Refining individualized medicine in older patients with breast cancer

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Colophon

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General introduction and outline of this thesis

Anna Z. de Boer

Den Haag, april 2020

GENERAL INTRODUCTION

Breast cancer in older patients

Breast cancer is the most frequently occurring cancer in women, with the second highest number of cancer deaths in the Netherlands after lung cancer.[1,2] In the Netherlands, up to a third of patients diagnosed with invasive breast cancer is 70 years or older at the time of diagnosis.[1] In the upcoming years, the number of older patients with breast cancer will rapidly rise due to ageing of Western populations.[3,4] Despite the fact that clinicians will face this growing population in the near future, the evidence base for age-specific treatment recommendations is still limited.[5] Older patients were underrepresented in the hallmark randomized clinical trials for breast conserving therapy and systemic treatments because an upper age limit of 70 years or even 65 years was generally used at the time.[6] As a results, for several treatments that are considered standard today, the actual treatment effect in this patient population is uncertain.

Defining the older patient

Previous studies have often used 65 years as a cut off to define the older patient. Due to the increasing longevity this definition seems not appropriate any more. In the Netherlands, in 2018, a 65 years old woman had an overall life expectancy of 21.5 years and a life expectancy in perceived good health of 12.6 years.[7] Because we live longer in good health, the Dutch government has recently increased the pension age to 67 years.[8] A cut off age of 70 years to define the older patients is therefore more appropriate, since substantial comorbidity, impaired functionality and other geriatric problems increase after this age. It remains an arbitrary definition because it is based on chronological age. As a result of the heterogenous ageing process, patients of the same age can vary widely in their general health and functional status. It is the physiological age of a patients that really matters. Obviously, treatment decisions should rather be based on a patients general health status than on chronological age alone.[9]

Weighing the benefits and risks

An important difference between older and younger patients with breast cancer is life expectancy. When life expectancy is short, patients may not live long enough to develop a recurrence, nor benefit from treatments aimed to prevent recurrences. The shorter the life expectancy, the likelier it is, that the actual recurrence risk and treatment effect are reduced (Figure 2). For example, a meta-analysis performed by the Early Breast Cancer Trialists' Collaborative Group showed that the absolute effect of radiotherapy after breast conserving surgery is substantially lower in patients aged 70 years and older.[10] Consequently, for certain patients, the benefit of treatment is too small to be considered worthwhile. In some cases, the treatment may even do more harm than good. This mostly occurs in patients with low-

risk breast cancer, since treatment effects are generally more robust when the risk of breast cancer recurrence is high. In other patients, the benefit of treatment is clearly outweighed by the risk of dying from other causes, for example in a patient with a 10-year risk of breast cancer death of 5% versus a risk of dying from other causes of 50%. Accurately estimating an older patient's life expectancy remains a challenge, and in addition to age, comorbidity shows a strong association with other-cause mortality in older patients with early stage breast cancer.[11,12]

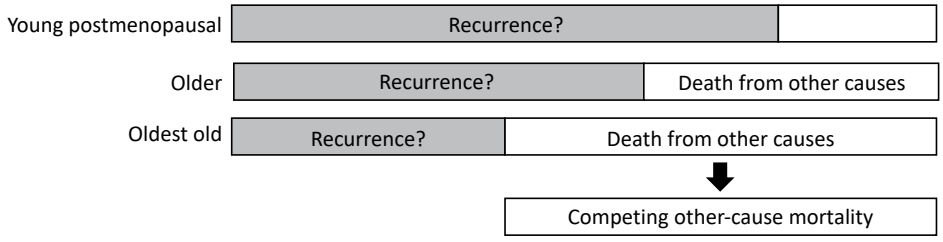

Figure 1. The risk of dying from other causes than breast cancer increases with age and competes with the risk of breast cancer recurrence.

The benefit of treatment should always be carefully weighed against the risks. This can be a delicate balance in older patients in whom the treatment effect is reduced by their life expectancy or the risk of adverse outcomes is increased due to a diminished physical reserve. Older patients can experience functional decline after surgical and adjuvant treatments.[13,14] Poorer physical function is the most important cause of distress in older patients with cancer.[15] Maintaining functionality is essential to preserve quality of life for most older patients.[16] As may be expected, patients with functional limitations or reduced physical strength at baseline, have a higher risk of functional decline after treatment.[17]

Toxicity is another important outcome, especially as the percentage of older patients who receive chemotherapy increased in recent years.[18] Older patients have a higher risk of experiencing toxicity from chemotherapy due to the reduced physical reserve, and therefore to complete their chemotherapy schedule.[19] It was found that results from a geriatric assessment independently predict chemotherapy toxicity in patients aged 65 years older, for example the number of falls in the preceding six months and being physically limited in walking one block.[19] These factors are incorporated in in the currently available prediction tool of the Cancer & Aging Research Group.[20] The International Society of Geriatric Oncology recommends a geriatric assessment to get more insight in a patient's risk of toxicity and functional decline.[5] A geriatric assessment may also help to make a better estimation of life-expectancy.

The research gap in geriatric oncology

Inclusion of older patients in cancer trials has somewhat improved. Very few cancer trials now use an upper age limit for inclusion,[21] and several trials were conducted that were specifically designed for older patients.[22] Unfortunately, the median age of the included patients with breast cancer remains 8 years younger than the actual patient population.[23] Even more important, in most trials, non-representative samples of fit older patients are included due to performance status inclusion criteria. Even in trials without such an explicit criterium, older trial participants have less comorbidity and a lower overall mortality risk compared to the general population.[24] Other trials have regrettably neglected to report parameters of general health which makes it impossible to evaluate the generalizability of the results.[25,26] Caution is therefore warranted in generalizing prognosis and treatment effect as observed in these trials to the general population.

Paradoxically, we seek treatment evidence for a patient population that is defined by its heterogeneity in terms of general health by performing randomized clinical trials that require homogeneity. A homogeneous study population strengthens the certainty with which the results apply to the included patients (internal validity), but inherently reduces the generalizability (external validity). This contradiction partly explains why many research gaps in geriatric oncology remain to be filled. If randomized data is not (yet) available, observational data can provide a good enough alternative under the right circumstances in which biases can be minimized.

Population-based data from hospital-based, regional and national registries provide the opportunity to perform retrospective cohort studies with generalizable results. However, direct comparisons of outcomes of differently treated patients are prone for bias due to confounding by indication.[27] This is particular an issue in older patients, when patient characteristics that influence treatment decisions are also directly associated with outcomes. Worse survival, observed in patients who did not undergo radiotherapy compared to patients who did undergo radiotherapy, is partially, if not completely, due to the fact that older age or a worse general health motivated the omission of radiotherapy in the first place. As general health parameters are not available in registries, and cannot be accurately retrieved in retrospect, conventional statistical techniques such as multivariable analysis and propensity score matching are unable to adjust for these parameters, and therefore leave residual confounding.[27] A technique called the instrumental variable method may avoid confounding by indication if treatment variation unrelated to patient factors, for example related to regions or hospitals, can be used.[28]

THESIS OUTLINE

The aim of this thesis is to investigate breast cancer outcomes in relation to other-cause mortality in a representative population of older patients with breast cancer, and to assess the effect of omission of treatments in selected patients with low-risk breast cancer or high competing mortality risk. Another aim was to assess geriatric outcomes in a subset of older patients with breast cancer.

In **Part I**, we evaluate the impact of age and comorbidity on locoregional and distant recurrence risk versus other-cause mortality. In **Part II**, the effect of omission of treatments in selected older patients is investigated using the instrumental variable method. In **Part III**, geriatric parameters are studied in relation to functional outcomes.

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

As older patients included in trials have less comorbidity and a higher life expectancy compared to the general population, the burden of other-cause mortality and the impact on breast cancer prognosis differs.[24] Population-based cohorts on the other hand, often lack detailed patient information or specific outcomes. A large database of the Netherlands Cancer Registry of over 27,000 patients aged 70 years or older diagnosed with invasive breast cancer between 2003 and 2009 was therefore supplemented with retrospectively collected data on comorbidity and long term locoregional and distant recurrence status for this thesis funded by ZonMw. Part I and II comprises projects performed with this unique database. In **Chapter 2**, the impact of older age on locoregional and distant recurrence is assessed while taking into account and presented against the risk of dying from other causes. Other-cause mortality can still compete with breast cancer mortality after a recurrence has occurred. In **Chapter 3**, we assess breast cancer mortality in relation to other-cause mortality after a locoregional or distant recurrence. As comorbidity is strongly associated with other-cause mortality, it could improve patient selection for treatment by distinguishing between patients with high and low risk of dying from other causes. **Chapter 4** evaluates the Charlson Comorbidity Index and comorbidity count as measurement methods for the prediction of other-cause mortality.

Part II: Omission of treatments in selected older patients

It is generally agreed on that there are older patients who do not benefit enough from certain treatments which thus should be omitted. Patient selection criteria for omission of standard treatments are however ill-defined in guidelines, despite results of randomized clinical trials specifically conducted in older patients for this purpose.[25,29,30] Inappropriate de-implementation of low value treatments makes older patients at risk of overtreatment. In **Chapter 5**, we used hospital variation in radiotherapy-use to investigate the effect of

radiotherapy after breast-conserving surgery on locoregional recurrence risk in patients aged 75 years and older with T1-2N0 breast cancer with endocrine treatment conform the Dutch treatment guideline. Selection criteria for primary endocrine therapy as alternative treatment for primary surgery also remain unclear as the original trials are outdated and performed in fit patients rather than in the frail patients in whom we would consider omission of surgery today.[30] In **Chapter 6**, we used hospital variation in primary surgery rates to investigate the effect of omission of surgery on survival in patients aged 80 years or older with early stage breast cancer. Clinicians state that patient preference is often the reason to still apply a low value treatment.[31,32] **Chapter 7** discusses patient perceived barriers and facilitators to omit radiotherapy after breast-conserving surgery, axillary lymph node dissection after a positive sentinel lymph node biopsy, and replace primary surgery by primary endocrine treatment.

Part III: Geriatric assessment and outcomes

During the last decade, researchers and clinicians have emphasized that for older patients, outcomes such as functional status, independence and quality of life are as important as recurrence, progression and survival outcomes.[33] This is especially true for patients with metastatic disease, when the aim of treatment is to maintain quality of life as long as possible.[34] **Chapter 8** presents the results of a study in which functional status, psychological wellbeing, and quality life of patients with metastatic breast cancer aged 70 years or older were followed over a 6 month period.

Chapter 9 provides the summary and general discussion.

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Part I

Evaluating breast cancer prognosis and other-cause mortality

2

Impact of older age and comorbidity on locoregional and distant breast cancer recurrence: a large population-based study

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ABSTRACT

Background. Studies have demonstrated worse breast cancer-specific mortality with older age, despite an increasing risk of dying from other causes due to comorbidity (competing mortality). However, findings on the association between older age and recurrence risk are inconsistent. The aim of this study was to assess incidences of locoregional and distant recurrence by age, taking competing mortality into account.

Methods. Patients surgically treated for nonmetastasized breast cancer between 2003 and 2009 were selected from The Netherlands Cancer Registry. Cumulative incidences of recurrence were calculated considering death without distant recurrence as competing event. Fine and Gray analyses were performed to characterize the impact of age (70-74 [reference group], 75-79, and ≥80 years) on recurrence risk.

Results. A total of 18,419 patients were included. Nine-year cumulative incidences of locoregional recurrence were 2.5%, 3.1%, and 2.9% in patients aged 70-74, 75-79, and ≥80 years, and 9-year cumulative incidences of distant recurrence were 10.9%, 15.9%, and 12.7%, respectively. After adjustment for tumor and treatment characteristics, age was not associated with locoregional recurrence risk. For distant recurrence, patients aged 75-79 years remained at higher risk after adjustment for tumor and treatment characteristics (75-79 years subdistribution hazard ratio [sHR], 1.25; 95% confidence interval [CI], 1.11-1.41; ≥80 years sHR, 1.03; 95% CI, 0.91-1.17).

Conclusion. Patients aged 75-79 years had a higher risk of distant recurrence than patients aged 70-74 years, despite the higher competing mortality. Individualizing treatment by using prediction tools that include competing mortality could improve outcome for older patients with breast cancer.

INTRODUCTION

Over 30% of all newly diagnosed patients with breast cancer are 70 years or older, and this proportion is likely to increase even further because of the aging of Western populations.[1] For this growing patient population, treatment decisions can prove challenging given the lack of evidence caused by underrepresentation of older patients in clinical trials. Generally, older patients tend to receive less extensive treatment compared with younger patients.[2] As ageing comes with comorbid diseases, the risk of dying from other causes than breast cancer, so-called competing mortality risk, strongly increases with age.[3,4] Therefore, it is essential to take competing mortality risks into account when estimating breast cancer outcomes and the benefit of treatment in the older population.

It has been suggested that age is an independent risk factor for worse breast cancer outcome.[5-7] Several studies have demonstrated that increasing age was associated with worse breast cancer-specific mortality, despite increasing competing mortality risks.[3,6,8] One would expect the worse breast cancer-specific mortality to be accompanied with a higher risk of disease recurrence. However, research findings on the association between age and recurrence risk are inconsistent, as some studies demonstrate a higher recurrence risk with age, whereas other studies do not find such association.[3,5-7,9,10] Different handling of competing mortality risks could play a role in the discrepant findings.

Therefore, the aim of this study was to assess the incidences of locoregional and distant recurrence by age at diagnosis among patients aged ≥70 years while taking competing mortality risks into account.

METHODS

All surgically treated patients diagnosed with nonmetastasized invasive breast cancer aged 70 years or older between 2003 and 2009 were selected from The Netherlands Cancer Registry (NCR), which is hosted by The Netherlands Comprehensive Cancer Organization (IKNL). The NCR receives reports of diagnosed malignancies from the nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA), which are completed by the national hospital discharge databank.

Trained data managers of the IKNL collect data on diagnosis, staging, and treatment directly from the medical records using international coding rules. Breast cancer stage was defined using the TNM Classification of Malignant Tumors (6th edition).[11] Clinical stage was used if pathological T or N stage was unknown. Estrogen receptor and progesterone receptor status

were considered positive if ≥10% of tumor cells demonstrated positive nuclear staining. For the current project, additional information on comorbidity at time of diagnosis and recurrences was retrospectively collected from the medical records. Five-year follow-up was available for the total cohort, and longer follow-up was available for a subcohort of 5,115 patients diagnosed between 2007 and 2009. Vital status was obtained through linkage of NCR data with the Municipal Personal Records database.

Patients were categorized into three groups based on age at diagnosis (70-74 (reference group), 75-79 and ≥80 years) following recommendations of the International Society of Geriatric Oncology (SIOG).[12] Comorbidity was aggregated using the Charlson Comorbidity Index (CCI).[13] Study endpoints were time from diagnosis to locoregional (ipsilateral breast, chest wall, axillary lymph nodes and supraclavicular lymph nodes) and distant recurrence by age group.[14] If a patient had both a locoregional and distant recurrence, the event was defined as distant recurrence.

Statistical analysis

The statistical analysis was performed with SPSS 23.0 and STATA 12.1. Multiple imputation by chained equation was performed to account for missing values, assuming that data were missing at random.[15] For each imputed variable, imputation models were applied that included incomplete and complete variables. Analyses were based on the pooled results of 25 imputed sets (according to Rubin's rules).[16] Differences between the age groups were assessed by means of Pearson's chi square tests. Cumulative incidences of recurrence were calculated using the Cumulative Incidence Competing Risk method with death without distant recurrence as competing event.[17] For locoregional recurrence, distant recurrence was also a competing event. Graphically depicted were cumulative incidences of locoregional and distant recurrence by age group, distant recurrence, and competing mortality within each age group and competing mortality by age and comorbidity status (CCI score, 0 and ≥1). In addition, distant recurrence risk was graphically depicted by age and comorbidity in a Supplementary Figure as exploratory analysis. The association between age and recurrence risk was assessed by performing univariable and multivariable Fine and Gray analysis using all available follow-up data, and the effect was expressed as subdistribution hazard ratio (sHR).[17] Covariates were included in the multivariable model if judged to be clinically relevant. Tumor characteristics (histologic grade, tumor size, nodal status, hormone-receptor status, Her2Neu overexpression) were included, as older patients generally present with more advanced disease. Furthermore, patients up to 75 years were included in the Dutch mass screening program, which accounts for the detection of more early stage disease below this age limit. Treatment characteristics that were included in the multivariable model were most extensive surgery, surgical margins, axillary lymph node dissection, radiotherapy, adjuvant endocrine treatment, and chemotherapy. Last, year of diagnosis was

included. Sensitivity analyses were performed with truncated 5-year follow-up to test the robustness of our results. All statistical tests were two-sided and a *p* value smaller than .05 was considered statistically significant.

RESULTS

Between 2003 and 2009, 19,748 patients aged 70 years or older were surgically treated for nonmetastasized breast cancer, and 18,419 patients with available follow-up were included in this study. At time of diagnosis, 7,793 patients (42.3%) were aged 70-74, 4,332 patients (23.5%) were aged 75-79, and 6,294 patients (34.2%) were aged ≥80 years, and the proportion of patients with a CCI score of 1 or higher increased with age (37.1%, 42.7%, and 46.5% in patients aged 70-74, 75-79, and ≥80 years, respectively; $p<0.001$). Tumor and treatment characteristics by age group are presented in Table 1. With increasing age, patients more often presented with larger tumors and more node-positive disease (27.7%, 36.6%, and 39.2% in patients aged 70-74, 75-79, and ≥80 years; $p<0.001$). Furthermore, patients aged 70-74 years more often presented with grade 1 tumors (28.7%) compared with patients aged 75-79 and ≥80 years (22.0% and 21.2%; $p<0.001$). With increasing age group, type of surgery was more often a mastectomy rather than a breast-conserving surgery (BCS), and the proportion radiotherapy after BCS was lower in patients aged ≥80 years (72.6%) compared with patients aged 70-74 and 75-79 years (97.5% and 95.3%; $p<0.001$). Notably, chemotherapy use was low in all age groups (4.1%, 1.6%, and 0.5% for patients aged 70-74, 75-79, and ≥80 years).

Median follow-up was 5.0 years (interquartile range [IQR], 3.1-5.0) for the total cohort and 6.3 years (IQR, 3.3-8.1 years) for the subcohort with longer follow-up. During follow-up, 815 of 7,793 patients aged 70-74, 693 of 4,332 patients aged 75-79, and 892 of 6,294 patients aged ≥80 years had a locoregional or distant recurrence. Figure 1 shows the cumulative incidences of locoregional and distant recurrence by age group. Nine-year cumulative incidences of locoregional recurrence were 2.5%, 3.1%, and 2.9% in patients aged 70-74, 75-79, and ≥80 years. Nine-year cumulative incidences of distant recurrence were 10.7%, 15.6%, and 12.7%, respectively (Table 2). The stacked cumulative incidences of distant recurrence and competing mortality for each age group are shown in Figure 2 which demonstrates the strong increase in competing mortality with age. Furthermore, Figure 3 confirms that having comorbidity clearly increases the competing mortality risk within each age category. No such trend was seen between having comorbidity and distant recurrence risk (Supplementary Figure).

Table 1. Tumor and treatment characteristics by age at diagnosis

Characteristic	All patients (n = 18,419), *n* (%)	%[a]	70-74 yr (*n* = 7,793), *n* (%)	%[a]	75-79 yr (*n* = 4,332), *n* (%)	%[a]	≥80 yr (*n* = 6,294), *n* (%)	%[a]	*p* value for trend
Charlson Comorbidity Index score									<0.001
0	4,459 (24.2)	58.4	2,109 (27.1)	62.9	1,004 (23.2)	57.3	1,346 (21.4)	53.5	
1	1,829 (9.9)	25.1	733 (9.4)	23.1	452 (10.4)	25.6	644 (10.2)	27.2	
≥2	1,220 (6.6)	16.5	450 (5.8)	14.0	321 (7.4)	17.1	449 (7.1)	19.3	
Unknown	10,911 (59.2)		4,501 (57.8)		2,555 (59.0)		3,855 (61.3)		
Histological grade									<0.001
1	4,198 (22.8)	24.6	2,098 (26.9)	28.7	872 (20.1)	22.0	1,228 (19.5)	21.2	
2	8,39 (45.6)	48.9	3,56 (45.7)	48.7	1,902 (43.9)	47.8	2,928 (46.5)	50.0	
3	4,587 (24.9)	26.5	1,649 (21.2)	22.6	1,235 (28.5)	30.2	1,703 (27.1)	28.8	
Unknown	1,244 (6.8)		486 (6.2)		323 (7.5)		435 (6.9)		
T size									<0.001
T1	9,827 (53.4)	53.4	5,53 (71.0)	71.1	2,125 (49.1)	49.1	2,172 (34.5)	34.6	
T2	7,421 (40.3)	40.4	1,987 (25.5)	25.5	1,936 (44.7)	44.8	3,498 (55.6)	55.7	
T3/4	1,138 (6.2)	6.2	266 (3.4)	3.4	262 (6.1)	6.1	610 (9.7)	9.7	
Unknown	33 (0.2)		10 (0.1)		9 (0.2)		14 (0.2)		
N status									<0.001
Negative	12,133 (65.9)	66.3	5,624 (72.2)	72.4	2,738 (63.2)	63.5	3,771 (59.9)	60.8	
Positive	6,193 (33.6)	33.7	2,153 (27.6)	27.7	1,582 (36.5)	36.6	2,458 (39.1)	39.2	
Unknown	93 (0.5)		16 (0.2)		12 (0.3)		65 (1.0)		
HR status									<0.001
ER and/or PR positive	15,053 (81.7)	85.8	6,497 (83.4)	87.3	3,474 (80.2)	84.0	5,082 (80.7)	85.2	
ER and PR negative	2,446 (13.3)	14.2	919 (11.8)	12.7	650 (15.0)	16.0	877 (13.9)	14.9	
Unknown	920 (5.0)		377 (4.8)		208 (4.8)		335 (5.3)		
Her2-receptor status									0.008

Table 1. Tumor and treatment characteristics by age at diagnosis (*continued*)

Characteristic	All patients (n = 18,419), *n* (%)	%[a]	70-74 yr (*n* = 7,793), *n* (%)	%[a]	75-79 yr (*n* = 4,332), *n* (%)	%[a]	≥80 yr (*n* = 6,294), *n* (%)	%[a]	*p* value for trend
Negative	11,178 (60.7)	89.1	4,908 (63.0)	90.2	2,594 (59.9)	87.9	3,676 (58.4)	88.6	
Positive	1,302 (7.1)	10.9	508 (6.5)	9.8	340 (7.9)	12.1	454 (7.2)	11.4	
Unknown	5,939		2,377 (30.5)		1,398 (32.3)		2,164 (34.4)		
Most extensive surgery									<0.001
Mastectomy	11,111 (60.3)		3,439 (44.1)		2,684 (62.0)		4,988 (79.3)		
BCS	7,308 (39.7)		4,354 (55.9)		1,648 (38.0)		1,306 (20.8)		
Surgical margins									<0.001
Free	17,204 (93.4)		7,348 (94.3)		4,052 (93.5)		5,804 (92.2)		
Not free	807 (4.4)		297 (3.8)		192 (4.4)		318 (5.1)		
Unknown	408		148 (1.9)		88 (2.0)		172 (2.7)		
ALND									<0.001
Yes	8,56 (46.5)		2,981 (38.3)		2,169 (50.1)		3,41 (54.2)		
No	9,859 (53.5)		4,812 (61.8)		2,163 (49.9)		2,884 (45.8)		
Radiotherapy after BCS									<0.001
Yes	6,761 (92.5)		4,243 (97.5)		1,57 (95.3)		948 (72.6)		
No	547 (7.5)		111 (2.6)		78 (4.7)		358 (27.4)		
Adjuvant endocrine therapy in HR+									<0.001
Yes	8,026 (53.3)	52.7	2,892 (44.5)	43.9	2,025 (58.3)	57.5	3,109 (61.2)	60.6	
No	7,027 (46.7)	47.3	3,605 (55.5)	56.1	1,449 (41.7)	42.5	1,973 (38.8)	39.4	
Chemotherapy									<0.001
Yes	420 (2.3)		319 (4.1)		70 (1.6)		31 (0.5)		
No	17,999 (97.7)		7474 (95.9)		4,262 (98.4)		6,263 (99.5)		

[a]Proportional distribution after multiple imputation. Abbreviations: ALND, axillary lymph node dissection; BCS, breast-conserving surgery; ER, estrogen receptor; HR, hormone receptor; PR, progesterone receptor.

Table 2. Risk of recurrence by age at diagnosis

	Cumulative incidence, % (95% CI)				Competing events, % (95% CI)				Univariable sHR		Multivariable sHR	*p* value
Age at diagnosis	5 yr		9 yr		5 yr		9 yr		(95% CI)	*p* value	(95% CI)*	
Locoregional recurrence												
70-74 years	2.1	(1.8-2.4)	2.5	(2.1-3.0)	16.3	(15.5-17.2)	30.9	(29.2-32.6)	Reference		Reference	
75-79 years	2.8	(2.3-3.3)	3.1	(2.6-3.7)	28.6	(27.3-30.0)	49.0	(46.6-51.4)	1.32 (1.05-1.66)	0.018	1.04 (0.82-1.33)	0.743
≥80 years	2.8	(2.5-3.3)	2.9	(2.5-3.4)	44.6	(43.4-45.8)	71.3	(69.3-73.2)	1.32 (1.07-1.63)	0.009	0.86 (0.68-1.09)	0.219
Distant recurrence												
70-74 years	7.4	(6.9-8.0)	10.9	(10.0-11.9)	9.5	(8.8-10.1)	21.2	(19.7-22.7)	Reference		Reference	
75-79 years	12.3	(11.4-13.3)	15.9	(14.5-17.3)	17.4	(16.3-18.5)	35.2	(32.9-37.6)	1.63 (1.46-1.83)	<0.001	1.25 (1.11-1.41)	<0.001
≥80 years	10.9	(10.1-11.7)	12.7	(11.8-13.7)	35.4	(34.2-36.6)	61.1	(59.0-63.1)	1.39 (1.25-1.55)	<0.001	1.03 (0.91-1.17)	0.606

*This multivariable analysis included year of diagnosis, histologic grade, tumor size, nodal status, hormone receptor status, Her2Neu overexpression, most extensive surgery, surgical margins, axillary lymph node dissection, adjuvant radiotherapy, adjuvant hormonal therapy and chemotherapy.

Abbreviations: CI, confidence interval; sHR, subdistribution hazard ratio.

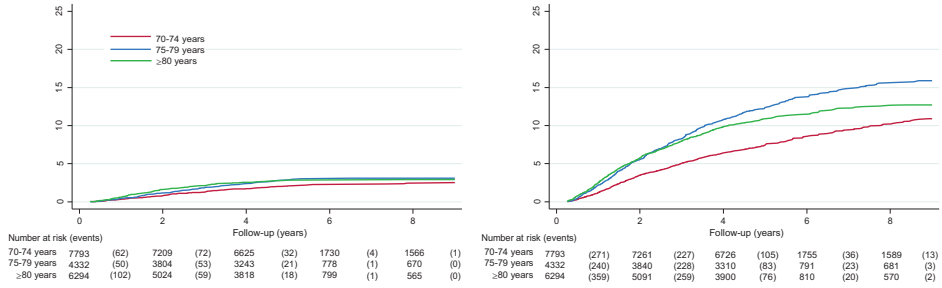

Figure 1. Cumulative incidence of locoregional recurrence and distant recurrence by age group.

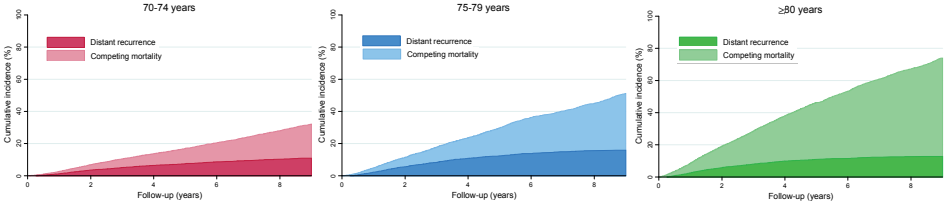

Figure 2. Stacked cumulative incidences of distant recurrence and competing mortality by age group.

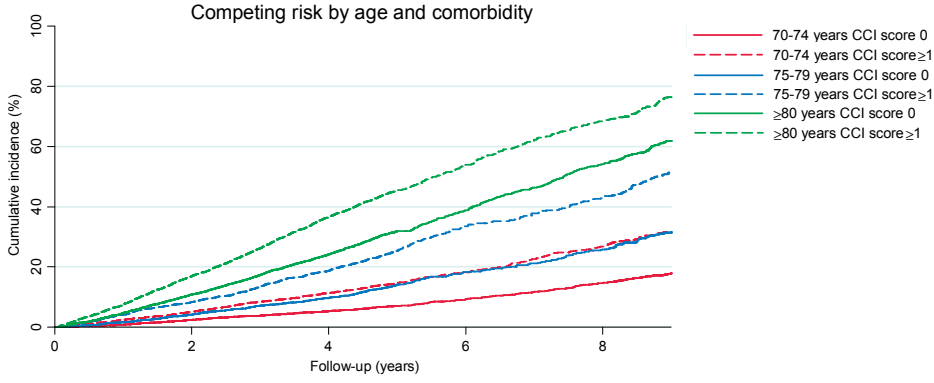

Figure 3. Competing mortality risk by age group and comorbidity status (CCI score 0 and ≥1).

Univariable analysis showed that patients aged 75-79 and ≥80 years had a higher risk of locoregional recurrence (75-79 years sHR, 1.32; 95% CI, 1.05-1.66; ≥80 years sHR, 1.32; 95% CI, 1.07-1.63) and distant recurrence (75-79 years sHR, 1.63; 95% CI, 1.46-1.83; ≥80 years sHR, 1.39; 95% CI, 1.25-1.55) compared with patients aged 70-74 years (Table 2). The association between age and locoregional recurrence risk was no longer significant after adjustment for tumor and treatment characteristics in multivariable analysis (75-79 years sHR, 1.04; 95% CI, 0.82-1.33; ≥80 years sHR, 0.86; 95% CI, 0.68-1.09), whereas the association between age and distant recurrence risk remained significant for patients aged 75-79 years (75-79 years sHR, 1.25; 95% CI, 1.11-1.41; ≥80 years sHR, 1.03; 95% CI,

0.91-1.17; Table 2). The sensitivity analysis with truncated 5-year follow-up yielded similar results (Supplementary Table).

DISCUSSION

The main finding of our study is that patients aged 75-79 years at diagnosis were at higher risk of distant recurrence compared with patients aged 70-74 years after adjustment for tumor and treatment characteristics, despite the higher competing mortality risk.

Our finding that age at diagnosis was not associated with locoregional recurrence risk is in line with previous studies.[6,7,9,10,18,19] Moreover, cumulative incidences of locoregional recurrence were low in all age groups despite the fact that we included all surgically treated patients with nonmetastasized breast cancer, and almost half of the patients was not treated systemically. Plausibly, some of the patients died from other causes than breast cancer before they could get a recurrence. Low locoregional recurrence risks among older patient have prompted research on the de-escalation of locoregional treatments for this population. The CALGB 9343 trial demonstrated that radiotherapy after breast-conserving surgery can be safely omitted in patients aged ≥70 years with stage 1 breast cancer who are treated with endocrine treatment.[20] Ongoing studies may confirm this for broader patient selections or other locoregional treatments such as the axillary treatment. The low cumulative incidences raise the question of how much there is to gain in reducing the locoregional recurrence risk in older patients and whether treatments that only reduce locoregional recurrence risk but do not affect breast cancer-specific survival, such as radiotherapy after BCS, are always appropriate.[12,21]

In contrast to consistent findings regarding the lack of association with locoregional recurrence risk, previous studies have reported inconsistent findings on the association between age and distant recurrence. One study reported an increasing risk of distant recurrence with age,[7] whereas other studies reported a non-significant trend,[3,6] or no association.[9,10] Different study populations and statistical models may play a role in the discordant findings. For example, in the randomized phase III Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial in which two endocrine regimens were compared, increasing age was associated with a higher risk of distant recurrence.[7] However, it is questionable whether these findings apply to the general population, as older patients included in trials are generally a healthy selection of the general population and, consequently, the impact of competing mortality is lower.[22] A second study, performed in a regional population-based cohort, demonstrated an association between increasing age and recurrence risk when combining locoregional and distant recurrence, but only a nonsignificant trend when distant recur-

rence was analyzed separately, possibly as a result of insufficient power.[6] With regard to statistical models, almost all previous studies used the Cox proportional hazards model that does not take competing mortality into account.[6,7,9,10] However, because the influence of competing mortality seems rather large in the older population of patients with breast cancer, the Fine and Gray model is considered more appropriate.[23]

We propose two possible explanations for our finding that patients aged 75-79 years were at higher risk of distant recurrence compared with patients aged 70-74 years. First, undertreatment could have played a role. Although the analyses were adjusted for treatment characteristics in the analysis, we lacked details on treatment extensiveness such as specific type and duration. Studies have demonstrated that older age is associated with increased discontinuation of and nonadherence to endocrine treatment.[8,24] Also, chemotherapy toxicity with subsequent dose reduction or discontinuation increases with age, although this could only have had a limited effect because few patients received chemotherapy.[25] Second, aging of the immune system could have played a role. Several studies have related decreased cellular immunity with decreased tumor defense or worse breast cancer prognosis.[26]

As the proposed explanations for the higher risk of distant recurrence in patients aged 75-79 both imply an age-dependent trend, a similar association among patients ≥80 years would be expected. The fact that we did not observe this can be explained by the higher competing mortality risk, but age-selective underdetection of recurrences may also have played a role. It is likely that underdetection increases with age because more patients refrain from visiting a doctor or do not wish to undergo diagnostic testing with age, and clinicians may refrain from diagnostic testing in patients with limited residual life expectancies. A study showed that 33% of nursing home patients with suspected breast cancer are not referred for further testing.[27]

The major strength of our study is that the results are applicable to the general population of older patients with breast cancer, as our study was performed in a nationwide population-based cohort. To our knowledge, this is one of the largest population-based cohort with information on comorbidity and recurrence. Furthermore, the prevalence of comorbidity was similar to the prevalence in two large population-based studies performed in the Danish and U.S. populations.[28,29] Of course, this study also has its limitations. First, no detailed information on treatment extensiveness and adherence was available. Furthermore, because we used observational follow-up data, age-selective underdetection is likely present and could not be taken into account. Notably, this could not have explained the higher distant recurrence risk for patients aged 75-79 years, because underdetection will increase with age.

Our findings suggest that some older patients may be undertreated, but they also demonstrate that older patients have a higher competing mortality risk. Therefore, patient selection for treatment should focus not only on breast cancer outcome but also on distinguishing patients with high from patients with low competing mortality risk, as only the latter may benefit from extensive treatment. In this context, prediction tools could play an important role in improving breast cancer management for older patients, as such tools could predict outcome with and without treatment, while taking into account competing mortality risk by including comorbidity as a predictor because it is well known and demonstrated in our study that having comorbidity increases the competing mortality risk. To facilitate the development of such prediction tools, prognostic studies should focus on the predictive value of comorbidity scores and geriatric parameters from geriatric screenings or assessments in addition to disease characteristics. The ultimate goal is to not only predict recurrence risk and survival but also to predict risk of toxicity, quality of life, and physical functioning, as these outcomes are (more) relevant for older patients.

Conclusion

Our study demonstrated that patients aged 75-79 years were at increased risk of distant recurrence compared with patients aged 70-74 years when differences in tumor and treatment characteristics were taken into account, regardless of the increasing competing mortality risks with age. Individualizing treatment by using prediction tools that include competing mortality could improve outcome for older patients with breast cancer.

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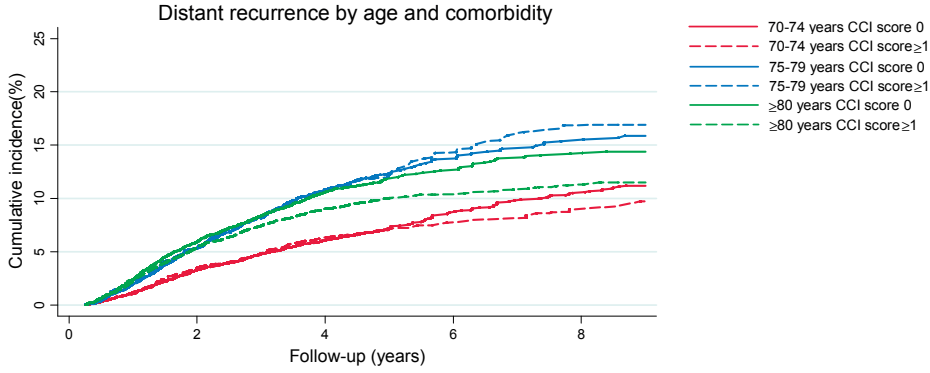
Supplementary Table. Risk of recurrence by age at diagnosis, sensitivity analysis with truncated five-year follow-up.

Age at diagnosis	Univariable R (95% CI)	*p* value	Multivariable sHR (95% CI)*	*p* value
Locoregional recurrence				
70-74 years	Reference		Reference	
75-79 years	1.35 (1.07-1.71)	0.013	1.05 (0.82-1.35)	0.676
≥80 years	1.38 (1.11-1.70)	0.003	0.90 (0.71-1.14)	0.369
Distant recurrence				
70-74 years	Reference		Reference	
75-79 years	1.71 (1.52-1.92)	<0.001	1.30 (1.14-1.47)	<0.001
≥80 years	1.50 (1.34-1.68)	<0.001	1.11 (0.98-1.26)	0.107

*This multivariable analysis included year of diagnosis, histologic grade, tumor size, nodal status, hormone-receptor status, Her2Neu overexpression, most extensive surgery, surgical margins, axillary lymph node dissection, adjuvant radiotherapy, adjuvant hormonal therapy and chemotherapy. sHR: subdistribution hazard ratio, CI: confidence interval.



Supplementary Figure. This is the univariable representation of cumulative incidence of distant recurrence stratified by age category and comorbidity. No trend was seen between having comorbidity and the risk of distant recurrence as patients with comorbidity had less distant recurrences among patients aged 70-74 years and ≥80 years, whereas patients with comorbidity had more distant recurrences in patients aged 75-79 years, compared to patients without comorbidity. Of note, potential differences in disease characteristics and treatment between the subgroups could not be taken into account in this representation.

3

Breast cancer mortality of older patients with and without recurrence analysed by multi-state models

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ABSTRACT

Introduction. In older patients with breast cancer, the risk of dying from other causes than breast cancer strongly increases after the age of 70. The aim of this study was to assess contributions of breast cancer mortality versus other-cause mortality after locoregional or distant recurrence in a population-based cohort of older patients analysed by multi-state models.

Methods. Surgically treated patients ≥70 years diagnosed with stage I-III breast cancer in 2003-2009 were selected from the Netherlands Cancer Registry. A novel multi-state model with locoregional and distant recurrence that incorporates relative survival was fitted. Other-cause and breast cancer mortality were indicated as population and excess mortality.

Results. Overall, 18,419 patients were included. Ten-year cumulative incidences of locoregional and distant recurrence were 2.8% (95%CI 2.6-3.1%) and 12.5% (95%CI 11.9-13.1%). Other-cause mortality increased from 23.9% (95%CI 23.7-24.2%) in patients 70-74 years to 73.8% (95%CI 72.2-75.4%) in those ≥80 years. Ten-year probabilities of locoregional or distant recurrence with subsequent breast cancer death were 0.4-1.3% and 10.2-14.6%, respectively. For patients with a distant recurrence in the first two years after diagnosis, breast cancer death probabilities were 95.3% (95%CI 94.2-96.4%), 93.1% (95%CI 91.6-94.6%), and 88.6% (95%CI 86.5-90.8%) in patients 70-74, 75-79, and ≥80 years.

Conclusion. In older patients without recurrence, prognosis is driven by other-cause mortality. Although locoregional recurrence is a predictor for worse outcome, given its low incidence it contributes little to breast cancer mortality after diagnosis. For patients who develop a distant recurrence, breast cancer remains the dominant cause of death, even at old age.

INTRODUCTION

The number of older patients with breast cancer will further increase in the upcoming years due to ageing of the population.[1] Despite having breast cancer, older patients often die from causes unrelated to breast cancer due to the shorter life expectancy and increasing comorbidity burden with age.[2-5] Above the age of 70 years, the risk of dying from other causes strongly increases.[6,7] It is therefore essential to consider this competing mortality risk while estimating prognosis in older patients[6,8] However, the impact of competing mortality after breast cancer recurrence has not been extensively studied so far, because most studies treat recurrence as an endpoint of the study and do not investigate what happens after this endpoint. This is an omission since more insight in the age-dependent prognosis after recurrence can help inform treatment decisions.

Locoregional recurrence rates (LRR) have greatly diminished over the last two decades due to advances in treatment modalities and patient selection for treatments.[9-11] Recent data showed that 4% of all-aged patients diagnosed with stage II or stage III experiences a LRR.[11] Yet, LRR remains a predictor for worse overall and breast cancer survival in line with previous data, possibly because this may be associated with concurrent micrometastases .[10-13] Prognosis after developing a distant recurrence (DR) is generally poor with a median time to death of 2.0 years.[14] However, the time to death is highly variable from several months up to more than ten years, which also leaves room for improving outcome prediction by taking into account age-related mortality.[14]

To our knowledge, no previous study has investigated the proportion of breast cancer versus other-cause mortality after LRR and DR.[15,16] We were capable of filling this gap thanks to our newly developed model in which we integrated relative survival techniques into a multi-state model, which enabled us to analyse observed events (recurrence and death) and unobserved events (cause of death) simultaneously. Therefore, the aim of this study was to assess all long-term outcomes in one integrated model and to compare them for different age groups. The study was performed in a nationwide population-based cohort of 18,419 older patients with stage I-III breast cancer with good quality long-term follow-up data.

METHODS

All surgically treated patients aged 70 years or older diagnosed with stage I-III breast cancer between 2003 and 2009 were selected from the Netherlands Cancer Registry (NCR) and included in this study. The NCR is a nationwide database on cancer diagnosis and treatment, hosted by the Netherlands Comprehensive Cancer Organization. The NCR receives

reports of diagnosed malignancies from the nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA) which are confirmed and completed by the national hospital discharge databank. The interval 2003 to 2009 was chosen to allow sufficiently long follow-up.

Data managers from NCR collect data on diagnosis, staging and treatment from medical records using international coding rules. Breast cancer stage is defined according to the sixth edition of the TNM classification of malignant tumors.[17] Clinical T or N stage was used when the pathological stage was unknown. Oestrogen receptor and progesterone receptor status were defined positive if ≥10% of the tumour cells showed positive nuclear staining. The nationwide population-based cohort of patients diagnosed from 2003 to 2009 was used. The whole cohort was hypothetically separated in two consecutive cohorts based on follow-up time available due to logistic reasons. Cohort I comprised patients diagnosed from 2003 to 2006 for which follow-up was artificially censored at 5 years, and in case of a LRR a consecutive DR was not recorded. Cohort II comprised patients diagnosed from 2007 to 2009. For this cohort follow-up was not censored at a particular time, and a DR after a LRR was recorded. Vital status was available until 31 January 2017 through linkage of NCR data with the Municipal Personal Records database.

Study endpoints were breast cancer mortality and other-cause mortality from diagnosis, after LRR, and after DR by age group over time. Survival time was defined as the time from diagnosis or landmark until death, with censoring of patients still alive at last follow-up visit. Breast cancer mortality was defined as death due to breast cancer or possibly due to its treatment in patients without a recurrence, whereas other-cause mortality was mortality that the patients would also have experienced independent of their disease.

LRR was defined as breast cancer in the ipsilateral breast, ipsilateral thoracic wall or ipsilateral lymph nodes.[18] If a patient presented with a LRR and DR at the same time, the patient was classified as having a DR given the impact on prognosis.

Statistical Analysis

Median follow-up duration was calculated using the reverse Kaplan-Meier method.[19] Cumulative incidences of recurrence were calculated by using competing risks methodology,[20] to take into account that patients with certain "competing" events are no longer at risk for the primary event. Death was considered a competing event for both LRR and DR. In addition, DR was considered a competing event for LRR.

Breast cancer mortality and other-cause mortality after diagnosis, after LRR, and after DR were assessed with a multi-state model with LRR and DR as intermediate events.[15,21] The

novelty of this multi-state model is that cause-specific mortality outcomes are estimated separately after diagnosis, LRR and DR, thus combining observed transitions (to recurrence and death) and unobserved transitions (population and excess death). Figure 1 shows the multi-state model. Statistical methods from the field of relative survival were used to split all mortality in population and excess mortality, since individual data on cause of death were not available. This method compares mortality in a study population to mortality in the general population matched by age, sex and year of diagnosis using country-specific life tables from the Human Mortality Database.[22] The observed (or total) death hazard is then assumed to be the sum of the population hazard and the excess hazard. In this study, excess mortality is indicated as breast cancer-related mortality. The population mortality is referred to as other-cause mortality.

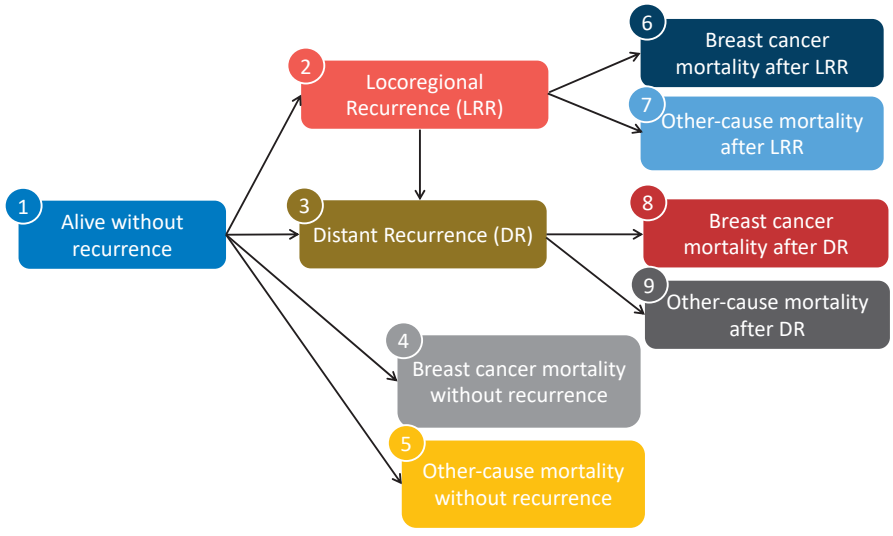

Figure 1. The multi-state relative survival model. All patients start in the state alive without recurrence (state 1). They can progress to locoregional recurrence (state 2), distant recurrence (state 3) or death (states 4 to 9). The model separates breast cancer mortality and other-cause mortality. Each arrow indicates the transition to the next state. Locoregional recurrence and distant recurrence are intermediate states between being alive without recurrence and death, which change the hazards for breast cancer and other-cause mortality, respectively. It cannot be discerned for individual patients if they die due to breast cancer or other-cause mortality. Techniques from relative survival are used to model this distinction, assuming that the hazard of other cause mortality is equal to that in the matched general population and that the remainder (observed minus population mortality) can be considered as breast cancer mortality, i.e., excess mortality due to the disease or possibly its treatment.

The relative survival technique can be used in patient populations in which the other-cause mortality risk is equal to that in the general population.[23,24] This is a reasonable assumption for older patients with breast cancer. First, it has been demonstrated that patients with breast cancer have similar comorbidity compared to the general population.[25] Second, for women aged 65 years and older, there is no longer a disparity in breast cancer incidence by

socioeconomic status.[26] Third, since our cohort is population-based, there was no selection of healthier patients in the study.

Finally, analyses were performed using landmark models describing the outcomes of patients who were alive 2 years after diagnosis and had developed a LRR or DR before. To investigate the impact of the choice of the landmark, we performed several sensitivity analyses: different landmark times were chosen and analyses were performed in which LRR or DR was the starting point. The potential differential impact of early and late DR was investigated by separately analysing survival after early (first three years after diagnosis) and later recurrence.

All analyses were performed in R version 3.6.2 (https://cran.r-project.org/), packages 'survival', 'prodlim', 'relsurv' and 'mstate', extended with functions specifically written for this new model.[20,21]

RESULTS

Patients

Between 2003 and 2009, 19,748 patients aged 70 years or older diagnosed with stage I-III breast cancer underwent surgery. Of these patients, 18,419 patients with available follow-up were included. Baseline characteristics are described in Table 1. At time of diagnosis, 7793 patients (42.3%) were aged 70-74 years, 4332 patients (23.5%) were aged 75-79 years, and 6294 patients (34.2%) were aged 80 years or older. Fifty-three percent received adjuvant endocrine therapy, and 1% was treated with adjuvant chemotherapy. Baseline characteristics per age group are described in the Supplementary Table 1.

Outcomes

Of cohort I, 15 patients (0.1%) were lost to follow up before 5 years. In cohort II, median follow-up was 9.0 years (95% CI 9.0-9.1). The number of patients in follow-up is shown in Supplementary Figure 1. Outcomes stratified by age are shown in Figure 2, and corresponding 5 and 10-year mortality outcome probabilities in Table 2. Ten-year probabilities of DR with subsequent breast cancer death were 10.2% (95%CI 9.1-11.3%), 14.6% (95%CI 13.3-15.8%), and 10.9% (95%CI 9.9-11.8%) for patients aged 70-74 years, 75-79 years, and ≥80 years respectively. For all age groups, few LRR with subsequent breast cancer death were observed (≤1.3%) or breast cancer mortality in patients without a recurrence (≤1.9%).

Table 1. Patient, disease and treatment characteristics at diagnosis of the 18419 patients in the study.

	N (%)
Age (years)	
70-74	7793 (42)
75-79	4332 (24)
≥80	6294 (34)
No. of comorbidities	
0	2205 (29)
1-2	4008 (53)
≥3	1296 (17)
Unknown	10910
Stage	
I	7752 (42)
II	8176 (44)
III	2463 (13)
Unknown	28
Histological grade	
1	4198 (24)
2	8390 (49)
3	4587 (27)
Unknown	1244
Hormone-receptor status	
ER and/or PR positive	15053 (86)
ER and PR negative	2446 (14)
Unknown	920
Her2-receptor status	
Negative	11178 (90)
Positive	1302 (10)
Unknown	5939
Type of surgery	
Mastectomy	11111 (60)
BCS	7308 (40)
Surgical margins	
Free	17204 (96)
Not free	807 (4)
Unknown	408
Radiotherapy after BCS	
Yes	6761 (93)
No	547 (7)
Adjuvant endocrine therapy*	
Yes	8026 (53)
No	7027 (47)
Adjuvant chemotherapy	
Yes	276 (1)
No	18143 (99)

*Percentage of the 15053 hormone-receptor positive patients. Abbreviations: ER, estrogen receptor-PR, progesterone receptor-BCS, breast-conserving surgery.

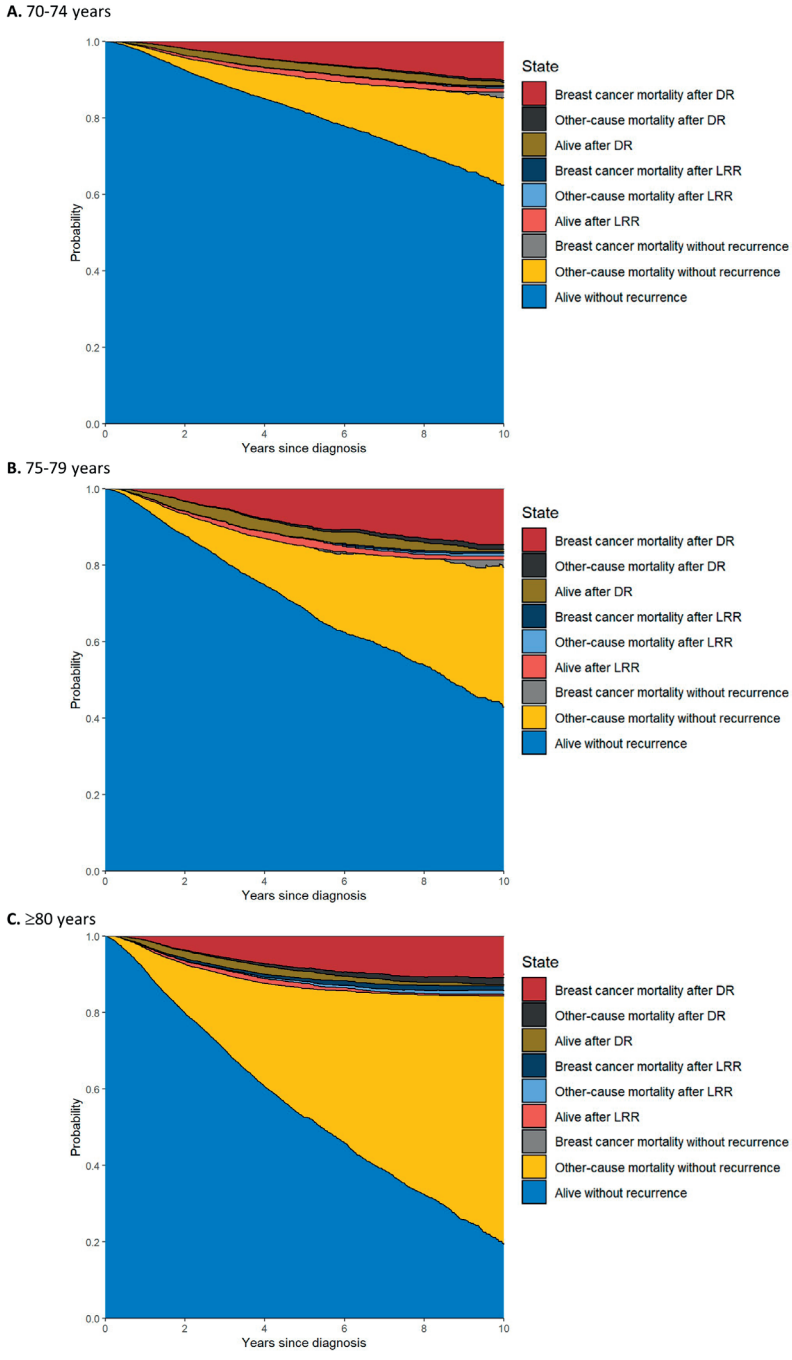

Figure 2. Outcome probabilities since diagnosis based on the multi-state model (see figure 1). Curves are stacked, meaning that the probabilities of the different outcomes are indicated by the distances between the lines. Probabilities are displayed for three age groups: **A.** 70-74 years. **B.** 75-79 years. and **C.** ≥80 years. Abbreviations: DR, distant recurrence; LRR, locoregional recurrence.

Table 2. Five- and ten-year breast cancer mortality and other-cause mortality probabilities (in %) from time of first diagnosis of breast cancer according to state from where the patients died (no recurrence, locoregional recurrence, and distant recurrence) stratified by age group. "Overall" indicates the sum of mortality from the no recurrence, locoregional and distant recurrence states (all mortality).

State	Without recurrence		Locoregional recurrence		Distant recurrence		Overall	
	Breast cancer mortality % (95% CI)	Other-cause mortality % (95% CI)	Breast cancer mortality % (95% CI)	Other-cause mortality % (95% CI)	Breast cancer mortality % (95% CI)	Other-cause mortality % (95% CI)	Breast cancer mortality % (95% CI)	Other-cause mortality % (95% CI)
At 5 years								
70-74 years	-0.9 (-0.3; 0)*	9.9 (9.8-10.0)	0 (0-0.3)	0.1 (0.1-0.1)	5.5 (5.0-6.0)	0.2 (0.2-0.2)	4.6 (3.8-5.4)	10.2 (9.5-14.5)
75-79 years	-0.6 (0-0.6)*	17.1 (16.8-17.3)	0 (0-0.3)	0.2 (0.2-0.3)	9.5 (8.8-10.3)	0.5 (0.4-0.6)	8.9 (7.3-10.5)	17.8 (17.6-18.0)
≥80 years	-6.1 (-4.7; 0)*	39.9 (39.3-40.5)	0.8 (0.2-1.3)	0.5 (0.3-0.8)	8.3 (7.7-9.0)	0.9 (0.8-1.0)	3.0 (1.3-4.8)	41.3 (40.6-42.0)
At 10 years								
70-74 years	1.4 (0-3.5)	23.0 (22.7-23.3)	0.4 (0-0.9)	0.3 (0.3-0.4)	10.2 (9.1-11.3)	0.5 (0.4-0.6)	12.0 (9.4-14.2)	23.9 (23.6-24.2)
75-79 years	1.9 (0-5.3)	36.7 (36.0-37.5)	0.4 (0-1.1)	0.7 (0.5-1.0)	14.6 (13.3-15.8)	1.3 (1.0-1.6)	16.8 (13.0-20.6)	38.8 (37.9-39.6)
≥80 years	-5.5 (-2.4; 0)*	70.5 (68.8-72.2)	1.3 (0.6-1.9)	1.0 (0.5-1.5)	10.9 (9.9-11.8)	1.7 (1.4-2.1)	6.6 (2.8-10.4)	73.3 (71.4-75.2)

*Since the total and population hazard must always be positive, their difference (the excess hazard) can under rare circumstances be negative, leading to negative probabilities. Although contra-intuitive, these negative quantities can be interpreted as meaning that for certain patient groups the survival is better than that of the general population since they represent a relatively fit group. CI, confidence interval.

Locoregional recurrence

Breast cancer and other-cause mortality probabilities after LRR are shown in Table 3 and Supplementary Figure 2. For patients alive after LRR at two years after diagnosis (and without a DR in this timeframe), the 10-year other-cause mortality probabilities were 16.2% (95%CI 11.7-20.6%), 30.9% (95%CI 21.9-39.8%), and 48.3% (95%CI 27.7-68.9%) in patients aged 70-74 years, 75-79 years, and ≥80 years respectively. Overall, the 10-year probabilities of breast cancer mortality were 48.3% (95%CI 23.2-73.5%), 35.4% (95%CI 6.7-64.2%), and 41.3% (95%CI 12.6-70.0%) respectively. For patients alive after LRR at two years after diagnosis, the 10-year probabilities of DR with subsequent breast cancer death were 32.0% (95%CI 8.7-55.4%), 28.2% (95%CI 8.0-48.4%), and 12.7% (95%CI 0-28.1%), respectively. Setting the landmark at 1 year led to worse outcomes at 10 years.

Table 3. Five- and ten-year breast cancer mortality and other cause mortality probabilities (in %) from time of diagnosis for patients alive and in the locoregional recurrence state at the two-year landmark by age group. "Overall" indicates the sum of mortality from the locoregional and distant recurrence states.

	Locoregional recurrence		Distant recurrence		Overall	
	Breast cancer mortality % (95% CI)	Other-cause mortality % (95% CI)	Breast cancer mortality % (95% CI)	Other-cause mortality % (95% CI)	Breast cancer mortality % (95% CI)	Other-cause mortality % (95% CI)
At 5 years						
70-74 years	3.0 (0-20.0)	5.1 (3.6-6.5)	16.5 (0-35.7)	0.7 (0-1.4)	19.5 (0-41.6)	5.7 (5.0-6.5)
75-79 years	-7.0 (0-3.4)	11.9 (9.4-14.3)	13.7 (0-29.3)	0.9 (0-1.8)	6.7 (0-27.2)	12.7 (10.7-14.8)
≥80 years	8.4 (0-35.8)	28.1 (17.5-38.7)	6.8 (0-20.6)	0.9 (0-2.8)	15.2 (0-43.3)	29.0 (19.4-38.7)
At 10 years						
70-74 years	16.3 (0-38.2)	14.4 (9.0-19.8)	32.0 (8.7-55.4)	1.7 (0.6-2.8)	48.3 (23.2-73.5)	16.2 (11.7-20.6)
75-79 years	7.2 (0-30.0)	27.6 (18.2-36.9)	28.2 (8.0-48.4)	3.3 (1.2-5.4)	35.4 (6.7-64.2)	30.9 (21.9-39.8)
≥80 years	28.6 (0-57.2)	45.5 (22.7-68.3)	12.7 (0-28.1)	2.8 (0-5.6)	41.3 (12.6-70.0)	48.3 (27.7-68.9)

Abbreviations: CI, confidence interval.

Distant recurrence

Breast cancer and other-cause mortality probabilities after DR are shown in Table 4 and Supplementary Figure 3. After a DR in the first two years after diagnosis for patients still alive at the two-year landmark, the 5-year probabilities of breast cancer mortality were 82.2% (95%CI 78.3-86.0%), 84.3% (95%CI 80.9-87.8%), and 83.4% (95%CI 80.0-87.2%) in patients aged 70-74 years, 75-79 years, and ≥80 years respectively. Ten-year probabilities were 95.3% (95%CI 94.2-96.4%), 93.1% (95%CI 91.6-94.6%), and 88.6% (95%CI 86.5-90.8%) respectively. The 10-year other-cause mortality probabilities were 3.8% (95%CI 3.2-4.4%), 6.3% (95%CI 5.3%-7.4%), and 11.1% (95%CI 9.0%-13.1%) respectively.

Setting the landmarks at 1 or 3 years only led to minimal changes. Breast cancer mortality was the 10 year-outcome for more than 90% of patients below the age of 80. When the

moment of DR was taken as starting point of the analysis, outcomes were somewhat better for patients with a recurrence later than 3 years after diagnosis (Supplementary Table 2).

Table 4. Five- and ten-year breast cancer mortality and other-cause mortality probabilities (in %) from time of diagnosis for patients alive and in the distant recurrence state at the two-year landmark by age group.

	Breast cancer mortality % (95% CI)	Other-cause mortality % (95% CI)
At 5 years		
70-74 years	82.2 (78.3-86.0)	2.8 (2.5-3.2)
75-79 years	84.3 (80.9-87.8)	5.0 (4.4-5.6)
≥80 years	83.4 (80.0-87.2)	9.6 (8.0-11.1)
At 10 years		
70-74 years	95.3 (94.2-96.4)	3.8 (3.2-4.4)
75-79 years	93.1 (91.6-94.6)	6.3 (5.3-7.4)
≥80 years	88.6 (86.5-90.8)	11.1 (9.0-13.1)

Abbreviations: CI, confidence interval.

DISCUSSION

This study showed that other-cause mortality is by far outweighed by the high breast cancer mortality following a DR. Although older patients mostly die from other causes, after developing a DR, the prognosis seems to be only determined by breast cancer. The different sensitivity analyses showed that, although age and moment of recurrence had some impact on outcomes, in all situations and independent of the model chosen, breast cancer mortality was high in the years following the recurrence. A previous hospital-based cohort study had similar findings, however other-cause mortality was not separated and probably less pronounced since no age selection-criteria were used.[14]

In line with previous literature,[10-13] LRR was a predictor for worse prognosis. For patients younger than 80 years, the 10-year probability of breast cancer mortality was 12-17%, whereas after developing a LRR, 49-53% of the patients died from breast cancer. Yet, it should be emphasized that for the whole cohort the chances of dying from breast cancer after a LRR are very low with 10-year probabilities between 0.8% to 1.5%. This is a result of the very low rates of LRR in the modern era.

We hypothesize that some patients already had distant (micro)metastases at time of LRR detection as many died without developing a DR first. This is supported by recent data showing that 27% of the patients who initially presented with a LRR were found to have synchronous DR.[11] Similarly, in our own cohort, 28% of the patients with a LRR had a DR at the same time (which were classified according to the latter). Furthermore, the classification of

LRR has changed since these data have been collected. Nowadays, contralateral tumours are not considered as recurrence, and a better distinction between ipsilateral second primary tumours and recurrences is possible. This implies that a modern patient with a LRR might even have a worse prognosis than the patients in the study since second primary tumours generally have a better prognosis than recurrences.

The multi-state model allows to estimate treatment-related mortality.[15] As patients with breast cancer have to develop a recurrence before dying from breast cancer, excess mortality in patients without a recurrence can be interpreted as treatment-related mortality. The treatment-related mortality at 10 years was 1-2% for patients younger than 80 years in our cohort. Since patients over 70 years were not treated with chemotherapy conform the Dutch treatment guideline, this is expected to be related to endocrine therapy such as tamoxifen-related thromboembolic events. Although breast cancer treatments are generally considered as low risk treatments, it is reassuring that our findings can confirm this for the older population in which predisposed factors related to ageing could increase the morbidity risk. Moreover, this is another indication of the quality of the data since unrecorded distant recurrences would falsely have resulted in breast cancer mortality in patients without a recurrence; the low probability of this event shows that underreporting was no serious issue.

Our finding that LRR and DR were strong predictors for breast cancer death reasons against omitting treatments in older patients with recurrent breast cancer because of the competing mortality risk. Recent population-based data showed an improvement in relative survival over time for patients aged ≥75 years with stage IV breast cancer, together with the increased use of CDK4/6 inhibitors.[27] Relative survival had also improved for patients aged 65-75 years with stage III breast cancer which was most likely explained by an increase in adjuvant chemotherapy.[27] These findings emphasize that at least some older patients will benefit from more extensive treatment.

This study was the first study to assess the occurrence of other-cause mortality after locoregional and distant recurrence separately which was possible thanks to the integration of methods from relative survival into a multi-state model. Furthermore, we used a large nationwide population-based cohort with detailed baseline information, long follow-up and available recurrence status. A limitation was that patients over 80 years had a better life expectancy than the matched general population (reflected in the negative breast cancer mortality probability in patients without a recurrence due to a larger expected other-cause mortality than the actual observed mortality). This indicates that the relative survival assumption that the patient population is a random subset of the general population was violated for the oldest patients. This is likely explained by the selection of surgically treated patients as frail patients may receive primary endocrine treatment instead (approximately

30% with hormone-receptor positivity).[28] Although this might lead to a small overestimation of other-cause mortality for the oldest age group, the general patterns are not affected by this.

In conclusion, our findings indicate that other-cause mortality plays a negligible role in the outcome of older patients once they develop a DR. LRR is a predictor for worse prognosis, yet leads to a small contribution of breast cancer death after LRR for the whole cohort since the incidence of LRR is low. Future studies need to investigate how these outcomes can be accurately incorporated in clinical prediction tools that could improve individualized treatments in older patients with breast cancer.

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Supplementary Table 1. Patient, disease and treatment characteristics by age group

	70-74 years N=7793	75-79 years N=4332	≥80 years N=6294	
	N (%)	N (%)	N (%)	*p* value
Age. median (IQR)	72.5 (71.2-73.7)	77.4 (75.9-78.7)	83.8 (81.9-86.3)	
No. of comorbidities				<0.001
0	1186 (36)	458 (26)	561 (9)	
1-2	1668 (51)	971 (55)	1369 (22)	
≥3	438 (13)	348 (20)	510 (8)	
Unknown	4501	2555	3854	
Stage				<0.001
I	4497 (58)	1622 (37)	1633 (26)	
II	2581 (33)	2060 (48)	3535 (56)	
III	706 (9)	644 (15)	1113 (18)	
Unknown	9	6	13	
Histological grade				<0.001
1	2098 (29)	872 (22)	1228 (21)	
2	3560 (49)	1902 (47)	2928 (50)	
3	1649 (23)	1235 (31)	1703 (29)	
Unknown	486	323	435	
Hormone-receptor status				<0.001
ER and/or PR positive	6497 (88)	3474 (84)	5082 (85)	
ER and PR negative	919 (12)	650 (16)	877 (15)	
Unknown	377	208	335	
Her2-receptor status				0.002
Negative	4908 (91)	2594 (88)	3676 (89)	
Positive	508 (9)	340 (12)	454 (11)	
Unknown	2377	1398	2164	
Type of surgery				<0.001
Mastectomy	3439 (44)	2684 (62)	4988 (79)	
BCS	4354 (56)	1648 (38)	1306 (21)	
Surgical margins				0.001
Free	7348 (94)	4052 (94)	5804 (92)	
Not free	297 (4)	192 (4)	318 (5)	
Unknown	148 (2)	88 (2)	172 (3)	
Radiotherapy after BCS				<0.001
Yes	4243 (97)	1570 (95)	948 (73)	
No	111 (3)	78 (5)	358 (27)	
Adjuvant endocrine therapy*				<0.001
Yes	3010 (39)	2109 (49)	3283 (52)	
No	4783 (61)	2223 (51)	3011 (48)	

Supplementary Table 1. Patient, disease and treatment characteristics by age group (*continued*)

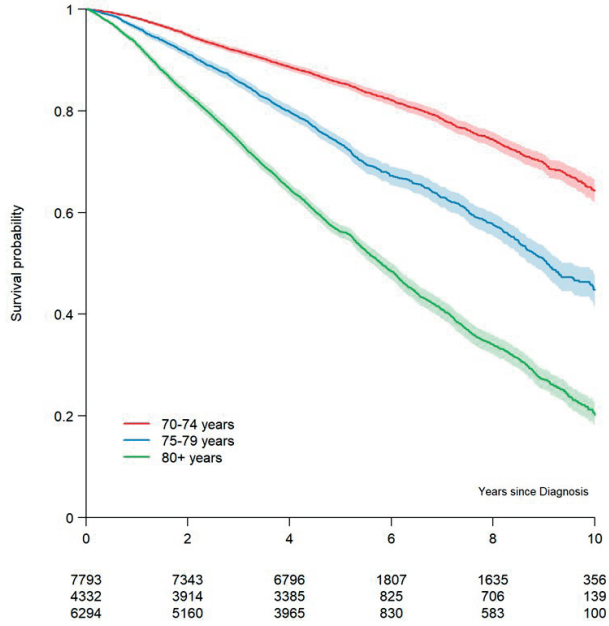
	70-74 years N=7793	75-79 years N=4332	≥80 years N=6294	
	N (%)	N (%)	N (%)	*p* value
Adjuvant chemotherapy				<0.001
Yes	237 (3)	31 (1)	8 (0)	
No	7556 (97)	4301 (99)	6286 (100)	

Differences between age groups were tested by means of Pearson's $\chi 2$ test. *Percentage of hormone-receptor positive patients. Abbreviations: ER, estrogen receptor; PR, progesterone receptor; BCS, breast-conserving surgery.

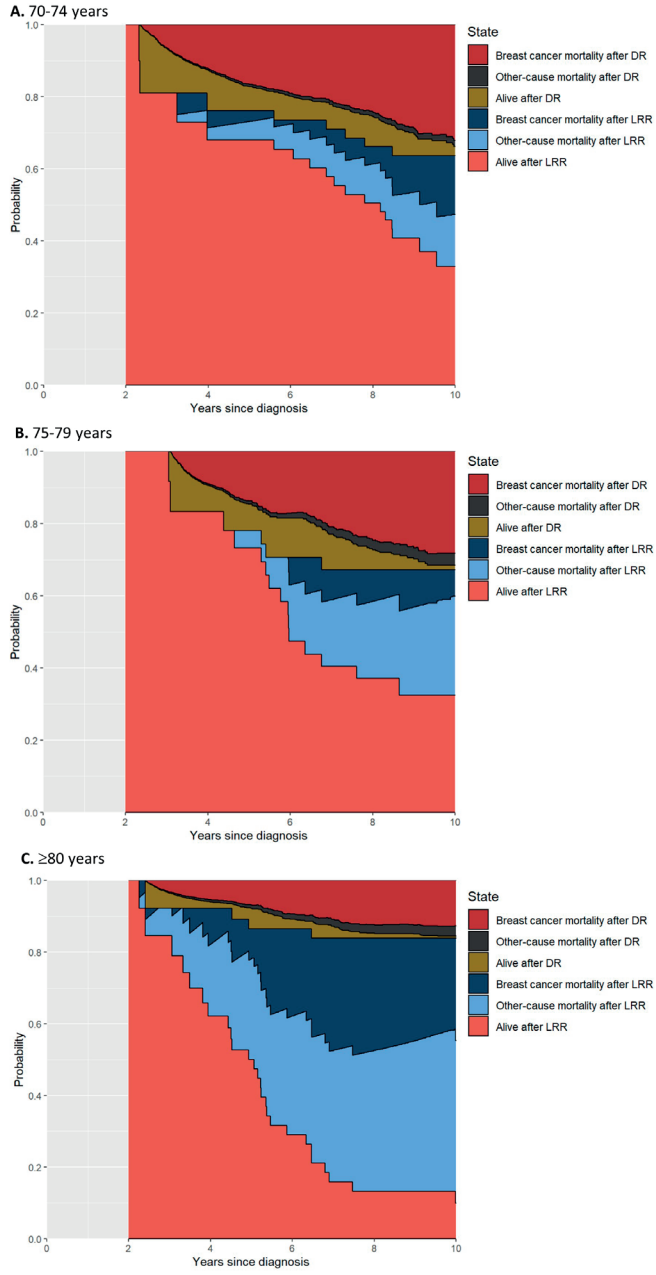
Supplementary Table 2. Three-year breast cancer mortality and other-cause mortality probabilities (in %) from time of distant recurrence by age group and by timing of recurrence.

	Breast cancer mortality % (95% CI)	Other-cause mortality % (95% CI)
Recurrence before 3 years		
70-74 years	85.0 (81.5-88.6)	2.5 (2.2-2.7)
75-79 years	84.0 (80.1-87.9)	4.5 (4.0-5.0)
≥80 years	82.2 (78.9-85.6)	8.4 (7.5-9.3)
Recurrence after 3 years		
70-74 years	78.6 (71.7-85.6)	4.6 (4.1-5.1)
75-79 years	73.6 (65.9-81.4)	8.0 (6.8-9.1)
≥80 years	73.7 (65.4-81.9)	13.4 (11.2-15.7)

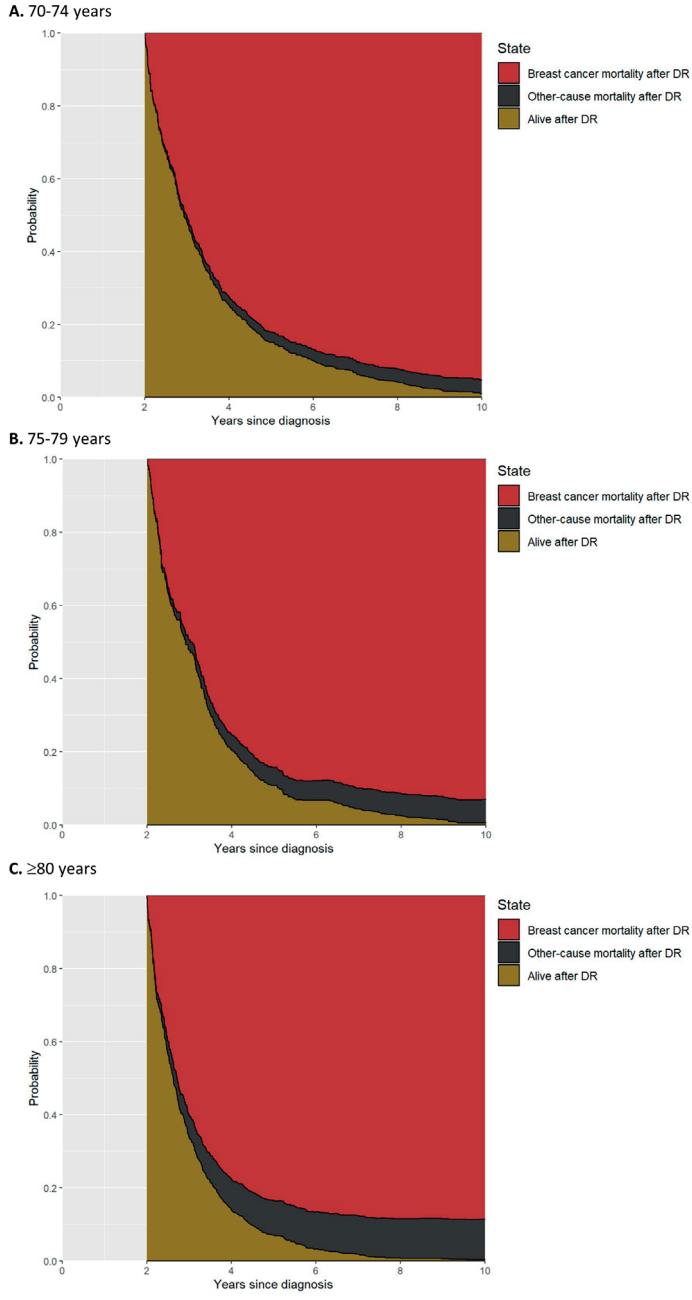
Abbreviations: CI, confidence interval.



Supplementary Figure 1. Kaplan Meier curves for overall mortality by age groups with the number of patients in follow-up in the analysis population.



Supplementary Figure 2. Outcome probabilities of patients alive at 2 years after diagnosis with a locoregional recurrence (but no distant recurrence) before 2 years, based on the multi-state model (see figure 1). All patients start at alive with locoregional recurrence without distant recurrence. Next states are distant recurrence and death. The observed mortality after locoregional occurrence has been split in two parts, based on mortality data for the general population: breast cancer mortality and other-cause mortality. The same has been done for mortality after distant recurrence. Curves are stacked, meaning that the probabilities of the different outcomes are indicated by the distances between the lines. Probabilities are displayed for three age groups: **A.** 70-74 years. **B.** 75-79 years. and **C.** ≥80 years. Abbreviations: DR, distant recurrence; LRR, locoregional recurrence.



Supplementary Figure 3. Outcome probabilities of patients alive at 2 years after diagnosis with a distant recurrence before 2 years, based on the multi-state model (see figure 1). All patient start at alive with distant recurrence. The only next state is death. The observed mortality has been split in two parts, based on mortality data for the general population: breast cancer mortality and other-cause mortality. Curves are stacked, meaning that the probabilities of the different outcomes are indicated by the distances between the lines. Probabilities are displayed for three age groups: **A.** 70-74 years. **B.** 75-79 years. and **C.** ≥80 years. Abbreviations: DR, distant recurrence.

4

Prediction of other-cause mortality in older patients with breast cancer using comorbidity

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ABSTRACT

Background. Individualized treatment in older patients with breast cancer can be improved by including comorbidity and other-cause mortality in prediction tools, as the other-cause mortality risk strongly increases with age. However, no optimal comorbidity score is established for this purpose. Therefore, this study aimed to compare the predictive value of the Charlson comorbidity index for other-cause mortality with the use of a simple comorbidity count and to assess the impact of frequently occurring comorbidities.

Methods. Surgically treated patients with stages I-III breast cancer aged ≥70 years diagnosed between 2003 and 2009 were selected from the Netherlands Cancer Registry. Competing risk analysis was performed to associate 5-year other-cause mortality with the Charlson index, comorbidity count, and specific comorbidities. Discrimination and calibration were assessed.

Results. Overall, 7,511 patients were included. Twenty-nine percent had no comorbidities, and 59% had a Charlson score of 0. After five years, 1,974 patients had died (26%), of which 1,450 patients without a distant recurrence (19%). Besides comorbidities included in the Charlson index, psychiatric disease was strongly associated with other-cause mortality (sHR 2.44 (95%-CI 1.70-3.50)). The c-statistics of the Charlson index and comorbidity count were similar (0.65 (95%-CI 0.64-0.65) and 0.64 (95%-CI 0.64-0.65)).

Conclusion. The predictive value of the Charlson index for 5-year other-cause mortality was similar to using comorbidity count. As it is easier to use in clinical practice, our findings indicate that comorbidity count can aid in improving individualizing treatment in older patients with breast cancer. Future studies should elicit whether geriatric parameters could improve prediction.

INTRODUCTION

Over 30% of patients diagnosed with breast cancer are 70 years or older.[1] The risk of dying from other causes than breast cancer strongly increases with age.[2, 3] Nine years after diagnosis, 21% of the patients aged 70-74 years have died from other causes compared to 61% over 80 years.[3] Selecting patients for adjuvant treatments is one of the challenges for clinicians who are treating this patient population since the effect of radiotherapy, endocrine therapy, or chemotherapy can be diminished by shorter life expectancies. The benefit of adjuvant treatments in patients that are likely to die from other causes is therefore questionable.[4-6] Hence, it is essential to take this other-cause mortality into account when estimating prognosis and treatment benefit.[2, 3] In addition to age, the presence of comorbidity is an important determinant for other-cause mortality.[7, 8]

The PREDICT tool has been demonstrated to accurately predict overall survival in older patients with breast cancer, but its implications for treatment decisions are unclear as mortality from breast cancer and other causes are not adjusted for individual comorbidities. Indeed, the predictions are less accurate if patients have multiple comorbidities.[9] The currently unavailable Adjuvant! Online tool did predict both cancer-specific and other-cause mortality, but inaccurate predictions were reported in patients over 65 years, especially when a higher number of comorbidities were present.[10] One proposed explanation is that Adjuvant! Online does not provide a definition of the incorporated comorbidity categories (including for example “minor problems” or “average for age”).

Up to now, an optimal comorbidity score to be used in prediction tools that aid in individualizing treatment decisions in older patients with breast cancer has not been established. The Charlson comorbidity index is frequently used to describe study populations’ general health status and adjust for differences in comparative effectiveness studies.[11, 12] The Charlson index comprises sixteen comorbidities, of which three are assigned extra weight. Since the Charlson index is widely known, it could be convenient to use it as a comorbidity score in a prediction tool. On the other hand, relevant comorbidities that are not included may be missed, and calculating the Charlson score requires some extra time from the clinician.

Therefore, the aim of this study was to assess the predictive value of the Charlson comorbidity index for other-cause mortality and to compare these predictions with using a simple comorbidity count. In addition, the aim was to assess the impact of frequently occurring comorbidities on 5-year other-cause mortality.

METHODS

Design and patients

This study was a nationwide population-based cohort study. Patients were selected from the database of the Netherlands Cancer Registry (NCR), of which data are currently used in over 200 publications annually (**https://iknl.nl/en/ncr**, accessed on 1 March 2021). The NCR receives reports of diagnosed malignancies from the nationwide network and registry of histopathology and cytopathology in the Netherlands (PALGA), which are confirmed and completed through the national hospital discharge databank. Data managers of the Netherlands Comprehensive Cancer Organization (IKNL) collect data on diagnosis, staging and treatment from medical records using international coding rules. The breast cancer stage is defined according to the TNM Classification of Malignant Tumors for breast cancer (6th edition).[13] Vital status is available through linkage of NCR data with the Municipal Personal Records database. Information on comorbidity and recurrence status was retrospectively collected from the medical records by trained data managers of the IKNL. All comorbidity, as present at the time of diagnosis, was recorded according to the categories in the ICD-10 classification, based on case record forms.

Patients diagnosed with stage I-III breast cancer aged 70 years or older diagnosed between 2003 and 2009, who underwent surgery, were included in this study. For patients diagnosed between 2003 and 2006, only patients from one of the nine Dutch registry regions were included, as information on comorbidity was at that time only available in this particular region. For patients diagnosed between 2007 and 2009, patients from all nine Dutch regions were included, as comorbidity and recurrence status were collected retrospectively specifically for this study. Patients with missing information on comorbidity and vital status were excluded. As death without distant recurrence was used as a proxy for other-cause mortality (described in next paragraph), patients with missing recurrence status were also excluded.

Definitions

The primary outcome was mortality from other causes than breast cancer, which was defined as death without distant recurrence, given that cause of death as registered on death certificates was not available. Another reason was that it is known that ascertaining the cause of death in older patients with breast cancer is prone to misclassification and tends to overattribute mortality to breast cancer.[14] As patients with early-stage breast cancer are unlikely to die from breast cancer without developing a distant recurrence, death without a distant recurrence was considered a valid proxy for other-cause mortality in prior research.[8, 15] Moreover, no treatment-related mortality is present. No lethal postoperative complications are described, and no chemotherapy toxicity occurs as chemotherapy was discouraged for patient over 70 years in national guidelines at the time.[16]

The specific comorbidities that were analyzed separately were comorbidities that are included in the Charlson comorbidity index or were present in at least 1% of the patients. Psychiatric diseases did not include dementia, which was reported separately. The Charlson comorbidity index was developed in 1987 to predict 1-year mortality in hospitalized patients (n = 604) and validated in patients with breast cancer.[11, 12] Solid tumors, leukemia, lymphoma and AIDS were omitted because breast cancer was the index disease, and AIDS did not occur. The remaining 12 comorbidities had weights from 1 to 3. The sum of these weights is called the Charlson score. The Charlson index was compared with comorbidity count as this is the simplest comorbidity score. Given that other-cause mortality is our outcome of interest, all comorbidities with a potential impact on life expectancy were included in the comorbidity count. These comprised all comorbidities that required medication at the time of diagnosis or were judged to impact life expectancy based on clinical knowledge.

Statistical analysis

Patients and treatment characteristics were described as frequencies and percentages. Comorbidity was described as frequencies and percentages of patients with specific comorbidities (yes; no), Charlson score (0; 1; 2; ≥3) and comorbidity count (0; 1; 2; ≥3). The distribution of the comorbidity scores was graphically presented. The relation between comorbidity and 5-year other-cause mortality was assessed by performing univariate and age-adjusted Fine and Gray analysis. Since the outcome of interest was other-cause mortality, distant recurrence was considered a competing event as aproxy for breast cancer deaths.[17] The associations are expressed as subdistribution hazard ratios (sHR) with 95% confidence intervals (CIs). For the specific comorbidities, patients without this comorbidity were used as reference. Charlson score 0 and zero comorbidities were used as a reference for the Charlson index and comorbidity count, respectively.

To compare the predictive value of the Charlson index and comorbidity count, first discrimination was assessed using c-statistics, which correspond to the area under the receiver operating characteristic (ROC) curve. The c-statistics of the univariable Charlson and comorbidity count Fine and Gray models were compared using the comorbidity scores as a continuous variable. To assess the additional value, improvements in c-statistics by adding the comorbidity scores to a model based on age alone were compared. A sensitivity analysis was performed to assess the potential effect of tumor characteristics on the relationship between comorbidity and other cause mortality by performing multivariate fine and gray models, including age, stage, grade and endocrine receptor status. The proportionality assumption was tested using Schoenfeld residuals. No violation of the assumption was found.

Next, calibration of the Fine and Gray models, including age and the comorbidity scores, was assessed by plotting the observed cumulative incidence of 5-year other-cause mortality

against the predicted 5-year other-cause mortality. Using the Cumulative Incidence Competing Risk method, distant recurrence was considered a competing event as a proxy for breast cancer deaths. To make the calibration plots, patients were grouped in tenths according to the predicted cumulative incidences of 5-year other-cause mortality. The calibration plots were visually compared with the ideal x = y line.

Finally, as the c-statistic is substantially lower in the presence of competing events, an additional analysis was performed to evaluate the impact of comorbidity in addition to age.[18] For this reason, the cumulative incidence curves of other-cause mortality by comorbidity count were presented stratified by age (70-74 years; 75-79 years; 80 years and older). Stata SE 12.0 was used for the statistical analysis. All statistical tests were two-sided, and a *p*-value < 0.05 was considered statistically significant.

RESULTS

Between 2003 and 2009, 19,748 patients aged 70 years or older were surgically treated for non-metastasized breast cancer, of which 1,329 (6.7%) were excluded due to missing follow-up for recurrence or vital status. A total of 7,511 patients with available information on comorbidity were included in the current study. The median age was 76.0 years (interquartile range 72.8-81.7 years). Patient and treatment characteristics are shown in Table 1. Most patients had stage I (43.9%) or stage II (43.4%) breast cancer. Of the 6,382 patients with hormone receptor-positive disease, 56.2% received adjuvant endocrine treatment in line with the Dutch treatment guideline stating that patients with favorable tumor characteristics (grade 1 up to 2 cm and grade 2 up to 1 cm) do not receive adjuvant endocrine treatment as the absolute survival benefit is very limited in patients with a low-risk tumor. Only 2.6% of all patients received adjuvant chemotherapy. Figure 1 shows the distribution of the Charlson index and comorbidity count. In 29% of patients, zero comorbidities were counted, and 59% had a Charlson score of 0 caused by a considerable number of patients having comorbidities not included in the Charlson index. The prevalence of specific comorbidities is presented in Table 2. Of the 4,460 patients with a Charlson score of 0, 2,206 patients (49.5%) had one or more comorbidities on the count, particularly hypertension (Supplementary Table S1). After five years of follow-up, 1,450 patients (19.3%) had died without a distant recurrence, 524 patients died after developing a distant recurrence (7.0%), and 135 were alive with a distant recurrence (1.8%).

Table 1. Patient and treatment characteristics.

	No. (%)
Total	7511
Year of diagnosis	
2003	309 (4.1)
2004	452 (6.0)
2005	548 (7.3)
2006	564 (7.5)
2007	1552 (20.7)
2008	1615 (21.5)
2009	2471 (32.9)
Age category	
70-74 years	3292 (43.8)
75-79 years	1778 (23.7)
≥80 years	2441 (32.5)
TNM stage	
1	3297 (43.9)
2	3259 (43.4)
3	944 (12.6)
Unknown	11 (0.2)
Tumor grade	
1	1847 (24.6)
2	3387 (45.1)
3	1803 (24.0)
Unknown	474 (6.3)
Hormone receptor status	
ER and/or PR positive	6382 (85.0)
ER and PR negative	968 (12.7)
Unknown	180 (2.3)
Her2 status	
Positive	610 (8.0)
Negative	5667 (75.1)
Unknown	1269 (16.8)
Type of surgery	
Mastectomy	4346 (57.9)
Breast conserving surgery	3165 (42.1)
Endocrine treatment*	
Yes	3584 (56.2)
No	2798 (43.8)
Chemotherapy	
Yes	194 (2.6)
No	7317 (97.4)

*Percentage of patients with hormone receptor-positive breast cancer.

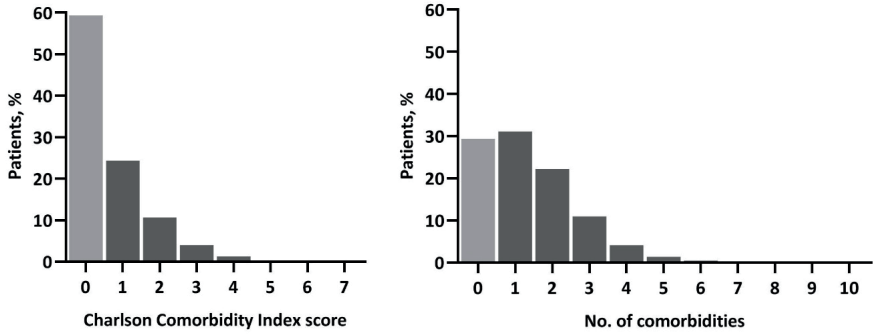

Figure 1. Distribution of comorbidity by measurement type.

Table 2. Prevalence of specific comorbidities.

	No. (%)
Comorbidities included in Charlson index	
Myocardial infarction	671 (8.9)
Congestive heart failure	216 (2.9)
Peripheral vascular disease	216 (2.9)
Cerebrovascular disease	545 (7.3)
Dementia	164 (2.2)
Chronic obstructive pulmonary disease	620 (8.3)
Connective tissue disease	212 (2.8)
Peptic ulcer disease	128 (1.7)
Liver disease	31 (0.4)
Diabetes without end-organ damage	1219 (16.2)
Diabetes with end-organ damage	162 (2.2)
Hemiplegia	16 (0.2)
Severe chronic renal disease	12 (0.2)
Other frequently occurring comorbidities*	
Hypertension	2971 (39.6)
Arrhythmia	342 (4.6)
Valvular heart disease	294 (3.9)
Thyroid disease	293 (3.9)
Venous thromboembolism/pulmonary embolism	213 (2.8)
Angina pectoris	166 (2.2)
Tuberculosis	100 (1.3)
Hypercholesterolemia	94 (1.3)
Psychiatric disease (excluding dementia)	90 (1.2)

*Present in ≥1% of the study cohort.

Specific comorbidities

All individual comorbidities included in the Charlson index increased the risk of 5-year other-cause mortality in the univariate analysis except for liver disease (Supplementary Table 2). The age-adjusted sHRs are presented in Figure 2, with the sHR of peptic ulcer disease no longer significant after adjustment for age. The highest sHR was seen for dementia, which was associated with a fourfold higher risk of other-cause mortality compared to patients without dementia (age-adjusted sHR 4.22, 95% CI 3.41-5.23). Of the specific comorbidities not included in the Charlson index, the presence of arrhythmia, psychiatric disease (excluding dementia), and valvular heart disease increased the risk of other-cause mortality in univariate analysis (Supplementary Table 2). The sHRs for psychiatric disease remained significant after adjustment for age (Figure 2). Patients with a psychiatric disease had a more than two-fold increased risk of other-cause mortality compared with patients without the psychiatric disease (age-adjusted sHR 2.44, 95% CI 1.70-3.50).

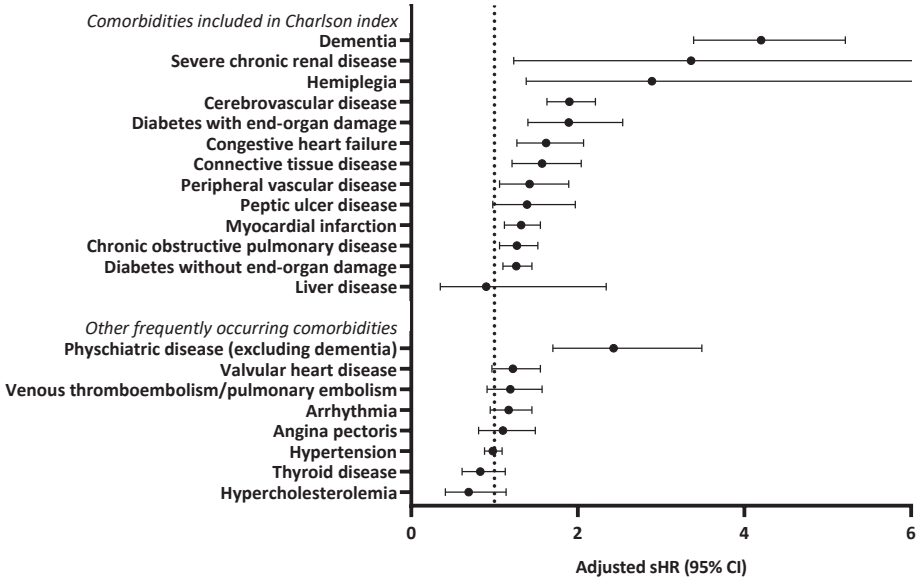

Figure 2. Adjusted subdistribution hazard ratios (sHRs) for 5-year other cause mortality by specific comorbidities. The multivariable model included all other specific comorbidities and age.

Charlson index

Table 3 and Figure 3 show the crude and age-adjusted sHR for other-cause mortality by comorbidity score. With each increasing comorbidity category, patients had a higher risk of dying from other causes than patients with a Charlson score of 0 or zero comorbidity count, respectively. The sensitivity analysis showed no effect of tumor characteristics on the relationship between comorbidity and age on other cause mortality (Supplementary Table S3).

Table 3. Crude and age-adjusted subdistribution hazard ratios for 5-year other-cause mortality by Charlson index and comorbidity count and corresponding model c-statistics.

	Charlson index		Comorbidity count	
Comorbidity category	Crude sHR (95% CI)	Age-adjusted sHR (95% CI)	Crude sHR (95% CI)	Age-adjusted sHR (95% CI)
0	Referent	Referent	Referent	Referent
1	1.80 (1.59 to 2.03)	1.69 (1.49 to 1.90)	1.60 (1.37 to 1.87)	1.42 (1.21 to 1.65)
2	2.05 (1.76 to 2.39)	1.80 (1.54 to 2.10)	2.01 (1.71 to 2.35)	1.73 (1.48 to 2.03)
≥3	2.96 (2.49 to 3.53)	2.82 (2.35 to 3.38)	3.04 (2.60 to 3.56)	2.45 (2.09 to 2.88)
Model c-statistic (95% CI)*	0.58 (0.57 to 0.59)	0.65 (0.64 to 0.66)	0.58 (0.58 to 0.59)	0.64 (0.64 to 0.65)

*The c-statistics of the age-adjusted models corresponds to the models including age and the comorbidity score.

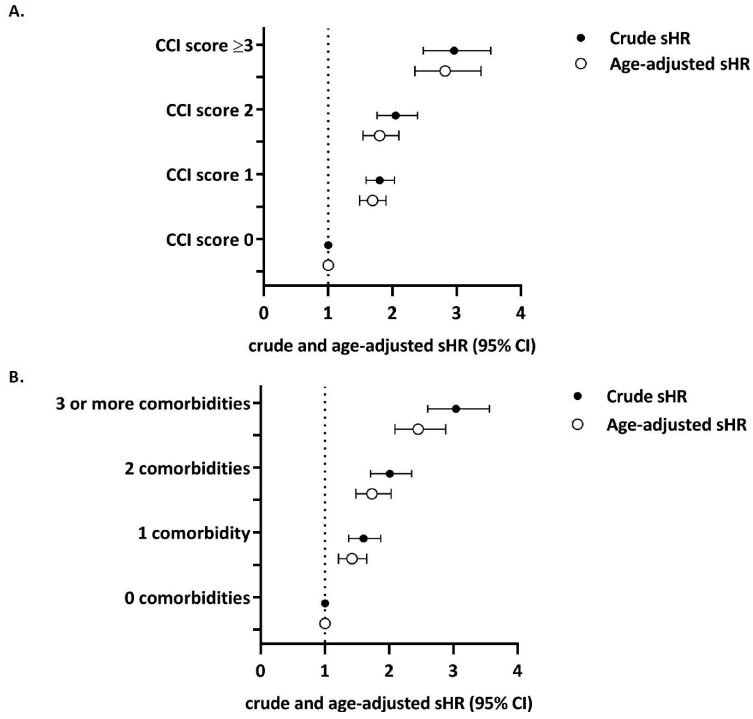

Figure 3. A. Crude (●) and age-adjusted (○) subdistribution hazard ratios (sHRs) for 5-year other-cause mortality by Charlson index. **B.** Crude (●) and age-adjusted (○) sHRs for 5-year other-cause mortality by comorbidity count.

The c-statistic for predicting 5-year other-cause mortality was similar between the univariable models of the Charlson index (0.58, 95% CI 0.57-0.59) and comorbidity count (0.58, 95% CI 0.58-0.59). The c-statistic for predicting 5-year other-cause mortality based on age alone was 0.62 (95% CI 0.62-0.63), which increased to 0.65 (95% CI 0.64-0.66) by adding the Charlson index, and to 0.64 (95% CI 0.64-0.65) by adding comorbidity count (Table 3).

Calibration was good for both the Fine and Gray models, including age and Charlson index and age and comorbidity count (Supplementary Figure S1).

The impact of comorbidity in addition to age was also evaluated by stratifying the cumulative incidence curves of death from other causes by age and comorbidity count (Figure 4). These cumulative incidence curves demonstrated a clear trend between a higher comorbidity count and increasing other-cause mortality in all three age groups.

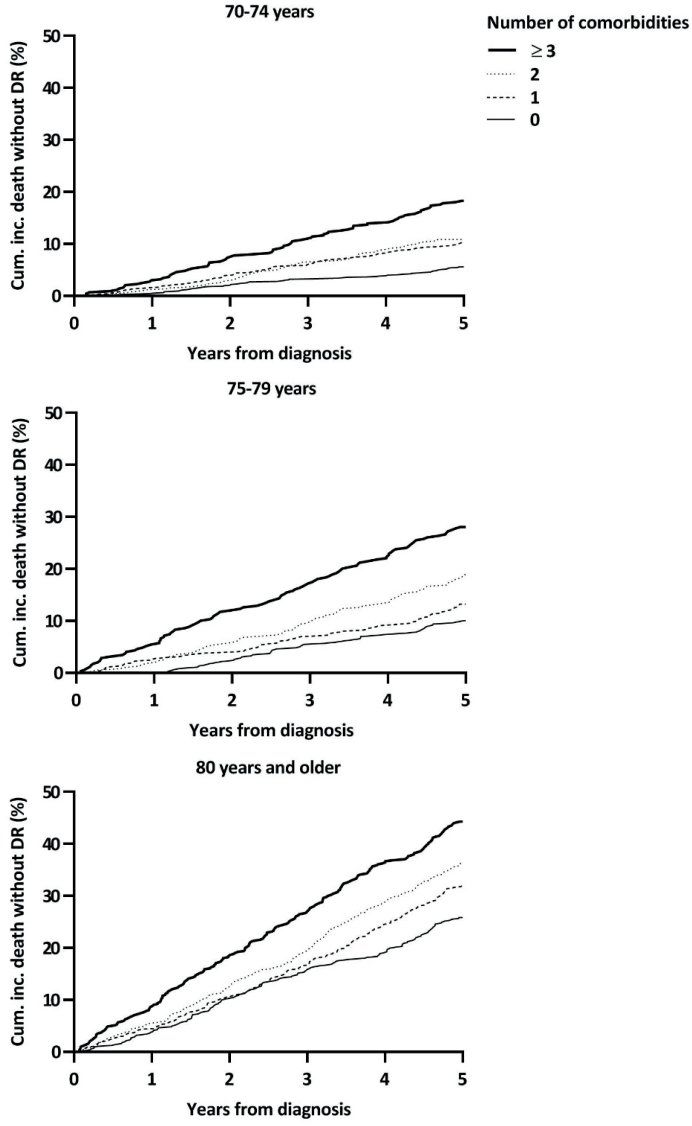

Figure 4. Cumulative incidences of other-cause mortality by age and number of comorbidities.

DISCUSSION

The main finding of this study is that the predictive value of the Charlson index for 5-year other-cause mortality is similar to that of comorbidity count. Furthermore, of the specific comorbidities not included in the Charlson index, the only psychiatric disease was associated with an increased risk of other-cause mortality after adjustment for age.

It is well-known that comorbidity is associated with overall and other-cause mortality in patients with breast cancer. This was demonstrated in population-based [19-25] and trial-based [8, 15] cohorts using the Charlson index [15, 19, 20, 22-24] or comorbidity count [8, 19, 21]. Unlike the current study, a previous study found that prediction of other-cause mortality was better for comorbidity count than for the Charlson index.[19] However, in this previous study, while calculating deaths from other causes, breast cancer-specific deaths were censored rather than explicitly taken into account as a competing event.[18] Our study found that the Charlson index had a similar predictive value as the comorbidity count. Our data provide some clues that could explain this finding.

First, the weights could play a role. Although dementia gave a fourfold risk of dying from other causes in the present study, dementia is only assigned a weight of one in the Charlson index. Others have also suggested that the original Charlson weights may no longer be appropriate. A SEER-Medicare population-based cohort study of 64,034 patients with breast cancer aged 66 years or older demonstrated that dementia, congestive heart failure and COPD would be assigned a higher weight if Charlson's method of assigning weights by rounding adjusted hazard ratio for overall mortality was applied.[20] Similarly, a Danish population-based cohort study of 59,673 postmenopausal patients with stage I-III breast cancer showed that dementia and COPD would be assigned a higher weight.[26]

A second explanation could be that the Charlson index misses comorbidities that are relevant for the remaining life expectancy. This is suggested because 60% of the patients in our cohort of patients over 70 years had a Charlson score of 0, of which 35% had one comorbidity, and 16% had two or more comorbidities that are not included in the Charlson index. Similar rates of patients with a Charlson score of 0 were seen in the aforementioned population-based cohorts.[20, 22] Psychiatric disease is not included in the Charlson index, but its presence was strongly associated with other-cause mortality in the present study. The association of psychiatric diseases with overall mortality also stood out in previous Dutch and American population-based studies.[21, 27] Possibly, this is due to improved recognition and diagnosis of psychiatric diseases over the past years.

As can be expected, the strongest predictor for other-cause mortality is age. However, in line with others, our study demonstrated that comorbidity provides additional predictive value. First, the association with other-cause mortality remained after adjusting for age. Second, although modestly, the c-statistic improved by adding comorbidity to the model based on age alone. Third, cumulative incidence curves showed a clear trend between comorbidity and other-cause mortality stratified by age. Hence, the question is raised how comorbidity should be incorporated in prediction tools for clinical practice. As the Charlson index is the most widely known standardized comorbidity score, the present study evaluated the Charlson index for this purpose. Comorbidity count was used as a reference because this is the simplest comorbidity score as no checklist of specific comorbidities is needed. Based on our finding that the Charlson index performed similar to comorbidity count, we would argue against using the original Charlson index in the development of new prediction tools for older patients with breast cancer. Although changing the weights and adding new comorbidities, such as psychiatric diseases, could improve the predictive value of the original Charlson index, the implication that all the separate comorbidities would need to be included in the prediction tool reduces its practicality. In our opinion, the advantage of using comorbidity count is that its simplicity enhances the applicability of the tool in clinical practice. Future studies must clarify to what extent updated Charlson weights could improve its predictive value in comparison to comorbidity count.

Interestingly, the c-statistics of our models based on age and comorbidity score were lower compared to previous studies performed in similar study populations.[10, 19] Several reasons could explain this. First, patients in the present study were somewhat older than previous studies, and the association between comorbidity and overall mortality seems to diminish with age.[21] Second, it is important to mention that the c-statistics in these previous studies are based on cox proportional hazards models, opposed to the competing risk models in the present study. This is relevant as the c-statistic is lower in the presence of competing events since patients with a high predicted risk of dying from other causes could still develop a distant recurrence.[18] It makes sense that if no such competing event can interfere with the prediction, the predictive accuracy will be better. Therefore, the predictive accuracy should not be based on the c-statistic alone, and the traditional interpretation may not be appropriate.[18] Since the age-adjusted sHRs and cumulative incidence curves stratified by age still showed a clear association between comorbidity and other-cause mortality, we believe that the modest improvement in c-statistic by adding comorbidity to a model based on age alone is a clinically relevant improvement.

Lastly, other geriatric parameters besides comorbidity status that discern life expectancy could improve prediction of other-cause mortality. For community-dwelling older individuals, it is known that prediction tools that include functional parameters obtained

from a geriatric assessment can more accurately predict life expectancy.[28] For patients with breast cancer, the evidence also accumulates that using geriatric parameters in addition to traditional prognostic factors improves prediction.[29-31] Therefore, geriatric parameters should also be considered for new prediction tools. Our research group is currently working on such a tool in the *prediction of outcome, risk of toxicity and quality of life in older patients treated for breast cancer* (PORTRET) study. The aim is to incorporate tumor characteristics, such as tumor stage, grade and estrogen receptor status, comorbidity and other geriatric parameters to predict breast cancer and other-cause mortality, but also focus on other relevant outcomes, such as toxicity and functional outcomes.

A strength of this study was that it was performed in a large nationwide cohort with detailed information on comorbidity and follow-up. The population-based character enhances the generalizability of our results. Another strength was that we selected patients aged 70 years and older, as comorbidity influences treatment decisions in this age category. Last, Fine and Gray regression models that considered distant recurrence as competing events were used. The lack of information on the cause of death can be seen as a limitation, although ascertaining the cause of death in older patients with cancer is prone to misclassification.[14] Furthermore, as patients with early breast cancer are unlikely to die from breast cancer without developing a distant recurrence, using death without distant recurrence is a valid proxy for other-cause mortality also used by others.[8, 15] It may be possible that we slightly underestimate other-cause mortality in *n* very small number of patients with limited recurrent disease (e.g., a solid bone metastasis), as these patients may be misclassified as having died due to breast cancer.

Conclusion

The Charlson index had no superior predictive value for other-cause mortality over comorbidity count in older patients with early breast cancer. To tailor a prediction tool to the older population with breast cancer, comorbidity status and other-cause mortality should be considered. To facilitate the application in clinical practice, we would argue the use of comorbidity count in new prediction tools. Future research is needed to assess the predictive value of other geriatric parameters for other-cause mortality, as these could further improve prediction.

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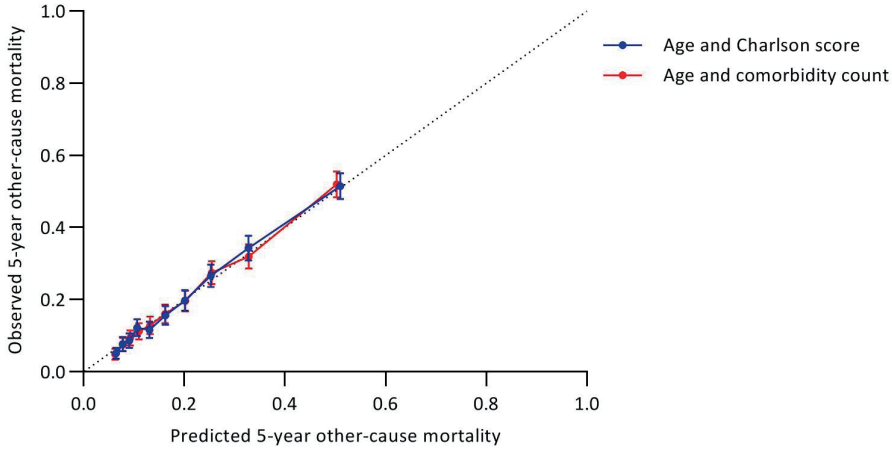

Supplementary Figure 1. Calibration of the two Fine and Gray models for prediction of 5-year other-cause mortality, including age and Charlson score (blue), and age and comorbidity count (red).

Supplementary Table 1. Comorbidity count and specific comorbidities in patients with a Charlson Comorbidity Index score 0 and ≥1

	Charlson score 0	Charlson score ≥1
	No. (%)	No. (%)
Comorbidity count		
0	2206 (49.5)	0 (0)
1	1556 (34.9)	782 (25.63)
2	536 (12)	1134 (37.17)
≥3	162 (3.6)	1135 (37.2)
Comorbidities not included in the CCI		
Hypertension	1503 (33.7)	1468 (48.1)
Arrhythmia	176 (4)	166 (5.4)
Valvular heart disease	157 (3.5)	137 (4.5)
Thyroid disease	169 (3.8)	124 (4.1)
Venous thrombo-/pulmonary embolism	102 (2.3)	111 (3.6)
Angina pectoris	57 (1.3)	109 (3.6)
Hypercholesterolemia	49 (1.1)	45 (1.5)
Psychiatric disease (excluding dementia)	57 (1.3)	33 (1.1)

Supplementary Table 2. Subdistribution hazard ratios (sHRs) with 95% confidence intervals of specific comorbidities for 5-year other-cause mortality. Patients without the specific comorbidity were used as referent.

	No. (%)	Crude sHR (95% CI)	Adjusted sHR* (95% CI)
Specific comorbidity included in CCI			
Myocardial infarction	671 (8.9)	1.57 (1.34 to 1.83)	1.32 (1.12 to 1.55)
Congestive heart failure	216 (2.9)	2.67 (2.15 to 3.31)	1.62 (1.27 to 2.07)
Peripheral vascular disease	216 (2.9)	1.45 (1.10 to 1.90)	1.42 (1.06 to 1.90)
Cerebrovascular disease	545 (7.3)	2.54 (2.19 to 2.93)	1.90 (1.63 to 2.21)
Dementia	164 (2.2)	5.95 (4.89 to 7.23)	4.22 (3.41 to 5.23)
Chronic obstructive pulmonary disease	620 (8.3)	1.38 (1.17 to 1.63)	1.26 (1.05 to 1.51)
Connective tissue disease	212 (2.8)	1.56 (1.21 to 2.01)	1.56 (1.21 to 2.03)
Peptic ulcer disease	128 (1.7)	1.63 (1.17 to 2.27)	1.38 (0.97 to 1.97)
Liver disease	31 (0.4)	0.85 (0.34 to 2.10)	0.90 (0.35 to 2.33)
Diabetes without end to organ damage	1219 (16.2)	1.30 (1.14 to 1.48)	1.26 (1.10 to 1.45)
Diabetes with end to organ damage	162 (2.2)	1.61 (1.22 to 2.14)	1.90 (1.41 to 2.55)
Hemiplegia	16 (0.2)	4.18 (2.07 to 8.45)	2.91 (1.38 to 6.10)
Severe chronic renal disease	12 (0.2)	4.74 (2.02 to 11.09)	3.38 (1.24 to 9.25)
Other frequently occurring comorbidities			
Hypertension	2971 (39.6)	1.07 (0.96 to 1.19)	0.98 (0.88 to 1.09)
Arrhythmia	342 (4.6)	1.67 (1.36 to 2.06)	1.18 (0.95 to 1.45)
Valvular heart disease	294 (3.9)	1.45 (1.15 to 1.83)	1.23 (0.97 to 1.55)
Thyroid disease	293 (3.9)	0.93 (0.70 to 1.24)	0.83 (0.61 to 1.13)
Venous thrombo-/pulmonary embolism	213 (2.8)	1.29 (0.98 to 1.71)	1.20 (0.91 to 1.58)
Angina pectoris	166 (2.2)	1.31 (0.97 to 1.78)	1.10 (0.81 to 1.49)
Hypercholesterolemia	94 (1.3)	0.73 (0.44 to 1.23)	0.69 (0.41 to 1.14)
Psychiatric diseases (excluding dementia)	90 (1.2)	1.64 (1.13 to 2.37)	2.44 (1.70 to 3.50)

*The multivariable model included all specific comorbidities and age.

Supplementary Table 3. Sensitivity analysis. Crude and multivariate subdistribution hazard ratios for 5-year other-cause mortality by Charlson index and comorbidity count. The first multivariate model was adjusted for age alone, and the second multivariate model was adjusted for age and tumor characteristics: stage, grade and endocrine receptor status.

Comorbidity category	Charlson index			Comorbidity count		
	Crude	Age-adjusted	Adjusted for age and tumor characteristics*	Crude	Age-adjusted	Adjusted for age and tumor characteristics*
	sHR (95% CI)	sHR (95% CI)	sHR (95% CI)	sHR (95% CI)	sHR (95% CI)	sHR (95% CI)
0	Referent	Referent	Referent	Referent	Referent	Referent
1	1.80 (1.59 to 2.03)	1.69 (1.49 to 1.90)	1.71 (1.50 to 1.94)	1.60 (1.37 to 1.87)	1.42 (1.21 to 1.65)	1.45 (1.24 to 1.71)
2	2.05 (1.76 to 2.39)	1.80 (1.54 to 2.10)	1.76 (1.50 to 2.07)	2.01 (1.71 to 2.35)	1.73 (1.48 to 2.03)	1.71 (1.45 to 2.01)
≥3	2.96 (2.49 to 3.53)	2.82 (2.35 to 3.38)	2.89 (2.38 to 3.50)	3.04 (2.60 to 3.56)	2.45 (2.09 to 2.88)	2.40 (2.03 to 2.84)

*Multivariate model including age, stage, grade and hormone receptor status.

Part II

Omission of treatments in selected older patients

5

Effectiveness of radiotherapy after breast-conserving surgery in older patients with T1-2N0 breast cancer

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ABSTRACT

Background. In the Netherlands, radiotherapy after breast-conserving surgery (BCS) is omitted in up to 30% of patients aged ≥ 75 years. Although omission of radiotherapy is considered an option for older women treated with endocrine treatment, the majority of these patients do not receive systemic treatment following Dutch treatment guidelines. Therefore, the aim of this study was to evaluate the effect of omission of radiotherapy on locoregional recurrence risk in this patient population.

Methods. Patients aged ≥ 75 years undergone BCS for T1-2N0 breast cancer diagnosed between 2003 and 2009 were selected from the Netherlands Cancer Registry. To minimize confounding by indication, hospital variation was used to assess the impact of radiotherapy-use on locoregional recurrence risk using cox proportional hazards regression. Hazards ratios with 95% confidence interval (CI) were estimated.

Results. Overall, 2390 patients were included. Of the patients with hormone receptor-positive breast cancer, 39.3% received endocrine treatment. Five-year incidences of locoregional recurrence were 1.9%, 2.8%, and 3.0% in patients treated at hospitals with higher (average radiotherapy-use 96.0%), moderate (88.0%), and lower radiotherapy-use (72.2%) respectively, and nine-year incidences were 2.2%, 3.1%, and 3.2% respectively. Adjusted hazard ratios were 1.46 (95% CI 0.77-2.78) and 1.50 (95% CI 0.79-2.85) for patients treated at hospitals with moderate and lower radiotherapy-use, compared to patient treated at hospitals with higher radiotherapy-use.

Conclusion. Despite endocrine treatment in only 39.3%, locoregional recurrence risk was low, even in patients treated at hospitals with lower radiotherapy-use. This provides reasonable grounds to consider omission of radiotherapy in patients aged ≥ 75 years with T1-2N0 breast cancer.

INTRODUCTION

Breast-conserving surgery (BCS) followed by radiotherapy is the standard treatment for early stage breast cancer. However, various randomized clinical trials (RCTs) have investigated omission of the radiotherapy in older patients as the additional benefit is expected to decrease with declining residual life expectancy and increasing risk of dying from other causes with age.[1-3] These RCTs demonstrated a small benefit in locoregional control from radiotherapy, but no effect on distant metastasis-free or disease-specific survival.

As no survival benefit was demonstrated and locoregional recurrences can be treated with surgery, in 2004, omission of radiotherapy was incorporated in the National Comprehensive Cancer Network (NCCN) guideline as treatment option for patients aged ≥70 years with stage 1 breast cancer provided that they are treated with endocrine therapy.[4] However, this recommendation had only limited effect on radiotherapy-use in clinical practice.[5] Furthermore, other guidelines such as recommendations from the Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA) still state that radiotherapy should be considered in all elderly patients because it decreases the risk of locoregional recurrence.[6]

The reluctance regarding omission of radiotherapy could be partially explained by concerns of clinicians about lower endocrine therapy-use and adherence in the true older population of patients with breast cancer compared to trial populations.[7,8] The RCTs exclusively included patients using endocrine therapy.[1,2] Moreover, adherence to endocrine treatment was supposedly higher than in the general older population. Although the aim of endocrine therapy is to reduce the risk of distant metastasis and improve breast cancer specific survival, the systemic therapy may also have a locoregional effect.

In the Netherlands, radiotherapy after BCS is omitted in up to 30% of patients aged ≥75 years, and the majority of these patients do not receive systemic treatment following Dutch treatment guidelines.[9] On the one hand, the omission of radiotherapy in the absence of endocrine treatment may potentially result in higher locoregional recurrence risks. On the other hand, older patients participating in trials are often a relatively young and healthy selection of the general older population[10] Due to higher competing mortality risks in the general older population, the radiotherapy benefit may actually be smaller than demonstrated in the selected trial populations.

Population-based data can give important insight in the effectiveness of radiotherapy after BCS for the general older population, provided that confounding by indication is appropriately handled. Because confounding by unmeasured factors was expected, a method

which can avoid such confounding was considered most effective in obtaining a valid effect estimate. Therefore, the aim of this study was to assess the effect of omission of radiotherapy after BCS on locoregional recurrence risk in patients aged ≥75 years with T1-2N0 breast cancer using hospital variation in radiotherapy-use as an instrumental variable-like approach.

METHODS

All patients aged ≥75 years who underwent BCS for T1-2N0 breast cancer between 2003 and 2009 were selected from the Netherlands Cancer Registry (NCR) and included in this study. The NCR is a database on cancer diagnosis and treatment. It is hosted by the Netherlands Comprehensive Cancer Organization (IKNL) and receives reports of diagnosed malignancies from the nationwide network and registry of histopathology and cytopathology in the Netherlands (PALGA), which are confirmed and completed by the national hospital discharge databank. Trained data managers of the IKNL regularly collect data on diagnosis, staging, and treatment from medical records using international coding rules. In addition, information on recurrence status and comorbidity is collected for specific research purposes.

Breast cancer stage is defined according to the TNM Classification of Malignant Tumors for breast cancer (6th edition).[11] Clinical T or N stage is used if pathological T or N stage is unknown. Recurrences are defined according to consensus-based definitions for classification of breast cancer recurrence.[12] Ipsilateral breast, chest wall, axillary and supraclavicular lymph nodes recurrence are considered a locoregional recurrence. For the current study, recurrence status was available for a minimum of five years after diagnosis for all patients. We used a Landmark approach to avoid bias due to immortal time between diagnosis, surgery and radiotherapy. Therefore, follow-up started 3 months after diagnosis. Endpoint for follow-up was time of recurrence, death, or last follow-up visit, whichever came first. Vital status was available until January 31st 2017 through linkage of NCR data with the Municipal Personal Records database. Information on comorbidity at time of diagnosis was retrospectively collected for patients diagnosed during incidence years 2007-2009.

Hospital radiotherapy variation

We used an instrumental variable-like approach to minimize confounding by indication by using hospital variation in radiotherapy-use. Treatment decisions in older patients with breast cancer are influenced by aspects of general health such as physical and cognitive functioning, which also affect outcome. As information regarding these factors is not available in cancer registries, conventional statistical methods are unable to take these factors into account. Consequently, results are at high risk of bias due to residual confounding.[13]

To minimize this problem, we used variation in radiotherapy-use among hospitals in which patients underwent surgery to assess the effect of radiotherapy. We assumed that hospitals are independent of breast cancer related prognostic factors, given that all hospitals in the Netherlands provide breast cancer care and older patients generally go to the nearest hospital. Three groups were constructed using tertiles of radiotherapy-use, based on the percentage of patients treated with radiotherapy within each hospital: higher level (range 92.3-100%), moderate (range 83.3-92.3%), and lower (range 0-83.3%) radiotherapy-use hospitals. Characteristics of patients treated at higher, moderate, and lower radiotherapy-use hospitals were presented. The characteristics of patients who were treated with and without radiotherapy were also presented to demonstrate the effect on confounding of using hospital variation instead of comparing treated and untreated patients directly.

Statistical analysis

Statistical analysis was performed with SPSS 23.0 and STATA 12.1. Multiple imputation by chained equation was performed to account for missing values, assuming that data were missing at random.[14] Imputation models were applied including incomplete and complete variables. Analyses were based on the pooled results of 25 imputed sets according to Rubin's rules.[15] Pearson's χ^2 tests were used to assess differences in characteristics between patients who were treated with and without radiotherapy, and between patients treated at hospitals with different levels of radiotherapy-use. Cumulative incidences of locoregional recurrence were calculated using the Cumulative Incidence Competing Risk method, considering distant recurrence and death without recurrence as competing events.[16] Cox proportional hazards models were used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) to compare locoregional recurrence risk in patients treated at hospitals with different levels of radiotherapy-use. The higher radiotherapy-use group was used as reference group. We adjusted by multivariable analysis for imbalances that were statistically significant. The scaled Schoenfeld residuals of the covariates over time were tested for a non-zero slope in a generalized linear regression. No violations were found. As recurrence status for patients diagnosed between 2003 and 2006 was not available after 5 years, a sensitivity analysis was performed with follow-up truncated at 5 years. To avoid immortal time bias, a Landmark approach was used, starting follow-up at 3 months after diagnosis. All statistical tests were two-sided.

RESULTS

Overall, 2390 patients with T1-2N0 breast cancer aged ≥75 years were included. Median age was 79.2 years (interquartile range (IQR) 76.4-82.5 years). Table 1 shows clear differences in characteristics between patients treated with and without radiotherapy. Patients treated with

radiotherapy were younger and had less comorbidity compared to patients treated without radiotherapy. With regard to tumor characteristics, patient treated with radiotherapy had smaller tumors, more often hormone receptor-positive tumors, and surgery was irradical in fewer patients. Furthermore, only 32.6% of the patients treated with radiotherapy received endocrine therapy, compared to 54.7% in patient treated without radiotherapy (p=0.023). Notably, of the patients with hormone receptor-positive tumors in this study, 39.3% received endocrine treatment.

The patients were divided into tertiles based on radiotherapy-use within each hospital (Table 2). The average radiotherapy-use was 96.0% in the higher-use, 88% in the moderate-use, and 72.2% in the lower-use hospitals. The groups included patients from 46, 35, and 47 different hospitals respectively. Comorbidity, an important determinant of receiving radiotherapy, and tumor characteristics were equally distributed over the groups. An imbalance in age distribution remained, patients treated in lower-use hospitals were older (17.8% of the patients was aged >85 years) compared to patients treated in higher-use and moderate-use hospitals (8.4% and 11.2%, p<0.001). Furthermore, endocrine treatment was more often prescribed in patients treated in lower-use hospitals (40.0%) compared to patients treated in higher-use and moderate-use hospitals (34.3% and 32.5% respectively, p=0.023). Another imbalance was observed for type of hospital as academic hospitals were overrepresented in the lower-use group (14.2% compared to 4.6% in the higher-use and 3.7% in the moderate-use group, p<0.001).

Out of the 2390 patients, 186 patients were lost to follow-up and 10 patients died during the first 3 months after diagnosis. For the 2194 patients included in the time-to-event analysis (Landmark approach), median follow-up was 4.8 years starting from 3 months after diagnosis (IQR 4.8-4.8, range 0.03-10.8 years), during which 61 patients had a locoregional recurrence. Cumulative incidences of locoregional recurrence by hospital level radiotherapy-use are graphically represented in Figure 1. Five-year cumulative incidences were 1.9%, 2.8%, and 3.0% in the higher-use, moderate-use and lower-use group, and nine-year cumulative incidences were 2.2%, 3.1%, and 3.2% respectively (Table 3).

Results of the Cox proportional hazards analysis are shown in Table 3. In univariable analysis, the HRs were 1.49 (95% CI 0.78-2.83) and 1.55 (95% CI 0.82-2.94) for patients treated at hospitals with moderate and lower radiotherapy-use respectively, compared to patients treated at hospitals with higher radiotherapy-use. After adjustment for age, endocrine treatment, and type of hospital, the HRs were 1.46 (95% CI 0.77-2.78) and 1.50 (95% CI 0.79-2.85) respectively. The sensitivity analysis with truncated five-year follow-up demonstrated comparable HRs compared to the primary adjusted analysis: HR 1.50 (95% CI 0.76-2.96) and 1.59 (95% CI 0.81-3.14) (Supplementary Table).

Table 1. Characteristics of patients treated with and without radiotherapy.

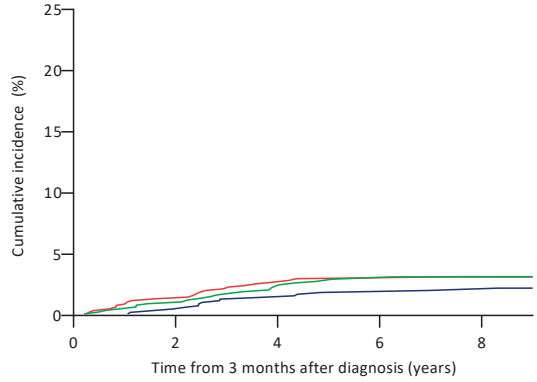
	Radiotherapy		No radiotherapy		
	n=2039		n=351		
	N (%)	(%)[a]	N (%)	(%)[a]	*p-value*
Age at diagnosis					**<0.001**
75-79	1286 (63.1)		69 (19.7)		
80-84	627 (30.8)		109 (31.1)		
>85	126 (6.2)		173 (49.3)		
CCI					**0.001**
0	531 (26.0)	(58.3)	52 (14.8)	(38.6)	
1	192 (9.4)	(24.0)	39 (11.1)	(35.6)	
>2	133 (6.6)	(17.7)	30 (8.6)	(25.8)	
Unknown	1183 (58.0)		230 (65.5)		
Tumor grade					0.455
1	570 (28.0)	(30.4)	100 (28.5)	(32.2)	
2	929 (45.6)	(48.8)	132 (37.6)	(42.0)	
3	407 (20.0)	(20.8)	85 (24.2)	(25.8)	
Unknown	133 (6.5)		34 (9.7)		
T stage					**<0.001**
T1	1449 (71.1)		213 (60.7)		
T2	590 (28.9)		138 (39.3)		
HR expression					**0.036**
ER+ and/or PR+	1682 (82.5)	(88.9)	280 (79.8)	(84.9)	
ER- and PR-	207 (10.2)	(11.1)	48 (13.7)	(15.1)	
Unknown	150 (7.4)		23 (6.6)		
Her2Neu overexpression					0.435
Negative	1283 (62.9)	(91.5)	208 (59.3)	(89.6)	
Positive	106 (5.2)	(8.5)	19 (5.4)	(10.4)	
Unknown	650 (31.9)		124 (35.3)		
Surgical margins					**<0.001**
Free	1912 (93.8)		302 (86.0)		
Not free	91 (4.5)		33 (9.4)		
Unknown	36 (1.8)		16 (4.6)		
Adjuvant endocrine therapy in HR+					**0.023**
Yes	565 (33.6)	(32.6)	157 (56.1)	(54.7)	
No	1117 (66.4)	(67.4)	123 (43.9)	(45.3)	
Chemotherapy					0.560
Yes	3 (0.2)		1 (0.3)		
No	2036 (99.9)		350 (99.7)		
Type of hospital					0.066
University hospital	146 (7.2)		35 (10.0)		
Non-university hospital	1892 (92.8)		316 (90.0)		

[a]Proportional distribution after multiple imputation. CCI: Charlson Comorbidity Index, HR: hormone receptor.

Table 2. Characteristics of patients by tertile of hospital radiotherapy-use.

	Higher-use		Moderate-use		Lower-use		
	n=802		n=775		n=813		
	n (%)	(%)[a]	n (%)	(%)[a]	n (%)	(%)[a]	*p-value*
Radiotherapy	770 (96.0)		682 (88.0)		587 (72.2)		**<0.001**
Age at diagnosis							**<0.001**
75-79	479 (59.7)		449 (57.9)		427 (52.5)		
80-84	256 (31.9)		239 (30.8)		241 (29.6)		
>85	67 (8.4)		87 (11.2)		145 (17.8)		
CCI							0.154
0	230 (28.7)	(57.9)	188 (24.3)	(56.4)	165 (20.3)	(52.0)	
1	78 (9.7)	(23.2)	73 (9.4)	(25.4)	80 (9.8)	(28.6)	
>2	66 (8.2)	(18.9)	46 (5.9)	(18.3)	51 (6.3)	(19.4)	
Unknown	428 (53.4)		468 (60.4)		517 (63.6)		
Tumor grade							0.083
1	243 (30.3)	(32.5)	224 (28.9)	(31.9)	203 (25.0)	(27.7)	
2	353 (44.0)	(47.1)	327 (42.2)	(45.9)	381 (46.9)	(50.4)	
3	155 (19.33)	(20.4)	166 (21.4)	(22.3)	171 (21.0)	(21.9)	
Unknown	51 (6.4)		58 (7.5)		58 (7.1)		
T stage							0.822
T1	564 (70.3)		534 (68.9)		564 (69.4)		
T2	238 (29.7)		241 (31.1)		249 (30.6)		
HR expression							0.699
ER+ and/or PR+	674 (84.0)	(89.8)	612 (79.0)	(86.0)	676 (83.2)	(89.2)	
ER- and PR-	77 (9.6)	(10.2)	97 (12.5)	(14.0)	81 (10.0)	(10.9)	
Unknown	51 (6.4)		66 (8.5)		56 (6.9)		
Her2Neu overexpression							0.692
Negative	519 (64.7)	(92.2)	478 (61.7)	(90.0)	494 (60.8)	(91.5)	
Positive	39 (4.9)	(7.9)	47 (6.1)	(10.0)	39 (4.8)	(8.5)	
Unknown	244 (30.4)		250 (32.3)		280 (34.44)		
Surgical margins							0.465
Free	747 (93.1)		723 (93.3)		744 (91.5)		
Not free	42 (5.2)		35 (4.5)		47 (5.8)		
Unknown	13 (1.6)		17 (2.2)		22 (2.7)		
Adjuvant endocrine therapy in HR+							**0.023**
Yes	238 (35.3)	(34.3)	202 (33.0)	(32.5)	282 (41.7)	(40.0)	
No	436 (64.7)	(65.7)	410 (67.0)	(67.5)	394 (58.3)	(60.0)	
Chemotherapy							0.186
Yes	1 (0.1)		0 (0)		3 (0.4)		
No	801 (99.9)		775 (100)		810 (99.6)		
Type of hospital							**<0.001**
University hospital	37 (4.6)		29 (3.7)		115 (14.2)		
Non-university hospital	764 (95.4)		746 (96.3)		698 (85.9)		

[a]Proportional distribution after multiple imputation. CCI: Charlson Comorbidity Index, HR: hormone receptor.



Number at risk (events)										
Higher-use	743	(4)	691	(7)	619	(3)	167	(1)	129	(1)
Moderate-use	718	(7)	644	(10)	571	(4)	137	(1)	112	(0)
Lower-use	733	(10)	659	(10)	559	(2)	125	(1)	94	(0)

Figure 1. Cumulative incidence of locoregional recurrence in high-use, moderate-use and low-use radiotherapy hospitals.

Table 3. Cox proportional hazards analysis for time to locoregional recurrence by hospital radiotherapy-use.

	Cumulative incidences (95% CI)		Univariable HR[b] (95% CI)	Multivariable HR[b,c] (95% CI)
	Five year follow-up[a]	Nine year follow-up[a]		
Higher-use	1.9 (1.1-3.1)	2.2 (1.3-3.6)	Reference	Reference
Moderate-use	2.8 (1.8-4.2)	3.1 (2.0-4.6))	1.49 (0.78-2.83)	1.46 (0.77-2.78)
Lower-use	3.0 (1.9-4.4)	3.2 (2.1-4.7)	1.55 (0.82-2.94)	1.50 (0.79-2.85)

[a]Follow-up from landmark at 3 months after diagnosis. [b]Calculated with complete follow-up time. [c]Adjusted for age (continuous), endocrine therapy and type of hospital. HR: hazard ratio, CI: confidence interval.

DISCUSSION

The present study shows that locoregional recurrence rates are low in patients aged ≥75 years who underwent BCS, even in patients treated in hospitals with lower radiotherapy-use. No association was found between radiotherapy-use and locoregional recurrence risk.

Our study adds to available evidence, since the low locoregional recurrence risks that were seen in previous RCTs were confirmed in this population-based cohort in which only 39.3% of the patients was treated with endocrine therapy. Therefore, concerns of an increased locoregional recurrence risk among older patients not treated with endocrine therapy are contradicted. We argue that this can be explained by the declining residual life expectancy and increasing risk of dying from other causes than breast cancer, so-called competing mortality, among the older population of patients with breast cancer.[17]

The low locoregional recurrence rates reported in this study support the allowance of omission of radiotherapy in patients aged ≥75 years, even when patients are not treated with

endocrine treatment. This is strengthened by the fact that we found locoregional recurrence risks in patients treated in hospitals with higher radiotherapy-use (average 96%) in our study (1.9% after 5 and 2.2% after 9 years), that were similar to patients in the radiotherapy-arm of the CALGB 9343 trial (1% after 5 and 2% after 10 years). This hallmark trial randomized patients aged ≥70 years with T1N0 breast cancer using endocrine treatment between radiotherapy or no radiotherapy after BCS. The trial exclusively included patients receiving endocrine treatment, whereas only 39.3% of the patients in our study was not treated with endocrine treatment conform Dutch treatment guidelines. Moreover, adherence to endocrine treatment was likely more typical for the true older population as population-based data were used.

Although RCTs provide the highest level of evidence for treatment efficacy, their external validity is often questioned. Therefore, results from observational studies can add to the generalizability. However, all observational studies are susceptible for confounding by indication because treatment allocation is likely based on reasons associated with outcomes. The validity of the results strongly depends on the ability to reduce such confounding.

Especially in older populations, directly comparing patients who are treated differently leads to biased effect estimates as treatment decisions are made on the combination and interaction of disease and patient related factors for which it appears impossible to adjust.[13] Furthermore, information on important confounding factors may be missing in observational studies, while conventional methods to reduce confounding such as multivariable analysis or propensity score matching rely on measured variables. Consequently, aspects of general health such as comorbidity, physical and cognitive functioning are often not taken into account. As a result, using conventional methods generally results in an overestimation of effect estimates, and may even demonstrate an opposite causal effect.[13,18,19]

Many previous observational studies addressed the omission of radiotherapy after BCS in older patients. Some advocate that radiotherapy may be omitted,[20-23] whereas others state that it is unsafe due to a higher risk of locoregional recurrence[24-26] or even worse breast cancer specific and overall survival[25,27-29]. Although different patient selections could play a role in the varying findings, results of these studies using conventional methods to adjust for confounding may have been biased to some extent. For example, the worse overall survival in patients treated without radiotherapy (not found in RCTs) could be in fact a reflection of the lower probability to receive radiotherapy in patients with higher competing mortality risk.[25,28] Furthermore, even when disease-specific outcomes are used, confounding by indication can still cause bias through differential censoring of patients dying from other causes.[30]

Instead of a conventional statistical approach, we used an instrumental variable-like approach by using hospital variation in radiotherapy-use to minimize confounding by indication.[13] We demonstrated that patients treated with and without radiotherapy differed in many aspects, but using hospital variation, the constructed radiotherapy groups were fairly similar. Comorbidity is an important confounding factor as it strongly influences whether a patient receives treatment, and at the same time, affects survival and disease-specific outcomes such as locoregional recurrence risk indirectly. Therefore, the fact that the groups were similar concerning comorbidity indicates that confounding by comorbidity was effectively resolved. Notably, we expected patients not treated with radiotherapy to have more favorable tumor characteristics, but on the contrary, we observed larger tumors and less hormone receptor-positivity. This may imply that the decision for radiotherapy depends more on patient related factors than on tumor characteristics.

Our study has important limitations. Foremost, although using hospital variation may result in more valid results, we could only assess the effect of a difference of 23.8% in radiotherapy-use. Consequently, the results apply to patients in whom the decision for radiotherapy was influenced by hospital variation, but this selection is not readily identifiable. However, we do not advocate that radiotherapy should be omitted in all patients, but rather advise against routinely treating all older patients with radiotherapy. Second, the low event rate prevented us from exploring subgroups with a differential radiotherapy-use effect. Third, residual confounding could not be completely ruled out because some imbalances between the radiotherapy-use groups persisted. For this reason, we also performed a multivariable analysis. Last, the absolute risk of locoregional recurrence for patients treated without radiotherapy could not be provided as a proportion of the patients treated in the lower-use hospitals still received radiotherapy.

To obtain the absolute locoregional recurrence risk for patients in whom radiotherapy after BCS is omitted, the ongoing TOP-1 (Tailored treatment in Older Patients) study (BOOG study number 2016-01) was recently initiated and is currently running in almost all breast cancer clinics in the Netherlands. This prospective cohort study includes patients aged ≥70 years with endocrine receptor-positive grade 1 tumors up to 2 cm and grade 2 tumors up to 1 cm who are treated without radiotherapy after BCS, and assesses whether the LRR remains below the prespecified limit of 3.9%. Notably, none of these patients is treated with endocrine therapy following Dutch treatment guidelines. To be able to assess the generalizability of the results, all patients are characterized by a geriatric assessment. Secondary outcomes are quality of life and toxicity.

In conclusion, despite endocrine treatment being prescribed in only 39.3% of the patients, locoregional recurrence risk after BCS in patients aged ≥75 years with T1-2N0 breast can-

cer was low, even in patients treated at hospitals with lower radiotherapy-use. Our study provides reasonable grounds to consider omission of radiotherapy after BCS. At older age, the frequent hospital visits required for radiotherapy can prove a substantial burden due to impaired mobility, lack of transportation, lack of social support, and caregiver responsibilities. Therefore, instead of routinely admitting radiotherapy after BCS, a shared-decision making approach is appropriate in all patients aged ≥75 years with T1-2N0 breast cancer.

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Supplementary Table. Sensitivity analysis. Cox proportional hazards analysis for time to locoregional recurrence by hospital radiotherapy-use with truncated five year follow-up.

	Univariable HR (95% CI)	Multivariable HR[a] (95% CI)
Higher-use	Reference	Reference
Moderate-use	1.53 (0.77-3.03)	1.50 (0.76-2.96)
Lower-use	1.67 (0.85-3.26)	1.59 (0.81-3.14)

[a]Adjusted for age (continuous), endocrine therapy and type of hospital. HR: hazard ratio, CI: confidence interval.

6

Effect of omission of surgery on survival in patients aged 80 years and older with early-stage hormone receptor-positive breast cancer

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ABSTRACT

Introduction. Surgery is increasingly being omitted in older patients with operable breast cancer in the Netherlands. Although omission of surgery can be considered in frail older patients, it may lead to inferior outcomes in non-frail patients. Therefore, the aim of this study was to evaluate the effect of omission of surgery on relative and overall survival in older patients with operable breast cancer.

Methods. Patients aged 80 years or older diagnosed with stage I–II hormone receptor-positive breast cancer between 2003 and 2009 were selected from the Netherlands Cancer Registry. An instrumental variable approach was applied to minimize confounding, using hospital variation in rate of primary surgery. Relative and overall survival was compared between patients treated in hospitals with different rates of surgery.

Results. Overall, 6464 patients were included. Relative survival was lower for patients treated in hospitals with lower compared with higher surgical rates (90.2 versus 92.4 per cent respectively after 5 years; 71.6 versus 88.2 per cent after 10 years). The relative excess risk for patients treated in hospitals with lower surgical rates was 2.00 (95 per cent c.i. 1.17 to 3.40). Overall survival rates were also lower among patients treated in hospitals with lower compared with higher surgical rates (48.3 versus 51.3 per cent after 5 years 15.0 versus 19.8 per cent after 10 years respectively; adjusted hazard ratio 1.07, 95 per cent c.i. 1.00 to 1.14).

Conclusion. Omission of surgery is associated with worse relative and overall survival in patients aged 80 years or more with stage I–II hormone receptor-positive breast cancer. Future research should focus on the effect on quality of life and physical functioning.

INTRODUCTION

The number of older patients with breast cancer is increasing owing to ageing of Western populations.[1,2] This age group differs in terms of co-morbidity, physical and cognitive functioning, and demands a personalized approach to cancer treatment. Less extensive treatments are often given when co-morbidity or a limited life expectancy is assumed to interfere with treatment benefit. criteria for treatments are, however, poorly defined in guidelines as evidence from RCTs is lacking.[3] Consequently, treatment variation is seen across countries, regions and hospitals.[4-6]

Previous studies have shown that the percentage of older patients who do not undergo primary surgical treatment has increased over the past decade in the Netherlands.[7-9] Most of these patients receive primary endocrine therapy instead of surgery. The assumption is that, with primary endocrine therapy, disruption of daily life may be minimized and risks of surgery can be avoided. After an uncertain length of time, disease progression will, however, occur and a change of treatment is required. Endocrine therapy can also have many side-effects affecting quality of life, especially in older patients.[10,11]

International recommendations state that primary endocrine therapy should be considered only in patients with a life expectancy of 2-3 years and who are unfit for, or refuse, surgery.[3] Although RCTs comparing surgical treatment and tamoxifen monotherapy reported high rates of local progression in patients treated with tamoxifen alone, none showed a survival difference before 3 years.[12,13] The applicability of data from these studies, undertaken in the 1980s, to current practice is questionable. Hormone receptor testing is now mandatory, and aromatase inhibitors have been shown to be superior to tamoxifen in both (neo) adjuvant and metastatic settings.[14-16] Furthermore, multiple lines of endocrine agents are available.[13,17,18] In addition, advances in anaesthetic techniques have made breast surgery a safe procedure, even in the very old.[19] Moreover, previous RCTs included only older patients who were considered fit enough to undergo surgery, which limits the generalizability of the results to the general population of older patients with breast cancer.[12]

Population-based data may provide more insight into the effect of omission of surgery in the older patient population in current practice. Comparison of patients treated with and without surgery in observational data is, however, susceptible to confounding by indication. Although statistical techniques may adjust for measured confounders, such as age and co-morbidity, residual confounding by unmeasured factors related to frailty is likely to be present. The variation in omission of surgery among hospitals provides the opportunity to use the instrumental variable approach, an alternative method to minimize confounding. The aim of this study was to evaluate the effect of omission of surgery on relative and overall

survival by comparing the outcomes of patients treated in hospitals with different rates of primary surgery.

METHODS

Patients aged 80 years or older diagnosed with stage I–II hormone receptor-positive breast cancer between 2003 and 2009 were selected from the Netherlands Cancer Registry (NCR) and included in this study. The NCR is a database on cancer diagnosis and treatment hosted by the Netherlands Comprehensive Cancer Organization (IKNL). It receives reports of diagnosed malignancies from the nationwide network and registry of histopathology and cytopathology in the Netherlands (PALGA), which are confirmed and completed by the national hospital discharge databank. The interval 2003-2009 was chosen to allow sufficiently long follow-up.

Trained data managers collect data on diagnosis, staging and treatment from medical records using international coding rules. Breast cancer stage is defined according to the sixth edition) of the TNM classification of malignant tumours.[20] Clinical tumour or node category was used when pathological stage was unknown. Oestrogen receptor and progesterone receptor status was considered positive if at least 10 per cent positive nuclear staining of tumour cells was demonstrated. Information on co-morbidity was collected for this study, but only for patients diagnosed in 2007-2009 for logistic reasons. For patients diagnosed between 2003 and 2006, data on co-morbidity were available only for those diagnosed in one of the nine regions in the Netherlands, as this is the only region that regularly collects such information. Missing co-morbidity data for the other regions were imputed (see below). Vital status was available until 31 January 2017 through linkage of NCR data with the Municipal Personal Records database.

Hospital variation

In clinical practice, the decision to omit surgery is based on disease characteristics, age, co-morbidity, and other aspects of general health and frailty, such as physical, cognitive and social functioning. As these latter factors are generally not measured or well recorded in observational databases, statistical techniques such as multivariable analysis or propensity score matching cannot fully adjust for them, leaving residual confounding. Previous studies have demonstrated that residual confounding can lead to implausible results.[21-23] To minimize confounding, an instrumental variable approach was used. Under certain assumptions, this method can adjust for unmeasured confounding. Variation in the percentage of patients undergoing primary surgery across hospitals (the instrument) was used, and outcomes of patients treated in hospitals with different rates of primary surgery were

compared. Hospital was used as instrument as rates of primary surgery varied substantially across hospitals, and no major differences in case mix between hospitals were expected as all hospitals in the Netherlands provide breast cancer care and older patients are assumed to go to the hospital nearest their home. Therefore, groups of hospitals are similar with respect to patients' prognosis and general health, and potential differences in outcomes can be attributed to the difference in surgery rates. Hospitals that contributed fewer than ten patients were excluded.

Three groups were defined by dividing 117 hospitals based on rates of primary surgery while ensuring equal numbers of patients in each group: hospitals with higher rates (range 75.9-100 per cent), moderate rates (63.2-75.8 per cent) and lower rates (37.6-63.1 per cent). Those treated in these hospitals are referred to as patients treated in hospitals with higher, moderate and lower rates of surgery respectively. The rate of surgery is defined as the rate of primary surgery. To evaluate the effect of using hospital variation to minimize confounding, patient characteristics of the three groups were compared.

Statistical analysis

Multiple imputation by chained equation was performed to account for missing values of grade, human epidermal growth factor receptor (HER) 2 status and co-morbidity. Missing values for these variables were assumed to be missing at random after examination of patterns.[24] Imputation models were applied including all variables as predictors. Results were based on the pooled results of 25 imputed sets according to Rubin's rules.[25] Pearson's χ^2 tests were used to assess differences in patient characteristics between groups.

In observational data, the time between diagnosis and the start of treatment is 'immortal time' as a patient had to survive this period to start the treatment. As the time to treatment was immortal for patients who underwent surgery in this study, a landmark approach was used to avoid immortal time bias.[26,27] Hence, follow-up time started 60 days after diagnosis. Patients who died before this landmark were excluded from the survival analysis. Follow-up ended at the date of death or last follow-up visit.

As older patients with breast cancer often die from causes other than those related to breast cancer, the primary outcome was relative survival. Relative survival was used as proxy for breast cancer-specific survival (BCSS) as cause of death is not available in the NCR. Moreover, ascertaining cause of death in older patients is susceptible to misclassification bias.[28] Relative survival is calculated by dividing the observed survival in a patient population by the expected survival in the general population matched by age, sex and year of diagnosis.[29] Hence, relative survival takes into account the patient population's background mortality and in the present study expresses the excess risk of death owing to breast cancer. Relative

survival estimates cancer-specific survival under the condition that the general population's mortality is representative of the background mortality in the patient population. In other words, the prevalence of co-morbid diseases should be similar in the patient population and the general population. Relative survival is considered a reliable outcome in older patients with breast cancer as it has been demonstrated that the prevalence of co-morbid diseases is indeed comparable among patients with breast cancer and those without cancer.[30] To compare relative survival, relative excess risks with 95 per cent confidence intervals were calculated using generalized linear Poisson models. Patients treated in hospitals with higher rates of surgery were used as reference group.

Kaplan-Meier estimates of overall survival were calculated. To compare overall survival, hazard ratios (HRs) with 95 per cent confidence intervals were calculated using Cox proportional hazard models. Patients treated in hospitals with higher rates of surgery were used as reference group. In addition, to explore different effects of omission of surgery in patients with and without co-morbidity, a stratified analysis was performed in groups with a Charlson Co-morbidity Index (CCI) score of 0 or at least 1.[31] As a statistically significant age difference across the groups remained despite applying the instrumental variable approach to reduce confounding, a multivariable analysis including age was undertaken. The proportionality assumption was tested by plotting the scaled Schoenfeld residuals. No violation of the assumption was found. All statistical tests were two-sided and $P < 0.05$ was considered statistically significant. Statistical analysis was done with SPSS version 23.0 and Stata version 12.1.

RESULTS

A total of 6464 older patients with stage I–II hormone receptor-positive breast cancer were included. Overall, 4465 patients (69.1 per cent) underwent surgery and 1999 (30.9 per cent) did not. There were differences in characteristics between the two groups (Table 1). Patients who did not have surgery were more often older; 69.2 per cent of these patients were aged 85 years or older compared with 35.7 per cent of patients who had surgery ($P < 0.001$). Among patients who did not undergo surgery, 58.3 per cent had a CCI score of 1 or more, compared to 45.7 per cent of those who had surgery ($P < 0.001$). No differences in stage, grade or HER2 status were observed after multiple imputation (Table 1). Of the patients who did not have surgery, 94.1 per cent received primary endocrine treatment.

Rates of surgery were on average 82.6, 69.7 and 54.8 per cent in the hospitals with higher, moderate and lower rates of surgery respectively. Furthermore, 15.2, 28.5 and 43.6 per cent received primary endocrine treatment, whereas 2.1, 1.8 and 1.6 per cent received no treat-

Table 1. Characteristics of patients who were treated with and without primary surgery.

	Surgery (*n*=4465)		No surgery (*n*=1999)		*p* value*
Age (years)					<0.001
80-84	2870	(64.3)	615	(30.8)	
85-89	1324	(29.7)	829	(41.5)	
≥90	271	(6.1)	555	(27.8)	
CCI score					<0.001
0	980	(54.3)	510	(41.7)	
1	468	(26.7)	386	(31.6)	
≥2	323	(19.0)	321	(26.8)	
Unknown	2694		782		
TNM stage					0.866
I	1458	(32.7)	657	(32.9)	
II	3007	(67.4)	1342	(67.1)	
Grade					0.159
1	1098	(26.2)	101	(31.5)	
2	2306	(55.2)	180	(51.8)	
3	784	(18.6)	61	(16.7)	
Unknown	277		1657		
HER2 status					0.689
Positive	217	(7.4)	79	(7.8)	
Negative	2864	(92.6)	977	(92.2)	
Unknown	1384		943		

Values in parentheses are percentages including missing data; percentages after multiple imputation. CCI, Charlson Comorbidity Index; HER2, human epidermal growth factor receptor 2. *Pearson's $\chi 2$ test.

ment (Table 2; Supplementary Figure 1). Patients treated in hospitals with lower rates of surgery were more often older than patients treated in hospitals with moderate and higher rates (48.5 per cent aged 85 years or more versus 46.1 and 43.7 per cent respectively; $P = 0.003$). No other differences were observed across the groups.

Of the 6464 patients, 6363 were included in the survival analysis as six patients were lost to follow-up and 95 died in the first 60 days after diagnosis. Relative survival is shown in Figure 1a. Relative survival was lower for patients treated in hospitals with lower compared with higher rates of surgery (90.2 versus 92.4 per cent after 5 years; 71.6 versus 88.2 per cent after 10 years) (Table 3). Compared with the reference group of patients treated in hospitals with higher rates of surgery, the relative excess risk of death was 2.00 (95 per cent c.i. 1.·17 to 3.40) for patients treated at hospitals with lower rates (Table 3). Of note, the relative survival curves are overlapping for the first 5 years (Figure 1a).

Table 2. Characteristics of patients who were treated at hospitals with higher, moderate or lower rates of primary surgery.

	Higher rates (*n*=2159)	Moderate rates (*n*=2158)	Lower rates (*n*=2147)	*p* value
Treatment				
Surgery	1784 (82.6)	1505 (69.7)	1176 (54.8)	
Primary endocrine treatment	329 (15.2)	615 (28.5)	937 (43.6)	
No treatment	46 (2.1)	38 (1.8)	34 (1.6)	
Age (years)				0.003
80-84	1216 (56.3)	1163 (53.9)	1106 (51.5)	
85-89	705 (32.7)	722 (33.5)	726 (33.8)	
≥90	238 (11.0)	273 (12.7)	315 (14.7)	
CCI score				0.985
0	448 (20.8; 50.5)	488 (22.6; 50.2)	554 (25.8; 50.6)	
1	260 (12.0; 27.9)	293 (13.6; 29.0)	301 (14.0; 27.7)	
≥2	209 (9.7; 21.6)	198 (9.2; 20.8)	237 (11.0; 21.8)	
Unknown	1242 (57.5)	1179 (54.6)	1055 (49.1)	
TNM stage				0.215
I	680 (31.5)	705 (32.7)	730 (34.0)	
II	1479 (68.5)	1453 (67.3)	1417 (66.0)	
Grade				0.511
1	475 (22.0; 28.1)	389 (18.0; 27.2)	335 (15.6; 28.3)	
2	946 (43.8; 54.1)	878 (40.7; 55.9)	662 (30.8; 52.4)	
3	318 (14.7; 17.8)	257 (11.9; 16.8)	270 (12.6; 19.3)	
Unknown	420 (19.5)	634 (29.4)	880 (41.0)	
HER2 status				0.554
Positive	96 (4.5; 7.7)	104 (4.8; 7.8)	96 (4.5; 7.1)	
Negative	1252 (58.0; 92.3)	1246 (57.7; 92.2)	1343 (62.6; 92.9)	
Unknown	811 (37.6)	808 (37.4)	708 (33.0)	
RT after BCS				0.066
Yes	251 (70.3)	310 (71.1)	234 (77.7)	
No	106 (26.7)	126 (28.9)	67 (22.3)	
RT after mastectomy				0.298
Yes	67 (4.7)	64 (6.0)	51 (5.8)	
No	1360 (95.3)	1005 (94.0)	824 (94.2)	
Adjuvant endocrine therapy				0.627
Yes	1015 (56.9)	875 (58.1)	663 (56.4)	
No	769 (43.1)	630 (41.9)	513 (43.6)	
Adjuvant chemotherapy				
Yes	7 (0.3)	1 (0.1)	1 (0.1)	
No	2152 (99.7)	2157 (99.9)	2146 (99.9)	

Values in parentheses are percentages including missing data; percentages after multiple imputation. CCI, Charlson Co-morbidity Index; HER2, human epidermal growth factor receptor 2; RT, radiotherapy; BCS, breast-conserving surgery. *Pearson's $\chi 2$ test.

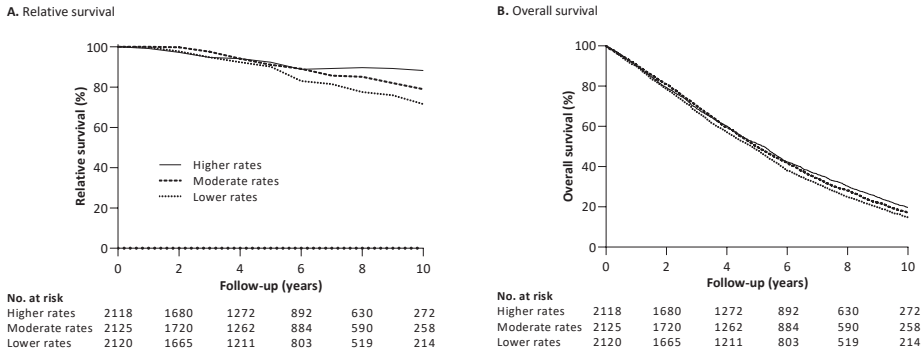

Figure 1. Cumulative relative survival (A) and overall survival (B) of patients treated in hospitals with different rates of primary surgery.

Table 3. Relative survival and relative excess risk for patients treated in hospitals with different rates of primary surgery.

	Surgically treated patients (%)	Relative survival (%)		Relative excess risk*	*p* value
		5 years	10 years		0.019
Higher rates	82.6	92.4 (88.5-96.2)	88.2 (80.4-96.3)	1.00 (reference)	
Moderate rates	69.7	91.1 (87.2-95.0)	79.0 (71.4-86.8)	1.29 (0.70-2.39)	
Lower rates	54.8	90.2 (86.2-94.2)	71.6 (64.1-79.4)	2.00 (1.17-3.40)	

Values in parentheses are 95 per cent confidence intervals. *Model included all available follow-up.

Overall survival rates were also lower for patients treated in hospitals with lower compared with higher rates of surgery (48.3 versus 51.3 per cent after 5 years; 15.0 versus 19.8 per cent after 10 years) (Figure 1b and Table 4). Compared with the reference group of patients treated in hospitals with higher rates of surgery, the adjusted HR for death was 1.07 (95 per cent c.i. 1.00 to 1.14) for patients treated at hospitals with lower rates (Table 4). Stratified by co-morbidity, the adjusted HR for death among patients treated in hospitals with lower compared with higher rates of surgery was 1.05 (0.95 to 1.16) in patients with a CCI score of 0, and 1.08 (0.98-1.20) among those with a CCI score of at least 1 (Table 4).

DISCUSSION

This study showed that omission of surgery had no effect during the first 5 years of follow-up, but was associated with worse relative and overall survival after 5 years in patients aged 80 years or older with stage I–II hormone receptor-positive breast cancer.

These findings support the recommendation of international guidelines that primary endocrine treatment is an alternative for patients with a life expectancy of 2-3 years, although,

Table 4. Cox proportional hazards analysis for overall survival of patients treated in hospitals with different rates of primary surgery stratified by comorbidity.

	Surgically treated patients (%)	Overall survival (%)					
		5 years	10 years	Hazard ratio*	*p* value	Age-adjusted hazard ratio*	*p* value
All patients					0.003		0.135
Higher rates	82.6	51.3 (49.2-53.4)	19.8 (18.0-21.6)	1.00 (reference)		1.00 (reference)	
Moderate rates	69.7	49.9 (47.8-52.0)	17.2 (15.5-18.9)	1.04 (0.98-1.12)		1.03 (0.96-1.09)	
Lower rates	54.8	48.3 (46.2-50.4)	15.0 (13.4-16.7)	1.12 (1.05-1.20)		1.07 (1.00-1.14)	
CCI score 0					0.060		0.646
Higher rates	88.2	60.4 (59.8-61.0)	25.9 (25.3-26.4)	1.00 (reference)		1.00 (reference)	
Moderate rates	74.4	57.9 (57.3-58.5)	22.4 (21.9-22.9)	1.06 (0.96-1.18)		1.02 (0.91-1.13)	
Lower rates	60.2	56.5 (55.9-57.1)	20.1 (19.6-20.6)	1.13 (1.03-1.25)		1.05 (0.95-1.16)	
CCI score ≥1					0.143		0.323
Higher rates	76.7	40.1 (39.7-40.5)	11.5 (11.2-11.8)	1.00 (reference)		1.00 (reference)	
Moderate rates	64.7	40.7 (40.2-41.1)	11.2 (10.9-11.5)	1.02 (0.99-1.14)		1.02 (0.92-1.15)	
Lower rates	48.8	39.1 (38.7-39.5)	10.3 (10.0-10.6)	1.10 (1.00-1.22)		1.08 (0.98-1.20)	

Values in parentheses are 95 per cent confidence intervals. *Model included all available follow-up. CCI, Charlson Comorbidity Index.

based on the data presented here, it could be argued that primary endocrine treatment is justified in patients with a life expectancy up of to 5 years. In a systematic review of six RCTs comparing surgery and tamoxifen monotherapy, only one trial demonstrated a survival advantage in favour of surgery.[12,13] Findings of the present study are in line with results from that trial, although with the finding of similar survival during the first 3 years compared with 5 years in the present study. The emergence of aromatase inhibitors might have improved the efficacy of primary endocrine treatment and contributed to this difference. This is substantiated by the findings of a cohort study in which 616 patients received primary endocrine treatment during the years when aromatase inhibitors were introduced; although 69.3 per cent of the patients received tamoxifen as first-line agent, the study demonstrated a median time to progression of 49 (range 4-132) months.[18] It is important to recognize that the early trials included only patients aged 70 years or more who were considered fit for surgery, whereas all patients aged 80 years or older in the Netherlands, including frail patients, were included in the present population-based cohort study. Because of this, the burden of mortality from non-breast cancer-related causes was considerably higher here, which could explain why the effect on survival was seen after a longer period.

There are no randomized data available comparing surgery and aromatase inhibitor monotherapy. The ESTEem (Endocrine +/- Surgical Therapy for Elderly women with Mammary cancer) trial was initiated to compare anastrozole with and without surgery, but unfortunately had to close owing to poor accrual. Patient preference for a specific treatment may

have contributed to the disappointing accrual. Furthermore, in clinical practice, omission of surgery is generally considered in frail older patients and the participation of this patient group in RCTs is often poor.

Several observational studies have compared outcomes of patients treated with primary surgery or primary endocrine treatment. The majority demonstrated superior BCSS and overall survival in patients who had primary surgery.[32,33] Only one study did not report a difference in 5-year BCSS between patients who had surgery versus primary endocrine treatment among those aged 80 years or more. Residual confounding owing to differences in general health and frailty between patients who had primary surgery and those who received primary endocrine treatment is usually not measured in observational databases, which makes direct comparisons at risk of bias.

In the present study, patients treated with and without primary surgery were not compared directly; instead, outcomes were compared in groups of patients treated in hospitals with different rates of primary surgery. As the measured patient and tumour characteristics were similar across the groups, the amount of residual confounding by unmeasured factors was reduced. An instrumental variable approach, however, requires further assumptions, such as similar quality of hospital care.[34] With a difference of 27.8 per cent in omission of surgery between the hospitals with higher and lower rates of surgery, both relative survival and overall survival were worse for patients treated in the hospitals with lower rates. As expected, overall survival rates are lower than relative survival rates owing to the high population mortality in this age group. Consequently, the impact of omission of surgery on relative survival translates into a smaller impact on overall survival, and for some patients with high competing mortality risks this absolute benefit is likely small enough to justify omission of surgery. On the other hand, the present data suggest that, if rates of surgery in patients aged 80 years and older were to increase, survival after 5 years may improve.

Given the overlapping survival curves, the present data may suggest that omission of surgery can be considered in patients with a life expectancy below 5 years. Yet, even in patients with limited life expectancy, there are reasons for being reluctant to offer primary endocrine treatment as an alternative to surgery. Endocrine therapy often has side-effects, such as hot flushes, joint pain and fatigue, which can impair activities of daily living and quality of life.[10,11] Furthermore, in the adjuvant setting, non-persistence with endocrine therapy has been demonstrated to increase with older age.[35] As patients with favourable tumour characteristics (grade 1 up to 2 cm in size; grade 2 up to 1 cm) do not receive adjuvant endocrine treatment in the Netherlands, such patients can be spared endocrine therapy completely after primary surgery.

Another disadvantage of primary endocrine treatment is that it is only effective for a limited period, after which a switch of treatment is needed. Although different lines of endocrine treatment are available, surgery may eventually be necessary. Furthermore, whereas primary endocrine treatment requires long-term regular hospital visits to evaluate disease progression, few hospital visits are required after surgery. The main advantage of primary endocrine treatment over surgery is that the risks and inconvenience of surgery can be avoided. Breast surgery, however, is associated with low morbidity rates, and age itself is not a risk factor for postoperative complications.[36,37] The inconvenience of primary endocrine treatment may persist for a long time, whereas the inconvenience of having surgery is generally temporary. Accurately estimating life expectancy is not straightforward. In 2018, the life expectancy of a Dutch woman aged 70 years was 17.3 years, and for a woman aged 80 years was 9.9 years.[19] Certain co-morbidities can decrease life expectancy, but impaired cognition, malnutrition and dependency in activities of daily living are also important predictors.[38] As these factors may not always be recognized, a geriatric assessment is advisable.[39] The present findings underline that estimating life expectancy is important for optimal treatment decisions, but unfortunately this is often difficult for patients aged over 80 years.

Strengths of this study were that hospital variation was used to minimize confounding by indication as much as possible, and relative survival was calculated, which takes into account mortality from other causes. All consecutive patients in a large, nationwide cohort were included with detailed information on tumour characteristics and co-morbidity. Limitations of this study were related to the data and methodology. Information on treatments was limited to the first year after diagnosis, and it is therefore unknown how many patients eventually had surgery after primary endocrine treatment. No information on specific endocrine agents and successive lines of endocrine therapy was available. Inherent to following the instrumental variable approach using hospital variation in rates of primary surgery, only the impact of a difference in rate of surgery of 27.8 per cent could be assessed, which reduced the statistical power. Although this was sufficient to demonstrate a survival difference in the primary analysis, the findings for the stratified analysis suggest a lack of power. Although confounding by unmeasured factors can theoretically be avoided using the instrumental variable approach, an instrument that meets all of the required assumptions is not always available in clinical data. There was a small age difference across the groups in the present study. Although age was adjusted for in multivariable analysis, residual confounding could not be ruled out completely.[34] Future research is needed to evaluate the side-effects of primary endocrine treatment using aromatase inhibitors, compliance and treatment switches, and to compare quality of life and physical functioning of patients treated with surgery or primary endocrine therapy.

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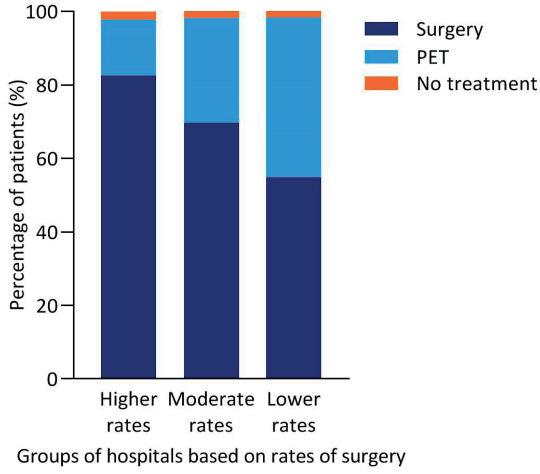

Supplementary Figure. Primary treatment in hospitals with higher, moderate and lower surgery rates. PET: primary endocrine therapy.

7

Older patients' barriers and facilitators for omission of locoregional breast cancer treatment

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ABSTRACT

Introduction. In older women with early breast cancer, individual components of locoregional treatment may have limited benefit with regard to recurrence and survival. Yet, the use of these treatments tends to persist after limited benefit is demonstrated. Patients play a crucial role in the decision to perform or omit treatment. This study therefore aims to assess patient barriers and facilitators for omission of specific locoregional treatments.

Methods. We conducted focus groups with patients aged ≥70 years to discuss omission of radiotherapy after breast-conserving surgery, axillary lymph node dissection (ALND) after positive sentinel node and replacement of primary surgery by endocrine treatment. Conventional content analysis was performed. Identified barriers and facilitators were presented as treatment scenarios in a survey among a larger group of older patients to identify the five most frequently occurring factors.

Results. Fifty-nine patients completed at least one treatment scenario in the survey. Fear of disease recurrence, feelings of receiving suboptimal treatment, and lack of social support were general barriers to omit radiotherapy and ALND. Barriers to omit surgery related to replacement by endocrine treatment. The relationship with the clinician and specialist nurse, information provision and trust in evidence were frequently mentioned general facilitators for all treatments. Avoiding long-term adverse effects of radiation and the risk of lymphedema after ALND were treatment-specific facilitators.

Conclusion. Reassurance on recurrence risks and involving family members for social support are two key actions clinicians and specialist nurses may take to enhance de-implementation of radiotherapy and ALND in patients with expected limited benefit.

INTRODUCTION

Since the number of older patients with breast cancer is increasing due to ageing of Western populations, efforts are made to improve the evidence for treatment effects in this patient population.[1, 2, 3, 4, 5] Previous studies have shown that for specific subgroups, the beneficial effect is very limited with regard to recurrence or survival due to a combination of low risk breast cancer and a shorter life expectancy. For example, it was shown that patients over 70 years with small tumors who are treated with endocrine treatment do not benefit from radiotherapy after breast-conserving surgery (BCS).[6] Surgery conferred no survival benefit over endocrine therapy alone in patients with hormone receptor-positive tumors and a life expectancy up to 2-3 years.[5, 7] Moreover, axillary lymph node dissection (ALND) did not add value for all aged patients with 1-3 positive sentinel lymph nodes who receive systemic treatment.[8]

However, to de-implement conventional treatments is more challenging than to implement a new treatment.[9, 10] Practice patterns show inconsistent de-implementation of individual treatments. Rates of radiotherapy after BCS have only modestly declined, whereas rates of ALND after a positive sentinel lymph node biopsy (SLNB) have decreased more rapidly.[11, 12] Furthermore, rates of surgery vary across countries and hospitals for patients over 80 years.[9, 13] Overall, practice patterns thus suggest that de-implementation could be improved, and that radiotherapy after BCS, as well as ALND after positive SLNB are likely still overutilized in older patients.

The differences in rates and varying trends of de-implementation cannot be explained by patient characteristics alone. Clinicians highlight that, besides their own views, patient views play an important role. In a survey on omission of radiotherapy (n=825), clinicians most frequently agreed on the statement that patients desire maximal treatment, even if the benefit is small.[14] Patient preference is the second most important factor after comorbidity to omit surgery according surgeons and specialist nurses (n=34).[15] Furthermore, patients' fear of lymphedema is mentioned as the strongest motivator (n=18) to omit ALND after a positive SLNB.[16] There could be other patient barriers preventing de-implementation, as well as facilitators that might help to overcome these barriers. Therefore, the aim of this study was to identify patient barriers and facilitators to omit radiotherapy after BCS, ALND after positive SLNB, and to replace primary surgery with endocrine treatment in older patients with early breast cancer.

METHODS

Study design

This was a mixed method study performed at the Leiden University Medical Center (LUMC) in collaboration with the national patient organization "Borstkankervereniging Nederland" (BVN). It was part of a larger project that aimed to identify locoregional treatments with limited added value in selected older patients with breast cancer. The current study was performed alongside to gain insight into factors influencing the de-implementation of such treatments.

In the first part, focus groups with patients were organized to identify barriers and facilitators for omission of treatments when proposed by the clinician. In the second part, the identified barriers and facilitators were presented to a larger group of older patients as treatment scenarios in a survey, to establish which five factors most frequently play a role. The study protocol and survey were approved by the medical ethical research committee of the LUMC (P17.152). The COREQ guidelines were used for reporting of the study.[17]

Participants and recruitment

Participants for the focus groups and survey were recruited through patient organization BVN by email and the outpatient Surgical and Medical Oncology departments of the LUMC, face-to-face or by mail. Consecutive patients who fulfilled the eligibility criteria were selected. Patients were eligible if they were treated for non-metastatic breast cancer aged 70 years or older. Time since diagnosis had to be at least six months to allow for recovery time and reflect on their experience. Understanding of the Dutch language was required. Patients with dementia were excluded. Participants for the focus groups were recruited until three groups of five participants could be organized.

Focus groups

In the period between February and May 2018, three focus groups were organized in the LUMC, each with five participants. The focus groups were conducted by a moderator (AB, MD, female) and assistant (NG, MD PhD, female). The assistant took notes and made sure all participants were heard and all relevant topics were covered. Both the moderator and assistant are experienced researchers in the field of breast cancer in older patients. Only the assistant was involved in clinical care at the time the focus groups were held, as a resident medical oncology. This information about the researchers was communicated with the participants, who had no prior relationship with either of the researchers. The researchers prepared for the conduct of the focus groups by studying literature, and guided by medical decision-making specialists experienced with conducting focus groups. A specific focus group guide was assembled based on literature and expert opinion (see appendix 1).

Each focus group took two hours. Three scenarios were discussed: the omission of radiotherapy after BCS, the omission of ALND after a positive SLNB, and the omission of primary surgery to be replaced by primary endocrine treatment (PET). The scenarios were introduced with the following question: "*if your doctor would propose treatment omission, would you have reasons to still want to undergo the treatment? If not, what are your considerations? If yes, what are your considerations?"* This question was sent by mail prior to the focus groups for preparation. The focus groups were audio-taped and transcribed verbatim. A conventional content analysis was performed by AB by deriving barriers and facilitators from the content, and coding similar items. The framework of Grol and Wensing was used to ensure the representation of factors on different levels. This generic framework was developed to assess barriers and facilitators for the implementation of new evidence on six levels of healthcare; the innovation itself, the professional and patient respectively, and the social, organizational, and financial context.[18] Data saturation was reached as no new items emerged during the third focus group. The transcripts and final results were not returned to the participants.

Patient perceived barriers were defined as reasons to insist undergoing treatment despite the proposition of the doctor to omit treatment. Facilitators were defined as reasons to follow the proposed treatment plan in which the treatment is omitted. A distinction was made between treatment-specific and general factors, with the latter applying to all three treatments.

Survey

Between May and October 2019, 90 patients agreed to participate in the survey. The survey included the same three scenarios as presented in the focus groups. All barriers and facilitators that were identified in the focus groups were included in a list of reasons following the statement "*I would still want to undergo the treatment despite the proposition of my clinician*" or "*I follow the proposition of my clinician not to undergo the treatment*." The respondent was asked to choose a maximum of five reasons. The barriers and facilitators were presented as quotes, for example *"because I think that more extensive treatment is always better*" or "*because I am afraid of the unknown long-term adverse effects of endocrine treatment*". An example scenario is presented in appendix 2. We computed the five most frequently mentioned barriers and the five most frequently mentioned facilitators for each treatment, while distinguishing between treatment-specific and general factors.

RESULTS

Patients

Median age of the 15 patients who participated in the focus groups was 74 years (range 71-86 years) and 72 years at time of diagnosis (range 70-85 years). All patients were surgically treated. Three underwent an ALND. Four patients underwent radiotherapy, out of 7 patients who underwent BCS. Four patients received adjuvant endocrine therapy, and 3 received chemotherapy.

Of 90 patients responding to the survey, 59 patients completed at least one scenario and were included in the analysis. Median age was 74 years (IQR 71-76 years) and 71 years at time of diagnosis (IQR 68-73 years). Three patients were treated with PET, and 56 patients underwent surgery of whom 13 underwent an ALND. Twenty-five patients underwent radiotherapy, out of 28 patients who underwent BCS. Thirty patients received adjuvant endocrine therapy, and 17 received chemotherapy.

General factors identified in the focus groups

We found factors applying to all three treatments on the level of the professional, the patient, and the social context (Table 1 including representative quotes). On the professional's level, all patients agreed that a trustful relationship with the clinician is the most important facilitator to agree with the proposal to omit treatment. Only one patient indicated a lack of trust as barrier. The feeling to be listened to and to be provided with sufficient information were other important facilitators. The specialist nurse was also valued by many patients.

Factors identified on the level of the patient were mostly barriers. It was mentioned that despite the knowledge that a treatment has no significant benefit, fear was a motivator to still want to undergo treatment. Similarly, some patients felt that more extensive treatment is always better. Others felt uncomfortable to receive substandard treatments, or different treatments than younger patients would receive. Similarly, trust in the scientific evidence was mentioned as barrier if patients were wary to be one of the first to be treated differently. Contrary, for others, trust in the scientific evidence was a facilitator.

Last, general factors on the level of the social context could act as either a barrier or a facilitator. For experiences from a familiar person, negative experiences seemed to have more impact than positive experiences. It was observed less often that a patient still wanted to undergo a treatment because of a familiar person with a good experience. Support from family members was predominantly brought up as facilitator.

Table 1. General barriers and facilitators for omission of treatments identified in the focus groups. B barrier; F facilitator.

Level	Barrier/facilitator	Sample quote	B	F
Professional	Relationship with doctor	"If you consider how clinicians guide you from the first step through surgery and after that, I don't believe they will make recommendations they don't support."		X
		"Clinicians don't tell you everything. Sometimes you come home and realize: if I had only put it like this, then maybe the clinician had explained it differently?"	X	
		"Trust in your clinician is most important. As a patient, you do not know much about scientific evidence."		X
	Relationship with specialist nurse	"I have consulted the specialist nurse several times. Her opinion and the fact that she examined me extensively gave me comfort during the process."		X
	Information provision	"The clinician took the time to explain everything and to let me talk. I really appreciated that he took the time to consider my personal preferences as well.		X
		"To be educated gives the patient comfort. Education is so important."		X
Patient	Fear of disease recurrence	"At the time, you don't give the surgical risks [of axillary lymph nodes dissection] a lot of thought. You think if only the cancer is gone."	X	
		"Fear is a bad advisor, but I can imagine that it can be a reason to choose to undergo the treatment anyway."	X	
	Trust in evidence	"You have to take a leap of faith. Back in the days it was only amputation, then there was breast conserving treatment. I think medical science will further move forward."		X
		"It is important to know how much research is done. You do not want to be the first they try it on."	X	
	Perception that extensive treatment is better	"[Despite the risk of lymph edema] I would still prefer to undergo an axillary lymph node dissection because if the cancer has spread to your lymph nodes, it also has access to the rest of your body."	X	
		"You want to do the best you can. If you are enjoying life, you do not want to die."	X	
	Important to receive the same treatment as younger patients	"I noticed that I had trouble with accepting treatments that are not standard, because it's effects are less known."	X	
		"The mass screening program stops at 75 years because there is no survival advantage, but what if you are an exception to the rule?"	X	
Social	Experience of family/friends	"One person I know told me I should never start with endocrine therapy, because it causes fatigue and painful joints."	X	
		"A person I know, her skin got really damaged by the radiotherapy."	X	
	Support by family/friends	"If you lack support at home, you may be more inclined to just undergo the treatment instead of considering different options."	X	
		"I had to get used to the idea not undergoing radiotherapy, but I discussed it with my husband and children."		X

Scenario 1. The clinician suggests to omit radiotherapy after BCS

The treatment-specific barriers and facilitators for omission of radiotherapy identified in the focus groups are presented with representative quotes in Table 2. Most patients expressed the fear of adverse effects due to radiation of the heart and lungs as a facilitator to omit radiotherapy. Some wondered whether the radiotherapy had something to do with general complaints they now experienced such as fatigue and sleeping problems. Several patients described that they were still very fit, and were afraid the radiotherapy would impact their physical condition. On the innovation level, some patients heard stories about poor wound healing, but this was not considered a strong facilitator. On the organizational context level, the avoidance of frequent hospital visits was a facilitator depending on the distance and functional status. Others did not mind the hospital visits, and some even felt they provided structure in their daily life.

From the survey, the five most frequently mentioned barriers and facilitators to omit radiotherapy are presented in Table 3. More respondents indicated facilitators (n=39, 66%) than barriers (n=20, 34%). The only treatment-specific factor was avoiding potential long-term adverse effects of radiation as facilitator. Most facilitators were on the level of the professional, whereas most barriers were on the patient level. If the clinician would propose to omit radiotherapy, a trustful relationship with the clinician and specialist nurse, and to be provided sufficient information could enhance this decision. In contrast, fear of disease recurrence, and wariness about the extensiveness of treatment were barriers. Lack of social support was also a frequently mentioned barrier. Trust in the scientific evidence was mentioned as both a barrier and facilitator.

Scenario 2. The clinician suggests to omit an ALND after a positive SLNB

The main facilitator discussed in the focus groups was avoiding the risk of lymphedema. The idea that lymphedema could diminish arm functionality was much feared. Some expressed worries about lymphedema being painful, potential sleeping difficulties, and the negative cosmetic effect. On the financial context level, it was mentioned that lymphedema therapy is only partially covered by insurance (Table 2).

The five most frequently mentioned barriers and facilitators in the survey for omission of ALND are presented in Table 3. More respondents indicated facilitators (n=29, 58%) than barriers (n=21, 42%). The only treatment-specific factor was avoiding the risk of pain and impaired arm function due to lymphedema as facilitator. Otherwise, the five most frequently mentioned barriers and facilitators were the same as for omission of radiotherapy.

Table 2. Treatment-specific barriers and facilitators identified in the focus groups. B barrier; F facilitator.

Level	Barrier/facilitator	Sample quote	B	F
Omission of radiotherapy after BCS				
Innovation	Risk of complications	"You might end up with all sorts of complaints such as painful ribs."		X
		"After surgery, the radiotherapy doesn't make the breast any prettier."		X
	Inconvenience	"The radiotherapy sessions were more inconvenient than the surgery. I had to keep my arm in a position which was almost unbearable."		X
Patient	Fear of adverse effects	"Since my tumor was located on the left side, my heart would be irradiated and I could end up becoming a heart patient."		X
		"The fatigue and sleeping problems, sometimes I think they are due to the radiotherapy. However, it could also be the endocrine therapy."		X
Organizational	Frequent hospital visits	"You already feel unfit, and then you have to go back and forth to the hospital. Sometimes you do not know what is best for you."		X
		"I did not mind the frequent hospital visits, the people were very kind and it gave me structure after the hectic period of diagnostics and surgery."	X	
Omission of ALND after SLNB+				
Innovation	Risk of lymph edema	"Due to lymph edema, the functionality of my right hand is reduced. I read about the surgical risks, but still, this was not what I expected."		X
		"Even if you are over 70 years of age, you still want to look good."		X
Financial	Costs of edema therapy	"You think it is something small the lymphedema [therapy], you get started, and then you have to pay hundreds of euros which insurance does not cover."		X
Omission of primary surgery by replacement with primary endocrine treatment				
Innovation	Breast cosmesis	"I could not at all endure the idea that my breast would be amputated. I just had a new partner. I would consider omission of surgery if it was safe."		X
	Risk or inconvenience of surgery	"Although my surgery went well, I would prefer not to undergo all the inconveniences, and they still have to cut in your body."		X
	Risk of side effects of endocrine treatment	"After a year on letrozole, I told my oncologist that I wanted to stop because the side effects had a negative impact on my quality of life."	X	
	Duration of surgery vs endocrine treatment	"I would choose surgery, because the inconveniences of surgery pass relatively quickly."	X	
		"I would say, gone is gone."	X	
Patient	Fear of surgery	"I would prefer the tablet. At my age, I have had enough surgeries."		X
	Perception about endocrine treatment	"A tumor does not belong there, thus should be removed [rather than controlled]."	X	
		"I think hormones are scary."	X	
	Fear of adverse effect endocrine treatment	"Nobody knows whether endocrine therapy is safe." "I heard on the television that endocrine therapy is harmful, that it can cause breast cancer."	X X	
Organizational	Hospital admission	"I had to arrange that my husband could stay in a nursing home for the days I was admitted to the hospital."		X

Abbreviations; BCS breast conserving surgery; ALND axillary lymph node dissection; SLNB+ positive sentinel lymph node biopsy; PET primary endocrine therapy.

Table 3. The five most frequently mentioned barriers and facilitators for omission of radiotherapy after breast-conserving surgery and omission of axillary lymph nodes dissection after positive sentinel lymph node biopsy in the survey.

Barriers	Level	Facilitators	Level
General factors for the omission of both treatments			
Fear of disease recurrence/progression	Patient	Trustful relationship with doctor	Professional
Perception that more extensive treatment is better	Patient	Trustful relationship with specialist nurse	Professional
Important to receive the same treatment as younger patients	Patient	Information provision	Professional
Lack of trust in evidence	Patient	Trust in evidence	Patient
Lack of support by family/friends	Social		
Treatment-specific factor for omission of radiotherapy after BCS			
		Avoiding fear of possible (unknown) long-term adverse effects of radiotherapy	Patient
Treatment-specific factor for omission of ALND after SLNB+			
		Avoiding risk of pain and impaired arm function due to lymphedema	Innovation

Scenario 3. The clinician suggests to omit surgery and treat with primary endocrine therapy

Facilitators discussed in the focus groups related to avoiding surgery. Some patients considered themselves too old to undergo surgery. One patient could not endure the idea of her breast being amputated. However, more patients preferred surgery because the inconveniences pass relatively quick, whereas side-effects of endocrine treatment persist for a longer time. It was emphasized that the advantage of avoiding surgery are outweighed by the risk of side-effects of endocrine treatment. Endocrine treatment was even considered unsafe by some patients. On an organizational context level, avoiding hospital admission could be a facilitator as one patient mentioned she had to arrange care replacement for her husband (Table 2).

The five most frequently mentioned barriers and facilitators in the survey for omission of surgery are presented in Table 4. In contrast to the previous two scenarios, respondents indicated mainly barriers (n=46 (87%)). Besides fear of disease progression, all barriers were treatment-specific. The risk of side-effects and fear of potential long-term adverse effects of endocrine treatment were frequently mentioned. Also, the fact that endocrine treatment should be used for a longer period, whereas you can have surgery and be done. Lastly, that a tumor needs to be removed instead of controlled. Again, the same four general facilitators were found with feeling too old to undergo surgery as the fifth facilitator.

Table 4. The five most frequently mentioned barriers and facilitators for omission of primary surgery by primary endocrine treatment replacement in the survey.

Barriers	Level	Facilitators	Level
General factors			
Fear of disease progression	Patient	Trustful relationship with doctor	Professional
		Trustful relationship with specialist nurse	Professional
		Information provision	Professional
		Trust in evidence	Patient
Treatment-specific factors			
Duration of surgery vs endocrine treatment	Innovation	Feeling too old to undergo surgery	Patient
Risk of side effects of endocrine treatment	Innovation		
Perception that a tumor needs to be removed instead of controlled with endocrine treatment	Patient		
Fear of possible (unknown) long-term adverse effects of endocrine therapy	Patient		

DISCUSSION

This study investigated patient barriers and facilitators to omit treatments demonstrated to have limited benefit in certain patient selections. In summary, the most frequently mentioned barriers and facilitators for omission of radiotherapy after BCS and ALND after positive SLNB were general factors; related to fear of disease recurrence and the relationship with health care professionals. Almost all respondents still wanted to undergo primary surgery if the clinician proposed PET, due to barriers related to PET; the risk of side-effects and treatment duration.

Our observations are mostly in line with a previous survey capturing patient views on omission of radiotherapy.[19] Similarly, it was indicated that worry about the cancer coming back was one the most important considerations. In contrast to our findings, receiving extensive treatment was considered less important in that survey. Also, avoiding potential long-term effects of radiotherapy was a frequently mentioned facilitator in our study, whereas in the previous survey, the avoidance of direct complications was more pronounced than the avoidance of irradiation per se. It should be noted that the studies had different designs.

In any case, clinicians opinion that patients seem to desire maximal treatment, even if the benefit is very small seems not justified based on both studies.[14] Although receiving extensive treatment and similar treatment to younger patients were important barriers, 66% (39 out of 59 patients) of our respondents reported that they would agree upon omission of radiotherapy if the clinician proposed so. The question to what extent treatment decisions

that can be based on patient preference are in fact based on the preference of the treating clinician was previously raised.[20] This treatment bias seems to occur both on the level of the patient and clinician.

In a recently study on barriers and facilitators to de-implement treatments that are considered unnecessary as part of the Choosing Wisely guideline, all 18 surgeons that were interviewed agreed on the omission of ALND in patients with a positive SLNB.[16, 21] However, a larger survey among 359 surgeons performed between 2013 and 2015 showed substantial variation in acceptance with approximately half still favoring ALND.[22] Furthermore, ALND rates of 45-46% after a positive SLNB are reported in Europe over 2015 and 2016 (most recent years available).[12] Although these studies did not address older patients specifically, overall, they indicate that ALND is overutilized. It was unexpected that 42% of our respondents (21 out of 50) still wanted to undergo ALND even when the clinician would suggest not to with fear of recurrence being an important factor. This observation emphasizes that in addition to focusing on the benefits of avoiding ALND, clinicians should inform and reassure a patient about the effect on recurrence risk.

The decision to omit surgery is a different situation since this requires replacement by endocrine treatment rather than omission of treatment only. Barriers and facilitators for both treatment options then have to be considered. Patient choice did not explain the omission of surgery in a UK cohort of 800 patients aged 70 years or older.[23] A smaller cohort study however showed that if surgery and PET were both discussed, which was the case in older patients with more comorbidities, 66 out of 112 chose to omit surgery.[24] We observed that 87% of the patients (46 out of 53) in our study still wanted to undergo surgery if PET was proposed as alternative treatment by the clinician. However, it should be kept in mind that almost all patients that participated in our study underwent surgery which likely influenced their opinion. The most frequently mentioned barriers related to the risk of side-effects of endocrine treatment and potential unknown long-term adverse effects, and that the inconvenience of PET lasts longer than of surgery. In light of the increased rates of omission of surgery, clinicians recommending this strategy may underestimate these barriers to PET.[25, 26] Moreover, PET is only a suitable strategy for a small fraction of the older patients, the very oldest or frail. Our recent study showed that even in patients over 80 years, omission of surgery is associated with worse survival.[13]

Based on the findings in the present study, several specific actions can be undertaken by clinicians and specialist nurses to support de-implementation. As can be expected, fear of disease progression is a major consideration that contributes to perceptions that extensive treatment is always better and treatments should be similar to younger patients. For omission of radiotherapy and ALND, facilitators were mostly general factors rather than related

to the treatment to be omitted specifically. The hospital visits and direct complications and inconveniences from radiotherapy were not among the frequently mentioned facilitators, nor were the general risks and inconveniences of surgery mentioned for omission of ALND. Avoiding potential long-term adverse effect of radiotherapy and the risk of lymphedema were the only frequently mentioned treatment-specific facilitators. Therefore, rather than focusing too much on the avoided risks when proposing to omit treatments, it is up to the clinician and specialist nurse to sufficiently inform and reassure the patient on recurrence risks. Furthermore, the survey also pointed out that a lack of social support was experienced as a barrier. It could therefore be helpful to involve patient family members in the treatment decision process to make sure that the patient receives sufficient social support for the decision made.

This study demonstrates how insight in patient barriers and facilitators could improve the actual omission of treatments with limited benefit in clinical practice. For health care professionals, they can guide actions that enhance de-implementation as best as possible. Also, a discordance between clinicians' perception on patient considerations and the actual considerations can come to the attention. Since performing this study, the American Society of Surgical Oncology has advocated not to perform an SLNB in patients aged 70 years or older if the results will not impact systemic therapy decisions.[27] Furthermore, the ongoing TOP-1 (Tailored treatment in Older Patients) study (BOOG study number 2016-01) investigates the omission of radiotherapy in patients aged 70 years or older with early breast cancer not receiving endocrine treatment. Therefore, the identification of patient barriers and facilitators will be needed to optimize future de-implementation of treatments once they prove to be of low value.

Our study had some limitations. Foremost, accrual of survey participants was slow, and a substantial part of the patients who agreed to participate did not manage to complete at least one treatment scenario. Despite a pilot survey (n=10), its complexity likely played a role, as patients had to imagine a hypothetical situation in which their clinician proposed to omit a treatment and objectify their considerations. This was mentioned in the survey remarks. Second, 12 survey participants were aged 66-69 years, and 8 were aged 60-65 years at diagnosis. We chose to include these patients to improve our sample size. Third, selection of older patients able and willing to participate in studies may have also reduced the generalizability of our findings. Last, it should be mentioned that patients are more likely to insist on a treatment they actually underwent based on a good experience, but also due to the need to justify previous decisions.

In conclusion, over half of the patients reported mainly facilitators to omit radiotherapy after BCS or ALND after a positive SLNB when proposed by the clinician, whereas up to

90% mainly reported barriers to omit primary surgery. Our findings indicated that reassurance on recurrence risks and involving family members for social support are two key actions that clinicians and specialist nurse could perform to enhance de-implementation of locoregional treatments with limited benefit in older patients with breast cancer.

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Appendix 1. Focus group guide

Introduction (10 minutes)

We have organized a group meeting to discuss your opinion on the treatment of breast cancer in women 70 year or older. You are asked to share your ideas and personal experiences. We would encourage you to react on each other and create a discussion. We ask that you respect one another's opinion. There are no wrong answers. We are interested in your opinion and what considerations play a role. To analyze the results, we will make an audio recording. The audio records will be anonymized. We will consider everything that is discussed here to be confidential and we ask you to do the same.

The aim of the study is to get insight in your opinion on the omission of parts of the breast cancer treatment. Scientific studies suggest that certain treatment can be safely omitted in selected patients. We would like to find out if patients have reasons to still want to undergo treatment if a clinician suggests to omission of a treatment. Some of you underwent the treatment we are discussing, others have not. If you did not undergo the treatment, please still try to imagine which factors you would consider if you had to make the decision or if a family member asks for your advice.

We will discuss the omission of three treatment separately. Before we start discussing a treatment, we ask you to write down on post-it's the factors that you would consider if your clinician would suggest to not undergo this treatment. We will use these post-it's as a way to guide the discussion. Of course, you can also introduce new factors during the conversation.

Participant introductions (*10 minutes*)

Situation 1. Omission of radiotherapy after breast conserving surgery (20 minutes)

We know from research that a selection of the older patients with breast cancer does not live longer with radiotherapy after breast conserving surgery than without the radiotherapy. There is always a small risk that the breast cancer recurs. Imagine the situation that new research shows that for selected patients, radiotherapy does not lower this risk of breast cancer recurrence either. You belong to this selection of patients, and therefore your clinician suggests to omit the radiotherapy. Do you have reasons to still want to be treated with radiotherapy? Or would you go for the suggestion of your clinician to omit radiotherapy? Could you write your considerations on the post-its? It may help to imagine what you would advise a family member or friend in this situation.

After finishing the post-its, ask if there are any questions about the treatment or side-effects. Try to let the participants answer each other's questions, but interfere or complement if needed. Use the post-it's to initiate and deepen the discussion.

Situation 2. Omission of surgery by replacement by endocrine treatment (20 minutes)

Imagine the situation that new research shows that for selected patients it is safe to treat the breast cancer with medication, endocrine treatment, instead of treated with surgery. You belong to this selection of patients, and therefore your clinician suggests to omit surgery by replacement by endocrine treatment. Do you have reasons to still undergo surgery? Or would you go for the suggestion of your clinician to omit surgery? Could you write your considerations on the post-its? It may help to imagine what you would advise a family member or friend in this situation.

After finishing the post-its, ask if there are any questions about the treatment or side-effects. Try to let the participants answer each other's questions, but interfere or complement if needed. Use the post-it's to initiate and deepen the discussion.

Break (15 minutes)

Situation 3. Omission of axillary lymph nodes dissection after a positive sentinel node biopsy (20 minutes)

During an axillary lymph nodes dissection, all lymph nodes in the axilla are removed. Imagine the situation that new research shows that this procedure can be safely omitted in selected patients with a positive sentinel lymph node biopsy. You belong to this selection of patients, and therefore your clinician suggests to omit the axillary lymph nodes dissection. Do you have reasons to still undergo the axillary lymph nodes dissection? Or would you go for the suggestion of your clinician to omit the procedure? Could you write your considerations on the post-its? It may help to imagine what you would advise a family member or friend in this situation.

After finishing the post-its, ask if there are any questions about the treatment or side-effects. Try to let the participants answer each other's questions, but interfere or complement if needed. Use the post-it's to initiate and deepen the discussion.

Extra time (20 minutes)

Appendix 2. Survey scenario for omission of radiotherapy after breast conserving surgery

Scenario 1 – Radiotherapy after breast conserving surgery

We know from research that a selection of the older patients with breast cancer does not live longer with radiotherapy after breast conserving surgery than without the radiotherapy. There is always a small risk that the breast cancer recurs. Imagine the situation that new research shows that for selected patients, radiotherapy does **not** lower this risk of breast cancer recurrence either. You belong to this selection of patients, and therefore your clinician suggests to omit the radiotherapy.

Question 1:

Do you have reasons to still want to be treated with radiotherapy? Check the box of one of the options and follow the instruction behind.

□ Yes → **answer question 2 and 3 on this page**

□ No → **answer question 4 and 5 on the next page**

Question 2:

Please check the boxes before the letters of reasons why you still want to be treated with radiotherapy. Try to choose as many reasons that are relevant for you, with a maximum of five reasons.

"Despite the suggestion of my clinician, I still want to be treated with radiotherapy..."

	A	"..due to a lack of trust in the clinician."
	B	"..due to a lack of a trustful relationship with the breast care nurse."
	C	"..because I was given insufficient explanation from the clinician."
	D	"..because I am afraid the cancer will come back. Even if I would know that radiotherapy would not lower this risk, because of this fear I would still want to be treated with radiotherapy."
	E	"..due to a lack of trust in the scientific evidence."
	F	"..because I think that more extensive treatment is always better."
	G	"..because the hospital visits give me structure in my daily routine after the surgery."
	H	"..because it is important to receive the same treatment as younger patients."
	I	"..because I am familiar with a person who has had a positive experience with radiotherapy."
	J	"..because the people around me support me in this."
	K	Other reason:

Question 3:

Please arrange the reasons that you just chose in order of importance from most to least important. Write down the letter of the most important reason in the box behind 1, the second most important reason in the box behind 2, and so on until you used all the reasons you chose in question 2. If you chose less than five reasons in question 2 not all boxes will be filled.

1		Most important
2		
3		
4		
5		Least important

Question 4:

Please check the boxes before the letters of reasons why you follow the suggestion of the clinician not to undergo radiotherapy. Try to choose as many reasons that are relevant for you, with a maximum of five reasons.

"I follow the suggestion of the clinician to not undergo radiotherapy..."

	L	"..because that is the advice of the clinician and I trust the clinician."
	M	"..because this is also recommended by the breast care nurse."
	N	"..because the clinician takes the time to explain everything."
	O	"..because I trust the scientific evidence."
	P	"..because I feel too old to undergo radiotherapy."
	Q	"..because I think it is important that new insights are tested in clinical practice."
	R	"..due to the risk of complications from the radiotherapy such as a thinning of the skin and poor wound healing."
	S	"..because I am scared for the (unknown) long term adverse effects due to irradiation of the heart and lungs."
	T	"..to avoid the direct inconvenience of radiotherapy that I have to lie and hold still in an uncomfortable position."
	U	"..because I am familiar with a person who has had a negative experience with radiotherapy."
	V	"..because the people around me support me in this."
	W	"..to avoid the frequent visits to the hospital (16-20 times) that are needed for the radiotherapy."
	X	"..to avoid being dependent on others for the frequent hospital visits (16-20 times)."
	Y	Other reason:

Question 5:

Please arrange the reasons that you just chose in order of importance from most to least important. Write down the letter of the most important reason in the box behind 1, the second most important reason in the box behind 2, and so on until you used all the reasons you chose in question 4. If you chose less than five reasons in question 4 not all boxes will be filled.

1		Most important
2		
3		
4		
5		Least important

Part III

Geriatric assessment and outcomes

8

Metastatic breast cancer in older patients: a longitudinal assessment of geriatric outcomes

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ABSTRACT

Introduction. Approximately 20% of older patients with breast cancer either present with metastatic disease or develop distant metastases after early breast cancer. The aims of this study were to assess the prevalence of psychosocial problems in older patients with metastatic breast cancer, and to assess longitudinal changes in functional status, psychosocial functioning, and quality of life.

Methods. For this prospective cohort study, patients with metastatic breast cancer aged 70 years and older were recruited in four Dutch hospitals. A baseline geriatric assessment was performed evaluating somatic, functional and psychosocial domains. Self-administered questionnaires were performed at baseline, three and six months: the Groningen Activity Restriction Scale, Geriatric Depression Scale, Loneliness scale, Apathy scale, Distress Thermometer and EORTC-QLQ-C30. Longitudinal changes on these scales were assessed by performing crude and adjusted linear mixed models.

Results. Of the 100 patients that were included and underwent a geriatric assessment, 85 patients completed the baseline self-administered questionnaires. Almost half of the patients (46%) had depressive symptoms, and up to 64% experienced distress. Apathy was present in 53%, and 36% experienced loneliness. Three- and six-month questionnaires were completed by 77 and 72 patients, respectively. Although a significant increase in loneliness between baseline and six months was seen, this size of this change was not clinically relevant. No other longitudinal changes were found.

Conclusion. The prevalence of distress, depressive symptoms, apathy and loneliness in older patients with metastatic breast cancer is high. Timely detection, for which a geriatric assessment is effective, could potentially improve quality of life.

INTRODUCTION

The number of older patients with breast cancer is rising due ageing of the Western population.[1] Within this older patient population, approximately 20% of patients present with metastatic disease at time of diagnosis or develop distant metastases after being initially treated for early breast cancer.[2] During the last decade, researchers and clinicians have stressed that for older patients, outcomes such as functional status, independence and quality of life are as important as recurrence and survival outcomes.[3,4] This is especially true for patients with metastatic disease, as this stage of disease is incurable. The primary treatment aim in this setting is to maintain quality of life for as long as possible, which may be achieved by controlling the disease via systemic treatment, reducing pain symptoms, and providing psychosocial support where needed.[5]

Older patients with metastatic disease potentially face a variety of problems that impact on quality of life.[6] Disease- and treatment-related symptoms can reduce functional status and threaten the ability to live independently. It was demonstrated that patients over 70 years do not completely regain their physical abilities after surgical and adjuvant treatment for non-metastatic disease.[7,8] Furthermore, their psychological well-being and ability to maintain a social network can be compromised, which may result in poor quality of life and distress.[6] Cross-sectional studies showed that up to 30% of patients with metastatic breast cancer had a depression and 6% had an anxiety disorder, but older patients were explicitly excluded in these studies.[9,10]

As no routine geriatric assessment is performed in this patient selection in most clinical practices, geriatric impairments may be missed. Geriatric characterization of older patients with metastatic breast cancer could help identify unmet needs, improve patient management and eventually quality of life. Therefore, the aims of this study were to assess the prevalence of psychosocial problems, and to assess longitudinal changes in functional status, psychosocial functioning, and quality of life.

METHODS

Design and population

This study is a multicenter prospective cohort study. The study was approved by the Medical Ethics Review Committee of the Leiden University Medical Center. Between February 2015 and September 2018, study participants were recruited at the medical oncology department of four hospitals in the Netherlands. In order to be eligible to participate, patients had to be 70 years or older and have primary or secondary metastatic breast cancer regardless of

time since diagnosis. Since informed consent had to be provided, patients with dementia were excluded. Understanding of the Dutch language was required to answer the self-administered questionnaires.

Patients underwent a baseline geriatric assessment evaluating comorbidity, polypharmacy, nutritional status, functional status, cognition and psychosocial well-being by researchers in geriatric oncology.[11] The geriatric assessment also included questionnaires that were completed by the patient (self-administered questionnaires). Comorbidity and medication use were evaluated with the patient, and confirmed and completed with the medical record.[12] Comorbidity was recorded as number of comorbidities, and polypharmacy was defined as five or more medications. The Malnutrition Universal Screening Tool (MUST) was used to evaluate nutritional status, the "Timed Up and Go (TUG)" test for mobility and the Mini-Mental State Examination (MMSE) for cognition.[13-15] Functional status and psychosocial functioning were further assessed using the self-administered questionnaires described hereafter. Breast cancer-related disease and treatment characteristics were collected from the medical record. Timing of inclusion was categorized as diagnosis of metastases, disease progression or follow-up visit. For patients who were included at disease progression, the new line of treatment was scored. Demographics were included in the questionnaires.

Longitudinal functional status, distress and quality of life were assessed by repeating the questionnaires three and six months after baseline. To minimize patient burden, the remaining questionnaires on psychosocial functioning were only repeated after six months. Patients who completed two or more questionnaire measurements were considered responders.

Self-administered questionnaires

Functional status

Functional status was assessed with the Groningen Activity Restriction Scale (GARS), a non-disease specific instrument including eleven items on activities of daily living (ADL) and 7seven items on instrumental activities of daily living (IADL) with answering options on a four-point scale. Various healthy and patient populations were used to develop the GARS, among which is a cohort of 475 patients with cancer.[16] Initially validated in patients with rheumatoid arthritis, the GARS was recently validated in hospitalized older patients (mean age 78 years).[17-19] The GARS was chosen because it can detect small changes in functional status due to the four point scale which was considered particularly important given the relatively short follow-up of six months, and because it combines ADL and iADL in one hierarchical scale. The eighteen items add up to a score of 18 to 72 points with a higher score corresponding to more disability.[20] Those who scored 4 ("No, I cannot do it fully independently; I can only do it with someone's help") in one or more items on the ADL subscale were considered ADL dependent.[20,21]

Psychosocial functioning

Psychosocial evaluation comprised depressive symptoms, apathy, loneliness and distress. Since the questionnaires have overlapping items, the rates of specific psychosocial problems are not completely independent. This comprehensive approach was still preferred to get a detailed overview as psychosocial wellbeing is particularly important in the metastatic setting. The fifteen-item Geriatric Depression Scale (GDS) was used to screen for depressive symptoms. The GDS is a widely used tool that was specifically developed for older individuals, and validated in older primary care patients (mean age 74 years).[12,22,23] Scores range from 0 to 15, and a cut-off of 5 indicates depressive symptoms.[23] Apathy was assessed with the Starkstein Apathy Scale. This scale was developed and validated in patients with Parkinson's disease, but also used to demonstrate isolated apathy in community-dwelling older persons.[24,25] The fourteen items add up to a score between 0 and 42 with a cut-off of 14 indicating apathy. Loneliness was assessed with the De Jong Gierveld Loneliness scale which is developed and validated in random subsets of general populations from different countries.[26,27] The eleven items add up to a score between 0 and 11 with a cut-off of 3 for moderate loneliness and a cut-off of 9 for severe loneliness.[28] Lastly, distress was evaluated with the Distress Thermometer.[29] Scores of this single-item tool range from 0 to 10 with a score of 0 corresponding to no distress and a score of 10 to maximum distress. A cut-off of 4 yielded optimal sensitivity and specificity in a cohort of ambulatory patients with cancer (median age 56 years), and was used in prior research on distress in older patients with cancer.[30,31]

Quality of life

The European Organization for Research and Treatment of Cancer quality of life questionnaire for patients with cancer was used.[32] The EORTC QLQ-C30 questionnaire is composed of five multi-item scales (physical, role, social, emotional and cognitive functioning) and nine single items (pain, fatigue, financial impact, appetite loss, nausea/vomiting, diarrhea, constipation, sleep disturbance and global quality of life), which can be combined to a summary score.[33] All scores range from 0 to 100. Global health and summary score are presented as these represent general quality of life. A higher score corresponds to better quality of life. In addition, the systemic treatment item of the breast-specific module (EORTC QLQ-BR23) was used.[34] For this outcome, a higher score corresponds to more symptoms.

Statistical analysis

Stata SE 12.0 was used for the statistical analysis. All statistical tests were two-sided with alpha set at 0.05. Patient characteristics are described with frequencies and percentages for categorical variables and age is described as median with interquartile range. The prevalence of baseline psychosocial problems were described for all patients who completed this measurement to minimize response bias. The aforementioned cut-offs were used.

The longitudinal analysis included patients who completed two or more questionnaire measurements; these were considered responders. Patients who completed less than two questionnaire measurements were considered non-responders. Patient characteristics of responders and non-responders were compared using chi-square tests and independent *t*-tests.

Linear mixed models for repeated measures were performed to assess longitudinal changes in functional status, psychosocial functioning and quality life.[35] The advantage of this technique is that it allows the use of incomplete measurements. Continuous questionnaire scores (dependent variable) were analyzed with time as a categorical factor (independent variable). Results are presented as linear beta coefficient (b) with 95% confidence intervals and p values. In a second model, predefined confounders were added as independent variables (the adjusted model).

Longitudinal changes were evaluated for clinical relevance. In accordance with Norman's rule-of-thumb, a change the size of at least half the standard deviation of the baseline mean was considered clinically relevant.[36] In other words, the change was considered clinically relevant if the beta coefficient (b) was larger than half the standard deviation. For the quality of life outcome, the expert opinion based guideline for the interpretation of changes in EORTC QLQ-C30 scores was followed.[37]

Sensitivity analysis

A sensitivity analysis was performed to assess whether changes in frail patients were different compared to non-frail patients. Frailty is a state of increased vulnerability due to decreased physiologic reserve caused by the accumulation of ageing processes across multiple organ systems. It has been demonstrated that more than half of the older patients with cancer are frail or pre-frail, and that these patients are at increased risk of adverse events such as toxicity from systemic treatment, decline in functional status and worse quality of life.[12,38,39]

For this sensitivity analysis, patients were considered frail if impairments in two or more domains were present: somatic (four or more comorbidities or polypharmacy), nutrition (MUST ≥ 2), functional status (ADL dependency or TUG test ≥14 s), cognition (MMSE < 24), and psychosocial domain (GDS ≥ 5). This is a definition of frailty that is frequently used in older patients with cancer.[38]

To assess whether longitudinal changes differed between frail and non-frail patients, interaction between frailty and time was tested for each outcome by adding interaction terms (frailty (yes;no))*time(baseline;3;6 months) to an adjusted model. Alpha was set at 0.10 for the interaction analysis. In order to interpret the interactions, these outcomes were stratified for frailty.

RESULTS

Patients

Overall, 100 patients were included in this study. Patient characteristics are shown in Table 1. Median age was 77 years (interquartile range 73-82 years). Most patients were married (47%), and lived independently at time of inclusion (96%). Thirty-one percent of patients was included at time of diagnosis of metastatic disease, 24% at time of disease progression, and 45% at any other point in the course of their disease. Most patients received first line treatment (53%), whereas 30% received second line treatment and 17% received third or higher lines of treatment at the time of inclusion. Five percent was treated with both endocrine therapy and chemotherapy, 78% was treated with endocrine treatment and 27% received chemotherapy, alone (72%) or in combination with a targeted therapy (23%) (Table 1).

Results of the geriatric assessment are shown in Table 1. Twenty-four percent of patients had zero or one comorbidity, 38% had two to three and 37% had four or more comorbidities. Polypharmacy was present in 58%. Eight percent was at high risk of malnutrition (MUST ≥ 2) and 9% had cognitive impairment (MMSE < 24). Seventy-six percent of patients were able to perform the TUG test, of whom 24% performed the test indicated impaired mobility (≥14 s).

Table 1. Demographic, disease and geriatric characteristics.

	N (%)
Demographics	
Age (median, IQR)	77 (73-82)
Marital status	
Married or living together	39 (47)
Unmarried or divorced	19 (23)
Widow	25 (30)
Unknown	17
Residential situation	
Independent housing	81 (96)
Nursing/Care homes	3 (4)
Unknown	16
Disease characteristics	
Hormone receptor status	
ER and/or PR positive	80 (85)
ER and PR negative	14 (15)
Unknown	6
Timing of inclusion	
Diagnosis of metastatic disease	30 (31)

Table 1. Demographic, disease and geriatric characteristics. (*continued*)

	N (%)
Disease progression	23 (24)
Follow-up visit	44 (45)
Unknown	3
Line of treatment at time of inclusion	
First line	58 (59)
Second line	24 (24)
Third or consecutive line	17 (17)
Unknown	1
Type of treatment at time of inclusion*	
Endocrine therapy	77 (78)
Chemotherapy	27 (27)
Targeted therapy	23 (23)
Unknown	1
Geriatric characteristics	
No. of comorbidities	
0-1	24 (24)
2-3	38 (38)
≥4	37 (37)
Unknown	1
No. of medications	
0-4	44 (44)
≥5	56 (56)
ADL dependency	
ADL independent	50 (59)
ADL dependent	35 (41)
Unknown	15
Risk of malnutrition	
Low	79 (81)
Medium-high	18 (19)
Unknown	3
MMSE score	
24-30	91 (91)
<24	9 (9)
Timed Up and Go test	
≤14 seconds	58 (76)
>14 seconds	18 (24)
Patient was not able to perform the test	23
Unknown	1

*Twenty-eight patients received a combination of treatments.

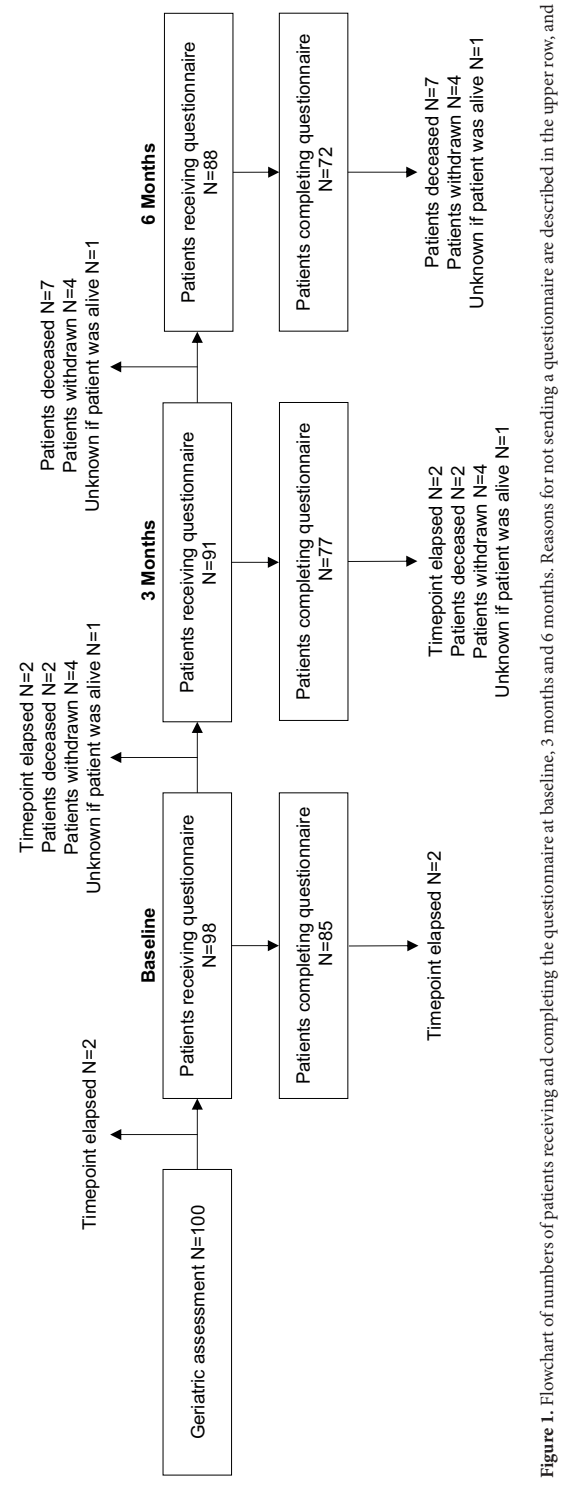

Figure 1. Flowchart of numbers of patients receiving and completing the questionnaire at baseline, 3 months and 6 months. Reasons for not sending a questionnaire are described in the upper row, and reasons for not completing a questionnaire are described in the bottom row.

The flowchart of patients receiving and completing the self-administered questionnaires on functional status, psychosocial functioning and quality of life is shown in Figure 1. The self-administered baseline questionnaires were completed by 85 patients, the three-month questionnaires by 77 patients and the six-month questionnaires by 72 patients. After completing the baseline questionnaires, four patients withdrew from participation due to deteriorating health. During the six-month follow-up of the study, seven patients died. Eighty out of the 100 included patients completed two or more questionnaire measurements, and were included in the longitudinal analysis. Compared to the responders, a higher percentage of the non-responders had cognitive impairment (25% versus 5%, p=0.005) (Table 2).

Table 2. Characteristics of responders and non-responders.

	Responder (N=80)	Non-responder (N=20)	
	N (%)	N (%)	p value
Age (median, IQR)	76 (73-81)	78 (76-83)	0.052
No. of comorbidities			0.119*
0-1	22 (28)	2 (10)	
2-3	31 (39)	7 (35)	
≥4	26 (33)	11 (55)	
Unknown	1	0	
No. of medications			0.158
0-4	38 (48)	6 (30)	
≥5	42 (53)	14 (70)	
Risk of malnutrition			0.140*
Low	65 (84)	14 (70)	
Medium or high	12 (16)	6 (30)	
Unknown	3	0	
MMSE score			0.005
≥24	76 (95)	15 (75)	
<24	4 (5)	5 (25)	
Timed Up and Go test			0.270*
≤14 seconds	46 (79)	12 (67)	
>14 seconds	12 (21)	6 (33)	
Unable to perform the test	18	1	
Unknown	4	1	

Patients were considered responders if at least two questionnaire measurements were completed. *p value without missing values. MUST: Malnutrition Universal Screening Tool; TUG: Timed Up and Go; MMSE: Mini-Mental State Examination.

Results self-administered questionnaires on psychosocial functioning, functional status, and quality of life

At baseline, almost half of the patients (46%) had depressive symptoms (GDS score ≥ 5), and up to 64% of the patients experienced significant distress (Distress Thermometer ≥ 4). Fifty-three percent of patients experienced cognitive-behavioral apathy (Apathy scale ≥ 14), in 36% the apathy appeared in the context of depressive symptoms and/or cognitive impairment, whereas apathy alone was seen in 17%. Overall, 36% of patients experienced loneliness (Loneliness scale ≥ 3), in 28% of patients this was graded as moderate and in 8% of patients this was graded as severe loneliness (Loneliness scale ≥9) (Figure 2). Furthermore, 41% of the patients who completed the baseline self-administered questionnaires were ADL dependent.

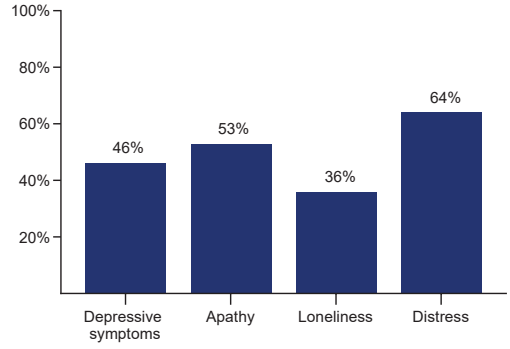

Figure 2. Prevalence of substantial psychosocial impairments at inclusion. Questionnaires (cut-off): Geriatric Depression Scale (5), Starkstein Apathy Scale (14), De Jong Gierveld Loneliness scale (3), and Distress Thermometer (4).

Longitudinal mean scores for functional status, psychosocial functioning and quality of life and results of the linear mixed models analysis to assess longitudinal changes are showed in Supplementary Table 1. An increase in loneliness was observed between baseline and six months in multivariate analysis (adjusted model; b 0.7, 95% CI 0.1-1.2, p=0.018). However, the size of this change was not clinically relevant. No other significant longitudinal changes were found.

Sensitivity analysis

Forty-eight patients were classified as frail and 37 patients as non-frail. For each outcome, interaction between frailty and time was tested to assess whether longitudinal changes differed between frail and non-frail patients. Interaction was found for depressive symptoms and quality of life summary score (Supplementary Table 2). The stratified analysis for depressive symptoms suggests an increase in depressive symptoms in non-frail patients (adjusted model; b 0.7, 95% CI -0.1;1.5, p=0.092), but the size of this change was not clinically relevant. For the quality of life summary score no clear picture emerged upon stratification (Figure 3).

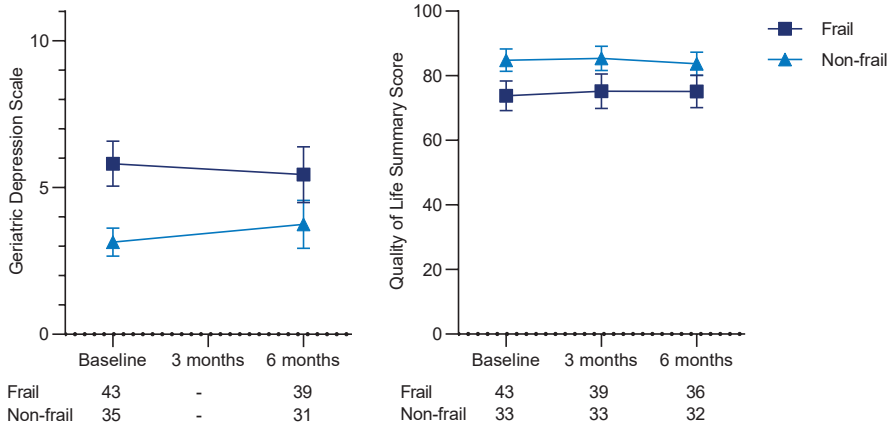

Figure 3. Depressive symptoms and quality of life stratified for frailty. The longitudinal scores are presented as means with 95% confidence intervals. Number of completed questionnaires are described below the graphs. For depressive symptoms, a higher score corresponds to more depressive symptoms. For quality of life summary score, a higher score corresponds to better quality of life.

DISCUSSION

In this study, a geriatric assessment was performed to characterize patients with metastatic breast cancer aged 70 years and older in different domains. The main finding is the high prevalence of psychosocial problems; distress, depressive symptoms, apathy and loneliness. Longitudinally, over a relatively short period of six months, psychosocial functioning did not change nor were changes in functional status and quality of life found that were both significant and clinically relevant.

Psychosocial functioning

Previous studies performed in older patients with cancer reported distress in 41%, and depressive symptoms is 18-26%.[31,40,41] Also, depressive symptoms were demonstrated to be more frequent in older patients with cancer compared to their counterparts without cancer.[40] These studies were all performed in the early stage disease setting, which can explain why higher rates of distress and depressive symptoms were found in the current study.[9] The incidence of depressive symptoms may even be higher, as a recent study has advocated to lower the cut-off of the GDS from 5 to 4 to improve its sensitivity.[42] In contrast, the prevalence of loneliness was similar to that previously reported in the early stage disease setting (35%).[43] Interestingly, the latter study demonstrated that older patients with cancer were equally lonely compared to older patients without cancer.[43] Although apathy is a symptom of neuropsychiatric diseases, it was demonstrated that isolated apathy occurs in community-dwelling older persons. In a cohort of persons aged 75 years or older, 3% of patients had apathy in combination with depressive symptoms or cognitive impairment,

and 8% had isolated apathy.[25] Moreover, it was suggested that this isolated apathy without concomitant depressive symptoms or cognitive impairment, particularly impacts quality of life.[25] In our cohort, isolated apathy was two times as frequent (17%) compared to a cohort of community-dwelling older persons (8%). Furthermore, the varying rates of specific psychosocial problems found in the present study reflect that there is not one psychosocial problem, but that different problems and combinations can be pronounced.

Several factors generally play a role in the psychosocial well-being of older patients with cancer. Cognitive impairment is related to distress and depressive symptoms.[44,45] Many concerns relate to functional status and independence. If physical decline hampers activities in daily living, a patient may lose the ability to live independently.[31,46] Moreover, many patients are informal caregivers for their partner as changes in health policy have increased the reliance on family caregivers. Furthermore, older individuals may have insufficient social support due to personal losses and diminishing social networks.

Although the psychosocial needs of younger patients with breast cancer may be more outspoken in clinical practice, our study emphasizes that older patients also require a psychosocial evaluation.[41,47] Preferably, a multi-domain geriatric assessment is performed as information on different domains (cognition, functional status, social network) helps to understand the nature of the psychosocial problems. If performing a geriatric assessment is not feasible, shorter screening tools may be useful. In any case, our findings underline the importance of asking the patient about psychosocial problems. Despite the gap of knowledge on psychosocial interventions improving quality of life, interventions should best be tailored to specific problems, including psychosocial support and specialized psychosocial care options. Furthermore, to improve psychosocial care, cooperation of health professionals secondary and primary care could play an important role.

Functional status and quality of life

In our cohort of patients aged 70 years and older with metastatic breast cancer, functional status and quality of life were maintained over a six-month period. These results cannot be directly compared to results of other studies. Although randomized clinical trials of metastatic disease are nowadays mandated to include quality of life as outcome (including a physical functioning domain), these studies often lack generalizability as relatively young and fit patients are included.[48] Based on the geriatric characteristics, our study population is probably more representative for all patients in the general population. Findings of the current study are somewhat in line with a previous cohort study of patients with advanced breast cancer of all ages that showed that both functional status and quality of life were maintained from inclusion to eleven weeks after inclusion.[49]

According to our findings, the course of metastatic disease and treatment had little impact on functional status and quality of life over a six-month period. Despite the fact that our study captured only a short follow-up period, seven patients died during the study period and 20 patients dropped out either due to deteriorating health or unknown reason. Assuming that at least some of these patients withdrew or died because of their disease, our findings may suggest that functioning of older patients with metastatic breast cancer remains stable during their disease until a rapid, rather than a gradual, deterioration leads to death. Notably, treatment comprised mainly endocrine treatment as only one in seven patients had hormone receptor negative disease. It should also be mentioned that part of the patients were included more than three months after diagnosis or disease progression (during a follow-up visit).

Strengths of our study are the generalizability of the results, and the availability of extensive baseline and longitudinal information on functioning on different domains. Our study also had limitations. The most important limitations relate to the type of study. Patients were selected who were fit enough to receive treatment and willing and able to participate in this self-administered questionnaire study. Although our study included both fit and frail patients, information on patients who were not included was not available to further evaluate selection. Response bias due to non-response of patients who might have not responded because of deteriorating health and function could not be prevented. Still, the response rate was quite high as 80 out of the 100 patients were considered responders. Second, the heterogeneity of the study population in terms of moment of inclusion, and the relatively short length of follow-up could have mitigated longitudinal changes. Lastly, the GARS has been validated in rheumatoid patients, primary care patients and older hospitalized patients, but not in patients with cancer specifically.

In conclusion, this study showed a high prevalence of distress, depressive symptoms, apathy and loneliness among older patients with metastatic breast cancer. Moreover, the rates of depressive symptoms and apathy are higher than in the healthy older population. Timely detection by a geriatric assessment or specific screening, and interventions for psychosocial problems could potentially increase quality of life for older patients with metastatic breast cancer. Future research is needed to confirm the absence of functional changes over a 6-month period in a larger cohort, to investigate potential risk groups, and to establish effective psychosocial interventions.

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Supplementary Table 1. Changes in functioning over 6 month period using linear mixed-effects models.

		Crude model			Adjusted model*		
	Mean (SD)	b	95% CI	p value	b	95% CI	p value
GDS							
Baseline	4.6 (2.5)						
6 months	4.7 (2.7)	0.1	(-0.5;0.72)	0.719	0.1	(-0.53;0.77)	0.711
Loneliness							
Baseline	2.6 (3.1)						
6 months	3.1 (3)	0.5	(-0.01;1.08)	0.054	0.7	(0.12;1.24)	0.018
Apathy							
Baseline	12.9 (5.4)						
6 months	13.2 (6.4)	0.3	(-0.69;1.27)	0.558	0.4	(-0.52;1.56)	0.330
Distress							
Baseline	4.3 (2.3)						
3 months	4.1 (2.4)	-0.1	(-0.62;0.34)	0.568	-0.2	(-0.73;0.28)	0.376
6 months	4.6 (2.4)	0.3	(-0.24;0.73)	0.325	0.3	(-0.25;0.78)	0.319
GARS (ADL/IADL)							
Baseline	28 (10.3)						
3 months	27.7 (10.3)	-0.2	(-1.57;1.14)	0.759	-0.2	(-1.64;1.24)	0.785
6 months	28.6 (11.7)	0.9	(-0.5;2.25)	0.211	0.9	(-0.55;2.37)	0.221
QLQ global health							
Baseline	73.7 (16.8)						
3 months	72.1 (18.3)	-1.9	(-5.74;1.9)	0.324	-1.8	(-6.08;1.95)	0.313
6 months	72.9 (19.1)	-0.8	(-4.68;3.1)	0.691	-1.1	(-5.49;2.66)	0.496
QLQ summary score							
Baseline	78.6 (14)						
3 months	79.9 (14.9)	0.8	(-1.43;3.09)	0.471	1.1	(-1.74;3.08)	0.586
6 months	79.1 (13.4)	0.1	(-2.2;2.43)	0.923	0.1	(-2.7;2.17)	0.830
QLQ systemic symptoms							
Baseline	18.6 (16.6)						
3 months	17.7 (17.7)	-0.4	(-2.91;2.2)	0.786	-0.8	(-3.38;1.9)	0.583
6 months	18.7 (16.4)	0.6	(-2.06;3.21)	0.669	0.6	(-2.1;3.33)	0.656

*Analyses were adjusted for age, timing of inclusion, comorbidity, polypharmacy, impaired physical function (ADL dependency or TUG test >14 seconds), malnutrition and cognitive impairment at baseline. GDS: Geriatric Depression Scale, GARS: Groningen Activities Restriction Scale, (I)ADL: (Instrumental) Activities of Daily Living, QLQ: Quality of Life Questionnaire.

Supplementary Table 2. Tests for interaction between frailty and time for each functioning score.

Interaction term frailty(yes, no)* time (baseline, 3 months, 6 months)	p value
GDS	0.058
Loneliness scale	0.697
Apathy scale	0.214
Distress scale	0.650
GARS	0.162
QLQ global health	0.571
QLQ summary score	0.067
QLQ systemic symptoms	0.176

GDS: Geriatric Depression Scale, GARS: Groningen Activity Restriction Scale, QLQ: Quality of Life Questionnaire.

Supplementary Table 3. Changes in functioning over 6 month period in frail and non-frail patients using linear mixed-effects models.

	Frail patients						
		Crude model			Adjusted model*		
	Mean (SD)	B	95% CI	p value	B	95% CI	p value
GDS							
Baseline	5.8 (2.5)						
6 months	5.4 (2.9)	-0.3	(-1.2;0.6)	0.484	-0.3	(-1.3;0.6)	0.482
QLQ summary score							
Baseline	73.8 (15.0)						
3 months	75.2 (16.5)	1.2	(-2.0;4.4)	0.468	1.2	(-2.1;4.5)	0.472
6 months	75.1 (14.8)	1.8	(-1.5;5.1)	0.282	1.7	(-1.7;5.1)	0.314
	Non-frail patients						
		Crude model			Adjusted model*		
	Mean (SD)	B	95% CI	p value	B	95% CI	p value
GDS							
Baseline	3.1 (1.4)						
6 months	3.7 (2.2)	0.7	(-0.1;1.4)	0.077	0.7	(-0.1;1.5)	0.092
QLQ summary score							
Baseline	84.8 (9.7)						
3 months	85.4 (10.5)	0.3	(-2.8;3.4)	0.845	-0.2	(-3.5;3.2)	0.926
6 months	83.7 (9.9)	-1.9	(-5.0;1.3)	0.240	-2.6	(-6.0;0.7)	0.124

*Analyses were adjusted for age, timing of inclusion, comorbidity, polypharmacy, impaired physical function (ADL dependency or TUG test >14 seconds), malnutrition and cognitive impairment at baseline. GDS: Geriatric Depression Scale, QLQ: Quality of Life Questionnaire.

9

Summary and general discussion

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Den Haag, mei 2020

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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Appendices

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NEDERLANDSE SAMENVATTING

Een derde van alle patiënten met borstkanker is 70 jaar of ouder en het aantal oudere patiënten met borstkanker zal de komende jaren verder toenemen door vergrijzing van de algemene bevolking. Oudere patiënten vormen een heterogene groep wat betreft comorbiditeit en algehele conditie, twee factoren die van grote invloed zijn op de levensverwachting. Bij oudere patiënten met laag risico borstkanker en een hoog risico op andere sterfte, is deze "concurrerende sterfte" bepalend voor de prognose. Er wordt wel gezegd dat deze patiënten overlijden mét de borstkanker in plaats van aan borstkanker. Dit betekent ook dat sommige oudere patiënten een beperkte winst hebben van standaardbehandelingen zodat het gerechtvaardigd kan zijn om onderdelen van de standaardbehandeling achterwege te laten.

Onderzoek heeft bijvoorbeeld aangetoond dat de behandelwinst van radiotherapie na een borstsparende operatie in een bepaalde selectie oudere patiënten met borstkanker zo beperkt is dat deze achterwege kan blijven.[1-3] Wat betreft het nalaten van primaire chirurgie suggereren onderzoeken dat primaire endocriene therapie een even goede behandeling is bij patiënten met een zeer beperkte levensverwachting. Het blijft echter lastig de juiste patienten voor gereduceerde behandeling te selecteren aangezien er geen harde selectiecriteria zijn.[4] Tot slot kan het zo zijn dat de bijwerkingen of andere nadelen van een behandeling voor een individuele patiënt zelf niet opwegen tegen een beperkte behandelwinst. Met het oog op kwaliteit van leven kan het weglaten van een behandeling voor deze patiënten een goede keuze zijn.

In dit proefschrift onderzochten we borstkanker specifieke uitkomsten en andere sterfte in een representatief cohort oudere patiënten. Daarnaast onderzochten we het effect van standaardbehandelingen. We maakten gebruik van een grote dataset van de Nederlandse Kanker Registratie met meer dan 18,000 patiënten van 70 jaar of ouder. Aangezien alle patiënten met borstkanker in Nederland worden geregistreerd is het gebruikte cohort per definitie representatief voor de ware patiëntenpopulatie. Hierdoor zijn de resultaten goed van toepassing op de oudere patiënt in de dagelijkse praktijk.

In deel I hebben we het risico op een borstkanker recidief, borstkanker gerelateerde sterfte en andere sterfte bestudeerd gebaseerd op leeftijd en comorbiditeit. In deel II hebben we het effect van het weglaten van onderdelen van de standaardbehandeling onderzocht en de barrières die patiënten ervaren en de faciliterende factoren die hierbij een rol spelen. In deel III worden resultaten van een prospectieve cohortstudie naar geriatrische uitkomsten bij oudere patiënten met gemetastaseerde borstkanker beschreven.

Deel I: Evaluatie van borstkanker specifieke uitkomsten en andere sterfte

Het risico op sterfte aan andere oorzaken dan borstkanker is meer uitgesproken in de algemene patiëntenpopulatie dan in de selectie fitte en relatief jonge oudere patiënten in gerandomiseerde onderzoeken.[5] Dit is relevant omdat een hoog risico op andere sterfte het risico op een borstkanker recidief en borstkanker sterfte in theorie kan verkleinen. Daarnaast is het voor de besluitvorming belangrijk het risico op overlijden aan borstkanker te interpreteren in de context van het risico op overlijden aan andere oorzaken.

In hoofdstuk 2 bestudeerden we de relatie tussen hogere leeftijd en het risico op een locoregionaal of afstandsrecidief in een op de populatie gebaseerd registratie cohort met meer dan 18,000 patiënten van 70 jaar of ouder met niet-gemetastaseerd borstkanker. Ondanks het hoge risico op andere sterfte hadden patiënten van 75-79 jaar een hoger risico op een afstandsrecidief dan de 70-74-jarigen, na correctie voor verschillen in tumorkenmerken en behandeling. Deze bevinding geeft aan dat sommige patiënten in de leeftijdscategorie 75-79 jaar onderbehandeld worden en mogelijk baat hebben bij intensievere behandeling. Het hoge concurrerende sterfterisico dat werd gevonden benadrukt hoe belangrijk het is om onderscheid te maken tussen oudere patiënten met een hoog en met een laag risico op andere sterfte. Dit is nodig om de juiste behandeling te kunnen bepalen voor een individuele patiënt, met name als het gaat om adjuvante behandelingen waarbij de verwachte behandelwinst klein is.

In hoofdstuk 3 bestudeerden we de borstkanker sterfte en andere sterfte na het optreden van een locoregionaal recidief of een metastase op afstand. We vonden dat overlijden aan borstkanker nagenoeg alleen optreedt na het ontwikkelen van een metastase op afstand. Een locoregionaal recidief was een voorspeller voor hogere borstkanker sterfte, maar het aandeel borstkanker sterfte na een locoregionaal recidief op de totale borstkanker sterfte was zeer beperkt door het lage percentage locoregionale recidieven. Voor alle leeftijdscategorieën gold dat de borstkanker sterfte overduidelijk de prognose bepaalde na het optreden van een metastase op afstand ondanks relatief hoge 10-jaars sterfte aan andere doodsoorzaken: 24% in patiënten van 75-79 jaar en zelfs van 73% in patiënten van 80 jaar of ouder. Hoofdstuk 2 en 3 benadrukken dat het essentieel is voor predictie modellen om rekening te houden met andere sterfte bij de voorspelling van borstkanker specifieke uitkomsten en om andere sterfte als aparte uitkomst te presenteren.

Er was nog geen eenduidig antwoord op de vraag welke comorbiditeit score het beste te gebruiken in predictie modellen.[6] In hoofdstuk 4 vergeleken we de voorspellende waarde voor andere sterfte van de Charlson Comorbidity index met de voorspellende waarde van het aantal comorbiditeiten.[7] Beide scores hadden voorspellende waarde voor andere sterfte in aanvulling op de voorspelling van leeftijd alleen. Onze belangrijkste bevinding was dat

de voorspellende waarde van de Charlson Comorbidity index voor 5-jaars andere sterfte vergelijkbaar was met de voorspellende waarde van het aantal comorbiditeiten. Op basis van deze resultaten in combinatie met het feit dat het tellen van het aantal comorbiditeiten eenvoudiger is, zouden wij willen betogen het aantal comorbiditeiten als score te gebruiken bij de ontwikkeling van nieuwe predictie modellen voor oudere patiënten met borstkanker.

Deel II: Weglaten van behandelingen in geselecteerde oudere patiënten

In het tweede gedeelte van dit proefschrift onderzochten we het effect van het achterwege laten van onderdelen van de standaardbehandeling van vroeg stadium borstkanker op het recidief risico en op de overleving in subgroepen. In de dagelijkse praktijk wordt de keuze voor deze behandelingen gemaakt op basis van meerdere factoren, namelijk de ziekte kenmerken, leeftijd, comorbiditeit en andere aspecten van de algehele conditie en het functioneren van een patiënt. Gegevens over deze laatste factoren zijn over het algemeen niet beschikbaar of van matige kwaliteit in observationele datasets. Dit heeft als consequentie dat conventionele statistische technieken bij het onderzoeken van behandeleffect helaas niet kunnen corrigeren voor ongemeten confounders zoals bijvoorbeeld performance status, wat leidt tot onbetrouwbare resultaten.[8]

Als oplossing hiervoor hebben wij een nieuwe methodologie toegepast genaamd de instrumentele variabele (IV) methode, waarmee confounding door ongemeten factoren kan worden vermeden. Deze methode creëert namelijk een pseudo-gerandomiseerde situatie als aan bepaalde voorwaarden wordt voldaan. Ziekenhuis werd gekozen als instrumentele variabele omdat bekend is dat de behandeling van borstkanker bij oudere patiënten varieert tussen ziekenhuizen. Tegelijkertijd is de verwachting dat oudere patiënten met borstkanker in verschillende ziekenhuizen vergelijkbaar zijn.

In hoofdstuk 5 onderzochten we het effect van weglaten van radiotherapie na een borstsparende operatie op het locoregionaal recidief risico in patiënten van 75 jaar of ouder met stadium T1-2N0 borstkanker. Volgens de IV-methode deden we dit door uitkomsten te vergelijken van patiënten die waren behandeld in ziekenhuizen met hogere (96%) en lagere (72%) percentages radiotherapie. Negenendertig procent werd behandeld met endocriene therapie, conform het verwachte percentage op basis van de Nederlandse behandelrichtlijn. Het locoregionaal recidief risico was laag (2.2%-3.2% na negen jaar), zelfs in de patiënten die werden behandeld in ziekenhuizen met lagere percentages radiotherapie (3.2%). Er werd geen associatie gevonden tussen radiotherapie gebruik en locoregionaal recidief risico.

In hoofdstuk 6 onderzochten we het effect van weglaten van primaire chirurgie op de overleving in patiënten van 80 jaar en ouder met stadium I-II hormoonreceptor positief borstkanker. Volgens de IV-methode deden we dit door uitkomsten te vergelijken van patiënten

behandeld in ziekenhuizen met hogere (83%) en lagere (55%) percentages chirurgie. Van alle patiënten die geen primaire chirurgie ondergingen werd 94% behandeld met primaire endocriene therapie. Zowel de 10-jaars relatieve overleving als de absolute overleving was lager voor patiënten behandeld in ziekenhuizen met lagere percentages chirurgie dan in de ziekenhuizen met hogere percentages chirurgie. Wel is belangrijk te noemen dat de overlevingsgrafieken in de eerste vijf jaar niet uiteenliepen.

In hoofdstuk 7 identificeerden we welke barrières en faciliterende factoren patiënten ervaren voor het weglaten van onderdelen van de behandeling van vroeg-stadium borstkanker als deze een beperkte behandelwinst hebben. We organiseerden focusgroepen met patiënten van 70 jaar en ouder die behandeld waren voor borstkanker. Vervolgens werd een survey uitgezet onder een grotere groep. In de survey gaf meer dan de helft van de respondenten aan in te stemmen met het voorstel radiotherapie of een okselklierdissectie weg te laten als dit voorgesteld zou worden door de arts. Bijna alle patiënten vermeldden daarentegen barrières voor het weglaten van primaire chirurgie, vooral door de noodzaak van primaire endocriene therapie als alternatieve behandeling. Barrières voor het weglaten van radiotherapie en een okselklierdissectie waren hoofdzakelijk algemene factoren gerelateerd aan angst voor een recidief, het gevoel suboptimale behandeling te krijgen en sociale support. Geruststelling over de recidief risico's en het betrekken van familieleden voor sociale support zijn daarom belangrijke acties om afzien van deze behandelingen te bevorderen.

Deel III: Geriatrisch assessment en uitkomsten

Het laatste deel van dit proefschrift, hoofdstuk 8, beschrijft de resultaten van een prospectieve cohortstudie naar geriatrische uitkomsten in patiënten van 70 jaar of ouder met gemetastaseerd borstkanker. Bij inclusie werd een uitgebreid geriatrisch assessment gedaan. Vervolgens werden veranderingen in functionele status, psychosociaal functioneren en kwaliteit van leven over een periode van 6 maanden gemeten. Patiënten werden geïncludeerd in vier Nederlandse ziekenhuizen. Bevindingen die in het oog sprongen waren de hogere prevalenties depressieve symptomen en apathie vergeleken met de gezonde populatie ouderen. Hoewel het geriatrische assessment effectief is in het signaleren van dergelijke problemen neemt een volledig geriatrisch assessment veel tijd in beslag, wat een kortere screening tool wenselijk maakt. Hier wordt op dit moment dan ook veel onderzoek naar gedaan. Daarnaast moet het effect van psychosociale interventies op kwaliteit van leven onderzocht worden in toekomstig onderzoek. Onze bevinding dat functionele status en kwaliteit van leven niet veranderden terwijl meerdere patiënten overleden tijdens de studie suggereert dat het functioneren eerder stabiel blijft tot een snelle achteruitgang voor het overlijden dan een graduele achteruitgang van het functioneren. Deze hypothese moet bevestigd worden in een groter cohort.

DISCUSSIE EN TOEKOMST PERSPECTIEVEN

Geïndividualiseerde behandeling

Borstkanker is niet één enkele ziekte entiteit. De prognose hangt sterk af van de tumor biologie en het stadium bij diagnose.[9] Door de introductie van het screenend bevolkingsonderzoek is het percentage premaligne afwijkingen met uitstekende prognose sterk toegenomen.[9,10] Hierdoor is de variatie in prognose nog meer uitgesproken geworden. Geïndividualiseerde behandeling, ook wel zorg op maat genoemd, houdt in voor elke patiënt de behandeling te kiezen die voor die individuele patiënt het meest geschikt. Predictiemodellen kunnen geïndividualiseerde behandeling bevorderen door het voorspellen van het recidief risico op basis van tumor en patiënten kenmerken. Het te verwachten behandeleffect kan ook ingeschat worden op basis van deze informatie. De behandeling kan soms verder geïndividualiseerd worden op basis van het genetisch risicoprofiel. Een groot gerandomiseerd onderzoek toont aan dat de Mammaprint de voorspelling van het recidief risico in aanvulling op de klassieke voorspellende factoren kan verbeteren in patiënten bij wie chemotherapie wordt overwogen.[11] Vooralsnog wordt de test alleen aanbevolen bij patiënten van jonge en middelbare leeftijd bij wie twijfel bestaat over wel of geen chemotherapie. Intussen loopt de individualisering van de behandeling van oudere patiënten achter. Tot dusver was het niet goed mogelijk om het effect van leeftijd en algemene conditie op borstkanker uitkomsten en behandeleffect te specificeren en diende de behandelend arts dit effect zelf in te schatten. Daarnaast wordt de keuze voor behandeling bij oudere patiënten vaak beïnvloed door de behandelcultuur in een land. Registratie data laat substantiële variatie in behandeling zien tussen verschillende landen en zelfs regio's. [12-14]

Voorspelling prognose verbeteren

De PREDICT tool is op het moment de meest gebruikte predictietool voor patiënten met borstkanker.[15] Alhoewel de tool het percentage andere sterfte presenteert naast het algehele sterfte risico, zijn deze schattingen niet gecorrigeerd voor comorbiditeit en dus niet voor het concurrerende sterfte risico. Uit een validatiestudie in patiënten van 65 jaar en ouder bleek dan ook dat de algehele sterfte onderschat werd in patiënten met nul tot één comorbiditeit. Daartegenover werd de algehele sterfte juist toenemend overschat in patiënten met twee en meer comorbiditeiten.[6] In andere woorden, deze tool houdt er geen rekening meer dat een patiënt van 75 jaar met twee comorbiditeiten een hoger risico op overlijden aan andere oorzaken heeft dan een patiënt die even oud is zonder comorbiditeit. De vervolgvraag rijst welke comorbiditeit score het beste gebruikt kan worden in een toekomstig predictiemodel. In hoofdstuk 4 vonden we dat de originele Charlson Comorbidity Index even goed andere sterfte voorspelde als het aantal comorbiditeiten. Vanwege het gemak zouden wij daarom pleiten voor het gebruik van aantal comorbiditeiten bij de ontwikkeling van een nieuw predictiemodel voor oudere patiënten met borstkanker.

Het is goed om op te merken dat in de literatuur is beschreven dat de invloed van comorbiditeit op resterende levensverwachting na 70 jaar steeds meer afneemt.[16] De oudere bevolking is van nature een heterogene groep door variatie in het verouderingsproces. Dit betekent dat ouderen met dezelfde kalenderleeftijd verschillen in fysiologische leeftijd met verschillen in fysieke reserve, comorbiditeit en functioneren. Echter, de nieuwe bevinding dat voorspellende waarde van comorbiditeit op resterende levensverwachting afneemt met de leeftijd suggereert dat deze variatie in fysiologische leeftijd vanaf een zekere leeftijd ook minder wordt. Als deze hypothese juist is, moet ook rekening worden gehouden met deze interactie tussen leeftijd en comorbiditeit in predictiemodellen. Tot slot kunnen geriatrische parameters waarschijnlijk ook de voorspelling van andere sterfte bij oudere patiënten met borstkanker verbeteren, zoals in modellen die gebruikt worden voor het voorpellen van de algemene levensverwachting in gezonde individuen.[17] Toekomstig onderzoek is nodig om de toegevoegde waarde van geriatrische parameters specifiek in patiënten met borstkanker te onderzoeken.

Voorspelling behandeleffect verbeteren

Naast de prognose geeft de PREDICT-tool ook de verwachte behandelwinst van adjuvante behandelingen op basis van verschillende gerandomiseerde data.[18,19] Echter, er moet rekening mee gehouden worden dat deze resultaten komen uit historische trials die bijna geen oudere patiënten includeerden. Bovendien waren de oudere patiënten die werden geïncludeerd ook nog eens een fitte selectie. Dit heeft tot gevolg dat het verwachtte behandeleffect dat de PREDICT-tool presenteert waarschijnlijk een overschatting is van het ware effect voor de meeste oudere patiënten in de dagelijkse praktijk. In de afgelopen jaren is het verbeteren van de bewijslast voor behandelingen van borstkanker bij oudere patiënten een belangrijk aandachtspunt geweest. Een van de belangrijkste doelen was, en is nog steeds, om subgroepen oudere patiënten te definiëren bij wie het weglaten van onderdelen van de standaardbehandeling van vroeg stadium borstkanker niet leidt tot slechtere uitkomsten. Aangezien het onwaarschijnlijk is dat er nog gerandomiseerde data beschikbaar komt, worden valide methoden gezocht om deze subgroepen te kunnen definiëren op basis van beschikbare observationele data.

Instrumentele variabele methodologie

Recent is een nieuwe veelbelovende methodologie geïntroduceerd voor het op een valide manier onderzoeken van behandeleffect in grote observationele datasets. De instrumentele variabele (IV) methode kan confounding door zowel gemeten als ongemeten factoren vermijden door een pseudo-gerandomiseerde situatie te creëren mits aan drie voorwaarden kan worden voldaan; de IV is geassocieerd met de behandeling (eerste voorwaarde), maar niet gerelateerd aan confounding factoren (tweede voorwaarde) of gerelateerd aan de uitkomst anders dan via de IV (derde voorwaarde). Geografische gebieden worden vaak gebruikt

als IV, omdat behandelvariatie wordt gezien tussen landen en regio's die niet verklaard kan worden door alleen case-mix. De IV-methodologie is in het bijzonder veelbelovend bij onderzoek naar behandeleffect in oudere patiënten met borstkanker, omdat directe vergelijking van behandelde en niet-behandelde patiënten gevoelig zijn voor confounding door ongemeten factoren gerelateerd aan algemene gezondheid en functioneren.[8]

In hoofdstuk 5 en hoofdstuk 6 van dit proefschrift pasten we de IV-methodologie toe waarbij we gebruik maakten van ziekenhuis als IV. Dit houdt in dat uitkomsten van patiënten behandeld in ziekenhuizen met verschillende behandelpercentages (hogere, gemiddelde en lagere) werden vergeleken. Onze resultaten in hoofdstuk 5 tonen aan dat het gebruik van radiotherapie na een borstsparende operatie verminderd kan worden in patiënten van 75 jaar of ouder met T1-2N0 borstkanker zonder het risico op een locoregionaal recidief te verhogen. De optie om radiotherapie achterwege te laten bij patiënten van 70 jaar of ouder met tumoren tot 3 centimeter die behandeld worden met adjuvante endocriene therapie is al langer opgenomen in internationale richtlijnen op basis van gerandomiseerde data.[1,2,3] Uit onderzoek blijkt echter dat er nauwelijks een afname van radiotherapie wordt gezien. Zorgen om de generaliseerbaard van de resultaten naar de algemene patiënten populatie met name wat betreft de therapietrouw bij endocriene therapie worden genoemd als een belangrijke reden voor de persisterende radiotherapie toepassing.[20] De resultaten van onze studie spreken deze zorgen om een hoger risico op een locoregionaal recidief in de afwezigheid van systemische therapie tegen, aangezien slechts een derde werd behandeld met endocriene therapie conform de Nederlandse behandelrichtlijn.[21]

In hoofdstuk 6 vonden we daarentegen dat het verhogen van het percentage primaire chirurgie de overleving kan verbeteren voor de patiënten van 80 jaar of ouder met stadium I-II hormoongevoelig borstkanker. Wat we wel constateerden was dat de overleving pas uiteenliep na de eerste vijf jaar. Hieruit kan opgemaakt worden dat primaire endocriene therapie als alternatief voor chirurgie gerechtvaardigd is bij patiënten met een levensverwachting van vijf jaar of minder. Dit is een ruimere indicatie dan de twee tot drie jaar resterende levensverwachting die momenteel wordt aanbevolen in internationale richtlijnen gebaseerd op historische trials.[4,22] Toch moeten ook de nadelen van primaire endocriene therapie, meest belangrijk de potentiële bijwerkingen, niet onderschat worden.

Over het geheel genomen werkte de IV-methodologie in ons populatie gebaseerde cohort goed. Om te beginnen was er genoeg behandelvariatie om groepen te maken met substantiële verschillen in behandelpercentage (ongeveer 25% tussen de hogere en lagere behandelpercentage groepen). In andere woorden, de IV was sterk genoeg om gevolgtrekkingen te doen over het effect op de uitkomst. Ten tweede, aangezien er slechts enkele kleine verschillen tussen de drie IV-groepen werden gezien kan ervan uit worden gegaan dat de verschillen

in ongemeten factoren ook minimaal waren. Aan de andere kant betekenen deze kleine verschillen tussen de IV-groepen ook dat de IV niet volledig aan alle voorwaarden kon voldoen. Om een voorbeeld te geven, in hoofdstuk 6 waren de patiënten die waren behandeld in ziekenhuizen met lagere percentages primaire chirurgie iets ouder dan de patiënten die waren behandeld in ziekenhuizen met hogere percentages primaire chirurgie. Dit betekent dat resterende confounding niet geheel uitgesloten kan worden. Daarnaast vermindert de IV-analyse de statistische power. Dit is af te leiden aan het wijde betrouwbaarheidsinterval dat werd gezien in hoofdstuk 5. Enorme datasets zijn daarom het meest geschikt voor een IV-analyse.

Het "*European Registration of Cancer Care (EURECCA)*" consortium is geïnitieerd om data van kankerregistraties van verschillende landen in Europa te combineren met als doel de behandeling en uitkomsten te vergelijken. Helaas verhinderen verschillen in gezondheidszorgsystemen en dientengevolge de verschillen in patiënten en borstkanker subtypen tussen de landen een formele IV-analyse. Natuurlijk blijft een dergelijke vergelijking tussen de landen waardevol om richting te geven aan toekomstige studies. Al met al is de IV-methodologie een geschikte analysemethode als confounding door ongemeten factoren waarschijnlijk wordt geacht. Het lijkt echter te optimistisch om in een klinische dataset een IV te vinden die aan alle voorwaarden voldoet en voldoende statistische power biedt.[23]

Toekomstig onderzoek naar behandeleffect

Randomized controlled trials (RCTs) blijven de gouden standaard om behandeleffect te onderzoeken, zelfs in de heterogene oudere populatie. Het is echter prioriteit de externe validiteit van RCTs te verbeteren zodat de resultaten ook daadwerkelijk toepasbaar zijn op de patiënt in de dagelijkse praktijk. Dit kan alleen worden bereikt door een representatieve selectie van de oudere populatie te includeren, inclusief kwetsbare patiënten en de allerouden. Op deze manier kunnen namelijk gestructureerde subgroep analyses worden gedaan gebaseerd op algehele gezondheid. Als gevolg van behandel bias worden oudere patiënten behandeld met nieuwe behandelingen die in hun doelgroep nog niet getest zijn. Tegenstrijdig genoeg persisteert bijvoorbeeld de toepassing van radiotherapie na een borstsparende operatie, terwijl nota bene RCTs hebben aangetoond dat de absolute behandelwinst zeer laag is.[20,24] Dit geeft weer dat als een behandeling eenmaal standaard is, het erg lastig is om het gebruik van deze behandeling te verminderen oftewel te de-implementeren. Het is niet haalbaar en niet realistisch om een RCT te herhalen met als enige doel het doen van subgroep analyses gebaseerd op algehele gezondheid. Ondanks de dwingende vraag en oproep om dergelijke secondaire trials zijn er slechts enkele opgezet.[25,26] Dit is niet verrassend gezien de tijd en kosten van een RCT. Misschien zouden beleidsmakers en fondsen de inclusie van oudere en kwetsbare patiënten moeten verplichten in een primaire trial of een secundaire trial verplicht stellen. Verder is de behandelend arts zich misschien niet

bewust dat de matige inclusie van oudere patiënten deels komt door hun eigen beslissing deze patiënten niet te includeren. Het komt frequent voor dat artsen deelname aan een studie voor hun eigen patiënten als een te grote belasting inschatten of de aanname doen dat een patiënt zelf niet zou willen deelnemen.

Patiënten laten zich niet gemakkelijk randomiseren voor reguliere standaardbehandelingen. Zo moest de *ESTEem ("Endocrine +/- Surgical Therapy for Elderly women with Mammary Care") trial* vroegtijdig sluiten door tegenvallende inclusie. In deze gevallen kan een prospectief cohort met gelijk behandelde patiënten een goed alternatief zijn. Een dergelijk cohort kan beschouwd worden als een single-arm trial. Een mooi recent voorbeeld is de "*Tailored treatment in Older Patients*" *(TOP)*-1 studie welke een prospectief cohort omvat van patiënten van 70 jaar of ouder met laag risico borstkanker die geen radiotherapie of endocriene therapie na een borstsparende operatie ondergingen.[27] Alle patiënten in deze studie ondergaan een geriatrische screening. Daarnaast is een van de secundaire doelen om te kijken naar subgroepen op basis van algemene gezondheid.

Voorspelling behandelschade verbeteren

Tot slot moet ook de voorspelling van negatieve effecten worden verbeterd om de behandeling verder te individualiseren. Oudere patiënten hebben een grotere kans op toxiciteit en functionele achteruitgang dan jongere patiënten. Daar staat tegenover dat de kwaliteit van leven door oudere patiënten vaak steeds belangrijker wordt gevonden dan de resterende levensduur. Het risico op bijwerkingen en achteruitgang in functioneren is dus essentiële informatie voor het kiezen van een behandeling op maat. De "*Cancer Research and Aging Group*" heeft een tool ontwikkeld waarmee het risico op toxiciteit van chemotherapie kan worden voorspeld. Deze tool bevat geriatrische parameters als voorspellende factoren.[28] Dezelfde onderzoeksgroep demonstreerde in een andere studie een achteruitgang in fysiek functioneren bij patiënten van 70 jaar of ouder die behandeld werden met chemotherapie.[29]

Risicogroepen voor bijwerkingen en achteruitgang in functioneren na een operatie, radiotherapie of bij endocriene therapie moeten worden onderzocht. Deze vragen worden hopelijk spoedig beantwoord door resultaten van lopende prospectieve cohortstudies naar functionele uitkomsten. De "*Bridging the Age Gap*" is een initiatief in het Verenigd Koninkrijk dat zich focust op de chirurgische behandeling van oudere patiënten met borstkanker.[30] In een cohort van meer dan 3000 patiënten van 70 jaar of ouder wordt het effect van chirurgische behandelingen op functionele status en kwaliteit van leven bestudeerd. Een vergelijkbare studie loop momenteel in Nederland. De "*Climb Every Mountain*" studie omvat een prospectief cohort van patiënten van 70 jaar of ouder waarin veranderingen in functioneren en kwaliteit van leven over de tijd worden onderzocht. Deze dataset wordt ook gebruikt in de "*Prediction of Outcome and Toxicity in older patients with bREasT cancer*

(PORTRET)" studie voor het ontwikkelen van een nieuwe predictie tool die specifiek ontwikkeld wordt voor oudere patiënten. In deze tool zullen het concurrerende sterfterisico, toxiciteit en functioneren als uitkomsten worden opgenomen. Alle patiënten in deze prospectieve cohortstudies zijn bij inclusie uitgebreid in kaart gebracht door middel van een geriatrisch assessment. In het bijzonder is het interessant welke geriatrische parameters een voorspellende waarde zullen hebben.

Het laatste hoofdstuk van dit proefschrift geeft een voorbeeld hoe functionele uitkomsten bestudeerd kunnen worden. Ondanks de geslaagde inclusie van zowel fitte als kwetsbare oudere patiënten, ondervonden we hoe moeilijk het is selectie bias en response bias te voorkomen. Deelnemende patiënten waren niet alleen fit genoeg voor behandeling, maar waren ook bereid en in staat om deel te nemen aan een survey die ze zelf moesten invullen. Patiënten met een slechte algehele gezondheid en beperkt functioneren zullen waarschijnlijk ondervertegenwoordigd zijn. Dit zijn de uitdagingen voor toekomstige prospectieve cohortstudies: om de juiste patiënten te includeren en om selectieve uitval in de follow-up zo veel als mogelijk te beperken. In de lopende "*Triaging Elderly Needing Treatment (TENT)*" studie ondergaan alle oudere patiënten die een grote behandeling nodig hebben, ongeacht de onderliggende ziekte, een geriatrisch assessment voorafgaand aan de behandeling. Naderhand worden gegevens over korte termijn uitkomsten verzameld uit het patiëntendossier en telefonisch door gespecialiseerde geriatrie verpleegkundigen bij de patiënt. [31] Een dergelijke systematische benadering kan de inclusie van kwetsbare patiënten verbeteren. Dat is namelijk essentieel om te bepalen welke kwetsbare patiënten een hoog risico hebben op negatieve uitkomsten. Een voorbeeld van response bias is het wegvallen van patiënten met achteruitgang in functioneren uit de follow-up juist door die achteruitgang. Telefonische evaluatie momenten of thuisbezoeken kunnen daarom helpen om deelname aan een studie minder belastend te maken en op die manier de response bias te verminderen.

Kortom, het aantal oudere patiënten met borstkanker zal in de aankomende jaren snel groeien. Predictie tools zijn hard nodig om de individualisatie van de behandeling van oudere patiënten te verbeteren. Alleen op die manier kan zowel onderbehandeling als overbehandeling zo veel mogelijk voorkomen worden. Gelukkig worden er op dit moment predictie tools ontwikkeld die specifiek zijn gericht op oudere patiënten met de voor hen relevante uitkomsten. De grootste uitdaging blijft om over de juiste data te beschikken om voorspellingen te doen over prognose en behandeleffect voor subgroepen van patiënten op basis van leeftijd, comorbiditeit en functioneren.

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CURRICULUM VITAE

Anna Zoë de Boer was born in The Hague on February 24, 1992. She graduated cum laude for her pre-university degree at the Christelijk Gymnasium Sorghvliet where she specialized in Science, Engineering and Health. In 2010, she started medical school at Leiden University. During her Master's degree she completed an internship in General Surgery at Muhammadiyah Hospital in Yogyakarta, Indonesia. She completed her final internship at the department of Internal Medicine at the HagaZiekenhuis in The Hague and graduated in 2017.

After graduation she started her PhD at the department of Surgery and the Geriatric Oncology Research Group at Leiden University Medical Center under the auspices of prof. dr. Portielje, dr. Bastiaannet and dr. Liefers. She studied the interplay between breast cancer mortality and other-cause mortality in older patients with low-risk breast cancer and the effect on absolute treatment benefits, using data from the Netherlands Cancer registry. The results are described in this thesis. In 2020 she started as a resident (ANIOS) at the department of Internal Medicine at the HagaZiekenhuis in the Hague.

Currently, Anna lives in The Hague and in January 2022, she started as a resident (AIOS) at the department of Internal Medicine at the Leiden University Medical Center and the HagaZiekenhuis under the supervision of prof. de Fijter and dr. Lagro.

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