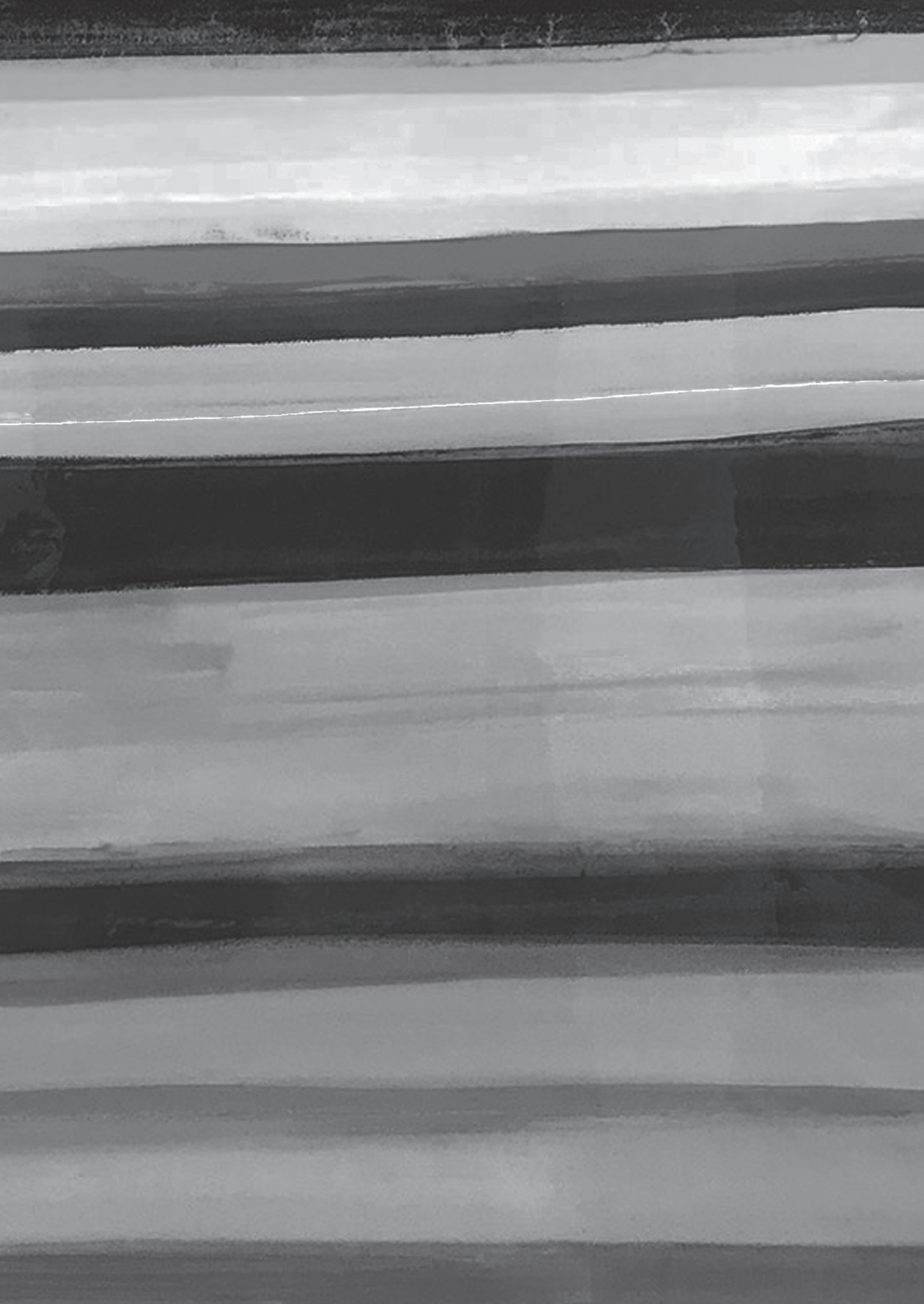
Coming of age : treatment and outcomes in older patients with breast cancer

Derks, M.G.M.



CHAPTER 10

Summary and discussion

M.G.M. Derks

Leiden, December 2017

SUMMARY

Part I: Evaluating treatment of older patients with breast cancer

In **Chapter 2,** data from five population-based national or regional cancer registries in Europe provided more insight into treatment strategies and survival outcomes among older patients with non-metastatic breast cancer. The design of this study allowed us to explore possible patterns between treatment strategies and survival outcomes as some treatment differences were most likely based on geographic factors. A notable finding was the low proportion of patients receiving adjuvant endocrine therapy in the Netherlands compared to the other countries in patients with stage I breast cancer. This reflects a difference in the national guidelines: in the Netherlands, endocrine therapy is only recommended in hormone receptor positive patients with lymph node positive disease or otherwise unfavourable tumour characteristics (high grade or size ≥ 2 cm),[1] while in other countries, adjuvant endocrine therapy is prescribed in all patients with hormone receptor positive breast cancer. This lower use of endocrine treatment in the Netherlands was not accompanied by poorer relative survival in the Netherlands suggesting potential overtreatment in countries other than the Netherlands. On the other hand, substantial variation in the omission of surgery was observed between the participating countries (Ireland vs Belgium) in patients with stage III breast cancer. The increase of omission of surgery was accompanied by a decreasing relative survival, potentially indicating undertreatment in this high risk group. Overall, these findings underline the lack of consensus in the international community on how to optimally treat older patients and reflect the struggle in clinical practice to treat this very heterogeneous population. Moreover, the variation in treatment probably contributes to variation in survival outcomes in Europe.

Chapter 3 described the primary outcomes of the long-term follow-up of the TEAM trial, investigating the effectiveness of exemestane monotherapy compared to sequential therapy with tamoxifen followed by exemestane for a total duration of five years, among post-menopausal patients with hormone receptor positive breast cancer. In line with the five year results,[2] no differences between these two strategies were observed for the primary endpoints. When considering cause of death, results of this analyses suggested there might be a small benefit of exemestane therapy on breast cancer-specific mortality but this was counterbalanced by an increase in non-breast cancer related mortality, resulting in similar overall survival rates for both treatment strategies. Literature has noted that tamoxifen bears a cardioprotective effect and therefore contributes to lower other cause mortality among patients with breast cancer.[3] This suggests that although exemestane might be more favourable for breast cancer related outcomes, it lacks the cardioprotective effect of tamoxifen. Therefore, tamoxifen might be preferred for patients with a relatively low risk breast

cancer and high risk cardiovascular profile, a finding that is particularly important for older patients.

In **Chapter 4**, we described the ability of physical recovery after surgical treatment and during endocrine treatment using two parameters of physical functioning among postmenopausal patients with breast cancer included in the TEAM trial. Patients aged 70 years or older did not improve in physical functioning between one and two years after diagnosis to the same extent as younger patients. Impairment in physical functioning could interfere with independent living and might influence quality of life. Therefore, these outcomes should be described in clinical studies, especially when the majority of the target population of the treatment under study is of older age.

Part II: Breast cancer prognosis in the presence of competing mortality

In the second part of this thesis we further investigated the prognosis of breast cancer in the presence of competing mortality. In **Chapter 5**, we evaluated the influence of age on breast cancer mortality and other cause mortality in ten year follow-up data from the TEAM trial. We applied Fine and Gray regression analysis to adjust for competing events. After ten years of follow-up, breast cancer mortality continued to increase among postmenopausal patients regardless of the increasing other cause mortality. In older patients, breast cancer mortality remained higher compared to younger patients and this was not outweighed by substantially higher other cause mortality. **Chapter 6** provides further insight into the role of comorbidities on the long-term risk of breast cancer mortality and other cause mortality in postmenopausal patients with early breast cancer, which especially for the older patient cohorts is very relevant. Despite the number of comorbidities or increasing age that both contributed to higher other cause mortality, no decrease in breast cancer mortality was observed. Most interestingly, we report that older patients without comorbidities are at higher risk of dying due to breast cancer, despite a higher other cause mortality. Both **Chapter 5** and **Chapter 6** underline the clinical challenge regarding decision making, balancing between undertreatment and overtreatment of older patients, and indicate that assessment of risk for both breast cancer mortality and other cause mortality is indispensable for treatment decision making in older patients.

Part III: From research setting to daily practice: improving methodology in studies in older patients

In the third section of this thesis, we explored some innovative methodological approaches to improve our understanding of health and disease among older patients with breast cancer. In **Chapter 7**, we shed further light on how scholars define successful aging using a citation network analysis to explore the literature. We described two distinct citation networks that form two mutually exclusive concepts of successful aging. The first network focused on suc-

cessful aging from the perspective of the older person themselves while the second cluster based the concept of successful aging on the objective measurements of aging as determined by the researchers. These findings emphasize how the concept of successful aging depends on whether the individual themselves or the outsider judge the situation.

In **Chapter 8**, we reported the use of absolute outcomes next to relative outcomes with the Aalen additive hazards model to improve our understanding of the impact of age in older patients with breast cancer. We illustrated that this model is easily applicable for time-to-event analysis while it preserves the possibility to adjust for confounders and test for statistical interaction similar to the traditional Cox model. Moreover, our results showed that the interpretation of effect of risk factors among subgroups can change depending on the relative or absolute scale of the effect measure due to variation in underlying baseline risk. As older patients are at higher baseline risk of dying compared to younger patients, it is important to take this into account when evaluating the clinical impact of risk factors.

Finally, in **Chapter 9** we proposed new endpoints that could be used for the evaluation of treatment in older patients with cancer. Ultimately, patients and clinicians aim to maximize both length and quality of life. Traditional quality of questionnaires include various domains of function (such as physical functioning and social functioning) defined by researchers that together sum up to a measurement of quality of life. However, the patient's perception of quality of life is highly dependent on individual thoughts, feelings, and preferences and is not necessarily reflected in a quality of life questionnaire based on functional outcomes. The proposed endpoints take into account both the perspective of the patient by evaluating the experienced happiness and life satisfaction and the objective measure overall survival. We combined the measure of happiness with the length of life to develop a balanced estimate of harms and benefits in the treatment of older patients with cancer (HAPPY endpoint).

DISCUSSION

IMPLICATIONS OF THE FINDINGS FOR CLINICAL PRACTICE

Balancing between undertreatment and overtreatment

There is a thin line between undertreatment and overtreatment in older patients with breast cancer. In **Chapter 2**, we described examples of both undertreatment and overtreatment. First, there is a group of older patients that, based on the breast cancer characteristics, has a low risk of disease recurrence and breast cancer mortality. Moreover, due to their older age their risk of dying due to other causes is substantially higher. In these patients, the additional benefit of adjuvant endocrine therapy might be minimal; despite the large variation in prescription of adjuvant endocrine therapy, relative survival was approaching 100% in

all participating countries, indicating almost no excess mortality due to breast cancer. Unfortunately, there is only circumstantial evidence that supports the omission of endocrine therapy in this low risk group. A study comparing treatment and survival in the Netherlands and Ireland reported similar findings.[4] In addition, a population-based study from Denmark identified a subgroup of older patients with low risk breast cancer not treated with adjuvant endocrine therapy that were not at increased risk of mortality.[5] Recently, a secondary analysis of a Swedish trial that compared adjuvant tamoxifen versus no tamoxifen was also able to define a ultralow risk group where adjuvant endocrine therapy did not lead to survival benefit over a course of 20 years.[6] While the beneficial effects of adjuvant endocrine therapy in this subgroup appear to be overestimated, harmful effects appear to be underestimated. Tamoxifen increases the risk of trombo-embolic events and is associated with decline in cognitive function and increasing risk of depression.[2,7,8] Aromatase-inhibitors are strongly associated with arthralgia and osteoporosis.[2] In a vulnerable older population, this might be even more pronounced and may lead to loss of independence, although data to underline these implications are lacking. For older patients with low risk breast cancer, the benefit of treatment may not outweigh the harms and this should be taken into consideration when deciding upon adjuvant endocrine therapy. Moreover, in older patients with cardiovascular disease tamoxifen might be more appropriate due to a possible cardioprotective effect but further research is needed to aid better profiling.

Second, there is a group of older patients with unfavourable tumour characteristics that have a high risk of recurrence and breast cancer mortality that are vulnerable for undertreatment: In **Chapter 2**, we reported that older patients with stage III breast cancer from countries that treat a higher proportion of patients with primary endocrine therapy (PET) have a poorer relative survival. Growing evidence suggests poor locoregional control with PET: a meta-analysis of randomised controlled trials and non-randomised studies has shown benefits for surgery over PET in treatment of older patients in better disease control and a probable survival benefit in patients with a life expectancy of more than five years.[9] It is therefore that the SIOG only recommends PET for patients with a life expectancy of less than 2 years, or for those patients considered unfit for surgery or refuse surgery.[10] Given these recommendations and the knowledge that women who reach the age of 75 have an average life expectancy of 13 years,[11] it is reasonable to assume that in countries such as England and Ireland, with up to 39% of the patients treated with PET, some of these patients were undertreated. Moreover, **Chapter 2** also showed that there is no international consensus on the prescription of chemotherapy among older patients. In the Netherlands, only very few patients aged over 70 years receive chemotherapy due to an upper age limit in our national guidelines. This might lead to undertreatment as the life expectancy of these patients may be high enough to gain benefit from chemotherapy. Especially among otherwise healthy older patients, withholding chemotherapy may contribute to poorer survival

outcomes that were described in Chapter 5 and 6. Unfortunately, little evidence exists on the efficacy, feasibility and toxicity of chemotherapy among older patients with breast cancer as they are often excluded from clinical trials. Only one trial specifically including older patients (aged >65 years, good performance score and no major organ dysfunction) compared standard chemotherapy (either cyclophosphamide, methotrexate, and fluorouracil (CMF) or cyclophosphamide/doxorubicin) with capecitabine, and noted better outcomes for disease recurrence and overall survival in the standard chemotherapy group.[12] In both therapy arms, however, a substantial percentage of patients experienced toxicity, needed dose reduction or stopped therapy early. The chemotherapy toxicity tool in older patients with cancer developed by Hurria and colleagues,[13] might be helpful in decision making regarding adjuvant chemotherapy.

Emphasizing the role of life expectancy

To reduce overtreatment and undertreatment and improve outcomes, treatment should be tailored to the needs of the older patient. The goal of many treatment strategies in breast cancer is to prevent future disease recurrence. Efficacy of treatment is often evaluated five years after initiation of treatment. Therefore, it is of key importance to estimate life expectancy. In older patients breast cancer occurs to the background of aging and therefore life expectancy is not only defined by the prognosis of breast cancer. There is a large heterogeneity in health status in older patients and calendar age alone is known to be a poor predictor of life expectancy. This is illustrated by Figure 1, that indicates how remaining life expectancy is influenced by the level of comorbidity in older individuals.[14] Many online tools have been developed to conceive a better estimation of life expectancy.[15] An overview of these tools is provided at www.eprognosis.com. In these tools, variables such as comorbidity, frailty and subjective health are included to more accurately predict life expectancy. The International Society of Geriatric Oncology recommends performing a geriatric assessment in all older patients with cancer.[10,16] Unfortunately, there is a large variety in tools that are used for the geriatric assessment and no consensus has yet been reached which tools should be included.[16] Nevertheless, several studies have indicated that some form of geriatric assessment could be used to predict the risk of toxicities and to provide a profound estimation of breast cancer mortality, other cause mortality and benefits and harms of treatment.[17]

On the other hand, recently published work by Kusumastuti et al described that the added value of geriatric indicators to calendar age to predict mortality decreases with increasing age.[18] Apparently, the process of aging makes older people intrinsically frail and variation in clinically visible signs of frailty do not appear to influence life expectancy. This is also visible in Figure 1,[14] where variation in life expectancy by comorbidity decreases with increasing age groups, especially after the age of 85 years. When extrapolating these findings to the treatment of breast cancer, we should question ourselves if there is a certain age threshold

at which invasive treatments such as chemotherapy should not be encouraged due to the intrinsic aging process, even when a patient is not showing any clinical signs of frailty.

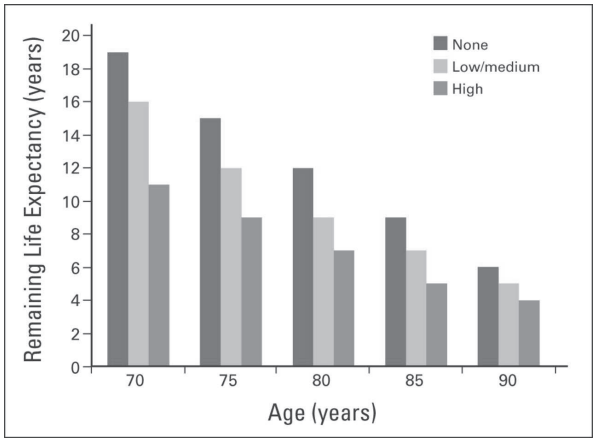


Figure 1. Estimated life expectancy by age and comorbidity level (none, low/medium, or high). Adapted from Muss et al.[14]

Taking competing mortality into account for breast cancer prognosis

Following the estimation of life expectancy, breast cancer prognosis should be evaluated to further define the extent of treatment. However, the tools that are currently available to estimate breast cancer prognosis such as Adjuvant! Online and PREDICT are not validated for the older population, and they do not incorporate geriatric parameters. Both tools are poorly equipped to take the heterogeneous health status of older patients, including comorbidity and functional status into account; in validation studies in the Dutch breast cancer population both tools overestimated breast cancer outcomes and the impact of treatment in older patients.[19-21] Therefore, tools specifically designed for older patients to estimate breast cancer prognosis are highly needed and they should take competing mortality into account to accurately predict breast cancer prognosis.

Over the last decade, the role of genomic profiling to better predict the value of adjuvant treatment in breast cancer is highly debated. In 2016, the results of the Microarray in Node-Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy (MINDACT) study were published and described that genetic profiling with the 70-gene signature test (MammaPrint) chemotherapy could be safely omitted among patients with a high clinical risk and low genomic risk.[22] Unfortunately, the MINDACT trial did not include patients aged over 70 years and therefore these results cannot easily be extrapolated to the older population. It is interesting to elaborate if genomic profiling could improve the predictive

value of adjuvant treatment in older patients. Recently, a secondary analysis of a Swedish trial that compared adjuvant tamoxifen versus no tamoxifen with a follow-up of twenty years showed that the MammaPrint could identify patients with ultra-low long-term risk of dying from breast cancer in whom adjuvant endocrine treatment could be safely omitted.[6]

IMPLICATIONS FOR RESEARCH IN THE OLDER POPULATION WITH BREAST CANCER

Include patients that are representative of the target population

Over the last years, the gap between efficacy observed in cancer trials and outcomes in daily practice became apparent.[23] Cancer trials aim to establish the efficacy of a drug or procedure on the disease of interest. They are performed in a highly controlled environment with highly selected and often younger patients.[24] Unfortynately, these patients and circumstances do not represent the daily practice where older patients carry a considerable burden of disease. Therefore, clinical trials ought to be more representative of the populations most affected by the disease for which treatments are being tested. This should increase the knowledge of effectiveness of treatments and improve translation of trial results to optimal care of older cancer patients.[25] For this reason, the Food and Drug Administration issued a guideline to encourage clinical trials to include patients aged 75 years and older when a disease is common among older patients.[23] Despite the encouragement of both governmental institutes and international research organisations, previous attempts have shown that it is challenging to include older patients in clinical trials.[10] Understandably, clinicians may feel uncomfortable with inclusion of frail older patients in trials with treatments with unknown efficacy and toxicity profiles. Therefore, 'level A' evidence will probably remain scarce for older patients.

To improve evidence based medicine in older patients, a reasonable addition to clinical trials are observational studies. They generate a large amount of data that are representative of the older population and clinical practice. To prevent bias due to so-called 'confounding by indication' when comparing treatment strategies, adequate methodological techniques should be used.[26] Unfortunately, many observational studies use inadequate methods that lead to incorrect interpretation of outcomes and thereby reduce the credibility of observational studies.[27] Novel methodological approaches such as the instrumental variable method can be applied in observational studies to compare treatment efficacy if certain assumptions are met.[26] To be able to use this type of research, large and high quality databases are necessary. One example is the EURECCA database, that is described in Chapter 2. In this project, patient, tumour and treatment variables were collected for all patients aged over 70 years diagnosed with breast cancer in defined regions or countries. Although only certified cancer registries were included, the quality of the data was highly variable making it

difficult to interpret findings. Moreover, various definitions for staging and treatment were applied hampering the possibility to merge and compare data. In the future, quality of these databases should be improved by reducing missing information and improving definitions of treatment. Furthermore, it would be very relevant to include more information on the health status of individual patients, such as comorbidities or polypharmacy, to improve our understanding of the interaction between age related factors and cancer outcomes.

Including relevant endpoints for older patients in research

To measure efficacy of treatment, outcomes in clinical trials in cancer emphasize the pharmacological or biological efficacy of the drug or surgery. This has resulted in cancer driven endpoints, such as progression free survival, disease free survival or pathological complete response.[28] Clinical trials should not only be concerned with prolonging life, but also focus on the needs and desires of patients.[28] From the perspective of patients, both length of life and quality of life are considered important aspects of treatment decision making and the balance might change during life course. In younger patients, increasing length of life might be the primary goal of treatment, while in older patients quality of life becomes an increasingly important aspect in treatment decision making.[29]

In the evaluation of health care, there has been an increasing awareness to include relevant measures for patients. In an influencing paper published in 2010, Michael Porter stated that ´value should always be defined around the customer´ and introduced value based health care that is rapidly being implemented in hospitals worldwide.[30] In line with this, Chapter 7 describes that successful aging can be described from the patient perspective along with the researchers perspective of successful aging. In addition, more emphasis has been given to so called patient reported outcomes such as functional outcomes, symptoms and quality of life to measure the value of care.[31] This line of reasoning should be extended to clinical research in geriatric oncology.[28] The value of treatment should not only be defined in terms of effectiveness but should also include the experience of the patient themselves. Current guidelines for the treatment of breast cancer do not provide any of this information as they are restricted to merely biomedical outcomes and are therefore insufficient for optimal treatment of older patients.

Ultimately, patients and clinicians aim to maximize both length and quality of life. Patient-related endpoints such as functional status, cognitive status and symptoms are important to provide further insight into this balance.[28] However, researchers and clinicians should be aware that functional outcomes should not be interpreted as a measurement of quality of life. As was outlined in Chapter 9, quality of life highly depends on individual needs and preferences and among older patients it is not one-to-one related to functional outcomes.[32] If we aim to measure quality of life from a patient perspective, wellbeing would be an ap-

propriate candidate to focus on. In older patients with cancer, the balance between length of life and quality of life should be reflected in the use of endpoints used in clinical trials. In Chapter 9, we proposed a new endpoint that includes both measures. In the near future, we hope to implement this new endpoint in a study including older patients with cancer to provide a better understanding of the balance between harms and benefits of treatment and disease from the perspective of the patients themselves.

Develop a prediction model specifically designed for older patients

The Climb Every Mountain Study is an observational cohort study including patients aged over 70 years with non-metastatic breast cancer and it opened in 2013. In addition, the Prospective Registration of Issues in Metastasized breast cancer in the Elderly (PRIME) study is including patients aged over 70 years with metastatic breast cancer and opened in 2014. Both studies collected data on geriatric indicators and tumour characteristics at baseline and measured various domains of functioning during follow-up. In the coming years, data from both studies will mature and provide us further insight into treatment and relevant outcomes in older patients with breast cancer. Another promising research project that will integrate data from the Climb study with data from other population based studies is the Prediction of Outcome, Risk of Toxicity and quality of life in older patients TREaTed for breast cancer (PORTRET) study. In this tool, geriatric indicators will be incorporated to predict cancer outcomes in the presence of competing mortality, risk of toxicity and quality of life.

In conclusion, similar to almost all other human malignancies, breast cancer is a disease of aging. This will lead to a growing number of older patients for whom optimal care is not yet available. It is important to provide studies and tools that are better suited to the needs and wishes of older patients. In the near future, important data from several observational studies will mature, setting foot to a prediction model for older patients with relevant outcomes to improve personalized care in older patients with breast cancer.

REFERENCES

1. NABON. Richtlijn Mammacarcinoom versie 2.0. 2012; www.oncoline.nl/mammacarcinoom. Accessed 10/4/2013, 2013.
2. van de Velde CJ, Rea D, Seynaeve C, et al. Adjuvant tamoxifen and exemestane in early breast cancer (TEAM): a randomised phase 3 trial. *Lancet.* 2011;377(9762):321-331.
3. Khosrow-Khavar F, Filion KB, Al-Qurashi S, et al. Cardiotoxicity of Aromatase Inhibitors and Tamoxifen in Post-Menopausal Women with Breast Cancer: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO.* 2016.
4. Kiderlen M, Walsh PM, Bastiaannet E, et al. Treatment strategies and survival of older breast cancer patients - an international comparison between the Netherlands and Ireland. *PLoSOne.* 2015;10(2):e0118074.
5. Christiansen P, Bjerre K, Ejlertsen B, et al. Mortality rates among early-stage hormone receptor-positive breast cancer patients: a population-based cohort study in Denmark. *J Natl Cancer Inst.* 2011;103(18):1363-1372.
6. Esserman LJ, Yau C, Thompson CK, et al. Use of Molecular Tools to Identify Patients With Indolent Breast Cancers With Ultralow Risk Over 2 Decades. *JAMA oncology.* 2017;3(11):1503-1510.
7. Boele FW, Schilder CM, de Roode ML, Deijen JB, Schagen SB. Cognitive functioning during long-term tamoxifen treatment in postmenopausal women with breast cancer. *Menopause (New York, NY).* 2015;22(1):17-25.
8. Schilder CM, Seynaeve C, Beex LV, et al. Effects of tamoxifen and exemestane on cognitive functioning of postmenopausal patients with breast cancer: results from the neuropsychological side study of the tamoxifen and exemestane adjuvant multinational trial. *JClinOncol.* 2010;28(8):1294-1300.
9. Hind D, Wyld L, Reed MW. Surgery, with or without tamoxifen, vs tamoxifen alone for older women with operable breast cancer: cochrane review. *BrJCancer.* 2007;96(7):1025-1029.
10. Biganzoli L, Wildiers H, Oakman C, et al. Management of elderly patients with breast cancer: updated recommendations of the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA). *Lancet Oncol.* 2012;13(4):e148-e160.
11. Life expectancy at 75 (NHSOF 1b). data.gov.uk 2017. Accessed 30-11-2017.
12. Muss HB, Berry DA, Cirrincione CT, et al. Adjuvant chemotherapy in older women with early-stage breast cancer. *NEnglJMed.* 2009;360(20):2055-2065.
13. Hurria A, Mohile S, Gajra A, et al. Validation of a Prediction Tool for Chemotherapy Toxicity in Older Adults With Cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2016;34(20):2366-2371.
14. Muss HB. Adjuvant chemotherapy in older women with breast cancer: who and what? *JClinOncol.* 2014;32(19):1996-2000.
15. Yourman LC, Lee SJ, Schonberg MA, Widera EW, Smith AK. Prognostic indices for older adults: a systematic review. *Jama.* 2012;307(2):182-192.
16. Wildiers H, Heeren P, Puts M, et al. International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. *JClinOncol.* 2014;32(24):2595-2603.

17. Li D, de Glas NA, Hurria A. Cancer and Aging: General Principles, Biology, and Geriatric Assessment. *Clinics in geriatric medicine.* 2016;32(1):1-15.

18. Kusumastuti S, Gerds TA, Lund R, Mortensen EL, Westendorp RGJ. Discrimination ability of comorbidity, frailty, and subjective health to predict mortality in community-dwelling older people: Population based prospective cohort study. *European journal of internal medicine.* 2017;42:29-38.

19. de Glas NA, Fontein DB, Bastiaannet E, et al. Physical activity and survival of postmenopausal, hormone receptor-positive breast cancer patients: Results of the Tamoxifen Exemestane Adjuvant Multicenter Lifestyle study. *Cancer.* 2014.

20. de Glas NA, Bastiaannet E, Engels CC, et al. Validity of the online PREDICT tool in older patients with breast cancer: a population-based study. *British journal of cancer.* 2016;114(4):395-400.

21. van Maaren MC, van Steenbeek CD, Pharoah PDP, et al. Validation of the online prediction tool PREDICT v. 2.0 in the Dutch breast cancer population. *European journal of cancer (Oxford, England : 1990).* 2017;86:364-372.

22. Cardoso F, van't Veer LJ, Bogaerts J, et al. 70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer. *The New England journal of medicine.* 2016;375(8):717-729.

23. Herrera AP, Snipes SA, King DW, Torres-Vigil I, Goldberg DS, Weinberg AD. Disparate inclusion of older adults in clinical trials: priorities and opportunities for policy and practice change. *American journal of public health.* 2010;100 Suppl 1:S105-112.

24. Singal AG, Higgins PD, Waljee AK. A primer on effectiveness and efficacy trials. *Clinical and translational gastroenterology.* 2014;5:e45.

25. Dunn C, Wilson A, Sitas F. Older cancer patients in cancer clinical trials are underrepresented. Systematic literature review of almost 5000 meta- and pooled analyses of phase III randomized trials of survival from breast, prostate and lung cancer. *Cancer epidemiology.* 2017;51:113-117.

26. Vandenbroucke JP. When are observational studies as credible as randomised trials? *Lancet.* 2004;363(9422):1728-1731.

27. de Glas NA, Kiderlen M, de Craen AJ, et al. Assessing treatment effects in older breast cancer patients: systematic review of observational research methods. *Cancer TreatRev.* 2015;41(3):254-261.

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

29. Meropol NJ, Egleston BL, Buzaglo JS, et al. Cancer patient preferences for quality and length of life. *Cancer.* 2008;113(12):3459-3466.

30. Porter ME. What is value in health care? *The New England journal of medicine.* 2010;363(26):2477-2481.

31. Rotenstein LS, Huckman RS, Wagle NW. Making Patients and Doctors Happier - The Potential of Patient-Reported Outcomes. *The New England journal of medicine.* 2017;377(14):1309-1312.

32. von FM, Bootsma-van der Wiel A, van EE, et al. Successful aging in the oldest old: Who can be characterized as successfully aged? *ArchInternMed.* 2001;161(22):2694-2700.