Pelvic floor function after gynaecological cancer treatment
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Summary, conclusions and implications for clinical practice and future research
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Chapter 1 is the general introduction and describes the objectives and outline of the thesis.

Part I: Effects of gynaecological cancer treatment on pelvic organ and sexual function, pelvic-floor-related quality of life and help-seeking behaviour

In Chapter 2 we describe the prevalence of and distress from pelvic floor symptoms in long-term cervical cancer survivors.

In a cross-sectional study we matched cervical cancer survivors (CCS) with a random female population sample (reference group). We assessed prevalence of and severe distress from bladder and bowel symptoms with pelvic floor-related questionnaires: the Uro-Genital Distress Inventory (UDI) and Defecation Distress Inventory (DDI). We dichotomized the symptom domain scores into severe and non-severe distress with the cut-off point at the 90th percentile of domain scores of a random female population. 146 CCS underwent radical hysterectomy and pelvic lymph node dissection (RH and LND), 49 underwent surgery and adjuvant radiotherapy (SART) and 47 primary radiotherapy (PRT).

Urge incontinence, difficulty to empty the bladder and incomplete emptying were reported by each treatment group more frequently than by the reference group. Patients, who were treated surgically, with or without adjuvant radiotherapy, reported more frequently straining to defecate in over one-quarter of times. In addition, both radiotherapy treatment groups reported more often to loose liquid stool.

Patients treated with RH and LND reported more distress from urinary incontinence, obstructive voiding and pelvic or abdominal pain as compared to levels of distress from their matched controls. Patients treated with PRT reported more distress than their controls from all uro-genital symptoms, i.e. urinary incontinence, obstructive voiding, overactive bladder and pelvic or abdominal pain. The RH and LND group reported more distress from constipation and obstructive defecation than the reference group. Patients who underwent primary or adjuvant radiotherapy reported more distress from anal incontinence than their matched controls.

In conclusion, the results show that treatment of cervical cancer is related to impaired pelvic floor function. Patients treated with PRT report the most frequently adverse effects on pelvic floor function. The results of our study enable physicians to inform patients that specific symptoms may occur after a certain treatment modality. Furthermore, to facilitate referral to pelvic floor specialists of patients who experience bothersome symptoms, we recommend evaluating pelvic floor symptoms as a routine procedure during follow up.

In Chapter 3 we identify associations between demographic, disease-related and psychological variables and severe distress from pelvic floor symptoms following cervical cancer treatment.
We cross-sectionally studied cervical cancer patients treated between 1997 and 2007 in the AMC, Amsterdam. Pelvic floor symptoms were assessed with patient-reported questionnaires: the UDI and DDI. We dichotomized the symptom domain scores as done in our previous study (Chapter 2). Disease-related variables were extracted from medical files. Psychological factors included mental and physical well-being, optimism and body image, which were assessed with standardized questionnaires. Uni- and multivariate logistic regression analyses were performed. 282 patients were included: 148 were treated RH+LND, 61 with SART, and 73 with PRT. Multivariate analyses showed no significant relation between demographic variables and symptoms. None of the disease-related variables were significantly associated in multivariate analyses. In all treatment groups multivariate associations were found between psychosocial variables and severe pelvic floor symptoms. In general, better mental and physical well-being was associated with non-severe pelvic floor symptoms.

In the RH+LND group statistically significant associations were found between mental well-being and severe uro-genital symptoms (OR 0.93, 95% CI: 0.88 – 0.97) and between physical well-being and severe defecation symptoms (OR: 0.90, 95% CI: 0.86 – 0.94). In the SART group, a significant association was found between physical well-being and severe defecation symptoms (OR 0.93, 95% CI: 0.87 – 0.99). In the PRT group a significant association was found between increased body-image disturbance and severe defecation symptoms (OR: 1.13, 95% CI: 1.01 – 1.27).

In conclusion, few associations were found between demographic and disease-related variables and distress from pelvic floor symptoms after cervical cancer treatment. However, better mental and physical well-being are associated with non-severe distress from uro-genital and defecation symptoms and more body-image disturbance with severe pelvic floor symptoms. Improving these factors might reduce distress from pelvic floor symptoms and should be the focus of future research.

Chapter 4 describes sexual function and explores associations between variables and sexual function after vulvar cancer treatment.

We identified vulvar cancer patients treated between 1997 and 2007 in the AMC, Amsterdam, and mailed them questionnaires assessing sexual function, mental and physical well-being, body image and optimism. Demographic and disease-related data were collected from medical files. Radical local excision with inguinal lymph node dissection and radical vulvectomy were considered ‘extensive treatment’; radical local excision, with or without sentinel node as ‘less extensive treatment’. Associations between sexual function and these variables were explored with univariate and multivariate linear regression analyses.

Of 120 eligible patients, 76 (63%) responded. Eighteen women with a male partner (43%) reported having sexual intercourse. Sexual function questionnaire (Female Sexual Function Inventory, FSFI) domain scores did not differ between extensively and less extensively treated women. Age was negatively associated with “Arousal” and “Desire”.

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Positive associations were found between having a partner and “Satisfaction”, optimism and “Desire” and physical well-being and “Orgasm”. Adjuvant inguinal radiotherapy was negatively associated with “Orgasm”. One woman reported having better sexual function after than before treatment, 50% reported a similar sexual function, and 42% a worse sexual function. These results indicate that the sexual function of women treated for vulvar cancer is influenced by multiple factors, and that gynaecologists, other physicians, and nurses should enquire about the sexual function of their patients before and after surgery. In the case of sexual dysfunction they should offer specialized help (by a sexologist).

Chapter 5 is an evaluation of routine renal ultrasound after treatment of early stage cervical cancer with a radical hysterectomy and pelvic lymph node dissection according to Wertheim-Okabayashi

Hydronephrosis can be a side effect of radical hysterectomy (RH) for cervical cancer. The incidence of clinically relevant hydronephrosis has not been studied in a large sample and the benefit of early detection of hydronephrosis is not clear. The objectives were to assess the incidence of hydronephrosis following RH and to evaluate the usefulness of routine renal ultrasound. We studied retrospectively cervical cancer patients (FIGO stage IBl-IIA) treated with RH and LND with or without adjuvant radiotherapy, without per-operative lesion of the ureter, and who had oncological follow-up of 6 months in the AMC, Amsterdam, between January 1998 and December 2008. Routine renal ultrasound was performed four weeks after RH, and some patients underwent imaging on indication before or after the routine ultrasound. We documented which interventions for hydronephrosis were performed and evaluated the profile of patients at risk for hydronephrosis.

281 patients were included: 252 (90%) underwent routine renal ultrasound and 29 (10%) underwent imaging on indication before routine ultrasound. The overall incidence of hydronephrosis was 12%. In symptomatic patients, the incidence was 21% and in asymptomatic women undergoing routine ultrasound the incidence was 9%. Four patients were invasively treated for hydronephrosis (1% of the total group) after imaging for clinical suspicion of hydronephrosis. Patients with hydronephrosis had been treated significantly more often with radiotherapy than patients without hydronephrosis (43% versus 25% (p=0.03). We concluded that there is no place for routine renal ultrasound following radical hysterectomy. Patients should be instructed about the symptoms that may be related to hydronephrosis, and contact the treating physician to find out whether there is an indication for renal ultrasound or other imaging techniques.

Chapter 6 focuses on personal reasons for not seeking medical help for severe pelvic floor symptoms in gynaecological cancer survivors.

With this qualitative study we aimed to explore (1) reasons for not seeking help for severe pelvic floor symptoms after gynaecological cancer treatment, (2) the willingness to undergo
treatment for these symptoms and (3) to invite suggestions to improve out-patient care. We interviewed semi-structured vulvar, endometrial or cervical cancer survivors treated in the AMC, Amsterdam between 1997 and 2007. The interviewees were a purposively selected sample from 138 eligible respondents to pelvic floor related questionnaires, who were severely bothered by symptoms (> 75th percentile of domain sum score of questionnaires) and who had not sought medical help. After each semi-structured interview a checklist with reasons for not seeking help was complemented with newly mentioned reasons. The interviews were stopped when data saturation was accomplished, i.e. three consecutive interviewees had not revealed new reasons. The interviews were analyzed by two researchers independently.

Fifteen interviews were conducted. Most reported reasons for not seeking help were that patients found their symptoms bearable in light of their cancer diagnosis and treatment, as most patients were informed about the consequences of treatment and felt fortunate to be alive, and because they lacked knowledge about possible treatments. Seven patients were willing to undergo treatment. Eleven patients stated that care should be improved, specifically by timely referral to pelvic floor specialists and additional care by oncology nurses.

There is need for standard attention to adverse effects on pelvic floor function after cancer treatment. This could be realized by quantifying symptoms using questionnaires, standard attention for such symptoms by gynaecological oncologists or oncology nurses and timely referral to pelvic floor specialists of those with bothersome pelvic floor symptoms.
Part II: Preventive and therapeutic measures for pelvic floor symptoms during and after gynaecological cancer treatment

In Chapter 7 the results are presented of a randomized clinical trial on the effect of pelvic physiotherapy on pelvic floor function after treatment of early stage cervical cancer. In this randomized clinical trial (RCT) in the AMC, Amsterdam we included early stage cervical cancer (FIGO stage IIB-IIBA) patients undergoing RH and LND, without previous bladder or bowel surgery or current pregnancy. The intervention (pelvic physiotherapy; PPT) and control (No PPT) groups received an illustrated brochure with instructions about pelvic exercises and voiding techniques. PPT patients additionally received advices and training by pelvic physiotherapists pre- and postoperatively.

Primary outcome was obstructive voiding domain score of the Uro-genital Distress Inventory. Secondary outcomes were other domain scores as assessed by the UDI, DDI and FSFI. Patients completed the set of questionnaires and voiding diaries preoperatively, 6 weeks, 3 and 12 months postoperatively. Flowcytometry and post void residual volumes were measured at 6 weeks, 3 and 12 months postoperatively. For analysis of the repeated measurements we used Generalized Estimation Equations (GEE).

Between September 2007 and January 2010, 82 patients were randomized, allocating 42 PPT patients and 40 No PPT patients. At 6 weeks the mean obstructive voiding domain score was in PPT patients 19 (Interquartile range: 0-33) and in No PPT patients 22 (Interquartile range: 0-33). No statistically significant differences were found on the primary and secondary outcomes between the PPT and the No PPT groups.

Before considering additional advices and training by specialized pelvic physical therapists for those patients, who are not able to fully understand the written information and exercises, their costs and potential benefits as well as patients’ preference should be studied. In conclusion, we did not find an effect of additional pelvic physiotherapy after early stage cervical cancer treatment to an illustrated brochure explaining voiding technique, with respect to post-operative pelvic floor function.

In Chapter 8 the results are reported of a pilot study about the feasibility and efficacy of intravesical instillations with chondroitin sulphate 0.2% to prevent or reduce acute radiation cystitis in gynaecological cancer patients treated with pelvic radiotherapy.

In this pilot study, we explored feasibility and efficacy of intravesical instillations with 40 ml chondroitin sulphate 0.2% solution to prevent or reduce acute radiation cystitis (RC) in women undergoing pelvic radiotherapy. We conducted a comparative study in 20 consecutive cervical and endometrial cancer patients. Half of the amount of included patients chose to receive instillations. We weekly assessed, during a period of eight weeks, bother from instillations with Visual Analogue Scores (VAS, 0-10), bladder pain with VAS and voiding-related-quality of life with the UDI. One of the patients receiving the intravesical instillations discontinued the instillations after the fourth treatment due to experienced urethral pain. The first median ‘bother’-VAS was 0 (range: 0 - 3); the last median was 1 (range: 0 - 3). ‘Bladder pain’-VAS peaked halfway treatment among controls.
(median: 1; range: 0–5) and after treatment in instilled patients (median: 1; range: 1-3).
Median UDI scores at follow up of instilled patients were at or below median baseline scores, whereas the median scores at follow up of the controls were at or above median baseline scores.

The results of this pilot study show that intravesical instillations with chondroitin sulphate 0.2% solution are well tolerated by patients undergoing pelvic radiotherapy for a gynaecological malignancy. Additionally, the instillations appear to reduce overactive bladder symptoms during the period of radiotherapy. Whether the restricted severity of symptoms following radiotherapy can be entirely explained by the efficacy of chondroitin sulphate itself, or by other factors such as additional attention that was given to the intervention group, needs to be assessed by a double-blind placebo-controlled RCT.

In Chapter 9 we describe two patients who were treated with a minimal invasive tension-free vaginal tape (TVT-Secur™) for stress urinary incontinence after cervical cancer treatment.

We presented two patients with bothersome stress urinary incontinence (SUI) following RH and LND for early stage cervical cancer. One patient underwent adjuvant radiotherapy. We expected altered anatomy due to major pelvic surgery in these two patients. Therefore we aimed to avoid the pelvic cavity. We selected a minimal invasive tension-free vaginal tape (TVT) not passing the obturatory foramen or the retropubic route: TVT-Secur™. Additionally, given results of a case series, we counted on low risk of developing bladder retention. Both patients were continent post-operatively. One patient presented with a small tape-erosion that was successfully corrected using local analgesics. The other patient developed urgency symptoms that disappeared after treatment with a cholinergic receptor antagonist, solifenacine. Both patients had detrusor hypo-activity at pre-operative urodynamics, but no bladder retention occurred following surgery.

In patients with a history of radical hysterectomy who present with SUI, we would advise to inform patients that satisfying results can be expected of a minimal invasive tension-free vaginal tape, but that it is likely that patients have to undergo additional treatments, such as removal of eroded mesh or medical treatment for side effects.
Conclusions

Part I

1. a. Cervical cancer patients treated with surgery, with or without adjuvant radiotherapy or with primary radiotherapy experience urinary incontinence and obstructive voiding and, when present, experience more frequently severe distress from these symptoms, as compared to matched controls from a random female population.

1. b. Cervical cancer patients treated with radical hysterectomy and pelvic lymph node dissection experience more frequently severe distress from constipation and obstructive defecation, as compared to matched controls from a random female population.

1. c. Cervical cancer patients treated with adjuvant or primary radiotherapy experience more frequently distress from anal incontinence, as compared to matched controls from a random female population.

2. a. In cervical cancer patients associations exist between general well-being and body image and severe distress from uro-genital and defecation symptoms: i.e. better mental and physical well-being is related to not severe distress from uro-genital and defecation symptoms and more body image disturbance to severe distress from defecation symptoms.

2. b. Sexual function of patients who have been treated for vulvar cancer is negatively affected by advanced age and adjuvant inguinal radiotherapy, but positively influenced by having a partner, better physical well-being and optimism.

3. a. The incidence of hydronephrosis after radical hysterectomy with pelvic lymph node dissection is 9% in asymptomatic patients and 21% in symptomatic patients during a period of 6 months postoperatively.

3. b. Routine renal ultrasound after radical hysterectomy and pelvic lymph node dissection does not have a proven benefit for patient outcome concerning hydronephrosis.

4. a. Most mentioned reasons for gynaecological cancer patients with severe pelvic floor symptoms for not seeking medical help were, that they consider these symptoms in the perspective of their previous cancer diagnosis and treatment, that most patients were informed about the consequences of treatment and feel fortunate to be alive, and because they were unaware of treatment options.

4. b. Most gynaecological cancer patients who have severe pelvic floor symptoms and did not seek medical help, would undergo treatment for these symptoms if this was proposed and efficacious.
Part II

5. a. No additional value was found of pelvic physiotherapy to an illustrated brochure explaining voiding techniques and pelvic floor exercises on pelvic floor function after radical hysterectomy with pelvic lymph node dissection for early stage cervical cancer.

5. b. Intravesical instillations in endometrial and cervical cancer patients receiving pelvic radiotherapy are feasible and intravesical instillations with chondroitin sulphate 0.2% solution may decrease bother related to bladder symptoms.

5. c. Minimal invasive sub-urethral tension-free vaginal tapes can possibly be a treatment option for bothersome stress urinary incontinence after cervical cancer treatment.
Implications for clinical practice and future research

In this thesis prevalence of and distress from pelvic floor symptoms were investigated after cervical cancer treatment. Associations between patient, disease and treatment, and psychological variables and distress from pelvic floor symptoms have been studied in patients after cervical and vulvar cancer treatment. As these symptoms are often present and patients report to experience distress from these symptoms, patients should be informed about the possible occurrence of these symptoms and the possible distress it may cause both before and after cervical and vulvar cancer treatment.

In accordance with our recommendation that routine renal ultrasound for early diagnosis of hydronephrosis should not be done after radical hysterectomy and pelvic lymph node dissection for early stage cervical cancer, the protocol in the AMC Amsterdam has been adjusted. Nowadays, only patients undergo renal ultrasound or other imaging techniques when clinical suspicion of hydronephrosis is present.

From the qualitative study we concluded that there is a need for routine attention for side effects from gynaecological cancer treatment. Patients have suggested that if pelvic floor symptoms occur, these should be diagnosed early. When patients experience distress from these symptoms, they would like to be timely referred to pelvic floor specialists. There is a need to study prospectively whether routine evaluation of pelvic floor and sexual symptoms before and after gynaecological cancer treatment leads to earlier detection and management of these symptoms and ultimately to better quality of life. For example, pelvic floor function could be routinely assessed by patient reported questionnaires before and up to two years after treatment. The post-treatment results of the questionnaires could be checked by an oncology or continence nurse at the out-patient clinic. Patients could then be divided between referral to a pelvic specialist and no referral by pre-randomization, i.e. without patients knowing they are randomized. This is a method to prevent drop-outs and non-compliance in the control-group. (1) Any interventions in both arms should be recorded. The results of all follow-up questionnaires should reveal whether the two groups differ in pelvic floor related quality of life.

Implications of the results of our study on pelvic physiotherapy after radical hysterectomy are that the brochure about pelvic exercises and voiding techniques is now handed out routinely in the AMC Amsterdam when patients undergo a radical hysterectomy with pelvic lymph node dissection. Pelvic physiotherapists are only consulted when patients are not able to understand the written information and additional information by the nurse about the exercises is not understood well.

The pilot study about the feasibility and efficacy of intravesical instillations with chondroitin sulphate 0.2% solution showed that the instillations were well tolerated and that there was a possible beneficial effect of the instillations on overactive bladder symptoms related to radiotherapy. These results have lead to a multicenter randomised clinical placebo-controlled trial which is currently conducted in the Netherlands: the PARIS study. The objectives of this study are to evaluate whether intravesical instillations with chondroitin
sulphate solution 0.2% reduce bother related to symptoms of acute radiation cystitis in patients undergoing pelvic radiotherapy for a gynaecological malignancy 12 weeks after radiotherapy. Also an economic evaluation is part of this study.

(www.studies-obsgyn.nl/paris).

The case report about treatment of urinary stress incontinence after cervical cancer treatment was meant as an illustration of a treatment possibility for these symptoms in those patients, i.e. a minimal invasive tension free vaginal tape. Its positive results and lack of publications for alternative treatment options might be the start of future randomized studies.
Reference List