Sexual rehabilitation after radiotherapy for gynaecological cancer

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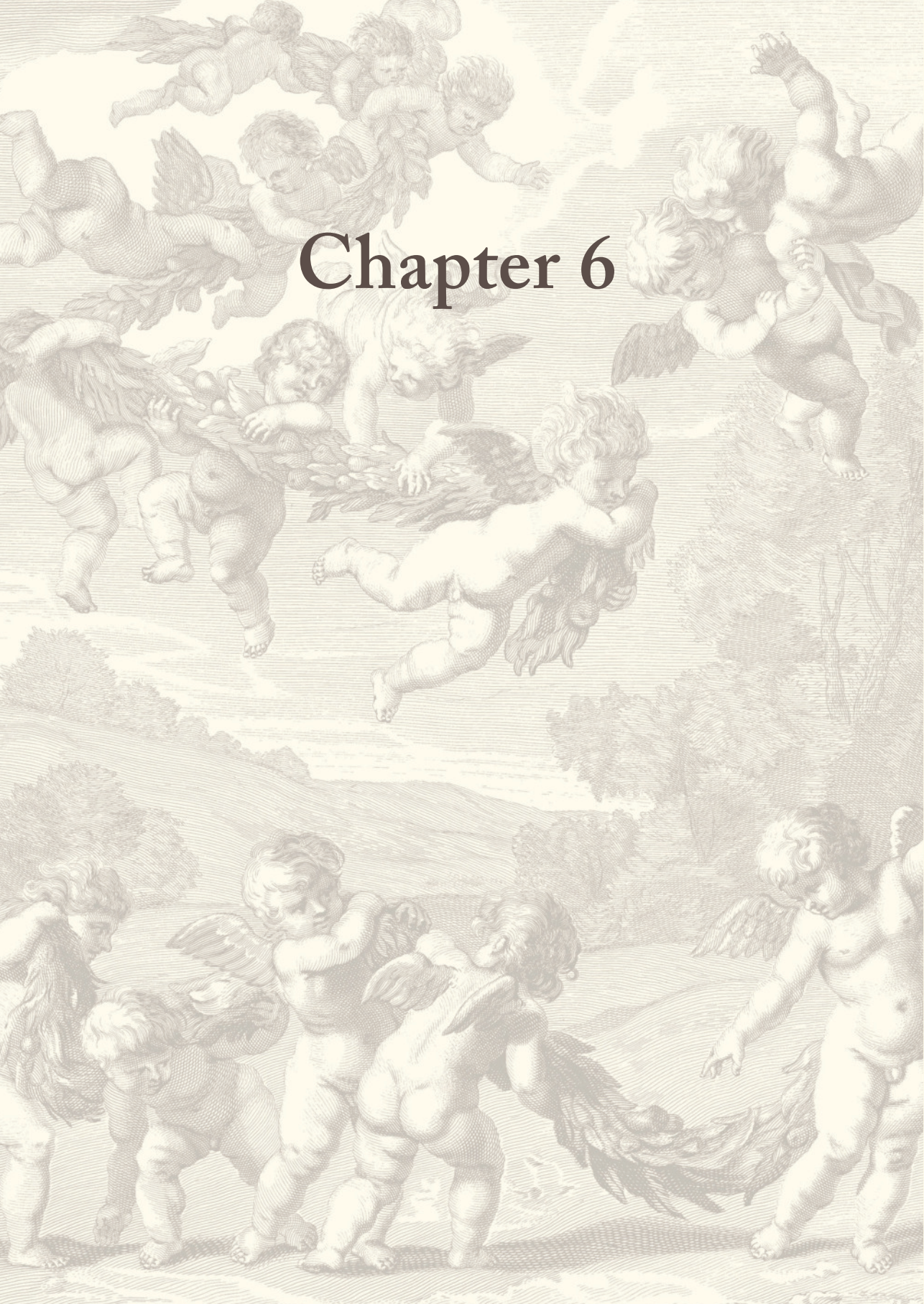

Chapter 6

General discussion

Many women who received radiotherapy for gynaecological cancers express a strong need for psychosexual aftercare, seeking more extensive and practical information rather than strictly medical details, along with reassurance and emotional support, with the active involvement of their partners[1-3]. Preferably, this support is provided by nurses. Randomized trials have shown that such support should include cognitive behavioural interventions aimed at improving vaginal and sexual functioning and increasing compliance with dilator use to prevent radiotherapy-induced vaginal mucosal changes, such as stenosis[4-7]. Additionally, involving the patient's partner, if available, is recommended[7]. However, these studies had limitations in methodological quality and inclusion rates. To address these limitations and to meet the needs of patients who received radiotherapy for gynaecological cancers, especially cervical carcinoma, a nurse-led sexual rehabilitation intervention was developed and pilot-tested[8]. The intervention supported sexual recovery and vaginal dilator use after radiotherapy. It was conducted by specialised nurses from various backgrounds (e.g., radiation oncology, gynaecology, general oncology), who had completed a 50-hour, study-specific training programme in sexology and basic cognitive behavioural interventions, as well as the treatment protocol itself, under the supervision of an experienced sexologist. To assess the intervention's effectiveness, the multicentre randomized SPARC trial was initiated. The trial aimed to evaluate its impact on sexual functioning, other sexual outcomes, vaginal dilation compliance, and cost-effectiveness compared to standard care.

This thesis focused on the evaluation of the SPARC trial outcomes regarding efficacy and cost-utility aspects, as well as on physician-assessed vaginal changes and patient-reported outcomes regarding vaginal and sexual functioning problems and sexual distress. In this chapter, the results of the various studies in this thesis and their clinical implications are discussed and put into perspective, with suggestions for future research.

MAIN FINDINGS

Vaginal and sexual functioning problems and rehabilitation

The prospective EMBRACE vaginal morbidity (VM) substudy evaluated physician-assessed vaginal changes and patient-reported outcomes on vaginal and sexual functioning problems in the first 2 years after radio(chemo)therapy with image-guided adaptive brachytherapy for locally advanced cervical cancer, and explored the association between these (**Chapter 2**). Physicians reported no or only mild vaginal changes for most women over time, with moderate and severe changes being very rare. At 24 months, almost half of the women reported not being sexually active, primarily because of losing interest in sex or the absence of a partner. The majority of the sexually

active women reported no or only minor vaginal functioning problems, with substantial problems being rare. Additionally, the rates of substantial sexual functioning problems in terms of sexual health (desire, arousal, orgasm, sexual satisfaction, and sexual enjoyment) were relatively low. Consistent with the findings from the prospective EMBRACE VM substudy, the randomised SPARC trial showed that most women in both study groups had no or little physician-reported vaginal stenosis (**Chapter 4**). Similarly, most sexually active women reporting no or only a little feeling of vaginal shortness, dryness and pain during intercourse at 12 months after radiotherapy. Substantial vaginal and sexual functioning problems were rare.

These positive outcomes regarding vaginal functioning problems are likely due to several factors. First, it is hypothesized that more advanced radiotherapy techniques with increased vaginal sparing (as implemented in EMBRACE-II) resulted in reduced vaginal mucosal changes. In both the VM and SPARC cohorts, radiotherapy according to the EMBRACE protocol was used, which is characterized by advanced dose optimization and image-guided adaptive brachytherapy[9]. This has been shown to significantly reduce vaginal stenosis[10]. However, it should be noted that the two cohorts are not directly comparable. The EMBRACE VM substudy included only women with no or very minimal vaginal tumour involvement, already leading to better outcomes[11-13]. Additionally, in the SPARC study, there was still a further transition toward improved radiotherapy techniques with even greater vaginal sparing between the VM substudy (mainly EMBRACE-I) and SPARC (EMBRACE-II techniques), as well as increased sexual rehabilitation awareness, factors that may have contributed to even better outcomes in the SPARC study cohort. The application of the EMBRACE-II protocol has been shown to lead to predictable performance and outcomes, with excellent and stable long-term disease control and very minimal substantial vaginal morbidity[14].

Second, it is hypothesized that improved psychosexual care and education led to better compliance with recommended dilator use, which in turn is thought to help prevent the development of fibrotic tissue that can lead to stenosis. As such, vaginal dilator use remains a central component of sexual rehabilitation after combined external beam radiotherapy with brachytherapy[15]. Current clinical guidelines recommend initiating vaginal dilation, an intervention carried out by women themselves using plastic cylinders of increasing size, approximately 2-4 weeks after radiotherapy, with a frequency of two to three times per week for at least one year to maintain vaginal patency. Silicone vibrators or sexual intercourse are often suggested as alternative methods[16,17]. Both the EMBRACE VM substudy and SPARC study included standard approaches for patient information and recommendations for vaginal dilation. In the SPARC study cohort, at 12 months, 85% of women in the intervention group and 75%

in the standard care group who received brachytherapy reported using some form of dilation at least twice a week, indicating high compliance (≥2 times per week using dilators, vibrators, dildos, fingers, or intercourse; **Chapter 4**). While frequent use of vaginal dilators is thought to reduce the risk of vaginal stenosis, the cause-effect relationship remains unclear.

Psychological factors likely contribute to high compliance with vaginal dilation, acting both directly and indirectly. For many women, dilator use involves confronting fears of pain, and has associations with the brachytherapy[18]. Therefore, regular engagement in vaginal dilation likely requires high levels of self-efficacy, motivation, and emotional readiness[19,20]. Based on the findings of Bakker et al.[18], the nurse-led sexual rehabilitation intervention incorporated specific motivational strategies, such as motivational interviewing[21], as well as fear-reducing techniques, such as gradual exposure exercises[22], to address these psychological barriers. These interventions may have supported women in the SPARC trial cohort to overcome avoidance behaviours and engage more consistently in vaginal dilation, even when physical discomfort or psychological distress were present. A psychologically informed, holistic approach may therefore enhance the effectiveness of both dilator use and improved radiotherapy techniques in preserving vaginal function. However, it is not yet known whether this also leads to fewer patient-reported vaginal and sexual functioning problems. It could be argued that because of the better radiotherapy techniques women experienced fewer vaginal and sexual functioning problems, thereby less negative emotions towards and during dilator use, making compliance easier. Based on the current studies in this thesis, it is not possible to determine the direction of this relationship.

Third, it was hypothesized that sexual activity itself, especially when involving arousal, may contribute to vaginal health through improved local circulation and could potentially provide similar benefits to those of dilator use in preventing vaginal stenosis. Evidence from an earlier EMBRACE-I study cohort suggests that dilator use following brachytherapy may be particularly important for women who are not sexually active, as it could potentially simulate some of the mechanical and vascular effects of penetrative activity, especially when combined with masturbation[23]. However, more recent studies have yet to confirm whether dilator use alone remains essential. One small, more recent randomised trial suggests a complementary relationship between dilator use and sexual activity[24]. Regular dilator use was shown to prevent the progression of vaginal stenosis, both its onset and worsening, and appeared to support the maintenance of sexual activity with less discomfort. These findings suggest that combining dilator use with sexual activity may be more effective than dilator use alone in promoting vaginal and sexual functioning. Findings from the EMBRACE VM substudy and SPARC

study further underscore the importance of sexual rehabilitation strategies that extend beyond dilator use. In both studies, most women reported sexual desire, arousal, vaginal lubrication and reaching an orgasm during sexual activity (**Chapter 2**; supplementary table S3, **Chapter 4**). Notably, 12 months after radiotherapy, a higher proportion of women in the SPARC trial were sexually active compared to the EMBRACE VM substudy (70% vs. 54%). Furthermore, 65% of women in both SPARC study groups had resumed sexual intercourse as early as three months after radiotherapy. These findings suggest that early-initiated sexual rehabilitation programmes, including psychoeducation provided by nurses and materials, may facilitate the resumption of sexual activity, which in turn could support vaginal function. The question whether vaginal dilator use remains necessary after brachytherapy, particularly when advanced radiotherapy techniques (as in EMBRACE-II) are combined with early, structured sexual rehabilitation and psychoeducation about the benefits of resuming sexual activity requires further research.

It is important to note that the absence of significant vaginal stenosis does not necessarily indicate the absence of vaginal functioning problems. These problems are often experienced during sexual activity, while mucosal changes such as stenosis are typically observed during clinical examination. Previous studies that compared physician-assessed vaginal morbidity and patient-reported vaginal functioning problems also showed that there is a high level of discrepancy between objective and subjective symptoms[25,26]. This underlines the necessity of reporting both physician-assessed and patient-reported vaginal functioning problems for a complete evaluation of changes after cancer treatment. Furthermore, the impact of mucosal changes on sexual functioning varies greatly between individuals. Some women report few or no symptoms despite evident mucosal abnormalities, while others experience persistent sexual difficulties even when clinical findings are minimal[15]. The psychosocial mechanisms underlying these individual differences remain poorly understood.

Understanding sexual functioning and distress after treatment

Despite the absence or only mild presence of vaginal stenosis and functioning problems, as well as high dilator compliance and frequent sexual activity, nearly half of the women in both SPARC study groups continued to report clinical levels of sexual distress at the 12 month follow-up (**Chapter 4**). Additionally, the lack of association between vaginal changes, vaginal functioning problems and sexual distress shows that sexual functioning is much more complex than vaginal morbidity alone (**Chapter 2**). These findings suggest that sexual distress cannot be fully explained by objective or subjective vaginal symptoms after radiotherapy, such as vaginal stenosis, pain, or feelings of a tight, short, and/or dry vagina during sexual activity. Furthermore,

even when substantial sexual functioning problems, such as decreased desire, arousal, orgasm, satisfaction, or enjoyment, were rare, and most women were sexually active, this did not mean that they did not experience sexual distress. This underlines the critical need to consider psychological and relational factors when evaluating sexuality after radiotherapy.

A few systematic reviews have already shown that sexual distress is more often driven by psychosocial than physiological factors[27-29]. Results show that many women experience significant difficulties adjusting to changes in their altered sexual lives after radiotherapy, including struggles with body image, intimacy with their partners, and partner support[27]. These emotional and relational challenges frequently persist even when physical symptoms are minor or well-managed through (sexual) rehabilitation interventions. Sexual distress, unlike vaginal changes or functioning problems, may be rooted in the psychological and emotional experience of sexual functioning and is commonly associated with anxiety, depression, and loss of sexual identity[27,30]. Bakker et al. also found that vaginal functioning problems are associated with sexual distress, defined as distress regarding sexual activity or worries about painful intercourse[31]. Additionally, body image concerns or fear of cancer recurrence, contribute significantly to post-treatment sexual distress, particularly in younger women who also suffer from premature menopause[28]. These physical changes resulting from cancer treatment alter the woman's sense of self and femininity, which has a profound impact on sexual wellbeing. Furthermore, long-term radiotherapy side effects such as fatigue and menopausal symptoms may contribute indirectly to sexual distress by diminishing energy, desire, and mood. It is shown that chronic fatigue following cancer treatment is significantly associated with depression and reduced sexual interest, particularly among younger women who received radiotherapy.

Relational factors are a critical yet often unrecognized component of sexual rehabilitation in gynaecological cancer survivors. Research shows that women frequently experience emotional withdrawal, lack of understanding, or even abandonment by partners who struggle to adapt to changes in female sexuality following treatment, further intensifying psychological distress[2,27]. Attachment style and marital adjustment significantly mediate the relationship between sexual satisfaction and distress in cervical cancer survivors, indicating that sexual activity alone does not guarantee emotional fulfilment, but that relational intimacy remains key to recovery[32]. These findings are reflected in the SPARC trial results: despite receiving a structured intervention, including coaching by a dedicated nurse with experience in cancer treatment, one-quarter of women in the intervention group continued to report clinically significant relationship dissatisfaction 12 months after radiotherapy (supplementary table S6, **Chapter 4**).

Notably, partner involvement in the intervention declined over time, underscoring the challenges of sustaining partner engagement and the relational strain that can persist after treatment ends.

Our findings and prior research highlight the need for future psychosexual research to move beyond physical symptoms and examine psychological factors such as body image, psychological distress, fatigue, and premature menopause. The SPARC trial has initiated the exploration of these factors, including relationship satisfaction, which remains an area of concern due to persistent difficulties reported despite targeted interventions. These results were beyond the scope of this thesis.

Sexual rehabilitation approaches after radiotherapy

To our knowledge, the SPARC trial is the first robustly powered randomised trial to investigate the efficacy of a nurse-led sexual rehabilitation intervention aimed to improve sexual recovery and compliance with dilator use for women treated with radiotherapy and brachytherapy for gynaecological cancers (**Chapter 3**). Contrary to expectations based on the pilot study[8], this trial did not show a significant benefit of the intervention over standard care in improving sexual functioning, dilator compliance, or in reducing vaginal functioning problems and sexual distress, one year after radiotherapy (**Chapter 4**). The SPARC trial results highlight the improvements in standard sexual rehabilitation care in the Netherlands, both prior to and during the study period. These findings emphasize the importance of awareness, education, and comprehensive care, which may have led to comparable sexual rehabilitation outcomes between the intervention and standard care groups. Therefore, we consider this standard care approach the best practice for improving sexual functioning and, ultimately, quality of life following treatment for gynaecological cancers. The standard care approach includes comprehensive patient education and a dedicated sexual rehabilitation consultation one month following radiotherapy. This consultation provides explicit guidance on dilator use and offers coaching on resuming sexual activity for women treated with external beam radiotherapy combined with brachytherapy. This is further supported from a health-economic perspective (**Chapter 5**). Rather than offering this care through additional or extended consultations with radiation oncologists or gynaecologists, a more cost-effective strategy involves providing sexual rehabilitation through a specifically trained and dedicated nurse. Furthermore, as women who received brachytherapy in both study arms were provided with an information session covering dilator use, structured follow-up on sexual functioning and dilator use throughout the first year after treatment completion is recommended to support long-term recovery and adherence.

When evaluating the content of the modules in our nurse-led sexual rehabilitation intervention (**Chapter 3**), it becomes evident that the intervention extended beyond a sole focus on radiotherapy-induced vaginal morbidity and dilator use. Instead, it conceptualized sexual functioning as a multidimensional construct, encompassing somatic, psychological, and relational factors, and recognized sexual well-being not merely just in terms of dysfunction or performance, but as a personal and psychosocial phenomenon. The programme was based on second-wave cognitive behavioural therapy (CBT), which evolved from behaviour therapy (first wave) by incorporating cognitive techniques, based on the premise that modifying maladaptive thought patterns can lead to improved emotional and behavioural outcomes. In the context of female sexual dysfunction, second-wave CBT has been used to help women reframe maladaptive beliefs about sexuality, enhance sexual communication, reduce avoidance behaviours, and mitigate sexual distress, a key mediator of quality of life in cancer survivorship[33-35].

Evidence supports the efficacy of CBT in oncology populations. A systematic review and meta-analysis demonstrated that CBT interventions significantly improved sexual functioning, increased sexual satisfaction, and reduced sexual distress among women with breast cancer[34,36]. Internet-based CBT has also shown durable improvements in sexual functioning and body image[33]. Although this evidence is drawn from breast cancer populations, the mechanisms targeted, such as cognitive distortions, anticipatory anxiety, and body-image issues, are also prominent in gynaecological cancer survivors[37]. Moreover, sexual distress remains highly prevalent among women treated for gynaecological cancer, often persisting even in those who resume sexual activity, possibly due to emotional disconnection, fear of pain, or altered self-perception[4,8], which is in line with our SPARC trial findings.

Whereas second-wave CBT primarily targets the modification of maladaptive cognitions to reduce psychological symptoms, third-wave approaches place greater emphasis on emotional acceptance and psychological flexibility. Rather than attempting to directly change the content of thoughts, third-wave CBT encourages individuals to relate to their thoughts and emotions in a more open and nonjudgmental way. This is often achieved through interventions such as mindfulness-based cognitive therapy (MBT) and acceptance and commitment therapy (ACT). MBT interventions have already shown promise in reducing sexual distress and enhancing sexual functioning after gynaecological cancer treatment by fostering nonjudgmental awareness of sexual and emotional experiences[4,35,38]. Research into the effectiveness of ACT on sexual dysfunction is still limited, and non-existing in a gynaecological cancer population. However, a recent randomized controlled trial showed that a relatively brief, guided, online version of ACT appeared to produce benefits for women who experience pain

during intercourse and related impacts on daily functioning, with improvements on both sexual functioning and sexual distress[39]. Although the nurse-led sexual rehabilitation intervention was not explicitly developed within a third-wave CBT framework, its emphasis on motivational support, relational dynamics, and self-management aligns with these principles and may form a foundation for integrating third-wave strategies in future iterations. Future randomized trials are needed to test the efficacy of ACT- or MBT-based interventions in the SPARC trial population.

Implementation of the nurse-led sexual rehabilitation into standard cancer aftercare

Although the multiple session nurse-led sexual rehabilitation intervention did not outperform standard rehabilitation care, our findings underscore the necessity of integrating sexual rehabilitation into routine clinical care to improve outcomes for women treated with radiotherapy for gynaecological cancers (**Chapter 4**). The trial's guidelines on sexual rehabilitation are consistent with international guidelines that underscore the importance of addressing sexual functioning following radiotherapy in patients with gynaecological cancers[40,41]. This integration into routine clinical care depends on ongoing training and education for nurses and other healthcare providers, ensuring they possess the knowledge and expertise to address sexual rehabilitation sensitively and effectively. Encouraging open conversations about sexuality can enhance communication between patients and providers and reduce barriers that prevent patients from voicing questions or concerns. Communication about sexuality was a key component of the SPARC-training. Nurse training was provided before, during (to accommodate staff turnover), and after the SPARC trial, securing sustained expertise and service delivery. The frequent requests for additional training from participating SPARC study centres and beyond underscore the ongoing demand and institutional commitment to advancing sexual rehabilitation care. To maintain these high standards, it is essential to continue offering these training courses in the coming years.

Since the SPARC trial and the preceding pilot study[8], awareness of the importance of sexual rehabilitation has increased among healthcare professionals and advocacy groups in the Netherlands. In addition to standard care implemented in the SPARC study centres, the development of accessible patient resources, such as the website of the Olijf advocacy group, has supported patient education and encouraged open dialogue about sexual functioning[42]. Post-hoc data also indicate that SPARC study centres implemented additional improvements in sexual rehabilitation care during the study period. Sexual health has been routinely addressed during follow-up appointments, reflecting a progressive shift toward comprehensive integration into standard care (**Chapter 4**).

Women with cervical cancer treated with external beam radiotherapy combined with brachytherapy constituted the large majority of the study population, making our study outcomes particularly relevant for these relatively young women treated with intensive combined chemoradiotherapy and brachytherapy. For patients treated with external beam radiotherapy alone, emphasis on broad and general sexual rehabilitation is more appropriate than interventions specifically focused on vaginal dilation, given the significantly lower risk of vaginal complications such as stenosis. As such, the use of vaginal dilators may represent an unnecessarily intensive approach for this group of women, including those treated with brachytherapy alone (not included in the SPARC trial). For these groups, it seems essential to address concerns and provide general rehabilitation support, including information and guidance on symptoms such as vaginal dryness, body image issues, relationship satisfaction, psychological and sexual distress, premature menopause, and fatigue - all of which can impact sexual functioning. Providing a designated contact person, such as a trained nurse, for follow-up questions seems essential. The training initiatives implemented during the study enhanced nurses' ability to provide personalized support, benefiting not only study participants but also a broader patient population. The sexual rehabilitation intervention may also be valuable for other gynaecological or pelvic cancer patients receiving radiotherapy and/or surgery, such as women treated for vulvar, rectal or bladder cancers. Studies show that women treated for vulvar cancer also deal with impaired sexual activity, fatigue, body image, and vaginal and sexual functioning, including pain[43,44]. Especially with vulvar cancer, physical changes, identity and relationship challenges have a negative impact on women's sexuality. With rectal or bladder cancer, the radiation exposure is comparable to that seen with external beam radiotherapy for gynaecological cancers. Trained SPARC study nurses can play an important role in supporting these patients.

As sex therapy is currently not reimbursed by Dutch health insurance, there is a need to embed sexual rehabilitation care within standard cancer aftercare. The sexual rehabilitation intervention, including nurse training, incurred additional costs estimated at €172 per patient (**Chapter 5**). While these expenses contributed to a modest increase in total one year follow-up costs (€478 versus €357 in standard care), they remain relatively low when considering the overall costs of cancer treatment. However, because standard care was slightly less expensive, it remains the preferred option from a health-economic perspective. Given that nurse-led care is generally less costly than the same care given by specialists, such as radiation oncologists and gynaecologists, this approach may offer a financially sustainable option. This suggest that incorporating sexual rehabilitation into routine clinical pathways is economically feasible and could support wider implementation without imposing significant financial

strain on healthcare systems. Specifically trained nurses in sexology are well equipped to deliver ongoing sexual rehabilitation and provide personalized support, as the content of the sexual rehabilitation intervention modules is tailored to the women's (and their partners') specific psychological, relational and somatic factors (**Chapter 3**). However, effective care requires collaboration within a multidisciplinary team, which includes radiation oncologists, gynaecologists, and psychologists/sexologists. This collaboration ensures comprehensive assessment, effective management of complex cases, and holistic, patient-centred care. Embedding sexual rehabilitation within standard follow-up protocols helps maintain sexual functioning as a priority throughout survivorship, ultimately enhancing quality of life and psychosocial well-being.

METHODOLOGICAL CONSIDERATIONS

The SPARC study had a number of methodological strengths, including the well-powered randomized trial design, a large sample size, the participation of all Dutch gynaecological oncology centres, a limited drop-out of study participants, the use of a clear treatment protocol and extensive training protocol, including an adherence and competency assessment by an independent panel, the relatively long follow-up period of 12 months, and the invitation to the women's partners to join the intervention sessions. However, the study also had some methodological limitations.

Contamination

One methodological limitation of the SPARC trial is the potential for contamination between the intervention and standard care groups (see also **Chapters 3** and **4**). As mentioned before, sexual rehabilitation care has evolved in the Netherlands. Elements of best practice, such as education about vaginal changes, dilator use, and early awareness of sexual rehabilitation, have become increasingly integrated into routine care. This may have reduced the contrast in content and support between the trial arms, potentially diminishing the observable effects of the intervention. Despite instructions given to physicians and nurses to manage the study groups separately, their involvement with both groups may have led to similar initial post-radiotherapy psychosexual care. This well-known issue of contamination in individually randomized intervention studies could have been avoided through cluster randomization (i.e., randomizing at the centre level rather than at the patient level). However, cluster randomization also introduces other potential threats to internal validity, particularly given the limited number of participating centres and the fact that only a subset (n = 8) could be randomized. Two centres had already completed training as part of the pilot study, precluding their inclusion in the randomization process[8]. Due to the variation in

patient populations, radiotherapy protocols, and follow-up procedures across centres, we ultimately chose to randomize at patient level.

In addition to our 'optimal' standard care, which includes a nurse-led consultation one month after radiotherapy and the provision of comprehensive patient information on sexual rehabilitation, post-hoc analyses showed that all centres consistently addressed sexuality during follow-up consultations with physicians (**Chapter 4**). Because the sexual rehabilitation sessions with the nurse were scheduled immediately after these appointments, sexuality was discussed at the same time points in both study groups. This may have resulted in both groups receiving support aligned with the first two levels of the PLISSIT model (*Permission*, *Limited Information*, Specific Suggestions, Intensive Therapy)[45]. Addressing sexuality and psychoeducation has been shown to positively influence sexual functioning, knowledge regarding physical and psychosexual side-effects and rehabilitation options of gynaecological cancer patients[35,46]. While this development reflects progress in clinical practice, it also limits the extent to which improved outcomes can be attributed solely to the intervention.

Measurement challenges in sexual health research

This study employed several validated self-report instruments to assess sexual functioning and sexual distress, including the Female Sexual Function Index (FSFI)[47], and the Female Sexual Distress Scale (FSDS)[48]. While both instruments are well-established in oncological and sexual functioning research, they have also limitations. The FSFI is designed primarily for sexually active women and defines sexual activity mainly in terms of heterosexual vaginal intercourse. This narrow operationalization could yield biased results for those who are sexually inactive due to factors such as lack of a partner, relationship quality, or reasons unrelated to cancer treatment effects[47,49]. Similarly, the EORTC QLQ-CX24, developed specifically for women with cervical cancer, includes items on sexual enjoyment and activity, but also tends to emphasize frequency and penetration, with limited attention to non-coital or emotionally intimate expressions of sexuality[50]. Additionally, both the FSFI and EORTC QLQ-CX24 use a fixed recall period of four weeks, which may result in misclassification. Women who were previously sexually active but not during that specific time frame may be inaccurately labelled as inactive, potentially underestimating vaginal or sexual functioning problems that have contributed to infrequent activity.

To mitigate some of these issues, participants in the SPARC trial were randomized with stratification based on partner status, and a "not applicable, no partner" response option was included in items concerning partner relationships (**Chapter 3**). Furthermore, we added two supplementary questions to the FSFI to assess the frequency of sexual

activity both with and without intercourse. Our results showed that most women who reported being sexually active also engaged in intercourse (**Chapter 4**). Despite these adjustments, studying sexual outcomes in cancer survivors remains complex. Not all women wish to resume sexual activity after radiotherapy, and their goals may vary widely. Some prioritize physical comfort, emotional closeness, or bodily autonomy over intercourse. Women included in the SPARC trial were required to have at least a wish to maintain or resume sexual activity in the short or long term (**Chapter 3**). Consequently, this study likely attracted relatively young, motivated participants with a partner. It could be argued that women find entering new relationships after cancer treatment particularly challenging. Building trust and emotional intimacy may be important factors in resuming sexual activity. This is also reflected in the SPARC trial population, where almost 80% of women who participated had a partner (Table 2, **Chapter 4**). The complexities of new relationships after radiotherapy require further research, as they may pose unique barriers to sexual recovery. Still, using sexual functioning as a primary outcome may not fully capture what recovery means to each individual, and this may risk "over-pathologizing" of low desire or abstinence when these are intentional or appropriate choices.

These challenges underscore the contrast between standardized definitions of sexual activity and women's lived experiences. Many women view sexual activity as encompassing a broader range of behaviours, including sensual touch or emotional intimacy. Moreover, research shows that vaginal intercourse alone is not the most effective stimulus for orgasm for many women[51], raising questions about the appropriateness of orgasm as a universal marker of sexual dysfunction. Dichotomizing women as "sexually active" or "inactive" based on narrow behavioural criteria may obscure meaningful aspects of post-radiotherapy sexual well-being.

A limitation of the FSDS is its limited specificity in measuring sexual dysfunction, as it appears to correlate more strongly with general psychological and relational distress than with physical aspects of sexual response such as arousal, lubrication, or orgasm[52]. Although vaginal functioning problems have been associated with sexual distress[31], the FSDS may primarily reflect broader emotional or relational concerns. This raises concerns about its discriminant validity and limits its utility as a standalone measure in sexology research. To address these limitation, the SPARC trial included a broader range of patient-reported outcomes in addition to the measures mentioned above, including the Hospital Anxiety and Depression Scale (HADS)[53] and the Maudsley Marital Questionnaire (MMQ)[54], which assess psychological distress and relationship satisfaction, respectively (**Chapter 3**).

IMPLICATIONS FOR FUTURE RESEARCH

Future research in sexual rehabilitation after radiotherapy for gynaecological cancer should move beyond symptom management to better address the complexity of sexual functioning and well-being. The SPARC trial provides a strong foundation, but several critical gaps remain to be addressed in upcoming publications.

Clarifying causal links between dilation, vaginal changes, and psychosocial and sexual outcomes

Although vaginal dilator use is widely recommended to prevent radiotherapy-induced vaginal changes such as stenosis, and results indicate that regular vaginal dilation (defined as the use of vaginal dilators, vibrators, dildos, fingers, or intercourse) is associated with a significantly lower risk of Grade ≥2 vaginal stenosis - potentially improving vaginal length and width in the vault area[23] - the precise impact of vaginal fibrosis and stenosis on patient-reported vaginal functioning, remains unclear. The SPARC trial offers a unique opportunity to investigate these complex relationships by combining physician-assessed vaginal changes with patient-reported outcomes on vaginal functioning (e.g., sensations of vaginal shortness, dryness, and pain)[50], sexual functioning (FSFI)[47], sexual distress (FSDS)[48], and sexual activity (including both penetrative and non-penetrative forms).

Planned in-depth analyses of the SPARC results will employ advanced statistical techniques, including stepwise multiple regression, to examine whether psychosocial factors such as sexual activity, body image, psychological distress or relationship dissatisfaction influence sexual functioning and distress. Mediation analysis will assess whether vaginal dilator use mediates the relationship between vaginal stenosis and sexual functioning. Optimizing sexual rehabilitation after radiotherapy requires a comprehensive understanding of these psychosocial processes that influence sexual functioning. Identifying which patients benefit most from different intervention strategies, will enable more personalized and cost-effective care.

Assessing long-term effects of interventions

Sexual functioning of cancer patients may further improve on the longer term, as part of broader physical recovery and ongoing adaptation to life after completion of treatment. Sexual recovery is a long-term process that often extends well beyond the first year post-treatment[55-57]. Most randomized controlled studies, including the SPARC trial, typically evaluate outcomes at relatively short follow-up intervals. Therefore, the SPARC trial included a longer-term follow-up at 24 months, providing a valuable opportunity to assess the durability of intervention effects on vaginal changes, sexual functioning, sexual distress, psychological well-being, and relationship satisfaction over

an extended period. This data is still to be analysed. Future research should continue to focus on long-term outcomes to capture the evolving nature of survivorship and inform sustained support strategies.

Evaluating applicability beyond the Netherlands

While the SPARC trial reflects current Dutch standards of care[41], its generalizability to other healthcare systems remains uncertain. Even what we consider 'optimal' standard care is not yet the norm in many countries, including some within Europe. Cross-cultural differences in sexual norms, healthcare access, and psychosocial support structures may influence both the feasibility and effectiveness of sexual rehabilitation programmes. In the Netherlands, women from different cultural backgrounds or with limited language proficiency may benefit from educational materials that make greater use of illustrations and culturally sensitive language. Such materials should be developed with dedicated input from psychologists, healthcare professionals from diverse cultural backgrounds, experts in low health literacy, and patients. Additionally, international replication studies are needed to evaluate the applicability and adaptability of the nurse-led sexual rehabilitation intervention across varied clinical and cultural contexts.

CONCLUSIONS

Results of the research presented in this thesis showed that most women treated with external beam radiotherapy and brachytherapy, who were informed and coached on vaginal and sexual issues throughout their recovery phase, experienced no or only mild vaginal and sexual functioning problems, with high levels of sexual activity and compliance with dilator use. However, nearly half of the women still reported clinical levels of sexual distress 12 months after radiotherapy. These findings highlight the complexity of sexual outcomes and suggest that sexual functioning is shaped by a range of biopsychosocial factors. They underscore the importance of early, comprehensive sexual rehabilitation delivered by specialized nurses.

The SPARC study was the first randomized trial to evaluate a nurse-led sexual rehabilitation intervention aimed at improving sexual functioning and dilator use in women treated with radiotherapy for gynaecological cancers. The intervention demonstrated similar effectiveness to standard care, with the latter being slightly more cost-efficient. As a result, standard care in the Netherlands now includes thorough patient information and a dedicated sexual rehabilitation session with trained nurses shortly after radiotherapy. Continuation to provide this training to nurses is therefore essential to ensure its availability to both current and future patients.

Future research should keep moving beyond assessments of vaginal mucosal changes and perceived vaginal functioning problems. Ultimately, this should lead to a shift towards more biopsychosocial, personalized, and accessible sexual rehabilitation for women after radiotherapy for gynaecological cancers. Tailoring interventions to patients' needs can foster greater engagement, enhance the efficacy of sexual rehabilitation, and provide truly patient-centred support that addresses the full spectrum of recovery after radiotherapy.

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