Chapter 1

Introduction

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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 1st 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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