



Universiteit
Leiden
The Netherlands

Early stage cervical cancer : quality of cancer care and quality of life
Pieterse, Q.D.

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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 life 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 maintenance 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 rise 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 lymphadenectomy (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 pelvis 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. Therefore, 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 until 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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