# Refining individualized medicine in older patients with breast cancer

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# Summary and general discussion

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# SUMMARY

## Part I: Evaluating breast cancer prognosis and other-cause mortality

Breast cancer outcomes in relation to other-cause mortality were previously studied in a trial population.[1] However, due to the selective inclusion of fit older patients in trials, competing mortality is more pronounced in the general population.[2] In **Chapter 2**, we assessed the relation of older age and the risks of locoregional and distant recurrence in a population-based cohort of over 18,000 patients aged 70 years or older with non-metastatic breast cancer. Other-cause mortality was considered by performing competing risk models, and presented as separate outcome. Despite the higher competing mortality, patients aged 75-79 years had a higher risk of distant recurrence than those aged 70-74 years after adjustment for tumor and treatment characteristics. This finding indicates that some patients in the 75-79 age category may benefit from more extensive treatment. The high competing mortality underpins that differentiating between patients with high and low risks of other-cause mortality is essential for patient selection, especially for adjuvant treatments.

Next, in **Chapter 3**, we studied breast cancer mortality and other-cause mortality after a locoregional or distant recurrence. Breast cancer mortality almost exclusively occurred after distant recurrence as first event. Locoregional recurrence as first event was a predictor for worse breast cancer mortality, but the contribution of breast cancer mortality after locoregional recurrence to all breast cancer mortality was limited. This is explained by the low rate of locoregional recurrences. Despite an increase in 10-year other-cause mortality from 24% in patients aged 75-79 years to 73% in patients aged 80 years or older, after a distant recurrence, other-cause mortality was evidently outweighed by breast cancer mortality. **Chapter 2** and **Chapter 3** emphasize that it is essential that prediction tools consider the competing mortality risk while estimating breast cancer outcomes in older patients, and present other-cause mortality as separate outcome.

In **Chapter 4**, we compared the predictive value of the Charlson Comorbidity Index for other-cause mortality with using a simple comorbidity count because an optimal comorbidity score to be used in prediction tools has not been established.[3,4] In addition to age, both comorbidity scores improved the prediction of other-cause mortality. Our main finding was that the predictive value of the Charlson Comorbidity Index for 5-year other-cause mortality was similar to the predictive value of the comorbidity count. As it is easier to use, we would argue the use of comorbidity count in the development of new prediction tools for older patients with breast cancer.

## Part II: Omission of treatments in selected older patients

In the second part of this thesis we have investigated the effect of omission of individual components of treatment for early breast cancer in subgroups of older patients on recurrence and survival. In clinical practice, these treatments are decided on based on disease characteristics, age, comorbidity, and other aspects of a patient's general health and functionality. As the latter factors are not available or not well-recorded in observational databases, conventional statistical techniques cannot adjust for these factors.[5] We applied a novel methodology which can avoid confounding by unmeasured factors by creating a pseudorandomized situation under certain assumptions; the instrumental variable (IV) method. Hospital was used as IV as treatment rates vary across hospitals, but no major differences in case-mix between hospitals is expected. In **Chapter 5**, we investigated the effect of omission of radiotherapy after breast-conserving surgery on locoregional recurrence by comparing the outcomes of patients treated in hospitals with higher (96%) and lower (72%) rates of radiotherapy in patients aged 75 years or older with T1-2N0 breast cancer. Thirty-nine percent received endocrine treatment conform Dutch treatment guidelines. Locoregional recurrence rates were low (2.2%-3.2% after nine years), even in the patients treated in hospitals with lower radiotherapy rates (3.2%). No association was found between radiotherapy use and locoregional recurrence risk.

In **Chapter 6**, we investigated the effect of omission of primary surgery in patients aged 80 years or older with stage I-II hormone-receptor positive breast cancer by comparing survival of patients treated in hospitals with higher (83%) and lower (55%) rates of surgery. Overall, 94% of the patients who did not have surgery were treated with primary endocrine treatment. Patients treated in hospitals with lower rates of surgery showed a worse 10-year relative and overall survival compared to patients treated in hospitals with higher rates of surgery. Interestingly, the survival curves did not diverge during the first five years.

In **Chapter 7**, we identified patient barriers and facilitators to omit components of treatment for early breast cancer with a limited beneficial effect. We organized focus groups with patients who were 70 years or older when they were treated for breast cancer and performed a survey among a larger group. More than half of the patients who responded to the survey stated they would agree to omit radiotherapy and axillary lymph node dissection if this was proposed so by the clinician. In contrast, almost all patients reported barriers to omit primary surgery related to the necessity of primary endocrine treatment. Barriers for omission of radiotherapy and axillary lymph node dissection were mostly general factors related to fear of recurrence, receiving suboptimal treatment and social support. Reassurance on recurrence risks and involving family members for social support are therefore key actions to enhance the de-implementation of these treatments.

### Part III: Geriatric assessment and outcomes

Chapter 8, the last part of this thesis, consists of a prospective cohort study of geriatric outcomes in patients aged 70 years or older with metastatic breast cancer. A comprehensive psychosocial assessment was performed at baseline, and longitudinal changes in functional status, psychosocial functioning and quality of life were assessment over a 6-month period. Patients were recruited in four Dutch hospitals. Most importantly, the prevalence of depressive symptoms and apathy were higher than in the healthy older population. Although the geriatric assessment effectively detected these psychosocial problems, a shorter screening may be more feasible. The optimal screening tool and the effect of psychosocial interventions on quality of life are subjects for future research. The finding that functional status and quality of life did not change while several patients died during the study period suggests that functioning remains stable until a rapid, rather than a gradual, deterioration leads to death. This should be confirmed in a larger cohort.

## DISCUSSION AND FUTURE PERSPECTIVES

### Prediction models facilitate individualized treatment

Breast cancer is not a single disease entity. The prognosis strongly depends on the tumor biology and the stage at which the disease is detected.[6] This prognostic variation has become even more pronounced since the detection of premalignant lesions with excellent prognosis has greatly increased due to screening programs.[6,7] Individualized treatment is defined as choosing the right treatment for each unique patient. Prediction models can facilitate individualized treatments by predicting the recurrence risk according to tumor and patient characteristics. The expected treatment effect can then also be estimated based on this profile. The role of genomic testing in individualized treatment in younger and middle-aged patients is much debated at the moment.[8] Meanwhile, individualized treatment in older patients lags behind. Foremost, we have thus far not succeeded to specify the effect of age and general health on breast cancer outcomes and treatment effects. For clinical practice this implies that it is up to the treating clinician to consider this impact. Furthermore, treatment decisions are more likely to be influenced by treatment "culture" in a country. Substantial treatment variation is observed across countries and regions in registration databases, indicating that older patients are prone to both overtreatment and undertreatment.[9-11]

### Improving the prediction of prognosis

It was demonstrated in the second part of this thesis that the risk of dying from other causes at 10 years strongly increases from 24% in patients aged 70-75 years to 73% in patients aged 80 years in our population-based cohort. When we considered this age-dependent

competing mortality risk, we found in Chapter 2 that patients aged 75-79 years had an increased risk of a distant recurrence. Furthermore, in Chapter 3, other-cause mortality was almost completely weight out by breast cancer mortality once a distant recurrence occured. While considering other-cause mortality on a population level as we did, these findings indicate that some patients aged 75-79 may benefit from more extensive primary treatment, as well as some patients with a recurrence may be undertreated. Patients with a high risk of breast cancer mortality and a low risk of competing mortality are the ones most likely to benefit. An accurate prediction of breast cancer mortality and other-cause mortality on the individual patient- level is therefore crucial for selecting the right patients. This way, undertreatment and overtreatment can be prevented as much as possible.

The PREDICT tool is currently the most frequently used prediction model for survival rates in patients with breast cancer.[12] Although this tool presents other-cause mortality in addition to overall mortality, these estimates are not adjusted for the presence of comorbidity and hence other cause mortality. This hampers the prediction for individual older patients. A validation study in patients aged 65 years or older demonstrated that overall mortality was *under*estimated in patients with zero or one comorbidity, and increasingly *over*estimated in patients with more than two.[13] In other words, this tool does not account for the fact that a patient aged 75 with two comorbidities has a higher chance of dying from other causes than a similar patient aged 75 without comorbidity. The question is then raised what comorbidity measurement should best be used in future prediction tools. In Chapter 4, it was found that the original Charlson Comorbidity Index performed similar to a simple comorbidity count. As it is easier to use, we would argue the use of comorbidity count in the development of new prediction tools for older patients with breast cancer.

Importantly, it has been noted in literature that the influence of comorbidity on remaining life expectancy diminishes with increasing age after 70 years.[14] The population of older adults is heterogenous by nature due to variation in the aging process. This means that older adults of the same calendar age have different physiological ages specified by differences in physical reserve, comorbidity, and functionality. However, the new insight indicates that this variation in physiological age diminishes with increasing calendar age. This understanding of the aging process is important because it implies that the interaction between age and comorbidity should be considered in prediction models. Also, geriatric parameters might improve the prediction of other-cause mortality as they are used in general life expectancy models for healthy individuals.[15] Future research is needed to investigate the added value in patients with breast cancer.

## Improving the prediction of treatment effects

In addition to the prediction of prognosis, the PREDICT tool presents the expected benefit of adjuvant treatments based on overviews of randomized data.[16,17] Since these overviews comprise historic trials including few older patients, who were also a fit selection, the effect presented there are likely an overestimation of the true effect for most older patients in clinical practice. In recent years, it has been a key focus to increase the evidence base for treatments in representative older patients. One of the main goals was, and still is, to define subgroups of older patients in whom omission of individual components of the established treatment for early breast cancer does not lead to worse outcomes. In particular, patients who already have a low recurrence risk without treatment or patients with a high risk of dying from other causes diminishing the effect of treatment. It is unlikely that randomized data will emerge to define these subgroups. Therefore, valid methods to do so by using observational data are sought.

## The instrumental variable methodology

A novel methodology has been proposed to allow for a valid analysis of treatment effects using large observational databases. This instrumental variable (IV) methodology avoids confounding by both measured and unmeasured factors by creating a pseudorandomized situation under certain assumptions; the IV is associated with the treatment (first assumption), but unrelated to confounding factors (second assumption) or to the outcome other than through the instrument (third assumption). Geographic areas are often used as IV, because treatment variation is observed across countries and regions beyond what variation explained by case-mix. The IV methodology seems a particularly promising method to use in research on treatment effects in older patients with breast cancer, because direct comparisons are prone for confounding by unmeasured factors related to general health and functionality.[5]

In Chapter 5 and Chapter 6 of this thesis, we investigated the effect of components of treatment for early breast cancer in subgroups of patients in which the beneficial effect of these treatments is questionable. We did this by performing the IV methodology using hospital as IV. The outcomes of patients treated in hospitals with different treatment rates (higher, moderate, lower) were compared. In Chapter 5, we found that the locoregional risk was low for all groups, even in patients treated in hospitals with lower radiotherapy use. Our findings indicate that the radiotherapy-use after breast conserving surgery in this subgroup of patients aged 75 years or older with T1-2N0 breast cancer can be lowered without increasing the rates of locoregional recurrence. Two RCTs showed that the beneficial effect of radiotherapy is very limited in patients aged 70 years or older with tumors up to 3 cm treated with endocrine treatment.[18,19] Based on results of these trials, international guidelines have adopted the omission of radiotherapy for this patient selection.[20] However, concerns regard-

ing the generalizability of these trial results, especially with regard to endocrine therapy adherence, are one of the reasons for persistent radiotherapy-use.[21] Our findings contradict these concerns about higher locoregional recurrence risks in the absence of systemic therapy as only a third received endocrine treatment conform Dutch treatment guidelines.[22]

In contrast, in Chapter 6, we found worse survival outcomes in patients treated in hospitals with lower rates of primary surgery. This indicates that increasing the rates of primary surgery can improve survival of this subgroup of patients aged 80 years or older with stage I-II hormone-receptor positive breast cancer. We did observe that the survival curves did not diverge until after five years. Consequently, it can be argued that primary endocrine therapy as alternative for surgery is justified in patients with a life expectancy of up to five years rather than two to three years which is currently recommended by international guidelines based on historical trials.[23,24] Yet, the disadvantages of primary endocrine treatment, most importantly the potential side effects, should not be underestimated.

Overall, the IV methodology worked well in our population-based cohort. Foremost, the variation in treatment was sufficient to construct groups with substantial different treatment rates (approximately 25% between the higher and lower rates groups). In other words, the IV was strong enough to make inferences about the effect on the outcome. Second, the few small differences between the three IV groups indicate that the unmeasured differences are also minimal. However, despite being small, these differences between the IV groups mean that our IV could not meet all assumptions. As an example, from Chapter 6, patients treated in the hospitals with lower rates of surgery remained somewhat older compared to patients treated in the hospitals with higher rates of surgery. Residual confounding could therefore not be completely ruled out. Also, in Chapter 5, it was apparent from the wider confidence interval that the IV analysis reduces the statistical power. Truly large databases are therefore most suitable for an IV analysis.

The European Registration of Cancer Care (EURECCA) consortium is initiated to combine cancer registry data from countries across Europe to compare treatments and outcomes. Unfortunately, differences in health care systems and subsequent differences in patients and breast cancer subtypes between countries hamper a formal IV analysis. Of course, such a comparison remains extremely valuable to give direction to future studies. Overall, the IV methodology is feasible if confounding by unmeasured variables exists. However, to find an instrument that meets all assumptions in a clinical database providing sufficient statistical power seems too optimistic.[25]

## Future research on treatment effects

Down the line, RCTs remain the golden standard to study treatment effects, even in the heterogenous older population. However, efforts need to be made to improve the external validity by including older and frail patients. This way, structured subgroup analyses based on general health can be performed. As a result of treatment bias, patients are treated with new treatments for which evidence in older patients is lacking. On the contrary, treatments for which RCTs have demonstrated that the beneficial effect is very low in subgroups of older patients are persistently used.[21,26] In other words, once a treatment is used, it is hard to turn back time and stop using the treatment. It is unfeasible to repeat an RCT for the sole purpose of doing general health subgroup analysis. Despite the urgent call for these secondary trials, few have arisen.[27,28] This is not surprising given the time and costs RCTs take. Maybe, policy makers and supporting funds should mandate the inclusion of older and frail patients in the primary trial or mandate the secondary trial. Furthermore, the clinicians urging for evidence for treatments in older patients may not realize that the poor accrual is partly due to their own decision not to include these patients. Clinicians frequently judge a patient unfit to participate in a study. If more attention is paid to older patients included in trials, clinicians may be more comfortable including them. Moreover, it is questionable whether all these excluded patients are truly unable or unwilling, or whether this is an unfortunate assumption.

For established treatments, patients do not let themselves be randomized any more, for example the ESTEem (Endocrine +/– Surgical Therapy for Elderly women with Mammary cancer) trial on the omission of primary surgery had to close early due to poor accrual. In these cases, prospective cohorts of similar treated patients, that can be considered single-arm trials, may be a valuable alternative. A recent example is the Tailored treatment in Older Patients (TOP)-1 study. This cohort comprises patients aged 70 years or older with low-risk breast cancer who do not undergo radiotherapy or endocrine therapy after breast-conserving surgery.[29] All patients undergo a geriatric screening, one of the secondary aims is to look into subgroups based on general health.

## Improving the prediction of treatment harms

Finally, in order to individualize treatments, the prediction of adverse effects should be improved. Older patients are more prone for toxicity and functional decline than younger patients. This is essential information as the quality of life may become more important with age, in addition to length of life. The Cancer Research and Aging group have developed a tool to predict toxicity from chemotherapy that includes findings from a geriatric assessment.[30] They have also demonstrated a decline in physical functioning in patients aged 70 years or older receiving chemotherapy.[31]

Risk groups for adverse effects after surgery, radiotherapy and endocrine therapy need to be identified and patient criteria be defined. These questions will hopefully be answered soon by prospective cohort studies which are collecting the final follow-up for functional outcomes. The Bridging the Age Gap is an initiative in the United Kingdom that focusses on the surgical treatment of older patients.[32] In a cohort of more than 3000 patients over 70 years, the effect of surgical treatments on functional status and quality of life will be studied in subgroups. Similarly, performed in the Netherlands, the Climb Every Mountain study comprises a prospective cohort of patients aged 70 years or older whose functional outcomes and quality of life are followed over time. This database will be used in the development of a new prediction tool specifically designed for older patients in the Prediction of Outcome and Toxicity in older patients with bREasT cancer (PORTRET) study. This tool is going to incorporate competing mortality, toxicity and functional outcomes. Patients included in these prospective studies are characterized by a baseline geriatric assessment. The predictive value of the separate parameters will be of special interest.

The last chapter of this thesis gives an example of how functional outcomes can be studied. Although we managed to include both fit and frail older patients, we experienced how selection and response bias are difficult to prevent. Participating patients were fit enough to receive treatment and willing and able to participate in a self-administered survey. It is however plausible that patients with deteriorating health and function were underrepresented among responders. These will be the challenges for future prospective cohort studies: to include the right patients and to minimize selective loss to follow-up. In the Triaging Elderly Needing Treatment (TENT) study, all older patients that are planned to undergo a major intervention, regardless of the disease, undergo a geriatric assessment prior to the intervention.[33] Afterwards, short term outcomes are collected from the medical files and a telephone call by geriatric specialist nurses. Such a systematic approach could improve the inclusion of frail patients. It is evident that the inclusion of frail patients is essential to determine whether frail patients are at risk for adverse outcomes. Response bias occurs for example if patients with functional decline are lost to follow-up partly due to their functional decline. To minimize the burden of the follow-up measurements, telephonic assessments or home visits could reduce response bias.

In conclusion, the number of older patients with breast cancer will grow rapidly in upcoming years. Prediction tools are urgently needed to improve individualized treatment and reduce undertreatment and overtreatment of older patients as much as possible. Fortunately, prediction tools specifically designed for older patients with relevant outcomes are being developed. The main challenge will be to provide the data that allows to estimate prognosis and treatment effect for the subgroups of the older patients based on age, comorbidity and functionality.

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