Chapter 1

General Introduction and Outline

Nienke A de Glas

Leiden, June 2014

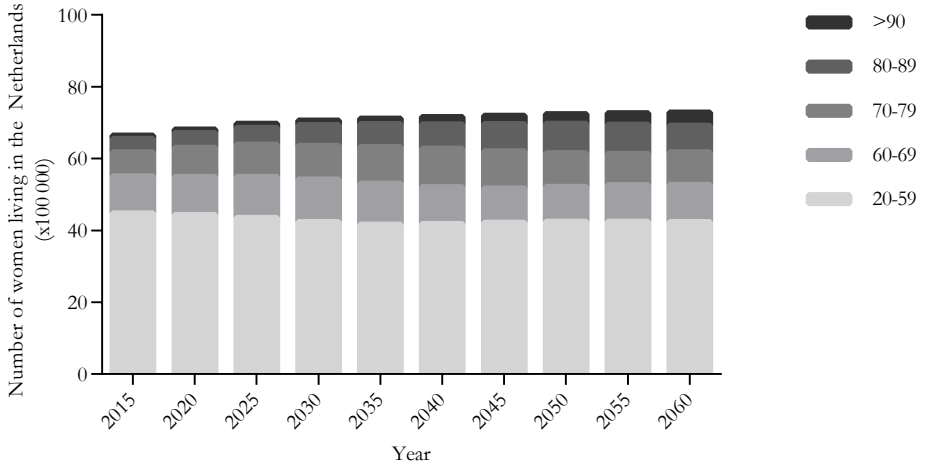
Introduction

Breast cancer is the leading contributor to cancer incidence and cancer mortality in women worldwide[1]. Currently, 35-45% of newly diagnosed breast cancer patients in developed countries is aged 65 years and older[2-4]. Due to ageing of the Dutch population, the number of women above the age of 65 is expected to increase with almost 1,000,000 women between 2015 and 2060[5] (Figure 1), and similar trends are expected in other developed countries. Consequently, the number of older women with breast cancer will strongly increase in the next years[2], resulting in a huge disease burden and a great concern for the health care system.

Breast cancer in older patients

Older women with breast cancer differ from younger women in many aspects. Older women tend to present with more advanced tumour stages and tumours are more often hormone-receptor positive[4;6]. In addition, older women with breast cancer comprise a heterogeneous group due to large differenes between patients with regard to concomitant diseases, physiological reserve and functional status[7], as breast cancer occurs in the background of physiological ageing[8]. These differences can strongly influence clinical decision making. It has been shown that older women with breast cancer are less concerned about body image and recurrence when it comes to surgical decision making[9]. In addition, older patients are generally prepared to undergo adjuvant treatment[10], but less willing to trade absolute survival gain for toxicity or loss of functional capacity[11;12]. With regard to shared decision making, older patients prefer a physician-based treatment advice more often than younger patients[13]. These differences must be taken into account in the clinical decision process with older patients.

Figure 1 *Prognosis of age-distribution of the Dutch Population*



With increasing age, women with breast cancer are at increased risk of dying from other causes than breast cancer[14]. Consequently, absolute benefits of breast cancer treatment may be less pronounced in older patients. However, ageing not only increases the risk of competing mortality, but also the risk of breast cancer mortality[14]. In addition, breast cancer survival in patients aged 75 years and older has not improved in recent years in the Netherlands, while survival of younger breast cancer patients has significantly improved, thereby increasing the survival gap between young and older breast cancer patients[15]. Similar trends have been observed in other European countries as well as in the United States[16-18]. Possibly, both undertreatment and overtreatment explain the lack of survival gain for older patients, indicating that specific individualized treatment strategies are essential to improve breast cancer care in older patients.

Non evidence-based medicine

Current guidelines for breast cancer are based on studies that were mostly performed in younger patients[4]. Due to the aforementioned differences between younger and older patients, general guidelines for breast cancer treatment do not automatically apply to the older population. However, the Dutch guidelines make few distinctions between young and older patients[19]. In 2007, the International Society for Geriatric Oncology (SIOG) published an international recommendation for treatment of older breast cancer patients based on the available evidence[4], which was updated in 2012[20]. The SIOG recommendations mentioned that treatment of older breast cancer patients is mostly not evidence based, as older breast cancer patients are generally underrepresented in clinical trials on which general guidelines are based[21]. The few trials that have been specifically designed for older breast cancer patients in the past, often suffer from poor patient accrual, probably due to strong patients' and physicians' preferences[22]. Furthermore, results from trials that did include older patients often cannot be extrapolated to the general population, as patients in clinical trials generally have fewer comorbid diseases, a higher socioeconomic status and more favourable tumour characteristics[21;23]. As a result, patients included in clinical trials tend to have a better prognosis than breast cancer patients in the general population[21;23]. Consequently, most of the SIOG recommendations were either based on trials that were performed in a non-representative population, or on small observational studies, resulting in a low level of evidence[4;20]. As it is unlikely that these issues in performing randomized clinical trials in older patients are easily overcome, it is essential to search for alternative methods to work towards evidence-based medicine for older patients. Observational studies may be a reasonable alternative, as they study "real" populations, provided that adequate methodological methods are used.

In conclusion, older patients differ from younger patients in many aspects. Treatment of older women with breast cancer is mostly not evidence-based, and it cannot be expected that

clinical trials will fill this gap of knowledge in the near future. Therefore, the aim of this thesis was to investigate several aspects of breast cancer treatment in older women by studying large, mostly population-based databases. This thesis is divided in two parts. In *Part I*, several aspects of treatment in older breast cancer patients are studied. *Part II* assesses several methodological aspects of studying breast cancer in older patients.

Outline

Part I: Choosing the right treatment for the right patient

Clinical decision making in older breast cancer patients is challenging due to many interacting factors and the heterogeneity of this population. Therefore, several aspects of treatment decisions in older breast cancer patients will be assessed. First, the value of mass breast cancer screening in older women will be investigated. It has been assumed that diagnosis at an earlier stage through screening programs could improve breast cancer prognosis, and may therefore be beneficial for older women[24]. However, previous breast cancer screening trials rarely included women over the age of 60[24]. Although there is no strong evidence for beneficial effects of breast cancer screening in older women, in 1998, in the Netherlands, the upper age limit of the mass screening program was extended from 70 to 75. In **Chapter 2,** the implementation of the mass breast cancer screening program in women aged 70-75 will be evaluated by studying incidence rates of early stage and advanced stage breast cancer before and after implementation of the mass screening program in this age-group.

Next, several aspects of surgical treatment for older patients are investigated. The SIOG recommendations from 2008 and 2012 state that all older breast cancer patients with a resectable tumour should receive either a mastectomy or breast conserving surgery with whole-breast radiotherapy.[4;20] However, older patients are often not treated in accordance with existing guidelines.[21;25] Deviation from guidelines may be justified in frail older patients, who may die from other causes, and may be at increased risk of adverse events of treatment. In **Chapter 3**, risk factors for postoperative complications and their association with survival of older patients are investigated. In **Chapter 4**, changing treatment strategies of early breast cancer in the past fifteen years as well as the effect on overall and relative survival of older patients are assessed. Similarly, time-trends in treatment and survival of patients with metastasized breast cancer are assessed in **Chapter 5**.

After completion of locoregional treatment, a large proportion of patients is treated with adjuvant therapy[6]. Currently, several prediction tools are used in clinical practice in order to estimate the gain of adjuvant treatment in individual patients. One of the most well-known prediction tools

is the online Adjuvant! program, which calculates 10-year breast-cancer mortality, other cause mortality and recurrence based on patient- and tumour characteristics. Also, the tool calculates expected benefits of adjuvant breast cancer treatment. The Adjuvant! program was developed in a large database that was derived from the SEER-database, which contained individual data from patients aged 35-69 years of age. Although the tool has been validated in several studies, these studies included highly selected populations with relatively few older patients. Since competing mortality risks strongly influence the absolute risk of breast cancer recurrence and death, the validity of the online Adjuvant! Program in older breast cancer patients in the population will be assessed in **Chapter 6**.

Part II : methodological aspects of research in older breast cancer patients

In Part II of this thesis, several methodological aspects of research in older breast cancer patients are assessed. For many years, researchers and clinicians in the geriatric oncology field have urged for new clinical trials that are specifically designed for older patients[26;27]. In addition, a recently published position paper of SIOG stated that it is important for trials that investigate treatment of older cancer patients to incorporate relevant endpoints such as functional status and quality of life[28]. These endpoints are essential to weigh the risks and benefits of treatment in older patients[28]. However, it remains unclear if currently ongoing trials address these outcomes strongly requested by the field of geriatric oncology. **Chapter 7** provides an overview of endpoints of all currently ongoing clinical trials on breast cancer, particularly in older patients. In **Chapter 8,** the role of competing events in methodology of studies in older breast cancer patients is studied. As older patients are at increased risk of dying from other causes than breast cancer, these so-called competing endpoints should be taken into account in the choice of study design. Several statistical models deal with competing endpoints in different ways, and this may influence the interpretation of study results. In this chapter, we will study this topic in further detail.

Due to the aforementioned poor and selective accrual of older breast cancer patients in clinical trials, it cannot be expected that the large gaps in knowledge will be (completely) filled by clinical trials. As observational studies are generally not limited by selection, they are expected to be of major importance to gain scientific evidence. However, the use of proper methodology in observational studies is essential to draw valid conclusions. **Chapter 9** includes an overview of all recently published observational studies on breast cancer treatment in older patients, and evaluates the methodology.

Finally, **Chapter 10** contains the general discussion and future perspectives.

References

(1) Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011;61(2):69-90.

(2) DeSantis C, Ma J, Bryan L, Jemal A. Breast cancer statistics, 2013. *CA Cancer J Clin* 2013.

(3) DeSantis C, Siegel R, Bandi P, Jemal A. Breast cancer statistics, 2011. *CA Cancer J Clin* 2011;61(6):409-418.

(4) Wildiers H, Kunkler I, Biganzoli L et al. Management of breast cancer in elderly individuals: recommendations of the International Society of Geriatric Oncology. *Lancet Oncol* 2007;8(12):1101-1115.

(5) Statistics Netherlands. Bevolking; prognose en waarneming. Omvang, groei, leeftijd, geboorte, vruchtbaarheid, sterfte en migratie 1950 - 2060. Accessed 9-1-2013. *statline.cbs.nl*

(6) Bastiaannet E, Liefers GJ, de Craen AJ et al. Breast cancer in elderly compared to younger patients in the Netherlands: stage at diagnosis, treatment and survival in 127,805 unselected patients. *Breast Cancer Res Treat* 2010;124(3):801-807.

(7) Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet* 2012;380(9836):37-43.

(8) Avis NE, Deimling GT. Cancer survivorship and aging. *Cancer* 2008;113(12 Suppl):3519-3529.

9) Bleicher RJ, Abrahamse P, Hawley ST, Katz SJ, Morrow M. The influence of age on the breast surgery decision-making process. *Ann Surg Oncol* 2008;15(3):854-862.

(10) Extermann M, Albrand G, Chen H et al. Are older French patients as willing as older American patients to undertake chemotherapy? *J Clin Oncol* 2003;21(17):3214-3219.

(11) Fried TR, Bradley EH, Towle VR, Allore H. Understanding the treatment preferences of seriously ill patients. *N Engl J Med* 2002;346(14):1061-1066.

(12) Kiebert GM, Stiggelbout AM, Kievit J, Leer JW, van de Velde CJ, de Haes HJ. Choices in oncology: factors that influence patients' treatment preference. *Qual Life Res* 1994;3(3):175-182.

(13) Levinson W, Kao A, Kuby A, Thisted RA. Not all patients want to participate in decision making. A national study of public preferences. *J Gen Intern Med* 2005;20(6):531-535.

(14) van de Water W, Markopoulos C, van de Velde CJ et al. Association between age at diagnosis and disease-specific mortality among postmenopausal women with hormone receptor-positive breast cancer. *JAMA* 2012;307(6):590-597.

(15) Bastiaannet E, Portielje JE, van de Velde CJ et al. Lack of survival gain for elderly women with breast cancer. *Oncologist* 2011;16(4):415-423.

(16) Foukakis T, Fornander T, Lekberg T, Hellborg H, Adolfsson J, Bergh J. Age-specific trends of survival in metastatic breast cancer: 26 years longitudinal data from a population-based cancer registry in Stockholm, Sweden. Breast Cancer Res Treat 2011;130:553-560.

(17) Jatoi I, Chen BE, Anderson WF, Rosenberg PS. Breast cancer mortality trends in the United States according to estrogen receptor status and age at diagnosis. J Clin Oncol 2007;25:1683-1690.

(18) Holleczek B, Brenner H. Trends of population-based breast cancer survival in Germany and the US: decreasing discrepancies,

but persistent survival gap of elderly patients in Germany. BMC Cancer 2012;12:317.

(19) NABON. Richtlijn Mammacarcinoom versie 2.0. Last updated 13-2-2012. Accessed 4-10-2013. *www.oncoline.nl/mammacarcinoom*

(20) Biganzoli L, Wildiers H, Oakman C et al. Management of elderly patients with breast cancer: updated recommendations of the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA). *Lancet Oncol* 2012;13(4):e148-e160.

(21) Zulman DM, Sussman JB, Chen X, Cigolle CT, Blaum CS, Hayward RA. Examining the evidence: a systematic review of the inclusion and analysis of older adults in randomized controlled trials. *J Gen Intern Med* 2011;26(7):783-790.

(22) Hamaker ME, Seynaeve C, Nortier JW et al. Slow accrual of elderly patients with metastatic breast cancer in the Dutch multicentre OMEGA study. *Breast* 2013;22(4):556-559.

(23) van de Water W, Kiderlen M, Bastiaannet E et al. External Validity of a Trial Comprised of Elderly Patients With Hormone Receptor-Positive Breast Cancer. *J Natl Cancer Inst* 2014;106(4):dju051.

(24) Paesmans M, Ameye L, Moreau M, Rozenberg S. Breast cancer screening in the older woman: an effective way to reduce mortality? *Maturitas* 2010;66(3):263-267.

(25) van de Water W, Bastiaannet E, Dekkers OM et al. Adherence to treatment guidelines and survival in patients with early-stage breast cancer by age at diagnosis. *Br J Surg* 2012;99(6):813-820.

(26) Pallis AG, Ring A, Fortpied C et al. EORTC workshop on clinical trial methodology in older individuals with a diagnosis of solid tumors. *Ann Oncol* 2011;22(8):1922-1926.

(27) Hurria A, Cohen HJ, Extermann M. Geriatric Oncology Research in the Cooperative Groups: A Report of a SIOG Special Meeting. *J Geriatr Oncol* 2010;1(1):40-44.

(28) Wildiers H, Mauer M, Pallis A et al. End points and trial design in geriatric oncology research: a joint European organisation for research and treatment of cancer-alliance for clinical trials in oncology-international society of geriatric oncology position article. *J Clin Oncol* 2013;31(29):3711-3718.

Part 1

Choosing the right treatment for the right patient