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Chapter 10

Summary, general discussion and future perspectives

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Summary and general discussion

Part I: choosing the right treatment for the right patient

In the first part of this thesis, results of common breast cancer practice are studied in population based cohorts of older breast cancer patients.

In **Chapter 2,** the implementation of breast cancer screening in older patients is evaluated. Older breast cancer patients tend to present with higher disease stages at diagnosis, which may contribute to the increased risk of breast cancer mortality[1]. In 1998, the upper age-limit of the mass screening program in the Netherlands was extended from 70 to 75 years in 1998. It was assumed that breast cancer screening would result in early detection , improving breast cancer outcome in older patients[2]. Contrary to high expectations of health policy makers, it was shown that the extension of the upper age limit to 75 years did not result in a large decrease in the incidence of advanced stage breast cancer, while the incidence of early stage tumours has strongly increased. For every advanced stage breast cancer that was prevented, 20 additional women were diagnosed with early stage disease. This implies that the effect of the screening program in older women is limited and leads to overdiagnosis, which may expose older patients to unnecessary treatment of small tumours risking harmful effects of these treatments.

Chapter 3 shows that the risk of postoperative complications strongly increases with age, and is especially high in patients with multiple comorbidities, but does not result in worse survival outcomes. Still, the increased risk of surgical complications may be a valid reason to omit surgical treatment in frail older patients with endocrine receptor-positive disease, for whom primary endocrine treatment may an alternative option[3]. In recent years, the proportion of older women with early stage breast cancer who were surgically treated has strongly decreased, as shown in **Chapter 4**. The decline in surgical treatment had no impact on overall survival, thereby indicating that primary endocrine treatment may be the optimal treatment for a subset of older patients. However, it must be kept in mind that previous clinical trials have shown that omission of surgical treatment may lead to poor locoregional control[3], which may result in declining functional status and quality of life. Unfortunately, there are no studies available on the effect of surgical treatment or primary endocrine therapy on either of these outcomes.

Chapter 5 shows that patients with metastasized breast cancer are increasingly treated with palliative chemotherapy and endocrine therapy at all ages. Although these changes have resulted in improved survival of patients with metastasized breast cancer below the age of 65, the survival of patients aged 65 years and older did not improve in the past 20 years. This lack of survival gain in the oldest patient group may be explained by poor selection of patients for specific

treatments, resulting in both over- and undertreatment. A recent, small study by van de Water et al. suggested that treatment of older patients with metastasized breast cancer in an oncogeriatric care program may result in an improved overall survival[4]. Oncogeriatric care could result in a better selection of patients for certain treatments based on a comprehensive geriatric assessment[4], thereby improving individualized treatment. Presumably, individualized treatment will result in improved outcome, both in terms of survival as well as quality of life and functional decline, and this should be addressed in future studies.

Throughout this thesis, the importance of individualized treatment is advocated, taking individual comorbidity into account. An example of a prediction tool that is currently used to provide patients and doctors with an individualized treatment advise is the Adjuvant! online program, which calculates 10-year breast cancer recurrence risk, breast cancer mortality risk, and risk of mortality due to other causes, as well as expected benefits of adjuvant treatment[5]. This tool is widely used and recommended in several guidelines[6;7], but it was developed in a generally young patient population[5]. Therefore, the validity of the tool was assessed for older women in **Chapter 6.** Adjuvant! Online classifies patients according to comorbidity status, ranging from "perfect health" and "average for age" to "major problems". No instructions are available on how patients should be classified into these categories. In order to assess the impact of specific comorbidities on the performance of the model, the validation was performed with two comorbidity classifications. First, all patients were entered into the model with the setting "average for age". Second, an expert panel categorized all patients into the categories used by Adjuvant! Online, in resemblance of daily clinical practice. It was shown that for both models, the tool does not accurately predict breast cancer recurrence and survival in older patients, which implies that the model should not be used in this population. Therefore, a new prediction tool for older patients is highly warranted, and this topic is discussed later in this chapter.

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

In part II, several methodological issues concerning studies that investigate treatment of older breast cancer patients are assessed[7;8]. One important methodological issue for future studies investigating breast cancer treatment of older patients is the choice of proper endpoints. The general consensus in the geriatric oncology field is that patient-related endpoints such as functional status, cognitive status and quality of life are essential in order to weigh benefits and disadvantages of specific treatments[9]. However, **Chapter 7** shows that these endpoints are rarely incorporated in current trials. In addition, the study showed that only 4% of currently ongoing breast cancer trials specifically target older patients. This implies that current ongoing trials are unlikely to add to the gap of knowledge in treating older patients with breast cancer.

Besides patient-related endpoints, breast cancer specific endpoints such as breast cancer survival are important in order to estimate benefits of specific treatments. However, establishing causes of death in older patients can be notoriously difficult, as patients with a breast cancer diagnosis who die from other causes such as cardiovascular incidents, are often registered as "death from breast cancer". Previous studies have shown that causes of death extracted from death certificates of cancer patients are not always accurate and can overestimated cancer as a cause of death[10;11]. This issue is of large importance in older patients, as the risk of competing mortality strongly increases with age[1], which can lead to an even larger overestimation of breast cancer mortality in elderly when death certificates are used. Therefore, breast cancer relapse is probably a more reliable breast cancer specific endpoint than breast cancer specific survival in older breast cancer patients.

In **Chapter 8**, it is shown that competing endpoints can strongly influence the interpretation of causal effects, especially when inappropriate statistical models are used for specific research questions. First, it is shown that in populations with a high prevalence of competing events, the Kaplan Meier method overestimates the absolute risk of the event of interest. In addition, it is shown that for etiological research questions, in which causal effects of specific factors of treatments are studied, statistical models should not incorporate the risk of competing risk. Survival analyses such as the Cox Proportional Hazard Model are most appropriate in this context. However, in prediction, "true" absolute risks of specific outcomes are studied, which means that it is essential to incorporate competing risks in the analyses. The survival analysis according to Fine & Gray is the most well-known model that takes competing endpoints into account[12]. In order to draw valid conclusions from studies that assess cause-specific endpoints, it is essential to use the correct type of analyses in order to estimate reliable effects of certain factors.

In **Chapter 9**, methodology of previously published observational studies that investigated breast cancer treatment in older patients is reviewed. Due to the poor and selective accrual of older patients in clinical trials, the very small number of trials that specifically target older patients, and the poor choice of endpoints of clinical trials, it is unlikely that clinical trials will fill the gap of knowledge on treatment of breast cancer in older patients in the next decade. Therefore, it is important to look for alternative study designs, such as observational research. However, it is essential to use proper methodology in such studies, as treatment is not allocated by randomization. Therefore, directly comparing two treatments in relation to patient outcome in observational studies can result in so-called confounding by indication. In this chapter, it is shown that the vast majority of observational studies directly compare treatment strategies, and therefore result in bias due to confounding by indication. This is a pity, as there are several methods that can be used as a proper alternative. For example, the instrumental variable analysis is a method to deal with confounding by indication. An instrumental variable is a factor

that allocates treatment, but is not related to the outcome[13]. Such a variable can therefore be considered as "pseudorandomization", provided that it is not related to the outcome through any other way than through the treatment. By using such inventive methods, observational studies could become an essential part in the path towards evidence-based treatment of older breast cancer patients.

Future perspectives

Individualized treatment

The key to improve outcome of older women with breast cancer, will be to individualize treatment. In general, Dutch breast cancer specialists tend to follow guidelines quite strict, although this is less the case in older breast cancer patients[14]. Indeed, due to the heterogeneity of the older breast cancer population, a "one-size-fits-all"-approach seems inappropriate. Therefore, this topic should be integrated in the guidelines, in order to improve individualized decision making. For example, guidelines could include specific treatment recommendations for certain subgroups of patients based on comorbidity status and functional status. Of course, it is also important to take tumour characteristics and tumour stage into account in order to estimate the risk of recurrence and breast cancer death. However, in older patients, it may even be more important to make treatment decisions in the context of physiological ageing and comorbid diseases. Although there is a certain group of patients that will die *from* breast cancer, an even larger group of older breast cancer patients will die *with* breast cancer but from another cause[1]. In this last group, it is essential to weigh the benefits and harms of treatment, as overtreatment may result in unnecessary harmful effects.

One of the priorities of future research should therefore be to develop a new prediction tool that can be used to aid decision making in daily clinical practice. As shown in this thesis, existing tools such as Adjuvant! online are not sufficient to predict breast cancer outcome in older breast cancer patients. Ideally, a new prediction tool should not only predict overall survival and breast cancer survival but also the risk of dying from other causes, functional decline and quality of life after specific treatments. Such a prediction tool should not only incorporate tumour characteristics as main predictors, but also detailed patient characteristics including comorbidity and functional status.

These patient characteristics may be gathered in a geriatric assessment, which is used to assess the whole spectrum of health issues and functional status in older patients[15]. It consists of validated measurements for comorbidity, medication, (instrumental) activities of daily living, nutrition, cognition, social status and depression[16]. Several previous studies have shown that it is a feasible

tool that can be used by oncologists in daily clinical practice[16-18]. Currently, 20-50% of treatment decisions is influenced by the geriatric assessment when it is performed[17], but no studies have investigated if this truly leads to improved outcomes for older patients[19]. However, a recent but small study has suggested that treatment of older patients with metastasized breast cancer in an oncogeriatric practice may result in improved survival of older patients, which may be explained by an improved selection of patients for certain treatments[4].

A major challenge in incorporating geriatric assessments in daily oncological practice, is the fact that there are many different forms of the geriatric assessment[19]. Until now, it remains unclear which tools are most useful in daily clinical practice[18-20]. Therefore, studies that investigate the value of the geriatric assessment in clinical practice will be essential in order to improve selection of patients for specific treatments. Furthermore, future studies should focus on certain cut-off points that can be used to aid clinical decision making. In addition, a full geriatric assessment may be time consuming and unnecessary in a subset of "fit" older patients. Possibly, the use of frailty screening instruments may be able to distinguish "fit" older patients, in whom a geriatric assessment may not be necessary, from more vulnerable patients in whom a full geriatric assessment is indicated[21]. Finally, the geriatric assessment could be used to initiate interventions to improve general health status before cancer treatment commences, but again, no previous studies have investigated this in breast cancer patients specifically. Hence, the use of the geriatric assessment in daily clinical practice is promising, but not yet evidence-based. However, the International Society of Geriatric Oncology (SIOG) does recommend performing a geriatric assessment in all older cancer patients, in order to detect unaddressed problems, improve their functional status, and possibly their survival[20].

A promising study on the use of geriatric assessments in daily clinical practice that is currently undertaken is the *"Climb Every Mountain Study"*, in which a geriatric assessment is performed at time of diagnosis, and which prospectively registers functional, cognitive, psychological and social decline as well as quality of life of older breast cancer patients. In a second phase, a tailor-made intervention will be developed, which will specifically target the problems that are encountered for each individual patient.

Individualized screening

Individualizing the approach of the older breast cancer patients is not only recommended for the choice of treatment, but may also be important in the context of breast cancer screening. As shown in Chapter 2, the current mass breast cancer screening program results in a proportion of overdiagnosis, with potentially harmful effects. It is well-known that screen-detected tumours are less aggressive than so-called interval-tumours[22]. Likely, a subset of older

patients are at increased risk of competing mortality, and therefore will not benefit from early detection. Therefore, we propose a more individualized approach toward the screening of older women. Currently, there are several existing tools that predict the risk of breast cancer[23]. In older women, future tools should not only incorporate the risk of breast cancer, but also of competing mortality, in order to assess which patients may benefit from breast cancer screening, and which patients may be "better off" without.

Shared decision making and management of breast cancer care

Another important aspect in clinical decision making in older patients, concerning both screening and treatment, is the patients' preference. In contrast to younger patients, older cancer patients are more affected by cancer and cancer treatment in terms of physical than psychological functioning[24]. This is of major importance, as functional limitations can result in loss of independence and institutionalization of older patients. Previous studies have suggested that although older patients are willing to accept adverse events of treatment, they are less willing to trade absolute survival gain for negative impact on quality of life, functional independence and cognitive function[25-28]. In addition, treatment choices of older patients are influenced by other factors than in younger patients[29;30]. For example, with regard to surgery, older patients value the risk of recurrence, body image or work-related issues less than younger patients [30]. Remarkably, older patients more often prefer a physician-based treatment decision than younger women[31], but this may be due to poor knowledge and education of older patients[29]. Hence, future studies should investigate the information needs and patients' preferences of older patients. Currently, the *"FOCUS on Choice"* study is undertaken as an extension of the FOCUS-project that was partly used for this thesis. The study investigates patients' preferences of older breast cancer patients with regard to surgical treatment, radiotherapy, systemic treatment, and information requirements, and will add to the process of shared decision making in daily clinical practice.

In the Netherlands, all individual breast cancer treatment plans are discussed in multi-disciplinary teams. The Dutch guideline states that this team should at least consist of a surgeon, a pathologist, a radiologist, a radiotherapist, a medical oncologist and a trained nurse, and can be extended by a plastic surgeon and a clinical geneticist[6]. With the growing population of older women with breast cancer, the team may be extended with a geriatrician. The increasing complexity of breast cancer care requires well-established cooperation of geriatrics and oncologists. In addition, the role of specialised nurses as case managers will become increasingly important in this process, as they are generally well accessible for patients, caregivers and medical specialists.

Future research in older breast cancer patients

Large observational studies will be essential to improve knowledge and gather data on

quality of life and functional decline after specific treatments. Currently, the general consensus in the medical world is that guidelines for any type of treatment should be based on findings of randomized clinical trials (so called Level A evidence)[32]. However, clinical trials are often not feasible in older individuals, because of ethical reasons and strong patient preferences[33]. Past and current clinical trials often exclude a large proportion of older patients based on age, comorbidity status or functional status. It was shown that older patients who participate in clinical trials, are not representative for the general older breast cancer population, as the "weakest" patients are generally not enrolled[33;34]. Also, it was shown in this thesis that current clinical trials rarely address endpoints that are of particular importance for older patients. This means that it is unlikely that clinical trials will provide the necessary evidence on treatment of older breast cancer patients. Therefore, "Level A evidence" will probably remain rare with regard to treatment of older breast cancer patients.

Observational studies can generate a large amount of reliable data, with adequate representation of the true population of older women with breast cancer[34]. In observational studies specific methodological pitfalls must be taken care of. Direct comparison of treatment strategies may induce bias due to "confounding by indication". As shown in this thesis, many observational studies use such inadequate methodological methods, which can result in incorrect assumptions. Unfortunately, this results in undervaluation of observational research. New, inventive methodological methods such as the use of an instrumental variable are of great value in this type of research[13], and should be explored in order to improve the evidence-base for treatment of older breast cancer patients. The main limitation of instrumental variable analyses is the identification of a proper instrumental variable that is truly unrelated to the outcome of patients through another way than the evaluated treatment. In order to use this methodology on a larger scale, large, quality-assured databases are necessary. The current practices of treatment of older breast cancer patients strongly differ across countries[35], and this provides researchers with the opportunity to compare outcomes of these different strategies. A promising project that may lead to new insights is the European Registration of Cancer Care (EURECCA) project[36]. This project was initiated by the European CanCer Organisation (ECCO) and aims to create a multidisciplinary European registration structure for patient, tumour, and treatment characteristics linked to outcome registration[36]. This type of multidisciplinary, international collaboration may become important to improve a more solid evidence base for treatment of older cancer patients. Ideally, clinicians and patients should also be able to access these data in order to create an open and informative structure. Major challenges in these international comparisons are how to account for differences in health systems, socioeconomic disparities and methods of registration across countries[37]. This topic deserves further attention before international comparisons can be widely implemented in clinical research and clinical practice.

Conclusion

In conclusion, older patients are at increased risk for overdiagnosis of breast cancer due to population-based screening. Despite changing treatment strategies, breast cancer prognosis of older women has not improved in recent years. Current treatment strategies and decisions tools that are used in older breast cancer patients are insufficient, and it is unlikely that randomized clinical trials will lead to major improvements in this area in the near future. Observational studies will become increasingly important in order to develop individualized treatment for older breast cancer patients, but it is essential that accurate methodological methods are used in these studies.

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