should therefore include self-report measures of sexual functioning as well as of depression, anxiety and quality of life issues including relationship parameters. The control group consisted of employees from the hospitals and relatives and friends of these employees, who had not undergone a hysterectomy in the past. Although the control group was not an a-select sample of the Dutch general population, the control group was matched for age, as this is related to sexual function (41). We used the Gynaecologic Leiden Questionnaire, which is the first developed Dutch questionnaire consisting of the items for sexual dysfunction, voiding- and bowel problems for women with cancer.

This study has an observational design. Despite this, we conclude that RHL for the treatment of early stage cervical carcinoma is associated with adverse effects mainly on sexual functioning. Adjuvant radiotherapy after RHL seemed not to be a major factor contributing to the complaints, in the present study. Whether or not the nerve sparing technique will lead to lower morbidity with comparable treatment results will have to be established.

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Chapter 7

# Vaginal blood flow after radical hysterectomy with and without nerve-sparing. A preliminary report.

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*Int J Gynecol Cancer 2007; in press*

## Abstract

**Objective:** Radical hysterectomy with pelvic lymphadenectomy (RHL) for cervical cancer causes damage to the autonomic nerves which are responsible for increased vaginal blood flow during sexual arousal. The aim of the study of which we now report preliminary data was to determine whether a nerve-sparing technique leads to an objectively less disturbed vaginal blood flow response during sexual stimulation.

**Methods:** Photoplethysmographic assessment of vaginal pulse amplitude (VPA) during sexual stimulation by erotic films was performed. Subjective sexual arousal was assessed after each stimulus. Thirteen women after conventional RHL, 10 women after nerve-sparing RHL and 14 healthy premenopausal women participated. Data were collected between January and August 2006. The main outcome measure was the logarithmically transformed mean VPA. To detect statistically significant differences in mean VPA levels between the three groups, a univariate analysis of variance was used.

**Results:** Mean VPA differed between the three groups ($p = 0.014$). The conventional group had a lower vaginal blood flow response than the control group ($p = 0.016$), which tended also to be lower than that of the nerve-sparing group ($p = 0.097$). These differences were critically dependent on baseline vaginal blood flow differences between the groups. The conventional group follows a vaginal blood flow pattern similar to postmenopausal women.

**Conclusions:** Conventional RHL is associated with an overall disturbed vaginal blood flow response compared to healthy controls. Since it is not observed to the same extent after nerve-sparing RHL, it seems that the nerve-sparing technique leads to a better overall vaginal blood flow caused by less denervation of the vagina.

## Introduction

Women with a history of radical hysterectomy with pelvic lymphadenectomy for cervical cancer (RHL) report a decrease in sexual interest, vaginal lubrication and genital swelling, which compromises sexual activity and results in considerable distress (1-4). Surgical damage to the pelvic autonomic nerves is responsible for a considerable part of the morbidity following radical hysterectomy (5-7). During radical hysterectomy the nerve supply to the blood vessels of the vaginal wall that is responsible for the neural control of the lubrication response is disrupted (1;4;5;8).

Psychophysiological assessment using photoplethysmographic vaginal pulse amplitude has been proven to be reliable in assessing the increase in vaginal blood flow during sexual arousal (9-11). The increased vaginal blood flow reflects a highly automated genital response mechanism, occurring irrespectively of subjective appreciation of the sexual stimulus (12;13). The genital physiological response is an involuntary reflex mediated by the (unconscious) autonomic nervous system (14;15). Maas et al. performed a study in which vaginal pulse amplitude during sexual stimulation by erotic films was assessed in women with a history of conventional RHL, women with a history of simple abdominal hysterectomy and in age-matched healthy controls. The results of the study indicated that conventional RHL is associated with a disturbed vaginal blood flow response during sexual arousal. The disturbed response could not be explained solely by uterus extirpation, since it was not observed to the same extent after simple hysterectomy. The difference in outcome might be related to a more extended denervation of the vagina with increasing radicality of surgery (10). A surgical technique in which the autonomic nerves are identified and subsequently preserved during surgery was developed at the Leiden University Medical Centre (LUMC) (6). The technique involved three steps: first, the identification and preservation of the hypogastric nerve in a loose tissue sheath underneath the ureter and lateral to the sacrouterine ligaments; second, the inferior hypogastric plexus in the parametrium is lateralized and avoided during parametrial transsection; third, the most distal part of the inferior hypogastric plexus is preserved during the dissection of the posterior part of the vesico-uterine ligament.

The aim of the study of which we now report preliminary data was to determine whether the nerve-sparing technique indeed leads to an objectively less disturbed vaginal blood flow response during sexual stimulation. Genital arousal was assessed by a photoplethysmograph, during sexual stimulation by erotic film in women with a history of a conventional RHL, in women with a history of a nerve-sparing RHL and in healthy premenopausal women. Subjective sexual arousal was assessed after each stimulus and self-report questionnaires were used to assess sexual functioning.

## Patients and Methods

*Study group*

Since 2000 we perform the nerve-sparing modification of the RHL. Patients were recruited by reviewing medical files, collected prospectively in a database, of 156 women who had consecutively undergone a conventional RHL and 70 women who had undergone a nerve-sparing RHL for the treatment of cervical cancer stage I-IIa at the LUMC. In all cases a RHL type III was performed (16). None of the patients had participated in the study of Maas et al. (10). All patients in the study were treated by the same team of gynaecologic oncologists. Surgery had to have been at least one year before entry in the current study. Exclusion criteria for the current study were: a history of adjuvant radiotherapy or chemotherapy or signs of recurrent or metastatic cervical cancer; a history of bilateral oophorectomy; other perineal or abdominal surgery; post- or perimenopausal status. The hormonal status of the patients was assessed through history-taking evaluating vasomotor symptoms, hormonal cycles and age. If there was any doubt, the patient was classified as postmenopausal. Twenty three out of 156 (15%) patients in the conventional RHL group participated. Ten of these 23 patients were postmenopausal and were excluded from the analysis. Participation was refused for various reasons: no interest because of a lack of sexual problems (30), lack of time (26), intrusive nature of the experiment (36), or no reason given (41).
In the nerve-sparing RHL group, 11 out of 70 (16%) patients participated. One of the 11 patients was postmenopausal and was excluded from the analysis. Participation was refused for similar reasons: no interest because of a lack of sexual problems (6), lack of time (10), intrusive nature of the experiment (18), or no reason given (25).
Premenopausal women without sexual problems and without a history of abdominal or pelvic surgery or radiotherapy/ chemotherapy were recruited from the general population. Women contacted the investigators after reading an advertisement in a local paper. The exclusion criteria were checked through a semi structured clinical interview. None of the 14 recruited healthy controls had ever participated in research on sexual arousal.

*Material and Response Measurements*

All the interviews and experiments were carried out by one female doctor (Q.D.P). The assessor was not blinded for patients operation. Informed consent was obtained. All women received travelling expenses. The study was approved by the local Medical Ethics Committee.
Stimulus material identical to the study of Maas et al.(10) was used; all the subjects were exposed to an experimental session, that contained two 5 minutes neutral stimuli (during which a non-erotic documentary film excerpt was shown), and two erotic 5.5 minutes stimuli (erotic films depicting cunnilingus and intercourse). The erotic film excerpts were taken from so-called women-made, female-initiated, and female-centred erotic film (12).

*Genital sexual arousal*

The physiological evaluation of the genital response was carried out using vaginal photoplethysmography. The plethysmograph is a menstrual tampon-sized device containing a
light-emitting diode and a phototransistor to detect light. The light source illuminates the capillary bed of the vaginal wall and the phototransistor responds to light reflected by the vaginal wall and the blood circulating within it. When the signal is connected to an alternating current (AC) amplifier, vaginal pulse amplitude (VPA) is measured, which reflects the phasic
changes in vaginal engorgement accompanying each heart beat, with larger amplitudes reflecting higher levels of vaginal blood flow. Vaginal pulse amplitude (VPA) is currently the most sensitive, specific, and reliable measure of vaginal vasocongestion (9) and is used in earlier /other studies (17;18) on sexual function in women with neurological damage

*Subjective sexual arousal*

Subjective sexual arousal was assessed through self-reported ratings of sexual arousal that were collected after the two neutral stimuli and the two erotic stimuli. Subjects were asked to assess on a seven-point Likert scale (19) their feeling of sexual arousal. Each point of the Likert scale was described by a verbal label: 1 representing "not sexually aroused at all" to 7 "very strongly sexually aroused".

*Assessment of sexual and psychological functioning*

*The Gyneacologic Leiden Questionnaire* (LQ) is a 21 item measure, which is the first Dutch list consisting of items for sexual function, voiding- and bowel problems for women with cancer. This questionnaire is currently being validated. This self-report questionnaire is validated in a Dutch population of patients with early stage cervical cancer (20).
The Dutch version of the *Female Sexual Function Index* (FSFI) (21;22) is a 19 items self-report measure of female sexual function that assess sexual desire, arousal, lubrication, orgasm, satisfaction and pain. The total FSFI score is an indication for sexual function.
The Dutch version of the *Hospital Anxiety and Depression Scale* (HADS) is a 14 items self-report measure to assess anxiety (7 items) and depression (7 items) (23;24), was used to assess the level of anxiety and depression.
The *European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30* (EORTC QLQ-C30) Dutch version 3.0 (25) is a 30 items self-report measure for assessing health-related quality of life of cancer patients. Only the global health status / quality of life scale (two items), was used for the current study.
The questionnaires were completed before the experiment.

*Data reduction and analysis*

The VPA was continuously recorded. VPA was sampled at 20 Hz across baseline and subsequent trials. A two-pass algorithm for automatic artefact removal (Molenkamp Technical Support Group, University of Amsterdam) was used to analyse the VPA data. After artefact deletion peak-to-trough amplitude was calculated for each remaining pulse and averaged over 60 second epochs.
Statistical calculations were performed with SPSS for Windows version 12. Prior to analysis, all dependent variables were examined for fit between their distributions and the assumptions of univariate analyses. To reduce the positive skew ness of the VPA data, all VPA data were logarithmically transformed (log10). For each stimulus (two neutral stimuli and two erotic stimuli), a log10 VPA mean score was calculated by averaging all epochs of the specific stimulus. To analyse differences in the log10 VPA scores between three groups for the four stimuli, the log10 VPA mean scores were submitted to 3 (group) x 4 (stimulus) repeated measures ANOVA. Furthermore, to control for baseline differences, the log10 VPA mean scores were also submitted to 3 (group) x 3(stimulus) repeated measures ANCOVA, using each individual's log10 mean baseline score of the first neutral stimulus as covariate. Following significant F ratios for each dependent measure, univariate post hoc analyses (multiple comparisons between all pairs of possible means) were performed to test specific stimulus effects. To analyse differences in the subjective sexual arousal between the three groups for the four stimuli, the mean subjective arousal scores were submitted to 3 (group) x 4 (stimulus) repeated measures ANOVA. To assess differences in subject's characteristics and dependent variables between the three groups, one-way analyses of variance or chi-square tests were used.
We were interested in a difference between the group of women with a nerve-sparing RHL and the group of women with a conventional RHL with a large size effect of at least $d$=0.8.
With an alpha value of 0.05, a power of 80% and an effect size of $d$=0.8, a number of minimal 26 women for each group is needed (26). We did not succeed to recruit this number of subjects for each group and it will take at least 3 years to collect enough subjects for this experiment. The results of the completed study will be reported later. In this preliminary report, with an alpha value of 0.05 and with the smallest number of ten patients in the nerve-sparing group and 13 patients in the conventional group, the power was 39 % to detect a difference with a large effect size between the two groups. Statistical significance was assigned at a level of $p<0.05$.

## Results

*Differences in biographical, medical status and psychological variables*

Table 1 shows characteristics and outcome of the questionnaires of the 37 women included. None of the women used hormone replacement therapy. The women in the nerve-sparing RHL group were younger than the women in the conventional RHL and control group. In the conventional RHL group

| Characteristics/ Questionnaires | Controls (n=14) | Conventional RHL (n=13) | Nerve-sparing RHL (n=10) | *F*/Chi-Square* | *p*-value |
|---|---|---|---|---|---|
| Age (y) | 46.9±5.9 | 46.7±5.5 | 40.1±6.3 | *F*=4.78 | 0.015 |
| **Operation-experiment(m)** | - | 107.7±41.1 | 25.6±18.4 | *F*=34.28 | 0.000 |
| **Gynaecologic LQ** | | | | | |
| **Marital status** | | | | | |
| With partner | 8(57) | 10(77) | 7(70) | $\chi^2$=1.24 | 0.538 |
| Without partner | 6(43) | 3(23) | 3(30) | | |
| **Bladder dysfunction** | | | | | |
| Incontinence complaints | 6(43) | 5(42) | 6(60) | $\chi^2$=0.91 | 0.634 |
| **Bowel dysfunction** | | | | | |
| Constipation complaints | 0 | 7(45) | 5(50) | $\chi^2$=10.85 | 0.004 |
| **Sexual dysfunction** | | | | | |
| Not sexually active | 4(29) | 4(31) | 3(30) | $\chi^2$=0.02 | 0.992 |
| **FSFI** | | | | | |
| Desire | 5.8±0.7 | 6.1±1.9 | 4.9±1.9 | *F*=1.21 | 0.318 |
| Arousal | 15.8±1.4 | 12.5±6.2 | 10.7±6.0 | *F*=2.02 | 0.156 |
| Lubrication | 17.3±3.2 | 17.1±6.2 | 14.9±7.5 | *F*=0.40 | 0.676 |
| Orgasm | 12.8±2.1 | 10.8±5.2 | 9.6±5.6 | *F*=0.93 | 0.409 |
| Satisfaction | 12.9±1.5 | 9.5±4.5 | 9.3±4.5 | *F*=2.23 | 0.131 |
| Pain | 12.6±3.9 | 11.7±6.2 | 11.6±5.6 | *F*=0.09 | 0.914 |
| Total FSFI | 77.1±5.7 | 67.7±24.8 | 60.9±29.1 | *F*=1.03 | 0.375 |
| **HADS** | | | | | |
| Anxiety | 7.3±1.8 | 6.6±3.2 | 9.6±7.1 | *F*=1.00 | 0.386 |
| Depression | 6.4±1.8 | 8.3±4.5 | 8.9±5.2 | *F*=0.81 | 0.456 |
| **EORTC QLQ-C30** | | | | | |
| Global health status | 6.4±0.7 | 5.2±1.2 | 5.1±1.2 | *F*=6.49 | 0.004 |

Tabel 1. Patients characteristics and outcome of the questionnaires. SD, standard deviation; RHL, radical hysterectomy with pelvic lymphadenectomy; y, years; m, months; LQ, Leiden Questionnaire; FSFI, Female Sexual Function Index (A higher score means a better sexual function); HADS, Hospital Anxiety and Depression Scale (A higher score means more complaints of anxiety or depression). EORTC QLQ-C30, The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (A higher score means a better global health status) *Observed two-tailed significance. Statistical significance at a level of p< 0.05. Data are presented as mean ± SD or n (%), unless otherwise indicated.

the time-interval between the operation and the experiment was three times as long as that of the nerve-sparing RHL group. Constipation complaints were more frequently reported by the conventional RHL and nerve-sparing RHL group compared to the controls. No differences were found for sexual and bladder dysfunction.

*Differences in genital arousal*

Figure 1 shows VPA responses in the three subjects groups throughout the whole experimental session. The VPA mean scores differed between the three groups ($F(2, 34) = 4.84$, $p = 0.014$); the conventional RHL group had overall, significantly lower VPA mean scores than the control group (p=0.016). The VPA mean scores of the conventional group tended also to be lower than the VPA mean scores of

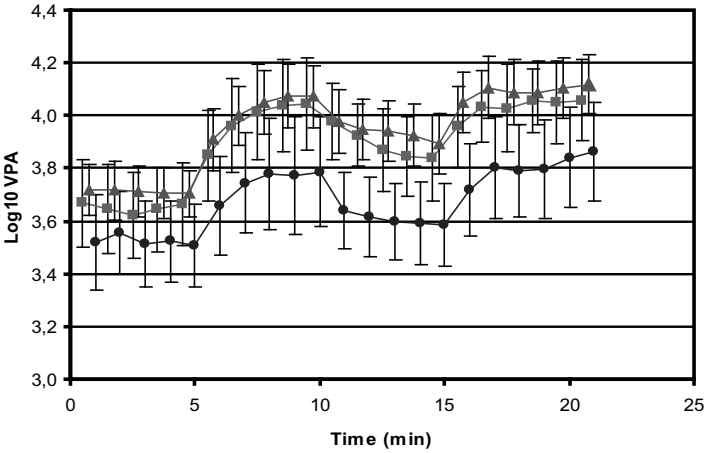


Figure 1. Change in logarithmically transformed mean vaginal pulse amplitude (log10VPA) during experimental session: Neutral stimulus 1 (Baseline assessment) (1-5 min), Erotic stimulus 1 (6-10 min), Neutral stimulus 2 (11-15 min), Erotic stimulus 2 (16-21 min).
–●–=Conventional RHL (n=13), –■–=Nerve-sparing RHL (n=10), –▲–=Controls (n=14). RHL, radical hysterectomy with pelvic lymphadenectomy. See colour figure page 153.

the nerve-sparing group (p=0.097). No differences were found between the control group and the nerve-sparing group (p=1.000). These results indicate that the VPA responses in the conventional RHL group were significantly lower throughout the whole experimental session. Moreover, the two erotic films were equally effective in enhancing genital arousal in the three groups which was reflected by significantly higher VPA mean scores of the two erotic stimuli compared to the mean VPA scores of the two neutral stimuli ($F(3, 102)=66.40$, $p<0.001$). Table 2 shows the untransformed VPA mean scores for the three groups and four stimuli.

As the conventional RHL group had significantly lower baseline VPA scores than the controls, we repeated the analysis while controlling for individual baseline differences. After controlling, the VPA responses in the three subject groups throughout the experimental session were comparable (p=0.140). This indicates that the differences in levels throughout the experimental session between the three subject groups were critically dependent on the baseline VPA scores (Fig. 1).

Because the women in the nerve-sparing group were significantly younger than the women in the other two groups and the time-interval between the operation and the experiment was longer for the conventional group, we performed the same analyses for VPA mean scores while controlling for age or time-interval between operation and experiment. After controlling for age or time interval the outcome did not change. These results indicate that the VPA responses throughout the whole experimental session are not affected by age or time-interval.

| | Controls (n=14) | Conventional RHL (n=13) | Nerve-sparing RHL (n=10) |
|---|---|---|---|
| **Objective report: vaginal pulse amplitude (mV)** | | | |
| Neutral stimulus 1 | 1.8±1.0 | 1.2±0.7 | 1.7±1.0 |
| Erotic stimulus 1 | 3.8±2.0 | 2.3±1.7 | 3.8±2.3 |
| Neutral stimulus 2 | 3.1±1.6 | 1.5±0.7 | 2.9±1.6 |
| Erotic stimulus 2 | 4.5±2.4 | 2.5±1.8 | 4.0±2.5 |
| **Subjective report: sexual arousal (Likert scale)** | | | |
| Neutral stimulus 1 | 1.6±0.4 | 1.2±0.6 | 1.2±1.1 |
| Erotic stimulus 1 | 3.6±1.6 | 3.2±1.2 | 3.3±1.1 |
| Neutral stimulus 2 | 1.2±0.6 | 1.5±0.7 | 1.3±0.5 |
| Erotic stimulus 2 | 4.4±1.5 | 4.2±1.4 | 3.7±1.4 |

Table 2. The mean and SD of the untransformed VPA mean scores in millivolt for the three groups and the mean and SD of the mean subjective arousal scores during the four stimuli. SD, standard deviation; VPA, Vaginal Pulse Amplitude; mV, millivolt. Data are presented as mean ± SD.

*Differences in subjective arousal*

The mean score on subjective arousal was significantly higher during erotic stimulus 1 and 2 compared to neutral stimulus 1 and 2 ($F(3, 102) = 108.36$, $p < 0.001$). The three subject groups reported the same level of subjective sexual arousal. These results indicate that the erotic films were equally effective in enhancing subjective sexual arousal in the three groups. Table 2 shows the mean subjective arousal scores of the three groups and four stimuli.

*Differences in postmenopausal and premenopausal status, post-hoc analyses*

Literature data show that postmenopausal women have a significantly lower baseline vaginal blood flow compared to premenopausal women (10;27;28). To explore the hypothesis that the vaginal blood flow response of the conventional RHL group follows a pattern comparable with that of postmenopausal women, we used our data of the postmenopausal controls (n=12) and postmenopausal women with a history of a conventional RHL (n=10) who were excluded from the earlier main analyses. These postmenopausal women met all the other inclusion criteria of our study.

Figure 2 shows the VPA responses in four different groups; post- and premenopausal controls and post-and premenopausal patients with a history of conventional RHL. Visual inspection of the data indicates that the premenopausal women of the conventional RHL group follow a pattern comparable with that of postmenopausal women. We subsequently performed statistical analyses to quantify the differences in VPA responses. A two subject groups (conventional vs controls) by hormonal status (premenopausal vs postmenopausal) by the four stimuli analysis revealed that the conventional RHL groups had overall lower VPA scores ($p=0.022$). Furthermore a trend for the interaction effect between group and hormonal status in VPA responses ($F(1, 45) = 2.87$, $p = 0.097$) was found. Post hoc analyses showed a significantly higher VPA response for the premenopausal controls compared to the premenopausal women with a history of conventional RHL ($p=0.024$), confirming the visual impression.

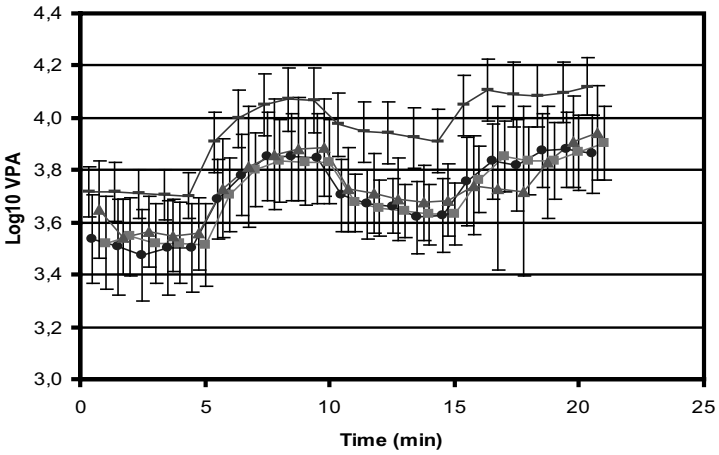


Figure 2. Postmenopausal versus premenopausal; change in logarithmically transformed mean vaginal pulse amplitude (log10VPA) during experimental session: Neutral stimulus 1 (Baseline assessment) (1-5 min), Erotic stimulus 1 (6-10 min), Neutral stimulus 2 (11-15 min), Erotic stimulus 2 (16-21 min).
–●– =Conventional RHL, postmenopausal (n=10), –■–=Conventional RHL, premenopausal (n=13), –▲–=Controls, postmenopausal (n=12), ——=Controls, premenopausal (n=14) RHL, radical hysterectomy with pelvic lymphadenectomy. See colour figure page 153.

## Discussion

This is the first study in which vaginal photoplethysmography was used to compare the functional results of a nerve-sparing modification of the RHL with the conventional RHL. Vaginal blood flow response during sexual stimulation was evaluated through objective assessment using photoplethysmography in women with a history of RHL, in women after nerve-sparing RHL and in healthy controls.
Although we did not yet succeed to recruit the number of subjects which we need according to our power calculation we decided to report preliminary data, because we feel that the results raise many interesting questions. The previous study from our group showed that damage to the autonomic nerves results in disrupted vaginal blood flow response during sexual stimulation. During sexual arousal a history of conventional RHL was associated with a significantly lower vaginal blood flow response compared to healthy controls (10). The results of the current study are partly in line with this; we also found that the conventional group had significantly lower VPA mean scores than the control group. The VPA mean scores of the conventional group tended also to be lower than the VPA mean scores of the nerve-sparing group. These differences in VPA were critically dependent on baseline differences between the three groups, and occurred despite the fact that these three groups felt an equally strong sexual arousal after the erotic stimulus condition. This implies that, in a non-stimulated situation,

patients with a history of conventional RHL probably have a lower vaginal blood flow than healthy controls and patients after a nerve-sparing RHL. Consequently, the vaginal blood flow during sexual stimulation does not reach the same high level in women with a history of conventional RHL.

The strength of the current study is the fact that all patients were treated by the same group of gynecologic oncologists, which ensures a uniform surgical technique.

The most ideal design would have been a pre-operative versus post-operative vaginal pulse amplitude assessment within subjects. We did not carry out such a study because we felt it was unethical to ask women in the period leading up to major cancer surgery to take part in an emotionally confronting psychophysiological sexual assessment.

In general, it has proven to be difficult to recruit women after they have had their treatment because of the intrusive nature of this experiment. For this reason it will take at least 3 years before we will have recruited a sufficient number of subjects for each group.

In interpreting the results of this preliminary analysis, the limits of the design and its size should be taken into account. The sample used was small. The fact that we did not find a significant difference between the conventional RHL group and the nerve-sparing RHL group could possibly be a consequence of relatively small power (39%) of the study so far (26).

Previous studies have shown that participants in sexuality studies tend to be more sexually liberal and permissive, and more sexually active than non-participants (29) which might influence the representativity of our sample. In the current study the control group showed mean FSFI total scores comparable with women without sexual problems (22). The two patients groups did not differ significantly from our control group. This could imply that women with more severe dysfunctions refrained from participating and that the difference in vaginal blood flow between the nerve-sparing RHL group and conventional RHL group might be an under-estimate.

The similarity of the VPA response curve of the women with a history of a conventional RHL and postmenopausal women is striking. In line with our findings, Laan et al.(27;30) also reported that postmenopausal women displayed significantly lower VPA responses than premenopausal women in the basal (unstimulated) state. They also found that the changes in VPA responses during erotic stimulation were similar in both premenopausal and postmenopausal women.

We suggest that a common pathophysiologic mechanism explaining the low basal vaginal blood flow in postmenopausal women and women with a history of conventional RHL could be an altered vascular smooth muscle contraction state in the vaginal blood vessels. We postulate that the observed altered vaginal blood flow in women with a history of a conventional RHL and postmenopausal women is in both cases the result of a reduced number of autonomic nerve fibres in the vascular smooth muscle cells in the vagina. Recent studies have shown both in animal models as well as in human tissue that the autonomic nerves which innervate the reproductive organs have been found to be responsive to circulating steroids such as oestrogen. These nerves express oestrogen receptor $\alpha$ (ER $\alpha$) and oestrogen receptor $\beta$ (ER $\beta$) (31-34). A changed number of autonomic nerve fibres in the vascular wall of

the vagina mediated by either direct nerve disruption (conventional RHL) or low oestrogen levels which modulate nerve density through oestrogen receptors in the vaginal wall (postmenopausal women) causes a changed contraction state of the vaginal arteries.

Chronic oestrogen exposure reduces the density of sympathetic nerves, but increases the density of parasympathetic nerves (31;32). Regarding vaginal blood flow, an increase of parasympathetic nerves would lead to vascular smooth muscle relaxation resulting in an increased VPA. This explains the higher baseline VPA in premenopausal women. Alternatively, a hypoestrogen status leads to a sympathetic hyperinnervation, causing vascular smooth muscle contraction resulting in a lower baseline VPA in postmenopausal women.

Interestingly, the typical sexual complaints reported by women with a history of conventional RHL (2-4) are similar to postmenopause-related sexual problems (35-37). These sexual complaints include dyspareunia, a dry vagina, reduced vaginal lubrication and a decline in sexual interest.

ER β, the receptor which is associated with human vaginal vascular smooth muscle has been documented to be expressed in the uterosacral ligaments (38). The critical modification of the conventional RHL into a nerve-sparing technique is the alternative surgical dissection of the uterosacral ligaments which contain essential parts of the pelvic autonomic nerves (6). Sparing the autonomic nerves expressing ER β could explain the higher baseline VPA in the premenopausal women with a history of nerve-sparing RHL.

The physiological model behind the subsequent 'normal' increase in VPA once the subject (after conventional RHL or in postmenopausal state) is erotically stimulated, i.e. after a low baseline, the vaginal blood flow increases to the same extent as in healthy controls but never reaches the high flow of controls, is the endothelin/ Nitric oxide (NO) system. Vessel walls react to sheer stress caused by blood pressure changes. Endothelin release results in vasoconstriction, while NO induces vasodilatation. This ability of the arteries to adapt to changes in the circulation is not regulated by the autonomic nervous system. This explains why a partly denervated vagina does show a relatively normal vaginal blood flow response.

In conclusion, the preliminary data from the present study show that women with a history of nerve-sparing surgery seem to have an overall better vaginal blood flow. Further research of the functional results of nerve-sparing modifications of RHL should therefore be performed, to prove without any doubt that nerve-sparing techniques lead to lower sexual morbidity with similar treatment results.

## Acknowledgements

We gratefully acknowledge P.H.C. Eilers (Ph.D.) from the Department of Statistics for his valuable advice on the statistical analysis. Furthermore, we want to thank C. Tuijnman (M.A.) for her practical explanation of the use of the plethysmography, B. Molenkamp and C. Kramer for technical support. The authors would also thank G.J. van Dijk (M.D., Ph.D.) for offering the possibility to perform this research project at the Department of Neurology.

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Chapter 8

# Summary, discussion and future perspectives

## Summary

Improving the quality of cancer care will lead to a better survival rate and less morbidity and, therewith, to a better quality of life for cancer patients. To achieve this goal, treatment-related information, like clinical data regarding treatment, survival items and the postoperative morbidity, is needed. This could be acquired by registries. A regular audit of this information will result in more awareness of individual differences, gain more insight into the existence of risk factors and comorbidity and could lead to other treatment modalities.
Furthermore, improving the quality of life is important when results of cancer treatment in terms of survival are good, because cancer treatment has its adverse effects. For cervical cancer patients these adverse side effects may include loss of fertility, bladder dysfunction, colorectal motility disorders and sexual dysfunction (1-10). It has been shown that for women with gynaecological cancer, the maintance of a positive self-image and feelings of sexuality is an issue of central importance in the provision of quality of their daily life (11). Because sexual function and satisfaction are based on both physical and psychological components, the treatment of gynaecological cancer can affect both of these aspects; particularly because of the anatomical nature of the cancer (12).
This thesis focused on the sequelae of treatment acquired by registries of women with early stage cervical cancer in order to improve the quality of treatment procedures and the quality of life. The results of these studies are summarized and discussed in this chapter.

A general introduction is presented in **chapter 1.** In this introduction aspects are reviewed about the quality control of cancer care, quality of life, morbidity after radical hysterectomy for the treatment of cervical cancer and different ways of monitoring morbidity. Finally, the role of the pelvic autonomous nerves in radical hysterectomy is described.

When radical hysterectomy with pelvic lymphadenectomy (RHL) is performed for women with early stage cervical cancer and adverse risk factors, such as lymph node involvement, parametrial invasion or positive surgical margins are present, postoperative radiotherapy is indicated (13-23). Several studies have suggested that patients with disease confined to the cervix but with certain other primary tumour related risk factors might also benefit from postoperative radiotherapy (13-28). In a study performed by the Gynecologic Oncology Group (GOG), Delgado et al. identified capillary lymphatic space involvement (CLS), clinical tumour size and depth of tumour invasion into the cervical stroma (DI) as predictors of prognosis and proposed a scoring system that identifies three separate risk groups for recurrence (14). Since 1997, patients with at least 2 of the following 3 risk factors also received postoperative radiotherapy in our centre (Leiden University Medical Centre, LUMC): tumour size ≥4omm, depth of invasion ≥ 15 mm and CLS. In **chapter 2,** the outcome of patients who received adjuvant radiotherapy on the basis of tumour related risk factors mentioned above was compared to

the outcome of patients with a similar risk profile treated before 1997 who did not receive radiotherapy. Furthermore, the prognosis of patients using our criteria for giving adjuvant radiotherapy (LUMC risk profile) was compared to those of the GOG prognostic scoring system (GOG risk score) (14). For this study prospectively collected data of 643 patients with stage I-IIa cervical carcinoma was used.
In line with the literature (14;21;22;29;30) the current study indicated that the high risk group according to the LUMC risk profile significantly benefited from postoperative radiotherapy. We found that a significantly larger percentage (41 vs 12%, p=0.02) of the high risk group who did not receive radiotherapy, had recurrence of disease. This occurred in the knowledge that apart from the number of deep infiltrating tumours (more frequent in the irradiated group), the other clinical important risk factors of the 2 groups were similar. The differences in the cancer specific survival (CSS) and the disease free survival (DFS) between the high risk group with adjuvant radiotherapy (86% and 85%, respectively) and high risk group without adjuvant radiotherapy (57% and 43%, respectively) were statistically significant (p=0.013 and p=0.006, respectively). Finally, this study showed that the LUMC modification of the GOG prognostic scoring system did not significantly differ from the GOG prognostic scoring system itself, with regard to risk of recurrence, CSS and DFS. It was concluded that the LUMC risk profile is simpler and more straightforward in use, has a slightly higher threshold to define patients as candidates for adjuvant radiotherapy as compared to the GOG prognostic scoring system, but without compromising their prognosis.

The goal of lymphadenectomy as part of the treatment of patient with early stage cervical cancer is to remove and diagnose cancer cells that have been transported to the lymphatic system draining the uterine cervix and the upper vagina. A systematic lymphadenectomy can reliably establish the presence or absence of lymph node involvement, with the attendant consequences for prognosis and treatment (31). For the treatment of early stage cervical cancer, the therapeutic value of lymphadenectomy is still a matter of debate, although some authors emphasized the possible beneficial effect of removing metastatic lymph nodes (31-38). Yet, it has never been proven that the removal of nodes itself leads to better survival figures (32). The aim of the study in **chapter 3** was to determine if the number of removed pelvic lymph nodes in RHL influences survival of patients with early stage cervical cancer. Furthermore the relation of patient, tumour and treatment factors on one hand and the number of nodes examined in node-negative early stage cervical cancer patients on the other hand was analyzed. For the first part of the study a group of 331 patients with negative nodes and without adjuvant therapy (group A) and a group of 136 patients with positive nodes (group B) were used. For the second part only group A was used. Lymphadenectomy consisted of removal of all the fatty tissue from 6 different pelvic stations. Parametrial nodes were not included in the counting of number of nodes. In the current study there were no para aortic lymph nodes removed in patients of group A and B.
The current study indicated that when all regional lymph nodes are pathologically negative, there is no relation between the number of nodes removed and CSS or DFS. However, the number of examined

lymph nodes effects DFS figures for patients with positive lymph nodes. Patients with early stage cervical cancer with positive lymph nodes consequently benefit from a sufficient number of removed lymph nodes. As such, the most important clinical consequence of this study is that one should complete the lymphadenectomy when frozen section reveals lymph node involvement during RHL. Finally, this study showed that the number of removed lymph nodes was not influenced by age, referral from Surinam, postmenopausal status, conisation before surgery, tumour size, infiltration depth and capillary lymphatic space involvement.

When a patient confronts the physician with questions about the exact risk of recurrence or death in their individual case by time, it can be difficult and sometimes even impossible to answer this adequately. Standard survival data measure the time span from some time origin until the occurrence of one type of event. If several types of events (like recurrence or death) occur, a model describing progression to each of these competing events is needed.
Multi-state models may be considered as a generalization of the basic framework for dealing with survival data to the case where several (possibly competing) events occur successively over time. The occurrence of successive events constitutes the transitions from an initial state to a final state. Here, the states of the cervical cancer patients are recurrence and death. Furthermore, these models allow the incorporation of prognostic factors in order to study the influence of these factors on each of the transition rates. Multi-state models can be used to predict the likelihood to reach a specific future state (e.g. recurrence) on the basis of their present state at various time intervals following initial treatment.
The aim of **chapter 4** was to evaluate the possibility to give a prediction of the future (disease free) survival, given the fact that a patient with a history of early stage cervical cancer has been disease free for a specific period after treatment. For this means the prospectively collected data were used of 615 patients with stage I-IIa cervical carcinoma who were treated with a RHL with or without adjuvant radiotherapy. Statistical analysis was done with multi-state risk models specifically designed for this purpose. The multi-state risk models estimate the influence of covariates and generate predicted survival curves by simulation. The covariates that have been taken into consideration in the analysis of individual patient survival were; lymph nodes involvement, tumour size, depth of invasion, capillary lymphatic space involvement, parametrial invasion, adenosquamous carcinoma and positive surgical margins. The simulations were done for patients with positive lymph nodes (n=492), patients with negative lymph nodes (n=123) and four hypothetical patients. The predicted probability of death of these 2 groups and the 4 hypothetical patients were demonstrated in predicted cumulative probability plots.
Until the results of other trials are known, the outcome of the present study shows the possibility to give a prediction of the future (disease free) survival, given the fact that a patient has been disease free for a specific period after treatment. This could provide information to individualise the treatment management and the (length of) programs of surveillance and this obviously will benefit cost and

time implications. Furthermore, improving the quality of cancer care will undoubtedly lead to a better quality of life for cancer patients. Therefore, it can be concluded that this possibility is an important step forward to improve the quality of cancer care.

To become aware of the morbidity that exists after a treatment and to obtain an impression of the impact of it on a patient's quality of life, self-report questionnaires may give more informative answers (39;40). Besides, self-report questionnaires might also give more comprehension of the patient's perception of symptom severity. We developed a Dutch self-report questionnaire, the Qynaecologic Leiden Questionnaire (LQ), which is the first developed Dutch list consisting of the items for sexual function, voiding- and bowel problems for women with cancer. The Gynaecologic LQ has one item for weariness, one item for lymphedema, 11 items for sexual functioning, 6 items for voiding and 2 items for bowel problems. The aim of **chapter 5** was to investigate the psychometric properties of the items concerning sexual functioning of the Gynaecologic LQ. The total study sample consisted of 198 subjects: 66 patients treated for cervical cancer, 66 patients with sexual complaints and 66 subjects from the general population. The patients treated with RHL for cervical cancer by a RHL were asked to complete the Gynaecologic LQ before, 3, 12 and 24 months after treatment. For the internal validation we used the Gynaecologic LQ that was completed 12 months after the operation. The patients with sexual problems, who solicited for therapy at an out-patient clinic for sexology, completed the questionnaire at the end of the first visit. The convergent and divergent construct validity of the Gynaecologic LQ was investigated using other validated instruments (questionnaires) measuring sexual functioning, sexual dissatisfaction, marital distress, general life distress and psychological distress.
By means of factor analysis three subscales were derived: Female Sexual Complaints, Female Sexual Function and Female Orgasm. The reliability of the subscales appeared to be satisfactory. The scores on the three subscales differentiated well between the patients treated for cervical cancer, patients with sexual complaints and the subjects from the general population. Furthermore, the subscales were sensitive to change within the patients treated for cervical cancer, since the score changed in the theoretically proposed direction following the treatment. The convergent and divergent validity of the Gynaecologic LQ was good, since the 3 subscales corresponded with subscales measuring similar complaints and discriminated from subscales measuring other (psychological) problems.
In conclusion, the results of the current study support the reliability and psychometric validity of Gynaecologic LQ in the assessment of sexual functioning and vaginal changes in gynaecological cancer patients.

The effects of the treatment for cervical carcinoma on the women's sexuality and the resulting distress, have received more attention in recent years (8;41-48). In **chapter 6** the results are described of the first longitudinal study of self-reported bladder, defecation, sexual and vaginal problems with a baseline score before the RHL with or without adjuvant radiotherapy. Women with early stage cervical cancer

who had to undergo RHL were enrolled in the study. For this study only 14 out of the 21 items of the self-report Gynaecologic LQ were used. The 14 items asked for lymphedema, sexual function, voiding and bowel problems and were completed before operation and at 3, 12, and 24 month after operation. We compared this group of patients with a group of age-matched controlled women from the general population. The control group was asked to complete the questionnaire once. Seventy-three patients filled in all the questionnaires. The control group consisted of 224 women.

Up to 1 year after the treatment the patients complained significantly more often of little or no urge to urinate and diarrhoea as compared to the controls. However, after 2 years follow-up, we found no significant difference anymore concerning bladder dysfunction and colorectal dysfunction compared to the control group and compared to the situation before surgery. Retrospective studies of frequency of late postoperative micturition and colorectal problems show various figures (2;4;9;49;50). The fact that in this study no significant difference was found after 2 years of follow-up might be a reflection of post-surgical recovery or an indication that perception of quality of life may be independent of objective measures. The relief resulting from the completion of potentially curative treatment may also have contributed to the subjective improvement despite changes in bowel and bladder function. And finally, most studies of colorectal and micturial dysfunction offer data collected from the medical files (4;9;49;50). This study used questionnaires and has a longitudinal design that makes a direct comparison with literature data problematic.

The patients showed significantly more negative effects on sexual function compared both to the controls as well as compared to their situation before the treatment throughout 2 years of follow-up. The problems included less lubrication, a narrow and short vagina, numb areas around the labia, dyspareunia, and sexual dissatisfaction. In agreement with the literature (1;3;44;51) it can be concluded that up to 2 years after the RHL, women with early stage cervical cancer experience negative effects mainly on sexual function. Adjuvant radiotherapy did not significantly increase the risk of bladder dysfunction, colorectal motility disorders and sexual functions.

It is known from several anatomical and clinical studies (52-55) that RHL for cervical cancer causes surgical damage to the pelvic autonomic nerves which are responsible for the increased vaginal blood flow during sexual arousal (56;57). It is conceivable that surgical damage to these autonomic nerves plays a crucial role in the aetiology of the postoperative morbidity that exist after RHL (52;58-62). Photoplethysmographic assessment of vaginal pulse amplitude has been proven to be reliable and reproducible to measure objectively the vaginal blood flow during sexual arousal (63;64).

**Chapter 7** reports preliminary data of a study with the aim to determine whether the nerve-sparing technique indeed leads to an objectively less disturbed vaginal blood flow response during sexual stimulation. Photoplethysmographic assessment of vaginal pulse amplitude (VPA) during sexual stimulation by erotic films was performed. Sexual and psychological functioning of the participating women was assessed by four self-report questionnaires: Gynaecologic LQ (65); FSFI (66;67) ; HADS

(68); EORTC-C30 (69). Subjective sexual arousal was assessed after each stimulus. Thirteen women with a history of a conventional RHL, 10 women with a history of a nerve-sparing RHL and 14 healthy controls participated.

The mean VPA differed between the three groups (p=0.014): the conventional group had overall a significantly lower vaginal blood flow response than the control group (p=0.016), and tended also to be lower than the nerve-sparing group (p=0.079). These differences in VPA were critically dependent on baseline differences between the three groups; the vaginal blood flow during the first 5 minutes lasting neutral stimuli, preceding the sexual stimuli, was already significant lower for the conventional RHL group compared to the control group. Furthermore, a trend was found between the conventional RHL group and nerve-sparing RHL group; the conventional RHL group had a lower baseline vaginal blood flow compared to the nerve-sparing RHL group. These differences occurred despite the fact that these three groups felt an equally strong subjective sexual arousal after erotic stimulus condition. Therefore, it seems that women with a history of nerve-sparing surgery have an overall better vaginal blood flow response. It is probably due to the low power of the study that differences with the women after conventional RHL were not statistically significant.

Furthermore, visual inspection of the data indicates that the conventional group follows a vaginal blood flow response pattern which is comparable to the vaginal blood flow pattern of postmenopausal women. This similarity could be explained by a changed number of autonomic nerve fibres in the vascular wall of the vagina mediated by either direct nerve disruption (after conventional RHL) or by low estrogen levels which modulate nerve density through estrogen receptors in the vaginal wall (in postmenopausal women).

This is the first study in which vaginal photoplethysmography was used to compare the functional results of the nerve-sparing modification of the RHL with the conventional RHL. However, a definite conclusion concerning the benefit of nerve-sparing surgery can only be made after inclusion of more subjects. Further research of the functional results of nerve-sparing modifications of RHL should therefore be performed, to prove without any doubt that nerve-sparing techniques lead to lower sexual morbidity.

## Discussion, recommendations and future perspectives

Summarizing from our studies it can be concluded first that treatment-related information from registries is a prerequisite to improve the quality of cancer care. Illustrative is the fact that UK studies reporting on the wide variety in outcomes in breast and colorectal cancer have had major consequences (70). The results of our studies, achieved by the use of our prospective clinical database, can also have consequences for the treatment of patients with early stage cervical cancer.

First of all the results of our study and data from the literature (14;24-28) may be used as argument to give adjuvant radiotherapy to patients with tumour related risk factors, without lymph node involvement, parametrial invasion or positive surgical margins, since these high-risk patients seem to benefit from adjuvant radiotherapy.
Another recommendation is that one should complete the lymphadenectomy when frozen section reveals lymph node involvement during RHL, because a greater number of examined lymph nodes leads to better disease free survival figures for patients with positive lymph nodes. Although in the literature the therapeutic value of lymphadenectomy is still a matter of debate, the results of our study confirm similar findings of a previous analysis (32).
Furthermore, we found a possibility to give an accurate prediction of the future (disease free) survival of an individual patient. This could provide information to individualise the treatment management and the (length of) programs of surveillance and this will also benefit cost and time implications. The future perspective could be that every gynaecologic-oncologist will have a program on his or her computer by which it will be possible to predict the future (disease free) survival for an individual patient. In the future these kinds of programs will become even more accurate because of the growing availability of new software for multi-state models. But also because the number of patients treated for early stage cervical cancer will increase in the database in which all clinical and pathological parameters of these patients are prospectively collected. Not only for this last purpose but also to maintain the possibility to be able to give recommendations like the other 2 mentioned above, it is necessary to collect treatment-related information in a registry. The Dutch Comprehensive Cancer Centres (IKC) only register new cases of cancer and do not collect other treatment-related data from these new patients apart from some study wise activities. Moreover, there are still hospitals and even several European countries that do not have (reliable) cancer registries (71;72). We therefore strongly recommend hospitals and also the IKC's to set up such registries, because they can provide valuable information on differences in treatment modalities, risk factors, morbidity or outcome and therefore form the basis of a strategy for monitoring, audit and improving of cancer care.

Secondly, it can be concluded from our studies that with the right tools it is possible to become aware of and to gain insight into the existence of morbidity after RHL for the treatment of cervical cancer. We validated the questions concerning sexual function of the self-report questionnaire, the Gynaecologic LQ, which is the first developed Dutch list consisting of the items for sexual function, voiding- and bowel problems for women with cancer. This questionnaire will help us to measure in a subjective way the complaints of patients after their treatment, and therefore might give insight in the necessity to develop other treatment modalities. Furthermore, this tool can be used to compare conventional therapy with new developed modalities.
Since we become more aware of the side effects of the treatment of cervical cancer and since the quality of life is nowadays an important issue, the number of studies about self-reported sexual function and vagi-

nal changes will undoubtedly increase in the future. It is however essential that these studies assessing sexual function use data of patients with the same diagnosis, treatment, stage, and follow-up periods. A longitudinal design, validated questionnaires and a baseline score are also important.

Photoplethysmographic assessment of vaginal pulse amplitude has been proven to be reliable and reproducible to measure objectively the vaginal blood flow during sexual arousal (63;73;74). RHL for cervical cancer causes damage to the autonomic nerves which are responsible for the increased vaginal blood flow during sexual arousal (1;52;75;76). Since this is known, several authors have proposed different nerve-sparing surgical approaches to avoid pelvic disruption during RHL (54;58;61;62;77-81). Vaginal photoplethysmography is therefore an important tool in the investigation of the functional results of these new developments.

In the LUMC we have also developed a nerve-sparing technique in an attempt to reduce the nerve damage during RHL without sacrificing oncological principles of radicality (59). The nerve-sparing modification of the RHL is performed since 2000. Recently we have started a multicentre observational study to assess the results of treatment in terms of DFS and the incidence of urinary, colorectal and sexual dysfunction after nerve sparing surgery in RHL for cervical carcinoma stage Ib1/IIa. The results of this study are to be expected in the coming years. The Gynaecologic LQ and the vaginal photoplethysmography are used in this study to investigate on a subjective and objective way the results of this new technique.

We made a start with the photplethysmographic assessments. For this part of the study a number of minimal 26 women with a history of conventional RHL and 26 women after nerve-sparing RHL is needed (82). We did not yet succeed to recruit this number of subjects. It has proven to be difficult to recruit women after they have had their treatment because of the intrusive nature of the experiment. For this reason it will take at least 3 years before a sufficient number of subjects for each group will be recruited. However, the preliminary data from the study show that a conventional RHL is associated with an overall disturbed vaginal blood flow response compared to healthy controls. Since it was not observed to the same extent after nerve-sparing RHL, it seems that the nerve-sparing technique leads to better overall vaginal blood flow caused by less denervation of the vagina.

The next years the recruitment of subjects for the multicentre observational study will be continued, to prove that the Leiden nerve-sparing modification of the RHL leads to lower morbidity with similar treatment results. This might lead to an improvement of the quality of life of women undergoing live-saving surgery for early stage cervical cancer.

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Chapter 9

# Nederlandse samenvatting

# Samenvatting

Verbetering in de kwaliteit van kanker zorg zal leiden tot betere overleving en minder morbiditeit, met als gevolg een betere kwaliteit van leven voor deze patiënten. Om dit doel te kunnen bereiken is informatie nodig over de behandeling. Dit kan worden verkregen uit databanken. Deze informatie bestaat onder andere uit klinische gegevens met betrekking tot de behandeling, gegevens ten aanzien van de overleving en postoperatieve morbiditeit. Het regelmatig nazien of controleren van deze informatie zal leiden tot meer bewustwording van individuele verschillen, zal meer inzicht geven in het mogelijke bestaan van risicofactoren en morbiditeit en kan resulteren in andere behandelingsmodificaties.
Wanneer op basis van overlevingscijfers kan worden gesteld dat de resultaten van de behandeling voor kanker goed zijn, wordt vervolgens de verbetering van de kwaliteit van leven belangrijk, dit omdat de behandeling van kanker ook zijn prijs heeft. Voor patiënten met baarmoederhalskanker betekent dit het verlies van vruchtbaarheid, disfunctioneren van de blaas, colorectale motiliteitstoornissen en problematiek op het gebied van de seksualiteit.
Het is aangetoond dat voor vrouwen met een gynaecologische vorm van kanker het behoud van een positief zelfbeeld en gevoelens van seksualiteit zeer belangrijk zijn voor de kwaliteit van leven. Omdat de seksuele functie en seksuele bevrediging gebaseerd zijn op zowel lichamelijke als psychische componenten, kan een behandeling voor een gynaecologische vorm van kanker deze beide aspecten aantasten, vooral vanwege de anatomische aard van de kanker.
Dit proefschrift bevat een aantal studies naar de gevolgen en de resultaten van de behandeling voor vrouwen met een vroeg stadium van baarmoederhalskanker (FIGO I-IIa) met als doel de kwaliteit van behandelingsprocedures en de kwaliteit van leven te verbeteren. De gegevens voor deze studies zijn onder meer verkregen uit een databank. In deze databank wordt sinds januari 1984 op prospectieve wijze meer dan 200 relevante klinische en pathologische parameters verzameld van vrouwen die in het Leids Universitair Medisch Centrum (LUMC) zijn behandeld voor baarmoederhalskanker.

In **hoofdstuk 1** worden aspecten zoals de kwaliteitscontrole op behandelingsprocedures en de kwaliteit van leven besproken. In dit inleidende hoofdstuk komen ook de verschillende vormen van morbiditeit na een radicale hysterectomie, de mogelijkheden om deze morbiditeit te meten en de rol van de autonome zenuwen aan bod.

Wanneer bij vrouwen met een vroeg stadium van baarmoederhalskanker blijkt dat er na de radicale hysterectomie met pelviene lymphadenectomie (RHL) ongunstige risico factoren aanwezig zijn, zoals positieve lymfeklieren, positieve snijranden en infiltratie in het parametrium, dan is postoperatieve radiotherapie geïndiceerd. Er zijn studies die hebben gesuggereerd dat patiënten ook baat hebben wanneer zij postoperatieve radiotherapie krijgen als de ziekte beperkt blijft tot de baarmoederhals, maar er wel bepaalde tumour gerelateerde risicofactoren aanwezig zijn. De Amerikaanse Gynaecologische

Oncologie Groep (GOG) toonde in hun studie aan dat vasoinvasie, tumor grootte en infiltratie diepte factoren zijn die een voorspellende waarde hebben voor de prognose. Zij ontwikkelde een scoringssysteem aan de hand van deze 3 factoren en vormde hiermee 3 risicogroepen voor het krijgen van een recidief. Sinds 1997 gebruikt het LUMC ook een scoringssysteem; patiënten met tenminste 2 van de volgende 3 tumor gerelateerde risico factoren krijgen postoperatieve radiotherapie: tumor grootte ≥40mm, infiltratiediepte ≥15mm en vasoinvasie. In **hoofdstuk 2** worden de resultaten vergeleken van de patiënten die op basis van bovengenoemde tumor gerelateerde risico factoren radiotherapie hebben gekregen met de groep patiënten met hetzelfde risico profiel, maar die voor 1997 zijn behandeld en dus geen radiotherapie hebben gekregen. Daarnaast is de overleving van patiënten die zijn behandeld volgens de criteria van het LUMC (LUMC risico profiel) vergeleken met de overleving van patiënten die zijn behandeld volgens het GOG prognostische scoringssysteem (GOG risico score). Voor deze studie zijn prospectief verzamelde data van 643 patiënten met baarmoederhalskanker stadium I-IIa gebruikt. In overeenstemming met de literatuur laat deze studie zien dat de hoge risico groep volgens het LUMC risico profiel significant baat heeft bij het krijgen van postoperatieve radiotherapie. Een significant hoger percentage ( 41 vs 12%, p=0.02) van de patiënten in deze hoge risico groep zonder radiotherapie, kreeg een recidief van de ziekte. Dit gebeurde ondanks het feit dat het aantal diep infiltrerende tumoren, een belangrijke risicofactor, meer voorkwam in de bestraalde groep. De overige klinisch prognostische factoren waren gelijk tussen de groepen. De verschillen in de kanker specifieke overleving en de ziekte vrije overleving tussen de hoge risico groep met adjuvante radiotherapie (86% en 85%, respectievelijk) en de hoge risico groep zonder adjuvante radiotherapie (57% en 43%, respectievelijk) waren statistisch significant (p=0.013 en p=0.006, respectievelijk). Tenslotte toonde deze studie aan dat de LUMC modificatie van het GOG prognostische scoringssysteem niet significant verschilde van dit laatste systeem ten aanzien van het risico op een recidief, de kanker specifieke overleving en de ziektevrije overleving. Geconcludeerd is dat het LUMC risico profiel eenvoudiger is in het gebruik. Het heeft wel een iets hogere drempel voordat het beslist om adjuvante radiotherapie te geven aan patiënten vergeleken met het GOG prognostische scoringssysteem, maar dit levert geen verschil op voor de resultaten.

Het doel van een lymfadenectomie als onderdeel van de behandeling van patiënten met het vroege stadium van baarmoederhalskanker is om kankercellen die zijn getransporteerd naar het lymfatische systeem dat baarmoederhals en het bovenste deel van de vagina draineert, te diagnostiseren en te verwijderen. Een systematisch uitgevoerde lymfadenectomie kan betrouwbaar de aan- of afwezigheid vaststellen van positieve lymfeklieren, wat consequenties heeft voor de prognose en de behandeling. De therapeutische waarde van de lymfadenectomie voor de behandeling van het vroege stadium van baarmoederhalskanker is nog steeds niet duidelijk, hoewel sommige auteurs het mogelijk gunstige effect van de verwijdering van gemetastaseerde lymfeklieren benadrukken. Toch is het nooit bewezen dat het verwijderen van klieren op zichzelf leidt tot betere overlevingscijfers. Het doel van **hoofdstuk 3** was om te kijken in hoeverre het aantal verwijderde pelviene lymfeklieren bij een RHL invloed heeft op

de overleving van patiënten met het vroege stadium van baarmoederhalskanker. Verder werd de relatie tussen patiënt, tumor en behandelingsfactoren aan de ene kant en het aantal onderzochte klieren van patiënten met negatieve klieren aan de andere kant vergeleken. Voor het eerste gedeelte van het onderzoek werd gebruik gemaakt van een groep van 331 patiënten met negatieve klieren en zonder adjuvante therapie (groep A) en een groep van 136 patiënten met positieve klieren (groep B). Voor het tweede gedeelte werd alleen groep A gebuikt.
Lymfadenectomie bestond uit het verwijderen van al het vetweefsel van 6 verschillende pelviene lymfeklierstations. Parametriale klieren werden niet bij het totale aantal verwijderde klieren geteld. Zowel in groep A als in groep B waren para-aortale klieren verwijderd.
Deze studie indiceert dat wanneer alle regionale lymfeklieren pathologisch negatief zijn, er geen relatie bestaat tussen het aantal verwijderde klieren en de kanker specifieke overleving of ziektevrije overleving. Echter, het aantal verwijderde klieren heeft wel invloed op de ziektevrije overleving van patiënten met positieve klieren. Patiënten met het vroege stadium van baarmoederhalskanker met positieve klieren hebben dus profijt wanneer een voldoende aantal klieren is verwijderd. Als zodanig, is de meest belangrijke klinische consequentie van deze studie dat men een volledige lymfadenectomie zou moeten verrichten wanneer tijdens de RHL uit de vriescoupe blijkt dat er sprake is van positieve lymfeklieren. Tot slot liet deze studie zien dat het aantal verwijderde klieren niet werd beïnvloed door leeftijd, Surinaamse afkomst, postmenopauzale status, conisatie in de voorgeschiedenis, tumor grootte, infiltratiediepte en vasoinvasie.

Wanneer een patiënt de dokter confronteert met vragen over haar exacte risico op een recidief of de kans op overlijden op een bepaald moment, kan het moeilijk zijn en zelfs onmogelijk om deze vragen adequaat te beantwoorden. Standaard overlevings data meten de tijdspanne van een beginpunt tot het moment van een gebeurtenis. Als meerdere type gebeurtenissen (zoals recidief of dood) zich voordoen, is een model nodig dat de progressie beschrijft van elk van deze concurrende gebeurtenissen. Multi-state modellen kunnen worden beschouwd als een algemeen basaal raamwerk dat zich bezighoudt met overlevingsdata waarbij meerdere (mogelijk concurrerende) gebeurtenissen zich achtereenvolgens kunnen voordoen in de tijd. Het zich voordoen van achtereenvolgende gebeurtenissen vormt de overgang van een begin toestand naar een eind toestand. Voor patiënten die een behandeling voor baarmoederhalskanker hebben ondergaan zijn dit respectivelijk het krijgen van een recidief en de dood. Daarnaast nemen deze modellen prognostische factoren mee in de analyse om de invloed van deze factoren op de snelheid van de overgang van de ene naar de andere gebeurtenis te kunnen bestuderen. Multi-state modellen kunnen worden gebruikt om de waarschijnlijkheid te voorspellen dat iemand een specifieke toestand (b.v. een recidief) in de toekomst bereikt, op basis van zijn of haar aanwezige toestand op verschillende tijdsintervallen die volgen op het moment van de initiële behandeling. Het doel van **hoofdstuk 4** was te onderzoeken of er een mogelijkheid bestaat een voorspelling van de toekomstige (ziektevrije) overleving te geven, gegeven het feit dat een patiënte met een vroeg

stadium van baarmoederhalskanker in de voorgeschiedenis, ziektevrij is geweest voor een specifieke periode na de behandeling. Gebruik is gemaakt van de prospectief verzamelde data van 615 patiënten met baarmoederhalskanker stadium I-IIa die zijn behandeld met een RHL met pelviene lymfadenectomie met of zonder adjuvante radiotherapie. Statistische analyses werden gedaan met multi-state risico modellen die speciaal voor dit doel zijn ontwikkeld. De multi-state modellen schatten de invloed van covariaten en maken voorspelde overlevingscurven door middel van simulatie. In de analyse van de overleving van de individuele patiënte is rekening gehouden met de volgende covarianten; positieve lymfeklieren, tumor grootte, infiltratiediepte, vasoinvasie, infiltratie in het parametrium, adenosquameus carcinoom en positieve snijranden. De simulaties zijn gedaan voor patiënten met positieve klieren (n=492), patiënten met negatieve klieren (n=123) en vier hypothetische patiënten. De voorspelde kans op overlijden van deze 2 groepen en de 4 hypothetische patiënten zijn gedemonstreerd in voorspelde cumulatieve waarschijnlijkheidsgrafieken. Totdat resultaten van andere studies bekend zijn, laat de huidige studie zien dat er een mogelijkheid bestaat om een meer gedetailleerde voorspelling van de toekomstige (ziektevrije) overleving te geven, gegeven het feit dat een patiënt ziektevrij is geweest voor een specifieke periode na de behandeling. Deze mogelijkheid zou informatie kunnen verschaffen om het behandelplan en (de duur van) het follow-up beleid te individualiseren. Dit zal duidelijk voordelige gevolgen kunnen hebben voor kosten en tijd. Daarnaast zal een verbetering in de kwaliteit van kanker zorg ongetwijfeld leiden tot een betere kwaliteit van leven voor kanker patiënten. Daarom kan worden geconcludeerd dat deze mogelijkheid een belangrijke stap vooruit is om de kwaliteit van kanker zorg te verbeteren.

Om bewust te worden van de morbiditeit die is ontstaan na de behandeling en om een indruk te krijgen van de impact hiervan op het leven van de patiënte, kunnen vragenlijsten informatieve antwoorden geven. Daarnaast kunnen deze vragenlijsten ook een beter begrip geven van de perceptie van de patiënte ten aanzien van de ernst van de symptomen. Wij ontwikkelden een Nederlandse vragenlijst, de Gynaecologische Leidse Vragenlijst (LV). Dit is de eerst ontwikkelde Nederlandse vragenlijst die items bevat over seksueel functioneren, mictie- en darmproblemen voor vrouwen met kanker. De Gynaecologische LV bevat 1 item over moeheid, 1 item over lymfoedeem, 11 items over het seksueel functioneren, 6 items over blaas- en 2 items over darmproblemen. Het doel van **hoofdstuk 5** was om de psychometrische eigenschappen van de items over het seksueel functioneren van de Gynaecologische LV te onderzoeken. De totale studie populatie bestond uit 198 vrouwen: 66 patiënten behandeld voor baarmoederhalskanker, 66 patiënten met seksuele klachten en 66 vrouwen uit de algemene bevolking.
De patiënten die een RHL hadden ondergaan voor de behandeling van baarmoederhalskanker werden gevraagd de Gynaecologische LV vóór, 3, 12 en 24 maanden na de operatie in te vullen. Voor de interne validatie werd alleen de Gynaecologische LV gebruikt die 12 maanden na de operatie was ingevuld. De patiënten met seksuele klachten gingen voor deze klachten naar een polikliniek seksuologie en vulde de vragenlijst in aan het einde van hun eerste bezoek. De convergente en divergente construct validiteit

werd onderzocht door gebruik te maken van andere gevalideerde vragenlijsten die de seksuele functie, seksuele ontevredenheid, relatie problemen, ontevredenheid over het algemene leven en psychologische problemen meten.
Door middel van factor analyse werden drie subschalen gevonden: Vrouwelijke Seksuele Klachten, Vrouwelijk Seksueel Functioneren en Vrouwelijk Orgasme. De betrouwbaarheid van de subschalen was voldoende. De score op de drie subschalen laat een goed onderscheid zien tussen de patiënten behandeld voor baarmoederhalskanker, de patiënten met seksuele problemen en de vrouwen uit de algemene bevolking. Daarnaast waren de subschalen gevoelig voor verandering binnen de groep patiënten behandeld voor baarmoederhalskanker, omdat de score veranderde in de theoretische verwachtte richting volgend op de behandeling. De convergente en divergente validiteit was goed, omdat de drie subschalen overeenkwamen met subschalen die dezelfde klachten meten en zich onderscheidde van subschalen die andere (psychologische) problemen meten. Kortom, de resultaten van deze studie steunen de betrouwbaarheid en de psychometrische validiteit van de Gynaecologische LV in de beoordeling van het seksueel functioneren en van vaginale veranderingen in gynaecologische kanker patiënten.

De effecten van de behandeling voor baarmoederhalskanker op de seksualiteit van de vrouw en de daaruit voortvloeiende droefheid en pijn, krijgt de laatste jaren steeds meer aandacht. In **hoofdstuk 6** worden de resultaten beschreven van de eerste longitudinale studie over zelfgerapporteerde blaas, darm, seksuele en vaginale problemen met een uitgangswaarde voor de RHL met of zonder adjuvante radiotherapie. Vrouwen met een vroeg stadium van baarmoederhalskanker die een RHL zouden ondergaan werden geincludeerd in de studie. Voor dit onderzoek werden 14 items van 21 items tellende Gynaecologische Leidse Vragenlijst (LV) gebruikt. De 14 items vragen naar lymfoedeem, seksueel functioneren, mictie- en darmproblemen. De Gynaecologische LV werd vóór de operatie en 3, 12, en 24 maanden na de operatie ingevuld. Drieënzeventig patiënten vulden alle vragenlijsten in. We vergeleken deze groep patiënten met een op leeftijd gesorteerde groep vrouwen uit de samenleving. De controle groep vulde de Gynaecologische LV eenmalig in. De controle groep bestond uit 224 vrouwen.
Patiënten klaagden tot 1 jaar na de behandeling significant vaker over weinig of geen aandrang om te urineren en diarree in vergelijking met de controle groep. Echter na 2 jaar follow-up werd er ten aanzien van blaas- en darmdisfunctie geen significant verschil meer gezien vergeleken met de controle groep en vergeleken met de situatie voor de operatie. Retrospectieve studies over de frequentie van voorkomen van mictie en darm problematiek, laten verschillende cijfers zien. Onze studie liet geen significant verschil zien na 2 jaar follow-up. Dit zou kunnen komen door postoperatief herstel of het zou kunnen wijzen op het feit dat de perceptie van kwaliteit van leven onafhankelijk is van objectieve metingen. De opluchting na een potentieel curatieve behandeling zou ook kunnen bijdragen aan de subjectieve verbetering ondanks veranderingen in darm- en blaasfunctie. Tot slot gebruiken veel studies over colorectale- en blaasdisfunctie verzamelde data uit medische statussen. Deze studie ge-

bruikte vragenlijsten en heeft een longitudinale opzet, zodat een direkte vergelijking met de literatuur hierdoor niet goed mogelijk is.
De patiënten hadden na 2 jaar follow-up wel significant meer seksuele problematiek, zowel in vergelijking met de controle groep als met hun situatie vóór de behandeling. De problemen waren minder lubricatie, een nauwe en korte vagina, gevoelloosheid rondom de labia, dyspareunie en ontevredenheid over hun seksleven. In overeenstemming met de literatuur kan worden geconcludeerd dat tot tenminste 2 jaar na de RHL, vrouwen met een vroeg stadium van baarmoederhalskanker negatieve gevolgen ondervinden vooral op het gebied van het seksueel functioneren. Adjuvante radiotherapie liet geen significante toename zien van het risico op blaasproblematiek, colorectale motiliteitsstoornissen en seksueel functioneren.
Uit verschillende anatomische en klinische studies is gebleken dat de RHL voor de behandeling van baarmoederhalskanker chirurgische schade veroorzaakt aan de pelviene autonome zenuwen. Deze zenuwen zijn verantwoordelijk voor de toename van de vaginale doorbloeding tijdens seksuele opwinding. Het is denkbaar dat chirurgische schade aan deze autonome zenuwen een cruciale rol spelen in de etiologie van de postoperatieve morbiditeit die ontstaat na RHL. Met behulp vant photoplethysmografie kan de vaginale doorbloeding tijdens seksuele opwinding betrouwbaar en objectief beoordeeld worden.

**Hoofdstuk 7** laat de voorlopige resultaten zien van een studie waarin wordt onderzocht of de zenuwsparende techniek inderdaad leidt tot een objectief minder verstoorde vaginale doorbloeding tijdens seksuele stimulatie. Photoplethysmografische beoordeling van de vaginale doorbloeding werd uitgevoerd tijdens seksuele stimulatie door erotische filmpjes. Het seksueel en psychologisch functioneren van de deelnemende vrouwen werd beoordeeld door vier vragenlijsten: Gynaecologische LV; FSFI; HADS; EORTC-C30. De subjectieve seksuele opwinding werd na iedere stimulus vastgesteld. Dertien vrouwen met een conventionele RHL in de voorgeschiedenis, 10 vrouwen met een zenuwsparende RHL in de voorgeschiedenis en 14 gezonde controles namen deel aan de studie.
De gemiddelde vaginale doorbloeding verschilde tussen de groepen (p=0.014): de conventionele RHL groep had over het geheel, een significant lagere vaginale doorbloeding dan de controle groep (p=0.016), en neigde ook lager te zijn dan de zenuwsparende RHL groep (p=0.079). Deze verschillen in vaginale doorbloeding werden veroorzaakt door verschillen in de baseline tussen de drie groepen; de vaginale doorbloeding tijdens de eerste 5 minuten durende neutrale stimuli, voorafgaand aan de seksuele stimuli, was al significant lager voor de conventionele RHL groep vergeleken met de controle groep. Verder werd een trendverschil gevonden tussen de conventionele RHL groep en de zenuwsparende RHL groep waarbij de conventionele groep een lagere vaginale baseline doorbloeding had in vergelijking met de zenuwsparende groep. Deze verschillen bestonden ondanks het feit dat deze 3 groepen dezelfde mate van subjectieve seksuele opwinding voelde na een erotische stimulus conditie. Het lijkt dus dat vrouwen na een zenuwsparende operatie een algeheel (basaal) betere vaginale door-

bloeding hebben. Dat het verschil met vrouwen na een conventionele RHL niet statistisch significant is, komt waarschijnlijk door de lage power van de studie.
Verder indiceerde het visuele beeld van de data dat de conventionele RHL groep een vaginaal doorbloedingspatroon heeft dat gelijkenis toont met die van postmenopauzale vrouwen. Deze gelijkenis zou verklaard kunnen worden door een veranderd aantal autonome zenuwvezels in de vaatwand van de vagina door enerzijds directe zenuwschade (na conventionele RHL) of anderzijds door een lage oestrogeen concentratie (bij postmenopauzale vrouwen). De oestrogeenconcentratie reguleert namelijk de zenuwdichtheid door middel van oestrogeen receptoren in de vagina wand.
Dit is de eerste studie die vaginale plethysmografie als meetinstrument gebruikt om de functionele resultaten van de conventionele RHL met de zenuwsparende RHL te vergelijken. Echter, een definitieve conclusie omtrent het nut van zenuwsparend opereren kan alleen worden gemaakt wanneer meer mensen worden geïncludeerd. Verder onderzoek naar de functionele resultaten van de zenuwsparende modificatie van de RHL moet daarom worden uitgevoerd, om zonder enige twijfel te bewijzen dat de zenuwsparende techniek leidt tot minder seksuele morbiditeit.

## Discussie, aanbevelingen en toekomst perspectieven

Samenvattend kan als eerste uit onze studies worden geconcludeerd dat informatie gerelateerd aan de behandeling, afkomstig uit databanken, een eerste vereiste is om de kwaliteit van kanker zorg te verbeteren. Illustratief is het feit dat de rapportage van Engelse studies over de grote variabiliteit in behandelingsresultaten van borst en colorectaal kanker grote consequenties heeft gehad. Evenzo kunnen de resultaten van onze studies, waarbij we gebruik hebben gemaakt van onze prospectieve klinische databank, consequenties hebben voor de behandeling van patiënten met een vroeg stadium van baarmoederhalskanker. Allereerst kunnen de resultaten van onze studie en gegevens uit de literatuur worden gebruikt als argument om radiotherapie te geven aan patiënten met tumor gerelateerde risico factoren, zonder positieve klieren, infiltratie in het parametrium of positieve snijranden. Dit wordt aanbevolen omdat deze hoog risico patiënten baat hebben bij adjuvante radiotherapie.
Een andere aanbeveling is dat men een volledige lymfadenectomie zou moeten doen wanneer uit de vriescoupe tijdens de RHL blijkt dat er positieve klieren aanwezig zijn, omdat een groter aantal onderzochte (verwijderde) klieren leidt tot een betere ziektevrije overleving voor patiënten met positieve klieren. In de literatuur wordt nog steeds gedebatteerd over de therapeutische waarde van de lymfadenectomie. De resultaten van onze studie bevestigen echter dezelfde soort bevindingen van een eerder door ons uitgevoerde studie.
Daarnaast hebben we een mogelijkheid gevonden om een accurate voorspelling te geven van de toekomstige (ziektevrije) overleving van een individuele patiënt. Dit zou informatie kunnen geven om het behandelplan en (de duur van) het follow-up beleid te individualiseren. Hierdoor kan de follow-up

kosteneffectiever worden. Het toekomst perspectief zou kunnen zijn dat elke gynaecoloog-oncoloog een programma op zijn of haar computer heeft staan, waarmee het mogelijk zal zijn om een gedetailleerde toekomstige (ziektevrije) overleving voor een individuele patiënt te voorspellen. Dit soort programma's zullen in de toekomst nog nauwkeuriger worden vanwege de toenemende beschikbaarheid van nieuwe software voor multi-state modellen. Maar ook omdat het aantal behandelde patiënten voor baarmoederhalskanker zal toenemen in de database, waarin alle klinische en pathologische parameters van deze patiënten prospectief worden verzameld. Het is niet alleen hiervoor noodzakelijk om behandelingsgerelateerde informatie te verzamelen in een databank. De databank is ook essentieel om in staat te zijn aanvullende aanbevelingen te kunnen geven, zoals de andere 2 aanbevelingen hierboven genoemd. De Nederlandse Integrale Kanker Centra (IKC) registreren alleen nieuwe gevallen van kanker en verzamelen gegevens voor enkele onderzoeksgerichte activiteiten, maar geen behandelingsgerelateerde data van deze nieuwe patiënten. Bovendien zijn er nog steeds ziekenhuizen en verscheidene Europese landen die geen (betrouwbare) databanken hebben om gegevens van kankerpatiënten in te kunnen verzamelen. Daarom willen wij ziekenhuizen en ook de IKC's ten zeerste aanbevelen zulke databanken op te zetten, omdat ze waardevolle informatie kunnen geven over verschillen tussen behandelingsbenaderingen, risicofactoren, morbiditeit en overleving. Het vormt daarom de basis om de kanker zorg te bewaken, te controleren en te verbeteren.

Ten tweede kan uit onze studies worden geconcludeerd dat, door gebruik te maken van de juiste middelen, het mogelijk is om bewust te worden van en inzicht te krijgen in de mate van morbiditeit na een RHL voor de behandeling van het vroege stadium van baarmoederhalskanker. Wij valideerden de vragen betreffende het seksueel functioneren van de zelfrapporterende vragenlijst, de Gynaecologische LV. Dit is de eerst ontwikkelde Nederlandse vragenlijst die bestaat uit onderwerpen over seksueel functioneren, blaas- en darmproblematiek voor vrouwen met kanker. Deze vragenlijst zal ons helpen om op een subjectieve manier de klachten van patiënten na hun behandeling te meten en kan daardoor inzicht geven in de noodzaak om andere behandelingsmodificaties te ontwikkelen. Bovendien kan de vragenlijst worden gebruikt om de conventionele therapie met de nieuw ontwikkelde modificaties te vergelijken.
Omdat we ons steeds meer bewust worden van de neveneffecten van de behandeling voor baarmoederhalskanker en omdat de kwaliteit van leven vandaag de dag een belangrijk onderwerp is, zullen het aantal studies met behulp van zelfrapporterende vragenlijsten over de seksuele functie en vaginale veranderingen ongetwijfeld in de toekomst toenemen. Het is echter essentieel dat deze studies die de seksuele functie beoordelen, gebruik maken van gegevens van patiënten met dezelfde diagnose, behandeling, stadium en follow-up periodes. Een longitudinale opzet, gevalideerde vragenlijsten en een uitgaanswaarde zijn ook belangrijk.
Het is bewezen dat photoplethysmografische beoordeling van de vaginale doorbloedingsamplitude betrouwbaar en reproduceerbaar is om op een objectieve manier de vaginale doorbloeding tijdens sek-

suele opwinding te meten. RHL voor de behandeling van baarmoederhalskanker veroorzaakt schade aan de autonome zenuwen die zorgen voor een toename van de vaginale doorbloeding tijdens seksuele opwinding. Sinds dit bekend is, hebben meerdere auteurs verschillende zenuwsparende chirurgische benaderingen voorgesteld. Vaginale plethysmografie is daarom een belangrijk hulpmiddel voor het onderzoek naar de functionele resultaten van deze nieuwe chirurgische technieken.
In het LUMC hebben wij ook een zenuwsparende techniek ontwikkeld in een poging de zenuwschade tijdens RHL te verminderen zonder dat de oncologische principes van de radicaliteit worden opgeofferd. Deze zenuwsparende modificatie van de RHL wordt sinds 2000 uitgevoerd.
Onlangs zijn wij begonnen met een multicentrum observationele studie ter evaluatie van de ziektevrije overleving en de incidentie van blaas, colorectale en seksueel disfunctioneren na een zenuwsparende RHL voor de behandeling van baarmoederhalskanker stadium I-IIa. De resultaten van deze studie zullen in de komende jaren worden verwacht. De Gynaecologische LV en de photoplethysmografie worden hiervoor gebruikt om op een subjectieve en objectieve wijze de resultaten van deze nieuwe techniek te onderzoeken.
We hebben een begin gemaakt met de photoplethysmografische metingen. Voor dit deel van de studie zijn minimaal 26 vrouwen met een voorgeschiedenis van een conventionele RHL en 26 vrouwen na een zenuwsparende RHL nodig. Op dit moment is het ons nog niet gelukt om voldoende vrouwen te werven. Het blijkt erg moeilijk te zijn vrouwen te includeren nadat ze zijn behandeld vanwege het indringende karakter van het onderzoek. Om die reden zal het zeker nog 3 jaar duren voordat voldoende mensen zijn verzameld in iedere groep. Echter, de voorlopige resultaten van de studie laten zien dat de conventionele RHL geassocieerd lijkt te zijn met een algeheel lagere basale vaginale doorbloeding. En omdat het niet in dezelfde mate werd gezien na een zenuwsparende RHL, lijkt het dat de zenuwsparende techniek leidt tot een algeheel betere vaginale doorbloeding door minder denervatie van de vagina. De komende jaren zal de werving van patiënten voor de multicentrum observationele studie worden voortgezet, om aan te tonen dat de Leidse zenuwsparende modificatie van de RHL leidt tot minder morbiditeit met overeenkomstige behandelingsresultaten. Dit zou voor een verbetering van de kwaliteit van leven kunnen zorgen van patiënten die een levensreddende operatie ondergaan voor het vroege stadium van baarmoederhalskanker.

# Abbreviations

| | |
|---|---|
| CLS | capillary lymphatic space involvement |
| CSS | cancer specific survival |
| DFS | disease free survival |
| DI | depth of tumour invasion |
| GOG | Gynecologic Oncology Group |
| HR | high risk |
| LQ | Leiden Questionnaire |
| RHL | radical hysterectomy with pelvic lymphadenectomy |
| RS | risk score |
| VPA | vaginal pulse amplitude |

# Colour figures

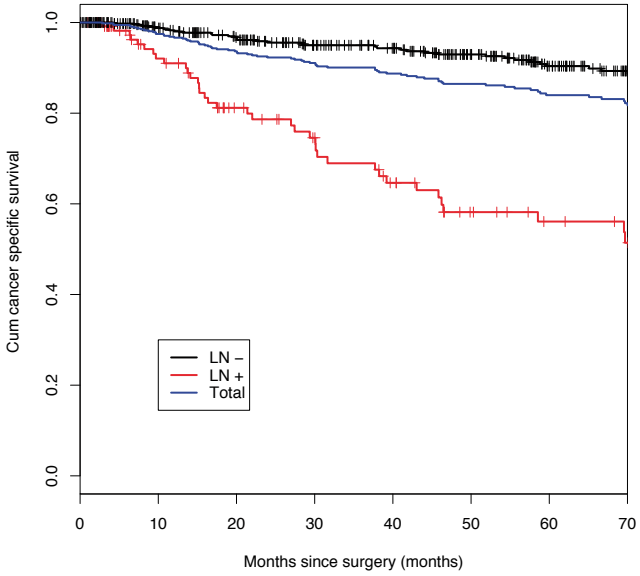


Figure 1. Cancer specific survival of the entire group (n=615), the patients with positive lymph nodes (n=123) and the patients with negative lymph nodes (n=492). Legend: Total, entire group; LN+, positive lymph nodes; LN-, negative lymph nodes. ( page 59 )

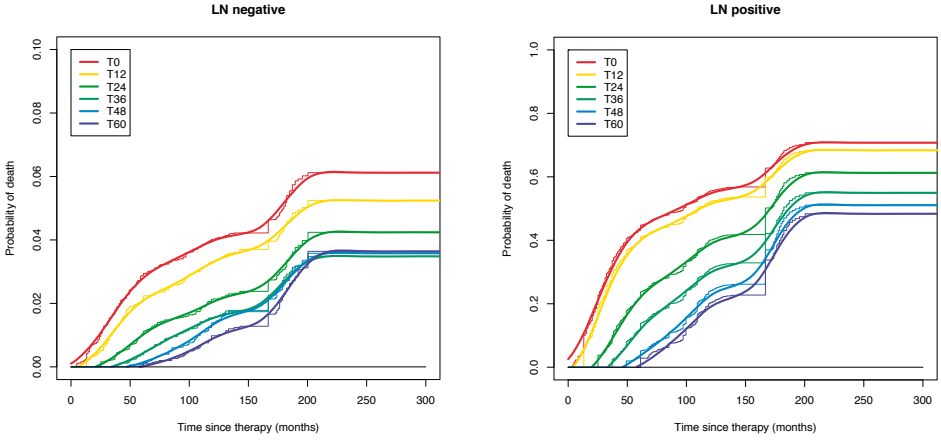


Figure 2. Predicted cumulative probability plots of patients with early stage cervical cancer with negative lymph nodes (LN negative) and with positive lymph nodes (LN positive).
Legend: To=0 months, T12= 12 months, T24=24 months, T36=36 months, T48=48 months and T60=60 months.
( page 60)

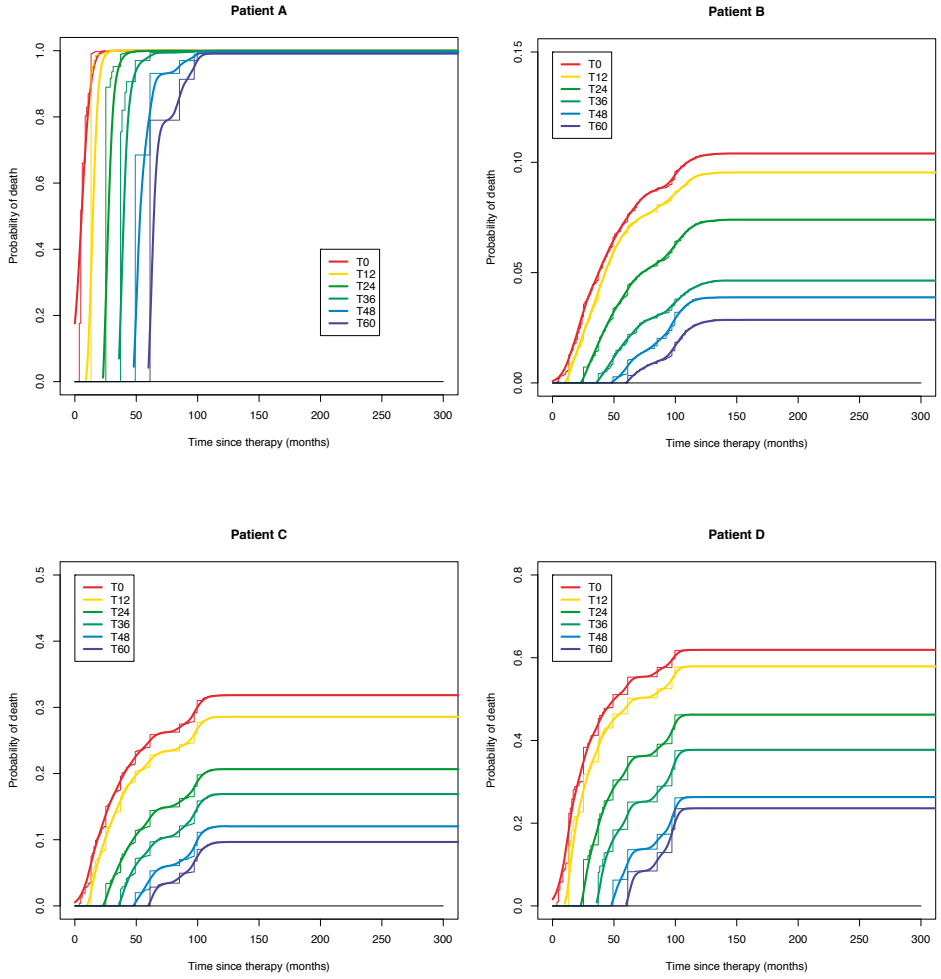


Figure 3. Predicted cumulative probability plots of patient A, B, C and D (Table 3). Legend: T0=0 months, T12= 12 months, T24=24 months, T36=36 months, T48=48 months and T60=60 months. ( page 61 )

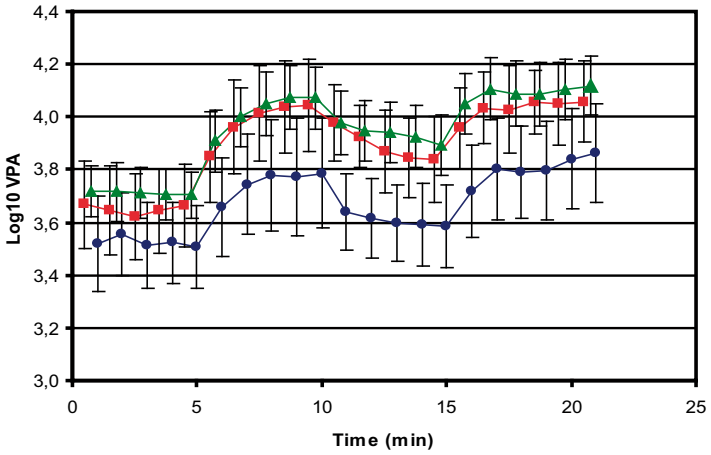


Figure 1. Change in logarithmically transformed mean vaginal pulse amplitude (log10VPA) during experimental session: Neutral stimulus 1 (Baseline assessment) (1-5 min), Erotic stimulus 1 (6-10 min), Neutral stimulus 2 (11-15 min), Erotic stimulus 2 (16-21 min).
–●–=Conventional RHL (n=13), –■–=Nerve-sparing RHL (n=10), –▲–=Controls (n=14). RHL, radical hysterectomy with pelvic lymphadenectomy. ( page 110 )

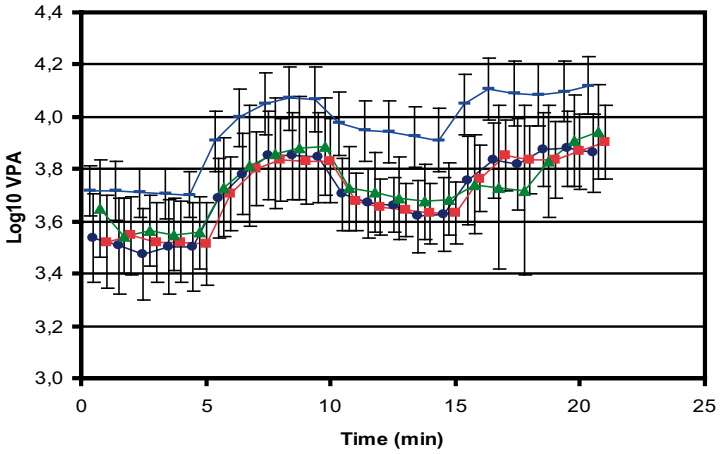


Figure 2. Postmenopausal versus premenopausal; change in logarithmically transformed mean vaginal pulse amplitude (log10VPA) during experimental session: Neutral stimulus 1 (Baseline assessment) (1-5 min), Erotic stimulus 1 (6-10 min), Neutral stimulus 2 (11-15 min), Erotic stimulus 2 (16-21 min).
–●– =Conventional RHL, postmenopausal (n=10), –■–=Conventional RHL, premenopausal (n=13), –▲–=Controls, postmenopausal (n=12), ——=Controls, premenopausal (n=14) RHL, radical hysterectomy with pelvic lymphadenectomy. ( page 112 )

# Curriculum vitae

Quirine Dionne Pieterse werd geboren op 24 juni 1975 te Dordrecht. Zij groeide op in Bussum waar zij balletlessen volgde, tenniste, leerde reddingszwemmen en als belangrijkste veel hockeyde. Zij behaalde het VWO diploma aan het Sint Vitus College te Bussum in 1994. In datzelfde jaar ving zij aan met de opleiding oefentherapie Cesar aan de Hogeschool van Utrecht. Na 9 maanden van deze studie te hebben afgerond, ging zij aan de Universiteit van Amsterdam Geneeskunde studeren. In 1996 behaalde zij cum laude haar propedeuse. Haar wetenschappelijke stage deed zij op de afdeling Gynaecologie en Verloskunde van het AMC onder leiding van Dr. W.M. Ankum naar de prevalentie van bekkenbodemproblematiek bij vrouwen die meer dan 10 jaar geleden waren bevallen van hun eerste kind. Na het cum laude behalen van haar doctoraal examen in 2000, heeft zij in de wachttijd voor haar co-schappen een extra verloskunde stage gedaan op de afdeling Gynaecologie en Verloskunde in het Bosch Medisch Centrum te Den Bosch. In december 1999 begon zij aan haar co-schappen. Tijdens haar co-schappen deed zij wetenschappelijk onderzoek op de afdeling Gynaecologie en Verloskunde in het AMC, onder leiding van Dr. J. van der Velden, naar de overleving van het klinisch stadium II endometriumcarcinoom waarbij een radicale uterusextirpatie werd verricht.

Na het behalen van het artsexamen in maart 2002 was zij een jaar werkzaam als AGNIO op de afdeling Gynaecologie en Verloskunde in het Medisch Centrum Alkmaar te Alkmaar (opleider Dr. J.B. Maathuis) en daarna anderhalf jaar in het Leyenburg Ziekenhuis, thans Haga Ziekenhuis, te Den haag (opleider Dr. P.A. de Jong). Tijdens haar werkzaamheden als AGNIO in het Haga Ziekenhuis deed zij wetenschappelijk onderzoek naar morbiditeit en kwaliteit van leven na een radicale uterusextirpatie voor de behandeling van het cervixcarcinoom onder leiding van Prof. Dr. G.G. Kenter op de afdeling Gynaecologie en Verloskunde in het LUMC. Deze studie was de aanleiding om in januari 2005 te starten als AGIKO voor full-time wetenschappelijk onderzoek. Dit onderzoek, dat plaatsvond op de afdeling Gynaecologie in het LUMC (Prof. Dr. G.G. Kenter en Prof. Dr. J.B.M.Z. Trimbos) leidde tot dit proefschrift.

Vanaf 1 april 2007 is zij in opleiding tot gynaecoloog in het Haga Ziekenhuis (opleider: Dr. E. van Rijssel) en het LUMC (opleiders: Prof. Dr. H.H.H. Kanhai en Prof. Dr. G.G. Kenter).

# Dankwoord

Dit proefschrift is mede tot stand gekomen door de steun en deskundigheid van een team van mensen om mij heen. De basisopstelling wil ik hier graag persoonlijk bedanken.
Allereerst de voorhoede, bestaande uit alle mensen op de werkvloer die mij hebben geholpen tijdens het onderzoekstraject. **Kees**, van je uitleg, je inzicht, je hulp, je anatomieles, je inzet en je altijd positieve instelling heb ik onbeschrijfelijk veel geleerd, heel veel dank daarvoor. Snap je? **Paul**, dat ik ooit in staat zou zijn om statistiek te bedrijven en het ook nog een heel klein beetje leuk ben gaan vinden, heb ik mede aan jou te danken. **Heleen**, dank voor je hulp met computers, je luisterend oor en al het geklets. Je bent een geweldige kamergenoot en collega! **Lot**, dank voor alles wat je me hebt geleerd over het praten over seks (poli) en het onder de knie krijgen van het sekslab. **Philomeen**, jij was altijd op de hoogte van de vorderingen van mijn onderzoek, bedankt voor al je belangstelling. **Alle medewerkers van de poli seksuologie**, dank voor al jullie medewerking. **Pauline** en **Irma**, met jullie eeuwige enthousiasme en hulp bij het werven van controles is het includeren zeker een stuk sneller gegaan! **Jessica, Fleur en Karijn**, het was altijd gezellig op de grootste kamer van J8. **Wendela**, al je adviezen en informatie hebben me veel geholpen. **Edgar** en **Sabine**, ik vond het echt fantastisch jullie als mijn paranimphen te hebben! Alle **collega-assistenten, klinisch verloskundigen, verpleging en gynaecologen** uit het LUMC en het Haga Ziekenhuis; bedankt voor al jullie adviezen, steun en collegialiteit. **Margriet** en **Anneke**, het was fijn met jullie samen te werken. Al jullie invoerwerk is de basis geweest van alle studies. **Bea, Wil en Ineke**, jullie kletspraat was heerlijk en jullie secretariële ondersteuning onmisbaar! Jullie zijn goud waard. En tot slot **alle vrouwen** die hebben deelgenomen aan mijn onderzoek. Zonder hen was het niet gelukt. Dank jullie wel!
Echter, een sterke voorhoede functioneert niet zonder een goed middenveld. Het zijn de mensen die naast mijn werk en familie een belangrijke rol spelen in mijn leven. Lieve **Nicole**, dank voor je grenzeloze vriendschap! **Dames 2 van HDM**; echt t allerleukste team van Den Haag! **Oud dames 1 van Gooische**; we blijven een team! **Urbian, Inge, Didi, Titia, Juliette, Roos, Karin, Leonie, Valérie,** en allen die ik ben vergeten, dank voor jullie vriendschap, steun en aanmoediging. **Familie Schoenaker**, ik geniet van jullie enthousiasme en warmte. **Jort** alias doctor Phil, je bent onvervangbaar. En tot slot **Delfien**, dank je wel voor het geven van inzicht.
Dan komen we bij de achterhoede, mijn achtergrond en basis. **Justin, Kevin en Rogier**, betere broers kan ik me niet wensen! **Jocelyne**, onze 'zusmomenten' zijn onvervangbaar! Lieve **mam**, thanx for all!
Eén speler in het team heb ik nog niet genoemd. Dat is de 'midden midden'; de belangrijkste speler in het veld, de spelverdeler, het middelpunt, het hart. Deze positie wordt ingenomen door mijn grote liefde, steun en toeverlaat; **Gerad**. Lieve **Surfer; love you!**

# Publications

The following papers were published or submitted on the basis of the studies in this thesis:

**Pieterse QD**, Trimbos JBMZ, Dijkman A, Creutzberg CL, Gaarenstroom KN, Peters AAW, Kenter GG.
Postoperative radiation therapy improves prognosis in patients with adverse risk factors in localized, early-stage cervical cancer: a retrospective comparative study.
*Int J Gynecol Cancer 2006; 16:1112-1118*

**Pieterse QD**, Maas CP, Ter Kuile MM, Lowik M, Van Eijkeren MA, Trimbos JBMZ, Kenter GG.
An observational longitudinal study to evaluate miction, defecation and sexual function after radical hysterectomy with pelvic lymphadenectomy for early stage cervical cancer.
*Int J Gynecol Cancer 2006; 16:1119-1129*

**Pieterse QD**, Kenter GG, Gaarenstroom KN, Peters AAW, Willems SM, Fleuren GJ, Trimbos JBMZ.
The number of pelvic lymph nodes in the quality control and prognosis of radical hysterectomy for the treatment of cervical cancer.
*Eur J Surg Oncol 2007; 33:216-221*

**Pieterse QD**, Kenter GG, Eilers PHC, Trimbos JBMZ.
An individual prediction of the future (disease free) survival of patients with a history of early stage cervical cancer; multi-state model.
*Int J Gynecol Cancer 2007; in press*

**Pieterse QD**, Ter Kuile MM, DeRuiter MC, Trimbos JBMZ, Kenter GG, Maas CP.
Vaginal blood flow after radical hysterectomy with and without nerve-sparing.
A preliminary report.
*Int J Gynecol Cancer 2007; in press*

**Pieterse QD**, Ter Kuile MM, Maas CP, Kenter GG.
The Gynaecologic Leiden Questionnaire: psychometric properties of a self-report questionnaire of sexual function and vaginal changes for gynaecological cancer patients.
*Submitted for publication*