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Chapter 1

General Introduction and Outline of This Thesis
Breast cancer is the most common type of cancer in women in the western world. In the Netherlands alone, one in eight women will develop breast cancer at some point in her lifetime, with a majority occurring after the age of 50. In postmenopausal women, the majority of breast tumors grow under the influence of the reproductive hormones, estrogen and progesterone. Characterized by the presence of hormone receptors, these tumors are frequently referred to as ‘endocrine’-sensitive.

The first major advancement in the treatment of endocrine-sensitive breast cancer was made in 1896 when the surgeon, Sir George Thomas Beatson, reported on a number of breast tumors that diminished in size after removal of the ovaries of these women. Beatson compared the growth of breast cancer to changes during lactation, describing that “…the changes that take place in the mammary gland in the process of lactation are almost identical, up to a certain point, with what takes place in a cancerous mamma.” He also writes that “…it is custom in certain countries to remove the ovaries of the cow after calving if it wished to keep up the supply of milk, and if this is done the cow will go on giving milk indefinitely.” Beatson proposed that the removal of the ovaries would “…arrest cell proliferation and [convert] the cells into fatty matter.” This observation marked the beginning of a new development in the treatment of breast cancer and, more than a century later, the principle withstands and breast cancer surgery is frequently accompanied by additional (adjuvant) endocrine therapy in patients whose tumors are estrogen receptor (ER)- and/or progesterone receptor (PR)-positive. Different types of endocrine therapy work by lowering the levels of circulating estrogens or by blocking the ER, reducing the risk of disease recurrence in patients with endocrine-sensitive breast cancer.

\section*{Adjuvant endocrine therapy}

In the early 1960s, tamoxifen, a selective modulator of the ER, was developed by Dr. Arthur L. Walpole and Dr. Dora Richardson, and was originally intended for contraceptive purposes. Around the same time, the presence of ER in breast tumors as well as estrogen-dependent breast cancer growth were confirmed, leading to the exploration of its potential use for endocrine-sensitive breast tumors. In the years that followed, tamoxifen established itself as standard adjuvant endocrine therapy for women with hormone-dependent breast cancer following several adjuvant clinical trials, showing significant reductions in both breast cancer recurrence and mortality.

In 1977, an alternative approach to improving breast cancer treatment through inhibition of the aromatase enzyme was proposed by Brodie and colleagues. Aromatase inhibitors (AIs) decrease the levels of circulating estrogens through inhibition of the aromatase enzyme, which facilitates the conversion of androgens to estrogens. The incorporation of aromatase inhibitors (AIs) into adjuvant endocrine therapy regimens in the years that followed harbored a great promise. Initially, AIs were studied as part of a sequential treatment regimen, following 2-3 years of tamoxifen. Trials that compared tamoxifen monotherapy with sequential treatment included the Intergroup Exemestane Study (IES), which compared 5 years of tamoxifen with...
2-3 years tamoxifen followed by exemestane for 3-2 years (total of 5 years). In this trial, significantly better disease-free survival (DFS) and overall survival (OS), as well as fewer recurrent breast cancer events were observed in patients in the sequential therapy group. In a combined analysis of the Austrian Breast and Colorectal Cancer Study Group (ABCSG)-8 trial and the Arimidex-Nolvadex (ARNO) 95 trial, sequential therapy consisted of switching to anastrozole after 2-2.5 years of tamoxifen. This analysis revealed small improvements in DFS (hazard ratio (HR), 0.6 (95%CI 0.44-0.81), p=0.0009) and treatment toxicities. Finally, the Italian Tamoxifen Anastrozole (ITA) trials, which compared 5 years of tamoxifen alone with tamoxifen followed by anastrozole, showed improvements in relapse-free survival (RFS) (HR 0.64 (95%CI 0.44-0.94), p=0.023).

Meanwhile, the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial had been initiated, which randomized postmenopausal, hormone receptor-positive breast cancer patients to 5 years of tamoxifen or anastrozole and revealed improvements in DFS and distant DFS, as well as a reduction in contralateral breast cancers (CBC). In addition, the Breast International Group (BIG) 1-98 and Tamoxifen and Exemestane Adjuvant Multinational (TEAM) trials compared the efficacy and safety of sequential treatment with AI monotherapy. The BIG 1-98 trial compared several five-year endocrine treatment regimens (letrozole, letrozole followed by tamoxifen, tamoxifen, and tamoxifen followed by letrozole). The analysis compared letrozole and letrozole followed by tamoxifen with tamoxifen and tamoxifen followed by letrozole. A meta-analysis of the different randomized trials comparing tamoxifen with different AI regimens (either alone or after 2-3 years of tamoxifen) by Dowsett et al. showed that 5 years after diagnosis, both AI monotherapy and sequential treatment markedly reduced absolute tumor recurrence rates when compared with 5 years of tamoxifen monotherapy (p<0000.1 in both cohorts).

The TEAM trial was originally designed to compare 5 years of exemestane with 5 years of tamoxifen in postmenopausal women with hormone receptor-positive breast cancer. After the results of IES were reported, however, the TEAM protocol was amended. Five years of exemestane monotherapy were compared with tamoxifen (for 2.5-3 years) followed by exemestane (for 2.5-2 years), also for a total of 5 years. In this multinational study, almost 10,000 patients were assigned either sequential treatment or exemestane alone. The aims of this study were to compare the efficacy and safety of exemestane alone with sequential treatment. After a median follow-up of 5.1 years, there were no statistically significant differences between the two treatment groups: 85% of the patients in the sequential treatment group and 86% in the exemestane alone group were disease free (HR 0.97, 95%CI 0.88-1.08; p=0.60).

**Extended adjuvant endocrine therapy**

In recent years, investigations of extended (more than 5 years) adjuvant therapy with an AI have been initiated and are showing improved outcomes when patients are treated with an AI for longer than 5 years. One of the first studies to investigate extended adjuvant endocrine therapy was the MA.17 study, a placebo-
controlled trial that randomized postmenopausal women after five years of tamoxifen, to five years of placebo or five years of letrozole. The study was un-blinded after the first interim analysis revealed a 43% reduction in disease recurrence (p=0.00008) in favour of letrozole. Patients treated with placebo were given the choice of switching to letrozole. A comparison of patients who chose letrozole compared to patients who stayed on placebo after un-blinding revealed a DFS and distant DFS benefit in patients who switched to letrozole. Currently, several trials are investigating the most optimal treatment schedule in the extended adjuvant treatment setting. The Investigation on the Duration of Extended Adjuvant Letrozole (IDEAL) trial is the first prospective, randomized controlled trial to compare 2.5 with 5 years of extended adjuvant letrozole, after 5 years of any adjuvant endocrine therapy regimen (tamoxifen, AI monotherapy or sequential therapy). The study comprises 1824 patients and final results of this trial are eagerly awaited.

**Neo adjuvant endocrine treatment**

It was not until the last part of the 20th century that the notion of pre-operative, also known as neoadjuvant, systemic therapy came into use. The advent of post-operative systemic therapy for early breast cancer had prompted the need for better control of both locoregional and micrometastatic tumor growth. This paradigm shift resulted in the use of neoadjuvant systemic therapy for treating large or inoperable breast cancers. One of the first trials to study neoadjuvant chemotherapy was the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 trial, which compared pre-operative with post-operative chemotherapy (doxorubicin (Adriamycin) and cyclophosphamide (Cytoxan; AC), every 21 days, 4 courses). The pre-operative treatment arm permitted more breast conservation, especially in women who had been candidates for mastectomy earlier, while survival outcomes did not differ between the pre-operative and post-operative study groups.

At the same time in 1984, the European Organization for Research and Treatment of Cancer (EORTC) Breast Cancer Cooperative Group devised two prospective, randomized trials (EORTC 10850 and 10851). The studies compared modified radical mastectomy (MRM) to wide local excision (WLE) with tamoxifen (EORTC 10850) and MRM to tamoxifen only (EORTC 10851) in older (≥70 years) breast cancer patients. OS was similar for both treatment groups in the two studies, and the time to distant disease progression was improved in tamoxifen- and WLE-treated patients (EORTC 10850). Both studies, however, showed shorter times to local disease progression in tamoxifen-treated patients. Although tamoxifen alone was not recommended for older breast cancer patients, based on the results of the EORTC 10851 study, it was evident that the addition of endocrine therapy might contribute to performing less extensive surgery. In the years that have since followed, several studies have investigated the use of neoadjuvant endocrine therapy for enabling downsizing and downstaging of large or inoperable hormone receptor-positive breast tumors, as well as allowing for a better insight into the effects of endocrine therapy on tumor biology and treatment response.
The scope of breast cancer treatment is multifactorial, and combines surgical intervention with systemic therapy, which comprises endocrine therapy, chemotherapy, potentially in combination with targeted therapy, as well as radiotherapy as the main treatment modalities. National and international treatment guidelines currently provide recommendations for surgical and pharmacologic interventions for breast cancer treatment.\textsuperscript{34, 35} Needless to say, these guidelines have targeted the entire population of breast cancer patients, and guidance for individual patients is less prominent. Conventional variables such as age, tumor stage, differentiation grade, overexpression of Human Epidermal growth factor Receptor 2 (HER2), and the presence of ERs and PRs are commonly used to guide treatment decisions, while more patient-specific features are less frequently accounted for. The patient also plays a key role in successful treatment and, having said this, we are seeing a growing trend towards tailoring breast cancer treatment to the individual at hand. In this thesis, we study tumor- and patient-specific characteristics and their capacity to aid the decision-making process with respect to endocrine treatment.

The studies that make up this thesis are based on patient cohorts from three separate clinical trials. All trials included postmenopausal, hormone receptor-positive early breast cancer patients. Data from patients enrolled in the TEAM trial was utilized for all studies of adjuvant endocrine therapy. The TEAM trial compares 2-3 years of tamoxifen followed by 3-2 years of exemestane (sequential therapy) with 5 years of exemestane only.\textsuperscript{22} The IDEAL (Investigation of the optimal Duration of Extended Adjuvant Letrozole) trial compares 2.5 years with 5 years of extended adjuvant letrozole, after completion of 5 years of any adjuvant endocrine therapy regimen (either tamoxifen or AI monotherapy or sequential therapy).\textsuperscript{36} Lastly, the TEAM IIA study is a single-arm, prospective clinical trial investigating 6 months of neoadjuvant endocrine therapy.

PART I – Patient and tumor characteristics

Part I of this thesis includes studies of a variety of patient and tumor characteristics that influence the success of different adjuvant endocrine therapy regimens in postmenopausal early breast cancer patients, focusing on ways to tailor endocrine treatment to the individual patient. In chapter 2 and chapter 3, we study the importance of tumor-biologic variations in the postmenopausal endocrine-sensitive breast cancer population with respect to choosing the optimal endocrine treatment regimen for certain patient subgroups.

Lifestyle interventions, including physical activity and diet have shown to improve disease outcomes and may be especially helpful for certain subgroups of patients. It has been suggested that body-mass index (BMI) has a significant effect on breast cancer outcomes and endocrine treatment efficacy. In chapter 4, we study the effect of BMI on breast cancer outcomes and whether BMI can influence the success of different endocrine treatment regimens. Several studies have addressed the importance of maintaining a healthy body weight, as high BMI has been found to be associated with poorer survival in breast cancer patients.
It is well-known that physical activity, in general, can help improve body weight and physical functioning as well as help decrease the risk of developing breast cancer. The effect of physical activity on breast cancer survival has not been as well-studied, especially in the elderly population of breast cancer patients. In addition to poorer breast cancer outcomes, the elderly breast cancer population is at risk of greater functional decline following breast cancer diagnosis and treatment. Therefore, we investigate the effect of physical activity on breast cancer outcomes in the elderly population in chapter 5 and chapter 6.

Current prediction models play an important role in determining prognosis and treatment outcomes for various cancers, but are suboptimal in providing long-term prognostic information for an individual patient. These so-called ‘static’ models also fail to take into account that cancer patients may experience treatment- or disease-related events after diagnosis, which may change their individual prognoses. ‘Dynamic prediction’, a very novel concept in medicine, has the capability to account for such events, permitting a continuous update of a patient’s individual prognosis as the time since breast cancer diagnosis prolongs. In chapter 7, we present a dynamic prediction model that can help predict an individual patient’s five-year OS probability at any point in time in the first three years after breast cancer diagnosis.

**PART II – Quality of life, treatment compliance and side effects**

In Part II, we discuss the impact of endocrine therapy and its side effects on the daily lives of breast cancer survivors. Although adjuvant endocrine therapy has brought about significant improvements in prognosis, treatment with AIs and/or tamoxifen are often accompanied by debilitating side effects such as hot flashes, night sweats, bone, joint and muscle pains, in addition to several other symptoms. These side effects can have a significant impact on the quality of life in women, as is described in chapter 8. Severe side effects also pose a major threat to premature discontinuation of endocrine treatment, and with the emergence of recent studies showing that longer treatment durations significantly benefit prognosis, ways to improve compliance to therapy need to be addressed. In chapter 9, we report on factors associated with early treatment discontinuation in patients treated with extended adjuvant endocrine therapy. In chapter 10 and chapter 11, we test the hypothesis that specific side effects including vasomotor symptoms (hot flashes, night sweats) and musculoskeletal symptoms (bone and joint pain, muscle pain) are related to treatment effectiveness in breast cancer patients. Not all patients develop specific side effects of endocrine therapy, even if we omit the possibility of this being because patients do not take their prescribed medication. In chapter 12, we explore variations in the aromatase gene (CYP19A1) and how these variations may be related to the development of specific side effects.

**PART III – Pre-operative and operative treatment possibilities**

Owing to the possibility of performing less extensive surgery as well as studying a tumor’s response to systemic treatment, neoadjuvant therapy has gained much popularity in recent years. Part III presents opportunities for incorporating both neoadjuvant chemotherapy and neoadjuvant endocrine therapy into the treatment regimens of postmenopausal early breast cancer patients. In chapter 13, we introduce
the concept of neoadjuvant endocrine therapy and its more widespread applicability for postmenopausal patients with endocrine-sensitive breast tumors. Following the literature review, chapter 14 presents a prospective clinical trial that investigates six months of neoadjuvant endocrine therapy in endocrine-sensitive breast cancer patients. A concluding topic that has enjoyed much attention in the last years is the surgical treatment of the axillary lymph nodes in patients undergoing pre-operative systemic treatment for breast cancer. We review this issue in relation to neoadjuvant chemotherapy in chapter 15 and provide recommendations based on the available evidence. Finally, chapter 16 discusses how the studies that make up this thesis contribute to further personalization of endocrine therapy for hormone receptor-positive breast cancer patients and proposes possibilities to further facilitate patient-tailored treatment.
Reference List

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