Chapter 11

Discussion

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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

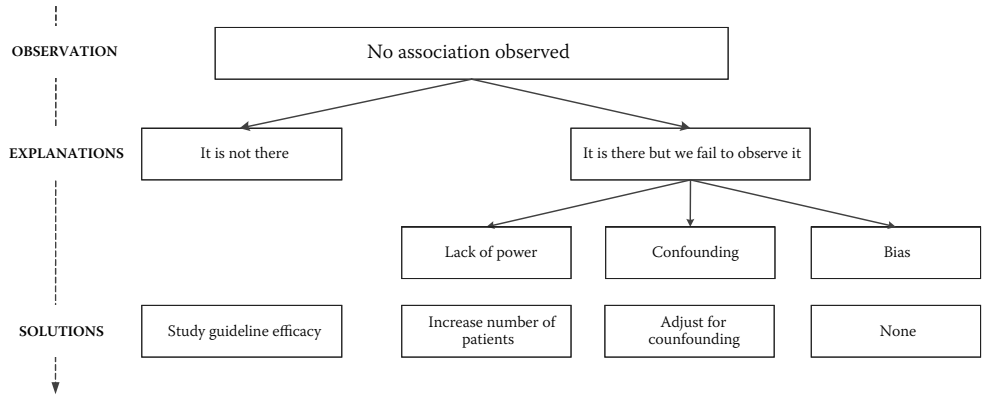

Figure 1. No association between guideline adherence and survival; explanations and solutions.

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).

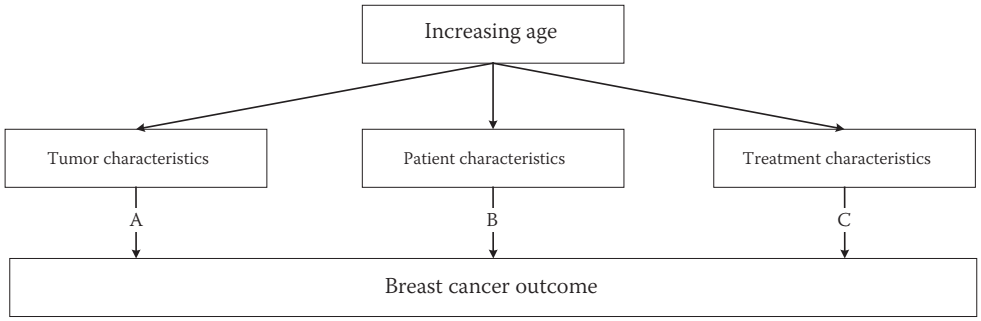

Figure 2. Relation between increasing age and prognosis.

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

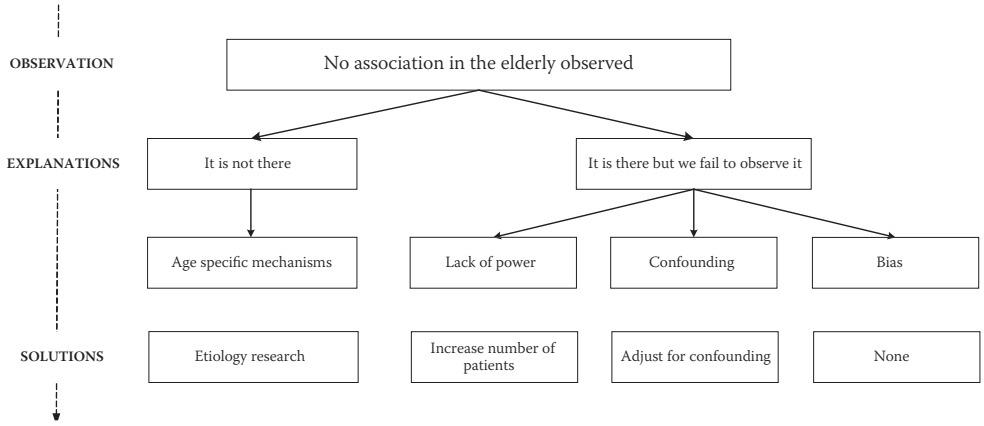

Figure 3. Explanations for the absence of an observed association.

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.

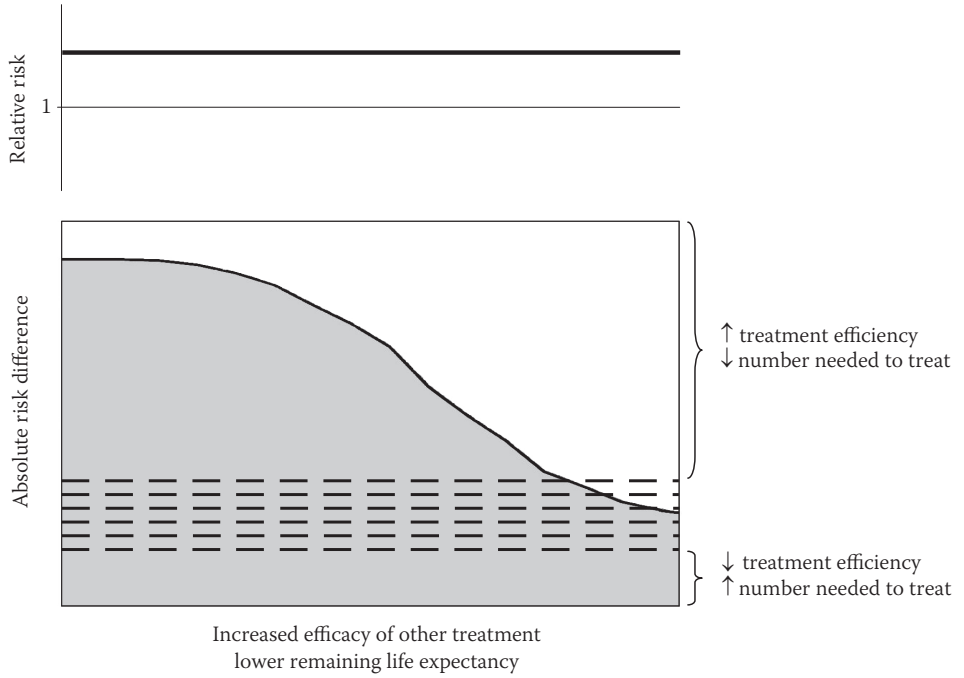

Figure 4. Evaluation of treatment efficiency by relative risk and absolute risk difference.

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

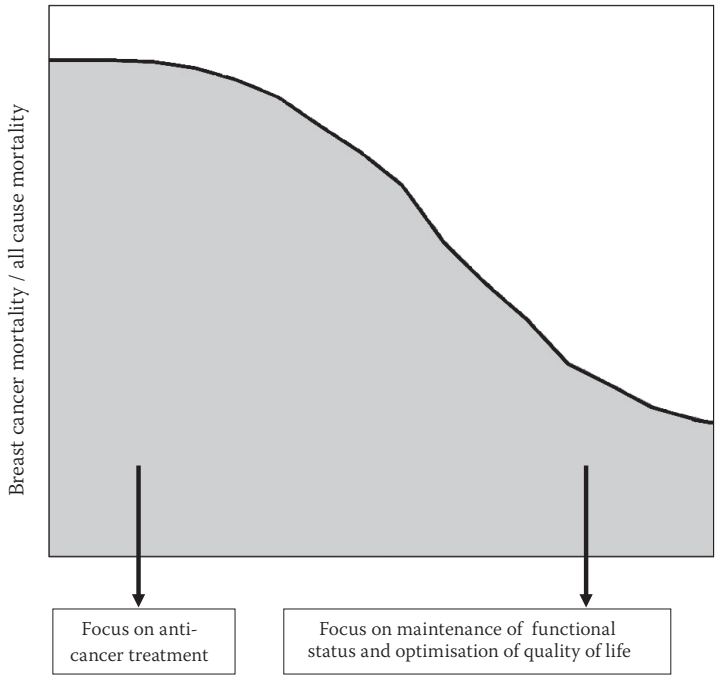

Figure 5. Treatment approach of different groups of elderly breast cancer patients.

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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