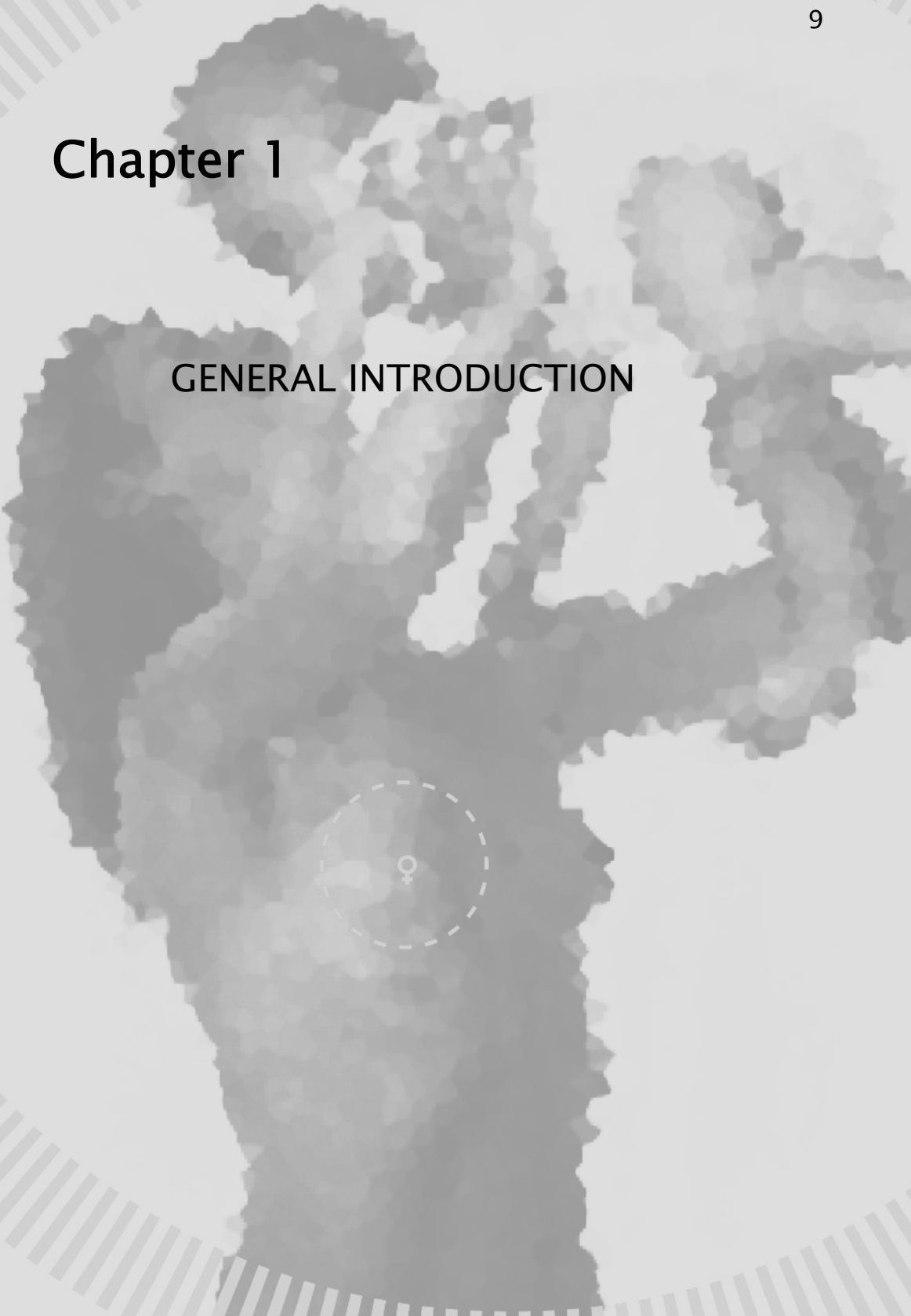
Chapter 1

GENERAL INTRODUCTION



GENERAL INTRODUCTION

Breast cancer is a major public health problem. It is the most common malignancy in women. Breast cancer accounts for one-third of all cancers in females and 24% of the patients are younger than 55 years of age. The number of women with breast cancer is increasing. Each year, over 1.1 million females worldwide are diagnosed with breast cancer and 410,000 women die of the disease. More than 10% all Dutch women will develop breast cancer and 70-80% of all breast cancer patients will survive over 5 years.
In the absence of distant metastases, patients receive loco-regional therapy with or without adjuvant systemic therapy. Loco-regional therapy consists of either a modified radical mastectomy, in some cases followed by local radiotherapy or breast-conserving surgery with removal of the primary tumor and axillary lymphadenectomy followed by irradiation. Adjuvant therapy is aimed at destroying micro metastases, and consists of chemotherapy, hormonal treatment and the antibody trastuzumab against the epidermal growth factor *HER2*, or a combination. These adjuvant treatments have successfully resulted in a lowering of the risk of recurrence and death of this disease. The side effects of adjuvant treatments however can cause physical and psychological problems and the number of patients receiving adjuvant systemic therapy is rising. On top of this the period over which hormonal therapy is administered has increased to several years. The higher change to survive in combination with the rising number of treated patients makes the long-term side effects of breast cancer treatment of utmost value. In 1948, Karnofsky et al reported the first efforts of physicians to assess the effect of cancer treatments on patients' quality of life, not just on the quantity of life. The recognition that the patient's well-being is an important issue has grown over the last quarter of a century. Health Related Quality of Life (HRQoL) is a broad concept, which takes many factors into account, including physical, emotional, sexual, social, and cognitive functions, as well as symptoms of disease and treatment. All these various functions and symptoms are assessed by and from the perspective of the patient. Better knowledge about the impact of adjuvant therapy on HRQoL is important for the evaluation of treatment, for adequate information to patients about future health effects, for treatment decision by physicians and patients and for interventions that reduce the negative effects of the treatment.

This thesis focuses on a number of potential long-term side effects of adjuvant breast cancer treatment. Because of the dismal prognosis of patients with

extensive axillary nodal involvement, over the last 10 years a variety of new treatment regimens has been tested. These include adjuvant dose-dense, as well as high-dose chemotherapy with hematopoietic stem-cell reinfusion. In a large multi center prospective Dutch study patients were randomized between a conventional and high-dose chemotherapy regimen, both followed by radiotherapy and tamoxifen. In this study HRQoL was included as a secondary endpoint.

CONTENTS OF THE THESIS

In **Chapter 2** we evaluated and compared Health Related Quality of Life (HRQoL) after conventional- and high-dose adjuvant chemotherapy in patients with high-risk breast cancer. Patients were randomized between a conventional and high-dose chemotherapy regimen, both followed by radiotherapy and tamoxifen. HRQoL was evaluated until disease progression, using the Short-Form 36 (SF-36), Visual Analogue Scale (VAS) and Rotterdam Symptom Checklist (RSCL) and assessed every 6 months for 5 years following randomization. For the SF-36, data from healthy Dutch women with the same age distribution served as reference value.

A frequently mentioned symptom by many patients in this study was fatigue. Other studies also found that many cancer survivors report fatigue after the completion of cancer treatment. Fatigue is reported to be highly distressing to patients and is limiting the quality of life. A better understanding of long-term fatigue in cancer survivors is, thus, fundamental to the development of appropriate intervention strategies. In **Chapter 3** fatigue after breast cancer treatment was addressed. We investigated whether standard or high-dose chemotherapy leads to changes in fatigue, hemoglobin (Hb), mental health, muscle and joint pain, and menopausal status from pre- to post-treatment and to evaluate whether fatigue is associated with these factors in disease-free breast cancer patients. Eight hundred eighty-five patients were randomly assigned between two chemotherapy regimens both followed by radiotherapy and tamoxifen. Fatigue was assessed using vitality scale, poor mental health using mental health scale both of Short-Form 36, muscle and joint pain with Rotterdam Symptom Checklist, and Hb levels were assessed before and 1, 2, and 3 years after chemotherapy.

Besides fatigue, hot flashes are often reported by patients with a history of breast cancer. Breast cancer patients experience more frequent and more severe hot flashes than healthy postmenopausal women. This is mainly the result of systemic breast cancer treatment such as chemotherapy and endocrine therapy.

Cytotoxic agents induce ovarian damage, which can become clinically manifest by the sudden onset of menopause. The abrupt and premature induction of menopause by chemotherapy may lead to exaggerated menopausal symptoms, including hot flashes.

Endocrine agents such as tamoxifen, aromatase inhibitors, and luteinizing hormone releasing hormone (LHRH) analogues are all used in the treatment of early or advanced breast cancer and hot flashes are a frequent side effect. Treatment of these hot flashes is relevant, because they may impair quality of life and may negatively influence adherence to endocrine treatment. In **Chapter 4** a literature search was conducted concerning the pathophysiologic mechanisms leading to hot flashes, their prevalence and severity in breast cancer patients, their influence on HRQoL, and the therapeutic options. Venlafaxine and clonidine are two non-hormonal treatment options. A randomized, prospective double blind study was performed comparing venlafaxine and clonidine as treatment of hot flashes in breast cancer patients. Side effects, efficacy, quality of life and sexual functioning were investigated and described in **Chapter 5**.

There are several types of endocrine treatment available such as selective estrogen receptor modulators (SERMs), non-steroidal and steroidal aromatase inhibitors, progestins and luteinising hormone-releasing hormone (LHRH) agonists. Endocrine treatment is based on the presence of estrogen receptor and/or progesterone receptor status of the breast cancer cells. These drugs are targeted either directly at the estrogen receptor (tamoxifen) or at eliminating the estrogen production. The latter is achieved by inhibiting the conversion of androgens into estrogens (aromatase inhibitors) or by blocking on the hypothalamic-pituitary axis (LHRH analogues). A more direct way is surgical removal of the ovaries. Endocrine treatment is an important treatment modality in the adjuvant and palliative setting for breast cancer patients. The long-term impact of endocrine therapies is increasingly relevant, as patients are treated for many years, the number of breast cancer survivors is increasing and more and younger women are treated with this modality. **Chapter 6** provides a literature-based overview of side effects of hormonal treatment in pre- and postmenopausal breast cancer patients, both in the early and advanced cancer and the influence on HRQoL and sexuality. The best-known drug for the treatment of breast cancer is tamoxifen, a non-steroidal anti-estrogen. Unfortunately tamoxifen may increase the risk of endometrial carcinoma two- to threefold, but this is exclusively described in postmenopausal women. In **Chapter 7** the frequent occurrence of hyperplasia of the stroma of the endometrium in a postmenopausal patient after 2 years of tamoxifen treatment is documented and reported. Data on gynaecological effects of tamoxifen in

premenopausal women are scarce. In **Chapter 7.1** a case report of a postmenopausal woman with breast cancer using tamoxifen is described which illustrates that tamoxifen can induce gynaecological changes that raise diagnostic problems.
In **Chapter 7.2** we investigated the influence of tamoxifen on the endometrium and the menstrual cycle in premenopausal breast cancer patients. Breast cancer patients using tamoxifen and 55 years of age or younger were investigated. Transvaginal ultrasonography was performed and serum levels of estradiol and follicle-stimulating hormone were determined. Patients with an endometrial response of >12 mm were offered an hysteroscopy and curettage.
Finally in **Chapter 8,** a summary is given of this thesis together with some future perspectives for further research in this area.