# Management of elderly patients with breast cancer

## towards evidence based medicine

Willemien van de Water

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# Management of elderly patients with breast cancer

## towards evidence based medicine

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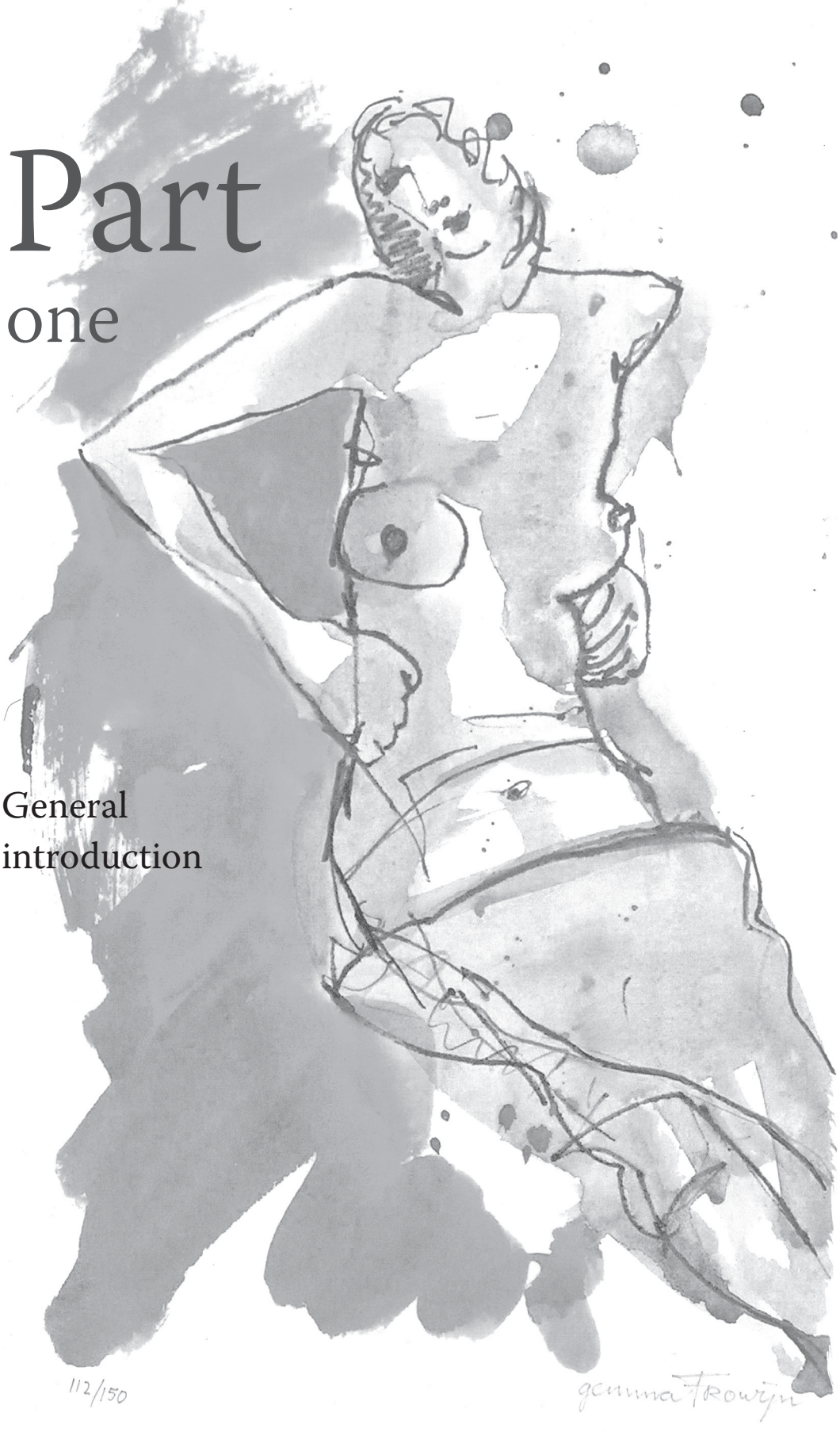
# Contents

# Part one




## General introduction

# Chapter 1

# Introduction

Willemien van de Water

# Introduction

The work presented in this thesis is part of the FOCUS project, 'Female breast cancer in the elderly; Optimizing Clinical guidelines USing clinico-pathological & molecular data', which was initiated in 2009 by a KWF program grant. The goal of the FOCUS project is to gain insight in breast cancer in elderly patients in order to improve care and cure in this patient group. The project consists of four domains; analysis of a large observational cohort of elderly patients; age specific analyses of clinical trial data; a prospective study investigating patient preferences; and a pathology study aiming to unravel differences and similarities in tumor biology of elderly breast cancer patients as compared to younger patients. The studies reported in this thesis cover analyses of observational cohort data, and age-specific analyses of clinical trial data.

Breast cancer is the most common malignancy diagnosed in women[1]. The incidence of breast cancer increases with age; currently, in developed countries more than 40% of breast cancer patients is 65 years or older at diagnosis[1]. In the Netherlands in 2011, 5,441 women aged 65 years or older were diagnosed with breast cancer[2]. The remaining life expectancy of persons aged 65 is still increasing, from almost 19 years in 1980, up to more than 21 years in 2010. Moreover, in last decades the birth rate has decreased, resulting in a higher proportion of older persons in the general population[3]. Both an increasing life expectancy and the increasing number of elderly in the population will further enhance the number of elderly women confronted with breast cancer;

Although a large proportion of all breast cancer patients is 65 years or older at diagnosis, there are no age specific guidelines for breast cancer treatment. However, elderly breast cancer patients differ from younger patients in several aspects. First, it is often reported that breast cancer in elderly patients may behave differently as compared to breast cancer in younger patients. Others have suggested a more aggressive as well as less aggressive disease in elderly patients; it has been shown that breast tumors of patients aged 70 years or older had slower growth rates, were genomically more stable and were more likely to be hormone receptor positive as compared to breast tumors in women younger than 45 years[4]. Of note, no variation with regards to hormone receptor status or histological grade was observed *within* postmenopausal patients[5]. On the other hand, tumor size and frequency of nodal involvement have been shown to increase with age[5], which may be partly due to a delayed diagnosis. However, nodal involvement in patients over 70 years was mainly observed in combination with smaller tumors, which may indicate a more aggressive disease in elderly[6]. Next to potential differences in tumor biology, age-related physiological changes may affect drug absorption, distribution and metabolism[7]. Moreover, concurrent disease and medication use may directly affect tolerability of treatment and increase toxicity[8;9]. Last, the definition of treatment efficacy may be different in elderly patients; a higher risk of death from any cause and a lower remaining life expectancy as compared to younger patients may result in

a lower absolute benefit of anticancer therapy, while long-term adverse events may be less relevant. Given these differences between older and younger breast cancer patients, guideline recommendations for younger patients may not be applicable to elderly breast cancer patients.

# Aim of this thesis

The aim of this thesis was to improve management of breast cancer in elderly patients by quantifying the evidence base for treatment, and by evaluating breast cancer outcomes and treatment efficacy.

# Overview of used patient cohorts

## FOCUS cohort

Data from the FOCUS cohort were used in chapters 2, 3 and 7. The FOCUS cohort is a population-based cohort of all incident breast cancer patients aged 65 years or older, who were diagnosed in the geographically defined Comprehensive Cancer Center Region West in The Netherlands, between 1997 and 2004. Overall 3,672 patients were included. The nationwide Dutch network and registry of histopathology and cytopathology regularly submits reports of all diagnosed malignancies to the regional cancer registries. The national hospital discharge data bank, which receives discharge diagnoses of admitted patients from all Dutch hospitals, completes case ascertainment. Information on patient characteristics, tumor characteristics, treatment, follow-up and outcome were recorded for all patients. Comorbidity was defined as presence of comorbidity at time of diagnosis, and categorized by the 10th edition of the International Statistical Classification of Diseases and Related Health Problems (ICD-10). Vital status was established either directly from the patient's medical record or through linkage with the municipal population registries, which record information on vital status (follow-up until January 1$^{st}$ 2011). One of the main advantages of this cohort is that we were able to collect detailed information of a large number of unselected patients, reflecting the large heterogeneity among elderly breast cancer patients in the general population.

## Netherlands Cancer Registry cohort

Data from the Netherlands Cancer Registry cohort were used in chapter 4. Patients were identified from the National Cancer Registry, which comprises all data from the regional cancer registries. Registry personnel collects data on diagnosis, staging and treatment from the medical records, including pathology and surgery reports, by using the registration and coding manual of the Dutch Association of Comprehensive Cancer Centers. Overall, 31,520 patients with early stage breast cancer, who were diagnosed between 2005 and 2008, and who were younger than 65 years or who were 75 years or older at diagnosis, were included in the cohort. The rationale behind this age restriction was that younger patients are deemed to be represented in clinical in trials upon which guideline recommendations are based, whereas

patients aged 75 years or older are included sporadically. Vital status was established through linkage with the municipal population registries, which record information on vital status (follow-up until January 1st 2011).

## TEAM trial

Data from the Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial were used in chapters 3, 5, 6 and 9. The TEAM trial is a randomized, phase 3, multinational, open-label study conducted in postmenopausal women with hormone receptor positive breast cancer. Overall, 9,766 patients were randomized to receive either exemestane 25 mg once daily for 5 years, or tamoxifen 20 mg once daily for 2.5 to 3 years, followed by exemestane 25 mg once daily for 2 to 2.5 years, for a total of 5 years. Patients were enrolled and included in 566 hospitals in Belgium, France, Germany, Greece, Japan, The Netherlands, the United Kingdom and Ireland, and the United States, between January 2001 and January 2006. Appropriate approvals from the ethical committees and written informed consent from all patients were obtained. Similar protocols were used in the 9 participating countries with minor differences to accommodate local treatment guidelines. In short, postmenopausal patients with histologically confirmed breast carcinoma who completed local therapy with curative intent (i.e. without evidence of metastatic disease) were eligible. Participants were randomized to receive endocrine treatment within 10 weeks of completion of surgery and chemotherapy, if indicated. Patients were ineligible if they had a previous malignancy with a disease-free interval of less than 5 years, an Eastern Cooperative Oncology Group (ECOG) performance status of more than 2, or significant cardiac disease or other illness interfering with study participation. Each patient's medical history was taken and clinical examination was performed at baseline, with further investigation as clinically indicated. Patients were assessed every 3 months during the first year of treatment and at least once a year thereafter. Mammography was performed every year. Adverse events were recorded at each visit; the data were obtained from elicited responses. Vital status was established by medical record review or, if information was missing, through linkage with the municipal population registries (follow-up until October 7th, 2010). One of the advantages of using data from the TEAM trial, was the structured follow-up with ascertainment of recurrence and cause of death, which provided a unique opportunity to study associations between age and breast cancer outcomes.

## Standard care cohort and oncogeriatric care cohort

Data from the standard care cohort and oncogeriatric care cohort were used in chapter 10. The standard care cohort is a population-based cohort of 104 elderly breast cancer patients who were treated in the Comprehensive Cancer Center West in The Netherlands. The oncogeriatric care cohort is a hospital-based cohort of 42 elderly patients treated at the H. Lee Moffitt Cancer Center and Research Institute in Tampa (Florida, United States). Patients were identified from the Moffitt Cancer Registry and the Total Cancer Care program.

All female patients with primary metastatic breast cancer, who were 70 years or older at diagnosis, and who were diagnosed between January 1st 2008 and December 31th 2011 were eligible. Inclusion in the oncogeriatric care cohort was extended to January 1st 2003 to increase the number of eligible patients. Patients with a history of breast cancer less than five years prior to diagnosis of metastatic breast cancer were excluded, as these were considered to have recurrent disease. By means of chart review, data were collected on tumor, patient and treatment characteristics. For the standard care cohort, vital status and date of last follow-up were established either directly from the patient's medical record or through linkage of cancer registry data with municipal population registries, which record information on vital status. For the oncogeriatric care cohort, vital status and date of last follow-up were established directly from the patient's medical record or through linkage of the Moffitt Cancer Registry data with the National Death Index. Patients who moved out of the region, were censored at time of last follow-up visit. Follow-up was recorded until July 1st 2012.

## Outline of this thesis

This thesis is divided in three parts. The first part consists of three studies evaluating the evidence base for treatment of elderly breast cancer patients. It is often mentioned that elderly are frequently underrepresented in clinical trials, and therefore the evidence base for breast cancer treatment in elderly is limited. However, it remains unknown how much and which type of elderly patients in particular are excluded from clinical trials. In chapter 2 we quantified and qualified the evidence base for locoregional treatment of elderly patients with early stage breast cancer. The study was based on all clinical trials on locoregional treatment, which were included in the national guideline recommendations. Another way to evaluate whether treatment is evidence based, is to assess the external validity of a trial. Therefore, in chapter 3 we compared characteristics and outcome of elderly breast cancer patients who participated in a trial with those of elderly breast cancer patients from the general population. Next, we evaluated whether adherence to national breast cancer treatment guidelines was associated with survival, as presented in chapter 4. Guidelines are merely based on clinical trial results; given a limited evidence base for treatment of elderly breast cancer patients, adherence to treatment guidelines may not necessarily improve outcomes in the elderly in the same way as it is expected in younger patients.

The second part of this thesis consists of three studies evaluating the association between age at diagnosis and breast cancer outcomes. A breast cancer patient who dies from causes unrelated to breast cancer is no longer at risk for progression of breast cancer or death due to breast cancer. This so called competing risk of death is particularly present in older populations and may affect breast cancer specific outcomes. In chapter 5 we investigated the association between age at diagnosis and breast cancer death, and death due to other causes among patients who participated in the TEAM trial. To gain further insight in the relationship between age at diagnosis and breast cancer outcome, in chapter 6 we studied the incidence

of breast cancer recurrence and contralateral breast cancer by age at diagnosis. Results obtained from clinical trial data may differ from results in the general population; competing mortality is likely to be higher in the general population, and administered treatment, as well as implications of treatment, may differ from a trial population. Therefore, the association between age and breast cancer outcomes was also assessed in the population-based FOCUS cohort, as described in chapter 7.

After evaluation of the evidence base for treatment of elderly breast cancer patients, and breast cancer outcomes by age of diagnosis, in the third part of this thesis we studied treatment outcomes in more depth. Chapter 8 consists of a systematic review and meta-analysis of radiotherapy after breast conserving surgery in elderly patients with early stage breast cancer. In chapter 9 we studied the outcomes after nonpersistence of adjuvant endocrine therapy by age at diagnosis among patients who participated in the TEAM trial. Next to specific treatment outcomes, we compared two different patterns of care. Management of elderly patients treated in a standard care setting in The Netherlands was compared with management of those treated in an oncogeriatric care setting in the United States. This study was performed in primary metastatic patients (chapter 10).

In chapter 11 the main conclusions of this thesis are summarized and discussed, and future studies and research goals are proposed.

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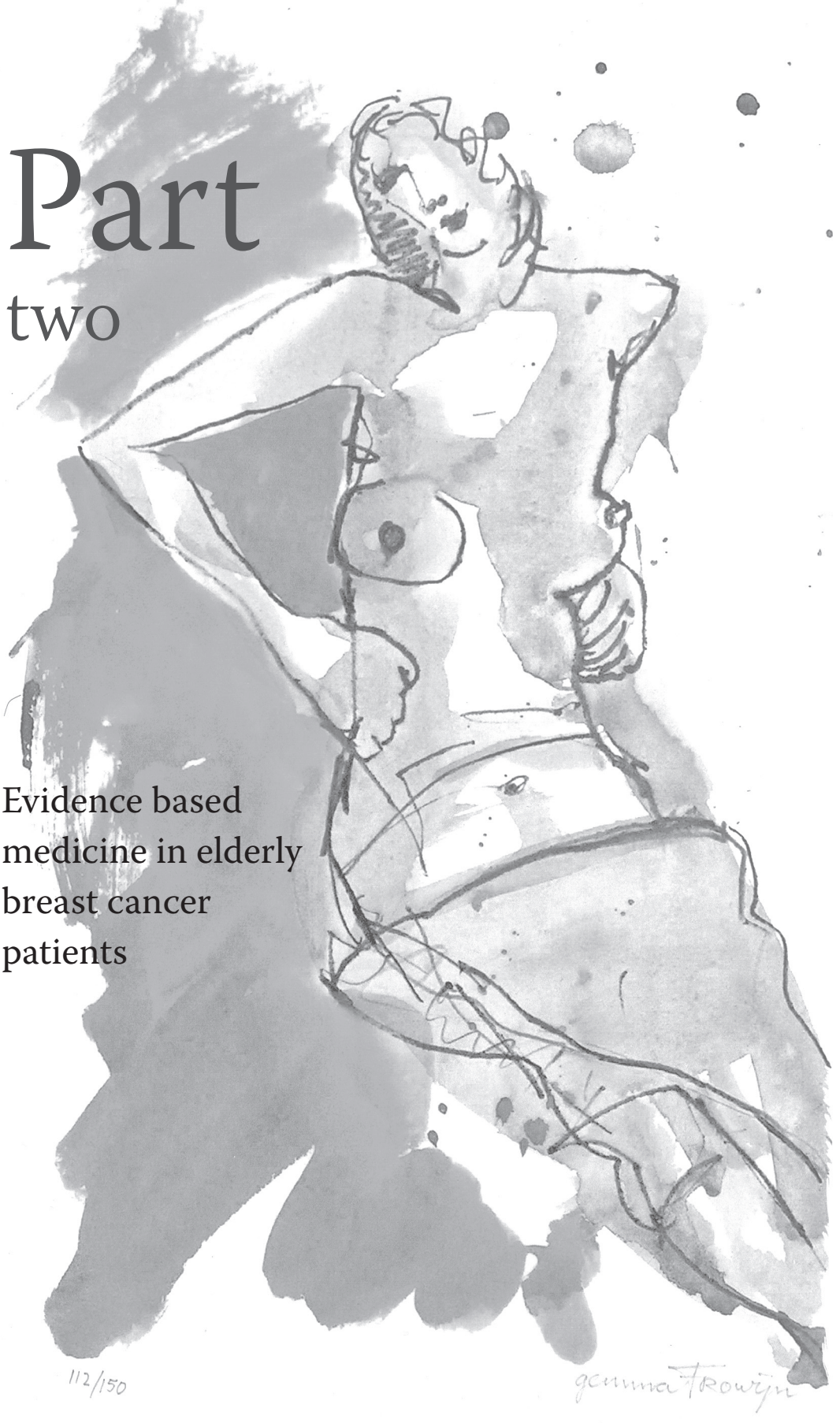
# Part two




## Evidence based medicine in elderly breast cancer patients

# Chapter 2

# Limited evidence base for locoregional treatment of patients aged 75 years or older with early stage breast cancer

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# Abstract

## Background

Treatment guidelines are merely based on randomized clinical trials, which are considered the evidence base for treatment of breast cancer. However, relatively few elderly are included in these trials. Therefore, the aim of this study was to quantify and qualify the evidence base for locoregional treatment of older women with early stage breast cancer.

## Methods

The 66 randomized clinical trials on locoregional trials included in the national breast cancer guidelines comprise the evidence for locoregional treatment. Eligibility criteria of these trials were applied to a population-based cohort of elderly breast cancer patients. The population-based cohort consisted of 2,662 patients aged ≥65 years at diagnosis of early stage breast cancer, who were diagnosed between 1997 and 2004 in the geographically defined Comprehensive Cancer Center Region West, in The Netherlands. For all patients we calculated the proportion of the randomized clinical trials from which they would be excluded due to eligibility criteria. Based on this proportion, the evidence base was deemed 1) present, 2) partial, or 3) limited; corresponding with exclusion from less than 30%; 30-60%; or more than 60% of the trials, respectively.

## Results

In patients aged 65-75 years, the evidence base was dependent on the number of comorbidities and whether patients had a previous malignancy. Contrary, the evidence base was limited for all patients aged 75 years or older; patients were excluded from more than 60% of the trials solely due to age. Overall, the evidence base for locoregional treatment was present for 35%, partial for 19%, and limited for 56% of elderly patients with early stage breast cancer.

## Conclusions

The evidence base for locoregional treatment is limited for the majority of elderly breast cancer patients, and for all patients aged 75 years or older in particular.

# Introduction

Up to 40% of breast cancer patients is 65 years or older at diagnosis[1]. As breast cancer incidence increases with increasing age[1], changing demographics and continuously increasing life expectancy will further enlarge the number of elderly women confronted with breast cancer. Recently it was shown that in postmenopausal patients, breast cancer mortality increased with increasing age[2]. Moreover, the risk of a distant recurrence in breast cancer patients aged 75 years or older was higher than in younger postmenopausal patients, which may be attributed to undertreatment of elderly patients[3].

The term undertreatment suggests less than optimal treatment. However, for elderly women with breast cancer it is largely unknown what optimal treatment is. The evidence base for treatment is mostly composed of randomized clinical trials. Despite comprising a large proportion of all breast cancer patients, elderly patients are underrepresented in these trials[4;5] because of physician factors[6;7], patients factors[8], but also due to exclusion criteria. Moreover, exclusion criteria may hamper participation of a certain type of elderly patients in particular. Consequently, trial results may not necessarily be extrapolated to all elderly breast cancer patients.

In early stage disease[9], the evidence for adjuvant chemotherapy is mostly based on the Early Breast Cancer Trialist's Collaborative Group meta-analyses[10;11]. It is known that few women older than 70 years of age, and very few older than 80 were randomized into the studies included in these meta-analyses[11], and therefore the evidence base for chemotherapy in elderly breast cancer patients is rather limited. It is also known that elderly breast cancer patients are relatively often included in clinical trials on adjuvant endocrine therapy[12]. However, there are few data on the evidence base for locoregional treatment in elderly patients with early stage breast cancer.

Therefore, the aim of this study was to quantify and qualify the evidence base for locoregional treatment of elderly patients with early stage breast cancer.

# Methods

Early stage breast cancer includes patients with T0–T2 N0–N1 M0 breast cancer according to the seventh edition of the tumor node metastasis (TNM) classification[9]. Locoregional treatment includes breast surgery, axillary surgery and postoperative radiotherapy.

The evidence base for locoregional treatment of early stage breast cancer patients was defined as all randomized clinical trials on locoregional treatment which are included in the national breast cancer guidelines. We chose to define the evidence base on the basis of the national breast cancer guidelines rather than on a systemic search strategy of the literature

to better meet the aim of the study; all randomized clinical trials which translate to clinical treatment decisions are incorporated in the guidelines. It was previously shown that national treatment recommendations in different countries exhibited a large degree of congruency[13]. Therefore, we used the Dutch guideline recommendations. In 2002, initiated by the Dutch Institute of Health Care Improvement CBO and the Dutch National Breast Cancer Society, the first national multidisciplinary guideline 'Breast Cancer Treatment' was implemented in the Netherlands[14]. Regular revisions ensure updated information and recommendations. For this study, the most recent Dutch national guidelines were used (February 2012)[14]. An overview of recommendations for locoregional treatment of early stage breast cancer, and the corresponding randomized clinical trials are shown in Supplementary tables 1 and 2.

The search engines Pubmed and Medline were used to retrieve the original articles. In case of a systematic review or a meta-analysis of multiple randomized clinical trials, all individual trials were retrieved and included. In case a study was used more than once, e.g. in more than one recommendation or in two meta-analyses, it was included in the analyses only once.

We then examined the inclusion and exclusion criteria of each of the randomized clinical trials. In case the authors referred to previous publications for extensive eligibility criteria, these publications were retrieved. Previously, van Spall and colleagues defined reasons for excluding individuals from a randomized clinical trial as poorly or strongly justified[15]. Exclusion criteria were defined to be poorly justified when based on, among others; age, physical ability or disability, or a chronic health condition. Consequently, eligibility criteria in the current study were categorized into three groups; 1) age, 2) a previous malignancy, and 3) comorbid disease. All criteria were reported as exclusion criteria[15].

Finally, we compared the exclusion criteria with a population-based cohort of breast cancer patients aged 65 years and older (FOCUS cohort), to see what proportion of patients would have been disqualified for the trials. Thereby we aimed to quantify and qualify the evidence base for locoregional treatment. The population-based FOCUS cohort (Female breast cancer in the elderly: Optimizing Clinical guidelines USing clinico-pathological & molecular data) comprises all consecutive incident breast cancer patients aged 65 years or older, who were diagnosed in the geographically defined Comprehensive Cancer Center Region West in The Netherlands, between 1997 and 2004. Information on patient characteristics, tumor characteristics, treatment, follow up and outcome were recorded for all patients. Comorbidity was categorized by the 10th edition of the International Statistical Classification of Diseases and Related Health Problems (ICD-10)[16].

## Statistical analyses

First, we calculated the frequency of all exclusion criteria. Second, we calculated what proportion of elderly patients from the population-based FOCUS cohort would have been

disqualified for the trials, based on the exclusion criteria. There is no standard definition or cut-off whether there is an evidence base for treatment. Therefore we propose a qualification based on the proportion of randomized clinical trials, i.e. the evidence base, from which patients are excluded. The evidence base was deemed *present* in patients who are excluded from less than 30% of the trials, i.e. in patients who could have been included in at least 70% of the trials; *partial* in patients who are excluded from 30-60% of the trials; and *limited* in patients who are excluded from more than 60% of the trials. In patients for which an evidence base is deemed present, we conclude that guideline recommendations, which are based on these trials, can be extrapolated. To further qualify the evidence base, we evaluated which patients are excluded in particular. Patients were categorized based on age (65-75 years; ≥75 years)[17], the number of comorbidities they had (0-1; 2-4; ≥5 comorbidities) and whether they had a previous malignancy.

# Results

## Population-based cohort

Overall, 2,662 patients with early stage breast cancer were included in the current study. Mean age was 75.7 years (standard deviation 7.3 years); 1,319 patients were 75 years or older at diagnosis (49.5%). Patient and tumor characteristics are shown in Table 1. The number of comorbid diseases varied from 0 up to 11; most patients had 0 or 1 comorbid disease. The most prevalent comorbidities were circulatory (e.g. heart failure, hypertension), endocrine (e.g. diabetes mellitus, hypothyroidism) and musculoskeletal comorbidities (e.g. arthrosis, osteoporosis). The majority of the patients had stage II disease (n=1,532 (58%)).

## Evidence base

The evidence base for locoregional treatment comprised 181 studies, among which six meta-analyses of 152 studies[18-23]. Overall, 40 studies were excluded because there was no report of the study methods (e.g. the results were presented at a conference or at a meeting only) or the study was not a randomized clinical trial. After elimination of duplicates, the evidence base for locoregional treatment was composed of 66 unique randomized clinical trials.

## Eligibility criteria

Adequate breast surgery or surgery with curative intent was required for participation in all clinical trials. As shown in Table 2, eligibility criteria on age, a previous malignancy and comorbid disease were defined in 67% (44/66); 58% (38/66) and 55% (36/66) of the randomized clinical trials, respectively. In case eligibility criteria on age were defined, patients aged 70 years and older were excluded in particular. Presence of comorbid disease was defined loosely in the majority of the trials, e.g. as 'a medical condition contra-indicating therapy, adherence or follow-up'. Therefore, consensus based definitions of comorbid disease (WW, EB) were used for further analyses. These are included in Table 2.

**Table 1.** Characteristics of the population-based cohort of elderly patients with early stage breast cancer (n=2,662).

| | n | % |
|---|---|---|
| Previous malignancy | | |
| Any | 391 | 14.7 |
| Excluding NMSC | 323 | 12.1 |
| Excluding BCC | 337 | 12.7 |
| Number of comorbidities | | |
| 0-1 | 1,304 | 49 |
| 2-4 | 1,098 | 41.2 |
| ≥5 | 260 | 9.8 |
| Type of comorbidity (presence) | | |
| Circulatory | 1,363 | 51.2 |
| Respiratory | 295 | 11.1 |
| Endocrine | 733 | 27.5 |
| Neurologic | 291 | 10.9 |
| Psychiatric | 247 | 9.3 |
| Digestive | 351 | 13.2 |
| Musculoskeletal | 652 | 24.5 |
| T stage | | |
| T0 | 1 | <0.1 |
| T1 | 1,45 | 54.4 |
| T2 | 1,172 | 44 |
| T3 | 39 | 1.5 |
| N stage | | |
| Negative | 1,857 | 69.8 |
| Positive | 805 | 30.2 |
| Hormone receptor status | | |
| Positive | 1,812 | 68.1 |
| Negative | 411 | 15.4 |
| Unknown | 439 | 16.5 |
| Histological subtype | | |
| Ductal | 1,938 | 72.8 |
| Lobular | 288 | 10.8 |
| Unknown | 436 | 16.4 |

SD: standard deviation; NMSC: non melanoma skin cancer; BCC: basal cell carcinoma

## Quantification and qualification of the evidence base

To quantify the evidence base, we calculated what proportion of elderly patients from the population-based FOCUS cohort would have been disqualified for the trials, based on the exclusion criteria. On average, elderly breast cancer patients were excluded from 52% (34/66, range 6% - 89%) of the randomized clinical trials which comprise the evidence base for locoregional treatment. Exclusion was evaluated for different groups of elderly patients, based on age, the number of comorbidities, and whether patients had a previous malignancy (Table 3). Overall, the evidence base for locoregional treatment was present for 35%, partial for 19%,

**Table 2.** Frequency of exclusion criteria of 66 randomized clinical trials comprising the evidence base for locoregional treatment.

| | n |
|---|---|
| Exclusion criteria on age (defined in 44/66 trials) | |
| <40 years | 2 |
| <50 years | 1 |
| <70 years | 1 |
| >65 years | 1 |
| >69 years | 1 |
| >70 years | 27 |
| >75 years | 8 |
| >80 years | 2 |
| Exclusion criteria on a previous malignancy (defined in 38/66 trials) | |
| Any | 20 |
| Excluding BCC | 13 |
| Excluding NMSC | 5 |
| Exclusion criteria on comorbid disease (defined in 36/66 trials)* | |
| ECOG performance status >2 | 6 |
| ECOG performance status >1 | 4 |
| Renal disorders | 5 |
| Hepatic disorders | 4 |
| Cardiac disorders | 4 |
| Psychiatric disorders | 10 |
| Hematological disorders | 7 |
| Non-malignant systemic disease | 5 |
| Serious non-malignant systemic disease | 5 |
| Medical condition contra-indicating therapy, adherence or FU | 18 |

BCC: basal cell carcinoma; NMSC: non melanoma skin cancer; ECOG: Eastern Cooperative Oncology Group; FU: follow-up. *Adds up to more than 36 because multiple criteria may apply. ECOG performance status >2: survival after diagnosis less than 6 months; psychiatric disorder. ECOG performance status >1: nursing home at time of diagnosis; survival after diagnosis <6 months; psychiatric disorder. Renal disorders: creatinin >1.5 ULN. Hepatic disorders: ASAT >1.5 ULN; ALAT >1.5 ULN. Cardiac disorders: myocardial infarction; heart failure plus one of the following disorders; valve disorder, conduction disorder, arrhythmia, peripheral arterial obstructive disease or cerebrovascular accident; three or more of the following conditions; heart failure, cerebrovascular accident, arrhythmia, valve disorder, conduction disorder, venous disease, thrombosis, hypertension. Psychiatric disorders: depression; severe psychiatric disorder; dementia. Hematological disorders: thrombocytes <1.5 ULN; leukocytes >1.5 ULN; hemoglobin <1.5 ULN. Non-malignant systemic disease: diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (ICD10-III); endocrine, nutritional and metabolic diseases (ICD10-IV); diseases of the musculoskeletal system and connective tissue (ICD10-XIII); hypertension; peripheral arterial obstructive disease; kidney failure. Serious non-malignant systemic disease: survival after diagnosis less than 6 months; psychiatric disorder. Medical condition contra-indicating therapy, adherence or FU: survival after diagnosis less than 6 months; psychiatric disorder.

and limited for 56% of elderly patients aged 65 years or older with early stage breast cancer. In patients aged 65-75 years, the evidence base was dependent on the number of comorbidities and whether patients had a previous malignancy. As depicted in Table 3 and in the Figure, an evidence base was present for patients who had 0-1 comorbid disease and no previous malignancy (659/1,343 or 49% of all patients aged 65-75 years); partial for those who had two or more comorbid disease and no previous malignancy (498/1,343 or 37% of all patients aged 65-75 years); and limited for all patients who had a previous malignancy (186/1,343 or 14% of all patients aged 65-75 years). Contrary, the evidence base was limited for all patients aged 75 years or older, irrespective of the number of comorbidities and whether they had a previous malignancy; they were excluded from more than 60% of the randomized clinical trials solely due to age.

**Table 3.** Exclusion of elderly patients with early stage breast cancer from 66 randomized clinical trials comprising the evidence base for locoregional treatment.

| | Number of patients (n=2,662) | Number of trials from which patients are excluded (n=66) | | Evidence base* |
|---|---|---|---|---|
| | | n | % | |
| 65-75 years (n=1,343) | | | | |
| No previous malignancy | | | | |
| 0-1 comorbidity | 659 | 18 | 27.3 | Present |
| 2-4 comorbidities | 414 | 25 | 37.9 | Partial |
| ≥5 comorbidities | 84 | 32 | 48.5 | Partial |
| Previous malignancy | | | | |
| 0-1 comorbidity | 102 | 43 | 65.2 | Limited |
| 2-4 comorbidities | 72 | 45 | 68.2 | Limited |
| ≥5 comorbidities | 12 | 45 | 68.2 | Limited |
| ≥75 years (n=1,319) | | | | |
| No previous malignancy | | | | |
| 0-1 comorbidity | 459 | 40 | 60.6 | Limited |
| 2-4 comorbidities | 517 | 42 | 63.6 | Limited |
| ≥5 comorbidities | 138 | 44 | 66.7 | Limited |
| Previous malignancy | | | | |
| 0-1 comorbidity | 84 | 52 | 78.8 | Limited |
| 2-4 comorbidities | 95 | 52 | 78.8 | Limited |
| ≥5 comorbidities | 26 | 52 | 78.8 | Limited |

* The evidence base was categorized as present (exclusion from less than 30% of the trials comprising the evidence base); partial (exclusion from 30-60% of the trials comprising the evidence base); or limited (exclusion from more than 60% of the trials comprising the evidence base).

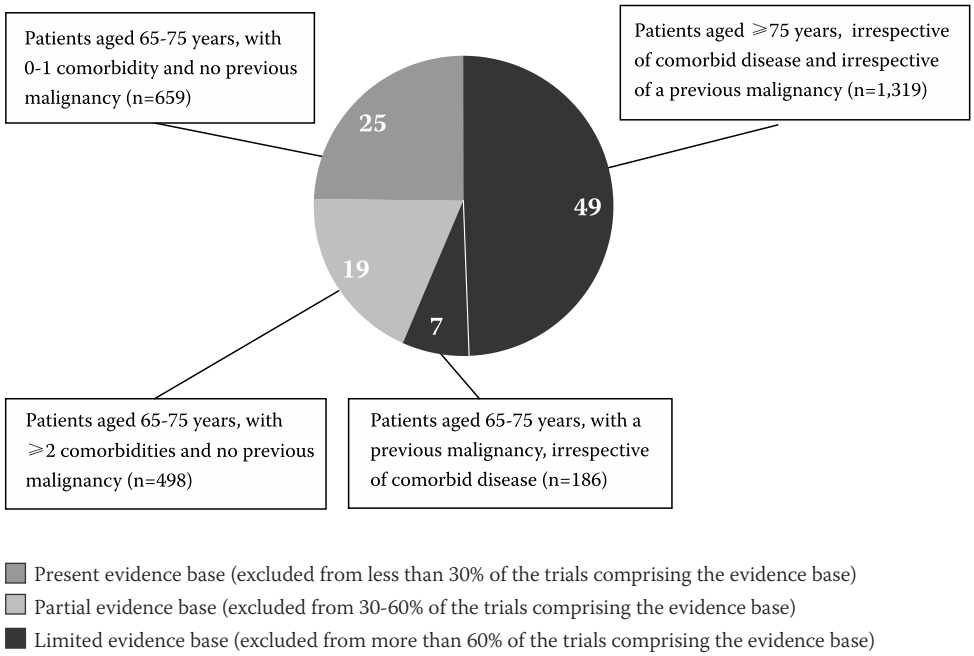


**Figure 1**. Qualification of the evidence base for locoregional treatment, for different groups of elderly breast cancer patients.

# Discussion

## Summary

Overall, the evidence base for locoregional treatment was present for 35%, partial for 19%, and limited for 56% of breast cancer patients aged 65 years or older with early stage disease. The evidence base for locoregional treatment in patients aged 65-75 years was dependent on the number of comorbidities, and whether patients had a previous malignancy. Contrary, the evidence base was limited in all patients aged 75 years or older. Hence, guideline recommendations regarding locoregional treatment may not necessarily be valid for patients aged ≥75 years with early stage breast cancer.

## Under- or overestimation of results

The current study showed that breast cancer patients aged 75 years or older are excluded from more than 60% of the trials, and hence the evidence base was deemed limited. The evidence base in this group may be *underestimated;* theoretically, a large and representative sample of elderly breast cancer patients may have been included in the remaining 40% of the trials they were eligible for. On the other end of the spectrum, patients aged 65-75 years with 0-1 comorbidity and no previous malignancy were excluded from only 27% of the clinical trials and therefore, an evidence base was deemed present. However, the evidence base in the latter

group of patients may be *overestimated*, since it is unknown how many and which type of elderly patients are actually included in the 73% of the trials they were eligible for. Unfortunately we did not have information on the number and type of elderly patients who were actually included, since individual trial data were not available.

The results of the current study are likely to be underestimated in another manner. Disqualification of patients was assessed by eligibility criteria. However, disqualification is multifactorial; therefore, actual exclusion of elderly patients is expected to be higher, and inclusion of elderly may be even more restricted and selected. Next to eligibility criteria, physician factors[7;8;24], patient factors[7], and factors related to trial logistics may affect inclusion[24]. These factors all favor inclusion of relatively healthy volunteers[25;26]. From a patient view, age has been shown to be no significant predictor as to whether a patient would participate, once they have been offered a trial[7;27]. Moreover, as exclusion criteria on comorbid disease were defined loosely, we had to specify the definition to calculate exclusion of elderly patients. As we have chosen to use a rather conservative definition, exclusion from trials due to comorbid disease is likely to be underestimated. In addition, other exclusion criteria may further affect exclusion of elderly patients. For example, 6% of the patients in the FOCUS cohort did not receive breast surgery and therefore would have been disqualified for all clinical trials in this study.

## Clinical implications

Others have published on the limited inclusion of elderly patients in clinical trials[4;5;28]. A recent literature review showed that of all clinical trials published in 2008 in five major medical journals, 20% excluded patients based on age[4]. In the remaining trials, almost half of the trials excluded patients with age-related diseases, which could disproportionally impact inclusion of elderly patients. The novelty of the current study is that we were able to actually assess exclusion from randomized clinical trials in a large population-based cohort of elderly breast cancer patients. Hence we were able not only to evaluate the magnitude of non-evidence based medicine in elderly breast cancer patients, but also to qualify for which patients in particular an evidence base for locoregional treatment is lacking.

Recently, Wolters and colleagues compared national breast cancer guidelines from the United States of America, Canada, Australia, the United Kingdom and Germany[13]. The authors concluded that most treatment recommendations exhibited a large degree of congruency. This was explained by the fact that they are based on the same evidence. Although the current study was based on the Dutch guideline recommendations, the study by Wolters suggests that our results may be valid to a large extent for locoregional treatment guidelines in other countries.

Breast cancer patients aged 75 years or older were excluded from the majority of the randomized clinical trials on locoregional treatment and thus, one should be aware that the evidence base for locoregional treatment in this population is limited. Extrapolation of trial results

obtained in a younger, selected population may not be justified and consequently, guidelines for locoregional treatment in early stage breast cancer may not be as valid in patients aged 75 years or older. The current findings are underlined by a previous finding that guideline adherence in elderly patients was not associated with survival[29]. To enlarge the evidence base, and thereby to optimize treatment, efforts should be made to perform age specific studies in elderly patients aged 75 years or older. Moreover, relaxation of eligibility criteria that could hamper inclusion of these patients in particular[30] and physician education[6] and awareness may increase the number of elderly study participants.

**Supplementary table 1.** The evidence base for locoregional treatment, as included in the national guidelines.

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|---|
| Breast conserving surgery followed by radiotherapy is equally effective compared with mastectomy in terms of survival. Omission of radiotherapy after breast conserving surgery has a negative impact on locoregional control and survival. [1-11]. Meta-analyses [6]: [3,4,12-37]; [7]: [1,3-5,12-50]; [8]: [15,33-36,39-41,51]. |
| A radiotherapy boost improves local control in all patients. The absolute benefit of a boost after complete resection declines with increasing age. [52,53] |
| An age of 40 years or younger is an independent predictor for a local recurrence after breast conserving surgery. [52-55]. Meta-analysis [54]: [56,57] |
| Good cosmesis after breast conserving surgery may be obtained in at least 70% of patients. [58] |
| Partial breast irradiation seems to be effective in a select group of patients with a low a priori risk for a local recurrence. [59] |
| Patients with large tumors (>5cm) and/or extensive nodal involvement (≥ 4 nodes involved) are at a higher risk for a locoregional recurrence, irrespective of irradical surgery and systemic therapy. [29,60,61] |
| In case of a mastectomy, postoperative locregional radiotherapy decreases the risk of a locoregional recurrence with 2/3 and increases survival. [6,29,60-62]. Meta-analyses: [6]: [3,4,12-37]; [62]: [23,25-31,61,63,64] |
| In case of a mastectomy, locoregional radiotherapy improves local control and overall survival at 15 years of follow up, if 5 years risk of locoregional recurrence is ≥15%. [7] Meta-analysis: [7]: [1,3-5,12-50] |
| In case of a mastectomy, in patients with 1 to 3 positive lymph nodes, postoperative locoregional radiotherapy improves locoregional control and overall survival. [29,60,61] |
| Hypofractionated radiotherapy of a patient with pT1-3aN0-1M0 breast cancer with a radical resection results in comparable five years survival, local control and cosmesis compared to conventional radiotherapy schemes. [65-69]; Meta-analysis: [65]: [70,71] |
| Surgery of the axillary and periclavicular lymph nodes yields similar survival, disease free survival and locoregional control compared with radiotherapy, in patients with clinically node negative, operable breast cancer. [3,48] |
| Surgery of the axillary lymph nodes seems to yield similar survival, disease free survival and locoregional control compared with radiotherapy, in patients with clinically node positive, operable breast cancer. [3] |
| Risk of lymph edema and other late morbidity is higher after axillary clearance compared with radiotherapy. [72] |

For references see Supplementary table 2.

**Supplementary table 2.** The evidence base for locoregional treatment, references.


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# Chapter 3

# The external validity of a clinical trial comprising elderly patients with hormone receptor positive breast cancer

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# Abstract

## Background

Despite comprising a large proportion of all breast cancer patients, elderly are underrepresented in clinical trials. Moreover, inclusion is likely to be selective. The aim of this study was to investigate to what extent elderly breast cancer patients in a randomized clinical trial are selected as compared to breast cancer patients from the general population.

## Methods

We compared characteristics and outcome of breast cancer patients who participated in a randomized clinical trial (Tamoxifen Exemestane Adjuvant Multinational trial) with unselected breast cancer patients of corresponding age from the general population. Dutch patients aged ≥65 years at diagnosis of hormone receptor positive breast cancer without distant metastases, with either nodal involvement, a tumor >3cm, or a 1-3cm histological grade III tumor, who completed local therapy were included. Analyses were stratified by age (65-75 years; ≥75 years). Primary outcome was overall mortality.

## Results

We included 1,325 breast cancer patients who participated in a trial and 1,056 breast cancer patients from the general population. Irrespective of age, patients who participated in the trial had fewer comorbid diseases, a higher socio-economic status, and smaller tumors (all p-values <0.001). In patients aged 65-75 years, those who participated in the trial had a similar overall mortality as patients from the general population after adjustment for patient, tumor, and treatment characteristics (hazard ratio 1.08 (95% confidence interval (CI) 0.73-1.60)). Contrary, in patients aged ≥75 years, those who participated in the trial had a lower overall mortality (multivariable hazard ratio 0.72 (95% CI 0.55-0.95)).

## Conclusion

Breast cancer trial participants aged ≥75 years do not represent elderly breast cancer patients of corresponding age from the general population. This may be explained by selective inclusion into a trial, which hampers the external validity of the trial. Hence, breast cancer trial results may not necessarily be extrapolated to the general elderly breast cancer patient aged ≥75 years.

# Introduction

In developed countries, over 40% of all breast cancer patients is 65 years or older[1;2]. Different factors may play a role in the evaluation of breast cancer treatment in elderly as compared to younger patients. Elderly suffer from a higher risk of competing mortality[3] and have a lower remaining life expectancy. Consequently, the absolute benefit of anticancer therapy may be smaller, while long term adverse events may be less relevant. Moreover, concurrent disease and medication use may directly affect tolerability of treatment and increase toxicity[4;5]. Therefore, it is important to evaluate treatment efficacy and outcomes specifically in elderly patients, and not to extrapolate results which were obtained in younger patients.

Despite comprising a large proportion of all breast cancer patients, elderly are frequently underrepresented in clinical trials[6-8]. This underrepresentation might not be problematic. As long as the included elderly are representative of the general population of elderly breast cancer patients, age specific subgroup analyses can be extrapolated. However, inclusion of elderly patients is likely to be selective[7].

The aim of the current study was to evaluate to what extent elderly breast cancer patients in a trial are selected as compared to breast cancer patients from the general population. Therefore, characteristics and outcome of elderly breast cancer patients who participated in a large trial without upper age limit, were compared with those of breast cancer patients of corresponding age from the general population.

# Methods

We included elderly patients who participated in a clinical trial, and elderly breast cancer patients from the general population. To ensure a valid comparison, similar inclusion criteria with regards to tumor and treatment characteristics were applied to all patients.

## Patients who participated in a trial

Patients who participated in the Tamoxifen Exemestane Adfuvant Multinational trial[9;10] were eligible for inclusion in the current study. Because five-years results of the TEAM trial showed no significant differences in efficacy endpoints between both treatment arms[9], we were able to conduct the current study regardless of randomized treatment. Between January 2001 and January 2006, 9,766 postmenopausal women with hormone receptor positive breast cancer without distant metastases, who completed local therapy with curative intent, were randomized to either exemestane 25 mg daily for 5 years or to a sequential regimen consisting of tamoxifen 20 mg daily for 2.5–3 years, followed by exemestane 25 mg daily for 2.5–2 years. Inclusion for patients in The Netherlands was restricted to those who either had nodal involvement, a tumor of >3cm, or a histological grade III tumor of 1-3cm[10].

## Patients from the general population

From the Netherlands Cancer Registry we identified all incident breast cancer patients aged 65 years or older, who were diagnosed in the geographically defined Comprehensive Cancer Center Region West in The Netherlands between January 1997 and December 2004. By means of chart review by trained personnel, additional information on patient characteristics, tumor characteristics, treatment, follow-up and outcome were recorded[11].

## Inclusion criteria

For a proper comparison between patients who participate in a trial and patients from the general population, similar inclusion criteria were applied to all patients. Hence, we restricted inclusion of patients who participated in a trial to patients from The Netherlands, who were 65 years and older at diagnosis. Likewise, the inclusion criteria that were used in the trial were applied to patients from the general population; those who had hormone receptor positive disease without distant metastases, and either one of the following; a tumor size of >3cm, a histological grade III tumor of 1-3cm, or nodal involvement, were eligible. In addition, they had to have received breast surgery with curative intent.

In all patients, prespecified forms including free text fields were used for data collection. Comorbidity was defined as presence of comorbidity at time of diagnosis. Comorbid diseases were categorized into presence or absence of the main categories included in the 10th edition of the International Statistical Classification of Diseases and Related Health Problems (ICD-10), namely endocrine, nutritional and metabolic diseases (chapter IV); mental and behavioural disorders (chapter V); diseases of the nervous system (chapter VI); diseases of the circulatory system (chapter IX); diseases of the respiratory system (chapter X); diseases of the digestive system (chapter XI); and diseases of the musculoskeletal and connective tissue (chapter XIII)[12]. In addition, comorbid diseases were categorized by number (0-1; 2-4; 5 or more comorbid diseases). Socio-economic status (SES) was assigned using an area-based measure according to place of residence at the time of diagnosis. The area-based SES was provided by the Netherlands Institute for Social Research, and is based on data concerning income, employment, and education[13]. In the current study, SES was categorized in tertiles (low, intermediate and high SES respectively).

## Statistical analyses

Statistical analyses were performed using SPSS 20.0 (SPSS, Chicago, IL) and Stata SE 12.0. In line with previous publications and in line with SIOG recommendations[14;15], the analyses were stratified by age at diagnosis (65-75 years and 75 years or older). To compare proportional differences in patient, tumor and treatment characteristics between patients who participated in a trial and patients from the general population, the Pearson $\chi^2$ test was used.

The primary outcome was overall mortality, defined as death from any cause. Vital status was established either directly from the patient's medical record or through linkage with the

municipal population registries (follow-up until January 1st 2011). Follow-up was truncated at five years to accommodate differences in total follow-up duration. Cumulative incidence of death was estimated by $1 - \widehat{S}(t)$ where $\widehat{S}(t)$ is the Kaplan–Meier estimator for the probability of survival at time (t), based on the life tables[16]. Corresponding 95% confidence intervals were calculated as the cumulative incidence at t(x) ± 1.96 * standard error. Cox proportional hazard models were used to evaluate the association between covariates and overall mortality. For both age groups, the proportional hazard assumption was evaluated by the link test (p=0.45; p=0.89 respectively) and based on the analysis of the Schoenfeld residuals[17] (p=0.20; p=0.75 respectively).

As breast cancer mortality contributes to overall mortality, disparities in breast cancer outcome may affect the primary endpoint. Therefore we evaluated distant breast cancer recurrence as secondary endpoint, which was defined as recurrence in skeleton, skin, liver, lung, brain, or other distant localization. We focused on distant recurrence because cause of death is more difficult to attribute to a certain cause with increasing age[18;19], and distant recurrence is a valid proxy for death due to breast cancer[20]. Detection method of a breast cancer recurrence was similar for all patients.

Cause-specific outcomes may be influenced by the risk of competing endpoints; for example, an individual who dies, is no longer at risk for a distant breast cancer recurrence. This risk of competing endpoints may be present in older populations in particular[3]. Therefore, distant breast cancer recurrence was estimated by regression analyses according to Fine and Gray[21;22]. A Fine and Gray analysis is used to assess the risk of a distant breast cancer recurrence while taking into account the risks of reaching other, competing endpoints. Competing endpoints were a locoregional recurrence (recurrence in the ipsilateral breast or chest wall, ipsilateral axillary or supraclavicular lymph node(s)), contralateral breast cancer, and death due to any cause.

Covariates were included in the multivariable model if they were judged to be clinically relevant. The fully adjusted multivariable model included tumor characteristics (histological grade [Bloom Richardson grade I; II; III; unknown], T stage [T1,T2; T3,T4; unknown], nodal stage [negative; positive; unknown]), treatment characteristics (most extensive surgery [breast conserving surgery; mastectomy], radiotherapy [yes; no; unknown], endocrine therapy [yes; no], and chemotherapy [yes; no; unknown]), and patient characteristics (age [continuous], year of diagnosis [continuous], socio-economic status [in tertiles; unknown], and number of comorbidities [0-1; 2-4; ≥5]). Sensitivity analyses were performed excluding missing values. All statistical tests were two-sided; p values <.05 were considered to be statistically significant.

# Results

Overall, we included 1,325 breast cancer patients who participated in a trial, and 1,056 unselected breast cancer patients from the general population. Mean age of patients who participated in a trial was 73.5 years, (standard deviation (SD) 5.7 years), versus 76.7 years (SD 7.1 years) in patients from the general population (p<0.001). First, we investigated whether the

**Table 1.** Patient and tumor characteristics of elderly breast cancer patients who participated in a trial, as compared to those of elderly breast cancer patients from the general population.

| | Age 65-75 years | | | | | Age ≥75 years | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Trial participants (n=852) | | General population (n=467) | | p | Trial participants (n=473) | | General population (n=589) | | p |
| | n | % | n | % | | n | % | n | % | |
| Socio-economic status (tertiles) | | | | | **<0.001** | | | | | **<0.001** |
| 1 (lowest) | 200 | 23.5 | 205 | 43.9 | | 108 | 22.8 | 250 | 42.4 | |
| 2 | 177 | 20.8 | 96 | 20.6 | | 106 | 22.4 | 122 | 20.7 | |
| 3 | 419 | 49.2 | 165 | 35.3 | | 238 | 50.3 | 217 | 36.8 | |
| Unknown | 56 | 6.6 | 1 | 0.2 | | 21 | 4.4 | 0 | 0 | |
| Number of comorbidities | | | | | **<0.001** | | | | | **<0.001** |
| 0-1 | 655 | 76.9 | 273 | 58.5 | | 306 | 64.7 | 262 | 44.5 | |
| 2-4 | 193 | 22.7 | 171 | 36.6 | | 165 | 34.9 | 263 | 44.7 | |
| ≥5 | 4 | 0.5 | 23 | 4.9 | | 2 | 0.4 | 64 | 10.9 | |
| Presence of comorbidity | | | | | | | | | | |
| Endocrine | 178 | 20.9 | 130 | 27.8 | **0.005** | 105 | 22.2 | 188 | 31.9 | **<0.001** |
| Psychiatric | 4 | 0.5 | 41 | 8.8 | **<0.001** | 7 | 1.5 | 72 | 12.5 | **<0.001** |
| Neurological | 31 | 3.6 | 38 | 8.1 | **<0.001** | 38 | 8.0 | 79 | 13.4 | **<0.001** |
| Circulatory | 334 | 39.2 | 225 | 48.2 | **0.002** | 220 | 46.5 | 334 | 39.2 | **<0.001** |
| Respiratory | 54 | 6.3 | 48 | 10.3 | **0.013** | 30 | 6.3 | 67 | 11.4 | **0.005** |
| Gastro-intestinal | 24 | 2.8 | 54 | 11.6 | **<0.001** | 16 | 3.4 | 83 | 14.1 | **<0.001** |
| Musculoskeletal | 104 | 12.2 | 86 | 18.4 | **0.002** | 100 | 21.1 | 167 | 28.4 | **0.008** |
| Histological grade (BR) | | | | | **<0.001** | | | | | **<0.001** |
| Grade 1 | 133 | 15.6 | 37 | 7.9 | | 69 | 14.6 | 67 | 11.4 | |
| Grade 2 | 380 | 44.6 | 138 | 29.6 | | 225 | 47.6 | 172 | 29.2 | |
| Grade 3 | 286 | 33.6 | 181 | 38.8 | | 134 | 28.3 | 193 | 32.8 | |
| Unknown | 53 | 6.2 | 111 | 23.8 | | 45 | 9.5 | 157 | 26.7 | |
| T stage | | | | | **<0.001** | | | | | **<0.001** |
| T1, T2 | 794 | 93.2 | 404 | 86.5 | | 429 | 90.7 | 466 | 79.1 | |
| T3, T4 | 58 | 6.8 | 61 | 13.1 | | 44 | 9.3 | 120 | 20.4 | |
| Unknown | 0 | 0 | 2 | 0.4 | | 0 | 0 | 3 | 0.5 | |
| Nodal status | | | | | 0.092 | | | | | 0.525 |
| Negative | 269 | 31.6 | 126 | 27 | | 149 | 31.5 | 181 | 307 | |
| Positive | 583 | 68.4 | 340 | 72.8 | | 322 | 68.1 | 402 | 68.3 | |
| Unknown | 0 | 0 | 1 | 0.2 | | 2 | 0.4 | 6 | 1 | |

BR: Bloom Richardson.

phenotype of patients who participated in a clinical trial differs from the phenotype of patients from the general population (Table 1). In both age groups, patients who participated in a trial had fewer comorbid diseases and more often had a high socio-economic status. Moreover, patients who participated in a trial had smaller tumors.

Second, we investigated whether treatment of patients who participated in a clinical trial differs from treatment of patients from the general population (Table 2). Needless to say, all patients who participated in the trial received endocrine therapy, whereas in both age groups 82% of patients from the general population received endocrine therapy, despite having hormone receptor positive disease and an indication for endocrine therapy. In patients aged 75 years or older, patients who participated in a trial more often had breast conserving surgery as the most extended type of breast surgery.

**Table 2.** Treatment characteristics of elderly breast cancer patients who participated in a trial, as compared to elderly breast cancer patients from the general population.

| | Age 65-75 years | | | | | Age ≥75 years | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Trial participants (n=852) | | General population (n=467) | | p | Trial participants (n=473) | | General population (n=589) | | p |
| | n | % | n | % | | n | % | n | % | |
| Most extended surgery | | | | | 0.164 | | | | | **<0.001** |
| BCS | 383 | 45.0 | 191 | 40.9 | | 114 | 24.1 | 75 | 12.7 | |
| Mastectomy | 469 | 55.0 | 276 | 59.1 | | 359 | 75.9 | 514 | 87.3 | |
| Radiotherapy | | | | | 0.446 | | | | | 0.052 |
| Yes | 500 | 58.7 | 288 | 61.7 | | 211 | 44.6 | 227 | 38.5 | |
| No | 351 | 41.2 | 179 | 38.3 | | 262 | 55.4 | 362 | 61.5 | |
| Unknown | 1 | 0.1 | 0 | 0 | | 0 | 0 | 0 | 0 | |
| Endocrine therapy | | | | | **<0.001** | | | | | **<0.001** |
| Yes | 852 | 100 | 384 | 82.2 | | 473 | 100 | 480 | 81.5 | |
| No | 0 | 0 | 83 | 17.8 | | 0 | 0 | 109 | 18.5 | |
| Chemotherapy | | | | | 0.054 | | | | | **<0.001** |
| Yes | 63 | 7.4 | 52 | 11.1 | | 0 | 0 | 19 | 3.2 | |
| No | 788 | 92.5 | 415 | 88.9 | | 473 | 100 | 570 | 98.6 | |
| Unknown | 1 | 0.1 | 0 | 0 | | 0 | 0 | 0 | 0 | |

BCS: breast conserving surgery.

Figure 1a and b show the unadjusted cumulative incidence of death for patients who participated in a trial and for patients from the general population, by age at diagnosis. In patients aged 65-75 years, five-years cumulative incidence of death was 14% (95% CI 9-16) for patients who participated in a trial and 19% (95% CI 16-23) for patients from the general population. For patients aged 75 years or older, five-years cumulative incidence of death was 28% (95% CI 23-32) and 48% (95% CI 44-52), respectively.

**Table 3.** Overall mortality for elderly breast cancer patients who participated in a trial, as compared to elderly patients from the general population, fully adjusted model.

| | Patients aged 65-75 years | | | Patients aged ≥75 years | | |
|---|---|---|---|---|---|---|
| | 5-years death, n | Multivariable* HR (95% CI) | p | 5-years death, n | Multivariable* HR (95% CI) | p |
| Patients | | | 0.693 | | | **0.019** |
| General population | 91 | 1 (reference) | | 281 | 1 (reference) | |
| Trial participants | 110 | 1.08 (0.73-1.60) | | 124 | 0.72 (0.55-0.95) | |
| Socio-economic status | | | 0.935 | | | 0.102 |
| Low | 58 | 1 (reference) | | 112 | 1 (reference) | |
| Intermediate | 65 | 0.97 (0.65-1.43) | | 124 | 1.03 (0.78-1.36) | |
| High | 69 | 0.90 (0.65-1.43) | | 162 | 1.27 (1.01-1.60) | |
| Missing | 9 | 0.87 (0.42-1.80) | | 7 | 1.74 (0.80-3.82) | |
| Number of comorbidities | | | **0.010** | | | 0.122 |
| 0-1 | 121 | 1 (reference) | | 199 | 1 (reference) | |
| 2-4 | 75 | 1.58 (1.18-2.11) | | 171 | 1.13 (0.92-1.40) | |
| ≥5 | 5 | 1.18 (0.47-2.93) | | 35 | 1.46 (1.00-2.12) | |
| Histological grade (BR) | | | **<0.001** | | | **0.007** |
| Grade 1 | 18 | 1 (reference) | | 50 | 1 (reference) | |
| Grade 2 | 55 | 0.97 (0.57-1.65) | | 126 | 0.90 (0.65-1.26) | |
| Grade 3 | 92 | 2.19 (1.30-3.69) | | 143 | 1.32 (0.95-1.84) | |
| Unknown | 36 | 1.81 (0.99-3.31) | | 86 | 0.89 (0.61-1.29) | |
| T stage | | | 0.656 | | | **0.002** |
| T1, T2 | 169 | 1 (reference) | | 313 | 1 (reference) | |
| T3, T4 | 31 | 1.22 (0.80-1.87) | | 91 | 1.56 (1.22-2.00) | |
| Unknown | - | Too low numbers | | 1 | 0.70 (0.10-5.09) | |
| Nodal stage | | | **0.007** | | | 0.058 |
| Negative | 44 | 1 (reference) | | 112 | 1 (reference) | |
| Positive | 156 | 1.82 (1.26-2.63) | | 288 | 1.32 (1.05-1.66) | |
| Unknown | - | Too low numbers | | 5 | 1.25 (0.50-3.16) | |
| Most extensive surgery | | | **0.001** | | | 0.518 |
| BCS | 58 | 1 (reference) | | 49 | 1 (reference) | |
| Mastectomy | 143 | 2.03 (1.35-3.04) | | 356 | 1.12 (0.80-1.57) | |
| Radiotherapy | | | 0.448 | | | 0.333 |
| Yes | 115 | 1 (reference) | | 148 | 1 (reference) | |
| No | 86 | 1.27 (0.88-1.84) | | 257 | 0.89 (0.70-1.13) | |
| Unknown | - | Too low numbers | | - | NA | |
| Endocrine therapy | | | **0.048** | | | 0.232 |
| Yes | 182 | 1 (reference) | | 347 | 1 (reference) | |
| No | 19 | 0.59 (0.35-1.00) | | 58 | 0.83 (0.61-1.13) | |
| Chemotherapy | | | 0.568 | | | 0.993 |
| Yes | 22 | 1 (reference) | | 10 | 1 (reference) | |
| No | 179 | 1.15 (0.71-1.88) | | 395 | 1.00 (0.52-1.91) | |
| Unknown | - | Too low numbers | | - | NA | |

* Hazard ratios adjusted for all other covariates mentioned in the Table, and age (continuous) and year of diagnosis (continuous). BR: Bloom Richardson; BCS: breast conserving surgery. Cox proportional hazard models were used to evaluate the association between covariates and overall mortality. All statistical tests were two-sided; p values <.05 were considered to be statistically significant.

Overall mortality of patients aged 65-75 years was lower for patients who participated in a trial (univariate HR 0.65 (95% CI 0.50-0.86)). To explore whether this difference in mortality could be explained by unequal distributions in patient, tumor and treatment characteristics, multivariable analyses were performed. The fully adjusted model (Table 3) showed that after adjustment for tumor, treatment and patient characteristics, the hazard ratio attenuated towards 1 (HR 1.08 (95%CI 0.73-1.60)). Patients aged 75 years or older who participated in a trial also had a lower overall mortality as compared to patients of corresponding age from

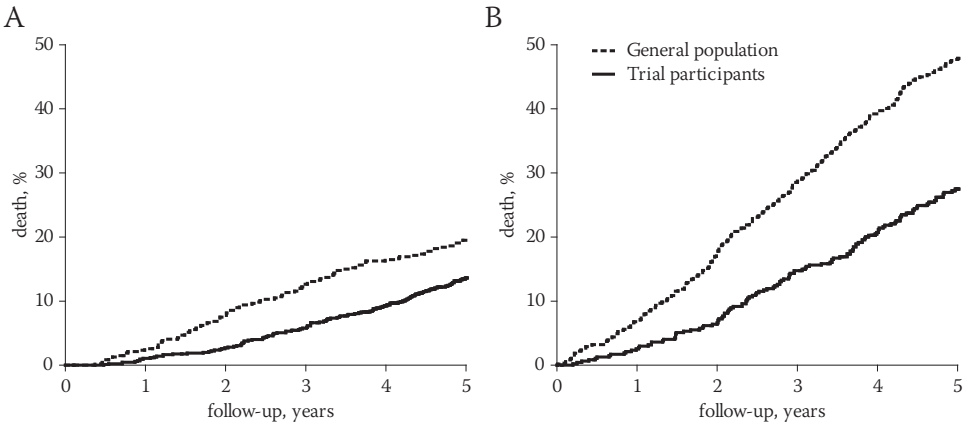


**Figure 1.** Cumulative incidence of death by age at diagnosis.

the general population (univariate HR 0.49 (95% CI 0.39-0.60)). These differences could not be explained by unequal distributions in patient, tumor and treatment characteristics; multivariable analysis consistently showed a lower overall mortality (HR 0.72 (95% CI 0.55-0.95)). To explore whether differences in overall mortality could be explained by differences in breast cancer outcome, we evaluated the risk of a distant recurrence (Table 4). Irrespective of age, multivariable analyses did not reveal any differences. Of note, in both age groups the absolute number of patients who developed a distant recurrence was exceeded by the number of patients who died. Among patients aged 75 years or older, the number of patients who died during five years of follow-up was 124 and 281. Contrary, the number of patients who developed a distant recurrence was 54 and 74. These data confirm that in those aged 75 years or older, the observed difference in overall mortality between patients who participated in a trial and patients from the general population is likely to resemble a non-breast cancer driven difference in overall fitness.

# Discussion

To warrant the internal validity of a clinical trial, inclusion of patients into a trial is often selective, even though this may compromise the external validity of the trial[23]. Indeed we

showed that patients who participated in a clinical trial had more favourable patient and tumor characteristics as compared to patients from the general population. In patients aged 65-75 years, those who participated in a trial had a similar overall mortality as patients from the general population after adjustment. Thus, selective inclusion can be overcome by taking into account patient, tumor and treatment characteristics. Selection of patients into a trial may be more pronounced with increasing age, given the larger heterogeneity of patients with increasing age. This hypothesis was confirmed in the current study; we showed that in patients aged 75 years or older, differences in overall mortality could not be explained by patient, tumor and treatment characteristics. Therefore other, unmeasured mechanisms may have played a role in the selection of elderly patients into a trial.

**Table 4.** Risk of distant breast cancer recurrence for elderly breast cancer patients who participated in a trial, as compared to elderly breast cancer patients from the general population.

| | 5-years distant recurrence n | 5-years competing events* n | Univariate HR (95%CI) | p | Multivariable HR** (95% CI) | p |
|---|---|---|---|---|---|---|
| 65-75 years | | | | 0.05 | | 0.737 |
| General population (n=467) | 61 | 59 | 1 (reference) | | 1 (reference) | |
| Trial participants (n=852) | 84 | 62 | 0.72 (0.52-1.00) | | 0.94 (0.64-1.37) | |
| ≥75 years | | | | 0.447 | | 0.269 |
| General population (n=589) | 74 | 228 | 1 (reference) | | 1 (reference) | |
| Trial participants (n=473) | 54 | 95 | 0.87 (0.66-1.24) | | 0.80 (0.53-1.19) | |

HR: Hazard ratio. * Competing events comprise intercurrent death; locoregional recurrence as first site of recurrence; contralateral breast cancer. ** Multivariable HRs were adjusted for histological grade, T stage, nodal stage, most extensive surgery, radiotherapy, endocrine therapy, chemotherapy, socio-economic status, comorbidity, age, year of diagnosis. Fine and Gray regression models were used to evaluate the association between covariates and distant breast cancer recurrence. All statistical tests were two-sided; p values <.05 were considered to be statistically significant.

A selective inclusion of patients into a trial may vary by type of study and study drug, and is multifactorial. First, eligibility criteria may hamper inclusion of elderly patients in general and inclusion of certain elderly in particular. Patients were ineligible for the TEAM trial if they had a malignancy within five years preceding breast cancer diagnosis, an Eastern Cooperative Oncology Group performance status of more than two, or a significant cardiac disease or other illness interfering with study participation and adequate follow-up[10]. Others have published about the impact of eligibility criteria on the inclusion in clinical trials[24]. Of all clinical trials published in 2008 in five major medical journals, 20% excluded patients based on age[7]. In the remaining trials, almost half of the studies excluded patients with age-related diseases, which could disproportionally impact inclusion of certain elderly patients. As compared with other randomized clinical trials, the TEAM trial had relatively few eligibility criteria, without an upper age limitation, enabling enrolment of many elderly patients[9]. Therefore it is expected that the discrepancy between trial patients and patients from the general population will also be present in other breast cancer trials including elderly patients. Next to eligibility criteria hampering the inclusion of elderly patients, physician factors[25-27], patient factors[26], and factors

related to trial logistics may affect participation[25]. From a patient point of view, age has been shown to be no significant predictor as to whether a patient would participate, once they have been offered a trial[26;28].

To summarize, the lower overall mortality of patients aged 75 years or older who participated in a trial may be the *result of* selective inclusion of patients into a trial. As was shown, those who participated in a trial had, among others, fewer comorbid diseases. Additionally, participation in a trial in itself may *result in* a lower overall mortality. One may argue that more attention is being paid to treatment of comorbid disease of elderly patients who participate in a trial, as compared to those from the general population, which may decrease overall mortality.

Others have published on the external validity of clinical trials[23]. The novelty of the current study is that we were able to perform a head-to-head comparison of patients participating in a clinical trial and patients from the general population. This way we could pinpoint that external validity is compromised for breast cancer patients aged 75 years or older in particular. Our study has some limitations. By applying identical inclusion criteria, we aimed to construct similar groups of patients. However, differences in design and data collection may have influenced our results. Although prespecified forms including free text fields were used for all patients, and baseline characteristics were reported extensively in the medical files of patients from the general population, we cannot exclude possible differences due to the prospective and retrospective nature of data collection. A strength of this study is that systematic misclassification of the primary endpoint overall mortality is unlikely; vital status was established through linkage with the municipal population registries for all patients. Regarding the secondary endpoint, the method of detection of a breast cancer recurrence was similar for all patients. Of note, those who participated in the trial had strict follow-up schemes, whereas this may not always be accomplished in general practice. Therefore, we cannot exclude the possibility of under diagnosis of breast cancer recurrence among patients from the general population. Regarding overall mortality, sample size was sufficient to detect a difference among patients aged 75 years or older. Among patients aged 65-75 years, given the confidence interval of the multivariable analysis (95% CI 0.73-1.60), we cannot exclude that those who participate in a trial do have a different overall mortality as compared to patients from the general population. Regarding the secondary endpoint, sample size may have been insufficient. However, it was also shown that the absolute number of patients who developed a distant recurrence was greatly exceeded by the absolute number of patients who died, especially in patients aged 75 years or older. Therefore, although the direct comparison of distant breast cancer recurrence between patients who participated in a trial and patients from the general population is possibly underpowered, the secondary endpoint does strengthen the main conclusion that the observed higher overall mortality in patients aged 75 years or older from the general population is likely to resemble a non-breast cancer driven difference in overall fitness.

## Clinical implications

Since treatment guidelines are mainly based on clinical trial results, the evidence base for treatment in patients aged 75 years or older may be limited. However, it is not likely that conduction of clinical trials will be sufficient to fill this 'evidence gap'. Even in the absence of eligibility criteria it is expected that elderly who are included in a trial will be selected[26;27;29]. Moreover, the large heterogeneity in the elderly population makes it difficult to conduct clinical trials including a representative sample of the general population; even with inclusion of large numbers, it remains a challenge to create comparable study arms. Therefore different study designs may be warranted. Restriction in research topics, design, and analysis may give observational research the chance to be as credible as randomized evidence[30]. Moreover, observational, population-based data reflect the heterogeneity of the general population. Among others, international comparisons of treatment strategies, using country as an instrumental variable, may increase insight in adequate treatment for different groups of elderly breast cancer patients.

## Conclusions

Inclusion in a breast cancer trial is more selective with increasing age. Breast cancer patients aged 75 years or older who participate in a trial are not representative of breast cancer patients of corresponding age from the general population, which may hamper the external validity of a trial; breast cancer trial results may not necessarily be extrapolated to the general breast cancer patient with corresponding age.

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Chapter 4

# Adherence to treatment guidelines and survival by age at diagnosis in patients with early stage breast cancer

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# Abstract


## Background

Elderly patients with breast cancer are underrepresented in clinical studies. Therefore, it is unknown whether treatment guidelines, based on clinical trials, can be extrapolated to this population. The aim of this study was to assess adherence to treatment guidelines by age at diagnosis, and to examine age-specific survival in relation to guideline adherence.

## Methods

Patients with early stage breast cancer aged younger than 65 years, or 75 years or older, diagnosed between 2005 and 2008, were identified from the Netherlands Cancer Registry. Adherence to treatment guidelines for breast and axillary surgery, radiotherapy, chemotherapy and endocrine therapy was determined. Nonadherence to the guidelines was defined as overtreatment or undertreatment. The primary endpoint was overall survival, assessed by means of an instrumental variable, the comprehensive cancer center region.

## Results

Overall, 24,959 patients younger than 65 years and 6,561 patients aged 75 years or older were included. Median follow-up was 2.8 years. Compared with patients younger than 65 years, those aged 75 years or older were less frequently treated in concordance with guidelines: 62.0% (15,487 patients) versus 55.6% (3,647 patients) ($p<0.001$). In both age groups, most patients received at least three out of five treatment modalities in concordance with guidelines: 98.8% (24,652 patients) and 93.8% (6,152 patients) respectively. Survival analysis using the instrumental variable showed that adherence to guidelines was not associated with overall survival in patients younger than 65 years ($p=0.601$) or those aged 75 years or older ($p=0.190$).

## Conclusions

Adherence to treatment guidelines was affected by age at diagnosis. However, adherence to the guidelines was not associated with overall survival in either age group.

# Introduction

The first national multidisciplinary guideline 'Breast Cancer Treatment', initiated by the Dutch Institute of Health Care Improvement CBO and the Dutch National Breast Cancer Society[1], was implemented in the Netherlands in 2002. The aim was to improve breast cancer care and cure by providing consensus and evidence based recommendations for treatment[1]. Deviation from the guidelines is possible, but reasons should be documented. Since 2002, regular revisions have ensured that information and recommendations are updated.

In 2008 in the Netherlands, almost 20% of breast cancer patients was 75 years or older at time of diagnosis[2]. Elderly patients differ from younger patients in many respects. The presence of comorbidities and concomitant medication may interact with treatment or survival from breast cancer[3-6]. In addition, there is evidence of different tumor biology in elderly breast cancer patients[7]. Moreover, a recent study showed that, in contrast to younger patients, survival of elderly breast cancer patients has not improved significantly in recent years[8].

Despite comprising a large proportion of those with breast cancer, elderly breast cancer patients have been underrepresented in trials[7]; it has been estimated that only 1 to 2% of the elderly participates in clinical trials[9]. Therefore, adherence to guidelines may not necessarily improve breast cancer cure and care in the elderly as it is expected in the younger population.

The aim of this study was to assess adherence to national breast cancer treatment guidelines by age at diagnosis, and to evaluate age specific survival in relation to adherence to the guidelines. Previous studies have investigated the association between guideline adherence and survival in an observational setting[10;11]. However, these studies all suffer from confounding by indication[12] and so alternative methods were applied in the present analysis.

# Methods

## Subjects

Female patients with incident early stage breast cancer, diagnosed between 2005 and 2008, were identified from the Netherlands Cancer Registry database. Early stage breast cancer was defined as T012, N01, M0 breast cancer, i.e. a tumor size smaller than five centimeters, with either no axillary metastases, or one or more metastases in movable ipsilateral level I or II axillary lymph nodes, without distant metastasis. PALGA (Pathologisch-Anatomisch Landelijk Geautomatiseerd Archief), the nationwide Dutch network and registry of histo- and cytopathology, regularly submits reports of all diagnosed malignancies to the regional cancer registries. The national hospital discharge databank, which receives discharge diagnoses of admitted patients from all Dutch hospitals, completes case ascertainment. Registry personnel collects data on diagnosis, staging, and treatment from the medical records, including

pathology and surgery reports, by using the registration and coding manual of the Dutch Association of Comprehensive Cancer Centers. All data from the regional cancer registries are merged into the Netherlands Cancer Registry.

Patients were categorized in age groups as discussed at the meeting of the International Society of Geriatric Oncology (SIOG) in 2009[13]. Inclusion was restricted to patients aged younger than 65 years and patients aged 75 years or older, since patients aged younger than 65 years at diagnosis are frequently included in trials upon which guidelines are based, while patients aged 75 years or older are included sporadically[9]. Primary endpoint was overall survival, which was defined as time from diagnosis to death from any cause. Relative survival, which takes into account the risk of dying from other causes than breast cancer, was also evaluated.

## Guideline adherence

Supplementary table 1 shows guideline recommendations with regards to breast and axillary surgery, radiotherapy, chemotherapy and endocrine therapy. Breast surgery and axillary surgery was recommended for all patients. Radiotherapy was recommended after a wide local excision, and after a mastectomy in case of non-radical surgery, involvement of the pectoral muscle, or positive axillary nodes at the apex. Chemotherapy was recommended in patients with nodal involvement, and in node negative patients with other unfavorable tumor characteristics. In patients aged 70 years or older, no general recommendations were given. With few exceptions, endocrine therapy was recommended in patients with estrogen and/or progesterone positive tumors.

Patients were adherent if they received treatment in concordance with guideline recommendations. Nonadherence was defined as undertreatment (omission of treatment despite recommendation), or overtreatment (administration of treatment despite no recommendation). The definitions of undertreatment and overtreatment were based on guidelines at time of diagnosis, and did not include reasons for treatment decisions. Adherence was assessed for all treatment modalities, summed, and then dichotomized in 100% adherence versus less than 100% adherence. As data on non-radicality, and localization of positive lymph nodes were not available, adherence with radiotherapy after a mastectomy could not be assessed and may therefore slightly differ from true adherence. Chemotherapy recommendations in some patients depend on general health. As these data were not available, adherence could not be assessed in these patients, and calculated adherence may again slightly differ from true adherence.

## Statistical analysis

SPSS 17.0 and STATA/SE 10.0 were used for statistical analyses. Descriptive statistics comprised median and interquartile range (i.q.r) and numbers (%). Pearson chi square test was used to compare differences in guideline adherence between age groups. A Cox proportional hazard model was used to assess overall survival, and reported with 95% confidence interval (CI). Relative survival was calculated by the Hakulinen method as the ratio of the observed

survival among the cancer patients and the survival that would have been expected based on the corresponding (age, sex and year) general population. National life tables were used to estimate expected survival. Relative Excess Risks of death (RER) were estimated using a multivariable generalized linear model with a Poisson distribution, based on collapsed relative survival data, using exact survival times.

Survival was assessed for patients who were treated 100% adherent and patients who were treated less than 100% adherent. As observational studies suffer from confounding by indication, additional survival analyses by means of an instrumental variable were performed. An instrumental variable may serve as a substitute for randomization in non-randomized studies, and may reduce confounding by indication under the assumptions that the instrumental variable is 1) associated with the exposure, 2) unrelated to the confounders (exclusion restriction), and 3) has no direct association with the outcome other than through the exposure (independence assumption)[14;15]. The geographically defined comprehensive cancer center regions (CCCRs) were used as an instrumental variable. CCCRs thus represented different proportions of patients who were treated 100% adherent, and were used as a substitute for randomization; the place of residence determines a patient's allocation to a CCCR and thereby to a probability of being treated 100% adherent. Analyses were performed to explore potential differences in tumor characteristics among CCCRs, although no large differences were expected a priori. Both multivariable and stratified analyses were performed. Covariates were included in the multivariable model if they were judged to be clinically relevant, and comprised histological grade (G1; G2; G3,4), T stage (T0,1; T2), nodal stage (negative; positive), estrogen receptor status (negative; positive), progesterone receptor status (negative; positive) and age (continuous). All statistical tests were two-sided. P values $<0.05$ were considered to be statistically significant.

Data were analyzed as intention to treat analyses; patients were categorized by theoretical allocation to CCCR based on postal code, which did coincide with CCCR of treatment in more than 95% of the patients. For survival analyses, CCCRs were ranked based on decreasing proportion of patients who were treated 100% adherent.

# Results

Between 2005 and 2008, 36,459 women, who were younger than 65 years or 75 years or older, were diagnosed with early stage breast cancer. Overall, 4,267 patients were excluded because of carcinoma in situ, or missing data regarding invasiveness, 649 patients because of missing data on estrogen and progesterone receptor status, and 23 patients because of missing data regarding therapy. This resulted in a study population of 31,520 patients, of whom 24,959 were younger than 65 years (median 52.3 years) and 6,561 were 75 years or older (median 82.5 years). Median follow-up (i.q.r) was 2.8 (1.8 to 3.9) years for all patients, 2.9 (1.9 to 3.9) years for patients younger than 65 years and 2.5 (1.5 to 3.5) years for patients aged 75 years or older.

**Table 1.** Treatment characteristics by age at diagnosis.

| | <65 years (n=24,959) | | ≥75 years (n=6,561) | | p |
|---|---|---|---|---|---|
| | n | % | n | % | |
| Most extensive surgery | | | | | <0.001 |
| Mastectomy | 9,037 | 36.2 | 3,473 | 52.9 | |
| Wide local excision | 15,805 | 63.3 | 1,677 | 25.6 | |
| No resection | 117 | 0.5 | 1,411 | 21.5 | |
| Most extensive AS | | | | | <0.001 |
| ALND | 9,699 | 38.9 | 2,211 | 33.7 | |
| SLN | 14,864 | 59.6 | 2,665 | 40.6 | |
| None | 396 | 1.6 | 1,685 | 25.7 | |
| Radiotherapy | | | | | <0.001 |
| Yes | 16,931 | 67.8 | 1,649 | 25.1 | |
| No | 8,028 | 32.2 | 4,912 | 74.9 | |
| Chemotherapy | | | | | <0.001 |
| Yes | 12,22 | 49.0 | 27 | 0.4 | |
| No | 12,739 | 51.0 | 6,534 | 99.6 | |
| Endocrine therapy | | | | | <0.001 |
| Yes | 10,547 | 42.3 | 3,776 | 57.6 | |
| No | 14,412 | 57.7 | 2,785 | 42.4 | |

AS: axillary surgery; ALND: axillary lymph node dissection; SLNB: sentinel lymph node biopsy.

Patients aged 75 years or older more often presented with an unknown histological grade and unknown nodal status, with larger tumors and a positive estrogen receptor status (all p values <0.001). Table 1 shows treatment characteristics by age. Patients aged 75 or older less often underwent breast and axillary surgery, and had a lower probability of receiving radiotherapy and chemotherapy, while endocrine therapy was administered more frequently.

As shown in Table 2, the proportion of patients who received all five treatment modalities in concordance with guidelines was significantly lower in patients aged 75 years or older; 15,487 (62.0%) patients versus 3,647 (55.6%) patients, respectively. In both age groups, the majority of patients received at least three out of five treatment modalities in concordance with guidelines; 24,652 (98.7%) patients and 6,152 (93.8%) patients, respectively.

**Table 2.** Number of treatments in concordance with guidelines, by age at diagnosis.

| | <65 years (n=24,959) | | ≥75 years (n=6,561) | | p |
|---|---|---|---|---|---|
| | n | % | n | % | |
| Number of treatments | | | | | <0.001 |
| 5 (100%) | 15,487 | 62.0 | 3,647 | 55.6 | |
| 4 (80%) | 5,722 | 22.9 | 1,266 | 19.3 | |
| 3 (60%) | 3,443 | 13.8 | 1,239 | 18.9 | |
| <3 (<60%) | 304 | 1.3 | 409 | 6.2 | |

Figure 1 shows the distribution of patients who were treated adherent, overtreated and undertreated for all treatment modalities according to the guidelines, by age at diagnosis. Patients aged 75 years or older had a marked lower adherence to surgical therapy recommendations as compared with patients who were younger than 65 years (breast surgery 99.5% (n=24,842) versus 78.5% (n=5,150), p<0.001; axillary surgery 98.4% (n=24,563) versus 74.3% (n=4,876), p<0.001). As surgical resection is recommended for all patients with early stage breast cancer, nonadherence to surgical therapy recommendations was fully explained by undertreatment. Adherence with endocrine therapy recommendations was slightly lower in patients aged 75 years or older (80.8% (n=20,167) versus 79.2% (n=5,194), p=0.003). In case of nonadherence, patients aged 75 years or older were overtreated more often as compared with patients younger than 65 years. Most patients aged 75 years or older were adherent with chemotherapy recommendations (73.9% (n=18,452) versus 99.6% (n=6,534), p<0.001), because specific chemotherapy recommendations for patients aged 70 years or older were not given.

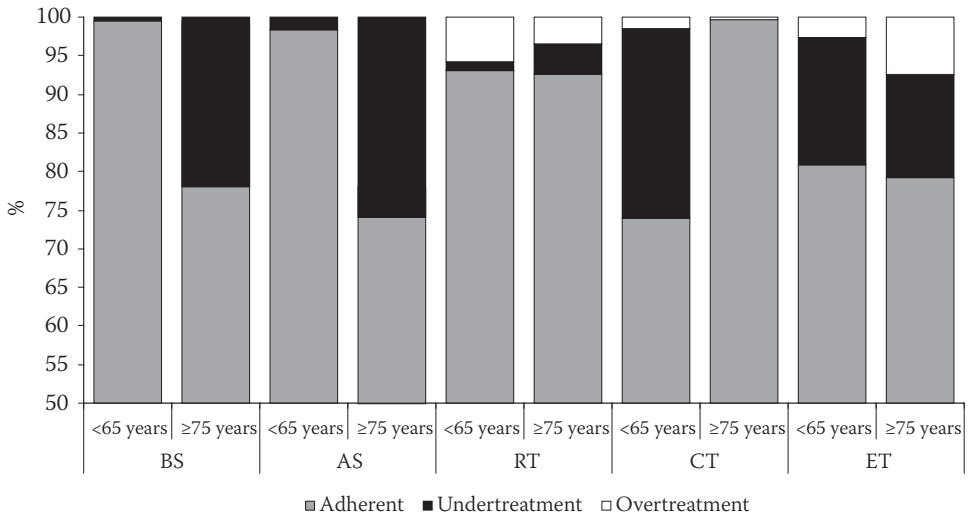


**Figure 1.** Adherence to guidelines, undertreatment and overtreatment per treatment, by age at diagnosis.

Number of deaths was 762 (3.1%) in patients younger than 65 years and 1,547 (23.6%) in patients aged 75 years or older. By conventional survival analyses, in patients younger than 65 years, overall survival was lower in patients who were treated less than 100% adherent as compared with those who were treated 100% adherent (patients who were treated 100% adherent functioned as reference category, univariate hazard ratio (HR) for patients who were treated less than 100% adherent was 1.68 (95% CI 1.46-1.94), p<0.001). In patients aged 75 years or older, these results were even more pronounced; HR 2.56 (95% CI 2.31-2.84), p<0.001. To account for unequal distribution of tumor characteristics and age, multivariable analyses were performed, which revealed comparable results (Table 3).

**Table 3.** Overall survival by adherence to guidelines and tumour characteristics, by age at diagnosis.

| | <65 years | | | ≥75 years | | |
|---|---|---|---|---|---|---|
| | 5-years survival (%) | HR (95% CI)* | p | 5-years survival (%) | HR (95% CI)* | p |
| Adherence | | | **<0.001** | | | **<0.001** |
| 100% | 95 | 1 (reference) | | 71 | 1 (reference) | |
| <100% | 92 | 1.75 (1.50-2.05) | | 48 | 1.62 (1.41-1.85) | |
| Histological grade | | | **<0.001** | | | **0.004** |
| G1 (well) | 98 | 1 (reference) | | 76 | 1 (reference) | |
| G2 (moderate) | 96 | 1.14 (0.86-1.50) | | 68 | 1.13 (0.95-1.36) | |
| G3, G4 (poor) | 89 | 1.83 (1.38-2.43) | | 59 | 1.39 (1.13-1.71) | |
| T stage | | | **<0.001** | | | **0.001** |
| T0 | 88 | 1 (reference) | | 51 | 1 (reference) | |
| T1 | 95 | 1.06 (0.26-4.28) | | 68 | 0.79 (0.69-0.91) | |
| T2 | 91 | 1.69 (1.34-1.83) | | 56 | 1.25 (1.09-1.44) | |
| N stage | | | **<0.001** | | | **0.002** |
| Negative | 95 | 1 (reference) | | 64 | 1 (reference) | |
| Positive | 92 | 1.57 (1.34-1.83) | | 56 | 1.25 (1.09-1.44) | |
| ER | | | **<0.001** | | | **0.001** |
| Positive | 96 | 1 (reference) | | 63 | 1 (reference) | |
| Negative | 86 | 2.82 (2.25-3.54) | | 52 | 1.40 (1.14-1.72) | |
| PR | | | **0.014** | | | **0.002** |
| Positive | 96 | 1 (reference) | | 65 | 1 (reference) | |
| Negative | 89 | 1.32 (1.06-1.64) | | 55 | 1.30 (1.10-1.53) | |
| Age (years) | - | 1.02 (1.01-1.03) | **<0.001** | - | 1.09 (1.07-1.10) | **<0.001** |

* Hazard ratios adjusted for all variables included in the model. HR: hazard ratio; CI: confidence interval; ER: estrogen receptor status; PR: progesterone receptor status.

In addition, survival was assessed by CCCR. The proportion of breast cancer patients who were treated 100% adherent varied among CCCRs in both age categories (in patients younger than 65 years 55.4% to 66.2%, p<0.001; in patients aged 75 years or older 50.0% to 59.8%, p=0.001). In both age groups, CCCR was not associated with overall survival (p=0.732; p=0.905 respectively). Multivariable analyses were performed to adjust for unequal distribution of tumor characteristics, which did not alter the results (Table 4). Analyses were stratified by T stage, N stage and histological grade, and adjusted for estrogen and progesterone receptor status. Again, results remained similar (data not shown). It was also studied whether CCCR was associated with relative survival (Supplementary table 2). Both in univariate and multivariable analyses the excess risk of death was similar among CCCRs.

Additional analyses restricted to the CCCR with the lowest and highest proportion of patients who were treated 100% in concordance with guidelines, did not alter the results. In patients younger than 65 years, the HR for the region with the lowest proportion of patients who were treated 100% adherent was 0.93 (95% CI. 0.69-1.26), p=0.657; in patients aged 75 years or older, HR was 0.87 (95% CI 0.60-1.11), p=0.262. Analyses were also stratified by year of diagnosis.

With a maximum median follow-up of 4.5 and 3.7 years respectively, similar results were observed (p=0.588 and p=0.335 respectively).

Since general recommendations for chemotherapy were not available for patients aged 75 years or older, survival analyses in this age group were repeated, in which 100% adherence was calculated without adherence to chemotherapy recommendations. Results were similar. Finally, an alternative definition of adherence was used, in which non adherence to guideline recommendations was defined as undertreatment only. In both age categories, again no difference in overall survival was observed among CCCRs (data not shown).

**Table 4.** Overall survival by Comprehensive Cancer Center Region, by age at diagnosis.

| | <65 years | | | ≥75 years | | |
|---|---|---|---|---|---|---|
| | 5-years survival (%) | HR (95% CI)* | p | 5-years survival (%) | HR (95% CI)* | p |
| CCCR** | | | 0.601 | | | 0.190 |
| 1 (highest) | 93 | 1 (reference) | | 60 | 1 (reference) | |
| 2 | 93 | 0.84 (0.61-1.15) | | 62 | 0.65 (0.49-0.88) | |
| 3 | 95 | 0.81 (0.55-1.18) | | 60 | 0.80 (0.59-1.08) | |
| 4 | 94 | 1.01 (0.73-1.41) | | 62 | 0.79 (0.58-1.09) | |
| 5 | 95 | 0.93 (0.66-1.32) | | 60 | 0.87 (0.63-1.20) | |
| 6 | 93 | 1.01 (0.74-1.38) | | 60 | 0.78 (0.59-1.03) | |
| 7 | 95 | 0.87 (0.62-1.22) | | 63 | 0.84 (0.63-1.13) | |
| 8 (lowest) | 93 | 1.09 (0.73-1.61) | | 63 | 0.77 (0.57-1.05) | |
| Histological grade | | | **<0.001** | | | **0.003** |
| G1 (well) | 98 | 1 (reference) | | 76 | 1 (reference) | |
| G2 (moderate) | 96 | 1.31 (0.99-1.72) | | 68 | 1.19 (0.90-1.42) | |
| G3, G4 (poor) | 89 | 2.07 (1.55-2.75) | | 59 | 1.43 (1.16-1.76) | |
| T stage | | | **<0.001** | | | **0.004** |
| T0 | 88 | 1 (reference) | | 51 | - | |
| T1 | 95 | 0.89 (0.22-3.58) | | 68 | 1 (reference) | |
| T2 | 91 | 1.35 (0.33-5.44) | | 56 | 1.23 (1.07-1.41) | |
| N stage | | | **<0.001** | | | **0.006** |
| Negative | 95 | 1 (reference) | | 64 | 1 (reference) | |
| Positive | 92 | 1.57 (1.34-1.84) | | 56 | 1.22 (1.06-1.40) | |
| ER | | | **<0.001** | | | **0.004** |
| Positive | 96 | 1 (reference) | | 63 | 1 (reference) | |
| Negative | 86 | 2.62 (2.08-3.30) | | 52 | 1.36 (1.10-1.67) | |
| PR | | | **0.017** | | | **0.008** |
| Positive | 96 | 1 (reference) | | 65 | 1 (reference) | |
| Negative | 89 | 1.31 (1.05-1.64) | | 55 | 1.26 (1.06-1.49) | |
| Age (years) | - | 1.02 (1.01-1.03) | **<0.001** | - | 1.10 (1.08-1.11) | **<0.001** |

* Hazard ratios adjusted for all variables included in the model. ** CCCR is ranked from highest to lowest proportion of patients who were treated 100% adherent. HR: hazard ratio; CI: confidence interval; ER: estrogen receptor status; PR: progesterone receptor status.

# Discussion

Overall adherence with breast cancer guidelines, and in particular adherence with surgical therapy recommendations, was lower in patients aged 75 years or older. By using an instrumental variable to reduce confounding by indication, comprehensive cancer center regions, representing a different proportion of patients who were treated 100% adherent, were not associated with overall survival nor with relative survival in both age categories.

A considerable number of papers have been published on adherence to breast cancer guidelines, in which most define nonadherence as undertreatment only[16-20]. Few studied guideline adherence by age at diagnosis. Most studies observed that increasing age was associated with nonadherence to either surgical treatment[18;20-22], radiotherapy[19;22], chemotherapy[18;19] or endocrine therapy[18]. Some studies have assessed the association between guideline adherence and survival in an observational setting. However, these studies all suffer from confounding by indication[12]; frailty status, age, tumor characteristics or presence of comorbidity may all affect both adherence as well as survival. Most studies showed that adherence with guideline recommendations was associated with worse breast cancer outcome[10;11;23;24]. The authors did acknowledge the risk of confounding by indication, and adjusted for multiple variables. By conventional survival analyses, this study confirmed in both age groups a higher overall survival for patients who were treated 100% adherent as compared with patients who were treated less than 100% adherent. Even after adjustment for confounders, the results from the multivariable model may suffer from residual confounding by indication. Therefore, a conventional survival analysis may yield insufficient results in this particular field of study.

The use of an instrumental variable may improve the quality of analyses by minimizing confounding by indication[15;25], provided certain assumptions are met. An association was observed between CCCR and the proportion of patients who were treated 100% adherent. Further, tumor characteristics were slightly different among CCCRs. Therefore, both multivariable and stratified analyses were performed, which did not alter the results. Regional differences in background mortality may affect survival by region in another way than through guideline adherence. However, no major differences in background mortality, or remaining life expectancy among regions have been observed in elderly patients[26]. Since treatment allocation of more than 95% of the patients coincided with allocated CCCR, effect modification by cross-over is unlikely. There seems to be reasonable ground to justify the use of CCCR as an instrumental variable. Using an instrumental variable, guideline adherence was not associated with survival in both age groups.

It was expected that in patients younger than 65 years, guideline adherence would be associated with an improved survival. The results from the present study did not confirm this hypothesis. The current study evaluated outcome of patients who received five treatment modalities in concordance with guideline recommendations, compared with patients who did not, which

may not be representative for outcomes of a single randomized clinical trial; most trials study one particular treatment at once.

This study has some critical limitations. The proportion of patients who were treated 100% adherent differed 10 to 11% among regions, which might have been too small to result in survival differences. Virtually all patients who were treated less than 100% adherent, received three or more treatment modalities in concordance with guidelines. Consequently, the difference between adherent and nonadherent patients may have been too small to detect substantial survival differences. Although additional analyses stratified by year of diagnosis were performed, the limited follow-up time may have reduced the statistical power of the analyses.

**Supplementary table 1.** Guideline recommendations early stage breast cancer* in The Netherlands.

| | |
|---|---|
| Breast surgery | Guideline 2005 – 2007: All.<br>Guideline 2008: No change. |
| Axillary surgery | Guideline 2005 – 2007: All.<br>Guideline 2008: No change. |
| Radiotherapy | Guideline 2005, 2006: Always after a wide local excision; radiotherapy may be considered after a mastectomy in case of a non-radical resection, involvement of pectoral muscle, or a positive axillary top.<br>Guideline 2008: No change. |
| Chemotherapy | Guideline 2005 – 2007: <70 years, node positive #; ≤35 years (except <1cm, BR I); >35<70 years, N0, >3cm#; >35<70 years, N0, 2-3cm, BR II#; >35<70 years, N0, >1cm, BR III#. In patients aged 70 years or older with nodal involvement, general recommendations cannot be given. Chemotherapy may be considered for those with unfavorable tumor characteristics.<br>Guideline 2008: <70, node positive; <35 years (except ≤ 1cm BR I); ≥35<70 years, N0, 1,1-2 cm, BR II/III; ≥35<70 years, N0, >2 cm. In patients aged 70 years or older, benefit of chemotherapy may be limited. It is advised to use AdjuvantOnline to calculate the expected benefit in individual cases. |
| Endocrine therapy$ | Guideline 2005 – 2007: Node positive; ≤35 years (except <1cm, BR I); >35 years, N0, ≥3cm; >35 years, N0, 2-3cm, BR II; >35 years, N0, >1cm, BR III.<br>Guideline 2008: Node positive; <35 years (except ≤ 1cm BRI); ≥ 35 years, N0, 1,1-2 cm, BR II/III; ≥ 35 years, N0, >2cm. |

BR: Histological grade according to Bloom Richardson. * Early stage breast cancer was defined as T0-2, N0-1, M0 breast cancer, i.e. a tumor size smaller than five centimeters, with either no axillary metastases, or one or more metastases in movable ipsilateral level I or II axillary lymph nodes, without distant metastasis. # Patients aged 50 to 59 years in good physical state with an estrogen receptor and/or progesterone receptor positive tumor, and patients aged 60 to 69 years with an unfavorable prognosis. $ Patients with estrogen and/or progresterone receptor positive tumors only.

**Supplementary table 2.** Relative survival by Comprehensive Cancer Center Region, by age at diagnosis.

| | 5-years RS (95% CI) | Univariate RER (95% CI) | p | Multivariable* RER (95% CI) | p |
|---|---|---|---|---|---|
| < 65 years | | | 0.726 | | 0.639 |
| CCCR1 (66.2)** | 95.4 (93.0-97.2) | 1 (reference) | | 1 (reference) | |
| CCCR2 (64.8%) | 95.2 (92.7-97.0) | 1.4 (0.8-2.4) | | 1.2 (0.7-2.1) | |
| CCCR3 (64.2%) | 96.8 (95.3-98.0) | 0.9 (0.5-1.5) | | 0.8 (0.5-1.3) | |
| CCCR4 (64.0%) | 95.7 (94.3-96.9) | 1.0 (0.6-1.7) | | 1.0 (0.6-1.6) | |
| CCCR5 (63.4%) | 96.5 (94.9-97.8) | 1.1 (0.6-1.8) | | 0.9 (0.6-1.5) | |
| CCCR6 (62.7%) | 95.3 (93.5-96.7) | 1.1 (0.7-1.8) | | 1.2 (0.7-1.9) | |
| CCCR7 (59.6%) | 96.6 (94.7-98.0) | 0.9 (0.5-1.6) | | 1.0 (0.6-1.7) | |
| CCCR8 (55.4%) | 95.2 (93.5-96.6) | 0.9 (0.5-1.5) | | 0.9 (0.6-1.4) | |
| ≥ 75 years | | | 0.873 | | 0.820 |
| CCCR1 (59.7%)** | 91.0 (76.4-100) | 1 (reference) | | 1 (reference) | |
| CCCR2 (58.7%) | 97.5 (86.5-100) | 0.3 (0.0-2.4) | | 0.5 (0.1-1.7) | |
| CCCR3 (58.2%) | 94.3 (85.1-100) | 0.6 (0.2-2.1) | | 0.6 (0.2-1.7) | |
| CCCR4 (56.4%) | 95.9 (89.0-100) | 0.5 (0.2-1.6) | | 0.9 (0.3-2.2) | |
| CCCR5 (56.1%) | 91.5 (79.0-100) | 0.6 (0.2-2.4) | | 0.8 (0.2-2.5) | |
| CCCR6 (55.7%) | 92.1 (80.2-100) | 0.5 (0.1-2.3) | | 0.8 (0.3-2.2) | |
| CCCR7 (54.2%) | 94.7 (85.8-100) | 0.6 (0.2-1.9) | | 0.9 (0.3-2.5) | |
| CCCR8 (49.9%) | 98.1 (89.7-100) | 0.3 (0.1-1.7) | | 0.5 (0.1-1.4 ) | |

*Hazard ratios adjusted for histological grade, T stage, nodal stage, estrogen receptor, and progesterone receptor.
** Percentage of patients treated 100% adherent. RS: relative survival; RER: relative excess risk of death.

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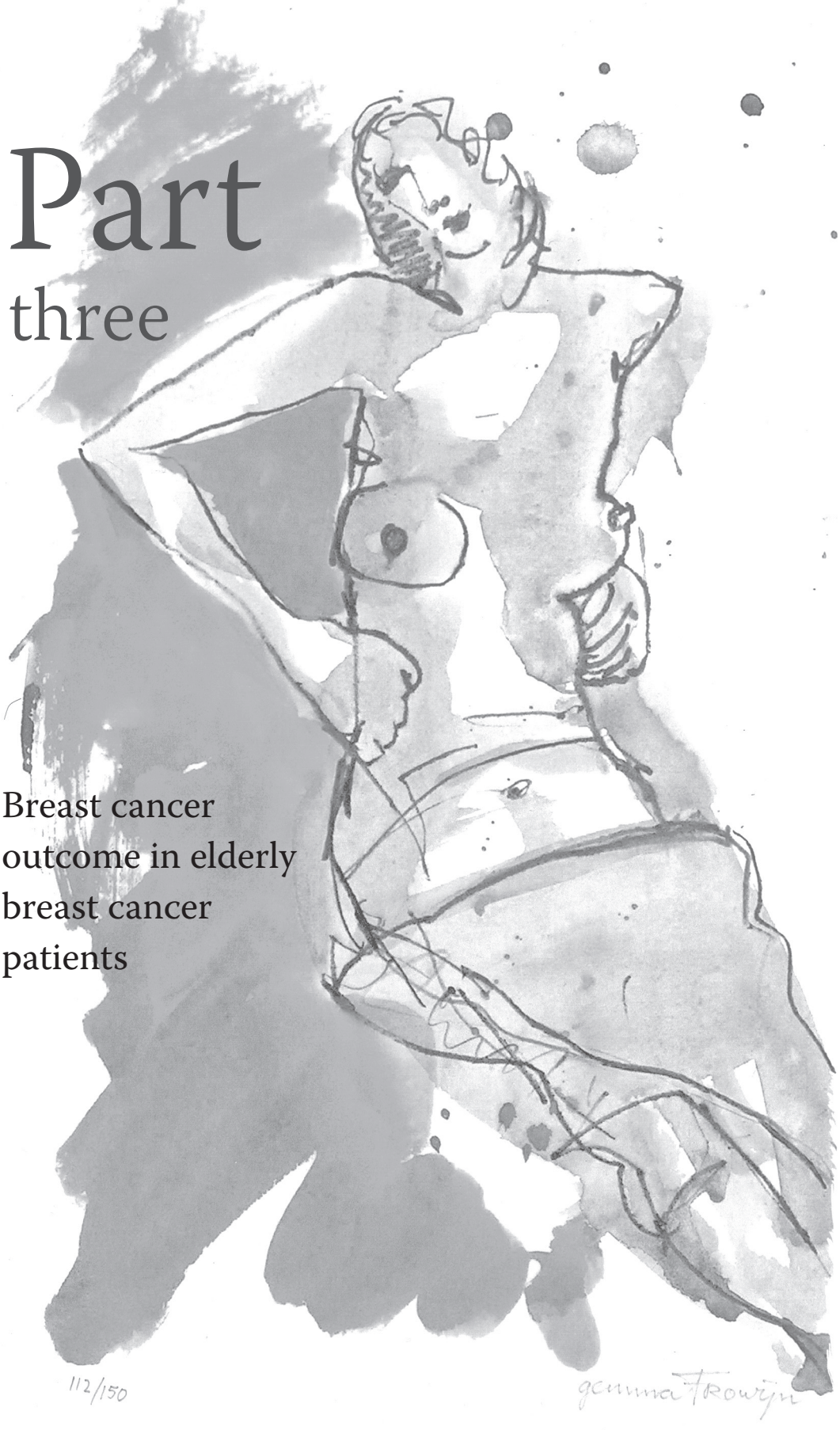
# Part three




## Breast cancer outcome in elderly breast cancer patients

# Chapter 5

# Association between age at diagnosis and disease specific mortality among postmenopausal women with hormone receptor positive breast cancer

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# Abstract

## Background

In addition to classical tumor related prognostic factors, patient characteristics may be associated with breast cancer outcome. The aim of this study was to assess the association between age at diagnosis and breast cancer outcome in postmenopausal women with hormone receptor positive breast cancer.

## Methods

Patients who were enrolled in the Tamoxifen Exemestane Adjuvant Multinational (TEAM) randomized clinical trial were included in the current study. Primary endpoint was disease specific mortality; secondary endpoints were other cause mortality and breast cancer recurrence. Age at diagnosis was categorized as <65 years, 65-75 years, and ≥75 years.

## Results

Overall, 9,766 patients were included; 5,349 were <65 years, 3,060 were 65-75 years, and 1,357 were ≥75 years. Disease specific mortality as a proportion of all cause mortality decreased with age (78%, 56%, 36% respectively; p<0.001). Disease specific mortality increased with age (multivariable analyses, patients aged <65 years functioned as a reference, hazard ratio for patients aged 65-75 years was 1.25 (95% CI 1.01-1.54); hazard ratio for patients aged ≥75 years was 1.63 (95% CI 1.23-2.16); p<0.001). Similarly, breast cancer recurrence and other cause mortality increased with age (patients aged <65 years functioned as a reference, breast cancer recurrence: hazard ratio for patients aged 65-75 years was 1.07 (95% CI 0.91-1.25); hazard ratio for patients aged ≥75 years was 1.29 (95% CI 1.05-1.60); p=0.061 – other cause mortality: hazard ratio for patients aged 65-75 years was 2.66 (95% CI 1.96-2.63); hazard ratio for patients aged ≥75 years was 7.30 (95% CI 5.29-10.07); p<0.001).

## Conclusion

Among postmenopausal women with hormone receptor positive breast cancer, increasing age was associated with a higher disease specific mortality.

# Introduction

Breast cancer is the leading contributor to cancer incidence and cancer mortality in women worldwide, with 1,383,500 new cases in 2008[1]. In the US in 2008, 41% of these women were 65 year or older at diagnosis[2]. As breast cancer incidence increases with increasing age[2], changing demographics and continuously increasing life expectancy will further enlarge the number of elderly women confronted with breast cancer.

In addition to classical tumor related prognostic factors, patient characteristics may be associated with breast cancer outcome; an individual who dies from causes unrelated to breast cancer is no longer at risk for progression of breast cancer or death due to breast cancer. The risk of death from another cause that is unrelated to either breast cancer or its therapy is termed a competing risk of death, and may be particularly present in elderly populations[3].

Observational data in breast cancer patients hint at an age specific association with mortality[4]. Observational data often lack data regarding treatment[5] and in retrospective studies cause of death is not always traceable. Clinical trials generally do not have these problems. Unfortunately, elderly patients are often not included in clinical trials due to age restrictions[6]. As one of few breast cancer trials, the Tamoxifen, Exemestane, Adjuvant, Multinational (TEAM) trial had no upper age limit, thereby providing a unique opportunity to focus on the association between age and disease specific mortality in postmenopausal patients diagnosed with hormone receptor positive breast cancer.

The aim of the current study was to assess disease specific mortality among age groups in postmenopausal patients with hormone receptor positive breast cancer. Secondarily, age specific other cause mortality and age specific breast cancer recurrence were evaluated.

# Methods

The TEAM trial is a randomized, phase 3, multinational, open label study conducted in postmenopausal breast cancer patients 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 (N=9766), and included between January 2001 and January 2006. Appropriate approvals from the ethical committee, and written informed consent from all patients were obtained[7]. The trial was registered with ClinicalTrials.gov, NCT00279448, NCT00032136, and NCT00036270; NTR 267; Ethics Commission Trial 27/2001; and UMIN, C000000057.

Similar protocols were used in the nine countries, with minor differences to accommodate local treatment guidelines[7;8]. In short, postmenopausal patients with histologically confirmed breast cancer, who completed local therapy with curative intent, i.e. without evidence of metastatic disease, were eligible. Participants commenced endocrine treatment assigned at random within 10 weeks of completion of surgery and chemotherapy, if indicated. Patients were ineligible if they had a previous malignancy with a disease free interval of less than five years, an Eastern Cooperative Oncology Group (ECOG) performance status of more than 2, or a significant cardiac disease or other illness interfering with study participation.

The final results of the TEAM trial showed no significant differences in efficacy endpoints between five years of exemestane alone versus the sequence of tamoxifen followed by exemestane[7]. Moreover, death from non breast cancer causes was comparable for both treatment arms[7]. Therefore we were able to investigate disease specific mortality for all patients regardless of randomized treatment.

The design of the current post hoc analysis was developed in December 2010. The database was locked on October 7th 2010. Patients were categorized in three age groups (<65 years, 65-75 years, ≥75 years) as discussed at the Meeting of the International Society of Geriatric Oncology (SIOG) in 2009[9] and in line with other publications[10;11]. Primary endpoint of this study was disease specific mortality, which was defined as time from randomization to death due to breast cancer, as indicated on the Case Report Form. Cause of death was ascertained by medical record review and categorized in one of ten prespecified groups. Classification was verified by the TEAM Central Statistical and Data-Center. Patients with distant metastases at time of death were considered to have died due to breast cancer. Overall, 7% (n=42) of deaths attributed to breast cancer was accounted to presence of distant metastases at time of death. The majority of these patients (57%, n=24) were formerly categorized as 'unknown' or 'other' cause of death. The secondary endpoints of this study were other cause mortality and breast cancer recurrence. Other cause mortality was calculated as all cause mortality minus disease specific mortality; breast cancer recurrence was defined as locoregional or distant breast cancer recurrence, or ipsi- or contralateral breast cancer. Ductal carcinoma in situ was not judged to be evidence of recurrence.

Statistical analyses were performed using SPSS 17.0 (SPSS, Chicago, IL) and R statistical package (R Development Core Team, 2008). To compare proportional differences among age categories, the Pearson chi-square test was used. Cumulative incidences of competing causes of death were calculated[12] using the mstate package in R[13]. Cox proportional hazard models were used to evaluate associations between covariates and cause specific hazards of disease specific mortality and other cause mortality. Additional regression analyses according to Fine and Gray[14] were performed in order to assess the risk of disease specific mortality and other cause mortality respectively, taken into account the risk of reaching the other endpoint. Covariates were included in the multivariable model if they were judged to be clinically

relevant, and comprised country, histological grade (G1; G2; G3,4), T stage (T0,Tis,T1; T2; T3,4), nodal stage (negative; positive), estrogen receptor (negative; positive), progesterone receptor (negative; positive), surgery, (mastectomy; wide local excision) radiotherapy (yes; no), chemotherapy (yes; no), endocrine therapy (tamoxifen followed by exemestane; exemestane) and persistence of endocrine therapy (discontinuation of allocated endocrine therapy because of either adverse events, intercurrent illness, patient refusal or other reasons; continuation of allocated endocrine therapy, or having an event while on study medication). All statistical tests were two-sided. P values <0.05 were considered to be statistically significant.

# Results

Overall 9,766 patients (age range 35-96, median age 64 years) were included in the multinational TEAM trial, of which 5,349 were <65 years at diagnosis (55%, median age 58 years), 3,060 were 65-75 years (31%, median age 69 years) and 1,357 were ≥75 years (14%, median age 79 years). Overall, 778 patients (8.0%) were lost to follow-up, 429 (8.0%) in patients aged <65 years, 214 (7.0%) in patients aged 65-75 years, and 135 (9.9%) in patients aged ≥75 years. Table 1 shows patient characteristics by age at diagnosis. We observed an age associated increase in larger tumors and estrogen receptor positive breast cancer. As shown in Table 2, the proportion of mastectomy increased significantly with age, whereas administration of chemotherapy, and administration of radiotherapy after a wide local excision an decreased.

At database lock, median follow-up (interquartile range) from randomization was 5.1 years (4.3; 6.0 years) in patients aged <65 years, 5.1 years (4.2; 6.0 years) in patients aged 65-75 years, and 5.0 years (3.8; 5.8 years) in patients aged ≥75 years. The number of deaths was 391 (7.3%), 341 (11.2%), and 311 (22.9%) respectively. Figure 1 illustrates cumulative incidence of death due to breast cancer, non breast cancer, and all causes by age at diagnosis. Cumulative incidence of death due to breast cancer increased from 5.7% in patients aged <65 years, 6.3% in patients aged 65-75 years, to 8.3% in patients aged ≥75 years. Cumulative incidence of non breast cancer death was 1.6%, 4.9% and 14.6% respectively.

Table 3 shows causes of death by age at diagnosis. Increasing age was associated with a lower number of deaths due to breast cancer as a proportion of all cause mortality (<65 years 78%, 65-75 years 56%, ≥75 years 36%; p<0.001). Deaths categorized as 'other' (n=100) were recorded to have died of old age, dementia, weakness or cachexia (n=41), infection or sepsis (n=20), sudden death not otherwise specified (n=7), accidents (n=6), a combination of recorded reasons (n=6), and other infrequent causes (n=20; gastro-intestinal perforation, urogential disorders, malignancy related disorders, suicide).

Univariate Cox regression analysis showed a higher risk of disease specific mortality with increasing age (patients aged <65 years functioned as a reference, hazard ratio (HR) for patients aged 65-75 years was 1.12 (95% confidence interval (CI) 0.94-1.34); HR for patients aged ≥75


**Figure 1.** Figure 1. Cumulative incidence of death due to breast cancer, non breast cancer and all causes by age at diagnosis. Non breast cancer death is defined as death due to all causes except breast cancer (second primary tumor, endometrial cancer, cardiac disorder, thromboembolism, pulmonary disorder, cerebral disorder, vascular disorder, other causes, and unknown causes).

**Table 1.** Patient characteristics by age at diagnosis.

| | <65 years (n=5,349) | | 65-75 years (n=3,060) | | ≥75 years (n=1,357) | | p |
|---|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) | |
| Histological grade | | | | | | | 0.06 |
| G1 (well) | 911 | (17.0) | 550 | (18.0) | 216 | (15.9) | |
| G2 (moderate) | 2,580 | (48.2) | 1,537 | (50.2) | 679 | (50.0) | |
| G3, G4 (poor) | 1,377 | (25.7) | 732 | (23.) | 329 | (24.2) | |
| Gx, unknown | 481 | (9.0) | 241 | (7.9) | 133 | (9.8) | |
| T stage | | | | | | | **<0.001** |
| T0, Tis | 6 | (0.1) | 0 | (0.0) | 0 | (0.0) | |
| T1 | 3,291 | (61.5) | 1,806 | (59.0) | 593 | (43.7) | |
| T2 | 1,793 | (33.5) | 1,122 | (36.7) | 676 | (49.8) | |
| T3, T4 | 244 | (4.6) | 125 | (4.1) | 88 | (6.5) | |
| Tx, unknown | 15 | (0.3) | 7 | (0.2) | 0 | (0.0) | |
| N stage | | | | | | | 0.14 |
| Negative | 2,799 | (52.3) | 1,622 | (47.1) | 690 | (50.8) | |
| Positive | 2,518 | (47.1) | 1,419 | (46.4) | 651 | (48.0) | |
| Unknown | 32 | (0.6) | 19 | (0.6) | 16 | (1.2) | |
| Estrogen receptor | | | | | | | **<0.001** |
| Positive | 5,218 | (97.6) | 3,022 | (98.8) | 1,344 | (99.0) | |
| Negative | 128 | (2.4) | 35 | (1.1) | 13 | (1.0) | |
| Unknown | 3 | (0.1) | 3 | (0.1) | 0 | (0.0) | |
| Progesterone receptor | | | | | | | 0.54 |
| Positive | 4,028 | (75.3) | 2,268 | (74.1) | 1,004 | (74.0) | |
| Negative | 915 | (17.1) | 554 | (18.1) | 255 | (18.8) | |
| Unknown | 406 | (7.6) | 238 | (7.8) | 98 | (7.2) | |
| Country | | | | | | | **<0.001** |
| Belgium | 265 | (5.0) | 106 | (3.5) | 43 | (3.2) | |
| France | 722 | (13.5) | 403 | (13.2) | 105 | (7.7) | |
| Germany | 871 | (16.3) | 454 | (14.8) | 146 | (10.8) | |
| Greece | 110 | (2.1) | 71 | (2.3) | 26 | (1.9) | |
| Japan | 98 | (1.8) | 66 | (2.2) | 20 | (1.5) | |
| The Netherlands | 1,428 | (26.7) | 852 | (27.8) | 473 | (34.9) | |
| UK/Ireland | 696 | (13.0) | 431 | (13.5) | 166 | (12.2) | |
| United States | 1,159 | (21.7) | 695 | (22.7) | 378 | (27.9) | |

UK: United Kingdom.

years was 1.66 (95% CI 1.34-2.06); p<0.001). Since tumor and treatment characteristics may be associated with disease specific mortality, multivariable analyses were performed in attempt to adjust for unequal distributions among age categories (Table 4). Overall, 8,030 (82.2%) patients were included in the multivariable model. Again, disease specific mortality increased with age (patients aged <65 years functioned as a reference, HR for patients aged 65-75 years was 1.25 (95% CI 1.01-1.54); HR for patients aged ≥75 years was 1.63 (95% CI 1.23-2.16); p<0.001).

**Table 2.** Treatment characteristics by age at diagnosis.

| | <65 years (n=5,349) | | 65-75 years (n=3,060) | | ≥75 years (n=1,357) | | p |
|---|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) | |
| Most extensive surgery | | | | | | | **<0.001** |
| Mastectomy | 2,120 | (39.6) | 1,372 | (44.8) | 841 | (62.0) | |
| WLE | 3,222 | (60.2) | 1,685 | (55.1) | 515 | (38.0) | |
| No resection | 2 | (<0.1) | 1 | (<0.1) | 0 | (0.0) | |
| Unknown | 4 | (0.1) | 2 | (0.1) | 1 | (0.1) | |
| Radiotherapy | | | | | | | **<0.001** |
| Yes | 3,980 | (74.4) | 2,030 | (66.3) | 687 | (50.6) | |
| No | 1,330 | (24.9) | 994 | (32.5) | 651 | (48.0) | |
| Unknown | 39 | (0.7) | 36 | (1.2) | 19 | (1.4) | |
| RT in case of WLE | | | | | | | **<0.001** |
| Yes | 3,042 | (94.4) | 1,543 | (91.6) | 451 | (87.6) | |
| No | 180 | (5.6) | 142 | (8.4) | 64 | (12.4) | |
| Chemotherapy | | | | | | | **<0.001** |
| Yes | 2,743 | (51.3) | 700 | (22.9) | 71 | (5.2) | |
| No | 2,605 | (48.7) | 2,357 | (77.0) | 1,284 | (94.6) | |
| Unknown | 1 | (<0.1) | 3 | (0.1) | 2 | (0.1) | |
| Endocrine therapy | | | | | | | 0.38 |
| Tam → Exe | 2,666 | (49.9) | 1,546 | (50.5) | 655 | (48.3) | |
| Exemestane | 2,682 | (50.1) | 1,514 | (49.5) | 702 | (51.2) | |
| Persistence of ET | | | | | | | **<0.001** |
| Yes | 4,142 | (77.4) | 2,376 | (77.6) | 980 | (72.2) | |
| No | 1,207 | (22.6) | 684 | (22.4) | 377 | (27.8) | |

WLE: wide local excision; RT: radiotherapy; Tam → Exe: tamoxifen followed by exemestane; ET: endocrine therapy.

**Table 3.** Causes of death by age at diagnosis.

| | <65 years (n=391) | | 65-75 years (n=341) | | ≥75 years (n=311) | |
|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) |
| Breast cancer | 303 | (77.5) | 192 | (56.3) | 113 | (36.3) |
| Second primary tumor | 35 | (9.0) | 50 | (14.7) | 31 | (10.0) |
| Endometrial cancer | 1 | (0.3) | 0 | (0.0) | 0 | (0.0) |
| Cardiac disorder | 14 | (3.6) | 25 | (7.3) | 39 | (12.5) |
| Thromboembolism | 0 | (0.0) | 2 | (0.6) | 10 | (3.2) |
| Pulmonary disorder | 5 | (1.3) | 12 | (3.5) | 14 | (4.5) |
| Cerebral disorder | 4 | (1.0) | 13 | (3.8) | 17 | (5.5) |
| Vascular disorder | 1 | (0.3) | 3 | (0.9) | 3 | (1.0) |
| Other | 17 | (4.3) | 26 | (7.6) | 57 | (18.3) |
| Unknown | 11 | (2.8) | 18 | (5.3) | 27 | (8.7) |

**Table 4.** Disease specific mortality by age at diagnosis.

| | 5-years death n | (%) | Multivariable* HR (95% CI) | p |
|---|---|---|---|---|
| Age | | | | **<0.001** |
| <65 years | 243 | (5) | 1 (reference) | |
| 65-75 years | 149 | (6) | 1.25 (1.01-1.54) | |
| ≥75 years | 92 | (8) | 1.63 (1.23-2.16) | |
| Histological grade (BR) | | | | **<0.001** |
| G1 | 27 | (2) | 1 (reference) | |
| G2 | 191 | (5) | 1.86 (1.28-2.70) | |
| G3,4 | 226 | (10) | 3.23 (2.21-4.72) | |
| T stage | | | | **<0.001** |
| T1 | 151 | (3) | 1 (reference) | |
| T2 | 282 | (9) | 1.91 (1.55-2.35) | |
| T3,4 | 49 | (12) | 2.01 (1.44-2.81) | |
| Nodal status | | | | **<0.001** |
| Negative | 121 | (3) | 1 (reference) | |
| Positive | 360 | (9) | 2.31 (1.85-2.87) | |
| Estrogen receptor | | | | **<0.001** |
| Positive | 459 | (6) | 1 (reference) | |
| Negative | 25 | (15) | 2.18 (1.44-3.31) | |
| Progesterone receptor | | | | **<0.001** |
| Positive | 293 | (5) | 1 (reference) | |
| Negative | 138 | (9) | 1.64 (1.35-2.00) | |
| Most extensive surgery | | | | **<0.001** |
| Mastectomy | 316 | (8) | 1 (reference) | |
| WLE | 168 | (4) | 0.59 (0.46-0.74) | |
| Radiotherapy | | | | **0.001** |
| Yes | 335 | (6) | 1 (reference) | |
| No | 146 | (6) | 0.68 (0.54-0.86) | |
| Chemotherapy | | | | 0.76 |
| Yes | 213 | (2) | 1 (reference) | |
| No | 271 | (2) | 0.97 (0.77-1.20) | |
| Endocrine therapy | | | | 0.08 |
| Tam → Exe | 246 | (6) | 1 (reference) | |
| Exe | 238 | (6) | 0.85 (0.71-1.02) | |
| Persistence of ET | | | | **0.001** |
| Persistent | 425 | (2) | 1 (reference) | |
| Nonpersistent | 79 | (2) | 0.64 (0.50-0.84) | |

HR: Hazard ratio; CI: confidence interval. * Hazard ratios adjusted for all other covariates mentioned in the Table, and country. WLE: wide local excision; Tam → Exe: Tamoxifen followed by Exemestane; ET: endocrine therapy.

To test the robustness of the age cut points, additional analyses were performed with age as a continuous variable, which confirmed an increased risk of breast cancer death per ten years increase in age (univariate HR per ten years was 1.20 (95% CI 1.10-1.31), p<0.001; multivariable HR per ten years 1.21 was (95% CI 1.08-1.36), p=0.001). Since increasing age was associated with larger tumors (Table 1), additional analyses were performed to exclude residual confounding by tumor size. Multivariable survival analyses adjusted for tumor size in centimeters instead of T stage revealed similar results (patients aged <65 years functioned as a reference, HR for patients aged 65-75 years was 1.25 (95% CI 1.01-1.55); HR for patients aged ≥75 years was 1.62 (95% CI 1.22-2.14); p=0.003). Moreover, within strata of tumor size in centimeters, increasing age was consistently associated with a higher disease specific mortality (Supplementary table 1).

As disease specific mortality may be underestimated due to increased other cause mortality with increasing age, we performed additional survival analyses using a Fine and Gray model, in which the risk of competing mortality is accounted for. Multivariable analyses yielded comparable results as those presented in Table 4 (patients aged <65 years functioned as a reference, HR for patients aged 65-75 years was 1.22 (95% CI 1.00-1.48); HR for patients aged ≥75 years was 1.50 (95% CI 1.16-1.94); p<0.001). Additionally, one may argue that comorbidity in itself, independent of associated competing mortality, may result in higher disease specific mortality. Data on comorbidity were available for Dutch and Belgian patients (n=3142, 32%). Survival analyses restricted to these patients showed that estimates were not affected by comorbidity (Supplementary table 2).

To investigate whether the association between age and disease specific mortality was of linear origin, or whether a specific turning point was present, age was categorized in seven groups (Supplementary table 3). Disease specific mortality was similar for patients up to 70 years of age. From this age onwards, disease specific mortality increased stepwise with increasing age.

**Table 5.** Other cause mortality and breast cancer recurrence by age at diagnosis.

| | 5-years events n | (%) | Univariate HR (95% CI) | p | Multivariable* HR (95% CI) | p |
|---|---|---|---|---|---|---|
| Other cause mortality | | | | **<0.001** | | **<0.001** |
| <65 years | 64 | (1) | 1 (reference) | | 1 (reference) | |
| 65-75 years | 126 | (5) | 2.99 (2.29-3.89) | | 2.66 (1.96-3.63) | |
| ≥75 years | 160 | (14) | 9.96 (7.74-12.80) | | 7.30 (5.29-10.07) | |
| Breast cancer recurrence | | | | **0.002** | | 0.061 |
| <65 years | 512 | (10) | 1 (reference) | | 1 (reference) | |
| 65-75 years | 282 | (10) | 1.00 (0.87-1.15) | | 1.07 (0.91-1.25) | |
| ≥75 years | 153 | (13) | 1.34 (1.13-1.59) | | 1.29 (1.05-1.60) | |

HR: Hazard ratio; CI: confidence interval. *Hazard ratios adjusted for country, histological grade, T stage, nodal stage, estrogen receptor, progesterone receptor, surgery, radiotherapy, chemotherapy, endocrine therapy and persistence of endocrine therapy.

Next, we studied whether other cause mortality and breast cancer recurrence were different among age categories (Table 5). Mortality from other causes increased with age (multivariable analyses, patients aged <65 years functioned as a reference, HR for patients aged 65-75 years was 2.66 (95% CI 1.96-3.63); HR for patients aged ≥75 years was 7.30 (95% CI 5.29-10.07); p<0.001). Next, increasing age was associated with a higher risk of breast cancer recurrence (multivariable analyses, patients aged <65 years functioned as a reference, HR for patients aged 65-75 years was 1.07 (95% CI 0.91-1.25); HR for patients aged ≥75 years was 1.29 (95% CI 1.05-1.60); p=0.061).

# Discussion

The major finding in this study is that disease specific mortality is higher in older breast cancer patients, independent of tumor and treatment characteristics. Similarly, breast cancer recurrence increased with increasing age. Disease specific mortality as a proportion of all cause mortality decreased with age.

Several factors were explored which potentially could have biased our findings. Increasing age was associated with larger tumors at diagnosis. Consequently, disease specific mortality would be higher in elderly patients. Multivariable analyses adjusted for treatment and tumor characteristics, and analyses stratified by tumor size did not alter the results. Selective misclassification, in which death is more often attributed to breast cancer with increasing age, is not likely to have biased our results, because additional analyses using the secondary endpoint breast cancer recurrence revealed similar results. Theoretically, this trial may have been subject to age specific inclusion bias, in which elderly were included with different tumors compared to younger patients (Table 1). However, since differences in tumor characteristics resemble observational data in postmenopausal patients receiving surgery[15], this was not likely to have had a major influence.

Our finding that disease specific mortality as a proportion of all cause mortality decreased with age is consistent with several observational studies[3;5;10;16-19]. Bastiaannet et al[4] found that within breast cancer patients the percentage of deaths attributed to breast cancer decreased with age. The decreased proportion of all cause mortality attributed to breast cancer may have led to the conclusion that disease specific mortality decreases with increasing age. Here we provide arguments that disease specific mortality increases with age. There are few studies in the literature addressing this topic. Besides, there are only little data available on disease specific mortality in breast cancer patients by age at diagnosis. Increased risk of disease specific mortality with increasing age is confirmed in two studies[4;20], however others observed an opposite association[5;17;18], or no association at all[16;19;21].

It is tempting to speculate on the underlying mechanisms which could explain the results presented in this study. First, elderly patients may experience undertreatment. Several studies

showed that elderly breast cancer patients have lower odds of receiving standard care[10;22-25]. Increased age at diagnosis predicts deviation from guidelines for surgical therapy[23], adjuvant radiotherapy[10;24;25], chemotherapy[23-25] and endocrine therapy[23;24]. All patients included in this trial received surgery and endocrine therapy. A previous TEAM study analysis showed that patients aged ≥75 years more frequently discontinued study medication, and received less often subsequent therapy. However, discontinuation within the first year of follow-up was not associated with disease specific mortality thereafter[11]. Radiotherapy after a wide local excision was administered less frequently with increasing age (Table 1). Moreover, while 48% of patients aged ≥75 years had nodal involvement, only 5.2% received adjuvant chemotherapy. Next, elderly patients may experience overtreatment, in which adverse events of breast cancer therapy result in mortality attributed to breast cancer. Older patients may have an increased toxicity risk when treated with chemotherapy and to a lesser degree with radiotherapy[26]. In these relatively healthy elderly trial participants, breast cancer recurrence was shown to be higher with increasing age as well. Therefore overtreatment is not likely to play a role in our findings.

Breast cancer in elderly might display a more aggressive tumor biology and thereby increase mortality from breast cancer. In this study, elderly presented more often with larger tumors, however nodal status was similar over age. Although this hypothesis cannot be tested in detail in this study, other studies suggest the opposite. Advanced age has been associated with a decrease in tumor proliferative factors[27], and elderly patients more often present with well differentiated tumors and positive hormone receptor status[19;28].

Adjustment for both treatment and tumor characteristics did not eliminate the association between age and disease specific mortality. Consequently, other, unknown factors might have contributed to our findings. Older patients might respond differently to a tumor than younger patients[29]. In addition, older patients might respond different to a certain therapy. Polypharmacy can cause drug interactions, and may alter pharmacokinetics of anticancer therapy[30].

Summarized, undertreatment, in particular undertreatment of either chemotherapy or radiotherapy, may explain age specific outcome in this relatively healthy population. Differences in tumor biology and age specific overtreatment are not likely to have influenced our findings. We cannot exclude a potential influence of an age specific response to either the tumor or anticancer therapy.

Effects of anticancer treatment cannot be estimated as precisely in patients with a high risk of competing mortality. As a consequence studies may be underpowered to detect treatment outcome differences in these populations[31]. Fine and Gray analyses accounting for the higher competing mortality with increasing age revealed similar effect sizes; despite the fact that 14.6% of patients aged ≥75 years died from causes other than breast cancer, estimates were

unaffected. These data suggest that competing mortality has to be substantial to affect disease specific outcome as estimated by Cox regression analysis.

## Strengths and limitations

The major strength of this study is the ability to study a large group of breast cancer patients followed as part of a clinical trial on endocrine therapy. Trial data comprise highly standardized treatment algorithms and virtually complete follow-up. The TEAM trial had very few exclusion criteria, among which there was no upper age limitation. This enabled us to study age specific mortality.

As enrollment in the TEAM trial was restricted to postmenopausal patients with estrogen and/or progesterone receptor positive disease, these results may not necessarily be extrapolated to all breast cancer patients. No data were available on compliance to non-randomized therapy. Although analyses were adjusted for non-randomized therapy, residual confounding and bias by noncompliance cannot be excluded. Although eligibility criteria of the TEAM trial were quite broad, it is known that trial populations generally comprise relatively healthy patients compared to the general population[32]. The results presented in this study may slightly differ from results in the general population. Competing mortality is likely to be higher in the general population, and administered treatment as well as implications of treatment may differ from a trial population. Replication of the current analyses in a detailed population based study may reveal additional evidence for one or more explanations of the findings presented in this study.

## Conclusion

In conclusion, regardless of a higher risk of other cause mortality and independent of tumor and treatment characteristics, disease specific mortality increases with age among postmenopausal women with hormone receptor positive breast cancer. These data underline the need for age specific breast cancer studies, in order to improve breast cancer outcome in all ages. Moreover, future detailed population based and translational studies may increase insight in causal factors of higher disease specific mortality and breast cancer recurrence with increasing age.

**Supplementary table 1.** Disease specific mortality by age at diagnosis, stratified by tumor size.

| | 5-years death n | (%) | Univariate HR (95% CI) | p | Multivariable* HR (95% CI) | p |
|---|---|---|---|---|---|---|
| <1 cm | | | | 0.827 | | 0.700 |
| <65 years | 3 | (1) | 1 (reference) | | 1 (reference) | |
| 65-74 years | 0 | (0) | 0.89 (0.16-4.85) | | 1.29 (0.21-7.97) | |
| ≥75 years | 1 | (1) | 1.84 (0.20-16.63) | | 2.82 (0.26-31.21) | |
| 1-2 cm | | | | 0.124 | | 0.073 |
| <65 years | 58 | (3) | 1 (reference) | | 1 (reference) | |
| 65-74 years | 44 | (2) | 1.31 (0.91-1.89) | | 1.52 (0.99-2.32) | |
| ≥75 years | 12 | (4) | 1.61 (0.95-2.74) | | 1.86 (0.97-3.58) | |
| 2-3 cm | | | | 0.208 | | 0.619 |
| <65 years | 80 | (7) | 1 (reference) | | 1 (reference) | |
| 65-74 years | 44 | (6) | 0.93 (0.67-1.29) | | 1.01 (0.69-1.47) | |
| ≥75 years | 76 | (9) | 1.32 (0.91-1.90) | | 1.24 (0.78-1.99) | |
| 3-4 cm | | | | 0.329 | | **0.022** |
| <65 years | 50 | (11) | 1 (reference) | | 1 (reference) | |
| 65-74 years | 21 | (8) | 0.95 (0.62-1.46) | | 1.11 (0.67-1.83) | |
| ≥75 years | 26 | (13) | 1.34 (0.86-2.07) | | 2.15 (1.20-3.82) | |
| 4-5 cm | | | | **0.034** | | 0.136 |
| <65 years | 15 | (9) | 1 (reference) | | 1 (reference) | |
| 65-74 years | 15 | (12) | 1.54 (0.81-2.90) | | 1.48 (0.70-3.14) | |
| ≥75 years | 13 | (20) | 2.51 (1.25-5.02) | | 2.32 (1.02-6.13) | |
| ≥5 cm | | | | 0.241 | | 0.397 |
| <65 years | 19 | (9) | 1 (reference) | | 1 (reference) | |
| 65-74 years | 18 | (18) | 1.51 (0.88-2.58) | | 1.53 (0.79-2.96) | |
| ≥75 years | 8 | (12) | 0.90 (0.43-1.88) | | 1.02 (0.37-2.82) | |

HR: Hazard ratio; CI: confidence interval. * Hazard ratios adjusted for country, histological grade, nodal stage, estrogen receptor, progesterone receptor, surgery, radiotherapy, chemotherapy, endocrine therapy and persistence of endocrine therapy.

**Supplementary table 2.** Disease specific mortality in Dutch/Belgian participants, adjusted for comorbidity.

| | 5-years death n | (%) | Multivariable HR (95% CI) | p |
|---|---|---|---|---|
| Model 1* | | | | 0.055 |
| <65 years | 135 | (9) | 1 (reference) | |
| 65-75 years | 74 | (9) | 1.16 (0.86-1.57) | |
| ≥75 years | 51 | (11) | 1.57 (1.09-2.26) | |
| Model 2** | | | | **0.048** |
| <65 years | 135 | (9) | 1 (reference) | |
| 65-75 years | 74 | (9) | 1.16 (0.86-1.58) | |
| ≥75 years | 51 | (11) | 1.60 (1.10-2.32) | |
| Model 3*** | | | | 0.064 |
| <65 years | 135 | (9) | 1 (reference) | |
| 65-75 years | 74 | (9) | 1.16 (0.86-1.57) | |
| ≥75 years | 51 | (11) | 1.55 (1.07-2.25) | |
| Model 4**** | | | | **0.047** |
| <65 years | 135 | (9) | 1 (reference) | |
| 65-75 years | 74 | (9) | 1.17 (0.87-1.59) | |
| ≥75 years | 51 | (11) | 1.59 (1.10-2.31) | |

HR: Hazard ratio; CI: confidence interval. * Hazard ratios adjusted for country, histological grade, T stage, nodal stage, estrogen receptor, progesterone receptor, surgery, radiotherapy, chemotherapy, endocrine therapy and persistence of endocrine therapy. ** Hazard ratios adjusted for variables included in Model 1 and comorbidity categories (cardiac, central nervous system, endocrine, musculoskeletal comorbidities). *** Hazard ratios adjusted for variables included in Model 1 and number of comorbidities (continuous). **** Hazard ratios adjusted for variables included in Model 1 and number of comorbidities (0, 1-2, >2).

**Supplementary table 3.** Disease specific mortality by age at diagnosis (7 groups).

| | 5-years death n | (%) | Univariate HR (95% CI) | p | Multivariable* HR (95% CI) | p |
|---|---|---|---|---|---|---|
| Age at diagnosis | | | | | | |
| <55 years | 63 | (5) | 1 (reference) | | 1 (reference) | |
| 55-60 years | 87 | (5) | 1.08 (0.81-1.44) | 0.611 | 1.02 (0.74-1.41) | 0.908 |
| 60-65 years | 93 | (5) | 1.09 (0.82-1.45) | 0.554 | 1.09 (0.79-1.51) | 0.610 |
| 65-70 years | 75 | (5) | 1.05 (0.78-1.41) | 0.767 | 1.18 (0.84-1.65) | 0.339 |
| 70-75 years | 74 | (7) | 1.38 (1.02-1.87) | **0.035** | 1.48 (1.04-2.11) | **0.029** |
| 75-80 years | 74 | (9) | 1.75 (1.27-2.40) | **0.001** | 1.73 (1.17-2.56) | **0.006** |
| ≥80 years | 29 | (7) | 1.81 (1.23-2.66) | **0.003** | 1.74 (1.11-2.74) | **0.017** |

HR: Hazard ratio; CI: confidence interval. * Hazard ratios adjusted for country, histological grade, T stage, nodal stage, estrogen receptor, progesterone receptor, surgery, radiotherapy, chemotherapy, endocrine therapy and persistence of endocrine therapy.

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Chapter 6

# Elderly postmenopausal patients with breast cancer are at increased risk for distant recurrence

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# Abstract

## Background

For postmenopausal patients with hormone receptor positive breast cancer, breast cancer survival decreases with increasing age at diagnosis. The aim of this study was to assess the incidence of breast cancer recurrence, both locoregional and distant recurrence, and contralateral breast cancer, by age at diagnosis.

## Methods

Patients enrolled in the Tamoxifen Endocrine Adjuvant Multinational (TEAM) trial were included. Primary endpoints were locoregional recurrence, distant recurrence and contralateral breast cancer. Age at diagnosis was categorized as younger than 65 years, 65-75 years, and 75 years or older.

## Results

Overall, 9,766 patients were included, of which 5,349 were younger than 65 years (reference group), 3,060 were 65-75 years, and 1,357 were 75 years or older. With increasing age, a decreased administration of radiotherapy after breast conserving surgery (94%; 92%; 88% respectively) and adjuvant chemotherapy (51%; 23%; 5% respectively) was observed. Risk of distant recurrence increased with age at diagnosis; multivariable hazard ratio for patients aged 65-75 years was 1.20 (95% CI 1.00-1.44), hazard ratio for patients aged 75 years or older was 1.39 (95% CI 1.08-1.79). Risks of locoregional recurrence and contralateral breast cancer were not significantly different across age groups.

## Conclusion

Elderly breast cancer patients were at increased risk for distant recurrence. Others have shown that the risk of distant recurrence is mainly affected by adjuvant systemic therapy. All TEAM patients received adjuvant endocrine treatment, however, chemotherapy was administered less often in elderly patients. These findings are suggestive for consideration of chemotherapy in relatively fit elderly breast cancer patients with hormone sensitive disease.

# Introduction

Breast cancer is the most common type of cancer in women in Western societies. Worldwide, nearly a third of all breast cancer patients are 65 years or older, and in more developed countries this proportion increases to over 40%[1]. Because of an increasing life expectancy and raised breast cancer incidence with increasing age, the disease will progressively affect the lives of elderly women[2].

Many have published on the worse prognosis of premenopausal compared with postmenopausal breast cancer patients[3-5]. However, evidence is lacking on age specific breast cancer outcome *within* postmenopausal women. Recently, we reported that breast cancer survival in postmenopausal patients decreased with increasing age[6]. To gain further insight in the relation between age at diagnosis and breast cancer outcome, we studied the incidence of breast cancer recurrence, both locoregional and distant recurrence, and contralateral breast cancer, by age at diagnosis in patients included in the Tamoxifen Exemestane Adjuvant Multinational (TEAM) Trial.

# Methods

## Study population

The TEAM trial has been described extensively in previous reports[6;7]. In short, 9,766 postmenopausal women with estrogen and/or progesterone receptor positive breast cancer, who completed local therapy with curative intent, were randomized to receive either exemestane 25 mg daily for five years or a sequential regimen consisting of tamoxifen 20 mg daily for 2.5–3 years, followed by exemestane 25 mg daily for 2.5–2 years. Adjuvant chemotherapy, if indicated, was given before start of endocrine therapy, and radiotherapy was administered according to local practice. Participants commenced the assigned endocrine study treatment within 10 weeks of completion of surgery and chemotherapy, if indicated. Patients were ineligible if they had a malignancy within five years preceding breast cancer diagnosis, an Eastern Cooperative Oncology Group (ECOG) performance status of more than two, or a significant cardiac disease or other illness interfering with study participation and adequate follow-up. Participants were enrolled in Belgium, The Netherlands, United Kingdom, Ireland, United States of America, Japan, Greece, Germany, and France. Similar protocols were used in the nine countries, with minor differences to accommodate the local treatment guidelines[8]. The trial was registered with ClinicalTrials.gov, NCT00279448, NCT00032136, and NCT00036270; NTR 267; Ethics Commission Trial 27/2001; and UMIN, C000000057.

As the final results of the TEAM trial showed no significant differences in efficacy endpoints between both treatment arms[7], we were able to investigate disease recurrence regardless of

randomized treatment. The database was locked on October 7th 2010; the design of the current post hoc analysis was developed in July 2011.

Patients were categorized in three groups, based on age at diagnosis (younger than 65 years, 65-75 years, and 75 years or older) as discussed at the Meeting of the International Society of Geriatric Oncology (SIOG) in 2009 and in line with other publications[6;9;10]. Study endpoints were 1) locoregional recurrence (recurrence in the ipsilateral breast or chest wall, recurrence in ipsilateral axillary or supraclavicular lymph node(s), or other locoregional localization), 2) distant recurrence (recurrence in bone, skin, liver, lung, brain, or other distant localization), and 3) contralateral breast cancer (new primary invasive tumor in the contralateral breast), whichever came first. In situ carcinoma was not considered to be a recurrence. For 61 patients with synchronously recurrent disease at more than one site, the localization most likely determining the prognosis was used as endpoint.

Statistical analyses were performed using SPSS 17.0 (SPSS, Chicago, IL). Cox proportional hazard models were used to evaluate the association between age at diagnosis and the endpoints. Covariates were included in the multivariable model if they were judged to be clinically relevant. First, estimates were adjusted for country and tumor characteristics (country of residence, histological grade (Bloom Richardson grade I; II; III), T stage (T1; T2; T3,4), nodal stage (negative; positive), estrogen receptor status (negative; positive), and progesterone receptor status (negative; positive)). Next, the fully adjusted model comprised both tumor and treatment characteristics (country, histological grade, T stage, nodal stage, estrogen receptor status, progesterone receptor status, type of surgery (mastectomy; wide local excision), radiotherapy (yes; no), chemotherapy (yes; no), allocated endocrine therapy

**Table 1.** Distribution of locoregional recurrence and distant recurrence by age at diagnosis.

| | <65 years | | 65-75 years | | ≥75 years | | p |
|---|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) | |
| Locoregional recurrence | | | | | | | 0.24 |
| Ipsilateral breast | 55 | (49.1) | 20 | (40.8) | 13 | (40.6) | |
| Chest wall | 23 | (20.5) | 16 | (32.7) | 11 | (34.4) | |
| Ipsilateral lymph node(s) | 16 | (14.3) | 5 | (10.2) | 6 | (18.7) | |
| Supraclavicular lymph node(s) | 8 | (7.1) | 2 | (4.1) | 0 | (0) | |
| Other | 10 | (8.9) | 6 | (12.2) | 2 | (6.3) | |
| Distant recurrence | | | | | | | 0.50 |
| Bone | 139 | (34.0) | 95 | (38.5) | 53 | (40.8) | |
| Liver | 144 | (35.2) | 77 | (31.2) | 37 | (28.5) | |
| Lung | 60 | (14.7) | 36 | (14.6) | 22 | (16.9) | |
| Skin | 9 | (2.2) | 7 | (2.8) | 1 | (0.8) | |
| Brain | 11 | (2.7) | 4 | (1.6) | 4 | (3.1) | |
| Other | 46 | (11.3) | 28 | (11.3) | 13 | (10.1) | |

(tamoxifen followed by exemestane; exemestane) and persistence of endocrine therapy (discontinuation of allocated endocrine therapy because of either adverse events, intercurrent illness, patient refusal or other reasons; continuation of allocated endocrine therapy, or having an event while on study medication)). Patients with missing data were not included in the multivariable model. All statistical tests were two-sided. P values <0.05 were considered to be statistically significant.

# Results

Overall, 9,766 patients (range 35-96, median age 64 years) were included; 5,349 were younger than 65 years (median 58 years), 3,060 were 65-75 years (median 69 years), and 1,357 were 75 years or older (median 79 years). Baseline characteristics by age groups were shown in an earlier report[6]; elderly patients presented with larger tumors, without differences in nodal status. With increasing age, the proportion of mastectomy increased significantly, while a marked decrease was observed in the administration of radiotherapy following a wide local excision (94%; 92%; 88% respectively, p<0.001) and administration of chemotherapy (51%; 23%; 5% respectively, p<0.001)[6].

At database lock, median follow-up (interquartile range) from randomization was 5.1 years (4.2-6.0 years), during which 1,062 first events were registered; 193 locoregional recurrences, 786 distant recurrences and 83 contralateral breast cancers. As shown in Table 1, the distribution of locoregional recurrence and distant recurrence was similar across age groups. Figure 1 shows the cumulative incidence of endpoints by age at diagnosis. Cumulative incidence of

**Table 2.** Breast cancer recurrence by age at diagnosis.

| | 5-years event | | Univariate | p | Multivariable* | p | Multivariable** | p |
|---|---|---|---|---|---|---|---|---|
| | n | (%) | HR (95% CI) | | HR (95% CI) | | HR (95% CI) | |
| Locoregional recurrence | | | | 0.10 | | 0.14 | | 0.10 |
| <65 years | 100 | (2) | 1 (reference) | | 1 (reference) | | 1 (reference) | |
| 65-75 years | 42 | (1) | 0.77 (0.55-1.08) | | 0.71 (0.49-1.04) | | 0.67 (0.45-0.99) | |
| ≥75 years | 27 | (3) | 1.24 (0.84-1.84) | | 1.10 (0.71-1.70) | | 1.00 (0.61-1.63) | |
| Distant recurrence | | | | **0.006** | | 0.08 | | **0.024** |
| <65 years | 378 | (8) | 1 (reference) | | 1 (reference) | | 1 (reference) | |
| 65-75 years | 219 | (8) | 1.06 (0.91-1.24) | | 1.14 (0.96-1.36) | | 1.20 (1.00-1.44) | |
| ≥75 years | 115 | (10) | 1.37 (1.13-1.68) | | 1.26 (1.01-1.57) | | 1.39 (1.08-1.79) | |
| Contralateral breast cancer | | | | 0.73 | | 0.79 | | 0.75 |
| <65 years | 34 | (1) | 1 (reference) | | 1 (reference) | | 1 (reference) | |
| 65-75 years | 21 | (1) | 0.98 (0.60-1.60) | | 0.99 (0.59-1.66) | | 1.03 (0.60-1.77) | |
| ≥75 years | 11 | (2) | 1.26 (0.68-2.33) | | 1.24 (0.64-2.38) | | 1.31 (0.64-2.68) | |

HR: Hazard ratio; CI: confidence interval. * Hazard ratios adjusted for country, histological grade, T stage, nodal stage, estrogen receptor, and progesterone receptor. ** Hazard ratios adjusted for country, histological grade, T stage, nodal stage, estrogen receptor, progesterone receptor, surgery, radiotherapy, chemotherapy, endocrine therapy and persistence of endocrine therapy.

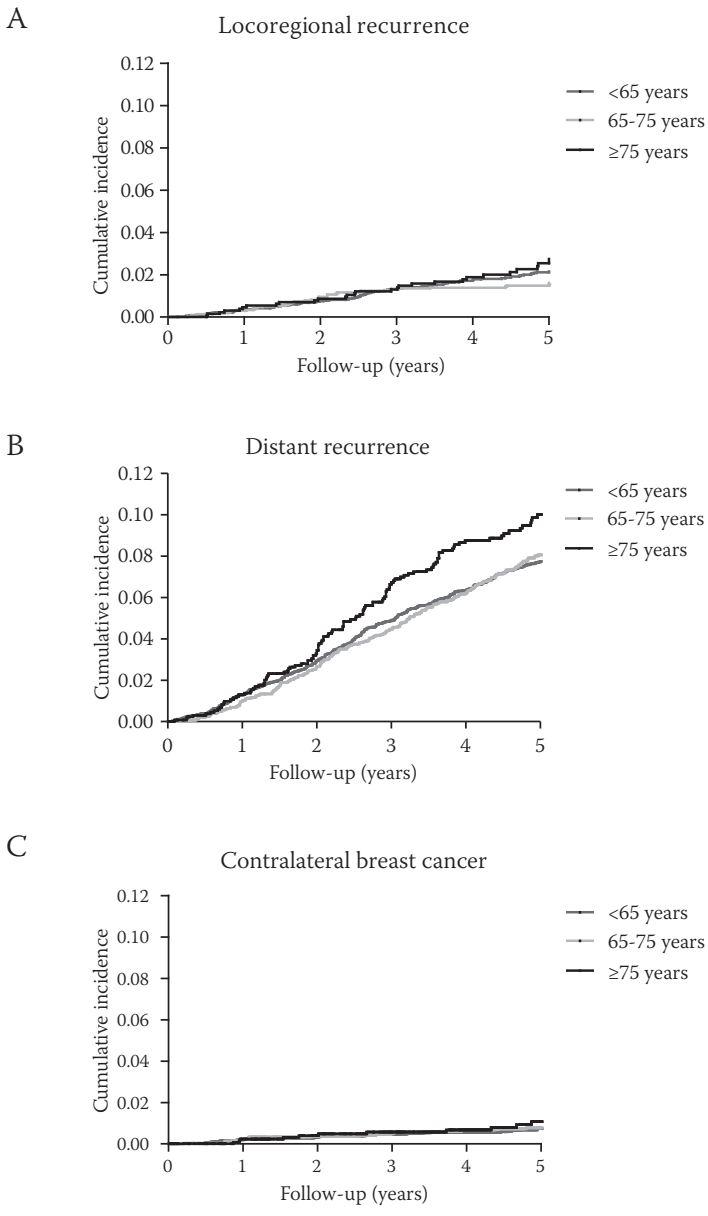


**Figure 1.** Cumulative incidence of A) locoregional recurrence, B) distant recurrence C) and contralateral breast cancer by age at diagnosis.

locoregional recurrence was 2.1%, 1.6%, and 2.4% respectively; cumulative incidence of distant recurrence increased from 7.6% in patients younger than 65 years, 8.1% in patients aged 65-75 years of age, to 9.6% in patients aged 75 years or older. Cumulative incidence of contralateral breast cancer was 0.8%, 0.8%, and 1.0% respectively.

Table 2 shows the results of Cox regression analyses. In both univariate and multivariable analyses, the risk of locoregional recurrence was similar across age categories. Contrary, the risk of distant recurrence increased with increasing age at diagnosis. Patients aged younger than 65 years functioned as a reference, univariate hazard ratio (HR) for patients aged 65-75 was 1.06 (95% confidence interval (CI) 0.91-1.24) and HR for patients aged 75 years or older was 1.37 (95% CI 1.13-1.68). Both the partly and fully adjusted model showed comparable results; the fully adjusted HR for patients aged 65-75 was 1.20 (95% CI 1.00-1.44); HR for patients aged 75 years or older was 1.39 (95% CI 1.08-1.79), p=0.024. The risk of contralateral breast cancer was not significantly different across age categories.

To test the sensitivity of the endpoints, three alternative analyses were performed. The results of these alternative analyses were similar to the main results. First, survival analyses were repeated without restriction to the *first* site of recurrence, i.e. all events irrespective of the sequence of occurrence were included in the analysis. Multivariable HR for locoregional recurrence was 0.79 (95% CI 0.57-1.09) for patients aged 65-75 years, and 0.94 (95% CI 0.62-1.43) for patients aged 75 years or older; multivariable HR for distant recurrence was 1.17 (95% CI 0.98-1.40) for patients aged 65-75 years, and 1.39 (95% CI 1.09-1.76) for patients aged 75 years or older; and multivariable HR for contralateral breast cancer was 0.90 (95% CI 0.53-1.52) for patients aged 65-75 years, and 0.92 (95% CI 0.46-1.83) for patients aged 75 years or older.

Second, synchronous endpoints (n=61) were recoded as locoregional recurrence, and contralateral breast cancer, respectively. Multivariable HR for locoregional recurrence, for patients aged 65-75 years was 0.76 (95% CI 0.54-1.06), HR for patients aged 75 years or older was 0.92 (95% CI 0.59-1.42), p=0.260; multivariable HR for distant recurrence, for patients aged 65-75 years was 1.20 (95% CI 0.99-1.46); HR for patients aged 75 years or older was 1.45 (95% CI 1.12-1.88), p=0.015; and multivariable HR for contralateral breast cancer, for patients aged 65-75 years was 1.05 (95% CI 0.62-1.80); HR for patients aged 75 years or older was 1.46 (95% CI 0.73-2.94), p=0.546.

Third, contralateral breast cancer was recoded as locoregional recurrence. Multivariable HR for locoregional recurrence, for patients aged 65-75 years was 0.77 (95% CI 0.56-1.06); HR for patients aged 75 years or older was 1.08 (95% CI 0.72-1.62), p=0.164.

Also, two additional analyses were performed to diminish selection bias. First, survival analyses for distant recurrence were stratified by T stage since increasing age was associated with larger tumors (Supplementary table 1). Although not significant, estimates were comparable to the main analysis. Second, survival analyses for locoregional recurrence were stratified by most extensive surgery since elderly patients more frequently underwent a mastectomy (Supplementary table 2). Again, the results remained similar.

# Discussion

To summarize, we found that elderly breast cancer patients had a higher risk of distant recurrence, while the risks of locoregional recurrence and contralateral breast cancer did not significantly differ across age groups. Additional analyses were performed to test the robustness of the endpoints and to explore whether our findings may have been biased. Inclusion of three alternative definitions of endpoints did not alter the results. Moreover, stratified analyses by T stage and most extensive surgery revealed comparable estimates.

Many have published on predictors of breast cancer recurrence in premenopausal compared to postmenopausal patients. Virtually all studies observed a higher risk of locoregional breast cancer recurrence in premenopausal compared to postmenopausal women[4;5;11-14]. Few studies addressed breast cancer recurrence *within* postmenopausal patients, and again most focused on locoregional recurrence[15-18]. It is tempting to speculate on the possible mechanisms which may explain our findings. Based on the literature, we hypothesize that locoregional recurrence may reflect suboptimal local[19] and/or systemic[20] treatment, while distant recurrence and contralateral breast cancer more likely reflect suboptimal systemic treatment[20-23]. As all TEAM patients received endocrine treatment, the decreased administration of chemotherapy with increasing age may have contributed to a higher distant breast cancer recurrence in elderly patients. Of note, the hazard ratio for contralateral breast cancer for patients aged 75 years or older was comparable with the hazard ratio for distant recurrence, but the distribution of contralateral breast cancer was not statistically different across age groups, possibly due to a low number of events.

Few have studied chemotherapy efficacy in elderly breast cancer patients. In the Early Breast Cancer Trialists' Collaborative Group meta-analysis, not enough women older than 70 years were included to be able to draw conclusions about chemotherapy efficacy in this age group[20]. However, a review of randomized clinical trials on chemotherapy in node positive breast cancer patients revealed that older patients derived similar reductions in breast cancer mortality and recurrence compared to younger patients[24]. Recently, Muss et al evaluated the efficacy of two regimens of adjuvant chemotherapy in older women with early stage breast cancer. Standard chemotherapy showed to be superior to oral capecitabine, especially in patients with hormone receptor negative tumors. Two studies aimed to evaluate the benefit of chemotherapy in elderly breast cancer patients, in which chemotherapy was compared with a no treatment arm[25;26]. Both trials failed to recruit and were closed early. The investigators suggested that a recruitment failure was due to the inability to convince patients to accept randomization in which a no treatment arm was incorporated[25]. Our findings suggest that addition of chemotherapy might be of benefit in relatively fit breast cancer patients with hormone receptor positive breast tumors. This needs to be evaluated in future studies.

As the association between age and distant recurrence was not eliminated by adjustment for both tumor and treatment characteristics, additional mechanisms may play a role, such as different tumor biology resulting in worse breast cancer outcome[27]; or interplay between tumor and patient characteristics including immunosenescence, which may result in a higher risk of disease progression[28;29]; or a different response to anti-cancer therapy due to interactions with comorbidity and polypharmacy[30].

One may argue that increasing age may be associated with a lower adherence to endocrine therapy and consequently may result in a higher rate of recurrence. No data were available on adherence by pill count. However, multivariable analyses were adjusted for nonpersistence, which was defined as discontinuing the assigned endocrine treatment because of adverse events, intercurrent illness, patient refusal, or other reasons. Previously, we reported a higher rate of nonpersistence of endocrine therapy with increasing age, in the Dutch and Belgian patients included in the TEAM study. However, both in patients aged 65-75 years as well as in patients aged 75 years or older, survival was not affected by nonpersistence[31]. The absence of a consistent association between nonpersistence and outcome suggests that the current findings cannot adequately be explained by age specific adherence.

## Strengths and limitations

A major strength of this study is the ability to study a large group of breast cancer patients followed as part of a clinical trial on endocrine therapy. Trial data comprise highly standardized treatment algorithms and virtually complete follow-up. The TEAM trial had very few exclusion criteria, among which there was no upper age limitation. This enabled us to study age specific breast cancer recurrence. However, although eligibility criteria of the TEAM trial were quite broad, it is known that trial populations generally comprise relatively healthy patients compared to the general population[32]. Additionally, as enrollment in the TEAM trial was restricted to postmenopausal patients with hormone receptor positive disease, these results may not necessarily be extrapolated to all breast cancer patients.

## Conclusion

In conclusion, elderly breast cancer patients included in the TEAM trial had a higher risk of distant recurrence. This risk may be due to underuse of chemotherapy, which therefore might be considered in relatively fit elderly patients.

**Supplementary table 1.** Distant recurrence of breast cancer by age at diagnosis, stratified by T stage.

| | 5-years event n | (%) | Univariate HR (95% CI) | p | Multivariable* HR (95% CI) | p |
|---|---|---|---|---|---|---|
| T1 | | | | 0.12 | | 0.11 |
| <65 years | 130 | (4) | 1 (reference) | | 1 (reference) | |
| 65-75 years | 70 | (4) | 0.93 (0.71-1.23) | | 1.03 (0.74-1.42) | |
| ≥75 years | 26 | (5) | 1.41 (0.97-2.05) | | 1.60 (1.01-2.51) | |
| T2 | | | | 0.54 | | 0.14 |
| <65 years | 199 | (12) | 1 (reference) | | 1 (reference) | |
| 65-75 years | 126 | (13) | 1.11 (0.90-1.37) | | 1.26 (0.98-1.62) | |
| ≥75 years | 76 | (13) | 1.12 (0.87-1.44) | | 1.29 (0.93-1.80) | |
| T3, T4 | | | | 0.76 | | 0.70 |
| <65 years | 46 | (21) | 1 (reference) | | 1 (reference) | |
| 65-75 years | 23 | (21) | 1.11 (0.69-1.78) | | 1.22 (0.70-2.12) | |
| ≥75 years | 13 | (17) | 0.86 (0.48-1.57) | | 1.30 (0.63-2.69) | |

HR: Hazard ratio; CI: confidence interval. * Hazard ratios adjusted for country, histological grade, nodal stage, estrogen receptor, progesterone receptor, most extensive surgery, radiotherapy, chemotherapy, endocrine therapy and persistence of endocrine therapy.

**Supplementary table 2.** Locoregional recurrence by age at diagnosis, stratified by most extensive surgery.

| | 5-years event n | (%) | Univariate HR (95% CI) | p | Multivariable* HR (95% CI) | p |
|---|---|---|---|---|---|---|
| Mastectomy | | | | 0.61 | | 0.57 |
| <65 years | 54 | (3) | 1 (reference) | | 1 (reference) | |
| 65-75 years | 32 | (3) | 0.84 (0.55-1.29) | | 0.80 (0.49-1.31) | |
| ≥75 years | 21 | (3) | 1.08 (0.67-1.74) | | 1.06 (0.58-1.92) | |
| Wide local excision | | | | 0.19 | | 0.11 |
| <65 years | 46 | (2) | 1 (reference) | | 1 (reference) | |
| 65-75 years | 10 | (1) | 0.60 (0.34-1.06) | | 0.49 (0.24-0.99) | |
| ≥75 years | 6 | (1) | 1.06 (0.51-2.24) | | 1.07 (0.45-2.52) | |

HR: Hazard ratio; CI: confidence interval. * Hazard ratios adjusted for country, histological grade, T stage, nodal stage, estrogen receptor, progesterone receptor, radiotherapy, chemotherapy, endocrine therapy and persistence of endocrine therapy.

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# Chapter 7

# Association between age at diagnosis and relative survival in elderly breast cancer patients from the general population

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# Abstract

## Background

Previously it was shown that breast cancer survival decreases with increasing age among a selected population of elderly who participated in a trial. However, patients who participate in a trial differ from patients in the general population. Therefore, the aim of this study was to evaluate the association between age and breast cancer outcome in an unselected group of elderly breast cancer patients.

## Methods

We included patients of the population-based FOCUS study, which comprises all incident breast cancer patients aged 65 years or older at diagnosis, who were diagnosed in the South Western part of The Netherlands between 1997 and 2004. All patients with non-metastasized breast cancer who received breast surgery were included. Age was categorized as 65-75 years and ≥75 years. Primary outcome was relative survival, which is an approximation of disease specific survival and the preferred way to describe the prognosis of elderly cancer patients in population-based studies. In addition, the relative excess risk of death was estimated.

## Results

Overall, 3,124 patients were included (1,617 aged 65-75 years; 1,507 aged ≥75 years), with a median age of 74.6 years. The five-years relative survival was 92.6% (95% CI 90.5-94.5) in patients aged 65-75 years, and 86.4% (95% CI 82.5-90.2) in patients aged ≥75 years. The lower relative survival in the oldest patients corresponded with a higher relative excess risk of death in patients aged ≥75 years as compared to patients aged 65-75 years (multivariable relative excess risk of death was 1.72 (95% CI 1.21-2.44)).

## Conclusions

Breast cancer outcome, in terms of relative survival, deteriorates with increasing age among unselected elderly patients from the general population.

# Introduction

Breast cancer is the most frequently diagnosed malignancy in females in the Western world, with over 40% of new diagnoses occurring in women aged 65 years and older[1]. It is often assumed that breast cancer phenotype is less aggressive in older women. Although elderly breast cancer patients more often present with larger tumors[2] and positive lymph nodes at diagnosis[3], they more often have hormone receptor positive disease and lower tumor differentiation grades[4]. In addition, a higher competing risk of death among elderly, in which a patient dies from causes unrelated to breast cancer, may affect breast cancer mortality[5].

However, recently we showed that breast cancer mortality increased with increasing age among 9,766 postmenopausal women with hormone receptor positive breast cancer who participated in a randomized clinical trial[6]. Moreover, elderly patients had a higher risk of breast cancer recurrence, and distant recurrence in particular[7].

Regardless of the disease and the age of the patients under study, it has been shown that the outlook of patients included in a clinical trial is usually better than those who do not participate[8]. In the general population, the risk of competing mortality is likely to be higher. In addition, both treatment[9] as well as implications of treatment may differ from patients who participate in a trial. Therefore it remains unknown whether the association of a worse breast cancer outcome with increasing age is also present in unselected elderly patients from the general population.

The aim of this study was to evaluate the association between age at diagnosis and breast cancer outcome in a large, unselected, population-based cohort of elderly patients with breast cancer.

# Methods

## FOCUS cohort

We included patients of the population-based FOCUS study. The FOCUS study (Female breast cancer in the elderly; Optimizing Clinical guidelines USing clinico-pathological & molecular data) comprises all incident breast cancer patients aged 65 years or older at diagnosis, who were diagnosed in the geographically defined Comprehensive Cancer Center Region West in The Netherlands between 1997 and 2004. Inclusion in the cohort is based on the National Cancer Registry, which contains data of all incident cancer cases. The nationwide Dutch network and registry of histopathology and cytopathology regularly submits reports of all newly diagnosed malignancies to the Regional Cancer Registries. The national hospital discharge data bank, which receives discharge diagnoses of admitted patients from all Dutch hospitals, completes case ascertainment. Trained personnel reviewed charts of these patients and collected information on patient, tumor, treatment and outcome characteristics. Vital

status was established either directly from the patient's medical record or through linkage with the municipal population registries, which record information on vital status (follow-up until January 1st 2011). Patients with in situ or invasive, non-metastatic breast cancer at diagnosis who received breast surgery were included in the current study.

## Outcome measures

Primary outcome measure was relative survival, which is an approximation of disease-specific survival. Relative survival is the preferred method for estimating disease-specific outcome in a population-based setting without requiring information on the cause of death[10;11].

Secondary outcome measures were time from diagnosis to occurrence of a locoregional recurrence, (recurrence in the ipsilateral breast or chest wall, or recurrence in ipsilateral axillary or supraclavicular lymph node(s); distant recurrence (recurrence in bone, skin, liver, lung, brain or other distant localization); or contralateral breast cancer, whichever came first. For patients with synchronously recurrent disease at more than one site, the localization most likely determining prognosis was used as endpoint. Ductal carcinoma in situ was not judged to be evidence of recurrence.

## Statistical analysis

Statistical analyses were performed using SPSS statistical software, version 20.0 (SPSS Chicago, IL) and STATA SE 12.0. Age at diagnosis was categorized as 65-74 years and ≥75 years, as discussed at the meeting of the International Society of Geriatric Oncology in 2009[12] and in line with other publications[6;13]. To compare proportional differences among age categories, the Pearson $\chi 2$ test was used.

Relative survival was calculated as the observed overall survival among patients in the study, divided by the expected overall survival in the sex-, age-, and year matched general population, using the 'strs' command in Stata[11]. Expected survival was obtained from population life-tables according to the Ederer II method[14]. An estimate of the five-years relative survival of less than 100% means that the survival of patients in the study is lower than expected, when compared to survival in the corresponding general population. This means that patients in the study had an excess risk of death, which can be attributed to breast cancer or breast cancer treatment.

The excess risk of death can be calculated as the observed number of deaths minus the expected number of deaths, divided by the total person-years. To compare whether the excess risk of death differed by age at diagnosis, we calculated the relative excess risk of death, which is the excess risk of death in patients aged ≥75 years divided by the excess risk of death in patients aged 65-75 years. The relative excess risk of death is estimated by a multivariable generalized linear model with a Poisson distribution, based on collapsed relative survival data based on exact survival times[14], and can be interpreted as the risk of death from breast cancer in patients aged ≥75 years as compared to the risk of death from breast cancer in patients aged

65-75 years. To assess the robustness of the results, the analyses were also stratified by stage (early stage: in situ, I, II; advanced stage: III)[15].

The relation between age at diagnosis and the secondary endpoints were evaluated by competing risk regression analyses according to Fine and Gray[16], since cause-specific outcomes may be influenced by the risk of competing endpoints. For example, an individual who dies, is no longer at risk for breast cancer recurrence. A Fine and Gray analysis is used to assess the risk of locoregional recurrence, distant recurrence and contralateral breast cancer, respectively, taking into account the risk of reaching competing endpoints. Competing endpoints for locoregional recurrence were distant recurrence, contralateral breast cancer, and death; competing endpoints for distant recurrence were locoregional recurrence, contralateral breast cancer, and death; and competing endpoints for contralateral breast cancer were locoregional recurrence, distant recurrence, and death. Sensitivity analyses were performed for overall recurrence, which was defined as either a locoregional recurrence, distant recurrence or contralateral breast cancer as a first event, with death as competing endpoint.

Covariates were included in the multivariable model if they were judged to be clinically relevant and comprised histological grade (Bloom Richardson G1; G2; G3; unknown), histological subtype (ductal; lobular; other), hormone receptor status (positive; negative; unknown), combined TNM stage (I; II; III; unknown), most extensive breast surgery (mastectomy; wide local excision), most extensive axillary surgery (axillary lymph node dissection; sentinel lymph node biopsy; none), radiotherapy (yes; no), chemotherapy (yes; no), endocrine therapy (yes; no); and comorbid disease (0-1; 2-4; 5 or more). All statistical tests were 2-sided. P values of less than 0.05 were considered to be statistically significant.

# Results

Overall, 3,124 patients with a median age of 74.6 years were included (range 65–98 years); 1,617 were 65-75 years (median age 69.8 years), and 1,507 were 75 years and older (median age 81.0 years). Median follow-up time was 7.3 years (interquartile range 4.2-9.7 years). Patient, tumor and treatment characteristics by age at diagnosis are shown in Table 1. Patients aged ≥75 years had a higher number of comorbid diseases. Moreover, they more often had a higher stage at diagnosis, and more often presented with hormone receptor positive tumors. The proportions of patients who received a mastectomy and endocrine therapy increased with increasing age, whereas axillary surgery, administration of radiotherapy after lumpectomy, and chemotherapy decreased.

When we compared overall survival of the patients in the current study to the expected overall survival as based on the corresponding general population, survival of patients in the study was lower than in the corresponding general population; the five-years relative survival was 92.6% (95% CI 90.5-94.5) in patients aged 65-75 years, and 86.4% (95% CI 82.5-90.2) in patients

**Table 1.** Patient, tumor and treatment characteristics by age at diagnosis.

| | Age 65-75 years (n=1,617) | | Age ≥75 years (n=1,507) | | p |
|---|---|---|---|---|---|
| | n | % | n | % | |
| Comorbid disease | | | | | **<0.001** |
| 0-1 | 919 | 56.8 | 602 | 39.9 | |
| 2 to 4 | 584 | 36.1 | 721 | 47.8 | |
| ≥5 | 114 | 7.1 | 184 | 12.2 | |
| Histological subtype | | | | | 0.116 |
| Ductal cancer | 1,224 | 75.7 | 1,092 | 72.5 | |
| Lobular cancer | 169 | 10.5 | 175 | 11.6 | |
| Other/unknown | 224 | 13.9 | 240 | 15.9 | |
| Histological grade (BR) | | | | | 0.813 |
| Grade 1 | 226 | 14.0 | 195 | 12.9 | |
| Grade 2 | 492 | 30.4 | 468 | 31.1 | |
| Grade 3 | 391 | 24.2 | 358 | 23.8 | |
| Unknown | 508 | 31.4 | 486 | 32.2 | |
| Hormone-receptor status | | | | | **<0.001** |
| Positive | 1,018 | 63.0 | 1,045 | 69.3 | |
| Negative | 256 | 15.8 | 232 | 15.4 | |
| Unknown | 343 | 21.2 | 230 | 15.3 | |
| TNM stage | | | | | **<0.001** |
| In situ | 137 | 8.5 | 61 | 4.0 | |
| I | 685 | 42.4 | 373 | 24.8 | |
| II | 627 | 38.8 | 803 | 53.3 | |
| III | 113 | 7.0 | 204 | 13.5 | |
| Unknown | 55 | 3.4 | 66 | 4.4 | |
| Most extensive breast surgery | | | | | **<0.001** |
| Mastectomy | 786 | 48.6 | 1,161 | 77.0 | |
| Wide local excision | 831 | 51.4 | 346 | 23.0 | |
| Most extensive axillary surgery | | | | | **<0.001** |
| ALND | 870 | 53.8 | 913 | 60.6 | |
| SLNB | 489 | 30.2 | 288 | 19.1 | |
| None | 258 | 16.0 | 306 | 20.3 | |
| Radiotherapy after wide local excision | | | | | **<0.001** |
| Yes | 751 | 90.4 | 238 | 68.8 | |
| No | 80 | 9.6 | 108 | 31.2 | |
| Endocrine therapy | | | | | **<0.001** |
| Yes | 550 | 34.0 | 704 | 46.7 | |
| No | 1,067 | 66.0 | 803 | 53.3 | |
| Chemotherapy | | | | | **<0.001** |
| Yes | 123 | 7.6 | 37 | 2.5 | |
| No | 1,494 | 92.4 | 1,47 | 97.5 | |

BR: Bloom Richardson; ALND: axillary lymph node dissection; SLNB: sentinel lymph node biopsy.

aged ≥75 years. This is depicted in Figure 1. This means that patients in the study had an excess risk of death, which can be attributed to breast cancer. We calculated the excess risk of death of patients in the current study as the difference between the observed and expected number of deaths, divided by the total person-years. Among patients aged 65-75 years, 261

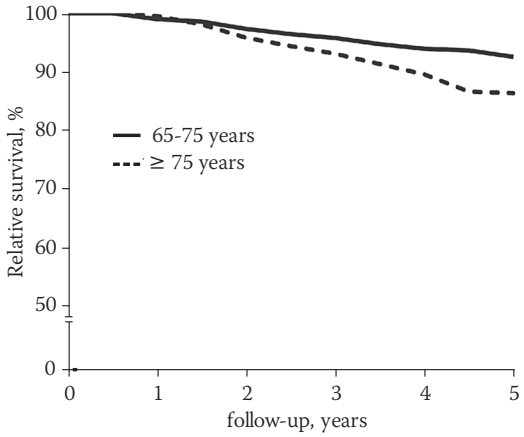



**Figure 1.** Survival of elderly patients with breast cancer as compared to the corresponding general population, by age at diagnosis.

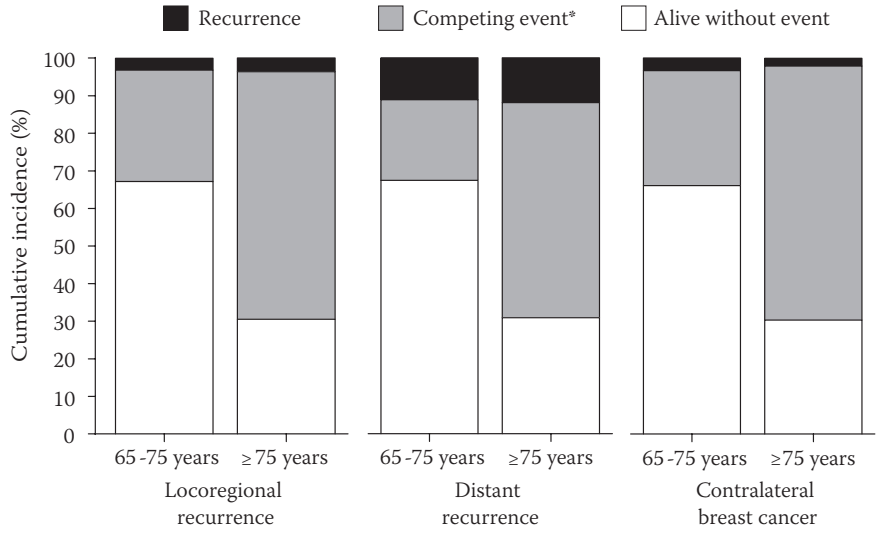
deaths occurred in 7470 person-years; among patients aged ≥75 years, 659 deaths occurred in 5894 person-years. The expected numbers of deaths were 147 and 496, respectively. Hence, the excess risk of death in patients aged 65-75 years was 15.2/1000 person-years, and 27.7/1000 person-years in patients aged ≥75 years. To compare whether the excess risk of death differed between both age groups, we calculated the relative excess risk of death. As shown in Table 2, the relative excess risk of death for patients aged ≥75 years as compared to patients aged 65-75 years was 1.88 (95% CI 1.25-3.83). Multivariable analyses confirmed a higher relative excess risk of death for patients aged ≥75 years (1.72 (95% CI 1.21-2.44)). As patients aged ≥75 years more often presented with a higher stage of disease, additional analyses were stratified by stage (Supplementary table). In patients with early stage breast cancer, again patients aged ≥75 years had a higher relative excess risk of death. Comparable results were observed in patients with advanced stage breast cancer, however these results were not statistically significant.

**Table 2.** Excess risk of death in elderly patients with breast cancer as compared to the corresponding general population, by age at diagnosis.

| | 5-years relative survival % | Excess risk of death / 1000py | Univariate relative excess risk of death (95% CI) | p | Multivariable* relative excess risk of death (95% CI) | p |
|---|---|---|---|---|---|---|
| Age | | | | **0.002** | | **0.003** |
| 65-75 years | 92.6 | 15.2 | 1 (reference) | | 1 (reference) | |
| ≥75 years | 86.4 | 27.7 | 1.88 (1.25-2.83) | | 1.72 1.21-2.44) | |

CI: confidence interval. * Multivariable analyses were adjusted for comorbidity, combined TNM stage, hormone receptor status, histological subtype, histological grade, most extensive breast surgery, most extensive axillary surgery, radiotherapy, endocrine therapy and chemotherapy.

During five years of follow-up, 523 patients developed a secondary endpoint, among which 80 developed a locoregional recurrence; 359 a distant recurrence; and 84 a contralateral breast cancer. Median follow-up time for recurrent disease was 5.9 years (interquartile range 2.9-7.9 years). As shown in Figure 2, for all three endpoints, the cumulative incidence of competing endpoints (death or another type of recurrence) was more than twice as high in patients aged




* Competing events for locoregional recurrence: distant recurrence, contralateral breast cancer, and death due to any cause. Competing events for distant recurrence: locoregional recurrence, contralateral breast cancer, and death due to any cause. Competing events for contralateral breast cancer: locoregional recurrence, distant recurrence, and death due to any cause.

**Figure 2.** Locoregional recurrence, distant recurrence, contralateral breast cancer and competing events, by age at diagnosis.

**Table 3.** Risk of locoregional recurrence, distant recurrence and contralateral breast cancer, by age at diagnosis.

| | 5-years recurrence, n | 5-years competing event, n | Univariate hazard ratio (95% CI) | p | Multivariable* hazard ratio (95% CI) | p |
|---|---|---|---|---|---|---|
| Locoregional recurrence | | | | 0.065 | | 0.293 |
| 65-75 years | 33 | 288 | 1 (reference) | | 1 (reference) | |
| ≥75 years | 47 | 680 | 1.52 (0.97-2.37) | | 1.30 (0.79-2.15) | |
| Distant recurrence | | | | **0.023** | | 0.435 |
| 65-75 years | 179 | 142 | 1 (reference) | | 1 (reference) | |
| ≥75 years | 180 | 547 | 1.30 (1.04-1.65) | | 1.12 (0.84-1.49) | |
| Contralateral breast cancer | | | | 0.061 | | 0.487 |
| 65-75 years | 53 | 268 | 1 (reference) | | 1 (reference) | |
| ≥75 years | 31 | 696 | 0.61 (0.39-0.95) | | 0.80 (0.42-1.51) | |

* Multivariable hazard ratios adjusted for comorbidity, combined TNM stage, hormone receptor status, histological subtype, histological grade, most extensive breast surgery, most extensive axillary surgery, radiotherapy, endocrine therapy and chemotherapy.

≥75 years as compared to those aged 65-75 years. As shown in Table 3, the risk of a distant breast cancer recurrence increased with increasing age in univariate analysis (hazard ratio for patients aged ≥75 years was 1.30 (95% CI 1.04-1.65). However, in multivariable analyses no significant differences were observed. Sensitivity analyses for overall recurrence did not alter the results (data not shown).

# Discussion

The main finding of our study is that the relative survival is lower for breast cancer patients aged ≥75 years as compared to patients aged 65-75 years. Patients aged ≥75 years had a higher excess risk of death. As the excess risk of death can be attributed to breast cancer, these results indicate that patients aged ≥75 years had a higher risk of death from breast cancer as compared to patients aged 65-75 years. We found no age-specific differences in the occurrence of locoregional recurrence, distant recurrence or contralateral breast cancer.

The design of the current study was based on the results of clinical trial data, which demonstrated a higher recurrence risk and worse breast cancer survival with increasing age[6;7;17]. Our main outcome that relative survival is lower among the oldest elderly breast cancer patients is confirmed by a previous study in The Netherlands[2], and by a population-based study in the United States, which showed a decreasing breast cancer specific survival[18]. However, other population-based studies have shown no association between age and breast cancer specific or relative survival[4;19;20] or even a higher breast cancer specific survival among elderly[21;22]. An explanation for the variation in results between our study and other publications could be the discrepancy in choice of endpoints. In the present study, we used relative survival as an approximation of breast cancer specific survival. As mentioned, the relative survival is the ratio of observed overall survival among patients in the study and the expected overall survival in the age-, sex-, and year-matched background file from the general population. Assuming all other factors being similar in the study cohort and the background file, the relative survival approximates breast cancer specific survival. The major advantage of using this endpoint is that there is no need to know the cause of death or cancer specific death data of all patients in the cohort, which is often described to be biased or overestimated in cancer registry data[10;23]. In addition, in population-based studies, relative survival has been shown to be comparable to cancer specific survival derived from death certificates[24].

It is tempting to speculate on the possible explanations of our finding that breast cancer outcome deteriorates with increasing age. First, elderly breast cancer patients may be undertreated. Less extensive treatment may be the result of careful weighing of the benefits and risk of therapy in patients with comorbid disease, but may also result from underestimation of the disease in elderly patients. As was shown, patients aged ≥75 years received less often axillary surgery, radiotherapy after a lumpectomy, and chemotherapy in particular. Overall, the differences in treatment were relatively small. Therefore it is expected that other mechanisms may play a role.

Although patients aged 75 years and older presented more often with more advances stages of disease, stratified analyse confirmed a worse breast cancer outcome in all stages. Additionally, it has been suggested that older patients may respond different to a tumor as well as to a certain therapy as compared to younger patients. Patients who are biologically older may experience more immunosenescence, and may thereby have an impaired immunoresponse to a tumor, which may impair prognosis[25]. Moreover, concomitant medication use and comorbid disease may alter pharmacokinetics of anticancer therapy[26]. Thus, a biologically older or frailer patient may be at higher risk for breast cancer events. Hence, a higher prevalence of biologically older or frailer patients among those aged ≥75 years may attribute to a worse breast cancer outcome.

We expected that the lower relative survival for the oldest elderly would be accompanied by an increase in breast cancer recurrence. However, after adjusting for patient and tumor characteristics, and after taking into account the risk of competing endpoints, we observed no difference in the occurrence of any type of recurrence. Insufficient power due to the shorter follow-up time for recurrences (median 5.9 years) and the limited number of events may have influenced the results. Another possible explanation could be under registration or under diagnosis of recurrent disease in medical files, especially in the frailest patients. From a clinical point of view, it is understandable that in an old patient with a history of breast cancer who presents with back pain, it is not always desired to further investigate the possibility of bone metastases, because either the patient does not wish to receive any therapy or it is not likely that life expectancy will be increased by administering further therapy. However, there is no literature that reports about this issue, and it would be interesting to investigate this prospectively in a future study.

A major strength of this study is the unselected population-based nature and the large number of consecutively diagnosed patients who were included; to our best knowledge, the FOCUS-cohort is the largest population-based cohort comprising elderly breast cancer patients with such detailed information. However, this study also has some limitations when interpreting the results. As mentioned before, due to the retrospective and observational character of the study we cannot exclude the possibility of under registration of recurrent disease. Next to breast cancer specific endpoints, it remains important to evaluate the impact of the disease and therapy on quality of life and daily functioning. Unfortunately, these data were not available in the current study.

To conclude, breast cancer outcome, in terms of relative survival, deteriorates with increasing age among unselected elderly patients from the general population. Of note, this was not accompanied by an increased risk of breast cancer recurrence.

**Supplementary table.** Excess risk of death in elderly patients with breast cancer as compared to the corresponding general population by age at diagnosis, stratified by stage.

| | 5-years relative survival (%) | Excess risk of death / 1000py | Univariate relative excess risk of death (95% CI) | p | Multivariable* relative excess risk of death (95% CI) | p |
|---|---|---|---|---|---|---|
| Early stage | | | | **0.04** | | **0.03** |
| 65-74 years | 94.5 | 11.1 | 1 (reference) | | 1 (reference) | |
| ≥75 years | 89.9 | 19.9 | 1.86 (1.03-3.36) | | 1.80 (1.07-2.99) | |
| Advanced stage | | | | 0.2 | | 0.2 |
| 65-74 years | 70.7 | 68.7 | 1 (reference) | | 1 (reference) | |
| ≥75 years | 60.1 | 96.4 | 1.39 (0.85-2.30) | | 1.42 (0.82-2.44) | |

CI: Confidence interval. * Multivariable analyses were adjusted for comorbidity, combined TNM stage, hormone receptor status, histological subtype, histological grade, most extensive breast surgery, most extensive axillary surgery, radiotherapy, endocrine therapy and chemotherapy.

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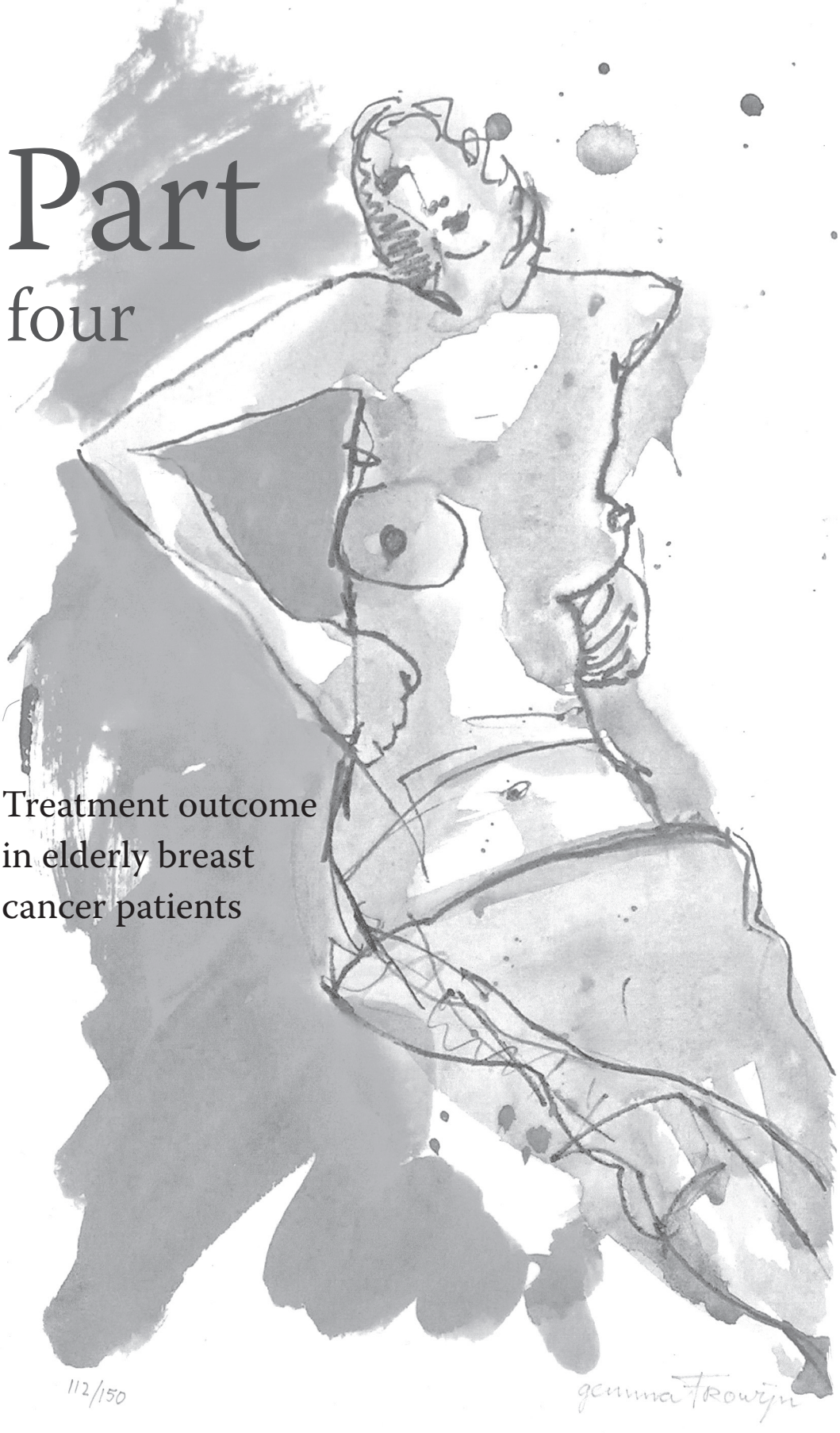
# Part four




## Treatment outcome in elderly breast cancer patients

Chapter 8

# Breast conserving surgery with or without radiotherapy in older patients with early stage breast cancer – a systematic review and meta-analysis

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# Abstract

## Background

In early stage breast cancer, radiotherapy is an integral part of locoregional treatment with breast conserving surgery. However, few older patients are included in the clinical trials upon which these recommendations are based. Therefore, we performed a systematic review and meta-analysis to evaluate outcomes of radiotherapy after breast conserving surgery in older patients.

## Methods

A systematic search of Pubmed and Embase was undertaken. Inclusion was restricted to randomized controlled trials in postmenopausal breast cancer patients. Pooled odds ratios were calculated for locoregional recurrence, distant recurrence and overall survival.

## Results

We included 5 randomized clinical trials comprising 3,190 patients. Overall, 39% of the patients was ≥70 years, and most had hormone receptor positive T1 tumors without nodal involvement. All patients received adjuvant systemic therapy. Patients who received radiotherapy had a lower relative risk of locoregional recurrence (pooled OR 0.36 (95%CI 0.25-0.50)). The 5-years absolute risk was 2.2% (95% CI 1.6-3.1) among patients who received radiotherapy, versus 6.5% (95% CI 5.3-7.9) among patients who did not. The absolute risk difference was 4.3% (95% CI 2.9-5.7), corresponding with a number needed to treat of 24. No differences were observed for distant recurrence or overall survival.

## Conclusion

Although patients who received radiotherapy had a lower relative risk of locoregional recurrence, the absolute risk was low and overall survival was not affected. We propose that the debate should not only focus on the *relative* risk but also on the *absolute* benefit of radiotherapy and the number needed to treat. Both treatment options may be reasonable in clinical practice.

# Introduction

In early stage breast cancer, adjuvant breast irradiation is an integral part of locoregional treatment with breast conserving surgery in order to obtain locoregional control[1]. However, with increasing age, patients are less often included in the clinical trials upon which these recommendations are based. Despite comprising more than 40% of new breast cancer patients, older patients are underrepresented in clinical trials[2]. Only 1-2% is estimated to participate in clinical trials, and only those who are considered fit enough are included[3].

Next to an underrepresentation in clinical trials, different factors may play a role in the evaluation of radiotherapy after breast conserving surgery in older as compared to younger patients. First, older patients suffer from a higher risk of competing mortality[4] and have a lower remaining life expectancy. Consequently, the absolute benefit of anticancer therapy may be smaller, while long term adverse events may be less relevant. Second, concurrent disease and medication use may directly affect tolerability of treatment and increase toxicity of systemic treatment[5;6]. Last, relevant treatment outcomes may vary with age[7]. Therefore, results obtained in a younger trial population may not necessarily be applicable to or appropriate for older breast cancer patients.

The outcome of radiotherapy after breast conserving surgery specifically in older patients has been studied by others. However, conclusions were inconsistent[8-15]. Meanwhile, observational studies show that administration of radiotherapy after breast conserving surgery decreases with increasing age[16;17]. Also among patients included in a randomized clinical trial on endocrine therapy, administration of radiotherapy after breast conserving therapy decreased with age[4]. It remains unclear whether this omission of radiotherapy is appropriate or whether radiotherapy should be an integral part of breast conserving surgery in older patients with early stage breast cancer.

Therefore, we performed a systematic review and meta-analysis to assess the efficacy of radiotherapy after breast conserving surgery in older patients with early stage breast cancer.

# Methods

The focus of this systematic review and meta-analysis was to specifically address the outcomes of breast conserving surgery with or without radiotherapy in older patients with early stage breast cancer. A systematic search of Pubmed and Embase was undertaken, using several different search strategies and keywords comprising early stage breast cancer, breast conserving surgery, and radiotherapy (Figure 1), without restriction of publication dates, until June 1st 2013. A priori inclusion criteria were the following; studies had to be a primary research article specifically addressing outcomes of breast conserving surgery with and without radiotherapy in early stage breast cancer. At least a subgroup analysis comprising older patients was to be

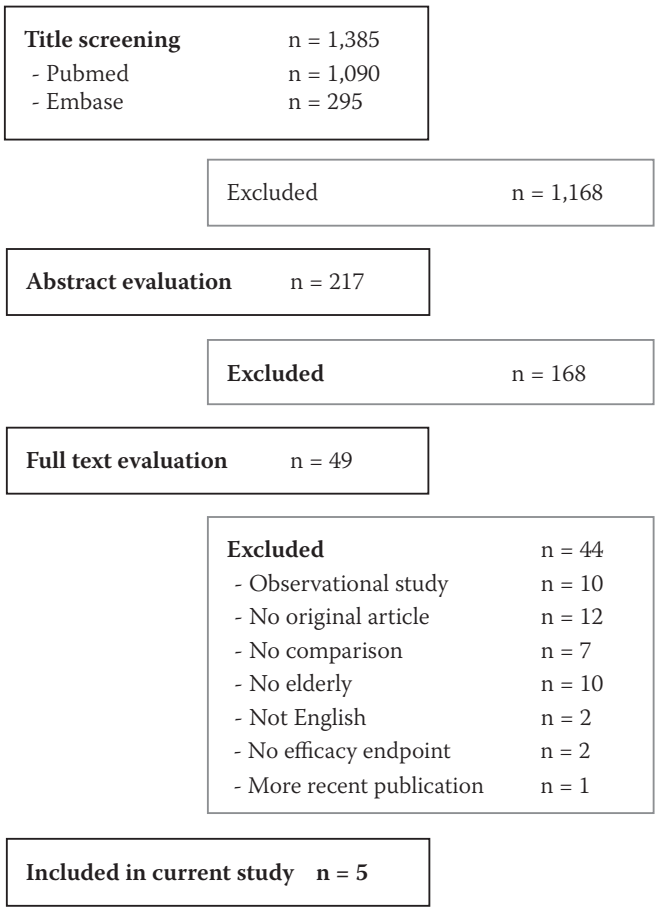



**Figure 1.** Search strategy and study selection.

reported. To increase the number of potentially interesting papers, older patients were defined as postmenopausal patients.

Studies were excluded if they were a review or meta-analysis on the subject. Published abstracts without complete articles were excluded because of the inability to obtain detailed information. All citations were independently reviewed by two of the authors (WW and EB) and categorized as relevant, potentially relevant, or not relevant. Citations categorized as relevant or potentially relevant by one of the authors, were selected for abstract review. After review of the abstract, potentially relevant and relevant abstracts were selected for full text evaluation. Upon full text evaluation, it was decided not to include any of the observational studies, as outcomes in observational data are prone to confounding by indication[18]. Therefore, inclusion in the current study was further restricted to randomized controlled trials.

For each included study, we recorded study characteristics (aim; randomization; eligibility criteria; number of patients), and main outcomes and conclusions as reported by the authors (primary and secondary outcomes; conclusions; comments). Numbers of events were extracted to conduct a meta-analysis of the different outcomes under study. If the numbers of events were not available, then survival graphs or survival rates were used to estimate the numbers of events. All data were obtained from the intention-to-treat analyses.

STATA SE 12 was used to pool the different outcome estimates. Outcomes were analysed as odds ratios. The $I^2$ statistic was used to test for heterogeneity across studies[19]. An $I^2$ value greater than 50% was considered to represent substantial heterogeneity. Publication bias was tested by using funnel plots; an inverted symmetrical funnel plot assumes the absence of publication bias[20].

Next to relative outcome measures, pooled absolute risks were calculated. The pooled absolute risk per study arm was calculated as Σ(number of events in study arm) / Σ(N study arm), including a 95% confidence interval (CI). The absolute risk difference was calculated as the pooled estimate of the absolute risk difference per study, including a 95% CI. Next, number needed to treat was calculated as 1 divided by the absolute risk difference.

# Results

## Results of search strategy

Overall, 1,385 unique citations were identified, of which 217 citations were selected for abstract review, and of those, full text evaluation was undertaken for 49 publications. Overall, 10 publications were excluded because they were observational studies; 12 publications were excluded because they were no original research article; 7 were excluded because they did not report on a direct comparison between breast conserving surgery versus breast conserving surgery plus radiotherapy; 10 were excluded because no (subgroup) analysis of older patients was included; 2 were excluded because they were not in English; 2 were excluded because no primary efficacy endpoint was included; and 1 was excluded because a more recent publication of the same study was available[21]. This resulted in 5 studies which were included the current systematic review and meta-analysis[11-13;22;23].

## Description of studies

Characteristics of the included studies are shown in Table 1. The total number of patients included in this systematic review and meta-analysis is 3,190. The studies included patients between 1981 and 2005 and were published between 2004 and 2013. Inclusion in all studies was restricted to patients with relatively favourable tumor characteristics; the majority of patients had T1 tumors, without nodal involvement, and with positive hormone receptor status. All patients received adjuvant systemic therapy; in the majority of the studies, patients

**Table 1.** Study characteristics of the included randomized clinical trials.

| Study | N | Aim | Randomization | Patient criteria | Tumor criteria | Exclusion criteria |
|---|---|---|---|---|---|---|
| Hughes (2013) | Total: 636<br>RT: 317<br>No RT: 319 | To evaluate whether elderly women with ER-positive EBC who had BCS, can be safely treated with tamoxifen instead of RT plus tamoxifen, | Tamoxifen 20mg + breast irradiation (45Gy) + boost (14Gy) versus Tamoxifen 20mg for 5 years. | ≥70 years | T1N0M0, positive/ unknown ER status** | Previous malignancy <5 years (except in situ cervical cancer or nonmelanoma skin cancer); no radical breast conserving surgery. |
| Tinterri (2009) | Total: 749<br>RT: 373<br>No RT: 376 | To assess the role of radical breast RT in postmenopausal women with EBC undergoing BCS. | Breast conserving surgery + breast irradiation (50Gy) + boost (10Gy) versus breast conserving surgery. Adjuvant treatment was based on nodal status and biological tumor parameters. | 50-75 years Postmenopausal | T12N01M0, <2.5cm | Multifocal breast cancer; multicentric breast cancer; extensive intraductal or vascular invasion like component; >3 axillary lymph nodes involved; previous malignancy. |
| Potter (2007) | Total 831<br>RT: 414<br>No RT: 417 | To assess the role of whole breast RT in women with a favorable subgroup of EBC. | Breast irradiation (mean 51Gy) + boost (mean 10Gy) + Tamoxifen 20mg for 2 years followed by Anastrozol 1mg for 3 years versus Tamoxifen 20mg for 2 years followed by Anastrozol 1mg for 3 years | Postmenopausal | T12N0M0, <3 cm, BRI/II IDAC, BRx ILAC, HR-status positive | Previous chemotherapy, radiotherapy or endocrine therapy; no radical breast conserving surgery. |
| Ford (2006) | Total: 400 (205*)<br>RT: 208 (104*)<br>No RT: 192 (101*) | To evaluate the need for RT following BCS in women with EBC. | Breast irradiation (max. 54Gy) ± regional irradiation (50Gy) + boost (10Gy) versus no irradiation. All patients received adjuvant therapy based on hormone receptor-status. | <70 years | T12N01M0 | Multifocal breast cancer; significant cardiac or renal impairment; previous malignancy. |
| Fyles (2004) | Total: 769<br>RT: 386<br>No RT: 383 | To define the role of adjuvant RT in women ≥50 years with EBC who had BCS. | Breast irradiation (40Gy) + boost (12.5Gy) + Tamoxifen 20mg for 5 years versus Tamoxifen 20mg for 5 years. | ≥50 years 734/769 (95%) postmenopausal | pT12N0M0 for patients <65 years; pT12c/ pN0M0 for patients ≥65 years *** | Bilateral breast cancer; multifocal breast cancer; previous malignancy <5 years (except in situ cervical cancer or nonmelanoma skin cancer); previous breast cancer <10 years; previous tamoxifen or chemotherapy; concurrent illness that would preclude use of tamoxifen. |

EBC: early breast cancer; BCS: breast conserving surgery; RT: radiotherapy; BR: Histological grade according to Bloom Richardson; IDAC: intraductal adenocarcinoma; ILAC: intralobular adenocarcinoma; HR: hormone receptor; ER: estrogen receptor. * Number of postmenopausal patients. ** Eligibility criteria were amended in 1996 to enhance inclusion: original criteria were T12N0M0, irrespective of estrogen receptor status. *** No criteria regarding hormone receptor-status.

received adjuvant tamoxifen; in one study patients received either tamoxifen or chemotherapy depending on hormone receptor status.

As shown in Table 2, most studies restricted inclusion to postmenopausal patients. Although Ford et al included patients under 70 years of age (range 25-69 years), subgroup analyses by menopausal status were performed and hence only the results of postmenopausal patients were included in the meta-analysis[11]. Fyles et al included patients aged 50 years or older with a median age of 68 years, and reported that more than 95% of the participants were postmenopausal, 3% were premenopausal and 2% had an unknown menopausal status[12]. Therefore, we decided to include all these patients in the meta-analysis. Although the overall median age of all studies could not be calculated directly, one can derive from the data that the median age was over 65 years of age. Moreover, at least 1,254/3,190 (39%) patients were 70 years or older.

The primary outcome of most studies was locoregional recurrence, which was defined as a recurrence or a secondary breast tumor in the ipsilateral breast, or a recurrence in ipsilateral axillary lymph nodes or infra- or supraclavicular lymph nodes[11;13;22;23] (Table 3). Frequent secondary outcomes were distant recurrence or distant disease free survival, and overall survival.

## Meta-analysis

The odds ratios for locoregional recurrence, distant recurrence and overall survival are shown in Figure 2. All studies observed a lower risk of locoregional recurrence for patients who were randomized to radiotherapy in addition to breast conserving surgery. The pooled analyses confirmed a lower relative risk of locoregional recurrence in patients who received radiotherapy; OR 0.36 (95% CI 0.25-0.50). There was no substantial heterogeneity across the studies ($I^2$ was 43%, p=0.130).

Since distant disease free survival was not uniformly described in all studies, we specifically extracted the number of distant recurrences in order to assess the pooled risk of a distant breast cancer recurrence. The relative risk of a distant recurrence was not affected by radiotherapy; the pooled OR was 0.96 (95% CI 0.68-1.36). Overall survival was also similar for both treatment modalities; the pooled OR for overall survival was 0.92 (95% CI 0.74-1.15). Again, there was no substantial heterogeneity among the studies for both outcomes.

Two sensitivity analyses were performed. First, the meta-analyses were repeated without the study results of Fyles et al[12], since a minority of the patients in this study may not have been postmenopausal. The results were unchanged (data not shown). Second, the analyses were repeated without the study results of Ford et al[11] and Hughes et al[13], since the median follow-up of these studies was twice as long, as compared to 4.5-5.6 years in the other studies. Instead we included the prior publication by Hughes et al, comprising the 5-years results[21]. Again,

the results were unchanged (data not shown). The associated funnel plots did not suggest significant publication bias (Supplementary figure 1).

**Table 2.** Age and tumor characteristics of patients in the included randomized clinical trials.

| Study | Age | Tumor characteristics |
|---|---|---|
| Hughes (2013) | All ≥70 years; 351/636 (55%) ≥75 years | 622/636 (98%) T1, 636/636 (100%) N0, 618/636 (97%) ER+ |
| Tinterri (2009) | All postmenopausal; range 50-75 years; 361/749 (48%) ≥65 years | 649/749 (87%) T1, 619/749 (83%) N0, 658/749 (88%) ER+ |
| Potter (2007) | All postmenopausal; range 46-80 years; median age 66 years; 587/831 (71%) ≥60 years; 293/831 (35%) >70 years | 753/831 (91%) T1, 831/831 (100%) N0, 831/831 (100%) HR+ |
| Ford (2006) | All postmenopausal; range 44-69 years; median age 59 years | 57/205 (28%) T1, 155/205 (76%) N0, 278/400 (70%) ER+* |
| Fyles (2004) | 734/769 (95%) postmenopausal; median age 68 years; 586/769 (76%) ≥60 years; 325/769 (42%) ≥70 years | 639/769 (83%) T1, 639/639 (100% N0, 621/769 (81%) HR+** |

ER+: estrogen receptor positive; HR+: hormone receptor positive. * Calculated for the whole population of pre- and postmenopausal patients; ** 127/769 (17%) unknown hormone receptor status, 46/769 (6%) negative hormone receptor status.

## Absolute risk

Additionally, we calculated the pooled absolute risk of locoregional recurrence, distant recurrence and all cause death for patients in both study arms. Since absolute risks are dependent on the duration of follow-up, the study by Ford et al[11] and Hughes et al[13] were not included in the calculation; the median follow-up of these studies was more than twice as much as compared to the other studies. For the study by Hughes et al, we used the prior publication in which the 5 years results were presented[21]. After a median follow-up of approximately 5 years, the absolute risk of a locoregional recurrence among those who received radiotherapy was 2.2% (33/1,490, 95% CI 1.6-3.1), versus 6.5% (97/1,495, 95% CI 5.3-7.9) among patients who did not receive radiotherapy. The absolute risk difference was 4.3% (95% CI 2.9-5.7), in favour of those who received radiotherapy in addition to breast conserving surgery, corresponding with a number needed to treat of 24 to prevent one locoregional recurrence in five years.

The 5-years absolute risk of a distant recurrence was 2.7% (40/1,490, 95% CI 1.9-3.5) in patients who received radiotherapy, versus 2.3% (35/1,495, 95% CI 1.6-3.1) in patients who did not receive radiotherapy. For all cause death, the 5-years absolute risks were 7.7% in both study arms (115/1,490, 95% CI 6.4-9.1; 115/1,495, 95% CI 6.3-9.0).

**Table 3.** Main outcomes and conclusions as reported by the authors of the included randomized clinical trials.

| Study | FU* | Primary outcomes | Secondary outcomes | Conclusions authors | Comment authors |
|---|---|---|---|---|---|
| Hughes (2013) | 10y | Locoregional recurrence (LR): supra- or infraclavicular, ipsilateral breast or lymph nodes); mastectomy for recurrence (MfR); breast cancer specific survival (DSS); distant recurrence (DR); overall survival (OS). | Cosmetic results; adverse events after up to 4 years | LR was higher in control arm. No differences were observed for MfR, DSS, DR or OS. Cosmetic results and adverse events were lower in the control arm[21]. | Irradiation adds no significant benefit in terms of survival, time to distant metastasis, or ultimate breast preservation. Omission of radiotherapy is a reasonable choice in this selection of patients. |
| Tinterri (2009) | 5y | In-breast recurrence (IBR: local recurrence, second primary in ipsilateral breast). | Distant disease free survival (DDFS; contralateral breast cancer, distant recurrence, second other primary cancer, death in the absence of cancer); overall survival (OS). | IBR was higher in the control arm, although not statistically significant. No differences were observed for DDFS and OS. | Breast irradiation after BCS can be avoided without exposing these patients to an increased risk of distant disease recurrence. |
| Potter (2007) | 4.5y | Local relapse free survival (LRFS). | Disease free survival** (DFS; local relapse or distant metastasis); overall survival (OS); contralateral breast cancer (CBC); distant recurrence (DR). | LRFS and DFS were lower in control arm. No differences were observed for OS and DR. | For patients with favorable early stage breast cancer as addressed in the study, radiotherapy remains the major integral part of adjuvant treatment after BCS. |
| Ford (2006) | 13.7y | Locoregional recurrence (LR); Distant recurrence (DR; not otherwise specified). | Overall survival (OS); disease free survival (DFS; not otherwise specified). | LR was higher in control arm. No differences were observed for DR, DFS or OS. | The results support a role for breast irradiation in patients who have had BCS for breast cancer, and it should be considered in every case. |
| Fyles (2004) | 5.6y | Disease free survival (DFS; locoregional or distant recurrence, or death). | Locoregional recurrence (LR; breast or axilla); overall survival (OS) | DFS was lower and LR was higher in control arm. No differences were observed for OS. | Radiotherapy significantly reduces the risk of breast and axillary recurrence after BCS in women with small, node negative, HR–positive breast cancer. |

FU: follow-up. * Median. ** The authors' definition of DFS corresponds with overall recurrence free period rather than disease free survival, since death is not included as an event.

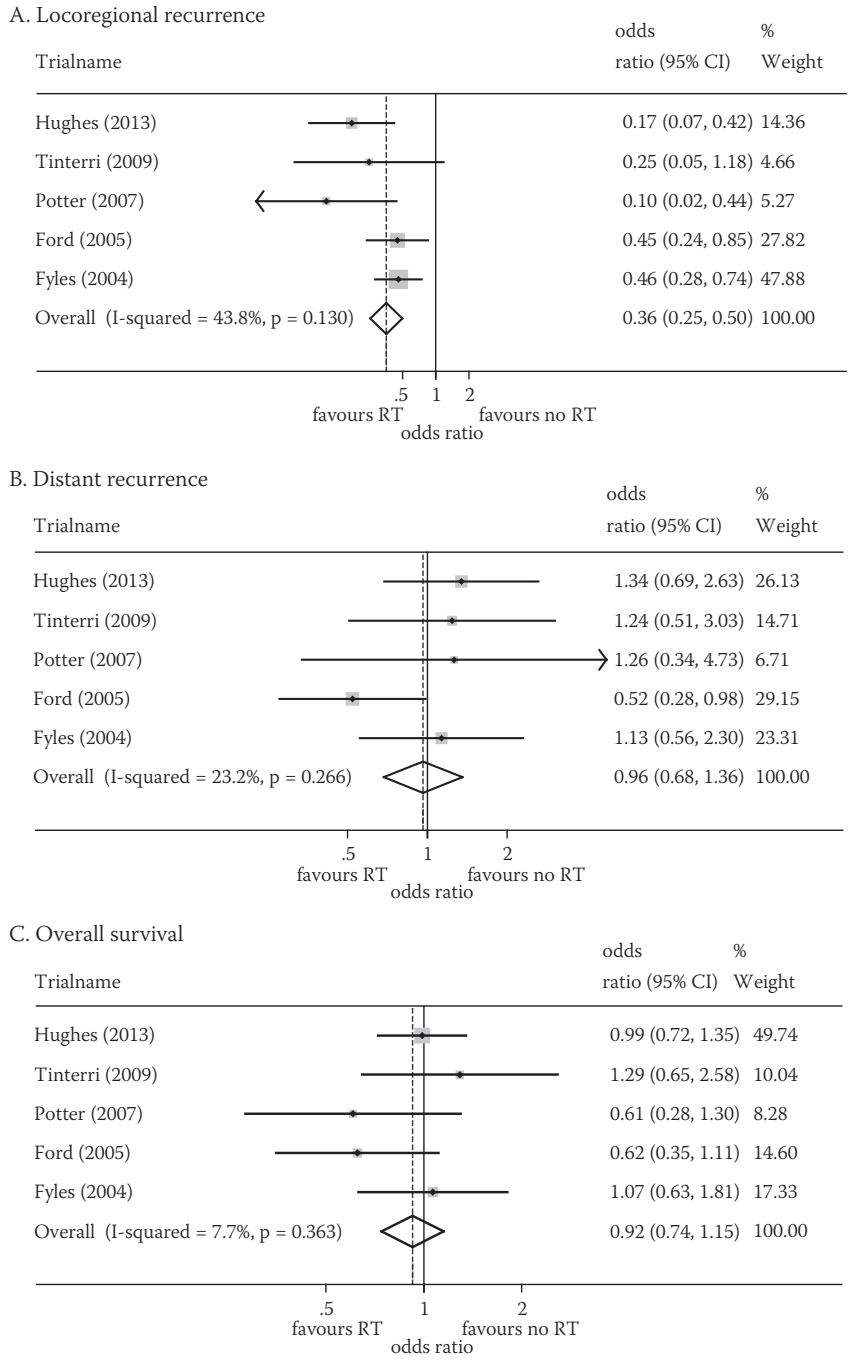



**Figure 2.** Odds ratios for locoregional recurrence, distant recurrence and overall survival.

# Discussion

## Summary of results

The current systematic review and meta-analysis clearly shows a decreased risk of locoregional recurrence for postmenopausal patients with early stage breast cancer who received radiotherapy after breast conserving surgery. The absolute risk difference for a locoregional recurrence was 4.3% after five years, corresponding with a number needed to treat of 24. No differences were observed with regards to the risks of a distant recurrence, or overall survival.

The effect of radiotherapy after breast conserving surgery has been evaluated by others[1;24]. However, few specifically studied older patients, or addressed age related considerations as competing mortality and remaining life expectancy. We decided not to include observational studies, as treatment outcomes in observational studies are confounded by indication[18]; frailty, age, tumour characteristics and presence of comorbidity all affect treatment decisions as well as outcome. As expected, most observational studies indeed observed a higher overall, disease specific or other cause mortality in patients who received breast conserving surgery as compared to patients receiving radiotherapy in addition to breast conserving surgery[8;9;25;26], although one study did not observe differences in overall survival between both treatment modalities[10]. With respect to locoregional recurrence, most observational studies[14;15;27;28], but not al[10] observed a higher risk for patients who received breast conserving surgery without radiotherapy. Recently, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) performed an age specific subgroup analysis of 7,287 node negative patients who received either breast conserving surgery plus or minus radiotherapy[1]. The relative risk reduction in 10-years locoregional recurrence by radiotherapy remained similar over age (overall relative risk 0.46 (95% CI 0.41-0.51)). The current study confirms a clear statistically significant benefit of radiotherapy in addition to breast conserving surgery in terms of prevention of a locoregional recurrence, even though the included patients were considered to have a low absolute risk of recurrence; the median age was over 65 years, and the majority of patients had T1 tumors without nodal involvement, with positive hormone receptor status.

To enhance the number of eligible studies, inclusion in the current study was permitted for all trials including postmenopausal patients. We are well aware of the discongruency between 'postmenopausal' and 'older', and the wide variation in age and phenotype among postmenopausal women. However, the median age of all patients in this study was over 65 years and 39% of the patients was 70 years or older. Moreover, sensitivity analyses were performed to exclude potential confounding of one study in which a minority of the patients may not have been postmenopausal. In addition, tumor and treatment characteristics were comparable among the included studies, and all patients received adjuvant systemic therapy. Nevertheless, the variation in phenotype of the included patients in the current study limits explicit recommendations for advocating omission or administration of radiotherapy. Rather than an attempt to indicate specific subgroups of patients, for clinical guidance we propose not

only to focus on relative risks but also on the absolute benefit of postoperative radiotherapy and the number needed to treat.

A low absolute risk results in a higher number needed to treat to prevent one recurrence. The number needed to treat in the current study was 24. This is expected to be higher in a non-trial population; Smith and colleagues evaluated the number of patients needed to be irradiated in order to prevent one local recurrence[15]. Patients of advanced age or those with moderate to severe comorbidity were less likely to benefit from radiotherapy, with an adjusted number needed to treat up to 125. In addition, the EBCTCG meta-analysis showed that the absolute risk reduction of radiotherapy decreased significantly with increasing age, from 24.6 (95% CI 13.2-36.0) to 8.9 (95% CI 4.0-13.8) in the oldest patients, due to a lower absolute recurrence rate[1]. This age specific decrease was also observed in other studies[12;22]. The more recently conducted randomized trials which were included in the current study seemed to observe an even lower locoregional recurrence rate[12;13;22;23]. This may be explained by the fact that studies included in the EBCTCG meta-analysis were mostly conducted in the 1970s and 1980s. These days, selection of patients may have been less precise, and hormonal status was not included in the selection criteria. Improvements in surgical treatment and the increased use and efficacy of currently available systemic treatment may have further tempered recurrence rates[29] and thereby limit the attributive effect of radiotherapy. As mentioned, all patients included in the current study received adjuvant systemic therapy. To summarize, the absolute risk of a locoregional recurrence decreases with increasing age and decreasing fitness. Moreover, the absolute risk has declined in more recent years.

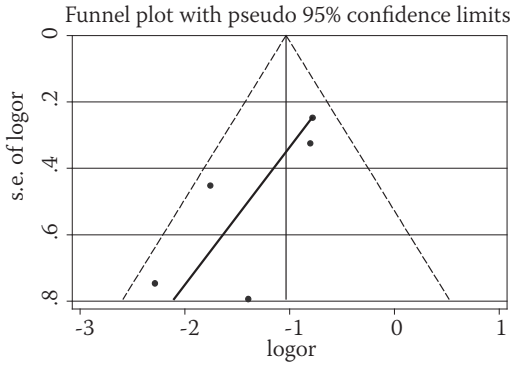
As mentioned, a low absolute risk results in a higher number needed to treat. To decrease the number needed to treat and to personalize treatment, others have tried to identify subgroups of patients in which radiotherapy could be safely omitted, based on the risk of a locoregional recurrence. The American College of Radiotherapy Appropriateness Criteria state that for women older than 70 years, with hormone receptor positive breast cancer less than two centimetre, who receive endocrine therapy, omission of radiotherapy may be reasonable[30]. A comparable statement was included in the most recent National Comprehensive Cancer Network treatment guidelines on senior adult oncology[31]. Although in the recently updated recommendations of the International Society of Geriatric Oncology (SIOG) it is stated that after breast conserving surgery, whole breast irradiation with a boost to the tumor bed should be considered in all older patients, room is left to balance pro and cons in individual cases[32].

In the debate whether or not to treat older breast cancer patients with radiotherapy in addition to breast conserving surgery, and in the identification of subgroups of patients in whom radiotherapy could be safely omitted, which outcome should be leading? The clinical significance of the observed relative risks should be considered critically: as mentioned, the absolute risk of a locoregional recurrence was low, and thereby the absolute risk reduction is rather small. Moreover, the risk of a distant recurrence and overall survival were not

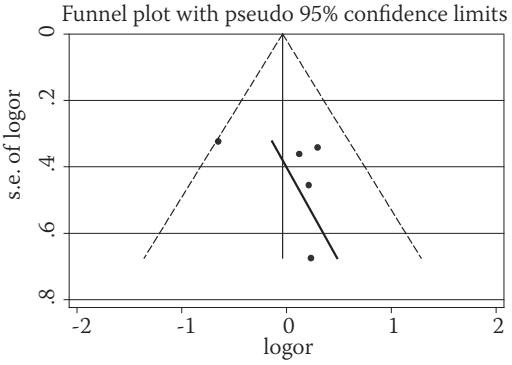
affected by radiotherapy. On the other hand, it was previously shown that older patients were less willing to exchange a prolonged survival for current quality of life[7]. Administration of radiotherapy requires frequent hospital visits, which may be impeded by decreased mobility in old age. Moreover, inferior cosmetic results and adverse events[21] may affect quality of life. Of note, development and treatment of a locoregional recurrence may also impact quality of life.

We propose that the debate should not only focus on the *relative* risk of a locoregional recurrence and on the identification of subgroups based on the relative risk of a locoregional recurrence, but instead should also be focused on the absolute benefit of radiotherapy and the number needed to treat. Both treatment options may be reasonable in clinical practice. The absolute recurrence risk should be discussed with respect to tumor characteristics, other treatment and estimated remaining life expectancy. Recently, a nomogram was developed to predict the absolute risk of mastectomy for a locoregional recurrence in older breast cancer patients in case of omission of adjuvant radiotherapy. These kind of decision tools may further aid in shared decision making when evaluating adjuvant treatment options[33]. Moreover, treatment options and quality of life in case of locoregional recurrence should be considered.

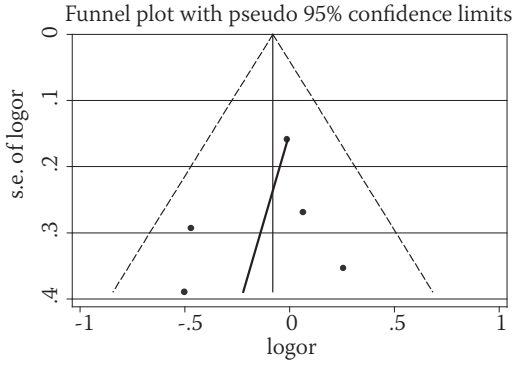
A. Locoregional recurrence




B. Distant recurrence




C. Overall survival




**Supplementary figure 1.** Funnel plots for evaluation of publication bias.

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Chapter 9

# Age specific nonpersistence of endocrine therapy in postmenopausal patients with hormone receptor positive breast cancer

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# Abstract

## Background

Early discontinuation of adjuvant endocrine therapy may affect outcome of treatment in breast cancer patients. Aim of this study was to assess age specific nonpersistence and age specific survival based on persistence status.

## Methods

Patients enrolled in the Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial were included. Nonpersistence was defined as discontinuing assigned endocrine treatment within one year of follow-up because of adverse events, intercurrent illness, patient refusal, or other reasons. Endpoints were breast cancer specific and overall survival. Analyses were stratified by age at diagnosis (<65, 65-75, ≥75 years).

## Results

Overall, 3,142 postmenopausal breast cancer patients were included; 1,682 were <65 years, 951 were 65-75 years and 509 were ≥75 years. Increasing age was associated with a higher proportion of nonpersistence within one year of follow-up (7.0%; 7.5%; 13.5% respectively, p<0.001). In patients aged <65 years, nonpersistent patients had a decreased breast cancer specific survival (multivariable HR 2.76 (95% CI 1.55-4.90), p=0.001) and overall survival (multivariable HR 2.83 (95% CI 1.65-4.85), p<0.001). In patients aged 65-75 years and in patients aged ≥75 years, survival of persistent and nonpersistent patients was similar.

## Conclusion

Nonpersistence within one year of follow-up was associated with lower breast cancer specific and overall survival in patients aged <65 years, but was not associated with survival in patients aged 65-75 years and in patients aged ≥75 years. These results suggest that extrapolation of outcomes from a young to an elderly breast cancer population may be insufficient and urge age specific breast cancer studies.

# Introduction

Breast cancer is the most frequently diagnosed malignancy in females[1]. The role of adjuvant endocrine therapy in middle aged hormone receptor positive breast cancer patients is well established; five years of endocrine treatment with tamoxifen results in an 11.8% absolute recurrence reduction and 9.2% reduction in breast cancer mortality after 15 years of follow-up[2].

Observational and non-observational studies, however, show a substantial proportion of nonpersistence or discontinuation during five years of endocrine therapy. A recent meta-analysis evaluated persistence with tamoxifen or an aromatase inhibitor in clinical trials and reported that overall, 23-28% of patients followed for at least 4 years, discontinued endocrine therapy earlier than recommended[3]. Observational studies show a comparable or even higher nonpersistence percentage[4-7] up to 49% nonpersistence after five years of follow-up[7].

In a recent review, Ruddy et al stated that nonpersistence has been associated with an increased consumption of health care resources, including more physician visits, higher hospitalization rates and longer stays[8]. Moreover, nonpersistence may impede efficacy of endocrine therapy. To date, however, little data are published on the effects of nonpersistence in oncology[8].

Especially in the elderly breast cancer population, evidence is scarce. Despite comprising a large proportion of all breast cancer patients, elderly breast cancer patients remain underrepresented in clinical trials[9]; an estimated 1-2% of the elderly participates in clinical trials[10]. Unlike many breast cancer trials, the Tamoxifen, Exemestane, Adjuvant, Multinational (TEAM) trial[11] had no upper age limitation, thereby providing a unique opportunity to focus on elderly breast cancer patients. The aim of this study was to assess age specific nonpersistence within one year of follow-up. Moreover, we evaluated age specific outcome by nonpersistence status at one year of follow-up.

# Methods

## Design TEAM trial

The TEAM trial is a randomized, adjuvant, phase 3, multinational, open label study conducted in postmenopausal women with estrogen and/or progesterone receptor positive breast cancer. 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 2–2.5 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 (N=9,766)[11]. Extensive eligibility criteria have been published in earlier reports[11;12]. 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.

## Design current study

Figure 1 shows the flow chart of the current study. Inclusion was restricted to patients from The Netherlands (n=2,753) and Belgium (n=414) because of available data on comorbidity. Patients who never started study medication and patients with missing data regarding duration of randomized therapy were excluded from analyses (n=25), which resulted in a study population of 3,142 subjects.

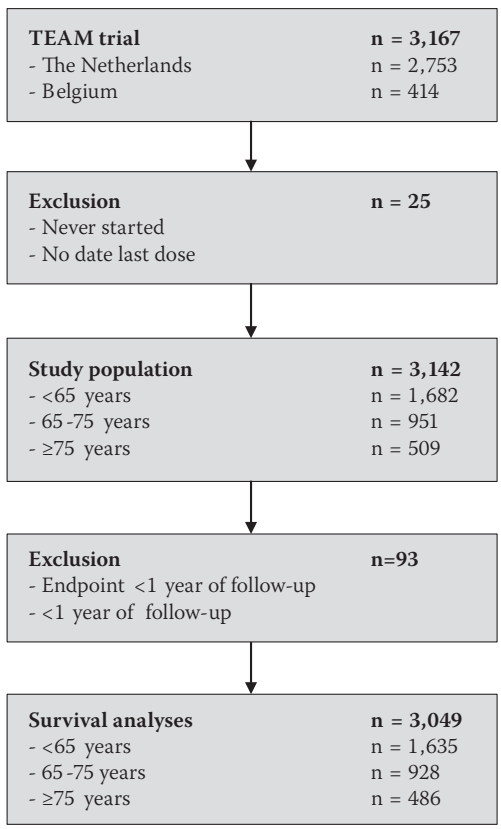


**Figure 1.** Flow chart.

## Persistence

Patients were categorized as persistent or nonpersistent, depending on whether they continued allocated treatment for at least one year. Nonpersistence was defined as discontinuation of allocated endocrine therapy within one year of follow-up because of adverse events, intercurrent illness, patient refusal not otherwise specified, or other reasons. Persistent patients continued allocated endocrine therapy for at least one year. Patients who died or developed a relapse within one year of follow-up while on study medication were considered to be persistent. Persistence

status was evaluated at each follow-up visit. Patients were assessed every three months during the first year of follow-up and at least once-yearly thereafter. At follow-up visits, patients were asked whether they (dis)continued randomized therapy. In case of nonpersistence, date and reason of nonpersistence were recorded by the treating physician. By calculating persistence in the first year, persistence could be used as a fixed covariate in survival analysis following the first year of follow-up (landmark method)[13]. Alternative endocrine therapy in case of nonpersistence was defined as none, cross-over, or other therapy.

Patients were categorized in three age groups (<65 years, 65-75 years, ≥75 years) according to recommendations at the Annual Meeting of the International Society of Geriatric Oncology (SIOG) in 2009[14]. Endpoints were breast cancer specific survival and overall survival. Breast cancer specific survival was defined as time from randomization to death due to breast cancer, whereas overall survival was defined as time from randomization to death from any cause.

## Statistical analysis

Statistical analyses were performed using SPSS 17.0 (SPSS, Chicago, IL) and R statistical package (R Development Core Team, 2008). To compare proportional differences among age categories, the Pearson chi-square test was used. Binary logistic regression analysis was used to assess predictive factors for nonpersistence within one year. Kaplan-Meier curves were plotted and a Cox proportional hazard model was used to assess survival differences with respect to persistence status at one year of follow-up. Persistence was treated according to the landmark method, using one year of follow-up as a landmark[13]. Subjects who reached an endpoint within the first year of follow-up and subjects on study medication who had less than one year of follow-up could not be taken into account and were excluded from survival analyses (n=93) (Figure 1). In line with others who investigated breast cancer outcome by adherence by means of a landmark analysis[15], a cutoff of one year was chosen because of a considerable proportion of nonpersistence but occurrence of few events within one year of follow-up. Moreover, we aimed to exclude bias due to nonpersistence because of switch issues in the sequential arm. Covariates were included in the multivariable model if they were of clinical significance; multivariable analyses included histological grade according to Bloom Richardson (G1; G2; G3,4), estrogen receptor status (positive; negative), progesterone receptor status (positive; negative), T stage (T1; T2; T3,4), N status (negative; positive), presence of cardiac, central nervous system, endocrine, gastro-intestinal, genitourinary and musculoskeletal comorbidity (no; yes), most extensive surgery (wide local excision; mastectomy), axillary surgery (yes; no), radiotherapy (yes; no), adjuvant chemotherapy (yes; no) and endocrine therapy (tamoxifen followed by exemestane; exemestane). Because of colinearity, influence of alternative treatment could be assessed in nonpersistent patients only. To assess whether the association between nonpersistence within one year of follow-up and survival was different among age categories, we tested for interaction between age and persistence status at one year of follow-up. To assess sensitivity of the landmark, alternative cutoff points were analyzed (0.5 and 1.5 years

respectively). All statistical tests were two-sided. A p value less than 0.05 was considered to be statistically significant.

# Results

Overall, 3,142 patients were included, of which 1,682 were <65 years (54%, median age 58.4 years), 951 were 65-75 years (30%, median age 69.7 years) and 509 were ≥75 years (16%, median age 79.3 years). Median follow-up from randomization was 5.0, 5.0 and 4.8 years respectively. Baseline characteristics by age at diagnosis are shown in Table 1. Increasing age was associated with a different histological grade (p=0.004) and larger tumors (p<0.001), nodal status however was similar among age categories. The presence of one or more cardiac, central nervous system, endocrine, gastro-intestinal, genitourinary and musculoskeletal comorbidity increased with age (all p values <0.001). In addition, the proportion of mastectomy increased significantly with age, whereas administration of radiotherapy and chemotherapy significantly decreased (all p values <0.001).

Overall, 256 subjects (8.1%) discontinued allocated endocrine therapy within one year of follow-up; 116 (7.4%) in the exemestane arm and 140 (8.9%) in the sequential arm (p=0.118). Nonpersistence within one year of follow-up increased with age (<65 years 7.0%, 65-75 years 7.5%, ≥75 years 13.2%; p<0.001). As shown in Table 2, reasons for nonpersistence within one year of follow-up did not differ among age categories (p=0.561). In all age categories, presence of adverse events was the most frequently reported reason for nonpersistence (85%; 83%; 89% respectively).

To gain insight in underlying mechanisms, we assessed predictive factors for nonpersistence within one year of follow-up in all age categories (Supplementary table 1a, 1b, 1c). In patients aged <65 years, presence of central nervous system, gastro-intestinal and genitourinary comorbidity, a mastectomy as most extensive surgery, and omission of radiotherapy were associated with nonpersistence within one year of follow-up. Multivariable analysis showed that gastro-intestinal comorbidity and omission of radiotherapy were independent predictive factors for nonpersistence within one year of follow-up. In patients aged 65-75 years, no predictive factors for nonpersistence could be identified. In patients aged ≥75 years, larger tumor size, a wide local excision as most extensive surgical treatment, and omission of radiotherapy were independent predictive factors for nonpersistence within one year of follow-up. In case of nonpersistence within one year of follow-up, increasing age was associated with less frequent administration of alternative endocrine treatment (78.8%, 80.3% and 61.2% respectively; p=0.013)(data not shown).

At database lock, the number of deaths was 173 (10.3%) in patients aged <65 years, 133 (14.0%) in patients aged 65-75 years, and 154 (30.3%) in patients aged ≥75 years. The number of deaths due to breast cancer was 146 (8.7%), 88 (9.3%) and 60 (11.8%) respectively. Figure 2 depicts

**Table 1.** Baseline characteristics by age at diagnosis.

| | <65 years (n=1,682) | | 65-75 years (n=951) | | ≥75 years (n=509) | | p |
|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | |
| Histological grade (BR) | | | | | | | **0.004** |
| Well | 240 | 14.3 | 142 | 14.9 | 70 | 13.8 | |
| Intermediate | 707 | 42.0 | 415 | 43.6 | 235 | 46.2 | |
| Poor | 647 | 38.5 | 339 | 35.6 | 157 | 30.8 | |
| Unknown | 88 | 5.2 | 55 | 5.8 | 47 | 9.2 | |
| Estrogen receptor | | | | | | | **0.002** |
| Positive | 1,629 | 96.8 | 942 | 99.1 | 503 | 98.8 | |
| Negative | 52 | 3.1 | 9 | 0.9 | 6 | 1.2 | |
| Not performed | 1 | 0.1 | 0 | 0.0 | 0 | 0.0 | |
| Progesterone receptor | | | | | | | 0.416 |
| Positive | 1,244 | 74.0 | 698 | 73.4 | 387 | 76.0 | |
| Negative | 347 | 20.6 | 209 | 22.0 | 104 | 20.4 | |
| Not performed | 91 | 5.4 | 44 | 4.6 | 18 | 3.5 | |
| T stage | | | | | | | **<0.001** |
| 0, is | 2 | 0.1 | 0 | 0.0 | 0 | 0.0 | |
| 1 | 802 | 47.7 | 443 | 46.2 | 128 | 25.1 | |
| 2 | 762 | 45.3 | 442 | 46.5 | 332 | 65.2 | |
| 3, 4 | 111 | 6.6 | 66 | 6.9 | 49 | 9.6 | |
| Unknown | 5 | 0.3 | 0 | 0.0 | 0 | 0.0 | |
| Nodal status | | | | | | | 0.090 |
| Negative | 486 | 28.9 | 299 | 31.4 | 168 | 33.0 | |
| Positive | 1,194 | 71.0 | 652 | 68.6 | 339 | 66.6 | |
| Unknown | 2 | 0.1 | 0 | 0.0 | 4 | 0.1 | |
| Presence of comorbidity | | | | | | | |
| Cardiac | 514 | 30.6 | 442 | 46.5 | 280 | 55.0 | **<0.001** |
| CNS | 151 | 9.0 | 104 | 10.9 | 79 | 15.5 | **<0.001** |
| Endocrine | 249 | 14.8 | 195 | 20.5 | 117 | 23.0 | **<0.001** |
| Gastro-intestinal | 356 | 21.2 | 272 | 28.6 | 151 | 29.7 | **<0.001** |
| Genitourinary | 466 | 27.7 | 220 | 23.1 | 145 | 28.5 | **0.020** |
| Musculoskeletal | 382 | 22.7 | 276 | 29.0 | 193 | 37.9 | **<0.001** |
| Most extensive surgery | | | | | | | **<0.001** |
| WLE | 863 | 51.3 | 424 | 44.6 | 129 | 25.3 | |
| Mastectomy | 818 | 48.7 | 527 | 55.4 | 380 | 74.7 | |
| Axillary surgery | | | | | | | 0.285 |
| Yes | 1,341 | 79.7 | 740 | 77.8 | 413 | 81.1 | |
| No | 341 | 20.3 | 211 | 22.2 | 96 | 18.9 | |
| Radiotherapy | | | | | | | **<0.001** |
| Yes | 1,201 | 71.4 | 597 | 62.8 | 243 | 47.7 | |
| No | 478 | 28.4 | 353 | 37.1 | 266 | 52.3 | |
| Unknown | 3 | 0.2 | 1 | 0.1 | 0 | 0.0 | |
| Chemotherapy | | | | | | | **<0.001** |
| Yes | 936 | 55.6 | 103 | 10.8 | 1 | 0.2 | |
| No | 746 | 44.4 | 847 | 89.1 | 508 | 99.8 | |
| Unknown | 0 | 0.0 | 1 | 0.1 | 0 | 0.0 | |
| Randomization | | | | | | | 0.880 |
| Tam → Exe | 837 | 49.8 | 483 | 50.8 | 255 | 50.1 | |
| Exemestane | 845 | 51.2 | 468 | 49.2 | 254 | 49.9 | |

BR: Bloom Richardson; CNS: central nervous system; WLE: wide local excision; Tam → Exe: tamoxifen followed by exemestane.

**Table 2.** Reasons for nonpersistence within one year of follow-up by age at diagnosis.

| | <65 years (n=118) | | 65-75 years (n=71) | | ≥75 years (n=67) | | p |
|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | |
| Reasons nonpersistence | | | | | | | 0.561 |
| Adverse events | 100 | 84.7 | 59 | 83.1 | 60 | 89.6 | |
| Intercurrent illness | 4 | 3.4 | 4 | 5.6 | 2 | 3.0 | |
| Patient refusal n.o.s. | 10 | 8.5 | 3 | 4.2 | 2 | 3.0 | |
| Other reason | 4 | 3.4 | 5 | 7.0 | 3 | 4.5 | |

n.o.s.: not otherwise specified.

**Table 3.** Breast cancer specific survival and overall survival from landmark by age at diagnosis.

| | 4-years survival# | Univariate HR (95% CI) | p | Multivariable* HR (95% CI) | p |
|---|---|---|---|---|---|
| Breast cancer survival | | | **0.001** | | **0.001** |
| <65 years | | | | | |
| Persistent ≥1 year | 94% | 1 (reference) | | 1 (reference) | |
| Persistent <1 year | 82% | 2.55 (1.51-4.33) | 0.356 | 2.76 (1.55-4.90) | 0.387 |
| 65-75 years | | | | | |
| Persistent ≥1 year | 92% | 1 (reference) | | 1 (reference) | |
| Persistent <1 year | 94% | 0.58 (0.18-1.84) | 0.731 | 0.59 (0.18-1.94) | 0.982 |
| ≥75 years | | | | | |
| Persistent ≥1 year | 90% | 1 (reference) | | 1 (reference) | |
| Persistent <1 year | 90% | 1.15 (0.52-2.56) | | 0.99 (0.37-2.62) | |
| Overall survival | | | **<0.001** | | **<0.001** |
| <65 years | | | | | |
| Persistent ≥1 year | 93% | 1 (reference) | | 1 (reference) | |
| Persistent <1 year | 80% | 2.49 (1.51-4.09) | 0.930 | 2.83 (1.65-4.85) | 0.659 |
| 65-75 years | | | | | |
| Persistent ≥1 year | 9% | 1 (reference) | | 1 (reference) | |
| Persistent <1 year | 66% | 1.03 (0.50-2.12) | 0.524 | 1.18 (0.57-2.47) | 0.942 |
| ≥75 years | | | | | |
| Persistent ≥1 year | 76% | 1 (reference) | | 1 (reference) | |
| Persistent <1 year | 76% | 1.17 (0.72-1.90) | | 0.98 (0.54-1.76) | |

HR: Hazard ratio; CI: confidence interval. # 4-years survival from landmark onwards; *Multivariable analyses were adjusted for histological grade, estrogen status, progesterone status, T stage, N status, cardiac / central nervous system / endocrine / gastro-intestinal / genitourinary and musculoskeletal comorbidity, most extensive surgery, axillary surgery, radiotherapy, adjuvant chemotherapy and endocrine therapy.

cumulative incidence of death due to breast cancer and death from other causes from landmark by persistence status at one year of follow-up, stratified by age at diagnosis. As shown in Table 3, patients aged <65 years who were nonpersistent within one year of follow-up, had a lower breast cancer specific survival (multivariable hazard ratio 2.76 (95% CI 1.55-4.90); p=0.001). For overall survival, comparable results were observed (multivariable hazard ratio 2.83 (95% CI 1.65-4.85); p<0.001). On the contrary, nonpersistence within one year of follow-up was not

associated with breast cancer specific survival nor overall survival in patients aged 65-75 years (multivariable p=0.387; p=0.659 respectively) and in patients aged ≥75 years (multivariable p=0.982; p=0.942 respectively).

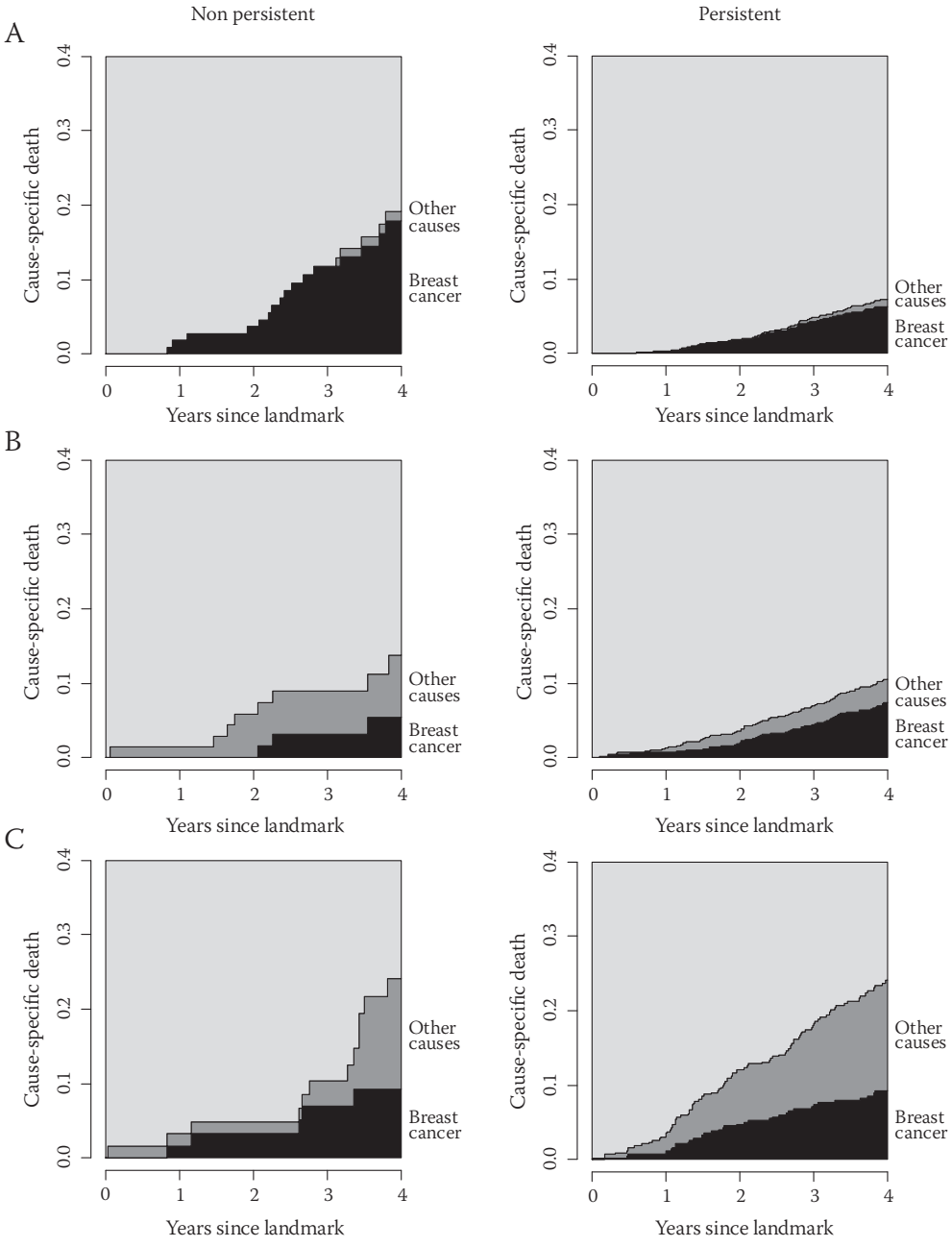


**Figure 2.** Cumulative incidence of death due to breast cancer and death from other causes by persistence status at one year of follow-up, by age at diagnosis. A) <65 years, B) 65-75 years, C) ≥75 years.

Additional survival analyses including an interaction term between persistence status at one year of follow-up and age confirmed significant interaction for breast cancer specific survival (p=0.031) but not for overall survival (p=0.140). To assess sensitivity of the landmark, we performed additional survival analyses comprising alternative landmark cutoffs (0.5 and 1.5 years respectively), which did not alter the results (data not shown). To account for a potential lack of power in patients aged ≥75 years, we performed additonal survival analyses in which patients aged 65-75 years and patients aged ≥75 years were combined. Again, nonpersistence within one year of follow-up was not associated with breast cancer specific survival (univariate hazard ratio 0.93 (95% CI 0.49-1.77), p=0.819; multivariable hazard ratio 0.81 (95% CI 0.39-1.69), p=0.675)). For overall survival, we observed comparable results (univariate hazard ratio 1.29 (95% CI 0.87-1.93), p=0.206; multivariable hazard ratio 1.19 (95% CI 0.76-1.87), p=0.440)). Additional analyses were performed to evaluate the influence of alternative treatment in case of nonpersistence (data not shown). In patients who were nonpersistent, alternative treatment was not associated with breast cancer specific or overall survival in all age categories (multivariable analyses breast cancer specific survival p=0.401; p=0.576; p=0.426 respectively; multivariable analyses overall survival p=0.314; p=0.325; p=0.328 respectively).

# Discussion

## Summary

In this study, increasing age was associated with a higher proportion of nonpersistence within one year of follow-up. Patients aged <65 years who were nonpersistent within one year of follow-up, had a marked decreased breast cancer specific and overall survival. However, no differences were observed for patients aged 65-75 years as well as for patients aged ≥75 years.

## Imbedding in literature

Nonpersistence has been evaluated in other endocrine therapy trials. The Intergroup Exemestane Trial randomized patients to receive 2-3 years tamoxifen or 2-3 years exemestane after 3-2 years of tamoxifen. Treatment was stopped early in 14% of the study population. As randomization took place after 2-3 years of tamoxifen, early nonpersistence has not been taken into account[16]. Of all patients included in the Arimidex and Tamoxifen Alone or in Combination trial, 76% of patients on anastrozole and 72% of tamoxifen-treated patients were persistent nearly 47 months after diagnosis[17]. Fisher et al evaluated efficacy of five years versus more than five years of tamoxifen in node negative breast cancer patients. During the first five years after randomization, 23% of patients discontinued assigned therapy[18]. Five years of tamoxifen in a preventive setting showed a nonpersistence proportion between 24% and 36%[19;20].

Several observational studies have reported on age specific persistence. Fink et al did not observe a relation between age and discontinuation within two years of follow-up in a cohort of 516 breast cancer patients on tamoxifen[4]. Similar results were found in a cohort study by

Demissie et al[6]. Hershman et al studied persistence and adherence in a historical cohort of 8,769 patients who received either tamoxifen or an aromatase inhibitor[21]. Persistence and adherence were evaluated by automated pharmacy records. Patients aged <40 years and patients aged ≥75 years were most likely to discontinue endocrine therapy within 4.5 years of follow-up. Partridge studied tamoxifen adherence in a cohort of 2,378 breast cancer patients[22]. Adherence was defined as the number of days covered by filled prescription in the first year of therapy. Both in women both aged <45 years as well as in patients aged ≥85 years a lower adherence was observed. These results are consistent with a cohort study by Barron among 2,816 breast cancer patients aged ≥35 years on tamoxifen[5]. Patients aged 35-44 years and patients aged ≥75 years were most likely to discontinue tamoxifen within one year of follow-up. In addition, a recent study among 961 breast cancer patients by Owusu showed that an age of ≥75 years was an independent predictor of tamoxifen discontinuation before completion of five years of therapy[7]. In most observational studies, high age is associated with lower persistence[5;7;21;22]. Differences in proportions may have been affected by the use of either adherence or persistence as primary endpoint. Persistence is defined as the duration of time over which a patient continues to fill prescriptions[23]. A related endpoint is adherence, which is defined as whether medication is taken as consistently as prescribed. This can be calculated by dividing the quantity of pills dispensed by the total days covered by prescription[22;24]. Contrary to other studies, we assessed persistence in the first year of follow-up in order to study survival by persistence status. In addition, inclusion in the current study was restricted to postmenopausal patients. Moreover, one has to take into account that the setting of a clinical trial generally results in higher persistence rates[23], possibly due to patient selection and attention[24-26].

## Exclusion of survival bias

Since patients were not randomized to persistence status, we acknowledge the limitations of discussing survival by persistence status at one year of follow-up. Patients with a worse prognosis or higher intrinsic mortality may have had a higher tendency to become nonpersistent and thereby bias survival analyses. In patients aged <65 years, nonpersistent patients more often had central nervous system, gastro-intestinal, and genitourinary comorbidity. However, in patients aged ≥75 years, who had more comorbid diseases, no differences between persistent and nonpersistent patients were observed. Moreover, no association between persistence status and overall survival was demonstrated. Therefore, it is unlikely that presence of comorbid disease has had a major impact on the association between persistence and survival in the eldest patients. In addition, administration of alternative endocrine therapy in case of nonpersistence may have biased survival analyses. However, additional analyses did not indicate survival benefit for nonpersistent patients who received alternative therapy. A lack of power was not likely to have had a major influence on our findings; analyses in which patients aged 65-75 years and patients aged ≥75 years were combined, showed similar results.

## Explanation of results

It is tempting to speculate on the underlying mechanisms which could explain the results presented in this study. Both patients and physicians might be more likely to discontinue treatment with increasing patients' age. It has been suggested that persistence in the elderly may be impaired by psychosocial issues such as decreased social supports and an increasing incidence of cognitive and functional impairment[27]. Sharkness et al showed that elderly patients with more than one chronic illness requiring the use of multiple drugs were more likely to be adherent[28]. Comparable associations have been observed for different numbers of prescriptions[4;29]. On the other hand, others observed lower adherence in patients using multiple drugs[30-32].

Although little is known about the implications of nonpersistence, it is well known that duration of adjuvant endocrine therapy is strongly associated with survival of young and middle aged breast cancer patients[2]. However, evidence in elderly is lacking. Elderly might respond different to a certain therapy; presence of comorbidity may affect anticancer therapy[33]. Polypharmacy may cause drug interactions[34] and may alter pharmacokinetics of anticancer therapy[33]. These findings hint at potential age specific therapy dynamics, but this should be investigated in further studies. Moreover, a higher competing risk of death with increasing age may play a role in assessing survival differences in elderly breast cancer patients.

## Strengths and limitations

The major strength of this study is the possibility to study a large group of incident breast cancer patients. Trial data comprise highly standardized treatment algorithms and virtually complete follow-up. The TEAM trial had very few exclusion criteria, among which there was no upper age limitation. This enabled us to study age specific persistence.

As enrollment in the TEAM trial was restricted to patients with postmenopausal hormone receptor positive disease, these results may not be extrapolated to all breast cancer patients. In addition, Ziller et al reported on the inconsistency between self-reported adherence and true adherence based on retrospective prescription check[35]. A recent study by Hershman et al showed that 28% of patients on endocrine treatment, who were persistent at 4.5 years of follow-up, were nonadherent[21]. These results indicate that persistence may not be as sensitive as adherence, especially when adherence is calculated by pharmacy data or prescriptions. In this report, we investigated nonpersistence. However, we were unable to assess adherence in patients who were persistent; therefore we cannot exclude that persistence may have been influenced by adherence.

## Conclusion

This study shows a higher proportion of adjuvant endocrine therapy nonpersistence within one year of follow-up with increasing age. Based on these data and study design we are unable to report on the efficacy of adjuvant endocrine therapy in elderly breast cancer patients.

However, we have shown that nonpersistence of adjuvant endocrine therapy within one year of follow-up was associated with breast cancer specific survival and overall survival in postmenopausal patients aged <65 years, but not in patients aged 65-75 years or in patients aged ≥75 years. The results presented in this study suggest that extrapolation of outcomes from a young, homogeneous population to a heterogeneous elderly population may be insufficient. Age specific breast cancer studies are needed to establish differential outcomes in young and elderly breast cancer patients

**Supplementary table 1a.** Predictive factors for nonpersistence within one year of follow-up for patients aged <65 years.

| | Univariate OR (95% CI) | p | Multivariable** OR (95% CI) | p |
|---|---|---|---|---|
| Histological grade (BR) | | 0.748 | | 0.923 |
| I | 1 (reference) | | 1 (reference) | |
| II | 1.24 (0.69-2.24) | | 1.05 (0.56-1.97) | |
| III, IV | 1.12 (0.61-2.05) | | 0.96 (0.49-1.86) | |
| Estrogen receptor | | 0.847 | | 0.953 |
| Positive | 1 (reference) | | 1 (reference) | |
| Negative | 0.90 (0.32-2.55) | | 0.97 (0.33-2.83) | |
| Progesterone receptor | | 0.813 | | 0.585 |
| Positive | 1 (reference) | | 1 (reference) | |
| Negative | 1.06 (0.66-1.71) | | 1.15 (0.69-1.90) | |
| T stage | | 0.095 | | 0.089 |
| 1 | 1 (reference) | | 1 (reference) | |
| 2 | 1.53 (1.04-2.27) | | 1.58 (1.03-2.45) | |
| 3, 4 | 1.11 (0.49-2.52) | | 0.97 (0.37-2.57) | |
| Nodal stage | | 0.856 | | 0.384 |
| Negative | 1 (reference) | | 1 (reference) | |
| Positive | 0.96 (0.64-1.45) | | 1.34 (0.69-2.58) | |
| Cardiac* | | 0.219 | | 0.292 |
| No | 1 (reference) | | 1 (reference) | |
| Yes | 1.28 (0.86-1.89) | | 1.27 (0.81-1.99) | |
| CNS* | | **0.035** | | 0.225 |
| No | 1 (reference) | | 1 (reference) | |
| Yes | 1.80 (1.04-3.09) | | 1.46 (0.79-2.68) | |
| Endocrine* | | 0.886 | | 0.757 |
| No | 1 (reference) | | 1 (reference) | |
| Yes | 1.04 (0.62-1.75) | | 0.91 (0.51-1.63) | |
| Gastro-intestinal* | | **0.011** | | **0.030** |
| No | 1 (reference) | | 1 (reference) | |
| Yes | 1.71 (1.13-2.57) | | 1.68 (1.05-2.69) | |
| Gentiourinary* | | **0.017** | | 0.065 |
| No | 1 (reference) | | 1 (reference) | |
| Yes | 1.61 (1.09-2.38) | | 1.50 (0.98-2.32) | |

**Supplementary table 1a.** (Cont.)

| | Univariate OR (95% CI) | p | Multivariable** OR (95% CI) | p |
|---|---|---|---|---|
| Musculoskeletal* | | 0.237 | | 0.732 |
| No | 1 (reference) | | 1 (reference) | |
| Yes | 1.29 (0.85-1.97) | | 1.09 (0.67-1.77) | |
| Other* | | 0.537 | | 0.525 |
| No | 1 (reference) | | 1 (reference) | |
| Yes | 1.12 (0.76-1.65) | | 0.86 (0.55-1.36) | |
| Most extensive surgery | | **0.010** | | 0.915 |
| WLE | 1 (reference) | | 1 (reference) | |
| Mastectomy | 1.65 (1.13-2.42) | | 1.03 (0.56-1.91) | |
| Axillary surgery | | 0.465 | | 0.341 |
| Yes | 1 (reference) | | 1 (reference) | |
| No | 1.18 (0.76-1.85) | | 1.41 (0.70-2.84) | |
| Radiotherapy | | **0.001** | | **0.040** |
| Yes | 1 (reference) | | 1 (reference) | |
| No | 1.87 (1.28-2.75) | | 1.89 (1.03-3.45) | |
| Chemotherapy | | 0.898 | | 0.839 |
| Yes | 1 (reference) | | 1 (reference) | |
| No | 1.03 (0.70-1.49) | | 1.05 (0.68-1.60) | |
| Endocrine therapy | | **0.026** | | 0.055 |
| Tam → Exe | 1 (reference) | | 1 (reference) | |
| Exemestane | 0.65 (0.44-0.95) | | 0.67 (0.44-1.01) | |

OR: odds ratio; CI: confidence interval; BR: Bloom Richardson: ER: estrogen receptor; PR: progesterone receptor; CNS: central nervous system; WLE: wide local excision; Tam → Exe: tamoxifen followed by exemestane. * Presence of comorbidity. ** All covariates were included in multivariable analysis.

**Supplementary table 1b.** Predictive factors for nonpersistence within one year of follow-up for patients aged 65-75 years.

| | Univariate OR (95% CI) | p | Multivariable** OR (95% CI) | p |
|---|---|---|---|---|
| Histological grade (BR) | | 0.262 | | 0.227 |
| I | 1 (reference) | | 1 (reference) | |
| II | 1.49 (0.70-3.16) | | 1.24 (0.57-2.70) | |
| III, IV | 0.98 (0.44-2.19) | | 0.74 (0.31-1.77) | |
| Estrogen receptor | | # | | # |
| Positive | # | | # | |
| Negative | # | | # | |
| Progesterone receptor | | 0.744 | | 0.887 |
| Positive | 1 (reference) | | 1 (reference) | |
| Negative | 0.91 (0.51-1.61) | | 0.96 (0.52-1.75) | |
| T stage | | 0.586 | | 0.224 |
| 1 | 1 (reference) | | 1 (reference) | |
| 2 | 1.07 (0.65-1.78) | | 1.15 (0.65-2.01) | |
| 3, 4 | 1.58 (0.66-3.74) | | 2.35 (0.89-6.22) | |
| Nodal stage | | 0.215 | | 0.263 |
| Negative | 1 (reference) | | 1 (reference) | |
| Positive | 0.73 (0.44-1.20) | | 0.65 (0.30-1.39) | |
| Cardiac* | | 0.140 | | 0.310 |
| No | 1 (reference) | | 1 (reference) | |
| Yes | 0.69 (0.42-1.13) | | 0.75 (0.44-1.30) | |
| CNS* | | 0.763 | | 0.743 |
| No | 1 (reference) | | 1 (reference) | |
| Yes | 0.88 (0.39-1.98) | | 1.16 (0.49-2.76) | |
| Endocrine* | | 0.634 | | 0.978 |
| No | 1 (reference) | | 1 (reference) | |
| Yes | 0.86 (0.46-1.60) | | (0.52-1.97) | |
| Gastro-intestinal* | | 0.721 | | 0.870 |
| No | 1 (reference) | | 1 (reference) | |
| Yes | 0.91 (0.53-1.56) | | 0.95 (0.51-1.78) | |
| Gentiourinary* | | 0.479 | | 0.454 |
| No | 1 (reference) | | 1 (reference) | |
| Yes | 0.80 (0.44-1.47) | | 0.77 (0.40-1.52) | |
| Musculoskeletal* | | 0.479 | | 0.764 |
| No | 1 (reference) | | 1 (reference) | |
| Yes | 0.82 (0.47-1.43) | | 0.91 (0.49-1.69) | |
| Other* | | 0.338 | | 0.854 |
| No | 1 (reference) | | 1 (reference) | |
| Yes | 0.78 (0.47-1.30) | | 0.95 (0.52-1.71) | |
| Most extensive surgery | | 0.168 | | 0.356 |
| WLE | 1 (reference) | | 1 (reference) | |
| Mastectomy | 0.72 (0.44-1.17) | | 0.68 (0.31-1.53) | |
| Axillary surgery | | 0.066 | | 0.681 |
| Yes | 1 (reference) | | 1 (reference) | |
| No | 1.64 (0.97-2.78) | | 1.19 (0.53-2.66) | |

**Supplementary table 1b.** (Cont.)

| | Univariate OR (95% CI) | p | Multivariable** OR (95% CI) | p |
|---|---|---|---|---|
| Radiotherapy | | 0.543 | | 0.581 |
| Yes | 1 (reference) | | 1 (reference) | |
| No | 0.85 (0.51-1.42) | | 1.25 (0.56-2.79) | |
| Chemotherapy | | 0.606 | | 0.173 |
| Yes | 1 (reference) | | 1 (reference) | |
| No | 0.83 (0.40-1.71) | | 0.57 (0.25-1.28) | |
| Endocrine therapy | | 0.988 | | 0.887 |
| Tam → Exe | 1 (reference) | | 1 (reference) | |
| Exe | 1.00 (0.61-1.61) | | 0.96 (0.58-1.61) | |

OR: odds ratio; CI: confidence interval; BR: Bloom Richardson: ER: estrogen receptor; PR: progesterone receptor; CNS: central nervous system; WLE: wide local excision; Tam → Exe: tamoxifen followed by exemestane. * Presence of comorbidity; ** All covariates were included in multivariable analysis. # Number too low to estimate.

**Supplementary table 1c.** Predictive factors for nonpersistence within one year of follow-up for patients aged ≥75 years.

| | Univariate OR (95% CI) | p | Multivariable** OR (95% CI) | p |
|---|---|---|---|---|
| Histological grade (BR) | | 0.738 | | 0.346 |
| I | 1 (reference) | | 1 (reference) | |
| II | 0.75 (0.34-1.63) | | 0.61 (0.27-1.41) | |
| III, IV | 0.88 (0.39-1.98) | | 0.95 (0.40-2.28) | |
| Estrogen receptor | | 0.166 | | 0.451 |
| Positive | 1 (reference) | | 1 (reference) | |
| Negative | 0.28 (0.05-1.65) | | 0.40 (0.04-4.37) | |
| Progesterone receptor | | 0.940 | | 0.783 |
| Positive | 1 (reference) | | 1 (reference) | |
| Negative | 0.98 (0.52-1.84) | | 0.90 (0.44-1.86) | |
| T stage | | 0.513 | | **0.021** |
| 1 | 1 (reference) | | 1 (reference) | |
| 2 | 0.92 (0.50-1.69) | | 0.82 (0.40-1.69) | |
| 3, 4 | 1.47 (0.61-3.56) | | 3.42 (1.10-10.61) | |
| Nodal stage | | 0.488 | | 0.850 |
| Negative | 1 (reference) | | 1 (reference) | |
| Positive | 0.83 (0.48-1.42) | | 1.08 (0.51-2.28) | |
| Cardiac* | | 0.572 | | 0.918 |
| No | 1 (reference) | | 1 (reference) | |
| Yes | 1.16 (0.69-1.96) | | 1.04 (0.53-2.01) | |
| CNS* | | 0.828 | | 0.744 |
| No | 1 (reference) | | 1 (reference) | |
| Yes | 1.08 (0.54-2.17) | | 1.15 (0.50-2.64) | |
| Endocrine* | | 0.852 | | 0.792 |
| No | 1 (reference) | | 1 (reference) | |
| Yes | 1.06 (0.58-1.94) | | 1.10 (0.54-2.26) | |
| Gastro-intestinal* | | 0.543 | | 0.537 |
| No | 1 (reference) | | 1 (reference) | |
| Yes | 1.19 (0.69-2.06) | | 1.24 (0.63-2.42) | |
| Gentiourinary* | | 0.398 | | 0.510 |
| No | 1 (reference) | | 1 (reference) | |
| Yes | 1.27 (0.73-2.20) | | 1.26 (0.64-2.47) | |
| Musculoskeletal* | | 0.872 | | 0.962 |
| No | 1 (reference) | | 1 (reference) | |
| Yes | 1.04 (0.62-1.77) | | 1.02 (0.52-1.98) | |
| Other* | | 0.997 | | 0.733 |
| No | 1 (reference) | | 1 (reference) | |
| Yes | 1.00 (0.60-1.67) | | 0.89 (0.46-1.73) | |

**Supplementary table 1c.** (Cont.)

| | Univariate OR (95% CI) | p | Multivariable** OR (95% CI) | p |
|---|---|---|---|---|
| Most extensive surgery | | 0.995 | | **0.016** |
| WLE | 1 (reference) | | 1 (reference) | |
| Mastectomy | 1.00 (0.55-1.80) | | 0.24 (0.07-0.76) | |
| Axillary surgery | | 0.261 | | 0.449 |
| Yes | 1 (reference) | | 1 (reference) | |
| No | 1.42 (0.77-2.62) | | 1.40 (0.59-3.35) | |
| Radiotherapy | | **0.038** | | **0.002** |
| Yes | 1 (reference) | | 1 (reference) | |
| No | 1.76 (1.03-3.00) | | 5.59 (1.90-16.49) | |
| Chemotherapy | | # | | # |
| Yes | # | | # | |
| No | # | | # | |
| Endocrine therapy | | 0.882 | | 0.947 |
| Tam → Exe | | | 1 (reference) | |
| Exe | | | 1.02 (0.56-1.85) | |

OR: odds ratio; CI: confidence interval; BR: Bloom Richardson: ER: estrogen receptor; PR: progesterone receptor; CNS: central nervous system; WLE: wide local excision; Tam → Exe: tamoxifen followed by exemestane. * Presence of comorbidity; ** All covariates were included in multivariable analysis; # Number too low to estimate.

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Chapter 10

# Management of primary metastatic breast cancer in the elderly – an international comparison of oncogeriatric versus standard care

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# Abstract

## Background

An oncogeriatric approach may affect management of elderly breast cancer patients. However, little is known about oncogeriatric care in the metastatic setting. Therefore, we performed an international comparison of management of elderly patients with primary metastatic disease who were treated in two different care settings.

## Methods

Patients who were ≥70 years at diagnosis of primary metastatic disease were eligible. The first cohort comprised a population-based cohort of 104 patients (Comprehensive Cancer Center West, The Netherlands), who all received standard care. The second cohort comprised a hospital-based cohort of 42 patients (H. Lee Moffitt Cancer Center, Florida, United States), who all received oncogeriatric care.

## Results

No large differences in patient and tumor characteristics were observed between both cohorts. Most patients in the standard care cohort received systemic therapy as primary therapy, whereas most patients in the oncogeriatric cohort received a combination of systemic and local therapy. Patients in the standard care cohort received fewer lines of treatment (mean number of treatments 2.1; 3.6, $p<0.001$), and particularly less breast surgery, chemotherapy and trastuzumab. Three-years overall mortality was 71% (95% CI 61-83) as compared to 58% (95% CI 42-75) among patients in the oncogeriatric care cohort (multivariable HR 0.63 (95% CI 0.35-1.15), $p=0.125$).

## Conclusions

In primary metastatic breast cancer, oncogeriatric care intensifies treatment and might improve survival in elderly patients. Future studies on a larger scale should investigate the potential for improved survival, and whether this is accompanied by a better (preservation of) quality of life and functional status.

# Introduction

Over 40% of all breast cancer patients is 65 years or older at diagnosis[1], and this proportion is expected to further increase due to increasing life expectancy[2]. Despite representing a large proportion of breast cancer patients, the elderly are frequently under accrued in clinical trials[3], and therefore breast cancer management in older women is limited by a lack of level 1 evidence[4]. Consequently, elderly are at risk for both under- and overtreatment.

A collaborative geriatric and oncology management can optimize care in elderly patients[4;5]. An oncogeriatric approach leads to greater attention being paid to comorbidity and geriatric issues, which may result in a better selection of adequate treatment on an individual basis, prevention of complications, and a lower risk of patient deconditioning. Previously it has been shown that use of a comprehensive geriatric assessment may result in changes in treatment strategy[6]. Through these mechanisms, an oncogeriatric approach may improve patient outcomes.

However, little is known about such an oncogeriatric approach in elderly with metastatic breast cancer[7]. Older women are more likely to present with more advanced disease as compared to younger patients[4]; 16.3% of patients aged 65 years and older present with distant metastases, versus 10.5% of patients younger than 65 years[2]. Therefore, we performed an international comparison of treatment and outcome of elderly patients with primary metastatic breast cancer who were treated in a standard care setting as compared to those who were treated in an oncogeriatric care setting.

# Methods

## Cohorts

The study flowchart is shown in Figure 1. Two patient cohorts were constructed. Cohort 1 comprised a population-based cohort of elderly breast cancer patients treated in the Comprehensive Cancer Center West in The Netherlands, who all received standard care (*standard care cohort*). Patients were identified from the Dutch Cancer Registry. Cohort 2 comprised a hospital-based cohort of elderly patients treated at the H. Lee Moffitt Cancer Center and Research Institute in Tampa, Florida, United States. All patients received oncogeriatric care (*oncogeriatric care cohort*). Patients were identified from the Moffitt Cancer Registry and the Total Cancer Care program.

All women with primary metastatic breast cancer, who were 70 years or older at diagnosis, and diagnosed between January 1st 2008 and December 31th 2011 were eligible. To increase the power of the analysis, inclusion in the oncogeriatric care cohort was extended to January 1st 2003. Patients with a history of breast cancer less than five years prior to diagnosis of metastatic breast cancer were excluded, as these were considered to have recurrent disease. By

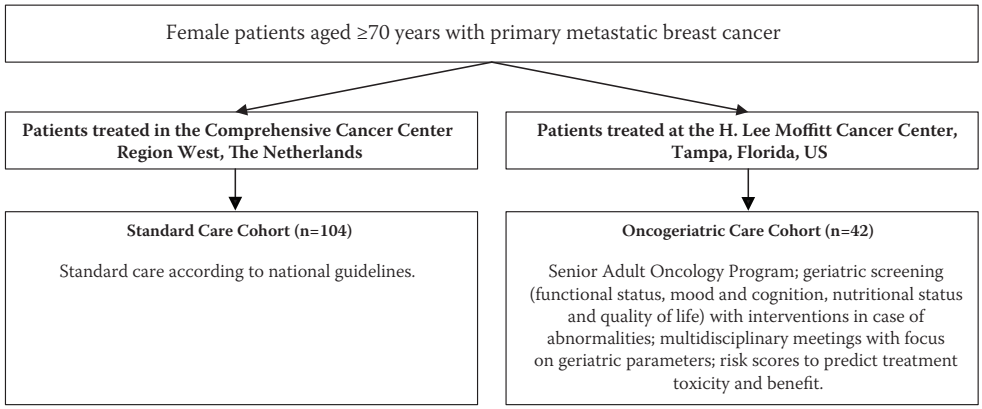


**Figure 1.** Flow chart.

means of chart review, data were collected on tumor, patient and treatment characteristics. For the oncogeriatric care cohort, vital status and date of last follow-up were established directly from the patient's medical record or through linkage of the Moffitt Cancer Registry data with the National Death Index. Patients who moved out of the region were censored at time of last follow-up visit. For the standard care cohort, vital status and date of last follow-up were established either directly from the patient's medical record or through linkage of cancer registry data with municipal population registries, which record information on vital status. Follow-up was recorded until July 1st 2012.

## Description of care

In the standard care cohort, no structured oncogeriatric approach was present. Irrespective of age at diagnosis, patients were discussed in multidisciplinary meetings, and treatment was based on national guidelines. Contrary, in the oncogeriatric care cohort a structured oncogeriatric approach was provided for all patients. Patients were seen in the Senior Adult Oncology Program and underwent a geriatric screening at first visit to evaluate functional status, mood and cognition, nutritional status and quality of life[6;8]. Any adverse finding prompted further evaluation and possible interventions[6]. All patients were discussed in a multidisciplinary meeting with a focus on geriatric parameters. Moreover, risk scores were used to predict benefit and toxicity from systemic therapy in order to personalize treatment[9].

## Statistical analysis

SPSS version 20.0 (SPSS, Chicago, Illinois, USA) was used for statistical analyses. Continuous data were presented as mean (standard deviation, SD). Differences in patient and tumor characteristics between the cohorts were analyzed by means of Pearson's $\chi 2$ test or the Fisher Exact test in the event of low numbers in any cell.

As the majority of patients with metastatic breast cancer die from breast cancer, the primary outcome of interest was overall mortality. A Cox proportional hazards model was used to assess

the association between care setting and overall mortality, with results reported as hazard ratio (HR) with 95% confidence interval (CI). Covariates were included in the multivariable model if they were judged to be clinically relevant, and comprised age (continuous) and the year of diagnosis (continuous). All statistical tests were two-sided. A p value of <0.05 was considered statistically significant.

### Instrumental variable

Differences in overall mortality were evaluated by means of cohort as an instrumental variable. An instrumental variable can be used as a substitute for randomization in non-randomized studies, and may reduce confounding by indication under the assumptions that the instrumental variable is associated with the exposure, unrelated to the confounders and has no direct association with the outcome other than through the exposure[10;11]. Thus, cohort membership was used as an instrumental variable, as a surrogate for type of care. The two geographically distinct cohorts represent different settings of care. The place of residence determines a patient's allocation to the cohort and thereby determines the probability of being treated in a standard or in an oncogeriatric care setting. The interpretation of the results strongly depends on the valid use of the instrumental variable. Therefore, sensitivity analyses and investigations were performed to assess whether the assumptions of the instrumental variable were met.

The standard care cohort is a population-based cohort in which all patients in a certain geographic area, who met the inclusion criteria, were included. Since the oncogeriatric care cohort is a hospital-based cohort, patients might be selected due to selective (self) referral. To assess whether patients included in the oncogeriatric care cohort were representative of the regional patient population, patient characteristics were compared with those treated in the other health facilities in the catchment area of the hospital (Pasco, Polk, Hillsborough, Pinellas, Hernando, Manatee, and Sarasota county). These data were retrieved from the Florida Cancer Data System (FCDS), Florida's statewide, population-based cancer registry[12]. All cancer cases seen in any health facility must be reported to FCDS within six months of diagnosis, as mandated by Florida statutes. Next, a comparison was made between the characteristics of patients who resided in the catchment area of the H. Lee Moffitt Cancer Center versus characteristics of patients who resided outside the catchment area.

## Results

Table 1 shows patient and tumor characteristics in both cohorts. Patients in the standard care cohort were older (p<0.001). Other patient characteristics and tumor characteristics were similar for patients in both cohorts.

Overall, 13/104 patients in the standard care cohort and 1/42 patients in the oncogeriatric care cohort did not receive any treatment. As shown in Figure 2, primary therapy was categorized

**Table 1.** Patient and tumor characteristics of patients treated in a standard care setting versus an oncogeriatric care setting.

| | Standard care (n=104) | | Oncogeriatric care (n=42) | | p | p* |
|---|---|---|---|---|---|---|
| | n | % | n | % | | |
| Age, years (mean, SD) | 81.1 | 5.8 | 76.1 | 5.2 | **<0.001** | **<0.001** |
| Comorbidities (number) | | | | | 0.590 | 0.590 |
| 0-1 | 33 | 31.7 | 10 | 23.8 | | |
| 2-4 | 53 | 51 | 25 | 59.5 | | |
| ≥5 | 18 | 17.3 | 7 | 16.7 | | |
| Polypharmacy | | | | | 0.194 | 0.194 |
| Yes | 67 | 64.6 | 22 | 52.4 | | |
| No | 37 | 35.6 | 20 | 47.6 | | |
| Localization metastases | | | | | 0.518 | 0.741 |
| Visceral | 21 | 20.2 | 11 | 26.2 | | |
| Non visceral | 49 | 47.1 | 18 | 42.9 | | |
| Both | 30 | 28.8 | 13 | 31 | | |
| Unknown | 4 | 3.8 | 0 | 0 | | |
| T stage | | | | | 0.793 | 0.574 |
| 0,1,2 | 45 | 43.3 | 24 | 57.1 | | |
| 3,4 | 45 | 43.3 | 16 | 38.1 | | |
| Unknown | 6 | 5.8 | 2 | 4.8 | | |
| N stage | | | | | 0.567 | 0.833 |
| Negative | 27 | 26 | 10 | 23.8 | | |
| Positive | 67 | 64.4 | 30 | 71.4 | | |
| Unknown | 10 | 9.6 | 2 | 4.8 | | |
| Hormone receptor status | | | | | 0.050 | 0.333 |
| Negative | 18 | 17.3 | 5 | 11.9 | | |
| Positive | 75 | 72.1 | 37 | 88.1 | | |
| Unknown | 11 | 10.6 | 5 | 11.9 | | |
| Her2Neu overexpression | | | | | 0.087 | 0.609 |
| No | 72 | 69.2 | 32 | 76.2 | | |
| Yes | 13 | 12.5 | 8 | 19 | | |
| Unknown | 19 | 18.3 | 2 | 4.8 | | |

SD: standard deviation. * p value excluding missing data.

as systemic therapy, local therapy, or a combination of systemic and local therapy. Patients in the standard cohort who received treatment, most often received a form of systemic therapy as primary therapy (49/91). Of these, the vast majority received endocrine therapy (43/49). Contrary, patients in the oncogeriatric cohort who received treatment, most often received a combination of systemic therapy and local therapy (23/41). In both cohorts, very few patients received local therapy of the breast or metastasis as primary therapy.

Patients in the standard care cohort less often received chemotherapy as primary therapy, irrespective of hormone receptor status, and less often received trastuzumab (Table 2). Contrary, they more often received endocrine therapy as monotherapy (41% versus 21%, p=0.024). In case patients received endocrine therapy as part of primary therapy, an aromatase-inhibitor was prescribed most frequently in both cohorts: 62/81 patients in the standard care cohort were treated with an aromatase-inhibitor (letrozole n=46; anastrozole n=15; exemestane n=1), and 31/32 patients in the oncogeriatric care cohort received an aromatase-inhibitor (letrozole

**Table 2.** Treatment characteristics of patients treated in a standard care setting versus an oncogeriatric care setting.

| | Standard care (n=104) | | Oncogeriatric care (n=42) | | p |
|---|---|---|---|---|---|
| | % | n | % | n | |
| *Primary therapy* | | | | | |
| Local therapy | | | | | |
| Surgery breast | 16 | 15.4 | 11 | 26.2 | 0.158 |
| Radiotherapy breast | 8 | 7.7 | 5 | 11.9 | 0.521 |
| Surgery metastasis | 2 | 1.9 | 4 | 9.5 | 0.057 |
| Radiotherapy metastasis | 26 | 25 | 11 | 26.2 | 0.881 |
| Systemic therapy | | | | | |
| Endocrine therapy | 81 | 77.9 | 32 | 76.2 | 0.829 |
| in HR + patients* | 72 | 96 | 32 | 86.5 | 0.113 |
| in HR – patients* | 5 | 27.8 | 0 | 0 | 0.545 |
| Chemotherapy | 6 | 5.8 | 8 | 19 | **0.025** |
| in HR + patients* | 1 | 1.3 | 5 | 13.5 | **0.015** |
| in HR – patients* | 4 | 22.2 | 3 | 60 | 0.142 |
| Trastuzumab | 4 | 3.8 | 6 | 14.3 | **0.034** |
| *Any therapy*** | | | | | |
| Local therapy | | | | | |
| Surgery breast | 19 | 18.3 | 17 | 40.5 | **0.010** |
| Radiotherapy breast | 10 | 9.6 | 8 | 19 | 0.162 |
| Surgery metastasis | 7 | 6.7 | 5 | 11.9 | 0.327 |
| Radiotherapy metastasis | 33 | 31.7 | 16 | 38.1 | 0.562 |
| Systemic therapy | | | | | |
| Endocrine therapy | 81 | 77.9 | 34 | 81 | 0.824 |
| in HR + patients* | 72 | 96 | 34 | 91.1 | 0.395 |
| in HR – patients* | 5 | 27.8 | 0 | 0 | 0.545 |
| Chemotherapy | 10 | 9.6 | 17 | 40.5 | **<0.001** |
| in HR + patients* | 5 | 6.7 | 14 | 37.8 | **<0.001** |
| in HR – patients* | 4 | 22.2 | 3 | 60 | 0.142 |
| Trastuzumab | 4 | 3.8 | 6 | 14.3 | **0.034** |

* Percentages were calculated based on the number of patients per subgroup. HR + patients: patients with positive hormone receptor status; HR – patients: patients with negative hormone receptor status. ** Any breast cancer therapy received between date of diagnosis until death or end of follow up, including primary therapy.

n=14; anastrozole n=10; and exemestane n=7). Additionally 13/81 patients in the standard care cohort received tamoxifen, and 6/81 patients received another form of endocrine therapy. In case patients received chemotherapy as part of primary therapy, the majority of patients in the standard care cohort received mono-chemotherapy (4/6), whereas patients from the oncogeriatric care cohort most often received a poly-chemotherapy regimen (6/8).

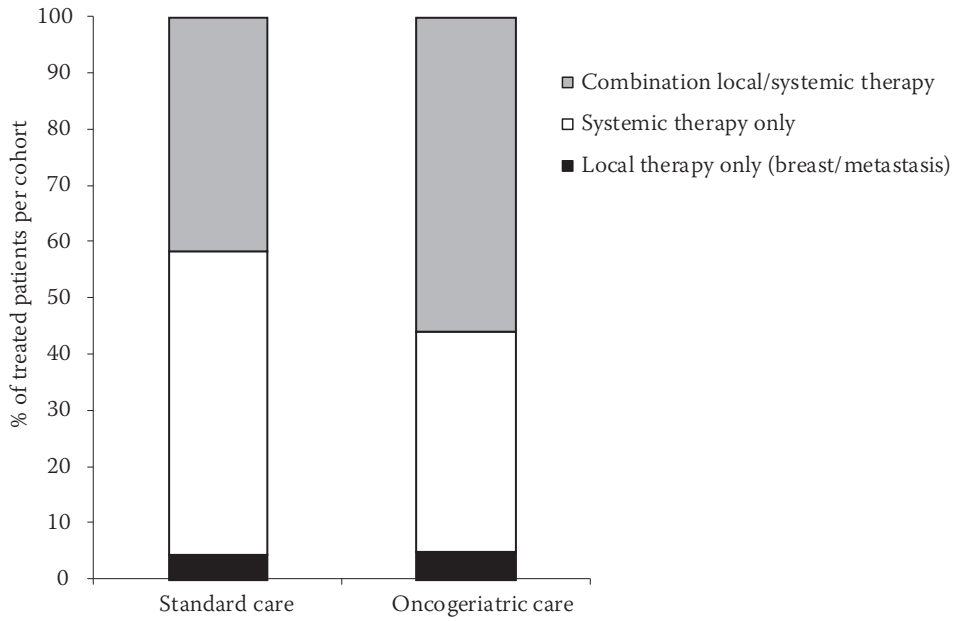


**Figure 2.** Primary therapy of patients treated in a standard care setting versus an oncogeriatric care setting.

Over the whole course of disease, patients in the standard care cohort received a lower number of treatments as compared to patients in the oncogeriatric care cohort (mean number of treatments was 2.1 (SD 1.8) versus 3.6 (SD 2.1), $p<0.001$), and received less often breast surgery, chemotherapy and tratuzumab in particular (Table 2). Comparable results were observed when the analysis was restricted to therapy received during the first two years of follow-up (data not shown). In both cohorts, progression of disease was the most frequent reason for another line of therapy.

Median follow-up among patients censored at July 1st 2012 was 2.1 years for patients in the standard care cohort, and 2.0 years for patients in the oncogeriatric care cohort. Figure 3 shows the cumulative incidence of death for both cohorts. For patients in the standard care cohort, three-years overall mortality was 71% (95% CI 61-83), as compared to 58% (95% CI 42-75) in the oncogeriatric care cohort, corresponding with a univariate HR of 0.62 (95% CI 0.38-1.02). Adjustment for year of diagnosis and age at diagnosis yielded comparable results (multivariable HR 0.63 (95% CI 0.35-1.14)).

**Table 3.** Overall mortality of patients treated in a standard care setting versus an oncogeriatric care setting.

| | 5-years death n (%) | Univariate HR (95% CI) | p | Multivariable* HR (95% CI) | p |
|---|---|---|---|---|---|
| Cohort | | | 0.057 | | 0.125 |
| Standard care | 62 (71) | 1 (reference) | | 1 (reference) | |
| Oncogeriatric care | 19 (58) | 0.62 (0.38-1.02) | | 0.63 (0.35-1.14) | |

HR: Hazard ratio; CI: confidence interval. * Multivariable analyses were adjusted for age and year of diagnosis.

Since patients in the oncogeriatric care cohort may be selected by (self) referral, we performed two sensitivity analyses. First, we compared patient characteristics of patients in the oncogeriatric care cohort with corresponding patients who were treated in other health facilities in the catchment area of the oncogeriatric care cohort (Supplementary table 1). Mean age of patients who were treated in other health facilities was 79.6 years (SD 6.4); as compared to 76.0 years (SD 5.2) for those who were included in the oncogeriatric care cohort (p=0.001). Otherwise, no marked differences were observed, which indicates that despite a possible selection of patients, patients in the oncogeriatric care cohort seem to be a representative patient sample. Second, we compared characteristics of patients who resided outside the catchment area of the H. Lee Moffitt Cancer Center with characteristics of patients who resided in the catchment area (Supplementary table 2). Patients who resided outside the catchment area were more often married; otherwise no marked differences were observed.

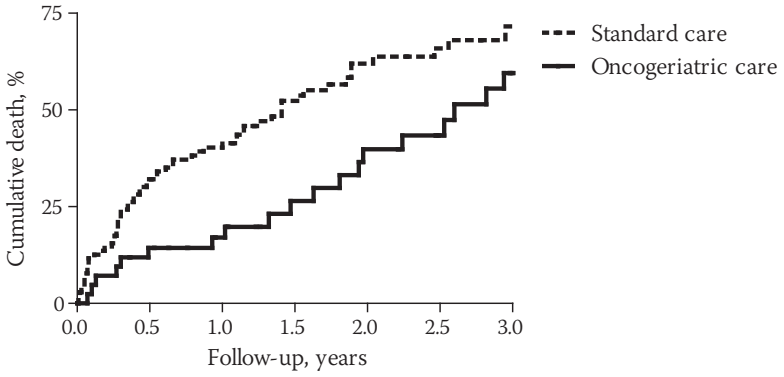


**Figure 3.** Cumulative incidence of death from all causes for patients treated in a standard care setting versus patients treated in an oncogeriatric care setting.

# Discussion

## Summary

Elderly patients with primary metastatic breast cancer who were treated in a standard care setting received a lower number of treatments, and in particular less often received chemotherapy, trastuzumab and local breast surgery, as compared to those treated in an oncogeriatric care setting. Moreover, our findings suggest that oncogeriatric care may be beneficial in elderly breast cancer patients with primary metastatic disease in terms of overall survival, although cautious interpretation is warranted given the relatively low number of patients and the older age profile in the standard care cohort.

## Instrumental variable

Randomized controlled trials are the preferred way to study specific treatment efficacy and should therefore be encouraged. However, the large heterogeneity of the elderly population renders difficult the conduct of clinical trials that are truly representative of that population. Eligibility criteria aimed at increasing the internal validity of a study, favor inclusion of relatively healthy participants, which tenders to weaken the external validity of the study[13]. Some authors have argued that even if all limits on eligibility were removed, the elderly who would be included in a trial would be a selected group[14;15]. Therefore different study designs may be warranted to obtain evidence based medicine in this large and growing population of patients. One option is the use of an instrumental variable in observational studies (e.g. regions within the same country or with similar settings, but with a different treatment approach).

In regular observational studies, the evaluation of treatment or treatment strategies is hampered by confounding by indication; frailty, age, tumor characteristics and presence of comorbidity might all affect both treatment and survival. An instrumental variable serves as a proxy for randomization and might thereby improve the quality of analyses in observational studies by minimizing confounding by indication[16], provided that certain assumptions are met. The instrumental variable has to be associated with the exposure of interest, should be unrelated to the confounders and must not have a direct association with the outcome other than through the exposure[10;11]. With regards to exposure, both cohorts represent a different care setting, which is displayed in the organization of care as well as in differences in administration of treatment. Next, the instrumental variable should not be related to the confounders, in other words, patients in both cohorts should be comparable. A priori we did not expect large differences in patient and tumor characteristics between patients diagnosed with metastatic disease in The Netherlands and the United States. As shown in Table 1, indeed no large differences were observed between both cohorts, except for age at diagnosis. Therefore, results were adjusted for age at diagnosis. Last, other than through care setting, there should be no direct association between the instrumental variable and overall mortality. Differences in background mortality might affect survival in other ways than through care setting. However, no major differences in background mortality or remaining life expectancy

were observed between the cohorts. In The Netherlands, women who were aged 65 years in 2007-2010 had an average remaining life expectancy of 21.2 years. For women aged 75 years the remaining life expectancy was 13.2 years[17]. This is comparable with the life expectancy of elderly women in the United States. White women who were aged 65 years in 2008-2009 had an average remaining life expectancy of 20.0-20.4 years. For women aged 75 years, the remaining life expectancy was 12.6-12.9 years[18]. Next, the year of diagnosis is associated with birth cohort and might thereby possibly affect life expectancy. To account for the different inclusion periods between the cohorts, the results were adjusted for year of diagnosis. Third, patients in the oncogeriatric care cohort were observed to be comparable to patients treated in other health facilities in the region, and are therefore deemed to be a representative sample. In summary, there seemed to be reasonable grounds for justifying the use of two cohorts with different care settings as an instrumental variable.

## Treatment differences

The main finding of this study is the less intensive treatment of patients in the standard care cohort. The current study does not allow separating the various reasons for a more intense management of patients in the oncogeriatric care cohort. A greater familiarity of the staff with the management and treatment of older breast cancer patients, the use of a geriatric assessment, a multidisciplinary coordination of care, the proactive use of preventive measures against complications, and the use of risk scores to predict treatment toxicity might all have contributed.

One of the most prominent treatment differences is the proportion of patients receiving chemotherapy. Others investigated chemotherapy effectiveness in elderly patients. A retrospective study based on the Surveillance Epidemiology End Results database among 1,519 patients aged 66 years and older with metastatic hormone receptor negative breast cancer, revealed that 33% received chemotherapy within 6 months of their diagnosis. Chemotherapeutic treatment was associated with a better overall survival, and age did not modify the survival effect of chemotherapy[19]. However, these results should be interpreted with caution, as they are prone to confounding by indication. A recent meta-analysis showed a similar relative benefit from adjuvant chemotherapy in older women as compared to younger patients[20], however the risk of toxicity increased with age[21]. Chemotherapy tolerability has also been investigated; in a study among 397 patients aged 60 years or older with metastatic breast cancer, women were randomized to either gemcitabine or epirubicin. Side effect wise, elderly patients tolerated chemotherapy well[22]. Moreover, older patients did not differ from their younger counterparts in their acceptance of chemotherapy, although they seemed to be less willing to trade survival for current quality of life[23].

Another marked treatment difference between both cohorts is the proportion of patients who received local therapy. Different studies suggest a beneficial effect of upfront breast surgery in metastasized breast cancer. A pooled analysis of 12 retrospective studies showed that patients

who underwent upfront surgery had a 35% higher survival[24]. Again, these results are prone to confounding by indication; it has been shown that patients who receive surgery have more favourable characteristics[25].

It is not expected that differences in treatment were explained by differences in treatment guidelines. Recently, Wolters and colleagues compared the national breast cancer guidelines of different countries and concluded that most treatment recommendations exhibited a large degree of congruency. This was explained by the fact that they are based on the same evidence[26]. Moreover, it is not expected that insight in oncogeriatric care, if applied, differed between both areas, since oncogeriatric guidelines are the result of collaborative efforts of experts from both Europe and the United States[4;27].

In addition, it is not expected that differences in treatment were explained by differences in *standard* care strategies between the United States and The Netherlands, beyond guideline recommendations. An international comparison between the United States and Europe has not shown a different willingness of patients to receive chemotherapy[28]. Unfortunately we were unable to confirm this hypothesis, since no information was present for elderly patients with primary metastatic breast cancer who were treated in a standard care setting in the United States. Since neither patients nor guidelines are different between both cohorts, different care setting is likely largely responsible for survival differences. Different care setting might include differences in multidisciplinary management, supportive or preventive measures, as well as differences in specific treatment, all of which support the use of oncogeriatric care.

## Survival differences

A second finding of this study was that patients in the oncogeriatric care cohort seemed to have a lower overall mortality. However, cautious interpretation is warranted, as patients in the standard care cohort did have a somewhat older age profile. This may be the result of small demographic differences between the geographic areas of both cohorts[17;29]. In addition, although we constructed two cohorts of unselected nature, inclusion in the oncogeriatric care cohort may have been affected by selective (self) referral of patients to the H. Lee Moffitt Cancer Center. However, sensitivity analysis showed no gross differences between patients who received oncogeriatric care, and patients who received standard care in other health facilities in the catchment area of the hospital. Of note, multivariable analyses were adjusted for age at diagnosis, which did not alter the results. Moreover, since we focused on different care settings for elderly patients with primary metastatic breast cancer, the number of eligible patients is limited, which hampers the power of the analyses. Therefore, the potential for improved survival by oncogeriatric care needs to be investigated on a larger scale.

Both a more intensive primary treatment as well as more subsequent treatment during the first year of follow-up might have contributed to the lower overall mortality among patients in the oncogeriatric care cohort. Moreover, oncogeriatric care might not only result in more intensive

treatment, but also in a better selection of treatment for individual patients. Additionally, a greater attention being paid to comorbidity and geriatric issues may have prevented complications and functional decline, with the net effect of improved overall survival.

## Survival versus quality of life

A review on metastatic breast cancer in the elderly states that in addition to controlling symptoms, care should include determination of comorbidity, assessment of functional status and patients' preferences[30]. In a setting with limited life expectancy due to both advanced age as well as advanced disease it remains a challenge to balance the benefit from therapy and the risk of adverse events which may impede quality of life or survival. Maintaining quality of life is one of the main aims in metastatic breast cancer[27]. From the oncogeriatric care setting we may deduce a greater attention for functional status and quality of life; however, no data on preservation of quality of life or functional status were available. Therefore, it is important to further investigate whether the deemed improved survival in the oncogeriatric care cohort is accompanied by a better (preservation of) quality of life, or contrary, counterbalanced by a decrease in quality of life because of treatment burden.

**Supplementary table 1.** Characteristics of patients in the oncogeriatric cohort as compared to those who were treated in other health facilities in the catchment area of the oncogeriatric care cohort (H. Lee Moffitt Cancer Center and Research Institute).

| | Oncogeriatric care (n=42) | | Other care* (n=341) | | p |
|---|---|---|---|---|---|
| | n | % | n | % | |
| Marital status | | | | | 0.199 |
| Married | 17 | 40.5 | 95 | 27.9 | |
| Other# | 25 | 59.5 | 242 | 71 | |
| Unknown | 0 | 0 | 4 | 1.2 | |
| Insurance | | | | | 0.457 |
| Uninsured | 1 | 2.4 | 3 | 0.9 | |
| Private | 4 | 9.5 | 17 | 5 | |
| Medicare^ | 37 | 88.1 | 305 | 89.4 | |
| Other governmental^^ | 0 | 0 | 9 | 2.6 | |
| Unknown | 0 | 0 | 7 | 2.1 | |
| Race | | | | | 0.672 |
| White | 312 | 91.5 | 40 | 95.2 | |
| Non white | 27 | 7.9 | 2 | 4.8 | |
| Unknown | 2 | 0.6 | 0 | 0 | |
| Ethnicity | | | | | 0.984 |
| Hispanic | 16 | 4.7 | 2 | 4.8 | |
| Non-hispanic | 325 | 95.3 | 40 | 95.2 | |

* Patients treated at other health facilities in the catchment area of the oncogeriatric care cohort. # widowed, divorced, single, separated. ^ plus or minus supplement. ^^ TRICARE, Veterans Affairs etc.

**Supplementary table 2.** Characteristics of patients in the oncogeriatric cohort who reside inside versus outside the catchment area of the H. Lee Moffitt Cancer Center and Research Institute.

| | In catchment area (n=26) | | Outside catchment area (n=16) | | p |
|---|---|---|---|---|---|
| | n | % | n | % | |
| Comorbidities (number) | | | | | 0.937 |
| 0-1 | 6 | 23.1 | 4 | 25 | |
| 2-4 | 16 | 61.5 | 9 | 56.2 | |
| 5 or more | 4 | 15.4 | 3 | 18.8 | |
| Marital status | | | | | **0.001** |
| Married | 5 | 19.2 | 12 | 75 | |
| Other# | 21 | 80.8 | 4 | 25 | |
| Education | | | | | 0.634 |
| Less than high school | 7 | 26.9 | 3 | 18.8 | |
| Some high school | 10 | 38.5 | 6 | 37.5 | |
| More than high school | 4 | 15.4 | 5 | 31.2 | |
| Unknown | 5 | 19.2 | 2 | 12.5 | |
| Insurance | | | | | 0.109 |
| Uninsured | 0 | 0 | 1 | 6.2 | |
| Private | 1 | 3.8 | 3 | 18.8 | |
| Medicare^ | 25 | 96.2 | 12 | 75 | |
| Other governmental^^ | 0 | 0 | 0 | 0 | |
| Race | | | | | 0.722 |
| White | 25 | 96.2 | 15 | 93.8 | |
| Non white | 1 | 3.8 | 1 | 6.2 | |
| Unknown | 0 | | 0 | 0 | |
| Ethnicity | | | | | 0.517 |
| Hispanic | 2 | 7.7 | 0 | 0 | |
| Non-hispanic | 24 | 92.3 | 16 | 100 | |

# widowed, divorced, single, separated; ^ plus or minus supplement; ^^ TRICARE, Veterans Affairs etc.

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# Part five


## Discussion

# Chapter 11

# Discussion

Willemien van de Water

# Summary

The three main conclusions of this thesis are that there is a limited evidence base for treatment of elderly women with breast cancer; that elderly women with breast cancer have a worse prognosis as compared to younger patients; and that the evaluation of treatment efficacy in elderly women with breast cancer differs from the evaluation in younger patients.

## I. Limited evidence base for treatment of elderly women with breast cancer

In the first part of this thesis, we investigated the evidence base for treatment of elderly breast cancer patients. Not only were we able to confirm an underrepresentation of elderly breast cancer patients in clinical trials, we were also able to pinpoint for which elderly patients an evidence base for treatment is lacking in particular. In chapter 2 we quantified the evidence base for locoregional treatment, based on the proportion of clinical trials from which elderly breast cancer patients are excluded. An evidence base for locoregional treatment in patients aged 65-75 years was dependent on their phenotype. Contrary, there was a limited evidence base for all patients aged 75 years or older. These results were supported by the findings in chapter 3, in which we evaluated the external validity of a clinical trial on endocrine therapy. Breast cancer patients aged 65-75 years who participated in a clinical trial were comparable with breast cancer patients from the general population of corresponding age, in terms of overall survival. However, with increasing age, inclusion in a clinical trial was more selected on fitness; trial participants aged 75 years or older did not represent elderly breast cancer patients from the general population. Hence, trial results may not necessarily be extrapolated to elderly breast cancer patients aged 75 years or older. Third, it was investigated whether adherence to guideline recommendations is associated with outcome (chapter 4). In line with the previous findings, we observed that guideline adherence was not associated with overall survival or with relative survival in patients aged 75 years or older. These results confirmed our hypothesis that non-evidence based guidelines do not improve breast cancer outcome. Surprisingly, we did not find an association between guideline adherence and breast cancer outcome in younger patients either.

There are two explanations for this absence of an association in both age groups; it is truly not there, or it is there but we fail to observe it (Figure 1). A true absence of an association may be explained by the fact that trials usually focus on the efficacy of one particular treatment. No trials have been performed comparing complete guideline adherence versus incomplete guideline adherence. In early stage breast cancer, both options may result in similar survival after five years of follow-up.

Other than a true absence of an association, we may fail to observe a true association. First, the study may have been underpowered. The contrast in adherence proportion among regions may have been too small (10%), or the contrast between adherent and nonadherent patients may have been too small; most patients who were not treated completely in accordance with

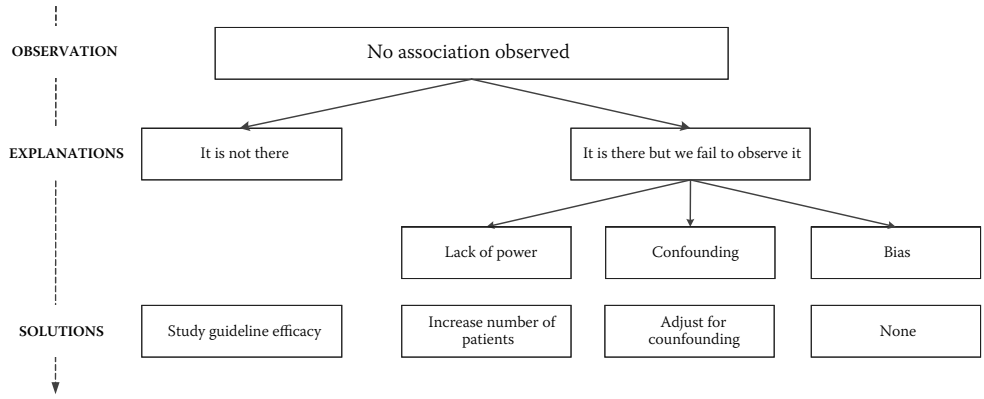


**Figure 1.** No association between guideline adherence and survival; explanations and solutions.

the guidelines received at least three out of five therapies in accordance with the guidelines. Second, confounding may blur the association in case patient or tumor characteristics, which may impact survival, differed among regions. However, background mortality and remaining life expectancy were similar among regions, and the analyses were adjusted for small differences in tumor characteristics. Third, bias may occur if a certain type of patients seeks medical help in another region than the region of residence. However, this was not the case in our study. In addition, information bias may occur when assessment of vital status differs across regions. However, vital status is established through linkage with the municipal population registries nationwide. Summarized, it seems likely that there is a true absence of an association, although we cannot exclude that a lack of power may have contributed to our findings.

## II. Elderly women with breast cancer have a worse prognosis

In in the second part of this thesis, we studied breast cancer outcomes in elderly patients. In patients who participated in a trial, we investigated the association between age at diagnosis and death from breast cancer and death due to other causes (chapter 5). As expected, we observed a higher risk of death due to other causes with increasing age. Surprisingly, we also observed a higher risk of breast cancer death in patients with higher age. To gain further insight in the relationship between age at diagnosis and breast cancer outcome, we studied the risk of breast cancer recurrence in the same cohort of patients (chapter 6). We found that with increasing age, patients had a higher risk of a distant recurrence, while the risks of locoregional recurrence and contralateral breast cancer were not different across age groups.

In the previous section we showed that elderly breast cancer patients who are included in a clinical trial may not represent elderly breast cancer patients from the general population. Therefore, the association between age and breast cancer outcome was also assessed in the population-based FOCUS cohort (chapter 7). Again we observed a worse breast cancer outcome with increasing age; patients aged 75 years or older had a lower relative survival as compared to younger patients. Of note, this was not accompanied by an increased risk of distant breast

cancer recurrence. The latter observation is probably explained by an age specific under diagnosis or under registration of recurrence; compliance with follow-up may differ in the general population as compared to compliance of patients who participate in a trial. Moreover, if a recurrence is detected outside the hospital, the patient and/or general practitioner may decide not to refer the patient to the hospital, and thus the recurrence is not recorded in the patient's hospital chart and consequently not reported in the cohort.

It is tempting to speculate on the underlying mechanisms of the surprising observation that breast cancer outcomes detoriate with increasing age. In general, patient, tumor and treatment characteristics may affect cancer outcome. Increasing age may affect breast cancer outcome by changes in tumor, patient and treatment characteristics (Figure 2).

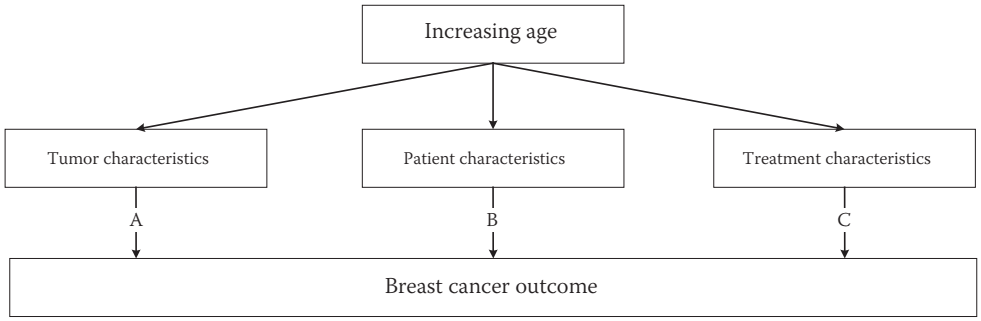


**Figure 2.** Relation between increasing age and prognosis.

As indicated by A, increasing age is associated with different tumor characteristics. Others have found a more frequent occurrence of hormone receptor positive breast cancer with increasing age[1;2], although this difference seems to be most pronounced in premenopausal versus postmenopausal women; *within* postmenopausal patients no large differences in hormone receptor status have been observed[3;4]. One may also speculate that it is not the tumor, but the surroundings of the tumor, i.e. the patient, that change with increasing age, and thereby may affect tumor characteristics and tumor phenotype. There is evidence that a patient's cellular immune response is able to control tumor development and progression, a process called immonosurveillance[5]. The mechanisms involved in immunosurveillance have been shown to alter with increasing age[6]. The functional decline in immune system with ageing is commonly defined as immunosenescence[7]. Thus, immunosenescence may impair immunosurveillance, which may result in increased cancer development and progression with increasing age[6].

As indicated by B in the Figure, increasing age is associated with certain patient characteristics. An individual who dies from other causes is no longer at risk for breast cancer death and therefore, death due to other causes is considered a competing endpoint. Competing endpoints may be particularly present in older populations[8]. If one is interested in causation ('does age

cause breast cancer death'), a Cox regression analysis may be suitable, since one would like to know the risk of death from breast cancer if a patient *would not have died* from other causes. In Cox regression estimations, patients who are lost to follow-up or experience a competing endpoint are censored; the assumption for censoring is that patients who are censored would in theory have the same probability to develop the outcome of interest as those who are still in the risk set. For prediction, or treatment decisions ('do I need to treat the breast cancer of this patient or will she die from something else before she will die from breast cancer'), a Cox regression analysis is not suitable, since one would like to know the risk of breast cancer death *in the presence* of the risk of other causes of death. In the presence of competing endpoints, the cause-specific cumulative incidence is overestimated in the conventional analysis[9]. Alternatively, in a Fine and Gray analysis the risk of breast cancer death is calculated in the presence of the risk of a competing event[10]. As described in chapters 5-7, Fine and Gray analyses did not substantially alter the results, which suggests that competing mortality needs to be substantial to significantly alter the results of Cox regression estimates.

As indicated by C, increasing age may affect treatment and thereby affect breast cancer outcome. It has been shown repeatedly that elderly patients receive less extensive treatment as compared to younger patients[11]. Consequently, they may suffer from undertreatment. The finding that elderly patients in the TEAM trial had a higher risk of a distant recurrence is suggestive for undertreatment with chemotherapy in particular. Next to undertreatment, treatment efficacy may change in elderly patients due to interactions between anticancer therapy and concurrent medication or comorbidity. Concurrent disease and medication use may affect tolerability of treatment and increase toxicity[12;13], which may result in suboptimal dosage of anticancer treatment. Moreover, drug absorption, distribution and metabolism can be affected by age-related physiological changes[14].

## III. Different treatment efficacy in older women with breast cancer

In the third part of this thesis, specific treatment and treatment strategies were evaluated. As reported in chapter 8, we evaluated the efficacy of radiotherapy in addition to breast conserving surgery in elderly patients with early stage breast cancer. A systematic review and meta-analysis of five randomized clinical trials showed a decreased risk of locoregional recurrence in favour of patients who received radiotherapy after breast conserving surgery. However, the absolute risk difference for a locoregional recurrence was low, and no differences were observed with regards to the risk of a distant recurrence, or overall survival. Therefore, omission of radiotherapy seems to be a reasonable option in elderly breast cancer patients.

As reported in chapter 9, we evaluated the outcome of patients who discontinued endocrine therapy. Patients younger than 65 years who discontinued endocrine therapy within one year of follow-up, had a worse overall and breast cancer specific survival after this first year. These results are in line with other studies showing a higher efficacy of five years of endocrine therapy as compared to one year of endocrine therapy[15]. Surprisingly, no association was observed

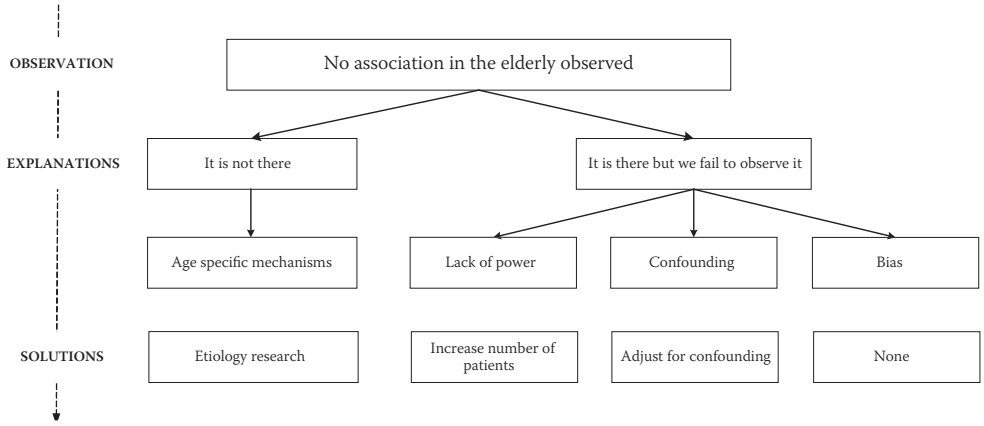


**Figure 3.** Explanations for the absence of an observed association.

between nonpersistence of endocrine therapy within one year and outcome after this year in patients aged 65 years or older. Again, there are two explanations for this absence of an association in the elderly; it is truly not there, or we fail to observe it (Figure 3).

If the association is truly not there, the explanation must be sought in age specific mechanisms or biology. As mentioned, absorption, distribution and metabolism of both types of endocrine treatment can be affected by age-related physiological changes[14], comorbidity or concurrent medication use. In addition, the quantitative expression of hormone receptors on the tumor surface may decline with age, or there may be less substrate for the hormone receptors with increasing age; both may hamper the absolute benefit of endocrine therapy. Of note, these suggestions are of hypothetical nature only, as there is no evidence to support them.

Alternatively, a lack of power, bias and confounding can blur a true association. In all three scenarios, these factors should be age specific, as the failure to observe an association would be present in the elderly only. In case of a lack of power, the number of patients in the oldest age category may have been too small. Second, competing mortality may decrease power because it negatively affects both the numerator and the denominator. In case of confounding, age specific treatment characteristics may have blurred the association. For example, administration of chemotherapy may decrease the risk of breast cancer death, but may also predict early discontinuation. A negative effect of early discontinuation may be counterbalanced by the positive effect of chemotherapy, with the net effect of no association between discontinuation and breast cancer death. Of note, no therapy was shown to predict early discontinuation of endocrine therapy. Second, tumor characteristics may confound the association; if patients with favourable tumor characteristics are more likely to discontinue endocrine treatment, a negative effect of early discontinuation could be counterbalanced by the positive effect of tumor characteristics. However, no tumor characteristics were predictive for early discontinuation. Third, the association may be confounded by patient characteristics. One may argue that those

who discontinue therapy within one year are healthier and have fewer comorbid diseases. Patients with fewer comorbid disease may be aged to a lesser extent, and consequently have a better preserved immune system function, and hence a better breast cancer outcome. Again, a negative effect of early discontinuation may be counterbalanced by the positive effect of fewer comorbid diseases, with the net effect of no association. However, evidence is lacking on the association between comorbidity and immunosensecence, and indicators of general health, i.e. comorbidity, were not predictive for discontinuation. Information bias, or systematic misclassification can occur when elderly who discontinue within one year, are also less compliant with follow-up visits. Consequently, there may be under registration of breast cancer recurrence and breast cancer death, thereby counterbalancing the higher risk of breast cancer death due to discontinuation. However, vital status was checked with the municipal population registries, so in the case of information bias we would still observe a higher overall risk of death in patients who discontinued endocrine therapy within one year. This was not the case.

In conclusion, despite the possibility of a lack of power, so far the results hint at evidence of absence rather than absence of evidence. The data appear to be robust and indicate that discontinuation of endocrine therapy within one year in patients aged 75 years or older is truly not as detrimental as in younger postmenopausal patients. Although the latter study design was unfit to report on the efficacy of adjuvant endocrine therapy in elderly breast cancer patients, these findings warrant further age specific studies. Few randomized clinical trials addressed the efficacy of endocrine therapy specifically in elderly patients. In one trial, a benefit of extended adjuvant endocrine therapy of letrozole treatment after five years of tamoxifen was only observed in patients younger than 60 years. However, no significant interaction between age and treatment efficacy was observed[16]. In 1993, Cummings et al reported on a clinical trial among 168 women aged 65 years or older, with mostly hormone receptor positive tumors, who were randomized to two years of tamoxifen or a placebo. After a median follow-up of 10 years, patients allocated to tamoxifen had a lower risk of a distant recurrence[17]. A meta-analysis including 2,805 patients aged 70 years or older with estrogen receptor positive disease, who were allocated to about five years of tamoxifen or to a control arm, showed a lower recurrence risk for those allocated to tamoxifen[18]. Of note, elderly patients comprised 3% of all patients included in the meta-analysis (2,805/105,623) and little was known about the phenotype of included elderly patients. Moreover, the majority of the trials included in the meta-analysis was conducted in the 1970s and 1980s; therapy regimens other than the randomized treatment have changed considerably since. Therefore, it remains subject of further investigation whether the association between nonpersistence and breast cancer outcome in the elderly it is truly not there, or whether we failed to observe it.

## Other treatment modalities

In the current thesis, not all treatment modalities were evaluated. Based on current literature, short notes are provided for breast surgery and chemotherapy. A Cochrane review investigating surgery versus primary endocrine therapy for operable breast cancer in women aged 70 years

or older concluded that primary endocrine therapy should only be offered to women with hormone receptor positive disease who are unfit for surgery, and to those who refuse surgical treatment[19]. Although the risk of postoperative complications seems to increase with increasing age[20], the majority of older patients tolerate surgery and anaesthesia with very low morbidity and virtually non-existent mortality[21]. A recent meta-analysis on adjuvant chemotherapy stated that age did not much affect the proportional risk reductions with taxane-based or anthracycline-based chemotherapy; elderly may have had somewhat greater immediate hazards from chemotherapy, but appeared to have similar reduction as younger women with regards to breast cancer outcomes. However, the gain in life expectancy from a given absolute reduction in the risk of death from breast cancer decreased with increasing age[22].

### Oncogeriatric care

Next to specific treatment, collaborative oncogeriatric management can optimize care and outcomes in elderly patients[23;24]. Therefore, we compared two different treatment strategies in elderly breast cancer patients. Chapter 10 describes the international comparison of treatment and outcome of elderly patients with primary metastatic breast cancer, who were treated in a standard care setting in The Netherlands, as compared to those who were treated in an oncogeriatric setting in the United States. We observed that patients who were treated in an oncogeriatric care setting were treated more extensively. Although not statistically significant, overall survival was deemed higher in the oncogeriatric care cohort, which was suggestive for a beneficial effect of oncogeriatric care in elderly breast cancer patients with metastatic disease. It needs yet to be determined whether this increase in survival is accompanied by a better (preservation of) quality of life and functional status, and whether similar results can be obtained in patients with early stage disease.

## Reflection

### Trial data versus population-based data

The work presented in this thesis indicates that elderly patients who participate in a clinical trial do not always represent breast cancer patients from the general population of corresponding age. However, some of the studies in this thesis comprise posthoc analyses of trial data. One may question to what extent these results can be extrapolated to the general population.

With regards to outcome, we observed a worse breast cancer outcome with increasing age, both in a trial setting as well as in a population-based cohort. Contrary, the higher risk of a distant recurrence in elderly trial patients could not be confirmed in the population-based cohort. This may be due to both under diagnosis and under registration in the latter cohort, as pointed out above. Another posthoc analysis of trial data comprised the association between early nonpersistence and breast cancer outcome thereafter. It is known that trial patients are generally more compliant with therapy as compared to patients in the general

population[25], but observational data confirm that higher age is predictive for nonpersistence and noncompliance[26].

## Calendar age

In geriatric oncology, it is recommended that treatment decisions are not (solely) based on calendar age, but rather on biological age or functional status. It is still being debated how biological age should be assessed and defined. Nevertheless, all our studies make use of calendar age rather than biological age. Therefore, one may question to which extent the results presented in this thesis are useful for daily practice. Although calendar age does not cover the whole spectrum of phenotypic variety in the elderly, it is strongly related with comorbidity, functional status and remaining life expectancy[27]. Until a definition and categorization of biological age is developed, calendar age may be appropriate to use as a proxy for biological age, whether or not in combination with another measurement of functional status, like comorbidity, polypharmacy or performance status.

## Outcome measures

In this thesis, the outcomes under study are overall survival and breast cancer outcomes. With increasing age, it is more difficult to establish cause of death to a single cause[28]. Relative survival can be used as a valid alternative of breast cancer specific survival[29]. Regardless of which survival endpoint is used, relevance of endpoints may differ between older and younger patients. Elderly are less likely to trade current quality of life for a prolonged survival[30]. Hence, maintenance of functional status, or preservation of quality of life may be more relevant outcomes that breast cancer specific survival. Unfortunately no data were available on quality of life or follow up of functional status.

In addition, the evaluation of treatment efficacy may differ depending on the outcome measure. As observed for radiotherapy after breast conserving surgery and adjuvant chemotherapy, the relative risk reduction was similar across age groups, while the absolute risk difference declined with increasing age. This is depicted in Figure 4. A smaller absolute risk difference corresponds with a larger number needed to treat to prevent one endpoint. The dotted lines resemble the hypothetical cut-off in absolute risk difference and numbers needed to treat, where treatment efficacy is considered not efficient anymore. This cut-off may vary per treatment and per patient. The number needed to treat may be a more useful instrument to evaluate whether a certain treatment is worthwhile, as compared to relative risk measures. Moreover, risks of serious adverse events should be included in evaluation of treatment efficacy. The delicate balance between absolute benefits of a certain therapy and potential impairment in functional status or quality of life due to adverse events, calls for patients and their peers to be actively involved in decision-making, and to take into account the patient's personal preferences with regards to risk of recurrent disease, functional status and risk of adverse events.

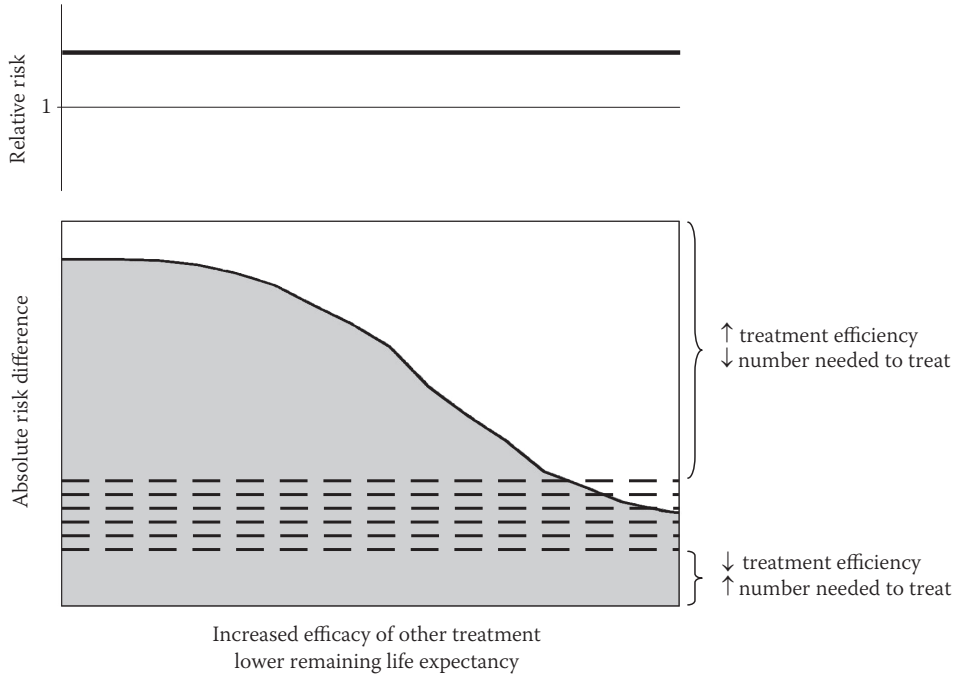


**Figure 4.** Evaluation of treatment efficiency by relative risk and absolute risk difference.

# Future studies

## Outcome prediction

The next phase in oncogeriatric research in breast cancer is aimed at individualized, tailored treatment. The key for appropriate care in the heterogeneous elderly breast cancer population is to predict who will die *with* and *from* breast cancer. As depicted in Figure 5, those who have a high risk of dying from breast cancer, i.e. those with a high risk of recurrent disease, should receive adequate anti-cancer therapy, aiming at minimal residual disease. However, those who will likely to die *with* breast cancer, i.e. those who have a low risk of recurrent disease and a higher risk of competing mortality, should receive adequate supportive care and optimal treatment of comorbid diseases, in order to maintain functional status and optimize quality of life. The X-axis of the Figure is yet undetermined as it needs to be investigated which combination of patient characteristics and tumor characteristics will predict breast cancer outcome best.

The online tool "Adjuvant Online" is frequently used as support for adjuvant treatment decisions in breast cancer. However, Adjuvant Online predictions have been shown to be less accurate in elderly patients[31]. Moreover, Adjuvant Online only predicts breast cancer recurrence and mortality, and does not include outcomes such as functional status. Maintaining functional

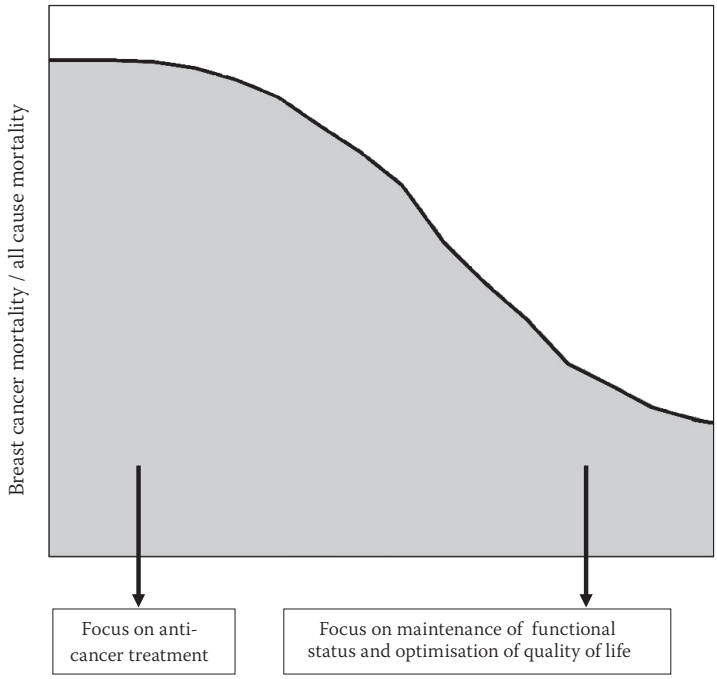


**Figure 5.** Treatment approach of different groups of elderly breast cancer patients.

status can make the difference between independent living and institutionalization, which may be more relevant in elderly patients than sec additional years added to survival. A prediction model based on patient and tumor characteristics, with relevant outcomes for elderly, can be used as a decision support tool when evaluating treatment options in elderly breast cancer patients. Moreover, such a model will aid in individualized treatment, taking into account the large heterogeneity in the elderly.

## Treatment

Currently, recommendations for management of breast cancer in elderly are limited by a lack of evidence[23], although the magnitude of this lack of evidence varies per type of treatment. To specifically assess treatment efficacy, conducting randomized controlled clinical trials in the elderly is inevitable. In some cases alternative designs, for example the use of an instrumental variable, may function as a surrogate for randomization in observational studies. Innovative designs may further enlighten efficacy and tolerability of treatment in elderly patients. As suggested by Martine Extermann, one could think of Phase I like studies; instead of increasing the dose of a certain treatment, one may increase the frailty status of patients receiving the treatment in order to assess tolerability of a certain therapy. Next to cancer specific treatment, supportive treatment is being investigated. Recently, the prospective study 'Climb Every Mountain' was initiated, in which elderly breast cancer patients undergo a geriatric assessment at diagnosis and during follow-up, to evaluate cognitive function, psychosocial issues and

physical activity. Aim of the study is to assess which domain is at highest risk for detoriation, and to identify predictive factors for detoriation. Afterwards, an intervention study will be conducted, aimed at preservation of the domain most at risk. In addition to treatment, the prospective study 'FOCUS on preferences' aims to unravel patient preferences with regards to surgical treatment, and to quantify the minimum expected benefit of adjuvant systemic therapy in order to opt for systemic treatment.

## Clinical implications

The work presented in this thesis primarily gained insight in the *unknown unknowns*. For example, we did not know whether the prognosis of elderly patients would be different as compared to younger patients. Now we know that elderly not only have a higher risk of non breast cancer death, but also have a higher risk of breast cancer death as well as a higher risk of distant disease recurrence. But we still do not know why. The question how to optimize breast cancer care and cure in elderly patients is yet unanswered. How to act in ignorance? Until the evidence gap is filled, the following remarks may be useful for clinical practice.

In line with the adagio 'primum non nocere', one should treat first what kills first. An older breast cancer patient who is likely to die *from* her breast cancer, or who is at high risk for disease recurrence, is a candidate for extensive anti-cancer treatment. On the other hand, treatment of an elderly breast cancer patient who will more likely die from other causes, i.e. *with* breast cancer should rather be focused on supportive care and optimal treatment of comorbid diseases. These outcome predictions can be based on the combination of tumor and patient characteristics.

A similar relative risk reduction of a certain treatment, may translate in only a minor absolute risk difference in elderly patients as compared to in younger patients. Therefore, elderly patients and their peers should be actively involved in decision-making, by discussing the absolute benefits and risks of different treatment options. In addition, the goals of treatment and the relevance of possible outcomes should be discussed.

A collaborative geriatric and oncology management may optimize care in elderly patients. A form of geriatric assessment and multidisciplinary meetings specifically addressing the needs of elderly patients may improve patient outcome.

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# Part six


## Appendices

# Appendices

## Nederlandse samenvatting

Willemien van de Water

# Introductie

Dit proefschrift maakt deel uit van het FOCUS-onderzoek (Female breast cancer in the elderly; Optimizing Clinical guidelines USing clinico-pathological & molecular data), wat gerealiseerd is middels een programmasubsidie van het Koningin Wilhelmina Fonds. Het doel van het FOCUS-onderzoek is om de behandeling en uitkomsten van oudere patiënten met borstkanker te verbeteren. Waarom onderzoek doen bij ouderen, en in het bijzonder bij oudere vrouwen met borstkanker? Borstkanker is de meest voorkomende vorm van kanker bij vrouwen en meer dan 40% van de borstkankerpatiënten is 65 jaar of ouder ten tijde van diagnose[1;2]. Hoewel oudere borstkankerpatiënten in meerdere opzichten verschillen van jongere patiënten, zijn er geen leeftijdsspecifieke richtlijnen voor de behandeling van oudere patiënten. Omdat er tot voor kort nauwelijks onderzoek verricht werd in deze grote en groeiende groep patiënten, is het dus onduidelijk hoe deze patiënten behandeld moeten worden.

# Doel van het proefschrift

Het doel van dit proefschrift is de zorg te verbeteren voor oudere patiënten met borstkanker, door het gebrek aan bewijs voor behandeling te kwantificeren, de borstkankeroverleving van oudere patiënten te onderzoeken en leeftijdsspecifieke effecten van verschillende behandelingen te evalueren.

# Gebruikte cohorten

Voor dit proefschrift zijn verschillende observationele patiëntcohorten samengesteld. Ook is gebruik gemaakt van gegevens van patiënten die deelnamen aan een grote klinische trial.

## FOCUS-cohort

Data uit het FOCUS-cohort zijn gebruikt in hoofdstuk 2, 3 en 7. Het FOCUS-cohort is een observationeel cohort van alle vrouwen in de regio West van het Integraal Kankercentrum Nederland, die tussen 1997 en 2004 gediagnosticeerd werden met borstkanker en 65 jaar of ouder waren ten tijde van de diagnose. In totaal werden 3.762 patiënten geïncludeerd. Middels statusonderzoek werden gedetailleerde gegevens verzameld over tumor-, patiënt- en behandelkarakteristieken, alsook follow-up en overleving.

## Nederlandse Kankerregistratie cohort

Data van dit cohort zijn gebruikt in hoofdstuk 4. De Nederlandse Kankerregistratie verzamelt gegevens over de diagnose, stagering en behandeling van alle patiënten met kanker in Nederland. In totaal werden 31.520 vrouwen geïncludeerd die tussen 2005 en 2008 gediagnosticeerd werden met vroeg stadium borstkanker, en ten tijde van diagnose jonger waren dan 65 jaar of ouder dan 75 jaar.

### TEAM trial

Data van de TEAM (Tamoxifen Exemestane Adjuvant Multinational) trial zijn gebruikt in hoofdstuk 3, 5, 6 en 9. De TEAM trial is een fase-3 studie in 9 landen, waarin tussen 2001 en 2006 9.766 borstkankerpatiënten gerandomiseerd werden voor twee verschillende vormen van endocriene therapie. Patiënten ontvingen 5 jaar exemestaan, of 2.5 jaar tamoxifen gevolgd door 2.5 jaar exemestaan. Postmenopauzale vrouwen met hormoonreceptorpositieve tumoren zonder afstandsmetastasen, die lokale therapie hadden afgerond, werden geïncludeerd.

### Standaard zorg- en oncogeriatrische zorg cohort

Data van dit cohort zijn gebruikt in hoofdstuk 10. Voor het standaard zorg cohort werden gegevens gebruikt van alle vrouwen van 70 jaar en ouder die tussen 2008 en 2011 werden gediagnosticeerd met een primair gemetastaseerd mammacarcinoom in de regio West van het Integraal Kankercentrum Nederland (n=104). Vergelijkbare criteria werden toegepast voor inclusie in het oncogeriatrische zorg-cohort; vrouwen van 70 jaar en ouder die tussen 2003 en 2011 in het H. Lee Moffitt Cancer Center and Research Institute in Tampa (Florida, Verenigde Staten) werden gediagnosticeerd met een primair gemetastaseerd mammacarcinoom, werden geïncludeerd (n=42). Middels statusonderzoek werden gedetailleerde gegevens verzameld over tumor-, patiënt- en behandelkarakteristieken, alsook follow-up en overleving.

## Overzicht van het beschreven onderzoek

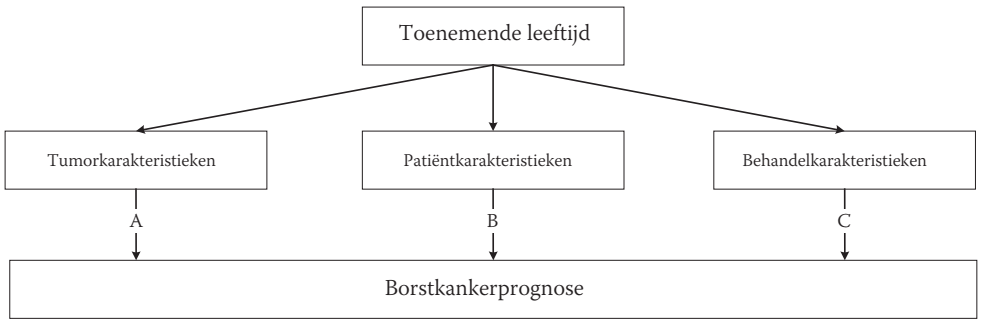
### Beperkte bewijsvoering voor de behandeling van oudere borstkankerpatiënten

Dit proefschrift bestaat uit drie delen; in het eerste deel wordt aangetoond dat de behandeling van borstkanker bij ouderen non-evidence based is. In hoofdstuk 2 wordt beschreven dat de meeste ouderen worden uitgesloten van deelname aan klinische trials. Voor borstkankerpatiënten van 65-75 jaar hangt het af van hun patiëntkarakteristieken hoe vaak zij worden uitgesloten van klinische trials waarop behandelrichtlijnen zijn gebaseerd. Borstkankerpatiënten van 75 jaar of ouder daarentegen worden alleen op basis van kalenderleeftijd uitgesloten van deelname aan de meerderheid van de klinische trials. In hoofdstuk 3 wordt onderzocht in hoeverre oudere borstkankerpatiënten in een klinische trial geselecteerd zijn ten opzichte van oudere borstkankerpatiënten in de algemene bevolking. Met name patiënten van 75 jaar of ouder die geïncludeerd worden in een klinische trial, zijn gezonder en hebben derhalve een betere algemene overleving dan hun leeftijdsgenoten in de algemene bevolking. Trialresultaten die zijn gebaseerd op een selecte groep ouderen zijn dus mogelijk niet extrapoleerbaar naar oudere borstkankerpatiënten in de algemene bevolking. Dit wordt bevestigd in hoofdstuk 4, waarin aangetoond wordt dat het naleven van behandelrichtlijnen die grotendeels zijn gebaseerd op klinische trials, niet geassocieerd is met een betere overleving van oudere borstkankerpatiënten.

## Oudere borstkankerpatiënten hebben een slechtere prognose

In het tweede deel van dit proefschrift wordt de prognose van oudere borstkankerpatiënten onderzocht. Het is een veel gehoorde opvatting dat borstkanker bij ouderen een minder grote bedreiging voor de gezondheid vormt in vergelijking met borstkanker bij jongere vrouwen. De prognose van oudere postmenopauzale borstkankerpatiënten blijkt echter slechter te zijn dan die van jongere patiënten. In hoofdstuk 5 worden de doodsoorzaken onderzocht van postmenopauzale patiënten die participeerden in de TEAM trial. Zoals verwacht neemt met het stijgen van de leeftijd de kans toe om te overlijden aan niet aan borstkanker gerelateerde oorzaken. Oudere patiënten hebben echter ook een grotere kans te overlijden aan borstkanker. In hoofdstuk 6 wordt de associatie tussen leeftijd en het optreden van een borstkankerrecidief onderzocht. De slechtere prognose van oudere patiënten wordt in deze studie bevestigd; het risico op afstandsmetastasen neemt toe met het stijgen van de leeftijd. Omdat in het eerste deel van dit proefschrift wordt gesteld dat resultaten uit een klinische trial niet altijd van toepassing zijn op oudere patiënten uit de algemene bevolking, wordt in hoofdstuk 7 de relatie tussen leeftijd en borstkankerprognose ook onderzocht in een cohort oudere borstkankerpatiënten uit de algemene bevolking. Wederom wordt aangetoond dat oudere borstkankerpatiënten een hoger risico hebben om aan borstkanker gerelateerde oorzaken te overlijden. In deze studie wordt dit echter niet ondersteund door een toename van het risico op afstandsmetastasen; dit is mogelijk het gevolg van onderdiagnose of onderregistratie.

Er zijn verschillende mogelijke verklaringen voor een hogere borstkankersterfte bij oudere borstkankerpatiënten, zoals weergegeven in Figuur 1. Zoals aangegeven met A, is een toenemende leeftijd geassocieerd met bepaalde tumorkarakteristieken. Hoewel oudere patiënten zich vaker presenteren met hormoonreceptorpositieve borsttumoren[3], blijkt dit verschil het meest uitgesproken tussen pre- en postmenopauzale patiënten[4]. Het is ook mogelijk dat de tumor zich anders gedraagt omdat de omgeving van de tumor, oftewel de patiënt, verandert; een slechter werkend immuunsysteem op hogere leeftijd kan mogelijk het risico op tumorontwikkeling en -metastasering vergroten[5]. Zoals aangegeven met B, is toenemende leeftijd ook geassocieerd met bepaalde patiëntkarakteristieken. Borstkankerspecifieke uitkomsten kunnen beïnvloed




**Figuur 1.** Relatie tussen toenemende leeftijd en borstkankerprognose.

worden door 'competing mortality'; het risico om aan andere, niet aan borstkanker gerelateerde oorzaken te overlijden alvorens men aan borstkanker zou overlijden. Dit risico neemt toe met het stijgen van de leeftijd en kan zo borstkankerspecifieke uitkomsten beïnvloeden[6]. Tenslotte kan een toenemende leeftijd invloed hebben op behandelkarakteristieken, zoals aangegeven met C. Het is bekend dat ouderen vaker minder uitgebreid worden behandeld; mogelijk worden zij in sommige gevallen onderbehandeld[7]. Daarnaast kunnen comorbide aandoendingen en het gelijktijdig gebruik van andere medicatie de werkzaamheid van antikankertherapie negatief beïnvloeden[8].

### Andere evaluatie van de effectiviteit van behandeling

In het derde deel van dit proefschrift wordt de werkzaamheid van verschillende therapieën en behandelstrategieën bij ouderen onderzocht. Een systematisch literatuuronderzoek en meta-analyse naar de effectiviteit van radiotherapie na borstsparende chirurgie bij oudere borstkankerpatiënten toont aan dat ook bij ouderen het relatieve risico op een locoregionaal recidief wordt verlaagd door radiotherapie (hoofdstuk 8). De absolute risicoreductie is echter klein, en het aantal te behandelen mensen om één recidief te voorkomen neemt toe met het stijgen van de leeftijd. Daarnaast beïnvloedt radiotherapie niet het risico op afstandsmetastasen en borstkankersterfte. Het achterwege laten van radiotherapie lijkt dan ook een reële optie en dient met de patiënt besproken te worden. In hoofdstuk 9 wordt onderzocht wat de associatie is tussen het vroegtijdig stoppen met endocriene therapie en de algemene overleving en borstkankerspecifieke overleving. Postmenopauzale patiënten die jonger zijn dan 65 jaar en binnen een jaar stoppen met endocriene therapie, hebben na dit jaar een slechtere algemene en borstkankerspecifieke overleving. Bij oudere patiënten wordt echter geen relatie gevonden tussen het vroegtijdig stoppen met endocriene therapie en overleving. De opzet van deze studie is niet geschikt om conclusies te trekken over de effectiviteit van endocriene therapie bij ouderen, maar suggereert wel dat het zinvol is hier nader onderzoek naar te doen. Naast de effectiviteit van specifieke therapie is ook gekeken naar verschillende zorgstrategieën (hoofdstuk 10). Een internationale vergelijking tussen Nederlandse patiënten met primair gemetastaseerde borstkanker die standaard zorg ontvingen, en patiënten in de Verenigde Staten die behandeld werden in een oncogeriatrisch centrum, suggereert dat een oncogeriatrische benadering van oudere borstkankerpatiënten resulteert in betere uitkomsten. Vervolgonderzoek moet aantonen of dit gepaard gaat met een beter behoud van functioneren en kwaliteit van leven, en of deze relatie ook aantoonbaar is in patiënten met borstkanker in een vroeg stadium.

## Reflectie

### Patiënten in een trial versus patiënten in de algemene populatie

Eén van de bevindingen in dit proefschrift is dat oudere patiënten in een trial niet representatief zijn voor oudere borstkankerpatiënten in de algemene bevolking. Toch is een aantal van de

onderzoeken in dit proefschrift uitgevoerd bij oudere patiënten die participeerden in een klinische trial. Men kan zich afvragen of de in deze studies beschreven resultaten ook van toepassing zijn op oudere patiënten uit de algemene bevolking. Wat betreft de studies over de prognose van oudere borstkankerpatiënten, werd ook bij patiënten uit de algemene bevolking gevonden dat het risico op borstkankersterfte toeneemt met de leeftijd. Dat dit niet gepaard ging met een hoger risico op afstandsmetastasen is mogelijk het gevolg van leeftijdsspecifieke onderdiagnose en -rapportage in een observationeel cohort.

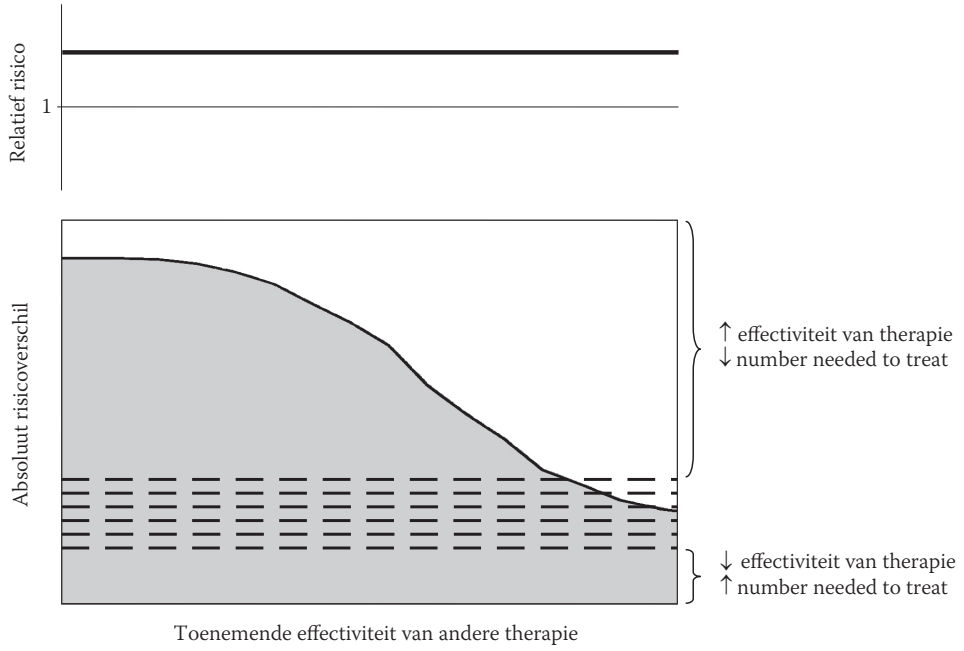
## Kalenderleeftijd versus biologische leeftijd

In de geriatrische oncologie wordt geageerd tegen het gebruik van kalenderleeftijd als (enige) criterium voor het aanbevelen of onthouden van behandeling; de grote heterogeniteit binnen de ouderen vraagt om andere criteria, zoals biologische leeftijd of functionele status. De studies in dit proefschrift zijn echter allemaal verricht met kalenderleeftijd als variabele. Hoewel dit niet volledig overeenkomt met biologische leeftijd, is kalenderleeftijd wel sterk geassocieerd met comorbiditeit en resterende levensverwachting. Totdat er een eenduidige definitie van biologische leeftijd is ontwikkeld kan kalenderleeftijd, al dan niet in combinatie met andere factoren, gebruikt worden in onderzoek.

## Uitkomstmaten

De in dit proefschrift gebruikte eindpunten zijn algemene overleving en borstkankerspecifieke eindpunten. Naast levensverlenging zijn er echter andere, wellicht relevantere uitkomstmaten voor oudere patiënten. Zo is bekend dat zij minder geneigd zijn kwaliteit van leven in te leveren voor een langere overleving[9]. Helaas waren andere uitkomsten zoals behoud van functioneren, zelfstandigheid of kwaliteit van leven niet voorhanden voor de in dit proefschrift gepresenteerde studies.

Naast de overweging welke uitkomstmaat relevant is voor oudere patiënten, is het ook belangrijk om onderscheid te maken in de weergave van de uitkomstmaat. Zoals geobserveerd voor radiotherapie na borstsparende therapie, kan met toenemende leeftijd het relatieve risico gelijk blijven, terwijl het absolute risicoverschil tussen wel of niet behandelen afneemt. Dit is weergegeven in Figuur 2. Hoe kleiner het absolute risicoverschil, hoe groter het aantal mensen dat behandeld moet worden om één uitkomst, bijvoorbeeld een borstkankerrecidief, te voorkomen. Het absolute risicoverschil, of de 'number needed to treat' is wellicht relevanter om in te schatten of een behandeling de moeite waard is. De stippellijn is het hypothetische afkappunt wanneer een bepaalde behandeling niet meer efficiënt geacht wordt. Dit afkappunt kan variëren per behandeling en per patiënt. Omdat elke behandeling bijwerkingen heeft, is het bovendien belangrijk dit absolute risicoverschil af te wegen tegen het risico op bijwerkingen en de mogelijke gevolgen hiervan. De voorkeur en afwegingen van de patiënt ten aanzien van het risico op een borstkankerrecidief, algemeen functioneren en behoud van kwaliteit van leven dienen meegenomen te worden in de besluitvorming rondom de behandeling. Het is daarom aan te raden om patiënten en hun naaste omgeving actief hierbij te betrekken.




**Figuur 2.** Effectiviteit van behandeling weergegeven als relatief risico en absoluut risicoverschil.

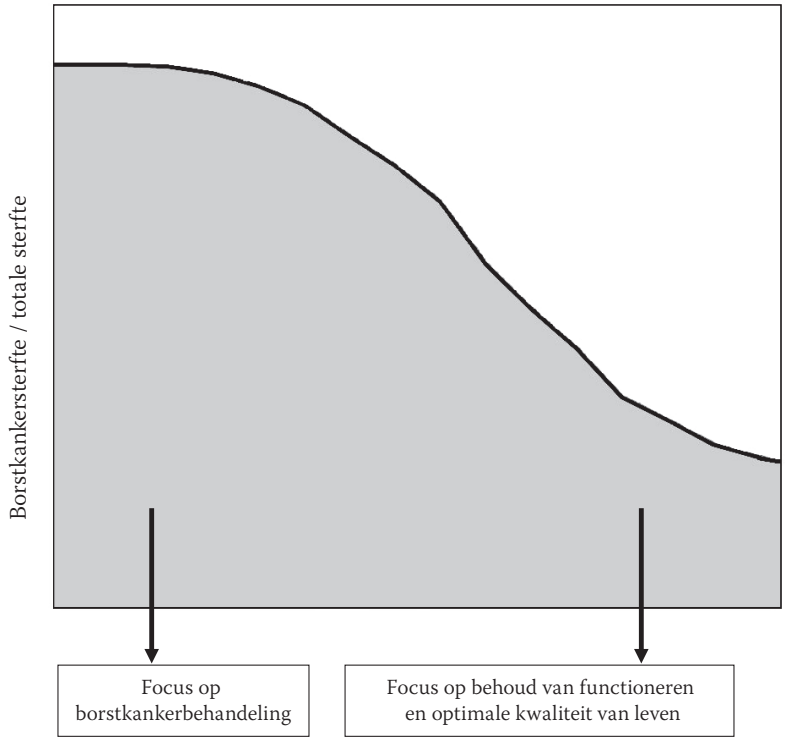
# Toekomstige studies

## Voorspellen van uitkomsten

De volgende stap in de geriatrische oncologie is gericht op geïndividualiseerde, op maat gesneden therapie. Gegeven de grote heterogeniteit binnen de ouderen is het moeilijk, zo niet onmogelijk, om algemene richtlijnen te formuleren over de behandeling van ouderen met borstkanker. Men dient datgene te behandelen waaraan men verwacht dat de patiënt het eerst zal overlijden. Wanneer voorspeld kan worden wie *aan* of juist *met* borstkanker overlijdt, kan de behandeling hier op aangepast worden (Figuur 3). Patiënten die op basis van tumor- en patiëntkarakteristieken een hoog risico hebben op terugkeer van de ziekte, hebben baat bij een adequate, uitgebreide borstkankerbehandeling. Patiënten die daarentegen een laag risico hebben op terugkeer van de ziekte, en een hoger risico hebben om aan andere, niet aan borstkanker gerelateerde oorzaken te overlijden, kunnen beter ondersteunend behandeld worden, met focus op het behoud van functioneren en adequate behandeling van eventuele andere comorbide aandoeningen. De ontwikkeling van een predictiemodel kan gebruikt worden als ondersteuning van de keuze om een bepaalde behandeling al dan niet in te zetten.

## Behandeling

Vanwege het gebrek aan bewijs voor een adequate borstkankerbehandeling moet verder onderzoek gedaan worden naar de effectiviteit van de verschillende behandelopties, specifiek




**Figuur 3.** Behandeling op basis van uitkomstvoorspelling.

bij ouderen. Hiervoor kunnen verschillende studie-opzetten gebruikt worden, waaronder gerandomiseerde klinische trials en internationale vergelijkingen van behandelstrategieën. Naast antikankerbehandeling dient ook ondersteunende behandeling onderzocht te worden; recent is de 'Climb Every Mountain' studie opgezet, waarin gekeken wordt welke functies met name achteruitgaan na de diagnose en behandeling van ouderen, met als doel gericht te kunnen interveniëren. Aanvullend op het onderzoek naar de effectiviteit van behandeling wordt onderzoek verricht naar de voorkeur van oudere patiënten voor verschillende behandelopties ('Focus on Preferences').

# Conclusies

De drie conclusies van dit proefschrift zijn dat er gebrekkige bewijsvoering is voor de behandeling van oudere patiënten met borstkanker; dat oudere patiënten met borstkanker een slechtere prognose hebben dan jongere patiënten; en dat het effect van therapie alsook de evaluatie van effectiviteit bij ouderen anders is dan bij jongeren.

Het onderzoek dat gepresenteerd is in dit proefschrift heeft ertoe geleid dat we beter weten wat we niet weten; zo weten we nu dat ouderen een slechtere borstkankerprognose hebben. We weten echter nog steeds niet waarom dat zo is. De vraag hoe de behandeling en uitkomsten van oudere borstkankerpatiënten geoptimaliseerd kunnen worden, is dus nog niet beantwoord. Hoe te handelen in onwetendheid? De volgende aanbevelingen kunnen bruikbaar zijn voor de dagelijkse praktijk:

Behandel als eerste datgene dat de meeste invloed op de gezondheid en overleving heeft. Patiënten die een hoog risico hebben op een borstkankerrecidief, hebben baat bij een adequate en uitgebreide borstkankerbehandeling. Patiënten met een laag risico op terugkeer van de ziekte en een hoger risico om aan andere oorzaken te overlijden, kunnen beter ondersteunend behandeld worden, met focus op behoud van functioneren en adequate behandeling van eventuele andere comorbide aandoeningen.

Oudere patiënten en hun naaste omgeving dienen actief betrokken te worden in de besluitvorming rondom de behandeling. Bij de evaluatie van het effect van therapie dient niet alleen gekeken te worden naar relatieve risicomaten, maar ook naar absolute risicoreductie en het aantal mensen dat behandeld moet worden om één borstkankereindpunt te voorkomen, alsook naar andere uitkomstmaten zoals kwaliteit van leven en behoud van functioneren.

Een oncogeriatrische benadering van ouderen met borstkanker kan de zorg en uitkomsten van oudere patiënten verbeteren.

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# Appendices

List of co-authors

List of publications

Curriculum vitae

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# Curriculum vitae

Willemien van de Water was born in Assen on May 28, 1984. After graduating cum laude at the Vincent van Gogh Gymnasium, she started Medicine at the University of Groningen in 2002. During her scientific internship at the department of Geriatrics and Gerontology at the Leiden University Medical Center (prof. dr. R.G.J. Westendorp en dr. A.J.M. de Craen), she became interested in the medical and social challenges regarding the elderly patient, and the surprising knowledge gap in the treatment and approach of this large group of patients.

She started her clinical rotations at the Leiden University and achieved her medical degree in 2009, after which she worked as a surgical resident at the 'Rijnland Ziekenhuis' in Leiderdorp. In 2010 she had the opportunity to combine her scientific interest in the elderly patient with her clinical ambition to specialize in surgery. For four years, she worked as a research fellow at the FOCUS study group, a collaboration between the departments of Surgical Oncology and Geriatrics and Gerontology at the Leiden University Medical Center (promotores prof. dr. C.J.H. van de Velde and prof. dr. R.G.J. Westendorp), funded by the Dutch Cancer Foundation. During these years, she achieved her registration as epidemiologist B. Thanks to, among others, a major fellowship of the European Society of Surgical Oncology, she got the opportunity to collaborate with the department of Senior Adult Oncology Program at the H. Lee Moffitt Cancer Center in Tampa, Florida (prof. dr. L. Balducci and prof. dr. M. Extermann), where she conducted part of her research.

In January 2014 she started her training in surgery at the 'Rijnland Ziekenhuis', under supervision of dr. A.M. Zeillemaker.

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