Sexual rehabilitation after radiotherapy for gynaecological cancer

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APPENDICES

ENGLISH SUMMARY

With the increasing incidence of cervical, vaginal, and endometrial cancers there is a growing emphasis on the management of health-related quality of life. Many women with gynaecological cancers receive radiotherapy in the course of their treatment. Radiotherapy, and particularly combined radiotherapy and brachytherapy, is associated with vaginal mucosal changes, such as stenosis, which may adversely affect sexual functioning. Frequently reported vaginal problems include dyspareunia, reduced lubrication, vaginal tightening and shortening, and bleeding, as well as sexual functioning problems, such as decreased sexual desire, arousal, enjoyment, and overall satisfaction. These vaginal and sexual functioning problems may be accompanied by sexual distress and may be influenced by a complex interplay of physiological, psychological, and relational factors, such as anxiety, altered body image, and relationship difficulties. To prevent vaginal stenosis, the use of vaginal dilators is recommended after treatment. However, compliance has remained low in previous studies.

Chapter 1 introduces a nurse-led sexual rehabilitation intervention for women treated with radiotherapy for gynaecological cancers. Research suggests that interventions combining psychoeducation and psychosexual-based cognitive-behavioural techniques, with partner involvement, can improve sexual functioning and dilator use compliance. Therefore, a nurse-led sexual rehabilitation intervention incorporating these elements was developed and pilot-tested, with promising results. The multicentre SPARC (Sexual rehabilitation Programme After Radiotherapy for gynaecological Cancer) trial was initiated to evaluate the (cost-)effectiveness of this intervention.

In this thesis, the aims were:

1. To evaluate physician-assessed vaginal changes and patient-reported outcomes regarding vaginal and sexual functioning problems, as well as sexual distress during the first two years after image-guided radio(chemo)therapy and brachytherapy for locally advanced cervical cancer.
2. To assess the efficacy of the nurse-led sexual rehabilitation intervention compared to standard care in terms of sexual functioning, distress, dilator use, and vaginal symptoms after external beam radiotherapy alone or in combination with brachytherapy for gynaecological cancers.
3. To compare the cost-effectiveness of the nurse-led sexual rehabilitation intervention with standard care in women treated with external beam radiotherapy, with or without brachytherapy, for gynaecological cancers.

Chapter 2 presents the results of the prospective EMBRACE vaginal morbidity substudy, which prospectively evaluated physician-assessed vaginal changes and patient-reported outcomes on vaginal and sexual functioning problems, and sexual distress in the first 2-years after radio(chemo)therapy with image-guided adaptive brachytherapy for locally advanced cervical cancer, and to explore the association between these. A total of 113 women with ≤5mm vaginal tumour involvement at diagnosis were analysed between 2012 and 2018. Compared to the full EMBRACE study cohort, this subset differed in lower tumour stage and less vaginal tumour extension, influencing treatment parameters. Overall, mostly mild vaginal changes (not interfering with sexual functioning) were reported, without clear changes during the 2-year follow-up. Higher grades were reported in <3% of the women. Over time, sexual inactivity decreased from 79% at baseline to 47% at 24 months after radiotherapy, mostly because of losing interest in sex or lacking a partner. Any vaginal and sexual functioning problems and distress were reported by almost half of the sexually active women over 2-years after radiotherapy. More substantial vaginal and sexual functioning problems and distress were reported by a up to 14%, 20% and 8% of the sexually active women, respectively. Most vaginal changes and sexual satisfaction differed significantly between baseline and follow-up, without further significant change between the first three months and later follow-up moments. Vaginal functioning problems and sexual distress, as reported in the patient-reported outcomes, were not or only weakly associated with the physician-assessed vaginal changes. This showed that sexual functioning is much more complex than vaginal morbidity alone.

Chapter 3 describes the design of the multicentre, randomized SPARC trial in which we investigated the (cost-)efficacy of the nurse-led sexual rehabilitation intervention in improving sexual functioning and dilator use of cervical, vaginal or endometrial cancer patients after radiotherapy. The primary outcome was sexual functioning as measured by the Female Sexual Function Index (FSFI). Secondary outcomes included body image, fear of sexual activity, sexual distress, treatment-related, and psychological distress, health-related quality of life and relationship satisfaction. We compared the nurse-led sexual rehabilitation intervention with standard care (optimal care-as-usual). Participants were randomized to either the intervention- or standard care group, and within each centre stratified by type of radiotherapy (External Beam Radiotherapy (EBRT) combined with Brachytherapy versus EBRT only) and having a partner (yes/no). Oncology nurses completed a 50-hour training in sexology, cognitive behavioural techniques, and the treatment protocol. They received monthly supervision from an experienced sexologist and attended additional training sessions on study-relevant topics. Standard care consisted of an information session with the trained nurse, information booklet and a dilator set (if applicable) one month after radiotherapy free of charge. The intervention group received sessions at 1, 3, 6, and 12 months after radiotherapy, with an additional 2-month session for women who received

brachytherapy. Partners were invited to the sessions, however, participation was not mandatory. Briefly, the intervention included 11 personalized modules covering topics such as education on cancer diagnosis and treatment, dilator use, fears related to dilator use and resuming sexual activity, promoting couples' coping and support, and addressing sexual and body image concerns. All women completed questionnaires at baseline (retrospective) and at 1, 3, 6, and 12 months after radiotherapy. Vaginal changes were assessed through standardized clinical assessments and recorded at the same timepoints.

Chapter 4 presents the efficacy results of the nurse-led sexual rehabilitation intervention compared to standard care. The SPARC trial enrolled 229 women between 2018 and 2021 across all Dutch gynaecological oncology centres (N=10). Results showed no statistically significant differences between the intervention and standard care groups in sexual functioning or most secondary outcomes at any timepoint after radiotherapy. While sexual functioning declined initially after radiotherapy in both study groups, they gradually improved over time (at 12-months, mean FSFI scores were 22.57 in the intervention group and 21.76 in the standard care group). Approximately 70% of women in both study groups reported being sexually active at 12 months, which is higher than the 40-50% sexual activity rates reported in previous studies. Clinical-level sexual distress persisted in approximately 50% of participants across both groups at one year. Vaginal changes, including stenosis, were generally mild or absent in the majority of women, and substantial vaginal morbidity was rare. High compliance with vaginal dilation after brachytherapy was observed in both groups: 85% of women in the intervention group and 75% in the standard care group reported using any form of dilation (e.g., dilators, intercourse, vibrators, fingers) at least twice weekly at 12 months after radiotherapy. Several factors could explain the absence of significant differences between study arms. Since the completion of the pilot study, sexual rehabilitation has become more integrated into standard gynaecologic oncology care in the Netherlands. Routine post-treatment consultations, increased awareness among healthcare providers, provision of vaginal dilators with instructions, and publicly available psycho-education resources likely enhanced care quality across both groups. The findings suggest that the enhanced standard care delivered during the study period may have been sufficiently comprehensive to support recovery in sexual functioning and vaginal health, thereby diminishing the added value of the multisession structured nurse-led sexual rehabilitation intervention. However, the trial underscores the importance and effectiveness of current best practices in post-radiotherapy sexual rehabilitation. Best practice involves a sexual rehabilitation appointment one month after radiotherapy, providing patient information and guidance on dilator use, preferably delivered by a trained nurse. Thereafter, during follow-up visits, general and sexual rehabilitation should remain a focus, with sexuality addressed as a standard topic throughout the sessions.

Chapter 5 presents the cost-efficacy of the nurse-led sexual rehabilitation intervention as compared to standard care. Results showed that women in the intervention group attended an average of 4.5 nurse-led sessions, with a total cost of €172 per participant, including nurse training. Overall, total one-year sexual rehabilitation costs were significantly higher in the intervention group (€478) compared to standard care (€357). Notably, women in the standard care group incurred higher non-intervention-related costs, particularly due to significantly more frequent sexual rehabilitation consultations with radiation oncologists early after radiotherapy. Despite the differences in healthcare utilization and cost, no statistically significant differences were observed in quality-adjusted life years (QALYs), utility scores, or sexual functioning outcomes between the study groups over 12 months. The intervention showed a 70% probability of being cost-effective at a willingness-to-pay threshold of €20,000 per QALY, but this did not translate into meaningful clinical superiority. The absence of outcome differences is likely attributable to significant improvements in standard sexual rehabilitation care in the Netherlands during the study period. The results showed that the nurse-led sexual rehabilitation intervention is not more cost-effective than standard care, however with low costs in both groups. Since the costs for standard care were slightly lower, the optimal approach is one session that includes information on sexual rehabilitation and coaching by a trained nurse, as this is preferred from a health-economic perspective. This session provides detailed patient education with a focus on sexual rehabilitation within the first three months after radiotherapy and can be delivered at a lower cost by a trained nurse.

Chapter 6 discusses the principal findings of the thesis within a biopsychosocial framework, alongside methodological considerations and implications for future research. Positive outcomes regarding vaginal mucosal changes and vaginal functioning problems from the EMBRACE vaginal morbidity substudy and the randomised SPARC trial reflect advances in radiotherapy techniques, such as optimised dose planning and vaginal sparing, and increased focus on sexual rehabilitation. Additionally, improved psychosexual care and patient education may have enhanced compliance with vaginal dilator use and increased sexual activity during the first year after cancer treatment. Psychological factors such as motivation, fear reduction, and emotional readiness, addressed through the nurse-led sexual rehabilitation intervention incorporating motivational interviewing and gradual exposure exercises, likely supported dilator use compliance. Besides, sexual activity itself may positively influence vaginal health through improved local circulation, potentially complementing the mechanical effects of dilator use.

The absence of vaginal stenosis does not necessarily indicate the absence of vaginal functioning problems, which often occur during sexual activity rather than clinical examination. Discrepancies between physician-assessed vaginal morbidity and patient-reported vaginal functioning problems highlight the importance of incorporating both perspectives. The impact of mucosal changes on sexual functioning problems varies considerably among individuals, which highlights the importance of psychological and relational factors. This broader influence is further illustrated by findings from the SPARC trial, where nearly half of the women reported clinically significant sexual distress 12 months after radiotherapy, emphasising that sexual functioning is influenced by more than just vaginal changes alone. Research shows that sexual distress is largely driven by psychosocial factors such as body image concerns, anxiety, depression, loss of sexual identity, and relational difficulties. Additionally, radiotherapy effects like premature menopause and chronic fatigue contribute indirectly to sexual distress. This suggests that future research should move beyond assessing vaginal mucosal changes and perceived vaginal functioning problems, aiming instead to develop more biopsychosocial, personalised, and accessible sexual rehabilitation for women following radiotherapy for gynaecological cancers. This includes exploring the complex interactions between vaginal changes, psychosocial factors, and sexual outcomes, with planned analyses to clarify the roles of vaginal dilation and psychosocial mediators. Long-term follow-up is crucial to evaluate the sustained effects of interventions beyond one year. The SPARC trial offers a unique opportunity to investigate these complex relationships. Furthermore, cross-cultural validation and adaptation of sexual rehabilitation programmes are necessary to ensure their broader applicability.

Ongoing nurse training and education are important for the continued implementation of sexual rehabilitation after radiotherapy. Multidisciplinary collaboration is vital to ensure comprehensive care and maintain sexual health as a priority throughout survivorship, ultimately improving the quality of life for gynaecological cancer survivors. This thesis supports a shift towards personalised, biopsychosocial approaches to sexual rehabilitation for women treated with radiotherapy for gynaecological cancers. The nurse-led intervention demonstrated feasibility and clinical value, reinforcing its role as a key component of standard care.