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Sexual rehabilitation after radiotherapy for gynaecological cancer

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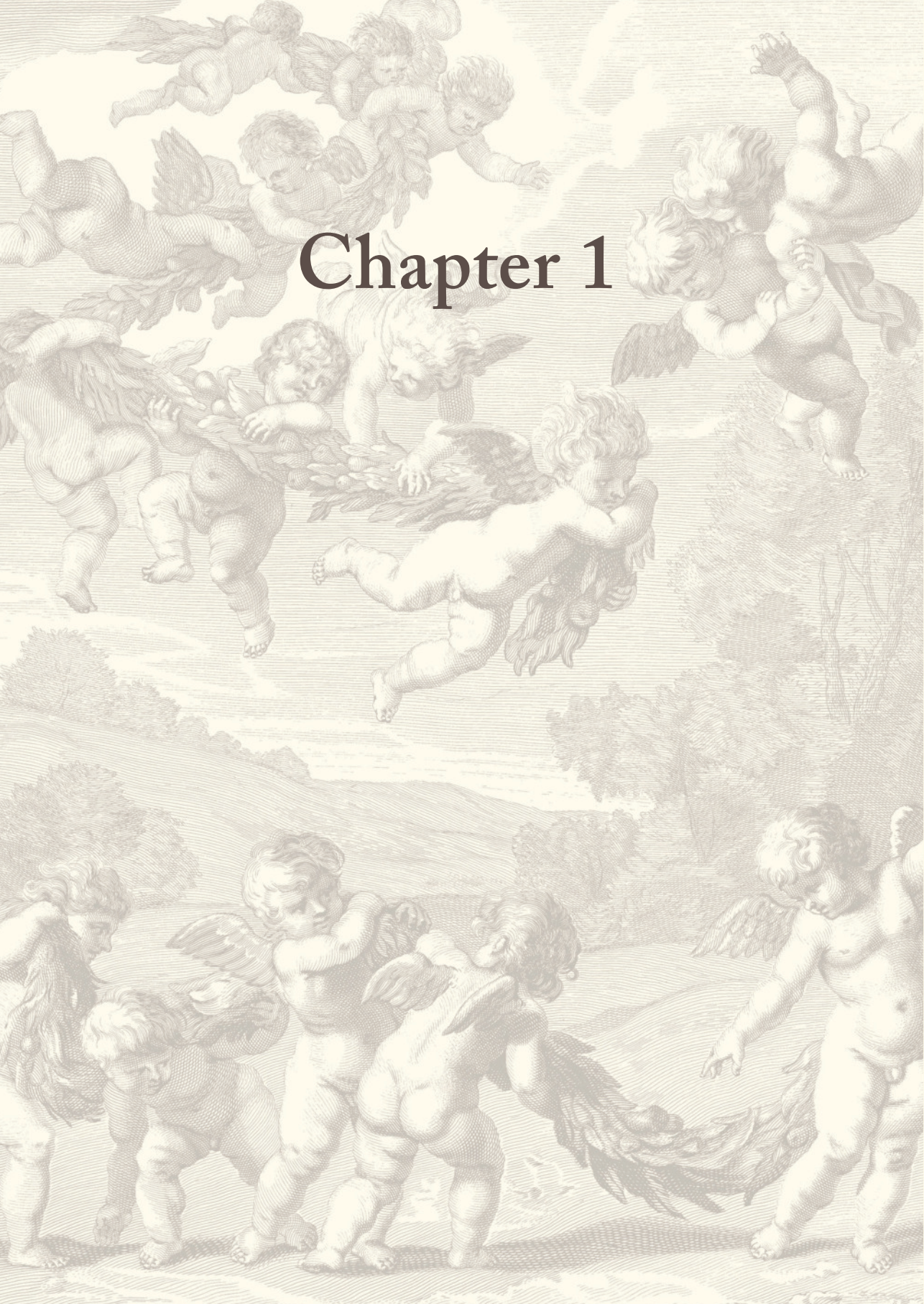
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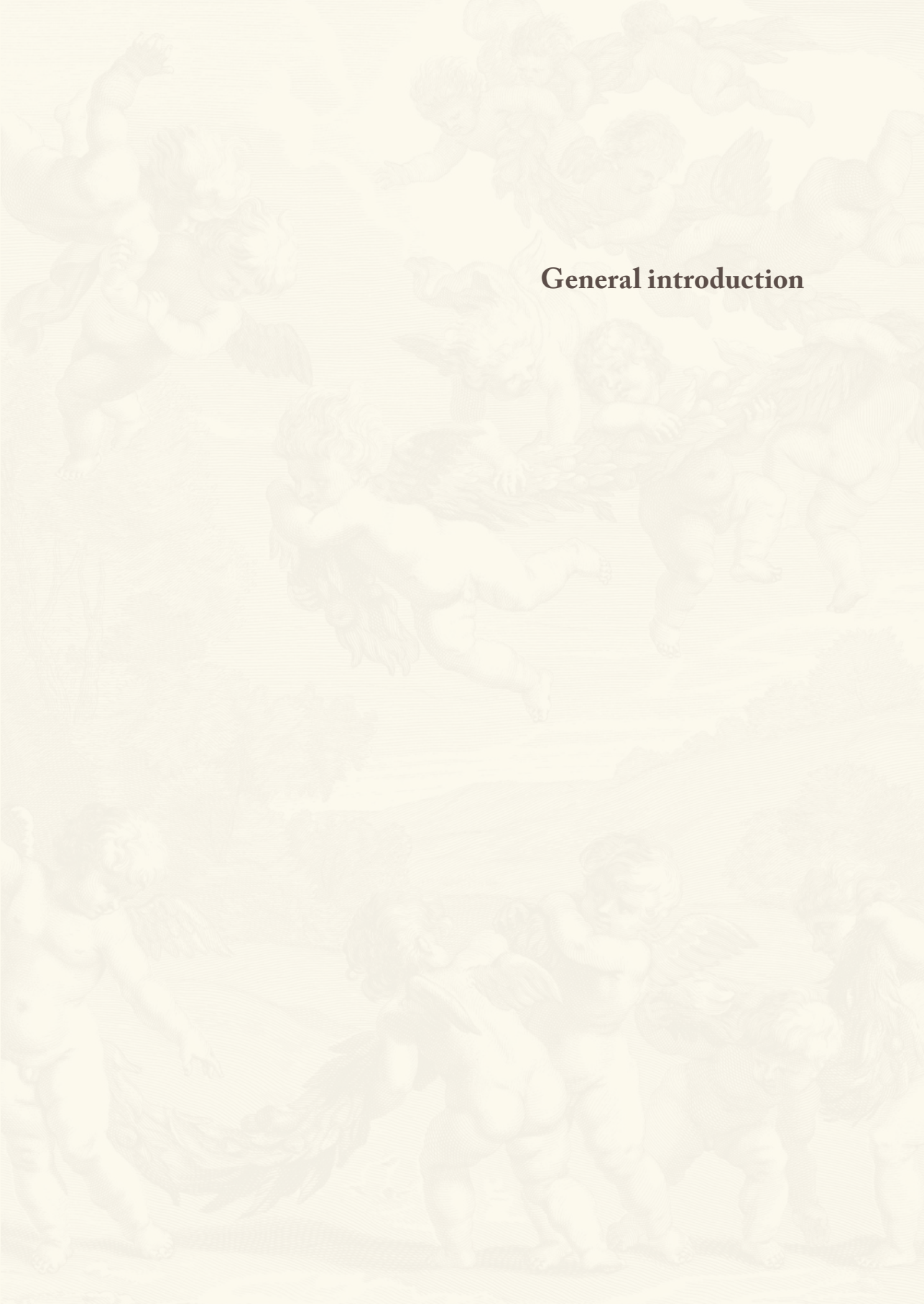
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Chapter 1





General introduction

Epidemiology and treatment of gynaecological cancers

The incidence of gynaecological cancers, including cervical, vaginal, and endometrial cancers, has been increasing¹. 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 surgery². Approximately 30–40% of patients receive radiotherapy, as adjuvant treatment in case of risk factors, and as primary treatment in more advanced stages of disease³. 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 fibrosis⁴. 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 group⁵, has significantly improved local disease control and survival rates in cervical cancer patients⁶. 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 treatment¹⁴. Despite its potential benefits, overall compliance has been low, with only about 30% of women adhering to the instructions, even after receiving counselling¹⁵⁻¹⁸. Common barriers to regular use include difficulty with planning, lack of time or privacy, forgetting, and other recovery-related challenges such as fatigue and anxiety¹⁹.

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 activity²⁰⁻²⁹. 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 intercourse³⁰. 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 changes¹⁴. 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 actively³³.

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 survivors³⁶⁻³⁹. 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 training³⁶. 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 radiotherapy⁴⁰. 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 study⁴⁰ 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**.

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