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TAILORING ENDOCRINE TREATMENT FOR EARLY BREAST CANCER

Duveken B.Y. Fontein

TAILORING ENDOCRINE TREATMENT FOR EARLY BREAST CANCER

Duveken B.Y. Fontein

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TAILORING ENDOCRINE TREATMENT FOR EARLY BREAST CANCER

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CONTENTS

INTRODUCTION

Chapter 1. General introduction and outline of this thesis 7

PART I. PATIENT AND TUMOR CHARACTERISTICS

Chapter 2. Preferential endocrine therapy for postmenopausal early breast cancer patients: a Dutch and Belgian TEAM trial sub-study 19

Chapter 3. Influence of semi-quantitative estrogen receptor expression on adjuvant endocrine therapy efficacy in ductal and lobular breast cancer 33

Chapter 4. Body-mass index as a prognostic indicator in breast cancer patients treated with adjuvant endocrine therapy: an international TEAM trial analysis 49

Chapter 5. Age and the effect of physical activity on breast cancer survival: a systematic review 65

Chapter 6. Age in relation to physical activity and survival in postmenopausal hormone receptor-positive breast cancer patients – results of the TEAM-lifestyle study 81

Chapter 7. Dynamic prediction in breast cancer – proving feasibility in clinical practice using the TEAM trial 97

PART II. QUALITY OF LIFE, TREATMENT COMPLIANCE AND SIDE EFFECTS

Chapter 8. Quality of life in relation to tamoxifen or exemestane treatment in postmenopausal breast cancer patients – a TEAM trial sub-study 117

Chapter 9. High non-compliance in patients treated with extended adjuvant letrozole. Results from the IDEAL randomized trial 131

Chapter 10. Relationship between specific adverse events and efficacy of exemestane therapy in early postmenopausal breast cancer patients 145

Chapter 11. Specific adverse events predict survival benefit in patients treated with tamoxifen or aromatase inhibitors – an international TEAM trial analysis 161

Chapter 12. Germline variants in the CYP19A1 gene are related to specific adverse events in aromatase inhibitor users: a sub-study of Dutch TEAM trial patients 177

PART III. PRE-OPERATIVE AND OPERATIVE TREATMENT POSSIBILITIES

Chapter 13. Neoadjuvant endocrine therapy in endocrine-sensitive breast cancer – a systematic review 197

Chapter 14. Efficacy of six months neoadjuvant endocrine therapy in postmenopausal, hormone receptor-positive breast cancer patients – a phase II trial 213

Chapter 15. Timing of the sentinel lymph node biopsy in breast cancer patients receiving neoadjuvant therapy – recommendations for clinical guidance 231

DISCUSSION

Chapter 16. General discussion 247

APPENDICES 259

Summary in English and Dutch (Nederlandse samenvatting)
Acknowledgements (Dankwoord)
List of Publications
Curriculum Vitae

CHAPTER

1

GENERAL INTRODUCTION AND OUTLINE OF THIS THESIS

INTRODUCTION

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.[1] 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.[2] 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."[2] 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."[2] Beatson proposed that the removal of the ovaries would "…arrest cell proliferation and [convert] the cells into fatty matter."[2] 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.[3, 4]

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.[5] Around the same time, the presence of ER in breast tumors as well as estrogen-dependent breast cancer growth were confirmed[6-9], leading to the exploration of its potential use for endocrine-sensitive breast tumors.[10] 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.[11-15]

In 1977, an alternative approach to improving breast cancer treatment through inhibition of the aromatase enzyme was proposed by Brodie and colleagues.[16] Aromatase inhibitors (AIs) decrease the levels of circulating estrogens through inhibition of the aromatase enzyme, which facilitates the conversion of androgens to estrogens.[17] 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.[18] 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.[19] 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).[20]

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).[21] 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.[22, 23] 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.[24] 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).[25]

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.[22] 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).[22]

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.[26] The study was un-blinded after the first interim analysis revealed a 43% reduction in disease recurrence (p=0.00008) in favour of letrozole.[27] 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.[28] 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).[29] The study comprises 1824 patients and final results of this trial are eagerly awaited.

Neoadjuvant 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.[30] 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).[30] 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.[31, 32] 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.[33]

OUTLINE OF THIS THESIS

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.[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.[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).[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.

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PART

I

PATIENT AND TUMOR CHARACTERISTICS

CHAPTER

2

PREFERENTIAL ENDOCRINE THERAPY FOR POSTMENOPAUSAL, EARLY BREAST CANCER PATIENTS: A DUTCH AND BELGIAN TEAM TRIAL SUB-STUDY

Duveken BY Fontein, Johanna GH van Nes, Johan WR Nortier, Hein Putter, Elma Meershoek-Klein Kranenbarg, Luc Y Dirix, Louk VAM Beex, Robert J Paridaens, Jan BE Smeets, John MS Bartlett, Cornelis JH van de Velde, Caroline Seynaeve

Submitted

ABSTRACT

Background

There is an ongoing effort to predict disease outcomes in breast cancer patients in order to personalize treatment. As adjuvant endocrine therapy plays a major role in the treatment of postmenopausal, endocrine-sensitive breast cancer patients, it is important to understand variations in this population and the preference of specific endocrine therapy regimens in various subgroups. We investigated preferential treatment benefits of sequential or upfront exemestane therapy in specific subgroups of Dutch and Belgian patients enrolled in the Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial.

Methods

The TEAM trial compares a sequential treatment regimen (tamoxifen 2.5-3 years followed by exemestane for 2.5-2 years) with exemestane alone for 5 years. Intention-to-treat analyses included 3168 Dutch and Belgian TEAM patients. Cox regression analyses, stratified by protocol-defined covariates, were performed to assess disease-free survival (DFS) and overall survival (OS). Additional analyses for DFS investigated quantitative hormone receptor expression according to the Allred score, and HER2 status in relation to treatment regimen.

Results

After a median follow-up of 6.91 years (range 0.06-11.41), overall hazard ratios (HR) for DFS and OS were 0.91 (95% confidence interval (CI) 0.85-1.04) and 0.93 (95%CI 0.80-1.08) respectively for upfront exemestane compared with sequential treatment. ER-rich patients had a significant DFS benefit when treated with upfront exemestane (HR 0.82 (95%CI 0.7-0.95), while ER-poor patients had an improved DFS with a sequential treatment regimen (HR 1.84 (95%CI 1.26-2.69), p-for-interaction=0.001). HER2 status did not show any treatment-by-marker interaction.

Discussion

Although exemestane alone compared with sequential treatment did not result in long-term differences in overall DFS or OS, certain subgroups of patients demonstrated a preferential treatment benefit for one over the other regimen.

INTRODUCTION

A majority of postmenopausal breast cancer patients have hormone receptor-positive breast tumors, their growth being driven by estrogens.[1, 2] Therapies have been developed to combat the effect of estrogens on tumor growth, either by selectively modulating the estrogen receptor (ER) as is the case with tamoxifen, or by blocking the conversion of androgens to estrogens through aromatase inhibitors (AIs). Tamoxifen and AIs both play a major role in the treatment of postmenopausal, hormone receptor-positive early breast cancer patients. In postmenopausal women, tamoxifen is usually followed by an AI, as the switch to an AI after 2-3 years of tamoxifen treatment showed benefits in disease-free survival (DFS) when compared with tamoxifen alone.[3, 4] AIs may be prescribed as part of a sequential treatment regimen (tamoxifen for 2-3 years followed by an AI for 3-2 years), upfront therapy for a period of five years, or extended treatment (following five years of tamoxifen therapy).[5-10] As adjuvant endocrine therapy assumes a long-term treatment commitment, it is important to understand variations in the population with hormone receptor-positive tumors and the role of endocrine therapy in relation to outcomes in different subgroups of patients.

Several prognostic factors are known to influence breast cancer survival, but data are limited regarding the predictive effects of these factors on the outcomes of different endocrine therapy regimens for specific subgroups of patients. For example, our analysis of semi-quantitative ER expression using the Allred score in relation to preferential treatment benefit in ductal and lobular breast cancer patients, specifically, showed a significant benefit of upfront exemestane over sequential treatment in ER-rich (ER Allred ≥7) patients.[11]

In establishing more tailored therapy for individual women, it is important to identify different predictive factors that can influence treatment success in order to enable physicians to select the most optimal treatment regimen together with their patients, whilst reducing the possibility of unnecessary side effects and minimizing the risk of disease recurrence. In the context of more extensive follow-up, we explored several tumor-specific factors in relation to preferential treatment benefit in Dutch and Belgian patients from the Tamoxifen Exemestane Adjuvant Multinational (TEAM) study.[10]

PATIENTS AND METHODS

TEAM Trial

The TEAM trial is a randomized, adjuvant, phase III, multinational, open label study conducted in postmenopausal breast cancer patients with ER- and/or progesterone receptor (PR)-positive tumors. Patients were randomized to receive a sequential treatment regimen, consisting of tamoxifen (20mg, once daily, orally) for 2.5-3 years, followed by exemestane (25mg, once daily, orally) for 2.5-2 years thereafter or five years of exemestane (25mg, once daily, orally). All patients provided written informed consent. The trial was registered in the Netherlands and Belgium with the Netherlands Trial Register, NTR 267.

Inclusion in the present study was limited to Dutch (n=2754) and Belgian (n=414) patients only (n=3168). The eligibility criteria for Belgium and the Netherlands comprised postmenopausal women with

histologically confirmed hormone receptor-positive early breast cancer, who had undergone primary surgery with curative intent and had an indication for adjuvant endocrine therapy according to Dutch and Belgian treatment guidelines.[12] Between July 2001 and February 2006, patients were enrolled in 79 hospitals throughout the Netherlands and Belgium. Database lock was on April 4th, 2013.

Data were collected locally on Case Report Forms and sent to the central datacenter in Leiden, the Netherlands. As part of the TEAM pathology study, central assessment of ER and PR status (according to the Allred score), and of HER2 status was performed in Edinburgh, United Kingdom.[13] The Allred score represents a combination of the percentage of cells that stain positive for hormone receptors and the intensity thereof.[14] Subgroup analyses investigated whether there was a beneficial effect on DFS for the different treatment arms in relation to three different biomarkers, including, ER Allred and PR Allred scores, and HER2 expression/gene amplification (positive/negative), with additional analyses for treatment-by-marker interactions.

The primary endpoint of the current investigation was disease-free survival (DFS), defined as the time from randomization to the earliest documentation of disease relapse (locoregional and/or distant recurrence or contralateral breast cancer) or death from any cause.[10] Secondary endpoints comprised overall survival (OS) and DFS outcomes for specific subgroups of patients, including age at randomization, ER Allred score (≤6/≥7), PR Allred score (≤4/≥5), and HER2 expression (positive/negative).

Statistical analyses

Statistical analyses were performed using SPSS 20.0 (SPSS, Chicago, IL). All analyses were performed as intention-to-treat analyses. To compare proportional differences between patients by randomized treatment, Pearson chi-square tests were used. Kaplan-Meier curves were plotted and Cox Proportional Hazard models investigated survival differences with respect to treatment arm (upfront exemestane compared with tamoxifen followed by exemestane). All analyses were stratified by protocol-defined stratification variables, including adjuvant chemotherapy (yes/no) and time between surgery and the start of randomized treatment (0-3 / 3-6 / >6 months). Interaction terms between treatment arm and grouping variable were included in the model to test for the presence of effect modification.

RESULTS

Patients

Out of 3168 patients, 1583 received sequential treatment and 1585 were allotted five years of upfront exemestane. Baseline tumor, patient, and treatment characteristics were equally distributed between the two treatment arms (Table 1). Median follow-up of patients alive was 6.91 years (range 0.06-11.41 years). Median age at randomization was 64.6 years (mean 63.5, range 38-96). Centrally revised information on ER, PR and HER2 status was available for approximately 85% of the patients.

Table 2 provides an overview of the major types of events and causes of death up to the most recent follow-up date. Disease relapse in both treatment arms mainly consisted of distant metastases. The majority of deaths in both the sequential treatment and the upfront exemestane groups were due to breast cancer (61.7% and 55.9% respectively), followed by second malignancy (10.8% and 14.5% respectively), and cardiovascular events (9.9% and 12.3% respectively; chi-squared p=0.036).

Table 1. **Baseline characteristics of Dutch and Belgian patients included in the TEAM trial**

	Tamoxifen → Exemestane (n=1583)		Exemestane only (n=1585)	
	n	%	n	%
Age				
<50	32	2.0	40	2.5
50-59	514	32.5	488	30.8
60-69	565	35.7	571	36.0
≥70	472	29.8	486	30.7
Tumor stage				
T1 (≤2cm)	670	42.3	718	45.3
T2 (>2-≤5cm)	788	49.8	757	47.8
T3 / T4 (>5cm)	122	7.7	106	6.7
unknown	3	0.2	4	0.3
Nodal stage				
Negative	487	30.8	476	30.0
Positive	1096	69.2	1106	69.8
unknown	0		3	0.2
Histological grade				
G1 (well)	226	14.3	232	14.6
G2 (moderate)	666	42.1	700	44.2
G3, G4 (poor)	602	38.0	551	34.8
unknown	89	5.6	102	6.4
Histological type				
Ductal	1096	69.2	1045	65.9
Lobular	220	13.9	243	15.3
Other	113	7.1	137	8.6
unknown	154	9.7	160	10.1
ER Allred score				
ER-poor (≤6)	172	10.9	151	9.5
ER-rich (≥7)	1188	75	1213	76.5
unknown	223	14.1	221	13.9
PR Allred score				
PR-poor (≤4)	325	20.5	311	19.6
PR-rich (≥5)	1014	64.1	1032	65.1
unknown	244	15.4	242	15.3
HER2 status				
Negative	1172	74.0	1175	74.1
Positive	165	10.4	153	9.7
unknown	246	15.5	257	16.2
Surgery				
Mastectomy	881	55.7	859	54.2
Wide local excision	702	44.3	725	45.7
No resection	0		1	0
Radiotherapy				
Yes	1023	64.6	1037	65.4
No	557	35.2	547	34.5
unknown	3	0.2	1	0.1
Chemotherapy				
Yes	530	33.5	527	33.2
No	1052	66.5	1058	66.8
unknown	1	0	0	

BR, Bloom&Richardson; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor-2.

Table 2. **Events in patients treated with sequential therapy or exemestane only**

	Tamoxifen → Exemestane		Exemestane only		
	n	%	n	%	p-value*
Total patients	**1583**		**1585**		
Total DFS events	431	27.2	407	25.7	0.251
Distant recurrence	223	14.1	187	11.8	
Locoregional recurrence	48	3	38	2.4	
Contralateral breast cancer	25	1.6	35	2.2	
Distant & locoregional recurrence	8	0.5	4	0.3	
Distant, locoregional and contralateral	1	0.1	1	0.1	
Unknown	2	0.1	4	0.3	
Total number of deaths	**334**	**21.1****	**317**	**20.0****	
Death due to breast cancer	*201*	61.7	*171*	55.9	0.036
Death due to second malignancy	*36*	10.8	*46*	14.5	
Cardiac causes	*33*	9.9	*39*	12.3	
Other causes	*64*	19.2	*61*	19.2	

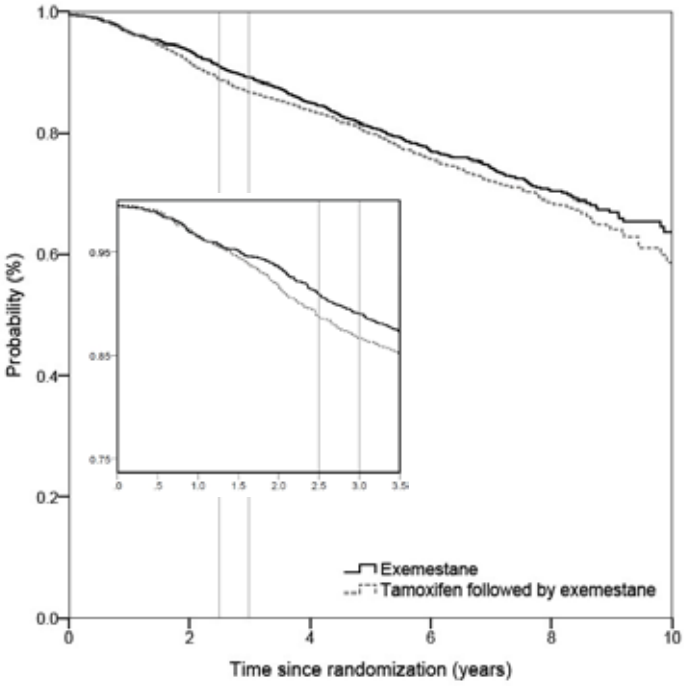
DFS, disease-free survival; *chi-squared p-value; **% deaths out of all patients.

Disease-free survival and overall survival

At the transition point from tamoxifen to exemestane (or 2.75 years for exemestane-treated patients), treatment with exemestane showed a significant DFS benefit when compared with tamoxifen (upfront exemestane: HR 0.780 (95%CI 0.631-0.965); p=0.022) (Figure 1). There was no difference in OS between sequential treatment and upfront exemestane at the time of treatment switch (HR 0.875 (95%CI 0.641-1.194); p=0.398).

Comparing sequential treatment with upfront exemestane until the most recent follow-up date, the previously observed difference between sequential treatment and upfront exemestane was no longer present. At 10 years of follow-up, DFS for the sequential treatment arm was 58.6% and was 63.6% for upfront exemestane (HR for upfront exemestane 0.911 (95%CI 0.795-1.044); p=0.179 (reference: tamoxifen followed by exemestane)) (Table 3). OS was 67.1% in the sequential arm and 68.6% in the upfront exemestane arm respectively (HR 0.927 (95%CI 0.795-1.081); p=0.333).

Figure 1. **Disease-free survival in patients treated with sequential treatment or exemestane only**



Time (years)	0	2	4	6	8	10
Sequential arm						
# of events		131	254	361	412	431
# Patients at risk	1583	1420	1276	781	306	35
Exemestane						
# of events		102	234	344	390	405
# Patients at risk	1585	1458	1313	799	314	54

Table 3. **Disease-free survival for exemestane only compared with sequential treatment in different subgroups of patients**

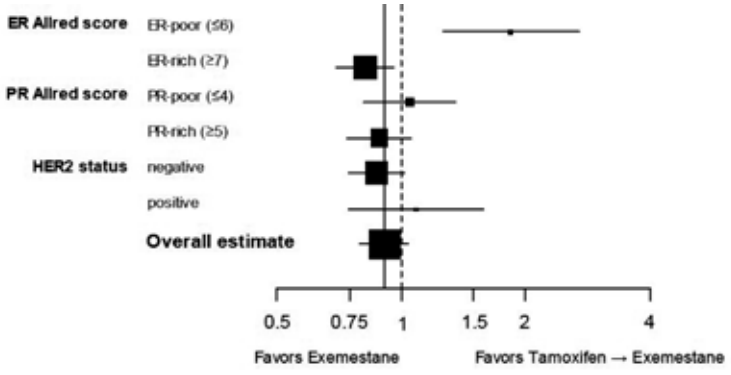
	n	# of events	Hazard Ratio (95%CI)*	p-value	*p* for interaction
All patients	3168	836	0.911 (0.795-1.044)**	0.179	-
ER Allred score					
ER-poor (≤6)	323	110	1.840 (1.257-2.694)	0.002	0.001
ER-rich (≥7)	2401	632	0.816 (0.698-0.954)	0.011	
PR Allred score					
PR-poor (≤4)	636	238	1.051 (0.815-1.356)	0.699	0.276
PR-rich (≥5)	2046	495	0.886 (0.742-1.056)	0.177	
HER2 status					
negative	2347	622	0.872 (0.745-1.020)	0.087	0.332
positive	318	108	1.084 (0.743-1.581)	0.676	

HR, Hazard Ratio; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor-2.
*univariate Cox regression analyses, sequential treatment served as the reference group (HR=1.0).
**multivariate analysis, stratified by adjuvant chemotherapy and time between surgery and the start of randomized treatment.

Biomarker analysis

The majority of patients (85%) had available data for ER and PR. Most patients had ER-rich (87%) and PR-rich (76%) tumors. In this cohort of patients, we found a significant treatment-by-marker interaction for ER Allred score and treatment regimen (p=0.001), with ER-rich patients having a significant DFS advantage when treated with upfront exemestane, and ER-poor patients showed better DFS with a sequential treatment regimen (reference: tamoxifen followed by exemestane: ER-poor: HR 1.840 (95%CI 1.257-2.694); p=0.002 and ER-rich: HR 0.816 (95%CI 0.698-0.954); p=0.011) (Figure 2).

Figure 2. **Forest plot depicting disease-free survival in relation to ER, PR and HER2 status in patients treated with five years of sequential treatment or upfront exemestane**



The impact of PR Allred scores (rich/poor) on preferential treatment for one of the two regimens was investigated in a similar fashion to ER Allred score. Unlike for ER expression, however, no preferential treatment benefit was demonstrated for PR Allred score in upfront exemestane-treated patients when compared with sequential treatment (PR-poor: HR 1.051 (95%CI 0.815-1.356); p=0.699 and PR-rich: HR 0.886 (95%CI 0.742-1.056); p=0.177, p-for-interaction=0.276).

Centrally reviewed HER2 status was also available for 2663 patients (84.1%). Approximately 12% of patients demonstrated HER2 overexpression (Table 1). Only two of the patients in this cohort were treated with trastuzumab (Herceptin®), owing to the year in which the TEAM study was conducted. HER2-positive patients showed poorer DFS outcomes than HER2-negative patients (DFS HR 1.375 (95%CI 1.121-1.687); p=0.002). However, neither preferential treatment benefit nor treatment-by-marker interaction were observed for HER2 status up to most recent follow-up for DFS (HER2-negative: HR 0.872 (95%CI 0.745-1.020); p=0.087, HER2-positive: HR 1.084 (95%CI 0.743-1.581); p=0.676, p-for-interaction=0.332).

DISCUSSION

In the present analyses, we report the intention-to-treat findings of the Dutch and Belgian TEAM patients with regard to DFS and OS outcomes of two commonly used endocrine therapy regimens in postmenopausal women with early breast cancer. At the time of switching from tamoxifen to exemestane, or 2.75 years for upfront exemestane-treated patients, treatment with exemestane showed better DFS outcomes when compared with tamoxifen. Needless to say, the survival curves converged again after this period. Both DFS and OS were similar with respect to endocrine therapy regimen after a median follow-up of almost 7 years. With respect to specific subgroups of patients, ER Allred score was associated with a preferential treatment benefit for one or the other treatment regimen. In the entire Dutch and Belgian TEAM trial cohort, ER-rich patients, as defined by the Allred score, had a significant DFS advantage when treated with five years of exemestane, when compared to a sequential treatment regimen. ER-poor patients, on the other hand, had an improved DFS with a sequential treatment regimen compared with upfront exemestane. Only ER Allred score demonstrated a significant treatment-by-marker interaction. PR Allred score and HER2 status were not predictive of a differential treatment benefit.

It is interesting to note that in the period until the switch from tamoxifen to exemestane, there were significant DFS and OS benefits in favour of the exemestane upfront treatment arm, although the curves converged thereafter and did not show a statistically significant difference in outcomes. This might be the result of switching from tamoxifen to exemestane in the sequential treatment arm. One may infer that the observed difference in risk reduction takes place during the initial years of treatment and recovers in the sequential group after the switch to exemestane is made. Of note, however, some patients treated with tamoxifen experienced side effects and discontinued treatment before the pre-designated switch-date. A majority of these patients changed to exemestane or another AI. Therefore, the true effect of a

sequential treatment regimen on disease outcomes may have been slightly overestimated. Although this can be considered a valuable representation of true clinical practices, this finding also limits the comparability of the two treatment arms in this study.

In our study, data on ER, PR and HER2 expression were centrally assessed and were available for the majority of patients, which confers a major strength of this investigation. We previously reported a significant benefit of exemestane upfront in ER-rich patients and of sequential therapy in ER-poor ductal and lobular breast cancer patients.[11] The current investigation includes all breast cancer subtypes of this cohort and confirms superior outcomes for upfront exemestane in ER-rich patients and of sequential treatment in ER-poor patients, with a significant treatment-by-marker interaction. Results show a strong preferential treatment benefit for upfront exemestane in ER-rich patients, but caution is warranted when interpreting results in ER-poor patients, as this subgroup comprises only 12% of the study population. The earlier prospectively planned analyses by Bartlett et al. found a similar benefit for five years of exemestane in ER-positive patients, but with a non-significant treatment-by-marker effect. The longer follow-up period in the current analyses, as well as our restriction to Dutch and Belgian TEAM participants who may differ slightly from the entire TEAM cohort may justify these findings.[13, 15] Previously, a combined analysis of the ABCSG 8 and ARNO 95 trials described that efficacy of anastrozole improved as quantitative ER expression increased, while effectiveness of tamoxifen did not improve with increasing ER expression.[16] Similarly, in the TransATAC (Arimidex, Tamoxifen, Alone or in Combination) study, increasing ER expression was associated with improved outcomes in anastrozole-treated patients, but not in patients treated with tamoxifen.[17] Nevertheless, results from the BIG 1-98 trial (using 80% expression as cut-off value) demonstrated improved outcomes with letrozole in patients with lower levels of ER expression than with higher ER expression.[18] The high cut-off point discriminating low from high ER expression in the latter study must be taken into account when comparing the results of these studies. Quantitative ER expression may be used to determine which regimen is most suitable for postmenopausal patients who are candidates for adjuvant endocrine therapy, if our data is confirmed and validated in future prospective studies.

HER2 overexpression is found in less than 20% of all breast cancers, and is associated with a poorer OS and relapse-free survival.[19, 20] In the current study, HER2 overexpression was observed in 12% of the patients (of which only two patients received trastuzumab) and was associated with a significantly worse DFS and OS. Studies have shown complex interactions between HER2 and ER pathways, with HER2-overexpressing tumors possibly more resistant to tamoxifen, a selective ER modulator.[21] Simultaneously, however, studies have presented conflicting results, also in the present investigation.[22-26] There is no evidence to suggest a preferential benefit of exemestane upfront in HER2-positive patients in this cohort. Bartlett et al. investigated differential treatment benefit by HER2 status and found a significant benefit of exemestane upfront in HER2-negative patients at 2.75 years, but the effect disappeared after five years.[27] The lack of a significant association after five years of treatment may reflect the consequences of switching from tamoxifen to exemestane after 2-3 years, hereby eliminating the effect of tamoxifen resistance.

The TEAM trial was conducted in nine different countries, with the Dutch and Belgian cohort of TEAM trial patients contributing to as much as 32% of all trial patients. The Dutch and Belgian study population represents a rather homogeneous group of patients, as similar eligibility criteria were employed. For this reason it was possible to investigate prognostic and predictive factors associated with treatment success in this cohort. In light of more tailor-made treatment of patients with breast cancer, the importance of determining the optimal adjuvant endocrine therapy regimen is ever increasing.

CONCLUSION

Overall, there were no differences in efficacy of the two endocrine therapy regimens in the Dutch and Belgian cohort of patients, which is in line with the results of all patients included in the international TEAM trial. A slight benefit was observed in this cohort at 2.75 years after the start of treatment in favour of exemestane upfront, but this effect disappeared after 5 years. Patients who had a lower ER Allred score (≤6) had improved outcomes when treated with tamoxifen followed by exemestane. These hypothesis-generating findings can have important consequences for daily clinical practice regarding the choice for a more personalized treatment regimen.

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CHAPTER

3

INFLUENCE OF SEMI-QUANTITATIVE ESTROGEN RECEPTOR EXPRESSION ON ADJUVANT ENDOCRINE THERAPY EFFICACY IN DUCTAL AND LOBULAR BREAST CANCER

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ABSTRACT

Background

Multiple studies suggest better efficacy of chemotherapy in invasive ductal breast carcinomas (IDC) than invasive lobular breast carcinomas (ILC). However, data on efficacy of adjuvant endocrine therapy regimens and histological subtypes is sparse. This study assessed endocrine therapy efficacy in IDC and ILC. The influence of semi-quantitative estrogen receptor (ER) expression by Allred score was also investigated.

Methods

Dutch and Belgian patients enrolled in the Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial were randomized to exemestane (25mg daily), alone or in sequence with tamoxifen (20mg daily) for 5 years. Inclusion was restricted to IDC and ILC patients. Histological subtype was assessed locally; ER expression was centrally reviewed according to Allred score (ER-poor (≤6;n=235); ER-rich (≥7;n=1789)). Primary endpoint was relapse-free survival (RFS), which was the time from randomization to disease relapse.

Results

Overall, 2140 (82%) IDC and 463 (18%) ILC patients were included. RFS was similar for both endocrine treatment regimens in IDC (HR for exemestane was 0.83 (95%CI 0.67-1.03)), and ILC (HR 0.69 (95%CI 0.45-1.06)). Irrespective of histological subtype, patients with ER-rich Allred scores allocated to exemestane alone had an improved RFS (multivariable HR 0.71 (95%CI 0.56-0.89)). In contrast, patients with ER-poor Allred scores allocated to exemestane had a worse RFS (multivariable HR 2.33 (95%CI 1.32-4.11)). Significant effect modification by ER-Allred score was confirmed (multivariable p=0.003).

Discussion

Efficacy of endocrine therapy regimens was similar for IDC and ILC. However, ER-rich patients showed superior efficacy to upfront exemestane, while ER-poor patients had better outcomes with sequential therapy, irrespective of histological subtype, emphasizing the relevance of quantification of ER expression.

INTRODUCTION

Treatment decisions in breast cancer therapy are increasingly dependent on a growing number of molecular tumor characteristics, consequently paving the way towards individual targeted treatment regimens. Invasive ductal carcinoma (IDC), is by far the most common type of breast cancer.[1] The second largest group, found in 10-15% of all female breast cancers is invasive lobular carcinoma (ILC); ILC patients tend to be older, and tumors are frequently larger in size, estrogen and progesterone receptor (ER and PR) positive, and human epidermal growth factor receptor[2] (HER2), p53, and epidermal growth factor receptor (EGFR) negative when compared to IDC.[2] ILC is also frequently associated with higher ER expression than IDC.[3, 4]

With regard to endocrine therapy, several reports have endorsed the association between higher levels of ER expression and the prediction of efficacy of endocrine therapy.[5-7] However, the association between histological subtype and adjuvant endocrine therapy efficacy is seldom addressed, as reports have frequently combined IDC and ILC in these efficacy analyses. In 1987, Smith and colleagues demonstrated similar survival after endocrine treatment with tamoxifen or ovarian ablation in IDC and ILC.[8] Another study investigated pathologic parameters and adjuvant tamoxifen response in IDC and ILC. But interaction analyses did not show significant differences in response to tamoxifen in IDC compared with ILC, and inclusion was restricted to premenopausal patients of whom fewer than 2% were treated with adjuvant chemotherapy.[4] A study by Rakha and colleagues, on the other hand, demonstrated a better response to various forms of endocrine therapy (ET) (tamoxifen, aromatase inhibitors (AIs), ovarian ablation or high-dose progestins) in ILC than IDC.[9] Thus, data comparing treatment response between the two major subtypes are scarce and inconsistent, and lack data on quantitative hormone receptor expression.

Upfront treatment with an AI or sequential therapy with tamoxifen followed by an AI for a total of five years is currently the most widely applied endocrine treatment regimen for postmenopausal hormone receptor-positive early breast cancer patients.[10] However, recommendations for prescribing adjuvant endocrine therapy make no distinction between IDC and ILC or quantitative hormone receptor expression.[11] In a recent report of the Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial by Bartlett and colleagues, a nonsignificant benefit for exemestane compared with tamoxifen was established in patients with high ER expression based on Allred scores, although follow-up was limited to 2.75 years.[12] The TransATAC (Arimidex, Tamoxifen Alone or in Combination) trial also demonstrated a significant improvement in time to relapse with respect to increasing ER expression in patients treated with anastrozole, while this could not be established for tamoxifen-treated patients.[13] At two years, recurrence rates were lower for ER-poor patients for tamoxifen versus anastrozole, but by about 5 years, rates were similar. However, no analyses by histological subtype were performed.

Current evidence is too inconsistent to establish a preferential treatment for histological subtypes in clinical practice. The reported variability in evidence regarding outcome after ET in IDC and ILC may be due to relatively small numbers of included ILC cases, as well as the retrospective nature of many studies previously reported. As ILC is more often ER-positive and frequently associated with stronger ER expression than IDC,

we investigated whether the histological subtype would translate to differential efficacies of two endocrine treatment regimens in Dutch/Belgian patients included in the TEAM trial on the basis of quantitative ER expression using the Allred score.[12, 14]

MATERIALS AND METHODS

International TEAM trial design

The TEAM trial is a randomized, adjuvant, phase III, multinational, open label study conducted in postmenopausal women with estrogen and/or progesterone receptor positive tumors. Patients were randomized to receive either exemestane 25 mg once-daily for five years or tamoxifen 20 mg once-daily for 2.5–3 years, followed by exemestane 25 mg once-daily for 2.5–2 years, for a total of five years. Participants were enrolled in Belgium, the Netherlands, United Kingdom, Ireland, United States of America, Japan, Greece, Germany and France. Eligibility criteria have been published in earlier reports.[10, 15] In short, postmenopausal patients with histologically confirmed breast adenocarcinoma, who completed local therapy with curative intent, i.e. without evidence of metastatic disease, were eligible. Appropriate approvals from the ethical committees were obtained. All patients provided written informed consent, and additional consent was obtained from patients in the tamoxifen group for the switch to exemestane.

Design of the current study

Inclusion in the present study was restricted to Dutch and Belgian patients, due to the central review of tumor characteristics in this population (n=3167). Patients with a lobular or ductal tumor subtype (n=2603) were eligible for inclusion. The remaining patients had invasive mixed (n=134, 4.2%), unspecified (n=24, 0.8%) and unknown (n=406, 12.8%) subtypes. The database was locked on February 23rd, 2011. Data collection was performed locally on specific study case report forms, and transferred to the central datacenter in Leiden, the Netherlands. Histological subtype was determined by the local pathologist conform international criteria as described in the literature.[16] The use of E-cadherin was not used routinely. Auditing of pathology reports was performed centrally in Leiden, the Netherlands. ER and PR expression was reassessed and quantified centrally in Edinburgh, United Kingdom. Detailed information is provided in a recent report by Bartlett and colleagues.[12] Estrogen and progesterone receptor expression were evaluated as binary categories according to the Allred score, with PR and ER cutoff at the median in line with those reported by Bartlett et al. (PR-poor ≤4 versus PR-rich ≥5; ER-poor ≤6 versus ER-rich ≥7).[12] Patients with unknown ER Allred scores (n=108) were not included in the survival analyses by Allred score, irrespective of their PR score. To assess the robustness of the findings, additional analyses were performed using the ER histoscore.[12] ER histoscore was dichotomized at the median. ER receptor expression and histoscore could be determined for 2461 patients (94.5%).

Endpoints

The primary endpoint of the current study was relapse-free survival (RFS), which was defined as the time from randomization to the earliest documentation of disease relapse. Disease relapse was defined as tumor recurrence (locoregional or distant), ipsilateral or contralateral breast cancer. Ductal carcinoma in situ was not considered a relapse.[10]

Statistical analysis

Statistical analyses were performed using SPSS 17.0 (SPSS, Chicago, IL) and R statistical package. To compare differences in proportions between patients with lobular and ductal breast tumors, Pearson chi-square tests and the Independent sample t-tests were used. Kaplan-Meier curves were plotted and Cox proportional hazard models were used to assess survival differences with respect to treatment arm. Survival analyses were stratified by histological subtype and ER Allred score. Interaction terms between treatment arm and histological subtype, and between treatment arm and ER Allred score respectively, were included in the Cox proportional hazard model to test for the presence of effect modification. Multivariable survival analyses by histological type were adjusted for age, histological grade (Bloom Richardson grade 1;2;3), T-stage (1;2;3,4), nodal stage (negative; positive), ER Allred score (ER-rich; ER-poor), PR Allred score (PR-rich; PR-poor), HER2 status (positive; negative), most extensive surgery (mastectomy; wide local excision), radiotherapy (yes; no), and chemotherapy (yes; no). Multivariable analyses by ER Allred score were adjusted for age, histological grade (Bloom Richardson grade 1;2;3), T-stage (1;2;3,4), nodal stage (negative; positive), PR Allred score (PR-rich; PR-poor), HER2 status (positive; negative), most extensive surgery (mastectomy; wide local excision), radiotherapy (yes; no), and chemotherapy (yes; no). To evaluate the interaction between randomized treatment and ER expression in more detail, we performed a sliding window STEPP analysis. [17, 18] All statistical tests were two-sided. A p-value of <0.05 was considered statistically significant.

RESULTS

Overall, 2603 patients from the Netherlands and Belgium who were included in the multinational TEAM trial, were included in this analysis, of which 2140 (82%) presented with IDC and 463 (18%) with ILC. Baseline characteristics of the included patients are shown by histological subtype in Table 1. Patients with a lobular subtype were significantly older ($p=0.004$), had larger tumors ($p<0.001$) and more frequently were node positive ($p=0.034$) and had an unknown tumor differentiation grade ($p<0.001$). Moreover, patients with ILC more frequently underwent a mastectomy ($p<0.001$) and received less chemotherapy ($p=0.024$). No differences were observed for other therapies applied.

Table 1: **Patient characteristics by histological subtype.**

	Ductal (n=2140)		Lobular (n=463)		
	n	%	n	%	p-value
Age (mean, SD)	65.0	9.2	66.3	9.4	0.004
Grade (BR)					
G1 (well)	318	14.9	58	12.5	<0.001
G2 (moderate)	897	41.9	236	51.0	
G3, G4 (poor)	848	39.6	88	19.0	
unknown	77	3.6	81	17.5	
Tumor stage					<0.001
T1 (≤2cm)	1041	48.6	133	28.7	
T2 (>2-≤5cm)	1002	46.8	251	54.2	
T3 / T4 (>5cm)	96	4.5	77	16.6	
unknown	0	0.0	2	0.4	
Nodal stage					0.034
Negative	662	30.9	120	25.9	
Positive	1475	69.0	343	74.1	
unknown	3	0.1	0	0.0	
ER Allred score					0.724
ER-poor (≤6)	235	11.0	56	12.1	
ER-rich (≥7)	1789	83.6	380	82.1	
unknown	116	5.4	27	5.8	
PR Allred score					0.062
PR-poor (≤4)	503	25.1	88	20.8	
PR-rich (≥5)	1498	74.9	336	79.2	
unknown	139	6.5	39	8.4	
HER2 status					<0.001
Negative	1719	80.3	394	85.1	
Positive	276	12.9	21	4.5	
unknown	145	6.8	48	10.4	
Most extensive surgery					<0.001
Mastectomy	1104	51.6	332	71.7	
Wide local excision	1036	48.4	131	28.3	
Adjuvant radiotherapy					0.397
Yes	1348	63.0	282	60.9	
No	789	36.9	181	39.1	
unknown	3	0.1	0	0.0	
Adjuvant chemotherapy					0.024
Yes	698	32.6	126	27.2	
No	1441	67.4	337	72.8	
Randomized treatment					0.152
Exemestane only	1096	51.2	220	47.5	
Tamoxifen → Exemestane	1044	48.8	243	52.5	

BR, Bloom&Richardson; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

At database lock, there were 338 (16%) relapses in patients with IDC and 83 (18%) in patients with ILC. Five-year RFS was 86% for IDC and 83% for ILC (reference: IDC, univariate hazard ratio (HR) for ILC 1.15 (95% confidence interval (CI) 0.90-1.46), p=0.257; ILC multivariable HR 1.18 (95%CI 0.89-1.57), p=0.257). Table 2 shows efficacy analyses stratified by histological subtypes. In patients with IDC, RFS was not significantly different for either treatment regimen (sequential therapy functioned as a reference, univariate HR for exemestane: 0.83 (95%CI 0.67-1.03), p=0.089; multivariable HR 0.90 (95%CI 0.72-1.13), p=0.373). Comparable results were observed in patients with ILC (univariate HR 0.69 (95%CI 0.45-1.06), p=0.089; multivariable HR 0.61 (95%CI 0.37-1.01), p=0.053). In order to assess whether efficacy analyses were modified by histological subtype, we included an interaction term between randomization and histological subtype. No significant interaction was observed (multivariable p=0.148).

Table 2. **Relapse-free survival by treatment regimen, stratified by histological subtype.**

	5 year RFS	Univariate HR (95%CI)	p-value	Multivariable** HR (95%CI)	p-value
IDC			0.089		0.373
Tam → Exe*	84%	1 (reference)		1 (reference)	
Exemestane	87%	0.83 (0.67-1.03)		0.90 (0.72-1.13)	
ILC			0.089		0.053
Tam → Exe	80%	1 (reference)		1 (reference)	
Exemestane	86%	0.69 (0.45-1.06)		0.61 (0.37-1.01)	

RFS, relapse-free survival; HR, hazard ratio; IDC, invasive ductal breast cancer; ILC, invasive lobular breast cancer; Tam, tamoxifen; Exe, exemestane.
* Tamoxifen followed by exemestane. ** HR adjusted for age, histological grade, tumor stage, nodal stage, ER Allred score, PR Allred score, HER2 status, most extensive surgery, radiotherapy, and chemotherapy.

The number of patients with an ER-rich tumor was 1789 (89.5%) in IDC patients, and 380 (87.6%) in ILC patients (p=0.234). Median ER Allred scores were similar in IDC and ILC patients (7 versus 7), mean ER Allred score was slightly lower in IDC patients (6.89 versus 6.98, p=0.042). Due to the fact that a previous study showed better RFS in patients with ER-rich Allred scores, and because patients with ILC more frequently present with ER-positive disease, survival by ER Allred score was assessed in patients with ductal and lobular subtypes separately.

For both histological subtypes, ER-rich Allred scores showed superior outcomes for upfront exemestane in both univariate and multivariable analyses (Supplementary Table 1). In contrast, in both IDC and ILC patients with ER-poor Allred scores, those who were allocated exemestane had a worse relapse-free survival. No significant effect modification by histological subtype was observed for ER-rich Allred scores (p=0.201) and ER-poor Allred scores (p=0.799).

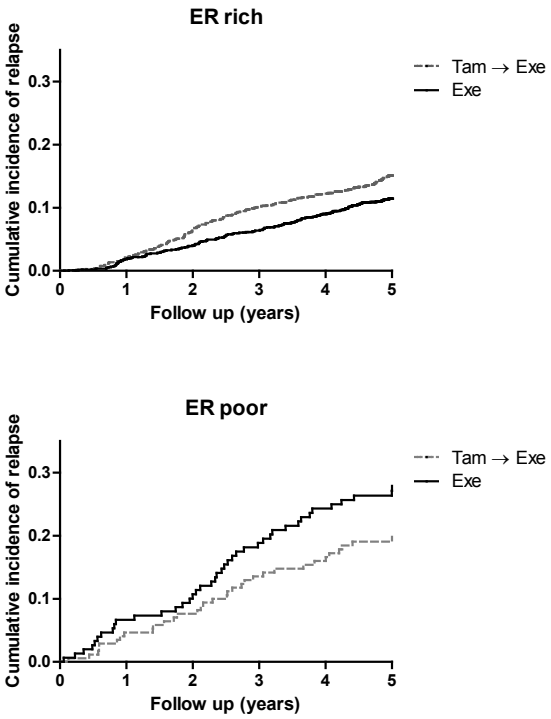
Because of the absence of effect modification, survival analyses were repeated for all patients. Cumulative incidence of breast cancer relapse by treatment regimen for both patients with ER-rich and ER-poor tumors is shown in Figure 1. As shown in Table 3, patients with ER-rich Allred scores and allocated 5 years of exemestane showed a more than 30% improved RFS when compared to patients allocated sequential treatment, which was confirmed in multivariable analyses (HR for exemestane: 0.72 (95%CI 0.57-0.90), p=0.004). In contrast, ER-poor Allred score in combination with allocation to exemestane monotherapy was associated with a worse RFS, which was even more pronounced after multivariable analyses (HR for exemestane: 1.85 (95%CI 1.11-3.09), p=0.019). ER Allred score was a significant effect modifier of endocrine therapy efficacy in all patients (multivariable p for interaction=0.003). Similar analyses were performed for PR Allred score, but no significant effect modification was observed (p for interaction=0.137).

Table 3. **Relapse-free survival by treatment regimen, stratified by ER Allred score.**

	5 year RFS	Univariate HR (95%CI)	p-value	Multivariable** HR (95%CI)	p-value
ER-rich			0.001		0.004
Tam → Exe*	80%	1 (reference)		1 (reference)	
Exemestane	73%	0.69 (0.56-0.86)		0.72 (0.57-0.90)	
ER-poor			0.031		0.019
Tam → Exe	82%	1 (reference)		1 (reference)	
Exemestane	74%	1.66 (1.05-2.63)		1.85 (1.11-3.09)	

RFS, relapse-free survival; HR, hazard ratio; Tam, tamoxifen; Exe, exemestane.
* Tamoxifen followed by exemestane. ** HR adjusted for age, histological subtype, histological grade, tumor stage, nodal stage, PR Allred score, HER2 status, most extensive surgery, radiotherapy, and chemotherapy. ER-rich was defined as an Allred score of ≤6; ER-poor was defined as an Allred score of ≥7.

Figure 1. **Cumulative breast cancer relapse by estrogen receptor Allred score.**



Supplement for Figure 1.

ER rich

	Year	0	1	2	3	4	5
Tam → Exe*	No. at risk	1088	1051	990	932	871	658
	No. events		23	50	40	20	27
Exemestane	No. at risk	1081	1050	1014	965	898	671
	No. events		20	23	26	28	21

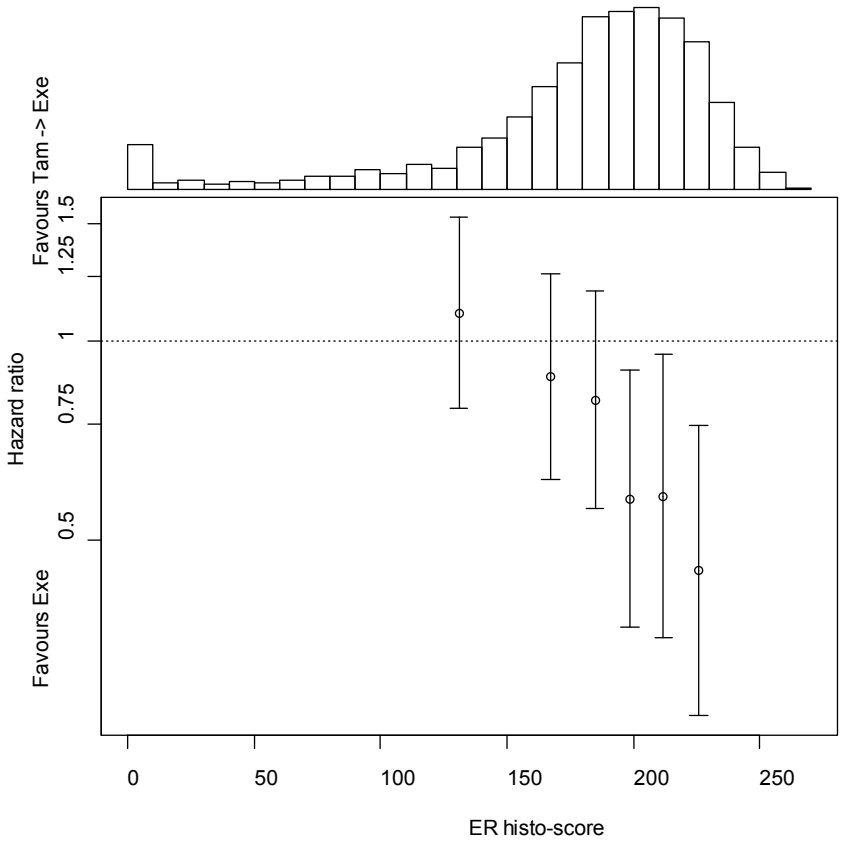
ER poor

	Year	0	1	2	3	4	5
Tam → Exe*	No. at risk	138	130	125	117	112	95
	No. events		6	4	6	3	5
Exemestane	No. at risk	126	117	111	100	93	81
	No. events		8	5	10	7	2

* Tamoxifen followed by exemestane

To assess the robustness of the findings, additional analyses were performed using the ER histoscore instead of the ER Allred score. ER histoscore was dichotomized at the median, which resulted in 1231 patients with ER-rich tumors and 1230 patients with ER-poor tumors. Results are shown in Supplementary Table 2. In both univariate and multivariable analyses, patients with a high histoscore derived a significant benefit from exemestane monotherapy (multivariable HR for exemestane was 0.56 (95%CI 0.39-0.80), p=0.001). No difference was observed for patients with a low histoscore (multivariable HR for exemestane was 1.04 (95%CI 0.80-1.34), p=0.779). Nevertheless, significant effect modification by histoscore (p=0.005) was observed. Additionally, a sliding window STEPP analysis was performed (Figure 2), which showed a dose-response relation. Moreover, only those patients with the lowest ER histoscores derived benefit from a sequential therapy regimen, while with increasing histoscore, the benefit of exemestane monotherapy increased. Lastly, as ILC patients received less chemotherapy, sensitivity analyses were also performed restricted to patients without prior chemotherapy. These analyses revealed similar results (data not shown).

Figure 2. **Sliding window STEPP analysis.**



DISCUSSION

This study showed no preferential benefit for endocrine therapy based on histological subtype in patients with either IDC or ILC. However, a major finding of the present study was that the efficacy of endocrine therapy regimens was modified by the ER Allred score: an improved RFS was demonstrated in ER-rich patients when treated with five years of exemestane, whereas ER-poor patients benefited more from the sequential treatment strategy.

Several analyses were performed to assess sensitivity of the used variables and robustness of our findings. First, survival analyses were repeated with ER histoscore instead of ER Allred score, which revealed comparable results. Next, a sliding window STEPP analysis was performed, which showed a dose-response relation between increasing ER histoscore and benefit of exemestane monotherapy. It was shown that only those patients with the very lowest ER histoscores derived benefit from sequential therapy. This is in line with the results of our Cox regression analyses, in which the effect in ER-rich patients is more outspoken than in ER-poor patients. Lastly, analyses were restricted to patients without prior chemotherapy, which did not alter the results.

Despite the numerous differences between IDC and ILC, histological subtype did not modify the efficacy of treatment regimen. As literature suggests different distributions of ER Allred scores for IDC and ILC patients[3, 4], survival analyses by Allred score for both IDC and ILC separately were performed. Again, similar effects in both IDC and ILC patients were observed, in which higher ER Allred scores were predictive of a better response to exemestane monotherapy, whereas a sequential treatment regimen was preferred in patients with lower ER Allred scores. These findings support the supposition of at least a similar efficacy of endocrine treatment in IDC and ILC. Of note, a prior publication by Pestalozzi et al. revealed changes in survival advantage for IDC and ILC over a 25-year period; up to six years, there is a survival benefit for ILC, after which the advantage changes to IDC.[19] It is therefore important to interpret our results in the context of longer-term findings.

Regardless of histological subtype, a significant effect modification by ER Allred score was ascertained. Patients with ER-rich tumors responded better to five years of exemestane, and patients with ER-poor tumors were better off with the sequential treatment regimen. It is tempting to speculate on the mechanisms which may explain the results observed. Although not the case in all patients, ER expression can decrease during tamoxifen treatment, also one of the mechanisms that contribute to reduced tolerability to endocrine treatment over time.[20, 21] We may thus contemplate that more rapid exhaustion of ER expression leads to an improved response to a new mechanism that counters the effect of estrogens on tumor growth, namely through the inhibition of aromatase. Therefore, in ER-poor tumors one can argue that these more readily develop endocrine resistance than ER-rich tumors, and thus the mechanism of switching therapy is more relevant than the therapy itself.

A recent report by Bartlett and colleagues in the international TEAM data suggested a beneficial effect of exemestane for ER-rich patients.[12] However, in contrast to the present investigation, no significant treatment effect modification by ER Allred score was observed. This may be explained by the restriction to the two major histological subtypes in the current study. Second, the present findings are based on the Dutch and Belgian TEAM participants only, who may display slightly different characteristics than the combined international data.[15] However, as nearly one third of the patients included in the international study are of Dutch/Belgian origin, this is not likely to have a major influence on our findings. Third, the analyses by Bartlett and colleagues were limited to 2.75 years of follow-up, whereas the median follow-up of the current study was 5.2 years.

Data are conflicting on the topic of prognostic value of quantitative hormone receptor expression. Previously, Mauriac and colleagues described prognostic risk factors that are associated with disease relapse, based on findings in the Breast International Group (BIG) 1-98 trial.[22] In these analyses, a beneficial effect of letrozole versus tamoxifen was found in patients with poorer prognoses (in terms of tumor burden and aggressiveness), regardless of the inclusion of quantitative ER expression in the analysis.[22] In the same cohort of patients, Viale et al. found that patients with lower levels of ER (<80%) had more benefit of letrozole monotherapy than patients with higher levels of ER (≥80%), while this was not established in another report by Regan et al.[23] In contrast, combined analyses of the ABCSG 8 and ARNO 95 trials concluded that treatment efficacy with anastrozole improved with increasing ER expression, while this was not the case in tamoxifen-treated patients.[24]

While our results remain to be confirmed in other studies, there is reason to believe that the differential response based on ER expression is of clinical relevance. The importance of quantitative associations between hormone receptor content and response to endocrine therapy has been documented in the past, and several semi-quantitative scoring systems have been proposed in order to reduce the number of borderline cases of ER-positive tumors. However, it is still infrequently used to determine treatment regimen clinically.

A major strength of the present investigation is the relatively large cohort of patients with ILC as well as the randomized design of this study, which assures quality controlled data and an extended record of patient and treatment characteristics. More importantly, the centrally reviewed ER expression excluded variation between pathology centers. Since histological subtype was assessed locally, we cannot exclude a potential bias in the inclusion of our patients. Inclusion in the TEAM study was restricted to ER-and/or PR-positive breast tumors, therefore it was not possible to elaborate on the proportion of ILC patients with ER-positive tumors compared to IDC patients. It is known that ILC patients more frequently present with ER-positive tumors, which predicts a superior response to endocrine therapy.[25-28] Although a significant effect modification by ER expression was observed, the sliding window STEPP analysis indicated that only those patients with very low ER expression may be better off with a sequential treatment, whereas patients with very high ER expression derive benefit from exemestane monotherapy. The retrospective, unplanned nature of this analysis renders our investigation hypothesis generating, and these results will need to be validated through further investigation prospectively in order to define a possible ER expression cutoff for treatment preference.

There was no difference in efficacy of endocrine treatment between IDC and ILC, and therefore endocrine therapy remains warranted in ILC patients. Instead, the extent of ER positivity may be superior in predicting treatment efficacy than histological subtype. In other words, our hypothesis was not confirmed on the basis of histological subtypes. Alternatively, an effect modification for treatment modality by ER expression in both subtypes was established. The semi-quantitative analysis of ER expression in postmenopausal early breast cancer patients may therefore be an important item in clinical decision-making to determining the optimal therapeutic regimen.

Supplementary Table 1. **Relapse-free survival by treatment regimen, stratified by ER Allred score and histological subtype.**

	5 year survival	Univariate HR (95%CI)	p-value	Multivariable** HR (95%CI)	p-value
ER-rich					
IDC			0.006		0.052
Tam → Exe*	85%	1 (reference)		1 (reference)	
Exemestane	89%	0.70 (0.55-0.90)		0.78 (0.60-1.00)	
ILC			0.061		0.014
Tam → Exe	80%	1 (reference)		1 (reference)	
Exemestane	86%	0.63 (0.39-1.02)		0.50 (0.29-0.87)	
ER-poor					
IDC			0.032		0.021
Tam → Exe	79%	1 (reference)		1 (reference)	
Exemestane	71%	1.72 (1.05-2.83)		1.89 (1.10-3.26)	
ILC			0.456		
Tam → Exe	87%	1 (reference)		Too few numbers	
Exemestane	80%	1.60 (0.47-5.51)			

RFS, relapse-free survival; IDC, invasive ductal breast cancer; ILC, invasive lobular breast cancer.
* Tamoxifen followed by exemestane. ** HR adjusted for age, histological grade, T stage, nodal stage, PR Allred score, HER2 status, most extensive surgery, radiotherapy, and chemotherapy. ER-rich was defined as an Allred score of ≤6; ER-poor was defined as an Allred score of ≥7.

Supplementary Table 2. **Relapse-free survival by treatment regimen, stratified by ER histoscore.**

	5 year RFS	Univariate HR (95%CI)	p-value	Multivariable** HR (95%CI)	p-value
High histoscore			<0.001		0.001
Tam → Exe*	87%	1 (reference)		1 (reference)	
Exemestane	92%	0.52 (0.37-0.73)		0.56 (0.39-0.80)	
Low histoscore			0.858		0.779
Tam → Exe	81%	1 (reference)		1 (reference)	
Exemestane	81%	1.02 (0.80-1.31)		1.04 (0.80-1.34)	

RFS, relapse-free survival; HR, hazard ratio; Tam, tamoxifen; Exe, exemestane.
* Tamoxifen followed by exemestane. ** HR adjusted for age, histological subtype, histological grade, tumor stage, nodal stage, PR Allred score, HER2 status, most extensive surgery, radiotherapy, and chemotherapy. ER histoscore was dichotomized at the median.

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CHAPTER

4

BODY MASS INDEX AS A PROGNOSTIC INDICATOR IN BREAST CANCER PATIENTS TREATED WITH ADJUVANT ENDOCRINE THERAPY: AN INTERNATIONAL TEAM TRIAL ANALYSIS

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Submitted

ABSTRACT

Background

The relationship between body-mass index (BMI, kg/m^2) and breast cancer outcomes in endocrine-sensitive early breast cancer patients is gaining recognition with regard to potential clinical relevance. Evidence suggests that obesity is associated with poorer outcomes following breast cancer diagnosis. We investigated the relationship between BMI and survival outcomes as well as BMI in relation to treatment efficacy in the Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial.

Methods

The TEAM trial is an international, randomized, phase III, study conducted in postmenopausal, endocrine-sensitive early breast cancer patients allocated sequential treatment with tamoxifen followed by exemestane or exemestane upfront, for a total of 5 years. Underweight (BMI<18.5kg/m^2) and severely obese (BMI>45kg/m^2) patients were excluded from the analyses. Univariable and multivariable Cox regression analyses assessed disease-free survival (DFS) and breast cancer-specific survival (BCSS) in relation to BMI and Kaplan-Meier curves were plotted. Interaction terms for BMI and treatment regimen tested for effect modification. Multiple imputations were performed in an additional analysis to account for missing data and 25 iterations were generated.

Results

After exclusion of patients without any available BMI data, as well as patients who were underweight or severely obese, 4711 patients were included. Overweight and obese patients showed similar hazard ratios (HR) for DFS and BCSS compared with normal-weight patients (DFS: overweight HR=0.91 (95%CI 0.79-1.05); obese HR=0.98 (95%CI 0.83-1.15). BCSS: overweight HR=1.07 (95%CI 0.82-1.40); obese HR=0.95 (95%CI 0.73-1.25)). BMI did not define benefit for one or the other treatment regimen with regard to DFS or BCSS. Imputed data analyses did not alter the results.

Discussion

BMI was not associated with differences in DFS or BCSS, nor was preferential treatment benefit affected by BMI.

INTRODUCTION

Obesity is affecting a growing number of women worldwide.[1] In Europe and other high-income countries, both age and obesity are on the rise, and are expected to continue to increase in the upcoming years.[2] Increasing weight is associated with the development of chronic diseases and multiple comorbid conditions including breast cancer, especially in the aging population. A growing global epidemic, obesity not only contributes to the risk of developing breast cancer[3, 4], but also to the clinical course of established disease.[5-7]

In early breast cancer patients, the relationship between body-mass index (BMI, kg/m^2) and breast cancer outcomes is of significant clinical importance. Obesity has been associated with poorer breast cancer outcomes overall and following primary treatment[5], including a higher risk of breast cancer recurrence.[6, 8] In their review, Chlebowski and colleagues demonstrated an almost two-fold increase in the risk of recurrence at 5 years in relation to BMI.[6]

Systemic treatment in endocrine-sensitive breast cancer patients is frequently accompanied by unintentional weight gain[9, 10], reported to range between 2.5 and 6.2 kg in the first year of diagnosis.[11] Older women especially are burdened by weight gain, both physiologically as time passes since menopause, and after breast cancer diagnosis and treatment. In addition to poorer outcomes after/during breast cancer treatment associated with increasing BMI, comorbidities and functional limitations associated with obesity are also considered risk factors for poorer breast cancer outcomes.[12] We investigated the impact of BMI on disease-free survival (DFS) and breast cancer-specific survival (BCSS) as well as the benefit of sequential versus upfront aromatase inhibitor (AI) treatment in relation to BMI in postmenopausal, endocrine-sensitive early breast cancer patients treated with adjuvant endocrine therapy.

MATERIALS AND METHODS

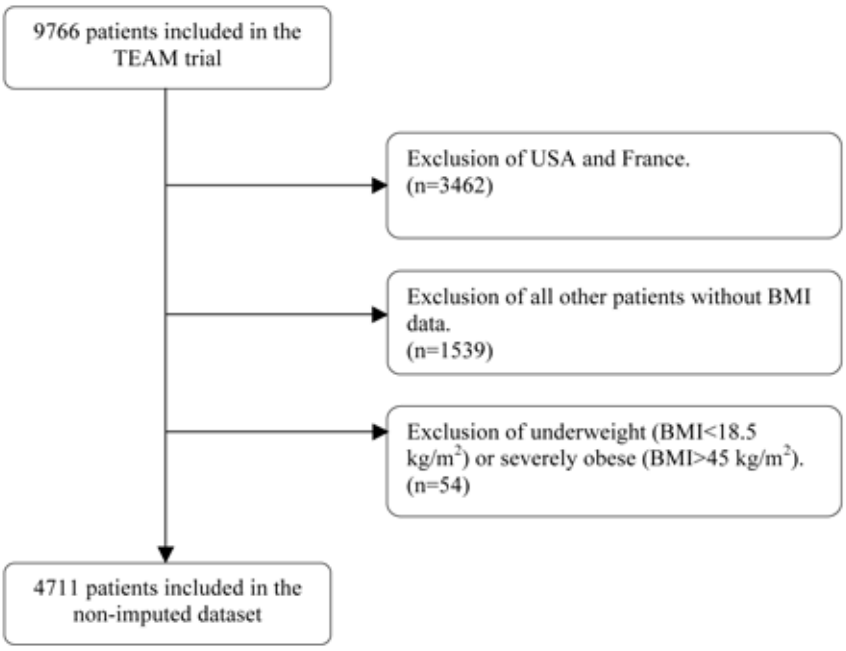
The Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial is a randomized, adjuvant, phase III, multinational, open label study conducted in postmenopausal early breast cancer patients with estrogen receptor (ER)- and/or progesterone receptor (PR)-positive tumors.[13] Relevant eligibility criteria comprised prior primary surgery with curative intent and an indication for adjuvant endocrine therapy. Patients were randomized to five years of exemestane (25mg, once daily) or a sequential treatment regimen, consisting of tamoxifen (20mg, once daily) for 2.5-3 years, followed by exemestane (25mg, once daily) for 2.5-2 years thereafter (for a total of 5 years). All patients provided written informed consent, and additional consent was obtained from patients in the sequential treatment group for the switch to exemestane. The trial was registered with ClinicalTrials.gov in France (NCT00279448), UK and Ireland (NCT00032136), USA (NCT00036270), with Ethics Commission Trial in Germany (27/2001), with University Hospital Medical Information Network-Clinical Trials Registry in Japan (C000000057), and in the Netherlands and Belgium with the Netherlands Trial Register (NTR 267).

Data were collected locally and transferred to the central datacenter in Leiden, the Netherlands. BMI was calculated using height and weight measurements, which were collected at baseline or randomization in Belgium, Germany, Greece, the Netherlands and UK/Ireland and were unavailable for France and USA. Patients were assessed every three months during the first year of treatment, and at least once yearly thereafter.

Statistical analyses

Statistical analyses were performed using SPSS 20.0 (SPSS, Chicago, IL). All analyses were performed by intention-to-treat. Patients from countries that did not provide any BMI data (USA and France), other patients without any BMI data, as well as underweight (BMI<18.5 kg/m^2, n=42) and severely overweight (BMI>45 kg/m^2, n=12) patients were excluded from the analyses (Figure 1). To compare proportional differences between patients by BMI, Pearson chi-square tests were used. DFS and BCSS in relation to BMI were modeled in univariable and multivariable Cox proportional hazard models (hazard ratio (HR) with 95% confidence intervals (95%CI)) and Kaplan-Meier curves were plotted. Multivariable Cox regression analyses were adjusted for age and country. Interaction terms for BMI and treatment regimen were incorporated to test for effect modification.

Figure 1. **CONSORT diagram of patients included in the non-imputed dataset**



Multiple imputation

Due to the large number of patients without BMI data, missing BMI data were imputed (multiple imputations) using a model that included country, treatment, BMI, height, weight, age, T- and N-stage, grade, histological type, ER, PR and HER2 (human epidermal growth factor receptor 2), and outcome measures for survival. France and USA were excluded from imputations, as these countries did not provide height and weight measurements for any of their patients. We generated 25 iterations and combined the estimates and standard errors using Rubin's Rules (micombine in STATA). Multiple imputation by chained equations was used, which assumes a multivariable distribution without specifying its form. In STATA, multiple imputation was performed using the Imputation by Chained Equations (ICE) model. Univariable and multivariable survival analyses were used to study associations between BMI and survival, and between randomized treatment and survival, stratified by BMI. Interaction terms between BMI and randomized treatment were included in the model. All variables with a p-value ≤0.05 after univariable analyses were entered in the multivariable model. DFS and BCSS were calculated using multivariable Cox proportional hazard models with any recurrence, death or breast cancer death as event. Kaplan-Meier survival estimates were used to plot the survival for randomized treatment, stratified by BMI.

RESULTS

BMI data (height and weight) was available for 4711 patients. BMI was normally distributed (median 26.2, standard deviation 4.68) and median follow-up of patients alive was 6.5 years (range 0-10.73 years). Table 1 shows patient, tumor and treatment characteristics for both the non-imputed and imputed datasets, and Table 2 depicts the distribution of characteristics according to BMI category for the non-imputed datasets. 2327 (49.4%) patients received tamoxifen followed by exemestane and 2384 (50.6%) patients exemestane upfront. BMI was higher in older than in younger patients, and the distribution of patients across the BMI categories differed between countries.

Patients with available BMI data had larger tumors with higher nodal stages and were younger than patients with missing BMI data (Supplementary Table 1). In addition, patients in whom BMI was known were more frequently treated with radiotherapy and chemotherapy. Nevertheless, DFS did not differ between patients with and without reported BMI data.

Table 1. **Baseline characteristics for the non-imputed and imputed datasets**

Baseline characteristics		Non-imputed dataset		Imputed dataset
		n	%	%
Country	Germany	1461	23.4	23.4
	Greece	207	3.3	3.3
	Japan	176	2.8	2.8
	Netherlands/Belgium	3145	50.3	50.3
	UK/Ireland	1261	20.2	20.2
	USA*	0	0	-
	France*	0	0	-
Treatment	Tamoxifen → Exemestane	3136	50.2	50.2
	Exemestane only	3114	49.8	49.8
Age	<50	208	3.3	3.3
	50 - 59	1911	30.6	30.6
	60 - 69	2430	38.9	38.9
	≥70	1701	27.2	27.2
BMI	18.5 - <25	1858	29.7	35.1
	25 - <30	1762	28.2	44.0
	30 - 45	1091	17.5	20.9
	missing	1539	24.6	-
Tumor stage	T1 (≤2 cm)	3079	49.3	49.4
	T2 (2-5 cm)	2757	44.1	44.2
	T3 or T4 (>5 cm)	394	6.3	6.4
	missing	20	0.3	-
Nodal stage	N0	2603	41.7	42.0
	N1	3170	50.7	51.1
	N2/N3	424	6.8	6.9
	missing	53	0.8	-
Grade (BR)	G1 (well)	673	10.8	11.8
	G2 (moderate)	3165	50.6	55.0
	G3, G4 (poor)	1904	30.5	33.2
	missing	508	8.1	-
Histological type	Invasive ductal/mixed	3570	57.1	57.1
	Invasive lobular	668	10.7	10.7
	other	2012	32.2	32.2
ER status	Positive	6110	97.7	97.8
	Negative	137	2.2	2.2
	missing	3	0.1	-
PR status	Positive	4472	71.5	80.2
	Negative	1110	17.8	19.8
	missing	668	10.7	-
HER2 status	Positive	511	8.2	15.0
	Negative	2267	36.3	85.0
	missing	3472	55.5	-
Surgery	Mastectomy	2912	46.6	46.6
	Breast conserving surgery	3331	53.3	53.3
	No resection / unknown	7	0.1	0.1
Radiotherapy	Yes	4242	67.9	67.9
	No	2008	32.1	32.1
Chemotherapy	Yes	2296	36.7	36.7
	No	3954	63.3	63.3

BR, Bloom&Richardson; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor-2.
*Excluded from multiple imputations (France and USA did not provide BMI data for any patients).

Table 2. **Baseline characteristics in relation to BMI category for patients included in the non-imputed dataset**

		18.5-25		25-30		>30-45		p-value
		n	%	n	%	n	%	
Total patients	n=4711	1858	39.4	1762	37.4	1091	23.2	
Randomized treatment	Tamoxifen → Exemestane	894	38.4	893	38.3	540	23.2	0.303
	Exemestane only	964	40.3	869	36.3	551	23.1	
Age	<50	95	57.9	44	26.8	25	15.2	<0.001
	50 - <60	665	44.2	526	35.0	308	20.5	
	60 - <70	695	37.5	692	37.3	461	24.9	
	≥70	403	33.5	500	41.6	297	24.8	
Country	Germany	419	42.7	365	37.2	195	19.9	<0.001
	Greece	8	32.0	7	28.0	10	40.0	
	Japan	115	65.3	55	31.2	6	3.4	
	Netherlands/Belgium	1068	38.0	1070	38.1	665	23.7	
	UK/Ireland	248	33.8	265	36.1	215	29.5	
Tumor stage	T1 (≤2cm)	970	42.0	837	36.2	497	21.6	0.003
	T2 (>2-≤5cm)	766	36.4	814	38.7	520	24.8	
	T3 or T4 (>5cm)	119	39.8	109	36.5	71	23.7	
	Tx/Tis/unknown	3	37.5	2	25.0	0	0	
Nodal stage	N0	746	39.5	694	36.7	442	23.5	0.050
	N1	938	38.2	946	38.5	567	23.1	
	N2/N3	152	44.6	112	32.8	77	22.6	
	Nx/unknown	22	59.5	10	27.0	5	13.5	
Histological grade	G1 (well)	214	39.4	214	39.4	113	20.9	0.767
	G2 (moderate)	931	40.0	856	36.8	535	23.0	
	G3, G4 (poor)	563	38.3	551	37.5	353	24.1	
	unknown	150	39.2	141	36.8	90	23.6	
Histological type	Invasive ductal/mixed	1056	38.2	1036	37.5	670	24.3	0.111
	Invasive lobular	201	39.0	195	37.9	119	23.1	
	other/unknown	601	41.9	531	37.0	302	21.1	
Surgery	Mastectomy	873	39.5	823	37.2	514	23.3	0.792
	Breast conserving surgery	983	39.3	939	37.6	577	23.1	
	No resection/unknown	2	100	0	0	0	0	
Radiotherapy	Yes	1302	39.5	1235	37.4	762	23.1	0.987
	No	553	39.3	526	37.4	328	23.3	
Chemotherapy	Yes	754	42.4	626	35.2	398	22.4	0.005
	No	1104	37.7	1135	38.7	693	23.6	
ER status	Positive	1815	39.3	1719	37.3	1067	23.2	0.778
	Negative	42	38.9	43	39.8	23	21.3	
	unknown	1	50.0	0	0	1	50.0	
PR status	Positive	1341	39.0	1284	37.3	806	23.5	<0.001
	Negative	384	43.7	325	37.0	167	19.1	
	unknown	133	32.9	153	37.9	118	29.2	
HER2 overexpression	Negative	658	39.3	626	37.4	391	23.3	0.135
	Positive	132	42.7	120	38.8	57	18.4	
	unknown	611	37.0	638	38.6	403	24.4	

BR, Bloom&Richardson; ER, estrogen receptor; PR, progesterone receptor.

Breast cancer outcomes

After a median follow-up of 6.5 years, DFS was 63.1%, 63.2% and 65.5% for normal-weight, overweight and obese patients respectively. Multivariable Cox regression analyses, adjusted for age and country, did not reveal any statistically significant differences between in DFS according to BMI. Compared with normal-weight patients, overweight and obese patients showed similar hazard ratios (HRs) for DFS (overweight HR 0.91 (95%CI 0.79-1.05) and obese HR 0.98 (95%CI 0.83-1.15)) (Table 3).

BCSS analyses also did not show any differences in cumulative incidence of breast cancer-related death in normal-weight, overweight and obese patients following both univariable and multivariable Cox regression analyses. BCSS was 24.4%, 24.5% and 24.6% for normal-weight, overweight and obese patients respectively (overweight HR 1.07 (95%CI 0.82-1.4); obese HR 0.95 (95%CI 0.73-1.25)) (Table 3).

Table 3. **Disease-free and breast cancer-specific survival in relation to BMI in patients treated with adjuvant endocrine therapy in the non-imputed and imputed datasets**

				Univariable analyses			Multivariable analyses**		
Original dataset	**n**	**Events**	**DFS (%)**	**HR**	**95%CI**	**p-value**	**HR**	**95%CI**	**p-value**
Disease-free survival									
Normal weight (BMI 18.5-25)	1858	390	63.1	1.0 (ref)		0.81†	1.0 (ref)		0.44†
Overweight (BMI 25-30)	1762	366	63.2	0.99	0.86 – 1.14	0.87	0.913	0.79 – 1.05	0.21
Obese (BMI >30)	1091	239	65.5	1.04	0.89 – 1.23	0.61	0.975	0.83 – 1.15	0.76
Breast cancer-specific survival									
Normal weight (BMI 18.5-25)	1858	284	24.4	1.0 (ref)		0.91†	1.0 (ref)		0.59†
Overweight (BMI 25-30)	1762	264	24.5	0.980	0.81-1.19	0.84	1.072	0.82-1.40	0.61
Obese (BMI >30)	1091	170	24.6	0.959	0.79-1.16	0.67	0.951	0.73-1.25	0.72
Imputed dataset	**%**	**Events (%)**	**DFS (%)**	**HR**	**95%CI**	**p-value**	**HR**	**95%CI**	**p-value**
Disease-free survival									
Normal weight (BMI 18.5-24.9)	35.1	21.7	65.1	1.0 (ref)		0.94†	1.0 (ref)		0.83†
Overweight (BMI 25.0-29.9)	44.0	22.3	65.8	1.01	0.89-1.14	0.89	0.96	0.85-1.09	0.56
Obese (BMI>30.0)	20.9	22.3	65.7	1.03	0.87-1.21	0.75	0.96	0.82-1.13	0.65
Breast cancer-specific survival									
Normal weight (BMI 18.5-24.9)	35.1	15.5	73.9	1.0 (ref)		0.93†	1.0 (ref)		0.98†
Overweight (BMI 25.0-29.9)	44.0	15.3	76.7	0.97	0.83-1.13	0.72	0.99	0.84-1.15	0.86
Obese (BMI>30.0)	20.9	15.5	75.2	1.00	0.82-1.21	0.99	1.00	0.82-1.21	0.96

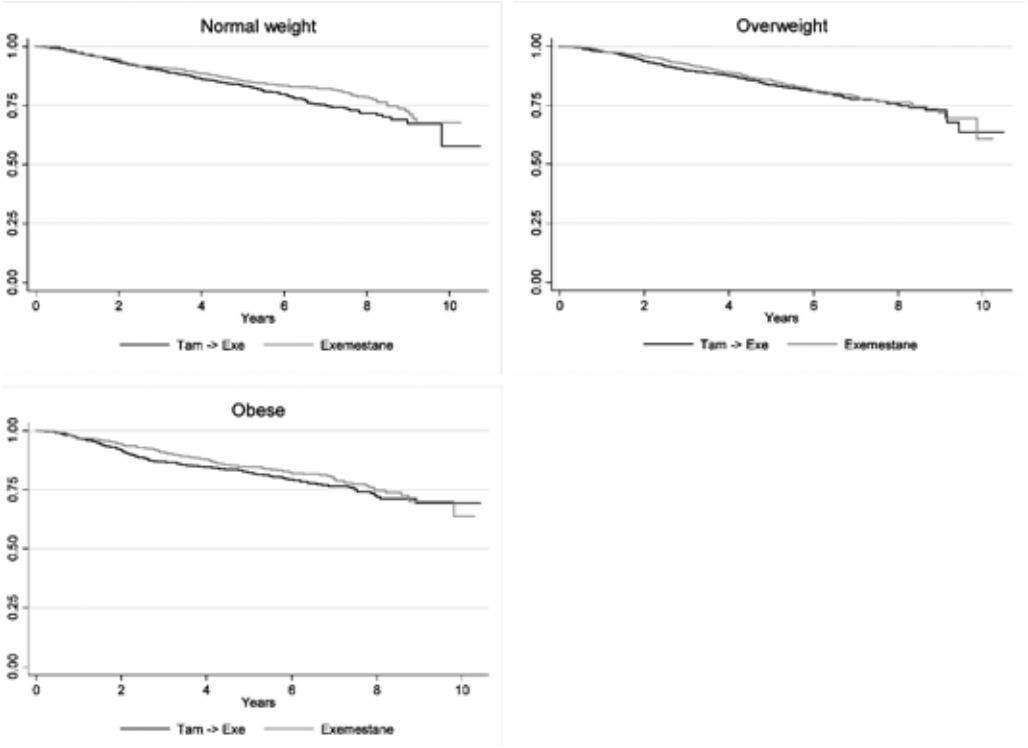
DFS, disease-free survival; BCSS, breast cancer-specific survival; HR, hazard ratio; 95%CI, 95% confidence interval.
[1]Cumulative incidence at 10 years, with death due to other causes as competing risk; †overall p-value.
*Multivariable Cox regression analyses, adjusted for age and country; **Multivariable Cox regression analyses adjusted for country, age, T stage, N stage, grade, subtype, ER, PR and treatment.

Treatment efficacy

Stratified analyses were performed to assess the effect of treatment benefit across the different BMI categories. Figure 2 depicts DFS outcomes for sequential treatment versus exemestane upfront in normal-weight, overweight and obese patients separately. In normal-weight patients, a tendency towards a benefit for exemestane upfront over sequential treatment was found (multivariable HR 0.80 (95%CI 0.65-0.97); p=0.025). However, treatment-by-marker analyses did not show significant effect modification for differential

treatment efficacy in relation to BMI (p-for interaction>0.05). In overweight and obese patients, analyses showed similar DFS outcomes for tamoxifen followed by exemestane and for exemestane only (Table 4).

Figure 2. **Kaplan-Meier survival figures for disease-free survival according to BMI category in the non-imputed dataset**



With respect to BCSS, normal-weight patients also demonstrated better outcomes with exemestane only compared to tamoxifen followed by exemestane (multivariable HR 0.76 (95%CI 0.60-0.95); p=0.018), although interaction tests did not reveal statistical significance (p-for interaction>0.05). There was no difference in treatment efficacy in overweight or obese patients (overweight: multivariable HR 0.90 (95%CI 0.71-1.15); obese: multivariable HR 0.90 (95%CI 0.66-1.21)) (Table 4).

Imputed data

Multiple imputations were performed to account for the large number of missing height and weight measurements encountered in our dataset. Following imputation, there were no changes in DFS and BCSS outcomes for normal-weight, overweight or obese patients compared with the non-imputed dataset (Table 3). Furthermore, imputed

analyses did not reveal a significant benefit for exemestane upfront in normal-weight patients for either DFS or BCSS (DFS: multivariable HR 0.90 (95%CI 0.74-1.10); p=0.32; BCSS: multivariable HR 0.85 (95%CI 0.67-1.07); p=0.16) (Table 4, Figure 3). Interaction tests between BMI and randomized treatment did not show significant effect modification (p>0.05 for both DFS and BCSS).

Figure 3. **Kaplan-Meier survival figures for disease-free survival according to BMI category following multiple imputation**

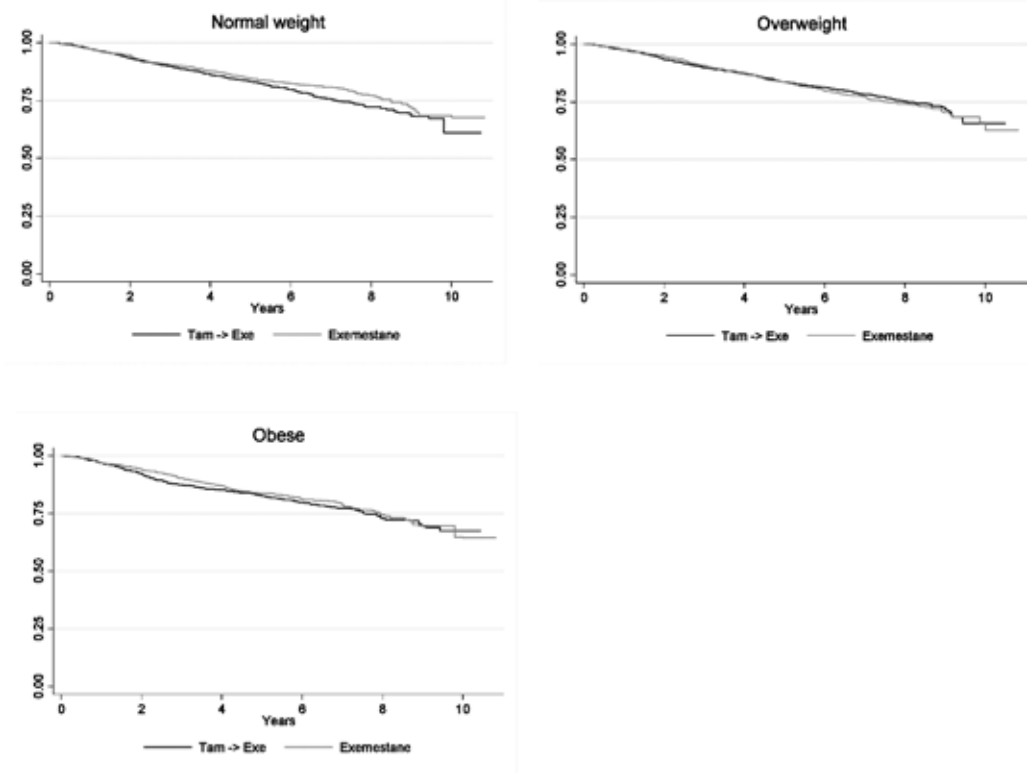


Table 4. **Univariable and multivariable Cox regression analyses of disease-free survival and breast cancer-specific survival according to BMI category in the non-imputed dataset**

Original dataset						**Univariable analyses**				**Multivariable analyses**		
Disease-free survival	**n**	**Event T→E**	**Events Exe**	**DFS T→E (%)**	**DFS Exe (%)**	**T→E**	**HR Exe**	**95%CI**	**p-value**	**HR Exe**	**95%CI**	**p-value**
Normal weight (BMI 18.5-25)	1858	207	183	57.8	67.7	Ref	0.78	0.64 – 0.95	0.015	0.80	0.65 – 0.97	0.025
Overweight (BMI 25-30)	1762	188	178	63.6	60.8	Ref	0.95	0.77 – 1.17	0.62	0.97	0.79 – 1.19	0.74
Obese (BMI >30)	1091	124	115	69.4	63.6	Ref	0.87	0.68 – 1.12	0.29	0.85	0.66 – 1.09	0.2
Breast cancer-specific survival	**n**	**Event T→E**	**Events Exe**	**BCSS T→E (%)**	**BCSS Exe (%)**	**T→E**	**HR Exe**	**95%CI**	**p-value**	**HR Exe**	**95%CI**	**p-value**
Normal weight (BMI 18.5-25)	1858	155	129	29.8	23.1	Ref	0.74	0.59-0.94	0.012	0.76	0.6-0.95	0.018
Overweight (BMI 25-30)	1762	140	124	24.4	22.0	Ref	0.88	0.70-1.13	0.34	0.90	0.71-1.15	0.400
Obese (BMI >30)	1091	86	84	24.4	22.9	Ref	0.92	0.68-1.24	0.59	0.90	0.66-1.21	0.479
Imputed dataset												
Disease-free survival	**%**			**DFS T→E (%)**	**DFS Exe (%)**	**T→E**	**HR Exe**	**95%CI**	**p-value**	**HR Exe**	**95%CI**	**p-value**
Normal weight (BMI 18.5-24.9)	35.1	-	-	61.0	68.4	Ref	0.84	0.70-1.02	0.08	0.90	0.74-1.10	0.32
Overweight (BMI 25.0-29.9)	44.0	-	-	65.6	66.0	Ref	1.05	0.88-1.24	0.61	1.04	0.88-1.24	0.64
Obese (BMI>30.0)	20.9	-	-	67.4	64.7	Ref	0.93	0.72-1.21	0.59	0.96	0.74-1.25	0.79
Breast cancer-specific survival	**%**			**BCSS T→E (%)**	**BCSS Exe (%)**	**T→E**	**HR Exe**	**95%CI**	**p-value**	**HR Exe**	**95%CI**	**p-value**
Normal weight (BMI 18.5-24.9)	35.1	-	-	68.5	78.3	Ref	0.78	0.62-0.99	0.04	0.85	0.67-1.07	0.16
Overweight (BMI 25.0-29.9)	44.0	-	-	74.5	78.7	Ref	0.97	0.79-1.19	0.76	0.95	0.77-1.17	0.62
Obese (BMI>30.0)	20.9	-	-	77.9	73.4	Ref	0.94	0.70-1.27	0.69	1.01	0.75-1.37	0.92

T→E: tamoxifen followed by exemestane; E, Exemestane only; 95%CI, 95% confidence interval; CI, cumulative incidence; HR, hazard ratio; DFS, disease-free survival; BCSS, breast cancer-specific survival.
*multivariable cox regression analyses, adjusted for age and country; †multivariable analyses adjusted for country, age, T stage, N stage, grade, subtype, ER, PR and treatment;**p for interaction>0.05.

DISCUSSION

In our cohort of postmenopausal, endocrine-sensitive breast cancer patients, BMI was not found to be an adverse prognostic factor for DFS or BCSS. Normal-weight patients, demonstrated a tendency towards superior results with exemestane upfront, but the treatment-by-marker interaction test did not reach statistical significance. In addition, no significant benefit for either tamoxifen followed by exemestane or upfront treatment with exemestane in relation to BMI was found following multiple imputation analyses.

In postmenopausal breast cancer patients, obesity is associated with an increased risk of the development of breast cancer.[3, 14] In addition, after breast cancer diagnosis, obesity has been described to have an adverse effect on survival[5-7], and an earlier meta-analysis demonstrated a significantly poorer survival in obese breast cancer patients when compared with non-obese patients.[15] The increase in breast cancer risk associated with higher BMI may be related to higher levels of circulating estrogens in postmenopausal women[16], as obesity is associated with increased estrogen synthesis, insulin resistance and altered inflammatory mediators, which play a role in promoting estrogen synthesis and breast cancer growth.[17-20] In contrast to earlier reports, however, our cohort showed that survival outcomes were similar in normal-weight, overweight and obese patients, implying that BMI does not compromise survival in this specific cohort of postmenopausal, endocrine-sensitive early breast cancer patients.

Evidence of a relationship between preferential treatment benefit and BMI is still relatively sparse. It has been implied that AIs are less effective in overweight or obese women, but only a limited number of studies have compared tamoxifen with AIs in relation to BMI.[21-25] Previously, Dignam and colleagues studied outcomes of 5 years of adjuvant tamoxifen versus placebo treatment in relation to BMI in the NSABP B14 trial. Treatment efficacy did not differ between obese (BMI ≥30 kg/m^2) and underweight/normal-weight patients (BMI <25 kg/m^2).[26] In postmenopausal women in the ATAC (Arimidex, Tamoxifen Alone or in Combination) and the BIG (Breast International Group) 1-98 trials, there was no significant benefit of tamoxifen over AIs in overweight or obese patients following 5 years of endocrine treatment.[21, 24] In the ATAC trial, a non-significant benefit of anastrozole over tamoxifen was reported in patients with a BMI <23 kg/m^2. Higher BMI was also not associated with a differential treatment benefit.[24] In another study by Wolters et al. a non-significant survival benefit in favor of AIs compared with tamoxifen in normal- and intermediate-weight endocrine-sensitive postmenopausal patients was demonstrated, and the opposite (also non-significant) was noted for obese patients.[25] In the present analyses, obese patients also did not benefit from sequential treatment over exemestane upfront. Of note, in contrast to the abovementioned studies, overall analysis of the TEAM trial did not reveal DFS or OS differences between sequential and upfront treatment.[13]

Although the currently available randomized studies have not provided striking evidence for a preferential treatment benefit in relation to BMI, it is tempting to speculate that there could be a biological rationale for differential efficacy between tamoxifen and exemestane treatment regimens in postmenopausal, endocrine-sensitive breast cancer patients. AIs reduce the peripheral conversion of androgens, also largely found in adipose tissue in postmenopausal women.[27] Moreover, aromatization of androstenedione to estrogens is related to body weight.[24, 28-30] Previously, Pfeiler and colleagues measured estradiol levels after 3 months of AI treatment and demonstrated that obese postmenopausal patients had (non-significantly) higher estradiol levels than non-obese patients.[31] Two groups have also studied variations in pharmacokinetics of letrozole and found that differential plasma letrozole concentrations were associated with variations in CYP2A6 and BMI.[32, 33] The lack of a differential treatment effect may hence be the result of suboptimal reductions in circulating estrogen levels in larger patients, in which case future research may need to focus on quantitative assessments of estrogen levels during endocrine treatment.

Approximately half of the entire TEAM cohort had BMI data available, and hence poses a limitation to the interpretation and wider applicability of our results. Despite prognostically less favorable breast cancer characteristics, DFS outcomes were not worse in patients with documented height and weight measurements when compared with those patients whose BMI data was not reported. Additional analyses by means of multiple imputation were performed to deal with the large amount of missing data. Multiple imputation can help reduce reporting bias to some degree, although it does not completely compensate for data not completely missing at random. A plausible explanation for the non-random nature of the missing data in relation to BMI may be more accurate documentation of height and weight in patients who require adjuvant chemotherapy, although this reasoning was not entirely supported by our cohort.

In conclusion, BMI was neither associated with survival outcomes nor variable treatment efficacy with respect to the two treatment regimens studied. Although more evidence for a stronger biological relationship is warranted before clinical decision-making is adapted to BMI, a progressively prevalent conception is that the dosage of AIs may need to be proportionally adjusted with increases in BMI in order to accomplish adequate aromatase inhibition.

Supplementary Table 1. **Baseline characteristics of patients with and without BMI data**

		BMI available		BMI not available		
Characteristics		**n**	**%**	**n**	**%**	**p-value**
Total patients	n=6250	4711	75.4	1539	24.6	
Disease-free survival	HR (95%CI)	1	(ref)	0.605	(0.235-1.558)	0.298
Treatment	Tamoxifen→Exemestane	2327	49.4	787	51.1	0.23
	Exemestane only	2384	50.6	752	48.9	
Age	<50	164	3.5	44	2.9	<0.001
	50-<60	1499	31.8	412	26.8	
	60-<70	1848	39.2	582	37.8	
	≥70	1200	25.5	501	32.6	
BMI	18.5-<25	1858	39.4	-	-	-
	25-<30	1762	37.4	-	-	
	≥30	1091	23.2	-	-	
Country	Germany	979	20.8	482	31.3	<0.001
	Greece	25	0.5	182	11.8	
	Japan	176	3.7	0	0	
	Netherlands/Belgium	2803	59.5	342	22.2	
	UK/Ireland	728	15.5	533	34.6	
Tumor stage	T1 (≤2cm)	2304	48.9	775	50.4	0.001
	T2 (>2-≤5cm)	2100	44.6	657	42.7	
	T3 or T4 (>5cm)	299	6.3	95	6.2	
	Tx/Tis/unknown	8	0.1	12	0.8	
Nodal stage	N0	1882	40.0	721	46.8	<0.001
	N1	2451	52.0	719	46.7	
	N2/N3	341	7.2	83	5.4	
	Nx/unknown	37	0.8	16	1.0	
Grade (BR)	G1 (well)	541	11.5	132	8.6	<0.001
	G2 (moderate)	2322	49.3	843	54.8	
	G3,G4 (poor)	1467	31.1	437	28.4	
	unknown	381	8.1	127	8.3	
Histological type	Invasive ductal	2762	58.6	808	52.5	<0.001
	Invasive lobular	515	10.9	153	9.9	
	Other/unknown	1434	30.4	578	37.6	
Surgery	Mastectomy	2210	46.9	702	45.6	0.006
	Wide local excision	2499	53.0	832	54.1	
	No resection/unknown	2	0.1	5	0.3	
Radiotherapy	Yes	3299	70.1	943	61.8	<0.001
	No	1407	29.9	582	38.2	
Chemotherapy	Yes	1778	37.7	518	33.7	0.004
	No	2932	62.3	1018	66.3	
ER Status	Positive	4601	97.7	1509	98.1	0.629
	Negative	108	2.3	29	1.9	
	unknown	2	0.0	1	0.1	
PR Status	Positive	3431	72.8	1041	67.6	<0.001
	Negative	876	18.6	234	15.2	
	unknown	404	8.6	264	17.2	
HER2 status	Negative	1675	46.1	592	57.1	<0.001
	Positive	309	8.5	202	19.5	
	unknown	1652	45.4	242	23.4	

HR, hazard ratio (multivariate); CI, confidence interval; BR, Bloom&Richardson; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor-2.

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CHAPTER

5

AGE AND THE EFFECT OF PHYSICAL ACTIVITY ON BREAST CANCER SURVIVAL: A SYSTEMATIC REVIEW

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ABSTRACT

The effect of physical activity (PA) on cancer survival is still the topic of debate in oncology research focusing on survivorship, and has been investigated retrospectively in several large clinical trials. PA has been shown to improve quality of life, fitness and strength, and to reduce depression and fatigue. At present, there is a growing body of evidence on the effects of PA interventions for cancer survivors on health outcomes. PA and functional limitations are interrelated in the elderly. However, the relationship between breast cancer survival and PA in older breast cancer patients has not yet been fully investigated. Our systematic review of the existing literature on this topic yielded seventeen studies. Most reports demonstrated an improved overall survival (OS) and breast cancer-specific survival (BCSS). Furthermore, in studies that compared younger women with older or postmenopausal women, it was suggested that the beneficial effect of PA may be even greater in older women. Understanding the interaction between physical functioning and cancer survival in older breast cancer patients is key, and may contribute to successful treatment and survival. In this population of cancer survivors it is therefore imperative to embark on research focused on improving physical functioning in the context of comorbidities and functional limitations.

INTRODUCTION

There is a growing body of evidence on the effects of physical activity (PA) interventions for cancer survivors on health outcomes. PA in breast cancer has shown to improve quality of life, fitness and strength and to reduce depression and fatigue.[1] Also, PA has shown to have an inverse association with postmenopausal breast cancer risk.[2] Previous randomized controlled trials have demonstrated better quality of life and other health outcomes in patients who undertake regular PA.[3] The effect of PA on cancer survival after breast cancer diagnosis, however, is still the topic of debate in oncology research.[4]

Breast cancer is increasingly becoming a disease of the elderly and, simultaneously, the number of breast cancer survivors is steadily rising.[5] For example, in the United Kingdom, 45% of breast cancer patients are older than 65 years at diagnosis.[6] In elderly patients, cancer occurs in a background of normal aging and comorbidity, thereby making this specific population heterogeneous in nature. Although older patients are known to have a higher disease-specific mortality, more than 65% of breast cancer patients older than 75 years die of other causes than breast cancer.[7] In contrast to younger patients, survival in the elderly breast cancer population has not improved in the last decade.[8] While breast cancer has a profound effect on psychological functioning and quality of life in younger females, elderly patients are affected by the disease physically more than psychologically.[9] At an older age, the decline in physical functioning may be induced or amplified as a result of local and/or systemic treatments. Regardless of age, decline in physical functioning is associated with higher mortality.[10] Therefore, new strategies to decrease the effect of breast cancer on physical decline and to improve overall and disease-specific survival are needed. The purpose of this study was to review the current literature in relation to the effect of PA on survival in breast cancer patients, with a focus on the elderly breast cancer patient in particular.

MATERIALS AND METHODS

Search strategy

Studies were identified through systematic review of the available literature in the PubMed database, EMBASe, Cochrane and Web of Science up to November 9th, 2012. PubMed, EMBASE, Cochrane and Web of Science were all searched using the following set of search terms which described breast cancer, physical activity, survival and elderly patients according to the following algorithm: ("Breast Neoplasms"[majr] OR "breast cancer"[ti] OR "Breast Neoplasm"[ti] OR "Breast Tumors"[ti] OR "Breast Tumor"[ti] OR "Breast Tumours"[ti] OR "Breast Tumour"[ti] OR "Breast Carcinoma"[ti] OR "Breast Carcinomas"[ti] OR "Cancer of the Breast"[ti] OR "Cancer of Breast"[ti]) AND ("physical activity" OR "Motor activity"[mesh] OR "Sports"[mesh] OR "Exercise"[mesh] OR Exercise[ti] OR Exercises[ti] OR "Resistance Training"[ti] OR Running[ti] OR Jogging[ti] OR Swimming[ti] OR Walking[ti] OR "Sports"[mesh] OR "Physical Exertion"[Mesh] OR exertion[ti]) AND (survival OR surviv* OR "Survival"[Mesh] OR "Mortality"[Mesh] OR "mortality"[Subheading] OR "Survival Rate"[Mesh] OR "Survival Analysis"[Mesh]) AND ("Aged"[mesh] OR Elderly OR aged OR Adult OR Adults OR

"Adult"[mesh] OR woman[tiab] OR women[tiab]) AND (eng[la]) AND ("Cohort Studies"[mesh] OR prognosis).

Selection criteria

Two independent reviewers (D.F., N.G.) selected studies for inclusion in the review. Only reports written in English were eligible. Articles included original studies in which the effect of PA on survival outcomes was investigated in breast cancer patients only. Studies were included if the primary or secondary outcome was related to the influence of PA on OS, BCSS or breast cancer recurrence after breast cancer diagnosis. PA was defined as any physical activity relating to aerobic, endurance, or strength training for the purposes of recreation, household, commuting, or work. Where evident, activities including yoga, Pilates, Tai Chi, or stretching were not included in the analyses. There were no restrictions with regard to patient characteristics, breast cancer subtype, treatment, age, condition, comorbidities, and other features. Only studies investigating leisure or total activity (occupational and/or non-occupational) were selected. Studies measuring PA using biological parameters (i.e. cardiorespiratory fitness, energy expenditure (in KJ or Kcal), oxygen use (in vO_2 /vCO_2), etc.) were not included in our selected abstracts. In case of an update of previously published data, the most recent publication was included. Reports on pilot data or descriptions of a study design were excluded from this review. Studies were also excluded if the PA intervention was combined with another intervention. To ensure that no other studies were missed for inclusion in the current review, additional articles were identified by a manual search of the reference list of the selected manuscripts.

Data extraction

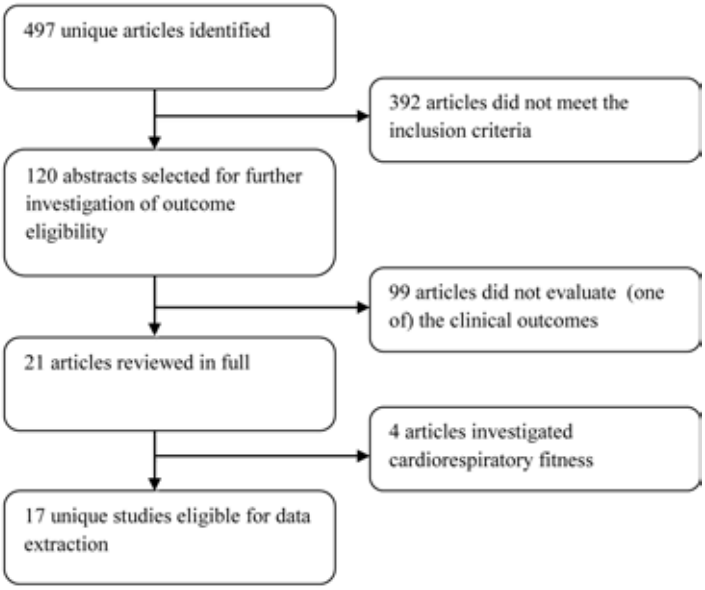
Data extraction was performed by 3 reviewers (D.F., N.G. and M.D.). Relevant data was determined prior to reading the selected articles. For all included studies, we documented the type of study, inclusion period, year of publication, primary and (where possible) secondary endpoints. Results from each study was documented and independently reviewed and verified by two independent reviewers (D.F. and N.G.). Aspects of PA were the type of activity, PA measurement unit (including frequency, duration and intensity, which were frequently converted into Metabolic Equivalent Task (MET) hours), time and timeframe of measurement(s), method of data collection, number of patients, mean and median age and age range, in- and exclusion criteria, as well as tumor- and patient-related characteristics. Results for specific population subgroups, including age (and/or menopausal status) and Body-Mass Index (BMI) were documented where available. Due to the fact that ages varied greatly between studies, we defined 'elderly' as 65 years or older. Primary and/or secondary endpoints included all-cause mortality, breast cancer-specific mortality, and breast cancer recurrence.

RESULTS

Patients

A total of 497 unique articles were identified in the PubMed, EMBASe, Cochrane and Web of Science searches, of which seventeen studies were deemed eligible after applying in- and exclusion criteria to the titles and abstracts (Table 1 and Figure 1). A total of 35,026 breast cancer patients were included in our review. Only one study investigated solely postmenopausal patients.11 In most studies, PA was measured in the first year after primary diagnosis. Two studies only included patients who were diagnosed with early-stage breast cancer. Fourteen studies also included patients with a more advanced breast cancer stage.

Figure 1. **Flow chart**



Studies

The majority of the studies assessed were prospective observational cohort studies.[11-23] Two studies were part of the same side study of a randomized controlled trial investigating dietary change.[24, 25] A final study was a retrospective analysis of PA in patients participating in a multicenter case-control study.[26]

Questionnaires

In all studies, data collection was through self-administered and/or interviewer-administered questionnaires, performed either in person or by telephone. Questionnaires were completed either once [12-15, 18, 19, 21-23, 25, 26]

Table 1. **Physical activity outcomes in all studies**

Study	Patients	Age	Type of study	Measurement of PA
Bertram et al.[24]	2361 BC survivors stage I-III, 1 year post-treatment	18-70, median age 54.3	Side study of randomized controlled trial of dietary change (WHEL-study)	9-item physical activity measure adapted from the WHI. Conversion to MET-hrs
Cleveland et al.[13]	1508 early-stage BC patients	Mean age 58.6	Population-based longitudinal study (Long Island Breast Cancer Study Project)	MET-hrs/week
Dal Maso et al.[26]	1453 BC patients	23-74, median age 55	Multicentre case-control study	Retrospective questionnaire on PA at various ages
Emaus et al.[12]	1364 BC patients	17-79, mean age 57.5	Population-based survival study (Norwegian Counties Study)	Questionnaire on pre-diagnostic PA
Friedenreich et al.[14]	1183 BC patients	Mean age 56	Population-based sample of breast cancer survivors	Assessment of lifetime PA. Conversion to MET-hrs
Hellman et al.[15]	528 primary BC patients	33-95, median age 66.9	Prospective population-based study (Copenhagen City Heart Study)	Self-administered questionnaire on PA
Holick et al.[27]	4482 BC patients, 91% postmenopausal.	20-79, mean age 58.5	Prospective population-based study (Collaborative Women's Longevity Study (CWLS))	CWLS questionnaire. Conversion to MET-hrs
Holmes et al.[16]	2987 nurses with stage I/II/III BC	30-55 on enrolment in NHS	Prospective observational study (Nurses' Health Study)	Questionnaire on PA, calculated in MET-hrs/wk (<3/3-8/9-14/15-23/>24)
Irwin et al.[17]	933 BC patients with local or regional breast cancer	Mean age 55.5 (6 months post-diagnosis)	Population based multicentre prospective cohort study (Health, Eating, Activity and Lifestyle (HEAL) Study)	Modifiable Activity Questionnaire in MET-hrs/wk (all types of PA) light (<3) moderate (3-6), vigorous (>6)
Irwin et al.[11]	4643 post-menopausal BC patients	50-79	Prospective longitudinal study (Women's Health Initiative (WHI))	Questionnaire on PA. Conversion to MET-hrs
Pierce et al.[25]	1490 early-stage BC patients	<70, mean age 50	Side study of randomized controlled trial of dietary change (WHEL-study)	9-item PA measure adapted from the WHI. Conversion to MET-hrs
Rohan et al.[19]	451 BC patients	20-74	Population-based cohort	Questionnaire on recreational PA. Conversion to total kcal expended per week
Sternfeld et al.[20]	1970 early-stage BC patients	18-79, mean 60.6	Prospective, observational study (Life After Cancer Epidemiology (LACE) Study)	Questionnaire based on the Arizona Activity Frequency Questionnaire. Conversion to MET-hrs
Keegan et al.[18]	4153 BC patients (320 patients excluded from Australian cases)	18-69	Population-based cancer registries (Breast Cancer Family Registry)	Questionnaires administered post-diagnosis. Conversion to MET-hrs.
West-Wright et al.[21]	3,539 BC patients with invasive BC	26-94, mean age 58.9	Prospective Cohort Study (California Teacher's Study)	PA questionnaire on recreational PA. hrs/week and months per year recorded.
Enger et al.[22]	717 BC patients with in situ or invasive BC	21-40	Population-based case-control study	Lifetime PA measured in hrs/week of recreational exercises.
Abrahamson et al.[23]	1264 BC patients with invasive BC	20-54, median 42	Population-based cohort study (parent study)	Relative MET scores for vigorous (9 METs) and moderate (5 METs) activities. Scores weighted by frequency of the activity per week.

BC, breast cancer; HR, Hazard Ratio; PA, physical activity; hrs, hours; MET-hrs, Metabolic Equivalent Task hours

Details of study	Primary outcome	Overall results
Questionnaire at baseline and 12-months. Post-treatment and change in PA	Invasive breast-cancer events and all-cause mortality	High baseline (post-treatment) PA (conform guidelines) lead to 35% reduction in all-cause mortality (HR 0.39 (0.21-0.72) for highest quintile total PA vs no PA). Change in PA had no effect on outcomes
Baseline interview post-diagnosis on pre-diagnosis recreational PA	5-year all-cause mortality and BC-specific mortality	Significant lower risk for BC-specific mortality (HR 0.63 (043-0.92)) (any total lifetime RPA vs no RPA), significantly lower risk for all-cause mortality (HR 0.58 (0.43-0.78))
Questionnaire completed once max 1 year post-diagnosis	All-cause mortality and BC-specific mortality	Leisure time PA was not associated with BC mortality: HR=0.85(0.68-1.07) for PA <2hr/wk vs. >2/wk Leisure time PA was not associated with all-cause mortality: HR=0.92 (0.67-1.01) for PA<2hr/wk. vs. >2/wk Occupational PA was not associated with BC mortality or all-cause mortality
Questionnaire on pre-diagnosis PA (for the year preceding each survey)	All-cause mortality and BC-specific mortality	Overall mortality was not significantly better in active patients (HR 0.74 (0.51-1.08)) (highest category vs lowest category of PA) or with BC-specific mortality (HR 0.75 (0.49-1.15))
Questionnaire on lifetime recreational, household and occupational PA, recorded at baseline only	All-cause mortality, BC-specific mortality, recurrence, progression, new primary	Vigorous intensity was not related to recurrence, BC-specific mortality and all-cause mortality. However, moderate intensity recreational physical activity was beneficial for all the outcomes (HR BC-specific mortality 0.66 (0.48-0.91), HR all-cause mortality 0.76 (0.58-1.06 with p=0.05), HR recurrence 0.48-0,91)
Self-reported pre-diagnosis PA	All-cause mortality	High PA (>4h/wk) vs moderate PA (2-4h/wk) vs no PA was not associated with reduced all-cause mortality after BC diagnosis (Moderate: HR=1.07, 0.77-1.49; High: HR=1.00, 0.69-1.45). High vs moderate vs no PA was not associated with reduced BC-specific mortality (Moderate: HR=0.73, 0.50-1.08; High: HR=0.70, 0.46-1.09).
Telephone interview within 2 years of diagnosis. Survivors completed a questionnaire for recent post-diagnosis PA.	All-cause mortality and BC-specific mortality	Compared with low recent post-diagnosis recreational PA (<2.8MET-hr/wk), higher PA was associated with a decreased risk of BC death. Overall mortality was also improved with increasing levels of PA. When stratified, moderate-intensity recreational PA had a significant beneficial effect on both outcomes, but vigorous-intensity PA did not
Questionnaires every 2 years from 1976-2004 for current PA.	BC-specific mortality	The HR for BC mortality was 0.80 (0.60-1.06) for 3- 8.9 MET-hrs/wk; 0.50 (0.31-0.82) for 9 to 14.9 MET-hr/wk; 0.56 (0.38- 0.84) for 15 to 23.9 MET-hr/wk; and 0.60 (0.40-0.89) for 24 or more MET-hr/wk
In-person baseline interview (4-8 months) post-diagnosis. Follow-up interview 3 years post-diagnosis	BC-specific mortality and all-cause mortality	Compared with inactive women (0 MET-hr/wk) BC mortality in pre-diagnostic PA: >9MET-hr was not significantly better (HR 0.69 (0.45-1.06)), but post-diagnosis PA was beneficial (HR 0.33 (0.15-0.73)). Increase in PA lead to non-significant 45% lower risk of all-cause mortality (HR 0.55,(0.22-1.38)); decrease in PA: HR=3.95 (1.45-10.5)
Questionnaire on recreational and household PA at baseline, year 3 and year 6 post-diagnosis	All-cause mortality and BC-specific mortality	Moderate- to vigorous-intensity post-diagnosis PA lead to a lower risk for all-cause mortality (HR 0.54 (0.38-0.79)) and a lower risk for BC-specific mortality (HR 0.61 (0.35-0.99)). Increase of PA after diagnosis of 9 MET-hr/wk or more lead to 33% less risk of all-cause mortality (HR 0.67 (0.46-0.96))
Baseline PA questionnaire	All-cause mortality	Compared with low PA (0-225 MET-min/wk), high PA was associated with lower all-cause mortality 225-636 MET-min/wk: HR=0.86, 636-1320 MET-min/wk: HR=0.76, 1320-6420 MET-min/wk: HR 0.58 (p=0.02, no 95%-CI reported)
Reported pre-diagnosis recreational PA (divided into winter and summer PA)	BC-specific mortality	There was no association between PA and BC-specific mortality in the whole study group (ref 0 kcal/wk). There was also no association between PA and BC-specific mortality when stratified by PA level (light, moderate, and vigorous PA).
Semi-annual questionnaire about primary outcomes (self-reported)	All-cause mortality, BC-specific mortality, BC recurrence	There was no association between total PA and all-cause mortality, BC-specific mortality and recurrence, but there was a significantly beneficial effect of moderate activity on all-cause mortality (HR 0.66 (0.42-1.03, p for trend=0.04)), but not on BC-specific mortality and recurrence.
Lifetime history of recreational PA and 3 years pre-diagnosis	All-cause mortality	Any recent moderate/vigorous PA versus no activity showed a significantly lower all-cause mortality (HR=0.73, (95%CI 0.60-0.89). Stratified by Estrogen Receptor (ER) status, only ER positive patients had a benefit of PA (HR=0.67 (95%CI 0.4-0.94)) for active vs non-active patients, ER-negative patients: HR=1.05 (95%CI 0.66-1.68)
PA questionnaire for long-term and recent pre-diagnosis recreational PA	BC-specific mortality, all-cause mortality	BC-specific mortality was significantly better for long-term intermediate PA HR 0.65 (95%CI 0.45-0.93) and high PA HR 0.53 (0.35-0.80) vs low PA, (p=0.003). For recent PA there was no beneficial effect for BC-specific mortality intermediate PA HR 1.17 (0.84-1.65), high PA HR 1.08 (0.73-1.58), p=0.69. Overall survival was better in long-term PA: intermediate PA HR 0.83 (0.65-1.07) and high PA (0.73 (0.55-0.96) vs low PA (p=0.03). Recent PA was borderline significantly beneficial for overall survival: intermediate PA HR 0.89 (0.71-1.11), high PA HR 0.78 (0.60-1.02) vs low PA (p=0.06)
In-person interview on lifetime PA (from first menses) up to 12 months pre-diagnosis	BC-specific mortality	There was no significant benefit of PA: 0.1-0.7hrs: HR 0.86 (0.56-1.32); 0.8-1.6 hrs: HR 0.59 (0.35-1.01); 1.7-3.7hrs: HR 0.87 (0.57-1.33); 3.8+hrs: HR 1.30 (0.81-2.09); p(trend)=0.88
In-person interview for average PA at 12-13 years, 20 years, and the year before diagnosis.	All-cause mortality	There was no significantly beneficial effect of PA in year before diagnosis for: Q2 HR 0.86 (0.63-1.18); Q3: HR 0.81 (0.6-1.12); Q4: HR 0.78 (0.56-1.08) vs quartile Q1. (p=0.10)

or on two or more occasions.[11, 16, 17, 20, 24, 27] Questionnaires included inquiries on occupational, recreational and/or household activities, either combined or separately. Furthermore, data were collected on either current, pre-diagnostic or post-diagnostic PA, or a combination of these. For most studies[11, 14, 16, 17, 20, 23-25, 27] Metabolic Equivalent Task (MET)-hours were used (or calculated) to assess PA in relation to survival outcomes. MET-hours are a validated measurement of PA, and are frequently used to define intensity and duration of PA. One MET-hour is defined as the equivalent of sitting quietly, or 3.5ml oxygen*kg-1 body weight*minute-1 (1 kcal*kg-1 body weight*hour-1).[28] The remaining studies used either the absolute number of hours of PA[12, 15, 21, 22, 26] or the total kcal expended per week[19] A majority of studies used validated questionnaires, including the Modifiable Activity Questionnaire [17] and the Collaborative Women's Longevity Study (CWLS) questionnaire.[27] In most studies, tumor and treatment characteristics, socio-demographic characteristics, lifestyle habits (education, occupation, smoking, alcohol use), menstrual and reproductive history, exogenous hormone use, and comorbidities were also documented.

Primary endpoints

Fourteen studies assessed all-cause mortality[11-15, 17, 18, 20, 21, 23-27], 12 studies assessed breast cancer-specific mortality[11-14, 16, 17, 19-22, 26, 27], and three studies investigated breast cancer recurrence as primary endpoint(s).[14, 20, 24] All hazard ratios (HR) reported in this review concern the highest amount of PA versus the lowest amount of PA, the lowest level of PA being the reference value. All reported HRs are multivariable adjusted.

Effects of physical activity on breast cancer-specific and all-cause mortality

Eight out of 12 studies that investigated the effect of PA on BCSS found a significant advantage of PA on survival, ranging from a 36-67% reduction in risk of death for the highest amount of PA versus no PA (HR ranging from 0.53 (95%CI 0.35-0.80) to 0.80 (no 95%CI reported[11-14, 16-18, 27]. Three of the remaining four studies found a non-significant benefit (HR 0.85 (95%CI 0.68-1.07), HR 0.72 (95%CI 0.29-1.81), HR 0.90 (95%CI 0.51-1.58))[19, 20, 26] while the fourth study found a non-significant worse BCSS (HR 1.30 (95%CI 0.81-2.09)).

Fourteen studies described the effect of PA on all-cause mortality, of which ten studies found a significant improvement in all-cause mortality with increasing PA.[13, 14, 17, 18, 20, 21, 24, 25, 27] This effect ranged from 14% to 56% (HR ranged from 0.39 (95%CI 0.21-0.72) to 0.73 (95%CI 0.60-0.89). The remaining studies reported a non-significant protective effect of PA on all-cause mortality.

Physical activity outcomes in elderly patients

There were no studies that investigated elderly patients (defined as older than 65 years) separately. However, eight studies stratified their analyses by menopausal status or age[12, 13, 15-19, 27], and one study included postmenopausal patients only (Table 2).[11] Five studies grouped their patients by pre- and postmenopausal status[11, 13, 15-17, 19], while the remaining studies stratified their analyses by age.[12, 17, 18, 27] Three studies found a significantly lower risk of either breast cancer-specific mortality[16] (HR 0.80 (95%CI 0.60-1.06)) or overall mortality[17] (HR 0.29 (95%CI 0.14-0.60)) in the older or postmenopausal active group (highest versus lowest amount of PA) (data from Keegan et al.[18] not shown). The study in which exclusively postmenopausal patients were included demonstrated a significantly lower risk of all-cause mortality (HR 0.67 (95%CI 0.46-

0.96)) and breast cancer-specific mortality (HR 0.61 (95%CI 0.35-0.99)) in patients who were moderate- to vigorously active after diagnosis.[11] The remaining five studies all reported a non-significant benefit of PA on outcomes.[12, 13, 15, 19, 27]

Differences in outcomes between pre- and post-diagnostic physical activity

Out of all studies, eleven investigated the effect of pre-diagnostic PA on overall mortality, breast cancer-specific mortality and/or disease-free survival.[12-15, 18, 19, 21-23, 25, 26] Three studies assessed the effect of post-diagnostic PA[16, 20, 27], one study investigated the effect of post-diagnostic PA at different time points[24], and the remaining two studies examined both pre- and post-diagnostic PA.[11, 17] These two studies looked at the effect of pre-diagnostic PA as well as the effect of change in PA after diagnosis on at least one of the outcomes.

Table 2. **Physical activity outcomes in older breast cancer patients**

Study	n	Age	Primary outcome	Age-specific results
Cleveland et al.[13]	1508	mean 58.6	5-year all-cause mortality and BC-specific mortality	Postmenopausal active women had a non-significant decreased risk of BC-specific mortality (HR 0.79 (0.45-1.39)), and a borderline significant decreased risk of all-cause mortality (HR 0.65 (0.42-1.00))
Emaus et al.[12]	1364	17-79, mean 57.5	All-cause mortality and BC-specific mortality	Non-significant decreased overall mortality in patients >55 (HR 0.60 (0.36-0.99) and non-significant risk of BC death (HR 0.57 (0.31-1.04))
Hellman et al.[15]	528	33-95, median 66.9	All-cause mortality	In active postmenopausal patients, HR for overall death was 1.71 (1.16-2.54) in highest amount of PA vs no PA
Holick et al.[27]	4482	20-79, mean 58.5	All-cause mortality and BC-specific mortality	The most active patients >59 years had a non-significantly lower risk of BC-mortality (HR 0.85 (0.47-1.54))
Holmes et al.[16]	2987	30-55	BC-specific mortality	Active postmenopausal women had a significantly lower risk of BC-death (HR 0.73 (0.54-0.98))
Irwin et al.[17]	933	mean 55.5	All-cause mortality and BC-specific mortality	Active women >55years had a significantly lower risk of all-cause mortality (HR 0.29 (0.14-0.60)
Irwin et al.[11]	4643	50-79	All-cause mortality and BC-specific mortality	Moderate- to vigorous-intensity post-diagnosis PA lead to a lower risk for all-cause mortality (HR 0.54 (0.38-0.79)) and a lower risk of BC-specific mortality (HR 0.61 (0.35-0.99)). Increase in PA after diagnosis of 9 MET-h/week or more lead to 33% decreased risk of all-cause mortality (HR 0.67 (0.46-0.96))
Rohan et al.[19]	451	20-74	BC-specific mortality	Postmenopausal active women did not have a decreased risk of BC mortality (HR 0.72 (0.29-1.81))
Keegan et al.[18]	4153	18-69	All-cause mortality	No difference between different ages at diagnosis of menopausal stage (no HRs reported)

BC, breast cancer; HR, hazard ratio; PA, physical activity; MET, Metabolic Equivalent Task.

Pre-diagnostic PA lead to a significantly better OS in five out of 11 studies[13, 14, 18, 21, 25], of which three studies also ascertained a significantly better BCSS[13, 14, 21] The remaining studies found beneficial effects, although they did not reach statistical significance. All studies investigating post-diagnostic PA found a beneficial effect on OS.[11, 16, 17, 20, 24, 27] BCSS was significantly lower in three out of five studies that had this endpoint.[16, 17, 27]

An increase in PA was beneficial in one out of two studies, with a HR of 0.67 (95%CI 0.46-0.99) (for the greatest increase in physical activity).[11] Although the second study investigating change in physical activity found a non-significant benefit of increased physical activity (HR 0.55 (95%CI 0.22-1.38)), a much higher risk of all-cause mortality was established in patients with a reduction in PA (HR 3.95 (95%CI 1.45-10.5)) (Table 3).[17]

Table 3. **Effect of physical activity on outcomes**

Study	n	Age	Breast cancer specific mortality	All-cause mortality	Breast cancer recurrence
Bertram et al.[24]	2361 BC survivors stage I-III, 1 year post-treatment	18-70 Median age 54.3	-	↓	-
Cleveland et al.[13]	1508 early-stage BC patients	Mean age 58.6	↓	-	-
Dal Maso et al.[26]	1453 BC patients	23-74 Median age 55	No difference	No difference	-
Emaus et al.[12]	1364 BC patients	17-79 Mean age 57.5	No difference	No difference	-
Friedenreich et al.[14]	1183 BC patients	Mean age 56	↓	↓	↓
Hellman et al.[15]	528 primary BC patients	33-95 Median age 66.9	No difference	No difference	-
Holick et al.[27]	4482 BC patients, 91% postmenopausal.	20-79 Mean age 58.5	↓	↓	-
Holmes et al.[16]	2987 nurses with stage I/II/III BC	30-55	↓	-	-
Irwin et al.[17]	933 BC patients with local or regional breast cancer	Mean age 55.5 (6 months post-diagnosis)	↓	-	-
Irwin et al.[11]	4643 post-menopausal BC patients	50-79	↓	↓	-
Pierce et al.[25]	1490 early-stage BC patients	<70 Mean age 50	-	↓	-
Rohan et al.[19]	451 BC patients	20-74	No difference	-	-
Sternfeld et al.[20]	1970 early-stage BC patients	18-79 Mean age 60.6	No difference	↓	No difference
Keegan et al.[18]	4153 BC patients (320 patients excluded from Australian cases)	18-69	-	↓	-
West-Wright et al.[21]	3,539 BC patients with invasive BC	26-94 Mean age 58.9	↓	↓	-
Enger et al.[22]	717 BC patients with in situ or invasive BC	21-40	No difference	-	-
Abrahamson et al.[23]	1264 BC patients with invasive BC	20-54 Median age 42	No difference	-	-

BC, breast cancer.

Physical activity in different BMI-groups

Nine studies stratified their analyses by different BMI-groups.[11-13, 17, 18, 20, 21, 23, 27] Two studies reported on breast cancer-specific mortality as well as all-cause mortality for the stratified groups, while one study reported on breast cancer-specific mortality only. The remaining six studies reported all-cause mortality only for the different groups. The study by Cleveland et al.[13] showed a non-significant lower risk of breast cancer-specific mortality in active patients with a BMI under 25 (HR 0.57 (95%CI 0.30-1.09)) and a significantly lower risk in active patients with a BMI over 25 (HR 0.63 (95%CI 0.40-0.99)).[13] Similarly, the study by Holick et al.[27] found a better BCSS for active patients with a BMI below 25 (although not statistically significant), and a borderline significant effect in patients with a BMI above 25 (HR 0.63 (95%CI 0.39-1.02)).[27] West-wright et al.[21] did not find a significant benefit for active patients with a BMI under 25 (HR 1.15 (95%CI 0.32-0.86)), but a significantly better BCSS in patients with a BMI above 25 (HR 0.41 (95%CI 0.23-0.74) for high PA versus low PA). In patients with a BMI below 25, all-cause mortality was significantly lower in four out of eight studies.[12, 13, 20, 27] One study reported a benefit that was even greater in patients who were 55 years or older.[13] Four studies found a lower all-cause mortality in active patients with a BMI over 25.[13, 17, 23, 27]

DISCUSSION

We present an overview of the available literature on the effect of PA on breast cancer outcomes. Most studies demonstrate that PA has a positive effect on OS and BCSS. Post-diagnostic PA was most beneficial for breast cancer outcomes. Most investigations were observational studies with low median ages, with the exception of one study that investigated only postmenopausal breast cancer patients. Although no study specifically addressed patients who were 65 years or older, we observed that older and/or postmenopausal patients acquired the greatest advantage of PA.

Several explanations have been proposed for the age-related benefit. In addition to concurrent comorbid conditions, aging is associated with declines in physical and cognitive functioning. A large cohort study of breast cancer survivors showed that functional limitations were associated with worse all-cause and competing-cause mortality.[29] Cancer patients are at increased risk of reporting limitations in their activities of daily living compared to non-cancer patients.[9, 30] Several exercise programs demonstrated varying positive effects in older people, including improved muscle strength and gait speed, reduction in falls, improved balance, bone mineral density and increased mental health.[31-37] The Canadian Study of Health and Aging showed that older persons who participated in high levels of PA had a lower risk of death than those who did little or no exercise; the absolute benefits were greatest for those with the highest number of health deficits.[37]

Investigators have speculated on the biological mechanism behind these findings. The effect of PA on breast cancer specific survival was stronger for overweight patients (BMI>25) than normal-weight patients. Although these findings were not paralleled for all-cause mortality, the effect of PA on the reduction in weight and, subsequently, on insulin levels are a likely explanation. It is well-known that postmenopausal patients with obesity and high insulin levels and/or diabetes mellitus have a greater risk of breast cancer.[38-40] Insulin resistance is thought to influence the risk of breast cancer recurrence and mortality[41-43] Pasanisi et al. found that higher insulin levels and insulin resistance syndrome are associated with breast cancer mortality.[41] Importantly, PA can significantly lower insulin levels in women with breast cancer. It has also been suggested that PA reduces breast cancer risk by improving metabolic profiles as well as by decreasing levels of endogenous estrogens and body fat.[44]

Aging is a strong predictor of functional decline and comorbidities, and literature suggests that older cancer patients are more likely to be affected by cancer in terms of physical than cognitive functioning.[9, 45, 46] Physical domains are especially important in elderly patients, as they can make the difference between independent and assisted living. As breast cancer in elderly patients is predominantly estrogen receptor (ER)-positive, systemic endocrine treatment is frequently warranted. Toxicities of endocrine therapy and the larger number of comorbid conditions with increasing age may result in patients being more vulnerable to the clinical consequences of adverse events. Previous reports have demonstrated that PA can improve

comorbid conditions and adverse effects of adjuvant treatment [47, 48], therefore, PA can provide an additional benefit in these patients.

Because of the heterogeneity of the data collected and different definitions of low, moderate and high intensity PA, we could not perform a pooled meta-analysis of the reported HRs. Furthermore, this study is limited to some extent by the lack of evidence that focuses on the effect of PA on breast cancer outcomes in the elderly breast cancer patients specifically. Consequently, the effect of PA on overall and breast cancer-specific mortality in elderly patients may reveal an even greater benefit, given the prevalence of more ER-positive tumors as well as frailer patients who are likely to gain most from PA. To add, it is important to realize that other factors may also influence the possibility for patients to partake in PA at all. One can presume that, generally speaking, patients without functional limitations are more likely to be healthy and capable of exercising, while patients who are restricted due to health deficits are already less physically active, and thus at an increased risk of adverse outcomes. For this reason, further investigations into the cancer-aging interface and the influence of breast cancer on functional decline in elderly patients are indispensable. We have initiated 'Climb Every Mountain', a longitudinal, prospective cohort study that measures physical, cognitive, and social health during and after breast cancer treatment. The purpose of this study is to generate new knowledge on the prevalence and impact of functional, cognitive, and social limitations in elderly breast cancer survivors. A second phase will use those domains most affected by cancer diagnosis and treatment, to develop a patient-tailored physical intervention study aimed specifically at the elderly breast cancer patient.

CONCLUSION

This review covers a very heterogeneous group of patients, consisting of pre-and postmenopausal breast cancer patients with varying tumor-biological and clinical characteristics. In older breast cancer patients specifically, the majority of studies demonstrated a decrease in both all-cause and breast cancer-specific mortality with increasing levels of PA. To add, the decrease in breast cancer-specific mortality was more prominent in overweight patients than in normal-weight patients. Overall, it can be concluded that some degree of PA leads to improved survival outcomes in breast cancer patients, which provides the prospect of employing a practical intervention that can act as a targeted treatment for breast cancer.

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CHAPTER

6

AGE IN RELATION TO PHYSICAL ACTIVITY AND SURVIVAL IN POSTMENOPAUSAL HORMONE RECEPTOR-POSITIVE BREAST CANCER PATIENTS – RESULTS OF THE TEAM-LIFESTYLE STUDY

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ABSTRACT

Background

Physical activity has been related to improved breast cancer outcomes in several previous studies. Especially in the older breast cancer population, physical activity may be of importance, as high age is associated with comorbidity and poor physical function. However, no previous studies investigated the relation between physical activity and breast cancer outcomes in older patients specifically. The purpose of this study was to investigate the relation between physical activity on overall survival (OS), breast cancer-specific survival (BCSS) and recurrence in postmenopausal breast cancer patients based on age-group

Methods

The TEAM-Lifestyle study is a side-study of the Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial, which prospectively investigated lifestyle habits of postmenopausal, hormone receptor-positive breast cancer patients. The effects of pre-diagnosis and post-diagnosis physical activity on OS, and BCSS and recurrence-free period (RFP) were calculated using Cox regression and competing risk regression models.

Results

Among 521 patients, high levels of physical activity before and after diagnosis were associated with a better OS (multivariable hazard ratio (HR) 0.50 (95%CI 0.26-0.98) and HR 0.57 (95%CI 0.26-1.40) for patients who were very active (upper quartile) before and after diagnosis respectively, compared to relatively inactive patients). This was most evident in patients aged 65 years and older. Physical activity was not significantly related to BCSS or RFP.

Discussion

OS was better in patients who were active before and after diagnosis, especially in older patients who were active before diagnosis. In contrast to previous studies, breast cancer survival and recurrence were not significantly associated with physical activity. These hypothesis-generating findings confirm the need for more studies investigating the use of physical activity to supplement breast cancer treatment in older patients.

INTRODUCTION

There is a growing body of evidence on the beneficial effects of physical activity in breast cancer patients. A recent meta-analysis showed that physical activity improves body composition, physical function, psychological complaints and quality of life in breast cancer patients.[1] To add, physical activity has been found to improve fitness and strength and reduce depression and fatigue.[2] Furthermore, a multitude of studies have demonstrated the positive effects of physical activity on decreasing the risk of developing breast cancer.[3] It has been suggested that these so-called 'modifiable' components, which are influenced by physical activity, may also favourably affect cancer survival.[4, 5] In a systematic review, we previously reported that physical activity is associated with overall survival (OS) and breast cancer-specific survival (BCSS), with post-diagnosis physical activity being most beneficial for these breast cancer outcomes.[6] However, none of the previous studies reported age-specific outcomes for patients over the age of 65, although this older breast cancer population in particular, may benefit from physical activity.

Older breast cancer patients deserve extra attention, as high age is related to poor physical function and other comorbidity[7, 8], and maintenance of pre-diagnosis physical activity levels could play an important role in sustaining functional mobility in this more vulnerable population. Older breast cancer patients differ from younger breast cancer patients in many other aspects; older patients generally present with higher tumor stages[9] and are more frequently affected by comorbid conditions affecting physical functioning than their younger counterparts.[10]

The aim of this study was to assess the relationship between recreational physical activity and OS, BCSS and relapse-free period (RFP) in postmenopausal, hormone-receptor positive breast cancer patients of different ages.

MATERIALS AND METHODS

The Tamoxifen Exemestane Adjuvant Multicenter (TEAM) trial is an international, open-label randomized controlled trial that compared two regimens of hormonal treatment in postmenopausal, hormone receptor-positive breast cancer patients. The study design and population of the trial have previously been described in detail.[11] The current study is a side-study of the TEAM trial, also known as the TEAM-Lifestyle side-study (TEAM-L). This side-study prospectively investigated lifestyle habits in a subset of 543 patients. The design and study population of the TEAM-L have also been described elsewhere.[12] Briefly, the TEAM-L consisted of two questionnaires at one and two years after diagnosis. In the first questionnaire, patients reported both pre-diagnosis (T0) and current (T1) physical activity levels, demographic factors, reproductive factors and other lifestyle habits. The second questionnaire (T2) consisted of the same questions, excluding pre-diagnosis lifestyle characteristics.

Data collection

Patient, tumor and treatment characteristics were collected by the TEAM datacenter (Leiden, the Netherlands). For this study, patients were included if they completed either one or both questionnaires. If a patient had a recurrence before completing the questionnaire, she was excluded from the analysis. Follow-up was defined as the time between completing the questionnaire (T0 and T1 at one year after diagnosis and T2 at two years after diagnosis), until an event last follow-up visit or loss to follow-up. Follow-up was complete until August 15th 2012.

Physical activity measures

Questions assessing physical activity were derived from the validated European Prospective Investigation into Cancer physical activity Questionnaire.[13] Patients were asked to report the amount of time they spent per week in summer and winter on the following activities: walking, cycling, gardening, housekeeping and sports (three different types of sport could be specified). The mean number of hours spent at these activities per week in summer and winter was calculated. Metabolic Equivalent Intensity Values (MET values) were calculated in order to include an estimate of the intensity of the reported physical activity.[14]

For this study, we evaluated recreational physical activity only, which was defined as walking, cycling, gardening and sports. For the analyses, patients were grouped into quartiles, based on the distribution of the total number of MET-hours of physical activity per week in the whole study population. Additionally, we performed all analyses in quartiles based on the total number of absolute hours spent on physical activity per week.

Statistical analyses

IBM SPSS statistics version 20.0 was used for all analyses, with an exception of the Fine and Gray analyses, which were performed in STATA version 12.0. All analyses were two-sided and p-values of 0.05 were considered statistically significant. If data were missing, patients were not excluded from the analyses, but analysed in a category "unknown" within the same variable, with the exception of patients with a missing status for physical activity measurements; these patients were excluded from the analyses.

The effect of pre-diagnosis physical activity (T0) and post-diagnosis physical activity (T2) on overall survival was calculated in univariable and multivariable Cox regression models. The multivariable models were adjusted for clinically relevant confounders (age, number of comorbidities, T-stage, N-stage, Body Mass Index (BMI, kg/m^2) and adjuvant chemotherapy). BCSS was defined as time until breast cancer death. RFP was defined as the time until disease recurrence or breast cancer death. Both BCSS and RFP were calculated using Fine and Gray analyses, which takes the risk of competing mortality into account. Again, these analyses were adjusted for clinically relevant confounders. Age-stratified (<65 vs ≥65 years) analyses were also performed for all outcome measures.

Due to small numbers of events in some subgroup analyses, we also performed sensitivity analyses that compared the three highest quartiles of physical activity (any physical activity) with the lowest quartile (very low). As the number of hours spent on physical activity at one year after diagnosis (T1) could be affected by

breast cancer treatment during this period, the effect of post-diagnosis physical activity was assessed based on the physical activity at two years after diagnosis (T2).

To assess potential effect modification by BMI, we performed a sensitivity analysis in which we assessed the effect of post-diagnosis physical activity on all outcomes in combination with BMI by creating a variable that combined physical activity and BMI. We distinguished four groups: low physical activity (defined as the two lower quartiles) and BMI ≥25 (reference group), low physical activity and BMI <25, high physical activity (defined as the two upper quartiles) and BMI ≥25, and high physical activity and BMI <25. To add, we performed analyses for BCSS and RFP using Cox Regression models, in order to assess the influence of competing risks on our results. Finally, we presented causes of death per physical activity level.

Table 1. **Patient characteristics**

All patients (n=521)	**n**	**%**		**n**	**%**
Age at T1, median (range)	63.6	44-88	**Estrogen receptor**		
Patient characteristics			Positive	511	98.1
Age at T1			Negative	9	1.7
<60	190	36.5	unknown	1	0.2
60-64	110	21.1	**Progesterone receptor**		
65-69	85	16.3	Positive	349	67.0
70-75	71	13.6	Negative	120	23.0
>75	65	12.5	unknown	52	10.0
Comorbidities					
0	146	28.0	***Therapy***		
1	158	30.3	**Surgery**		
2	117	22.5	No resection	1	0.2
3 or more	100	19.2	Wide local excision	256	49.1
BMI			Mastectomy	262	50.3
<25	78	32.4	unknown	2	0.4
25-30	107	44.4	**Axillary surgery**		
>30	42	17.4	Sentinel node	117	22.5
unknown	14	5.8	Axillary lymph node dissection	398	76.4
			unknown	6	1.2
Tumor characteristics			**Radiotherapy**		
Grade (BR)			No	174	33.4
G1 (well)	83	16.6	Yes	340	65.3
G2 (moderate)	232	46.5	unknown	7	1.3
G3, G4 (poor)	172	34.5	**Chemotherapy**		
unknown	12	2.4	No	334	64.1
Tumor stage			Yes	187	35.9
T1 (≤2cm)	255	48.9	**Endocrine therapy**		
T2 (>2-≤5cm)	232	44.5	Tam→Exe	263	50.5
T3 / T4 (>5cm)	31	5.9	Exemestane only	258	49.5
unknown	3	0.6			
Nodal status					
Negative	143	27.4			
Positive	376	72.2			
unknown	2	0.4			

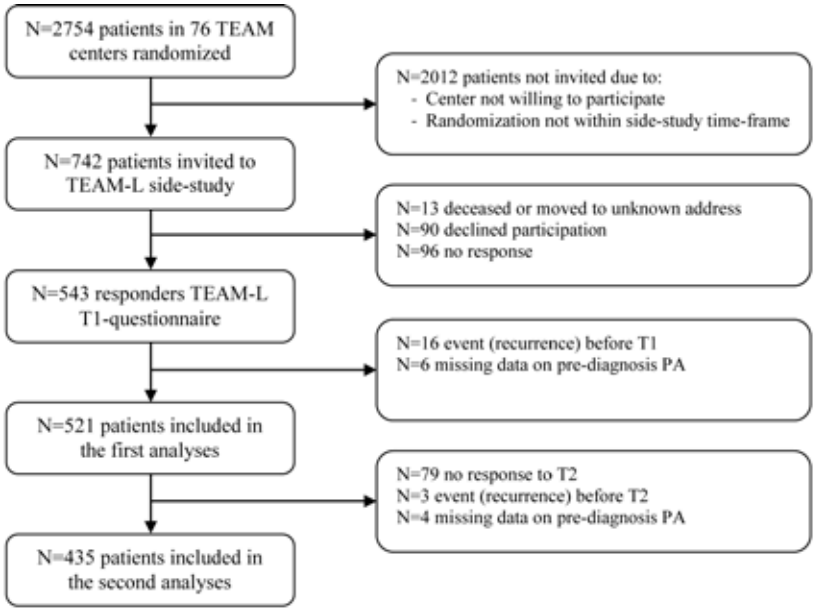
BMI, body-mass index; BR, Bloom&Richardson; Tam→Exe, Tamoxifen followed by exemestane; Exe, exemestane.

RESULTS

Patient characteristics

Overall, 521 patients who completed the first questionnaire were included in the analyses regarding pre-diagnosis physical activity. For the second analyses investigating post-diagnosis physical activity, 436 patients were included (Figure 1). The median age of the patient population was 63.6 years (Table 1). Most patients had one or more comorbidities (72%), and the majority of patients (55%) had a BMI of 25 or higher. Patient-, tumor- and treatment-characteristics were not different between the four quartiles of pre-diagnosis physical activity, with the exception of age and chemotherapy (Supplementary Table 1). Mean pre-diagnosis physical activity level was 10.9 hours per week, while the mean post-diagnosis physical activity level was 10.0 hours per week.

Figure 1. **Patients included in this study**



Pre-diagnosis physical activity

Overall survival was better in patients who were physically active before diagnosis, both in the analyses based on MET-hours as well as in the analyses based on the absolute number of hours. This effect remained similar with additional adjustments for number of comorbidities, T-stage, N-stage, mean BMI and chemotherapy (Hazard Ratio (HR) 0.57, 95% Confidence Interval (CI) 0.31-1.05 for low physical activity, 0.48, 95% CI 0.25-0.91 for high physical activity and 0.50, 95% CI 0.26-0.98 for very high physical activity, compared to the very low physical activity, p=0.10, Table 2).

Table 2. **Physical activity in relation to survival outcomes**

	Overall survival				Breast cancer-specific survival				Recurrence-free period			
	Events	HR*	95% CI	p-value	Events	HR**	95% CI	p-value	Events	HR***	95% CI	p-value
Pre-diagnosis PA (n=521)												
MET-hrs / wk												
Very low (0-22.3)	34	Ref		0.10	17	Ref		0.75	21	Ref		0.74
Low (22.6-41.5)	17	0.57	(0.31-1.05)		13	0.81	(0.35-1.87)		21	1.07	(0.55-2.11)	
High (41.8-70.8)	15	0.48	(0.25-0.91)		8	0.51	(0.22-1.18)		14	0.67	(0.33-1.38)	
Very high (>70.8)	14	0.50	(0.26-0.98)		12	0.83	(0.38-1.80)		20	1.04	(0.53-2.02)	
Hrs / wk												
Very low (0-5.0)	37	Ref		0.20	19	Ref		0.87	26	Ref		0.60
Low (5.3-8.5)	14	0.50	(0.27-0.95)		9	0.81	(0.35-1.86)		15	1.08	(0.55-2.11)	
High (8.8-14.0)	13	0.40	(0.21-0.77)		9	0.51	(0.22-1.16)		15	0.68	(0.33-1.39)	
Very high (>14.1)	16	0.65	(0.35-1.21)		13	0.84	(0.39-1.82)		20	1.04	(0.53-2.04)	
Post-diagnosis PA (n=435)												
MET-hrs / wk												
Very low (0-21.0)	24	Ref		0.34	14	Ref		0.95	17	Ref		0.79
Low (21.3-40.0)	10	0.43	(0.19-0.94)		6	0.44	(0.15-1.35)		9	0.54	(0.23-1.29)	
High (40.1-65.5)	13	0.60	(0.29-1.24)		11	1.00	(0.13-1.32)		18	0.97	(0.44-2.13)	
Very high (66.0-258)	11	0.57	(0.26-1.40)		8	0.77	(0.28-2.12)		14	0.90	(0.39-2.10)	
Hrs / wk												
Very low (0-4.6)	25	Ref		0.51	15	Ref		0.77	19	Ref		0.69
Low (4.8-6.3)	9	0.40	(0.18-0.89)		8	.	.		12	0.22	(0.02-2.25)	
High (8.5-13.5)	11	0.48	(0.23-1.03)		7	2.45	(0.40-14.95)		11	1.37	(0.35-5.38)	
Very high (>13.5)	13	0.63	(0.31-1.32)		9	0.89	(0.16-4.94)		16	0.72	(0.22-2.33)	

MET-hrs/wk, Metabolic Equivalent Intensity Value (MET) hours per week; Ref, reference value; HR, hazard ratio; 95%CI, 95% confidence interval.
*Cox Regression analyses, adjusted for age (T1), no of comorbidities, T-stage, N-stage, BMI (mean), chemotherapy
** Fine & Gray analyses, adjusted for age (T1), no of comorbidities, T-stage, N-stage, BMI (mean), chemotherapy
***Fine & Gray analyses, adjusted for age (T1), T-stage, N-stage, BMI (mean), chemotherapy

Breast cancer specific survival according to Fine and Gray analysis was not statistically significant in association with physical activity levels. Also, the recurrence-free period according to Fine and Gray was not statistically significant in relation to the four quartiles. The analyses performed with categories based on the absolute hours per week showed similar results (Table 2).

Post-diagnosis physical activity

Post-diagnosis survival was calculated in all patients who completed T2 and did not have a recurrence before T2. Overall, 435 patients were included in these analyses. Overall survival was statistically significantly

better in patients who were relatively active (HR 0.43, 95% CI 0.19-0.94 for low physical activity, HR 0.60, 95% CI 0.29-1.22 for high physical activity and HR 0.57, 95% CI 0.26-1.40 for very high physical activity compared to very low physical activity, p=0.34, Table 2). Breast cancer specific survival and recurrence-free period did not differ between the four quartiles of physical activity (Table 2).

Age-specific results

With regard to pre-diagnosis physical activity, age-stratified analyses (<65 vs ≥65 at breast cancer diagnosis) demonstrated that overall survival was significantly better in active patients aged 65 years and older compared to relatively inactive patients (multivariable HR 0.63, 95% CI 0.30-1.35 for low physical activity, HR 0.44, 95% CI 0.19-1.03 for high physical activity and HR 0.34, 95% CI 0.11-1.01 for very high physical activity compared to very low physical activity, Table 3). No statistically significant differences between the four quartiles were observed for any of the outcomes in patients aged 65 years and younger, although all estimates for overall survival were below one and the number of evens was very small. Breast cancer specific survival and relapse-free period were not significantly associated with physical activity levels.

Sensitivity analyses

Additional sensitivity analyses in which the upper three quartiles in the age-specific analyses were combined showed similar results in both age-groups (Table 3).

Table 3. **Pre-diagnosis physical activity in relation to survival outcomes, stratified by age at diagnosis**

	Overall survival				Breast cancer-specific survival				Recurrence-free period			
	Events	HR*	95% CI	p-value	Events	HR**	95% CI	p-value	Events	HR***	95% CI	p-value
Age < 65 at diagnosis												
MET-hrs / wk												
Very low (0-22.3)	7	Ref		0.73	4	Ref		0.82	7	Ref		0.80
Low (22.6-41.5)	7	0.59	(0.21-1.72)		5	0.71	(0.17-2.91)		9	0.74	(0.26-2.13)	
High (41.8-70.8)	7	0.60	(0.21-1.72)		6	0.90	(0.27-3.08)		7	0.61	(0.21-1.74)	
Very high (>71.0)	10	0.73	(0.28-1.95)		8	1.02	(0.33-3.20)		12	0.92	(0.36-2.30)	
MET-hrs / wk												
Very low (0-22.3)	7	Ref		0.32	4	Ref		0.83	7	Ref		0.54
Any physical activity (>22.3)	24	0.65	(0.28-1.52)		19	0.89	(0.30-2.59)		28	0.76	(0.33-1.79)	
Age > 65 at diagnosis												
MET-hrs / wk												
Very low (0-22.3)	27	Ref		0.04	13	Ref		0.40	14	Ref		0.70
Low (22.6-41.5)	10	0.63	(0.30-1.35)		8	0.97	(0.35-2.66)		12	1.60	(0.68-3.74)	
High (41.8-70.8)	8	0.44	(0.19-1.03)		2	0.25	(0.06-1.01)		7	0.73	(0.27-2.01)	
Very high (>71.0)	4	0.34	(0.11-1.01)		4	0.62	(0.19-2.02)		8	0.98	(0.37-2.59)	
MET-hrs / wk												
Very low (0-22.3)	27	Ref		0.02	13	Ref		0.26	14	Ref		0.80
Any physical activity (>22.3)	22	0.49	(0.27-0.91)		14	0.61	(0.26-1.45)		26	1.10	(0.53-2.30)	

MET-hrs/wk, Metabolic Equivalent Intensity Value (MET) hours per week; Ref, reference value; HR, hazard ratio; 95%CI, 95% confidence interval.
*Cox Regression analyses, adjusted for age (T1), no of comorbidities, T-stage, N-stage, BMI (mean), chemotherapy
** Fine & Gray analyses, adjusted for age (T1), no of comorbidities, T-stage, N-stage, BMI (mean), chemotherapy
***Fine & Gray analyses, adjusted for age (T1), T-stage, N-stage, BMI (mean), chemotherapy.

We investigated the influence of high BMI and physical activity in relation to outcomes by stratifying by BMI category. Normal-weight (BMI<25) and overweight or obese (BMI≥25) patients were assessed separately. The combination of post-diagnosis physical activity and BMI was not statistically significant in relation to overall survival, breast cancer specific survival or relapse-free period (Supplementary Table 2).

Furthermore, Cox Regression analyses for both prediagnostic and postdiagnostic physical activity in relation to breast cancer specific survival and relapse-free period showed similar results as the Fine & Gray analyses (data not shown). Finally, causes of death per physical activity level show that the majority of patients who died, died from breast cancer, second malignancies or cardiovascular death (Supplementary Table 3).

DISCUSSION

This study shows that physical activity was associated with an improvement in overall survival, both before and after diagnosis. Especially in patients older than 65, a high level of pre-diagnosis physical activity was related to a better overall survival compared to lower levels of physical activity. Breast cancer specific survival and recurrence-free period were not significantly associated with physical activity levels, and no trends towards a better breast cancer specific survival or recurrence-free period were observed.
Although we did not observe a statistically significant association between physical activity and breast cancer death or recurrence, many previous studies have demonstrated favourable effects of physical activity on breast cancer-specific survival in breast cancer survivors.[4, 6, 15] Several mechanisms could explain these contradicting results. First, the Dutch population is, in general, more active compared to other Western societies[16], especially when compared to the United States, where most of the previous studies were performed.[4, 15] Furthermore, the TEAM-trial included postmenopausal women who generally had a high socio-economic status and a low comorbidity burden compared to the general population.[17] For this reason, it is possible that even the "very low physical activity" category was, in fact, quite active in which case the differences in outcomes were absent. Second, the TEAM-trial included relatively many older patients.[18] Since the risk of dying from other causes than breast cancer (competing causes of death) strongly increases with age[18], possibly, the absolute benefits of physical activity could be less pronounced in this population. However, competing risk analyses did not differ from regular analyses in our data. Especially cardiovascular mortality could be improved in active patients[19], but the number of events was too small to investigate this in further detail (Supplementary Table 3).

The biological mechanism behind improved breast cancer outcomes in physically active patients, as was observed in previous studies, remains to be elucidated. It has been suggested that obesity and insulin resistance play an important role in influencing the risk of breast cancer recurrence and mortality.[20, 21] Obesity and high levels of insulin and diabetes have been associated with increased breast cancer risk[22, 23],

and physical activity is known to lower insulin levels and improve insulin sensitivity. Furthermore, it has been suggested that physical activity could result in a reduction in endogenous oestrogen levels and body fat, which could lead to slower progression of breast cancer.[24] Previous studies have also shown that obesity can lead to poorer breast cancer outcomes.[21] Pierce et al. investigated interactions between specific lifestyle factors and mortality in breast cancer patients and found significant improvements in 10-year mortality in patients who were physically active and had a healthy dietary pattern, regardless of BMI.[5] Although we did not take into account dietary patterns, the interaction between BMI and physical activity in relation to outcome was not statistically significant and there was no statistically significant association between BMI, physical activity and survival. Of note, in the older population, high BMI may even have a protective effect on overall survival, as was shown in a study by Reeves et al[25], and which may reflect the absence of an association in our results.

Interestingly, the results based on the number of MET-hours gave similar results to the analyses based on the absolute number of hours. This implies that the intensity of physical activity is not related to the association between physical activity and the improved overall survival. Presumably, any form of physical activity is beneficial compared to a sedentary lifestyle. This could be of major importance in developing future physical activity interventions for breast cancer patients.

Concerning the age-specific results, we found the strongest association between physical activity and overall survival in patients aged 65 years and older. This is of particular interest in this vulnerable population, as high age is associated with comorbidity and poor physical function.[26, 27] In developed countries, over 40 percent of the breast cancer population is 65 years or older and this percentage is expected to increase even further in the upcoming years.[28] Treatment of breast cancer in older patients is still not evidence-based, due to the fact that older patients are often not included in clinical trials due to restrictions of age, comorbidity and physical function.[29] This leads to a large diversity in treatment strategies and poor adherence to guidelines among treating specialists.[30] Consequently, breast cancer specific mortality increases with age, even amidst competing causes of death in older patients.[18] Therefore, new treatment strategies for elderly breast cancer patients are urgently needed.

Although physical activity was not related to breast cancer outcome in our data, it could play an important role in preventing adverse-events and non-compliance to hormonal therapy in the older breast cancer population.[31] Breast cancer in older patients is often hormone-receptor positive[32], and consequently, many patients receive hormonal therapy. Aromatase inhibitors often cause side-effects such as arthralgia, musculoskeletal pain and diminished bone mineral density.[31] Older patients are especially at increased risk for the development of fractures after hormonal treatment.[31] In the TEAM-study, older patients were more likely to be non-compliant within the first year of hormonal treatment than younger patients. The most important reasons for non-persistence were adverse events.[33] Therefore, maintaining physical activity levels might be extra beneficial in the older breast cancer population.

Strengths and limitations

A major strength of this study is its prospective design. Data were registered at various timepoints during follow-up using validated questionnaires, resulting in a homogeneous study population with well-registered, reliable data. Furthermore, patients in this side study were a representative subset of the international TEAM trial, as demonstrated in an earlier report by Voskuil et al.[12] To our knowledge, this is the first study to investigate differences in PA levels on survival outcomes in older breast cancer patients compared to younger patients. Needless to say, our study is limited by the number of events, which was relatively small when compared with other studies.[4, 15, 34] Furthermore, patients who exercise regularly may also be more likely to adopt other healthy lifestyles.[35] The more favourable outcomes demonstrated in patients older than 65 may therefore be the result of selection, as patients who are capable of participating in physical activity are fit enough to be able to exercise and hence survive for longer than unfit patients. In order to establish a causal relation between physical activity and breast cancer outcomes, randomized clinical trials should be performed, but inevitably, these kinds of trials are not feasible. Therefore, data such as our present study can still be of much value for investigating the association between physical activity levels and breast cancer outcomes.

Finally, the reported number of hours of physical activity was relatively high in comparison with other studies, and this may be due to over-reporting of pre-diagnosis physical activity. Nevertheless, the Dutch population is known to engage in high levels of physical activity, especially in walking, cycling, gardening and sports.[16] Most women in the Netherlands (76%) spend at least 30 minutes on moderate-to-vigorous physical activity on at least 5 days of the week.[36]

In conclusion, overall survival was better in patients who were active before and after diagnosis, while breast cancer recurrence and survival were not associated with physical activity. Especially in women over the age of 65, high physical activity levels before diagnosis were associated with an improved overall survival. These hypothesis-generating findings confirm the need for more studies investigating the use of physical activity to supplement breast cancer treatment in older patients. Physical activity could play an important role in improving survival, maintaining physical function and improving quality of life both during and after breast cancer treatment, especially in older patients.

Supplementary Table 1. **Patient characteristics per quartile of pre-diagnosis physical activity**

Characteristic	n	%
Age (median, range)	(63.7)	*(44-93)*
Grade (BR)		
G1 (well)	219	*14.7*
G2 (moderate)	646	*43.5*
G3, G4 (poor)	528	*35.6*
Gx (unknown)	92	*6.2*
Tumor stage		
T1 (≤2cm)	680	*45.8*
T2 (>2cm - ≤5cm)	703	*47.3*
T3, T4 (>5cm)	98	*6.6*
Tx,Tis	4	*0.3*
Nodal stage		
Positive	1043	*70.2*
Negative	442	*29.8*
ER status		
Positive	1459	*98.2*
Negative	25	*1.7*
Not performed	1	*0.1*
PR status		
Positive	1108	*74.6*
Negative	304	*20.5*
Not performed	73	*4.9*
Most extensive surgery		
Mastectomy	803	*54.1*
Wide local excision	681	*45.9*
No resection	1	*0.1*
Adjuvant radiotherapy		
Yes	983	*66.2*
No	501	*33.7*
Unknown	1	*0.1*
Adjuvant chemotherapy		
Yes	501	*33.7*
No	984	*66.3*

BR, Bloom & Richardson; ER, estrogen receptor; PR, progesterone receptor

Supplementary Table 2. **Survival analyses for post-diagnosis PA AND BMI combined**

	Overall survival				Breast cancer-specific survival				Recurrence-free period			
BMI & post-diagnosis PA	**Events**	**HR***	**95% CI**	**p-value**	**Events**	**HR****	**95% CI**	**p-value**	**Events**	**HR*****	**95% CI**	**p-value**
BMI>25 & Low/very low	18	Ref		0.78	10	Ref		0.12	15	Ref		0.72
BMI<25 & Low/very low	14	1.40	(0.69-2.84)		8	1.22	(0.43-3.47)		9	1.18	(0.50-2.79)	
BMI>25& High/very high	15	1.04	(0.51-2.11)		12	1.49	(0.59-3.79)		14	0.97	(0.43-2.18)	
BMI<25 & High/very high	9	0.97	(0.42-2.23)		7	1.31	(0.44-3.88)		18	2.11	(0.98-4.54)	

**Cox Regression analyses, adjusted for age (T1), no of comorbidities, T-stage, N-stage, chemotherapy*
*** Fine & Gray analyses, adjusted for age (T1), no of comorbidities, T-stage, N-stage, chemotherapy*
****Fine & Gray analyses, adjusted for age (T1), T-stage, N-stage, chemotherapy*

Supplementary Table 3. **Causes of death**

	Alive		Breast cancer death		Other malignancy		Cardiovascular death		Other cause of death	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Pre-diagnosis physical activity (MET-hrs per week)										
Very low (0-22.3)	95	(73.6)	17	(13.2)	5	(3.9)	5	(3.9)	7	(5.4)
Low (22.6-41.5)	115	(87.1)	13	(9.8)	1	(9.8)	2	(1.5)	1	(0.8)
High (41.8-70.8)	112	(88.2)	8	(6.3)	2	(6.3)	3	(2.4)	2	(1.6)
Very high (>70.8)	115	(89.1)	12	(9.3)	2	(9.3)	0	(0.0)	0	(0.0)
Post-diagnosis physical activity (MET-hrs per week)										
Very low (0-21.0)	85	(78.0)	14	(12.8)	3	(2.8)	4	(3.7)	3	(2.8)
Low (21.3-40.0)	99	(90.8)	6	(5.5)	3	(2.8)	0	(0.0)	1	(0.9)
High (40.1-65.5)	96	(88.1)	11	(10.1)	1	(0.9)	0	(0.0)	1	(0.9)
Very high (66.0-258)	98	(89.9)	8	(7.3)	1	(0.9)	1	(0.9)	1	(4.7)

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CHAPTER

7

DYNAMIC PREDICTION IN BREAST CANCER – PROVING FEASIBILITY IN CLINICAL PRACTICE USING THE TEAM TRIAL

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Submitted

ABSTRACT

Background

Predictive models are an integral part of current clinical practice and help determine optimal treatment strategies for individual patients. A drawback is that covariates are assumed to have constant effects on overall survival (OS), when in fact, these effects may change during follow-up. Furthermore, breast cancer patients may experience events that alter their prognosis from that time onwards. We investigated the 'dynamic' effects of different covariates on OS and developed a nomogram to calculate 5-year dynamic OS (DOS) probability at different prediction timepoints (t_P) during follow-up.

Methods

Dutch and Belgian postmenopausal, endocrine-sensitive, early breast cancer patients enrolled in the TEAM trial were included. We assessed time-varying effects of specific covariates and obtained 5-year DOS predictions using a proportional baselines landmark supermodel. Covariates included age, histological grade, hormone receptor and HER2 status, T- and N-stage, locoregional recurrence (LRR), distant recurrence, and treatment compliance. A nomogram was designed to calculate 5-year DOS based on individual characteristics.

Results

2602 patients were included (mean follow-up 6.2 years). N-stage, LRR, and HER2 status demonstrated time-varying effects on 5-year DOS. Hazard ratio (HR) functions for LRR, high-risk N-stage(N2/N3) and HER2 positivity were $HR=(8.427 \cdot 0.583t_P)$, $HR=(3.621 \cdot 0.816t_P)$ and $HR=(1.235 \cdot 0.851t_P)$, respectively. Treatment discontinuation was associated with a higher mortality risk, but without a time-varying effect (HR 1.263 (95%CI 0.867-1.841)). All other covariates were time-constant.

Conclusion

The current nomogram accounts for elapsed time since starting adjuvant endocrine treatment and optimises prediction of individual 5-year DOS during follow-up. The nomogram can facilitate in determining whether further therapy will benefit an individual patient.

INTRODUCTION

Breast cancer comprises a heterogeneous disease with diverse features that can interact with outcomes, making it difficult to obtain estimations of individual prognoses. The overwhelming popularity of tools such as Adjuvant! or the Nottingham Prognostic Index (NPI) illustrates the importance of prediction models for physicians and patients, providing guidance for adjuvant treatment decisions.[1, 2] Most prediction models, however, cannot be used for cancer patients at specific timepoints during the follow-up period, as these models have been designed for use immediately after diagnosis. Apart from the caveats associated with available 'static' prediction models, there are some important reasons why these models may give misleading results when used during follow-up. First, the fact that patients have already survived a number of years after diagnosis may change a patient's prognosis. For instance, breast cancer recurrence rates peak at 1-2 years after diagnosis and decline thereafter, resulting in an improved prognosis.[3-5] Second, in the time between diagnosis and the moment of prediction, important events may have taken place, such as locoregional recurrence (LRR) and/or distant recurrences (DR) or premature discontinuation of treatment, which may alter a patient's prognosis. Third, some variables included in current models may exhibit time-varying effects on outcome, resulting in a change in mortality risk as time progresses. Consequently, too much emphasis may be placed on variables with a strong impact on outcome early in the follow-up period, whereas this effect might be much smaller later on.

Available static models are based on probabilities of survival at the time of diagnosis and may not accurately portray a patient's survival probability later on in the follow-up period. The concept of updating survival probabilities by both incorporating time-varying covariates and allowing for time-varying effects is called dynamic prediction. By design, these variables are not included in the static risk prediction models, and these considerations illustrate a need for better prediction models for cancer patients.

To investigate the clinical applicability of dynamic prediction, we utilized a dataset from a large randomized clinical trial of postmenopausal hormone receptor-positive early breast cancer patients treated with endocrine treatment (ET) in the Netherlands and Belgium. The aim of the current analysis was to develop a clinically applicable nomogram to facilitate the prediction of an individual patient's probability of surviving an additional 5 years at any prediction timepoint (t_P) up to three years after starting adjuvant ET. This concept of continually updating 5-year overall survival (OS) from a certain t_P is referred to as 5-year dynamic overall survival (DOS). We designed a dynamic predictive model, taking into account various patient- and tumor-specific covariates with time-varying and time-constant effects during follow up.

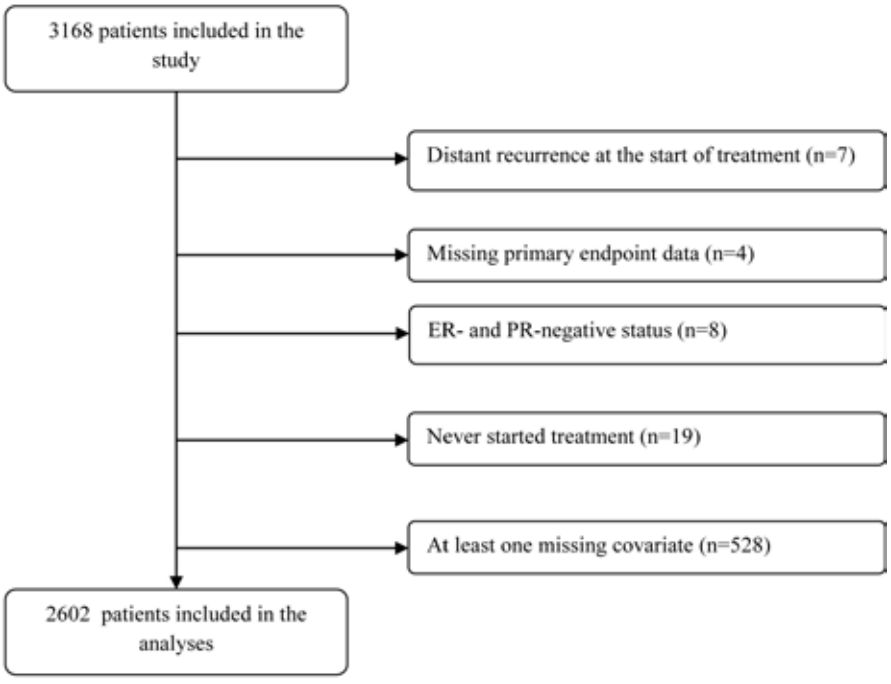
MATERIALS AND METHODS

The Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial is a randomized, phase III, multinational, open-label study conducted in postmenopausal women with hormone receptor-positive breast cancer, who

were eligible for adjuvant ET and randomized to either 5 years of exemestane (25mg) or 2.5-3 years of tamoxifen (20mg) followed by exemestane (25mg) for 2.5-2 years.[6] The TEAM trial protocol was approved by regulatory and ethics authorities of all participating centers in all participating countries. The trial was registered in the Netherlands and Belgium with the Netherlands Trial register, NTR 267. All patients provided written informed consent. Details of the study and data collection have been published previously.[6] In the Netherlands and Belgium, 3168 postmenopausal, early breast cancer patients were enrolled in the TEAM trial. Patients who did not start randomized treatment (n=19) or had missing endpoint data (n=4), metastatic disease before the start of ET (n=7), and patients with missing data regarding covariates used in the model (n=528) were excluded (Figure 1). Patients with estrogen receptor (ER) and progesterone receptor (PR)-negative disease (n=8) were excluded.

The primary outcome of the present investigation was OS, which was the time from randomization to the date of death or last recorded follow-up. LRR was defined as any breast cancer recurrence in the ipsilateral breast and/or lymph nodes as well as in supraclavicular lymph nodes. DR comprised all other accounts of breast cancer recurrence.

Figure 1. **CONSORT diagram of patients included in the analyses**



Statistical analysis

Statistical analyses were performed using the programs SPSS (version 20) and R (version 2.15.1). We used the proportional baselines landmark supermodel[7, 8] to obtain dynamic predictions of the 5-year DOS probability. The model requires a number of landmark timepoints (t_{LM}); in the current model t_{LM} was established at every third month between 0 and 3 years after the start of ET. A prediction model for 5-year DOS at a specific t_{LM} is constructed by selecting the individuals at risk at that t_{LM} and incorporating the values of any time-dependent covariates at that respective t_{LM} in a Cox proportional hazards model.[9] The landmark prediction models at different t_{LM}s may be combined into a single supermodel (Appendix 1). Using this analysis in the clinical setting, we can obtain DOS predictions at any prediction timepoint, t_P, between 0 and 3 years after starting adjuvant ET. For this specific model, the prediction window was set to 5 years after the established t_P .

Baseline patient- and tumor-specific factors included in the model comprised age at diagnosis (continuous, linear and quadratic terms), Bloom&Richardson (BR) histological grade (I,II,III), tumor stage (1,2,3/4), nodal stage (N0,N1,N2/N3), ER and PR status (positive,negative), HER2 status (positive,negative, missing), most extensive surgery (mastectomy,breast conserving surgery), radiotherapy (yes,no), chemotherapy (yes,no). ER and PR status were considered positive if at least 10% of tumor cells stained positively following immunohistochemical staining, as defined by the Dutch breast cancer treatment guidelines.[10]

The model also included three dynamic variables whose values may change during ET, namely current ET status (on versus off ET), LRR (yes,no) and DR (yes,no). To assess whether a patient had stopped treatment, we used the last treatment date, as reported on the case-report forms. If no last treatment date was available, the patient was assumed to be on-treatment. According to the TEAM trial protocol, patients with LRR or DR discontinued or switched ET.

In order to test for time-varying covariate effects, interactions between covariates and t_{LM} (both linear and quadratic) were included in the model. A backward selection procedure was then performed in two steps. In the first step all quadratic t_{LM} interactions with the covariates were tested. Non-significant quadratic interactions were removed, and those covariates which did not have significant interactions in the first step were then tested in the second step for linear t_{LM} interactions. Again, only significant interactions were retained. Wald-tests, based on robust standard errors, were used and a p-value of 0.05 was considered statistically significant (Appendix 1). Main effects of the covariates and of t_{LM} and t_{LM}^2 were included, irrespective of statistical significance. The model was then validated by internal calibration using the heuristic shrinkage factor by van Houwelingen et al.11 The model's ability to correctly discriminate between patients was evaluated using the dynamic cross validated c-index. A c-index of 1 resembles a model that can perfectly discriminate between patients, while with a c-index of 0.5, the prediction is as good as chance.[7]

Nomogram

The nomogram is a user-friendly tool for calculating survival probabilities based on a prediction model, and graphically computes 5-year DOS based on an individual patient's unique characteristics. For each prognostic

factor, a number of risk points are assigned to each corresponding covariate, which can be read off the nomogram. The sum of the risk points represents a total risk point score, from which the corresponding 5-year DOS probability can be assessed at any t_P (between 0 and 3 years) after the start of ET.

RESULTS

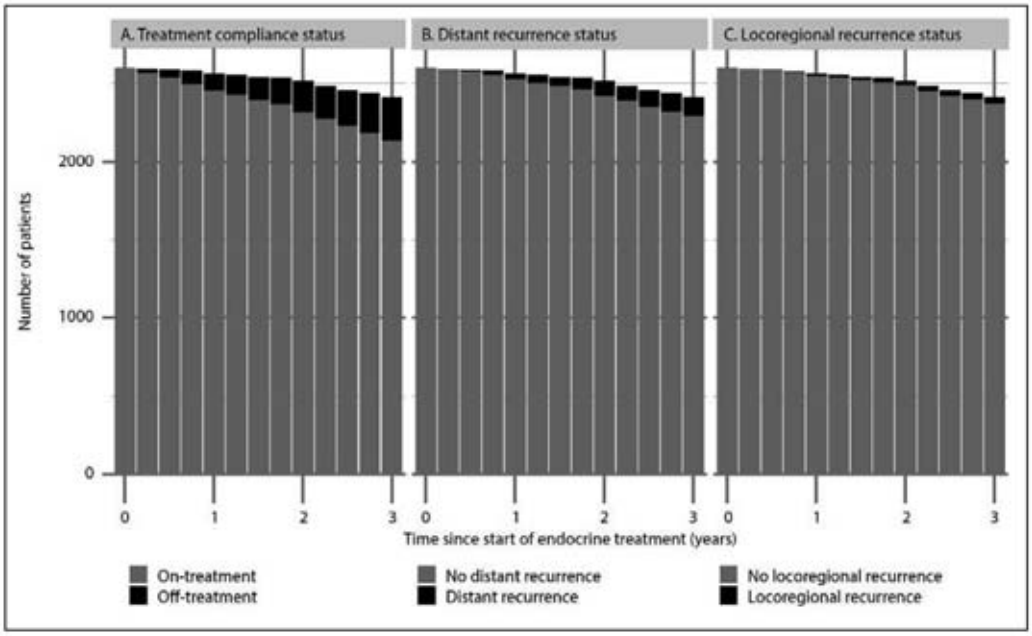
In total, 2602 TEAM trial patients with a median age of 64.8 years (range 38-92 years), were included in the analyses (Figure 1). Baseline characteristics of included patients are depicted in Table 1. The majority of patients included in this trial had adjuvant radiotherapy (66%) and did not receive adjuvant chemotherapy (68%). Figure 2 provides an overview of the total number of patients in the landmark datasets at successive t_{LM}s in relation to treatment compliance and disease recurrence status.

Table 1. **Baseline characteristics of patients included in the cohort (n=2602)**

Characteristic	n	%
Age at diagnosis (years) (*mean, standard deviation*)	*64.8*	*(9.19)*
Tumor stage		
T1 (≤2cm)	1135	44
T2 (>2-≤5cm)	1276	49
T3 / T4 (>5cm)	191	7
Nodal stage		
N0	821	32
N1	1344	52
N2/N3	437	17
Histological grade (BR)		
G1 (well)	382	15
G2 (moderate)	1202	46
G3, G4 (poor)	1018	39
Estrogen receptor status		
Negative	57	2
Positive	2545	98
Progesterone receptor status		
Negative	579	22
Positive	2023	78
HER2 status		
Negative	1898	73
Positive	257	10
Missing	447	17
Most extensive surgery		
Mastectomy	1422	55
Breast conserving surgery	1180	45
Radiotherapy		
Yes	1718	66
No	884	34
Chemotherapy		
Yes	843	32
No	1759	68

BR, Bloom&Richardson

Figure 2. **Number of patients at risk in relation to follow-up time since the start of endocrine treatment**

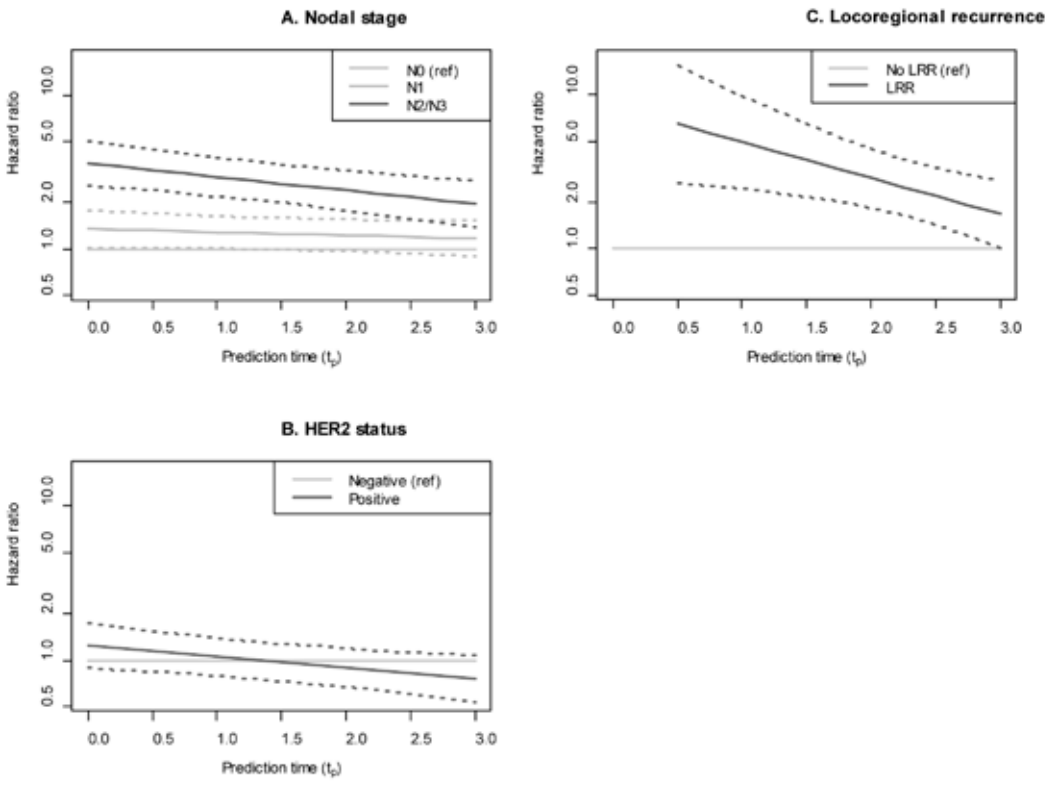


Number of patients in the landmark datasets (i.e. at risk) over time (t_{LM})since the start of adjuvant endocrine treatment in relation to (A) treatment compliance status (on-treatment/off-treatment) (B) distant recurrence status (yes,no) and (C) locoregional recurrence status (yes,no).

Table 2 depicts the regression coefficients and hazard ratios (HR) with 95% confidence intervals (95% CI) of the covariates included in the model. Covariates with time-constant effects and covariates with time-varying effects on 5-year DOS are shown. Age at diagnosis demonstrated a time-constant effect, with 5-year DOS being a quadratic function of age (Appendix 2). Interestingly, high-risk nodal stage (N2/N3), compared to N0, demonstrated a significant time-varying effect on 5-year DOS with each successive t_P, while nodal stage N1 did not (Figure 3A). To illustrate, the HR of a patient with nodal stage N2/N3 immediately after primary treatment compared to a patient with nodal stage N0 (reference) is 3.621, (calculated by the following formula: HR=[(constant) · (time-varying effect)t_P]=3.621 · 0.8510)(Table 2), but decreases to 2.411 (HR=3.621 · 0.8512 =2.411) at two years after the start of ET. HER2 positive status also demonstrated a significant time-varying effect on 5-year DOS (Table 2, Figure 3B).

Next, covariates whose status have the potential to change over time (i.e. treatment compliance status and disease recurrence) were investigated for their influence on 5-year mortality risk. Patients who went off-treatment during the follow-up period had a higher residual mortality risk compared to patients who remained compliant, although this was not statistically significant. The effect of treatment discontinuation was constant over time (Table 2). Simultaneously, LRR had a time-varying influence on 5-year DOS, revealing a subsiding mortality risk with each successive t_{LM} (Figure 3C). Compared with no LRR, having a LRR at 1, 2, and 3 years after the start of ET increased 5-year mortality risk with HR=4.913 (2.444-9.877), HR=2.864 (1.851-4.431), and HR=1.670

Figure 3. **Time-varying hazard ratios for Nodal stage, HER2 status and Locoregional Recurrence status**



t_P , prediction timepoint; LRR, Locoregional Recurrence.
Hazard ratios for nodal stage, HER2 status and locoregional recurrence status as time since the start of endocrine treatment (t_P) increases (depicted as a hazard ratio with 95% confidence interval).

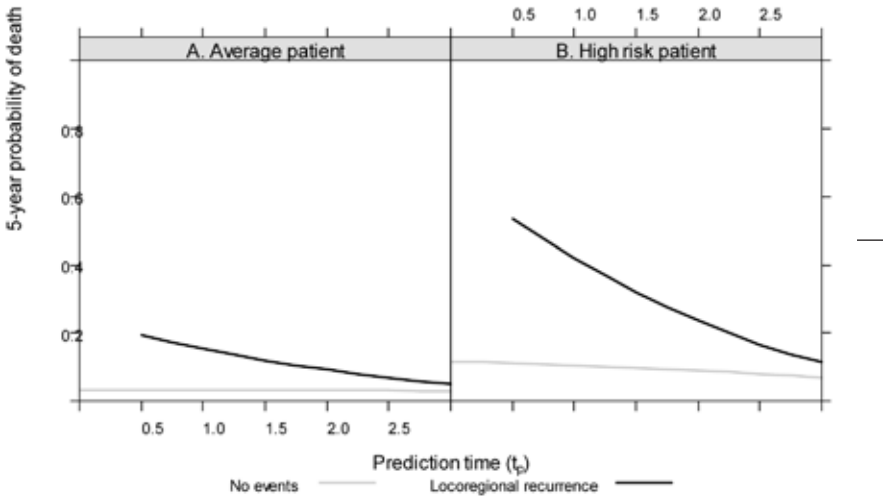
(1.005-2.773), respectively (Table 2). In contrast, developing distant metastases (versus no distant metastases) was associated with an increased 5-year mortality risk, with a constant effect over time (HR=15.018 (9.934-22.705)).

Figure 4 illustrates differences in the 5-year DOS in the event of a LRR in a patient who presents with the most commonly occurring baseline characteristics (average patient) found in this cohort, as well as in a high-risk patient. In the absence of a LRR, 5-year mortality probabilities are approximately 3% and 10%, respectively, at all t_Ps. However, in case of a LRR, 5-year mortality probabilities in both the average patient and the high-risk patient are initially high, and decrease with time.

Internal model validation

The heuristic shrinkage factor was 0.995, indicating good calibration of the model. Furthermore, the model's discriminatory accuracy had a dynamic cross validated c-index of 0.70, 0.72, 0.76 and 0.79 at 0, 1, 2 and 3 years respectively.

Figure 4. **Change in 5-year dynamic probabilities of death based on the occurrence of a locoregional recurrence in two example patients**



t_P , prediction timepoint; LRR, Locoregional Recurrence; ER, Estrogen Receptor; PR, Progesterone Receptor.

This figure illustrates how 5-year dynamic probabilities of death changes if a patient who is on-treatment throughout the entire follow-up period develops a LRR during follow-up. Two example patients are depicted in A and B.
A. Average patient with the following characteristics: age at diagnosis=65 years, tumor stage T2, nodal stage N1, histological grade 2 (Bloom&Richardson), HER2 negative, ER and PR positive, treated with breast conserving surgery, adjuvant radiotherapy and adjuvant chemotherapy.
B. High-risk patient with the following characteristics: age at diagnosis=65 years, tumor stage T3, nodal stage N2, histological grade 3 (Bloom&Richardson), HER2 negative, ER and PR positive, treated with mastectomy, adjuvant radiotherapy and adjuvant chemotherapy.

Using the nomogram

The nomogram (Figure 5) provides estimates for 5-year DOS probabilities at different t_Ps from the start of ET and onwards, provided that adequate surgery has been performed. The probabilities can be calculated by adding the risk points for each covariate corresponding to the patient's individual characteristics. For each characteristic, the number of associated risk points can be determined by drawing a vertical line straight up from the covariate's corresponding value to the axis with risk points (0 to 80). While the majority of covariates are considered 'static' and defined at the start of ET, some covariates are 'dynamic', such as treatment compliance status and the occurrence of LRR or distant metastases during follow-up. In addition, three covariates (nodal stage (N2/N3), HER2 status (positive) and LRR) demonstrated time-varying effects on 5-year DOS. Hence, 5-year DOS for these specific covariates depends on the t_P, and for these specific covariates each subgroup has an individual time-interaction axis.

Table 2. **The dynamic prediction model with time-constant and time-varying covariates**

	Regression coefficient	Hazard ratio	(95% CI)	p-value
Covariates with time-constant effects				
Age at diagnosis (ref: 65years, per 10years)				<0.001
Age	0.365	1.440	(1.254-1.653)	
Age^2	0.154	1.166	(1.067-1.275)	
Tumor size (ref: T1 (<2cm))				<0 .001
T2 (2-<5cm)	0.256	1.291	(1.052-1.585)	
T3/T4 (≥5cm)	0.306	1.357	(0.956-1.928)	
Histological grade (BR) (ref: BR I)				0.001
BR II	-0.018	0.982	(0.729-1.323)	
BR III	0.346	1.413	(1.038-1.923)	
Estrogen receptor status (ref: positive)				0.073
Negative	0.566	1.761	(0.948-3.271)	
Progesterone receptor status (ref: positive)				<0.001
Negative	0.456	1.557	(1.301-1.913)	
Most extensive surgery (ref: mastectomy)				0.683
Breast conserving surgery	0.055	1.057	(0.811-1.377)	
Radiotherapy (ref: yes)				0.157
No	0.195	1.216	(1.928-1.592)	
Chemotherapy (ref: yes)				0.384
No	0.127	1.136	(0.853-1.512)	
Treatment status (ref: on-treatment)				0.224
Off-treatment	0.234	1.263	(0.867-1.841)	
Distant recurrence (ref: no)				<0.001
Yes	2.709	15.018	(9.934-22.705)	
Covariates with time-varying effects*				
Prediction time (ref: years since start of treatment‡)				0.057
t_P	0.017	1.017	(0.920-1.125)	
t_P^2	-0.034	0.967	(0.945-0.989)	
Nodal stage (ref: N0)				
Constant				<0.001
N1	0.303	1.354	(1.021-1.795)	
N2/N3	1.287	3.621	(2.596-5.052)	
Time-varying effect				0.026
N1 (t_P)	-0.047	0.954	(0.869-1.048)	
N2/N3 (t_P)	-0.204	0.816	(0.722-0.922)	
HER2 status (ref: HER2 negative)				
Constant				0.214
Positive	0.211	1.235	(0.885-1.724)	
Time-varying effect				0.015
Positive (t_P)	-0.162	0.851	(0.747-0.969)	
Locoregional recurrence (ref: no LRR)				
Constant				<0.001
LRR	2.131	8.427	(2.885-24.617)	
Time-varying effect				0.013
LRR (t_P)	-0.540	0.583	(0.380-0.893)	

CI, confidence interval; yrs, years; t_P, prediction timepoint; BR, Bloom&Richardson; LRR, locoregional recurrence; Age^2 refers to the quadratic effect of age at diagnosis on 5-year dynamic overall survival (DOS); t_P^2 refers to the quadratic effect of prediction time (t_P) on 5-year DOS.
*Specific hazard ratios (HR) for time-varying covariates are calculated by the following formula: HR=[(constant) · (time-varying effect)^{t_P}].
‡Time elapsed (years) since the start of adjuvant endocrine treatment.

The sum of the risk points is equal to the total risk point score, which is depicted on the axis of the nomogram entitled "Total Points". From here, a vertical line can be drawn towards the axis labelled "5 Year Survival Probability", which is the corresponding 5-year DOS at that specific t_P.

To illustrate, we consider a 69-year-old postmenopausal woman (14 points) who has been using ET for two years (t_P=2, 5 points). She had a grade III tumor (13 points) with a diameter of 1.5cm (0 points), ER-positive (0 points), PR-positive (0 points) and HER2-negative (0 points), and 5 tumor-positive lymph nodes (at t_P=2, 55 points). The patient has undergone breast conserving surgery (2 points) with adjuvant radiotherapy (0 points) and adjuvant chemotherapy (0 points). She is still on-treatment (0 points) and disease-free (0 points) (no locoregional or DR). To calculate her 5-year DOS probability, we take her total risk point score (89 points) and draw a vertical line down to the '5-year survival probability' axis. For this patient, the 5-year DOS is 94%. If our patient had developed a LRR in the 2-year period since ET, one must add an additional 40 points (total=129 points) to her total risk prediction score, resulting in a 5-year DOS of 84%.

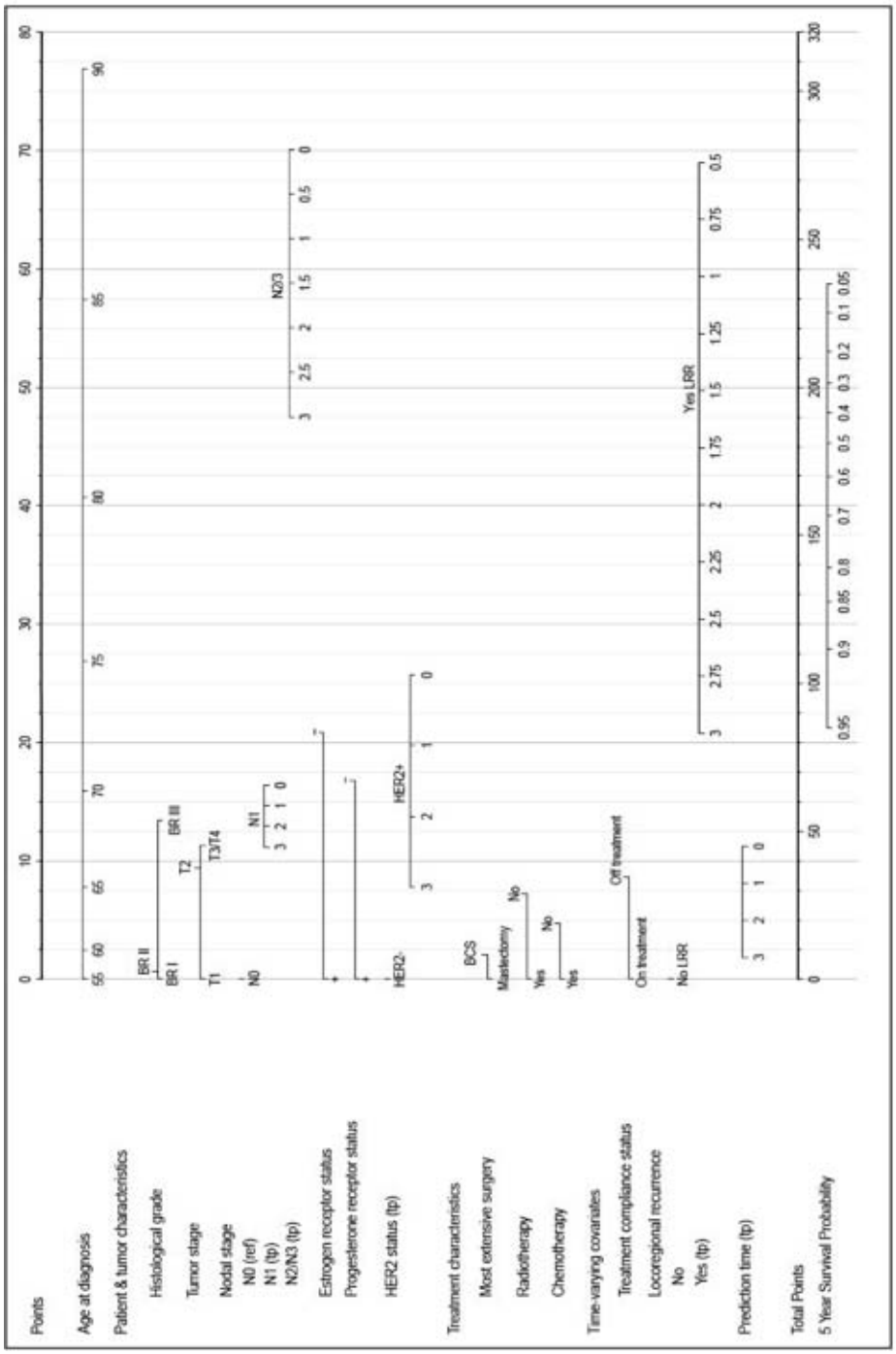
DISCUSSION

To our knowledge this is the first dynamic prediction model in clinical oncology, designed to optimise the prediction of the 5-year DOS at specific timepoints after the start of adjuvant ET. The key advantage of this model is that it takes into account dynamic factors that can influence a patient's prognosis after some time has passed since starting ET, including treatment compliance and the occurrence of LRR or distant metastases. Moreover, covariates with time-varying effects are also accounted for in the model, including high-risk nodal stage (N2/N3) and HER2 positive status.

Current nomograms are suboptimal for cancer patients, because their reference point is commonly the time of diagnosis or the start of adjuvant ET. Aiming at further personalized breast cancer treatment, continuous re-evaluation of the residual risk of breast cancer recurrence and mortality during follow-up is crucial. Patients may develop disease recurrences or discontinue ET before the pre-designated end-date, which may alter a patient's prognosis from that timepoint onwards. Additionally, the effect of a covariate on 5-year survival probabilities may not be constant over time. These changes are more prominent than current statistical models account for, which could lead to the risk of developing less effective treatment guidelines. Therefore, survival prediction models need to be adapted for long-term outcome prediction in individual patients. Specifically, dynamic prediction models can be used to determine whether a patient will benefit from further adjuvant systemic therapy or, conversely, whether ET can be discontinued at a certain timepoint during follow-up.
The current nomogram can be applied to postmenopausal, hormone receptor-positive breast cancer patients undergoing adjuvant ET and have had an axillary lymph node dissection in case of macrometastases. For patients who have had breast-conserving surgery, the model assumes that the breast was irradiated. The current nomogram also assumes that disease relapse implies discontinuation of ET from that moment onwards. In case of disease recurrence, data on subsequent treatment were not available for all patients, hence our ability to draw conclusions for this subgroup is limited.

LRR is considered a 'dynamic' covariate, as patients can develop a LRR at any moment during follow-up. LRR also had 'time-varying' properties, as the event of a LRR revealed a changing impact on 5-year DOS at different timepoints after starting ET. Our findings parallel those of several other studies, which have

Figure 5. **Nomogram for dynamic prediction of the 5-year survival probability**



BR, Bloom&Richardson; BCS, breast-conserving surgery; t_p, prediction timepoint.

The 5-year dynamic overall survival probability (DOS) is calculated by taking the sum of the risk points, according to patient-, tumor-, and treatment-specific characteristics. For each covariate, the number of associated risk points can be determined by drawing a vertical line straight up from the covariate's corresponding value (as determined by the individual patient's characteristics) to the axis with risk points (0 to 80). All covariates marked with '(t_p)' have time-varying effects and require that the time since the start of endocrine treatment are taken into account.

shown that early LRRs convey a worse prognosis than late LRRs.[12-16] It can therefore be of major clinical importance to include this factor in dynamic survival prediction. Moreover, this model could potentially help evaluate the need for additional adjuvant chemotherapy in case of LRR. Data on the benefit of additional chemotherapy are still relatively lacking, although the nomogram could be useful in this setting. The current model also revealed a time-varying relationship between high nodal stage (N2/3) and 5-year DOS probability. A similar time-varying effect was shown with regard to 5-year DOS in HER2-positive patients, although no patients received anti-HER2 treatment. To our knowledge, no prior reports have investigated the time-varying effects of these two prognostic factors, hence warranting further investigation. Our dynamic prediction model also accounts for the effect of early treatment discontinuation for reasons other than breast cancer relapse. Although the effect of treatment discontinuation did not reach statistical significance, possibly due to the low number of patients who discontinued treatment within three years (Figure 2, left panel), we retained this data in our model, as an earlier review revealed the importance of treatment compliance on survival outcomes.[17]

The number and site(s) of DR are known to be prognostic for subsequent survival.[18-20] The dynamic prediction model incorporates the occurrence of distant metastases, but does not include this in the nomogram due to insufficient data concerning first site of DR and subsequent treatment. For this reason, it is not advised to use the dynamic prediction model for patients with distant metastases as first site of disease recurrence.

Internal validation demonstrated that the model had a good ability to discriminate between patients. To elucidate, internal validation of Adjuvant! showed a c-index of 0.71 for discriminatory accuracy (the ability for the model to distinguish patients who will versus those who will not die from breast cancer) and a predictive accuracy of 0.73 at diagnosis, which is similar to that of our prediction model.[21] The predictive accuracy of Adjuvant! after diagnosis has not been studied; in contrast, our dynamic prediction model showed a cross-validated c-index that improved from 0.70 to 0.79 three years after the start of adjuvant ET. Further external validation of the prediction model is required in greater (non-trial) cohorts to allow for full applicability in the clinical setting. A web-based dynamic prediction tool is currently underway to facilitate decision making in clinical practice.

CONCLUSION

The importance of using dynamic prediction models for clinical guidance, not only at the start of treatment, but also during follow-up, permits continuous revision of a patient's residual mortality risk and can help motivate a patient to continue treatment, improve compliance, and ultimately improve survival. This proof-of-principle study demonstrates a novel technique for performing dynamic prediction of breast cancer survival probabilities over time, enabling a more individualized prediction of the 5-year DOS in individual patients at various timepoints during adjuvant ET. The most important advantage of this model is that it takes into account factors that can influence an individual patient's prognosis after some time has passed since starting adjuvant ET. Notwithstanding the feasibility of our dynamic prediction model, further external validation with longer follow-up is necessary to enable implementation in clinical practice.

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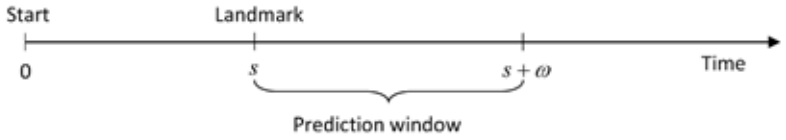
TECHNICAL APPENDIX

Landmarking

The method of landmarking was introduced by Anderson et. al (1983) as a way to deal with time-dependent covariates in survival analysis, to avoid immortal time bias. The idea behind landmarking is, for a pre-specified landmark time point s, to construct a landmark data set consisting of only subjects at risk at s, i.e. those still alive and under follow-up. For a time-dependent covariate $Z(t)$, such as distant recurrence, the current value $Z(s)$ at s is used. An analysis using standard methods such as the log-rank test or Cox regression can then be performed using $Z(s)$ as a time-constant covariate.

Dynamic prediction using landmarking

Van Houwelingen (2007) was the first to suggest using landmarking for dynamic prediction and Van Houwelingen & Putter (2008) were the first to apply the method in the current of context time-dependent covariates. Again subjects at risk, at time s, are selected for analysis (left-truncation). The prediction window is fixed at ω and right-censoring is imposed at time $s+\omega$, see figure below.



A Cox model is then applied to link covariates with prediction of survival at ω time units after s. The hazard λ is thus assumed to be linked in a proportional way to the baseline hazard λ_0 ;

$$\lambda(t \mid Z(s), s) = \lambda_0(t \mid s)\exp(\beta(s)Z(s)).$$

Note that the proportionality factor $\exp(\beta(s)Z(s))$ depends on the covariates $Z(s)$, again fixed at their current value at the landmark time s, and their effect $\beta(s)$.

After having fitted the model, obtaining estimates of $\lambda_0(t \mid s)$ and $\beta(s)$, we want to use them to predict the conditional probability $S(s+\omega \mid Z^*(s), s)$ of surviving ω time units after s given alive at time s, for a new subject with covariate values $Z^*(s)$. To this end the relation between the survival- and hazard function is applied

$$\hat{S}(s+w \mid Z^*(s), s) = \exp\left(-\int_s^{s+\omega} \hat{\lambda}(t \mid Z^*(s), s)dt\right), \quad (1)$$

where the estimated hazard for the subject is given by

$$\hat{\lambda}(t \mid Z^*(s), s) = \hat{\lambda}_0(t \mid s)\exp\left(\hat{\beta}(s)Z^*(s)\right).$$

This method can be applied for one or for several landmark times. However we would like to be able to predict survival for any time between start and up to some natural limit (we cannot predict beyond end of follow-up). This is what motivates the use of landmark supermodels.

Landmark supermodels

The general idea of the landmark super model is to select not just one, but several landmark time points $\{s_1,...,s_K\}$. For each of these landmark times a landmark data set is created, as described above, by imposing left-truncation and right-censoring. The K datasets are then stacked into a super landmark data set. This is similar to longitudinal survival data, where a subject can contribute with several observations.

A Cox model can be applied to the super landmark data set, where possible landmark-varying effects of covariates can be modelled by a function of s;

$$\lambda(t \mid Z(s), s) = \lambda_0(t) \cdot \exp(\theta(s) + \beta(s)Z(s)).$$

The parameter function $\theta(s)$ describes how the baseline changes over s and similarly $\beta(s)$ is a vector of functions that describes changes in the covariates' effect. These parameter functions will in practice be chosen to be smooth functions. In our analysis we took

$$\theta(s) = \theta_0 s + \theta_1 s^2,$$

where θ_0 and θ_1 are parameters to be estimated. With this choice of function the baseline hazard is allowed to vary non-linearly across landmark time. Similar functions are chosen for β, see below (2). The interpretation of the parameters in the super model is comparable to the interpretation in the traditional Cox model; the effect of the covariates $\exp(\beta(s)Z(s))$ works multiplicatively on the baseline hazard.

Predictions of survival can now be made for any time s, between s_1 and s_K, using the same formula as before (1).

The longitudinal nature of the new data set gives rise to the possibility of dependence between observations, because we can have repeated observations on the same subject. To account for this possible dependence one can use the robust sandwich estimator of Lin & Wei (1989) to estimate the variance.

In summary, the difference between the landmark supermodel and having separate models for each selected landmark is that we can predict at any time between s_1 and s_K, and not just at those exact times. This is due to the fact that the supermodel assumes a structure for how the hazard and the covariate effects change with s.

Model building

The first step of the model building process was to select covariates that are known to be predictors of overall survival. In the second step we investigated whether any of these covariates had (landmark) time-varying effects by allowing them to be non-linear. A model including all covariates was therefore fitted, where all covariate effects were of the form

$$\beta(s) = \beta_0 + \beta_1 s + \beta_2 s^2 \quad , \qquad (2)$$

where β_0, β_1 and β_2 are parameters.

A model selection procedure was then applied in two steps: In each one a backward selection was used to decide in which order to remove terms. In the first step the quadratic time interactions were tested, i.e. for each covariate the hypothesis $\beta_2 = 0$ was tested. Non-significant quadratic interactions, at the 0.05 level,

were removed. In the second step all linear interactions, $\beta_1 = 0$, were tested, but only if the quadratic time interaction was removed in the first step. The resulting model is then what is presented in the paper. It was decided to also retain covariates for which the effect was not significant, because they are known to be important predictors.

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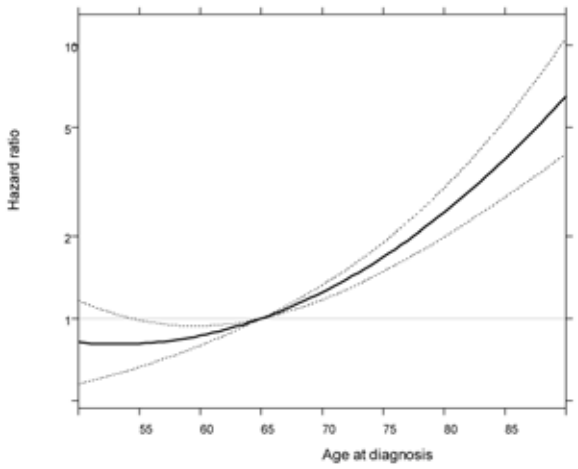
Appendix 2. **5-year dynamic overall survival (DOS) as a quadratic function of age at diagnosis**



PART

II

QUALITY OF LIFE, TREATMENT COMPLIANCE AND SIDE EFFECTS

CHAPTER

8

QUALITY OF LIFE IN RELATION TO TAMOXIFEN OR EXEMESTANE TREATMENT IN POSTMENOPAUSAL BREAST CANCER PATIENTS – A TEAM TRIAL SUB-STUDY

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ABSTRACT

Background

Tamoxifen and aromatase inhibitors are associated with different side effects which can significantly impact quality of life (QOL). We assessed QOL in Dutch patients receiving tamoxifen or exemestane in the Tamoxifen Exemestane Adjuvant Multinational (TEAM) Trial.

Methods

A total of 2754 Dutch postmenopausal early breast cancer patients were randomized between five years of exemestane or 2·5-3 years of tamoxifen followed by 2·5-2 years of exemestane. A total of 742 patients were invited to participate in the QOL side-study and complete questionnaires at one (T1) and two (T2) years after start of endocrine treatment. Questionnaires comprised the EORTC QLQ-C30 and BR23 validated questionnaires, supplemented with FACT-ES questions.

Results

543 patients completed questionnaires at T1 and by 454 patients (84%) at T2. For both treatment arms, overall QOL improved during follow-up. Most functioning scales improved over time, except for physical functioning, sexual functioning and sexual enjoyment. The only clinically relevant and statistically significant treatment difference between the treatment types concerned insomnia, with exemestane-treated patients reporting more insomnia than patients using tamoxifen (8 points difference at both timepoints; $p=0·001$).

Discussion

Certain QOL issues are treatment- and/or time-specific and deserve attention by oncology health care providers. Patients using exemestane reported more insomnia compared to patients using tamoxifen. There is a need for careful inquiry into QOL issues by those prescribing endocrine treatment to optimize QOL and ensure treatment adherence.

INTRODUCTION

The majority of breast cancer patients is diagnosed at postmenopausal age and most have hormone-receptor positive tumors. Over time, adjuvant endocrine therapy has increasingly been used to reduce disease recurrence and improve survival.[1] Presently, optimal endocrine therapy consists of at least five years of treatment including an aromatase inhibitor (AI), either given upfront or as part of a sequential treatment regimen following tamoxifen.2 Both regimens are appropriate treatment options for postmenopausal hormone receptor positive breast cancer patients.[2, 3] However, many patients on endocrine therapy are confronted with adverse effects, which may negatively impact quality of life (QOL), treatment compliance, and may then lead to a reduced survival.[4, 5] The impact of long-term endocrine treatment on QOL in postmenopausal breast cancer patients may therefore be an important issue of deliberation regarding the choice for a specific adjuvant treatment strategy.

Both tamoxifen, a selective estrogen receptor modulator, and AIs, which potently inhibit the aromatase enzyme (involved in the conversion of androgens to estrogen), are associated with a variety of adverse effects. Tamoxifen is associated with thromboembolic complications and endometrial cancer while AIs show fewer life-threatening side effects but more readily give rise to sometimes invalidating symptoms such as hot flashes, arthralgias, vaginal dryness and osteoporosis.[6, 7] Variations in the types and severities of adverse effects associated with the use of either tamoxifen or an AI may result in differences in the domains of QOL affected in patients using either endocrine treatment.

So far, several trials have investigated QOL in patients using adjuvant endocrine therapy, but only four have compared QOL in patients treated with tamoxifen versus an AI.[8-12] It is difficult to compare these studies due to variations in trial design, starting time of the AI and type of AI used. To our knowledge, the ATAC QOL study is the only large trial that compared QOL from the start of endocrine therapy in patients treated with tamoxifen versus an AI upfront.[9] In the Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial (Netherlands Trial Register NTR267), postmenopausal, hormone receptor-positive early breast cancer patients were randomized to either 5 years of exemestane upfront or 2.5-3 years tamoxifen followed by 2-2.5 years of exemestane.[2] There was a major participation in the TEAM study from the different hospitals throughout the Netherlands, therefore, this study provided a good opportunity for studying the effects of exemestane and tamoxifen on QOL in a homogeneous cohort of Dutch breast cancer patients. Moreover, we were able to relate relevant QOL issues reported by patients in this side study to the adverse events involved with these issues reported by the same patients in the main study using the registered adverse events.

PATIENTS AND METHODS

Study design

The study design and patient eligibility criteria for the TEAM trial have been described previously.[2] In the Netherlands, the study was initiated in 76 hospitals and details also have been described previously.[13] The

TEAM QOL side study was an open, multicenter study in which 45 Dutch TEAM centers participated. The side study protocol was approved separately by central and local ethics authorities before the enrollment of patients.

Patients and data collection

Patients who were randomized between January 2nd, 2003 and December 29th, 2004 and were event-free were invited to participate in the TEAM QOL side study. Patients received a letter together with the first QOL questionnaire one year after treatment randomization (further referred to as timepoint 1; T1). Participating patients who returned the first questionnaire and were disease-free two years after randomization received the second questionnaire one year after T1 (further referred to as timepoint 2; T2). Patients included in the sequential arm received the second questionnaire before the switch from tamoxifen to exemestane. No questionnaire was sent at baseline (time of diagnosis and treatment) as the results regarding QOL may potentially be biased, due to the recent knowledge of breast cancer diagnosis and impending treatment, which is known to have a negative impact on QOL. Furthermore, treatment was allocated by randomization, hence there is essentially no indication for baseline imbalance in QOL data between both treatment arms.[14] Patient, tumor, treatment and survival data were collected through the main TEAM Datacenter in Leiden, the Netherlands. In the main trial, patients were seen every three months in the first year, twice yearly in the second year and at least yearly thereafter.

Questionnaires

Data on QOL were obtained using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Version 3.0 (EORTC QLQ-C30) and the EORTC Breast Cancer Module questionnaire (QLQ-BR23), both translated into Dutch and previously validated.[15, 16] Both questionnaires were used after authorization by the EORTC Quality of Life Study Group. The EORTC QLQ-C30 is composed of five functioning scales (physical functioning, role functioning, cognitive functioning, emotional functioning, and social functioning), a global health status/QOL scale, three symptom scales (fatigue, pain, nausea/vomiting), and six single items (dyspnea, appetite loss, sleep disturbance, constipation, diarrhea and financial impact). The EORTC QLQ-BR23 is a validated tool designed for breast cancer patients with varying disease stages and treatment modalities and consists of 23 items that assess disease symptoms, side effects, body image, sexual functioning, future perspectives, therapy side effects, breast and arm symptoms and hair loss. Items that specifically assess side effects of chemotherapy were not applicable for the current study. In addition, the Functional Assessment of Cancer Therapy – Endocrine Subscale (FACT-ES) questionnaire was designed and validated to measure QOL in breast cancer patients treated with endocrine therapies.[17] Of the 18 items, 13 were included in our questionnaire (as other items were already included through the EORTC QLQ-C30 or BR23 questionnaires), resulting in three endocrine symptom scales (menopausal complaints, weight complaints, and vaginal complaints).

Based on standard EORTC scoring procedures, all scales were linearly converted to a zero-to-100 scale. Missing data were treated according to published recommendations.[18] For scales evaluating global health and functioning, higher scores represent higher levels of functioning and health status. For the evaluation of symptoms, higher scores correspond to more problems and higher levels of complaints.

Relevant patient-reported outcomes

Regarding QOL, the following items were investigated: (1) the difference between the QOL scores for patients using tamoxifen versus exemestane, (2) the difference between the two timepoints (T1 and T2), and (3) the interaction between treatment arm and time. A difference in score of at least eight points between groups was considered clinically relevant, and has been demonstrated to be a reasonable cut-off for clinical significance for a range of QOL endpoints.[19] Prior surgery was taken into account for analyses of body image, sexual functioning and sexual enjoyment.

Statistical analysis

All data were analyzed using the statistical package SPSS for Windows 17.0 (SPSS Inc, Chicago, IL, USA). Descriptive data are given as mean (SD) or median (range). The t-test was used to compare frequencies between groups. Linear mixed models were used to assess changes over time for overall QOL and for separate components of QOL.

RESULTS

Demographics

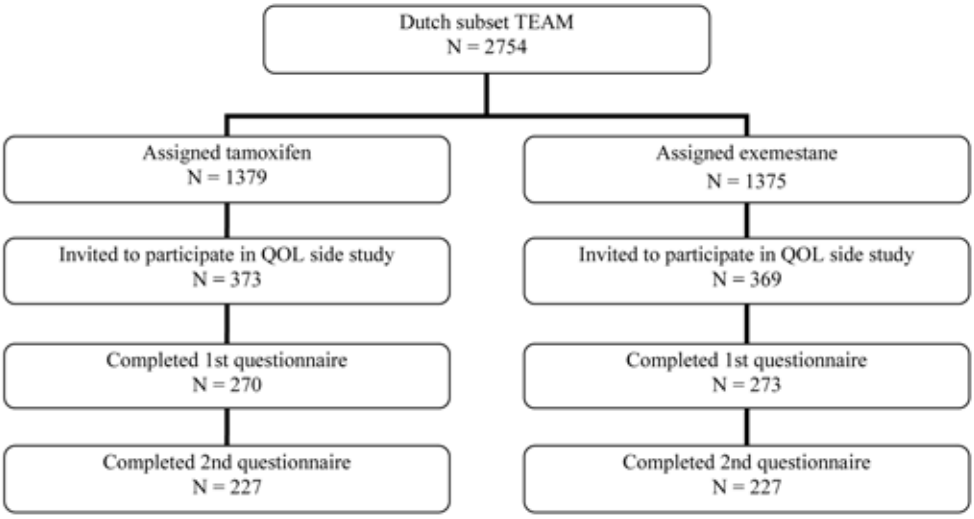
A total of 742 Dutch patients were invited to participate in the QOL side study (Figure 1). 543 patients (73%) completed the first questionnaire, of which 454 (84%) also completed the second questionnaire. Baseline characteristics of the responding patients and the total group of Dutch TEAM patients are shown in Table 1. The distribution of clinical, pathological and treatment characteristics of patients participating in the QOL side study was similar to that of the entire cohort of Dutch TEAM trial patients, except for the distribution of age, hormone receptor status and prior chemotherapy (yes/no). Of the patients participating in the TEAM QOL side study, most were older than 60 years, had node-positive disease and underwent a sentinel lymph node procedure followed by an axillary lymph node dissection. Almost 50% of the tumors were smaller than 20mm and approximately half of the patients were surgically treated by mastectomy.

Table 1. **Clinical and pathological data of responders compared to all Dutch TEAM trial patients**

		Responders		TEAM NL		
		n	%	n	%	p-value
Total		**543**		**2753**		
Age	<50-59	200	37	914	33	0.039
	60-69	200	37	965	35	
	≥70	143	26	874	32	
Body-mass index	≤25	190	39	919	38	0.589
	25-30	188	39	931	38	
	≥30	109	22	601	25	
Tumor stage	T1 (≤2cm)	267	49	1235	45	0.158
	T2 (>2-≤5cm)	241	45	1329	48	
	T3 / T4 (>5cm)	32	6	183	7	
Nodal stage	pN0	150	29	834	31	0.166
	pN1-3	275	53	1387	52	
	pN4-9	77	15	327	12	
	pN≥10	18	3	131	5	
Histological grade	G1 (well)	85	17	420	16	0.896
	G2 (moderate)	244	48	1218	47	
	G3, G4 (poor)	179	35	934	36	
Type of tumor	Ductal	404	75	2047	75	0.891
	Lobular	84	16	442	16	
	Ductolobular	27	5	129	5	
	Other	21	4	109	4	
Hormone receptor	ER+ PR+	350	64	1950	71	0.001
	ER+ PR-	129	24	595	22	
	ER+ PRnp	54	10	153	6	
	ER- PR+	10	2	47	2	
	ER- PR-	0	0	6	0	
Local therapy	MST, RT-	188	35	1127	41	0.051
	MST, RT+	92	17	401	15	
	BCS, RT-	7	1	36	1	
	BCS, RT+	255	47	1188	43	
Axillary surgery	SLNB-, ALND-	0	0	3	0	0.882
	SLNB-, ALND+	172	32	885	32	
	SLNB+, ALND-	127	23	632	23	
	SLNB+, ALND+	244	45	1233	45	
Chemotherapy	No	348	64	1941	71	0.002
	Yes	195	36	812	30	

ALND, axillary lymph node dissection; BCS, breast-conserving surgery; ER, estrogen receptor; MST, mastectomy; np, not performed; PR, progesterone receptor; RT, radiotherapy; SLNB, sentinel lymph node biopsy.

Figure 1. **Patient selection**

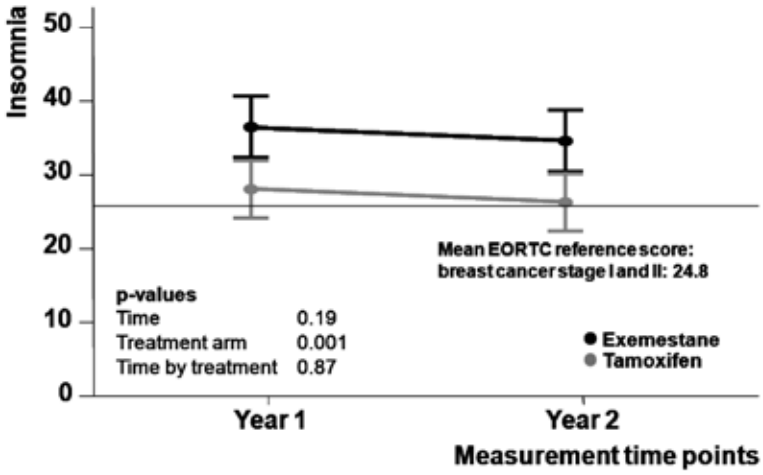


Quality of Life: Tamoxifen versus exemestane

The results regarding QOL items are shown in Table 2. In general, the scores for the various items did not differ significantly between patients using tamoxifen versus exemestane. Patients allocated tamoxifen showed superior scores for emotional functioning and sexual functioning ($p=0.048$ and $p=0.024$ respectively) than exemestane-users. Treatment with exemestane did not show superior results compared to tamoxifen for any of the functioning scales. Regarding individual symptoms, patients who received tamoxifen had fewer complaints of fatigue, dyspnoea, insomnia, and arm symptoms than patients receiving exemestane. For fatigue, the results were unrelated to the administration of chemotherapy (data not shown). Only for insomnia, the differences between the two treatment types were clinically significant (more than 8 points difference between tamoxifen and exemestane), observed at both timepoints (Figure 2). The endocrine symptom scales that were assessed using the FACT-ES included menopausal, weight and vaginal complaints. These scores did not differ between the two treatment arms.

The global health status scale represents an overall summary measurement of QOL. With respect to either treatment group, there was no difference in global health status/overall QOL (Table 2). Interestingly, the reported overall QOL was higher than the reference value of the EORTC QLQ-C30 (>75 versus 62 points).

Figure 2. **Insomnia in relation to treatment and time in the TEAM QOL side study**



Quality of Life: Changes over time

Changes in QOL items were assessed over the one-year period between T2 and T1 for the total group of patients, as there were no relevant differences between the two treatment arms. We found that over time, most functioning scales improved, except for physical functioning, sexual functioning and sexual enjoyment ($p<0.01$). Of note, fewer patients completed the questions concerning sexual functioning and enjoyment compared to the other items (Table 2). Over time, neither improvement nor deterioration was observed for global health status. Concerning the individual symptom scales, a significant improvement was found for the following items: fatigue, nausea and vomiting, appetite, breast symptoms and side effects of systemic therapy. Again, these results for fatigue were unrelated to the administration of chemotherapy (data not shown). A clinically significant difference over time was only established for breast symptoms.

Quality of Life: Interaction between treatment arm and time

Irrespective of treatment, most assessed items improved from T1 to T2. Only for the functioning scale 'Future perspective', did an interaction exist between treatment and time: patients using exemestane improved more compared to patients using tamoxifen.

DISCUSSION

The impact of adjuvant endocrine therapy on QOL is an ongoing discussion in the treatment of breast cancer patients prescribed long-term endocrine therapy. The current standard of practice advocating five

Table 2. **Overview of the different functioning and symptom scales by time and treatment arm**

	T1		T2		p-value		
	Tamoxifen Mean (SD)	Exemestane Mean (SD)	Tamoxifen Mean (SD)	Exemestane Mean (SD)	Treatment	Time	Time by treatment
EORTC QLQ-C30							
Functioning scales							
Physical functioning	80 (18)	78 (18)	79 (18)	79 (17)	0.732	0.508	0.132
Role functioning	80 (25)	79 (28)	82 (26)	82 (25)	0.741	0.028	0.826
Cognitive functioning	83 (21)	79 (25)	85 (19)	83 (22)	0.082	0.002	0.179
Emotional functioning	80 (21)	75 (21)	83 (20)	81 (21)	0.048	<0.001	0.273
Social functioning	87 (20)	86 (19)	90 (19)	90 (19)	0.861	0.001	0.397
Global health scale							
Global health status	78 (18)	75 (19)	78 (17)	76 (17)	0.074	0.458	0.281
Symptom scales							
Fatigue	30 (25)	34 (26)	24 (23)	29 (23)	0.026	<0.001	0.661
Pain	20 (24)	21 (25)	18 (24)	20 (25)	0.216	0.234	0.643
Nausea and vomiting	6 (15)	6 (17)	4 (14)	3 (14)	0.917	0.004	0.395
Symptom single items							
Dyspnoea	15 (24)	20 (25)	14 (23)	18 (24)	0.032	0.234	0.490
Appetite loss	9 (22)	9 (19)	5 (16)	6 (15)	0.697	0.001	0.511
Insomnia	28 (32)	37 (31)	27 (30)	35 (31)	0.001	0.188	0.869
Constipation	12 (24)	12 (23)	13 (24)	10 (55)	0.319	0.507	0.337
Diarrhoea	4 (15)	6 (17)	4 (15)	5 (15)	0.236	0.458	0.823
Financial difficulties	8 (18)	5 (15)	9 (22)	6 (16)	0.076	0.431	0.791
EORTC QLQ-B23							
Functioning scales							
Body image*	84 (25)	83 (22)	87 (20)	84 (26)	0.327	0.004	0.294
Sexual functioning*	20 (19)	17 (19)	21 (19)	16 (19)	0.024	0.755	0.208
Sexual enjoyment*	50 (30)	46 (23)	48 (22)	44 (22)	0.172	0.162	0.829
Future perspective	67 (27)	64 (26)	70 (25)	72 (25)	0.710	<0.001	0.028
Symptom scales							
Syst. therapy side effect	19 (17)	19 (18)	17 (17)	18 (17)	0.964	0.040	0.426
Breast symptoms	22 (19)	19 (19)	16 (19)	14 (19)	0.152	<0.001	0.523
Arm symptoms**	19 (21)	17 (21)	20 (20)	16 (20)	0.027	0.728	0.213
EORTC FACT-ES							
Menopausal complaints	26 (21)	26 (21)	24 (20)	26 (20)	0.572	0.093	0.196
Weight complaints	14 (20)	16 (20)	15 (19)	16 (19)	0.186	0.207	0.972
Vaginal complaints	18 (27)	20 (27)	20 (26)	23 (26)	0.337	0.412	0.793

*Stratified by type of surgery (mastectomy versus breast-conserving surgery)
**Stratified by axillary lymph node dissection (yes/no)

or more years of endocrine treatment can therefore be considered cumbersome in those experiencing severe adverse effects. Both tamoxifen and AIs have been associated with the development of various menopausal symptoms like sleeping disorders and sexual problems related to the depletion of circulating estrogens, some of which being severe to the point of significantly diminishing QOL. The present investigation of QOL in patients in the TEAM trial offers further insight into the impact of either tamoxifen or exemestane on a woman's QOL during endocrine therapy for breast cancer.

In the present investigation, a clinically significant difference was found between the two treatment arms for insomnia, observed at both timepoints, indicating more problems for exemestane users versus those taking tamoxifen. In general, insomnia is underreported and frequently overlooked in the context of breast cancer treatment. Approximately half of all breast cancer patients experience sleeping disorders

up to several years post-diagnosis.[20] The pathophysiological mechanism behind insomnia in breast cancer patients suggests a relation with nocturnal hot flashes.[21] Both hot flashes and musculoskeletal symptoms have also been associated with the depletion of circulating estrogens.[22] As exemplified by the MA.17 trial, a significant increase in the incidence of hot flashes and musculoskeletal symptoms was found in patients treated with letrozole compared to placebo.[11] Our data regarding more sleeping disorders in exemestane-users suggests that further lowering of postmenopausal estrogen levels with exemestane may lead to more sleeping disorders. Unfortunately this cannot be verified with blood samples, as these were not collected for our cohort of TEAM patients.

Patients using exemestane reported less sexual enjoyment and more sexual functioning problems than patients using tamoxifen. This is similar to the results as found after one year of therapy in the US Oncology side study of the TEAM trial concerning menopausal symptoms.[10] Our data do show that also after 2-2.5 years of therapy, menopausal symptoms persisted over time. In physiological menopause, the lack of circulating estrogens reduces vaginal lubrication, resulting in vaginal dryness and, consequently, dyspareunia.[23] Tamoxifen affects sexual functioning in terms of decreased libido and the ability to become aroused and experience orgasm, while AIs cause vaginal dryness and dyspareunia. Although tamoxifen is known to have anti-estrogenic properties on breast tissue, it exerts an estrogen agonist effect on the female genital tract in postmenopausal women and increases the risk of endometrial cancer.[24] Furthermore, under tamoxifen treatment, the vaginal squamous epithelium is weakly stimulated and undergoes proliferation and maturation.[25] It is possible that the abovementioned reasons explain why sexual functioning may be less affected in tamoxifen-treated patients than in those treated with exemestane. Another contributing factor may be that as already said, exemestane induces further lowering of postmenopausal estrogens in breast cancer patients. Fewer reports investigated vaginal dryness and dyspareunia in studies with AIs, but Morales et al. suggest that AIs induce more symptoms of vaginal atrophy (vaginal dryness and dyspareunia) than tamoxifen, which parallels our findings that exemestane-treated patients reported more sexual functioning problems than tamoxifen-treated patients.[26]

Other quality of life studies

To date, only a few large randomized trials comparing adjuvant tamoxifen with AIs have reported on QOL data (Table 3).[8-12]

Also, it is difficult to compare the different randomized trials with each other and with our QOL side study, due to differences in patient populations, countries of residence, AIs used, timing and of start of treatment, and the instruments used to assess QOL. However, regardless of these variations, no large differences in QOL were seen between tamoxifen and AIs.

The planned nature of the QOL side study using validated questionnaires as well as the high response rate for both T1 and T2 questionnaires lends confidence to our findings. The absence of a baseline measurement

Table 3. **Overview of other quality of life studies in trials comparing tamoxifen with an aromatase inhibitor in postmenopausal early breast cancer patients**

Study	Author	Intervention	Sample size	Follow-up	QOL Instrument	Outcome QOL study	Insomnia
ATAC (main)	Howell et al. 2005	Arm 1: Ana Arm 2: Tam (Arm 3: Combi)	9366	n.r.	None	AI: Fewer gyn and vascular disorders; more arthralgia and fractures than Tam.	n.r.
ATAC (QOL)	Fallowfield et al. 2004	Arm 1: Ana Arm 2: Tam (Arm 3: Combi)	1021	Baseline, 3, 6, 12, 18, and 24 months	FACT-B+ES	No sign differences across both groups. AI: fewer cold sweats and vaginal discharge Tam: more vaginal dryness, painful intercourse and loss of sexual interest.	n.r.
IES (main)	Coombes et al. 2007	Tam → Tam Tam → Exe	4724	Baseline, 3, 6, 9, 12, 18 and 24 months	None	Switching to Exe had no adverse effect on QOL. Exe: Fewer gyn complications than Tam.	Tam: 16.8% Exe: 19.6% p=0.02
IES (QOL)	Fallowfield et al. 2006	Tam → Tam Tam → Exe	582	Baseline, 3,6,9,12,18,24,30, 36,48 and 60 months.	FACT-B +ES	No differences in QOL or in the endocrine subscale.	Tam: 34.5%, Exe: 34.6%
MA 17 (main)	Goss et al. 2005	After 5 years of Tam: Plac 5 years Let 5 years	3612	Baseline, 6 months and annually	None	Vaginal bleeding more common in placebo vs letrozole (6% vs 8% p=0.005).	Let: 6% Plac: 5% p=0.06
MA.17 (QOL)	Whelan et al. 2005	After 5 years Tam: Plac 5 years Let 5 years	3612	Baseline, 6 months and annually	SF-36 MENQOL	Small differences in bodily pain and vasomotor symptoms. No differences in overall QOL.	n.r.
TEAM (main)	Van de Velde et al. 2011	Tam → Exe Exe	9779	Baseline, every 3 months in year 1, yearly thereafter	None	Sequential arm: more gyn/endometrial symptoms and venous thrombosis; Exe alone: more musculoskeletal effects, hypertension and hyperlipidemia	Tam: 10% Exe: 13% p≤0.001
TEAM (QOL)	Jones et al. 2007	Tam → Exe Exe	1614	Baseline and every 3 months	Ten common symptoms	More sleeping disorders for exemestane	n.r.
TEAM (QOL)	Current: Van Nes/Fontein et al. 2012	Tam → Exe Exe	543	After 1 and 2 years of start hormonal therapy	EORTC C30 EORTC B23 FACTB-ES	No difference in overall QOL between both groups	Exe > Tam p=0.001

Ana, anastrozole; combi, combination; ES, endocrine symptom subscale; Exe, exemestane; FACT, Functional Assessment of Cancer Therapy-Breast; MENQOL, Menopause Specific Quality of Life Questionnaire; Let, letrozole; n.r., not reported; Plac, placebo; SF-36, Short Form 36-item health Study; Tam, tamoxifen; Gyn, gynaecological.

may be considered a shortcoming when assessing changes in QOL over time; notably, however, baseline measurements of QOL are likely biased due to recent knowledge of breast cancer diagnosis in our patient population at the start of treatment. Due to the randomized nature of this trial, differences in baseline QOL with respect to treatment arms are unlikely.[14]

In summary, our findings indicate that overall QOL and most functioning scales improve with longer therapy duration, both for patients treated with tamoxifen and exemestane. Nevertheless, certain QOL issues are treatment-specific and deserve attention by oncology health care providers. Also, the large number of patients who reported complaints of sexual functioning, fatigue and insomnia in the QOL study was not mirrored by the reported adverse events related to these complaints in the main TEAM trial database. There is a need for careful inquiry by those seeing patients throughout the duration of endocrine treatment in order to optimize QOL and ensure adherence to treatment.

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CHAPTER

9

HIGH NON-COMPLIANCE IN PATIENTS TREATED WITH EXTENDED ADJUVANT LETROZOLE. RESULTS FROM THE IDEAL RANDOMIZED TRIAL

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ABSTRACT

Background

The aim of this study was to investigate non-compliance to aromatase inhibitors and factors associated with early treatment discontinuation in the extended adjuvant setting.

Methods

The IDEAL trial is a prospective, open-label phase-III trial comparing 2.5 with 5 years of extended adjuvant letrozole in hormone receptor-positive postmenopausal early breast-cancer patients after 5 years of adjuvant endocrine therapy. The purpose of this study was to assess non-compliance in the first 2.5 years of extended adjuvant therapy. Non-compliance was defined as early discontinuation of letrozole for all reasons, excluding death or recurrence.

Results

At 2.5 years, 1215 patients were included in the analysis. Overall non-compliance probability was 18.4%, of which 85.1% discontinued due to toxicities. Analyses showed that patients with prior sequential therapy were less likely to discontinue treatment than when treated with an aromatase inhibitor (AI) or tamoxifen upfront (logrank-p=0.004). Longer treatment-free intervals also predicted more non-compliance (logrank-p=0.011). Age was not predictive of non-compliance (p=0.571). Prior surgery (mastectomy vs breast conserving surgery), both with or without radiotherapy and/or chemotherapy were also not associated with early treatment discontinuation (p=0.228 and p=0.585 respectively). Although having fewer than four positive lymph nodes predicted more non-compliance (logrank-p=0.050), age, tumor-type and locoregional treatment did not.

Conclusions

High non-compliance to extended adjuvant endocrine therapy was confirmed. Toxicities were the major reason for discontinuation, and this was not influenced by age. Longer treatment-free intervals and fewer positive lymph nodes predicted more non-compliance. Patients who underwent sequential therapy were least likely to discontinue extended adjuvant endocrine therapy.

INTRODUCTION

Aromatase inhibitors (AIs) have shown improvements in reducing both mortality and recurrence rates in postmenopausal hormone receptor-positive early breast cancer patients.[1-5] AIs are commonly prescribed as part of a sequential treatment regimen for 2-3 years after 3-2 years of tamoxifen, or as monotherapy for five years, although it has been suggested that more than five years of adjuvant treatment provides an additional benefit, even after a period of treatment discontinuation.[6] Despite prominent developments in breast cancer therapy directed at improving survival and reducing recurrence, early discontinuation of adjuvant endocrine therapy in the first five years of treatment is persistently high.[7, 8] Non-compliance rates are similar in patients treated with AIs, tamoxifen, or a sequence of both, and ranges between 40-60%. Reports confirm that these high rates are largely attributable to the presence and severity of adverse effects.[8-12]

AIs function by inhibiting the enzyme aromatase, which plays a role in converting estradiol to estrogen. Estrogen deprivation by AIs has shown profound effects on breast cancer survival and a significant reduction in recurrence rates.[13] However, inducing an early artificial menopausal status by depriving the body of circulating estrogens also gives rise to symptoms imitating menopause, including arthralgias, hot flashes, vaginal dryness, and osteoporosis.[14, 15] Steps have been undertaken to reduce the number of adverse effects that derive from the depletion of estrogens. Third-generation AIs were developed to be more selective and potently lower plasma estrogen levels through near-complete suppression of aromatase.[13, 16]

Studies show that treatment duration is directly related to clinical outcome.[17] Current standard of care is tamoxifen or an AI only or a sequence of both for the duration of five years, although evidence suggests that continuing treatment after five years may be beneficial in terms of survival.[1, 6]

Although data implies that treatment compliance is lower in patients who are older (≥85 years) or younger (<45 years), have a lower socio-economic status, experience side effects, and are prescribed therapy for longer duration, these associations are inconsistent across studies.[18, 19] These differences may, in part, result from differences in study populations, as well as variations in definitions of adherence. Patients' personal perceptions and beliefs about their illness as well as the risks, benefits and costs of their prescribed medication were found to be strong predictors of non-compliance, and have been the focus of investigations.[18-20]

To date, no other prospective clinical trial has studied non-compliance to extended adjuvant therapy in-depth. The MA.17 trial, one of the first trials to investigate more than five years of adjuvant endocrine treatment, conveyed high rates of adverse effects, but medication adherence was not reported.[21] In light of determining the optimal duration of adjuvant endocrine therapy, efficacy may be compromised when treatment is discontinued before the predetermined stop date is reached, in which case extended therapy is prescribed in vain.

This investigation discusses high rates of non-compliance found in the extended adjuvant setting in a Dutch trial on prolonged endocrine therapy, and determines which patients are at risk of early treatment discontinuation. Discerning which patients are at highest risk of non-compliance is imperative for tackling this issue effectively.

MATERIALS AND METHODS

Patient selection

The Investigation on the Duration of Extended Adjuvant Letrozole (IDEAL) trial is a prospective, randomized, open-label phase III trial evaluating the efficacy and safety of 2.5 with 5 years of adjuvant letrozole in breast cancer patients after five years of adjuvant endocrine therapy. The purpose of the present study was to assess non-compliance in the first 2.5 years of extended adjuvant therapy. Postmenopausal patients were diagnosed with hormone receptor-positive, early stage (I-IIIa) breast cancer, and adequately treated with five years of adjuvant endocrine therapy. Patients were disease-free at time of randomization. Adjuvant endocrine therapy consisted of five years of AIs only (anastrozole, exemestane or letrozole), or a sequence of 2-3 years of tamoxifen followed by 3-2 years of AIs. When AIs are contraindicated, five years of tamoxifen monotherapy is warranted. The IDEAL trial is registered with the Netherlands Trial Register (NTR3077). Appropriate approvals from local ethical committees were obtained and all patients provided written informed consent. 1262 patients from 72 hospitals were included in the present analysis and were randomized to either 2.5 or 5 years of letrozole (2.5mg once daily, orally) between April 2007 and April 2011.

Non-compliance

Non-compliance was defined as early discontinuation of letrozole before the predetermined end date for any reason, with the exception of early discontinuation due to cancer recurrence or death. Switching to a different form of endocrine therapy before the predetermined stop date was also considered non-compliance. The duration of letrozole therapy was determined by calculating the number of days between the first and last dose of letrozole during the first 2.5 years of follow-up. An intermittent break from therapy was permitted for a maximum of four weeks. Patients who died during the follow-up period and who had not reported treatment discontinuation before their death were considered compliant. Patients who never started letrozole were excluded from the analyses.

Patient and tumor characteristics

Tumor characteristics were recorded using clinical TNM classification (tumor size, regional lymph node metastases and distant metastases), estrogen receptor (ER), and progesterone receptor (PR) status. We collected data on tumor and pathological characteristics, including histological subtype, pathological grade and mitotic activity, and prior curative and locoregional therapy (type of surgery, type and duration of chemotherapy, type and duration of endocrine therapy). Patients were stratified by nodal status (node-negative or node-positive), time from last dose of prior endocrine therapy (0-<6, 6-<12, 12-27 months) and prior chemotherapy (yes/no). Treatment discontinuation was assessed during patient visits at 6 months, 1, 2 and 2.5 years after starting extended adjuvant treatment with letrozole, or in case of intermittent adverse events. Date of last follow-up, cancer recurrence or death were used as censoring, and further administrative censoring was applied at 2.5 years after randomization. The date of treatment discontinuation as well as reasons for non-compliance and (if relevant) subsequent therapy were documented prospectively.

Statistical analysis

Kaplan-Meier survival curves were used to demonstrate early discontinuation of letrozole over the follow-up period. We performed Cox regression analyses to identify factors associated with early treatment discontinuation. All analyses were performed with SPSS version 17.0 Statistical Software (SPSS Inc., Chicago Ill.).

Table 1. **Baseline characteristics of 1215 patients who started letrozole**

Characteristic	n	%	Characteristic	n	%
Age (years)			**Histological grade (BR)**		
<55	322	26.5	G1 (Well)	188	15.5
55-65	510	42	G2 (Moderate)	506	41.7
65-75	292	24	G3, G4 (Poor)	362	29.8
>75	91	7.5	unknown	159	13
ER/PR status			**Prior endocrine therapy**		
ER+ PR+	903	74.8	5 yrs tam	141	11.6
ER+ PR-	232	19.2	5 yrs AI	291	24
ER+ PR unk	29	2.4	2-3 tam → 3-2 AI	729	60
ER- PR+	39	3.2	unknown	54	4.4
ER- PR-	3	0.2	**Endocrine therapy type**		
ER unk PR+	1	0.1	Tamoxifen	141	11.6
Treatment-free period			Exemestane	185	15.2
0-<6 months	1069	88	Tam → exemestane	302	24.9
6-<12 months	64	5.3	Letrozole	31	2.6
12-27 months	82	6.7	Anastrozole	75	6.2
Tumor type			Tam → letrozole	111	9.1
Ductal	942	77.5	Tam → anastrozole	316	26
Lobular	190	15.6	unknown	54	4.4
other	83	6.8	**Prior chemotherapy**		
Tumor stage			no	401	33
pT0/pTis	4	0.4	yes	814	67
pT1 (≤2cm)	550	45.3	**Prior radiotherapy**		
pT2 (>2-≤5cm)	544	44.8	no	343	28.2
pT3 (>5cm)	72	5.9	yes	860	70.8
pT4a-c/pT4d	28	2.3	unknown	12	1
unknown	17	1.4			
Nodal status					
pN0/pN0(i+)	293	24.1			
pN1(mi)/pN1(1-3)	730	60.1			
pN2 (4-9)/pN3(≥10)	179	14.7			
unknown	13	1.1			

unk, unknown; BR, Bloom&Richardson; tam, tamoxifen; AI, aromatase inhibitor;

RESULTS

Patient and treatment characteristics

1262 patients were randomized for 2.5 or 5 years of treatment with letrozole. 1215 patients had at least one dose of letrozole during the follow-up period. 31 patients (2.6%) had a recurrence and seven patients (0.6%) died over the follow-up period. Most patients (1069, 88%) started letrozole within six months of the end of prior adjuvant endocrine therapy. Prior treatment consisted of five years tamoxifen (n=141) or an AI only (n=291), or sequential therapy of 2-3 years with an AI after 3-2 years of tamoxifen (n=729) (Table 1). Information about the number of follow-up visits was available for 1103 patients. Compliant patients visited the breast unit more frequently than non-compliant patients (median 2.07 (range 0.79-10.53) versus 2.03 visits (range 0.02-7.14), p=0.011).

The overall non-compliance probability was 18.4% within the 2.5-year follow-up period. The median follow-up time for non-compliant and compliant patients was 1.88 years (range 0.19-2.50) and 1.11 years (range 0.19-2.50) respectively, (p=0.003). Highest discontinuation rates were found in the first six months of treatment with letrozole (49.7%). A vast majority of patients (n=154, 85.1%) discontinued due to adverse events. Most commonly reported adverse events included musculoskeletal, neurological, and dermatological/skin disorders, based on the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (Table 2). Other reasons for early discontinuation of letrozole included treatment refusal (n=18), protocol deviation (n=4), intercurrent illness (n=1) and other reasons (n=4). No difference existed between the randomized treatment groups (2.5 years vs 5 years letrozole) (logrank p=0.695). 35 patients discontinued follow-up altogether (13 non-compliant and 22 compliant patients).

Table 2. **Reasons for treatment discontinuation by adverse event***

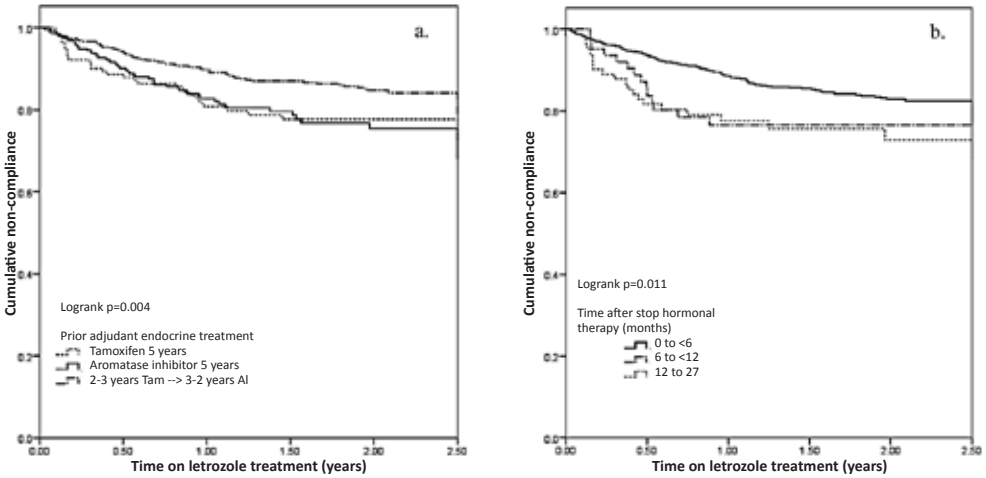
Adverse event	n	%
Cardiac symptoms	6	3.9
Constitutional symptoms	15	9.7
Dermatological / skin	17	11.0
Endocrine	7	4.5
Gastrointestinal	14	9.1
Haemorrhage / bleeding disorder	1	0.6
Infection	1	0.6
Metabolic / laboratory disorder	1	0.6
Musculoskeletal / soft tissue	29	18.8
Neurological	23	14.9
Ocular/visual	3	1.9
Pain (general)	8	5.2
Pulmonary / upper respiratory	1	0.6
Renal / genitourinary	1	0.6
Sexual / reproductive function	5	3.2
Unknown	22	14.3

* based on the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0

Risk factors for non-compliance

A significant difference was found between treatment discontinuation and prior endocrine treatment regimen (logrank p=0.004). Patients previously treated with sequential therapy of 2-3 years tamoxifen followed by an AI for 3-2 years had the lowest probability of treatment discontinuation after 2.5 years (Figure 1a). There was no difference between the two 5-year therapies (p=0.829). Patients who had used letrozole earlier, either five years upfront or after switching from tamoxifen, were most likely to persevere

Figure 1. **Kaplan-Meier curve of early treatment discontinuation based on prior endocrine treatment regimen and treatment-free interval after 5 years of adjuvant endocrine therapy.**



a. Early treatment discontinuation based on prior endocrine treatment regimen b. Early treatment discontinuation based on treatment-free interval (months)

Figure 1a. **Early treatment discontinuation based on prior endocrine treatment regimen**

Prior treatment regimen	Non-compliance probability (%)	Discontinued treatment	(%)	HR (95% CI)	Logrank p value
Tamoxifen 2-3 → AI 3-2 years	15.6	92	12.6	1 (ref)	0.004
Aromatase inhibitor only	24.1	54	18.6	1.588 (1.056 - 2.388)	
Tamoxifen only	22.5	31	22.0	1.667 (1.191 - 2.335)	

Figure 1b. **Early treatment discontinuation based on treatment-free interval (months**

Treatment-free interval	Non-compliance probability (%)	Discontinued treatment	(%)	HR (95% CI)	Logrank p value
0 - <6	17.5	146	(13.7)	1 (ref)	0.011
6 - <12	23.4	14	(21.9)	1.702 (0.983 - 2.947)	
12 - 27	27.1	21	(25.6)	1.804 (1.140 - 2.855)	

with letrozole in the extended adjuvant setting (3.5% non-compliance, hazard ratio (HR) 0.170 (95%CI 0.066-0.437); logrank p=0.001) compared to tamoxifen only. No significant difference existed between the other treatment groups (data not shown). A significant difference was also found in the number of patients discontinuing treatment early based on the treatment-free interval between the last dose of prior endocrine therapy and the first dose of letrozole (logrank p=0.011). Longer intervals predicted more non-compliance (Figure 1b).

Patients were categorized by age (<55, 55-65, 65-75, >75 years), tumor size and nodal status based on the TNM classification, prior surgery and prior chemotherapy. No differences in early discontinuation rates between older and younger postmenopausal patients could be established (p=0.571) (data not shown). Tumor size did not show any differences in early discontinuation rates (logrank p=0.370). However, there was a barely significant difference in non-compliance based on the number of positive lymph nodes; having fewer than four positive lymph nodes predicted more non-compliance (logrank p=0.050) (Figure 2).

Figure 2. **Early discontinuation of letrozole based on nodal status**

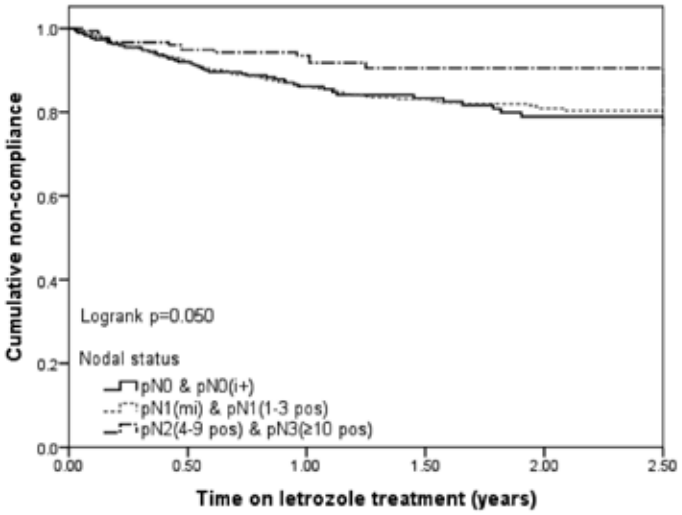


Figure 2. **Number of positive lymph nodes and treatment discontinuation**

Nodal status	Non-compliance probability (%)	Discontinued treatment	(%)	HR (95% CI)	Logrank p value
pN0 & pN0(i+)	21.1	47	16.0	1.889 (1.071 - 3.331)	0.050
pN1(mi) & pN1(1-3 pos)	19.7	117	16.0	1.874 (1.111 – 3.160)	
pN2(4-9 pos) & pN3(≥10 pos)	9.5	16	8.9	1 (ref)	

Type of surgery (mastectomy or breast conserving surgery (BCS)) was not associated with non-compliance (logrank p=0.822). Non-compliance was not associated with prior adjuvant chemotherapy (logrank p=0.585) or radiotherapy (logrank p=0.383) separately. We investigated whether the combination of surgery type with or without radiotherapy were correlated with non-compliance. Only nine patients received BCS without radiotherapy and were therefore grouped together with other breast conserving surgery patients. No differences were established between the different treatment groups (logrank p=0.228). Additional analyses were performed where patients who switched to another AI were also considered compliant. Patients with mastectomy and radiotherapy were more compliant than patients who underwent mastectomy without radiotherapy or BCS with or without radiotherapy (HR 1.740 (95%CI 1.047-2.892) and HR 1.785 (95%CI 1.113-2.864); logrank p=0.043 for the two treatment combinations respectively). After termination of letrozole, most patients discontinued extended therapy altogether (78.5%). 35 patients continued with another AI (4 patients unknown). 32 out of 35 patients switched back to the AI used prior to starting letrozole (14 exemestane, 18 anastrozole).

DISCUSSION

Risk factors for non-compliance

Non-compliance to adjuvant endocrine therapy can be detrimental for women in their treatment of hormone-receptor positive early breast cancer. More than half of the patients prescribed adjuvant AIs discontinue treatment before the five-year regimen has passed.[9, 11, 22] The present study shows that even after persisting five years of endocrine therapy, approximately 15% of patients still choose to discontinue treatment with AIs. Longer intervals between adjuvant and extended adjuvant treatment, prior endocrine therapy with tamoxifen or AI only, and fewer than four positive lymph nodes were associated with more non-compliance.

Research on non-compliance in the extended adjuvant setting after enduring five years of endocrine therapy is lacking. We found several factors that were predictive of early treatment discontinuation. The kind of endocrine therapy was an independent predictor of non-compliance. Patients previously treated with letrozole only or as part of a sequential treatment regimen were more likely to persist treatment than patients who had previously been treated with a different agent. The most plausible reasoning lies in the fact that patients are accustomed to letrozole and its toxicities.

Evidence for the impact of certain patient- and therapy-related factors on treatment non-compliance is variable. Previous reports indicate that older and younger breast cancer patients have higher rates of early treatment discontinuation.[19] Increased age is often associated with multiple comorbidities, which also affects treatment compliance.[19, 23] Non-compliance probability did not differ significantly based on age in our cohort. It should be taken into consideration that the current population may differ from other populations

reported in prior literature. Perceived benefit of extended adjuvant treatment may also be the cause of the obliterated differences in non-compliance based on age commonly described in previous studies.[18, 19] In addition, the present study population consists of patients who could be considered more compliant than the general population of postmenopausal early breast cancer patients with hormone-receptor positive disease, due to the fact that they have already completed five years of endocrine therapy.

Partridge et al. indicated that patients who underwent mastectomy instead of BCS had higher rates of tamoxifen non-compliance.[19] On the other hand, Owusu et al. reported more treatment discontinuation in patients who received BCS without radiotherapy.[22] Our results were similar to those reported by Owusu et al. only after considering patients who switched from letrozole to another AI as being compliant: patients who underwent mastectomy with radiotherapy were more compliant than those who underwent mastectomy without radiotherapy or BCS. Although mortality rates do not differ between BCS and mastectomy, a pooled analysis of randomized trials found more locoregional recurrences in patients with BCS.[24] It is therefore disquieting to discover that patients who underwent BCS with or without radiotherapy are at greater risk of non-compliance.

The observed protective effect of more positive lymph nodes on non-compliance starkly contrasts findings by Fink and colleagues.[18] Fink et al. investigated tamoxifen discontinuation in women 65 years and older with newly diagnosed hormone receptor-positive breast cancer and discovered that patients with four or more positive nodes had a two and a half times greater likelihood of discontinuing tamoxifen than patients with no positive nodes. Contrary to these findings, our study showed that patients with four or more positive lymph nodes were more compliant than patients with fewer positive nodes. This discovery suggests that patients' perceptions on the benefit of treatment and the knowledge of risk factors for disease recurrence could influence treatment persistence, as was demonstrated in earlier investigations of the role of patients' beliefs on treatment adherence.[18] All patients in our study already persisted five years of adjuvant endocrine therapy. Accordingly, patients who discontinued treatment in the first five years were not included in the present analysis. Differences between the two populations may thus explain the dissimilarity in the observations by Fink and colleagues.[18]

Adverse effects

Previous studies have recognized that non-compliance is largely attributable to the presence and severity of adverse effects.[9, 10, 19] Treatment efficacy can be compromised when AIs are not taken for the full prescribed duration.17 Adverse events were the cause of 85.1% of the cases of early treatment discontinuation, which is consistent with other studies on non-compliance in the first five years of endocrine therapy, where adverse events also posed the greatest threat to non-compliance.[9, 10, 19]

It has also been suggested that adherence to endocrine therapy is at least partially dependent on the (lack of) communication between patients and their physicians, who fail to adequately explain the importance of enduring adjuvant endocrine therapy and the potential adverse effects of the prescribed therapy.[25] As

adverse effects are a major contributor to early treatment discontinuation, it is crucial that physicians and nurse practitioners take the time to explain and prepare the patient for the possibility of adverse effects. Greater adherence was found in patients previously prescribed a sequential treatment regimen than those with upfront treatment regimens. One might infer that active reinforcement of the importance of endocrine treatment when a patient visits her physician to switch from tamoxifen to an AI provides an additional advantage to treatment adherence, because the importance of therapy is reiterated. This supposition is based on reported methods of improving adherence, which include adequately explaining and reinforcing the benefits and side effects of the prescribed medication.[25]

Several methods have been proposed to objectively measure drug compliance, including self-reports, pill counts, prescription analysis, serum or urine drug levels and microelectronic monitoring systems.[26] Although one or more of these methods is unmistakably more effective for objectively assessing compliance while on treatment, this was not possible in the current study. Given the results of the present analysis, however, it is more important to reflect whether prescribing endocrine therapy for 2.5 years or longer will be advantageous if almost 20% of patients already discontinue treatment within 2.5 years.

After discontinuing letrozole, most patients stopped treatment altogether. The decision to discontinue treatment may be a relief for patients experiencing adverse effects that interfere with daily functioning and quality of life. Conversely, other patients are more reluctant to stop treatment, given the knowledge that a growing number of studies are finding that longer treatment with AIs provide additional survival benefit. The Dutch treatment guidelines currently recommend five years of adjuvant endocrine therapy for patients with hormone receptor-positive disease. Extended adjuvant therapy is not yet standard practice, and physicians and patients may therefore decide to discontinue treatment completely rather than switch to another AI. On the other hand, almost 20% of patients who discontinued letrozole did persist with another AI, which suggests that outside of clinical trials physicians are already prescribing AIs for longer. Information on drug adherence and treatment duration after switching from letrozole to another AI were not available, and is therefore a limitation of this study. Additionally, information on why non-compliant patients had fewer follow-up visits per year was not reported. It is therefore not possible to conclude whether missing a follow-up visit was due to adverse events or due to other reasons unrelated to treatment compliance.

Treatment efficacy and drug metabolism

Although endocrine therapy is known to cause multiple toxicities of varying severity, not all patients report adverse effects. With respect to tamoxifen, patients may differ in their metabolic responses to convert tamoxifen into the active metabolite endoxifen, depending on the activity of the Cytochrome P450 2D6 (CYP2D6) enzyme.[27] Treatment efficacy seems highest in patients considered extensive metabolizers.[27-29] Goetz and colleagues found that extensive metabolizers had the highest rates of adverse effects such as hot flashes.[28] If this also holds true for AIs, it is important to determine which patients are at highest risk of non-compliance resulting from adverse events based on their metabolic characteristics. If differences in drug

efficacy are associated with variations in AI metabolism, and treatment toxicities are subsequently linked to these variations in AI metabolism, one can infer that patients with more severe adverse reactions will derive additional benefit from AI therapy. Simultaneously, these are the same patients who will have the greatest risk of non-compliance. To date, this has only been demonstrated in CYP2D6 metabolism studies with tamoxifen.[27-29] Considering that an individual-tailored approach to endocrine treatment of postmenopausal breast cancer patients is most favourable, it is crucial that future studies determine which patients are at highest risk of adverse events, and consequently, non-compliance.

Patients are frequently prescribed adjuvant therapies to further reduce the risk of relapse. However, reductions in recurrence can only be attained when patients comply with the prescribed treatment and duration. Despite promising reports of superior efficacy when endocrine treatment duration exceeds five years, many patients are plagued by adverse effects, and the risk of non-compliance raises questions on the efficacy of extended treatment in all patients. 40-60% of patients have discontinued treatment after five years of treatment [19], and an additional 18% stop in the extended adjuvant setting. This alarmingly high non-compliance reiterates the need for tackling this issue effectively. Furthermore, it is important to discern which patients are most likely to encounter adverse effects and prevent their non-compliance, as it is likely that these patients may derive most benefit from extended adjuvant endocrine therapy with AIs.

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CHAPTER

10

RELATIONSHIP BETWEEN SPECIFIC ADVERSE EVENTS AND EFFICACY OF EXEMESTANE THERAPY IN POSTMENOPAUSAL EARLY BREAST CANCER PATIENTS

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ABSTRACT

Introduction

Many adverse events (AEs) associated with aromatase inhibitors (AI) involve symptoms related to the depletion of circulating estrogens, and may be related to efficacy. We assessed the relationship between specific AEs (hot flashes (HF) and musculoskeletal AEs (MSAE)) and survival outcomes in Dutch and Belgian patients treated with exemestane in the Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial. Additionally, the relationship between hormone receptor expression and AEs was assessed

Methods

Efficacy endpoints were relapse-free survival (RFS), overall survival (OS) and breast cancer-specific mortality (BCSM), starting at 6 months after the start of exemestane treatment. AEs reported in the first 6 months of treatment were included. Specific AEs comprised HF and/or MSAE. Landmark analyses and Cox proportional hazards models assessed survival differences up to 5 years.

Results

1485 exemestane patients were included. Patients with HF had a better RFS than patients without HF (multivariate HR 0.393 (95%CI 0.19–0.813); p=0.012). The occurrence of MSAE versus no MSAE did not relate to better RFS (multivariate HR 0.677 (95%CI 0.392–1.169); p=0.162). Trends were maintained for OS and BCSM. Quantitative hormone receptor expression was not associated with specific AEs.

Discussion

Some AEs associated with estrogen depletion are related to better outcomes and may be valuable biomarkers in AI treatment.

INTRODUCTION

Five years of adjuvant treatment with third-generation aromatase inhibitors (AI) have shown improvements in disease-free survival, distant disease-free survival, and contralateral breast cancer, without significant improvements in overall survival, when compared with tamoxifen in postmenopausal hormone receptor-positive breast cancer patients. This has been observed in several large trials.[1, 2] In addition, superiority of AIs has also been shown when used as part of a sequential treatment regimen, following 2-3 years of tamoxifen, including survival benefit in the IES study.[3-5] Although the toxicity profile shows fewer acute and potentially life-threatening adverse events (AEs) than tamoxifen, such as pulmonary embolisms and endometrial cancer, AIs are also associated with inconvenient adverse effects, mostly related to the body's depletion of circulating estrogens such as hot flashes (HF), vaginal dryness, osteoporosis and musculoskeletal symptoms (MSAE) such as arthritis, arthrosis, arthralgia and myalgia.[6] Adverse effects of AIs also play an important role in treatment compliance and, essentially, treatment efficacy.[7]

By virtue of their mechanism of action, aromatase inhibitors decrease the levels of circulating postmenopausal estrogens.[8] Polymorphisms in the aromatase gene, CYP19A1, have also been described and are associated with variations in circulating estrogen levels.[9]. In addition, it has been suggested that a relationship exists between CYP19A1 polymorphisms and efficacy of aromatase inhibitors based on alterations in aromatase activity.[10]. The presence of specific AEs including HF and MSAE may also be related to lower levels of circulating estrogens.[11-13] Based on this assumption, AEs may be a predictor and valuable biomarker of treatment efficacy of AIs.[14-16] Regarding tamoxifen, it has also been suggested that patients who developed vasomotor symptoms during tamoxifen treatment had a lower risk of breast cancer relapse, and were CYP2D6 extensive metabolizers, but data are inconclusive and immature to implement preemptive CYP2D6 testing in the clinic.[15-18] Cuzick and colleagues assessed the relationship between endocrine symptoms and breast cancer recurrence in both tamoxifen- and anastrozole-treated patients in the ATAC study, and found that the presence of specific endocrine symptoms were predictive of a better response to endocrine therapy.[14]

The level of hormone receptor expression is possibly also predictive of response to endocrine therapy. Results from the TransATAC and TEAM trials showed that higher levels of estrogen receptor (ER) expression were beneficial in terms of longer time to relapse in both patients treated with aromatase inhibitors and tamoxifen; in highly hormone-sensitive patients AIs were more effective than tamoxifen.[19, 20] Quantitative hormone receptor expression may therefore be predictive of the occurrence of specific adverse effects related to the depletion of circulating estrogens, and thus influence treatment efficacy in patients treated with exemestane. We hypothesized that more specific AEs would be present in patients with higher levels of hormone receptor expression.

In the current investigation in postmenopausal hormone-sensitive breast cancer patients using exemestane therapy, we assessed the relationship between the occurrence and types of AEs and efficacy, as well as the association between specific AEs and quantitative ER and progesterone receptor (PR) expression based on the Allred score. For this purpose, data from hormone-receptor positive Dutch and Belgian early breast cancer patients treated with the steroidal aromatase inhibitor, exemestane, in the Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial was utilized.

MATERIALS AND METHODS

The TEAM trial is a randomized, phase 3, multinational, open label study conducted in postmenopausal women with ER and/or PR positive tumors who were eligible for adjuvant hormonal treatment. Patients were randomized to receive either exemestane 25 mg once-daily for five years or tamoxifen 20 mg once-daily for 2.5–3 years, followed by exemestane 25 mg once-daily for 2.5–2 years, for a total of five years.[21] Participants were enrolled in nine countries worldwide. The TEAM Trial protocol was approved by the regulatory and ethics authorities of all participating centers in all participating countries. The trial was registered in the Netherlands and Belgium with the Netherlands Trial Register, NTR 267. All patients provided written informed consent, and additional consent was obtained from patients in the tamoxifen group for the switch to exemestane. Details of eligibility criteria have been published in earlier reports.[21]

In the Netherlands and Belgium, 3167 patients were randomized in the TEAM study. 1584 patients were allocated to 5 years of exemestane. Patients randomized to the sequential treatment arm (tamoxifen to start with, n=1583) and patients who did not start randomized treatment (n=8) were excluded from the current analyses. Furthermore, patients who had an event (recurrence or death) (n=8) and/or discontinued the randomized therapy within six months of treatment initiation (n=94) were also excluded as patients had to fulfill the first six months of treatment in order to be included in the follow-up. All AEs reported in the first six months of starting adjuvant endocrine therapy were included in the analyses.

Data collection was performed by case report forms and transferred to the central data center in Leiden, the Netherlands. For almost all Dutch, and a subset of the Belgian patients, ER and PR expression on the tumor blocks were reviewed centrally in Edinburgh, United Kingdom, as has been reported by Bartlett and colleagues.[20] Quantitative ER and PR expression were evaluated as binary categories according to the Allred score, PR-poor ≤4 versus PR-rich ≥5; ER-poor ≤6 versus ER-rich ≥7.20 Only those patients whose ER and PR expression could be reviewed centrally were included in the analyses with quantitative HR expression. Patients with unknown ER Allred scores (n=212) or unknown PR Allred scores (n=231) were excluded.

Complete follow-up data was available for the first five years, and was carried out every 3 months in the first year, and twice yearly until year 5 (end of randomized therapy). All AEs were obtained from patient responses during follow-up visits, a symptom checklist was not utilized. Severity of AEs was assessed using the National Cancer Institute Common Toxicity Criteria, and were centrally recoded using the Medical Dictionary for Regulatory Activities (version 12.1).[21] HF was defined as a subjective and transient sensation of heat, including night sweats. MSAE included all accounts of arthralgia, arthritis, arthrosis and myalgia. For the current analysis, osteoporosis was not considered an MSAE. Due to the fact that both HF and MSAE are specifically related to the immediate decrease in concentration of circulating estrogens, the symptoms combined are referred to as 'specific' AEs. Specific AEs of all severities reported within the first 6 months of treatment were included in the analyses.

The endpoints of the current analyses were relapse free survival (RFS), overall survival (OS), and breast cancer-specific mortality (BCSM) starting as of six months after start of exemestane therapy. RFS was defined as the time on treatment to the earliest documentation of disease relapse (local or distant recurrence, contralateral breast cancer or death from breast cancer, as defined on the case report form), or end of follow-up (5 years). Breast cancer mortality was confirmed by medical record review and categorized into 1 of 10 pre-specified groups, and classification was verified by the TEAM central datacenter. If patients had distant metastases at the time of death, the cause of death was considered breast cancer-related.

Statistical analysis

Statistical analyses were performed using SPSS 17.0 (SPSS, Chicago, IL). Landmark analyses were conducted, with follow-up starting at 6 months after randomization. Kaplan-Meier curves were plotted for time-to-relapse. Cox Proportional Hazard Models with 95% confidence intervals (CI) were used to assess survival differences with respect to the presence or absence of HF or MSAE. Multivariate survival analyses were adjusted for age at diagnosis, tumor size, nodal status, histological grade, most extensive surgery, radiotherapy and chemotherapy. Interaction terms between HF and age, size, nodal status, histological grade, surgery, prior radiotherapy and prior chemotherapy, and between MSAE and age, size, nodal status, histological grade, surgery, prior radiotherapy and prior chemotherapy were incorporated in the Cox model to test for the presence of effect modification.

RESULTS

Study population

In total, 1485 exemestane patients were included. Median age was 63.7 years (range 44-93 years), and further patient characteristics are shown in Table 1. Supplementary Figure 1 portrays the reported treatment-related AEs within the predetermined 6-month period by age. Of note, the majority of patients did not report any AEs, while 39.3% of the patients reported any AE within the first six months of starting exemestane. Specific AEs were reported by 23.7% of the patients. Specific AEs were more frequently reported by younger patients (chi-squared $p<0.001$). The number of patients who discontinued exemestane because of AEs during the follow-up period (starting as of six months post-randomization) was 95 (6.4%). No difference was found in discontinuation rates between patients with and without HF. However, in the presence of MSAE, significantly more patients discontinued exemestane therapy than when no MSAE were experienced (18.9% versus 11.4%, $p=0.029$).

Adverse events and breast cancer recurrence

Characteristics of patients who reported specific AEs versus none or nonspecific AEs are shown in Table 2. Younger patients and patients who had also been treated with chemo- and/or radiotherapy generally reported more specific AEs.

Table 1. **Baseline characteristics in patients treated with exemestane**

Characteristic	n	%
Age (median, range)	(63.7)	*(44-93)*
Grade (BR)		
G1 (well)	219	14.7
G2 (moderate)	646	43.5
G3, G4 (poor)	528	35.6
unknown	92	6.2
Tumor stage		
T1 (≤2cm)	680	45.8
T2 (>2-≤5cm)	703	47.3
T3 / T4 (>5cm)	98	6.6
Tx/Tis	1	0.1
unknown	3	0.2
Nodal stage		
Positive	1043	70.2
Negative	442	29.8
ER status		
Positive	1459	98.2
Negative	25	1.7
Not performed	1	0.1
PR status		
Positive	1108	74.6
Negative	304	20.5
Not performed	73	4.9
Most extensive surgery		
Mastectomy	803	54.1
Wide local excision	681	45.9
No resection	1	0.1
Adjuvant radiotherapy		
Yes	983	66.2
No	501	33.7
Unknown	1	0.1
Adjuvant chemotherapy		
Yes	501	33.7
No	984	66.3

BR, Bloom & Richardson; ER, estrogen receptor; PR, progesterone receptor

Using univariate Cox regression analyses, the presence of HF versus no HF (with or without MSAE) was not significantly associated with a lower risk of disease relapse (21 versus 144 events), although the hazard ratio (HR) was much reduced (HR 0.704 (95% confidence interval (CI) 0.441-1.123); p=0.141) (Table 3). However, after correcting for age at diagnosis, histological grade, T-stage, nodal stage, ER and PR status, type of surgery, radiotherapy and chemotherapy in multivariate analyses, patients with HF showed a significantly lower risk of disease recurrence (HR 0.393 (95%CI 0.19-0.813); p=0.012) (Figure 1).

The presence of MSAE versus no MSAE (with or without HF) was not associated with a better RFS (15 versus 150 events), using both univariate and multivariate Cox regression analyses (HR 0.727 (95%CI 0.427-1.236);

p=0.239 and HR 0.677 (95% CI 0.392-1.169); p=0.162 respectively). No significant correlation was found between RFS and the severity of AEs.(Figure 1)

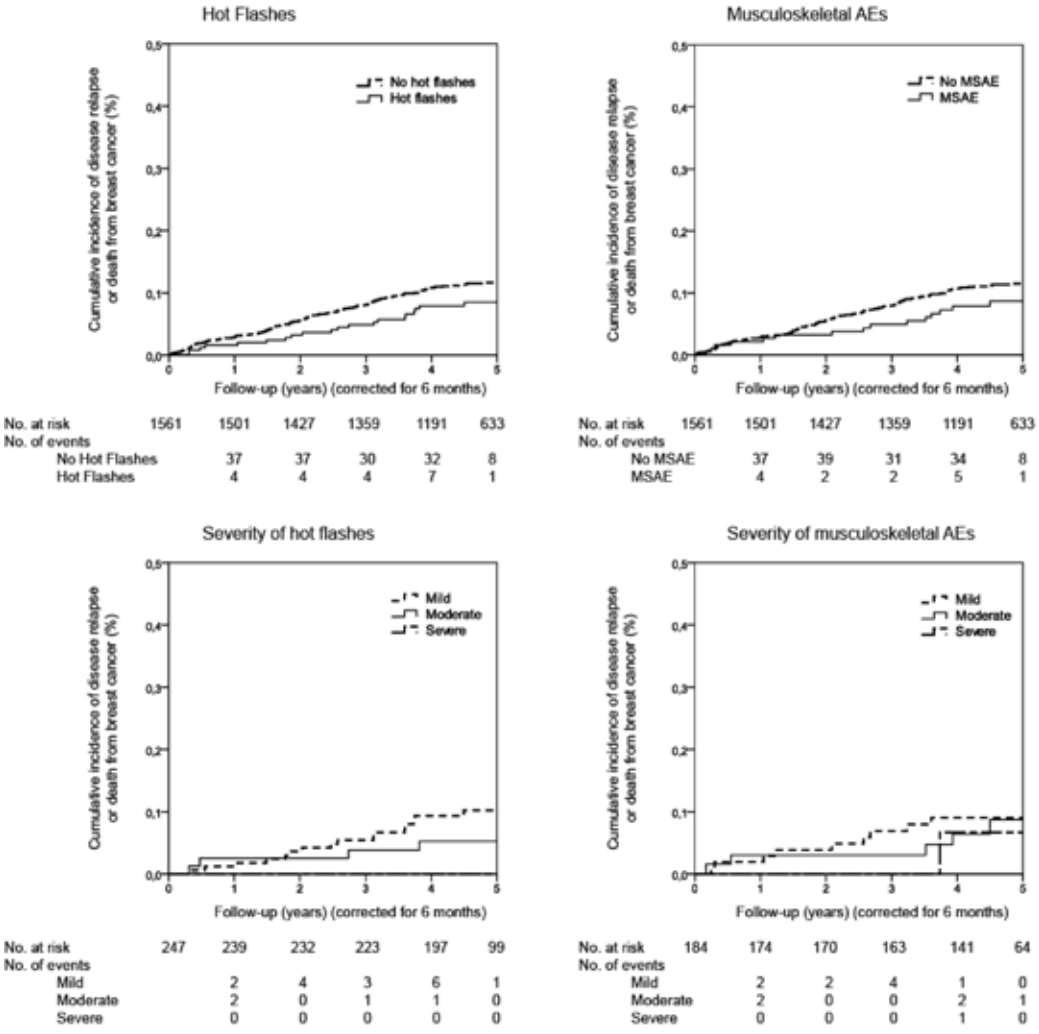
Patients who received chemotherapy reported HF and MSAE more frequently than patients not treated with chemotherapy: (HF, 20.2% versus 14.0%, p=0.002 and MSAE, 20.4% versus 7.6%, p<0.001) (Supplementary Table 1). Because earlier studies described a relationship between adjuvant chemotherapy and menopausal symptoms, we also tested for effect modification by chemotherapy, but this did not influence the relationship between specific AEs and survival (logrank p=0.688).

Table 2. **Characteristics of patients with and without specific adverse events**

	No or non-specific AEs		Specific AEs		
	n	%	n	%	p-value*
Age category					<0.001
<50	24	61.5	15	38.5	
50-59	313	66.9	155	33.1	
60-69	420	77.8	120	22.2	
≥70	376	85.8	62	14.2	
Grade (BR)					0.068
G1 (well)	182	83.1	37	16.9	
G2 (moderate)	483	74.8	163	25.2	
G3, G4 (poor)	396	75.0	132	25.0	
unknown	72	78.3	20	21.7	
Tumor stage					0.819
T1 (≤2cm)	517	76.0	163	24.0	
T2 (>2-≤5cm)	534	76.0	169	24.0	
T3 / T4 (>5cm)	79	80.6	19	19.4	
unknown	3	75.0	1	25.0	
Nodal stage					0.192
Positive	786	78.5	95	21.5	
Negative	347	75.4	257	24.6	
ER status					0.2
Positive	1114	76.4	345	23.6	
Negative	19	76.0	6	24.0	
not performed	0	0.0	1	100.0	
PR status					0.002
Positive	853	77.0	255	23.0	
Negative	237	78.0	67	22.0	
not performed	43	58.9	30	41.1	
Most extensive surgery					0.139
Mastectomy	620	77.2	183	22.8	
Wide local excision	513	75.3	168	24.7	
Adjuvant radiotherapy					0.015
Yes	731	74.4	252	25.6	
No	401	80.0	100	20.0	
Adjuvant chemotherapy					<0.001
Yes	332	66.3	169	33.7	
No	801	81.4	183	18.6	

AEs, adverse events; BR, Bloom&Richardson; ER, estrogen receptor; PR, progesterone receptor.
*Pearson chi-squared.

Figure 1. **Relation between adverse event and severity and relapse-free survival for hot flashes and musculoskeletal adverse events**

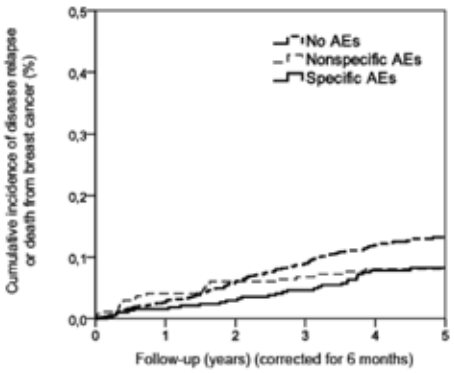


MSAE, musculoskeletal adverse events

When investigating the association between disease relapse and specific AEs (HF and/or MSAE) versus nonspecific (all other AEs) or no AEs, as reported within the first six months of exemestane treatment, we found that patients reporting specific AEs had a lower risk of disease relapse than patients who reported none or nonspecific AEs in the univariate analysis (Figure 2) (specific AEs: HR 0.608 (95%CI 0.404-0.914);

nonspecific AEs: HR 0.638 (95%CI 0.4-1.015); no AEs (ref); overall p=0.019). Even more so, multivariate analyses (correcting for the same variables as previously mentioned), also showed a significant correlation between specific AEs and better RFS (specific AEs: HR 0.559 (95%CI 0.368-0.849); nonspecific AEs: HR 0.583 (95%CI 0.365-0.931); no AEs (ref); overall p=0.005).

Figure 2. **Relapse-free survival for specific adverse events versus nonspecific or no adverse events**



No. at risk	1561	1500	1426	1358	1190	632
No. of events						
No AEs		24	31	26	25	8
Nonspecific AEs		11	5	2	3	0
Specific AEs		7	4	6	11	1

AEs, adverse events

We also investigated whether the trends were maintained when analyses were performed for OS and BCSM. There was a significant relationship between patients who reported specific AEs versus nonspecific or no AEs with respect to OS and BCSM.(Table 3) Assessed separately, however, neither HF nor MSAE was significantly associated with a better outcome for OS or BCSM.

During the follow-up period of the current analysis, 95 patients (6.4%) still discontinued exemestane treatment because of AEs (both specific and nonspecific). Most patients who discontinued exemestane due to toxicities reported no or nonspecific AEs (n=64, 67.4%). When looking at the group discontinuing therapy due to specific AEs, results were similar for patients experiencing HF only (n=13, 13.7%), MSAE only (n=11, 11.6%) or both HF and MSAE (n=7, 7.4%). Prior chemotherapy (yes/no) did not influence the results (chi-squared p=0.267).

Quantitative hormone receptor expression using Allred scores

Although PR and ER Allred scores were predictive of RFS based on earlier findings by Bartlett and colleagues[20], no association was found in our analysis between PR and ER Allred scores and the occurrence of specific versus nonspecific or no AEs (Supplementary Table 2), or with the occurrence of HF and/or MSAE separately (data not shown). Therefore, PR and ER Allred scores were not predictive of better RFS.

Table 3. **Relation between adverse events and outcomes**

Hot Flashes		Univariate HR* (95%CI)	p-value	Multivariate HR (95% CI)	p-value
RFS	Yes	0.704 (0.441-1.123)	0.141	0.393 (0.19-0.813)	0.012
	No	1 (ref)		1 (ref)	
OS	Yes	0.617 (0.388-0.982)	0.042	0.646 (0.404-1.034)	0.068
	No	1 (ref)		1 (ref)	
BCSM	Yes	0.681 (0.390-1.190)	0.177	0.703 (0.399-1.239)	0.223
	No	1 (ref)		1 (ref)	
Musculoskeletal AEs		**Univariate HR (95%CI)**	**p-value**	**Multivariate HR* (95% CI)**	**p-value**
RFS	Yes	0.727 (0.427-1.236)	0.239	0.677 (0.392-1.169)	0.162
	No	1 (ref)		1 (ref)	
OS	Yes	0.602 (0.349-1.038)	0.068	0.645 (0.369-1.125)	0.122
	No	1 (ref)		1 (ref)	
BCSM	Yes	0.772 (0.415-1.437)	0.415	0.586 (0.138-2.489)	0.469
	No	1 (ref)		1 (ref)	
Specific AEs		**Univariate HR (95%CI)**	**p-value**	**Multivariate HR* (95% CI)**	**p-value**
RFS	Specific AEs	0.608 (0.404-0.914)	0.019	0.559 (0.368-0.849)	0.005
	Nonspecific AEs	0.638 (0.4-1.015)		0.583 (0.365-0.931)	
	No AEs	1 (ref)		1 (ref)	
OS	Specific AEs	0.532 (0.356-0.795)	0.003	0.538 (0.357-0.811)	0.001
	Nonspecific AEs	0.656 (0.428-1.007)		0.570 (0.369-0.897)	
	No AEs	1 (ref)		1 (ref)	
BCSM	Specific AEs	0.576 (0.356-0.930)	0.009	0.573 (0.351-0.933)	0.004
	Nonspecific AEs	0.494 (0.28-0.871)		0.430 (0.244-0.788)	
	No AEs	1 (ref)		1 (ref)	

*HR, hazard ratio; RFS, relapse-free survival; OS, overall survival; BCSM, breast cancer-specific mortality; AEs, adverse events

DISCUSSION

This analysis in Belgian and Dutch patients participating in the TEAM trial and randomized to exemestane therapy investigated the relationship between the occurrence of specific AEs related to the depletion of (circulating) estrogens and RFS. Only AEs reported while on-treatment and occurring within six months of starting exemestane treatment were considered for the analyses, in order to ascertain that the AEs were attributed to the study medication.

In the cohort of exemestane treated patients, HF were strongly associated with improved RFS, while MSAE were not predictive of better RFS. Currently, we did not find any evidence from previous clinical studies that estrogen levels were correlated with improved survival in patients treated with aromatase inhibitors. Nevertheless, variations in circulating estrogens may occur due to polymorphisms in the aromatase gene in postmenopausal women.[10]

HF are a commonly reported toxicity of aromatase inhibitors, and are strongly related to the degree of lowered estrogen levels occurring both naturally during menopause, and artificially in relation to chemotherapy and with aromatase inhibitors for breast cancer.[13] MSAE include arthralgia, arthritis, arthrosis, myalgia, bone pain and joint disorders, and are also frequently prevalent in postmenopausal patients. The mechanism behind MSAE is relatively unknown, although several studies have also demonstrated an association with decreased estrogen levels.[12, 22] Felson and colleagues reported that estrogen has antinociceptive effects and that the depletion of circulating estrogens influences the sensitivity to pain in articular structures.[12] It is also suggested that lowered estrogen levels increase levels of pro-inflammatory cytokines.[23] The inflammation of joints subsequently gives rise to increased levels of prostaglandins and bradykinin, thereby activating receptors on peripheral nociceptors and enhancing their sensitivity to pain.[12] We could not demonstrate an association between the presence of MSAE and treatment efficacy, although there is some evidence in support of this hypothesis.

MSAE and HF may both be associated with decreased estrogen levels, and may thus be valuable biomarkers for treatment efficacy. Our study's finding that patients on exemestane therapy who reported specific AEs had a lower risk of disease recurrence is supported by Cuzick et al. in a previous study.[14] In contrast, however, Cuzick et al. found an association between breast cancer recurrence and both vasomotor and joint symptoms, with the presence of MSAE being more predictive of RFS than HF, the latter not being in accordance with our data. Nevertheless, a trend showing a better RFS in our patients with MSAE was seen. Of note, we assessed MSAE arising in the first 6 months of treatment, and results might be different when MSAE occurring over the full duration of the follow-up period were included. Cuzick et al. investigated patients who had been treated with either an aromatase inhibitor or tamoxifen; as we investigated a subgroup of the patients randomized to exemestane in the TEAM trial, this may lead to some degree of selection bias, although baseline characteristics and adverse events reported did not differ between the two randomized treatment groups (data not shown).
The effect of chemotherapy on the relationship between specific AEs and survival is difficult to assess due to

possible confounders such as age and disease stage. Our findings revealed that patients who have previously been treated with adjuvant chemotherapy reported more MSAE and HF than patients who did not undergo prior chemotherapy. It is well-known that chemotherapy is correlated with more menopausal symptoms[24], and for this reason our analyses were adjusted for prior chemotherapy. With respect to MSAE, a relationship has also been found between plasma levels of inflammatory cytokines and musculoskeletal symptoms in breast cancer patients undergoing paclitaxel chemotherapy in a previous study.[25] However, this study only investigated short-term symptoms, while evidence is relatively lacking with respect to late-onset musculoskeletal symptoms in patients who received prior chemotherapy. Nevertheless, it is plausible to assume a relationship with the prolonged suppression of circulating estrogens, and subsequent increases in nociception and circulating inflammatory cytokines.[12, 23]

All patients who were treated and event-free for at least six months were included in the analyses. The number of patients who discontinued treatment during the follow-up period was similar for both HF and MSAE or both, and lower than previously reported. Noncompliance is known to be similar in patients treated with AIs, tamoxifen, or a sequence of both, and can be as high as 50%.[26] These high rates are largely attributable to the presence and severity of adverse effects.[26] As such, if RFS is superior in patients who experience specific AEs, but who are also at greatest risk of noncompliance, there is a clinically relevant paradox that those patients who may potentially derive most benefit from adjuvant endocrine treatment have a significant risk of disease relapse because of treatment discontinuation. The absence of a relationship between MSAE on RFS may therefore be explained by the fact that patients experiencing MSAE discontinued treatment early, whereas this did not occur for patients with HF. When dealing with AEs, it is therefore important to ask patients specifically about their symptoms, as not all patients will report toxicities spontaneously, and may not link their complaints with the study medication. The absence of checklists for complaints in the TEAM study may have led to some degree of under-reporting of AEs in this trial. Nonetheless, in clinical practice it is important to effectively inform and warn patients of possible toxicities. In addition, treatment compliance should be actively promoted by all health care providers in order to optimize treatment.

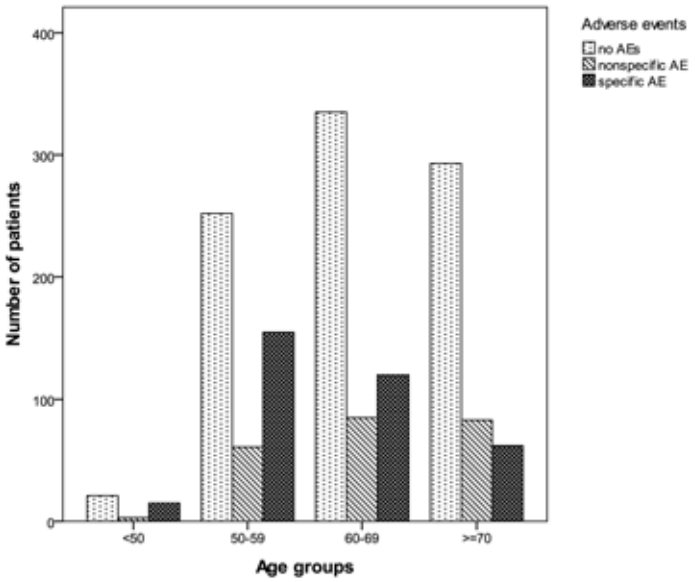
There was no correlation with the occurrence of specific AEs in patients with PR- or ER-rich tumors in our analyses. It is suggested that in the presence of any level of ER, tumors expressing high levels of PR increase the benefit of endocrine treatment, and consequently patients may encounter more specific side effects.[27] However, we could not confirm these findings with the current data.

Patients using adjuvant AIs who experience specific AEs may have a better RFS than patients without these specific AEs. However, not all patients undergoing endocrine treatment for breast cancer experience specific AEs, and therefore, individual genetic factors may also play a role in the response to therapy and the emergence of specific AE based on differences in drug metabolism. The most logical explanation would be that these specific AEs act as a surrogate marker for estrogen depletion and thus treatment efficacy. The aromatase enzyme is the most prominent candidate enzyme. It is encoded by the CYP19A1 gene and is involved in the

peripheral conversion of androgens to estrogens.[28] Several reports suggest that variations in CYP19A1 may influence AI treatment efficacy and also the incidence of specific AEs in hormone-positive early breast cancer patients, although this requires further investigation.[10, 22]

To conclude, although these results are hypothesis-generating, our findings suggest that the side effects caused specifically by the depletion of estrogens predict a better outcome and may thus act as a valuable biomarker in AI treatment. Future studies on biomarkers predictive of treatment outcome are eagerly warranted, eventually aiming at further personalization of therapy.

Supplementary Figure 1. **Adverse events occurring within 6 months in patients treated with Exemestane by age**



	No AEs		Nonspecific AEs		Specific AEs					
	N	%	N	%	HF	%	MSAE	%	Both	%
<50	21	*0.54*	3	*7.7*	6	*15.4*	5	*12.8*	4	*10.3*
50-59	252	*0.54*	61	*13.0*	62	*13.2*	62	*13.2*	31	*6.6*
60-69	335	*0.62*	85	*15.7*	71	*13.1*	29	*5.4*	20	*3.7*
≥70	293	*0.67*	83	*18.9*	36	*8.2*	17	*3.9*	9	*2.1*

Supplementary Table 1. **Relationship between prior chemotherapy and hot flashes and musculoskeletal adverse events**

	Chemotherapy		No Chemotherapy		
	n	%	n	%	p-value*
Hot flashes	101	20.2	138	14.0	0.002
No hot flashes	400	79.8	846	86.0	
MSAE	102	20.4	75	7.6	<0.001
No MSAE	399	79.6	909	92.4	

*Pearson chi-squared; MSAE, musculoskeletal adverse events

Supplementary Table 2. **Adverse events according to PR and ER Allred score**

	Specific AEs		Nonspecific AEs		No AEs		
	n	%	n	%	n	%	p-value*
PR-rich	214	22.2	149	15.5	601	62.3	0.563
PR-poor	56	19.3	45	15.5	189	65.2	
ER-rich	248	21.9	177	15.6	706	62.4	0.926
ER-poor	30	21.1	21	14.8	91	64.1	

*Pearson chi-squared; AEs, adverse events

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CHAPTER

11

SPECIFIC ADVERSE EVENTS PREDICT SURVIVAL BENEFIT IN PATIENTS TREATED WITH TAMOXIFEN OR AROMATASE INHIBITORS – AN INTERNATIONAL TEAM TRIAL ANALYSIS

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ABSTRACT

Introduction

Specific adverse events (AEs) associated with endocrine therapy and related to depletion or blocking of circulating estrogens may be related to treatment efficacy. We investigated the relationship between survival outcomes and specific AEs including vasomotor symptoms (VMS), musculoskeletal adverse events (MSAE) and vulvovaginal symptoms (VVS) in postmenopausal breast cancer patients participating in the international Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial.

Methods

Primary efficacy endpoints were disease-free survival (DFS), overall survival (OS) and distant metastases (DM). VMS, MSAE and VVS arising in the first year of endocrine treatment were considered. Patients who did not start or who discontinued their allocated therapy and/or had an event (recurrence/death) within one year after randomization were excluded. Landmark analyses and time-dependent multivariate Cox proportional hazards models assessed survival differences up to five years from the start of treatment.

Results

9325 patients were included. Patients with specific AEs (versus nonspecific or no AEs) had better DFS and OS (multivariate hazard ratio (HR) (95% confidence interval (CI)) for DFS: VMS 0.731 (0.618-0.866); MSAE 0.826 (0.694-0.982); VVS 0.769 (0.585-1.01); multivariate HR (95%CI) for OS: VMS 0.583 (0.424-0.803); MSAE 0.811 (0.654-1.005); VVS 0.570 (0.391-0.831)) and fewer DM (VMS 0.813 (0.664-0.996); MSAE 0.749 (0.601-0.934); VVS 0.687 (0.436-1.085)) than patients not reporting these symptoms. Increasing numbers of specific AEs were also associated with better survival outcomes. Outcomes were unrelated to treatment allocation.

Discussion

Certain specific AEs are associated with superior survival outcomes, and may therefore be useful in predicting treatment responses in breast cancer patients treated with endocrine therapy.

INTRODUCTION

Since the 1980s, adjuvant endocrine therapy by means of tamoxifen, a selective estrogen receptor modulator, has been a beneficial agent for breast cancer patients, being most effective in hormone-sensitive breast cancer.[1, 2] Later, five years of tamoxifen therapy became the gold standard for adjuvant endocrine treatment. Over the last 15 years, several studies have been performed to assess the value of third-generation aromatase inhibitors, showing benefit in terms of overall survival (OS), disease-free survival (DFS), distant disease-free survival and contralateral breast cancer (CBC) recurrence in postmenopausal breast cancer patients with hormone receptor positive disease when compared with tamoxifen.[3-5] Other studies showed beneficial effects of a sequential treatment regimen consisting of 2-3 years of tamoxifen followed by 2-3 years of an aromatase inhibitor when compared with tamoxifen alone.[3, 4, 6, 7]

Both tamoxifen and aromatase inhibitors are associated with inconvenient and sometimes debilitating adverse effects resembling menopausal symptoms, and which may be related to lower levels of peripherally circulating estrogens or the blocking of the estrogen receptor (ER) in particular tissues, depending on the type of endocrine therapy used.[8-11] Some relevant and commonly reported adverse events (AEs) associated with adjuvant endocrine therapy for early breast cancer comprise vasomotor symptoms (VMS), musculoskeletal and joint symptoms (MSAE), and vulvovaginal symptoms (VVS). After menopause, estrogen production is derived from peripheral tissues including adipose tissue, muscle, liver, skin, brain, bone marrow and breast tissue.[12, 13] VMS are a well-known side effect of estrogen deprivation, occurring both naturally during menopause and artificially in relation to chemotherapy and endocrine therapy administered in early breast cancer patients.[11] Estrogen is considered a factor that affects temperature regulation by promoting vasodilation, which influences blood flow to the skin.[14] Through decreased estrogen levels associated with endocrine therapy, the body lacks the ability to maintain normal body temperatures.[15] Estrogen deprivation has also been linked to the development of MSAE in patients on endocrine therapy.[9] Estrogen has antinociceptive effects that influence the body's sensitivity to pain in articular structures as well as increased levels of pro-inflammatory cytokines, which is thought to be associated with MSAE.[9, 16] With respect to VVS, aromatase inhibitors (further) lower postmenopausal estrogen levels, causing vaginal atrophy, and possibly resulting in vaginal dryness and dyspareunia.[17, 18] Tamoxifen, on the other hand, has known agonist effects on the uterus.[19, 20]

Adverse effects during long-term treatment can significantly impact quality of life as well as treatment compliance. Earlier studies on adjuvant breast cancer therapy recognized that non-compliance is largely attributable to the presence of adverse effects.[21-25] Furthermore, treatment outcomes can be compromised when adjuvant endocrine treatment is not taken for the full prescribed duration.[26]

In earlier reports, the relationship between VMS as well as MSAE and breast cancer recurrence in patients treated with adjuvant endocrine therapy was investigated.[27, 28] The presence of both symptoms was predictive of fewer breast cancer recurrences. Recently, we reported results of Dutch and Belgian patients treated with exemestane alone, and found a significant relapse-free survival (RFS) benefit in patients who

reported VMS and MSAE.[29] Similarly, a recent investigation by Huober and colleagues in the BIG 1-98 trial found associations between arthralgia, myalgia and vasomotor symptoms and improved DFS.[30] Stearns and colleagues, however, also investigated the association between endocrine symptoms and RFS in the MA.27 trial, but did not find a benefit in patients who reported VMS and/or MSAE.[31] Another issue is that patients treated with either tamoxifen or aromatase inhibitors commonly complain of VVS. Vaginal dryness was addressed in the study by Huober et al., which was considered a VVS. To the author's knowledge, no other reports exist on the relationship between VVS and breast cancer recurrence.

In the present analysis, we investigated the relationship between specific AEs (VMS, MSAE and VVS) arising in the first year of endocrine therapy and treatment efficacy in postmenopausal early breast cancer patients enrolled in the Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial. In addition, the influence of early treatment discontinuation within the five-year treatment period in relation to outcome in patients with and without specific AEs was assessed.

MATERIALS AND METHODS

TEAM trial

The TEAM trial is a randomized, phase 3, multinational, open label study conducted in postmenopausal women with ER and/or PR positive breast cancer and who were eligible for adjuvant endocrine treatment. Patients were randomized to receive either exemestane 25mg once-daily for five years or tamoxifen 20mg once-daily for 2.5-3 years, followed by exemestane 25mg once-daily for 2.5-2 years (sequential regimen).[6] Participants were enrolled in 599 hospitals in nine countries worldwide (Belgium, France, Germany, Greece, Japan, the Netherlands, UK and Ireland, and the USA.6 Similar trial protocols were used in all countries, with minor differences to accommodate the regional treatment guidelines; the TEAM trial protocols were approved by the regulatory and ethics authorities of all participating centers in all participating countries.[6] All patients provided written informed consent, and additional consent was obtained from patients using tamoxifen for the switch to exemestane. The study was conducted in compliance with the guidelines of the Declaration of Helsinki, International Conference on Harmonisation and Good Clinical Practice. Appropriate approvals from the ethical committee were obtained.[6] Data collection was performed locally by case report forms and regularly transferred to a local data center, after which the Central Statistical and Data Center collected and analyzed the pooled data. Follow-up was carried out every three months in the first year, and twice yearly until year 5 (end of randomized therapy), with yearly mammography. Details of eligibility criteria have been published in earlier reports.[6]

In the TEAM trial, 9766 patients were allocated to five years of exemestane or to a sequential treatment with tamoxifen followed by exemestane for a total of five years in the TEAM trial. For the current analyses,

we excluded patients who did not start the randomized treatment, who discontinued their allocated therapy within the first year, or who had an event (recurrence or death) within the first year of starting endocrine therapy.

Adverse events

All AEs reported in the first year of starting adjuvant endocrine therapy were included in the analyses. AEs were obtained from patient responses during follow-up visits, and a standard symptom checklist was not utilized. Severity of AEs was assessed using the National Cancer Institute Common Toxicity Criteria, and were centrally recoded using the Medical Dictionary for Regulatory Activities (version 12.1).[6] VMS were defined as a subjective and transient sensation of heat, including hot flashes and night sweats. MSAE were all accounts of arthralgia, arthritis, arthrosis, myalgia and bone pain. For the current analysis, osteoporosis was not considered a MSAE due to the fact that osteoporosis is a long-term process, likely to take more than 1 year to become evident. VVS included all accounts of vaginal dryness/itching, vaginal discharge, dyspareunia, endometrial and libido disorders.

Endpoints

The efficacy endpoints of the present investigation were DFS, OS, and distant metastases (DM), starting as of the second year of therapy. DM comprised all cases of metastases of the skeleton, skin, liver, lung, brain, and contralateral lymph nodes, and excluded locoregional recurrences (including ipsilateral breast cancer, ipsilateral lymph nodes, ipsilateral chest wall recurrences), CBC and new primary tumors. DFS was defined as the time on-treatment to the earliest documentation of disease relapse or death (all-causes) or end of follow-up, whichever came first. OS was defined as the time on-treatment to the date of death.

The relationship between the occurrence of specific AEs (VMS, MSAE and VVS) and survival and recurrence outcomes was assessed. Furthermore, we evaluated the relationship between outcome measures and the sum of the different kinds of specific AEs reported per patient.

Statistical analysis

Statistical analyses were performed using SPSS 17.0 (SPSS, Chicago, IL). It was possible to combine the patients in the two treatment groups, as the primary efficacy analysis found no differences in outcome between the two treatment arms.[6] Landmark analyses were conducted, with follow-up starting at one year after randomization. Accounts of specific AEs reported in the first year after randomization were used to classify patients into the yes/no cohorts for VMS, MSAE and VVS. Kaplan-Meier curves were plotted for time-to-event. Early treatment discontinuation is an important factor in patients who experience AEs of endocrine treatment, as shorter time on-treatment may negatively influence outcomes.[26] Multivariate time-dependent Cox Proportional Hazards Models with specific adverse event (yes/no), on-treatment (yes/no), and their interaction assessed differences in survival with respect to the presence or absence of VMS, MSAE and VVS, in relation to time on-treatment. All multivariate analyses were adjusted for age at diagnosis,

country, histological grade, tumor size, nodal stage, most extensive surgery, radiotherapy and chemotherapy. Interaction terms between the AEs and all abovementioned adjusted variables were incorporated in the Cox model to test for the presence of effect modification.

RESULTS

Study population

In total, 9325 patients (95%) were included in the current analyses; reasons for exclusion are shown in Figure 1. We excluded patients who never started treatment or who had an unknown start date (n=93), and patients who discontinued their allocated therapy (n=174) or who had an event (recurrence or death) within the first year of treatment (n=174). 4694 patients were allocated to receive 5 years of exemestane and 4631 patients were allocated to receive the sequential treatment regimen. Median follow-up was 5.13 years (range 0.01 – 9.23 years), and median age was 63.8 years (range 34.9 – 96.1 years). Baseline characteristics were similar between the two treatment groups.[6]

Figure 1. **Patients included in the analyses of adverse events and breast cancer outcomes**

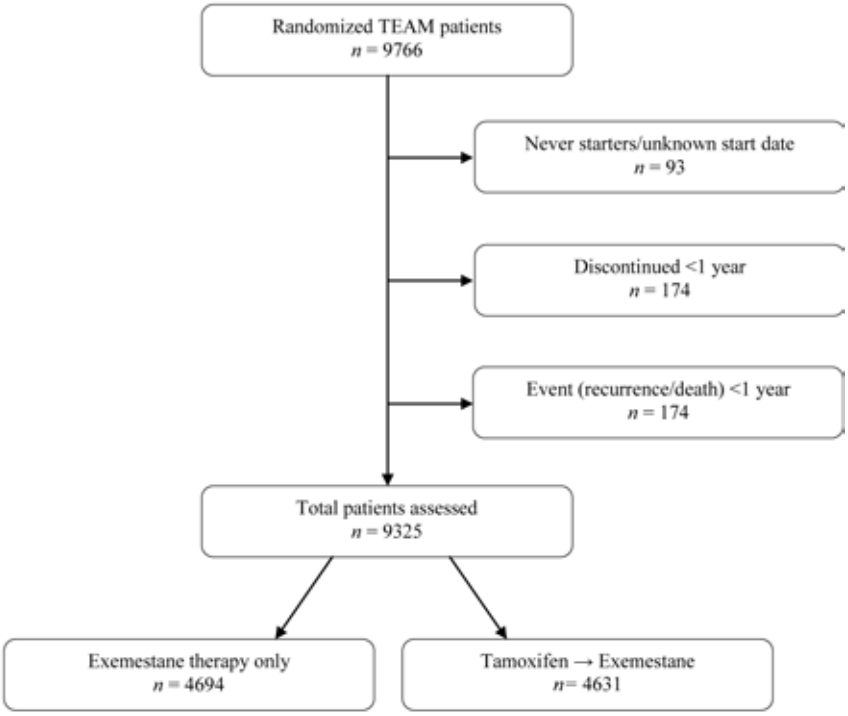


Table 1. **Baseline characteristics for specific versus none or nonspecific adverse events**

	None or non-specific AEs		Specific AEs		
	n	%	n	%	p-value
Age (median, range)	(65.5)	(34.9-92.5)	(62.1)	(35.8-96.1)	
Randomized treatment					0.270
Exe	2389	50.9	2305	49.8	
Tam → Exe	2304	49.1	2327	50.2	
Age at diagnosis					<0.001
<60	1352	28.8	1823	40.5	
60-69	1778	37.9	1789	38.6	
≥70	1563	33.3	970	20.9	
Grade (BR)					<0.001
G1 (well)	713	15.2	888	19.2	
G2 (moderate)	2339	49.8	2262	48.8	
G3, G4 (poor)	1276	27.2	1034	22.3	
unknown (Gx)	365	7.8	448	9.7	
Tumor stage					<0.001
T1 (≤2cm)	2519	53.7	2974	64.2	
T2 (>2-≤5cm)	1906	40.6	1478	31.9	
T3 / T4 (>5cm)	257	5.5	168	3.6	
Tx/Tis	3	0.1	3	0.1	
unknown	8	0.2	9	0.2	
Nodal stage					<0.001
Negative	2223	47.4	2704	58.4	
Positive	2470	52.6	1928	41.6	
ER status					0.195
Positive	4606	98.1	4558	98.4	
Negative	87	1.9	72	1.6	
not performed	0	0	2	0	
PR status					<0.001
Positive	3412	72.7	3578	77.2	
Negative	825	17.6	796	17.2	
not performed	456	9.7	258	5.6	
Most extensive surgery					<0.001
Mastectomy	2170	46.2	1921	41.5	
Breast-conserving surgery	2519	53.7	2707	58.4	
No resection/unknown	4	0.1	4	0.1	
Adjuvant radiotherapy					<0.001
Yes	3139	67.4	3298	72.0	
No	1521	32.6	1284	28.0	
unknown					
Adjuvant chemotherapy					<0.001
Yes	1466	31.3	1890	40.8	
No	3223	68.7	2742	59.2	

BR, Bloom & Richardson; ER, estrogen receptor; PR, progesterone receptor

Baseline characteristics of the patients who reported specific AEs versus none or nonspecific AEs are shown in Table 1. Overall, there was no difference in the presence of specific versus none or nonspecific AEs between randomized treatments. Assessed separately, patients allocated sequential treatment reported fewer VMS and MSAE, but more VVS (chi-squared p-value<0.001 for all comparisons). Younger patients were more likely to report specific AEs, while older patients were more likely to report nonspecific AEs (<60/60-<75/≥75 years: 16.3%/22.2%/31.5% nonspecific AEs reported respectively). In addition, patients who reported specific AEs more frequently had well-differentiated and low-grade tumors, node-negative disease, underwent breast-conserving surgery, and had adjuvant radiotherapy and chemotherapy when compared with patients who did not report specific AEs. Within the first year of treatment, 3003 patients (32.2%) reported VMS (with or without other specific or nonspecific adverse effects), 2635 patients reported MSAE (28.3%) and 1150 patients reported VVS (12.3%).

Disease-free survival

DFS outcomes are depicted in Table 2 and Figure 2. Using both univariate and multivariate Cox regression analyses (adjusted for age at diagnosis, country, histological grade, tumor size, nodal stage, most extensive surgery, radiotherapy and chemotherapy), patients who reported VMS or MSAE had a better DFS than those who did not report these symptoms (multivariate hazard ratio (HR) for VMS: 0.731 ((95% confidence interval (CI) 0.618-0.866); MSAE: 0.826 (95%CI 0.694-0.982)). DFS was significantly better in patients who reported VVS after univariate analyses, and borderline significant following multivariate analyses (univariate HR 0.566 (95%CI 0.437-0.733); multivariate HR 0.769 (95%CI 0.585-1.01)).

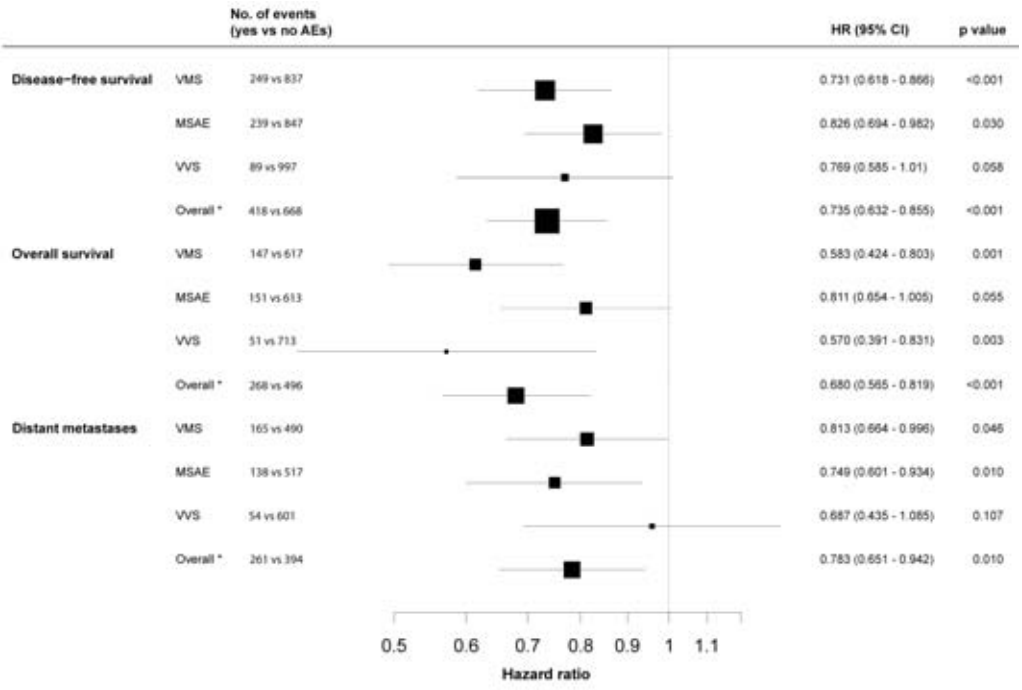
Overall survival

Figure 2 shows OS outcomes for VMS, MSAE and VVS respectively. Both univariate and multivariate Cox regression analyses showed that patients who reported VMS or VVS had better outcomes in terms of OS than those who did not report these symptoms (multivariate HR for VMS: 0.583 (95%CI 0.424-0.803); for VVS: 0.570 (95%CI 0.391-0.831)). There was a borderline significance for improved OS with respect to MSAE versus no MSAE after multivariate analyses (multivariate HR 0.811 (95%CI 0.654-1.005)). (Table 2)

Distant metastases

Further investigations into the occurrence of VMS and MSAE in relation to DM revealed that patients who reported these symptoms had fewer accounts of DM than when these symptoms were not reported (for VMS, multivariate HR 0.813 (95%CI 0.664-0.996); MSAE 0.749 (95%CI 0.601-0.934)). VVS were associated with significantly fewer DM following univariate analyses, but not for multivariate analyses. (Table 2) There was no effect modification for treatment discontinuation and the risk of DM for VMS, MSAE and VVS.(Table 2)

Figure 2. **Outcomes for disease-free survival, overall survival and distant metastases in relation to specific adverse events**



*Overall outcomes for VMS, MSAE and VVS combined. HR: Hazard ratio; VMS: vasomotor symptoms; MSAE: musculoskeletal adverse events; VVS: vulvovaginal symptoms
Multivariate Cox regression analyses were adjusted for age, country, histological grade, tumor size, nodal stage, most extensive surgery, radiotherapy and chemotherapy. There were no significant interactions between specific adverse events and the relevant covariates.

Table 2. **Survival outcomes and distant metastases for vasomotor symptoms, musculoskeletal adverse events and vulvovaginal symptoms**

Disease-free survival		Univariate HR (95%CI)	p-value	Multivariate HR* (95% CI)	p-value	Interaction AE and time on-treatment
Vasomotor symptoms	Yes	0.591 (0.502-0.697)	<0.001	0.731 (0.618-0.866)	<0.001	p=0.398
	No	1 (ref)		1 (ref)		
Musculoskeletal AEs	Yes	0.678 (0.575-0.80)	<0.001	0.826 (0.694-0.982)	0.030	p=0.233
	No	1 (ref)		1 (ref)		
Vulvovaginal symptoms	Yes	0.566 (0.437-0.733)	<0.001	0.769 (0.585-1.01)	0.058	p=0.134
	No	1 (ref)		1 (ref)		
Overall survival						
Vasomotor symptoms	Yes	0.460 (0.372-0.570)	<0.001	0.583 (0.424-0.803)	0.001	p=0.19
	No	1 (ref)		1 (ref)		
Musculoskeletal AEs	Yes	0.621 (0.506-0.762)	<0.001	0.811 (0.654-1.005)	0.055	p=0.802
	No	1 (ref)		1 (ref)		
Vulvovaginal symptoms	Yes	0.40 (0.279-0.575)	<0.001	0.570 (0.391-0.831)	0.003	p=0.016
	No	1 (ref)		1 (ref)		
Distant metastases						
Vasomotor symptoms	Yes	0.664 (0.545-0.809)	<0.001	0.813 (0.664-0.996)	0.046	p=0.183
	No	1 (ref)		1 (ref)		
Musculoskeletal AEs	Yes	0.615 (0.498-0.760)	<0.001	0.749 (0.601-0.934)	0.010	p=0.063
	No	1 (ref)		1 (ref)		
Vulvovaginal symptoms	Yes	0.639 (0.471-0.866)	0.004	0.687 (0.435-1.085)	0.107	p=0.870
	No	1 (ref)		1 (ref)		

HR, hazard ratio; CI, confidence interval; AEs adverse events.
*Multivariate analyses were adjusted for age, country, histological grade, tumor size, nodal stage, most extensive surgery, radiotherapy and chemotherapy

Early Treatment discontinuation

Time-dependent Cox regression analyses were performed to investigate the relationship between time on-treatment and survival outcomes. Pertaining to VMS and MSAE, treatment discontinuation did not affect the improved DFS and OS in patients who reported these specific AEs. Therefore, even if patients discontinued treatment before the pre-designated stop-date (which was five years after the start of randomized therapy), a survival benefit persisted in those who reported specific AEs. This was also the case for DFS in relation to VVS, but not for OS (p for interaction=0.016).(Table 2)

Sum of specific adverse events

A patient could have a maximum of 3 types of specific AEs, which was the sum of VMS, MSAE and VVS (yes/no outcome). Improved outcomes for DFS, OS and DM were found for increasing numbers of specific AEs reported.(Table 3/Figure 3)

Figure 3. **Outcomes for disease-free survival, overall survival and distant metastases based on the number of specific adverse events reported**

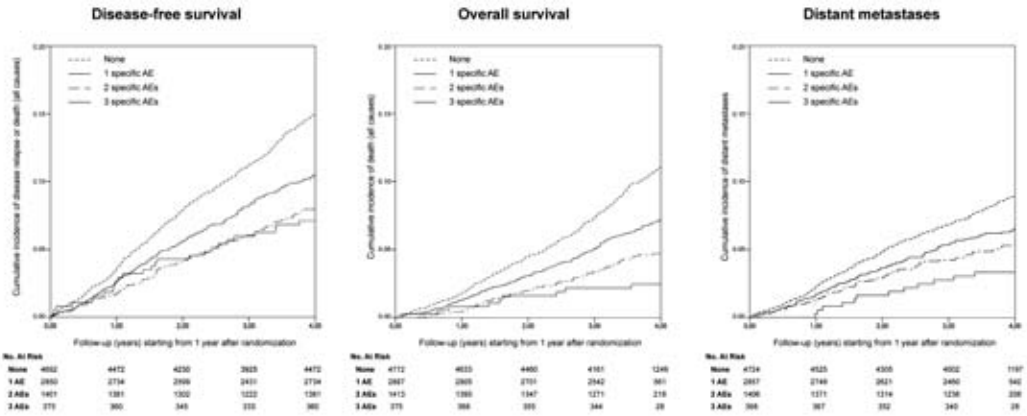


Table 3. **Outcome based on the number of specific adverse events reported**

Disease-free survival		N	Univariate HR (95%CI)	p-value	Multivariate HR* (95% CI)	p-value
No. of specific AEs	0	4658	1 (ref)	<0.001	1 (ref)	0.001
	1	2825	0.647 (0.551-0.760)		0.769 (0.651-0.909)	
	2	1384	0.501 (0.396-0.634)		0.668 (0.522-0.853)	
	3	373	0.432 (0.273-0.683)		0.624 (0.388-1.004)	
Overall survival						
No. of specific AEs	0	4740	1 (ref)	<0.001	1 (ref)	<0.001
	1	2862	0.587 (0.483-0.713)		0.744 (0.608-0.910)	
	2	1402	0.405 (0.299-0.548)		0.579 (0.423-0.794)	
	3	374	0.189 (0.084-0.423)		0.296 (0.130-0.673)	
Distant metastases						
No. of specific AEs	0	4689	1 (ref)	<0.001	1 (ref)	0.049
	1	2832	0.694 (0.57-0.845)		0.805 (0.657-0.987)	
	2	1389	0.554 (0.417-0.734)		0.762 (0.568-1.024)	
	3	374	0.358 (0.191-0.672)		0.563 (0.294-1.079)	

HR hazard ratio; AEs adverse events; * Multivariate analyses were adjusted for age, country, histological grade, tumor size, nodal stage, most extensive surgery, radiotherapy and chemotherapy

Adjuvant chemotherapy in relation to specific adverse events

Patients who received adjuvant chemotherapy more frequently reported specific AEs when compared with patients who had not been treated with adjuvant chemotherapy (56.3% versus 43.7%, p<0.001). There is a known relationship between adjuvant chemotherapy and menopausal symptoms, although the relation with late-onset symptoms has not been fully investigated[32] We tested for effect modification by chemotherapy for VMS and VVS and MSAE. No effect could be demonstrated (data not shown).

DISCUSSION

The present analyses showed that postmenopausal breast cancer patients who received at least one year of adjuvant endocrine therapy and who reported one or more treatment-related AEs during the first year of treatment had better subsequent outcomes in terms of DFS and OS, and fewer DM than patients who do not report these symptoms. The strongest effect on distant recurrence and survival outcomes was observed for VMS. A decreasing incidence of DM, disease relapse and death was noted in patients reporting increasing numbers of different specific AEs. Furthermore, even if patients who reported specific AEs were not on-treatment for the full duration, they still had better outcomes than patients who were on-treatment for longer, but did not experience specific AEs. No difference in effect was found between the two TEAM trial treatment arms.

The present investigation only included patients who reported symptoms in the first year of endocrine therapy. Due to the unplanned nature of these analyses, pre-existing symptoms were not recorded. The effect observed may therefore be larger when the occurrence of specific AEs over the entire follow-up period is considered. Reporting of AEs may not be uniform across countries or study centers within countries, therefore it is conceivable that results may be influenced by reporting bias. The incidence of reported specific AEs varied considerably by country and survival outcomes were better in countries where more specific AEs were reported (Supplementary Table 1). These results must be interpreted with caution, as no information was available for individual study centers. All AEs were patient-reported AEs and no standardized symptom checklist was utilized. Cultural differences between countries may therefore also reflect differences in reporting of AEs. A symptom checklist that actively inquires about a patient's symptoms and severity thereof will undoubtedly lead to a more accurate assessment and potentially observe a stronger relationship between specific AEs, severity, and improved outcomes. Also of note, characteristics of patients reporting specific versus no or nonspecific AEs revealed that patients with specific AEs were younger, more frequently had lower-grade tumors, node-negative disease, underwent breast-conserving surgery and adjuvant radiotherapy and chemotherapy. Although it is conceivable that older patients may be less likely than younger patients to report any AE at all, older patients reported more nonspecific AEs than younger patients in our cohort. Nonetheless, even after adjusting for these possible confounders, the correlation between specific AEs and superior outcomes was still present.

Previously, a relationship was found between VMS and MSAE and disease recurrence in breast cancer patients participating in the ATAC trial[27], and between hot flashes and outcomes in tamoxifen-treated patients in a study by Mortimer and colleagues.[28] Our earlier manuscript regarding Dutch and Belgian exemestane users reports a relationship between MSAE and VMS and disease recurrence.[29] In the current analyses, we aimed to assess whether results varied in a much more heterogeneous population. Minor variations in protocols between countries accommodated regional treatment guidelines. Additionally, in the context of cultural differences between countries, variations in reporting may exist. Most importantly, however, we address time on-treatment in relation to the occurrence of AEs. In contrast to what is generally

expected, Cuzick and colleagues noted a better treatment adherence in patients experiencing vasomotor and joint symptoms. Yet noncompliance resulting from side effects plays an important role in adjuvant endocrine therapy for postmenopausal, hormone receptor-positive breast cancer patients, and several studies have reported that patients who discontinue treatment before the pre-designated end-date do so largely because of AEs[21-25] Patients who discontinue the prescribed treatment regimen may not enjoy the full benefit of treatment due to shorter time on-treatment.[26] Pritchard sharply points out that the reporting of AEs may depend on the kind of patient who reports these symptoms; this may be related to treatment compliance, which would hence explain improved treatment outcomes in these patients.[33] Similarly, patients who do not report specific AEs may not have taken the prescribed treatment. Therefore, we performed a time-dependent Cox regression analysis for time on- and off-treatment. The positive effect of specific AEs on outcomes did not change for patients who went off-treatment. Accordingly, even if patients who experience specific AEs discontinued treatment before the designated stop-date, they still had a survival benefit over patients who did not experience specific AEs.

Although our results must be considered hypothesis generating, our findings show an association between specific side effects caused by endocrine therapy and outcomes, and may thus potentially be a valuable predictor and biomarker for treatment efficacy. Future prospective studies, however, are warranted in order to advance the personalization of treatment strategies for breast cancer patients.

Supplementary Table 1. **Disease-free and overall survival outcomes for specific adverse events versus nonspecific adverse events by country**

Disease-free survival	**Specific AEs**		**No or nonspecific AEs**		**p-value***	**Disease-free survival (%)**	
Country	**n**	**%**	**n**	**%**		**Specific AEs**	**No/nonspecific AEs**
France	777	65.0	418	35.0	<0.001	92.6	91.4
Germany	745	53.0	660	47.0		91.2	88.8
Greece	13	7.0	172	90.0		84.6	87.6
Japan	108	61.7	67	38.3		86.6	87.4
Netherlands/ Belgium	1040	34.2	1999	65.8		86.6	82.0
UK/Ireland	361	29.3	873	70.7		87.1	85.6
USA	1588	75.9	504	24.1		92.4	85.4
Overall survival	**Specific AEs**		**No or nonspecific AEs**		**p-value***	**Overall survival (%)**	
Country	**n**	**%**	**n**	**%**		**Specific AEs**	**No/nonspecific AEs**
France	782	65.0	422	35.0	<0.001	97.2	94.9
Germany	751	52.7	673	47.3		95.3	93.4
Greece	13	6.8	177	93.2		100	93.2
Japan	112	61.9	69	38.1		95.3	94.8
Netherlands/ Belgium	1061	34.2	2042	65.8		90.3	85.9
UK/Ireland	364	29.2	884	70.8		91.4	88.4
USA	1605	75.9	509	24.1		94.5	90.0

AEs, adverse events. *chi-squared p-value

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CHAPTER

12

GERMLINE VARIANTS IN THE CYP19A1 GENE ARE RELATED TO SPECIFIC ADVERSE EVENTS IN AROMATASE INHIBITOR USERS: A SUB-STUDY OF DUTCH TEAM TRIAL PATIENTS

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ABSTRACT

Background

Musculoskeletal adverse events (MSAE) and vasomotor symptoms (VMS) are known side-effects of aromatase inhibitors (AIs), and may be related to genetic variations of the aromatase gene (CYP19A1). We investigated the relationship between these specific AEs and single nucleotide polymorphisms (SNPs) in the CYP19A1 gene in postmenopausal, hormone receptor-positive early breast cancer patients treated with adjuvant exemestane for five years.

Methods

Dutch patients who were randomized to receive 5 years of exemestane in the Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial were included. A tagging SNP approach was performed, covering 80% of variations of the CYP19A1 gene with 30 SNPs. Logistic regression analyses were used to assess the risk of reporting VMS or MSAE in relation to genotypes within selected SNPs.

Results

Of 737 included patients, 281 patients reported at least one MSAE (n=210) or VMS (n=163). Homozygous AA genotype of rs934635 was associated with a significantly higher odds of MSAE (multivariate odds ratio (OR) 4.66, p=0.008) and VMS (multivariate OR 2.78, p=0.044). Regarding both rs16964189 and rs7176005, the homozygous variant genotypes (TT) were associated with a higher odds of VMS, but not MSAE (OR 1.758, p=0.025 and OR 6.361, p=0.021 respectively).

Discussion

Our exploratory analysis demonstrated that some CYP19A1 gene variations may be associated with MSAE and/or VMS. Specifically, patients with the homozygous variant rs934635 genotype reported more MSAE and VMS. Although further confirmatory studies are warranted, genomic profiling can help identify patients at an increased risk of reporting these specific AEs, potentiating further personalized breast cancer treatment.

INTRODUCTION

Aromatase inhibitors (AIs) are well-integrated in the treatment of post-menopausal patients with hormone-sensitive breast cancer, and have shown improvements in both mortality and recurrence rates in the adjuvant as well as the palliative setting.[1] The mechanism of action of AIs consists of the inhibition of the aromatase enzyme, which plays a significant role in estrogen biosynthesis in postmenopausal women.[2] The inhibition of the aromatase enzyme causes a significant decline in estrogen levels in this setting, thus having its positive effect on breast cancer suppression in postmenopausal women.

Joint pain and hot flashes have emerged as major side-effects in patients treated with AIs.[3, 4] In the clinical setting 30-40% of the patients report musculoskeletal adverse events (MSAE) and these AI-associated adverse events (AEs) contribute to a decrease in patient function[5] and compliance to therapy, affecting both quality of life and drug effectiveness. The precise pathophysiological mechanism of AI-induced MSAE remains unclear. The marked estrogen deprivation in postmenopausal breast cancer patients is hypothesised to play an important role. This hypothesis has been strengthened by the fact that the time from menopause is associated with the incidence of MSAE, with a shorter time since the last menstruation being predictive of more MSAE.[6] In addition, hot flashes and night sweats, collectively known as vasomotor symptoms (VMS), are common side effects associated with endocrine therapy, and have been related to the degree of lowered estrogen levels occurring both naturally during menopause, and artificially in relation to chemotherapy and endocrine therapy for the treatment of breast cancer.[7] Recent studies[8, 9] demonstrated that the occurrence of MSAE and/or VMS predicted for improved efficacy of AI treatment, reinforcing the hypothesis that estrogen deprivation in postmenopausal patients may be one of the major factors in the development of specific AEs during AI treatment.

Variation in the CYP19A1 gene coding for the aromatase enzyme is associated with altered estrogen levels in serum and urine[10] and increased breast cancer risk according to several studies.[11, 12] Furthermore it was demonstrated that polymorphisms in CYP19A1 cause a different in-vitro response to AIs and alter aromatase activity in postmenopausal women.[13, 14] It is thus possible that polymorphisms in the CYP19A1 gene are associated with different responses to AIs in patients. This differential response may be influenced by the degree of estrogen deprivation and may affect the efficacy of AI treatment and the development of AEs.

The objective of this study was to evaluate whether single nucleotide polymorphisms (SNPs) in the CYP19A1 gene were associated with AEs in postmenopausal early breast cancer patients treated with adjuvant exemestane. We performed a genetic analysis in patients enrolled in the TEAM (Tamoxifen Exemestane Adjuvant Multinational) trial in the Netherlands.

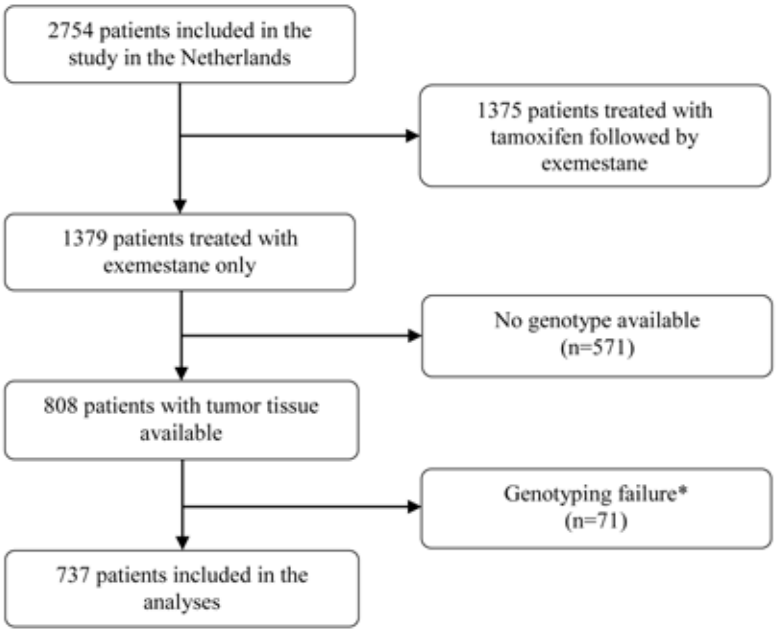
MATERIALS AND METHODS

Study design and patient population

Patients were selected from the cohort of Dutch TEAM patients (n=2754) only. Patients who received five years of exemestane (n=1379) and who had available tumor tissue were eligible (n=808). After genotyping, 71 patients were excluded because of genotyping failures (Figure 1). In total 737 Dutch patients who were treated with five years of adjuvant exemestane were available for analysis.

The TEAM trial is a randomized, phase III, multinational, open-label study conducted in postmenopausal women with estrogen receptor (ER-) and/or progesterone receptor (PR)-positive tumors who were eligible for adjuvant endocrine therapy. Patients were allocated to receive exemestane (25 mg once-daily for 5 years) or tamoxifen (20 mg once-daily for 2.5-3 years), followed by exemestane (25 mg once-daily for 2.5-2 years), for a total of 5 years.15 Study participants were enrolled in nine countries worldwide. Details of eligibility criteria have been published in an earlier report.[15] Data were collected locally and transferred to the central datacenter in Leiden, the Netherlands. Complete follow-up data were available for at least the first five years from the start of treatment, with follow-up visits performed every 3 months in the first year. Medical history

Figure 1. **Flow diagram of patients included in the current study**



*Samples were repeated once on the same platform and were considered genotyping failures if a re-run generated poor results for a second time.

issues were classified according to the International Classification of Diseases (ICD), version 10 (http://apps.who.int/classifications/icd10/browse/2010/en).

Outcome measurements

The objective of the current study was to evaluate whether SNPs in the CYP19A1 gene were associated with AEs in patients treated with exemestane. The primary endpoint was the occurrence of MSAE and VMS during the first year of treatment in relation to CYP19A1 SNPs. All AEs were obtained from patient responses during follow-up visits, and a standard symptom checklist was not used. AE severity was assessed using the National Cancer Institute's Common Terminology Criteria for Adverse Events (v3.0) and was centrally recoded using the Medical Dictionary for Regulatory Activities (version 12.1). MSAE included arthralgia, arthritis, and osteoarthritis, myalgia and other musculoskeletal problems. Osteoporosis was not considered a MSAE. VMS were defined as subjective and/or transient sensations of heat, including night sweats.

Selection of polymorphisms and genotyping procedures

Thirty polymorphisms in the CYP19A1 gene were selected using a tagging SNP approach, aiming for an 80% coverage of variation in the gene. CYP19A1 data was gathered from HapMap, with 200Kb distance from the start and end of the gene. Pairwise tagging with a minimal distance between two SNPs of 50Kb was used to narrow the selection. This approach captured 211 SNPs with an R^2 of 0.8 or higher. The 80% coverage consisted of 28 SNPs with a mean R^2 of 0.962. Polymorphisms with a minor allele frequency below 5% were excluded. Two SNPs (rs7176005 and rs6493497) were included because of a suggested association.[14]

DNA was isolated from paraffin embedded tissue samples with the Maxwell 2000 system (Promega Leiden, the Netherlands). Taqman assays were obtained from Life Technologies (Life Technologies, Nieuwerkerk aan den Ijssel, the Netherlands) for 26 polymorphisms. All those SNPs were initially determined by the LC480 system (Roche, Almere, the Netherlands) according to the manufacturer's protocol. Taqman assays were unavailable for 4 SNPs, and a pyrosequence (Qiagen, Venlo, the Netherlands) assay was designed. Both platforms yielded comparable results. Since tumor tissue was used, a preamplification step was introduced. Details of this procedure have been published elsewhere.[16]

Genotyping validity

Two assays were excluded because of assay failure. Failed samples were repeated once on the same platform and were considered genotyping failures if a re-run generated poor results for a second time. On the occasion of more than 10 genotyping failures in an individual patient, this patient was excluded. The average success rate of the other 28 assays and the individual samples was 98.4%. The lowest success rate of an individual assay was 92%. For quality control, 10% of all DNA samples were genotyped in duplicate for all SNPs. No inconsistencies were observed. The allelic frequencies of the 28 included SNPs with adequate

assays were tested for Hardy-Weinberg equilibrium (HWE). Six genotype assay results did not meet HWE. However, of four of these, frequencies were comparable with allelic frequencies as reported on the National Center for Biotechnology Information website (NCBI, http://www.ncbi.nlm.nih.gov) for the Caucasian population. Of the two remaining SNPs, no frequencies were available from the NCBI Web site. The homozygote wild-type frequencies of both SNPs were allowed for the analysis because of a low number of homozygous patients and good quality controls. We assessed whether HWE deviation was caused by loss of heterozygosity (LOH).[17] Almost all patients were heterozygous for at least one SNP in the CYP19A1 gene, therefore we rejected the possibility of LOH. Furthermore, there is currently no available evidence that LOH is a relevant issue in the CYP19A1 gene.

Since germline DNA was not available, tumor DNA was utilized, extracted from paraffin embedded tissue. Prior research has demonstrated the concordance between germline DNA and tumor DNA in multiple genes and numerous SNPs, although there is no direct evidence available with regard to the CYP19A1 gene.[18, 19] In addition, solid evidence of an association between CYP19A1 polymorphisms and breast cancer risk is still lacking.

Statistical analysis

Statistical analyses were performed using SPSS 17.0 (SPSS, Chicago, IL). Chi-squared tests initially compared proportions of VMS versus no VMS and proportions of MSAE versus no MSAE for different genotypes. Univariate and multivariate logistic regression analyses assessed whether the occurrence of VMS and MSAE differed with respect to CYP19A1 genetic variants. The primary analysis was performed using a general model, after which the most appropriate model was fitted (general, dominant or recessive). With respect to both MSAE and VMS, our multivariate logistic regression analyses were adjusted for age, body-mass index (BMI), and adjuvant chemotherapy. Data on patient ethnicity was not taken up in the trial protocol and was therefore not included in the multivariate analyses. Any musculoskeletal and/or vasomotor symptoms that were reported to have occurred before the start of treatment were excluded from the analyses. The explained variance was tested for using the Nagelkerke R^2 test. Due to the exploratory nature of these analyses, which comprises testing multiple hypotheses of which a selection will require further investigation, we did not correct for multiple testing.[20]

RESULTS

Successful DNA extraction from tumor samples was achieved in 737 patients, who were subsequently included in the analyses. Table 1 provides an overview of the baseline characteristics of these 737 patients. Median age was 64 years (range 45-91 years) and median BMI (kg/m^2) was 26.6 (range 16.9-47.8) There were no statistically significant differences in patient, tumor, or treatment characteristics between included and excluded patients (Supplementary Table 1). There was a borderline proportional difference with respect

to prior chemotherapy being administered in 27.1% and 32% respectively (chi-squared p=0.05). Only one patient who received adjuvant chemotherapy and reported MSAE and VMS was treated with taxanes.

Table 1. **Baseline characteristics of patients included in the analyses**

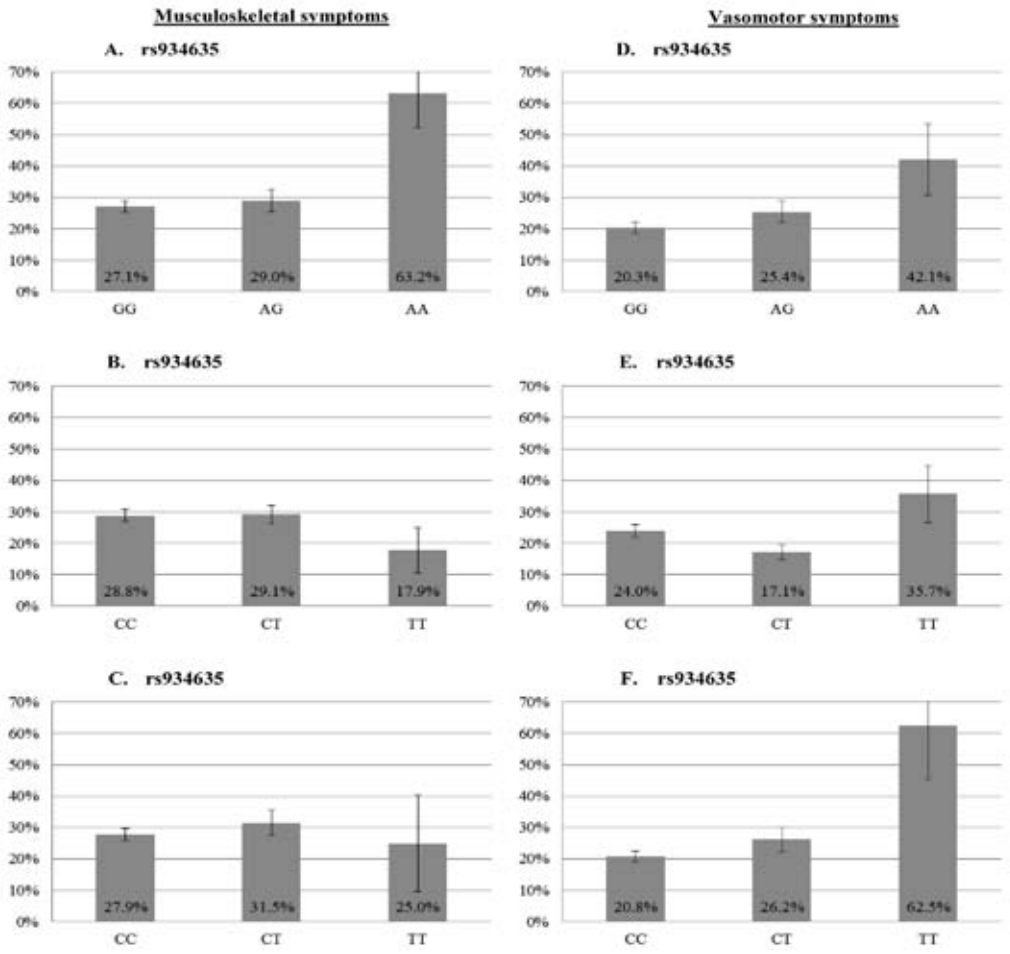
Baseline Characteristic	n	%
Age category (years)		
<59	222	30.1
60-69	272	36.9
≥70	243	33.0
BMI category (g/cm^3)		
<18.5	3	0.5
18.5 - <25	235	35.7
25 - <30	247	37.5
≥30	174	26.4
Tumor grade (BR)		
G1 (well)	130	18.6
G2 (moderate)	338	48.4
G3, G4 (poor)	231	33.0
ER status		
Positive	726	98.5
Negative	11	1.5
HER2 status		
Positive	85	12.3
Negative	605	87.7
Most extensive surgery		
Mastectomy	394	53.5
Wide local excision	343	46.5
no resection	0	0
Adjuvant radiotherapy		
Yes	445	60.4
No	292	39.6
Adjuvant chemotherapy		
Yes	200	27.1
No	537	72.9
Adverse event during the first year of treatment		
Musculoskeletal AEs		
Yes	210	28.5
No	527	71.5
Vasomotor symptoms		
Yes	163	22.1
No	574	77.9

BR, Bloom&Richardson; ER, estrogen receptor; PR, progesterone receptor; AEs, adverse events.

Musculoskeletal adverse events

MSAE were reported by 210 patients during the first year of exemestane treatment (Table 1). 98 patients (47.6%) reported mild symptoms, while 108 patients (52.4%) reported moderate/severe MSAE. The genotype of one SNP (rs934635) consisting of a G>A polymorphism, was associated with MSAE (Table 2), although genotype was not associated with AE severity (chi-squared p=0.15). Figure 2 shows that homozygous AA patients reported more MSAE compared to wild-type GG and GA, with an odds ratio (OR) of 4.62 (95% confidence interval (CI) 1.79-12.0) following univariate analysis (p=0.007). Multivariate analyses were adjusted for age, BMI and adjuvant chemotherapy and revealed an OR of 5.08 (95%CI 1.8-14.3) (p=0.007). No association was found with regard to the other SNPs (Supplementary Table 2).

Figure 2. **Percentage of specific adverse events according to genotype**



Musculoskeletal adverse events (A-C) and vasomotor symptoms (D-F) in relation to genotype.

Supplement for Figure 2

	Musculoskeletal adverse events							Vasomotor symptoms						
rs934635	**GG**	**%**	**AG**	**%**	**AA**	**%**	**p-value***	**GG**	**%**	**AG**	**%**	**AA**	**%**	**p-value***
No	399	(75.9)	120	(22.8)	7	(1.3)	0.003	436	(76.1)	126	(22)	11	(1.9)	0.038
Yes	148	(70.8)	49	(23.4)	12	(5.7)		111	(68.5)	43	(26.5)	8	(4.9)	
rs16964189	**CC**	**%**	**CT**	**%**	**TT**	**%**	**p-value***	**CC**	**%**	**CT**	**%**	**TT**	**%**	**p-value***
No	326	(61.9)	178	(33.8)	23	(4.4)	0.444	348	(60.6)	208	(36.2)	18	(3.1)	0.023
Yes	132	(62.9)	73	(34.8)	5	(2.4)		110	(67.5)	43	(26.4)	10	(6.1)	
rs7176005	**CC**	**%**	**CT**	**%**	**TT**	**%**	**p-value***	**CC**	**%**	**CT**	**%**	**TT**	**%**	**p-value***
No	417	(81.4)	89	(17.4)	6	(1.2)	0.685	458	(82.2)	96	(17.2)	3	(0.5)	0.009
Yes	161	(78.9)	41	(20.1)	2	(1)		120	(75.5)	34	(21.4)	5	(3.1)	

*chi-squared p-value

Musculoskeletal adverse events (A-C) and vasomotor symptoms (D-F) in relation to genotype.

Vasomotor symptoms

163 out of 737 patients experienced VMS during the first year of exemestane treatment, of which the majority (69.1%, n=112) were mild and 30.9% were moderate/severe (n=50). Associations with VMS were found for three SNPs, namely rs934635, rs7176005, and rs16964189 and are depicted in Figure 2. With respect to rs934635, the homozygous AA genotype was found to be associated with VMS, revealing an OR of 2.86 (95%CI 1.12-7.27) following univariate analysis (p=0.044) and an OR of 2.78 (95%CI 1.02-7.56) after multivariate analysis (p=0.044), which were also adjusted for age, BMI and adjuvant chemotherapy.

There was no correlation between genotype and AE grade (data not shown). In addition, both univariate and multivariate analyses showed a statistically significant association with rs7176005 (Table 2). Patients with a homozygous TT genotype reported more VMS than patients with at least one C allele (univariate OR 6.36 (95%CI 1.5-27.0) (p=0.021) and multivariate OR 4.9 (95%CI 1.02-23.5) (p=0.06)).

Lastly, the rs16964189 SNP was associated with the occurrence of VMS for the homozygous TT genotype (univariate OR 1.76 (95%CI 0.79-3.92) (p=0.025) and multivariate OR 1.86 (95%CI 0.76-4.59) (p=0.06)). No other SNPs demonstrated an association with VMS (Supplementary Table 2).

Explained variance

The explained variances (R2) for rs934635, rs16964189 and rs7176005 were 0.074, 0.054 and 0.057 respectively for MSAE and VMS combined. Assessed separately, the respective R2 values were 0.077, 0.060, and 0.057 for MSAE and 0.043, 0.043 and 0.044 for VMS. Sensitivity analyses revealed increased R2 values with the addition of more covariates in the regression model (data not shown).

Table 2. **Single nucleotide polymorphisms of the aromatase (CYP19A1) gene associated with musculoskeletal adverse events and vasomotor symptoms**

Musculoskeletal AEs	Genotype	Patients n	AEs n	Univariate OR (95%CI)	p-value	Multivariate OR* (95%CI)	p-value
	GG	547	209	1 (ref)	0.007	1 (ref)	0.007
rs934635	AG	169	49	1.101 (0.75-1.61)		1.213 (0.81-1.82)	
	AA	19	12	4.622 (1.79-12.0)		5.083 (1.8-14.3)	
Vasomotor symptoms	**Genotype**	**Patients n**	**AEs n**	**Univariate OR**	**p-value**	**Multivariate OR* (95%CI)**	**p-value**
	GG	547	111	1 (ref)	0.044	1 (ref)	0.044
rs934635	AG	169	43	1.34		1.45 (0.95-2.21)	
	AA	19	8	2.857		2.775 (1.02-7.56)	
	CC	458	110	1 (ref)	0.025	1 (ref)	0.06
rs16964189	CT	251	43	0.654		0.695 (0.46-1.05)	
	TT	28	10	1.758		1.863 (0.76-4.59)	
	CC	578	120	1 (ref)	0.021	1 (ref)	0.06‡
rs7176005	CT	130	34	1.352		1.406 (0.88-2.25)	
	TT	8	5	6.361		4.9 (1.02-23.5)	

AEs, adverse events; OR, odds ratio; *multivariate OR adjusted for age, body-mass index and adjuvant chemotherapy; CI, confidence interval.
‡ homozygous genotype statistically significantly associated with increased incidence of vasomotor symptoms (p=0.047).

DISCUSSION

Our analyses suggest an association between three CYP19A1 SNPs, namely rs7176005 (TT genotype), rs934635 (AA genotype), and rs16964189 (TT genotype), and the increased incidence of MSAE and/or VMS in the first year of adjuvant exemestane treatment in postmenopausal hormone receptor-positive breast cancer patients. MSAE and VMS associated with endocrine treatment can influence patient function and compliance to AI therapy and can significantly affect quality of life. Simultaneously, these specific AEs have been related to lowered levels of circulating estrogens.[7, 21] Although our findings are limited by the unavailability of estrogen levels in our cohort, clinical data have shown associations between MSAE and VMS and breast cancer outcome, also in the TEAM trial.[8, 9] Differential responses to AIs and the incidence of these specific AEs may result from genetic variations in the genes encoding the drug target or drug-metabolizing enzymes. With respect to treatment with AIs, the aromatase gene comprises a multitude of SNPs, some of which may be relevant for predicting treatment response and/or variations in drug metabolism leading to the presence or absence of treatment toxicities.

It is widely accepted that higher estrogen levels in postmenopausal women are associated with augmented breast cancer risk, and are related to increased transcription of aromatase.[22, 23] An earlier study showed that two SNPs of the CYP19A1 gene, rs6493497 and rs7176005, were associated with increased plasma

estrogen levels, which plays an important role in promoting the growth of estrogen-sensitive breast cancer.[14, 24] Another study investigated sex hormone levels in relation to genetic polymorphisms of the aromatase gene, finding lower estrone concentrations in women with multiple SNPs.[25] Finally, Wang et al. showed that variations in CYP19A1, including rs6493497 and rs7176005 caused changes in the transcription of aromatase in tumor tissue, causing a greater decrease in aromatase activity in AI-treated patients.[14] To add, rs7176005, was associated with higher estradiol levels in patients both before and after AI treatment.[14]
As mentioned previously, both MSAE and VMS have been linked to lower levels of circulating estrogens in AI users. Ingle and colleagues demonstrated the existence of a strong correlation between four SNPs in the TCLA1 gene and MSAE in a genome wide association study[26], and associations have also been found in relation to osteoporosis.[27, 28] Although these SNPs are different from those in our analyses, the relationship that was found between CYP19A1 SNPs and MSAE (and osteoporosis) suggest that genetic variations may have an effect on circulating estrogens in AI users. No reports exist on genetic variations in relation to VMS specifically, although reports have verified variations in circulating sex hormone levels in relation to SNPs of CYP19A1.[10, 13, 25] Straume et al. suggested that the variant allele of the rs7176005 was associated with enhanced CYP19 transcription in breast cancer patients, possibly resulting in higher plasma and tissue estrogen levels.[24] The effect of treatment with AIs on triggering AEs may, in this case, be influenced by baseline estrogen levels.

Both AEs and clinical outcomes have been linked to a number of SNPs previously [14, 26-31], with several SNPs showing endocrine treatment benefit in both the adjuvant and neoadjuvant settings.[31, 32] Results with respect to the SNP rs7176005, however, are still somewhat inconclusive. Analyses by Ghimenti et al.[33] failed to show an association with response to neoadjuvant anastrozole treatment.

A major advantage of the tagging-SNP approach is that it allows for a systematic investigation of associated SNPs, providing almost complete coverage of the entire CYP19A1 gene. Although tumor material may not truly represent a patient's germline genetic profile, the CYP19A1 gene is reported to be quite stable and identical to that in the patient's non-breast cancer tissue.14 Furthermore, the large number of patients used in this study (737 patients) strengthens the assertion that specific SNPs could be associated with more MSAE or VMS following treatment with exemestane. To our knowledge, this is currently the largest study to date investigating the association between SNPs in CYP19A1 and treatment toxicities. Although many patients did not have tumor material available for assessment (n=808), characteristics of subjects with available tumor material (n=737) did not differ from excluded patients (Supplementary Table 1). Despite the substantial size of our cohort, the number of patients with homozygous variants for specific SNPs was low and limited the ability to draw definite conclusions about the results and the implication for clinical practice. Consequently, further validation of these SNPs is eagerly awaited.

Our study did not reveal an association between AE severity and genotype. All AEs were obtained from spontaneous patient reports and specific responses during follow-up visits. No standard symptom checklist

was utilized, which could imply relative under-reporting of AEs in this study. It is therefore conceivable that our findings may be influenced by reporting bias and the effect observed may be stronger if inquiry into specific MSAE- and VMS-severity was standardized. Previously, we also found that patients who reported MSAE and VMS had better outcomes following endocrine treatment than patients who did not report these symptoms.9 Although speculative, drug metabolism might vary between patients, indicating a possible dose-response relationship with regard to endocrine treatment. As patients who develop AEs also risk early treatment discontinuation, dose reduction to minimize AEs while maintaining treatment benefit may be an acceptable approach to optimising treatment in these patients. Likewise, patients who receive adjuvant endocrine therapy, but do not develop toxicities may require a higher dosage to maximize their benefit.

Despite the large number of patients in our study, the low number of homozygous variants limits our interpretations. Nevertheless, patients with a heterozygous genotype for rs934635 also showed an increased odds of reporting specific MSAE and VMS, albeit less striking. The clinical benefit of identifying these patients susceptible to AEs following AI treatment is especially important given the influence of treatment compliance on breast cancer outcomes. Consequently, these personalized approaches can enable clinicians to find the optimal treatment for their patients that balances toxicities, compliance and effectiveness of endocrine therapy.

These hypothesis-generating results provide the prospect of using variations in the CYP19A1 gene to facilitate decision-making for a particular adjuvant endocrine therapy in postmenopausal breast cancer patients. Future studies on SNPs associated with variations in responses to endocrine treatment are eagerly awaited and will have to be performed in large cohorts of patients. It is hopeful that this will lead to better ways of predicting optimal treatment strategies in postmenopausal breast cancer patients who are candidates for adjuvant endocrine therapy.

Supplementary Table 1. **Characteristics of included and excluded exemestane-treated patients**

	Included patients		Excluded patients		
Characteristic	**n**	**%**	**n**	**%**	**p-value***
Age category					0.154
<59	222	30.1	223	35.0	
60-69	272	36.9	215	33.7	
≥70	243	33.0	200	31.3	
BMI category (kg/m^2)					0.680
<18.5	3	0.5	5	0.9	
18.5 - <25	235	35.7	215	37.7	
25 - <30	247	37.5	209	36.6	
≥30	174	26.4	142	24.9	
Tumor grade (BR)					0.101
G1 (Well)	130	18.6	84	14.4	
G2 (Moderate)	338	48.4	285	48.9	
G3, G4 (Poor)	231	33.0	214	36.7	
ER status					0.902
Positive	726	98.5	628	98.6	
Negative	11	1.5	9	1.4	
HER2 status					0.164
Positive	85	12.3	57	9.8	
Negative	605	87.7	522	90.2	
Most extensive surgery					0.354
Mastectomy	394	53.5	357	56.0	
Wide local excision	343	46.5	280	43.9	
no resection	0	0	1	0.2	
Adjuvant radiotherapy					0.446
Yes	445	60.4	396	62.1	
No	292	39.6	241	37.8	
Adjuvant chemotherapy					0.050
Yes	200	27.1	204	32.0	
No	537	72.9	434	68.0	
Musculoskeletal AEs**					0.224
Yes	210	28.5	201	31.5	
No	527	71.5	437	68.5	
Vasomotor symptoms**					0.568
Yes	163	22.1	133	20.8	
No	574	77.9	505	79.2	

BMI, body-mass index; BR, Bloom & Richardson; AEs, adverse events.
*chi-squared p-value.
**self-reported AEs in the first year of endocrine treatment.

Supplementary Table 2. **Specific adverse events in relation to single nucleotide polymorphisms of the aromatase (CYP19A1) gene**

				MSAE				Vasomotor symptoms			
	RS number	Genotype	n	Univariate OR	p-value	Multivariate OR*	p-value	Univariate OR	p-value	Multivariate OR*	p-value
1	rs17522553	GG	526	1 (ref)	0.765	1 (ref)	0.695	1 (ref)	0.436	1 (ref)	0.561
		AG	190	1.012		1.146		0.902		0.966	
		AA	19	0.662		0.769		0.398		0.442	
2	rs12324478	CC	207	1 (ref)	0.482	1 (ref)	0.435	1 (ref)	0.864	1 (ref)	0.743
		CT	363	1.188		1.289		0.917		0.942	
		TT	165	0.950		1.080		1.019		1.131	
3	rs1075681	GG	410	1 (ref)	0.143	1 (ref)	0.531	1 (ref)	0.696	1 (ref)	0.386
		AG	276	1.230		1.165		1.137		1.100	
		AA	48	0.607		0.791		1.256		1.661	
4	rs934635	GG	547	1 (ref)	**0.007**	1 (ref)	**0.007**	1 (ref)	**0.044**	1 (ref)	**0.044**
		AG	169	1.101		1.213		1.340		1.450	
		AA	19	4.622		5.083		2.857		2.775	
5	rs4775928	CC	350	1 (ref)	0.48	1 (ref)	0.857	1 (ref)	0.068	1 (ref)	0.093
		CT	301	0.868		0.954		0.850		0.892	
		TT	82	1.177		1.117		1.619		1.671	
6	rs16964189	CC	458	1 (ref)	0.455	1 (ref)	0.502	1 (ref)	**0.025**	1 (ref)	0.06
		CT	251	1.013		1.040		0.654		0.695	
		TT	28	0.537		0.528		1.758		1.863	
7	rs934633	CC	617	1 (ref)	0.372	1 (ref)	0.411	1 (ref)	1.00	1 (ref)	0.933
		CT	117	0.896		0.882		1.001		1.099	
		TT	3	4.972		4.520		too few numbers		too few numbers	
8	rs6493489	TT	226	1 (ref)	0.43	1 (ref)	0.579	1 (ref)	0.083	1 (ref)	0.144
		CT	269	1.180		1.220		0.632		0.646	
		CC	181	0.901		1.012		0.687		0.727	
9	rs4775935	GG	322	1 (ref)	0.682	1 (ref)	0.945	1 (ref)	0.436	1 (ref)	0.614
		GT	309	1.076		1.059		0.947		0.903	
		TT	99	0.858		1.068		0.683		0.740	
10	rs17703883	TT	440	1 (ref)	0.299	1 (ref)	0.43	1 (ref)	0.587	1 (ref)	0.831
		CT	223	0.960		1.054		0.815		0.944	
		CC	48	0.550		0.586		0.872		0.755	
11	rs16964211	GG	629	1 (ref)	0.604	1 (ref)	0.874	1 (ref)	0.427	1 (ref)	0.32
		AG	67	1.314		1.168		1.116		1.061	
		AA	4	too few numbers		too few numbers		3.558		4.669	
12	rs2414099	TT	541	1 (ref)	0.896	1 (ref)	0.914	1 (ref)	0.651	1 (ref)	0.85
		CT	182	1.032		0.924		1.155		1.122	
		CC	13	0.754		1.105		0.659		0.889	
13	rs12901187	GG	244	1 (ref)	0.178	1 (ref)	0.236	1 (ref)	0.262	1 (ref)	0.448
		AG	353	1.364		1.334		1.228		1.121	
		AA	136	1.017		0.973		1.509		1.396	
14	rs936307	CC	576	1 (ref)	0.476	1 (ref)	0.652	1 (ref)	0.175	1 (ref)	0.614
		AC	138	1.269		1.221		0.660		0.903	
		AA	20	0.874		0.998		1.414		0.740	
15	rs28757122	TT	668	1 (ref)	0.409	1 (ref)	0.704	1 (ref)	0.367	1 (ref)	0.243
		CT	64	1.443		1.286		0.811		0.775	
		CC	4	0.000		too few numbers		3.514		4.653	
16	rs1004982	TT	320	1 (ref)	0.609	1 (ref)	0.353	1 (ref)	0.52	1 (ref)	0.263
		CT	283	1.167		1.094		1.241		1.266	
		CC	115	1.210		1.447		1.204		1.513	
17	rs4774585	GG	467	1 (ref)	0.647	1 (ref)	0.369	1 (ref)	0.289	1 (ref)	0.165
		AG	204	1.156		1.191		1.322		1.375	
		AA	21	1.324		1.834		1.546		1.997	
18	rs6493497	GG	591	1 (ref)	0.793	1 (ref)	0.57	1 (ref)	0.72	1 (ref)	0.463
		AG	110	0.936		0.829		1.075		1.056	
		AA	17	1.362		1.529		1.522		2.054	

				MSAE				Vasomotor symptoms			
	RS number	Genotype	n	Univariate OR	p-value	Multivariate OR*	p-value	Univariate OR	p-value	Multivariate OR*	p-value
19	rs2445765	GG	522	1 (ref)	0.957	1 (ref)	0.788	1 (ref)	0.614	1 (ref)	0.567
		CG	190	1.039		0.914		1.027		0.970	
		CC	23	1.116		1.260		1.584		1.641	
20	rs2124873	GG	513	1 (ref)	0.349	1 (ref)	0.2	1 (ref)	0.386	1 (ref)	0.322
		AG	202	1.007		0.993		0.881		0.885	
		AA	21	1.922		2.338		1.730		1.919	
21	rs8031311	GG	327	1 (ref)	0.567	1 (ref)	0.17	1 (ref)	0.208	1 (ref)	0.108
		GT	333	0.891		0.825		1.192		1.205	
		TT	64	1.193		1.459		1.702		1.979	
22	rs28757184	CC	674	1 (ref)	0.55	1 (ref)	0.867	1 (ref)	0.332	1 (ref)	0.463
		CT	63	1.185		1.054		1.337		1.267	
23	rs17523014	AA	692	1 (ref)	0.393	1 (ref)	0.5	1 (ref)	0.72	1 (ref)	0.888
		AG	16	0.576		0.638		0.793		0.911	
24	rs767199	AA	190	1 (ref)	0.505	1 (ref)	0.655	1 (ref)	0.157	1 (ref)	0.162
		AG	361	1.194		1.211		0.667		0.660	
		GG	186	0.975		1.095		0.771		0.847	
25	rs1062033	CC	235	1 (ref)	0.51	1 (ref)	0.656	1 (ref)	0.467	1 (ref)	0.364
		CG	316	1.193		1.124		1.041		0.916	
		GG	163	0.967		0.921		1.318		1.279	
26	rs7176005	CC	578	1 (ref)	0.686	1 (ref)	0.995	1 (ref)	**0.021**	1 (ref)	**0.06**
		CT	130	1.193		0.990		1.352		1.406	
		TT	8	0.863		0.919		6.361		4.900	
27	rs2470169	TT	652	1 (ref)	0.856	1 (ref)	0.498	1 (ref)	0.978	1 (ref)	0.819
		GT	69	1.023		0.980		0.971		0.901	
		GG	8	1.503		2.518		1.166		1.580	
28	rs6493496	TT	410	1 (ref)	0.932	1 (ref)	0.373	1 (ref)	0.462	1 (ref)	0.137
		AT	271	1.006		1.087		0.947		0.981	
		AA	52	1.126		1.609		1.441		1.941	

* adjusted for age, chemotherapy and body-mass index

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PART

III

PRE-OPERATIVE AND OPERATIVE TREATMENT POSSIBILITIES

CHAPTER

13

NEOADJUVANT HORMONAL THERAPY FOR ENDOCRINE SENSITIVE BREAST CANCER: A SYSTEMATIC REVIEW

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ABSTRACT

In recent years, studies investigating neoadjuvant therapies have been emerging, because of the additional benefits it provides in terms of facilitating less extensive surgery and the possibility of investigating tumor biological features and response. Neoadjuvant hormonal therapy (NHT) is, in general, considered to be a suitable option for hormone receptor-positive patients who are unfit for chemotherapy or surgery, and is increasingly being utilized to achieve tumor downsizing before surgery in postmenopausal women. Studies investigating NHT were reviewed for tumor response data. NHT demonstrated similar efficacy to neoadjuvant chemotherapy (NCT) in hormone receptor-positive breast cancer patients. Clinical responses ranged from 13.5-100%, with treatment periods between 3-24 months. In studies comparing tamoxifen with aromatase inhibitors, the latter were superior in terms of tumor response and rates of breast-conserving surgery (BCS). In most studies with treatment durations longer than 3 months, tumor response rates increased. Therefore, longer durations of NHT are feasible and should be considered as an alternative to NCT in selected patients.

INTRODUCTION

Targeted treatment for breast cancer was described as early as 1895, when Beatson performed an oophorectomy on a woman with extensive breast cancer, inspired by techniques for promoting lactation in cattle.[1] Today, breast cancer treatment has adopted a multifactorial approach, combining surgery, systemic therapy and radiotherapy as main treatment modalities. Early studies investigated neoadjuvant chemotherapy (NCT) in women with large, operable breast cancer, revealing tumor shrinkage that facilitated more breast-conserving surgery (BCS), while survival rates were unaffected when compared with postoperative chemotherapy.[2] More recently, neoadjuvant hormonal therapy (NHT) trials have been emerging and its clinical application is gaining recognition. During the 13th St. Gallen International Breast Cancer Conference, 94% of breast cancer experts' consensus panel voted for the use of NHT in patients with hormone receptor-positive breast cancer.[3] A great advantage of preoperative systemic therapy is the prospect of downsizing and downstaging large tumors, facilitating the possibility of rendering inoperable tumors operable and achieving more BCS. Moreover, neoadjuvant studies can efficiently provide insight into the effects of drugs on biochemical, molecular and histological tumor features, on the basis of which surrogate prognostic biomarkers can be identified. Moreover, research questions can be answered sooner and in fewer patients. In recent years, several targeted systemic treatments have been developed, using molecular and biological tumor characteristics to further guide treatment decisions.[4] For example, adjuvant chemotherapy is less effective in hormone receptor-positive than hormone receptor-negative tumors.[5, 6] It is therefore plausible to assume similar efficacy profiles in the neoadjuvant setting. Here, we provide a systematic review of studies reporting response to NHT.

MATERIALS AND METHODS

Search method

Studies were identified through systematic review of the available literature in the PubMed database up to February 13th, 2013. PubMed was searched using a set of search terms which described breast cancer and neoadjuvant hormonal therapy with different agents. The specific search strategy used is outlined in Appendix 1 and was conducted with the help of the institution's information specialist (J.S.). Additional articles were included after searches through reference lists of selected articles.

Selection criteria

Two independent reviewers (D.F. and A.C.) selected studies for inclusion in the systematic review. Only reports written in English were eligible. Articles included original studies in which NHT was investigated in relation to tumor response. Studies were included if the primary or secondary outcome was related to our research questions. In the case of an update of previously published data or multiple reports of a single study, only the most recent publication was selected. In the case of disagreement, the independent reviewers discussed the study and, where necessary, the decision was made by a third independent reviewer (J.M). Only studies including patients with nonmetastatic breast cancer were included.

Data extraction

Data extraction was performed by two independent reviewers (D.F. and A.C.). Relevant data was determined prior to reading of the selected articles. For all studies, we documented the type of study, year of publication, patient and treatment characteristics, primary and (where possible) secondary endpoints, treatment duration, tumor response evaluation method(s), and study results. Data from each study was documented and independently reviewed and verified by the two independent reviewers.

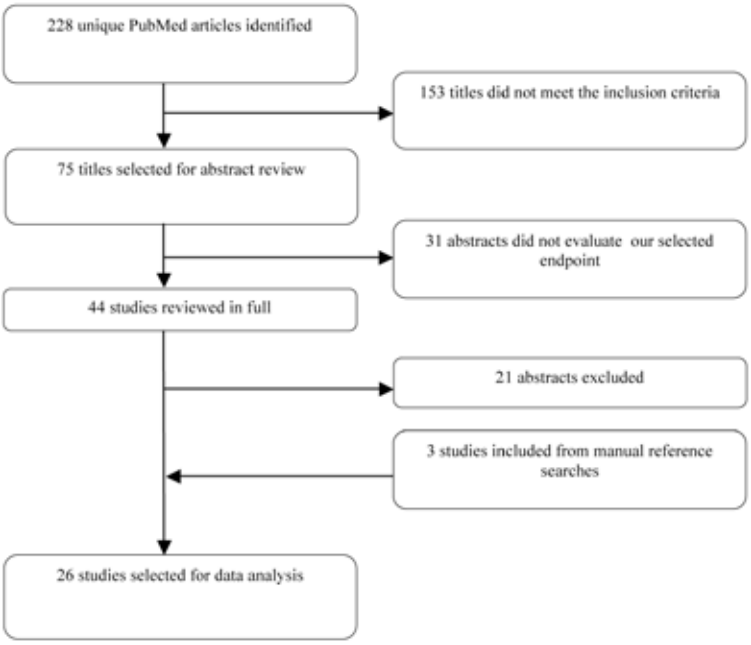
RESULTS

Study selection

A total of 228 unique articles were identified in the original database search. 153 studies were excluded based on our predefined inclusion criteria after reading the abstracts. 46 articles were fully read and evaluated for reporting of clinical and/or pathological response data. Three additional manuscripts were included after a manual search through the reference lists of the selected studies. 26 studies were deemed eligible for our systematic review. The study selection process is summarized in Figure 1.

Selected studies included 13 single-armed studies,[7-19] 4 studies investigating an aromatase inhibitor (AI) versus tamoxifen,[20-23] 5 studies comparing different AI regimens [24-28] and 4 studies that compared NHT with NCT.29-32

Figure 1. **Selection of studies included in this review**



Overall responses

26 studies were included in our analyses (Table 1). 23 studies investigated clinical response based on calliper measurement or palpation.[7, 9-14, 16, 18-32] Clinical responses ranged from 13.5% to 100% for endocrine therapy, with treatment durations between 3 and 24 months. Radiological responses, as measured with ultrasound or mammography ranged from 20% to 91.7% and 16% to 85.4% respectively. Table 1 provides an overview of the clinical responses based on measurement modality. The lowest clinical response rate was found in a study that included both hormone receptor-positive and hormone receptor-negative patients.[18]

Chemotherapy versus hormonal therapy

Four studies compared NHT with NCT.[31-34] Overall clinical response rates for the NHT arm ranged from 48%-89% and from 64% to 85% for the NCT arm. Three studies included hormone receptor-positive patients only.[29-31] Results from the large comparative study by Semiglazov et al. (n=239) showed that NHT is at least as effective as NCT with regard to response rate.[31] Furthermore, BCS was performed slightly more often in the NHT arm (33% vs. 24%, p=0.058). Likewise, Alba et al. did not find a significant difference in clinical response following NHT when compared with NCT in a retrospective analysis of 95 luminal breast cancer patients (p=0.075).[29]

Tamoxifen versus aromatase inhibitors

In four phase III trials, differences in neoadjuvant treatment outcomes between AIs and tamoxifen were studied.[20-23] Clinical response rates ranged from 38% to 70% for AIs and from 36% to 51% for tamoxifen. In two studies,[21, 22] AIs were as least as effective as tamoxifen, and in two other studies,[20-23] AI treatment resulted in a significantly better clinical response. The first published phase III trial comparing an AI to tamoxifen was a study by Eiermann and colleagues.[21] This double-blind double-dummy, randomized, multicenter study compared four months of letrozole with tamoxifen in women with hormone receptor-positive tumors who were ineligible for BCS. Letrozole was found to be more effective than tamoxifen in terms of clinical and radiologic (ultrasound and mammography) response rates, and in relation to BCS. The advantage of letrozole was higher in estrogen receptor (ER)-positive and HER2-positive breast tumors. Although most studies focused on AI treatment for postmenopausal women, Masuda et al.[22] conducted a neoadjuvant study with premenopausal patients, all treated with ovarian suppression with goserelin, and who were randomized to treatment with either anastrozole or tamoxifen. Clinical response was observed more frequently with anastrozole than with tamoxifen (70.4% vs. 50.5%, p=0.004). Similarly, ultrasound and MRI response was significantly better in the anastrozole group. In all four studies, AIs rendered tumors more suitable for BCS. Higher BCS rates were observed in favour of AIs in two studies, although only significant in the study by Eiermann et al.[21, 22]

Only one study was prospectively planned to investigate differences between four months of neoadjuvant treatment with exemestane, anastrozole or letrozole in the ACOSOG Z1031 trial.[24] Although letrozole exhibited the highest response rate (74.8%), this was not significantly different from that of exemestane or anastrozole (62.9% and 69.1% respectively). Also, BCS rates were not significantly different for the letrozole, exemestane, and anastrozole arms (60.8%, 67.8%, and 77% respectively; 52%, 50% and 57.7% were lumpectomy candidates before neoadjuvant therapy).

Table 1. **Studies included in this review**

Author	Age, HR status	Treatment	Treatment Duration (months)	Clinical response†	p-value	Radiological response‡	p-value	Ultrasound response	p-value	Mammography response	p-value	Pathologic response	Conversion (%)[j]	BCS	p-value
Single-arm studies															
Llombart-Cussac[7] 2012	66-91 HR+	Letrozole (n=70)	12 m	76.8% (43/56)		51.8% (29/56)									
Hille[8] 2011	52-102 ER+	Aromatase Inhibitor* (n=56)	5-92 m			66.6% (38/57)									
Dixon[9] 2011	55-91 ER+	Letrozole (n=61)	≥3 m	91.7% (55/60)				80.4% (41/51)		85.4% (41/48)		56.1% (23/41)	61% (25/41)		
Olson[10] 2009	48-89 HR+	Letrozole (n=115)	4-6 m	62% (62/100)				38% (29/77)		38% (21/56)			50% (48/96)		
Dixon[12] 2009	55-95 ER+	Letrozole (n=182)	3 m ≥3 m	69.8% (127/182) 83.5% (152/182)♦									60% (81/134) 72% (96/134)		
Krainick-Strobel[11] 2008	56-85 HR+	Letrozole (n=32)	2-8 m	72.4% (21/29)				62.1% (18/29)		24.1% (7/29)			75.9% (22/29)		
Torrisi[13] 2007	33-54 HR+	Letrozole + GnRH analogue (n=39)	4 m	50% (16/32)		47% (15/32)						3% (1/32)**		47% (15/32)	
Salmon[14] 2006	58-91 HR+	Anastrozole (n=75)	6 m	98.7% (74/75)										86% (65/75)	
Miller[15] 2006	PM ER+	Letrozole (n=63)	3 m					76.2% (48/63)				75.8% (47/62)			
Cappeletti[16] 2004	65-90 ER+	Toremifene (n=47)	3 m	68.4% (26/38)											
Milla-Santos[19] 2004	56-73 ER+	Anastrozole (n=74)	3 m	83% (61/74)[3]											
Ciatto[17] 1996	>69 HR+/-	Tamoxifen (n=120)	≥6 m							56.6% (68/120)					
McDonald[18] 1990	34-94 HR+/-	Tamoxifen (n=58)[ΞΞ] Tamoxifen (n=37)[ΞΞΞ]	6 m	34.5% (20/58) 13.5% (5/37)											
Endocrine therapies compared															
Masuda[22] 2012	20-59 ER+	Anastrozole + Goserelin (n=98) Tamoxifen + Goserelin (n=99)	6 m	70.4% (69/98) 50.5% (50/99)	p=0.004	64.3% (63/98)[β] 37.4% (37/99)[β]	p=0.0002	58.2% (57/98) 42.4% (42/99)	p=0.027			84.7% (83/98) 71.7% (71/99)		85.7% (84/98) 67.6% (67/99)	
Ellis[24] 2011	43-90 ER+	Exemestane (n=124) Letrozole (n=127) Anastrozole (n=123)	4 m	62.9% (78/124) 74.8% (95/127) 69.1% (85/123)										22.6% (26/115) 20.8% (25/120) 28.3% (33/117)	

Baselga[26] 2009	43-88 ER+	Letrozole + Placebo (n=132)	4 m	59.1% (78/132)	p=0.0616	47% (62/132)	p=0.035	29.4% (52/132)	p=0.704			
		Letrozole + Everolimus (n=138)		68.1% (94/138)		58% (80/138)		36.2% (50/138)				
Chow[25] 2008	48-93 HR+	Exemestane (n=24)	3 m	54.5%	NS							
		Letrozole (n=28)		62.0%								
		Exemestane + Celecoxib (n=30)		58.6%								
Cataliotti[20] 2006	44-96 HR+	Anastrozole (n=228)	4 m	50% (114/228)	p=0.37	39.5% (90/228)	p=0.29			38.1% (77/228)		p=0.11
		Tamoxifen (n=223)		46.2% (103/223)		35.4% (79/223)				29.9% (55/223)		
Smith[23] 2005	50-90 ER+	Tamoxifen (n=108)	3 m	36%	p=0.87^	20%	p=0.53*			31%		p=0.23
		Anastrozole (n=113)		37%		24%				44%		
		Tamoxifen + Anastrozole (n=109)		39%		29%				24%		
Dixon[27] 2001	PM ER+	Letrozole 2.5 mg (n=12)	3 m	100% (12/12)		66.6% (8/12)		66.6% (8/12)				
		Letrozole 10 mg (n=12)		75% (9/12)		50% (6/12)		58.3% (7/12)				
Eiermann[21] 2001	PM HR+	Letrozole (n=154)	4 m	55% (85/154)	p<0.001	35% (54/154)	p=0.042	34% (52/154)	p<0.001	45% (70/154)		p=0.022
		Tamoxifen (n=170)		36% (61/170)		25% (43/170)		16% (27/170)		35% (60/170)		
Dixon[28] 2000	PM ER+	Anastrozole 1 mg (n=12)	3 m	100% (12/12)♭		91.7% (11/12)♭		75% (8/12)♭				
		Anastrozole 10 mg (n=12)		90.1% (10/11)♭		63.6% (7/11)♭		54.5% (6/11)♭				
Endocrine therapy versus chemotherapy												
Alba[29] 2011	32-74 ER+	Exemestane (+/- Goserelin) (n=48)	6 m	48%	p=0.075					56%		p=0.24
		Chemotherapy (n=47)		66%						47%		
Generali[30] 2009	62-94 ER+	Letrozole (n=57)	6 m	73.2% (41/56)								
		Letrozole + Chemotherapy (n=57)		87.7% (50/57)								
Semiglazov[31] 2007	PM ER+	Anastrozole (n=61) or Exemestane (n=60)	3 m	64.5% (78/121)	p>0.5	40% (49/121)	p=0.80	60% (73/121)	p=0.50	33% (40/121)		p=0.058
		Chemotherapy (n=118)		63.6% (75/118)		46% (55/118)		63% (74/118)		24% (28/118)		
Thomas[32] 2007	28-90 HR+	Letrozole (n=53)	3 m	88.7%	p=0.757							
		Chemotherapy (n=50)		85.0%								

HR Hormone Receptor; ER Estrogen Receptor; BCS Breast Conserving Surgery; PM Postmenopausal;
†Clinical Responses defined as measured by calliper or palpation; ‡Radiological response: radiological modality not otherwise defined; ∫Conversion from inoperable to operable or mastectomy to BCS (not otherwise defined); Δ clinical and/or radiological response, confirmed by 2 evaluations; *Aromatase inhibitor not defined, **Pathological Complete Response reported only, ♦up to 24 months, ‡‡early stage breast cancer patients, ‡‡‡late-stage breast cancer patients, ^anastrozole versus tamoxifen, ∫∫MRI response, ♭interpreted data.

Table 2. Studies with longer than three months neoadjuvant hormonal therapy duration

Author	Age	Treatment duration	Treatment	Clinical response†	Radiological response‡	BCS	Response details
Dixon[12]	55-95	3 months (n=182)	Letrozole	69.8%		60%	Mean reduction at 3 months 46.7%, 3-6 months (46.6%), 6-12 months (47.8%), and 12-24 months (35.8%)
		≥3 months (n=63)		83.5%		72%	
Dixon[9]	55-91	3 months (n=61)	Letrozole	91.6% (55/60)	72.5% (37/51) US, 85.4% (41/48) MG		Mean reduction in clinical volume at 3 months was 66.1%; 22 patients continued letrozole as sole treatment for a median of 2.8 years
		≥3 months (n=22)	Letrozole			81%	
Olson[10]	48-89	4-6 months	Letrozole	62% (62/100)	38% (29/77) US, 38% (21/56) MG	50%*	Median clinical tumor size after letrozole treatment significantly smaller than pretreatment size (4.9 vs. 3.0 cm; p=0.0001)
Llombart-Cussac[7]	66-91	4 months	Letrozole		55% (30/56)		Median time to response 3.9 months; 20 patients (37.1%) achieved maximal response within 6-12 months
		4-12 months			80% (40/50)	43%	
Krainick-Strobel[11]	56-85	4 months	Letrozole	55.2%			Median tumor size reduced by 70% at individual end, compared with 62.5% at month 4
		8 months		60%		75.9%	
Masuda[22]	20-59	6 months	Anastrozole + Gosereline	70.4% (69/98)	64.3% (63/98)**	85.7%	
		6 months	Tamoxifen + Gosereline	50.5% (50/99)	37.4% (37/99)	67.6%	
Generali[30]	62-94	6 months	Letrozole	73.2% (41/56)			
		6 months	Letrozole + CT	87.7% (50/57)			
Salmon[14]	58-91	6 months	Anastrozole	98.7% (74/75)		86%	

BCS, Breast-conserving surgery

†Clinical responses as measured by calliper or palpation; ‡Radiological response: modality not otherwise defined; *Total conversion from inoperable to operable or mastectomy to BCS (not otherwise defined)

Duration

In most studies investigating NHT, patients were treated for 3 to 4 months prior to surgery. We identified eight studies that reported responses following treatment periods longer than 3-4 months.(Table 2) In one study by Dixon et al.[12] postmenopausal patients (median age 78) with operable or locally advanced ER-positive breast cancer received neoadjuvant letrozole for 3 months or longer. Treatment was continued after three months in 63 of the 182 patients for reasons including insufficient response for operability (n=15) or BCS (n=26), patients were unfit or unsuitable for surgery (n=13) or refused surgery (n=9).12 A continued clinical reduction in volume was observed hereafter. The overall response rate increased from 69.8% at three months to 83.5% after prolonged treatment in 63 patients. Importantly, the overall BCS rate improved from 60% to 72%. Several other studies also attempted to identify the optimal duration of NHT.[7, 11] In the phase II trial by Llombart-Cussac et al., the median time to objective response was 3.9 months and the median time to maximum response (i.e. time until the lesion had reached stabilization at evaluation) was 4.2 months. A third of the responders reached maximum reduction in tumor volume after 6 months, although few responders were reported hereafter. In another study, patients were treated with neoadjuvant letrozole for up to 8 months.[11] While only 50% of patients were initially considered to be eligible, BCS was performed in 68% of the patients after 4 months of neoadjuvant letrozole.

Hormone receptor status and histological subtype

All but three studies included hormone receptor-positive patients only. In these three studies[17, 18, 32], clinical response rates were as low as 34.5% and 13.5% for early-stage and late-stage breast cancer respectively. No reports existed on quantitative hormone receptor-expression in patients treated with NHT.

Eight studies reported the inclusion of both ductal and lobular breast cancer patients.[8, 10, 11, 14, 16, 26, 30, 35] None of these studies discriminated between lobular and ductal subtypes of breast cancer in their analysis of response. Only one single-armed study by Dixon reported on NHT in patients with lobular breast cancer exclusively and found response rates of almost 92% after more than three months of treatment. The mean reduction in tumor volume at 3 months was 66%.[9]

DISCUSSION

NHT is gaining popularity and is becoming standard of care in hormone receptor-positive breast cancer patients with large inoperable tumors, and in patients deemed unfit for NCT. With the prospect of an additional modality for downsizing large tumors as well as providing an early measurement tool for evaluating response to endocrine therapy, NHT is increasingly becoming an integral part of preoperative breast cancer management. Here we present a systematic overview of the available studies involving NHT to date. Compared to NCT, our evidence suggests that NHT has comparable response rates. AIs have demonstrated superior results when compared with tamoxifen in postmenopausal patients. In a majority of studies, NHT duration was between 3 and 4 months. Where data on longer treatment duration were available, continuing NHT beyond 3-4 months demonstrated additional clinical responses and further reductions in tumor size.

One of the main benefits of neoadjuvant systemic treatment is the higher chance that BCS is feasible in patients initially opting for mastectomy. In most studies investigating NHT, patients were treated for 3 to 4 months prior to surgery. One of the first investigators to study longer durations of NHT was Dixon et al., who treated elderly patients for up to 24 months.[12] Extending treatment beyond the predefined end-date revealed further reductions in tumor size in several studies, and in one study, response rates reached 100% when extending treatment indefinitely.[27] The 13th St. Gallen Breast Cancer Expert Panel recently (March 2013) voted in favor of a preferred maximal response duration beyond 4 to 8 months (62%).[3] With ever increasing data suggesting that longer treatment durations are suitable[7, 8, 12, 17], there is a growing interest in using NHT in (older) breast cancer patients deemed unfit for NCT or surgical intervention. Prolonged NHT could therefore be a valid alternative, and an earlier meta-analysis showed no differences in overall survival in elderly breast cancer patients treated with NHT alone versus surgery.[35] An additional advantage is the relatively mild toxicity profile of NHT when compared with NCT.[29, 31] Semiglazov and colleagues found more adverse events in NCT-treated patients than in NHT-treated patients.[31] In contrast to NCT-treated patients, no serious adverse events were reported by patients undergoing NHT. Therefore, NHT could be a safe alternative to NCT for certain patients for whom a low toxicity profile is preferred, especially in the elderly hormone receptor-positive breast cancer population. Although several studies are integrating NHT into their study design, available data on trials addressing the question of whether NCT is superior to NHT before surgery in hormone receptor-positive breast cancer patients is limited to a single trial (NEST trial, NCT01622361), whose completion is expected in 2016.[36] Trials with combined NHT and targeted therapy are also expected soon. Our study group recently completed a phase II trial with 6 months of neoadjuvant exemestane, in postmenopausal hormone receptor-positive breast cancer patients (TEAM IIA trial, ISRCTN17633610). Results of this trial will be available shortly. Considering the limited evidence comparing NCT to NHT, further trials are warranted, especially focusing on the question of neoadjuvant treatment duration for NHT and NCT. A comparative study of 6 months NHT versus standard durations of NCT could be feasible, keeping in mind that the objective is to downsize tumors for surgery.

In the adjuvant setting, studies have shown that hormonal therapy is more effective than chemotherapy when treating hormone-receptor positive breast cancer.[37, 38] Previously, an association was demonstrated between higher levels of ER expression and efficacy of endocrine therapy.[39] Petit and colleagues demonstrated an inverse relation between ER expression and pathological complete response following neoadjuvant chemotherapy in hormone receptor-positive breast cancer patients.[37] In the current investigation, all but three studies included hormone receptor-positive patients only. In the two single-arm studies, relatively lower response rates were observed when compared with the other single-arm studies.[17, 18] Ciatto et al. observed a strong association between response and ER content. While 100% had progressive disease in patients with no tumor immunostaining, only 6% of tumors with >60% immunostaining progressed.[17] These findings suggest that NHT could be a valuable substitute to NCT in ER-rich breast cancer patients. Furthermore, in clinical-decision making, the percentage of ER-immunostaining might be a more predictive number for treatment efficacy than a dichotomous ER-status based on a cut-off value of 1 or 10%. The majority

of studies have not reported on the effects of NHT on different tumor subtypes, such as invasive lobular carcinoma. Consequently, the effect of NHT in patients with hormone receptor-positive breast cancer may reveal an even greater benefit in specific subgroups. Invasive lobular breast carcinomas, in particular, may be best off when treated with NHT rather than NCT, due to the fact that they commonly present with large, ER-rich tumors relatively insensitive to NCT.[9, 39-41]

A superior efficacy for AIs over tamoxifen was found in a majority of the comparative studies.[20-23] Previously, it has been suggested that tamoxifen resistance in ErbB1- and ErbB2-positive tumors may play an important role in hormone-receptor positive patients.[42] Therefore, in postmenopausal hormone receptor-positive patients, we recommend NHT treatment with an AI rather than tamoxifen.

Because of the heterogeneity of the data collected and the use of varying classifications of tumor response (e.g. WHO and UICCC criteria)[43, 44], it was not possible to perform a pooled meta-analysis of the reported response rates. Hence, we have provided a comprehensive overview of the studies investigating response to NHT. In addition, it is difficult to draw conclusions for BCS rates, as baseline assessments of BCS versus mastectomy candidates differed between studies.

An additional feature of neoadjuvant therapy is facilitating investigations of possible predictive biomarkers. It has been suggested that measurements of the proliferation marker Ki-67 can be used to tailor neoadjuvant treatment shortly after starting treatment.[45] Dowsett et al. found that in patients treated with letrozole, the change in Ki-67 level after two weeks of treatment was of prognostic value for relapse-free survival (RFS), rather than baseline Ki-67 levels.[46] Ellis et al. concluded that a single tumor Ki-67 assessment 2 to 4 weeks after initiating AI treatment can identify ER-positive breast cancer patients with poor outcomes.[47] Furthermore, since the neoadjuvant setting provides a convenient model for examining tumor biology, post-neoadjuvant data may be used in preparation of further adjuvant studies or to predict outcomes in the adjuvant setting.[48] For example, post-treatment Ki67 can be of prognostic value, as shown by Ellis et al., who developed a preoperative endocrine prognostic index (PEPI) score for the prediction of RFS. The PEPI score incorporates post-treatment pathological tumor size, pathological node status, ER status and Ki67[49] Results from biomarker studies like these will help pave the way to a more personalized approach using neoadjuvant therapy.

NHT rivals NCT in its potential for downsizing primary tumors and rendering them operable, as well as increasing conversion rates from mastectomy to BCS in postmenopausal, hormone receptor-positive breast cancer patients. Moreover, the favourable toxicity profile of NHT makes it a very suitable treatment option for patients unfit for chemotherapy. Studies have shown that AIs, rather than tamoxifen, are the preferred agents for NHT in postmenopausal patients. Longer treatment durations demonstrated greater clinical responses and BCS rates with acceptable tolerability, and our findings are largely supported by the St. Gallen Breast Cancer Expert Panel 2013.[3] Treatment with AIs can still be optimised by selecting the most potent agent and by defining optimal treatment durations. Furthermore, in our endeavour for more personalized approaches to

breast cancer management, investigations into subgroups of patients most likely to attain a beneficial clinical response to NHT are needed. Results from future neoadjuvant trials in which these subgroups are studied will unquestionably contribute to further establishment of optimized treatment regimens in individual patients.

Appendix 1. PubMed search algorithm for relevant studies

PubMed was searched using a set of search terms which described breast cancer and neoadjuvant hormonal therapy according to the following algorithm:

("neoadjuvant hormonal therapy" OR "preoperative hormonal therapy" OR "neoadjuvant endocrine therapy" OR "preoperative endocrine therapy" OR "primary endocrine therapy" OR "primary hormonal therapy" OR "primary hormone therapy" OR (("Antineoplastic Agents, Hormonal"[Pharmacological Action] OR "Aromatase Inhibitors"[Pharmacological Action] OR "anastrozole"(Supplementary Concept) "ICI D1033" OR "ZD-1033" OR ZD1033 OR Arimidex R "exemestane"(Supplementary Concept) OR "FCE 24304" OR "FCE-24304" OR Aromasil OR Aromasin OR "letrozole"(Supplementary Concept) OR Femara OR "CGS 20267" OR "CGS-20267" OR "Tamoxifen"[mesh] OR ICI47699 OR Zitazonium OR Soltamox OR Tomaxithen OR "ICI-46474" OR "ICI 46474" OR ICI46474 OR "ICI-46,474" OR "ICI 46,474" OR "ICI46,474" OR Nolvadex OR "hormonal therapy" OR "hormone therapy" OR "endocrine therapy") AND ("Neoadjuvant Therapy"[Mesh] OR Neoadjuvant OR "primary systemic" OR "primary therapy"))) AND ("Breast Neoplasms"[mesh] OR "breast cancer") AND ("Clinical Trial"[Publication Type] OR "Comparative Study" [Publication Type]).

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CHAPTER

14

EFFICACY OF SIX MONTHS NEOADJUVANT HORMONAL THERAPY IN POSTMENOPAUSAL, HORMONE RECEPTOR-POSITIVE BREAST CANCER PATIENTS – A PHASE II TRIAL

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ABSTRACT

Introduction

Neoadjuvant hormonal therapy (NHT) is playing an increasing role in the clinical management of breast cancer and may improve surgical outcomes for postmenopausal, estrogen receptor (ER)-positive breast cancer patients. However, there is currently no consensus on the optimal duration of NHT before surgery. Here, we present the outcomes of the TEAM IIA trial, a multicentre, phase II trial investigating the efficacy of six months of neoadjuvant exemestane in postmenopausal, strong ER-positive (≥50%) breast cancer patients.

Methods

102 patients (stage T2-T4ac) were included in the study after exclusion of ineligible patients. Primary endpoint was clinical response at 3 and 6 months as measured by palpation. Secondary endpoint was radiological response as measured by MRI, mammography and/or ultrasound. Linear mixed models (95%confidence interval (CI)) were used to compare changes in mean tumor size (in mm) between baseline, 3 and 6 months after the start of hormonal therapy. Conversion rates from mastectomy to breast-conserving surgery (BCS) were evaluated.

Results

Median age of all patients was 72 years (range 53-88). Overall response rate by clinical palpation was 64.5% in all patients with a final palpation measurement. 4 patients had clinically progressive disease. 63 patients had both 3-month and >3-month palpation measurements. Overall response was 58.7% at 3 months and 68.3% at final palpation (>3 months). Mean tumor size by clinical palpation at T=0 was 39.1mm (95%CI 34.8-43.4mm), and decreased to 23.0mm (95%CI 18.7-27.2mm) and 16.7mm (95%CI 12.6-20.8) at T=3 and T>3 months respectively (p=0.001). Final radiological response rates at the end of treatment for MRI (n=37), ultrasound (n=77) and mammography (n=56) were 70.3%, 41.6% and 48.2% respectively. Feasibility of BCS improved from 61.8% to 70.6% (McNemar p=0.012).

Discussion

6 months of neoadjuvant exemestane therapy helps reduce mean tumor size further in strongly ER-positive breast cancer patients without significant side effects compared to 3 months. Nevertheless, some patients still experience disease progression under exemestane. Feasibility of breast conservation rates improve by almost 10%.

INTRODUCTION

Neoadjuvant hormonal therapy (NHT) with aromatase inhibitors has been gaining recognition due to its ability to improve surgical outcomes for hormone sensitive breast cancer patients with stage II or III breast cancer. In recent years, NHT has come to play a major role in the treatment of large breast tumors, attesting its ability to render inoperable tumors suitable for mastectomy and for breast conservation in patients who would otherwise undergo ablative surgery.[1] Moreover, NHT provides the prospect of investigating the effects of hormonal treatment, with or without new targeted antitumor agents, on biochemical, molecular and histological tumor response features, which can help guide subsequent treatment decisions.[2]

Although long-term survival benefit of adjuvant chemotherapy do not differ between ER-positive and ER-negative tumors based on an Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis[3], neoadjuvant studies have demonstrated that ER-positive tumors are less sensitive to chemotherapy than ER-negative tumors in terms of pathological Complete Response (pCR).[4-7]

In estrogen receptor-positive, postmenopausal breast cancer patients, NHT is an appropriate option for patients who are considered unfit for neoadjuvant chemotherapy. Not infrequently, NHT is also prescribed for long-term treatment in elderly patients who are too fragile to undergo surgical intervention. During the 13th St. Gallen International Breast Cancer Consensus Conference, the majority of the breast cancer experts' consensus panel voted in favour of the use of NHT for postmenopausal patients with highly endocrine-responsive disease.[8]

Currently, the most commonly applied treatment duration of NHT in early breast cancer patients with large inoperable tumors is three months. Arguably, however, this may be too short a period for aromatase inhibitors to work to their full potential, as tumor response may continue if treatment is extended.[9, 10] Importantly, the St. Gallen 2013 preliminary summary of the consensus discussion reported that 62.2% of panelists were in favour of continuing NHTtreatment until maximal response[8], with only 11% of panelists recommending a treatment duration of 3-4 months.[11] 26.7% of panelists were in favour of a treatment duration of 4-8 months.[11] Clinical studies investigating the optimal duration of NHT in order to optimize operability of large tumors otherwise unsuitable for breast conservation are still relatively lacking.[2, 12] We report the results of the TEAM IIA study, a nationwide, multi-institutional, phase II trial that investigated six months of neoadjuvant therapy with exemestane on tumor response in strongly endocrine-sensitive breast cancer patients, which was developed to address the optimal duration of NHT.

MATERIALS AND METHODS

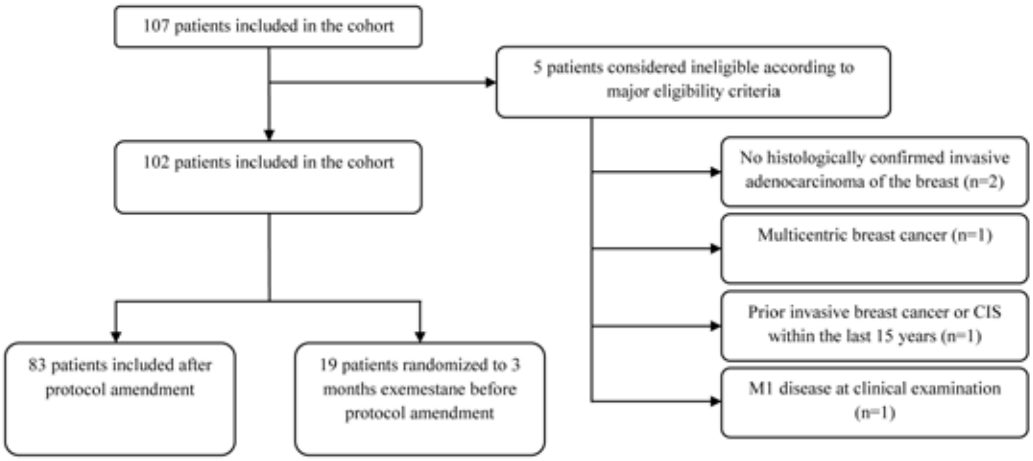
Trial design

The TEAM IIA trial was originally designed as a phase III, randomized clinical trial investigating three versus six months of neoadjuvant exemestane therapy on clinical response. Due to unexpectedly slow accrual, the TEAM IIA trial protocol was changed to a phase II single-arm study investigating six months of NHT on clinical response following an amendment in June 2009. The TEAM IIA trial was conducted in 11 hospitals throughout the Netherlands between March 2007 and May 2012. Database lock was on October 15th, 2013.

Patients

107 patients were enrolled in the study. 20 patients were randomized to 3 months of neoadjuvant treatment with exemestane before the amendment. 87 patients were included after the amendment and were allotted 6 months of NHT.(Figure 1) Patients randomized to 3 months and on-treatment were offered to continue until 6 months. Eligibility criteria included postmenopausal patients with histologically confirmed invasive adenocarcinoma (stage I-III) of the breast that was strongly ER-positive (≥50% based on core biopsies) and ≥2cm in diameter. Patients with metastatic disease (M1) were considered ineligible. In addition, patients with multicentric, bilateral, or inflammatory (cT4d) breast cancer were ineligible.

Figure 1. **CONSORT diagram showing patients included in the study.**



The protocol as well as the amendment were reviewed and approved by each participating institution and registered with the Netherlands Trial Register (NTR785) in compliance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent.

Tumor response was assessed monthly by clinical palpation and at 3-month intervals for MRI, bidirectional mammography or ultrasound. Clinical palpation response was measured in terms of the largest diameter (in millimetres). For radiological response, perpendicular dimensions of the largest measurable primary tumor and lymph nodes were measured. Cut-off points for response categories included complete response (disappearance of all target lesions), partial response (≥30% decrease in tumor size), stable disease (<20% increase or ≤30% decrease in tumor size), and progressive disease (≥20% increase in tumor size, as well as an absolute increase of at least 5mm), and were based on the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.13

Endpoints

The primary endpoint was overall clinical response at three and six months, as measured by clinical palpation. Only patients who enrolled in the study after the implementation of the amendment are included in these analyses.

Secondary endpoints consisted of objective radiological response; imaging modality was opted by the treating physician. Other secondary endpoints included pCR of the primary breast cancer and lymph nodes, and the feasibility of breast conserving surgery in all patients. pCR was defined as the absence of invasive tumor cells in the resection specimen and dissected lymph nodes (pT0/pN0) as reported by the pathology laboratories.

Tumor pathology data

Core biopsies were obtained before the start of treatment and resection specimens were acquired at final surgery. Biopsies were evaluated by immunohistochemistry with conventional light microscopy at pathology laboratories.

Assessment of safety

Patient-reported toxicities were assessed at 1-month intervals. The National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0, was used to classify adverse events following exemestane treatment.

Statistical analyses

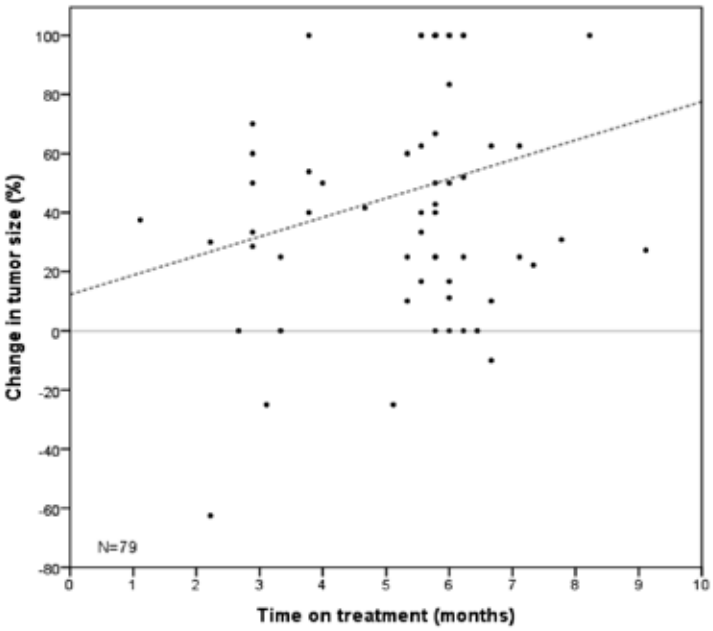
Cross tabs with McNemar tests for paired samples were used to assess palpability and clinical response at baseline, three and six months. If treatment was discontinued before six months due to progressive disease or due to patient or investigator request, response up to the last clinical examination was used. Mean changes in tumor size from baseline to 3 months and 6 months after the start of exemestane were assessed in linear mixed models with 95% confidence intervals (CI) for clinical palpation, MRI, bi-directional mammography, and/or ultrasound. All available radiological modalities were included in the analyses. If more than one modality was used for tumor size measurement, we used radiological modality in order of accuracy (MRI followed by mammography, followed by ultrasound).[13]

RESULTS

Study population

107 patients were included in the study, of which 20 patients were allocated 3 months of exemestane before implementation of the protocol amendment. After exclusion of ineligible patients (n=5), the final cohort comprised 102 (stage T2-T4a-c) patients.(Figure 1) Median treatment time for all patients was 5.78 months

Figure 2. **Scatter plot of the percentage change in tumor size as measured by palpation in relation to time on treatment (months) in patients treated with neoadjuvant exemestane in all included patients.**



(mean 5.32, range 0.89-9.11 months) and 3.33 months (mean 3.46, range 2.22-5.78 months) for patients randomized to 3 months of treatment before the amendment. The scatter plot that makes up Figure 2 reveals the percentage change in tumor size as measured by palpation in relation to time on exemestane treatment for all patients in the cohort. Mean age was 72 years (range 53-88). Baseline characteristics of patients at the start of treatment (T=0) are presented in Table 1, with primary tumor characteristics representing the results following core needle biopsy.

Tumor downstaging

Clinical response to exemestane was quantified and classified as complete response, partial response, stable disease and progressive disease. Overall response rates at the end of treatment for palpation, MRI, ultrasound and mammography are shown in Table 2. At the end of neoadjuvant exemestane treatment, overall clinical response (complete response + partial response) was 64.5% (51 out of 79 evaluable patients). There were 22 complete clinical responses, 29 partial responses, 24 stable diseases and 4 progressive diseases according to palpation assessments. Of the 4 patients with progressive disease based on clinical palpation, only 2 were also radiologically confirmed progressive diseases (2 stable disease). Mean percentage reduction in tumor size was 47.35% (range -63% - 100%). 63 patients had palpation measurements at 3 months and

Table 1. **Baseline characteristics of patients included in this study**

Before surgery	**n**	**%**
Age		
Median (range)	*72*	*(53-88)*
Tumor size		
<3cm	43	42.2
3-5cm	41	40.2
>5cm	15	14.7
T4a-c	3	2.9
Nodal status		
cN-	77	75.5
cN+	25	24.5
Tumor type		
Ductal	66	64.7
Lobular	30	29.4
other/unknown	6	5.8
Histological grade (BR)		
G1 (well)	12	11.8
G2 (moderate)	27	26.5
G3, G4 (poor)	7	6.9
unknown	56	54.9
PR status		
Positive (≥10%)	70	68.6
Negative	32	31.4
HER2 status		
Positive	9	8.8
Negative	85	83.3
unknown	8	7.9
Feasibility of BCS before surgery		
Not feasible	34	32.5
Feasible	68	67.5

BR, Bloom&Richardson; BCS, breast-conserving surgery.

a final measurement at the end of neoadjuvant treatment (>3 months). At the end of treatment, overall clinical palpation response (compared to 3 months) increased from 58.7%to 68.3% at last palpation. (McNemar p=0.031).

Mean tumor size was 39mm at the start of treatment, and decreased significantly after 3 and >3 months of exemestane treatment (Table 3). Mean reductions in tumor size at 3 and >3 months were 16mm and 22mm respectively (p<0.001). After >3 months of neoadjuvant treatment, there was a statistically significant decrease in tumor size when compared with 3 months of treatment (p=0.003).

Table 2. **Overall response at final assessment in all patients, as determined by clinical palpation, MRI, mammography and ultrasound.**

Response modality‡	n	%
Clinical palpation	*(n=79)*	
Complete response	22	21.6
Partial response	29	28.4
Stable disease	24	23.5
Progressive disease	4	3.9
Not available	23	22.5
*Overall response**	*51*	*64.5*
MRI	*(n=37)*	
Complete response	9	8.8
Partial response	17	16.7
Stable disease	8	7.8
Progressive disease	3	2.9
Not available	65	63.7
*Overall response**	*28*	*70.2*
Mammography	*(n=56)*	
Complete response	2	2.0
Partial response	25	24.5
Stable disease	26	25.5
Progressive disease	3	2.9
Not available	46	45.1
*Overall response**	*27*	*48.2*
Ultrasound	*(n=77)*	
Complete response	3	2.9
Partial response	29	28.4
Stable disease	39	38.2
Progressive disease	6	5.9
Not available	25	24.5
*Overall response**	*32*	*41.6*

‡Final response assessment at any time since the start of neoadjuvant treatment; *Out of all evaluable patients.

Radiological assessment

93 patients had a radiological assessment (91.2%). Based on radiological assessment, overall clinical response rate was 54.8%. There were 11 complete responses (11.8%), 40 partial responses (43%), 35 stable diseases (37.6%) and 7 patients with progressive disease (7.5%). Patients who had MRI measurements (n=37) had larger tumors at palpation than patients without MRI measurements (n=65) (35mm versus 47mm, p=0.003). In the MRI group there was a greater proportion of invasive lobular carcinomas (45.7%) than in the group without MRI measurements (20.3%). Patients who had both MRI in addition to mammography or ultrasound measurements did not have larger tumors on MRI than on mammography or ultrasound (independent samples T-test p=0.694 and p=0.142). Figure 3 shows the mean tumor sizes (95% confidence interval, CI) for individual radiological modalities. In addition, Table 3 depicts mean reductions in tumor

Table 3. **Mean tumor size and mean change in tumor size at 3 months and at the end of neoadjuvant exemestane treatment in patients enrolled after protocol amendment**

	Time (months)	n	Mean size (mm)	SE	(95% CI)	Mean reduction in size (mm)	(95% CI)	p-value
Palpation	T=0	63	39.08	2.16	(34.82 – 43.35)	0 (ref)		
	T=3	64	22.98	2.15	(18.73 – 27.23)	16.11	(11.87 – 20.35)	<0.001
	T=last**	72	16.68†	2.07	(12.59 – 20.78)	22.4	(18.28 – 26.53)	<0.001
MRI	T=0	37	41.15	3.35	(35.65 – 46.65)	0 (ref)		
	T=3	24	24.66	3.42	(17.85 – 31.46)	16.5	(8.09 – 24.9)	<0.001
	T=last	25	19.77*	2.76	(13.11 – 26.44)	21.38	(13.05 – 29.7)	<0.001
Mammo-graphy	T=0	62	32.99	1.65	(29.71 – 36.26)	0 (ref)		
	T=3	37	21.85	1.93	(18.02 – 25.67)	11.38	(7.62 – 14.66)	<0.001
	T=last	38	22.22*	1.92	(18.43 – 26.01)	10.77	(7.31 – 14.22)	<0.001
Ultra-sound	T=0	69	27.81	1.37	(25.1 – 30.52)	0 (ref)		
	T=3	50	20.67	1.48	(17.73 – 23.6)	7.15	(4.65 – 9.64)	<0.001
	T=last	49	18.39*	1.49	(15.44 – 21.35)	9.42	(6.87 – 11.96)	<0.001

SE, standard error; CI, confidence interval.
†p=0.003 (statistically significant) with respect to T=3 months; *p>0.05 (not statistically significant) with respect to T=3 months; **last measurement after >3 months of neoadjuvant hormonal therapy

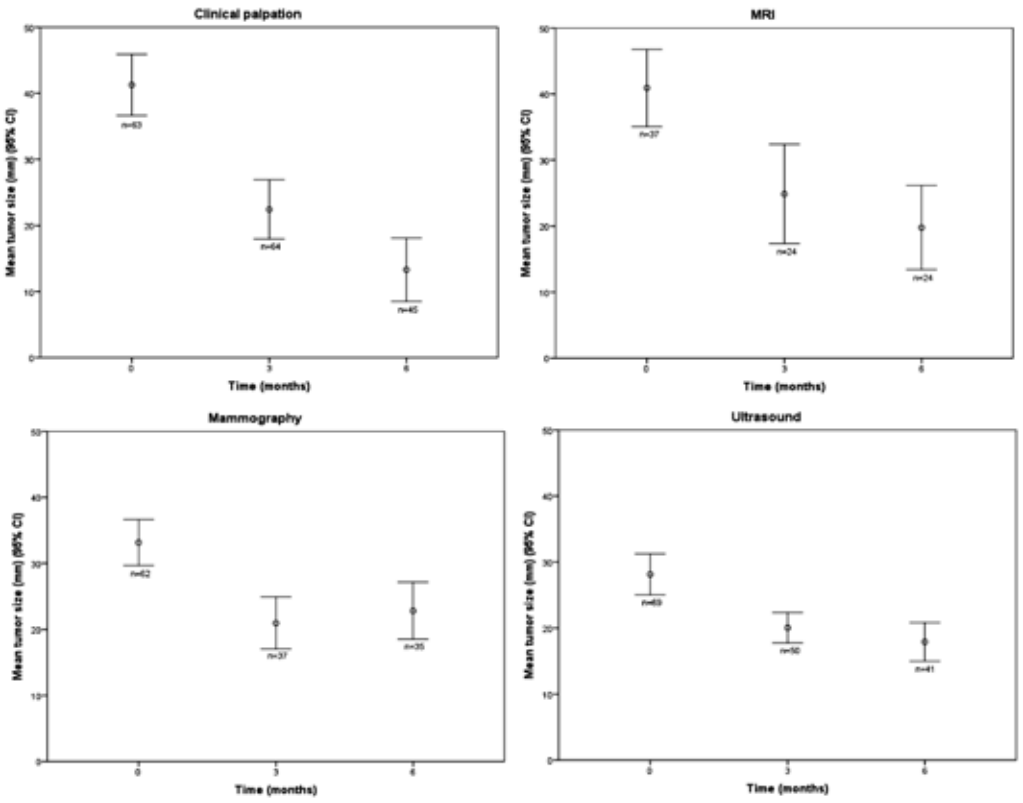
size for each radiological modality separately. For all modalities, there was a significant decrease in mean tumor size over time. Mean tumor size was not statistically significantly lower after 6 months of exemestane than after 3 months (p>0.05).

8 patients (8.8%) had confirmed HER2-positive disease after surgery, of whom 5 had clinical response assessments available (2 complete responses (25%), 1 partial response (12.5%), 2 stable diseases (25%)). All patients had radiological response data available, which showed 1 complete response (12.5%), 1 partial response (12.5%), 3 stable diseases (37.5%) and 3 progressive diseases (37.5%).

Feasibility of breast-conserving surgery

Median time to surgical intervention was 28 weeks (range 8 – 47 weeks). Tumor and nodal stage, grade, histology, and hormone receptor status were also determined after final surgery and are presented in Supplementary Table 1. The number of patients with feasible BCS increased from 63 before treatment to 72 at the end of treatment (McNemar p=0.012) (Table 4). A total of 98 patients (96.1%) underwent surgical resection of their tumor. Primary surgery consisted of BCS in 58 patients (56.9%) and mastectomy in 40 patients (39.2%). 9 patients (9.2%) deemed ineligible for BCS at the start of treatment had successful breast conservation. 9 patients (8.8%) required a re-excision (5 mastectomy, 4 BCS) following tumor-positive resection margins (invasive carcinoma and/or carcinoma in situ).

Figure 3. **Mean change in tumor size after 3 and 6 months after the start of neoadjuvant treatment in patients enrolled after protocol amendment.**



Patient preference for either mastectomy or BCS was also assessed. 79 patients reported a surgical preference at baseline and at the end of treatment. Patient preference regarding the type of breast surgery shifted from 13.7% in favour of mastectomy (n=14) at the start of treatment to 23.5% (n=24) in favour of mastectomy at the end of treatment. Preference for BCS was 66.7% (n=68) at baseline and decreased to 63.7% (n=65) at the end of exemestane treatment.

Sentinel lymph node biopsy

25 out of 102 patients (24.5%) had clinically or cytologically confirmed node-positive disease at the start of exemestane treatment. In total, 71 patients underwent a sentinel lymph node biopsy (SLNB) (9 patients before neoadjuvant therapy and 62 patients after neoadjuvant therapy). Three out of the 25 patients (12%) who were clinically node-positive before the start of exemestane became pathologically node-negative after neoadjuvant treatment. Forty-two out of 62 patients (67.7%) who had a SLNB after neoadjuvant treatment were also node-negative (pN0 or pN0(i+)).

Table 4. **Feasibility of breast conserving surgery before and after neoadjuvant treatment in all patients**

	Before treatment		End of treatment		McNemar p-value
	n	%	n	%	
Feasibility of breast-conserving surgery					
not feasible	39	38.2	24	23.5	0.012
feasible	63	61.8	72	70.6	
unknown	0	0.0	3	2.9	
Conversion rate*	-	-	9	9.2%	
Performed surgery					
breast conserving surgery	-	-	58	56.9	
mastectomy	-	-	40	39.2	
no resection	-	-	4	3.9	
Re-excision required	-	-	*9*	*(8.8%)*	
Patient preference					
breast conserving surgery	68	66.7	65	63.7	
mastectomy	14	13.7	24	23.5	
no resection	2	2.0	1	1.0	
not reported	18	17.6	12	11.8	

*conversion from mastectomy before treatment to breast conserving surgery after treatment.

Safety and toxicities

Adverse events were graded according to the CTC-AE version 3.0. All toxicities that make up >1% of all reported adverse events (n=188) are included in Supplementary Table 2. Only 10 toxicities (4.1%) were reported to be grade 3-4 toxicities. Pain, fatigue, and sensory neuropathy make up the majority of grade III-IV toxicities reported in this study. Importantly, only three patients discontinued exemestane due to toxicities. There were no serious unexpected adverse events.

DISCUSSION

Six months of neoadjuvant exemestane resulted in improved clinical and radiological responses, without an increased risk of toxicity. Overall clinical response rate was 64.5% after 6 months of neoadjuvant exemestane. Radiologically confirmed progressive disease was limited to four patients. In addition, neoadjuvant treatment resulted in a greater feasibility of breast conservation, although the number of patients who required a re-excision for tumor-positive margins was 8.8%.

Two earlier studies have shown that in patients with ER-positive breast cancer, hormonal therapy may be at least as effective as chemotherapy for inducing tumor response.[14, 15] In the last decade, neoadjuvant therapy has gained popularity, owing to the prospect of downsizing tumors to facilitate breast conservation and to evaluate biological features associated with tumor response to treatment.[2] Neoadjuvant chemotherapy

(NCT) with several cycles comprising around 4 months (e.g. TAC chemotherapy for 6 x 3-week cycles), of which it is suggested that early clinical response to the first few cycles is predictive for survival after surgery.[16] Conversely, however, NHT demonstrates a more gradual tumor response rate and may thus require longer treatment durations in order to attain maximum effect.[9] Our investigation revealed that prolonged treatment with neoadjuvant exemestane therapy results in sustained tumor response, with a reduction in mean tumor size of more than 2cm at the end of treatment.

Previous prospective, randomized studies have investigated the feasibility of aromatase inhibitors in inducing tumor downsizing in endocrine-sensitive breast cancer patients. The P024 and PROACT studies investigated 4 months of aromatase inhibitor therapy compared with tamoxifen therapy and found response rates of 55% and 50% respectively in the aromatase inhibitor arm.[17, 18] Similarly, the IMPACT study by Smith and colleagues reported a response rate of 37% following 3 months of anastrozole.[19] Aromatase inhibitor therapy in these phase III studies showed lower response rates than those found in our study, possibly related to the longer treatment duration in our cohort.

For practical purposes, tumor size assessed by clinical palpation defined the primary endpoint of this study. There was a steady decrease in the number of patients with palpable tumors between baseline and 6 months of NHT. Although the greatest decrease in tumor size was observed between baseline and 3 months of treatment, tumor size continued to fall after more than 3 months of NHT, suggesting that prolonged treatment duration may be required to achieve maximum response to optimize surgery. In an earlier report by Dixon and colleagues, more than a third of the patients included in the study continued NHT beyond 3-4 months for various reasons, causing a rise in overall response rates to more than 80% and facilitating more BCS.[9] Furthermore, maximum response in other studies was achieved approximately 4-6 months after the start of NHT.[20, 21] Similar results were recently reported in a study by Carpenter et al, who showed that the median duration of neoadjuvant letrozole to allow for BCS in patients otherwise ineligible for breast conservation was 7.5 months.[22] These findings demonstrate that extended duration of NHT achievable optimal tumor response and is well-accepted by patients.

Radiological response as measured by MRI is considered the best available response assessment modality followed by mammography.[13, 23] Although our study is limited by the inconsistent use of MRI to assess tumor response, the highest overall response rate was observed with MRI (70.2%), suggesting that the lower response rates measured by mammography and ultrasound may underestimate the true response to NHT. Although recommended, the use of MRI was not required and was up to the local investigator. The RECIST criteria (1.1) were used to evaluate MRI data in this study.[13] It must be noted that those tumors which were reduced to scattered fragments should be regarded as responders to NHT, although accurate response assessment based on RECIST is not possible. In 2012, the ACRIN 6657/I-SPY study concluded that volumetric assessment of breast tumors is a better predictor of response than measuring the longest tumor diameter in patients treated with neoadjuvant chemotherapy.[24] Since the patients in this study were included between 2010 and 2012, routine volumetric assessments were not yet standard of care, but should be considered for use in clinical practice.

Our study comprised strongly ER-positive breast cancer patients, as studies have shown that the degree of quantitative ER expression might be a valuable discriminating factor to predict hormonal therapy efficacy. In this study, we utilized percentage of positively staining tumor cells (according to the Dutch National Breast Cancer guidelines)[25] to select our patients. The ACOSOG Z1031 study selected ER-positive patients based on the Allred score (Allred score 6-8), which may be of added value in predicting response to hormonal therapy.[26] When considering staining intensity in addition to percentage of positively staining cells when selecting eligible patients, response rates may be even higher than those reported in the current study and deserves further investigation. In the adjuvant setting, efficacy of hormonal therapy was superior with incremental increases in ER expression.[27-30] NHT may be a valid alternative to neoadjuvant chemotherapy in strong ER-positive patients, and quantitative ER expression may aid the decision to opt for NHT as opposed to NCT. Petit et al. found an inverse relation between ER expression and pCR in hormone receptor-positive breast cancer patients treated with neoadjuvant chemotherapy.[31] NHT provides the prospect of improving operability of large tumors, thereby opening up new domains for further improvements in breast cancer care.

pCR is a frequently used endpoint in patients treated with NCT. In our study, however, only one patient had a pCR in both tumor and regional lymph nodes. Accordingly, it is questionable whether pCR should be the aim in breast cancer patients undergoing NHT. Apart from much longer time to maximal response when compared with NCT, one must bear in mind that the primary objective of preoperative treatment is to allow for adequate tumor downsizing to enable breast conservation in patients who would alternatively require mastectomy, and breast surgery in otherwise inoperable patients.[1] As patients may differ in the time to maximum response, monitoring tumor downsizing up to response stagnation may be more important in anticipation of surgical resection as opposed to determining a set treatment duration.

Feasibility of BCS improved from 61.8% (n=63) to 70.6% (n=72) after completion of NHT, although breast conservation was performed in 58 patients. Of note, BCS can be considered a challenging endpoint for determining NHT efficacy and must be interpreted with caution, as type of surgery can also be driven by several other factors than post-treatment tumor size alone (i.e. patient preference, surgeon preference and/or experience).

A major advantage of NHT is its application in translational research, especially with regard to predicting efficacy of hormonal therapy.[32] Measurements of the proliferation marker Ki-67 can be used to tailor neoadjuvant treatment soon after the initiation of treatment.[33] In patients treated with letrozole, the change in Ki-67 level after two weeks of treatment was of prognostic value for RFS, as was demonstrated in an earlier study.[33] Ellis et al. concluded that a single tumor Ki-67 assessment after 2 to 4 weeks after initiating aromatase inhibitor treatment might identify ER-positive breast cancer patients with poor outcomes.[34] Although this is not always feasible in daily clinical practice, results from biomarker studies like these will help pave the way to a more personalized treatment approach pertaining to hormonal therapy.

The conversion of our study from a double-arm phase III study investigating 3 versus 6 months of NHT to a single-arm phase II study of the efficacy and safety of 6 months of NHT is in part related to slow accrual and

Supplementary Table 1. **Patient and tumor characteristics after final surgery in all patients**

All patients	N	%
Feasibility of BCS (after surgery)		
not feasible	24	23.5
feasible	72	70.6
unknown	6	5.9
Final surgery performed		
breast conserving surgery	58	56.9
mastectomy	40	39.2
no resection	4	3.9
Axillary lymph node dissection		
yes	43	42.2
no	56	54.9
unknown	3	2.9
Pathological complete response (pCR)*		
pCR (pT0)	2	2.0
pCR (pTmicro)	3	2.9
No pCR	93	91.2
No surgery	4	3.9
Pathological tumor status		
pT0	2	2.0
pT1 (≤2cm)	42	41.2
pT2 (>2 - ≤5cm)	46	45.1
pT3 (>5cm)	5	4.9
pTx/unknown	7	6.9
Pathological nodal status		
pN-	55	53.9
pN+	41	40.2
unknown	6	5.9
Tumor type		
ductal	57	55.9
lobular	26	25.5
other/unknown	19	18.6
Tumor grade (BR)		
Well (G1)	32	31.4
Moderate (G2)	45	44.1
Poor (G2, G3)	9	8.8
Unknown (Gx)	16	15.7
PR status		
positive (≥10%)	54	52.9
negative	44	43.1
unknown	4	3.9
HER2 status		
positive	8	7.8
negative	83	81.4
unknown	11	10.8

BCS, breast-conserving surgery; pCR, pathological complete response.
*pCR in tumor only; BR, Bloom&Richardson

limits the assertion of our findings. During the early phases of this study, the reluctance to treating patients with NHT resulted in much resistance in the inclusion of patients in our trial. More than half of the patients allocated to 3 months of NHT continued for more than 3 months, suggesting that longer treatment duration has already gained acceptance by patients in clinical practice. Of crucial importance is the late St. Gallen consensus meeting, which confirmed that neoadjuvant hormonal treatment should be continued until maximum treatment response.[8]

CONCLUSION

A sustained response to neoadjuvant treatment with the aromatase inhibitor, exemestane, was observed up to 6 months, exceeding the generally accepted neoadjuvant treatment period of three months. Feasibility of BCS improved, consequently facilitating better cosmetic outcomes. Based on the results of this study and in line with current consensus, it is advised that the duration of NHT durations should be at least 6 months, in the absence of progressive disease. The potential to predict efficacy of adjuvant hormonal treatment based on initial response in the preoperative setting requires further exploration.

Supplementary Table 2. **Adverse events reported by all patients in this study**

	Overall		Grade 3 or 4 toxicities	
Adverse event	**N**	**%**	**N**	**%**
All adverse events*	236	100	11	100
Pain	35	14.8	3	1.3
Hot flashes	26	11.0	1	0.4
Fatigue	24	10.2	2	0.8
Insomnia	10	4.2	0	0
Mood alteration	11	4.7	0	0
Sensory neuropathy	10	4.2	2	0.8
Joint-function	9	3.8	0	0
Dizziness	8	3.4	0	0
Nausea	7	3.0	1	0.4
Hair loss/alopecia (scalp or body)	6	2.5	0	0
Rash/desquamation	6	2.5	0	0
Diarrhea	6	2.5	0	0
Dry mouth/salivary gland (xerostomia)	6	2.5	0	0
Dermal change lymphedema, phlebolymphedema	6	2.5	0	0
Musculoskeletal/Soft Tissue	6	2.5	0	0
Sweating (diaphoresis)	5	2.1	0	0
Gastrointestinal	4	1.7	0	0
Constipation	4	1.7	0	0
Weight gain	3	1.3	0	0
Infection	3	1.3	0	0
Dyspnea (shortness of breath)	3	1.3	0	0
Weight loss	1	0.4	1	0.4
Mucositis	1	0.4	1	0.4
Other (<1%)	36	14.2	-	-

*Only adverse events that make up >1% of all reported AEs or grade ¾ toxicities are specified in this table.

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CHAPTER

15

TIMING OF THE SENTINEL LYMPH NODE BIOPSY IN BREAST CANCER PATIENTS RECEIVING NEOADJUVANT THERAPY – RECOMMENDATIONS FOR CLINICAL GUIDANCE

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ABSTRACT

Neoadjuvant chemotherapy (NCT) is an increasingly important component in the treatment of both locally advanced and early-stage breast cancer. With this, a debate on the timing of the sentinel lymph node biopsy (SLNB) has emerged. At the end of the last century, the SLNB was introduced as an axillary staging modality, and this paper aims to further elucidate this issue in the context of NCT. We compiled available data on the SLNB after NCT and provide clinical guidance for the timing of the SLNB in this context. On the basis of our findings, we recommend that the SLNB can be performed after NCT in all cases. In patients with a clinically node-negative (cN0) status prior to NCT, the SLNB should be performed after NCT, and in case of a histologically confirmed negative SLNB, a completion axillary lymph node dissection (ALND) has no added value and can be omitted. In patients with clinically positive nodal involvement (cN+) prior to NCT, all axillary surgery can also be performed after NCT.

INTRODUCTION

Nodal status is one of the most important determinants of breast cancer prognosis.[1, 2] Axillary staging is successfully achieved by sentinel lymph node biopsy (SLNB), [3, 4] followed by a completion axillary lymph node dissection (ALND) in patients with proven sentinel node metastases. Needless to say, the SLNB is a means of staging and not a treatment modality. Earlier, some have questioned the need for completion ALND in patients with sentinel lymph node (SLN) involvement[5, 6]; about half of the patients with a positive SLN are known to have additional axillary nodal involvement[7-9], and even in case of omitting an ALND, the risk of developing an axillary recurrence in the presence of a positive SLN is less than one per cent.[10]

The American College of Surgeons Oncology Group (ACOSOG) Z0011 trial was initiated to investigate whether there were differences in axillary recurrences and survival in patients who underwent a completion ALND versus a SLNB alone.[11] In 2009 Bilimoria and colleagues investigated differences in axillary recurrences and survival in women with histologically confirmed node-positive breast cancer who underwent a SLNB with or without ALND.[5] All had clinically node-negative (cN0) disease. After a median follow-up of 63 months, there were no differences in axillary recurrence and survival for SLNB alone versus ALND. Even when assessing micrometastases and macrometastases separately, no differences were found in axillary recurrence and overall survival.[5] Despite evidence pointing towards equally good outcomes in terms of recurrence and survival when the ALND is withheld, we still largely perform a completion ALND in patients with a positive SLNB.

In the context of neoadjuvant chemotherapy (NCT), a similar debate has emerged on the subject of the appropriate use and optimal timing of the SLNB. Multiple studies confirm downstaging of the tumor and the axilla during NCT, increasing the likelihood of less extensive surgery.[12, 13] At present, one school of thought advocates performing a SLNB before commencing NCT, while the latter proclaim that the SLNB can be safely performed after completion of the NCT regimen. With the increasing use of NCT, clinicians are currently short of sound clinical guidelines for the management of the SLN in the context of NCT. The objective of this study was to aggregate available data on the SLNB after NCT and to provide clinical guidance for timing of the SLNB in the context of NCT.

METHODS

Search strategy

The databases Pubmed and Medline were searched until May 1st 2012 using free text and MeSH (Medical Subject Headings) terms for “breast cancer”, “Neoadjuvant chemotherapy” and “sentinel lymph node biopsy”. Only papers written in English were eligible. Included, were original studies in which accuracy or feasibility of the SLNB after NCT in invasive breast cancer was evaluated. There were no restrictions with regard to clinical nodal stage or tumor size. Completion of an ALND after a SLNB was mandatory for inclusion. Additionally, references of the included papers, and of three meta-analyses[14-16] and a systematic

review were checked.[17] Abstracts and data solely presented at conferences were excluded. In case of an update of previously published data, the most recent publication was chosen to be included.

Data extraction

For all included studies we recorded year of publication, number of patients, inclusion period, inclusion criteria, clinical nodal status, type of NCT, and conclusions made by the authors. For reason of comparison, accuracy parameters were calculated using a standard definition, and comprised 1) sentinel node identification rate (IR), 2) false negative rate (FNR), and 3) overall accuracy. IR was calculated as the number of patients with a successful SLNB divided by the total number of patients in whom a SLNB was attempted. True positive SLNB was defined as the number of patients with a positive SLNB, with or without additional positive lymph nodes at ALND. True negative SLNB was defined as the number of patients with a negative SLNB which was confirmed by a negative ALND. A false negative SLNB was defined as the number of negative SLNBs with a positive ALND. FNR was calculated as false negative / (true positive + false negative). Accuracy was calculated as (true positive + true negative) / number of patients with a successful SLNB. Whenever possible, these numbers were also calculated for subgroups based on nodal status. Weighted means were calculated based on the number of patients in each study.

RESULTS

A total of 40 original studies were retrieved for analyses, including 3328 patients. The studies were published between 2000 and 2011, and patients were included between 1994 and 2009. As some studies published data on various subgroups of patients along with overall accuracy data, these studies were included more than once. Results are shown by clinical nodal status before and after NCT.

Node-negative before NCT

An overview of the 17 studies including 1738 patients who were clinically node-negative (cN0) prior to NCT (pre-NCT) is shown in Table 1. The studies were published between 2001 and 2009, patients were included between 2001 and 2007. Mean sentinel lymph node IR was 95.0% (range 83.3%-100%); mean FNR was 11.4% (range 0%-28%); mean overall accuracy was 95.6% (range 80.6%-100%).

In patients who were cN0 prior to NCT, performing a SLNB after NCT was determined to be accurate in 14 out of 17 studies (Table 1). Three studies concluded otherwise.[18-20] The study by Papa and colleagues prospectively investigated performing a SLNB before NCT versus after NCT and found a significantly lower IR (87% versus 100%, $p<0.05$) and higher FNR (15.8% versus 0%, $p=0.04$) in patients who underwent a SLNB after— versus before NCT.[19] The other two studies found comparable higher FNRs.[18,20]

Table 1. **Overview of the results and conclusions of the included studies, cN0 preNCT**

cN0 preNCT Author	Year	n	SLN identification method	IR	FNR	Accuracy	Conclusion*
Cheung[48]	2009	78	Periaureolar Tc99; and periaureolar blue dye (patent blue, 2mL).	83.3%	16.7%	87.7%	Accurate
Hunt[37]	2009	575	At the discretion of the surgeon. Tc99 (0.5-2.5mCi) alone; or blue dye alone (isosulfan 3-5mL.); or a combination of both.	97.4%	6.0%	97.0%	Accurate
Tausch[49]	2008	121	At the discretion of the surgeon. Blue dye alone; or radioactive colloid alone; or a combination of both.	-	5.9%	-	Accurate
Gimbergues[50]	2008	82	Periaureolar (at the site of tumor localization) Tc99 (1.6mCi).	93.9%	0.0%	100.0%	Accurate
Classe[51]	2008	130	Peritumoral or periaureolar 99Tc, and peritumoral and periaureolar blue dye (patent blue, 2mL).	94.6%	7.5%	97.6%	Accurate
Yu[34]	2007	127	Peritumoral and periaureolar blue dye (5mL).	91.3%	7.2%	95.7%	Accurate
Kinoshita[38]	2007	54	Peritumoral Tc99 (30-80mBq); and periaureolar blue dye (patent blue, 3mL).	96.3%	14.3%	92.6%	Accurate
Tanaka[23]	2006	17	Peritumoral blue dye (indigocarmine, 4mL).	100.0%	0.0%	100.0%	Accurate
Mamounas[52]	2005	326	Radioactive colloid alone; or blue dye alone (isosulfan); or a combination of both.	-	12.4%	-	Accurate
Shimazu[53]	2004	25	Periaureolar Tc99 (30-80mBq); and blue dye (isosulfan, 2mL).	96.0%	7.1%	95.8%	Accurate
Lang[54]	2004	30	Peritumoral Tc99 (0.5-1mCi) (1997-2003); and blue dye (isosulfan, 1997-2002).	96.7%	0.0%	100.0%	Accurate
Reitsamer[55]	2003	17	Peritumoral Tc99 (30-60mBq); and periaureolar blue dye (patent blue).	100.0%	-	-	Accurate
Piato[56]	2003	42	Peritumoral Tc99 (15mBq).	97.6%	16.7%	92.7%	Accurate
Tafra[57]	2001	29	Peritumoral Tc99 (37mBq, 1 mCi); and peritumoral blue dye (isosulfan, 2-5mL).	93.1%	0.0%	100.0%	Accurate
Papa[19]	2008	31	Tc99; and periaureolar blue dye (isosulfan).	87.1%	15.8%	88.9%	Inaccurate
Jones[18]	2005	17	At the discretion of the surgeon.	94.1%	10.0%	94.1%	Inaccurate
Vigario[20]	2003	37	Peritumoral Tc99 (14.8mBq).	97.3%	28.0%	80.6%	Inaccurate
Overall		**1738**		**95.0%**	**11.4%**	**95.6%**	

* Conclusion according to the authors of the original paper.

Node-positive before NCT

Fifteen studies in which 839 patients who were clinically node-positive (cN+) prior to chemotherapy were included, is shown in Table 2. The studies were published between 2003 and 2011, patients were included between 1994 and 2009. Mean SLN IR was 86.5% (range 68.4%-100%); mean FNR was 10.3% (range 5.1%-29.6%); mean overall accuracy was 92.8% (range 81.8%-96.7%).

Performing a SLNB after NCT was concluded to be accurate in 11 out of 15 studies (Table 2). Four studies concluded otherwise.[18, 21-23] Various reasons exist for the studies with negative conclusions. Reasons were lower IR [18] and higher FNR [21, 22] than when performing a SLNB before NCT. Controversy still exists on this issue, as some negative studies reported lower IR but satisfactory FNR after NCT [18] while others reported that the latter was unsatisfactory with a similarly high IR.[21, 22] Therefore, there is still no exact reason for the different negative studies. Another study did not state conclusions, because this was not the main research question of the study.[24]

Node-negative and node-positive before NCT

Some studies included both patients who were cN0 or cN+ prior to NCT, and only provided data for the whole study population. Results of these 11 studies comprising 480 patients are shown in Table 3. The studies were published between 2000 and 2010, patients were included between 1994 and 2007. Mean sentinel lymph node IR was 83.6% (range 70.9%-100%); mean FNR was 9.5% (range 0%-20%); mean overall accuracy was 97.4% (range 87.5%-100%).

Performing a SLNB after NCT (post-NCT) was concluded to be accurate in 9 out of 11 studies. Two studies concluded otherwise.[25, 26] Reasons were lower IR and high FNR (18.2%26 and 20%25 respectively).

Node-negative after NCT

An overview of the 8 studies including 348 patients who were cN0 after NCT, and whom, before NCT, were either cN0 or cN+ is shown in Table 4. The studies were published between 2000 and 2010, patients were included between 1996 and 2008. Mean SLN IR was 92.0% (range 85%-100%); mean FNR was 8.5% (range 0%-33.3%); mean overall accuracy was 94.6% (range 76.9%-100%).

Performing a SLNB after NCT was considered accurate in 7 out of 8 studies. One study concluded otherwise.[27] Nason and colleagues investigated 82 patients with a clinically negative axilla and who underwent a SLNB followed by an ALND, of which only 15 patients underwent NCT. This study found an IR of 80% and an increased FNR (33%); out of 9 patients with histologically confirmed positive axillary lymph nodes, three patients had a false-negative SLN.

DISCUSSION

We performed an in-depth investigation of the different studies performed to date. Studies included either cN+ or cN0 patients only, or both (pre-NCT). We assessed a selection of studies that combined cN0 and cN+ patients before NCT and, on the basis of these results it was concluded that overall, performing a SLNB after NCT is accurate. In the majority of the studies, it was concluded that the SLNB can be performed after NCT in patients with a clinically node-negative (cN0) disease before NCT. In case of a histologically confirmed negative SLNB, a completion axillary lymph node dissection (ALND) has no added value. Similarly, in patients with clinically positive nodal involvement (cN+) before NCT, all axillary surgery can be performed after NCT.

Staging procedure

Historically, the SLNB was introduced in order to indicate disease stage and prognosis more accurately and to add value to treatment decisions based on prognostic indicators. The SLNB was not intended as a therapeutic procedure. Consequently, staging accuracy is not an endpoint in itself.[28] Although a false-

Table 2. **Overview of the results and conclusions of the included studies, cN+ preNCT**

cN+ preNCT							
Author	**Year**	**n**	**SLN identification method**	**IR**	**FNR**	**Accuracy**	**Conclusion***
Canavese[58]	2011	64	Peritumoral Tc99 (0.2mCi).	93.8%	5.1%	96.7%	Accurate
Tausch[69]	2008	46	At the discretion of the surgeon. Radioactive colloid alone; or blue dye alone; or a combination of both.	-	-	-	Accurate
Gimbergues[50]	2008	47	Periaureolar (at the site of tumor localization) Tc99 (1.6mCi).	93.6%	29.6%	81.8%	Accurate
Classe[51]	2008	65	Peritumoral or periaureolar 99Tc; and peritumoral and periaureolar blue dye (patent blue, 2mL).	81.5%	12.0%	94.3%	Accurate
Newman[59]	2007	54	Tc99; and blue dye (isosulfan).	98.1%	7.7%	94.3%	Accurate
Lee[39]	2007	219	Tc99 alone; or peritumoral blue dye alone (isosulfan, indigocarmine); or a combination of both.	77.6%	5.6%	95.9%	Accurate
Kinoshita[38]	2007	50	Peritumoral Tc99 (30-80mBq; and periaureolar blue dye (patent blue, 3mL).	90.0%	7.7%	95.6%	Accurate
Khan[24]	2005	20	Periaureolar Tc99; and blue dye (isosulfan).	100.0%	7.1%	95.0%	Accurate
Mamounas[52]	2005	102	Radioactive colloid alone; or blue dye alone (isosulfan); or a combination of both.	-	7.0%	-	Accurate
Lang[54]	2004	23	Peritumoral Tc99 (0.5-1mCi) (1997-2003); and blue dye (isosulfan, 1997-2002).	91.3%	9.1%	95.2%	Accurate
Reitsamer[55]	2003	13	Peritumoral Tc99 (30-60mBq); and periaureolar blue dye (patent blue).	69.2%	-	-	Accurate
Shen[21]	2007	69	Peritumoral Tc99 alone; or peritumoral blue dye alone (isosulfan); or a combination of both.	92.8%	25.0%	82.1%	Inaccurate
Jones[18]	2005	19	At the discretion of the surgeon.	68.4%	12.5%	92.3%	Inaccurate
Tanaka[23]	2006	26	Peritumoral blue dye (indigocarmine, 4mL).	100.0%	6.3%	96.2%	Inaccurate
Shimazu[53]	2004	22	Periaureolar Tc99 (30-80mBq); and blue dye (isosulfan, 2mL).	90.9%	15.8%	85.0%	Inaccurate
Overall		**839**		**86.5%**	**10.3%**	**92.8%**	

* Conclusion according to the authors of the original paper.

Table 3. **Overview of the results and conclusions of the included studies, cN0, cN+ preNCT**

cN0, cN+ preNCT							
Author	**Year**	**n**	**SLN identification method**	**IR**	**FNR**	**Accuracy**	**Conclusion***
Reitsamer[33]	2010	143	Peritumoral 99Tc (30mBq); and periaureolar blue dye (patent blue, 2mL).	81.1%	8.3%	95.7%	Accurate
Hino[60]	2008	55	Peritumoral 99Tc (1mL).	70.9%	0.0%	100.0%	Accurate
Yamamoto[61]	2007	20	Radioactive colloid; and blue dye (isosulfan).	100.0%	14.3%	95.0%	Accurate
Balch[62]	2003	32	Peritumoral 99Tc (0.45mCi); and peritumoral blue dye (isosulfan 5mL).	96.9%	5.3%	96.8%	Accurate
Stearns[63]	2002	34	Peritumoral blue dye (isosulfan 3-5mL).	85.3%	14.3%	89.7%	Accurate
Brady[64]	2002	14	Peritumoral blue dye (isosulfan 1mL).	92.9%	0.0%	100.0%	Accurate
Haid[65]	2001	33	Peritumoral 99Tc (0.3-1.2mCi); and peritumoral blue dye (patent blue 4mL).	87.9%	0.0%	100.0%	Accurate
Cohen[66]	2000	38	Peritumoral blue dye alone (isosulfan); or in combination with Tc99.	81.6%	16.7%	90.0%	Accurate
Breslin[67]	2000	51	Peritumoral Tc99; and blue dye; or blue dye alone.	77.4%	12.0%	93.0%	Accurate
Hidar[26]	2009	20	Peritumoral or periaureolar blue dye (patent blue, 2 mL).	80.0%	18.2%	87.5%	Inaccurate
Fernandez[25]	2001	40	Peritumoral 99Tc (111mBq).	94.4%	20.0%	88.2%	Inaccurate
Overall		**480**		**83.6%**	**9.5%**	**97.4%**	

*Conclusion according to the authors of the original paper.

Table 4. **Overview of the results and conclusions of the included studies, cN0 postNCT**

cN0 postNCT							
Author	**Year**	**N**	**SLN identification method**	**IR**	**FNR**	**Accuracy**	**Conclusion***
Ozmen[68]	2010	77	Tc99; and blue dye (isosulfan, 5mL).	92.2%	13.7%	90.1%	Accurate
Kinoshita[38]	2007	104	Peritumoral Tc99 (30-80mBq); and periaureolar blue dye (patent blue, 3mL).	93.3%	10.0%	95.9%	Accurate
Aihara[69]	2004	20	Peritumoral blue dye (indigocarmine, 5ml).	85.0%	8.3%	92.9%	Accurate
Patel[70]	2004	42	Peritumoral Tc99 (1mCi) alone; or peritumoral blue dye alone (isosulfan 5mL); or a combination of both.	95.2%	0.0%	100.0%	Accurate
Schwartz[71]	2003	21	Peritumoral blue dye (isosulfan, 1mL).	100.0%	9.1%	95.2%	Accurate
Miller[72]	2002	35	Peritumoral Tc99 (1mCi); and peritumoral blue dye (isosulfan 3-5mL).	85.7%	0.0%	96.7%	Accurate
Julian[73]	2002	34	Peritumoral Tc99 alone; or peritumoral blue dye alone (isosulfan 5mL); or a combination of both.	91.2%	0.0%	100.0%	Accurate
Nason[27]	2000	15	Peritumoral Tc99 (1mCi); and peritumoral blue dye (isosulfan, 5mL).	86.7%	33.3%	76.9%	Inaccurate
Overall		**348**		**92.0%**	**8.5%**	**94.6%**	

* Conclusion according to the authors of the original paper.

negative result, i.e. a negative SLN in the presence of positive axillary lymph nodes, may lead to incorrect nodal staging and thus to potential undertreatment with regard to adjuvant therapy, the clinical implications of false-negative results in the neoadjuvant setting are not as critical. The decision to administer systemic therapy has already been made, and undertreatment is unlikely.[22] We must bear in mind that current adjuvant treatment also incorporates breast and axillary irradiation to further reduce the probability of axillary recurrences.[29, 30] Surgical overtreatment, however, is conceivable, and the impact of additional comorbidity following more extensive surgery where it could be prevented cannot be ignored.[31] Furthermore, the risk of developing an axillary recurrence at 5 years when an ALND has been omitted in the presence of a positive SLN remains low.[10, 32]

Axillary Downstaging

One of the major advantages of axillary surgery after neoadjuvant therapy is the potential for less extensive surgery as well as reducing surgery to a single procedure. Overall, 20-44% of node-positive patients achieves a complete pathological response in the axilla with NCT[12, 13] and may thereby be spared an ALND, with its well-known comorbidities.[31] Moreover, patients who are clinically node-negative before NCT may also be spared a second surgical procedure when the SLNB is performed after NCT.[33]

Axillary response to NCT

One of the arguments restraining the progression of clinical guidelines is the potentially selective complete response following NCT in the SLN, but not in the axillary lymph nodes.[34] Dixon and colleagues correctly state in an earlier editorial that the areas of concern for surgeons as well as other physicians dealing with breast cancer patients include the alteration in lymphatic drainage leading to potentially lower IR and higher FNR.[28] Excessive fibrosis of the tumor involved lymphatics after neoadjuvant chemotherapy and the potential obstruction of lymphatic channels with cellular debris or tumor emboli may lead to inaccurate lymphatic

mapping[35], although the latter has never been proven.[28, 33] Alteration in lymphatic drainage is a heterogeneous process, and multiple studies have found that NCT does not influence mapping success.[27, 36] Fringuelli evaluated the influence of NCT on lymphatic drainage using lymphoscintigraphy before and after NCT in 129 patients; in 123 patients (95.3%), no change in drainage pattern between before and after NCT was observed.[36]

Several studies observed a uniform axillary response to NCT.[16] The SLN was shown to accurately predict axillary status, also after NCT.[37-39] We must also acknowledge that only 40-60% of patients with a positive SLN have additional axillary nodal involvement.[7] Moreover, it is important to bear in mind that there will always be a risk of axillary lymph node involvement, also in the absence of a positive SLN, and that the introduction of breast and axillary irradiation has further reduced axillary recurrences. Therefore, in patients with a histologically confirmed negative SLNB, an ALND has little added value.

Accuracy and Safety

In light of the results of previous practice-changing studies that lead to the introduction of the standard staging procedure using the SLNB, accuracy rates in terms of IR and FNR were similar to the current findings in the neoadjuvant setting. Some have commented that because these were early studies, rates are no longer acceptable in current clinical practice.[18] However, several studies have also found that IR improves with augmenting experience.[38-40] Furthermore, several direct comparisons of the accuracy of the SLNB with- versus without NCT have been conducted recently, and all have observed a similar accuracy for both strategies.[39,41] Of note, patients included in these studies were cN0 prior to NCT.

Although results are comparable across studies, some consider it safe and accurate to perform a SLNB after NCT, whereas others do not recommend the procedure. The false-negative rate is a probability of axillary nodal involvement when the SLN is negative. Currently, no FNR standard has been set, but an FNR of 5% has been deemed reasonable by several investigators.[23,43,44]

The current SENTINA trial, a substudy of the German Geparquinto neoadjuvant trial, is a four-arm trial in which the role of the sentinel lymph node (cN0 and cN+) is being investigated in patients undergoing NCT.[40,42] Recent results from the San Antonio Breast Cancer Symposium (SABCS) in 2012 showed that FNR is less favorable in patients who underwent SLNB after NCT than when the SLNB is performed before NCT.[40] The other trial is the ACOSOG Z1071 trial, a phase II study in which a SLNB + ALND after NCT is performed in T0-4, N1-2, M0 patients.[41] The primary objective is to determine FNR for sentinel lymph node surgery in women with node-positive breast cancer at initial diagnosis. To the author's knowledge, the latter has currently been suspended, however, results presented at SABCS 2012 revealed that NCT results in conversion to node-negative disease in 40% of node-positive cases, with a FNR of 12.8%.[41]

Some argue that the FNR may not be the best endpoint to use in the neoadjuvant setting and that its value is slightly overrated. Instead, looking at the risk of locoregional recurrences when an ALND is withheld may be a better approach to determining the future of the management of the axilla. Adjuvant locoregional

and systemic treatment has had a tremendous impact on improving locoregional control in recent years. In the 1980s, several studies reported on the effectiveness of radiotherapy following breast conserving therapy in patients with a positive and/or negative SLN. The majority of studies reported axillary recurrence rates below 4%, with the exception of one study reporting a 16% axillary recurrence rate.[42] A later study investigated the effect of axillary radiotherapy on locoregional recurrences in patients with a positive SLN who did not undergo an ALND.[43] Out of 73 patients, only one developed an axillary recurrence (median follow-up 32 months). All patients received adjuvant systemic treatment. In the context of NCT, all patients will already have been systemically treated, therefore axillary radiotherapy may be a suitable alternative to axillary surgery in these patients. Furthermore, the majority of hormone receptor-positive patients will also receive adjuvant endocrine therapy for a period of five years or longer to further reduce recurrence rates.

Based on comparable results, some consider it safe and accurate to perform a SLNB after NCT, whereas others do not recommend the procedure. The discrepant conclusions extend beyond individual studies. To date, three meta-analyses[15-17], and one systematic review[18] were completed. Although there is considerable overlap in the studies included, conclusions vary. Several contained studies with cN0 and cN+ patients prior to neoadjuvant therapy.[15, 17, 18] and one restricted inclusion to studies consisting of patients with cN0 after NCT only.[16] As different studies have investigated groups of patients that are all at different risks of presenting with involved lymph nodes, there is a great variability in FNR. Unfortunately, small sample sizes may also obscure statistical analyses and outcomes. No evident publication bias was shown in previous reports.[16, 17]

SLN identification method

In the reviewed studies, we summarize the identification rates based on different detection methods. (Supplementary Table 1) Several methods of SLN identification were utilized, and a majority of studies applied a combination of blue dye and radioactive colloid (usually Technetium-99m (Tc99)). Studies also varied with respect to injection location. It is difficult to draw conclusions based on these results, as they vary across studies with respect to the different clinical presentations and procedures. Zhang et al. attempted to compare SLN identification techniques in different studies and found that a combined technique resulted in a higher IR than either dye or isotope alone.[44]

CONCLUSION

In the context of NCT, clinicians are still at a loss, given the discrepancies demonstrated in conflicting guideline recommendations. The ASCO guidelines dating from 2005[45] state that performing a SLNB after NCT is not recommended. Contrary, the more recent St. Gallen expert consensus meeting in 2009 concluded that 'results of sentinel node biopsy after NCT are reliable, as described in a meta-analysis and supported by experience at a single institution'.[46] As stated earlier, NCT is an essential element in the

treatment of breast cancer in patients with large operable tumors with the potential of being downstaged and undergoing breast conserving therapy. NCT is equally effective as adjuvant chemotherapy when adequate local treatment ensues.[47] Similarly, adjuvant radiation therapy is of critical significance in reducing axillary recurrences. In this multidisciplinary approach, surgical intervention is but one of the components of the entire treatment regimen. It is therefore unjustified not to adjust surgical treatment if downstaging of the tumor and axilla occurs through valid treatment. This would certainly undermine the true potential of NCT, especially if neglecting to do so brings additional comorbidity to patients already burdened by multiple demanding treatments.

Supplementary Table 1. **Identification rate by detection method***

	Studies *N*	Patients *N*	Identification Rate
cN0 preNCT			
Combination blue dye and radioactive colloid	8	394	92%
Either blue dye or radioactive colloid	5	305	94%
cN+ preNCT			
Combination blue dye and radioactive colloid	7	247	89%
Either blue dye or radioactive colloid	3	137	95%
cN0, cN+ preNCT			
Combination blue dye and radioactive colloid	4	228	86%
Either blue dye or radioactive colloid	5	163	85%
cN0 postNCT			
Combination blue dye and radioactive colloid	4	231	91%
Either blue dye or radioactive colloid	2	41	93%

*Studies not reporting on IR or where IR was at the discretion of the surgeon were excluded from this table.

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CHAPTER

16

GENERAL DISCUSSION

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GENERAL DISCUSSION

Personalized medicine is the practice of using established and novel techniques to optimize the management of an individual patient's disease based on unique patient and tumor characteristics whilst addressing personal needs and expectations in order to choose the most optimal treatment approach with the greatest possibility of achieving the best medical outcomes. With regard to breast cancer, rapid advances in biotechnology have enabled us to look more profoundly at the biological and disease processes taking place in each patient and her tumor. Consequently, the terms 'personalized' or 'tailored' treatment have been coined to describe treatment that is fitted to the individual patient, combining conventional clinical and non-clinical characteristics with more recent molecular markers and involving patients in the decisions pertaining to their cancer.

In postmenopausal, endocrine-sensitive, early breast cancer patients, personalized endocrine treatment is still relatively unknown. Thus far, it has not yet been possible to choose the most optimal endocrine therapy regimen based on the combination of tumor biological factors and personal characteristics including demographics, comorbidities, anticipated side effects, and quality of life (QOL) and lifestyle issues. Being able to determine the best endocrine therapy regimen may be difficult when all the elements that define a patient and her disease are not completely taken into consideration. Furthermore, continuous monitoring and updating of a patient's prognosis based on subsequent events over time (such as disease events as well as other non-disease-related incidents) are needed as these may require re-evaluation of the prescribed treatment regimen. Aiming at successful therapy, whilst preventing over- or under-treatment, it is crucial to take into account all aspects of the individual patient and her disease. Above all, it is important to engage a patient in her own disease and treatment decision-making processes.

Predicting individual outcomes in breast cancer

Prognosis in medicine means estimating the probability or risk of a future outcome in an individual based on his or her characteristics. In daily clinical practice, a doctor will, directly or indirectly, make use of an array of elements to estimate the risk or probability of a certain outcome in an individual patient. In clinical trials, it is equally important to account for these characteristics using prognostic and predictive models in order to allow for more accurate estimations for individual patients. Using different cohorts of endocrine-sensitive, postmenopausal early breast cancer patients (Tamoxifen Exemestane Adjuvant Multinational (TEAM), Investigation on the Duration of Extended Adjuvant Letrozole (IDEAL), and TEAM IIA trials), we studied several prognostic and predictive factors associated with outcomes of endocrine treatment.[1, 2]

Tumor- and patient-specific factors

Endocrine-sensitive breast tumors, characterized by the expression of hormone receptors (estrogen receptor (ER) and/or progesterone receptor (PR)) on the cell surface, grow under the influence of estrogen and/or progesterone. In postmenopausal breast cancer patients, anti-estrogens (tamoxifen and aromatase inhibitors (AIs)) are the mainstay of endocrine treatment and, at present, are prescribed either as sequential treatment consisting of tamoxifen followed by an AI, or as upfront treatment with an AI for a total of 5 years.[2-6]

Over the last few years, accumulating evidence is showing improvements in long-term survival when treatment with AIs is continued beyond the standard 5-year treatment period, although it is insufficiently clear for which patients extended adjuvant endocrine therapy is suitable, and the optimal duration thereof in terms of offering maximal survival benefit with minimal toxicities.[7, 8] Primarily, however, it is essential to emphasize the importance of successfully completing the initial 5-year treatment period in the absence of disease relapse and with the best possible prognosis, while taking into consideration individual QOL and treatment compliance issues. The studies included in this thesis largely focus on determining the best endocrine therapy regimen for each individual, based on different patient- and tumor-specific features.

Based on national and international treatment guidelines, adjuvant endocrine therapy is generally prescribed in patients whose tumors express a certain level of hormone receptors, although currently no distinction is made between quantitative hormone receptor expression with respect to preference for either a sequential or upfront endocrine treatment regimen.[9, 10] Analysis of Dutch and Belgian patients included in the TEAM trial showed a preferential treatment benefit for exemestane upfront in patients whose tumors displayed a relatively high level of ER expression (Allred score 7 and 8), while a sequential treatment regimen was more beneficial in tumors with lower levels of ER expression (Allred score ≤6)(chapter 3).[11] In considering the mechanism for these findings, greater estrogen dependency and the reduction in ER expression during tamoxifen treatment may play an important role.[12] In breast tumors, ER expression is heterogeneous and it is possible that, through clonal selection, primary treatment with tamoxifen allows for the selective survival of tumor cells lacking ER expression.[12] As tolerability and effectiveness of tamoxifen treatment may diminish following ER down-regulation, the effect of switching to an AI may instigate a new and enhanced response that counters estrogen-induced tumor growth in patients with lower levels of ER expression. More detailed documentation and utilization of quantitative ER expression in the clinical setting could therefore provide further tailored treatment recommendations and improve outcomes for individual patients.

After menopause, the main source of estrogen is the body's adipose tissue. A direct relationship has been established between body-mass index (BMI, kg/m^2) and levels of circulating estrogens.[13] As obesity is associated with heightened estrogen synthesis, as well as hormone-dependent breast cancer growth,[14-16] it is conceivable that adiposity could contribute to lower efficacy of treatment with AIs. There have been several studies regarding the influence of obesity on survival after breast cancer.[15, 17, 18] Our study of patients with available BMI data in the international TEAM trial did not show an association between BMI and survival. (chapter 4) Furthermore, there was no evidence of a preferential treatment benefit for sequential or upfront endocrine treatment in different BMI categories. Some of the major trials comparing different endocrine therapy regimens have also touched upon the issue of BMI in relation to preferential treatment benefit,[19-22] but results vary tremendously. A direct comparison of the results of these studies is limited by the diversity of BMI cut-off points, and a meta-analysis of the major studies would be justified. To add, a better insight into the role of adjusting the prescribed doses of endocrine treatment may also be relevant.

With respect to other, potentially modifiable, lifestyle factors, physical activity (PA) can play an important role in improving breast cancer outcomes. PA contributes to benefiting daily physical, emotional and social functioning, with a subsequent positive effect on QOL as well as reducing the burden of side-effects arising from endocrine treatment.[23, 24] Particularly in the aging population, a decline in physical functioning is also associated with decreased social functioning, subsequent worsening of QOL as well as increased mortality.[25, 26] Few studies, however, have addressed the role of PA in affecting breast cancer survival. In our systematic review (chapter 5), we found that PA significantly improved overall survival as well as breast cancer-specific survival in elderly patients.[27] In addition, our analysis regarding PA in the TEAM-Lifestyle side-study (chapter 6) showed that overall survival improved in patients who were physically active before and after breast cancer diagnosis. In older patients especially, pre-diagnosis PA revealed better overall survival.

Quality of life, treatment compliance and side effects

In considering the individual breast cancer patient with an indication for adjuvant endocrine treatment, maximal effectiveness can only be achieved if the patient also maintains a good QOL while adhering to her prescribed treatment regimen. Side effects of adjuvant endocrine treatment can seriously hamper daily functioning and QOL of breast cancer patients, and are the greatest cause of non-compliance to endocrine treatment. Approximately half of all patients prescribed adjuvant endocrine treatment discontinue before the pre-designated end-date.[28] As observed in our study on compliance to extended adjuvant endocrine therapy (chapter 9), an additional 20% of patients discontinue treatment in this setting.[7] Considering that the goal of (extended) adjuvant endocrine therapy is to further improve individual survival outcomes, it is important to address alternative ways of reducing toxicities and improving compliance while maintaining maximal QOL and treatment benefit.

Insight into the different side effects associated with endocrine therapy and understanding its impact on QOL and daily functioning is essential, given the growing acceptance of extended adjuvant endocrine treatment durations (chapter 8). In clinical practice, it is important to carefully weigh potential treatment benefits against potential sacrifices in QOL and daily functioning. It is likely that a combination of patient- and/or tumor-biological as well as lifestyle mechanisms contributes to the presence and severity of AEs, and understanding the underlying mechanism for the manifestation of AEs in some, but not all patients is of much clinical interest.

When determining the optimal endocrine treatment strategy while maintaining QOL, a patient's susceptibility to these specific AEs of treatment is seldom taken into account. With respect to AIs, several specific side-effects, including vasomotor symptoms (hot flashes, night sweats) and musculoskeletal symptoms, may derive from the body's response to a further reduction in circulating estrogen levels.[29] Accordingly, we predicted that specific side effects of endocrine treatment may be related to improved endocrine treatment outcomes, while taking into account confounders such as non-compliance. Longer survival was noted in patients who reported one or more specific AEs (vasomotor symptoms and/or musculoskeletal AEs) than

patients who did not report these symptoms (chapter 10 and chapter 11).[30,31] Some critics have suggested that reporting is selective, and patients who report their AEs may be inherently different from patients who do not report these specific AEs. For example, patients who report specific side effects are more likely to engage in other healthy lifestyles, which could contribute to better outcomes than in women who do not report these symptoms.[32] It is plausible, however, that the majority of reported side effects does not distinguish patients by their lifestyle habits. Bearing this in mind, we performed additional analyses which revealed that survival outcomes were still superior for patients with specific AEs when compared with patients who reported nonspecific AEs and patients who did not report any AE separately (data not shown).[33]

Not all patients undergoing endocrine therapy will develop specific AEs, implying that AEs may also be the result of variable estrogen levels in AI-treated patients. Polymorphisms in the aromatase gene, CYP19A1, have been associated with differences in circulating estrogen concentrations previously[34], and may be related to the diversity of responses to AIs among breast cancer patients.[35] CYP19A1 gene polymorphisms may thus play a causal role in the development of specific AEs. This hypothesis was tested in chapter 12, which revealed that specific AEs were more commonly reported by patients who expressed one of three CYP19A1 variants. Genetics-based treatment decisions have rapidly advanced in recent years and companies now market genetic tests (such as Oncotype DX and Mammaprint) capable of predicting added benefit of treatment based on a tumor's genetic profile.[36] With these tests, patients and doctors alike use this information to weigh potential treatment advantages with important lifestyle and QOL issues. For patients, it signifies more insight and fewer feelings of uncertainty about the risk of disease recurrence, and with this data, patients can better understand their disease process and actively engage themselves in the treatment decision-making process.

Dynamic prediction

The various studies described in this thesis demonstrated that several conventional and unconventional clinical factors are associated with predicting treatment success, QOL, and survival in postmenopausal, endocrine-sensitive early breast cancer patients. The majority of determinants that influenced individualized treatment decisions were based on patient- and tumor-specific features that were measured at the time of diagnosis or at the start of adjuvant endocrine treatment. In considering individualized treatment strategies, it is also important to re-evaluate a patient's health and disease status during treatment and over time, using this knowledge to modify therapy where deemed necessary. As described in chapter 7, current statistical models still fall short of taking into account changes in a patient's health status or the occurrence of specific events throughout the course of treatment, which may alter previously predicted survival outcomes. The following example illustrates our need for better prediction models for all cancer patients. We consider our 69-year-old postmenopausal breast cancer patient from chapter 7 who was diagnosed with a grade III, 1.5cm, ER- and PR-positive tumor two years earlier. At the time, she underwent breast-conserving surgery, adjuvant radiotherapy and chemotherapy, and started adjuvant endocrine therapy. During her regular yearly visit she tells that she is suffering a number of side effects and discusses the possibility of discontinuing

her endocrine treatment. At the time of diagnosis two years earlier, the woman and her physician solicited Adjuvant![37] to calculate her probability of being alive 10 years later. Without additional chemotherapy or endocrine therapy, this probability was 38.9%, and with additional chemotherapy and endocrine therapy meant an additional 12.7% chance of being alive 10 years later. What Adjuvant! could not take into account at that time was whether this patient's survival probability would still be the same two years later. Does this woman still have a 38.9% chance of being alive 10 years after her initial breast cancer diagnosis? Two years earlier it was not possible to know whether this woman would suffer a relapse, or that she might discontinue endocrine treatment because of side effects that obstructed her QOL and daily functioning.

Time has shown to play a vital role in predicting as well as modifying survival outcomes, and in our endeavour to tailor treatment to the individual patient, the occurrence of events and the capacity for a patient's health and disease status to change over time is frequently neglected. Furthermore, it is important to keep in mind that the individual's QOL and daily functioning can be seriously affected by endocrine treatment, and dynamic prediction can help the patient and her doctor weigh the benefits and harms of discontinuing treatment against improvements in QOL. We have developed a clinically applicable dynamic prediction model which incorporates the key factor, time, into a survival model for breast cancer patients. Although external validation and fine-tuning of this prediction model needs to be performed, our analysis reiterates the importance of continuously re-evaluating the previously prescribed treatment regimens. It is our obligation as physicians to help patients weigh the benefits and detriments of treatment against mortality risk and personal preferences during this long-term treatment relationship in order to attain the best possible treatment advice, tailored to suit the individual's needs.

Dynamic prediction can be considered a novel concept that provides more sophisticated estimates of survival probabilities based on a more realistic reflection of the course of a patient's health and disease status over time. At present, we are developing a more refined, user-friendly, web-based dynamic prediction tool that can be accessed during clinical follow-up visits so as to re-evaluate and, where necessary, modify individual treatment recommendations. Implementing and improving dynamic prediction in current clinical practice entails expanding existing multidisciplinary as well as national and international collaborations in order to develop better models based on more extensive datasets. Ultimately, these models will help guide patients and clinicians during the course of treatment, not only with respect to breast cancer, but over the full scope of clinical oncology, and likely, other 'chronic' conditions.

Pre-operative treatment

The final part of this thesis is dedicated to pre-operative (neoadjuvant) systemic treatment for breast cancer patients and the role of the sentinel lymph node biopsy (SLNB) in this context. Neoadjuvant treatment allows for downsizing and downstaging of large (≥2cm) or locally advanced and/or inoperable primary tumors prior to surgical resection. In addition, neoadjuvant treatment provides the convenience of efficiently gaining insight into the effects of systemic treatment on various biochemical, molecular and histological

tumor features, on the basis of which valuable biomarkers can be identified and clinical decisions can be made.

In some patients, it can be challenging to determine the best neoadjuvant treatment regimen. Neoadjuvant chemotherapy may not be the most appropriate treatment option for elderly and/or frailer patients, as well as in patients whose tumors have high levels of ER expression. Especially in these kinds of patients, neoadjuvant endocrine treatment has been proposed as a valid alternative to neoadjuvant chemotherapy. In strongly endocrine-sensitive breast cancer patients, neoadjuvant endocrine therapy is gaining popularity, although there remains considerable uncertainty about issues such as the optimal treatment duration and the most suitable modality for response assessment. Neoadjuvant endocrine therapy trials have typically treated patients for 3 or 4 months prior to surgery, but emerging evidence suggests that longer treatment durations are feasible and that tumors continue to regress during longer treatment periods, without serious threats concerning safety and toxicity. In our phase II trial, we observed sustained tumor downsizing as well as more breast conservation (chapter 14). Similar results were described in our earlier review of the literature on neoadjuvant endocrine therapy (chapter 13), with maximal responses when treatment was extended beyond 3-4 months.[38] Our results strongly suggest that treatment periods of at least 6 months should be sought after in clinical practice.

The role and timing of the sentinel lymph node biopsy (SLNB) as well as the axillary lymph node dissection (ALND) in the context of neoadjuvant treatment still prompts much debate, and clinical guidelines are largely lacking or inconclusive.[9, 39, 40] The SLNB was originally introduced to accompany surgical tumor excision as a means of specifying disease stage and prognosis, as well as to guide further treatment decisions concerning systemic, locoregional and additional surgical intervention. As neoadjuvant treatment causes a shift in the timing of surgery, it may seem logical to perform the SLNB at the moment of primary surgery. Needless to say, some have argued that neoadjuvant chemotherapy can reduce staging accuracy of the sentinel lymph node, although the clinical implications may be slightly overstated. Potential under-treatment resulting from increased false-negative rates may not be as relevant, as the decision to administer systemic treatment has already been made and the risk of developing an axillary recurrence after a positive SLN without an additional ALND is low.[41] Yet the risk of surgical over-treatment and the impact of additional comorbidity following surgical intervention is significant. With the advent of neoadjuvant systemic treatment as an important contributor to current breast cancer treatment, it is justified to adjust surgical treatment if downstaging of the tumor and axilla has occurred.

Tailored endocrine treatment - a pursuable goal?

"Individualization of drug therapy is an evolution, not a revolution", was the statement by Lesko and Schmidt [42], who describe that 'personalized' apothecary practice dates back to 2600 B.C. as evidenced by medical texts and prescriptions written on clay tablets.[42] Although up until the late 19th and early 20th centuries the concoction of formulations to treat the individual patient was common practice, the expansion

of our medical knowledge and intensified production of one-size-fits-all treatments made way for more efficient drug development and the evolution of evidence-based medicine which now sets the standard for new treatments. With the advent of evidence-based medicine, some critics convey that the use of clinical trials does not truly allow for personalized medicine as the majority of these trials maintain strict in- and exclusion criteria in which case only a certain subset of patients can be included and results cannot be applied to the more general population.[42, 43]

Personalized medicine requires more than an overall cohort benefit. In modern medicine, we have reached a tipping point, where treatment decisions based on large clinical trials and overall treatment benefits for large groups of patients are replaced by more complex models targeting individual patients. In addition, the physician's individual clinical expertise as well as the patient's more active involvement with her condition in order to convey important issues driving individual preferences and maximizing the probability of successful treatment have become an integral part of a treatment plan.

In current clinical practice, there is a need for more accurate and easily accessible personalized prediction models that surpass the currently available selection of genetic tests such as Mammaprint and OncotypeDX.[36] A major limitation of genetic tests is that they lack the capacity to account for issues associated with daily functioning in individual patients, including QOL, compliance, and side effects. We demonstrated that patients vary in their responses to endocrine therapy. The studies that make up this thesis show that we are capable of combining a wide range of patient- and tumor-specific features into a single model that offers opportunities to adjust treatment advice over time, aimed at further personalized medicine. Moreover, the presented dynamic prediction model can help empower individual patients to convey personal preferences and partake in their own treatment decisions in order to put into perspective side effects and QOL aspects beside treatment benefit. For the scientific community, the need for solid prediction models underlines the importance of further in-depth investigations and more large-scale collaboration to permit additional fine-tuning of our dynamic prediction model for an even broader target audience. Based on statistics, we can establish the best objective outcome for the disease, but based on an array of unique characteristics, we can provide the best care for the individual patient.

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APPENDICES

Summary of the research
Nederlandse samenvatting
List of co-authors
List of publications
Acknowledgements / Dankwoord
Curriculum Vitae

SUMMARY OF THE RESEARCH

This thesis describes several important aspects of adjuvant endocrine therapy for postmenopausal women with endocrine-sensitive, early-stage breast cancer. In our ongoing efforts to tailor treatment so as to provide the best possible care for each of our patients, we studied the influence of various tumor- and patient-related factors on outcomes of adjuvant endocrine therapy. These factors include quantitative hormone receptor expression, body weight, age and physical activity, changes in prognosis over time, quality of life, treatment compliance, treatment-specific side effects, and single nucleotide polymorphisms (SNPs) of the aromatase gene (CYP19A1). The results of these studies contribute to further individualization of hormone receptor-positive early breast cancer and can improve survival outcomes while maintaining a good quality of life. In addition, the effect of preoperative (neoadjuvant) endocrine therapy in strong endocrine-sensitive, postmenopausal breast cancer patients is described. Finally, this thesis includes a chapter on the optimal timing of the sentinel lymph node procedure in breast cancer patients treated with neoadjuvant systemic therapy in general.

Approximately 75% of postmenopausal breast cancer patients have tumors that grow under the influence of the hormone estrogen, and are thus classified as endocrine-sensitive. These tumors are characterized by the presence of hormone receptors (estrogen receptors (ER) and/or progesterone receptors (PR)) lining the tumor cells. The decision to administer adjuvant endocrine therapy is largely dependent on the presence and level of expression of these hormone receptors, after earlier studies revealed that endocrine therapy is most effective in patients whose breast tumors express these receptors. Adjuvant endocrine therapy for postmenopausal, endocrine-sensitive early breast cancer patients is generally prescribed for a period of 5 years or more. In the early years of adjuvant endocrine therapy, the anti-estrogen, tamoxifen, initially prescribed for 2, and later 5 years, significantly improved breast cancer survival when compared with no treatment at all. Later, with the introduction of aromatase inhibitors, also prescribed for five years or following 2-3 years of tamoxifen treatment (either regimen totaling 5 years of treatment), further improvements in prognosis were established in these patients. More recently, studies have revealed that the addition of aromatase inhibitors for additional 2 to 5 years after 5 years of tamoxifen provides an even greater survival benefit in high-risk patients.

Part I – Patient- and tumor-specific characteristics

Part I of this thesis concerned the identification of a variety of factors that drive breast cancer outcomes in postmenopausal, endocrine-sensitive patients who participated in the Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial. In the TEAM trial, patients who had undergone adequate local treatment were randomized to receive either sequential therapy (2-3 years of tamoxifen followed by 3-2 years of the aromatase inhibitor, exemestane) or five years of exemestane. The TEAM trial was executed in nine different countries and included 9779 breast cancer patients, of which 3168 were included in the Netherlands and Belgium. Central data management was carried out at the Datacenter of the Department of Surgery at Leiden University Medical Center in the Netherlands. In 2011, the main results of the TEAM trial were published in the Lancet: there were no differences in disease-free survival (DFS) between the two study

groups. Central revision of the available tumor material following publication of the main manuscript has provided opportunities for further biomarker research.

In chapter 1, we provide a general introduction of adjuvant endocrine therapy, its development over time and its application for treating postmenopausal, endocrine sensitive breast cancer patients. In chapter 2, we made use of the centrally reviewed tumor material of patients included in the Dutch and Belgian TEAM trial cohort to study the influence of several tumor-specific biomarkers (ER, PR, and human epidermal growth factor receptor 2 (HER2)) on endocrine treatment efficacy. Treatment with upfront exemestane resulted in a better DFS than sequential treatment in women whose tumors expressed high levels of the ER. In chapter 3, survival outcomes were studied in relation to histological subtype (ductal or lobular breast cancer) in Dutch and Belgian TEAM trial patients (n=3168). We compared the two treatment regimens in relation to histological subtype and quantitative ER expression (based on the Allred score). The Allred score evaluates the percentage and intensity of tumor cells staining positively for hormone receptors (ER and PR). Lobular breast tumors frequently express higher levels of ER when compared to ductal breast tumors and may thus show better survival outcomes. Although our results, did not reveal any differences in efficacy of the two endocrine treatment regimens between patients with ductal and lobular breast cancer, patients who were considered ER-rich, regardless of histological subtype had better outcomes when treated with 5 years of exemestane, while the sequential treatment regimen was superior for ER-poor patients.

Obesity, defined as a body-mass index (BMI, kg/m^2) of ≥30, has been related to increased estrogen synthesis as well as to hormone-dependent breast cancer growth. After termination of ovarian estrogen synthesis after menopause, estrogen production occurs in other tissues, including adipose tissue. It has been suggested that the increased estrogen synthesis in obese patients could reduce the efficacy of adjuvant endocrine therapy, especially pertaining to aromatase inhibitors. Aromatase inhibitors function by lowering the conversion of androgens to estrogens. In chapter 4, BMI was studied in relation to breast cancer outcomes in postmenopausal, endocrine-sensitive, early breast cancer patients in the international TEAM cohort. BMI data were available for 4711 patients (median BMI 26.2 kg/m^2 (SD 6.68)). 29.7% of patients were normal-weight (BMI between 18.5 and 25 kg/m^2), 28.2% were overweight (BMI between 25 and <30 kg/m^2), and 17.5% were obese (BMI between >30 and 45 kg/m^2; 24.6% of patients were missing BMI data). After a follow-up of 6.5 years, no differences in 5-year DFS or breast cancer-specific survival (BCSS) were observed between the treatment arms in relation to BMI, which is in contrast to what is generally reported in the currently available literature. The lack of a statistically significant differences between the two treatment arms in relation to BMI may be due to the relatively short follow-up period. It is also possible that adiposity negatively influences effectiveness of aromatase inhibitor treatment, which could explain the absence of a preferential benefit for upfront exemestane therapy in overweight and obese patients in our cohort.

In studying so-called 'modifiable' variables that can improve breast cancer outcomes as well as QOL, physical activity is an element where the individual patient can play an active role. In chapters 5 and 6, we investigated

the influence of physical activity (PA) on breast cancer outcomes. First, we performed a systematic review of the available evidence on the relation between physical activity and survival in postmenopausal breast cancer patients, which is described in chapter 5. Seventeen studies (n=497) investigated physical activity in relation to overall survival (OS), DFS and/or BCSS and met the inclusion criteria. In this review, we showed that, in older breast cancer patients, any form of physical activity improved the aforementioned survival outcomes. In chapter 6, we studied physical activity in relation to breast cancer recurrence and survival in the TEAM-Lifestyle side-study (n=521) using the validated European Prospective Investigation into Cancer Physical Activity Questionnaire. Metabolic Equivalent Task (MET)-hours, a measure of the intensity and duration of a particular activity, were used to study physical activity in relation to OS and BCSS. 521 Dutch and Belgian TEAM trial patients completed questionnaires 1 and 2 years following breast cancer diagnosis, and the number of hours spent on various activities (walking, cycling, gardening, household activities and sport, both before and after breast cancer diagnosis) were recorded. Our results showed that physical activity, both before and after breast cancer diagnosis, improved OS, especially in women over the age of 65 years. Predictive models based on patient- and tumor-specific characteristics at the time of breast cancer diagnosis are commonly used to help make decisions regarding adjuvant systemic therapy. When considering long-term endocrine treatment, however, certain events that can have an effect on prognosis (such as early treatment discontinuation or disease recurrence) may occur during the course of endocrine treatment. Furthermore, the impact of certain patient- and tumor-specific characteristics (such as age, HER2 status and nodal status) on prognosis have shown to vary over time. Surprisingly, cancer prediction models to date have never before accounted for these prognosis-modifying events, therefore long-term outcome predictions are limited. Chapter 7 describes an innovative dynamic prediction model based on Dutch and Belgian TEAM trial patients and which consolidates conventional 'static' variables with time-changing and time-varying 'dynamic' variables. This dynamic prediction model shows us that as the time since diagnosis elapses, predictions concerning a patient's prognosis, in fact, need to be updated. Patients and their doctors can utilize this model throughout endocrine treatment in order to adjust treatment strategies and/or lifestyle behaviors where reckoned necessary in order to improve prognosis and maintain quality of life. Although external validation and further fine-tuning of the dynamic prediction model is still awaited (and awaiting longer follow-up), this model is informative and it is conceivable that it will lead to the development of more elaborate dynamic prediction models that can be consulted in clinical practice.

Part II – Quality of life, treatment compliance and side effects

Part II of this thesis addressed a variety of issues concerning adjuvant endocrine therapy that influence treatment outcomes for individual patients. Adjuvant endocrine therapy is associated with a variety of side effects that, in addition to the psychological impact of the diagnosis breast cancer per se, can be of detriment to treatment compliance and significantly impair quality of life (QOL) and daily functioning in breast cancer patients. Determining which elements of QOL and daily functioning carry more weight than others is key when selecting the most appropriate treatment regimen, and chapter 8 describes differences in QOL of 543 Dutch TEAM trial patients who participated in the TEAM-Lifestyle side study (study setup

described above for chapter 6). No differences in overall QOL were found between the two randomized endocrine treatment regimens. However, emotional and sexual functioning, as well as symptoms of fatigue, insomnia and shortness of breath were statistically significantly worse in women treated with exemestane compared to women treated with tamoxifen. Only those differences pertaining to fatigue were considered clinically relevant. Importantly, our study also revealed that overall QOL as well as the majority of functioning and symptom scales improved between the 1st and 2nd measurements in the TEAM-Lifestyle side study. This implies that improvement and/or habituation occurs and can be of use to those involved in the care of women experiencing these symptoms.

QOL also plays an important role in early treatment discontinuation and non-compliance, particularly with regard to long-term treatment. Previous studies have shown that 40% to 60% of patients undergoing adjuvant endocrine treatment discontinue within the first 5 years. Simultaneously, there is accumulating evidence that longer endocrine treatment durations are beneficial for breast cancer survival. The IDEAL (Investigation on the Duration of Extended Adjuvant Letrozole) study investigates the efficacy of extended adjuvant letrozole treatment (2.5 versus 5 years), after 5 years of adjuvant endocrine therapy in postmenopausal early breast cancer patients. Because non-compliance can significantly influence treatment success in some patients, we investigated how many patients discontinued letrozole treatment and reasons therefore in chapter 9. Out of 1215 studied patients, 18.4% were non-compliant within the first 2.5 years of extended treatment. In more than 85% of the cases, non-compliance was caused primarily by debilitating adverse events (AEs). Risk factors for early treatment discontinuation were: prior treatment with either tamoxifen or exemestane alone, a longer treatment-free interval between the first 5 years of adjuvant treatment and the start of letrozole, and low-risk nodal stage at diagnosis. Age was not a risk factor for non-compliance.

Hot flashes and night sweats (collectively known as vasomotor symptoms) as well as musculoskeletal adverse events are frequently occurring side effects of aromatase inhibitors and may be related to further lowering of circulating estrogen levels in postmenopausal women. We investigated the intricate relationship between specific adverse events and treatment efficacy in patients who experience these specific side effects in chapters 10 and 11, first in the Dutch/Belgian cohort and subsequently in the international TEAM trial cohort. In both studies, we found that women who reported vasomotor symptoms and/or musculoskeletal adverse events had a better DFS than women who did not report these symptoms (respective hazard ratios (HR) 0.731 (95% confidence interval (CI) 0.616-0.866) and 0.826 (95%CI 0.694-0.982)). The strongest effect was found in patients who reported vasomotor symptoms. These data conclude that specific side effects of adjuvant endocrine treatment are associated with better survival outcomes and can be used in clinical practice to predict endocrine treatment efficacy.

It has yet to be discovered why some women undergoing adjuvant endocrine treatment develop specific adverse events while others do not. One hypothesis for the presence of these specific adverse events in some patients, but not in others, is that genetic variants in the aromatase gene (CYP19A1) drive differences

in aromatase inhibitor metabolism and hence, treatment effectiveness. In chapter 12, we study genetic variations ('single nucleotide polymorphisms'; SNPs) of the aromatase gene (CYP19A1) in relation to the occurrence of the abovementioned specific adverse events. Using a 'tagging SNP' approach, we were able to study approximately 80% of the CYP19A1 gene for genetic variants. Based on the results of 737 exemestane-treated Dutch TEAM trial patients, 3 SNPs (rs934635, rs16964189 and rs7176005) were found to be associated with reporting specific adverse events. These hypothesis-generating results require further investigation before implementation in clinical practice.

Part III – Pre-operative and operative treatment

In Part III of this thesis, we focus on the role of pre-operative, or neoadjuvant, systemic therapy as part of personalized breast cancer treatment. Neoadjuvant systemic therapy can be used to downsize and downstage large (or inoperable) tumors before surgical resection. In recent years, neoadjuvant treatment has facilitated in studying a tumor's 'in-vivo' response to systemic treatment and in monitoring changes in biomarkers for the development of novel targeted treatments. Neoadjuvant chemotherapy (NCT) is now well-integrated in current clinical practice, although studies have also shown that the effectiveness NCT decreases in stronger ER-positive tumors. Therefore, neoadjuvant endocrine therapy, also known as neoadjuvant hormonal therapy (NHT), with aromatase inhibitors has rapidly been gaining recognition for strongly endocrine-sensitive breast cancers as well as for patients who are considered unsuitable for neoadjuvant chemotherapy. The time it takes for a tumor to attain maximal response is, however, longer for NHT than for NCT, and no consensus has been reached as of yet concerning the optimal duration of neoadjuvant treatment with aromatase inhibitors. In previous clinical studies, patients have commonly been treated for 3-4 months, although our systematic review (chapter 13) presented ample evidence for the beneficial effect of longer endocrine treatment durations on sustaining further reductions in tumor size. In the TEAM IIA study, we investigated the tumor downsizing and down-staging in 102 strongly endocrine sensitive (>50% ER positivity), postmenopausal breast cancer patients treated with neoadjuvant exemestane for more than 3 months (chapter 14). After a median treatment duration of 5.78 months, this study confirmed a continuing reduction in tumor size after 3 months of NHT. It was concluded that in strongly ER-positive breast cancer patients who are eligible for NHT and whose tumor response to neoadjuvant therapy, the treatment should be continued beyond 3 months.

In chapter 15, the timing of the sentinel lymph node biopsy (SLNB) and the necessity of performing a completion axillary lymph node dissection (ALND) in patients undergoing neoadjuvant systemic treatment was investigated, as there is no clear consensus on this topic. The SLNB replaced the conventional ALND at the end of the last century and is now used for axillary staging. An additional advantage is that a number of women now do not need to undergo an ALND, which has also lead to a significant decrease in the comorbidities associated with an ALND. Neoadjuvant systemic treatment is generally prescribed to achieve tumor downsizing as well as downstaging, with subsequent surgical resection. An advantage of performing the SLNB after completion of neoadjuvant treatment is that all surgery can be performed in a single surgical procedure. Our systematic review revealed that the SLNB can be safely performed after neoadjuvant treatment in both clinically node-positive and node-negative patients.

A variety of different elements that contribute to the intricate web of personalized breast cancer treatment are presented in this thesis. Chapter 16 discusses the findings presented in the different studies in the context of personalized therapy. Aside from the known tumor-specific characteristics that determine whether or not to prescribe adjuvant endocrine therapy, we show how a variety of patient-, treatment-, and tumor-specific specific characteristics are also important drivers of adjuvant endocrine treatment success. In particular, our study of dynamic prediction marks a pivotal point in oncology research, presenting a novel way of continual evaluation of endocrine treatment benefit in individual patients.

NEDERLANDSE SAMENVATTING

In dit proefschrift wordt ingegaan op verschillende aspecten van adjuvante hormonale therapie bij de postmenopauzale vrouw met een hormoongevoelig mammacarcinoom. De bestudeerde aspecten betreffen patiënt-gerelateerde en tumor-gerelateerde factoren, waarbij de mate van hormoonreceptorexpressie, het lichaamsgewicht, het effect van fysieke activiteit in relatie tot de leeftijd, de verandering van de prognose tijdens follow-up, kwaliteit van leven, therapietrouw, de relatie tussen het optreden van wel of geen specifieke bijwerkingen en impact van kiembaanveranderingen in het aromatasegen (CYP19A1) tijdens de behandeling met hormonale therapie aan de orde komen. De resultaten beschreven in de verschillende studies van dit proefschrift dragen bij aan een verdere geïndividualiseerde behandeling van het hormoongevoelig mammacarcinoom bij de postmenopauzale vrouw, met als doel verhogen van de overlevingskansen met behoud van kwaliteit van leven. Daarnaast wordt ingegaan op het effect van preoperatieve (neoadjuvante) hormonale therapie bij de postmenopauzale vrouw met een hormoongevoelig mammacarcinoom en tot slot, het optimale tijdstip voor het uitvoeren van de schildwachtklierprocedure bij vrouwen die behandeld worden met neoadjuvante systemische therapie in het algemeen.

Bij ongeveer 75% van de postmenopauzale vrouwen met borstkanker is er sprake van een hormoongevoelig mammacarcinoom. De tumor groeit in deze gevallen onder invloed van het vrouwelijk hormoon oestrogeen en wordt gekenmerkt door de aanwezigheid van hormoonreceptoren ter hoogte van de tumorcellen. In de loop van de tijd is duidelijk geworden dat hormonale therapie met name effectief is bij patiënten met een hormoongevoelige tumor (oestrogeen receptor (ER)-positief en/of progesteron receptor (PR)-positief). De aanwezigheid van deze receptoren, en in het bijzonder de mate van ER positiviteit, vormt de basis voor verdere therapeutische beslissingen. Bij postmenopauzale vrouwen met een hormoongevoelig mammacarcinoom wordt veelal gekozen voor een adjuvante hormonale behandeling van 5 jaar of langer. Behandeling met tamoxifen, een anti-oestrogeen, werd aanvankelijk gedurende 2, en later 5 jaar gegeven, en heeft de prognose bij deze patiënten aanzienlijk verbeterd ten opzichte van de prognose zonder adjuvante hormonale therapie. De introductie van aromataseremmers (non-steroidaal: anastrozol, letrozol; steroidaal: exemestaan), gegeven hetzij gedurende 5 jaar of in een sequentie na tamoxifen (voor een totaalperiode van 5 jaar) resulteerde in een verdere verbetering van met name de ziektevrije overleving. Ondertussen is gebleken dat verlengde hormonale therapie voor een verdere periode van 2-5 jaar voor hoog-risico patiënten ook meerwaarde heeft.

Deel I – Patiënt- en tumorspecifieke kenmerken

In Deel I van dit proefschrift, werd onderzoek gedaan naar verschillende factoren die mogelijk geassocieerd zijn met de effectiviteit van adjuvante hormonale therapie bij postmenopauzale, hormoongevoelige borstkankerpatiënten die deelnamen aan de Tamoxifen Exemestane Adjuvant Multinational (TEAM) studie. Respectievelijke borstkankerpatiënten die een adequate lokale behandeling kregen en in aanmerking kwamen voor adjuvante systemische hormonale therapie werden in de TEAM studie gerandomiseerd tussen een sequentiële behandelingsstrategie (2-3 jaar tamoxifen gevolgd door 3-2 jaar exemestaan) en

uitsluitend exemestaan gedurende 5 jaar. De TEAM studie was geactiveerd in 9 landen, en includeerde in totaal 9779 patiënten, waarvan 3168 in Nederland en België. Centraal datamanagement vond plaats via het datacenter Heelkunde van het Leids Universitair Medisch Centrum. In 2011 publiceerde de studiegroep het hoofdmanuscript in de Lancet. Na vijf jaar follow-up werden géén verschillen in ziektevrije overleving gevonden tussen de twee behandelingsstrategieën. De centrale revisie van het tumorweefsel bood hierna mogelijkheden voor nader biomarker onderzoek.

Hoofdstuk 1 betreft een algemene inleiding over adjuvante hormonale therapie, de doorgemaakte ontwikkelingen van de laatste jaren en huidige toepassingen bij postmenopauzale vrouwen met borstkanker. In hoofdstuk 2 worden de resultaten beschreven van onderzoek in het Nederlands/Belgische TEAM cohort naar de impact van verschillende tumor-specifieke biomarkers (ER, PR, en human epidermal growth factor receptor-2 (HER2)) die mogelijk gerelateerd zijn aan de effectiviteit van de verschillende hormonale behandelingsstrategieën. Hierbij werd gebruik gemaakt van de resultaten verkregen na centrale revisie van het tumorweefsel. Bij vrouwen met borsttumoren met een hoge mate van ER expressie werd een betere 5-jaars overleving gevonden indien zij behandeld waren met uitsluitend exemestaan in vergelijking met de sequentiële behandelingsstrategie.

In hoofdstuk 3 werd de behandeling met exemestaan vergeleken met de sequentiële behandelingsstrategie in respectievelijk ductale en lobulaire tumoren in het Nederlands/Belgische cohort (n=3168), en werd de impact van de gekwantificeerde ER expressie (op basis van de Allred score) hierbij geëvalueerd. De Allred score voor hormoonreceptoren wordt gekwantificeerd op basis van het percentage positief aankleurende tumorcelkernen en de intensiteit daarvan. Lobulaire borsttumoren zijn vaker sterk ER-positief in vergelijking met ductale tumoren, hetgeen zou kunnen resulteren in een verschillende effectiviteit van de twee onderzochte behandelingsstrategieën. Er werden geen statistisch significante verschillen in effectiviteit gevonden tussen de twee behandelingen bij ductale en lobulaire tumoren. Een betere ziektevrije overleving werd echter wel geobserveerd bij vrouwen met sterk ER-positieve tumoren die behandeld waren met exemestaan ten opzichte van een sequentiële behandeling. Bij vrouwen met een minder sterk hormoongevoelige tumor resulteerde de sequentiële behandelingsstrategie tot een betere ziektevrije overleving.

Obesitas, gedefinieerd als een body-mass index (BMI, kg/m^2) van ≥30, is geassocieerd met een verhoogde aanmaak van oestrogenen, en hierdoor met hormoon-afhankelijke borstkanker groei. Het termineren van de oestrogeenproductie door de ovaria na de menopauze zorgt ervoor dat oestrogeen elders wordt geproduceerd, onder anderen in vetweefsel. Bij vrouwen met obesitas kan de verhoogde oestrogeenproductie mogelijk leiden tot een verminderde effectiviteit van adjuvante hormonale therapie in het algemeen, en aromataseremmers in het bijzonder. Aromataseremmers blokkeren het aromatase enzym, hetgeen nodig is bij de omzetting van androgenen naar oestrogenen bij de postmenopauzale vrouw, en welke ook in vetweefsel aanwezig is. Hoofdstuk 4 beschrijft de relatie tussen BMI en borstkankeruitkomsten voor de twee behandelingsstrategieën in het internationale TEAM cohort. BMI data waren beschikbaar voor 4711 TEAM patiënten. De mediane BMI was 26.2 (SD 6.68) en

de verdeling in de verschillende BMI groepen was als volgt: 29.7% had een BMI tussen 18.5 en 25 kg/m^2, 28.2% een BMI tussen 25 en <30 kg/m^2, en 17.5% tussen 30 en 45 kg/m^2. Bij 24.6% van de patiënten was er geen BMI data beschikbaar. Na een follow-up van 6.5 jaar werden geen verschillen in de 5-jaars ziektevrije en borstkanker-specifieke overleving van de twee behandelingsstrategieën voor de verschillende BMI groepen aangetoond, in tegenstelling tot wat er in de recente literatuur is beschreven. De afwezigheid van een statistisch significant verschil tussen de twee behandelingsstrategieën is mogelijk te wijten aan een vooralsnog te korte follow-up periode en/of de switch van tamoxifen naar exemestaan na ongeveer 2.5 jaar, waardoor eventuele verschillen zouden kunnen afnemen door toevoeging van een aromataseremmer. Verder onderzoek hiernaar is dus wenselijk.

Er zijn aanwijzingen dat de uitkomst van borstkanker beter is bij patiënten die fysiek actief zijn, hetgeen suggereert dat de patiënt door beïnvloeding van leefstijlfactoren een actieve en leidende rol zou kunnen spelen als het gaat om borstkankeroverleving. In hoofdstukken 5 en 6 werd de invloed van fysieke activiteit op de overleving van postmenopauzale borstkankerpatiënten onderzocht. Hoofdstuk 5 betreft een systematisch overzicht van de bestaande literatuur over de invloed van fysieke activiteit op de borstkankeroverleving bij postmenopauzale vrouwen. Op grond van de 17 studies (n=497 patiënten) die geïncludeerd werden in het overzicht werd geconcludeerd dat bij oudere vrouwen met borstkanker, enige vorm van fysieke activiteit een positieve invloed heeft op de overlevingsuitkomsten. In hoofdstuk 6 maken we gebruik van de gegevens verkregen in het kader van de TEAM-Lifestyle nevenstudie. Nederlandse patiënten vulden 1 jaar en 2 jaar na de start van de adjuvante hormonale therapie gevalideerde vragenlijsten over de kwaliteit van leven en leefgewoonten in. In dit hoofdstuk werd de invloed van fysieke activiteit op borstkankeroverleving en borstkanker-specifieke sterfte onderzocht bij 521 patiënten. Het aantal uren per week die besteed werden aan de volgende activiteiten: lopen, fietsen, tuinieren, huishouden en sport, zowel voor als na de diagnose borstkanker werden omgerekend naar Metabolic Equivalent Task (MET-uren), een mate van de duur en intensiteit van verschillende activiteiten. Wij toonden in dit hoofdstuk aan dat fysieke activiteit, zowel voor als na de diagnose borstkanker, de algehele overleving van postmenopauzale borstkankerpatiënten, in het bijzonder bij vrouwen boven de leeftijd van 65 jaar verbeterde.

Predictieve modellen zijn een belangrijk onderdeel van de dagelijkse praktijk en kunnen faciliteren bij het bepalen van de beste behandelingsstrategieën voor individuele patiënten. In de huidige klinische praktijk wordt veelal gebruik gemaakt van prognostische modellen die gebaseerd zijn op o.a. tumor- en patiënt-specifieke kenmerken op het moment van de diagnose borstkanker. Gedurende de langdurige hormonale behandeling kunnen zich echter bepaalde gebeurtenissen (vroegtijdig staken van de hormonale therapie, ziekte-recidief waarvoor eventuele nieuwe behandeling) voordoen die de prognose van een patiënte kunnen beïnvloeden. Ook is gebleken dat de impact van bepaalde patiënt- en tumorkenmerken (bijvoorbeeld leeftijd, HER2 status en lymfklierstatus) op de prognose niet stabiel is over de tijd. Een nadeel van bestaande predictiemodellen bij borstkanker is dat er vooralsnog geen rekening

wordt gehouden met deze prognose-modificerende gebeurtenissen en variabelen. In hoofdstuk 7 wordt een innovatief dynamisch predictiemodel voor hormoongevoelige borstkankerpatiënten beschreven, ontwikkeld aan de hand van het Nederlands/Belgische TEAM cohort, waarbij conventionele 'statische' variabelen en nieuwe 'dynamische' variabelen worden meegenomen. Uit dit predictiemodel blijkt dat naarmate de tijdsperiode vanaf de diagnose borstkanker vordert, er in feite een nieuwe situatie ontstaat, waarbij de prognose van een patiënte opnieuw geëvalueerd moet worden. Dit dynamische predictiemodel kan gedurende de hele behandelingsperiode overlevingsvoorspellingen doen en zowel arts als patiënte ondersteunen bij beslissingen omtrent de hormonale behandeling op dat moment. Hoewel externe validatie in andere patiëntencohorten nog moet plaatsvinden en het model verder uitgewerkt moet worden o.a. bij een langere follow-up periode, is het huidige dynamische predictiemodel erg informatief en is het niet ondenkbaar dat dit zal leiden tot de uitwerking van dynamische predictiemodellen die voor de klinische praktijk ingezet kunnen worden.

Deel II – Kwaliteit van leven, therapietrouw en bijwerkingen

Deel II van dit proefschrift richtte zich op verschillende patiënt-specifieke en therapie-specifieke factoren die individuele uitkomsten kunnen beïnvloeden. De adjuvante hormonale behandeling van het hormoongevoelige mammacarcinoom kan immers gepaard gaan met hinderlijke bijwerkingen die de therapietrouw, de kwaliteit van leven en het dagelijks functioneren van een patiënte nadelig kunnen beïnvloeden. Bij het bepalen van de beste behandelingsstrategie is het nuttig om te weten op welke aspecten van de kwaliteit van leven en het dagelijks functioneren, en in welke mate dit een impact heeft bij vrouwen met borstkanker. In hoofdstuk 8 werd de kwaliteit van leven van 543 Nederlandse TEAM patiënten onderzocht in de TEAM-Lifestyle nevenstudie (studieopzet eerder beschreven bij hoofdstuk 6). Er werd geen verschil gevonden in de globale kwaliteit van leven tussen de twee behandelingsstrategieën. De resultaten toonden echter wel aan dat vrouwen die behandeld werden met exemestaan statistisch significant slechter scoorden met betrekking tot emotioneel en seksueel functioneren, en vaker te maken hadden met klachten van moeheid, slapeloosheid en kortademigheid dan vrouwen die tamoxifen gebruikten. Het verschil tussen de twee behandelgroepen werd echter alleen als klinisch significant beschouwd voor wat betreft slapeloosheid. Informatief, maar ook geruststellend is de observatie dat de kwaliteit van leven en de meerderheid van de verschillende functionele en symptoommetingen van vrouwen die deelnamen aan het kwaliteit van leven onderzoek tussen de 1e en 2e meting verbeterden, hetgeen aangeeft dat er in de loop van de tijd verbetering en/of gewenning optreedt. Deze informatie is belangrijk voor hulpverleners van respectievelijke patiënten die bijwerkingen ervaren.

Meer en meer blijkt uit onderzoek dat adjuvante hormonale therapie binnen de eerste 5 jaar vroegtijdig gestopt wordt door 40% tot 60% van de vrouwen die dit geadviseerd krijgen, wat nadelig kan zijn voor de overleving en de kans op ziekterecidief. De IDEAL (Investigation on the Duration of Extended Adjuvant Letrozole) studie onderzoekt de effectiviteit van verlengde behandeling met de aromataseremmer letrozol (2.5 of 5 jaar) nadat postmenopauzale borstkankerpatiënten al vijf jaar met adjuvante hormonale therapie

zijn behandeld. Het thema therapietrouw is onderzocht in de patiëntenpopulatie (n=1215) van de IDEAL studie (hoofdstuk 9), waaruit blijkt dat 18.4% van de vrouwen tijdens de eerste 2.5 jaar van de verlengde hormonale therapie vroegtijdig stopten met letrozol. In meer dan 85% van de gevallen was dit vanwege bijwerkingen. Risicofactoren voor het vroegtijdig stoppen betroffen: eerdere monotherapie met hetzij tamoxifen of een aromataseremmer, een langer therapievrij interval tussen de eerste 5 jaar van de adjuvante behandeling en de start van de verlengde hormonale therapie, en een gunstiger lymfklierstatus bij diagnose. Leeftijd was geen risicofactor voor vroegtijdig stoppen van letrozol.

Opvliegers en nachtzweten (verzamelnaam vasomotorische symptomen) en spier- en gewrichtsklachten zijn veel voorkomende bijwerkingen van aromataseremmers en zijn mogelijk gerelateerd aan de verdere daling van al lage postmenopauzale oestrogeenspiegels. In hoofdstukken 10 en 11 wordt gerapporteerd over de bevindingen naar de relatie tussen deze 'specifieke bijwerkingen' en borstkankeroverleving, hetgeen werd onderzocht in het TEAM cohort. In zowel het Nederlands/Belgische cohort als in het internationale TEAM cohort werd gevonden dat vrouwen die vasomotorische symptomen en/of spier- en gewrichtsklachten rapporteerden een betere ziektevrije overleving hadden dan vrouwen zonder deze klachten (respectievelijke hazard ratio's (HR) 0.731 (95%CI 0.616-0.866) en 0.826 (95%CI 0.694-0.982)). Het sterkste effect werd geobserveerd bij vrouwen die vasomotorische symptomen rapporteerden. Deze data geven aan dat specifieke bijwerkingen geassocieerd zijn met betere overlevingsuitkomsten en in de toekomst mogelijk gebruikt kunnen worden in de klinische praktijk om de effectiviteit van de hormonale therapie te voorspellen.

Waarom sommige vrouwen met borstkanker specifieke bijwerkingen ontwikkelen en anderen niet is tot op heden niet bekend. In hoofdstuk 12 wordt ingegaan op de verschillende genetische variaties ('single nucleotide polymorphisms', SNPs) van het aromatasegen (CYP19A1) in relatie tot het optreden van deze specifieke bijwerkingen. Met behulp van een zogenaamde 'tagging SNP' approach werd ruim 80% van het CYP19A1 gen onderzocht voor genetische variaties. Op basis van de resultaten bij 737 met exemestaan behandelde Nederlandse TEAM patiënten werd geconcludeerd dat 3 SNPs (rs934635, rs16964189 en rs7176005) geassocieerd waren met het rapporteren van specifieke bijwerkingen. Verder onderzoek hiernaar is wenselijk, voordat het toepasbaar is in de klinische praktijk.

Deel III – Preoperatieve en operatieve behandelingsmogelijkheden

In Deel III van dit proefschrift werd de rol van preoperatieve (neoadjuvante) systemische therapie als onderdeel van de geïndividualiseerde borstkankerbehandeling verder onderzocht. Neoadjuvante systemische therapie wordt voorafgaande aan de chirurgische behandeling toegepast om grote of niet-operabele tumoren in grootte of stadium te doen afnemen, terwijl het ook de mogelijkheid biedt om 'in vivo' te beoordelen hoe de tumor reageert op de neoadjuvante behandeling. Eerdere studies hebben aangetoond dat de effectiviteit van neoadjuvante chemotherapie (NCT) afneemt naarmate tumoren sterker ER positief zijn. In de laatste jaren is de populariteit van neoadjuvante hormonale therapie (NHT) bij sterk hormoongevoelige borstkanker en/

of bij patiënten die de behandeling met chemotherapie niet of moeilijk kunnen verdragen sterk toegenomen. De tijd tot maximale tumorrespons is echter langer bij NHT dan bij NCT, en er bestaat op dit moment nog geen consensus over de optimale duur van de neoadjuvante behandeling met aromataseremmers. In de meerderheid van de studies betreffende NHT met aromataseremmers worden patiënten gedurende 3 tot 4 maanden behandeld, hoewel er aanwijzingen zijn dat een behandelingsduur van langer dan 3 maanden voordelig is bij vrouwen bij wie de afname in tumorgrootte aanhoudt (hoofdstuk 13). In de TEAM IIA studie werd de afname in tumorgrootte onderzocht bij 102 sterk hormoongevoelige (>50% ER positiviteit), postmenopauzale borstkankerpatiënten die gedurende meer dan 3 maanden behandeld werden met neoadjuvant exemestaan (hoofdstuk 14). Na een mediane behandelingsduur van 5.78 maanden werd een voortgaande afname in tumorgrootte bij een behandelingsduur van langer dan 3 maanden bevestigd. In deze studie werd aangetoond dat vrouwen die langer dan 3 maanden behandeld werden met exemestaan, een aanhoudende afname in tumorgrootte plaatsvond, op basis waarvan geconcludeerd kan worden dat sterk hormoongevoelige borstkankerpatiënten die in aanmerking komen voor NHT en waarbij de tumor op de neoadjuvante behandeling reageert, een behandelingsduur van langer dan 3 maanden dient te worden aangehouden.

Hoofdstuk 15 behandelt de vraag wanneer de schildwachtklierprocedure en de eventuele aansluitende okselklier-dissectie te verrichten bij patiënten die behandeld worden met neoadjuvante systemische therapie, omdat hierover momenteel geen duidelijke consensus bestaat. De introductie van de schildwachtklierprocedure voor stadiëring en prognose bepaling heeft in het verleden geleid tot een significante daling in de comorbiditeiten die gepaard gaan met een volledige okselklier-dissectie (zowel op korte als lange termijn). De neoadjuvante behandeling met systemische therapie wordt veelal voorgeschreven om een afname in tumorgrootte of tumorstadium te bereiken, waarna chirurgische resectie van de resterende tumor volgt. Een voordeel van het verrichten van de schildwachtklierprocedure na afloop van de neoadjuvante systemische behandeling betekent dat de operatieve verwijdering van de tumor en de schildwachtklier in een enkele chirurgische procedure kunnen plaatsvinden. Ons systematisch overzicht van de bestaande bewijsvoering toonde aan dat de schildwachtklierprocedure na afloop van de neoadjuvante behandeling veilig kan worden uitgevoerd, zowel bij de aanwezigheid (cN+) als afwezigheid van klinisch aangetoonde tumorpositieve lymfklieren (cN0). Tot slot worden de bevindingen van de verschillende studies verricht in het kader van dit proefschrift bediscussieerd en in perspectief geplaatst (hoofdstuk 16).

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LIST OF PUBLICATIONS

Fontein DBY, Seynaeve C, Bastiaannet E, Nortier JWR, Meershoen-Klein Kranenbarg E, Putter H, Hozumi Y, Dirix LY, Hasenburg A, Bartlett JMS, Rea D, Markopoulos C, van de Velde CJH. Body-mass index as a prognostic indicator in breast cancer patients treated with adjuvant endocrine therapy: an international TEAM trial analysis. Submitted

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CURRICULUM VITAE

Duveken Fontein was born in Kogarah, Australia on June 23rd, 1984. Until the age of 17, she grew up in a number of different countries, together with her parents and 5 siblings, after which she returned to the Netherlands to complete the International Baccalaureate Program at the American School of the Hague (2002) and to attend medical school at Leiden University. After completing medical school in 2010, Duveken worked as a resident in general surgery at the Groene Hart Hospital in Gouda for six months before starting clinical PhD research in breast cancer at Leiden University Medical Center. In 2012, she was awarded the Niall O'Higgins Award for best abstract (3rd place) during the 32nd European Society of Surgical Oncology (ESSO) conference in Valencia, Spain. In 2014, Duveken undertook clinical observerships at the Department of Plastic Surgery at the Brigham and Women's hospital (prof. dr. E. Eriksson) in Boston and at the Breast Service, Department of Surgery at Memorial Sloan-Kettering Cancer Center (prof. dr. M. Morrow) in New York (USA). At present, Duveken is serving on Steering Committees of the European Young Surgeons and Alumni Club (EYSAC), an ESSO affiliate, and the Flims Alumni Club (FAC), both of which focus on helping young clinicians form a solid basis for high-quality clinical and scientific training in order to follow in the footsteps of those currently leading in the field of (surgical) oncology. Duveken has a passion for running, outdoor sports, learning languages and traveling. She has recently moved to Switzerland with her fiancé Otto, where she will continue her specialty training in surgery.