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CHAPTER 1

General Introduction

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Background

Breast cancer is the most common cancer in women in Western countries. In the Netherlands, nearly 17,000 new breast cancer cases were diagnosed in 2016. Although the disease affects women of all ages, it is more common among older women. Currently, about 40% of all cases are in women aged ≥65 years and this percentage is expected to increase as the population ages. Older patients also have a greater breast cancer mortality than younger patients. Consequently, there has been much concern about how to optimize cancer care for this patient population.

Despite this significant and growing patient population, little evidence is available to guide the management of breast cancer in older patients. Randomized clinical trials have frequently excluded older women based on their age or comorbid conditions. Consequently, the benefits and risks of treatment are often uncertain for older patients and results from trials conducted in younger patients can possibly not be extrapolated to the geriatric population. In addition, the few older patients that have been included in trials may not reflect the older patients in daily clinical practice, as they are generally healthier and might have more favourable tumour characteristics.

An important aspect in cancer treatment decision-making for older patients, is the patient’s preference. Currently, decision-making of breast cancer treatment is often done without the input of patients. Lack of shared decision-making between the clinician and the patient could potentially entail a decrease in satisfaction and treatment adherence of the patients. Therefore, it is stipulated that shared decision-making should be made a priority in breast cancer treatment in older patients, especially as it is often not clear which treatment option is most appropriate. Given this background, this thesis is directed towards exploring treatment decision-making between clinicians and older patients, with a focus on the preferences of the latter.

Tailoring treatment to the older patient’s context

Treatment decision-making for older patients is generally complex. Older patients frequently suffer from other medical conditions besides breast cancer and may take multiple medications, which may place them at increased risk of adverse outcomes. Further, the older patient population is highly heterogeneous, with patients of the same chronological age having large differences in physiological reserves, life expectancies, physical and cognitive functioning, geriatric health conditions, and possibly in preferences. These aspects make it difficult to determine the best individual treatment decision.

Due to a lack of treatment evidence, current (inter)national practice guidelines for breast
cancer are not able to recommend treatment options in older breast cancer patients.\textsuperscript{22} This means that with the absence of age-specific guidelines, clinicians are left with general treatment recommendations. However, for many older patients with breast cancer, the general treatment recommendations are difficult to apply to. Since 2007, an international group of experts of the European Society of Breast Cancer Specialists and the International Society of Geriatric Oncology have put efforts in releasing a set of recommendations for the management of breast cancer in older patients.\textsuperscript{9,10} Their recommendations state that treatment plans should not be based solely on the patient’s chronological age alone, but be tailored to the individual older patient’s context (e.g., general health status, comorbid conditions, and estimated life expectancy). In addition, it is recommended that as evidence about the best treatment option is often inconclusive, a shared decision-making approach between the clinician and the older patient should be an essential part of this process.

Shared decision-making

In recent years, it has become increasingly accepted that it is important to involve patients in medical decision-making and to elicit their preferences to make good individualized health care decisions.\textsuperscript{23} Shared decision-making is a process in which clinicians inform patients about all possible treatment options and encourage them to consider the potential benefits and risks, so that patients can form their preferences. The patient’s preferences are then combined with the best available medical evidence to decide which option best suits the patient.\textsuperscript{24} Assessment and prioritization of the patient’s preferences is particularly essential in decisions when there is more than one reasonable treatment option from a medical standpoint\textsuperscript{25} or when trade-offs between potential benefits and risks have to be made for which patient preferences vary.\textsuperscript{26} This is the case in the treatment of early-stage breast cancer as will be illustrated in following subparagraphs.

Treatment of early stage breast cancer

The majority of patients with breast cancer are diagnosed with stage 0-II (‘early stage’) disease,\textsuperscript{27,28} which typically refers to small tumours (i.e., a clinical lesion size ≤ 5.0 cm) that have not spread beyond the breast or lymph nodes close to the breast.\textsuperscript{22} Depending on the type and extension of the early BC, its treatment often involves a combination of different modalities (i.e., primary surgery potentially followed by adjuvant systemic therapies). Generally, patients with this diagnosis and their clinicians face a difficult decision-making process, which revolves around whether to perform a mastectomy or a breast-conserving surgery, potentially followed by adjuvant systemic therapies (hormonal or chemotherapies). Each of the abovementioned modalities involves risks and benefits, which clinicians clearly need to discuss with the patients, so that they can develop informed treatment preferences.\textsuperscript{24} Moreover, as this is a high impact decision-making process, it is preferable to elicit their
preferences in the early stages of this process.

**Type of surgery**

Primary treatment for patients with ductal carcinoma in situ (the most common type of stage 0) and stage I-II breast cancer consists of surgery. In most cases, patients of all ages are eligible for two surgical treatment options, namely a mastectomy or a breast-conserving surgery. Mastectomy involves a surgical procedure in which the breast is removed, while breast-conserving surgery is a less invasive procedure, but is followed by radiotherapy. Trials comparing the outcomes of both options have shown similar overall survival rates.\(^{29-31}\) However, the surgical options are different with respect to cosmetic outcome, local recurrence, and use of additional surgery or radiotherapy.\(^{32}\) As there is no best surgical treatment option from a medical standpoint, the decision between breast-conserving surgery and mastectomy can be made according to the patient’s individual preferences and values.

**Adjuvant systemic therapy**

After surgery, the next step in the treatment of stages I and II breast cancer may be chemotherapy and/or hormonal therapy. Adjuvant systemic therapy is generally recommended for patients with unfavourable tumour characteristics and a 10-year disease recurrence risk of ≥25%, and when treatment would result in an absolute benefit of ≥10%.\(^{22}\) Although these adjuvant systemic therapies have been shown to reduce breast cancer recurrence,\(^{33}\) each of these therapies may cause side effects.\(^{34}\)

In the Dutch treatment guidelines for BC treatment options, decision-making about adjuvant hormonal therapy is driven by the hormone receptor status and not by the patient’s age. With regard to adjuvant chemotherapy, the benefits of this systemic therapy are less clear for patients aged ≥70 years. The guidelines currently recommend that adjuvant chemotherapy may be considered for patients aged ≥70 years who are in good general health.\(^{22}\)

In general, older patients diagnosed with early breast cancer may benefit from adjuvant systemic therapy,\(^{35,36}\) however the benefits in this patient group may only be marginal. This means that both accepting and declining the therapies are clinically possible options. As there is no best treatment option, the patient’s informed treatment preference in which the benefits and risks are weighed should determine the treatment decision.

**Differences in treatment by age**

Population-based studies have reported that older patients less often receive standard treatment than younger patients. Despite the fact that the decision between breast-conserving surgery and mastectomy can be made independent of the patient’s age,\(^{22}\) lower rates of breast-conserving surgery in older patients have been observed.\(^{37,38}\) Also,
radiotherapy is more likely to be omitted after breast-conserving surgery in older patients and they less frequently receive (guideline recommended) adjuvant chemotherapy than younger patients with similar disease severity.\textsuperscript{35,39,40} After taking into account differences in patient and tumour characteristics (e.g., comorbid conditions, tumour size), there was still substantial variation between different age groups. This has directed the focus towards the preferences of patients and clinicians as potential important determinants of the decision-making process for older patients.\textsuperscript{41}

**Older patients’ decision-making about breast cancer treatment**

Extensive research to date has been performed on the factors that patients with breast cancer consider important when facing a decision between breast-conserving surgery with radiotherapy and mastectomy.\textsuperscript{42} Various influencing factors have been found, including fear of cancer recurrence\textsuperscript{43} and the impact of the surgery on body image.\textsuperscript{44} Studies on the association between age and breast cancer treatment have implied that a patient's preference for a specific treatment option or willingness to undergo treatment is influenced by a patient's age.\textsuperscript{45} For example, it is often believed that older patients may attach less importance to body image than younger patients and that they consider several weeks of radiotherapy to be a larger burden,\textsuperscript{46,47} and therefore are more likely to prefer mastectomy over breast-conserving surgery. It is also often assumed that many older patients judge that the small possible survival benefits of adjuvant systemic therapy do not outweigh the possible side effects\textsuperscript{48} and therefore they are more likely to refuse therapy. Also, it is often thought that older patients’ preferences may be based on other aspects than prolongation of life only, for example, on maintaining mobility and independence and quality of life.\textsuperscript{47}

Older patients’ treatment preferences are however an understudied topic in the field of breast cancer,\textsuperscript{47,49} in particular with regard to their preferences for adjuvant systemic therapy. A systematic review of studies on older cancer patients’ preferences found that none of the studies focused on adjuvant treatment for breast cancer.\textsuperscript{49} The few studies that have concentrated on older patients with breast cancer involved only patients aged ≥65 or ≥70 years,\textsuperscript{50-56} making it hard to decide whether the decision-making process of older patients is actually different from that of younger patients. In addition, other studies including breast cancer patients of all ages have generally not aimed to determine age-differences in treatment preferences or in the reasons for choosing one treatment over the other.\textsuperscript{57}

**Clinicians’ decision-making about breast cancer treatment**

Clinician preference has also been proposed to strongly influence the treatments that older patients undergo.\textsuperscript{58} Firstly, although the majority of patients want to be involved in treatment decision-making, it is often suggested that decision-making role preferences differ by patient
Older patients are thought to more often prefer to leave the decision to their clinician, thereby indicating that the treatment decision mainly depends on the clinician’s preference rather than on the patient’s preference. Secondly, there are indications that for their older patient clinicians often make unilateral decisions with regard to which treatment options are relevant based on the patient’s chronological age. Making decisions without having complete information available about the patient (e.g., comorbid conditions, social situation, concerns and preferences), may not result in a decision that is right for that particular older patient.

Previous research on clinicians’ preferences for treatment of older patients has mainly focused on oncologists of one specialty. In the Netherlands, it is nowadays standard of care that treatment plans are discussed in multidisciplinary team meetings. The team constitutes of at least a surgical, a radiation and a medical oncologist who collaborate together to come to a treatment advice that is in their patient’s best interest. Each of these different specialties is expected to approach the same patient from their own perspective, which could result in different treatment recommendations. This may be particularly present with regard to older patients, as clinicians can make different interpretations of the clinical evidence, since the benefits to older patients are not clearly defined and since the content of the treatment guidelines leaves room for alternative interpretations. Thus, opinions of the specialists involved in the treatment of older patients also require examination.

Aims of this thesis

FOCUS study
The research in this thesis is part of the FOCUS project (Female breast cancer in the elderly: Optimizing Clinical guidelines Using clinico-pathological and molecular data). This project was funded by a grant of the Dutch Cancer Society in 2007, and aimed to increase knowledge about tumour biology, treatment and survival outcomes of older patients with breast cancer. Amongst others, this resulted in a data set with detailed treatment and patient-related information of more than 3,000 female breast cancer patients of ≥65 years and who were diagnosed in the South West region of the Netherlands between 1997 and 2004. During data collection it became apparent that data about the preferences of older patients were largely absent. Consequently, older patients’ preferences was added to the FOCUS project as a new research topic.

This thesis
It is often suggested that older patients may have different preferences and motivations than younger patients, because of different life circumstances, values, priorities and medical conditions. However, little attention has been paid to assessing possible differences in the
perspectives of younger and older patients. With the addition of data on older patients’ treatment preferences and the factors that distinctively affect their preferences, clinicians will be able to better inform, support and guide older patients in decision-making. To better understand the process of treatment decision-making for older patients, it is also relevant to understand the opinions of their clinicians and which factors of the older patient they consider important when making treatment recommendations.

The overall aim of this thesis therefore is to gain a greater understanding of the preferences of both older patients with early breast cancer and clinicians with regard to treatment, with the first group being the central focus of this thesis.

Outline of this thesis

The first part of this thesis describes the perspectives of patients with early breast cancer on decision-making about surgical and adjuvant systemic therapy. Chapter 2 presents the results of a systematic literature review which identified studies on patients’ preferences for surgery and adjuvant systemic therapy in early breast cancer. PubMed and EMBASE databases were searched up to October 2012. The aim of this systematic review was to provide an overview of the factors that affect patients’ preferences for type of surgery and the minimal survival benefit that patients require from adjuvant systemic therapy to consider the therapy worthwhile.

Chapter 3 to 5 report on a prospective study which was carried out among patients with early-stage breast cancer who were scheduled to undergo primary surgery and who were eligible for both breast-conserving surgery and mastectomy. This study had a unique design characteristic where preferences were measured before patients had seen a surgical or medical oncologist to decide upon a treatment plan. Based on a psychological mechanism (i.e., cognitive dissonance reduction or post-hoc justification), individuals may have a strong preference for the treatment they are recommended. To minimize the impact of this phenomenon, we conducted this study in patients who had not yet been informed about their clinician’s advice.

Chapter 3 describes the preferences for type of surgery of both younger and older patients, and the factors they consider important when making the decision between breast-conserving surgery with radiotherapy versus mastectomy. Secondarily, older patients’ preferences for breast reconstruction following mastectomy are compared to those of younger patients. In Chapter 4, we assess whether there are differences in younger and older patients’ willingness to undergo adjuvant systemic therapy (i.e., adjuvant chemotherapy and adjuvant hormonal therapy) and their motivations for or against undergoing therapy. Chapter 5 presents a
comparison of both age groups’ preferred and perceived roles in making the decision about surgery and adjuvant systemic therapy.

The final chapter of this thesis focuses on the perspectives of clinicians about treatment of older patients. **Chapter 6** describes the treatment recommendations of breast cancer specialists concerning older patients. Via an anonymous, online questionnaire, we presented hypothetical cases of older patients (aged ≥70 years) to surgical, radiation and medical oncologists to identify how different patient-related characteristics affect their treatment recommendations, and whether the specialties differ in their recommendations.

In **Chapter 7**, the main findings, the implications for clinical practice and health care policy, and the future perspectives for research in this field are discussed. A summary in Dutch of this thesis is given in **Chapter 8**.
Reference list


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