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

Citation

Version: Corrected Publisher’s Version
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Downloaded from: https://hdl.handle.net/1887/12312

Note: To cite this publication please use the final published version (if applicable).
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 maintenance 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 ≥40mm, 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 benefitted 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 Gynaecologic 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;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;49;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
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 significantly 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 photoplethysmographic 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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