Sexual rehabilitation after radiotherapy for gynaecological cancer

Suvaal, I.

SEXUAL REHABILITATION

AFTER RADIOTHERAPY FOR

GYNAECOLOGICAL CANCERS

ISABELLE SUVAAL

Sexual rehabilitation after radiotherapy for gynaecological cancers

Isabelle Suvaal

Sexual rehabilitation after radiotherapy for gynaecological cancers
PhD thesis – Leiden University Medical Center – Leiden, the Netherlands

ISBN:	978-94-6537-102-3
Cover design and artwork:	Creations of Curiosity
Lay-out and print:	Ridderprint | www.ridderprint.nl

The SPARC study was supported by a grant from the Dutch Cancer Society - Alpe d'HuZes Fund (grant 10674). The EMBRACE vaginal morbidity substudy was supported through unrestricted grants and study sponsorship by Elekta AB and Varian Medical Systems. Financial support for printing this thesis was provided by Leiden University Libraries and the Department of Radiation Oncology of the Leiden University Medical Center.

Sexual rehabilitation after radiotherapy for gynaecological cancers

Proefschrift

ter verkrijging van
de graad van doctor aan de Universiteit Leiden,
op gezag van rector magnificus prof. dr. S. de Rijcke,
volgens besluit van het college voor promoties
te verdedigen op donderdag 5 maart 2026
klokke 14:30 uur

door

Isabelle Suvaal

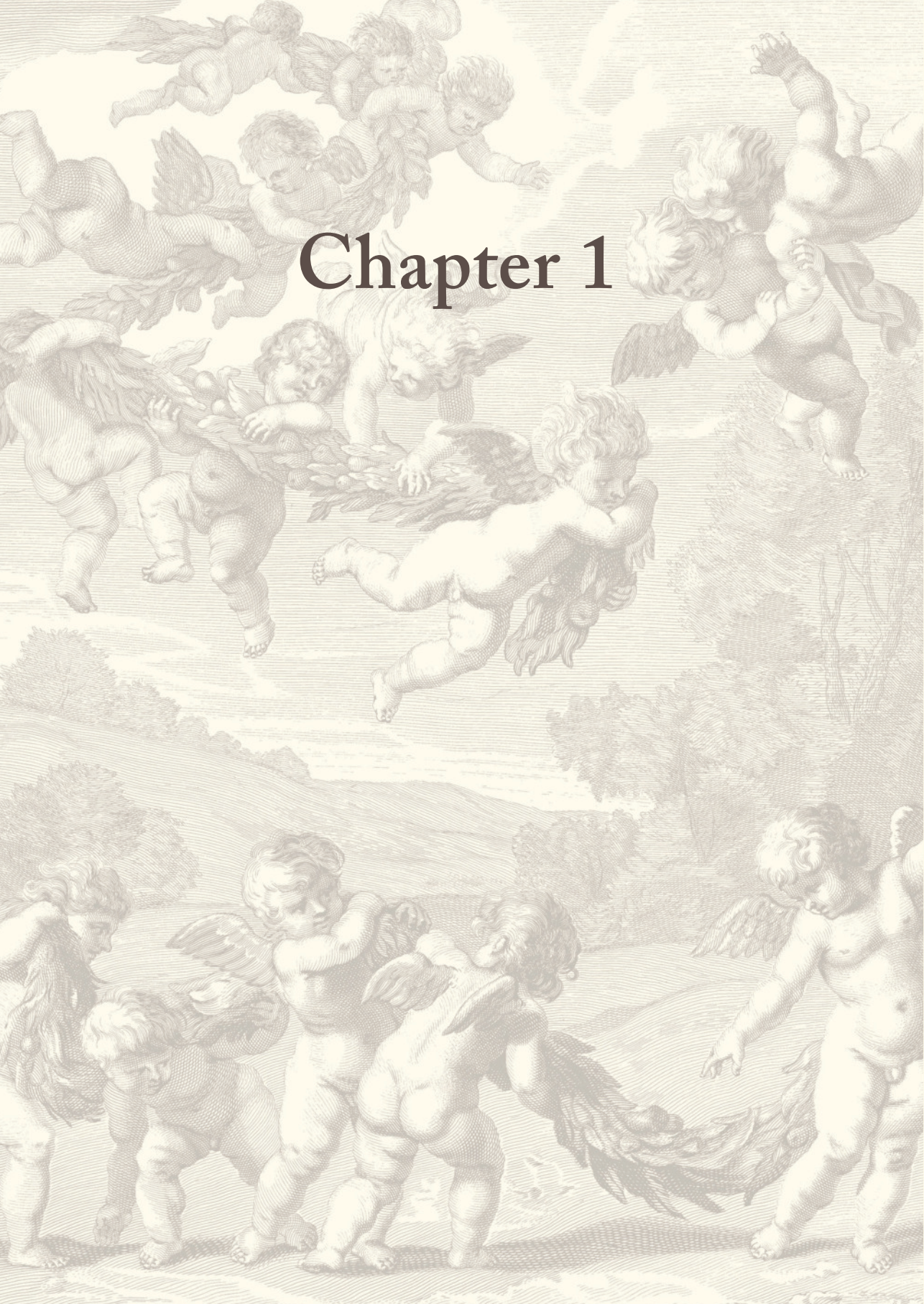
Promotores

Prof. dr. C.L. Creutzberg
Dr. M.M. ter Kuile

Leden promotiecommissie

Prof. dr. E.M.A. Bleiker
Prof. dr. J.J.D.M. van Lankveld (Open Universiteit)
Prof. dr. L.V. van de Poll-Franse (Universiteit van Tilburg)
Dr. H.C. van Doorn (Erasmus MC, Rotterdam)
Dr. C.D. de Kroon

Contents



Chapter 1

General introduction

Epidemiology and treatment of gynaecological cancers

The incidence of gynaecological cancers, including cervical, vaginal, and endometrial cancers, has been increasing[1]. Their classification, treatment and prognosis depend on the tumour type, organ of origin and stage of disease. Endometrial and cervical cancers are among the most common types worldwide. In the Netherlands, more than 5000 women are diagnosed with gynaecological cancers each year, including approximately 2200 endometrial cancers, 900 cervical cancers, and 60 vaginal cancers in 2024. Cervical and vaginal cancers are primarily caused by persistent infection with high-risk human papillomavirus (HPV) types, with additional risk factors including smoking and sexual behaviour. Endometrial cancer is strongly influenced by hormonal factors, particularly prolonged oestrogen exposure, obesity, and strongly increases with age. The peak incidence of endometrial cancer is between 60 and 80 years of age, while cervical cancer has the highest incidence between 30 and 45 years of age.

Standard treatment of most early stage gynaecological cancers is surgery[2]. Approximately 30-40% of patients receive radiotherapy, as adjuvant treatment in case of risk factors, and as primary treatment in more advanced stages of disease[3]. Women with locally advanced cervical and vaginal cancers are primarily treated with external beam radiotherapy, with concurrent weekly cisplatin-based chemotherapy and followed by MRI-guided adaptive intracavitary and interstitial brachytherapy. Image-guided brachytherapy is used to deliver a high dose of radiation to the residual tumour, while minimizing exposure to the surrounding tissues. Patients with early stage cervical or endometrial cancers may receive postoperative adjuvant external beam radiotherapy, with or without brachytherapy boost, in case of adverse risk factors such as lymph node involvement or lymph-vascular space invasion, close or involved surgical margins, deep invasion, or a combination of such risk factors.

Women who undergo primary or postoperative external beam radiotherapy combined with brachytherapy are at risk of radiotherapy-induced vaginal mucosal changes, such as vaginal dryness, tightening and stenosis due to fibrosis[4]. The combination of modern image-guided external beam radiotherapy with concurrent cisplatin-based chemotherapy and image-guided adaptive brachytherapy, as developed and implemented by the international EMBRACE group[5], has significantly improved local disease control and survival rates in cervical cancer patients[6]. Furthermore, this approach has shown to reduce both short-term and long-term toxicities compared to older treatment techniques[7-9]. As a result, attention to health-related quality of life of gynaecological cancer survivors increased.

Vaginal changes after radiotherapy for gynaecological cancers

While treatment options have improved significantly, many patients still experience vaginal mucosal changes after external beam radiotherapy and brachytherapy[4,10-12]. These changes may include mucositis, microvascular alterations leading to atrophy and telangiectasia, reduced lubrication, adhesions, and fibrosis in the upper vagina. As a result, women may face vaginal changes with impact on their sexuality, such as vaginal stenosis and shortening. Many of those changes are classified as low-grade adverse events according to the Common Terminology Criteria for Adverse Events (CTCAE). However, it is important to acknowledge that these treatment-induced morphological vaginal mucosal changes, known as vaginal morbidity, may negatively affect vaginal and sexual functioning.

Some smaller studies suggested that frequent dilator use following the combination of external beam radiotherapy and brachytherapy for locally advanced cervical and vaginal cancers may help prevent vaginal stenosis, with the goal of maintaining the possibility of vaginal penetration in the long term[13,14]. It is generally recommended that women use vaginal dilators for 9-12 months after treatment[14]. Despite its potential benefits, overall compliance has been low, with only about 30% of women adhering to the instructions, even after receiving counselling[15-18]. Common barriers to regular use include difficulty with planning, lack of time or privacy, forgetting, and other recovery-related challenges such as fatigue and anxiety[19].

Vaginal and sexual functioning problems, and distress after radiotherapy for gynaecological cancers

Gynaecological cancer survivors, particularly those who have undergone external beam radiotherapy in combination with brachytherapy, often experience vaginal function issues during intercourse or other sexual activity[20-29]. Common problems include dyspareunia (pain), reduced lubrication, vaginal tightening and shortening, and bleeding, as well as sexual functioning problems. These may include decreased sexual desire, arousal, enjoyment, and overall satisfaction. Additionally, it has been shown that vaginal functioning problems are associated with sexual distress, defined as distress regarding sexual activity or worries about painful intercourse[30]. It is important to note that sexual dysfunction - including problems with desire, arousal, orgasm, satisfaction, and enjoyment - is not solely linked to vaginal function. Other reported long lasting psychosocial symptoms of cancer treatment, such as anxiety, depression, diminished body-image, fatigue and relationship dissatisfaction, also play a role. Additionally, the consequences of vaginal mucosal changes vary between individuals. Some women do not report any vaginal functioning problems, even when significant mucosal changes are observed, while others experience persistent sexual issues despite

only minor mucosal changes[14]. This highlights that sexual dysfunction results from a complex interaction of physiological, psychological, and relational factors.

Sexual rehabilitation after radiotherapy for gynaecological cancers

Previous research has indicated that women and their partners have a strong need for psychosexual aftercare after cancer treatment, which includes more extensive and practical information rather than strictly medical details, and also reassurance and emotional support about sexuality and relationship consequences[31,32]. Nurses are especially equipped to give such support as they can devote more time to patient interaction than physicians, possibly also at lower cost. Furthermore, it has been shown to be beneficial to involve partners actively[33].

Two small randomized trials demonstrated that a psychoeducational group intervention, which focused on motivating regular dilator use, can increase dilator compliance significantly[17,34]. This suggests that gynaecological cancer survivors may benefit from additional professional support. However, it is important to note that interventions aimed solely at increasing dilator use did not have a positive impact on the psychosexual effects of gynaecological cancer treatment, such as sexual distress and (worries about) pain during intercourse[17,20,35]. To date, only four randomized trials have evaluated psychosexual rehabilitation interventions for gynaecological cancer survivors[36-39]. These trials have incorporated cognitive-behavioural techniques, psychoeducation, and counselling. However, three of these studies were of low methodological quality and had low participant inclusion rates (ranging from 27% to 42%). Only one high quality randomized trial (N=94) is available, which revealed that couple-coping training significantly enhanced sexual relationship satisfaction and intimacy, as compared to standard medical education or patient-only coping training[36]. Notably, sexual functioning - as measured in terms of sexual desire, arousal, and orgasm - was not improved. Therefore there was a clear need for a practical, cost-effective, and condensed sexual rehabilitation intervention that integrates psychoeducation with elements of psychosexual-based cognitive-behavioural therapy for gynaecological cancer patients and their partners after radiotherapy.

A nurse-led sexual rehabilitation intervention was developed and pilot-tested to support sexual functioning and encourage the use of vaginal dilators after radiotherapy[40]. The intervention had several aims/objectives, including motivating women and their partners (if applicable), offering tailored advice, strengthening self-management, promoting mutual coping and support between partners, and providing information and coaching on vaginal dilator use for women who had received external beam radiotherapy combined with brachytherapy.

Prior to delivering the intervention, the nurses completed a 50-hour specific training programme in sexology, basic cognitive-behavioural interventions, and the treatment protocol itself. Following this training, they reported feeling confident in their ability to guide and support the women throughout the process. Results from the pilot study[40] on the feasibility of this intervention demonstrated that it supported women in their dilator use, improved sexual functioning, and that they highly valued the support provided by the nurses.

Aims and outline of the thesis

Based on the promising results of the pilot study on the feasibility of the nurse-led sexual rehabilitation intervention, the multicentre randomized SPARC (Sexual rehabilitation Programme After Radiotherapy for gynaecological Cancer) trial was initiated to investigate the (cost-)effectiveness of the nurse-led sexual rehabilitation intervention in improving sexual functioning and dilator use of gynaecological cancer patients after radiotherapy. The design, analysis and primary and secondary outcomes of this trial are discussed in the following chapters of this thesis.

The aims of this thesis 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 explores vaginal changes, sexual functioning, and distress in women with locally advanced cervical cancer treated in the EMBRACE vaginal morbidity substudy. **Chapter 3** describes the study design of the multicentre randomized SPARC trial, including its rationale and methodology. **Chapter 4** outlines the primary results of the SPARC trial, evaluating the efficacy of the nurse-led sexual rehabilitation intervention compared to standard care following radiotherapy for gynaecological cancers. **Chapter 5** presents the cost-effectiveness and cost-utility of the nurse-led sexual rehabilitation intervention compared to standard care. The thesis concludes with a general discussion of the research findings, with clinical implications and future directions in **Chapter 6**.

REFERENCES

1. Dutch Cancer Registry. Nederlandse Kankerregistratie Cijfers. 2025. https://iknl.nl/nkr-cijfers (accessed 5th of May 2025).
2. Waggoner SE. Cervical cancer. *Lancet* 2003; **361**(9376): 2217-25. doi:10.1016/S0140-6736(03)13778-6.
3. Vale C, Tierney JF, Stewart LA, et al. Reducing Uncertainties About the Effects of Chemoradiotherapy for Cervical Cancer: A Systematic Review and Meta-Analysis of Individual Patient Data From 18 Randomized Trials. *J Clin Oncol* 2008; **26**(35): 5802-12. doi:10.1200/Jco.2008.16.4368.
4. Viswanathan AN, Lee LJ, Eswara JR, et al. Complications of pelvic radiation in patients treated for gynecologic malignancies. *Cancer* 2014; **120**(24): 3870-83. doi:10.1002/cncr.28849.
5. Embrace Collaborative G. EMBRACE study. 2025. www.embracestudy.dk (accessed 5th of May 2025).
6. Rijkmans EC, Nout RA, Rutten IH, et al. Improved survival of patients with cervical cancer treated with image-guided brachytherapy compared with conventional brachytherapy. *Gynecol Oncol* 2014; **135**(2): 231-8. doi:10.1016/j.ygyno.2014.08.027.
7. Potter R, Tanderup K, Schmid MP, et al. MRI-guided adaptive brachytherapy in locally advanced cervical cancer (EMBRACE-I): a multicentre prospective cohort study. *Lancet Oncol* 2021; **22**(4): 538-47. doi:10.1016/S1470-2045(20)30753-1.
8. Potter R, Tanderup K, Kirisits C, et al. The EMBRACE II study: The outcome and prospect of two decades of evolution within the GEC-ESTRO GYN working group and the EMBRACE studies. *Clin Transl Radiat Oncol* 2018; **9**: 48-60. doi:10.1016/j.ctro.2018.01.001.
9. Sturdza A, Potter R, Fokdal LU, et al. Image guided brachytherapy in locally advanced cervical cancer: Improved pelvic control and survival in RetroEMBRACE, a multicenter cohort study. *Radiother Oncol* 2016; **120**(3): 428-33. doi:10.1016/j.radonc.2016.03.011.
10. Kirchheiner K, Fidarova E, Nout RA, et al. Radiation-induced morphological changes in the vagina. *Strahlenther Onkol* 2012; **188**(11): 1010-7. doi:10.1007/s00066-012-0222-0.
11. Kirchheiner K, Nout RA, Lindegaard JC, et al. Dose-effect relationship and risk factors for vaginal stenosis after definitive radio(chemo)therapy with image-guided brachytherapy for locally advanced cervical cancer in the EMBRACE study. *Radiother Oncol* 2016; **118**(1): 160-6. doi:10.1016/j.radonc.2015.12.025.
12. Westerveld H, de Leeuw A, Kirchheiner K, et al. Multicentre evaluation of a novel vaginal dose reporting method in 153 cervical cancer patients. *Radiother Oncol* 2016; **120**(3): 420-7. doi:10.1016/j.radonc.2016.05.002.
13. Damast S, Jeffery DD, Son CH, et al. Literature review of vaginal stenosis and dilator use in radiation oncology. *Pract Radiat Oncol* 2019; **9**(6): 479-91. doi:10.1016/j.prro.2019.07.001.
14. International Clinical Guideline Group. International guidelines on vaginal dilation after pelvic radiotherapy. 2012. https://www.pocd.com.au/core/media/media.nl/id.47537/c.3923593/.f?h=f2e5bc493442741b7e6c (accessed 2nd of March 2020).
15. Friedman LC, Abdallah R, Schluchter M, Panneerselvam A, Kunos CA. Adherence to vaginal dilation following high dose rate brachytherapy for endometrial cancer. *Int J Radiat Oncol Biol Phys* 2011; **80**(3): 751-7. doi:10.1016/j.ijrobp.2010.02.058.
16. Law E, Kelvin JF, Thom B, et al. Prospective study of vaginal dilator use adherence and efficacy following radiotherapy. *Radiother Oncol* 2015; **116**(1): 149-55. doi:10.1016/j.radonc.2015.06.018.
17. Robinson JW, Faris PD, Scott CB. Psychoeducational group increases vaginal dilation for younger women and reduces sexual fears for women of all ages with gynecological carcinoma treated with radiotherapy. *Int J Radiat Oncol Biol Phys* 1999; **44**(3): 497-506. doi:10.1016/s0360-3016(99)00048-6.
18. Schover LR, Fife M, Gershenson DM. Sexual dysfunction and treatment for early stage cervical-cancer. *Cancer* 1989; **63**(1): 204-12. doi:10.1002/1097-0142(19890101)63:1<204::Aid-Cncr2820630133>3.0.Co;2-U.

19. Bakker RM, Vermeer WM, Creutzberg CL, Mens JWM, Nout RA, ter Kuile MM. Qualitative accounts of patients' determinants of vaginal dilator use after pelvic radiotherapy. *The Journal of Sexual Medicine* 2015; **12**(3): 764-73. doi:10.1111/jsm.12776.

20. Abbott-Anderson K, Kwekkeboom KL. A systematic review of sexual concerns reported by gynecological cancer survivors. *Gynecologic Oncology* 2012; **124**(3): 477-89. doi:10.1016/j.ygyno.2011.11.030.

21. Kirchheiner K, Smet S, Jurgenliemk-Schulz IM, et al. Impact of Vaginal Symptoms and Hormonal Replacement Therapy on Sexual Outcomes After Definitive Chemoradiotherapy in Patients With Locally Advanced Cervical Cancer: Results from the EMBRACE-I Study. *Int J Radiat Oncol Biol Phys* 2022; **112**(2): 400-13. doi:10.1016/j.ijrobp.2021.08.036.

22. Ye S, Yang J, Cao D, Lang J, Shen K. A systematic review of quality of life and sexual function of patients with cervical cancer after treatment. *Int J Gynecol Cancer* 2014; **24**(7): 1146-57. doi:10.1097/IGC.0000000000000207.

23. Pieterse QD, Kenter GG, Maas CP, et al. Self-reported sexual, bowel and bladder function in cervical cancer patients following different treatment modalities: longitudinal prospective cohort study. *Int J Gynecol Cancer* 2013; **23**(9): 1717-25. doi:10.1097/IGC.0b013e3182a80a65.

24. Nout RA, Putter H, Jurgenliemk-Schulz IM, et al. Five-year quality of life of endometrial cancer patients treated in the randomised Post Operative Radiation Therapy in Endometrial Cancer (PORTEC-2) trial and comparison with norm data. *Eur J Cancer* 2012; **48**(11): 1638-48. doi:10.1016/j.ejca.2011.11.014.

25. Incrocci L, Jensen PT. Pelvic radiotherapy and sexual function in men and women. *J Sex Med* 2013; **10 Suppl 1**: 53-64. doi:10.1111/jsm.12010.

26. Jensen PT, Groenvold M, Klee MC, Thranov I, Petersen MA, Machin D. Longitudinal study of sexual function and vaginal changes after radiotherapy for cervical cancer. *Int J Radiat Oncol Biol Phys* 2003; **56**(4): 937-49. doi:10.1016/s0360-3016(03)00362-6.

27. Jensen PT, Froeding LP. Pelvic radiotherapy and sexual function in women. *Transl Androl Urol* 2015; **4**(2): 186-205. doi:10.3978/j.issn.2223-4683.2015.04.06.

28. Bae H, Park H. Sexual function, depression, and quality of life in patients with cervical cancer. *Support Care Cancer* 2016; **24**(3): 1277-83. doi:10.1007/s00520-015-2918-z.

29. Roussin M, Lowe J, Hamilton A, Martin L. Factors of sexual quality of life in gynaecological cancers: a systematic literature review. *Arch Gynecol Obstet* 2021; **304**(3): 791-805. doi:10.1007/s00404-021-06056-0.

30. Bakker RM, Kenter GG, Creutzberg CL, et al. Sexual distress and associated factors among cervical cancer survivors: a cross-sectional multicenter observational study. *Psycho-Oncology* 2017; **26**(10): 1470-7. doi:10.1002/pon.4317.

31. Vermeer WM, Bakker RM, Kenter GG, Stiggelbout AM, Ter Kuile MM. Cervical cancer survivors' and partners' experiences with sexual dysfunction and psychosexual support. *Support Care Cancer* 2016; **24**(4): 1679-87. doi:10.1007/s00520-015-2925-0.

32. Vermeer WM, Bakker RM, Kenter GG, de Kroon CD, Stiggelbout AM, ter Kuile MM. Sexual issues among cervical cancer survivors: how can we help women seek help? *Psychooncology* 2015; **24**(4): 458-64. doi:10.1002/pon.3663.

33. Scott JL, Kayser K. A review of couple-based interventions for enhancing women's sexual adjustment and body image after cancer. *Cancer J* 2009; **15**(1): 48-56. doi:10.1097/PPO.0b013e31819585df.

34. Jeffries SA, Robinson JW, Craighead PS, Keats MR. An effective group psychoeducational intervention for improving compliance with vaginal dilation: a randomized controlled trial. *Int J Radiat Oncol Biol Phys* 2006; **65**(2): 404-11. doi:10.1016/j.ijrobp.2005.12.009.

35. Flynn P, Kew F, Kisely SR. Interventions for psychosexual dysfunction in women treated for gynaecological malignancy. *Cochrane Database Syst Rev* 2009; **2009**(2): CD004708. doi:10.1002/14651858.CD004708.pub2.

36. Scott JL, Halford WK, Ward BG. United we stand? The effects of a couple-coping intervention on adjustment to early stage breast or gynecological cancer. *J Consult Clin Psychol* 2004; **72**(6): 1122-35. doi:10.1037/0022-006x.72.6.1122.

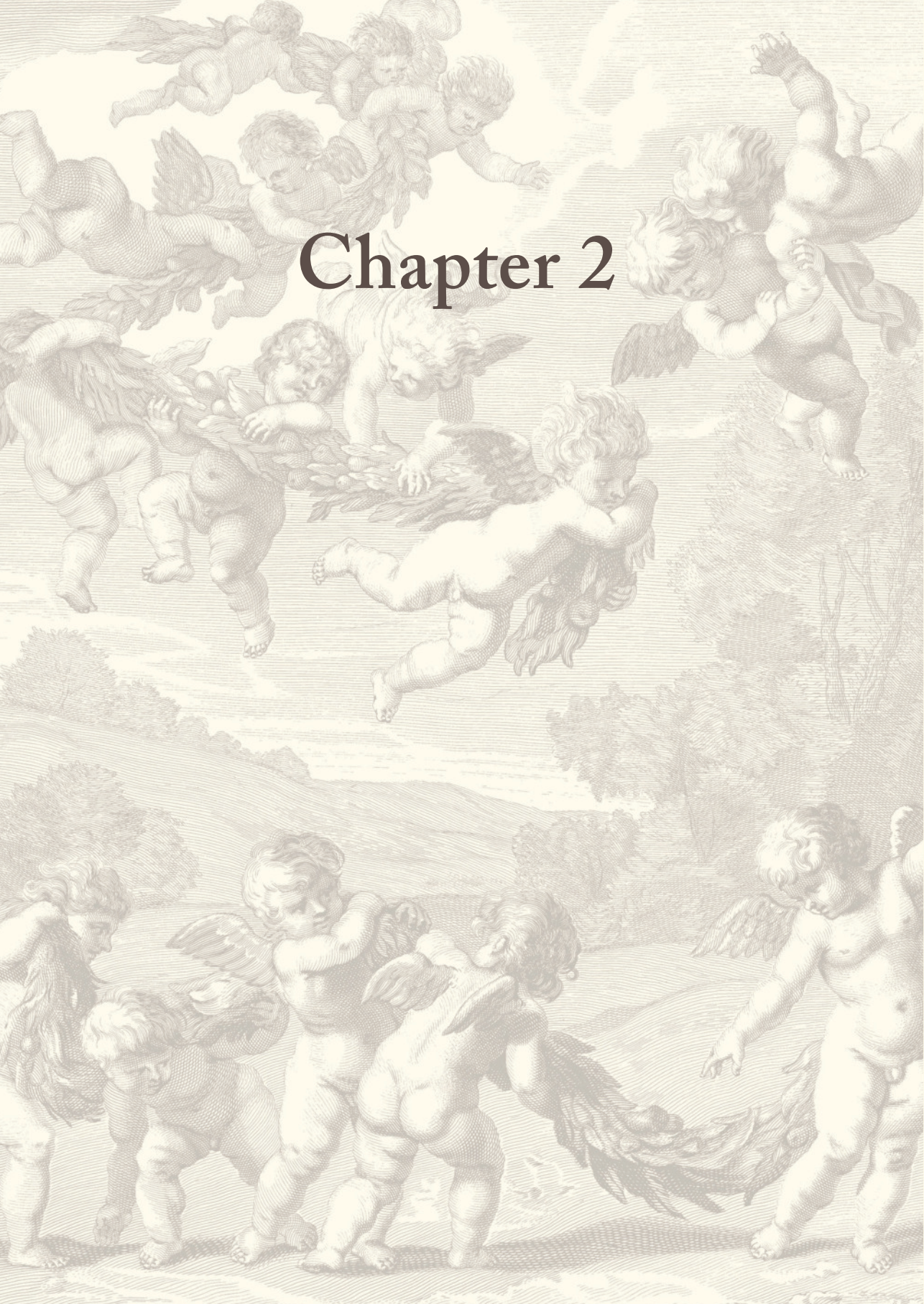
37. Brotto LA, Erskine Y, Carey M, et al. A brief mindfulness-based cognitive behavioral intervention improves sexual functioning versus wait-list control in women treated for gynecologic cancer. *Gynecol Oncol* 2012; **125**(2): 320-5. doi:10.1016/j.ygyno.2012.01.035.

38. Cain EN, Kohorn EI, Quinlan DM, Latimer K, Schwartz PE. Psychosocial benefits of a cancer support group. *Cancer* 1986; **57**(1): 183-9. doi:10.1002/1097-0142(19860101)57:1%3C183::aid-cncr2820570135%3E3.0.co;2-3.

39. Classen CC, Chivers ML, Urowitz S, et al. Psychosexual distress in women with gynecologic cancer: a feasibility study of an online support group. *Psychooncology* 2013; **22**(4): 930-5. doi:10.1002/pon.3058.

40. Bakker RM, Mens JW, de Groot HE, et al. A nurse-led sexual rehabilitation intervention after radiotherapy for gynecological cancer. *Supportive Care Cancer* 2017; **25**(3): 729-37. doi:10.1007/s00520-016-3453-2.

Chapter 2



Vaginal changes, sexual functioning and distress of women with locally advanced cervical cancer treated in the EMBRACE vaginal morbidity substudy

Gynecologic Oncology, 2023; 170:123-132
doi: 10.1016/j.ygyno.2023.01.005

Isabelle Suvaal
Kathrin Kirchheiner
Remi A. Nout
Alina E. Sturdza
Evert van Limbergen
Jacob C. Lindegaard
Hein Putter
Ina M. Jürgenliemk-Schulz
Cyrus Chargari
Kari Tanderup
Richard Pötter
Carien L. Creutzberg
Moniek M. ter Kuile

ABSTRACT

Objectives

The EMBRACE vaginal morbidity substudy prospectively evaluated physician-assessed vaginal changes and patient-reported-outcomes (PRO) on vaginal and sexual functioning problems and distress in the first 2-years after image-guided radio(chemo) therapy and brachytherapy for locally advanced cervical cancer.

Methods

Eligible patients had stage IB1-IIIB cervical cancer with ≤5mm vaginal involvement. Assessment of vaginal changes was graded using CTCAE. PRO were assessed using validated Quality-of-Life and sexual questionnaires. Statistical analysis included Generalized-Linear-Mixed-Models and Spearman's rho-correlation coefficients.

Results

113 eligible patients were included. Mostly mild (grade 1) vaginal changes were reported over time in about 20% (range 11-37%). At 2-years, 47% was not sexually active. Approximately 50% of the sexually active women reported any vaginal and sexual functioning problems and distress over time; more substantial vaginal and sexual problems and distress were reported by up to 14%, 20% and 8%, respectively. Physician-assessed vaginal changes and patient-reported sexual satisfaction differed significantly ($p \leq .05$) between baseline and first follow-up, without further significant changes over time. No or only small associations between physician-assessed vaginal changes and PRO vaginal functioning problems and sexual distress were found.

Conclusions

Mild vaginal changes were reported after image-guided radio(chemo)therapy and brachytherapy, potentially due to the combination of tumours with limited vaginal involvement, EMBRACE-specific treatment optimization and rehabilitation recommendations. Although vaginal and sexual functioning problems and sexual distress were frequently reported, the rate of substantial problems and distress was low. The lack of association between vaginal changes, vaginal functioning problems and sexual distress shows that sexual functioning is more complex than vaginal morbidity alone.

INTRODUCTION

The combination of modern image-guided external beam radiotherapy with concurrent cisplatin-based chemotherapy and image-guided adaptive brachytherapy (EBRT+IGABT), as developed and implemented by the international collaborative EMBRACE-group (international studies on MRI-guided brachytherapy in locally advanced cervical cancer[1]), has substantially improved local disease control and survival in cervical cancer patients, and led to reduced toxicity compared to older treatment techniques[2-4]. A growing number of cervical cancer survivors, mostly young or middle-aged, may still experience long-term bowel and bladder symptoms, fatigue and sexual problems that may compromise their health-related quality of life (QoL)[5-9]. Sexual problems experienced by survivors include decreased sexual desire, arousal, enjoyment, satisfaction and vaginal functioning problems during intercourse or other sexual activity, such as pain, reduced lubrication, tightening and shortening of the vagina, and blood loss at sexual activities[7,8,10,11]. These adverse effects of radiotherapy may be caused by treatment-induced morphological vaginal mucosal changes, known as vaginal morbidity (VM)[12].

Common vaginal changes after EBRT+IGABT include mucositis, changes to the microvasculature leading to atrophy, telangiectasia, reduced lubrication, adhesions, and fibrosis in the upper vagina which may lead to vaginal stenosis and shortening. Only in very rare cases ulceration, necrosis and fistulae are seen[13,14]. Vaginal changes are mostly rated by physicians as low-grade adverse events according to Common Terminology Criteria for Adverse Events (CTCAE), and their direct impact on sexual QoL remains unclear[7,15,16]. As vaginal functioning problems are experienced by patients during sexual activity, and vaginal mucosal changes are observed by the physician during vaginal examination, the consequences of these vaginal mucosal changes for vaginal and sexual functioning vary between individuals. Some women do not report vaginal functioning problems even when significant mucosal changes are observed, while others experience persisting sexual problems with clinically minor mucosal changes[17]. It has been shown that vaginal functioning problems are associated with sexual distress, defined as distress regarding sexual activity or worries about painful intercourse[18]. However, sexual functioning problems in terms of sexual health (desire, arousal, orgasm, sexual satisfaction, and sexual enjoyment) may not be related only to vaginal functioning problems. As sexual functioning problems are a complex interplay between physiological, psychological and relationship factors, there remains a lack of knowledge to which extent these factors are relevant for overall sexual functioning of cervical cancer survivors. Improved understanding of vaginal mucosal changes and the relation to vaginal functioning problems as experienced by survivors will provide rationale and focus for strategies to improve their sexual health. The VM substudy was initiated to evaluate physician-assessed vaginal changes and patient-reported outcomes

(PRO) on vaginal functioning problems, sexual functioning problems and sexual distress in the first 2-years after treatment; and the association between physician-assessed vaginal changes and PRO.

METHOD AND MATERIALS

The VM study was a prospective longitudinal study designed as a substudy of the EMBRACE-I study and continued during initial years of the EMBRACE-II study[1]. The background, rationale, design, and results of the EMBRACE studies have been published previously[2,3]. Recruitment and data collection for the VM substudy were conducted in 6 of 24 gynaecologic radiation oncology centres participating in the EMBRACE-I study. The VM substudy was approved in all participating centres by their Ethics Committees.

Women who participated in the EMBRACE studies were eligible for the VM substudy when diagnosed with cancer of the uterine cervix, Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) 2009 stage IB1-IIIB, with biopsy-proven squamous-cell carcinoma, adenocarcinoma, or adeno-squamous cell carcinoma, with no or only limited (≤5 mm) vaginal involvement. Exclusion criteria were pre-existent major vaginal morbidities, or severe medical or psychological conditions. All participating women provided written informed consent.

Treatment

Women were treated in accordance with the EMBRACE-I or II protocols[1-3,6]. In summary, pelvic EBRT was given either by three-dimensional (3D) conformal or intensity-modulated radiation therapy (IMRT) to a total dose of 45-50 Gy in 1.8-2 Gy daily fractions, with concomitant weekly cisplatin chemotherapy (≥5 cycles of cisplatin 40mg/m^2), and IGABT to a total dose of 30-50 Gy EQD2 specified to the high-risk clinical target volume (HR-CTV). Target volume doses and constraints for organs at risk (OAR) were according to the EMBRACE protocols. In the VM substudy, all women received counselling on sexual rehabilitation after treatment, and a set of four different dilators was made available to them (free of cost). Women were recommended to start dilation 4-6 weeks after treatment (after resolving of acute VM), for at least 3 times per week at least during the first 2-years after treatment.

Assessments

In addition to the EMBRACE assessments on disease, morbidity and QoL, the VM substudy included a detailed extra VM assessment by vaginal and pelvic examination and additional questionnaires on vaginal and sexual functioning problems and sexual

distress. Timepoints of clinical assessments were baseline, 4-6 weeks after completion of treatment, and at 3, 6, 12 and 24 months follow-up. PRO questionnaires were completed at the same timepoints, except for 4-6 weeks.

Vaginal morbidity assessed by the physician

Vaginal morbidity was assessed by the treating radiation oncologists and/or gynaecologic oncologists. The Common Terminology Criteria for Adverse Events (AE) version 3 (CTCAE v3.0) and a detailed and comprehensive assessment protocol were used to grade vaginal changes, including dryness, stenosis, mucositis, and bleeding (for CTCAE definitions see supplementary table S1). Vaginal length and width were measured with standardized cylinders. Vaginal adhesions, fibrosis, telangiectasia, mucosal colour, fragility/bleeding, and ulceration were scored on four or five-point scales. The scoring was based on a comprehensive photographic atlas with detailed description of morphological vaginal changes as assessed with vaginoscopies (for details see Kirchheiner, 2012[12]).

Patient-reported outcomes (PRO)

The PRO measurements consisted of a combination of internationally established and validated questionnaires. *Vaginal functioning problems and sexual distress* were assessed with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Gynaecological Cancer Module (EORTC QLQ-CX24, completed in conjunction with the EORTC QLQ-C30 core questionnaire[19,20] and the Sexual Activity Questionnaire (SAQ[21])). *Sexual functioning problems* were assessed with the EORTC QLQ-CX24[20] and the gynaecologic Leiden Questionnaire (LQ[22]). The SAQ also includes a section regarding reasons for sexual inactivity[21]. Patients who were not sexually active were asked to indicate the reasons and if they would like to become sexually active again. Finally, all women were asked how important sexuality in general was for them.

Statistical methods

While the overall study design was explorative without restriction of exact case number calculation, a total number of at least 100 women was intended for prospective evaluation of vaginal changes and PRO, and approximately 40 of these 100 women were expected to be sexually active, based on the proportion of sexually active women in the EMBRACE-I study. Data were reported with mean (M) and standard deviation (SD) or median (Md) and interquartile range (IQR). Proportions were given as number of women with and without the characteristic and as a percentage (mean and range). Statistical significance was considered for $p \leq .05$. Analyses were conducted with the Statistical Package for Social Scientists (SPSS, version 25) and the Generalized-Linear-Mixed-Models (GLMM)-adaptive package in R.

To evaluate differences between physician-assessed vaginal changes and patient-reported sexual functioning problems and sexual distress at baseline (pre-treatment) and the follow-up moments, a GLMM analysis based on the continuation ratio model for ordinal data was conducted[23]. The GLMM models handle missing values as 'missing at random'. The scores on vaginal changes, patient-reported sexual functioning problems and sexual distress were entered as dependent variables, with 'patient' as random effect and follow-up moments (time) as fixed factors. When ≤5 women scored in one category (e.g. CTCAE grade 3), this category was merged with one category below (e.g. grade 2). The same method was used to evaluate potential differences between vaginal changes, and patient-reported sexual functioning problems and sexual distress immediately after treatment and subsequent follow-up moments, using Wald tests based on appropriately defined contrasts. Due to the limited number of sexually active women, we refrained from analysis of changes over time for these PRO results because of lack of power. Spearman's rho correlation coefficients (r) were conducted to examine the associations between the physician assessments and patient-reported vaginal and sexual functioning problems. Observations were pooled over all timepoints of follow-up. We report associations with an effect size of medium and above ($r \geq .3$)[24].

RESULTS

Participants

Between June 2012 and November 2018, a total of 118 women were included in the VM substudy; 5 women were excluded because vaginal involvement at diagnosis exceeded 5mm, leaving 113 women in the analysis. Data of 36 women (32%) were not available at different timepoints during the 24 month-follow up period (for an overview, see Figure 1): 22 women (20%) died because of the disease, and for 13 women (12%) data were largely incomplete due to non-compliance with assessments or follow-up.

Patient, disease and treatment characteristics are summarized in Table 1. The characteristics of the VM study cohort differed from the overall EMBRACE cohorts regarding FIGO stage and vaginal tumour extension. These differences were reflected in several treatment parameters (key characteristics are depicted in supplementary table S2). Results of QoL functioning and symptom subscales over time are provided in supplementary tables S3 and S4. In line with findings of previous EMBRACE reports, fatigue and insomnia were present at baseline and slightly increased after treatment, after which they remained at similar rates over the follow-up period (supplementary table S3)[9,15].

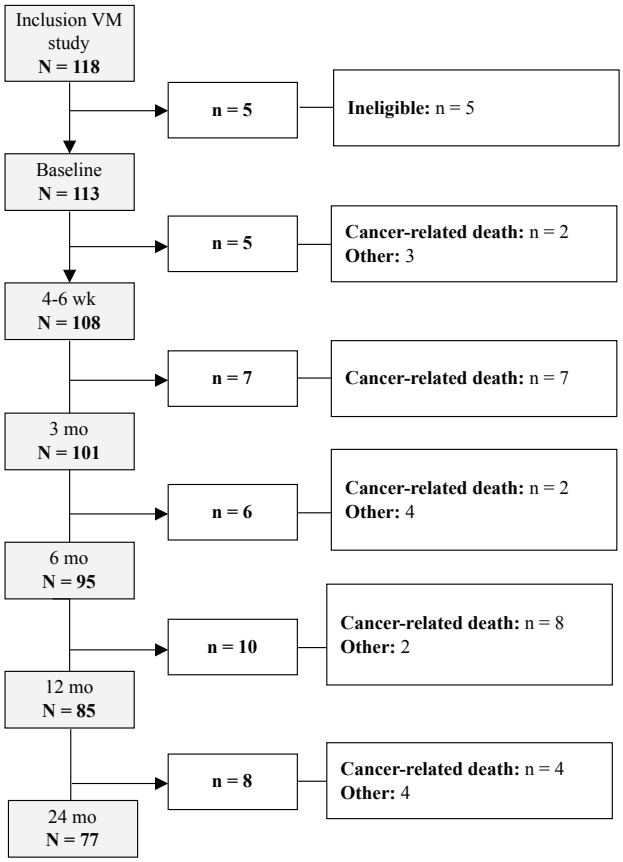


Figure 1 Inclusion overview and reasons of data unavailable per timepoint.
mo = months; N = total sample; n = subsample; Other = non-compliance with assessments or follow-up; VM = Vaginal Morbidity; wk = weeks

Vaginal changes assessed by the physician

Significant differences between baseline and follow-up were found for all physician-assessed vaginal changes (See Figures 2A and 2B-II-VIII). However, for most vaginal changes, there was no further change between the first and later follow-up timepoints. The prevalence rates of physician-reported vaginal mucositis, width, fibrosis, and adhesions significantly differed between 4-6 weeks and later follow-up timepoints. In more detail, the prevalence rates for grade 1 vaginal dryness increased from 17% at 4-6 weeks to 23% at 6 months and slightly decreased again to 18% at 24 months. Grade 1 stenosis gradually increased from 11% at 4-6 weeks to 37% at 24 months.

Table 1 Patient, disease and treatment characteristics in 113 EMBRACE VM study patients

Patient and disease characteristics (at time of diagnosis) of N = 113 patients analysed		
Age	Median in years (IQR)	48 (40.5-59.0)
BMI	Normal (18.8-24.9)	58 (51.3%)
	Underweight (<18.5)	5 (4.4%)
	Overweight (25-19.9)	31 (27.4%)
	Obese (>30)	19 (16.8%)
Partner	Yes	79 (69.9%)
	No	34 (30.1%)
Vaginal delivery*	Yes	53 (46.9%)
	No	15 (13.3%)
	Missing N (%)	45 (39.8%)
Menopausal status	Premenopausal	59 (52.2%)
	Postmenopausal	51 (45.1%)
	Missing N (%)	3 (2.7%)
WHO performance score	WHO PS0	85 (75.2%)
	WHO PS1	25 (22.1%)
	WHO PS2	3 (2.7%)
	WHO PS3	0
FIGO 2009 stage	1B	28 (24.8%)
	2A	5 (4.4%)
	2B	62 (54.9%)
	3A	0
	3B	16 (14.2%)
	4A	2 (1.8%)
Tumour extension in the vagina (clinical)	Not involved	91 (80.5%)
	Upper third	22 (19.5%)
	Middle third	0
Treatment characteristics (at time of diagnosis) of N = 113 patients analysed		
EBRT PTV-E total dose	Median dose (Gy) (IQR)	45 (45-45)
	Missing N (%)	0
EBRT technique	3D conformal	20 (17.7%)
	IMRT/VMAT	93 (82.3%)
EBRT PTV-N Nodal boost	Yes	43 (38.1%)
	No	70 (61.9%)
Concomitant chemotherapy given	Yes	111 (98.2%)
	No	0
	Missing N (%)	2 (1.8%)
EBRT+BT HR-CTV D90 in EQD2	Median dose (Gy) (IQR)	91.1 (89.4-93.6)
	Missing N (%)	2 (1.8%)
Total ICRU Rectum in EQD2	Median dose (Gy) (IQR)	62.2 (57.8-65.3)
	Missing N (%)	5 (4.4%)

Note. 3D = three-dimensional; BMI = Body Mass Index; BT = brachytherapy; EBRT = external beam radiotherapy; EBRT PTV-E = external beam radiotherapy total dose prescribed to the elective planning target volume; EBRT PTV-N = external beam radiotherapy total dose prescribed to the lymph nodes planning target volume; EBRT+BT HR-CTV D90 = external beam radiotherapy + brachytherapy dose received by 90% of the high-risk clinical target volume; EMBRACE = image guided intensity modulated External beam radiochemotherapy and MRI based adaptive BRAchytherapy in locally advanced Cervical cancer; EQD2 = equivalent dose in 2-Gy fractions; FIGO = Fédération Internationale de Gynécologie et d'Obstétrique; Gy = gray; IMRT = intensity modulated radiotherapy; IQR = interquartile range; N = total sample; VM = vaginal morbidity; VMAT = volumetric modulated arc radiotherapy; WHO PS = World Health Organization performance status.
* = only EMBRACE-I VM study patients, not assessed in EMBRACE-II VM study patients.

The prevalence rates for grade 1 vaginal mucositis decreased over time (from 29% at 4-6 weeks to 13% at 24 months). Grade 1 vaginal bleeding, at baseline caused by the tumour, decreased from 44% to 15% at 4-6 weeks post-treatment, with no further changes over time. During follow-up, vaginal morbidity prevalence of moderate (up to 2% grade 2 on average) and especially severe (<1% grade 3 on average) -related adverse events of dryness, stenosis, mucositis and bleeding were rare.

The median vaginal length assessed by physicians varied over time between 9 and 10cm. For vaginal width, 3cm and 3.5cm were most often reported, at all timepoints. Regarding the degree of fibrosis, in most women (79%, range: 72-89%) the vaginal tissue was reported to be soft and mobile during the follow-up period. Adhesions in the proximal vagina were reported shortly after treatment in 20% of the women and these proportions remained comparable during follow-up. Adhesions in the middle third of the vagina were reported in 7% at 24 months. Erythema and/or moderate surface fragility with minimal bleeding at examination were reported in 14% (range: 11-17%) of the women. Telangiectasia up to 4 cm^2 had developed after treatment in 27% of the women at 4-6 weeks, increasing over time to 79% at 24 months. The mucosal colour changed over time from uniform pink at baseline (95%) to mildly mottle pale (79%) at 24 months. Some superficial ulceration was reported in 6% of the women shortly after treatment, which healed over time, with none reported at 24 months.

Patient-reported sexual activity

Up to 29% of the women reported that sexuality in general was 'not at all' important in their life (see Table 2). Many women reported not to be sexually active at baseline (79%), most often because of disease related problems (54%), followed by 'loss of interest in sex' (40%). From 3 to 24 months post-treatment the proportion not being sexually active decreased to 47% at 24 months, with the most frequently reported reason being 'loss of interest in sex' (69%), followed by 'not having a partner' (47%). At three months after treatment, about 25% of the non-sexually active women stated that they would 'very much like to become sexually active again', which decreased to 6% at 24 months.

Figure 2A Vaginal morbidity clinical measurements over time. The proportion of women is shown in percentages. BM = baseline measurement; CTCAE = Common Terminology Criteria for Adverse Events; M = months; N = number of women at risk at the specific timepoint, O = observed number of women at the specific timepoint, W = weeks.
*p < .05, **p < .01, ***p < .001

Figure 2B Vaginal morbidity clinical measurements over time. The proportion of women is shown in percentages, except for vaginal length, which is shown in median length in centimeter. BM = baseline measurement; Dm = diameter; cm = centimeter; M = months; Med = Median; N = number of women at risk at the specific timepoint, O = observed number of women at the specific timepoint, W = weeks.
*p < .05, **p < .01, ***p < .001

Table 2 Sexual activity (SAQ)

	Baseline (N=113)	**3 months (N=101)**	**6 months (N=95)**	**12 months (N=85)**	**24 months (N=77)**
Importance of sexuality in general life					
Not at all	29 (25.7%)	24 (23.8%)	26 (27.4%)	25 (29.4%)	20 (26.0%)
A little	17 (15.0%)	22 (21.8%)	11 (11.6%)	17 (20.0%)	14 (18.2%)
Quite a bit	27 (23.9%)	23 (22.8%)	32 (33.7%)	18 (21.2%)	18 (23.4%)
Very much	31 (27.4%)	19 (18.8%)	17 (17.9%)	18 (21.2%)	12 (15.6%)
Missing	9 (8.0%)	13 (12.9%)	9 (9.5%)	7 (8.2%)	13 (16.9%)
Subgroup of non-sexually active women* (N)	89 (78.8%)	57 (56.4%)	41 (43.2%)	39 (45.9%)	36 (46.7%)
Reasons, because (more answers are possible):					
I do not have a partner (yes)	24 (27.0%)	19 (33.3%)	21 (51.2%)	22 (56.4%)	17 (47.2%)
I have lost interest in sex (yes)	36 (40.4%)	34 (59.6%)	23 (56.1%)	26 (66.7%)	25 (69.4%)
My partner has a problem (yes)	4 (4.5%)	5 (8.8%)	2 (4.9%)	1 (2.6%)	2 (5.6%)
Because of disease/treatment related problems (yes)	48 (53.9%)	16 (28.1%)	3 (7.3%)	3 (7.7%)	5 (13.9%)
Would you like to become sexually active again					
Not at all	25 (28.1%)	16 (28.1%)	20 (48.8%)	20 (51.3%)	20 (55.6%)
A little	7 (7.9%)	20 (35.1%)	12 (29.3%)	11 (28.2%)	7 (19.4%)
Quite a bit	18 (20.2%)	4 (7.1%)	2 (4.9%)	2 (5.1%)	2 (5.6%)
Very much	36 (40.4%)	14 (24.6%)	4 (9.8%)	4 (10.3%)	2 (5.6%)
Missing	3 (3.4%)	3 (5.3%)	3 (7.3%)	2 (5.1%)	5 (13.9%)

N*ote.* N = 113 at baseline, N = 101 at 3 months, N = 95 at 6 months, N = 85 at 12 months, N = 77 at 24 months. N = total sample. SAQ = Sexual Activity Questionnaire.
*Non-sexually active in the past four months (according to the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Gynaecological Cancer Module (EORTC QLQ-CX24) question regarding sexual activity).

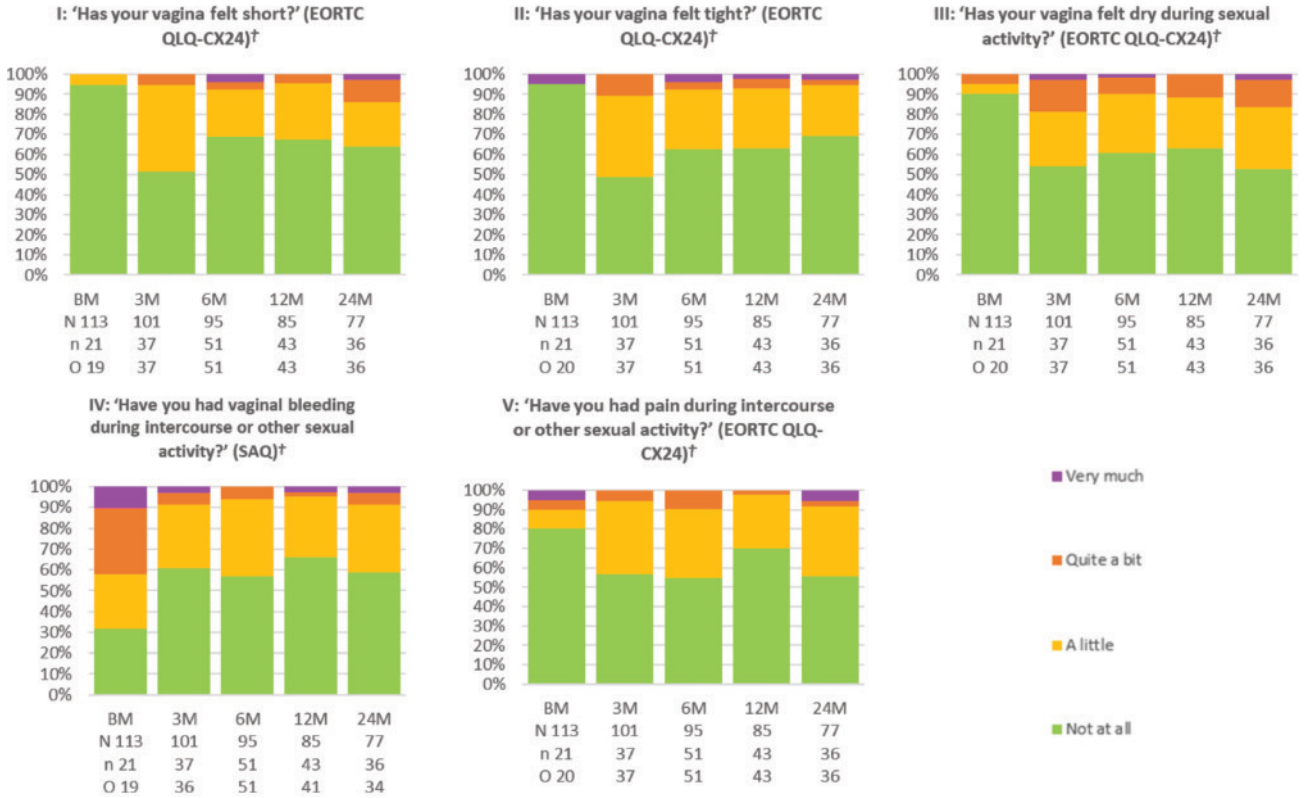


Figure 3 Patient-reported vaginal functioning problems of sexually active women in the past four weeks on single item level over time. The proportion of women is shown in percentages with the answer categories "not at all", "a little", "quite a bit" and "very much". BM = baseline measurement; EORTC QLQ-CX24 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Gynaecological Cancer Module; M = months; N = number of women at risk at the specific timepoint, n = number of sexually active women at risk at the specific timepoint, O = observed number of women at the specific timepoint, SAQ = Sexual Activity Questionnaire.
†GLMM-analysis were only conducted with PRO including the total population, so not with PRO including the sexually active subgroup only.

Patient-reported vaginal functioning

The time pattern of prevalence rates of vaginal functioning problems of sexually active women is shown in Figure 3. Any vaginal tightness, shortness, dryness, and pain (response categories 'a little', `quite a bit` and 'very much') showed an immediate increase from the proportions at baseline (5%, 5%, 10%, and 20% for feelings of tightness, shortness, dryness and pain, respectively) to 3 months after treatment (51%, 47%, 46%, and 43%, respectively), when they reached a plateau. Any vaginal bleeding during intercourse or other sexual activity was most often reported at baseline (68%), being a symptom of the disease, and decreased to 39% (range: 34-43%) of the sexually active women in follow-up, being a symptom of fragility of vaginal mucosa after treatment. During follow-up, more substantial feelings of tightness, shortness, dryness, pain and bleeding during intercourse or other sexual activity ('quite a bit' and 'very much') was reported by 8%, 8%, 14%, 7% and 7% on average of the sexually active women, respectively.

Patient-reported sexual distress and sexual functioning problems

Sexual dissatisfaction decreased significantly between baseline and follow-up, with no further change between the earliest and later follow-up timepoints (see Figure 4-II). No significant differences were found between sexual desire and worries about painful intercourse over time (see Figures 4-I and 4-III). In more detail, 31% of all women were 'dissatisfied' or 'very dissatisfied' with their present sexual life at baseline, which decreased to 15% at 24 months, while 24% reported being 'quite a bit' or 'very much' worried that sex would be painful at baseline, which decreased to 13% at 24 months. During the study period, up to 46% of all women reported that they 'seldom' or 'never' felt sexual desire.

Among the sexually active women, 4% reported that they 'seldom' or 'never' felt sufficient lubrication during sexual arousal at baseline, which increased to 20% at 24 months after treatment. At baseline, about 22% reported that they 'seldom' or 'never' experienced an orgasm during intercourse, which remained comparable over time (30% on average, range: 38-23%). In addition, 6% reported to 'seldom' or 'never' reached an orgasm during masturbation at baseline, which decreased to 0% at 24 months. Over all timepoints, around 20% (range: 16-25%) of the sexually active women reported that sexual activity had been 'a little' or 'not at all' enjoyable, and around 8% (range: 5-11%) reported that they were 'quite a bit' or 'very much' distressed about sexual activity.

Figure 4 Patient-reported sexual functioning problems and sexual distress on single item level over time. The proportion of women is shown in percentages. BM = baseline measurement; EORTC QLQ-CX24 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Gynecological Cancer Module; LQ = gynecologic Leiden Questionnaire; M = months; N = number of women at risk at the specific timepoint, n = number of sexually active women at risk at the specific timepoint, O = observed number of women at the specific timepoint, SAQ = Sexual Activity Questionnaire.
Panel II: *p < .05, **p < .01, ***p < .001. Panel I and III: #No significant differences were found. †GLMM-analysis were only conducted with PRO including the total population, so not with PRO including the sexually active subgroup only.

Associations between physician-assessed vaginal changes and patient-reported vaginal functioning problems and sexual distress

There was only a significant negative association (r=-.34) with a medium effect size found between patient-reported dryness and physician-assessed vaginal width, suggesting a trend for women who reported a dryer vagina to have a narrower vagina (as measured in cm) (See supplementary table S5).

DISCUSSION

The EMBRACE vaginal morbidity substudy prospectively evaluated physician-assessed vaginal changes and patient-reported outcomes (PRO) 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. Mostly mild physician-assessed vaginal changes were reported, such as grade 1 (not interfering with sexual functioning) mucositis (13%) and stenosis (37%) at 24 months after treatment, without clear changes during the 2-year follow-up. Higher grades were reported in less than 3% of the women. Almost half of the women in the total cohort reported not being sexually active at 24 months, 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 treatment. More substantial 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 earliest and later follow-up moments. Vaginal functioning problems and sexual distress, as reported in the PRO outcomes, were not or only weakly associated with the physician-assessed vaginal changes.

No or only mild physician-assessed vaginal changes were reported over time for most women, and moderate and severe vaginal changes were very rare. Although mild vaginal stenosis increased after treatment, in the large majority a 'normal' range for average vaginal length[25] and width[26] were reported. An explanation for our relatively favourable results as compared to earlier literature data could be that women who were eligible for the VM substudy had no or very minimal vaginal involvement at baseline. A previous EMBRACE-I analysis showed that the risk of developing mild or moderate stenosis by 2-years after treatment was 15% for women with cancers without vaginal involvement, compared to 28% for those with vaginal involvement[27]. Martins et al.[13] found that a more advanced tumour stage (IIIA or IIIB) resulted in more frequent and severe reductions in vaginal diameter and length. With more advanced tumours with more extensive vaginal involvement a higher vaginal volume

and longer segment of the vagina will receive the full target dose, resulting in more subsequent vaginal changes, especially vaginal stenosis[27,28]. As the VM study cohort consisted of women with none to limited vaginal involvement, the vaginal length receiving the full EBRT dose and a significant dose contribution from brachytherapy will have been relatively limited[28]. In addition, these women were treated according to EMBRACE protocol. It has already been shown that the EMBRACE-related dose optimization decreases VM substantially[29]. Besides, the 6 centres that participated in the VM substudy were relatively large and experienced gynaecological radiation oncology centres participating in EMBRACE from early on. These centres had already introduced standard approaches for patient information and awareness on sexual issues and vaginal dilation as standard of care before the VM substudy[17,30-33]. Women who chose to participate in the VM study were also likely to be motivated to comply to vaginal dilation and resume sexual activities (now or when no partner present, with future partners), as they were also regularly reminded by receiving the follow-up measurements and questionnaires regarding these topics. Martins et al.[33] showed that daily vaginal dilator use positively influence the maintenance of sexual activity with less discomfort, preventing the progression from grade 1 to grade 2 stenosis. Women in the VM study who were under 50 years of age at diagnosis were recommended to receive hormonal replacement therapy until age of about 50.

The VM results show that only about one out of four women were sexually active before treatment, most likely due to symptoms of their cervical cancer, and that sexual activity increased to only about half of the women at 24 months. Even in this motivated cohort of women participating in the VM study, the proportion resuming sexual activity remained relatively low. Previous studies reported similar prevalence rates of sexual activity varying between 40-60% after treatment for cervical cancer survivors with primary chemoradiation and brachytherapy[7,10,34,35]. Importantly, these rates are like those reported after radical surgery alone, and after surgery with postoperative EBRT, thus suggesting that the diagnosis and treatment of cervical cancer as such has a profound impact on subsequent sexual functioning, activity and distress[10,34].

Compared to the analysis of the EMBRACE-I cohort[7], sexually active women in the VM substudy reported less often substantial vaginal functioning problems such as vaginal dryness, shortness, tightness, or pain during sexual activity. The reported prevalence rates of substantial vaginal functioning problems, sexual functioning problems and sexual distress in an older, non-EMBRACE study cohort[35] were even higher, with 40% reporting vaginal dryness, 29% vaginal shortening and tightening, 17% vaginal pain during intercourse, and 35% persistent lubrication problems, compared to 12% dryness, 5% shortening and 7% tightening, 2% pain, and 4% lubrication

problems in our study at 12 months after treatment. In addition to the more favourable selection of motivated patients in the VM substudy, excluding tumours with more than minimal vaginal involvement, the EMBRACE-treatment standards may have added to reduction of severe changes. While vaginal bleeding during intercourse was a symptom of the disease before treatment, about a third of the women reported minor bleeding during sexual activity or examination at 24 months, in line with previous data[35,36].

Even though most of the women in the VM study had no or only mild physician-reported vaginal changes over time, any vaginal functioning problems (mild to substantial) were reported by half of the sexually active women. These findings highlight the complexity of interpreting sexual outcomes. In the current study, even after pooling observations over all timepoints of follow-up, we found that the subjective perception of vaginal changes and sexual distress as experienced by the women during sexual activity were not or only weakly associated with the objective assessments of the physicians. Previous studies that compared physician-assessed vaginal CTCAE items and patient-reported symptoms also showed that there is a high level of discrepancy between objective and subjective symptoms[37,38]. This underlines the necessity of reporting both physician-assessed and patient-reported vaginal functioning problems for a complete evaluation of changes after cervical cancer treatment, as done in the VM study. In addition, as vaginal functioning problems such as pain, and feeling of a tight, short and/or dry vagina are subjective symptoms, they can be influenced by additional biopsychosocial factors, such as pelvic floor functioning, menopause and infertility as result of treatment, fatigue, and relationship and work-related problems. Interpretation of vaginal functioning problems in relation to these factors might be helpful.

Substantial sexual functioning problems, such as 'seldom' or 'never' reaching an orgasm during masturbation, 'seldom' or 'never' lubricated during sexual arousal and 'a little' or 'not at all' enjoyable sex, were reported by up to 20% of the sexually active women. For 'seldom' or 'never' reaching an orgasm during sexual intercourse, this percentage was higher (30%), however, from previous research we know that for many women sexual intercourse alone is not the best stimulus to climax[39]. Therefore, we did not define this as a substantial sexual problem. For sexual distress, approximately 30% of all women reported being 'a little', 'quite a bit' or 'very much' worried that sex would be painful at 24 months. This result is comparable with findings of a previous study, where 29% of all women were worried about painful intercourse after treatment for cervical cancer, even when in their cohort the minority (29%) received EBRT+BT and brachytherapy[18]. Bakker[18] also showed that higher levels of vaginal functioning problems were associated with higher levels of sexual distress. In a subsequent study a nurse-led intervention for sexual rehabilitation after cervical cancer treatment with

EBRT and brachytherapy was developed and pilot tested, aiming to reduce such distress and improve sexual outcomes by coaching women to use vaginal dilation and resume sexual activities[40]. The effects of frequency of dilator use and early resuming and frequency of sexual activity in the VM study on vaginal and sexual functioning problems and distress will be further evaluated and be topic of a subsequent analysis.

This non-randomized study has obvious limitations. Although the CTCAE is the most comprehensive grading system, the reporting of vaginal changes relies on the thoroughness and interpretation of vaginal and pelvic examination, which can be cumbersome for the patient both before and after treatment. However, both physicians and patients were strongly motivated by the rational and the standardized structure of the VM study protocol. Another limitation is that the time frame of the questions of the EORTC QLQ-CX24[20] is set with 'in the past 4 weeks'. Women who were sexually active before, but not during the past 4 weeks might be inaccurately categorized as inactive. The proportion of vaginal functioning problems for such women could therefore have been underestimated, as these might have contributed to very infrequent sexual activity. In addition, although the questions of the EORTC QLQ-CX24 are vaginal penetration oriented, 'sexual activity' is not well operationalized, leading to a lack of knowledge regarding the meaning in terms of vaginal intercourse or any other sexual activity, both in the EORTC QLQ-CX24 and SAQ[21]. Although standard approaches for patient information and coaching on sexual issues and recommendations for vaginal dilation were included in the VM study, there was no information on compliance of centres with such rehabilitation measures.

In conclusion, in the EMBRACE VM substudy, most of the women treated with primary radio(chemo)therapy and image-guided brachytherapy for locally advanced cervical cancer had no or only mild vaginal changes over time. The results are favourable compared to previous data, potentially due to the combination of no or only limited vaginal involvement and EMBRACE-related dose optimization and rehabilitation recommendations. About half of the women were sexually active at 24 months after treatment, and although any vaginal and sexual functioning problems and distress were frequently reported, the rate of more substantial vaginal and sexual functioning problems was relatively low. The lack of association between vaginal changes, vaginal problems and sexual distress shows that sexual functioning is much more complex than vaginal morbidity alone.

SUPPLEMENTARY MATERIAL

Table S1 CTCAE version 3.0 definitions

		Grade		
Adverse event	**Short name**	**1**	**2**	**3**
Vaginal stenosis/ length	Vaginal stenosis	Vaginal narrowing and/ or shortening not interfering with function	Vaginal narrowing and/ or shortening interfering with function	Complete obliteration; not surgically correctable
Vaginal dryness	Vaginal dryness	Mild	Interfering with sexual functioning; dyspareunia; intervention indicated	-
Vagina bleeding	Haemorrhage, GU - Vagina	Minimal or microscopic bleeding; intervention not indicated	Gross bleeding, medical intervention, or urinary tract irrigation indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., haemostasis of bleeding site)
Vaginal mucositis	Vaginal mucositis	Erythema of the mucosa; minimal symptoms	Patchy ulcerations; moderate symptoms or dyspareunia	Confluent ulcerations; bleeding with trauma; unable to tolerate vaginal exam, sexual intercourse or tampon placement

Note. CTCAE = Common Terminology Criteria for Adverse Events; GU = genitourinary

Table S2 Comparison of patient, disease and treatment characteristics (at time of diagnosis) between patients included in the VM study and patients not included in the VM study (EMBRACE-I and II; up to and including 12-11-2018)

Patient and disease characteristics (at time of diagnosis) in EMBRACE patients (I and II)		**N = 113 (Subgroup Vaginal Morbidity study)**	**N = 1551 (EMBRACE participants not in Vaginal Morbidity study)**	**z or t - value**
Age	Median in years (IQR) Missing N (%)	48 (40.5-59.0) 0	50 (41.8-61) 5 (0.3%)	1.7
BMI	Normal (18.8-24.9) Underweight (<18.5) Overweight (25-19.9) Obese (>30) Missing N (%)	58 (51.3%) 5 (4.4%) 31 (27.4%) 19 (16.8%) 0	680 (43.8%) 71 (4.6%) 446 (28.8%) 324 (20.9%) 30 (1.9%)	-1.5
Partner[#]	Yes No Missing N (%)	79 (69.9%) 34 (30.1%) 0	N.A.	N.A.
Vaginal delivery[#**]	Yes No Missing N (%)	53 (46.9%) 15 (13.3%) 45 (39.8%)	N.A.	N.A.
Menopausal status[#]	Premenopausal Postmenopausal Missing N (%)	59 (52.2%) 51 (45.1%) 3 (2.7%)	N.A.	N.A.
WHO performance score	WHO PS0 WHO PS1 WHO PS2 WHO PS3 Missing N (%)	85 (75.2%) 25 (22.1%) 3 (2.7%) 0 0	1093 (70.5%) 396 (25.5%) 39 (2.5%) 3 (0.2%) 20 (1.3%)	-.9
FIGO 2009 stage	1B 2A 2B 3A 3B 4A Missing N (%)	28 (24.8%) 5 (4.4%) 62 (54.9%) 0 16 (14.2%) 2 (1.8%) 0	13 (0.8%) 299 (19.3%) 817 (52.7%) 244 (15.7%) 127 (8.2%) 16 (1.0%) 35 (2.3%)	**-3.2*****
Tumour extension in the vagina (clinical)	Not involved Upper third Middle third Lower third Missing N (%)	91 (80.5%) 22 (19.5%) 0 0 0	823 (53.1%) 580 (37.4%) 83 (5.4%) 43 (2.8%) 22 (1.4%)	**-5.7*****

Table S2 *Continued*

Treatment characteristics (at time of diagnosis) in EMBRACE patients (I and II)		**N = 113 (Subgroup Vaginal Morbidity study)**	**N = 1551 (EMBRACE participants not in Vaginal Morbidity study)**	**z or t - value**
EBRT PTV-E total dose	Median dose in Gy (IQR) Missing N (%)	45 (45-45) 0	45 (46-45) 34 (2.2%)	**7.9*** **
EBRT technique	3D conformal IMRT/VMAT Missing N (%)	20 (17.7%) 93 (82.3%) 0	774 (49.9%) 743 (47.9%) 34 (2.2%)	**6.8*** **
EBRT PTV N Nodal boost	Yes No Missing N (%)	43 (38.1%) 70 (61.9%) 0	560 (36.1%) 957 (61.7%) 34 (2.2%)	.2
Concomitant chemotherapy given	Yes No Missing N (%)	111 (98.2%) 0 2 (1.8%)	1405 (90.6%) 94 (6.1%) 52 (3.4%)	**2.7** **
EBRT+BT HR-CTV D90 in EQD2	Median dose (Gy) (IQR) Missing N (%)	91.1 (89.4-93.6) 2 (1.8%)	90.3 (85.6-94.2) 63 (4.1%)	**-3.1** **
Total ICRU Rectum in EQD2	Median dose (Gy) (IQR) Missing N (%)	62.2 (57.8-65.3) 5 (4.4%)	64.1 (59.5-70.4) 80 (5.2%)	**3.9*** **

Note. 3D = three-dimensional; BMI = Body Mass Index; BT = brachytherapy; EBRT = external beam radiotherapy; EBRT PTV-E = external beam radiotherapy total dose prescribed to the elective planning target volume; EBRT PTV-N = external beam radiotherapy total dose prescribed to the lymph nodes planning target volume; EBRT+BT HR-CTV D90 = external beam radiotherapy + brachytherapy dose received by 90% of the high-risk clinical target volume; EMBRACE = image guided intensity modulated External beam radiochemotherapy and MRI based adaptive BRAchytherapy in locally advanced Cervical cancer; EQD2 = equivalent dose in 2-Gy fractions; FIGO = Fédération Internationale de Gynécologie et d'Obstétrique; Gy = gray; IMRT = intensity modulated radiotherapy; IQR = interquartile range; N = total sample; VM = vaginal morbidity; VMAT = volumetric modulated arc radiotherapy; WHO PS = World Health Organization performance status.

= Only assessed in Vaginal Morbidity study patients. * = only EMBRACE-I Vaginal Morbidity study patients, not assessed in EMBRACE-II Vaginal Morbidity study patients

*p < .05, **p < .01, ***p < .001

Table S3 EORTC QLQ-C30 generic health related QoL functioning and symptom scales

	Baseline (N=113)	3 months (N=101)	6 months (N=95)	12 months (N=85)	24 months (N=77)
Range in number patients responding (n)	109 - 110	91 - 95	91 - 94	81 - 82	71 – 72
Global health/QoL (M ± SD)	67.4 ± 21.0	78.1 ± 20.1	79.8 ± 15.9	80.0 ± 17.2	79.8 ± 19.8
Functioning scales (M ± SD)					
Physical functioning	83.1 ± 19.9	90.0 ± 12.4	90.5 ± 14.5	92.5 ± 14.1	90.7 ± 15.6
Role functioning	67.1 ± 33.3	80.3 ± 24.1	86.4 ± 23.7	85.6 ± 24.0	83.3 ± 26.1
Emotional functioning	66.2 ± 23.2	79.1 ± 21.7	83.3 ± 17.9	85.1 ± 18.7	83.9 ± 17.9
Cognitive functioning	85.3 ± 22.1	85.8 ± 20.2	87.1 ± 16.8	87.9 ± 18.8	85.9 ± 19.0
Social functioning	77.4 ± 29.2	87.0 ± 23.0	92.0 ± 16.8	89.6 ± 19.5	88.7 ± 19.9
Multi-item symptom scales (M ± SD)					
Fatigue	34.1 ± 29.9	22.7 ± 22.0	21.4 ± 24.1	19.5 ± 23.2	20.4 ± 24.0
Nausea/vomiting	8.2 ± 15.4	4.4 ± 11.2	4.5 ± 13.0	3.7 ± 13.1	1.6 ± 5.7
Pain	27.6 ± 30.7	10.0 ± 15.8	14.7 ± 24.0	13.0 ± 24.3	13.6 ± 23.3
Single item symptom scales (M ± SD)					
Dyspnoea	14.2 ± 24.9	9.9 ± 21.2	7.9 ± 20.5	10.6 ± 23.4	13.0 ± 22.8
Sleep disturbance	28.5 ± 34.6	20.7 ± 28.4	22.6 ± 29.1	19.1 ± 27.2	19.9 ± 28.9
Appetite loss	23.0 ± 31.5	9.1 ± 22.0	8.2 ± 19.5	5.8 ± 17.3	4.6 ± 12.9
Constipation	10.0 ± 21.9	5.3 ± 14.8	5.7 ± 14.4	5.7 ± 18.7	3.7 ± 11.9
Diarrhoea	8.2 ± 19.3	8.4 ± 17.5	6.2 ± 14.8	5.7 ± 17.2	11.6 ± 22.5
Financial impact	12.8 ± 27.6	16.7 ± 29.6	12.1 ± 24.6	12.2 ± 23.7	11.7 ± 25.3

Note. EORTC QLQ-C30 subscales were calculated and linearly transformed according to the scoring manual of the EORCT QoL group. N = 113 at baseline, N = 101 at 3 months, N = 95 at 6 months, N = 85 at 12 months, N = 77 at 24 months; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; M = Mean; n = subsample; N = total sample; QoL = quality of life; SD = Standard Deviation.

Table S4 EORTC QLQ-CX24 symptom scales

	Baseline (N=113)	**3 months (N=101)**	**6 months (N=95)**	**12 months (N=85)**	**24 months (N=77)**
Range in number patients responding QLQ-CX24 (N)	110	93 - 94	94	82	71-72
Multi-item symptom scales (M ± SD)					
Symptom experience	16.0 ± 11.3	8.2 ± 7.5	9.2 ± 9.3	8.0 ± 9.2	8.5 ± 9.0
Body image	17.3 ± 24.0	16.1 ± 23.8	11.7 ± 19.6	12.1 ± 20.4	15.5 ± 22.1
Single-item symptom scales (M ± SD)					
Lymphedema	7.9 ± 20.2	12.8 ± 23.5	11.0 ± 25.6	13.0 ± 26.6	15.3 ± 29.6
Peripheral Neuropathy	9.4 ± 21.0	15.2 ± 27.1	18.4 ± 30.8	18.3 ± 30.2	19.0 ± 32.1
Menopausal symptoms	18.2 ± 29.8	37.9 ± 35.9	30.5 ± 32.3	28.5 ± 31.5	33.8 ± 35.6

Note. EORTC QLQ-CX24 subscales were calculated and linearly transformed according to the scoring manual of the EORCT QoL group. N = 113 at baseline, N = 102 at 3 months, N = 95 at 6 months, N = 85 at 12 months, N = 77 at 24 months. EORTC QLQ-CX24 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Gynaecological Cancer Module; M = Mean; N = total sample; SD = Standard Deviation.

Table S5 Associations of pooled observations over all time points of follow-up between patient-reported feelings of vaginal shortness, tightness, dryness, bleeding, pain during intercourse or other sexual activity, sexual distress regarding sexual activity and worries about painful intercourse at the one hand and vaginal length, width, fibrosis, stenosis, adhesions, dryness and fragility/bleeding measured by the physician during vaginal examination at the other hand

Vaginal examination by the physician **Patient-reported outcome**	Vaginal Length	Vaginal Width	Vaginal fibrosis	Vaginal stenosis (CTCAE)	Vaginal adhesions	Vaginal dryness (CTCAE)	Vaginal fragility/ Bleeding with examination
Has your vagina felt short? (EORTC QLQ-CX24)	-.13	-.18*	.19**	.17*	.19*	.23**	.20**
Has your vagina felt tight? (EORTC QLQ-CX24)	-.18*	-.15*	.14	.23**	.19*	.21**	.24**
Has your vagina felt dry during sexual activity? (EORTC QLQ-CX24)	-.03	**-.34****	-.02	.23**	.05	.29**	.02
Have you had vaginal bleeding during intercourse or other sexual activity? (SAQ)	.12	-.14	.07	-.03	-.03	.08	.24**
Have you had pain during intercourse or other sexual activity? (EORTC QLQ-CX24)	-.01	-.21**	.13	.16*	.22**	.11	.19**
Has sexual activity been distressing for you? (SAQ)	-.03	-.21**	.16*	.12	.17*	.03	.18*
Have you worried that sex would be painful? (EORTC QLQ-CX24)	-.10	-.12*	.04	.11*	.05	.07	.05

Note. Spearman Rank Order (rho) Correlations; CTCAE = Common Terminology Criteria for Adverse Events; EORTC QLQ-CX24 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Gynaecological Cancer Module; SAQ = Sexual Activity Questionnaire.
r ≥ .10, .30 and .50 mark small, medium, and large effects, respectively[24].
*p < .05, **p < .01

REFERENCES

1. Embrace Collaborative G. EMBRACE study. 2025. www.embracestudy.dk (accessed 5th of May 2025).
2. Potter R, Tanderup K, Schmid MP, et al. MRI-guided adaptive brachytherapy in locally advanced cervical cancer (EMBRACE-I): a multicentre prospective cohort study. *Lancet Oncol* 2021; **22**(4): 538-47. doi:10.1016/S1470-2045(20)30753-1.
3. Potter R, Tanderup K, Kirisits C, et al. The EMBRACE II study: The outcome and prospect of two decades of evolution within the GEC-ESTRO GYN working group and the EMBRACE studies. *Clin Transl Radiat Oncol* 2018; **9**: 48-60. doi:10.1016/j.ctro.2018.01.001.
4. Sturdza A, Potter R, Fokdal LU, et al. Image guided brachytherapy in locally advanced cervical cancer: Improved pelvic control and survival in RetroEMBRACE, a multicenter cohort study. *Radiother Oncol* 2016; **120**(3): 428-33. doi:10.1016/j.radonc.2016.03.011.
5. Spampinato S, Jensen NBK, Potter R, et al. Severity and Persistency of Late Gastrointestinal Morbidity in Locally Advanced Cervical Cancer: Lessons Learned From EMBRACE-I and Implications for the Future. *Int J Radiat Oncol Biol Phys* 2022; **112**(3): 681-93. doi:10.1016/j.ijrobp.2021.09.055.
6. Vittrup AS, Tanderup K, Bentzen SM, et al. Persistence of Late Substantial Patient-Reported Symptoms (LAPERS) After Radiochemotherapy Including Image Guided Adaptive Brachytherapy for Locally Advanced Cervical Cancer: A Report From the EMBRACE Study. *Int J Radiat Oncol Biol Phys* 2021; **109**(1): 161-73. doi:10.1016/j.ijrobp.2020.08.044.
7. Kirchheiner K, Smet S, Jurgenliemk-Schulz IM, et al. Impact of Vaginal Symptoms and Hormonal Replacement Therapy on Sexual Outcomes After Definitive Chemoradiotherapy in Patients With Locally Advanced Cervical Cancer: Results from the EMBRACE-I Study. *Int J Radiat Oncol Biol Phys* 2022; **112**(2): 400-13. doi:10.1016/j.ijrobp.2021.08.036.
8. Ye S, Yang J, Cao D, Lang J, Shen K. A systematic review of quality of life and sexual function of patients with cervical cancer after treatment. *Int J Gynecol Cancer* 2014; **24**(7): 1146-57. doi:10.1097/IGC.0000000000000207.
9. Smet S, Potter R, Haie-Meder C, et al. Fatigue, insomnia and hot flashes after definitive radiochemotherapy and image-guided adaptive brachytherapy for locally advanced cervical cancer: An analysis from the EMBRACE study. *Radiother Oncol* 2018; **127**(3): 440-8. doi:10.1016/j.radonc.2018.03.009.
10. Pieterse QD, Kenter GG, Maas CP, et al. Self-reported sexual, bowel and bladder function in cervical cancer patients following different treatment modalities: longitudinal prospective cohort study. *Int J Gynecol Cancer* 2013; **23**(9): 1717-25. doi:10.1097/IGC.0b013e3182a80a65.
11. Nout RA, Putter H, Jurgenliemk-Schulz IM, et al. Five-year quality of life of endometrial cancer patients treated in the randomised Post Operative Radiation Therapy in Endometrial Cancer (PORTEC-2) trial and comparison with norm data. *Eur J Cancer* 2012; **48**(11): 1638-48. doi:10.1016/j.ejca.2011.11.014.
12. Kirchheiner K, Fidarova E, Nout RA, et al. Radiation-induced morphological changes in the vagina. *Strahlenther Onkol* 2012; **188**(11): 1010-7. doi:10.1007/s00066-012-0222-0.
13. Martins J, Vaz AF, Grion RC, Esteves SCB, Costa-Paiva L, Baccaro LF. Factors associated with changes in vaginal length and diameter during pelvic radiotherapy for cervical cancer. *Arch Gynecol Obstet* 2017; **296**(6): 1125-33. doi:10.1007/s00404-017-4553-z.
14. Viswanathan AN, Lee LJ, Eswara JR, et al. Complications of pelvic radiation in patients treated for gynecologic malignancies. *Cancer* 2014; **120**(24): 3870-83. doi:10.1002/cncr.28849.
15. Kirchheiner K, Potter R, Tanderup K, et al. Health-Related Quality of Life in Locally Advanced Cervical Cancer Patients After Definitive Chemoradiation Therapy Including Image Guided Adaptive Brachytherapy: An Analysis From the EMBRACE Study. *Int J Radiat Oncol Biol Phys* 2016; **94**(5): 1088-98. doi:10.1016/j.ijrobp.2015.12.363.

16. Kirchheiner K, Nout RA, Tanderup K, et al. Manifestation pattern of early-late vaginal morbidity after definitive radiation (chemo)therapy and image-guided adaptive brachytherapy for locally advanced cervical cancer: an analysis from the EMBRACE study. *Int J Radiat Oncol Biol Phys* 2014; **89**(1): 88-95. doi:10.1016/j.ijrobp.2014.01.032.

17. International Clinical Guideline Group. International guidelines on vaginal dilation after pelvic radiotherapy. 2012. https://www.pocd.com.au/core/media/media.nl/id.47537/c.3923593/.f?h=f2e5bc493442741b7e6c (accessed 2nd of March 2020).

18. Bakker RM, Kenter GG, Creutzberg CL, et al. Sexual distress and associated factors among cervical cancer survivors: a cross-sectional multicenter observational study. *Psycho-Oncology* 2017; **26**(10): 1470-7. doi:10.1002/pon.4317.

19. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *Journal of the National Cancer Institute* 1993; **85**(5): 365-76. doi:10.1093/jnci/85.5.365.

20. Greimel ER, Kuljanic Vlasic K, Waldenstrom AC, et al. The European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life questionnaire cervical cancer module: EORTC QLQ-CX24. *Cancer* 2006; **107**(8): 1812-22. doi:10.1002/cncr.22217.

21. Vistad I, Fossa SD, Kristensen GB, Mykletun A, Dahl AA. The sexual activity questionnaire: pychometric properties and normative data in a norwegian population sample. *J Womens Health (Larchmt)* 2007; **16**(1): 139-48. doi:10.1089/jwh.2006.0052.

22. Pieterse QD, Ter Kuile MM, Maas CP, Kenter GG. The Gynaecologic Leiden Questionnaire: psychometric properties of a self-report questionnaire of sexual function and vaginal changes for gynaecological cancer patients. *Psychooncology* 2008; **17**(7): 681-9. doi:10.1002/pon.1294.

23. Rizopoulos D. GLMMadaptive: Generalized Linear Mixed Models using Adaptive Gaussian Quadrature. R package version 0.8-2. 2021. https://drizopoulos.github.io/GLMMadaptive/ (accessed 1st of June 2022).

24. Cohen J. Statistical power analysis for the behavioral sciences 2nd ed. Mahwah, New Jersey: Lawrence Erlbaum Associates, Inc.; 1988.

25. Lloyd J, Crouch NS, Minto CL, Liao LM, Creighton SM. Female genital appearance: "normality" unfolds. *BJOG* 2005; **112**(5): 643-6. doi:10.1111/j.1471-0528.2004.00517.x.

26. Weber AM, Walters MD, Schover LR, Mitchinson A. Vaginal Anatomy and Sexual Function. *Obstet Gynecol* 1995; **86**(6): 946-9.

27. Kirchheiner K, Nout RA, Lindegaard JC, et al. Dose-effect relationship and risk factors for vaginal stenosis after definitive radio(chemo)therapy with image-guided brachytherapy for locally advanced cervical cancer in the EMBRACE study. *Radiother Oncol* 2016; **118**(1): 160-6. doi:10.1016/j.radonc.2015.12.025.

28. Westerveld H, de Leeuw A, Kirchheiner K, et al. Multicentre evaluation of a novel vaginal dose reporting method in 153 cervical cancer patients. *Radiother Oncol* 2016; **120**(3): 420-7. doi:10.1016/j.radonc.2016.05.002.

29. Lindegaard JC, Fokdal LU, Nielsen SK, Juul-Christensen J, Tanderup K. MRI-guided adaptive radiotherapy in locally advanced cervical cancer from a Nordic perspective. *Acta Oncol* 2013; **52**(7): 1510-9. doi:10.3109/0284186X.2013.818253.

30. Bakker RM, ter Kuile MM, Vermeer WM, et al. Sexual rehabilitation after pelvic radiotherapy and vaginal dilator use: consensus using the Delphi method. *International Journal of Gynecological Cancer* 2014; **24**(8): 1499-506. doi:10.1097/igc.0000000000000253.

31. Miles T, Johnson N. Vaginal dilator therapy for women receiving pelvic radiotherapy. *Cochrane Database Syst Rev* 2014; (9): CD007291. doi:10.1002/14651858.CD007291.pub3.

32. Damast S, Jeffery DD, Son CH, et al. Literature review of vaginal stenosis and dilator use in radiation oncology. *Pract Radiat Oncol* 2019; **9**(6): 479-91. doi:10.1016/j.prro.2019.07.001.

33. Martins J, Vaz AF, Grion RC, Costa-Paiva L, Baccaro LF. Topical estrogen, testosterone, and vaginal dilator in the prevention of vaginal stenosis after radiotherapy in women with cervical cancer: a randomized clinical trial. *BMC Cancer* 2021; **21**(1): 682. doi:10.1186/s12885-021-08274-w.

34. Greimel ER, Winter R, Kapp KS, Haas J. Quality of life and sexual functioning after cervical cancer treatment: a long-term follow-up study. *Psychooncology* 2009; **18**(5): 476-82. doi:10.1002/pon.1426.

35. Jensen PT, Groenvold M, Klee MC, Thranov I, Petersen MA, Machin D. Longitudinal study of sexual function and vaginal changes after radiotherapy for cervical cancer. *Int J Radiat Oncol Biol Phys* 2003; **56**(4): 937-49. doi:10.1016/s0360-3016(03)00362-6.

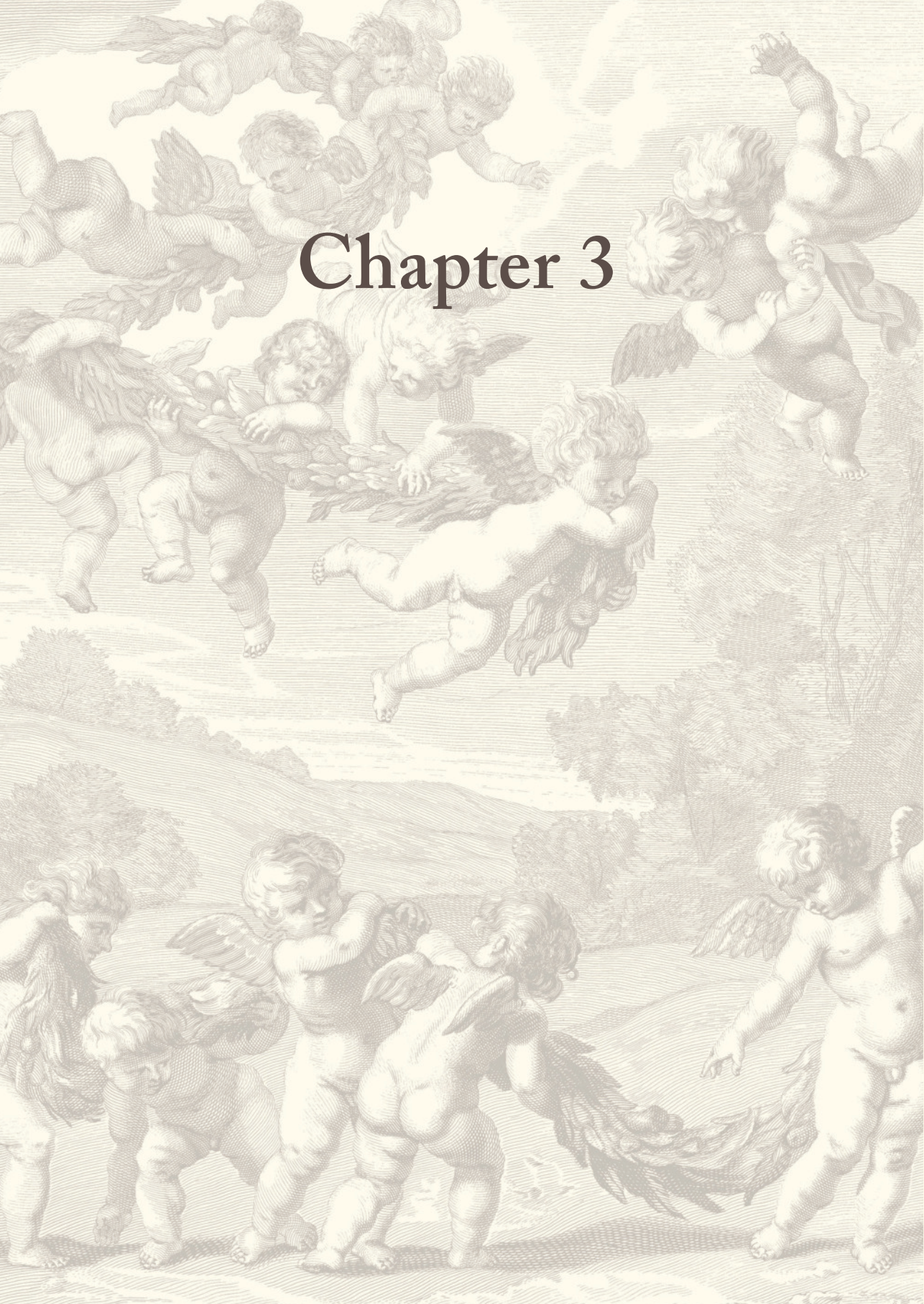
36. Grion RC, Baccaro LF, Vaz AF, Costa-Paiva L, Conde DM, Pinto-Neto AM. Sexual function and quality of life in women with cervical cancer before radiotherapy: a pilot study. *Arch Gynecol Obstet* 2016; **293**(4): 879-86. doi:10.1007/s00404-015-3874-z.

37. Kirchheiner K, Nout R, Lindegaard J, et al. Do clinicians and patients agree regarding symptoms? A comparison after definitive radiochemotherapy in 223 uterine cervical cancer patients. *Strahlenther Onkol* 2012; **188**(10): 933-9. doi:10.1007/s00066-012-0156-6.

38. Vistad I, Cvancarova M, Fossa SD, Kristensen GB. Postradiotherapy morbidity in long-term survivors after locally advanced cervical cancer: how well do physicians' assessments agree with those of their patients? *Int J Radiat Oncol Biol Phys* 2008; **71**(5): 1335-42. doi:10.1016/j.ijrobp.2007.12.030.

39. Laan E, Rellini AH. Can we treat anorgasmia in women? The challenge to experiencing pleasure. *Sex Relatsh Ther* 2011; **26**(4): 329-41. doi:10.1080/14681994.2011.649691.

40. Bakker RM, Mens JW, de Groot HE, et al. A nurse-led sexual rehabilitation intervention after radiotherapy for gynecological cancer. *Supportive Care Cancer* 2017; **25**(3): 729-37. doi:10.1007/s00520-016-3453-2.



Chapter 3

A sexual rehabilitation intervention for women with gynaecological cancer receiving radiotherapy (SPARC study): design of a multicentre randomized controlled trial

BMC Cancer, 2021; 21(1):1295
doi: 10.1186/s12885-021-08991-2

Isabelle Suvaal
Susanna B. Hummel
Jan-Willem M. Mens
Helena C. van Doorn
Wilbert B. van den Hout
Carien L. Creutzberg
Moniek M. ter Kuile

ABSTRACT

Objectives

Sexual problems are frequently reported after treatment with radiotherapy (RT) for gynaecological cancer (GC), in particular after combined external beam radiotherapy and brachytherapy (EBRT+BT). Studies demonstrate that psychosexual support should include cognitive behavioural interventions and involvement of the patient's partner, if available. Therefore, we developed a nurse-led sexual rehabilitation intervention, including these key components. The intervention was previously pilot-tested and results demonstrated that this intervention improves women's sexual functioning and increases dilator compliance. The objective of the current study is to investigate the (cost-)effectiveness of the intervention compared to optimal care as usual (CAU). We expect that women who receive the intervention will report a statistically significant greater improvement in sexual functioning and - for women who receive EBRT+BT - higher compliance with dilator use, from baseline to 12 months post-RT than women who receive optimal CAU.

Methods

The intervention is evaluated in the SPARC (Sexual rehabilitation Programme After Radiotherapy for gynaecological Cancer) study, a multicentre, randomized controlled trial (RCT). The primary endpoint is sexual functioning. Secondary outcomes include body image, fear of sexual activity, sexual-, treatment-related- and psychological distress, health-related quality of life and relationship satisfaction. A cost-effectiveness analysis (CEA) will be conducted in which the costs of the intervention will be related to shifts in other health care costs and the impact on patient outcome. The study sample will consist of 220 women with GC treated with RT in specialized GC treatment centres (N = 10). Participants are randomized to either the intervention- or CAU control group (1:1), and within each centre stratified by type of radiotherapy (EBRT+BT vs EBRT only) and having a partner (yes/no). All women complete questionnaires at baseline (T1) and at 1, 3, 6, and 12 months post-RT (T2, T3, T4 and T5, respectively).

Conclusions

There is a need to improve sexual functioning after RT for GC. This RCT will provide evidence about the (cost-)effectiveness of a nurse-led sexual rehabilitation intervention. If proven effective, the intervention will be a much needed addition to care offered to GC survivors and will result in improved quality of life.

BACKGROUND

In the Netherlands, more than 4500 women are diagnosed with gynaecological cancers (GC) annually[1]. Approximately one-third of GC patients, especially those with cervical, uterine and vaginal cancers, receive radiotherapy (RT) as primary or post-surgical treatment; most often external beam radiotherapy (EBRT) with or without brachytherapy (BT). Sexual problems, such as dyspareunia, vaginal dryness and a decrease of sexual satisfaction and desire are frequently reported after treatment with RT for GC[2-9]. The negative effects of RT, and in particular of the combination of EBRT with BT (EBRT+BT), on sexual functioning are due to vaginal changes such as fibrosis with vaginal shortening and tightening, mucosal atrophy, and reduced flexibility and decreased lubrication of the upper vagina[10]. EBRT+BT is the standard combination for primary treatment of more advanced stages of cervical, vaginal and endometrial cancer, while postoperative BT is only added in case of involved or tight vaginal margins.

To prevent or reduce vaginal shortening and tightening during the period of fibrosis formation after EBRT+BT, it is generally recommended to use vaginal dilators for a period of 9-12 months after completion of treatment[11]. Such use may prevent or minimise vaginal stenosis with the purpose to maintain the option of vaginal penetration in the long term[11,12]. Despite the proposed benefits of regular dilator use, most GC patients (75%) fail to use dilators regularly even after counselling and instructions for use[13-16]. Frequently reported barriers to dilator use are difficulties with planning, lack of time or privacy, forgetting, and other problems in the recovery phase such as fatigue and worry[17]. To increase compliance, it is important to provide sufficient patient information tailored to the woman's need, clear instructions and psycho-education regarding dilator use[18]. In addition, the process of recovery from cancer diagnosis and treatment and the associated physical and psychological problems is already demanding. A broader view on rehabilitation, counselling and support would be needed to help multi-dimensional recovery and increase compliance with regular dilator use.

A recent study demonstrated that GC patients treated with RT benefit from a psychosexual rehabilitation information booklet[19]. Women reported more knowledge regarding physical and psychosexual side-effects and rehabilitation options in the first 6 months post-RT than women wo received standard information materials. However, the psychosexual rehabilitation booklet did not increase compliance with dilator use. In addition to psycho-education, two studies demonstrated that a psychoeducational group intervention, including a focus on motivation to engage in regular dilator use, increased dilator compliance[15,20]. Indicating that GC survivors could benefit from additional professional support targeting dilator use. However, such an intervention targeting dilator use only did not affect the psychosexual consequences of treatment

of GC, such as decreased sexual desire, dyspareunia, diminished body image, and relationship dissatisfaction[15]. Therefore, psychosexual rehabilitation interventions should focus on preventing and reducing RT-induced vaginal changes, as well as on increasing psychosexual and relationship satisfaction[21].

Only few studies have evaluated psychosexual rehabilitation interventions - which used cognitive behavioural techniques, psycho-education and counselling - for GC survivors[22-26]. Results demonstrated that women who received the psychosexual rehabilitation interventions experienced better sexual functioning, less sexual distress[23] and a decrease in sexual problems[22]. Only one of the studies actively involved the partner in the intervention and demonstrated that a couple-coping training improved sexual relationship satisfaction to a greater extent than medical information education or patient-coping training only[26].

It can be concluded that psychosexual support after treatment for GC should include motivational issues and psychosexual interventions to increase dilator compliance and improve sexual functioning. Furthermore, involvement of the partner is preferred. There is a need for a condensed, practical and (cost-)effective sexual rehabilitation intervention, consisting of psycho-education combined with elements of psychosexual-based cognitive behavioural therapy for GC patients and their partners after RT[27-31]. Therefore, based on the results of our previous studies[17,18,21], we developed a nurse-led sexual rehabilitation intervention to support sexual improvement and vaginal dilator use after RT. The intervention has multiple aims: motivating women, giving tailored advice, strengthening self-management, promoting couples' mutual coping and support processes and, for women who received EBRT+BT, providing information and coaching on use of vaginal dilators on a regular basis. The results of our pilot study regarding the feasibility of the intervention demonstrated that this intervention improved women's sexual functioning and that it supported them in their dilator use[32]. Furthermore, the nurses who were trained and supervised to guide the intervention felt capable to support the women.

In this chapter we present the design of the SPARC (Sexual rehabilitation Programme After Radiotherapy for gynaecological Cancer) study, a multicentre randomized controlled trial (RCT) which evaluates the (cost-)effectiveness of the nurse-led sexual rehabilitation intervention in improving sexual functioning and dilator use of GC patients after RT. Participants are randomized to either the intervention- or optimal care as usual (CAU) control group (1:1). We expect that women who receive the intervention will report a statistically significant greater improvement in sexual functioning and - for women who receive EBRT+BT - higher compliance with dilator use, from baseline to 12 months post-RT than women who receive CAU.

METHODS

The study design and main procedures of the RCT are displayed in Figure 1.

Ethical issues, safety aspects and (medical) complications

The SPARC study has been approved by the Medical Ethical Committee Leiden-Den Haag-Delft (number NL62767.058.17) and by the institutional review boards of the 10 participating GC centres (for an overview, see supplementary table S1, chapter 4). Recruitment and data collection started in August, 2018 and was still ongoing at the date of publication of this chapter. This study is monitored on data and safety by an independent certificated study monitor. All study-related adverse events, i.e. dilator-use-related, will be recorded and reported as an adverse event. Events related to the undergone cancer treatments are not considered study-related events.

Study Sample

The study sample will consist of 220 women diagnosed with cervical, vaginal or endometrial cancer and who will receive primary or postoperative EBRT+BT (BT boost by intra-uterine and/or vaginal brachytherapy) or postoperative EBRT alone. This also includes curative treatment with EBRT+BT for local relapse after previous surgery. Participants are recruited in specialized GC treatment centres in the Netherlands. Women are eligible for study participation if they (1) are 18 years or older, (2) receive treatment with RT for GC as specified above and (3) wish to retain their sexual activity in the short- or long term. Women are excluded from study participation if they (1) are unavailable for follow-up, (2) have insufficient command of the Dutch language or (3) have a major affective disorder, psychotic disorder, substance abuse disorder or posttraumatic stress disorder resulting from abuse in the pelvic floor area and/or genitals. To ensure appropriate treatment of these women with more severe psychological and/or psychiatric problems, they are referred to a specialized psychologist/sexologist connected to the own GC centre or are advised to consult their general practitioner to be referred to a specialized psychologist/sexologist or psychiatrist.

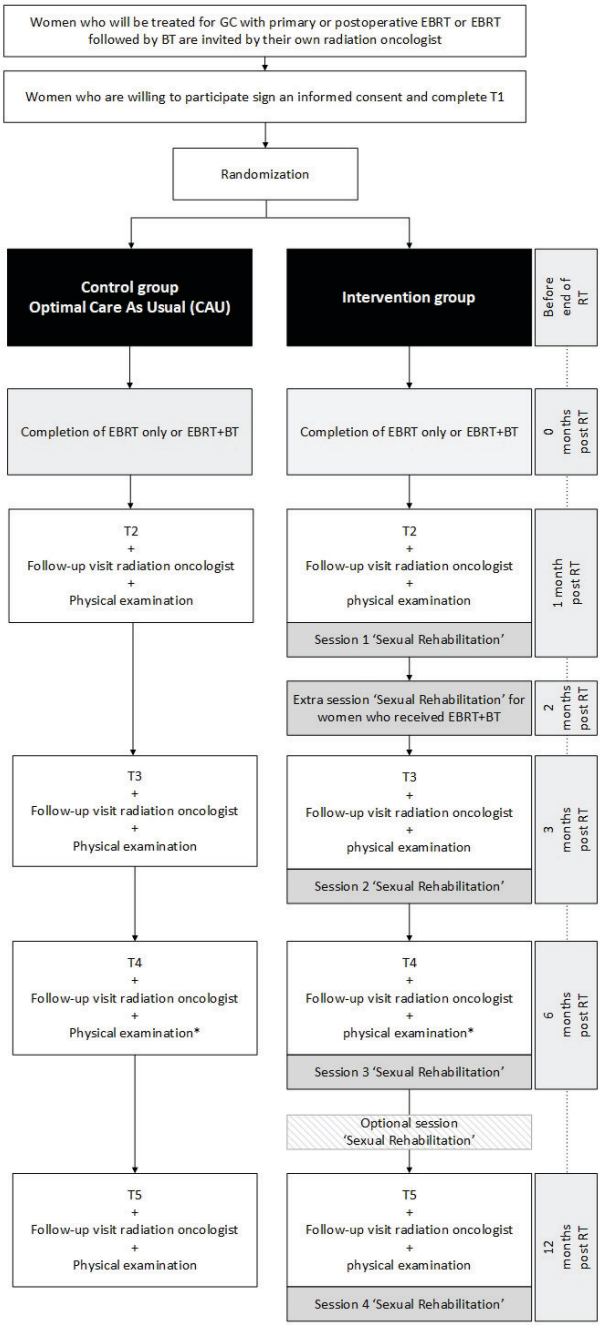


Figure 1 Overview of study procedures. *The physical examination at the 6 months follow-up visit might also be conducted by the gynaecologist (depending on the centre). BT = Brachytherapy; EBRT = External Beam Radiotherapy; GC = Gynaecological cancer; RT = Radiotherapy; T1 = Self-report baseline questionnaire, T2-5 = Self-report follow-up questionnaires

Recruitment and randomization

The treating radiation oncologists screen potential participants with regard to the inclusion and exclusion criteria. Eligible women are informed about the background, rationale and specifics of the study protocol. Women who want to participate in the study provide written informed consent and complete a paper-and-pencil baseline questionnaire before randomization. After inclusion, participants are assigned a unique study identifier by the local data manager, which will be filled out on all questionnaires and used in the data files. Inclusion and randomization take place before the completion of RT. Participants are randomized to either the intervention- or the optimal CAU control group (1:1), and within each centre stratified by type of radiotherapy (EBRT+BT versus EBRT only) and having a partner (yes/no). The randomization is block stratified with varying block sizes, and is performed by the local data manager, using a secured web-based data-management system.

Study groups

One month after completion of RT, women in both study groups receive an information booklet. The information booklets, which contain specific information to improve knowledge and coping strategies regarding sexual rehabilitation after either EBRT+BT or EBRT only, are based on the booklet developed in the pilot study[32]. The booklets are provided in both a printed and online version. Women in both study groups who received EBRT+BT are given a dilator set and are advised to start vaginal dilation for 1 to 3 minutes, 2 to 3 times a week around 4 weeks after RT when the vagina is sufficiently healed[11,18].

Training of the nurses

The intervention is conducted by oncology nurses who have completed a 50-hour study-specific training in sexology and simple cognitive behavioural interventions and the treatment protocol itself. The nurses are supervised by an experienced sexologist once per month. Every six months, the oncology nurses and their supervisors attend an additional day of training that is focused on a specific theme that is relevant for the study (i.e. vaginal stenosis and dilator use, emotional reactions after loss of participants due to cancer recurrence, and the partner relationship).

Intervention group: the nurse-led sexual rehabilitation intervention

The intervention consists of four one-hour face-to-face sessions at 1, 3, 6, and 12 months post-RT. These sessions are planned synchronously with women's radiation oncologist follow-up visits. An additional session is scheduled for women who received EBRT+BT at 2 months, during which potential barriers and problems with dilator use are discussed. Furthermore, if preferred, an extra follow-up session/telephone consultation of 30 minutes can be scheduled between 6 and 12 months after RT. If a woman is in a relationship, the partner is invited to accompany her in the sessions.

Table 1 Description of the sexual rehabilitation intervention modules

Module 1: Brief sexual history	This module describes how the nurse can question the patient in-depth about sexual problems on various domains of sexual functioning, including sexual interest/ arousal, orgasm, pain and sexual satisfaction. It also covers psycho-education about sexuality and the sexual response curve[33] and provides information about frequently occurring sexual problems and solutions.
Module 2: Pain during intercourse	This module includes practical guidelines that the nurse can provide regarding pain during intercourse after radiotherapy-, with referrals to module 3, 4, 6 and 7, and explains how to provide psycho-education about the circular model of dyspareunia[34], which is based on a cognitive behavioural framework.
Module 3: Vaginal dryness and health	This module provides the nurse with instructions on how to give advice with regard to treatment of vaginal dryness, pain or irritation. It also includes information regarding vaginal health, such as the use of vaginal creams, avoidance of scratching in response to irritated skin or avoidance of washing with soap.
Module 4: Alternatives for intercourse	The exercise in this module helps the woman and her partner (if available) to explore and discuss non-penetrative alternatives for sexual intercourse.
Module 5: The partner and possible sexual problems	This module can be consulted by the nurse when partners experience temporary sexual problems, such as erectile dysfunction during intercourse. The module also includes a reference to module 1.
Module 6: Gradual exposure towards sexual intercourse	The aim of the steps in this module, which are based on a cognitive behavioural gradual exposure therapy for Genito-Pelvic/ Penetration Disorder[29], is to learn the woman and her partner how to re-engage in sexual intercourse. The steps include: touching of the vaginal opening with the erect penis without penetration, stepwise vaginal insertion of the erect penis without moving, and vaginal insertion of the erect penis with moving.
Module 7: Pelvic floor exercise	This module includes several pelvic floor relaxation exercises for women who experience tension in the pelvic floor muscles.
Module 8: Difficulties with dilator use at home	This module is suitable for women who experience problems with dilator use and who already practiced under supervision of a nurse (see module 9) or for women who do not want to practice under supervision. This module provides the nurse with instructions on how to give specific advice on how to overcome experienced difficulties, after first exploring the problems during dilator use (e.g. pain/discharge, loss of blood or difficulties with inserting the dilator).
Module 9: Using dilators under supervision at the outpatient clinic	This module focuses on women who experience fear with regard to dilator use or who experience difficulties when using vaginal dilators, due to for example tension of the pelvic floor. The nurse-led session is based on therapist-aided exposure therapy for Genito-Pelvic/Penetration Disorder[29]. The goal is to reduce fear of dilator use by using a stepwise exposure session in which the woman - who performs the vaginal dilation by herself - is facilitated by the nurse. During the session, tips are given with regard to a correct and more comfortable use of the dilators. Furthermore, the nurse helps to evaluate and articulate any unhelpful cognitions about what could (or could not) occur during dilator use. In these instances, the exposure is used as a behavioural experiment, to test the tenability of these cognitions. The module also includes advice on how to handle problems that might occur during practicing at home.

Table 1 *Continued*

Module 10: Exploring and resolving ambivalence with regard to dilator use	The aim of the exercise in this module is to motivate the woman for dilator use, by acknowledging, exploring and resolving ambivalent feelings towards dilator use by motivational interviewing technique[35]. By exploring pros and cons of both dilator use and no dilator use, the woman can be supported in making an informed choice about dilator use. If she decides to use dilators, problems with dilator use are discussed in more detail and how to overcome them. If a woman decides not to use dilators, tampons covered in petroleum jelly (Vaseline) are recommended and guidelines on how to use these are provided to the woman (see module 11).
Module 11: Petroleum jelly (Vaseline) tampons	This module follows module 10, when a woman decides not to use dilators. The module covers guidelines on how to use tampons covered in petroleum jelly (Vaseline).

The sexual rehabilitation intervention consists of 11 modules. A description of the content of the modules is provided in Table 1. The modules include topics such as education regarding the specific cancer diagnosis and treatment, education on the importance of regular use of vaginal dilators (if applicable), discussing potential experienced barriers to dilator use (if applicable) and lubricant use, fear of penetration with dilators (if applicable) and fear of resuming sexual activity after cancer, promoting couples' mutual coping and support processes and addressing sexual and body image concerns. The content of the intervention programme is a personalized programme tailored to the participant-specific psychological, relational and somatic factors. During a session, the oncology nurse selects the specific module(s) that fits the woman's (and her partner's) needs. The decision tree for module selection is provided in Figure 2.

All sessions will be audio-taped allowing a direct check on the oncology nurses' adherence and competency. A random check of 30% of audio-taped sessions on adherence of the treatment protocol will be performed by two independent researchers. Furthermore, these audio-taped treatment sessions will be used for supervision purposes.

Control group: Optimal Care As Usual

All participating women are offered an information session, information booklet and a dilator set (if applicable) post-RT free of charge. Hereby, we optimized the CAU control group in our current study. Although CAU cannot be completely standardized, as the procedure is dependent on the local standard practice, it will not involve a structured, tailored nurse-led sexual rehabilitation intervention.

Data collection

Participants are requested to complete questionnaires prior to randomization (T1, baseline) and at 1, 3, 6, and 12 months post-RT (T2, T3, T4 and T5, respectively, see Figure 1). The T1 questionnaire is completed on paper. The T2-T5 study questionnaires can be completed either online (a link is sent by email) or on paper, depending on the preference of the participant. An online reminder is sent to participants who do not complete and return the questionnaire within one week. If a participant does not complete the questionnaire in the week following the reminder, she is contacted by telephone. Vaginal symptoms, assessed by standardized clinical examination during a physical examination, are synchronously collected at the timepoints of the T1-T5 questionnaires through Case Report Forms (CRFs) and medical records. For women who withdraw early from study participation, data collected until the moment of withdrawal will be available for analysis.

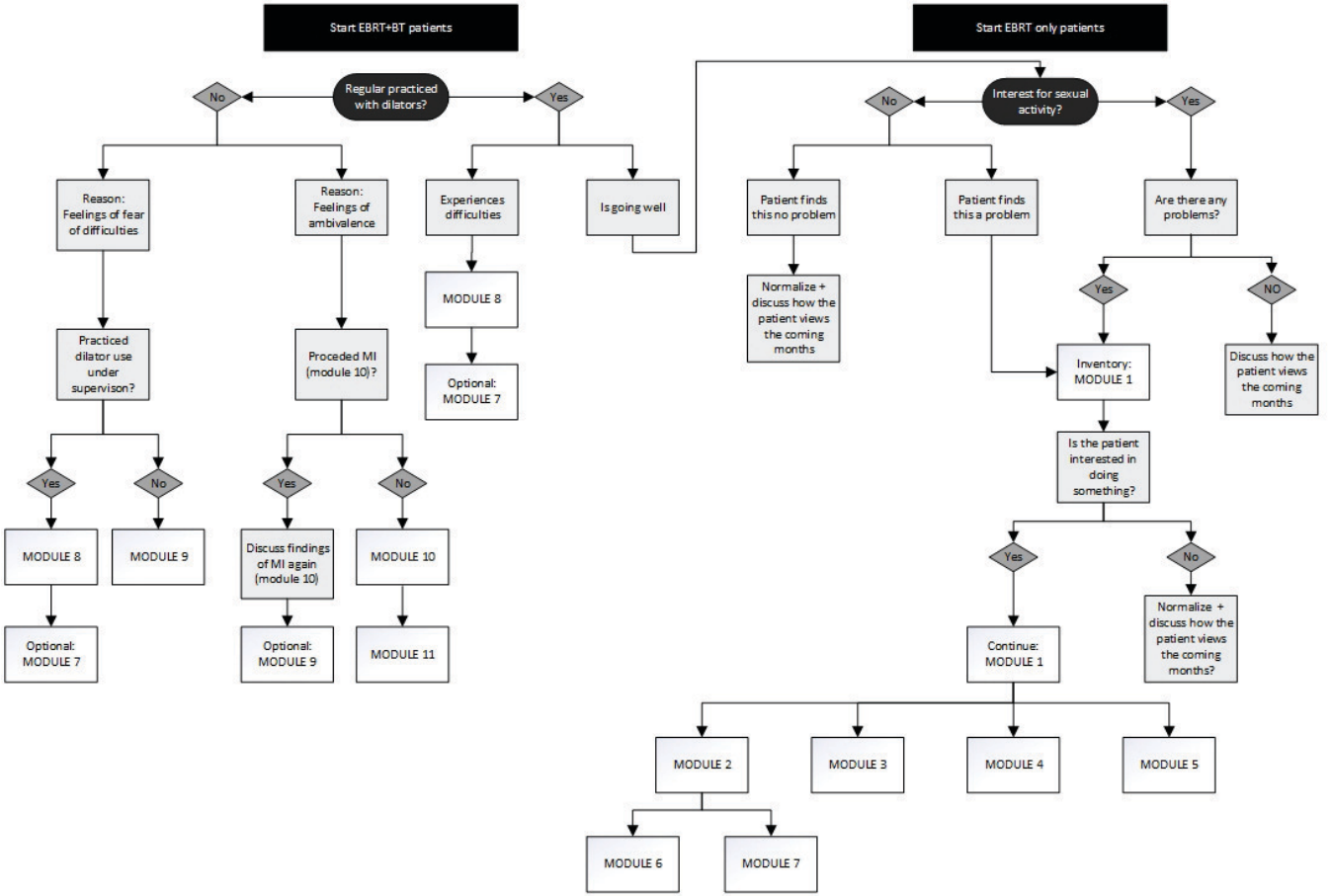


Figure 2 Decision Tree intervention modules. BT = Brachytherapy; EBRT = External Beam Radiotherapy; MI = Motivational Interviewing[35]; Module 1 = Brief sexual history; Module 2 = Pain during intercourse; Module 3 = Vaginal dryness and health; Module 4 = Alternatives for intercourse; Module 5 = The partner and possible sexual problems; Module 6 = Gradual exposure towards sexual intercourse; Module 7 = Pelvic floor exercise; Module 8 = Difficulties with dilator use at home; Module 9 = Using dilators under supervision at the outpatient clinic; Module 10 = Exploring and resolving ambivalence with regard to dilator use. Module 11 = Petroleum jelly (Vaseline) tampons

Measures

Sociodemographic and clinical data

Sociodemographic data are obtained via the T1-questionnaire and include age, relational status, living situation, having children, education, and work status. Clinical data are collected from medical records and through CRFs at T1 and include date of gynaecological cancer diagnosis, type of gynaecological cancer (cervical/endometrial/vaginal) and characteristics (histological type, Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) stadium, lymph node metastases), treatment(s) received (surgery, chemotherapy, type of radiotherapy, hypothermia), height and weight, and smoking. In addition, World Health Organisation (WHO) performance status, menopausal status and medication use (including hormonal replacement therapy) are collected from medical records and through CRFs at T1-T5.

Outcome measures

Detailed descriptions of the outcome measures are provided in Table 2. The primary outcome measure is a standardized patient-reported outcome measure (PROM) assessing sexual functioning (Female Sexual Function Index (FSFI)[36]). The secondary outcome measures include PROMs assessing vaginal symptoms and body image concerns (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Gynaecological Cancer Module (EORTC QLQ-CX24)[37]), fear of coital and non-coital sexual activity (Fear of Sexuality Questionnaire (FSQ)[38]), sexual distress (Female Sexual Distress Scale (FSDS)[39]), treatment-related distress (Impact of Event Scale (IES)[40]), generic health-related quality of life (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)[41]), urological and gastrointestinal symptoms and sexual interest (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Endometrial Cancer Module (EORTC QLQ-EN24)[42]), psychological distress (Hospital Anxiety and Depression Scale (HADS)[43]), and relationship satisfaction (Maudsley Marital Questionnaire (MMQ)[44]). To minimize respondent burden, the T1-questionnaire includes only the FSFI[36] and the FSDS[39].

Additionally, the secondary outcome measures include a 4-item questionnaire for women treated with EBRT+BT regarding the frequency of dilator use: (1) 'How often have you used the dilator in the past month?', (2) 'Which size(s) dilator(s) did you use?', (3) 'How often did you have other kinds of penetration (including penile penetration) in the past month?', and (4) 'How often did you use petroleum jelly (Vaseline) tampons?'.

Furthermore, the following vaginal symptoms are assessed by standardized clinical examination for all participants: dryness, shortening/tightening, mucositis, discharge, blood loss, fibrosis, atrophy, pain, length (in millimetre) and dyspareunia. Vaginal symptoms will be recorded using the Common Terminology Criteria Sexual rehabilitation after RT for gynaecological cancers for Adverse Events (CTCAE), version 4.037.

Cost-effectiveness

A cost-effectiveness analysis (CEA) will be conducted in which the costs of the intervention will be related to shifts in other health care costs and the impact on patient outcome. A cost-price analysis will be performed for the nurse-led sexual rehabilitation intervention (including training, counselling hours and materials). Other healthcare use will be limited to sexuality-related health care utilization (including gynaecologist, radiation oncologist, general practitioner, psychologist and sexologist) and medication use, estimated from patient reports and valued using standard prices.

Estimated costs will be related to the impact on the number of women with sexual improvement after 12 months (costs-per-improved-patient, defined as a Reliable Change Index (RCI)[55] >1.96 on the FSFI[36] total score) and to the impact on quality-adjusted life years (cost-per-QALYs). In the primary analysis, consistent with Dutch guidelines, QALYs will be calculated using the Dutch tariff for the 5-level EuroQol-5D (EQ-5D-5L)[49,50,56]. As a secondary analysis, QALYs will also be estimated using the EuroQol visual analogue scale (EQ-VAS, with power transformation) as predicted by a mapping from the FSFI to the EQ-VAS. This secondary analysis is included because the Dutch tariff for the EQ-5D-5L does not explicitly value sexuality and mapping from the FSFI will make the approach more sensitive to change.

Other study parameters

In addition to treatment- and patient characteristics, treatment credibility and expectancy for improvement will be assessed using the 4-item Credibility and Expectancy Questionnaire (CEQ)[47]. These parameters will be measured at T3. Additionally, at T2-T5 all women will be requested to report the use of any counselling or therapy in the course of their rehabilitation period. Furthermore, the type (face-to-face or by telephone) and the duration of the session, and modules used during the session are documented by the oncology nurses in CRFs. Finally, for each participant, the date of the completion of study participation and the reason for ending study participation are registered in web-based CRFs.

Table 2 Study outcome measures and corresponding questionnaires

Variable	Questionnaire	Details
Primary Outcome		
Sexual functioning	FSFI[36,45]	• Assesses overall sexual functioning • 19 items; 5- and 6-point Likert scales • Subscales: sexual desire; arousal; lubrication; orgasm; satisfaction; pain • Total score*: 2-36/Subscale scores*: desire 1.2-6; arousal 0-6; lubrication 0-6; orgasm 0-6; satisfaction 0-6. Higher score indicates better overall sexual functioning. A subscale score of 0 indicates no sexual activity • Time frame: past 4 weeks • Cronbach's alpha in a gynaecologic cancer survivors group[46]: total score: $\alpha = 0.94$; subscale scores: • $0.85 \leq \alpha \leq 0.94$ • We added 4 items (6- and 7-point Likert scales) to assess the average frequency and amount of pleasure experienced during sexual activity without sexual intercourse and sexual activity with sexual intercourse • As our study sample consists of partnered as well as unpartnered women, we added an answer option 'not applicable, no partner' to the two items concerning the partner relationship.
Secondary Outcomes		
Credibility of analogue therapy rationales	CEQ[47]	• Assesses the credibility of the rationales and procedures of the intervention and the optimal CAU control group • 4 items; 9-point Likert scale • Subscales: credibility; 1 single item (expectancy) • Cronbach's alpha: credibility subscale: $0.81 \leq \alpha \leq 0.86$[48]
Generic health-related quality of life related to gynaecological cancer	EORTC QLQ-C30[41]	• Assesses QoL of cancer patients • 30 items; 4- and 7-point Likert scales • Subscales: 5 function subscales: physical; role; emotional; cognitive; social and 3 symptom subscales: fatigue; nausea/vomiting; pain. Single items: dyspnoea; sleep disturbance; appetite loss; constipation; diarrhoea; financial impact. One global QoL scale • Subscale scores: 0-100. Higher score indicates higher level of functioning (for the function subscales) and greater degree of symptoms (for symptom subscales and/or single items) • Time frame: past week • Cronbach's alpha: subscales: $0.54 \leq \alpha \leq 0.86$[41]

Table 2 *Continued*

Variable	Questionnaire	Details
Vaginal symptoms and body image concerns	EORTC QLQ-CX24[37]	• Assesses disease-specific and treatment-specific aspects of QoL in patients with cervical cancer • 24 items; 4-point Likert scale • Subscales: symptom experience; body image; sexual/vaginal functioning. Single-items: lymphedema; peripheral neuropathy; menopausal symptoms; sexual worry; sexual activity; sexual enjoyment • Subscale score: 0-100. Higher score indicates better level of functioning (for items regarding sexual activity and sexual enjoyment) and higher level of symptoms (for all other items and scales) • Time frame: past week (for the subscales and single-items lymphedema, peripheral neuropathy and menopausal symptoms); past 4 weeks (for the single-items sexual worry, sexual activity and sexual enjoyment) • Cronbach's alpha: subscales: $0.72 \leq \alpha \leq 0.87$[37]
Urological and gastrointestinal symptoms and sexual interest	EORTC QLQ-EN24[42]	• Assesses urological and gastrointestinal symptoms, and sexual functioning • 10 items[#]; 4-point Likert scale • Subscales: urological symptoms; gastrointestinal symptoms. Single-item: sexual interest • Subscale score: 0-100. Higher score indicates higher level of urological and gastrointestinal symptoms and higher sexual interest • Time frame: past week • Cronbach's alpha: subscales: $0.74 \leq \alpha \leq 0.75$[42]
Quality of life	EQ-5D-5L[49,50]	• Assesses (general) health • 5 items; 5-point Likert scale & Visual Analogue Scale (VAS) • 5 dimensions: mobility; self-care; usual activities; pain/discomfort; anxiety/depression. One VAS for general health • Time frame: today
Sexual distress	FSDS[39,45]	• Assesses distress related to sexual dysfunction • 12 items; 5-point Likert scale • Total score: 0-48. Higher score indicates higher level of sexual distress • Time frame: past 30 days • Cronbach's alpha: $0.86 \leq \alpha \leq 0.94$[39]
Fear of coital and non-coital sexual activity	FSQ[38]	• Assesses aspects of fear of sexuality • 8 items; 5-point Likert scale • Subscales: fear of non-penetration sexual activity; fear of coitus/vaginal penetration • Subscale scores: fear of non-coital sexual activity 0-20; fear of coitus 0-12. Higher score indicates higher fear • Cronbach's alpha: $0.82 \leq \alpha \leq 0.86$[38]

Table 2 *Continued*

Variable	Questionnaire	Details
Psychological distress	HADS[43,51]	• Assesses psychological distress • 14 items; 4 point Likert scale • Subscales: depression (HADS-D); anxiety (HADS-A) • Total score: 0-42/Subscale scores: 0-21. Higher score indicates more psychological distress • Time frame: past week • Cronbach's alpha: HADS-D: $0.67 \leq \alpha \leq 0.90$; HADS-A: $0.68 \leq \alpha \leq 0.93$[52]
Gynaecological cancer treatment related distress	IES[40,53]	• Assesses current treatment related distress • 15 items; 4-point scale • Subscales: intrusion; avoidance • Total score: 0-75/Subscale scores: intrusion 0-35; avoidance 0-40. Higher score indicates: higher tendency to be triggered by stimuli associated with the traumatic event(s) (for items regarding intrusion); higher tendency to avoid situations that are reminders of the treatment (for items regarding avoidance) • Time frame: past week • Cronbach's alpha: total score: $0.87 \leq \alpha \leq 0.96$; intrusion subscale: $0.85 \leq \alpha \leq 0.95$; avoidance subscale: $0.77 \leq \alpha \leq 0.91$[53]
Relationship dissatisfaction	MMQ_Marital scale[44,54]	• Assesses marital dissatisfaction • 10 items; 9-point Likert scale (range 0-8) • Total scale-score: 0-80. Higher score indicates higher marital dissatisfaction • Time frame: past 2 weeks • Cronbach's alpha in non-distressed group: $0.87 \leq \alpha \leq 0.88$[54]

*The score is calculated based on weighted items.
#Due to the overlap between 4 items from the QLQ-EN24 and QLQ-CX24, we only included the remaining 6 items.
CAU = Care as usual; CEQ = Credibility/Expectancy Questionnaire; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-CX24 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Gynaecological Cancer Module; EORTC QLQ-EN24 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Endometrial Cancer Module; EQ-5D-5L = EuroQol 5D-5L; FSDS = Female Sexual Distress Scale; FSFI = Female Sexual Function Index; FSQ = Fear of Sexuality Questionnaire; HADS = Hospital Anxiety and Depression Scale; IES = Impact of Event Scale; MMQ = Maudsley Marital Questionnaire; QoL = Quality of Life.

Statistical methods

Power and sample size calculation

The FSFI[36] is the primary outcome measure on which sample size calculations are based. With a total sample of 128 women (64 per group), and under the assumption of no interaction, the study will have a 80% power to detect a 0.5 standard deviation difference (Cohen's effect size[57]) for the main effects of the sexual rehabilitation intervention, with the p-value set at 0.05 (two-sided test). Based on our pilot study we expect an attrition rate of 40% (i.e., women who discontinue participation in the study due to somatic reasons such as cancer recurrence)[32]. Consequently, we have to include at least 107 women in both study groups ultimately resulting in an intended sample size of 220 women[57].

Statistical analysis

T-tests or appropriate non-parametric statistics for independent samples will be used to evaluate the comparability of the intervention and control group at baseline in terms of sociodemographic and clinical characteristics. If, despite the stratified randomization procedure, the groups are not comparable on one or more background variables, those variables will be employed routinely as covariates in subsequent analyses.

Questionnaire scores will be calculated according to published scoring algorithms. Differences in changes in the primary outcome measure and secondary outcome measures between groups (intervention vs. control group) over time (T1-T5) will be evaluated using multilevel models and are based on an intention-to-treat approach. Effect sizes will be calculated using standard statistical procedures.

Furthermore, multilevel models will be used to investigate if improvement in sexual functioning in the intervention group is moderated by treatment/cancer characteristics and patient characteristics or mediated by e.g. sexual symptoms and vaginal symptoms or frequency of dilator use. Cost-effectiveness will be analysed using net benefit analysis, with multiple imputation to account for missing data.

Per protocol analyses will also be carried out (as a secondary analysis), comparing women who meet minimal compliance levels with the intervention with the control group. We will use correlation analyses to examine the relationship between degree of intervention adherence and intervention effect.

DISCUSSION

Sexual problems, such as dyspareunia, vaginal dryness and a decrease of sexual satisfaction and desire, are frequently reported by GC survivors after treatment with RT, and occur in particular after combined EBRT+BT. Previous studies have shown that psychosexual support after treatment for GC should include cognitive behavioural interventions to increase dilator compliance and improve sexual functioning[2,15,20-26]. Furthermore, including the patient's partner, if available, is preferred[26]. Therefore, we developed a nurse-led sexual rehabilitation intervention, including these key components, to support sexual improvement and vaginal dilator use after RT. This RCT will provide evidence about the efficacy of this nurse-led sexual rehabilitation intervention in terms of sexual functioning as measured by the FSFI[36], as well as evidence on other sexual outcome measures, compliance with vaginal dilation and the cost-effectiveness of the rehabilitation intervention. We expect that women who received the intervention will report a statistically significantly greater improvement in sexual functioning and - for women who receive EBRT+BT - higher compliance with dilator use, from baseline to 12 months post-RT than women who receive optimal CAU. If proven effective, the rehabilitation intervention will be a valuable addition to the care offered to GC survivors and will contribute to improved quality of life after GC.

The SPARC study has several notable strengths, including the randomized trial design, the multicentre nature (with participation of all Dutch GC centres), the comparison of the intervention group with a control group, the use of a clear treatment protocol and training protocol, the use of intention-to-treat analyses and the long-term follow-up assessments of outcomes. This trial also has several limitations. First, even though the FSFI is one of the most widely used questionnaires to measure sexual functioning among female cancer survivors, it produces biased results for women who have not been sexually active in the past month[36,58]. The majority of the questions (15 out of 19) include a response option of 'No sexual activity' or 'Did not attempt intercourse', scored as zero. This is problematic because lower scores indicate more severe dysfunction whereas not engaging in sexual activity during four weeks does not necessarily imply sexual dysfunction. Sexual inactivity could have multiple reasons, such as the absence of a partner. As our study sample consists of partnered as well as unpartnered women, we chose to randomize participants stratified by having a partner. Second, despite the proposed benefits of regular dilator use (i.e., preventing or minimising vaginal stenosis), unequivocal evidence for its effectiveness in reducing vaginal complaints and better sexual functioning is still limited. The consequences of stenosis remain individually determined, with some women unaffected by significant vaginal complaints, while others experience long-lasting sexual problems[11]. However, because dilator use aims to prevent or minimise stenosis, we expect that this could positively affect vaginal

complaints and sexual functioning indirectly. Therefore, we will include dilator use as a mediator instead of an outcome measure in the statistical analyses. Third, because RT-induced sexual problems develop soon after treatment, we start evaluating GC survivors early in the recovery phase and continue until 12 months post-RT. A longitudinal study that analysed functioning and symptom scores for quality of life of cervical cancer patients who underwent EBRT+BT demonstrated that RT-induced sexual problems increased to a clinically relevant degree in the first three months, after which it stayed elevated, even after 12 months[59]. This study did not include a sexual rehabilitation intervention. By offering a nurse-led sexual rehabilitation intervention we hope to find significant greater improvement in sexual functioning between the intervention- and optimal CAU control group at 12 months follow-up. However, it is possible that sexual functioning among GC survivors might improve further after 12 months post-RT. Therefore, we intend to plan an additional long-term follow-up measure at 24 months post-RT. Fourth, the possibility of contamination of our optimal CAU control group exists. In the past few years, the Dutch CAU regarding sexual problems after RT improved and was aligned nationwide, possibly as a consequence of the findings of our pilot study[32]. This resulted in fewer differences between the participating centres in the current trial, as all participating women are offered an information session, information booklet and a dilator set (if applicable) post-RT free of charge. In the current study, this improved CAU, combined with the possibility that the specialized trained nurses also come into contact with the control group, may result in the control group receiving better post-RT psychosexual care than intended - as the nurses might find it difficult not to use the additional trained skills to help these patients. This well-known problem of contamination within individually randomized intervention studies could be avoided by cluster randomization (i.e., on centre level instead of patient level). However, this method also introduces other potential threats to internal validity, as the number of centres in our study is limited and only a part of the centres could be randomized (n = 8, as a consequence of the training that was already completed in two centres for the pilot study)[32]. Because of the specific variation in the patient population, RT treatment procedures and follow-up procedures across centres, we decided to randomize on patient level, with the risk of contamination. During their training, the nurses received clear instructions on the procedure to be followed in both study groups and about the contamination risks.

The importance of the availability of a sexual rehabilitation intervention is evident from the British[60], Australian[61] and Dutch guidelines[62] which state that more attention has to be paid to sexual functioning after RT for GC. To our knowledge, this is the first RCT evaluating the (cost-)effectiveness of a nurse-led sexual rehabilitation intervention in improving sexual functioning and dilator use compliance of GC patients

after RT. If proven to be effective, the intervention will be a valuable addition to GC survivors' standard care. It will ultimately improve the quality of life of patients (and their partners). The intervention can be implemented nationwide directly after study completion, as all end-users were involved in the preparatory studies[17,18,32] and nurses in all Dutch GC centres are trained in the treatment protocol. Implementation is further enhanced by the relatively low costs of personnel and materials. In addition, if successful, the intervention could be extrapolated to women with other types of pelvic cancer (e.g., rectal cancer, anal cancer and bladder cancer).

REFERENCES

1. Dutch Cancer Registry. Nederlandse Kankerregistratie Cijfers. 2025. https://iknl.nl/nkr-cijfers (accessed 5th of May 2025).
2. Abbott-Anderson K, Kwekkeboom KL. A systematic review of sexual concerns reported by gynecological cancer survivors. *Gynecologic Oncology* 2012; **124**(3): 477-89. doi:10.1016/j.ygyno.2011.11.030.
3. Bae H, Park H. Sexual function, depression, and quality of life in patients with cervical cancer. *Support Care Cancer* 2016; **24**(3): 1277-83. doi:10.1007/s00520-015-2918-z.
4. Incrocci L, Jensen PT. Pelvic radiotherapy and sexual function in men and women. *J Sex Med* 2013; **10 Suppl 1**: 53-64. doi:10.1111/jsm.12010.
5. Jensen PT, Groenvold M, Klee MC, Thranov I, Petersen MA, Machin D. Longitudinal study of sexual function and vaginal changes after radiotherapy for cervical cancer. *Int J Radiat Oncol Biol Phys* 2003; **56**(4): 937-49. doi:10.1016/s0360-3016(03)00362-6.
6. Jensen PT, Froeding LP. Pelvic radiotherapy and sexual function in women. *Transl Androl Urol* 2015; **4**(2): 186-205. doi:10.3978/j.issn.2223-4683.2015.04.06.
7. Pieterse QD, Maas CP, ter Kuile MM, et al. An observational longitudinal study to evaluate miction, defecation, and sexual function after radical hysterectomy with pelvic lymphadenectomy for early-stage cervical cancer. *Int J Gynecol Cancer* 2006; **16**(3): 1119-29. doi:10.1111/j.1525-1438.2006.00461.x.
8. Pieterse QD, Kenter GG, Maas CP, et al. Self-reported sexual, bowel and bladder function in cervical cancer patients following different treatment modalities: longitudinal prospective cohort study. *Int J Gynecol Cancer* 2013; **23**(9): 1717-25. doi:10.1097/IGC.0b013e3182a80a65.
9. Nout RA, Putter H, Jurgenliemk-Schulz IM, et al. Five-year quality of life of endometrial cancer patients treated in the randomised Post Operative Radiation Therapy in Endometrial Cancer (PORTEC-2) trial and comparison with norm data. *Eur J Cancer* 2012; **48**(11): 1638-48. doi:10.1016/j.ejca.2011.11.014.
10. Viswanathan AN, Lee LJ, Eswara JR, et al. Complications of pelvic radiation in patients treated for gynecologic malignancies. *Cancer* 2014; **120**(24): 3870-83. doi:10.1002/cncr.28849.
11. International Clinical Guideline Group. International guidelines on vaginal dilation after pelvic radiotherapy. 2012. https://www.pocd.com.au/core/media/media.nl/id.47537/c.3923593/.f?h=f2e5bc493442741b7e6c (accessed 2nd of March 2020).
12. Damast S, Jeffery DD, Son CH, et al. Literature review of vaginal stenosis and dilator use in radiation oncology. *Pract Radiat Oncol* 2019; **9**(6): 479-91. doi:10.1016/j.prro.2019.07.001.
13. Friedman LC, Abdallah R, Schluchter M, Panneerselvam A, Kunos CA. Adherence to vaginal dilation following high dose rate brachytherapy for endometrial cancer. *Int J Radiat Oncol Biol Phys* 2011; **80**(3): 751-7. doi:10.1016/j.ijrobp.2010.02.058.
14. Law E, Kelvin JF, Thom B, et al. Prospective study of vaginal dilator use adherence and efficacy following radiotherapy. *Radiother Oncol* 2015; **116**(1): 149-55. doi:10.1016/j.radonc.2015.06.018.
15. Robinson JW, Faris PD, Scott CB. Psychoeducational group increases vaginal dilation for younger women and reduces sexual fears for women of all ages with gynecological carcinoma treated with radiotherapy. *Int J Radiat Oncol Biol Phys* 1999; **44**(3): 497-506. doi:10.1016/s0360-3016(99)00048-6.
16. Schover LR, Fife M, Gershenson DM. Sexual dysfunction and treatment for early stage cervical-cancer. *Cancer* 1989; **63**(1): 204-12. doi:10.1002/1097-0142(19890101)63:1<204::Aid-Cncr2820630133>3.0.Co;2-U.
17. Bakker RM, Vermeer WM, Creutzberg CL, Mens JWM, Nout RA, ter Kuile MM. Qualitative accounts of patients' determinants of vaginal dilator use after pelvic radiotherapy. *J Sex Med* 2015; **12**(3): 764-73. doi:10.1111/jsm.12776.

18. Bakker RM, ter Kuile MM, Vermeer WM, et al. Sexual rehabilitation after pelvic radiotherapy and vaginal dilator use: consensus using the Delphi method. *Int J Gynecol Cancer* 2014; **24**(8): 1499-506. doi:10.1097/igc.0000000000000253.

19. Lubotzky FP, Butow P, Hunt C, et al. A psychosexual rehabilitation booklet increases vaginal dilator adherence and knowledge in women undergoing pelvic radiation therapy for gynaecological or anorectal cancer: a randomised controlled trial. *Clin Oncol (R Coll Radiol)* 2019; **31**(2): 124-31. doi:10.1016/j.clon.2018.11.035.

20. Jeffries SA, Robinson JW, Craighead PS, Keats MR. An effective group psychoeducational intervention for improving compliance with vaginal dilation: a randomized controlled trial. *Int J Radiat Oncol Biol Phys* 2006; **65**(2): 404-11. doi:10.1016/j.ijrobp.2005.12.009.

21. Bakker RM, Kenter GG, Creutzberg CL, et al. Sexual distress and associated factors among cervical cancer survivors: a cross-sectional multicenter observational study. *Psycho-Oncology* 2017; **26**(10): 1470-7. doi:10.1002/pon.4317.

22. Aktaş D, Terzioğlu F. Effect of home care service on the sexual satisfaction of patients with gynecologic cancer. *Sexuality and Disability* 2014; **33**(2): 243-52. doi:10.1007/s11195-014-9370-8.

23. Brotto LA, Erskine Y, Carey M, et al. A brief mindfulness-based cognitive behavioral intervention improves sexual functioning versus wait-list control in women treated for gynecologic cancer. *Gynecol Oncol* 2012; **125**(2): 320-5. doi:10.1016/j.ygyno.2012.01.035.

24. Cain EN, Kohorn EI, Quinlan DM, Latimer K, Schwartz PE. Psychosocial benefits of a cancer support group. *Cancer* 1986; **57**(1): 183-9. doi:10.1002/1097-0142(19860101)57:1%3C183::aid-cncr2820570135%3E3.0.co;2-3.

25. Classen CC, Chivers ML, Urowitz S, et al. Psychosexual distress in women with gynecologic cancer: a feasibility study of an online support group. *Psychooncology* 2013; **22**(4): 930-5. doi:10.1002/pon.3058.

26. Scott JL, Halford WK, Ward BG. United we stand? The effects of a couple-coping intervention on adjustment to early stage breast or gynecological cancer. *J Consult Clin Psychol* 2004; **72**(6): 1122-35. doi:10.1037/0022-006x.72.6.1122.

27. Gunzler C, Berner MM. Efficacy of psychosocial interventions in men and women with sexual dysfunctions - a systematic review of controlled clinical trials: part 2 - the efficacy of psychosocial interventions for female sexual dysfunction. *J Sex Med* 2012; **9**(12): 3108-25. doi:10.1111/j.1743-6109.2012.02965.x.

28. Heima JR, Meston CM. Empirically validated treatment for sexual dysfunction. *Annu Rev Sex Res* 1997; **8**: 148-94.

29. ter Kuile MM, Both S, van Lankveld JJ. Cognitive behavioral therapy for sexual dysfunctions in women. *Psychiatr Clin North Am* 2010; **33**(3): 595-610. doi:10.1016/j.psc.2010.04.010.

30. Vermeer WM, Bakker RM, Kenter GG, Stiggelbout AM, Ter Kuile MM. Cervical cancer survivors' and partners' experiences with sexual dysfunction and psychosexual support. *Support Care Cancer* 2016; **24**(4): 1679-87. doi:10.1007/s00520-015-2925-0.

31. Vermeer WM, Bakker RM, Stiggelbout AM, Creutzberg CL, Kenter GG, ter Kuile MM. Psychosexual support for gynecological cancer survivors: professionals' current practices and need for assistance. *Support Care Cancer* 2015; **23**(3): 831-9. doi:10.1007/s00520-014-2433-7.

32. Bakker RM, Mens JW, de Groot HE, et al. A nurse-led sexual rehabilitation intervention after radiotherapy for gynecological cancer. *Support Care Cancer* 2017; **25**(3): 729-37. doi:10.1007/s00520-016-3453-2.

33. Basson R. The female sexual response: a different model. *J Sex Marital Ther* 2000; **26**(1): 51-65. doi:10.1080/009262300278641.

34. Spano L, Lamont JA. Dyspareunia: a symptom of female sexual dysfunction. *Can Nurse* 1975; **71**(8): 22-5.

35. Miller WR, Rollnick S. Motivational interviewing: helping people change. 3 ed: Guilford Press; 2013.

36. Rosen R, Brown C, Heiman J, et al. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. *J Sex Marital Ther* 2000; **26**(2): 191-208. doi:10.1080/009262300278597.

37. Greimel ER, Kuljanic Vlasic K, Waldenstrom AC, et al. The European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life questionnaire cervical cancer module: EORTC QLQ-CX24. *Cancer* 2006; **107**(8): 1812-22. doi:10.1002/cncr.22217.

38. ter Kuile MM, van Lankveld JJ, de Groot E, Melles R, Neffs J, Zandbergen M. Cognitive-behavioral therapy for women with lifelong vaginismus: process and prognostic factors. *Behav Res Ther* 2007; **45**(2): 359-73. doi:10.1016/j.brat.2006.03.013.

39. Derogatis LR, Rosen R, Leiblum S, Burnett A, Heiman J. The Female Sexual Distress Scale (FSDS): initial validation of a standardized scale for assessment of sexually related personal distress in women. *J Sex Marital Ther* 2002; **28**(4): 317-30. doi:10.1080/00926230290001448.

40. Horowitz M, Wilner N, Alvarez W. Impact of Event Scale: a measure of subjective stress. *Psychosom Med* 1979; **41**(3): 209-18. doi:10.1097/00006842-197905000-00004.

41. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *Journal of the National Cancer Institute* 1993; **85**(5): 365-76. doi:10.1093/jnci/85.5.365.

42. Greimel E, Nordin A, Lanceley A, et al. Psychometric validation of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Endometrial Cancer Module (EORTC QLQ-EN24). *Eur J Cancer* 2011; **47**(2): 183-90. doi:10.1016/j.ejca.2010.08.014.

43. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983; **67**(6): 361-70. doi:10.1111/j.1600-0447.1983.tb09716.x.

44. Crowe MJ. Conjoint marital therapy: a controlled outcome study. *Psychol Med* 1978; **8**(4): 623-36. doi:10.1017/s0033291700018833.

45. ter Kuile MM, Brauer M, Laan E. The Female Sexual Function Index (FSFI) and the Female Sexual Distress Scale (FSDS): psychometric properties within a Dutch population. *J Sex Marital Ther* 2006; **32**(4): 289-304. doi:10.1080/00926230600666261.

46. Baser RE, Li Y, Carter J. Psychometric validation of the Female Sexual Function Index (FSFI) in cancer survivors. *Cancer* 2012; **118**(18): 4606-18. doi:10.1002/cncr.26739.

47. Borkovec TD, Nau SD. Credibility of analogue therapy rationales. *J Behav Ther Exp Psychiatry* 1972; **3**(4): 257-60. doi:10.1016/0005-7916(72)90045-6.

48. Devilly GJ, Borkovec TD. Psychometric properties of the credibility/expectancy questionnaire. *J Behav Ther Exp Psychiatry* 2000; **31**(2): 73-86. doi:10.1016/s0005-7916(00)00012-4.

49. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011; **20**(10): 1727-36. doi:10.1007/s11136-011-9903-x.

50. Versteegh MM, Vermeulen KM, Evers SMAA, de Wit GA, Prenger R, Stolk EA. Dutch tariff for the five-level version of EQ-5D. *Value Health* 2016; **19**(4): 343-52. doi:10.1016/j.jval.2016.01.003.

51. Spinhoven P, Ormel J, Sloekers PPA, Kempen GIJM, Speckens AEM, VanHemert AM. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. *Psychol Med* 1997; **27**(2): 363-70. doi:10.1017/S0033291796004382.

52. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res* 2002; **52**(2): 69-77. doi:10.1016/s0022-3999(01)00296-3.

53. van der Ploeg E, Mooren TT, Kleber RJ, van der Velden PG, Brom D. Construct validation of the Dutch version of the impact of event scale. *Psychol Assess* 2004; **16**(1): 16-26. doi:10.1037/1040-3590.16.1.16.

54. Arrindell WA, Boelens W, Lambert H. On the psychometric properties of the Maudsley Marital Questionnaire (MMQ): Evaluation of self-ratings in distressed and 'normal' volunteer couples based on the Dutch version. *Personality and Individual Differences* 1983; **4**(3): 293-306.

55. Jacobson NS, Truax P. Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. *J Consult Clin Psychol* 1991; **59**(1): 12-9. doi:10.1037/0022-006X.59.1.12.

56. Janssen MF, Pickard AS, Golicki D, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. *Qual Life Res* 2013; **22**(7): 1717-27. doi:10.1007/s11136-012-0322-4.

57. Cohen J. Statistical power analysis for the behavioral sciences 2nd ed. Mahwah, New Jersey: Lawrence Erlbaum Associates, Inc.; 1988.

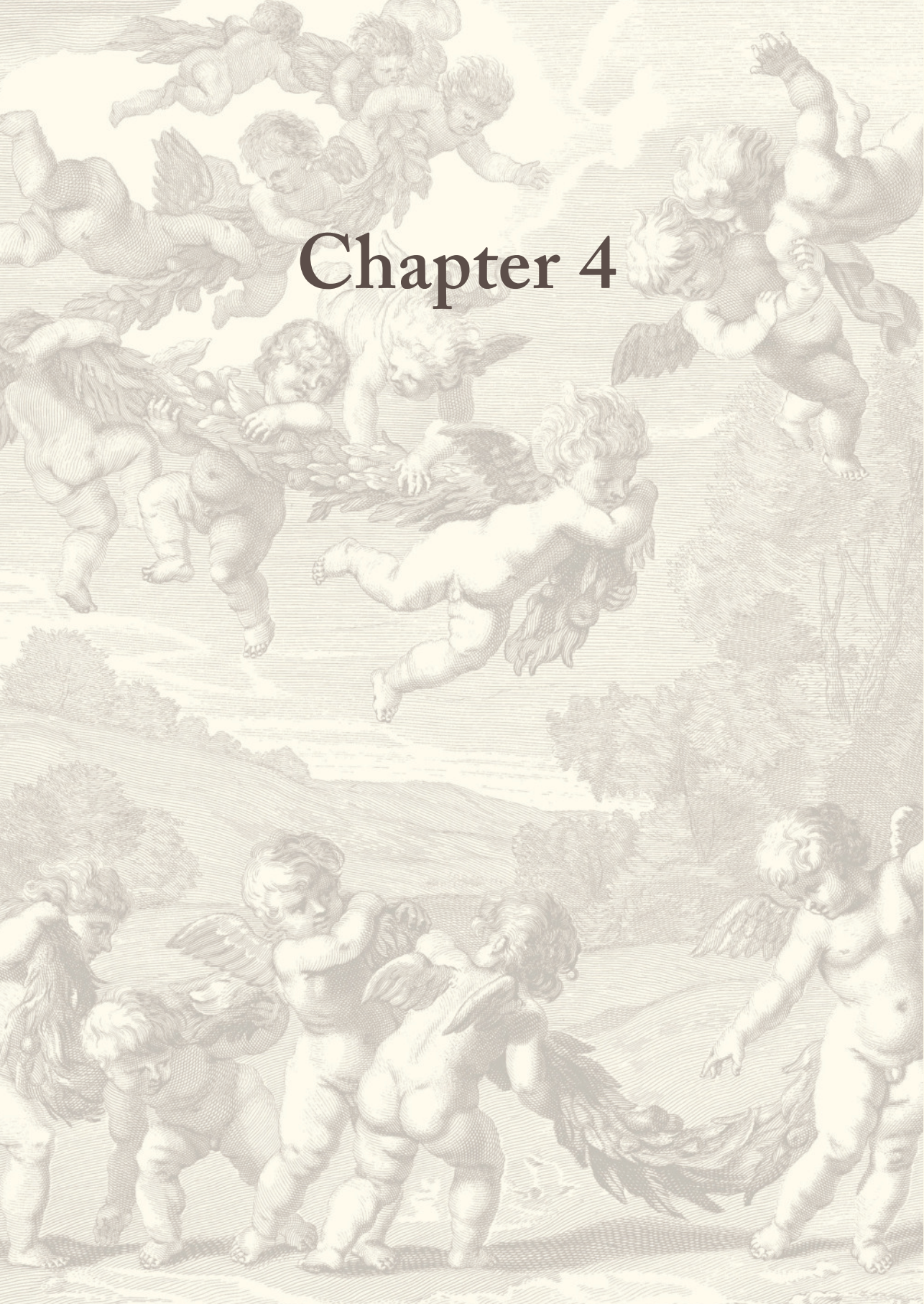
58. Meyer-Bahlburg HFL, Dolezal C. The female sexual function index: a methodological critique and suggestions for improvement. *J Sex Marital Ther* 2007; **33**(3): 217-24. doi:10.1080/00926230701267852.

59. Kirchheiner K, Potter R, Tanderup K, et al. Health-related quality of life in locally advanced cervical cancer patients after definitive chemoradiation therapy including image guided adaptive brachytherapy: an analysis From the EMBRACE Study. *Int J Radiat Oncol* 2016; **94**(5): 1088-98. doi:10.1016/j.ijrobp.2015.12.363.

60. Reed N, Balega J, Barwick T, et al. British Gynaecological Cancer Society (BGCS) cervical cancer guidelines: recommendations for practice. *Eur J Obstet Gynecol Reprod Biol* 2021; **256**: 433-65. doi:10.1016/j.ejogrb.2020.08.020.

61. Cancer Australia. Psychosexual care of women with gynaecological cancers. 2021. https://www.cancerlearning.gov.au/topics/psgc (accessed May 7 2021).

62. Integraal Kankercentrum Nederland. Cervixcarcinoom Landelijke richtlijn, Versie: 3.0. 2012. http://www.med-info.nl/Richtlijnen/Oncologie/Gynaecologische%20tumoren/Cervixcarcinoom.pdf (accessed 7th of December 2020).



Chapter 4

Efficacy of a nurse-led sexual rehabilitation intervention for women with gynaecological cancers receiving radiotherapy: results of a randomised trial

British Journal of Cancer, 2024; 131(5):808-819
doi: 10.1038/s41416-024-02775-8

Isabelle Suvaal
Susanna B. Hummel
Jan-Willem M. Mens
Charlotte C. Tuijnman-Raasveld
Roula Tsonaka
Laura A. Velema
Henrike Westerveld
Jeltsje S. Cnossen
An Snyers
Ina M. Jürgenliemk-Schulz
Ludy C.H.W. Lutgens
Jannet C. Beukema
Marie A.D. Haverkort
Marlies E. Nowee
Remi A. Nout
Cor D. de Kroon
Wilbert B. van den Hout
Carien L. Creutzberg
Helena C. van Doorn
Moniek M. ter Kuile

ABSTRACT

Objectives

The multicentre randomized SPARC trial evaluated efficacy of a nurse-led sexual rehabilitation-intervention on sexual functioning, distress, dilator use, and vaginal symptoms after radiotherapy for gynaecological cancers.

Methods

Eligible women were randomised to the rehabilitation intervention or care-as-usual. Four intervention-sessions were scheduled over 12-months, with concurrent validated questionnaires and clinical assessments. Primary outcome was the Female Sexual Function Index (FSFI). A generalized-mixed-effects model compared groups over time.

Results

229 women were included (n=112 intervention; n=117 care-as-usual). No differences in FSFI total-scores were found between groups at any timepoint (p=0.37), with 12-month scores of 22.57 (intervention) versus 21.76 (care-as-usual). The intervention did not significantly improve dilator use, reduce sexual distress or vaginal symptoms compared to care-as-usual. At 12-months, both groups had minimal physician-reported vaginal stenosis; 70% of women were sexually active and reported no or mild vaginal symptoms. After radiotherapy and brachytherapy, 85% (intervention) versus 75% of participants reported dilation twice weekly.

Conclusions

Sexual rehabilitation for women treated with combined (chemo)radiotherapy and brachytherapy improved before and during the SPARC trial, which likely contributed to comparable study groups. Best-practice involves a sexual rehabilitation-appointment one-month post-radiotherapy, including patient-information, with dilator guidance, preferable by a trained nurse, and follow-up during the first year after treatment.

BACKGROUND

Women with locally advanced cervical and vaginal cancer are primarily treated with external beam radiotherapy with concurrent cisplatin-based chemotherapy and MRI-guided adaptive brachytherapy. Those with early stage cervical or endometrial cancer treated with upfront surgery receive adjuvant external beam radiotherapy (with or without brachytherapy boost) in case of lymph node involvement, close or involved surgical margins or a combination of risk factors. The impact of these gynaecological cancer treatments on sexual functioning can be substantial, and is more pronounced when radiotherapy is included, as compared to surgery alone[1,2]. Especially treatment with both external beam radiotherapy and brachytherapy has been shown to impact vaginal and sexual functioning by causing morphological changes in the vaginal mucosa, such as atrophy, adhesions, and fibrosis which may lead to vaginal stenosis and shortening[3-5].

Regular vaginal dilation has been shown to help preventing and reducing vaginal stenosis[6]. However, many women (75%) fail to use dilators regularly, even with counselling and specific instructions[7,8]. Some studies suggested that additional professional support, including psycho-education and motivation, can improve compliance[6], but not all studies showed such benefit[9,10]. In addition, reported interventions targeting dilator use did not address other psychosexual consequences of treatment of gynaecological cancer, such as sexual distress and (worries about) pain during intercourse[3,7,11].

Some small studies have investigated psychosexual interventions such as cognitive-behavioural techniques, psycho-education and counselling to address sexual problems after radiotherapy[5,11-13]. Results indicated that such interventions can lead to improved sexual functioning, reduced sexual distress, and when the partner was actively involved, enhanced relationship satisfaction.

In a previous pilot study, a specifically developed nurse-led sexual rehabilitation intervention combining psycho-education and cognitive-behavioural therapy was shown to improve sexual functioning and compliance with dilator use in women treated with chemoradiotherapy and brachytherapy[14]. Subsequently a randomised trial was designed to evaluate the effectiveness of this rehabilitation intervention as compared to care-as-usual. We hypothesized that women receiving this nurse-led rehabilitation intervention would experience significantly greater improvement in sexual functioning at 12-months after radiotherapy. Additionally, we anticipated improved compliance with dilator use and fewer vaginal functioning problems and sexual distress.

METHODS

Study design and participants

The SPARC (Sexual rehabilitation Programme After Radiotherapy for gynaecological Cancer, NCT03611517) study was a multicentre randomised trial conducted in all 10 Dutch gynaecological oncology centres. Participating centres, including their study teams, are listed in supplementary table S1. A detailed description of the trial design has been previously reported[15].

Before start of the trial, a study-specific 50-hour training programme was held, to which each participating centre sent at least two designated oncology nurses (for details, see Table 1)[14,15]. Only after completing this programme nurses were allowed to conduct the intervention. An additional training programme and annual focused training days were organised during the years of the study.

Eligible women had a histological diagnosis of cervical, vaginal or endometrial cancer; received primary or postoperative external beam radiotherapy with or without concurrent chemotherapy and brachytherapy, or postoperative radiotherapy alone; were 18 years or older, and intended to retain sexual activity. Both single and partnered women, regardless of their sexual orientation, could participate. Exclusion criteria were unavailability for follow-up; insufficient Dutch language proficiency; major affective, psychotic or substance abuse disorder, or posttraumatic stress disorder related to pelvic floor/genital abuse.

The radiation oncologists at the participating centres screened potential participants. Eligible women were informed about the background, rationale and specifics of the study protocol. All participating women provided written informed consent and completed a baseline questionnaire before completion of radiotherapy. In this baseline questionnaire they retrospectively completed questions about sexual functioning and distress prior to cancer symptoms and diagnosis.

The protocol was approved by the Scientific Review Board of the Dutch Cancer Society, by the Medical Ethics Committee Leiden-Den Haag-Delft (number NL62767.058.17), and by the Institutional Review Boards and/or Ethics Committees of the participating centres.

Randomisation and masking

Participants were assigned unique study identifiers by the local data manager for use in all questionnaires and data files. Participants were randomly assigned (1:1) to the nurse-led rehabilitation intervention or care-as-usual, using block stratified

randomisation (block sizes of 2 and 4). Stratification was based on radiotherapy type (brachytherapy yes/no) and partner status (yes/no). Participants were registered by the local data manager through a secured web-based system, and randomised after completing baseline measurements. Participants, physicians, nurses, and investigators were not masked to treatment allocation.

Procedures

In the intervention group, all women were counselled and followed by the specifically trained nurse[14]. The content of this nurse-led sexual rehabilitation intervention has been described in detail elsewhere[15] and is summarized in Table 1 and Figure 1. In short, the intervention comprised four one-hour face-to-face sessions at 1, 3, 6, and 12 months post-radiotherapy, synchronized with visits to the radiation oncologist, with an extra session at 2 months for women who received brachytherapy. All nurse-led intervention sessions were audio-taped for checks of adherence to the protocol and assessment of competence by an independent panel. The aim was to conduct random checks of 15% of the sessions, which is customary in this type of research, where a minimum of 10% is considered acceptable within large cohorts[16].

Both the intervention and care-as-usual groups had a first follow-up session 4-5 weeks after completion of radiotherapy with their radiation oncologist, to evaluate recovery, tumour regression and vaginal healing, and to assess symptoms. All women received a specially developed information booklet which was based on the pilot study[14]. Those who had received radiotherapy with brachytherapy also received a vaginal dilator set (Amielle Comfort®; Owen Mumford) and two tubes of lubrication gel (K-Y Jelly; Johnson & Johnsen) free of charge. They were advised to start vaginal dilation for 1 to 3 minutes, 2 to 3 times a week, provided the vagina was sufficiently healed, and to continue regular vaginal dilation throughout the first year after radiotherapy. If sexual intercourse was resumed, this was also considered as part of vaginal dilation, which could be complemented with the use of the dilator set. Women with cervical or vaginal cancers who were under 50 years of age were recommended to receive hormone replacement therapy until the age of about 50.

Prior to the study, the study team at the centres had been queried about their standard protocols regarding sexual rehabilitation within their centre ('care-as-usual'). In most of the centres (90%), specific counselling on sexual rehabilitation and dilation was already a standard topic of information after treatment and during follow-up appointments with their physician. Although the guidance offered to the care-as-usual group could not be completely standardized due to these local practices, it did not involve the structured, tailored nurse-led sexual rehabilitation intervention during follow-up.

Table 1 Description of the sexual rehabilitation programme

General Features
Nurses • Each participating centre sent at least two designated oncology nurses; or brachytherapy technicians (two centres); or radiotherapy medical assistants (one centre). In total, 25 oncology nurses were involved in the study, divided over 10 Dutch oncology centres. • The training programme was developed during the pilot study by one clinical psychologist, and two healthcare psychologists, all with at least 25 years expertise in sexology, conceptualization, methods and skills[14]. • Prior to the start of the trial, all nurses completed a 50-hour study-specific training in the basic principles of sexology, motivational interviewing, simple cognitive behavioural interventions, and the treatment protocol itself. Because of changes in employment the training was repeated in 2020 for new nurses from some participating centres and for an additional participating centre. • The nurses were supervised by experienced sexologists (N = 12), who were also trained in the treatment protocol. • Over a period of approximately 4 years, the nurses attended six additional training days that focused on a specific theme that was relevant for the study (i.e., vaginal stenosis and dilator use; emotional reactions after loss of participants due to cancer recurrence; the partner relationship; implementation of the intervention). During five of these training days, the supervisors were also present. One of these training days took place online due to the COVID-19 pandemic.
Structure of the sexual rehabilitation programme (see also figure 1) • The intervention consisted of four one-hour face to face sessions at 1, 3, 6, and 12-months after radiotherapy. • An additional session was scheduled at 2-months after radiotherapy for women who received external beam radiotherapy combined with brachytherapy, during which potential barriers and problems with dilator use were discussed. • An extra follow-up session/telephone consultation of 30 minutes was scheduled between 6 and 12-months post-treatment, if preferred by the participant. • The sexual rehabilitation intervention consisted of 11 modules (see also description of modules below). The modules included topics such as education regarding the specific cancer diagnosis, treatment and importance of long-term regular dilator use, discussing potential experienced barriers to dilator or lubricant use, fear of penetration with dilators and resuming sexual activity, promoting couples' mutual coping and support processes and addressing sexual, body image and relationship concerns. If sexual problems appeared to beyond the scope of the modules, referral options to a psychologist-sexologist were given. • The content of the intervention was personalized for each individual person and was tailored to the participant-specific psychological, relational and somatic factors. During each session, the nurse selected the specific module(s) that fitted the woman's (and her partner's) needs best. See Suvaal et al[15] (chapter 3) for the decision tree for module selection. • The sessions were designed to be face-to-face; however, during the COVID-19 pandemic, sessions could also take place by telephone or video.
Involvement of the partner • Partners were invited and encouraged to accompany the sessions. Their presence was however not obligatory.
Costs of the sexual rehabilitation programme • The sexual rehabilitation programme was provided at no cost to the women.

Table 1 *Continued*

Description of modules
Module 1: Brief sexual history This module describes how the nurse can question the patient in-depth about sexual problems on various domains of sexual functioning, including sexual interest/arousal, orgasm, pain and sexual satisfaction. It also covers psycho-education about sexuality and the sexual response curve and provides information about frequently occurring sexual problems and solutions.
Module 2: Pain during intercourse This module includes practical guidelines that the nurse can provide regarding pain during intercourse after radiotherapy-, with referrals to module 3, 4, 6 and 7, and explains how to provide psycho-education about the circular model of dyspareunia, which is based on a cognitive behavioural framework.
Module 3: Vaginal dryness and health This module provides the nurse with instructions on how to give advice with regard to treatment of vaginal dryness, pain or irritation. It also includes information regarding vaginal health, such as the use of vaginal creams, avoidance of scratching in response to irritated skin or avoidance of washing with soap.
Module 4: Alternatives for intercourse The exercise in this module helps the woman and her partner (if available) to explore and discuss non-penetrative alternatives for sexual intercourse.
Module 5: The partner and possible sexual problems This module can be consulted by the nurse when partners experience temporary sexual problems, such as erectile dysfunction during intercourse. The module also includes a reference to module 1.
Module 6: Gradual exposure towards sexual intercourse The aim of the steps in this module, which are based on a cognitive behavioural gradual exposure therapy for Genito-Pelvic/Penetration Disorder, is to learn the woman and her partner how to re-engage in sexual intercourse. The steps include: touching of the vaginal opening with the erect penis without penetration, stepwise vaginal insertion of the erect penis without moving, and vaginal insertion of the erect penis with moving.
Module 7: Pelvic floor exercise This module includes several pelvic floor relaxation exercises for women who experience tension in the pelvic floor muscles.
Module 8: Difficulties with dilator use at home This module is suitable for women who experience problems with dilator use and who already practiced under supervision of a nurse (see module 9) or for women who do not want to practice under supervision. This module provides the nurse with instructions on how to give specific advice on how to overcome experienced difficulties, after first exploring the problems during dilator use (e.g. pain/discharge, loss of blood or difficulties with inserting the dilator).
Module 9: Using dilators under supervision at the outpatient clinic This module focuses on women who experience fear with regard to dilator use or who experience difficulties when using vaginal dilators, due to for example tension of the pelvic floor. The nurse-led session is based on therapist-aided exposure therapy for Genito-Pelvic/Penetration Disorder. The goal is to reduce fear of dilator use by using a stepwise exposure session in which the woman - who performs the vaginal dilation by herself - is facilitated by the nurse. During the session, tips are given with regard to a correct and more comfortable use of the dilators. Furthermore, the nurse helps to evaluate and articulate any unhelpful cognitions about what could (or could not) occur during dilator use. In these instances, the exposure is used as a behavioural experiment, to test the tenability of these cognitions. The module also includes advice on how to handle problems that might occur during practicing at home.
Module 10: Exploring and resolving ambivalence with regard to dilator use The aim of the exercise in this module is to motivate the woman for dilator use, by acknowledging, exploring and resolving ambivalent feelings towards dilator use by motivational interviewing technique. By exploring pros and cons of both dilator use and no dilator use, the woman can be supported in making an informed choice about dilator use. If she decides to use dilators, problems with dilator use are discussed in more detail and how to overcome them. If a woman decides not to use dilators, tampons covered in petroleum jelly (Vaseline) are recommended and guidelines on how to use these are provided to the woman (see module 11).
Module 11: Petroleum jelly (Vaseline) tampons This module follows module 10, when a woman decides not to use dilators. The module covers guidelines on how to use tampons covered in petroleum jelly (Vaseline).

Note. N = total number of supervisors involved in the study.

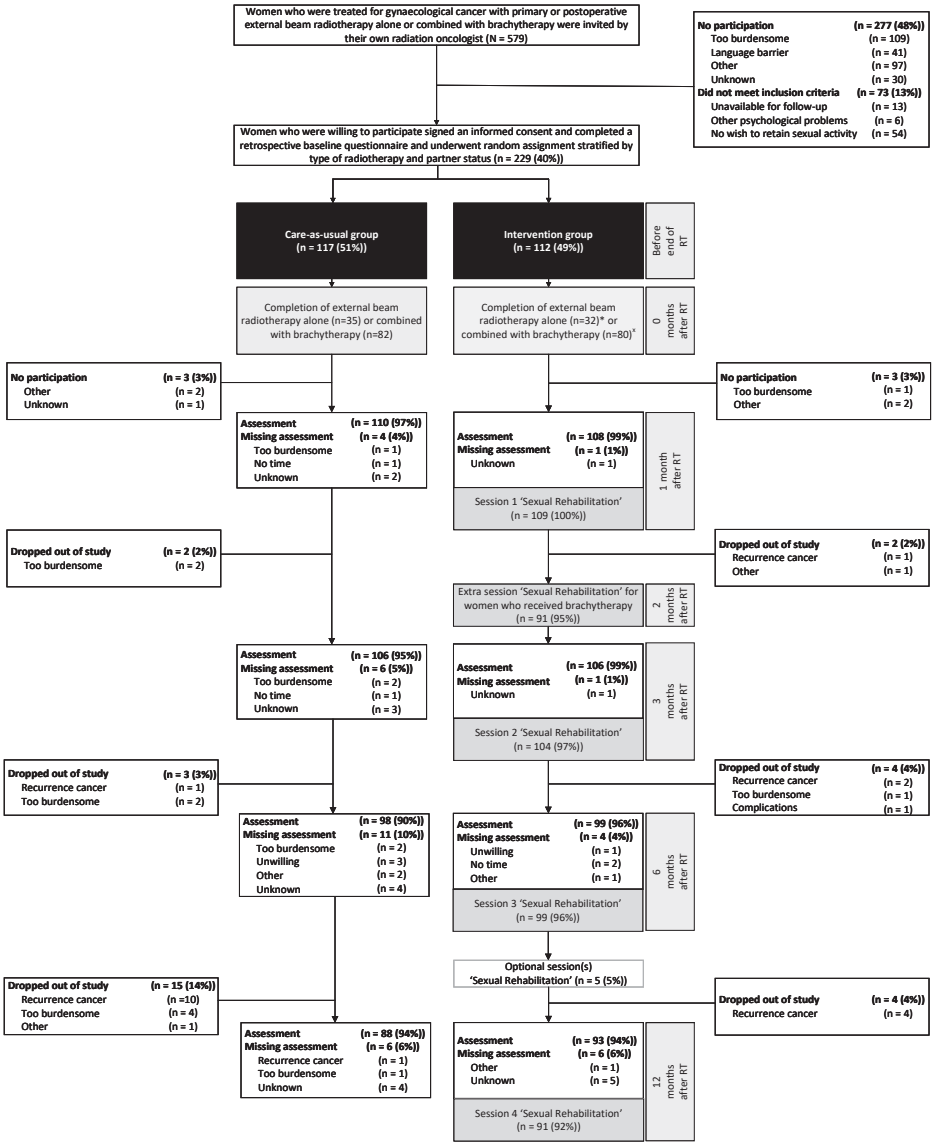


Figure 1 CONSORT diagram. N = total number of patients invited for the study; n = subgroup of patients; RT = Radiotherapy

*One patient was initially stratified for external beam radiotherapy combined with brachytherapy, but ultimately received external beam radiotherapy alone. Consequently, her rehabilitation trajectory was according to external beam radiotherapy alone; therefore she was moved to external beam radiotherapy alone.

xOne patient was initially stratified for external beam radiotherapy alone, however she received an additional external beam radiotherapy boost. This led to modification in her rehabilitation trajectory to align external beam radiotherapy combined with brachytherapy; therefore she was moved to external beam radiotherapy combined with brachytherapy.

Outcomes

The primary outcome was overall sexual functioning, as measured with the Female Sexual Function Index (FSFI)[17]. A total score of ≤26.55 has been validated as cut-off score for diagnosis of female sexual dysfunction[18]. We added 2 questions to the FSFI to assess the frequency of sexual activity with and without sexual intercourse. Secondary outcomes included sexual distress, as measured by the Female Sexual Distress Scale (FSDS; scores ≥15 have been signified to establish the presence of sexual distress)[19], compliance with dilator use (assessed using a 4-item questionnaire regarding frequency, duration, sexual intercourse and other vaginal penetration activities), vaginal functioning problems such as shortness, dryness and pain during intercourse (measured by the Cervical Cancer Module of the European Organization for Research and Treatment of Cancer (QLQ-CX24)[20]), and physician-reported vaginal dryness, shortening and/or tightening, and dyspareunia (assessed by standardized clinical examination using the Common Terminology Criteria for Adverse Events (CTCAE, version 4.03)). See supplementary table S2 for additional specific patient and physician-reported outcome measures, with cut-off scores if applicable.

Outcomes were assessed before radiotherapy (retrospective baseline) and 1, 3, 6 and 12-months after radiotherapy. To minimize respondent burden, the baseline questionnaire included only the FSFI and the FSDS. Adverse events related to dilator use were documented. Cancer treatment related adverse events were not considered study-related.

Statistical analysis

An effect size of d=0.50 indicates a moderate and clinically relevant effect size[21]. This corresponds with a difference of 3.4 points on the primary outcome measure (FSFI), with a standard deviation of 6.8. To achieve 80% power at a 0.05 significance level, each study group required a minimum of 64 evaluable women at 12-months. Considering the 40% dropout rate observed in the pilot study[14], at least 107 women in both the intervention and care-as-usual group were required, stratified by radiotherapy type and partner status.

During participant recruitment, it became evident that women undergoing both external beam radiotherapy and brachytherapy were more likely to participate, probably due to more advanced age and milder side effects in those receiving pelvic radiotherapy alone. Consequently, the study population comprised relatively young women with cervical carcinoma primarily treated with external beam radiotherapy, concurrent cisplatin-based chemotherapy, and image-guided adaptive brachytherapy. Given the intervention's relevance to these younger women with intensive treatment for cervical

and vaginal carcinomas, we decided to continue enrolment of eligible women regardless of radiotherapy type to a total of 220 women. The study was amended accordingly.

Analyses were based on intention-to-treat, and were conducted with the Statistical Package for Social scientists (version 29) and the GLMM-adaptive package in R (version 4.2.1)[22]. Questionnaire scores were calculated using published algorithms[17,19,20]. Missing values were replaced by the average score of completed items in the same scale for each individual, when ≥75% of items were completed. When a scale consisted of only two items, 100% of the items had to be completed.

To address differences in changes in the primary and secondary outcome measures between groups (intervention versus care-as-usual) over time we modelled either the mean scores, log expected counts or log-odds (depending on the type of variable) as a function of time, of the intervention group and their interaction. In addition, radiotherapy with or without brachytherapy was added as factor to the model. For the physician-reported variables, when fewer than 15 women scored within CTCAE grade 2 and/or 3 events, these scores were combined into a single category with CTCAE grade 1 ('toxicity'), and then compared to CTCAE grade 0 ('no toxicity'). Differences between groups were evaluated based on a generalized linear mixed effects model, specifically depending on the outcome considered we used mixed effects poisson regression (count measurements) or mixed effects logistic regression (dichotomous outcomes). We used a beta distribution instead of a normal distribution for our continuous outcomes, because of the bounded nature of these outcomes (e.g. the FSFI total score takes values between 2-36[17]). In addition, we used a random effects model (i.e., random intercepts and random slopes) to capture the within-subjects correlation. We further explored if there was considerable between-hospital variability. Regarding missing data, the generalized linear mixed effects models give valid results under the missing at random mechanism. To account for any potential model misspecification robust standard errors were computed. We used the Likelihood Ratio Test to test whether the improvement of the intervention group over time was statistically significantly different from the care-as-usual group. The significance level was set at 0.05.

This study was monitored for trial and data compliance by an independent certified monitor and registered under ClinicalTrials.gov number NCT03611517.

RESULTS

Between Aug 7, 2018, and Dec 31, 2021, 229 women were enrolled and randomly assigned to the nurse-led sexual rehabilitation intervention (n=112, 49%) or to care-as-usual (n=117, 51%) (see Figure 1). 36 Women (16%) discontinued participation before the 12-month assessment. Drop-out was significantly lower in the intervention group (n=13, 12%) than the care-as-usual group (n=23, 20%) ($p<0.001$). Follow-up and/or questionnaire data of 39 women (17%); were not available at one or more timepoints during the 12-month follow-up period: 12 (11%) in the intervention group; 27 (23%) in the care-as-usual group).

Patient, disease and treatment characteristics were well balanced between the two groups (see Table 2). Most women were treated with primary or postoperative external beam radiotherapy combined with brachytherapy (80 (71%) in the intervention group; 82 (70%) in the care-as-usual group) for cervical cancer (98 (87.5%) for the intervention group; 104 (89%) for the care-as-usual group), and had a partner (88 (79%) for the intervention group; 90 (77%) for the care-as-usual group); with mostly male partners (86 (98%) for the intervention group; 90 (100%) for the care-as usual group). Approximately 70% of the women under the age of 50 with cervical cancer received hormonal replacement therapy during follow-up.

Women in the intervention group had on average 4.4 (SD=1.1) intervention sessions, lasting on average 31 minutes (SD=14.6) per session. Most sessions were face-to-face: 102 (94%), 49 (56%), 80 (77%), 68 (69%), 65 (71%) for 1, 2, 3, 6 and 12-months after radiotherapy, respectively. The participation of partners declined over time: among the 88 women in the intervention group with a partner, 40 partners (45.5%) participated at the 1-month session, 31 (35%) at 3-months, 21 (24%) at 6-months, and 14 (17%) at 12-months after radiotherapy. Twenty partners of the 74 partnered women in each arm in the radiotherapy with brachytherapy group (27%) participated in the 2-month session focusing on dilator use. Random checks of protocol adherence and competence assessment indicated a 90% adherence and competence rate. There were no sexual rehabilitation or dilator use related serious adverse events.

Table 2 Patient, disease and treatment characteristics

		Intervention group n = 112 (48.9%)	Care as Usual group n = 117 (51.1%)
	Patient characteristics		
Age	Median in years (±IQR)	42 (17)	41 (19)
Partner	Yes	88 (78.6%)	90 (76.9%)
	Male	86 (97.7%)	90 (100%)
	Female	2 (2.3%)	0
	No	24 (21.4%)	27 (23.1%)
Highest completed level of education	Primary education	7 (6.3%)	6 (5.1%)
	Secondary education	50 (44.6%)	54 (46.2%)
	Higher education	54 (48.2%)	56 (47.9%)
	Missing	1 (0.9%)	1 (0.9%)
Menopausal status before diagnosis	Premenopausal	75 (67.0%)	75 (64.1%)
	Perimenopausal	10 (8.9%)	3 (2.6%)
	Postmenopausal	23 (20.5%)	33 (28.2%)
	Unknown	4 (3.6%)	6 (5.1%)
Vaginal delivery	Yes	68 (60.7%)	69 (59.0%)
	No	40 (35.7%)	43 (36.8%)
	Unknown	2 (1.8%)	5 (4.3%)
	Missing	2 (1.8%)	0
Body Mass Index	Underweight (<18.5)	5 (4.5%)	5 (4.3%)
	Healthy weight (18 .8-24 .9)	59 (52.7%)	44 (37.6%)
	Overweight (25-19 .9)	20 (17.9%)	40 (34.2%)
	Obese (>30)	27 (24.1%)	25 (21.4%)
	Missing	1 (0.9%)	3 (2.6%)
Current smoker	Yes	18 (16.1%)	14 (12.0%)
	No	94 (83.9%)	102 (87.2%)
	Unknown	0	1 (0.9%)
World Health Organization performance score	0	85 (75.9%)	89 (76.1%)
	1	24 (21.4%)	25 (21.4%)
	2	2 (1.8%)	3 (2.6%)
	Unknown	1 (0.9%)	0
	Disease characteristics		
Type of carcinoma	Cervical carcinoma	98 (87.5%)	104 (88.9%)
	Endometrial carcinoma	7 (6.3%)	8 (6.8%)
	Vaginal carcinoma	7 (6.3%)	5 (4.3%)
Histological type	Cervical		
	• Squamous cell	80 (81.6%)	85 (81.7%)
	• Other	18 (18.4%)	19 (18.3%)
	Endometrium		
	• Endometrioid carcinoma	5 (71.4%)	5 (62.5%)
	• Serous carcinoma	0	1 (12.5%)
	• Mixed or other	2 (28.6%)	2 (25.0%)
	Vagina		
	• Squamous cell	6 (85.7%)	4 (80.0%)
	• Other	1 (14.3%)	1 (20.0%)

Table 2 *Continued*

		Intervention group n = 112 (48.9%)	Care as Usual group n = 117 (51.1%)
FIGO stage (2009)	Cervical		
	• IB	29 (29.6%)	32 (30.8%)
	• IIA/B	52 (53.1%)	56 (53.8%)
	• IIIA/B	11 (11.2%)	11 (10.6%)
	• IVA	1 (1.0%)	1 (1.0%)
	• Not applicable (if recurrence)	5 (5.1%)	4 (3.8%)
	Endometrium		
	• IA/B	3 (42.9%)	2 (25.0%)
	• II	1 (14.3%)	3 (37.5%)
	• IIIA-C	3 (42.9%)	3 (37.5%)
	Vagina		
	• I	4 (51.7%)	2 (40.0%)
	• II	3 (42.9%)	1 (20.0%)
	• III	0	0
	• IVA	0	2 (40.0%)
Lymph node metastases	Yes	59 (52.7%)	68 (58.1%)
	No	53 (47.3%)	49 (41.9%)
	Treatment characteristics		
Treatment centre	Amsterdam Medical Center	16 (14.3%)	15 (12.8%)
	Catharina hospital	13 (11.6%)	12 (10.3%)
	Erasmus Medical Center	24 (21.4%)	26 (22.2%)
	Leiden University Medical Center	23 (20.5%)	22 (18.8%)
	Maastro	6 (5.4%)	10 (8.5%)
	Netherlands Cancer Institute	3 (2.7%)	2 (1.7%)
	Radboud University Medical Center	11 (9.8%)	13 (11.1%)
	Radiotherapiegroep	2 (1.8%)	3 (2.6%)
	University Medical Center Groningen	5 (4.5%)	4 (3.4%)
	University Medical Center Utrecht	9 (8.0%)	10 (8.5%)
Chemotherapy (concurrent)	Yes	90 (80.4%)	87 (74.4%)
	No	22 (19.6%)	30 (25.6%)
Hyperthermia[#]	Yes	4 (3.8%)	15 (13.8%)
	No	101 (96.2%)	94 (86.2%)
Type of Radiotherapy	Primary EBRT+BT	80 (71.4%)	82 (70.1%)
	Postoperative EBRT+BT	16 (14.3%)	15 (12.8%)
	External Beam Radiotherapy only	14 (12.5%)*	19 (16.2%)
	EBRT with EBRT boost	2 (1.8%)[x]	1 (0.9%)
Target area External Beam Radiotherapy	Pelvic region	84 (75.0%)	89 (76.1%)
	Pelvic and para-aortal regions	22 (19.6%)	22 (18.8%)
	Pelvic and inguinal regions	6 (5.4%)	4 (3.4%)
	Pelvic, para-aortal, and inguinal regions	0	2 (1.7%)
External Beam Radiotherapy total dose	Median dose in Gy (±IQR)	45 (0)	45 (0)
Brachytherapy	Yes	96 (85.7%)	97 (82.9%)
	No	16 (14.3%)	20 (17.1%)

Table 2 *Continued*

		Intervention group n = 112 (48.9%)	**Care as Usual group n = 117 (51.1%)**
Target area Brachytherapy	Intrauterine/vaginal Brachytherapy primary	80 (83.3%)	87 (89.7%)
	Vaginal vault boost postoperative	9 (9.4%)	8 (8.2%)
	Vaginal intracavitary and interstitial (primary or recurrence)	6 (6.3%)	2 (2.1%)
	Vaginal intracavitary primary	1 (1.0)	0

Note. EBRT+BT = External Beam Radiotherapy combined with Brachytherapy; FIGO = Fédération Internationale de Gynécologie et d'Obstétrique; IQR = interquartile range; N = total sample; n = subgroup sample.
= Only applicable for cervical and vaginal carcinoma.
* = One participant was stratified as EBRT+BT radiotherapy, however she was treated with EBRT only. Her rehabilitation trajectory was according to EBRT alone; therefore she was moved to EBRT alone.
ˣ = One participant was stratified as EBRT alone, however she received an additional EBRT boost. Her rehabilitation trajectory was according to EBRT+BT; therefore she was moved to EBRT+BT.

Regarding the primary outcome FSFI, for both study groups scores were clearly decreased after radiotherapy (compared to the retrospective baseline scores), whereafter they increased over time. At 12-months FSFI total-scores were 22.57 in the intervention group versus 21.76 in the care-as-usual group, see Figure 2I-II. As the FSFI is very sensitive to sexual activity, we also show the mean scores of sexually active women (with or without intercourse) and women not sexually active. At 12-months, 67 (71%) women in the intervention group and 60 (69%) women in the care-as-usual group were sexually active, with 65 (69%) women in the intervention group and 56 (64%) women in the care-as-usual group reporting sexual intercourse (see supplementary table S3). As shown in Figure 2I-II, FSFI scores for women not sexually active were lower than for sexually active women, while the pattern of decrease and increase over time was similar in both groups.

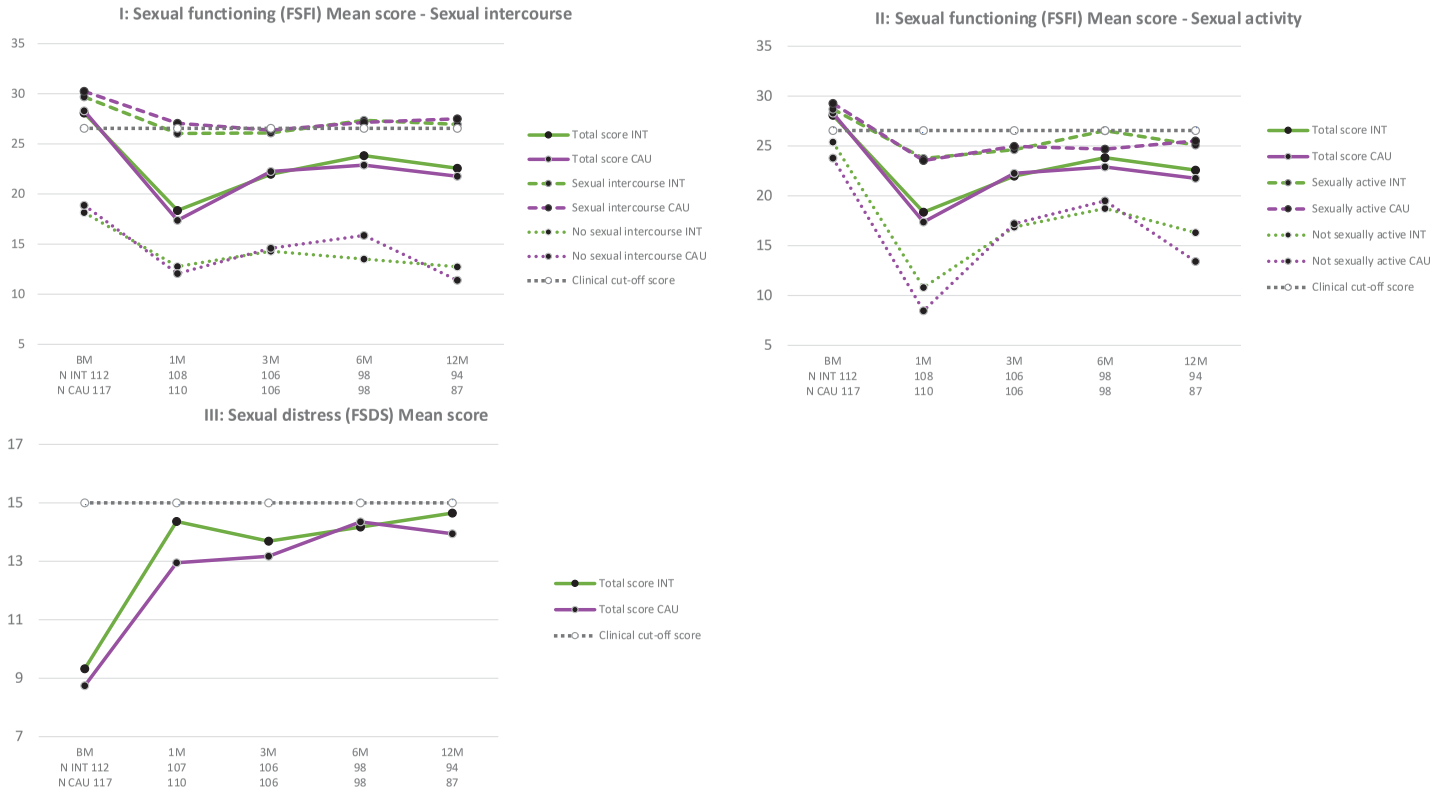


Figure 2 Patient-reported average scores on sexual functioning and sexual distress. BM = baseline measurement; CAU = Care As Usual group; FSDS = Female Sexual Distress Scale (higher score is more sexual distress); FSFI = Female Sexual Function Index (higher score is better sexual functioning); INT = Intervention group; M = months; N = observed number of women at the specific timepoint.

Regarding our secondary outcomes, compared to the situation prior to diagnosis, sexual distress as measured by the FSDS was strongly increased after radiotherapy, whereafter it remained elevated over time (see Figure 2-III). Almost half of the women reported sexual distress to a clinical degree at 12-months after radiotherapy in both study groups (42 (45%) women in the intervention group versus 40 (46%) women in the care-as-usual group, see supplementary table S6).

Figure 3 I-III shows that the majority of the women in both groups had no physician-reported vaginal stenosis, dryness, and dyspareunia during follow-up, followed by grade 1 (not interfering with sexual functioning). Grade 1 vaginal stenosis was seen in 8 (7.5%, intervention group) and 4 (3%, care-as-usual group) women at baseline (before radiotherapy), gradually increasing to 21 (24%) women in the intervention group and 20 (23%) women in the care-as-usual group at 12-months after radiotherapy. Grade 1 vaginal dryness was reported in 2 (2%, intervention group) and 4 (4%, care-as-usual group) women before radiotherapy, increasing to 18 (21%) and 26 (32%) women, respectively, at 12-months after radiotherapy. Grade 1 dyspareunia was assessed in 3 (4%, intervention group) and 10 (12%, care-as-usual group) women before radiotherapy, increasing to 24 (29%) and 14 (20%) women, respectively, at 12-months after radiotherapy. There was no clear increase or decrease in patient-reported feelings of vaginal shortness, dryness and pain during intercourse in the follow-up period (Figure 3 IV-VI), with most sexually active women reporting 'none' or 'a little' (respectively 61 (87%), 55 (78.5%), and 64 (91.5%) in the intervention group and 54 (87%), 54 (87%), and 58 (93.5%) in the care-as-usual group at 12-months after radiotherapy). At 12-months, more substantial ('quite a bit' or 'very much') feelings of vaginal shortness, dryness and pain during intercourse were reported by 9 (13%), 15 (21%), and 6 (9%) sexually active women in the intervention group versus 8 (13%), 8 (13%), and 4 (6.5%) sexually active women in the care-as-usual group, respectively. See supplementary figures S4 and S5 for additional physician and patient-reported outcomes on vaginal functioning.

Figure 3 Physician-reported clinical measurements and patient-reported vaginal functioning problems (of sexually active women in the past four weeks) on single item level over time. The proportion of women is shown in percentages. BM = baseline measurement; CTCAE = Common Terminology Criteria for Adverse Events; EORTC QLQ-CX24 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Gynaecological Cancer Module; M = months; N = number of women at risk at the specific timepoint; n = number of sexually active women at risk at the specific timepoint according to EORTC QLQ-CX24 item 19; O = observed number of women at the specific timepoint.

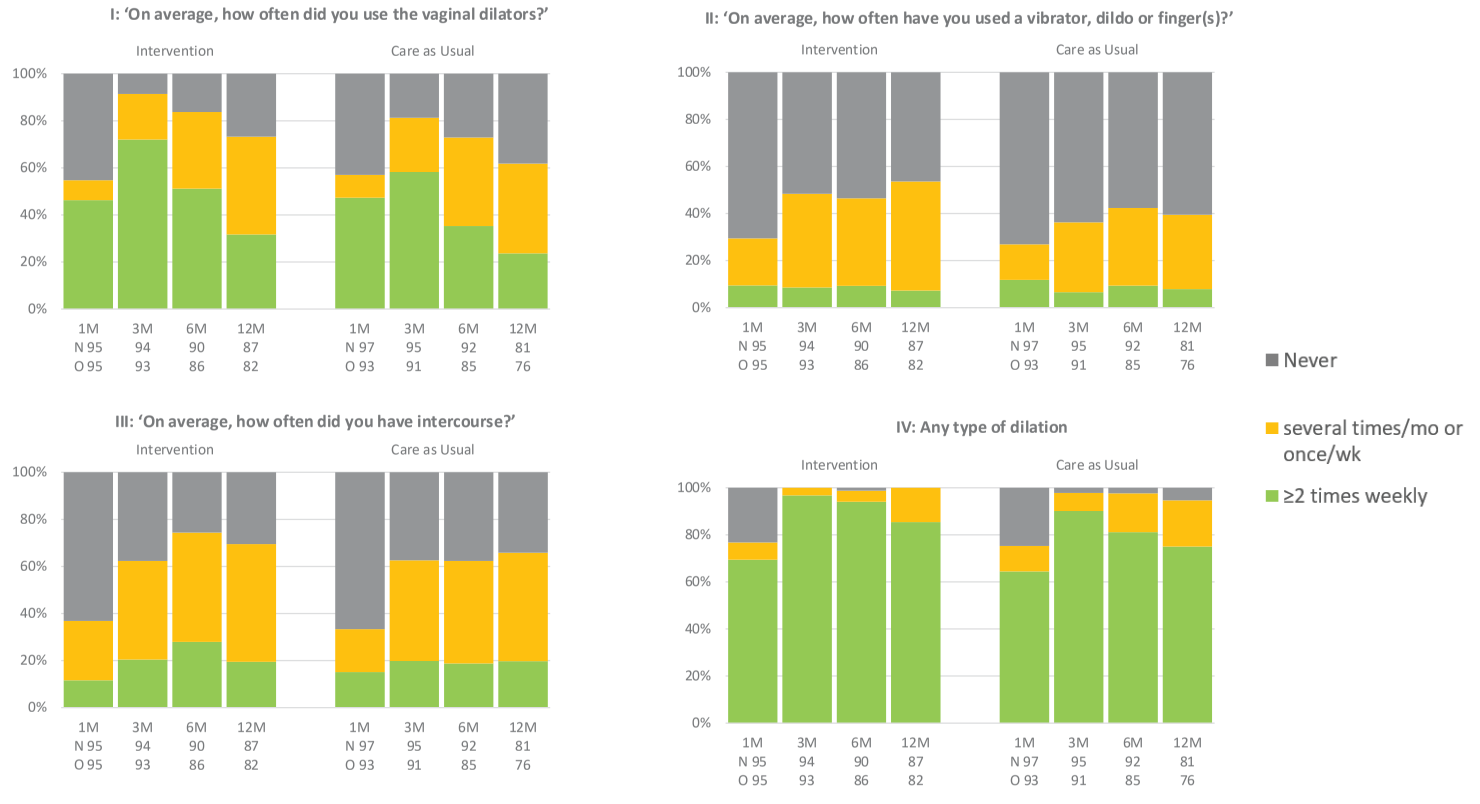


Figure 4 Patient-reported dilation in the past four weeks over time. The proportion of women is shown in percentages. M = months; mo = month, N = number of women at risk who received dilators; O = observed number of women at the specific timepoint; wk = week.

Figure 4 shows the patient-reported dilation by arm for women in the external beam radiotherapy combined with brachytherapy group. Any type of dilation used at least two times per week, including dilators, vibrators, dildos, fingers or intercourse combined, that was employed by women who received brachytherapy, was reported by 66 (69.5%) women in the intervention group and 60 (64.5%) women in the care-as-usual group at 1-month after radiotherapy, increasing to 90 (97%) women and 82 (90%) women at 3-months after radiotherapy, respectively (Figure 4-IV). Any type of dilation ≥2 times per week slightly decreased to 70 (85%) women in the intervention group, and 57 (75%) women in the care-as-usual group at 12-months after radiotherapy.

Likelihood ratio tests indicated no significant improvement in model fit when including the treatment group ($p>0.05$). No differences in FSFI total scores were found between the groups at any timepoint ($p=0.37$). This suggests that the sexual rehabilitation intervention had no significant impact on better sexual functioning compared to the care-as-usual group. This result applied to most (95%) of the other outcomes (for more details, see supplementary table S3).

DISCUSSION

The SPARC trial is to our knowledge the first robustly powered randomised trial to investigate the efficacy of a nurse-led sexual rehabilitation intervention to improve sexual recovery and compliance with dilator use for women treated with radiotherapy and brachytherapy for gynaecological cancers. Contrary to expectations based on the pilot study[14], this trial did not show a significant benefit of the nurse-led sexual rehabilitation intervention over care-as-usual in improving sexual functioning, dilator compliance, and reducing sexual distress and vaginal symptoms, one year after radiotherapy. However, compared to previous data on similar treatments, women in both study groups had relatively high rates of sexual activity, with overall 70% reporting to be sexually active at 12-months, compared to 40-50% in previous studies[1,2,4]. Most women in both study groups had no or little physician-reported vaginal stenosis, with 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. Also, any dilation ≥2 times weekly, including dilators, vibrators, dildos, fingers or intercourse combined, was reported by 85% of the participants in the intervention group and by 75% of the participants in the care-as-usual group at 12-months, similar to the pilot study[14]. Almost half of the women in both groups continued to experience clinical-level sexual distress even at the 12-month post-radiotherapy follow-up, indicating the complexity of sexual functioning.

The lack of notable differences in outcomes between the two groups is likely explained by the fact that both healthcare professionals in gynaecological oncology and patient advocacy groups have become more aware of the importance of early sexual rehabilitation care and associated issues since the start of the trial. Since the completion of the pilot study[14], standard sexual rehabilitation care in the Netherlands already involved a one-month post-radiotherapy appointment with a physician or nurse. During this appointment, women received comprehensive verbal and written information on sexual rehabilitation. Additionally, a vaginal dilator set with lubrication gel was provided free of charge to women who had undergone pelvic radiotherapy with brachytherapy, along with explicit guidance on use, both within and outside of trial participation. The comprehensive training of the nurses conducting the intervention in the SPARC trial led to further in-depth knowledge, and to increased skills in informing and coaching and addressing specific personal issues and questions for these women across all centres, including in most centres those randomised to the care-as-usual group. In addition, during the study, the Dutch patient advocacy group for women with gynaecological cancers (Olijf) developed a specialized patient website focused on sexual rehabilitation[23]. The website's widespread visibility and accessible information on sexuality and post-treatment rehabilitation were shared with all trial participants, fostering informal discussions among patients in online forums and with caregivers, both at the treatment centres and beyond.

To gain a more comprehensive understanding of the coaching and information of the women randomised to the care-as-usual group, we incorporated post-hoc questionnaires for the centres about their standard care. The responses revealed that six out of ten centres had implemented additional improvements to standard sexual rehabilitation care during the study period, and that half of the centres had arranged at least one additional care pathway appointment within the first year after radiotherapy, with a specific focus on sexuality. Moreover, all centres ensured that sexuality remained a standard topic in all follow-up appointments with physicians. As the sexual rehabilitation sessions with the nurse were directly scheduled after these appointments, sexuality was discussed at the same timepoints in both study groups.

Women with cervical cancer constituted the large majority (88%) of the current study population, making our study outcomes particularly relevant for these relatively young women treated with intensive combined chemoradiotherapy and brachytherapy. The trial's guidelines on sexual rehabilitation align with recent guidelines that advocate for heightened attention to post-radiotherapy sexual functioning in gynaecological cancer patients, including those treated with pelvic radiotherapy alone, albeit with more emphasis on rehabilitation after treatment in general and less on vaginal dilation[24,25]. Considering that nurses can devote more time to patient interaction, are often easily

accessible for patients, and can integrate their role in information and counselling in other clinical tasks, their role would be a cost-effective strategy for dedicated sexual rehabilitation. The cost-effectiveness of the nurse-led intervention versus care-as-usual is topic of subsequent analysis.

This trial has several notable strengths, including the well-powered randomised trial design, 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, and the invitation to the women's partners to join the intervention sessions. This study also has some limitations. First, as it turned out, the improvements in standard sexual rehabilitation after completion of radiation therapy may have unintentionally impacted on care of the care-as-usual group. Despite instructions to physicians and nurses to manage both study groups differently, their involvement with both study groups may have resulted similar initial post-radiotherapy psychosexual care. This well-known problem of contamination within individually randomized intervention studies could have been avoided by cluster randomization (i.e., on centre level instead of patient level). However, this method also introduces other potential threats to internal validity, as the number of centres in our study is limited and only a part of the centres could be randomized (n = 8, as a consequence of the training that was already completed in two centres for the pilot study)[14]. Because of the specific variation in the patient population, radiotherapy treatment procedures and follow-up procedures across centres, we decided to randomize on patient level. Furthermore, the FSFI which is widely employed to evaluate sexual functioning in female cancer survivors, could yield biased results for sexually inactive women due to lack of a partner, relationship quality, or reasons unrelated to cancer treatment effects[17,26]. To mitigate this, we randomised participants with stratification based on partner status, and included the response option 'not applicable, no partner' for items concerning the partner relationship, thereby minimising potential imbalance in the study outcomes. It is also possible that sexual functioning may further improve on the longer term. To investigate potential further recovery and to assess if the high rates of sexual activity will be sustained over time, a long-term evaluation at 24 months after radiotherapy was added per protocol amendment and results will be available next year. Finally, it could be argued that this study attracted relatively young and motivated participants, and that the improvement in vaginal and sexual functioning in both study groups was due to recovery over time. However, prospective studies involving cohorts of women treated with radio(chemo)therapy and brachytherapy for advanced or recurrent cervical cancer, without any standard sexual rehabilitation care, reported clearly higher prevalence rates of feelings of vaginal shortness, dryness and pain during sexual activity, vaginal stenosis and lower compliance with dilator use[4,7,8,27,28].

The prospective EMBRACE vaginal morbidity substudy, which did recommended sexual rehabilitation counselling after treatment, along with clear instructions on dilator use, demonstrated similar outcomes to our study regarding stenosis (physician-reported), vaginal shortness, dryness, and dyspareunia (patient-reported)[29]. Half of sexually active women reported feelings of vaginal shortness, dryness, and intercourse-related pain, which was also the case in our study cohort, although in vast majority rated as 'a little'. However, in the EMBRACE vaginal morbidity substudy cohort 54% reported to be sexually active at 12 months, while this was approximately 70% in the SPARC trial, possibly reflecting the effects of the increased patient education and awareness on early sexual rehabilitation. Regarding vaginal stenosis, either no or only mild stenosis was found at 12 months in both study cohorts, probably resulting from the improved radiotherapy and brachytherapy techniques causing less severe vaginal effects than in historical cohorts[30] along with more frequent vaginal dilation reported by the participants. In the SPARC trial, 85% (intervention) versus 75% (care-as-usual) of women who received brachytherapy, reported using any form of dilation at least twice a week at 12 months, indicating high compliance.

The results of the SPARC trial highlight the improved sexual rehabilitation care for women undergoing intensive radio(chemo)therapy and brachytherapy in the Netherlands, both before and during the study period, emphasizing the importance of awareness, education, and comprehensive care. This may have resulted in comparable sexual rehabilitation for both study groups. We therefore regard this care-as-usual approach as best practice to improve sexuality and thus quality-of-life after gynaecological cancer treatment. This approach encompasses thorough patient information, as well as a sexual rehabilitation appointment with a specifically trained dedicated nurse at one-month post-radiotherapy, including explicit guidance on dilator use and coaching on resuming sexual activities for women who underwent radiotherapy combined with brachytherapy, and dedicated follow-up regarding sexual functioning and dilator use over the first year after completion of treatment.

SUPPLEMENTARY MATERIAL

Table S1 Participating centres including study teams

Centre	Principle Investigator (and Associated Investigators)	Nurses	Supervisors
Amsterdam Medical Center	Henrike Westerveld	Wilma van der Ham-Paalman Sandra Diergaarde Wendy Lesterhuis	Ellen Laan† Hanneke Termeer
Catharina Hospital	Jeltsje Cnossen Hetty van den Berg	Noor Vincent Ivonne Oomen	Rian Brus Simone Speelman
Erasmus Medical Center	Jan Willem Mens Helena van Doorn Remi Nout	Claudia Mangelaars Karin Dupree Nicoline Schuur – van 't Hof Sabine Blom Christel de Jager-Blom	Hanneke Bolt
Leiden University Medical Center	Carien Creutzberg Cor de Kroon Laura Velema	Corine de Jong Mirjam Laman	Charlotte Tuijnman-Raasveld Ellen de Groot
Maastro	Ludy Lutgens	Moniek Kamps Charlotte Penders	Reinhilde Melles
Netherlands Cancer Institute	Marlies Nowee	Kirsten de Greef Erin Gardebroek-de Boer	Ilaniek Zantingh
Radboud University Medical Center	An Snyers	Annemieke Janssens Lotte Knapen	Marianne Vergeer
Radiotherapiegroep	Dorien Haverkort	Janine de Neeff Truus Kroeze	Irma Bosman
University Medical Center Groningen	Jannet Beukema	Bianca Kramer-Medema Nina van Linde	Ria Bosgraaf
University Medical Center Utrecht	Ina Jurgenliemk-Schulz	Nicole van den Berg Catharina van der Linden-Hunziker Ankie Krol Veraar	Ilaniek Zantingh

Table S2 Additional patient and physician-reported outcomes

Variable	Questionnaire	Clinical cut-off score
Sexual functioning	FSFI	≤26.55
Sexual desire	FSFI	NA
Sexual arousal	FSFI	NA
Vaginal lubrication	FSFI	NA
Orgasmic function	FSFI	NA
Sexual satisfaction	FSFI	NA
Sexual pain	FSFI	NA
Sexual distress	FSDS	≥15
Symptom experience	EORTC QLQ-CX24	NA
Body image	EORTC QLQ-CX24/QLQ-EN24	NA
Sexual/vaginal functioning (dryness, shortness, tightness, pain during intercourse)	EORTC QLQ-CX24/QLQ-EN24	NA
Vaginal tightness	EORTC QLQ-CX24/QLQ-EN24	NA
Lymphedema	EORTC QLQ-CX24/QLQ-EN24	NA
Peripheral neuropathy	EORTC QLQ-CX24	NA
Menopausal symptoms	EORTC QLQ-CX24	NA
Sexual worry	EORTC QLQ-CX24	NA
Sexual activity	EORTC QLQ-CX24/QLQ-EN24	NA
Sexual enjoyment	EORTC QLQ-CX24/QLQ-EN24	NA
Urological symptoms	EORTC QLQ-EN24	NA
Gastrointestinal symptoms	EORTC QLQ-EN24/QLQ-EN24	NA
Sexual interest	EORTC QLQ-EN24	NA
Fear of non-penetration sexual activity	FSQ	NA
Fear of coitus/vaginal penetration	FSQ	NA
Relationship dissatisfaction	MMQ	≥20
Psychological distress	HADS	≥14
Depression	HADS	≥7
Anxiety	HADS	≥7
Physical function	EORTC QLQ-C30	NA
Role function	EORTC QLQ-C30	NA
Emotional function	EORTC QLQ-C30	NA
Cognitive function	EORTC QLQ-C30	NA
Social function	EORTC QLQ-C30	NA
Fatigue	EORTC QLQ-C30	NA
Nausea/vomiting	EORTC QLQ-C30	NA
Pain	EORTC QLQ-C30	NA
Dyspnoea	EORTC QLQ-C30	NA

Table S2 *Continued*

Variable	Questionnaire	Clinical cut-off score
Sleep disturbance	EORTC QLQ-C30	NA
Appetite loss	EORTC QLQ-C30	NA
Constipation	EORTC QLQ-C30	NA
Diarrhoea	EORTC QLQ-C30	NA
Financial impact	EORTC QLQ-C30	NA
Global QoL	EORTC QLQ-C30	NA
Treatment related stress – intrusion	IES	NA
Treatment related stress – avoidance	IES	NA
Cost-effectiveness		
Sexual health care use	-	NA
Quality of life	EQ-5D-5L	NA
Credibility of analogue therapy rationales	CEQ	NA
Physician-reported Bleeding	CTCAE	≥grade 3 = severe
Physician-reported Mucositis	CTCAE	≥grade 3 = severe
Physician-reported Discharge	CTCAE	≥grade 3 = severe
Physician-reported Fibrosis	CTCAE	≥grade 3 = severe
Physician-reported Atrophy/ telangiectasia	CTCAE	≥grade 3 = severe
Physician-reported Pain	CTCAE	≥grade 3 = severe
Physician-reported Dyspareunia	CTCAE	≥grade 3 = severe
Physician-reported vaginal estradiol/ estriol	CRF	NA
Physician-reported hormone replacement therapy	CRF	NA

Note. CEQ = Credibility/Expectancy Questionnaire; CRF = Case Report Form; CTCAE = Common Terminology Criteria for Adverse Events; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-CX24 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Gynaecological Cancer Module; EORTC QLQ-EN24 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Endometrial Cancer Module; EQ-5D-5L = EuroQol 5D-5L; FSDS = Female Sexual Distress Scale; FSFI = Female Sexual Function Index; FSQ = Fear of Sexuality Questionnaire; HADS = Hospital Anxiety and Depression Scale; IES = Impact of Event Scale; MMQ = Maudsley Marital Questionnaire; NA = not applicable

Table S3 Total and subscale mean values at retrospective baseline (for FSFI and FSDS) 1, 3, 6 and 12 months after radiotherapy and GLMM likelihood ratio test outcomes of primary and secondary continuous outcome measures

	Assessment															GLMM outcomes	
	T1			T2			T3			T4			T5				
Outcome measure (range score)	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**LRT(df)**	**P (overall model)**
Primary																	
Sexual functioning																	
FSFI total (2-36)																10.88(10)	0.37
Intervention	112	28.08	6.48	108	18.36	10.27	106	21.98	9.45	98	23.82	8.83	94	22.57	9.30		
Care-as-usual	117	28.30	7.07	110	17.38	10.64	106	22.26	9.10	98	22.89	8.74	87	21.76	10.42		
Sexual desire																	
FSFI sexual desire (1.2-6)																7.59(10)	0.67
Intervention	112	3.81	0.99	108	2.92	1.25	106	3.05	1.27	99	3.31	1.30	94	2.99	1.32		
Care-as-usual	117	3.76	0.99	110	2.80	1.24	106	2.99	1.23	98	3.04	1.18	88	3.08	1.34		
Sexual arousal																	
FSFI arousal (0-6)																13.16(10)	0.21
Intervention	112	4.75	1.40	108	2.93	2.09	106	3.63	1.95	98	3.90	1.89	94	3.52	1.98		
Care-as-usual	117	4.81	1.35	110	2.72	2.31	106	3.67	1.90	98	3.75	1.91	88	3.69	2.07		
Vaginal lubrication																	
FSFI lubrication (0-6)																4.06(10)	0.95
Intervention	112	5.14	1.49	108	3.10	2.43	106	3.76	2.19	98	4.15	2.11	94	3.88	2.23		
Care-as-usual	117	5.24	1.52	110	2.89	2.52	106	3.93	2.14	98	4.17	2.13	88	3.80	2.40		
Orgasmic function																	
FSFI orgasm (0-6)																6.52(10)	0.77
Intervention	112	4.80	1.32	108	3.15	2.35	106	3.88	2.10	98	4.05	1.91	94	3.95	1.98		
Care-as-usual	117	4.97	1.54	110	2.98	2.49	106	4.03	2.11	98	4.19	2.11	88	3.84	2.32		
Sexual satisfaction																	
FSFI satisfaction (0-6)																1.49(10)	0.99
Intervention	112	4.88	1.19	108	3.77	1.54	106	4.11	1.59	98	4.40	1.35	94	4.18	1.53		
Care-as-usual	117	4.77	1.36	110	3.62	1.58	106	4.11	1.52	98	4.20	1.49	87	4.06	1.54		

Table S3 *Continued*

	Assessment															GLMM outcomes	
	T1			T2			T3			T4			T5				
Outcome measure (range score)	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**LRT(df)**	**P (overall model)**
Sexual pain																	
FSFI pain (0-6)																10.75(10)	0.37
Intervention	112	4.70	1.82	108	2.49	2.52	106	3.54	2.28	98	4.02	2.08	94	4.03	2.25		
Care-as-usual	117	4.75	1.89	110	2.37	2.45	106	3.54	2.28	98	3.54	2.18	87	3.38	2.52		
Sexual activity																0.54(5)	0.99
Intervention																	
Never	20	18.0	..	45	41.7	..	36	34.0	..	34	34.7	..	27	28.7	..		
Several times per month	33	29.7	..	26	24.1	..	32	30.2	..	29	29.6	..	36	38.3	..		
1 time/week	20	18.0	..	17	15.7	..	17	16.0	..	16	16.3	..	15	16.0	..		
≥2 times/week	38	34.2	..	20	18.5	..	21	19.8	..	19	19.4	..	16	17.0	..		
Care-as-usual																	
Never	22	19.0	..	45	40.9	..	37	34.9	..	34	34.7	..	27	31.0	..		
Several times per month	37	31.9	..	28	25.5	..	34	32.1	..	37	37.8	..	37	42.5	..		
1 time/week	28	24.1	..	11	10.0	..	16	15.1	..	11	11.2	..	11	12.6	..		
≥2 times/week	29	25.0	..	26	23.6	..	19	17.9	..	16	16.3	..	12	13.8	..		
Sexual Intercourse																3.36(3)	0.34
Intervention																	
Never	15	13.6	..	62	57.9	..	37	34.9	..	25	25.5	..	29	30.9	..		
Several times per month	33	30.0	..	19	17.8	..	24	22.6	..	28	28.6	..	22	23.4	..		
1 time/week	18	16.4	..	14	13.1	..	22	20.8	..	20	20.4	..	26	27.7	..		
≥2 times/week	44	40.0	..	12	11.2	..	23	21.7	..	25	25.5	..	17	18.1	..		
Care-as-usual																	
Never	20	17.1	..	71	64.5	..	37	34.9	..	37	37.8	..	31	35.6	..		
Several times per month	37	31.6	..	13	11.8	..	32	30.2	..	26	26.5	..	25	28.7	..		
1 time/week	25	21.4	..	7	6.4	..	17	16.0	..	13	13.3	..	13	14.9	..		
≥2 times/week	35	29.9	..	19	17.3	..	20	18.9	..	22	22.4	..	18	20.7	..		

Table S3 *Continued*

	Assessment															GLMM outcomes	
	T1			T2			T3			T4			T5				
Outcome measure (range score)	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**LRT(df)**	**P (overall model)**
Secondary																	
Sexual Distress																	
FSDS (0-48)																7.57(10)	0.67
Intervention	112	9.32	9.40	107	14.37	10.49	106	13.69	10.55	98	14.17	10.31	94	14.65	12.07		
Care-as-usual	117	8.74	9.36	110	12.95	10.01	106	13.17	9.92	98	14.35	11.36	87	13.94	10.97		
Vaginal dilation																5.25(4)	0.24
Dilator use																	
Intervention																	
Never	..	..	..	43	45.3	..	8	8.6	..	14	16.3	..	22	26.8	..		
Several times per month	..	..	..	3	3.2	..	6	6.5	..	8	9.3	..	19	23.2	..		
1 time/week	..	..	..	5	5.3	..	12	12.9	..	20	23.3	..	15	18.3	..		
2 times/week	..	..	..	10	10.5	..	27	29.0	..	16	18.6	..	17	20.7	..		
3 times/week	..	..	..	29	30.5	..	38	40.9	..	25	29.1	..	9	11.0	..		
4-6 times/week	..	..	..	5	5.3	..	2	2.2	..	3	3.5	..	0	0	..		
Daily	..	..	..	0	0	..	0	0	..	0	0	..	0	0	..		
Care-as-usual																	
Never	..	..	..	40	43.0	..	17	18.7	..	23	27.1	..	29	38.2	..		
Several times per month	..	..	..	4	4.3	..	12	13.2	..	13	15.3	..	23	30.3	..		
1 time/week	..	..	..	5	5.4	..	9	9.9	..	19	22.4	..	6	7.9	..		
2 times/week	..	..	..	16	17.2	..	21	23.1	..	15	17.6	..	10	13.2	..		
3 times/week	..	..	..	25	26.9	..	29	31.9	..	13	15.3	..	6	7.9	..		
4-6 times/week	..	..	..	1	1.1	..	3	3.3	..	1	1.2	..	2	2.6	..		
Daily	..	..	..	2	2.2	..	0	0	..	1	1.2	..	0	0	..		

Table S3 *Continued*

	Assessment															GLMM outcomes	
	T1			T2			T3			T4			T5				
Outcome measure (range score)	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**LRT(df)**	**P (overall model)**
Vaginal dilation																1.90(4)	0.75
Vibrator/dildo/fingers																	
Intervention																	
Never	..	..	..	67	70.5	..	48	51.6	..	46	53.5	..	38	46.3	..		
Several times per month	..	..	..	12	12.6	..	25	26.9	..	21	24.4	..	28	34.1	..		
1 time/week	..	..	..	7	7.4	..	12	12.9	..	11	12.8	..	10	12.2	..		
2 times/week	..	..	..	4	4.2	..	6	6.5	..	6	7.0	..	2	2.4	..		
3 times/week	..	..	..	4	4.2	..	2	2.2	..	2	2.3	..	4	4.9	..		
4-6 times/week	..	..	..	1	1.1	..	0	0	..	0	0	..	0	0	..		
Daily	..	..	..	0	0	..	0	0	..	0	0	..	0	0	..		
Care-as-usual																	
Never	..	..	..	68	73.1	..	58	63.7	..	49	57.6	..	46	60.5	..		
Several times per month	..	..	..	12	12.9	..	21	23.1	..	23	27.1	..	19	25.0	..		
1 time/week	..	..	..	2	2.2	..	6	6.6	..	5	5.9	..	5	6.6	..		
2 times/week	..	..	..	7	7.5	..	2	2.2	..	2	2.4	..	5	6.6	..		
3 times/week	..	..	..	2	2.2	..	2	2.2	..	3	3.5	..	1	1.3	..		
4-6 times/week	..	..	..	1	1.1	..	1	1.1	..	2	2.4	..	0	0	..		
Daily	..	..	..	1	1.1	..	1	1.1	..	1	1.2	..	0	0	..		
Vaginal dilation																2.33(4)	0.68
Intercourse																	
Intervention																	
Never	..	..	..	60	63.2	..	35	37.6	..	22	25.6	..	25	30.5	..		
Several times per month	..	..	..	10	10.5	..	18	19.4	..	24	27.9	..	18	22.0	..		
1 time/week	..	..	..	14	14.7	..	21	22.6	..	16	18.6	..	23	28.0	..		
2 times/week	..	..	..	9	9.5	..	13	14.0	..	16	18.6	..	11	13.4	..		
3 times/week	..	..	..	2	2.1	..	5	5.4	..	6	7.0	..	3	3.7	..		
4-6 times/week	..	..	..	0	0	..	0	0	..	1	1.2	..	2	2.4	..		
Daily	..	..	..	0	0	..	1	1.1	..	1	1.2	..	0	0	..		

Table S3 *Continued*

	Assessment															GLMM outcomes	
	T1			T2			T3			T4			T5				
Outcome measure (range score)	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**LRT(df)**	**P (overall model)**
Care-as-usual																	
Never	..	..	..	62	66.7	..	34	37.4	..	32	37.6	..	26	34.2	..		
Several times per month	..	..	..	12	12.9	..	27	29.7	..	28	32.9	..	23	30.3	..		
1 time/week	..	..	..	5	5.4	..	12	13.2	..	9	10.6	..	12	15.8	..		
2 times/week	..	..	..	6	6.5	..	9	9.9	..	10	11.8	..	8	10.5	..		
3 times/week	..	..	..	5	5.4	..	6	6.6	..	4	4.7	..	3	3.9	..		
4-6 times/week	..	..	..	2	2.2	..	2	2.2	..	1	1.2	..	3	3.9	..		
Daily	..	..	..	1	1.1	..	1	1.1	..	1	1.2	..	1	1.3	..		
Any type of vaginal dilation ≥2 times/week																1.39(4)	0.85
Intervention																	
Yes	..	..	..	66	69.5	..	90	96.8	..	81	94.2	..	70	85.4	..		
No	..	..	..	29	30.5	..	3	3.2	..	5	5.8	..	12	14.6	..		
Care-as-usual																	
Yes	..	..	..	60	64.5	..	82	90.1	..	69	81.2	..	57	75.0	..		
No	..	..	..	33	35.5	..	9	9.9	..	16	18.8	..	19	25.0	..		
Sexual functioning EORTC QLQ-CX24 (0-100)																10.64(8)	0.22
Intervention	..	..	..	52	26.44	19.65	76	22.59	20.18	77	21.43	18.75	70	18.69	19.32		
Care-as-usual	..	..	..	50	23.67	18.62	70	22.74	17.60	66	22.60	16.06	62	19.49	21.65		
Vaginal symptoms EORTC QLQ-CX24 (0-100)																3.92(8)	0.86
Intervention	..	..	..	107	16.30	14.90	106	11.43	11.83	98	11.0	12.71	94	10.99	13.19		
Care-as-usual	..	..	..	109	16.00	14.46	106	12.06	13.38	97	10.20	12.39	87	10.47	13.38		

Table S3 *Continued*

	Assessment															GLMM outcomes	
	T1			T2			T3			T4			T5				
Outcome measure (range score)	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**LRT(df)**	**P (overall model)**
Sexual/vaginal functioning EORTC QLQ-CX24																	
Vaginal dryness																0.83(8)	0.99
Intervention																	
Not at all	..	..	..	20	38.5	..	35	46.1	..	35	45.5	..	36	51.4	..		
A little	..	..	..	25	48.1	..	22	28.9	..	27	35.1	..	19	27.1	..		
Quite a bit	..	..	..	5	9.6	..	11	14.5	..	12	15.6	..	11	15.7	..		
Very much	..	..	..	2	3.8	..	8	10.5	..	3	3.9	..	4	5.7	..		
Care-as-usual																	
Not at all	..	..	..	25	50.0	..	30	42.9	..	26	39.4	..	31	50.0	..		
A little	..	..	..	14	28.0	..	33	47.1	..	31	47.0	..	23	37.1	..		
Quite a bit	..	..	..	9	18.0	..	3	4.3	..	7	10.6	..	4	6.5	..		
Very much	..	..	..	2	4.0	..	4	5.7	..	2	3.0	..	4	6.5	..		
Sexual/vaginal functioning EORTC QLQ-CX24																	
Vaginal shortness																1.18(8)	0.99
Intervention																	
Not at all	..	..	..	24	46.2	..	41	53.9	..	42	54.5	..	40	57.1	..		
A little	..	..	..	21	40.4	..	22	28.9	..	20	26.0	..	21	30.0	..		
Quite a bit	..	..	..	3	5.8	..	10	13.2	..	11	14.3	..	7	10.0	..		
Very much	..	..	..	4	7.7	..	3	3.9	..	4	5.2	..	2	2.9	..		
Care-as-usual																	
Not at all	..	..	..	23	46.0	..	35	50.0	..	29	43.9	..	34	54.8	..		
A little	..	..	..	21	42.0	..	27	38.6	..	28	42.4	..	20	32.3	..		
Quite a bit	..	..	..	4	8.0	..	8	11.4	..	8	12.1	..	4	6.5	..		
Very much	..	..	..	2	4.0	..	0	0	..	1	1.5	..	4	6.5	..		

Table S3 *Continued*

	Assessment															GLMM outcomes	
	T1			T2			T3			T4			T5				
Outcome measure (range score)	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**LRT(df)**	**P (overall model)**
Sexual/vaginal functioning EORTC QLQ-CX24																	
Vaginal tightness																3.23(8)	0.92
Intervention																	
Not at all	..	..	..	22	42.3	..	47	61.8	..	54	70.1	..	51	72.9	..		
A little	..	..	..	19	36.5	..	24	31.6	..	14	18.2	..	14	20.0	..		
Quite a bit	..	..	..	7	13.5	..	5	6.6	..	8	10.4	..	5	7.1	..		
Very much	..	..	..	4	7.7	..	0	0	..	1	1.3	..	0	0	..		
Care-as-usual																	
Not at all	..	..	..	25	50.0	..	33	47.1	..	38	57.6	..	39	62.9	..		
A little	..	..	..	22	44.0	..	28	40.0	..	20	30.3	..	16	25.8	..		
Quite a bit	..	..	..	1	2.0	..	7	10.0	..	8	12.1	..	4	6.5	..		
Very much	..	..	..	2	4.0	..	2	2.9	..	0	0	..	3	4.8	..		
Sexual/vaginal functioning EORTC QLQ-CX24																	
Pain during intercourse																1.24(8)	0.99
Intervention																	
Not at all	..	..	..	18	34.6	..	31	40.8	..	34	44.2	..	37	52.9	..		
A little	..	..	..	29	55.8	..	38	50.0	..	35	45.5	..	27	38.6	..		
Quite a bit	..	..	..	4	7.7	..	6	7.9	..	8	10.4	..	6	8.6	..		
Very much	..	..	..	1	1.9	..	1	1.3	..	0	0	..	0	0	..		
Care-as-usual																	
Not at all	..	..	..	18	36.0	..	27	38.6	..	26	39.4	..	37	59.7	..		
A little	..	..	..	28	56.0	..	38	54.3	..	35	53.0	..	21	33.9	..		
Quite a bit	..	..	..	1	2.0	..	4	5.7	..	5	7.6	..	4	6.5	..		
Very much	..	..	..	3	6.0	..	1	1.4	..	0	0	..	0	0	..		

Table S3 *Continued*

Outcome measure (range score)	Assessment															GLMM outcomes	
	T1			T2			T3			T4			T5				
	N	M/ %	SD	N	M/ %	SD	N	M/ %	SD	N	M/ %	SD	N	M/ %	SD	LRT(df)	P (overall model)
Sexual worry EORTC QLQ-CX24 (0-100)																2.99(8)	0.94
Intervention	..	..	..	107	39.25	32.96	105	26.98	28.53	98	21.43	27.60	94	22.34	29.89		
Care-as-usual	..	..	..	109	37.00	32.18	106	25.47	25.43	98	24.15	30.57	87	19.92	28.96		
Sexual activity EORTC QLQ-CX24 (0-100)																8.89(8)	0.35
Intervention	..	..	..	107	21.18	24.40	105	33.97	27.34	98	39.80	26.93	94	36.17	26.62		
Care-as-usual	..	..	..	109	22.94	29.29	106	30.82	27.87	98	30.95	27.18	87	34.87	28.26		
Sexual enjoyment EORTC QLQ-CX24 (0-100)																11.58(8)	0.17
Intervention	..	..	..	52	58.97	26.09	76	59.65	29.47	77	62.77	24.76	70	62.38	28.33		
Care-as-usual	..	..	..	50	60.67	29.11	70	62.38	27.76	66	60.10	23.55	62	63.98	27.86		
Sexual interest EORTC QLQ-EN24 (0-100)																4.2(8)	0.84
Intervention	..	..	..	107	30.84	27.36	105	34.92	27.50	98	38.78	27.78	94	34.04	29.32		
Care-as-usual	..	..	..	109	30.28	25.88	106	34.91	27.36	98	35.71	24.99	87	34.48	28.05		
Symptom experience EORTC QLQ-CX24 (0-100)																3.01(8)	0.93
Intervention	..	..	..	107	15.89	10.55	105	13.45	8.82	98	14.13	9.63	94	13.38	10.10		
Care-as-usual	..	..	..	109	16.51	10.75	106	14.47	11.12	97	13.93	10.04	87	13.27	9.97		

Table S3 *Continued*

	Assessment															GLMM outcomes	
	T1			T2			T3			T4			T5				
Outcome measure (range score)	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**LRT(df)**	**P (overall model)**
Body image EORTC QLQ-CX24 (0-100)																4.17(8)	0.84
Intervention	..	..	..	107	31.67	27.59	105	27.41	27.99	98	27.55	27.60	94	29.55	28.25		
Care-as-usual	..	..	..	109	29.46	26.47	104	28.95	26.02	98	27.89	25.04	87	26.44	24.80		
Lymphedema EORTC QLQ-CX24 (0-100)																6.16(8)	0.63
Intervention	..	..	..	107	11.22	21.45	106	11.32	21.52	98	14.97	26.70	94	13.83	23.14		
Care-as-usual	..	..	..	109	8.26	19.85	106	11.01	23.33	98	10.88	21.29	87	15.33	27.28		
Peripheral neuropathy EORTC QLQ-CX24 (0-100)																2.68(6)	0.85
Intervention	..	..	..	107	11.84	20.09	106	16.67	26.53	98	15.99	24.51	94	17.02	25.28		
Care-as-usual	..	..	..	109	10.70	19.71	106	14.78	26.46	98	14.63	25.80	87	15.33	24.80		
Menopausal symptoms EORTC QLQ-CX24 (0-100)																4.27(8)	0.83
Intervention	..	..	..	107	36.76	32.68	106	37.11	32.31	98	32.65	33.15	94	30.85	30.23		
Care-as-usual	..	..	..	109	31.19	31.84	106	30.82	33.40	98	28.91	30.13	87	23.37	28.36		
Urological symptoms EORTC QLQ-CX24 (0-100)																3.32(8)	0.91
Intervention	..	..	..	107	18.77	18.28	105	13.41	14.36	98	15.14	15.48	94	13.21	12.78		
Care-as-usual	..	..	..	109	17.74	15.92	106	15.17	16.34	98	15.05	14.88	87	14.56	14.45		

Table S3 *Continued*

	Assessment															GLMM outcomes	
	T1			T2			T3			T4			T5				
Outcome measure (range score)	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**LRT(df)**	**P (overall model)**
Gastrointestinal symptoms EORTC QLQ-CX24 (0-100)																9.28(8)	0.32
Intervention	..	..	..	107	10.67	10.60	106	12.81	13.67	98	12.50	13.18	94	12.59	13.54		
Care-as-usual	..	..	..	109	13.91	14.35	106	13.13	14.36	98	14.20	14.86	87	11.59	12.48		
Fear of sexuality - FSQ_ fear of non-penetration sexual activity (0-20)																7.19(8)	0.51
Intervention	..	..	..	107	4.33	4.10	106	3.56	3.94	98	3.58	4.39	94	4.11	4.73		
Care-as-usual	..	..	..	109	3.83	4.10	106	3.40	3.83	98	3.30	3.80	87	3.32	4.30		
Fear of sexuality - FSQ_ fear of coitus/vaginal penetration (0-12)																2.41(8)	0.97
Intervention	..	..	..	107	1.65	2.52	106	1.65	2.26	98	1.45	2.16	94	1.90	2.61		
Care-as-usual	..	..	..	109	1.39	2.32	106	1.69	2.81	98	1.43	2.28	87	1.66	2.59		
Relationship dissatisfaction MMQ_Marital scale																4.79(8)	0.78
Intervention	..	..	..	90	10.06	11.53	89	9.97	11.57	83	10.29	11.74	78	11.45	13.30		
Care-as-usual	..	..	..	84	11.76	15.35	80	10.75	12.44	72	10.08	9.58	66	10.85	11.16		
Psychological distress HADS Total (0-42)																5.87(8)	0.66
Intervention	..	..	..	107	9.95	7.30	105	9.87	7.14	98	9.46	7.33	94	8.93	7.74		
Care-as-usual	..	..	..	107	9.93	7.65	106	9.80	7.32	98	10.00	6.83	87	9.32	6.63		

Table S3 *Continued*

	Assessment															GLMM outcomes	
	T1			T2			T3			T4			T5				
Outcome measure (range score)	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**LRT(df)**	**P (overall model)**
Psychological distress HADS depression (0-21)																5.96(8)	0.65
Intervention	..	..	..	107	4.22	3.68	105	4.13	3.89	98	3.87	3.62	94	3.47	3.79		
Care-as-usual	..	..	..	107	4.36	4.03	106	4.01	3.86	98	4.21	3.64	87	3.41	3.36		
Psychological distress HADS anxiety (0-21)																7.48(8)	0.49
Intervention	..	..	..	107	5.74	4.29	105	5.73	3.89	98	5.59	4.36	94	5.38	4.48		
Care-as-usual	..	..	..	107	5.57	4.34	106	5.79	4.27	98	5.79	4.07	87	5.91	4.03		
Physical function EORTC QLQ-C30 (0-100)																8.28(8)	0.41
Intervention	..	..	..	107	82.12	16.60	105	85.91	16.39	98	88.57	13.02	94	92.27	10.81		
Care-as-usual	..	..	..	109	81.22	16.89	106	86.04	14.59	98	88.10	13.17	86	91.32	11.57		
Role function EORTC QLQ-C30 (0-100)																17.12(8)	0.03*
Intervention	..	..	..	107	66.04	30.45	106	71.23	27.65	98	72.79	29.05	94	80.50	24.15		
Care-as-usual	..	..	..	109	66.67	25.36	106	69.81	25.73	98	75.17	23.96	87	82.95	23.29		
Emotional function EORTC QLQ-C30 (0-100)																9.16(8)	0.33
Intervention	..	..	..	107	70.25	20.92	106	71.78	20.88	98	71.51	21.37	94	73.49	23.02		
Care-as-usual	..	..	..	109	66.67	23.07	106	67.37	23.60	98	67.18	23.32	87	73.85	19.70		

Table S3 *Continued*

	Assessment															GLMM outcomes	
	T1			T2			T3			T4			T5				
Outcome measure (range score)	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**LRT(df)**	**P (overall model)**
Cognitive function EORTC QLQ-C30 (0-100)																11.47(8)	0.18
Intervention	..	..	..	107	71.18	23.52	106	74.06	20.97	98	68.71	25.02	94	72.87	24.32		
Care-as-usual	..	..	..	109	68.65	24.19	106	70.44	23.15	98	72.11	25.19	87	76.05	23.80		
Social function EORTC QLQ-C30 (0-100)																9.7(8)	0.29
Intervention	..	..	..	107	67.76	27.31	106	73.74	25.09	98	76.53	24.27	94	83.51	19.48		
Care-as-usual	..	..	..	109	68.20	26.11	106	73.11	24.08	98	77.38	20.20	87	82.38	20.70		
Fatigue EORTC QLQ-C30 (0-100)																22.63(8)	0.004*
Intervention	..	..	..	107	41.85	22.41	106	36.16	23.36	98	36.40	20.54	94	30.14	23.98		
Care-as-usual	..	..	..	108	44.65	23.63	105	40.42	23.22	98	36.84	22.82	87	28.86	23.57		
Nausea/vomiting EORTC QLQ-C30 (0-100)																6.45(6)	0.38
Intervention	..	..	..	107	5.61	10.97	106	7.55	16.92	97	7.05	14.60	94	6.74	13.23		
Care-as-usual	..	..	..	109	8.26	12.75	106	5.35	14.47	98	5.61	10.42	87	4.02	8.79		
Pain EORTC QLQ-C30 (0-100)																6.34(8)	0.61
Intervention	..	..	..	107	20.09	20.57	106	19.18	21.18	97	20.96	23.97	94	16.67	22.0		
Care-as-usual	..	..	..	109	19.88	23.18	106	19.81	24.03	98	20.41	23.88	87	14.18	19.94		

Table S3 *Continued*

	Assessment															GLMM outcomes	
	T1			T2			T3			T4			T5				
Outcome measure (range score)	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**LRT(df)**	**P (overall model)**
Dyspnoea EORTC QLQ-C30 (0-100)																3.23(8)	0.92
Intervention	..	..	..	107	17.45	23.50	106	11.95	17.33	98	9.18	18.40	94	10.28	20.75		
Care-as-usual	..	..	..	109	16.82	21.58	106	14.47	18.98	98	11.22	21.38	87	7.66	15.83		
Sleep disturbance EORTC QLQ-C30 (0-100)																9.71(8)	0.29
Intervention	..	..	..	107	36.14	29.0	106	32.39	31.02	98	31.63	29.65	94	30.14	31.71		
Care-as-usual	..	..	..	109	30.89	29.64	106	28.62	30.32	98	29.59	26.17	87	27.20	27.15		
Appetite loss EORTC QLQ-C30 (0-100)																1.82(6)	0.94
Intervention	..	..	..	107	9.66	15.87	106	10.06	19.61	98	8.84	18.88	94	6.74	16.0		
Care-as-usual	..	..	..	109	13.76	22.32	106	7.86	17.55	98	7.48	16.25	87	6.13	15.69		
Constipation EORTC QLQ-C30 (0-100)																1.53(8)	0.99
Intervention	..	..	..	107	10.28	18.55	106	10.06	18.50	97	12.72	21.75	94	10.28	18.31		
Care-as-usual	..	..	..	109	10.40	22.54	106	6.60	15.55	98	11.57	24.92	87	7.28	18.63		
Diarrhoea EORTC QLQ-C30 (0-100)																3.51(8)	0.90
Intervention	..	..	..	107	13.08	19.83	106	14.78	22.58	98	15.31	23.04	94	11.35	18.65		
Care-as-usual	..	..	..	109	19.57	24.52	106	17.61	26.11	98	18.37	23.02	87	12.64	19.85		

Table S3 *Continued*

	Assessment															GLMM outcomes	
	T1			T2			T3			T4			T5				
Outcome measure (range score)	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**LRT(df)**	**P (overall model)**
Financial impact EORTC QLQ-C30 (0-100)																2.9(8)	0.94
Intervention	..	..	..	107	12.46	23.58	106	13.21	23.76	98	11.91	20.45	94	11.35	21.06		
Care-as-usual	..	..	..	109	15.60	25.49	106	11.01	22.41	98	10.20	20.54	87	14.18	25.74		
Global QoL EORTC QLQ-C30 (0-100)																7.2(8)	0.51
Intervention	..	..	..	107	64.95	16.42	106	69.18	18.59	98	69.98	16.91	94	73.49	16.71		
Care-as-usual	..	..	..	109	67.05	17.98	106	68.24	17.06	98	69.05	18.27	87	75.58	15.29		
Gynaecological cancer treatment related stress IES Total (0-75)																6.03(8)	0.64
Intervention	..	..	..	107	24.09	16.61	105	20.05	15.83	98	19.12	16.46	94	17.49	16.24		
Care-as-usual	..	..	..	107	24.24	17.33	106	21.65	16.06	98	20.95	15.93	87	18.66	16.10		

Table S3 *Continued*

	Assessment															GLMM outcomes	
	T1			T2			T3			T4			T5				
Outcome measure (range score)	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**LRT(df)**	**P (overall model)**
Physician-assessed																	
Stenosis (shortening/ tightening) CTCAE																8.83(5)	0.12
Intervention	96	90.6	..	75	83.3	..	62	70.5	..	57	64.0	..	56	63.6	..		
Grade 0	8	7.5	..	11	12.2	..	20	22.7	..	26	29.2	..	21	23.9	..		
Grade 1	1	0.9	..	4	4.4	..	5	5.7	..	2	2.2	..	10	11.4	..		
Grade 2	1	0.9	..	0	0	..	1	1.1	..	4	4.5	..	1	1.1	..		
Grade 3																	
Care-as-usual	110	94.0	..	82	79.6	..	77	78.6	..	66	67.3	..	56	65.1	..		
Grade 0	4	3.4	..	19	18.4	..	14	14.3	..	22	22.4	..	20	23.3	..		
Grade 1	3	2.6	..	2	1.9	..	4	4.1	..	8	8.2	..	8	9.3	..		
Grade 2	0	0	..	0	0	..	3	3.1	..	2	2.0	..	2	2.3	..		
Grade 3																	
Dryness CTCAE																4.64(5)	0.46
Intervention																	
Grade 0	99	96.1	..	77	85.6	..	57	65.5	..	59	68.6	..	60	70.6	..		
Grade 1	2	1.9	..	12	13.3	..	20	23.0	..	17	19.8	..	18	21.2	..		
Grade 2	1	1.0	..	1	1.1	..	10	11.5	..	8	9.3	..	6	7.1	..		
Grade 3	1	1.0	..	0	0	..	0	0	..	2	2.3	..	1	1.2	..		
Care-as-usual																	
Grade 0	103	92.8	..	80	78.4	..	73	74.5	..	69	72.6	..	55	67.1	..		
Grade 1	4	3.6	..	19	18.6	..	24	24.5	..	24	25.3	..	26	31.7	..		
Grade 2	4	3.6	..	2	2.0	..	1	1.0	..	2	2.1	..	1	1.2	..		
Grade 3	0	0	..	1	1.0	..	0	0	..	0	0	..	0	0	..		

Table S3 *Continued*

	Assessment															GLMM outcomes	
	T1			T2			T3			T4			T5				
Outcome measure (range score)	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**LRT(df)**	**P (overall model)**
Bleeding CTCAE																7.6(5)	0.18
Intervention																	
Grade 0	47	42.3	..	94	87.0	..	81	86.2	..	76	82.6	..	78	83.0	..		
Grade 1	32	28.8	..	11	10.2	..	13	13.8	..	15	16.3	..	14	14.9	..		
Grade 2	26	23.4	..	3	2.8	..	0	0	..	1	1.1	..	2	2.1	..		
Grade 3	6	5.4	..	0	0	..	0	0	..	0	0	..	0	0	..		
Care-as-usual																	
Grade 0	51	43.6	..	102	91.1	..	88	81.5	..	78	77.2	..	72	80.0	..		
Grade 1	32	27.4	..	10	8.9	..	19	17.6	..	22	21.8	..	17	18.9	..		
Grade 2	31	26.5	..	0	0	..	1	0.9	..	1	1.0	..	1	1.1	..		
Grade 3	3	2.6	..	0	0	..	0	0	..	0	0	..	0	0	..		
Mucositis CTCAE																11.04(5)	0.05*
Intervention																	
Grade 0	104	97.2	..	51	53.1	..	68	74.7	..	74	86.0	..	72	80.9	..		
Grade 1	3	2.8	..	41	42.7	..	21	23.1	..	10	11.6	..	13	14.6	..		
Grade 2	0	0	..	4	4.2	..	2	2.2	..	1	1.2	..	3	3.4	..		
Grade 3	0	0	..	0	0	..	0	0	..	1	1.2	..	1	1.1	..		
Grade 4	0	0	..	0	0	..	0	0	..	0	0	..	0	0	..		
Care-as-usual																	
Grade 0	111	95.7	..	54	50.9	..	68	71.6	..	81	84.4	..	70	82.4	..		
Grade 1	4	3.4	..	46	43.4	..	21	22.1	..	12	12.5	..	13	15.3	..		
Grade 2	1	0.9	..	5	4.7	..	2	2.1	..	2	2.1	..	2	2.4	..		
Grade 3	0	0	..	1	0.9	..	3	3.2	..	1	1.0	..	0	0	..		
Grade 4	0	0	..	0	0	..	1	1.1	..	0	0	..	0	0	..		

Table S3 *Continued*

	Assessment															GLMM outcomes	
	T1			T2			T3			T4			T5				
Outcome measure (range score)	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**LRT(df)**	**P (overall model)**
Discharge CTCAE																1.65(5)	0.90
Intervention																	
Grade 0	73	67.0	..	57	53.8	..	60	64.5	..	66	73.3	..	65	70.7	..		
Grade 1	23	21.1	..	45	42.5	..	30	32.3	..	23	25.6	..	24	26.1	..		
Grade 2	13	11.9	..	4	3.8	..	3	3.2	..	1	1.1	..	3	3.3	..		
Grade 3	0	0	..	0	0	..	0	0	..	0	0	..	0	0	..		
Care-as-usual																	
Grade 0	70	61.4	..	56	50.5	..	66	63.5	..	69	70.4	..	62	68.9	..		
Grade 1	33	28.9	..	43	38.7	..	29	27.9	..	20	20.4	..	27	30.0	..		
Grade 2	11	9.6	..	12	10.8	..	9	8.7	..	9	9.2	..	1	1.1	..		
Grade 3	0	0	..	0	0	..	0	0	..	0	0	..	0	0	..		
Fibrosis CTCAE																3.03(5)	0.70
Intervention																	
Grade 0	104	98.1	..	93	97.9	..	74	85.1	..	66	77.6	..	58	67.4	..		
Grade 1	2	1.9	..	2	2.1	..	13	14.9	..	18	21.2	..	25	29.1	..		
Grade 2	0	0	..	0	0	..	0	0	..	1	1.2	..	2	2.3	..		
Grade 3	0	0	..	0	0	..	0	0	..	0	0	..	1	1.2	..		
Care-as-usual																	
Grade 0	111	96.5	..	88	88.9	..	79	85.9	..	77	80.2	..	60	72.3	..		
Grade 1	3	2.6	..	11	11.1	..	13	14.1	..	15	15.6	..	22	26.5	..		
Grade 2	1	0.9	..	0	0	..	0	0	..	3	3.1	..	1	1.2	..		
Grade 3	0	0	..	0	0	..	0	0	..	1	1.0	..	0	0	..		

Table S3 *Continued*

	Assessment															GLMM outcomes	
	T1			T2			T3			T4			T5				
Outcome measure (range score)	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**N**	**M/ %**	**SD**	**LRT(df)**	**P (overall model)**
Dyspareunia CTCAE																1.37(5)	0.93
Intervention																	
Grade 0	74	91.4	..	45	80.4	..	45	62.5	..	50	61.7	..	54	64.3	..		
Grade 1	3	3.7	..	9	16.1	..	21	29.2	..	24	29.6	..	24	28.6	..		
Grade 2	2	2.5	..	2	3.6	..	5	6.9	..	5	6.2	..	4	4.8	..		
Grade 3	2	2.5	..	0	0	..	1	1.4	..	2	2.5	..	2	2.4	..		
Care-as-usual																	
Grade 0	73	84.9	..	34	64.2	..	49	63.6	..	50	64.9	..	50	71.4	..		
Grade 1	10	11.6	..	15	28.3	..	18	23.4	..	17	22.1	..	14	20.0	..		
Grade 2	3	3.5	..	3	5.7	..	9	11.7	..	8	10.4	..	5	7.1	..		
Grade 3	0	0	..	1	1.9	..	1	1.3	..	2	2.6	..	1	1.4	..		

Note. CTCAE = Common Terminology Criteria for Adverse Events; df = degrees of freedom; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-CX24 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Gynaecological Cancer Module; EORTC QLQ-EN24 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Endometrial Cancer Module; FSDS = Female Sexual Distress Scale; FSFI = Female Sexual Function Index; FSQ = Fear of Sexuality Questionnaire; GLMM = Generalized Linear Mixed effects Model; HADS = Hospital Anxiety and Depression Scale; IES = Impact of Event Scale; IQR = interquartile range; M = mean; Md = median; MMQ = Maudsley Marital Questionnaire; N = observed number of women at the specific timepoint; QoL = Quality of Life; SD = standard deviation.
*$p < 0.05$.

Figure S4 Physician-reported clinical measurements on single item level over time. The proportion of women is shown in percentages. BM = baseline measurement; CTCAE = Common Terminology Criteria for Adverse Events; M = months; N = number of women at risk at the specific timepoint; O = observed number of women at the specific timepoint.

Figure S5 Patient-reported vaginal functioning problems on single item level over time. The proportion of women is shown in percentages. Figure I and IV only includes sexually active women. EORTC QLQ-CX24 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Gynaecological Cancer Module; EORTC QLQ-EN24 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Endometrial Cancer Module; M = months; N = number of women at risk at the specific timepoint; n = number of sexually active women at risk at the specific timepoint according to EORTC QLQ-CX24 item 19; O = observed number of women at the specific timepoint.

Table S6 The prevalence of women scoring at a clinical level on sexual functioning, sexual distress, relationship dissatisfaction, and psychological distress

	N	n cut-off*	% cut-off*
Primary Outcome			
FSFItotal BM			
Intervention (total group)	112	33	29.5
Care-as-usual (total group)	117	29	24.8
Sexually active	185	47	25.4
Not sexually active	42	14	33.3
Sexual intercourse	192	33	17.2
No sexual intercourse	35	28	80.0
FSFItotal 1M			
Intervention (total group)	108	80	74.1
Care-as-usual (total group)	110	82	74.5
Sexually active	128	79	61.7
Not sexually active	90	83	92.2
Sexual intercourse	84	38	45.2
No sexual intercourse	133	123	92.5
FSFItotal 3M			
Intervention (total group)	106	67	63.2
Care-as-usual (total group)	106	65	61.3
Sexually active	139	78	56.1
Not sexually active	73	54	74.0
Sexual intercourse	138	67	48.6
No sexual intercourse	74	65	87.8
FSFItotal 6M			
Intervention (total group)	98	49	50.0
Care-as-usual (total group)	98	54	55.1
Sexually active	128	59	46.1
Not sexually active	68	44	64.7
Sexual intercourse	134	48	35.8
No sexual intercourse	62	55	88.7
FSFItotal 12M			
Intervention (total group)	94	53	56.4
Care-as-usual (total group)	87	47	54.0
Sexually active	127	59	46.5
Not sexually active	54	41	75.9
Sexual intercourse	121	45	37.2
No sexual intercourse	60	55	91.7

Table S6 *Continued*

	N	n cut-off*	% cut-off*
Secondary Outcomes			
FSDStotal BM			
Intervention	112	29	25.9
Care-as-usual	117	30	25.6
FSDStotal 1M			
Intervention	107	54	50.5
Care-as-usual	110	49	44.5
FSDStotal 3M			
Intervention	106	49	46.2
Care-as-usual	106	45	42.5
FSDStotal 6M			
Intervention	98	43	43.9
Care-as-usual	98	46	46.9
FSDStotal 12M			
Intervention	94	42	44.7
Care-as-usual	87	40	46.0
MMQtotal 1M			
Intervention	90	13	14.4
Care-as-usual	84	16	19.0
MMQtotal 3M			
Intervention	89	16	18.0
Care-as-usual	80	15	18.8
MMQtotal 6M			
Intervention	83	17	20.5
Care-as-usual	72	11	15.3
MMQtotal 12M			
Intervention	78	15	19.2
Care-as-usual	66	13	19.7
HADStotal 1M			
Intervention	107	32	29.9
Care-as-usual	107	33	30.8
HADStotal 3M			
Intervention	105	33	31.4
Care-as-usual	106	27	25.5
HADStotal 6M			
Intervention	98	27	27.6
Care-as-usual	98	31	31.6
HADStotal 12M			
Intervention	94	21	22.3
Care-as-usual	87	21	24.1
HADS depression 1M			
Intervention	107	28	26.2
Care-as-usual	107	28	26.2

Table S6 *Continued*

	N	n cut-off*	% cut-off*
HADS depression 3M			
Intervention	105	25	23.8
Care-as-usual	106	20	18.9
HADS depression 6M			
Intervention	98	22	22.4
Care-as-usual	98	21	21.4
HADS depression 12M			
Intervention	94	21	22.3
Care-as-usual	87	16	18.4
HADS anxiety 1M			
Intervention	107	41	38.3
Care-as-usual	107	38	35.5
HADS anxiety 3M			
Intervention	105	43	41.0
Care-as-usual	106	41	38.7
HADS anxiety 6M			
Intervention	98	37	37.8
Care-as-usual	98	35	35.7
HADS anxiety 12M			
Intervention	94	31	33.0
Care-as-usual	87	36	41.4

Note. BM = baseline measurement; FSFI = Female Sexual Function Index; FSDS = Female Sexual Distress Scale; HADS = Hospital Anxiety and Depression Scale; M = months; MMQ = Maudsley Marital Questionnaire; N = observed number of women at the specific timepoint (for the MMQ, this number only includes women with a partner).
* = women that scored above/below the clinical cut-off point.

REFERENCES

1. Pieterse QD, Kenter GG, Maas CP, et al. Self-reported sexual, bowel and bladder function in cervical cancer patients following different treatment modalities: longitudinal prospective cohort study. *Int J Gynecol Cancer* 2013; **23**(9): 1717-25. doi:10.1097/IGC.0b013e3182a80a65.
2. Jensen PT, Groenvold M, Klee MC, Thranov I, Petersen MA, Machin D. Longitudinal study of sexual function and vaginal changes after radiotherapy for cervical cancer. *Int J Radiat Oncol Biol Phys* 2003; **56**(4): 937-49. doi:10.1016/s0360-3016(03)00362-6.
3. Abbott-Anderson K, Kwekkeboom KL. A systematic review of sexual concerns reported by gynecological cancer survivors. *Gynecologic Oncology* 2012; **124**(3): 477-89. doi:10.1016/j.ygyno.2011.11.030.
4. Kirchheiner K, Smet S, Jurgenliemk-Schulz IM, et al. Impact of Vaginal Symptoms and Hormonal Replacement Therapy on Sexual Outcomes After Definitive Chemoradiotherapy in Patients With Locally Advanced Cervical Cancer: Results from the EMBRACE-I Study. *Int J Radiat Oncol Biol Phys* 2022; **112**(2): 400-13. doi:10.1016/j.ijrobp.2021.08.036.
5. Roussin M, Lowe J, Hamilton A, Martin L. Factors of sexual quality of life in gynaecological cancers: a systematic literature review. *Arch Gynecol Obstet* 2021; **304**(3): 791-805. doi:10.1007/s00404-021-06056-0.
6. Damast S, Jeffery DD, Son CH, et al. Literature review of vaginal stenosis and dilator use in radiation oncology. *Pract Radiat Oncol* 2019; **9**(6): 479-91. doi:10.1016/j.prro.2019.07.001.
7. Robinson JW, Faris PD, Scott CB. Psychoeducational group increases vaginal dilation for younger women and reduces sexual fears for women of all ages with gynecological carcinoma treated with radiotherapy. *Int J Radiat Oncol Biol Phys* 1999; **44**(3): 497-506. doi:10.1016/s0360-3016(99)00048-6.
8. Bakker RM, Vermeer WM, Creutzberg CL, Mens JWM, Nout RA, ter Kuile MM. Qualitative accounts of patients' determinants of vaginal dilator use after pelvic radiotherapy. *J Sex Med* 2015; **12**(3): 764-73. doi:10.1111/jsm.12776.
9. Hanlon A, Small W, Jr., Strauss J, et al. Dilator Use After Vaginal Brachytherapy for Endometrial Cancer: A Randomized Feasibility and Adherence Study. *Cancer Nurs* 2018; **41**(3): 200-9. doi:10.1097/NCC.0000000000000500.
10. Kozak MM, Usoz M, Fujimoto D, von Eyben R, Kidd E. Prospective randomized trial of email and/or telephone reminders to enhance vaginal dilator compliance in patients undergoing brachytherapy for gynecologic malignancies. *Brachytherapy* 2021; **20**(4): 788-95. doi:10.1016/j.brachy.2021.03.010.
11. Flynn P, Kew F, Kisely SR. Interventions for psychosexual dysfunction in women treated for gynaecological malignancy. *Cochrane Database Syst Rev* 2009; **2009**(2): CD004708. doi:10.1002/14651858.CD004708.pub2.
12. Huffman LB, Hartenbach EM, Carter J, Rash JK, Kushner DM. Maintaining sexual health throughout gynecologic cancer survivorship: A comprehensive review and clinical guide. *Gynecol Oncol* 2016; **140**(2): 359-68. doi:10.1016/j.ygyno.2015.11.010.
13. Scott JL, Halford WK, Ward BG. United we stand? The effects of a couple-coping intervention on adjustment to early stage breast or gynecological cancer. *J Consult Clin Psychol* 2004; **72**(6): 1122-35. doi:10.1037/0022-006x.72.6.1122.
14. Bakker RM, Mens JW, de Groot HE, et al. A nurse-led sexual rehabilitation intervention after radiotherapy for gynecological cancer. *Support Care Cancer* 2017; **25**(3): 729-37. doi:10.1007/s00520-016-3453-2.
15. Suvaal I, Hummel SB, Mens JM, et al. A sexual rehabilitation intervention for women with gynaecological cancer receiving radiotherapy (SPARC study): design of a multicentre randomized controlled trial. *BMC Cancer* 2021; **21**(1): 1295. doi:10.1186/s12885-021-08991-2.
16. Rakovshik SG, McManus F, Vazquez-Montes M, Muse K, Ougrin D. Is supervision necessary? Examining the effects of internet-based CBT training with and without supervision. *J Consult Clin Psychol* 2016; **84**(3): 191-9. doi:10.1037/ccp0000079.

17. Rosen R, Brown C, Heiman J, et al. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. *J Sex Marital Ther* 2000; **26**(2): 191-208. doi:10.1080/009262300278597.

18. Wiegel M, Meston C, Rosen R. The female sexual function index (FSFI): cross-validation and development of clinical cutoff scores. *J Sex Marital Ther* 2005; **31**(1): 1-20. doi:10.1080/00926230590475206.

19. Derogatis LR, Rosen R, Leiblum S, Burnett A, Heiman J. The Female Sexual Distress Scale (FSDS): initial validation of a standardized scale for assessment of sexually related personal distress in women. *J Sex Marital Ther* 2002; **28**(4): 317-30. doi:10.1080/00926230290001448.

20. Greimel ER, Kuljanic Vlasic K, Waldenstrom AC, et al. The European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life questionnaire cervical cancer module: EORTC QLQ-CX24. *Cancer* 2006; **107**(8): 1812-22. doi:10.1002/cncr.22217.

21. Cohen J. Statistical power analysis for the behavioral sciences 2nd ed. Mahwah, New Jersey: Lawrence Erlbaum Associates, Inc.; 1988.

22. Rizopoulos D. GLMMadaptive: Generalized Linear Mixed Models using Adaptive Gaussian Quadrature. R package version 0.8-2. 2021. https://drizopoulos.github.io/GLMMadaptive/ (accessed 1st of June 2022).

23. (Olijf) DPAG. Living with cancer - Sexuality. 2021. https://olijf.nl/leven-met-kanker/seksualiteit (accessed May 26 2024).

24. Reed N, Balega J, Barwick T, et al. British Gynaecological Cancer Society (BGCS) cervical cancer guidelines: recommendations for practice. *Eur J Obstet Gynecol Reprod Biol* 2021; **256**: 433-65. doi:10.1016/j.ejogrb.2020.08.020.

25. Integraal Kankercentrum Nederland. Cervixcarcinoom Landelijke richtlijn, Versie: 3.0. 2012. http://www.med-info.nl/Richtlijnen/Oncologie/Gynaecologische%20tumoren/Cervixcarcinoom.pdf (accessed 7th of December 2020).

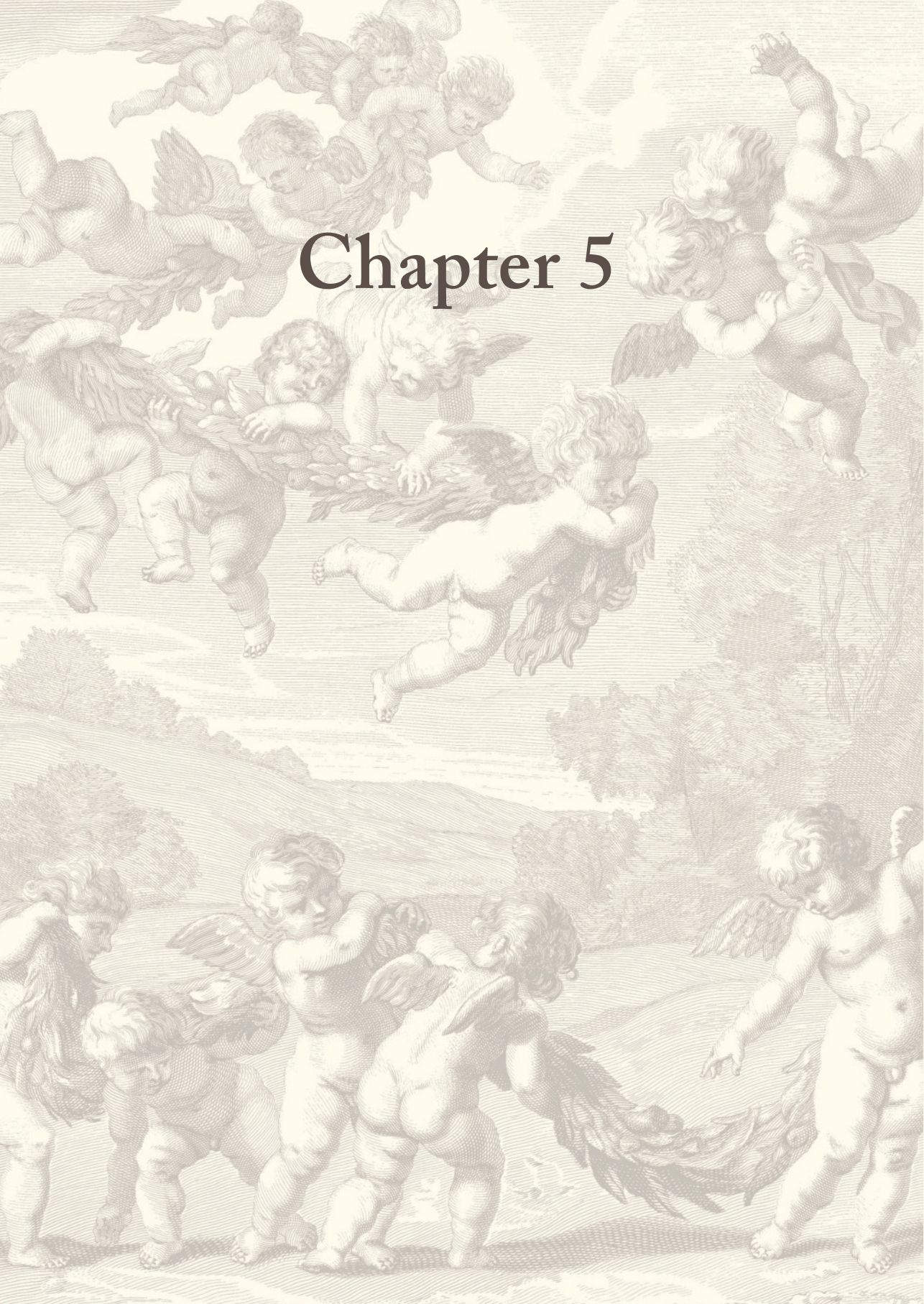
26. Meyer-Bahlburg HFL, Dolezal C. The female sexual function index: a methodological critique and suggestions for improvement. *J Sex Marital Ther* 2007; **33**(3): 217-24. doi:10.1080/00926230701267852.

27. Kirchheiner K, Potter R, Tanderup K, et al. Health-Related Quality of Life in Locally Advanced Cervical Cancer Patients After Definitive Chemoradiation Therapy Including Image Guided Adaptive Brachytherapy: An Analysis From the EMBRACE Study. *Int J Radiat Oncol Biol Phys* 2016; **94**(5): 1088-98. doi:10.1016/j.ijrobp.2015.12.363.

28. Jensen PT, Froeding LP. Pelvic radiotherapy and sexual function in women. *Transl Androl Urol* 2015; **4**(2): 186-205. doi:10.3978/j.issn.2223-4683.2015.04.06.

29. Suvaal I, Kirchheiner K, Nout RA, et al. Vaginal changes, sexual functioning and distress of women with locally advanced cervical cancer treated in the EMBRACE vaginal morbidity substudy. *Gynecol Oncol* 2023; **170**: 123-32. doi:10.1016/j.ygyno.2023.01.005.

30. Kirchheiner K, Nout RA, Lindegaard JC, et al. Dose-effect relationship and risk factors for vaginal stenosis after definitive radio(chemo)therapy with image-guided brachytherapy for locally advanced cervical cancer in the EMBRACE study. *Radiother Oncol* 2016; **118**(1): 160-6. doi:10.1016/j.radonc.2015.12.025.



Chapter 5

Cost-effectiveness of a nurse-led sexual rehabilitation intervention for women treated with radiotherapy for gynaecological cancer in a randomized trial

Radiotherapy and Oncology, 2025; 203:110683
doi: 10.1016/j.radonc.2024.110683

Isabelle Suvaal
Wilbert B. van den Hout
Susanna B. Hummel
Jan-Willem M. Mens
Charlotte C. Tuijnman-Raasveld
Laura A. Velema
Henrike Westerveld
Jeltsje S. Cnossen
An Snyers
Ina M. Jürgenliemk-Schulz
Ludy C.H.W. Lutgens
Jannet C. Beukema
Marie A.D. Haverkort
Marlies E. Nowee
Remi A. Nout
Cor D. de Kroon
Helena C. van Doorn
Carien L. Creutzberg
Moniek M. ter Kuile

ABSTRACT

Objectives

To compare the cost-effectiveness of a nurse-led sexual rehabilitation intervention with standard care in women treated with external beam radiotherapy, with or without brachytherapy, for gynaecological cancers.

Methods

Eligible women were randomly assigned to the intervention (n=112) or standard care (n=117). Primary endpoint was sexual functioning at 12-months post-radiotherapy, assessed by the Female Sexual Function Index (FSFI). Nurses documented frequency and duration of intervention sessions, patients reported sexual healthcare and functioning at 1, 3, 6, and 12-months. Costs were related to quality-adjusted-life-years (QALYs) using the EuroQol-5 Dimensions and visual analogue scale, and to sexual functioning improvement at 12-months. T-tests compared mean QALYs and costs, with multiple imputation for missing data.

Results

The nurse-led intervention added €172 per patient, including training costs and 4-5 sessions. Other sexual rehabilitation costs were higher in the standard care group (€107 versus €141, p=0.02). Total costs were €478 for the intervention group and €357 for standard care (p=0.03). Valued at €20.000 per QALY, the intervention was 60%-70% likely to be cost-effective and less than 50% likely to be cost-effective in terms of improved sexual functioning.

Conclusions

The nurse-led sexual rehabilitation intervention is not more cost-effective than standard care, however with low costs in both groups. Since costs for standard care were slightly lower, it is preferred from a health-economic perspective. It includes detailed patient education and a dedicated sexual rehabilitation session within the first three months post-radiotherapy, which is better provided at lower cost by a trained nurse.

INTRODUCTION

Gynaecological cancer treatment, especially treatment involving intensive combined external beam (chemo)radiotherapy (EBRT) and brachytherapy, is associated with sexual problems, particularly pain during intercourse and vaginal symptoms such as dryness, shortness, and/or tightening[1-3]. Women who receive EBRT and brachytherapy have a higher risk of radiotherapy-induced vaginal stenosis than women receiving EBRT alone[4]. To prevent stenosis, regular vaginal dilation is recommended, however, many women (75%) fail to use dilators regularly, even with specific instructions[5].

Randomized trials targeting dilator use and psychosexual consequences after radiotherapy for gynaecological cancer are rare. Therefore, we developed and pilot tested a nurse-led sexual rehabilitation intervention that includes psycho-education combined with elements of psychosexual-based cognitive-behavioural therapy for gynaecological cancer patients and their partners after radiotherapy, which seemed promising[6,7]. We set up a multicentre randomized trial to evaluate the effectiveness of this intervention[7,8].

Besides evaluation of effectiveness, the implementation of a new intervention requires an economic evaluation to determine whether the clinical benefits are gained at reasonable cost. Up to date, randomized trials and studies of sexual rehabilitation programmes after radiotherapy for gynaecological cancer have not involved explicit cost comparisons. Therefore, the purpose of the present study was to estimate, from a societal perspective, the cost-effectiveness and cost-utility of the nurse-led sexual rehabilitation intervention, compared to standard care.

MATERIALS AND METHODS

The cost-effectiveness analysis (CEA) and cost-utility analysis (CUA) were part of the multicentre randomized SPARC trial (NCT03611517), involving 10 Dutch gynaecologic oncology centres. This trial has been described in detail elsewhere[7,8]. The SPARC trial was approved by the Scientific Review Board of the Dutch Cancer Society, the Medical Ethics Committee Leiden-Den Haag-Delft (number NL62767.058.17), and the Institutional Review Boards and/or Ethics Committees of the participating centres. Participants were randomly assigned (1:1) to standard care or the nurse-led sexual rehabilitation intervention, stratified by radiotherapy type (brachytherapy yes/no) and partner status (yes/no).

Participants

Women treated for cervical, endometrial or vaginal cancers with primary or postoperative EBRT with or without concurrent chemotherapy and brachytherapy, or postoperative radiotherapy alone, were eligible for the trial. They had to be 18 years or older, intend to engage in sexual activity, possessed sufficient Dutch language proficiency, and had no major affective psychotic or substance abuse disorder, or posttraumatic stress disorder related to pelvic floor/genital abuse. Both single and partnered women, regardless of their sexual orientation, could participate. Women were informed and included after eligibility screening by their radiation oncologist[7,8].

Standard care

Both the intervention and standard care groups had a follow-up session 4-5 weeks after radiotherapy with their radiation oncologist (or gynaecologist), to evaluate recovery, tumour regression and vaginal healing, and to assess symptoms. All women received a specially developed information booklet based on the pilot study[6]. Those who had received brachytherapy also received a vaginal dilator set (Amielle Comfort®; Owen Mumford) and two tubes of lubrication gel (K-Y Jelly; Johnson & Johnsen). Women under 50 with cervical or vaginal cancers were recommended hormone replacement therapy until age of about 50. If they received brachytherapy, they were also advised to use vaginal estriol ovules for 5-6 weeks during recovery.

Nurse-led sexual rehabilitation Intervention

Before initiation of the trial, a study-specific 50-hour training programme was held, to which each participating centre sent at least two designated nurses. Only after completing this programme nurses were allowed to conduct the intervention. In the intervention group, all women were counselled and followed by these nurses. The intervention comprised four one-hour face-to-face sessions at 1, 3, 6, and 12-months post-radiotherapy, synchronized with visits to the radiation oncologist, with an extra session at 2-months for women who received brachytherapy. Optionally, a 30-minute follow-up session/phone call was offered between 6 and 12-months after radiotherapy. The intervention consisted of 11 modules, personalized based on individual psychological, relational, and somatic factors, with modules selected during each session to meet each woman's specific needs[7,8]. Partners were welcome to participate in the sessions.

Measurements

Patient and disease characteristics, as well as sexual functioning before the cancer diagnosis, were reported by patients before radiotherapy. Details regarding the nurse-led sexual rehabilitation intervention sessions (such as duration) were documented

in Case Report Forms (CRFs) by the trained nurses after each session. Additionally, sexuality-related healthcare and sexual functioning were reported by the patients at 1, 3, 6, and 12-months after radiotherapy. Sexual functioning was measured by the Female Sexual Function Index (FSFI), a validated 19-item scale with total scores ranging from 2-36, where higher scores indicate better sexual functioning[9].

Costs and cost-effectiveness analysis

An economic evaluation was conducted, relating the difference in sexuality-related healthcare costs to the impact on patient-reported outcomes. Costs are reported in euros (€) at price level 2023. Costs for the nurse-led sexual rehabilitation intervention included nurse training (€1000/nurse - covering materials, one trainer, location, and food and beverage expenses), recorded direct nurse time with patients (max 60min/session), and indirect nurse time (5min/session). Other included healthcare utilization was limited to sexuality-related healthcare and valued using Dutch reference prices or market prices[10].

For the CEA, the estimated costs were related to the intervention's impact on the number of women with sexual improvement, measured by the FSFI (costs-per-improved-patient), defined as a Reliable Change Index (RCI) >1.96 on the FSFI total score between 1 and 12-months after radiotherapy[9,11]. The RCI is calculated by subtracting the FSFI total score at 1-month from the score at 12-months, then dividing by the Standard error of difference (Sdiff)[11]. The Sdiff was computed from the standard error of measurement using the formula $\sqrt{2}(SE)^2$, with the SE calculated from the Dutch population's standard deviation (SD=3.9) and the FSFI test-retest reliability (=.93)[12].

For the CUA, estimated costs were related to the impact on quality-adjusted-life-years (QALYs). In the primary analysis, following Dutch guidelines, QALYs were calculated as the area under the curve of the Dutch tariff for the 5-level EuroQol-5D (EQ-5D)[13,14], consisting of 5 questions on mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. From the EQ-5D classification system, the EQ-5D utility index was calculated, which is anchored at 1 (full health) and 0 (as bad as dead)[15]. This measure reflects how the general public values the health status described by the patient, which is preferred for economic evaluations from a societal perspective[10].

As the EQ-5D does not explicitly value sexuality, QALYs were also estimated using the EuroQol visual analogue scale (EQ-VAS), where patients rated their personal health ranging from worst imaginable health (0) to best imaginable health (100). The EQ-VAS was transformed to a utility scale, using the power transformation

1-(1-EQ-VAS/100)[1.61].[16] Instead of using individually observed EQ-VAS scores, we used a mapping to predict the EQ-VAS from the individually observed FSFI, estimated from our own trial data using linear regression, to make the QALY as sensitive to change as possible.

The cost-effectiveness of the sexual rehabilitation intervention compared to standard care depends on the difference in costs and QALYs, and the willingness-to-pay (WTP) per QALY. Statistical uncertainty was analysed using the net benefit approach, using a cost-effectiveness acceptability curve to graph the probability that the intervention was cost-effective (i.e. had higher net benefit) compared with standard care[17]. Based on the 5-year survival rate of 68% of women with cervical cancer who received EBRT with brachytherapy[18], the relevant Dutch WTP threshold for our study population is €20.000 per QALY[10].

All analyses used data collected during the 12-months follow up, according to intention-to-treat as initially assigned. Multiple imputation with predictive mean matching accounted for missing data. We imputed 100 data sets, using randomization group, type of radiotherapy, partner status (yes/no), type of gynaecological cancer, age at diagnosis, sexual functioning (FSFI scores[9]) and sexual distress (Female Sexual Distress Scale (FSDS) scores[19]), sexuality-related healthcare use, costs, and utilities as predictors. To investigate changes in sexual functioning from 1 to 12-months between groups, a 2 Group (intervention, standard care) by 2 Time (1-month, 12-months) repeated measures analyses of variance (ANOVAs) were applied, with FSFI scores as within-subject factors. T-tests assessed differences in mean 1-year QALYs and costs. Analyses were conducted with the Statistical Package for Social Scientists (SPSS, version 29).

RESULTS

Between August 7, 2018, and December 31, 2021, 229 women were enrolled[8]. Patient, disease, and treatment characteristics were well balanced between the study groups (see Table 1). Women in the intervention group and standard care group were, on average, respectively 43 and 44 years old. Most were treated with primary or postoperative EBRT combined with brachytherapy (80 (71%) in the intervention group; 82 (70%) in the standard care group) and for cervical cancer (98 (87.5%) for the intervention group; 104 (89%) for the standard care group).

Table 2 shows the mean one-year sexual healthcare use and costs per patient. Women in the sexual rehabilitation intervention attended an average of 4.5 sessions. The total average time spent for all sessions per patient was 162 minutes, including 22 minutes

indirect time for preparing the sessions. The total costs of the nurse-led intervention, including the training course for the nurse, were estimated at €172 per participant. Total costs of standard healthcare regarding sexual rehabilitation were estimated at €107 for the intervention group and €141 for the standard care group (see Table 2). These costs were significantly higher in the standard care group (p=.02), mostly because women in the standard care group consulted their radiation oncologist regarding sexual issues more frequently in the first three months after radiotherapy. Other or additional sexual healthcare use and costs were similar between the study groups. No statistically significant differences in total non-intervention standard sexual rehabilitation costs were found between the groups at 12-months. Total sexual rehabilitation costs over the one-year follow-up period, including intervention costs, were significantly higher for the intervention group (€478) compared to the standard care group (€357; p=.03).

Table 1 Patient, disease and treatment characteristics

		Intervention group n = 112 (48.9%)	**Standard care group n = 117 (51.1%)**	**p Value (X^2 or t-test)**
	Patient characteristics			
Age	Mean in years (SD)	43 (10.3)	44 (11.7)	.06
Partner	Yes	88 (78.6%)	90 (76.9%)	.75
	No	24 (21.4%)	27 (23.1%)	
Menopausal status before diagnosis	Premenopausal	75 (67.0%)	75 (64.1%)	.12
	Perimenopausal	10 (8.9%)	3 (2.6%)	
	Postmenopausal	23 (20.5%)	33 (28.2%)	
	Unknown	4 (3.6%)	6 (5.1%)	
World Health Organization performance score	0	85 (75.9%)	89 (76.1%)	.57
	1	24 (21.4%)	25 (21.4%)	
	2	2 (1.8%)	3 (2.6%)	
	Unknown	1 (0.9%)	0	
Incapacitated for work	Yes	25 (22.3%)	19 (16.4%)	.26
	No	87 (77.7%)	97 (82.9%)	
	Unknown	0	1 (0.9%)	
	Disease characteristics			
Type of carcinoma	Cervical carcinoma	98 (87.5%)	104 (88.9%)	.79
	Endometrial carcinoma	7 (6.3%)	8 (6.8%)	
	Vaginal carcinoma	7 (6.3%)	5 (4.3%)	
Histological type	Cervical			.99
	• Squamous cell	80 (81.6%)	85 (81.7%)	
	• Other	18 (18.4%)	19 (18.3%)	
	Endometrial			.62
	• Endometrioid carcinoma	5 (71.4%)	5 (62.5%)	
	• Serous carcinoma	0	1 (12.5%)	
	• Mixed or other	2 (28.6%)	2 (25.0%)	
	Vaginal			.79
	• Squamous cell	6 (85.7%)	4 (80.0%)	
	• Other	1 (14.3%)	1 (20.0%)	

Table 1 *Continued*

		Intervention group n = 112 (48.9%)	Standard care group n = 117 (51.1%)	p Value (X^2 or t-test)
FIGO stage (2009)	Cervical			.99
	• IB	29 (29.6%)	32 (30.8%)	
	• IIA/B	52 (53.1%)	56 (53.8%)	
	• IIIA/B	11 (11.2%)	11 (10.6%)	
	• IVA	1 (1.0%)	1 (1.0%)	
	• Not applicable (if recurrence)	5 (5.1%)	4 (3.8%)	
	Endometrial			.57
	• IA/B	3 (42.9%)	2 (25.0%)	
	• II	1 (14.3%)	3 (37.5%)	
	• IIIA-C	3 (42.9%)	3 (37.5%)	
	Vaginal			.18
	• I	4 (51.7%)	2 (40.0%)	
	• II	3 (42.9%)	1 (20.0%)	
	• III	0	0	
	• IVA	0	2 (40.0%)	
	Treatment characteristics			
Chemotherapy (concurrent)	Yes	90 (80.4%)	87 (74.4%)	.28
	No	22 (19.6%)	30 (25.6%)	
Hyperthermia[#]	Yes	4 (3.8%)	15 (13.8%)	**.01**
	No	101 (96.2%)	94 (86.2%)	
Type of Radiotherapy	Primary EBRT+BT	80 (71.4%)	82 (70.1%)	.79
	Postoperative EBRT+BT	16 (14.3%)	15 (12.8%)	
	External Beam Radiotherapy only	14 (12.5%)*	19 (16.2%)	
	EBRT with EBRT boost	2 (1.8%)[x]	1 (0.9%)	
Target area External Beam Radiotherapy	Pelvic region	84 (75.0%)	89 (76.1%)	.49
	Pelvic and para-aortal regions	22 (19.6%)	22 (18.8%)	
	Pelvic and inguinal regions	6 (5.4%)	4 (3.4%)	
	Pelvic, para-aortal, and inguinal regions	0	2 (1.7%)	
External Beam Radiotherapy total dose	Median dose in Gy (±IQR)	45 (0)	45 (0)	.09
Brachytherapy	Yes	96 (85.7%)	97 (82.9%)	.56
	No	16 (14.3%)	20 (17.1%)	
Target area Brachytherapy	Intrauterine/vaginal Brachytherapy primary	80 (83.3%)	87 (89.7%)	.34
	Vaginal vault boost postoperative	9 (9.4%)	8 (8.2%)	
	Vaginal intracavitary and interstitial (primary or recurrence)	6 (6.3%)	2 (2.1%)	
	Vaginal intracavitary primary	1 (1.0)	0	

Note. EBRT+BT = External Beam Radiotherapy combined with Brachytherapy; FIGO = Fédération Internationale de Gynécologie et d'Obstétrique; IQR = interquartile range; N = total sample; n = subgroup sample; SD = standard deviation.
= Only applicable for cervical and vaginal carcinoma.
* = One participant was stratified as EBRT+BT radiotherapy, however she was treated with EBRT only. Her rehabilitation trajectory was according to EBRT alone; therefore she was moved to EBRT alone.
[x] = One participant was stratified as EBRT alone, however she received an additional EBRT boost. Her rehabilitation trajectory was according to EBRT+BT; therefore she was moved to EBRT+BT.

Figure 1 shows participants' utility scores, mean QALYs and RCI scores above 1.96 over the 12-months follow-up. Utilities according to the EQ-5D and the EQ-VAS were similar between the study groups throughout the follow-up period. At 12-months, the results show utilities of 0.82 for both groups according to the EQ-5D and of 0.88 and 0.87 for the intervention group and the standard care group, respectively, according to the EQ-VAS. Over the full year, the QALYs according to the EQ-5D the EQ-VAS did not statistically significantly differ between the intervention group and standard care group (p=.43 and .39, respectively). The total FSFI score increased significantly between 1 and 12-months after radiotherapy (F (1, 227)=30.09, p<.001, η^2_p=.12). In the total group, 94 of 229 women (41%; n=46 (41%) intervention group, n=48 (41%) standard care group) had a RCI score above 1.96, meaning a clinically relevant improvement in sexual functioning at 12-months. No significant differences in Time X Group interaction, and RCI scores above 1.96 between the intervention group and standard care group were found (p=.77 and .97, respectively).

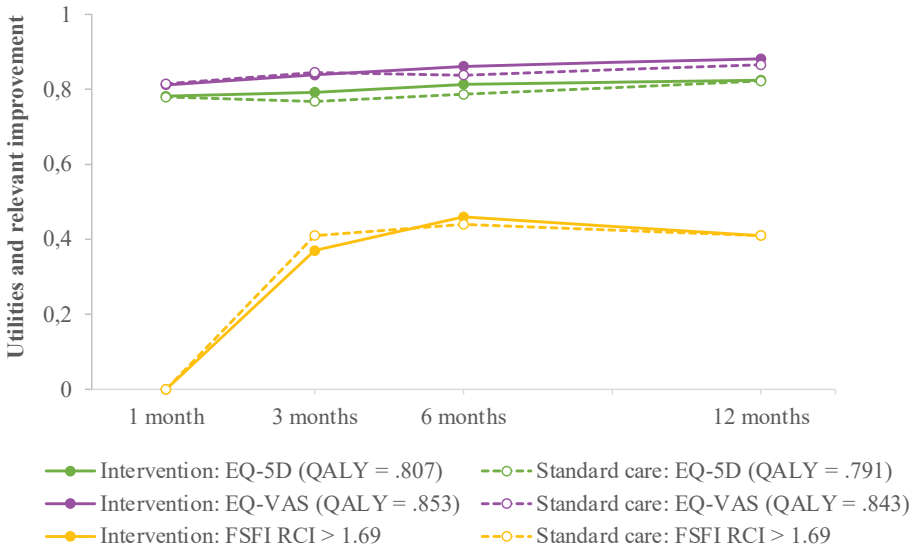


Figure 1 Participants' utility scores, mean quality-adjusted life years (QALY) and RCI scores above 1.96 over the 12-months of follow-up. QALY was measured as the area under the curve over 12-months with the EuroQol 5 dimensions (EQ-5D) utility score (Dutch tariff) and EQ-5D visual analogue scale (EQ-VAS) ranging from 0 (worst health status) to 1 (best health status). FSFI = Female Sexual Function Index; RCI = Reliable Change Index (% reliable change compared to 1 month after radiotherapy).

Table 2 Mean one-year healthcare use and costs per patient, by randomization group

	Intervention group (N = 112)		**Standard care group (N = 117)**		**Difference in costs (€)**	**p Value difference in Costs**
	Use	**Cost (€)**	**Use**	**Cost (€)**		
Sexual rehabilitation intervention						
Direct patient contact (sessions and total minutes)	4.49; 140min	119	-	-		
Indirect time (minutes)	22min	19	-	-		
Training costs		33		-		
Total intervention costs		*172*		-	*172*	***<.001***
Standard sexual rehabilitation healthcare						
Gynaecologist (visits 1-3 months)	.13	12	.18	18	-6	.37
Radiation oncologist (visits 1-3 months)	.30	31	.59	59	-28	**.01**
Materials:						
• Dilator set*	.88	39	.84	38	1	.42
• Lubrication jelly*	1.75	12	1.68	12	0	.42
• Patient information brochure	1	8	1	8	0	1.00
• Local oestrogens (days)	5.74	1	7.04	1	0	.42
• Other out of pocket expenses (e.g. dildo, Vaseline tampons) (days)	2.70	3	4.47	6	-3	.17
Total non-intervention standard sexual rehabilitation costs		*107*		*141*	*-34*	***.02***
Other sexuality-related healthcare						
General practitioner (visits)	.38	12	.38	12	0	.97
Sexologist/psychologist/psychotherapist (visits)	.30	37	.30	38	-1	.97
Gynaecologist (visits 4-12 months)	.44	44	.46	46	-2	.86
Radiation oncologist (visits 4-12 months)	.57	57	.56	56	1	.94
Pelvic floor therapist (visits)	.78	32	.92	37	-5	.76

Table 2 *Continued*

	Intervention group (N = 112)		Standard care group (N = 117)		Difference in costs (€)	p Value difference in Costs
	Use	**Cost (€)**	**Use**	**Cost (€)**		
Other healthcare providers (e.g. nurse, case manager, urologist, physiotherapist) (visits)	.27	13	.36	19	-6	.35
Other materials:						
• Moistening gel/cream (e.g. premeno Duo ovules) (days)	5.13	4	7.45	5	-1	.45
• Anaesthetic ointment (Lidocaine) (days)	.56	1	1.36	2	-1	.07
Total other sexuality-related costs		*200*		*216*	*-16*	*.73*
Total sexuality-related healthcare costs		*478*		*357*	*121*	***.03***

Note. N = sample size; € = Euro.
* = Every participant treated with External Beam Radiotherapy combined with Brachytherapy received 1 dilator set and 2 lubrication jelly (82 gram per tube).

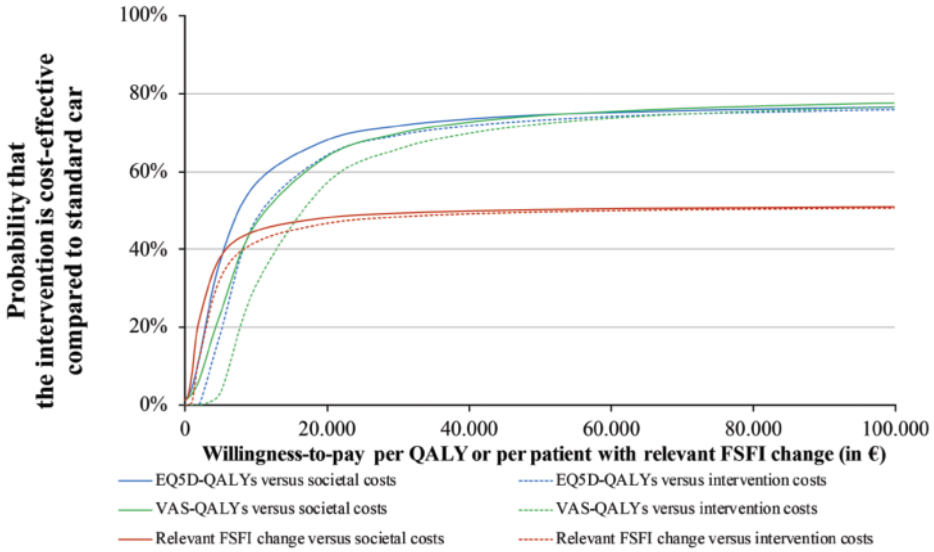


Figure 2 Cost-effective acceptability curves from a societal perspective (solid lines) and interventional perspective (dashed lines), showing the probability that the sexual rehabilitation intervention is cost-effective compared to standard care depending on the willingness to pay for patient outcomes. EQ-5D = EuroQol-5 Dimensions 5 Levels; FSFI = Female Sexual Functioning Index; QALY = quality-adjusted life years; VAS = Visual Analogue Scale.

Figure 2 shows the cost-effective acceptability curves. In the base-case analysis comparing societal costs to EQ-5D QALYs, the probability that the intervention was cost-effective ranged from 3% for low WTP/QALY to about 70% at €20.000 and higher WTP/QALY. Taking only the intervention costs into account, the probability that the intervention was cost-effective ranged from 0% for low WTP/QALY to about 68% at €20.000 and higher WTP/QALY. The probability that the sexual rehabilitation intervention is cost-effective based on the EQ-VAS ranged from 3% for low WTP/QALY to 68% at €20.000 WTP/QALY from a societal perspective and to 60% from a narrower interventional cost perspective. Based on the FSFI RCI above 1.96, the probability that the sexual rehabilitation intervention is cost-effective ranged from 3% for low WTP/QALY to about 45% at €20.000 and higher WTP/QALY, also when taking only the intervention costs into account.

DISCUSSION

The study aimed to estimate the cost-effectiveness of a nurse-led sexual rehabilitation intervention for women treated with radiotherapy for gynaecological cancer compared to standard care. To our knowledge, this is the first well-powered randomized trial that explored the cost-effectiveness of such a sexual rehabilitation intervention (albeit as a secondary outcome).

The costs of the nurse-led sexual rehabilitation intervention including nurse training, were estimated at €172 per patient. Total costs over the one-year follow-up period, including these intervention costs, were significantly higher for the intervention group compared to the standard care group. Of note, the cost differences were small (€478 versus €357), especially in light of overall cancer treatment costs. If the sexual rehabilitation intervention had been found more effective than standard care, it would likely be worth its cost. While 41% of women showed reliable improvement in sexual functioning between 1 and 12-months after radiotherapy, there were no significant differences in reliable FSFI improvement between the study groups. This is in line with the results of the randomized SPARC trial, which showed no significant benefit for the nurse-led rehabilitation intervention[8]. At 12-months post-radiotherapy, both groups reported similar improvements in sexual functioning, with relatively high sexual activity rates (71% in the intervention group vs. 69% in the standard care group). Moreover, dilatation compliance ≥2 times weekly after brachytherapy (dilators, vibrators, dildos, fingers or intercourse combined) was high (85% in the intervention vs. 75% in the standard care group). Most women had no or little physician-reported vaginal stenosis, with the majority of sexually active women reporting little to no feeling of vaginal shortness, dryness, or pain during intercourse. Similarly, the current economic evaluation showed no differences in QALYs or in the number of patients with improved sexual functioning between the groups. The lack of difference in outcomes between the study groups is likely explained by the substantial improvement and awareness of sexual rehabilitation care as a standard in the Netherlands during the initiation and course of the trial. As a result, standard care nowadays consists of thorough patient information, which includes a sexual rehabilitation appointment at 4-6 weeks post-radiotherapy, often with a trained nurse, or radiation oncologist or gynaecologist. During this appointment explicit guidance on dilator use is provided for women who underwent radiotherapy combined with brachytherapy; and coaching on sexual health in the recovery phase for all women. Additionally, there is dedicated follow-up regarding sexual functioning and dilator use over the first year after completion of treatment.

Differences in non-intervention sexual healthcare costs should be interpreted with caution, since differences in almost all specific cost categories were not statistically significant. However, we did find a significant difference in total non-intervention standard sexual rehabilitation healthcare costs between the study groups (i.e., costs incurred in the first three months after radiotherapy), with higher costs for the standard care group. Specifically, costs for radiation oncologist visits regarding sexual issues were significantly higher in the standard care group than the intervention group. During the first three months after radiotherapy, women received the most guidance and coaching regarding sexual rehabilitation. Nurses can devote more time to patient interaction than radiation oncologists, and at lower cost. A visit with a specifically trained nurse would cost only €38 per patient on average (see Table 2). In addition, nurses are often easier accessible for patients and can integrate their role in information and counselling into other clinical tasks. Therefore, their involvement in standard information and coaching of these patients could still be an economically sound strategy for dedicated sexual rehabilitation.

The CUA consistently estimated that the nurse-led sexual rehabilitation intervention was about 70% likely to be the more cost-effective policy (at €20.000 WTP/QALY), regardless whether we valued health from a more societal or a more individual perspective (EQ-5D versus EQ-VAS), and regardless of the scope of the cost estimates (societal versus intervention only). While the Netherlands has thresholds for the WTP to achieve a certain QALY gain, no such thresholds exist for the WTP for improved sexual functioning.

Strengths of this study are the well-powered randomized trial design, the participation of all Dutch gynaecological oncology centres, a limited drop-out of study participants, the use of different methods to estimate QALYs, the comprehensive societal cost perspective, a net benefit approach for statistical uncertainty and multiple imputation for missing values. There are also some limitations. First, we utilized patient-reported sexual healthcare use. The primary drawback of relying on patients is that it necessitates their recall, which can be challenging and may result in inaccurate estimates[20]. Especially between 6 and 12-months after radiotherapy, recall bias may have occurred, possibly resulting in underreporting of healthcare use. It would have been beneficial if we had also included questions regarding additional sexual healthcare use to be answered by patients during each follow-up visit with the physician. Second, the costs of the nurse-led intervention included the training expenses for the nurses, but we chose not to account for their time spent away from clinical duties to enable attendance at the 50-hour training course. In the Netherlands, time spent on additional professional training is incorporated into continuous professional education, and our

training was also directed at general communication skills on sexual topics for daily patient care, and was accredited for this. The costs of sexual rehabilitation healthcare were specific to the Netherlands and University Medical Centres and may not be generalizable to other, international, healthcare systems. Third, it could be argued that this study attracted relatively young and (sexually) motivated participants. Women with cervical cancer constituted the large majority (88%) of the study population, making our findings particularly relevant for these relatively young women treated with intensive combined chemoradiotherapy and brachytherapy. Last, the FSFI which is widely employed to evaluate sexual functioning in female cancer survivors, could yield biased results for sexually inactive women due to lack of a partner, relationship quality, or reasons unrelated to cancer treatment effects[9,21]. To mitigate this, we randomized participants with stratification based on partner status, and included the response option 'not applicable, no partner' for items concerning the partner relationship, thereby minimizing potential imbalance in the study outcomes[7,8].

CONCLUSIONS

In conclusion, our study estimated that the effectiveness of the sexual rehabilitation intervention provided by trained nurses is similar to standard care, with costs that are low for both approaches to sexual rehabilitation care. However, as costs for standard care were slightly lower, the preferred treatment from a health-economic perspective is standard care. This standard approach encompasses thorough patient information, as well as a sexual rehabilitation appointment with explicit guidance on dilator use and coaching on resuming sexual activities. Instead of providing this care in additional or extended consultations with the radiation oncologist or gynaecologist, this sexual rehabilitation care is better provided at lower costs by a specifically trained dedicated nurse.

REFERENCES

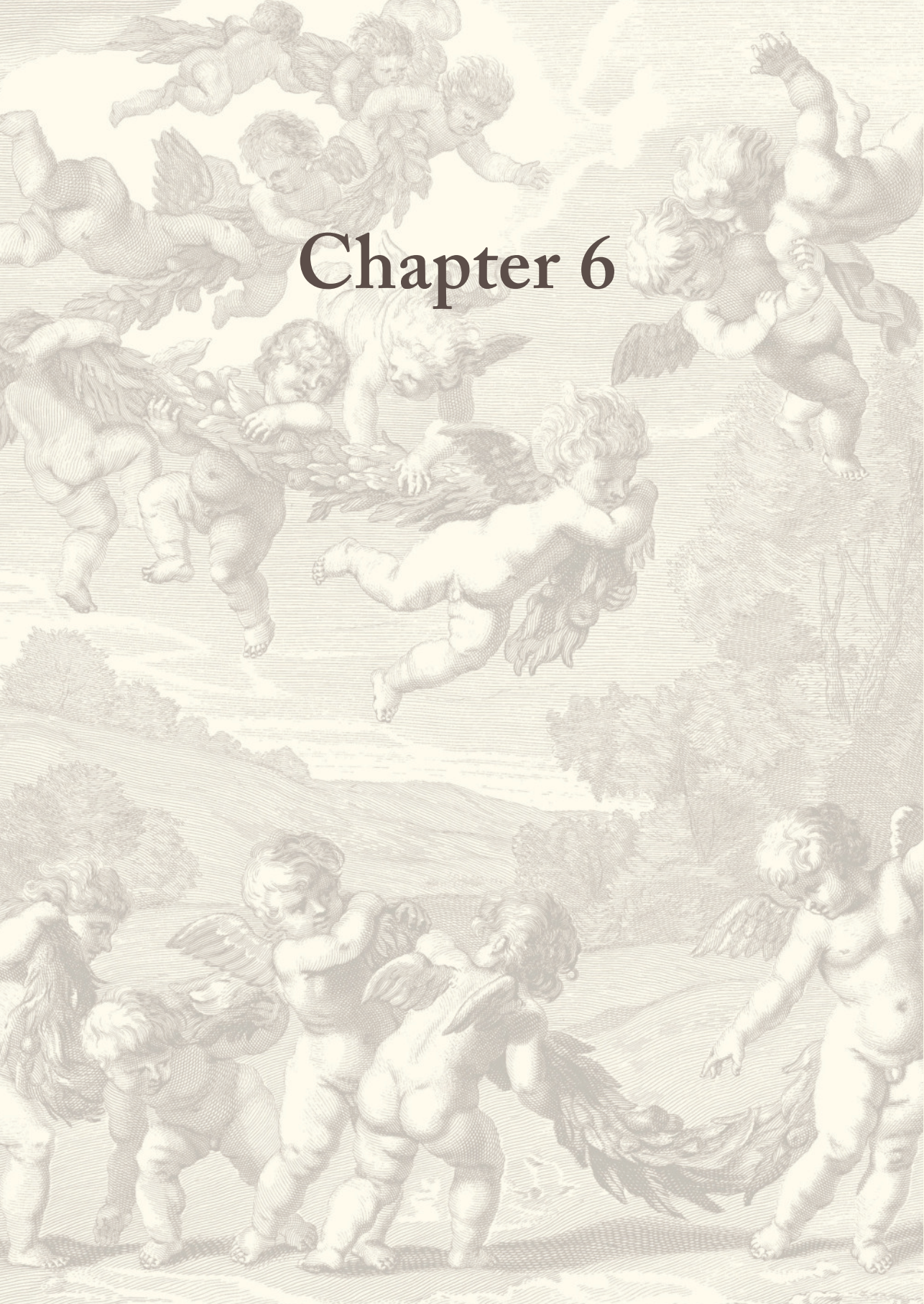
1. Jensen PT, Groenvold M, Klee MC, Thranov I, Petersen MA, Machin D. Longitudinal study of sexual function and vaginal changes after radiotherapy for cervical cancer. *Int J Radiat Oncol Biol Phys* 2003; **56**(4): 937-49. doi:10.1016/s0360-3016(03)00362-6.
2. Abbott-Anderson K, Kwekkeboom KL. A systematic review of sexual concerns reported by gynecological cancer survivors. *Gynecologic Oncology* 2012; **124**(3): 477-89. doi:10.1016/j.ygyno.2011.11.030.
3. Roussin M, Lowe J, Hamilton A, Martin L. Factors of sexual quality of life in gynaecological cancers: a systematic literature review. *Arch Gynecol Obstet* 2021; **304**(3): 791-805. doi:10.1007/s00404-021-06056-0.
4. Damast S, Jeffery DD, Son CH, et al. Literature review of vaginal stenosis and dilator use in radiation oncology. *Pract Radiat Oncol* 2019; **9**(6): 479-91. doi:10.1016/j.prro.2019.07.001.
5. Bakker RM, Vermeer WM, Creutzberg CL, Mens JWM, Nout RA, ter Kuile MM. Qualitative accounts of patients' determinants of vaginal dilator use after pelvic radiotherapy. *J Sex Med* 2015; **12**(3): 764-73. doi:10.1111/jsm.12776.
6. Bakker RM, Mens JW, de Groot HE, et al. A nurse-led sexual rehabilitation intervention after radiotherapy for gynecological cancer. *Support Care Cancer* 2017; **25**(3): 729-37. doi:10.1007/s00520-016-3453-2.
7. Suvaal I, Hummel SB, Mens JM, et al. A sexual rehabilitation intervention for women with gynaecological cancer receiving radiotherapy (SPARC study): design of a multicentre randomized controlled trial. *BMC Cancer* 2021; **21**(1): 1295. doi:10.1186/s12885-021-08991-2.
8. Suvaal I, Hummel SB, Mens JM, et al. Efficacy of a nurse-led sexual rehabilitation intervention for women with gynaecological cancers receiving radiotherapy: results of a randomised trial. *Br J Cancer* 2024. doi:10.1038/s41416-024-02775-8.
9. Rosen R, Brown C, Heiman J, et al. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. *J Sex Marital Ther* 2000; **26**(2): 191-208. doi:10.1080/009262300278597.
10. National Health Care Institute Netherlands. Costing Manual: Methods and Reference Prices for Economic Evaluations in Healthcare. 2024. https://english.zorginstituutnederland.nl/publications/reports/2024/01/16/guideline-for-economic-evaluations-in-healthcare (accessed August 30 2024).
11. Jacobson NS, Truax P. Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. *J Consult Clin Psychol* 1991; **59**(1): 12-9. doi:10.1037/0022-006X.59.1.12.
12. ter Kuile MM, Brauer M, Laan E. The Female Sexual Function Index (FSFI) and the Female Sexual Distress Scale (FSDS): psychometric properties within a Dutch population. *J Sex Marital Ther* 2006; **32**(4): 289-304. doi:10.1080/00926230600666261.
13. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011; **20**(10): 1727-36. doi:10.1007/s11136-011-9903-x.
14. Versteegh MM, Vermeulen KM, Evers SMAA, de Wit GA, Prenger R, Stolk EA. Dutch tariff for the five-level version of EQ-5D. *Value Health* 2016; **19**(4): 343-52. doi:10.1016/j.jval.2016.01.003.
15. Dolan P. Modeling valuations for EuroQol health states. *Med Care* 1997; **35**(11): 1095-108. doi:10.1097/00005650-199711000-00002.
16. Stiggelbout AM, Eijkemans MJ, Kiebert GM, Kievit J, Leer JW, De Haes HJ. The 'utility' of the visual analog scale in medical decision making and technology assessment. Is it an alternative to the time trade-off? *Int J Technol Assess Health Care* 1996; **12**(2): 291-8. doi:10.1017/S0266462300009648.
17. Stinnett AA, Mullahy J. Net health benefits: a new framework for the analysis of uncertainty in cost-effectiveness analysis. *Med Decis Making* 1998; **18**(2 Suppl): S68-80. doi:10.1177/0272989X98018002S09.

18. Potter R, Tanderup K, Schmid MP, et al. MRI-guided adaptive brachytherapy in locally advanced cervical cancer (EMBRACE-I): a multicentre prospective cohort study. *Lancet Oncol* 2021; **22**(4): 538-47. doi:10.1016/S1470-2045(20)30753-1.

19. Derogatis LR, Rosen R, Leiblum S, Burnett A, Heiman J. The Female Sexual Distress Scale (FSDS): initial validation of a standardized scale for assessment of sexually related personal distress in women. *J Sex Marital Ther* 2002; **28**(4): 317-30. doi:10.1080/00926230290001448.

20. Goossens ME, Rutten-van Molken MP, Vlaeyen JW, van der Linden SM. The cost diary: a method to measure direct and indirect costs in cost-effectiveness research. *J Clin Epidemiol* 2000; **53**(7): 688-95. doi:10.1016/S0895-4356(99)00177-8.

21. Meyer-Bahlburg HFL, Dolezal C. The female sexual function index: a methodological critique and suggestions for improvement. *J Sex Marital Ther* 2007; **33**(3): 217-24. doi:10.1080/00926230701267852.



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.

REFERENCES

1. Vermeer WM, Bakker RM, Kenter GG, Stiggelbout AM, Ter Kuile MM. Cervical cancer survivors' and partners' experiences with sexual dysfunction and psychosexual support. *Support Care Cancer* 2016; **24**(4): 1679-87. doi:10.1007/s00520-015-2925-0.
2. Vermeer WM, Bakker RM, Kenter GG, de Kroon CD, Stiggelbout AM, ter Kuile MM. Sexual issues among cervical cancer survivors: how can we help women seek help? *Psychooncology* 2015; **24**(4): 458-64. doi:10.1002/pon.3663.
3. Scott JL, Kayser K. A review of couple-based interventions for enhancing women's sexual adjustment and body image after cancer. *Cancer J* 2009; **15**(1): 48-56. doi:10.1097/PPO.0b013e31819585df.
4. Brotto LA, Erskine Y, Carey M, et al. A brief mindfulness-based cognitive behavioral intervention improves sexual functioning versus wait-list control in women treated for gynecologic cancer. *Gynecol Oncol* 2012; **125**(2): 320-5. doi:10.1016/j.ygyno.2012.01.035.
5. Cain EN, Kohorn EI, Quinlan DM, Latimer K, Schwartz PE. Psychosocial benefits of a cancer support group. *Cancer* 1986; **57**(1): 183-9. doi:10.1002/1097-0142(19860101)57:1%3C183::aid-cncr2820570135%3E3.0.co;2-3.
6. Classen CC, Chivers ML, Urowitz S, et al. Psychosexual distress in women with gynecologic cancer: a feasibility study of an online support group. *Psycho-Oncology* 2013; **22**(4): 930-5. doi:10.1002/pon.3058.
7. Scott JL, Halford WK, Ward BG. United we stand? The effects of a couple-coping intervention on adjustment to early stage breast or gynecological cancer. *J Consult Clin Psychol* 2004; **72**(6): 1122-35. doi:10.1037/0022-006x.72.6.1122.
8. Bakker RM, Mens JW, de Groot HE, et al. A nurse-led sexual rehabilitation intervention after radiotherapy for gynecological cancer. *Supportive Care Cancer* 2017; **25**(3): 729-37. doi:10.1007/s00520-016-3453-2.
9. Embrace Collaborative G. EMBRACE study. 2025. www.embracestudy.dk (accessed 5th of May 2025).
10. Lindegaard JC, Fokdal LU, Nielsen SK, Juul-Christensen J, Tanderup K. MRI-guided adaptive radiotherapy in locally advanced cervical cancer from a Nordic perspective. *Acta Oncol* 2013; **52**(7): 1510-9. doi:10.3109/0284186X.2013.818253.
11. Kirchheiner K, Nout RA, Lindegaard JC, et al. Dose-effect relationship and risk factors for vaginal stenosis after definitive radio(chemo)therapy with image-guided brachytherapy for locally advanced cervical cancer in the EMBRACE study. *Radiother Oncol* 2016; **118**(1): 160-6. doi:10.1016/j.radonc.2015.12.025.
12. Westerveld H, de Leeuw A, Kirchheiner K, et al. Multicentre evaluation of a novel vaginal dose reporting method in 153 cervical cancer patients. *Radiother Oncol* 2016; **120**(3): 420-7. doi:10.1016/j.radonc.2016.05.002.
13. Martins J, Vaz AF, Grion RC, Esteves SCB, Costa-Paiva L, Baccaro LF. Factors associated with changes in vaginal length and diameter during pelvic radiotherapy for cervical cancer. *Arch Gynecol Obstet* 2017; **296**(6): 1125-33. doi:10.1007/s00404-017-4553-z.
14. Pötter R, Tanderup K, Schmid MP, et al. 2638 EMBRACE II - a multicenter prospective interventional cohort study on IGRT-IMRT+cisplatin+MR-IGABT in locally advanced cervix cancer: overall results. *Radiother Oncol* 2025; **206**: S837-S40. doi:10.1016/S0167-8140(25)01194-6.
15. International Clinical Guideline Group. International guidelines on vaginal dilation after pelvic radiotherapy. 2012. https://www.pocd.com.au/core/media/media.nl/id.47537/c.3923593/.f?h=f2e5bc493442741b7e6c (accessed 2nd of March 2020).
16. Varyte G, Bartkeviciene D. Pelvic Radiation Therapy Induced Vaginal Stenosis: A Review of Current Modalities and Recent Treatment Advances. *Medicina (Kaunas)* 2021; **57**(4). doi:10.3390/medicina57040336.
17. Haddad NC, Soares Brollo LC, Pinho Oliveira MA, Bernardo-Filho M. Diagnostic Methods for Vaginal Stenosis and Compliance to Vaginal Dilator Use: A Systematic Review. *J Sex Med* 2021; **18**(3): 493-514. doi:10.1016/j.jsxm.2020.12.013.

18. Bakker RM, Vermeer WM, Creutzberg CL, Mens JWM, Nout RA, ter Kuile MM. Qualitative accounts of patients' determinants of vaginal dilator use after pelvic radiotherapy. *The Journal of Sexual Medicine* 2015; **12**(3): 764-73. doi:10.1111/jsm.12776.

19. Basson R. Human sex-response cycles. *J Sex Marital Ther* 2001; **27**(1): 33-43. doi:10.1080/00926230152035831.

20. Schwarzer R, Lippke S, Luszczynska A. Mechanisms of health behavior change in persons with chronic illness or disability: the Health Action Process Approach (HAPA). *Rehabil Psychol* 2011; **56**(3): 161-70. doi:10.1037/a0024509.

21. Miller WR, Rollnick S. Motivational interviewing: helping people change. 3 ed: Guilford Press; 2013.

22. ter Kuile MM, Both S, van Lankveld JJ. Cognitive behavioral therapy for sexual dysfunctions in women. *Psychiatr Clin North Am* 2010; **33**(3): 595-610. doi:10.1016/j.psc.2010.04.010.

23. Kirchheiner K, Zaharie A, Smet S, et al. Association Between the Regular Use of Vaginal Dilators and/or Sexual Activity and Vaginal Morbidity in Locally Advanced Cervical Cancer Survivors: An EMBRACE-I Study Report. *Int J Radiat Oncol Biol Phys* 2025; **121**(2): 452-64. doi:10.1016/j.ijrobp.2024.09.011.

24. Martins J, Vaz AF, Grion RC, Costa-Paiva L, Baccaro LF. Topical estrogen, testosterone, and vaginal dilator in the prevention of vaginal stenosis after radiotherapy in women with cervical cancer: a randomized clinical trial. *BMC Cancer* 2021; **21**(1): 682. doi:10.1186/s12885-021-08274-w.

25. Kirchheiner K, Nout R, Lindegaard J, et al. Do clinicians and patients agree regarding symptoms? A comparison after definitive radiochemotherapy in 223 uterine cervical cancer patients. *Strahlenther Onkol* 2012; **188**(10): 933-9. doi:10.1007/s00066-012-0156-6.

26. Vistad I, Cvancarova M, Fossa SD, Kristensen GB. Postradiotherapy morbidity in long-term survivors after locally advanced cervical cancer: how well do physicians' assessments agree with those of their patients? *Int J Radiat Oncol Biol Phys* 2008; **71**(5): 1335-42. doi:10.1016/j.ijrobp.2007.12.030.

27. Pizetta LM, Reis ADC, Mexas MP, Guimaraes VA, de Paula CL. Management Strategies for Sexuality Complaints after Gynecologic Cancer: A Systematic Review. *Rev Bras Ginecol Obstet* 2022; **44**(10): 962-71. doi:10.1055/s-0042-1756312.

28. Cianci S, Tarascio M, Arcieri M, et al. Post Treatment Sexual Function and Quality of Life of Patients Affected by Cervical Cancer: A Systematic Review. *Medicina (Kaunas)* 2023; **59**(4). doi:10.3390/medicina59040704.

29. Tsatsou I, Parpa E, Tsilika E, et al. A Systematic Review of Sexuality and Depression of Cervical Cancer Patients. *J Sex Marital Ther* 2019; **45**(8): 739-54. doi:10.1080/0092623X.2019.1610125.

30. Levin AO, Carpenter KM, Fowler JM, Brothers BM, Andersen BL, Maxwell GL. Sexual morbidity associated with poorer psychological adjustment among gynecological cancer survivors. *Int J Gynecol Cancer* 2010; **20**(3): 461-70. doi:10.1111/IGC.0b013e3181d24ce0.

31. Bakker RM, Kenter GG, Creutzberg CL, et al. Sexual distress and associated factors among cervical cancer survivors: a cross-sectional multicenter observational study. *Psycho-Oncology* 2017; **26**(10): 1470-7. doi:10.1002/pon.4317.

32. do Rosario Ramos Nunes Bacalhau M, Pedras S, da Graca Pereira Alves M. Attachment style and body image as mediators between marital adjustment and sexual satisfaction in women with cervical cancer. *Support Care Cancer* 2020; **28**(12): 5813-9. doi:10.1007/s00520-020-05423-y.

33. Hummel SB, van Lankveld J, Oldenburg HSA, et al. Efficacy of Internet-Based Cognitive Behavioral Therapy in Improving Sexual Functioning of Breast Cancer Survivors: Results of a Randomized Controlled Trial. *J Clin Oncol* 2017; **35**(12): 1328-40. doi:10.1200/JCO.2016.69.6021.

34. Xu J, Xue B, Li L, Qiao J, Redding SR, Ouyang YQ. Psychological interventions for sexual function and satisfaction of women with breast cancer: A systematic review and meta-analysis. *J Clin Nurs* 2023; **32**(9-10): 2282-97. doi:10.1111/jocn.16194.

35. Brotto LA, Heiman JR, Goff B, et al. A psychoeducational intervention for sexual dysfunction in women with gynecologic cancer. *Arch Sex Behav* 2008; **37**(2): 317-29. doi:10.1007/s10508-007-9196-x.

36. Brotto LA, Walker L, Sears C, Woo S, Millman R, Zdaniuk B. A randomized comparison of online mindfulness-based group sex therapy vs supportive group sex education to address sexual dysfunction in breast cancer survivors. *J Sex Med* 2024; **21**(5): 452-63. doi:10.1093/jsxmed/qdae022.

37. Huffman LB, Hartenbach EM, Carter J, Rash JK, Kushner DM. Maintaining sexual health throughout gynecologic cancer survivorship: A comprehensive review and clinical guide. *Gynecol Oncol* 2016; **140**(2): 359-68. doi:10.1016/j.ygyno.2015.11.010.

38. Carney LM, Schnur JB, Morgan O, et al. Psychosocial interventions to improve sexual functioning in women with cancer: a systematic review of randomized controlled trials. *Sex Med Rev* 2024; **12**(2): 142-53. doi:10.1093/sxmrev/qead052.

39. Buhrman M, Hallstrom H, Friden A, et al. Guided internet-based acceptance and commitment therapy for provoked vestibulodynia: A randomized controlled trial. *Eur J Pain* 2024; **28**(7): 1185-201. doi:10.1002/ejp.2253.

40. Reed N, Balega J, Barwick T, et al. British Gynaecological Cancer Society (BGCS) cervical cancer guidelines: recommendations for practice. *Eur J Obstet Gynecol Reprod Biol* 2021; **256**: 433-65. doi:10.1016/j.ejogrb.2020.08.020.

41. Integraal Kankercentrum Nederland. Cervixcarcinoom Landelijke richtlijn, Versie: 3.0. 2012. http://www.med-info.nl/Richtlijnen/Oncologie/Gynaecologische%20tumoren/Cervixcarcinoom.pdf (accessed 7th of December 2020).

42. (Olijf) DPAG. Living with cancer - Sexuality. 2021. https://olijf.nl/leven-met-kanker/seksualiteit (accessed May 26 2024).

43. Olesen ML, Seibaek L, Sekse RJT. Impaired sexual health among women treated for vulvar cancer: An integrated review. *J Clin Nurs* 2023; **32**(17-18): 6212-28. doi:10.1111/jocn.16753.

44. Thimm AM, Hansson EH, Wraae KB, Olesen ML. Symptom Experience After Surgical Treatment for Vulvar Cancer-A Scoping Review. *Scand J Caring Sci* 2025; **39**(2): e70037. doi:10.1111/scs.70037.

45. Annon JS. The PLISSIT Model: A Proposed Conceptual Scheme for the Behavioral Treatment of Sexual Problems. *Journal of Sex Education and Therapy* 1976; **2**(1). doi:https://doi.org/10.1080/01614576.1976.11074483.

46. Lubotzky FP, Butow P, Hunt C, et al. A psychosexual rehabilitation booklet increases vaginal dilator adherence and knowledge in women undergoing pelvic radiation therapy for gynaecological or anorectal cancer: a randomised controlled trial. *Clin Oncol (R Coll Radiol)* 2019; **31**(2): 124-31. doi:10.1016/j.clon.2018.11.035.

47. Rosen R, Brown C, Heiman J, et al. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. *J Sex Marital Ther* 2000; **26**(2): 191-208. doi:10.1080/009262300278597.

48. Derogatis LR, Rosen R, Leiblum S, Burnett A, Heiman J. The Female Sexual Distress Scale (FSDS): initial validation of a standardized scale for assessment of sexually related personal distress in women. *J Sex Marital Ther* 2002; **28**(4): 317-30. doi:10.1080/00926230290001448.

49. Meyer-Bahlburg HFL, Dolezal C. The female sexual function index: a methodological critique and suggestions for improvement. *J Sex Marital Ther* 2007; **33**(3): 217-24. doi:10.1080/00926230701267852.

50. Greimel ER, Kuljanic Vlasic K, Waldenstrom AC, et al. The European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life questionnaire cervical cancer module: EORTC QLQ-CX24. *Cancer* 2006; **107**(8): 1812-22. doi:10.1002/cncr.22217.

51. Laan E, Rellini AH. Can we treat anorgasmia in women? The challenge to experiencing pleasure. *Sex Relatsh Ther* 2011; **26**(4): 329-41. doi:10.1080/14681994.2011.649691.

52. ter Kuile MM, Brauer M, Laan E. The Female Sexual Function Index (FSFI) and the Female Sexual Distress Scale (FSDS): psychometric properties within a Dutch population. *J Sex Marital Ther* 2006; **32**(4): 289-304. doi:10.1080/00926230600666261.

53. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983; **67**(6): 361-70. doi:10.1111/j.1600-0447.1983.tb09716.x.

54. Crowe MJ. Conjoint marital therapy: a controlled outcome study. *Psychol Med* 1978; **8**(4): 623-36. doi:10.1017/s0033291700018833.

55. Kirchheiner K, Nout RA, Czajka-Pepl A, et al. Health related quality of life and patient reported symptoms before and during definitive radio(chemo)therapy using image-guided adaptive brachytherapy for locally advanced cervical cancer and early recovery - a mono-institutional prospective study. *Gynecol Oncol* 2015; **136**(3): 415-23. doi:10.1016/j.ygyno.2014.10.031.

56. Kirchheiner K, Smet S, Jurgenliemk-Schulz IM, et al. Impact of Vaginal Symptoms and Hormonal Replacement Therapy on Sexual Outcomes After Definitive Chemoradiotherapy in Patients With Locally Advanced Cervical Cancer: Results from the EMBRACE-I Study. *Int J Radiat Oncol Biol Phys* 2022; **112**(2): 400-13. doi:10.1016/j.ijrobp.2021.08.036.

57. Jensen PT, Groenvold M, Klee MC, Thranov I, Petersen MA, Machin D. Longitudinal study of sexual function and vaginal changes after radiotherapy for cervical cancer. *Int J Radiat Oncol Biol Phys* 2003; **56**(4): 937-49. doi:10.1016/s0360-3016(03)00362-6.

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.

NEDERLANDSE SAMENVATTING

De incidentie van baarmoederhals-, vaginale en endometriumcarcinomen neemt toe in Nederland. Door verbeterde radiotherapietechnieken en daarmee hogere overlevingskansen is er steeds meer aandacht gekomen voor het behoud van kwaliteit van leven. Veel vrouwen gediagnosticeerd met gynaecologische kanker ondergaan radiotherapie als deel van hun behandeling. Radiotherapie kan worden toegepast als (beeldgestuurde) uitwendige bestraling, inwendige bestraling (brachytherapie) of een combinatie daarvan. Vooral de combinatie van uitwendige en inwendige radiotherapie kan leiden tot veranderingen van het vaginale slijmvlies, die een negatieve invloed kunnen hebben op seksueel functioneren. Veelvoorkomende klachten zijn dyspareunie, verminderde lubricatie, vernauwing en verkorting van de vagina (stenose), evenals seksuele functiestoornissen, zoals een afname van seksueel verlangen, opwinding, plezier en tevredenheid. Deze vaginale veranderingen, klachten en seksuele functiestoornissen gaan vaak gepaard met seksuele distress (persoonlijk ervaren hinder met betrekking tot seksuele problemen) en worden beïnvloed door een complex samenspel van lichamelijke, psychologische en relationele factoren, zoals angst, een veranderd lichaamsbeeld en relatieproblemen. Ter preventie van vaginale stenose wordt het gebruik van vaginale pelottes aanbevolen, maar eerdere studies toonden een lage therapietrouw bij het volhouden van het gebruik.

Hoofdstuk 1 introduceert een seksuele rehabilitatie interventie voor vrouwen die behandeld zijn met radiotherapie voor gynaecologische kanker. Eerder onderzoek suggereert dat interventies die psycho-educatie combineren met cognitief-gedragstherapeutische technieken en de partner betrekken, kunnen bijdragen aan verbetering van het seksueel functioneren en aan het beter volhouden van pelottegebruik. Op basis hiervan werd een door verpleegkundigen geleide seksuele rehabilitatie interventie ontwikkeld en in een pilotstudie getest, met veelbelovende resultaten. De multicenter SPARC studie (Seksueel rehabilitatie Programma nA Radiotherapie voor gynaeCologische kanker) werd opgezet om de (kosten)effectiviteit van deze interventie te evalueren.

De doelstellingen van dit proefschrift waren:

1. Het evalueren van door artsen beoordeelde vaginale veranderingen en door patiënten gerapporteerde vaginale klachten en seksuele functiestoornissen en seksuele distress gedurende de eerste twee jaar na beeldgestuurde radio(chemo) therapie en brachytherapie bij lokaal gevorderde baarmoederhalskanker.
2. Het onderzoeken van de effectiviteit van de door verpleegkundigen geleide seksuele rehabilitatie interventie ten opzichte van standaardzorg op het gebied van seksueel functioneren, seksuele distress, pelottegebruik en vaginale klachten na uitwendige radiotherapie, al dan niet in combinatie met brachytherapie, voor gynaecologische kanker.
3. Het vergelijken van de kosteneffectiviteit van de door verpleegkundigen geleide seksuele rehabilitatie interventie met standaardzorg bij vrouwen die uitwendige radiotherapie, al dan niet in combinatie met brachytherapie, ondergingen voor gynaecologische kanker.

Hoofdstuk 2 presenteert de resultaten van de prospectieve, Europese EMBRACE substudie naar vaginale morbiditeit. In deze studie werden zowel door artsen beoordeelde vaginale veranderingen als door patiënten gerapporteerde uitkomsten met betrekking tot vaginale klachten, seksuele functiestoornissen en seksuele distress in de eerste twee jaar na beeldgestuurde radio(chemo)therapie met brachytherapie voor lokaal gevorderde cervixcarcinoom prospectief geëvalueerd. Daarnaast werd de associatie tussen arts-gerapporteerde en patiënt-gerapporteerde uitkomsten onderzocht. In totaal werden 113 vrouwen geïncludeerd tussen 2012 en 2018. In vergelijking met de volledige EMBRACE-cohortpopulatie kenmerkte deze subgroep zich door een lager tumorstadiëring en minder vaginale tumorextensie, wat van invloed was op de radiotherapeutische behandelparameters. Over het algemeen werden na radiotherapie voornamelijk milde vaginale veranderingen gerapporteerd door artsen, zonder duidelijke toename gedurende de twee jaar follow-up. Substantiëlere vaginale veranderingen kwamen voor bij minder dan 3% van de vrouwen. In vergelijking met baseline waren de meeste vaginale veranderingen op alle follow-up momenten (4-6 weken, 3, 6, 12 en 24 maanden) significant verslechterd. Tussen de follow-up momenten traden geen verdere significante verbeteringen of verslechteringen op. De mate van seksuele activiteit nam in de loop van de tijd toe van 21% bij baseline tot 53% 2 jaar na radiotherapie. Op 24 maanden rapporteerden vrouwen voornamelijk seksueel inactief te zijn als gevolg van verminderde interesse in seks of het ontbreken van een partner. Vaginale klachten, seksuele functiestoornissen en seksuele distress werden gedurende twee jaar na de behandeling gerapporteerd door bijna de helft van de seksueel actieve vrouwen. Meer substantiële vaginale klachten, seksuele functiestoornissen en seksuele distress werden respectievelijk gerapporteerd door 14%, 20% en 8% van de seksueel actieve vrouwen.

Seksuele tevredenheid was op baseline significant lager in vergelijking met de follow-up momenten. Er werden verder geen significante veranderingen gevonden tussen de latere follow-up momenten. De door vrouwen gerapporteerde vaginale klachten en seksuele distress waren niet, of slechts zwak, geassocieerd met de door artsen beoordeelde vaginale veranderingen. Deze bevinding onderstreept dat seksueel functioneren een veel complexer fenomeen is dan vaginale morbiditeit alleen.

Hoofdstuk 3 beschrijft het ontwerp van de multicenter, gerandomiseerde SPARC trial, waarin de (kosten)effectiviteit werd onderzocht van een door verpleegkundigen geleide seksuele rehabilitatie interventie ter verbetering van het seksueel functioneren en het gebruik van pelottes bij patiënten met cervix-, vaginale of endometriumcarcinoom na radiotherapie. De primaire uitkomstmaat was seksueel functioneren, gemeten met de Female Sexual Function Index (FSFI). De FSFI is internationaal een van de meest gebruikte gevalideerde meetinstrumenten voor het in kaart brengen van vrouwelijk seksueel functioneren. Secundaire uitkomstmaten omvatten lichaamsbeeld, angst voor seksuele activiteit, seksuele distress, kanker behandeling-gerelateerde- en psychologische distress, gezondheids-gerelateerde kwaliteit van leven en relatietevredenheid. Alle vrouwen vulden vragenlijsten in op baseline (retrospectief) en op 1, 3, 6 en 12 maanden na radiotherapie. Vaginale veranderingen werden beoordeeld via gestandaardiseerde klinische evaluaties en op dezelfde meetmomenten geregistreerd. De door verpleegkundigen geleide seksuele rehabilitatie interventie werd vergeleken met standaardzorg (optimale gebruikelijke zorg). Participanten werden gerandomiseerd naar de interventiegroep of de standaardzorggroep, en binnen elk centrum gestratificeerd op type radiotherapie (uitwendige radiotherapie gecombineerd met brachytherapie versus alleen uitwendige radiotherapie) en op het hebben van een partner (ja/nee). De standaardzorg bestond uit een informatiesessie één maand na afronding van de radiotherapie, gegeven door een getrainde verpleegkundige of specialist, waarbij seksuele rehabilitatie werd besproken en waarbij de vrouwen een uitgebreide, specifieke informatiebrochure en (indien van toepassing) een pelotteset kosteloos verstrekt kregen. De interventiegroep ontvingen zittingen met een getrainde verpleegkundige op 1, 3, 6 en 12 maanden na radiotherapie, met een extra zitting na 2 maanden voor vrouwen die brachytherapie hadden ondergaan. Partners werden uitgenodigd om deel te nemen aan de zittingen, maar deelname was niet verplicht. Kort samengevat bestond de interventie uit 11 gepersonaliseerde modules met thema's zoals voorlichting over de kankerdiagnose en behandeling, gebruik van pelottes, angst voor pelottegebruik en het hervatten van seksuele activiteit, het bevorderen van coping en onderlinge steun binnen de partnerrelatie, en het bespreken van zorgen omtrent seksualiteit en lichaamsbeeld. Voorafgaande aan de studie volgden oncologieverpleegkundigen (behandelaars) een training van 50 uur op het gebied van

seksuologie, cognitieve gedragstherapie-technieken en het behandelprotocol. Tijdens de studie hadden zij maandelijks supervisie van een ervaren seksuoloog en namen deel aan aanvullende landelijke trainingsdagen over studierelevante onderwerpen.

Hoofdstuk 4 beschrijft de resultaten over de effectiviteit van de door verpleegkundigen geleide seksuele rehabilitatie interventie in vergelijking met standaardzorg. Tussen 2018 en 2021 werden in totaal 229 vrouwen, afkomstig uit alle Nederlandse gynaecologische oncologiecentra (N=10), geïncludeerd in de SPARC trial. Er werden geen statistisch significante verschillen gevonden tussen de interventiegroep en de standaardzorggroep in seksueel functioneren of in de meeste secundaire uitkomstmaten op enig tijdsmoment na radiotherapie. Hoewel seksueel functioneren aanvankelijk afnam na de behandeling in beide groepen, trad in het eerste jaar na radiotherapie geleidelijk herstel op. Op 12 maanden bedroegen de gemiddelde FSFI-scores 22.57 in de interventiegroep en 21.76 in de standaardzorggroep en gaf ongeveer 70% van de vrouwen in beide groepen aan seksueel actief te zijn, wat een hoger percentage is dan de 40-50% die in eerdere studies is gerapporteerd. Klinisch relevante seksuele distress (zoveel hinder door seksuele problemen dat dit als belangrijk wordt beschouwd om hier (professioneel) aandacht aan te besteden) bleef echter aanwezig bij ongeveer 50% van de participanten in beide groepen één jaar na behandeling.

Bij de meerderheid van de vrouwen waren vaginale veranderingen en klachten over het algemeen afwezig of mild. Substantiële vaginale veranderingen en klachten werd zelden gezien. De therapietrouw ten aanzien van vaginale dilatatie 12 maanden na uitwendige radiotherapie in combinatie met brachytherapie was hoog in beide groepen: 85% van de vrouwen in de interventiegroep en 75% in de standaardzorggroep rapporteerden dat zij ten minste tweemaal per week enige vorm van dilatatie toepasten (bijvoorbeeld pelottes, geslachtsgemeenschap, vibrator of vingers).

Verschillende factoren kunnen de afwezigheid van significante verschillen tussen de studiearmen verklaren. Sinds de voltooiing van de pilotstudie in 2016 is seksuele rehabilitatie sterker geïntegreerd in de standaard gynaecologisch-oncologische zorg in Nederland. Routinematige nazorgconsultaties waarbij het bespreken van seksualiteit aan bod kwam, toegenomen bewustzijn onder zorgverleners, de verstrekking van vaginale pelottes met instructie, en de beschikbaarheid van het psycho-educatief materiaal, dat ontwikkeld was voor de pilot studie, hebben waarschijnlijk de kwaliteit van de zorg in beide groepen verbeterd. Seksuele rehabilitatie werd een standaard onderdeel van gesprek tijdens het eerste jaar na radiotherapie. De bevindingen suggereren dat de verbeterde standaardzorg die tijdens de studieperiode werd aangeboden mogelijk al voldoende uitgebreid was om herstel van seksueel functioneren en vaginale gezondheid

te ondersteunen, waardoor de toegevoegde waarde van de meer gestructureerde verpleegkundige interventie van 4-5 zittingen beperkt werd. Niettemin benadrukt deze studie het belang en de effectiviteit van de huidige best practices in seksuele rehabilitatie na radiotherapie in Nederland. Optimale zorg omvat een consult voor seksuele rehabilitatie één maand na afronding van de radiotherapie, met patiëntgerichte schriftelijke informatie en begeleiding over het gebruik van pelottes, bij voorkeur uitgevoerd door een getrainde verpleegkundige. Tijdens de daaropvolgende follow-upbezoeken dienen algemene én seksuele rehabilitatie aandacht te blijven krijgen, waarbij seksualiteit als een vast onderdeel van de nazorggesprekken wordt beschouwd.

Hoofdstuk 5 presenteert de kosteneffectiviteit van de door verpleegkundigen geleide seksuele rehabilitatie interventie in vergelijking met standaardzorg. De resultaten toonden aan dat vrouwen in de interventiegroep gemiddeld 4.5 zittingen bijwoonden, met een totale kostprijs van €172 per deelneemster, inclusief de kosten voor de training van de verpleegkundigen. De totale kosten voor seksuele rehabilitatie gedurende één jaar waren significant hoger in de interventiegroep (€478) dan in de standaardzorggroep (€357). Opvallend was dat vrouwen in de standaardzorggroep hogere zorgkosten maakten gedurende de eerste maanden na radiotherapie, voornamelijk doordat deze vrouwen significant frequenter hun radiotherapeut raadpleegde over seksueel herstel. Ondanks deze verschillen in zorggebruik en kosten werden geen statistisch significante verschillen gevonden tussen de studiegroepen in quality-adjusted life years (QALY's; een maat die laat zien hoeveel gezonde levensjaren iemand wint), utiliteitscores (hoe kwaliteit van leven wordt ervaren) of seksueel functioneren-uitkomsten gedurende de 12 maanden follow-up. De interventie liet een kans van 70% zien om kosteneffectief te zijn bij een willingness-to-pay-drempel van €20.000 per QALY, maar dit vertaalde zich niet in een klinisch relevante meerwaarde. Het ontbreken van significante uitkomstverschillen is waarschijnlijk toe te schrijven aan de substantiële verbeteringen in de standaard seksuele rehabilitatiezorg in Nederland tijdens de studieperiode. De resultaten tonen aan dat de door verpleegkundigen geleide seksuele rehabilitatie interventie niet kosteneffectiever is dan standaardzorg, hoewel de kosten in beide groepen relatief laag waren. Aangezien de kosten voor standaardzorg iets lager uitvielen, lijkt de optimale benadering vanuit gezondheidseconomisch perspectief te bestaan uit één zitting waarin informatie en coaching over seksuele rehabiliatie wordt gegeven. Deze zitting biedt gedetailleerde patiënteneducatie met nadruk op seksuele rehabilitatie in de eerste drie maanden na radiotherapie en kan tegen lagere kosten worden uitgevoerd door een opgeleide verpleegkundige dan door een medisch specialist.

Hoofdstuk 6 bespreekt de belangrijkste bevindingen van dit proefschrift binnen een biopsychosociaal kader, aangevuld met methodologische overwegingen en implicaties voor toekomstig onderzoek. De gunstige uitkomsten met betrekking tot vaginale veranderingen (o.a. stenose), zoals gerapporteerd in de EMBRACE substudie naar vaginale morbiditeit en in de gerandomiseerde SPARC trial, weerspiegelen de vooruitgang in radiotherapietechnieken, waaronder geoptimaliseerde dosisplanning van zowel de uitwendige radiotherapie als brachytherapie, en betere vaginale sparing (het zoveel mogelijk sparen van gezond vaginawandweefsel tijdens de bestraling). Daarnaast heeft verbeterde psychoseksuele rehabilitatie zorg waarschijnlijk bijgedragen aan een betere therapietrouw ten aanzien van het gebruik van vaginale pelottes en aan een toename van seksuele activiteit in het eerste jaar na de radiotherapiebehandeling. Psychologische factoren, zoals motivatie, angstvermindering en emotionele gereedheid, spelen vermoedelijk een rol bij therapietrouw en kunnen het gebruik van pelottes ondersteunen, ongeacht of dit onderdeel is van een gestructureerde interventie of van de standaardzorg. Bovendien kan seksuele activiteit zelf een gunstig effect hebben op de vaginale gezondheid door verbeterde lokale doorbloeding, wat mogelijk een aanvullende werking heeft op de mechanische effecten van pelottegebruik.

De afwezigheid van door artsen gerapporteerde vaginale veranderingen betekent echter niet noodzakelijk dat vrouwen geen vaginale klachten ervaren. Veel van deze klachten doen zich vaak voor tijdens seksuele activiteit en zijn niet altijd zichtbaar bij klinisch onderzoek. De discrepantie tussen door artsen beoordeelde vaginale veranderingen en door patiënten gerapporteerde vaginale klachten benadrukt het belang van het combineren van beide perspectieven. Daarnaast varieert de impact van slijmvliesveranderingen op het seksueel functioneren aanzienlijk tussen vrouwen. Dit onderstreept dat seksuele problemen niet uitsluitend door somatische factoren worden bepaald, maar dat ook psychologische, seksuologische en relationele factoren een belangrijke rol spelen. De bevindingen uit de SPARC trial illustreren dit: ondanks de afwezigheid bij de meerderheid van de vrouwen van vaginale veranderingen, rapporteerden bijna de helft klinisch significante seksuele distress op 12 maanden na radiotherapie. Dit laat zien dat seksueel functioneren door veel meer wordt beïnvloed dan alleen vaginale veranderingen. Uit eerder onderzoek blijkt bovendien dat seksuele distress grotendeels wordt bepaald door psychosociale factoren, zoals zorgen over het lichaamsbeeld, angst, depressie, verlies van seksuele identiteit en relatieproblemen. Ook lichamelijke gevolgen van radiotherapie, zoals vroegtijdige menopauze en chronische vermoeidheid, dragen hier aan bij. Daarom moet toekomstig onderzoek verder gaan dan de beoordeling van vaginale slijmvliesveranderingen (artsen) en gerapporteerde vaginale klachten (patiënten). De reeds verzamelde gegevens binnen de SPARC trial bieden een waardevolle mogelijkheid om de complexe interacties tussen

vaginale veranderingen, psychosociale factoren en seksuele uitkomsten te onderzoeken. Geplande analyses kunnen bijvoorbeeld meer inzicht gaan geven in de rol van vaginale dilatatie en psychosociale mediatoren. Daarnaast is langdurige follow-up essentieel om de bestendigheid van interventie-effecten op de lange termijn te evalueren. Om deze rede heeft de SPARC trial een meetmoment op 24 maanden toegevoegd. Bovendien zijn crossculturele validatie en aanpassing van seksuele rehabilitatieprogramma's noodzakelijk om de bredere toepasbaarheid ervan te waarborgen.

Voortgezette training en educatie van verpleegkundigen zijn cruciaal voor de duurzame implementatie van seksuele rehabilitatie na radiotherapie. Multidisciplinaire samenwerking is essentieel om integrale zorg te waarborgen en seksuele gezondheid als prioriteit te behouden gedurende het gehele nazorgtraject, met als uiteindelijk doel de kwaliteit van leven van vrouwen die behandeld zijn voor gynaecologische kanker te verbeteren. Dit proefschrift ondersteunt een verschuiving richting gepersonaliseerde, biopsychosociale benaderingen van seksuele rehabilitatie bij vrouwen die radiotherapie hebben ondergaan voor gynaecologische kanker. De inzet van verpleegkundigen blijkt daarbij goed uitvoerbaar en waardevol voor het bieden van systematische en toegankelijke ondersteuning binnen de standaardzorg.

LIST OF PUBLICATIONS AND PRESENTATIONS

Publications

Suvaal I, Hummel SB, Mens JM, van Doorn HC, van den Hout WB, Creutzberg CL, Ter Kuile MM. **A sexual rehabilitation intervention for women with gynaecological cancer receiving radiotherapy (SPARC study): design of a multicentre randomized controlled trial**. *BMC Cancer* 2021; 21(1): 1295. doi:10.1186/s12885-021-08991-2.

Suvaal I, Kirchheiner K, Nout RA, Sturdza AE, Van Limbergen E, Lindegaard JC, Putter H, Jürgenliemk-Schulz IM, Chargari C, Tanderup K, Pötter R, Creutzberg CL, Ter Kuile MM. **Vaginal changes, sexual functioning and distress of women with locally advanced cervical cancer treated in the EMBRACE vaginal morbidity substudy**. *Gynecol Oncol* 2023; 170:123-132. doi: 10.1016/j.ygyno.2023.01.005.

Suvaal I, Hummel SB, Mens JM, Tuijnman-Raasveld CC, Tsonaka R, Velema LA, Westerveld H, Cnossen JS, Snyers A, Jürgenliemk-Schulz IM, Lutgens LCHW, Beukema JC, Haverkort MAD, Nowee ME, Nout RA, de Kroon CD, van den Hout WB, Creutzberg CL, van Doorn HC, Ter Kuile MM. **Efficacy of a nurse-led sexual rehabilitation intervention for women with gynaecological cancers receiving radiotherapy: results of a randomised trial**. *Br J Cancer* 2024; 131(5):808-819. doi: 10.1038/s41416-024-02775-8.

Suvaal I, van den Hout WB, Hummel SB, Mens JM, Tuijnman-Raasveld CC, Velema LA, Westerveld H, Cnossen JS, Snyers A, Jürgenliemk-Schulz IM, Lutgens LCHW, Beukema JC, Haverkort MAD, Nowee ME, Nout RA, de Kroon CD, van Doorn HC, Creutzberg CL, Ter Kuile MM. **Cost-effectiveness of a nurse-led sexual rehabilitation intervention for women treated with radiotherapy for gynaecological cancer in a randomized trial**. *Radiother Oncol* 2025; 203:110683. doi: 10.1016/j.radonc.2024.110683.

Myrtveit-Stensrud L, Ekholm E, Flink I, Ter Kuile MM, Engman L, Suvaal I, Groven KS, Reme SE. **Partner responses to pain among male partners of women with provoked vestibulodynia - a cross-sectional study**. *Pain Rep* 2025; 10(2):e1265. doi: 10.1097/PR9.0000000000001265.

(Inter)national conference presentations

January 2020:	Oral presentation at the annual EMBRACE meeting in Vienna, Austria
November 2020:	Oral presentation at the 57th Gynaecongress (online)
November 2021:	Oral presentation in the lecture series Sexual Medicine & Oncology (AASM) (online)
June 2022:	Oral presentation at the lustrum congress of NVVS, TvS, VVS in Ede, Netherlands
February 2023:	Oral presentation at the European Society for Sexual Medicine (ESSM) congress in Rotterdam, Netherlands
March 2023:	Oral presentation at the annual EMBRACE meeting (online)
October 2023:	Oral poster discussion at the European Society of Gynaecological Oncology (ESGO) congress in Berlin, Germany
September 2023:	Oral presentation at the World Congress of the International Psycho-Oncology Society (IPOS) in Milan, Italy
March 2024:	Poster presentation at the European Society of Gynaecological Oncology (ESGO) congress in Barcelona, Spain
September 2024:	Workshop at the World Congress of the International Psycho-Oncology Society (IPOS) in Maastricht, Netherlands
December 2024:	Oral presentation at the Masterclass Gynaecologic Oncology for nurses provided by Stichting Oncowijs in Amersfoort, Netherlands
March 2025:	Oral presentation at the 25th IGO-Doelencongress in Rotterdam, Netherlands
December 2025:	Oral presentation at the Masterclass Gynaecologic Oncology for nurses provided by Stichting Oncowijs in Amersfoort, Netherlands

CURRICULUM VITAE

Isabelle Suvaal werd geboren op 7 december 1990 in Rotterdam. In 2010 behaalde zij haar vwo-diploma aan het Luzac College te Leiden, waarna zij in 2011 begon met de bachelor Psychologie aan de Vrije Universiteit Amsterdam. Na het afronden van deze studie startte zij in 2015 met de tweejarige master Seksuologie aan de Katholieke Universiteit Leuven in België. Aansluitend volgde zij haar master Klinische Psychologie aan de Vrije Universiteit Amsterdam, waarbij zij haar klinische- en thesis stage deed bij de LUMC-polikliniek Psychosomatische Gynaecologie en Seksuologie. In 2019 begon Isabelle, naast haar werk als onderzoeksassistent, met haar promotietraject rond de SPARC studie (huidig proefschrift). Naast haar (wetenschappelijke) onderzoek bleef Isabelle werkzaam als psycholoog/seksuoloog op de polikliniek Psychosomatische Gynaecologie en Seksuologie. In 2024 was zij medeoprichter van De Intimiteitspraktijk in Amsterdam, een praktijk voor mensen met seksuele disfuncties. In 2025 begon Isabelle met de tweejarige post-masteropleiding tot GZ-psycholoog bij de afdeling Psychiatrie en Psychologie van het LUMC. In het eerste jaar werd zij gedetacheerd naar GGZ Rivierduinen, polikliniek Volwassenen, te Katwijk. Zij verwacht haar opleiding eind 2026 af te ronden, waarna zij hoopt haar klinische interesses en (wetenschappelijke) onderzoeksambities, in één functie te kunnen blijven combineren.

DANKWOORD

Iedereen die heeft bijgedragen aan de SPARC studie en aan de totstandkoming van mijn proefschrift wil ik bedanken. Graag bedank ik een aantal personen in het bijzonder, uiteraard in willekeurige volgorde van belangrijkheid.

Allereerst gaat mijn grote dank uit naar alle vrouwen en hun partners die, na een intensieve behandeling voor gynaecologische kanker, bereid waren om mee te doen aan de SPARC studie. Hun inzet om bij te dragen aan beter inzicht en een betere kwaliteit van leven voor toekomstige patiënten is bijzonder waardevol. Tevens dank ik Patiëntenvereniging Olijf voor haar waardevolle betrokkenheid tijdens verschillende fases van deze studie.

Dank aan alle radiotherapeut-oncologen, gynaecologisch-oncologen, verpleegkundigen, brachytherapie-laboranten, seksuologen en research-nurses afkomstig uit alle tien gynaecologische oncologiecentra in Nederland. Zonder jullie samenwerking en grote inzet was het deelnemersaantal van 229 vrouwen nooit behaald en hadden we de SPARC studie nooit kunnen uitvoeren.

In het bijzonder wil ik mijn promotoren Moniek ter Kuile en Carien Creutzberg bedanken voor hun grote betrokkenheid en geduld tijdens mijn promotietraject. Dank voor het overbrengen van jullie diepgaande wetenschappelijke kennis, zowel op het gebied van de radiotherapie en oncologie als de psychologie en seksuologie. Jullie steun en geloof in mij hebben in belangrijke mate bijgedragen aan het voltooien van dit eindproduct. Lisanne Hummel, ook jou dank ik voor het mij wegwijs maken in de fijne kneepjes van onderzoeksland, ik had me geen fijnere postdoc kunnen wensen.

Dank aan al mijn (ex)collega's van de poli Seksuologie (Aart, Ellen, Johanneke, Lotte, Rosemarije, Sandra, Stephanie, stagiaires). Jullie collegialiteit hebben dit traject bijzonder gemaakt. In het speciaal bedank ik Charlotte Tuijnman-Raasveld. Zonder jou was er geen behandelprotocol en geen training geweest. Dank voor alles wat je me hebt geleerd en dat ik altijd bij je terechtkon voor steun en gezelligheid.

Dank aan mijn mede-Gyn/Verlos-PhD-collega's, die er waren, kwamen en promoveerden tijdens mijn aanstelling: Angelos, Anne, Anne-Fleur, Géraldine, Kim B., Kim v. B., Kim v. N., Liseanne, Margot, Merlijn, Renske, Romy, Rozemarijn, Yaël en Yentl - zowel voor de vriendschap als het vinden van herkenning bij elkaar. Zonder jullie was promoveren nooit zo leuk geweest! En daarnaast: Ivanka, zonder jouw ondersteuning zouden wij als PhD'ers nergens zijn.

Anne-Sophie, dank dat jij aan mijn zijde staat als paranimf. Je begrijpt, een puur tactische keuze uiteraard, want mocht ik flauwvallen tijdens de verdediging, weet ik dat jij het wel kan overnemen. Ik kon bij jou altijd terecht als ik weer eens iets niet begreep van het medische, radiotherapeutisch-oncologische vakgebied. Maar daarnaast vonden wij elkaar in humor en vriendschap, die ik uiteraard zeer koester.

David, jij staat niet alleen aan mijn zijde in het leven, maar ook als paranimf tijdens een van de meest bijzondere dagen in mijn leven. Ik had het niet anders willen zien. Voor jouw onvoorwaardelijke steun en geduld tijdens mijn promotietraject ben ik je eeuwig dankbaar. En ja, ik beloof dat ik voorlopig even geen nieuwe opleidingen start.

Lieve Monique, mama, dank voor zoveel. Mijn grootste cheerleader, onvoorwaardelijke liefde en de (vaak nodige) peptalks tijdens dit proces hebben mij er doorheen gesleept. Mijn doorzettingsvermogen heb ik absoluut van jou meegekregen. Ik hou van jou, van hier tot aan de maan en drie rondjes eromheen.

Dank aan al mijn lieve (bonus- en schoon)familie. In het bijzonder dank ik Peter: van het brengen naar balletlessen toen ik een klein meisje was, tot het brengen van muziek en huisdieren in mijn leven en het altijd luisterende oor aan de telefoon; Sylvia, want ik ben toch ook een beetje jouw kind? Et Alicia, ma chère petite sœur, nous formons une véritable équipe.

Last but not least, dank aan al mijn vriendinnen en vrienden voor de ontspanning, steun, wijze raad en enthousiaste reacties op tussentijdse mijlpalen. Jullie betrokkenheid en vriendschap betekenen meer dan woorden kunnen uitdrukken. Lisa, 1000 maal dank voor het maken van de kaft en illustraties. Mara, al 30 jaar mijn bestie: ontpop nu die mini Piper Heidsiecks maar!