Patterns of care and prognosis of older women with breast cancer

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Chapter 5

Impact of comorbidity on outcome of older breast cancer patients: a FOCUS cohort study

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ABSTRACT

Purpose. Older breast cancer patients often suffer from comorbid diseases, which may influence life expectancy. The aim of this study was to assess the impact of specific comorbidities on overall survival and distant recurrence free period (DRFP) of older breast cancer patients.

Methods. Patients were included from the population-based FOCUS cohort, which contains 3,672 breast cancer patients aged 65 years or older. The impact of comorbidity on overall survival and DRFP were analyzed using multivariable Cox proportional hazard models and Poisson regression models.

Results. Median follow-up time was 6.8 years (range 0-14.0). Irrespective of age, the number of comorbid diseases was significantly associated with worse overall survival (hazard ratio (HR) per increasing number of comorbid diseases: 1.20, 95% confidence interval (CI) 1.13-1.27 and HR 1.09, 95% CI 1.05-1.13 for age <75 and age ≥75 respectively). Median follow-up time for DRFP was 5.7 years (range 0-14.0). An increasing number of comorbid diseases was associated with a decreasing risk of metastases among patients aged ≥75 (HR 0.94, 95% CI 0.87-1.02), whereas an increasing risk was shown for patients aged <75 (HR 1.09, 95% CI 1.01-1.19).

Conclusions. This study shows that in older breast cancer patients overall survival and DRFP are influenced by comorbidity. This reiterates that patient outcome is not only influenced by breast cancer, and non-cancer related factors should be taken into account.

INTRODUCTION

Breast cancer among the elderly comprises 40% of all breast cancer cases in the Western society.[1] Due to age and other restrictions to inclusion of older patients in clinical trials, there is a lack of evidence for the treatment of this specific and growing patient category.[2]

One of the most important differences between older and younger patients is the heterogeneity of the former in terms of general fitness. Furthermore, older patients have a high competing risk of mortality, which is the risk of dying from another cause than cancer before developing a cancer-specific event, such as a recurrence or cancer-related death.[3] This competing risk of death unsurprisingly increases with age, but is also affected by the presence and severity of comorbid diseases.[4] With increasing age, the proportion of breast cancer deaths among all-cause mortality has been shown to decrease.[5-7]. In contrast, recently a higher cumulative incidence of distant recurrences and breast cancer mortality has been reported among the oldest patients (≥75 years).[5-8]

With the knowledge that competing risk of mortality increases with age and comorbidity[4], and the number of prevalent comorbid diseases increase with age in general[9], the competing risk of other cause-mortality should always be taken into account when studying breast cancer specific endpoints among older patients. When studying older patients included in clinical trials (with or without age restrictions), one should constantly be aware of the effect of selection, as only the fittest and most motivated patients will be included in trials.[10,11] Therefore, to be able to get a reliable impression of the 'real world' patient, observational cohorts with detailed information on patient, disease, treatment and follow up, are pivotal when studying the older cancer patient.

The aim of the present study is to assess the impact of the extent of comorbidity and specific comorbid diseases on overall survival and distant recurrence free period in two age strata of a large population-based cohort of older breast cancer patients in The Netherlands.

METHODS

Patients

The FOCUS cohort study (Female breast cancer in the elderly; Optimizing Clinical guidelines USing clinico-pathologocial & molecular data) is based on the National Cancer Registry in The Netherlands, which contains data of all newly diagnosed malignancies. The FOCUS database contains information on all consecutive female

patients aged 65 years and older with invasive and in situ breast cancer who were diagnosed between 1997 and 2004 in the South-West part of the Netherlands. Trained personnel reviewed the charts of these patients, and collected information on tumor characteristics, specific treatments, comorbidity, adverse events, geriatric parameters, and recurrence.

All comorbidity, as present at the time of diagnosis, was recorded according to the categories in the ICD-10 classification[12], on the basis of the case record forms and extracted from the medical charts by an experienced research nurse.

Follow up on survival status was available until January 1st 2011 through linkage of cancer registry data with municipal population registries. For this study, all patients with breast cancer stage I–IV and in situ of all histological subtypes were included. Stage was described using the tumor-node-metastasis (TNM) classification, as valid in the year of diagnosis. If the data on T- or N- stage from pathological reports were missing (pT or pN), data from clinical reports (cT or cN) were used to complete the combined TNM stage. Hormone receptor status was analyzed in a combined dichotomized variable for estrogen receptor status and/or progesterone receptor status. If patients received breast-conserving surgery followed by mastectomy, the most extensive surgery was used for analyses. Axillary surgery was defined as a sentinel node procedure or an axillary lymph node dissection, and dichotomized for analyses. Again, the most extensive surgery was used for the analyses. To compare different age groups, patients were categorized into two groups: 65–74 years and 75 years or older, as discussed at the meeting of the International Society of Geriatric Oncology (SIOG) in 2009[13] and in line with other publications.[5,7] The number of comorbid diseases was categorized in three groups: 0 or 1 concomitant diseases, 2-4 concomitant diseases, and 5 or more concomitant diseases. Specific groups of comorbid disease were defined according to the ICD-10 classification.[12] Endocrine diseases, psychiatric diseases, neurologic diseases, cardiovascular diseases, respiratory diseases, digestive diseases and musculoskeletal diseases were considered as the clinically most important subgroups defined in the ICD-10 and were analyzed separately. The remaining comorbidities were defined as a category “other comorbidity”.

Statistical analyses

The primary study endpoints were overall survival and distant recurrence free period (DRFP), defined as time from breast cancer diagnosis to death of any cause and time to first distant recurrence respectively.

Overall survival and DRFP were calculated using univariable and multivariable Cox Regression models. All multivariable analyses were adjusted for age (continuous), tumor stage (in situ, I, II, III, IV or missing), tumor grade (1, 2, 3 or missing),

hormone receptor status (negative, positive or missing), morphology (ductal, lobular or other/unknown), local surgical treatment (none, breast conserving surgery or mastectomy), axillary surgery (dichotomous), radiation therapy (dichotomous), endocrine therapy (dichotomous) and chemotherapy (dichotomous). Analyses of specific comorbid disease categories according to the ICD-10 were additionally adjusted for the number of additional comorbidities. In case of missing data, patients were not excluded from the analyses, but analyzed in a separate group. For DRFP analyses, patients with primary metastatic disease (stage IV) were excluded. Also for DRFP analyses, sensitivity analyses using Poisson regression models were performed, comparing incidence rates of distant recurrences per 1000 person years, taking account of the actual follow-up time of each patient, to rule out the impact of short life expectancy of the oldest patients with more comorbidity.

In all statistical analyses, a p-value smaller than 0.05 was considered statistically significant. All statistical tests were performed two-sided. All statistical analyses were performed in IBM SPSS Statistics 20, except for Poisson regression analyses, which were performed in STATA SE 12.0.

RESULTS

Characteristics of patients

All 3,672 patients in the FOCUS cohort were included for the analyses. Of all patients, 1747 (48%) were aged 65-74 years at diagnosis, and 1925 (52%) patients were 75 years or older. Patient, tumor and treatment characteristics per age group are shown in Table 1A. Patients in the older age group (≥75) more frequently had advanced (stage III or IV) tumors, more missing data on grade and morphology, reflecting the fewer surgeries (and consequently less histology) performed among the ≥75 (no surgery: 6.1% among patients aged <75, 20.1% among patients aged ≥75). Also, patients aged ≥75 years received radiotherapy and chemotherapy less often, and received endocrine monotherapy more often.

Comorbidity

Table 1B shows the distribution of comorbidity. The mean number of comorbidities was higher in the group aged ≥75 years (2.2 vs. 1.6 among the patients aged <75 years; p<0.001). The larger proportion of comorbidity in the older group can be explained by a significantly higher burden of psychiatric diseases, neurologic diseases, cardiovascular diseases, digestive diseases and musculoskeletal diseases.

Table 1 - patient, tumor and treatment characteristics

	all patients (N=3,672)		<75 (N=1747)		≥75 (N=1925)		
Mean age in years (SD)	76.5 (7.4)		70.0 (2.9)		82.3 (4.9)		
	N	%	N	%	N	%	P*
Stage							**<0.001**
In situ	208	5.7	142	8.1	66	3.4	
I	1,130	30.8	704	40.3	426	22.1	
II	1,532	41.7	639	36.6	893	46.4	
III	368	10	121	6.9	247	12.8	
IV	212	5.8	72	4.1	140	7.3	
missing	222	6	69	3.9	153	7.9	
Tumor grade							**<0.001**
1	437	11.9	233	13.3	204	10.6	
2	1,005	27.4	507	29.0	498	25.9	
3	784	21.4	403	23.1	381	19.8	
missing	1,446	39.4	604	34.6	842	43.7	
HR status							0.215
ER and PR negative	540	14.7	274	15.7	266	13.8	
ER or PR positive	2,290	62.4	1,068	61.1	1,222	63.5	
missing	842	22.9	405	23.2	437	22.7	
Morphology							**<0.001**
Ductal	2,560	69.7	1,294	74.1	1,266	65.8	
Lobular	400	10.9	175	10	225	11.7	
other/unknown	712	19.4	278	15.9	434	22.5	
Surgery							**<0.001**
None	493	13.4	107	6.1	386	20.1	
BCS	1,194	32.5	839	48	355	18.4	
Mastectomy	1,985	54.1	801	45.9	1,184	61.5	
Axillary surgery	2,614	71.2	1,385	79.3	1,229	63.8	**<0.001**
Adjuvant radiotherapy	1,532	41.7	981	56.2	551	28.6	**<0.001**
Endocrine therapy	1,661	45.2	638	36.5	1023	53.1	**<0.001**
Endocrine monotherapy	371	10.1	74	4.2	297	15.4	
Adjuvant endocrine therapy	1,290	35.1	564	32.3	726	37.7	
Chemotherapy	306	8.3	184	10.5	122	6.3	

*p for difference between age categories (Chi square)

Overall survival

As shown in Figure 1, in multivariable Cox regression models, overall survival was worse for patients with an increasing number of comorbidities in both age groups (multivariable Hazard Ratio (HR) for patients with 5 or more comorbidities compared to 0-1 comorbidities: 2.61 (95% Confidence Interval (CI) 1.92-3.56) and HR 1.51 (95% CI 1.24-1.83) respectively for the <75 and ≥75 group. In patients aged <75, specific categories of comorbidity that were associated with a worse overall survival were psychiatric diseases (HR 1.41, 95% CI 1.07-1.85), neurologic diseases (HR 1.94, 95% CI 1.50-2.52), cardiovascular diseases (HR 1.52, 95% CI 1.28-1.81) and other comorbidity (HR 1.47, 95% CI 1.03-1.30). Among the highest age group, only psychiatric diseases (HR 1.62, 95% CI 1.12-1.93) and cardiovascular diseases (HR 1.16, 95% CI 1.03-1.30) were associated with a worse overall survival.

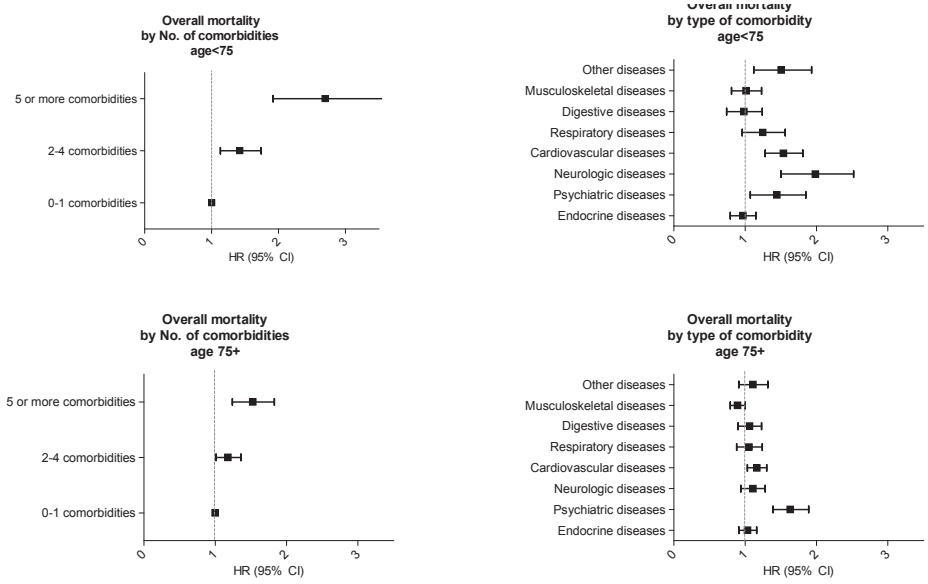

Figure 1. All-cause mortality, multivariable Cox regression analyses.

Distant recurrence free period

Overall, the proportion of patients who developed distant metastases among stage 0 to III patients did not differ between the age categories (11% in both categories). Among the patients aged ≥75, the majority of breast cancer patients died without registered distant metastases (62%), in other words: they died due to a "competing event", This proportion was almost three times smaller in the younger elderly (22%) (Figure 2).

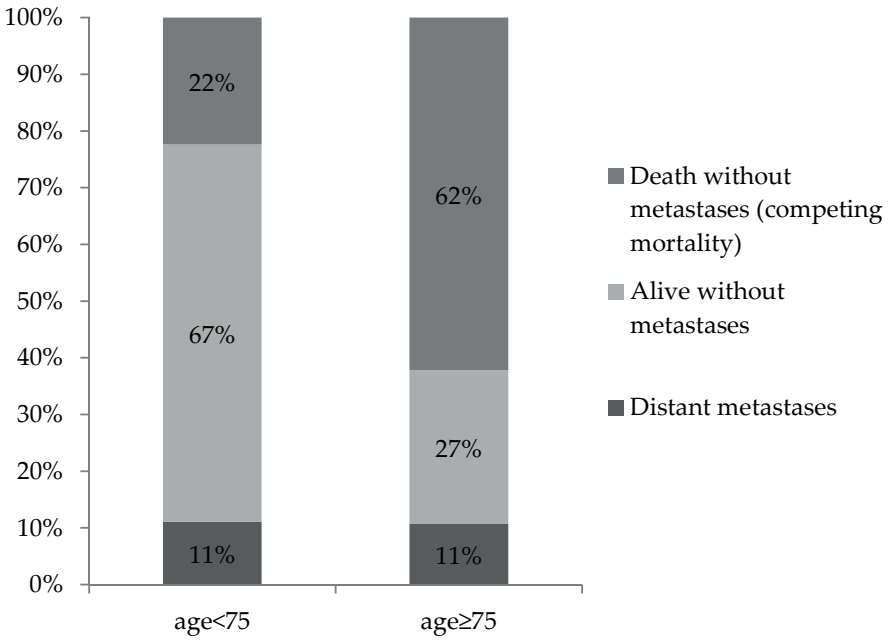

Figure 2. Distant recurrences and competing mortality.

Results of the multivariable Cox regression analysis on Distant recurrence free period (DRFP) are shown in Figure 3. In the patients aged <75, an association between the number of comorbidities and a higher risk of distant recurrences was found, the HR for each increase in number of comorbidities was 1.09 (95% CI 1.01-1.19). With the exception of neurologic diseases (HR 1.82, 95% CI 1.10-3.01, p=0.02) and cardiovascular diseases (HR 1.34, 95% CI 0.98-1.82), no association was observed between any of the specific comorbidities and DRFP. Among the patients aged ≥75, there was also an association between the number of comorbidities and DRFP, multivariable Cox regression analyses showed a trend to decreased risk of distant metastases among the oldest group (HR per unit increase in number of comorbidities: 0.94, 95% CI 0.0.87-1.02, p=0.12). The finding that the number of comorbidities is associated with fewer distant metastases in older patients is endorsed by categorizing the number of comorbidities, showing that patients aged 75 or older having 5 or more comorbid diseases have a significantly lower HR for DRFP (HR 0.54, 95% CI 0.30-0.96, p=0.036). In addition, a lower risk on distant metastases was shown for patients with psychiatric comorbidity (HR 0.42, 95% CI 0.20-0.90, p=0.026).

Poisson regression analyses, adjusted for the same factors as the Cox regression analyses, and taking account with the actual time a patient was followed in the study, showed an increasing trend for the incidence rate of distant recurrences in

the <75 group with increasing number of comorbidities (Webtable 1) (multivariable Incidence Rate Ratio (IRR) 1.09 (95%CI 1.00-1.18; p=0.046); whereas a decreasing trend was shown in the patients aged ≥75 (IRR 0.93 (95% CI 0.86-1.01; p=0.094).

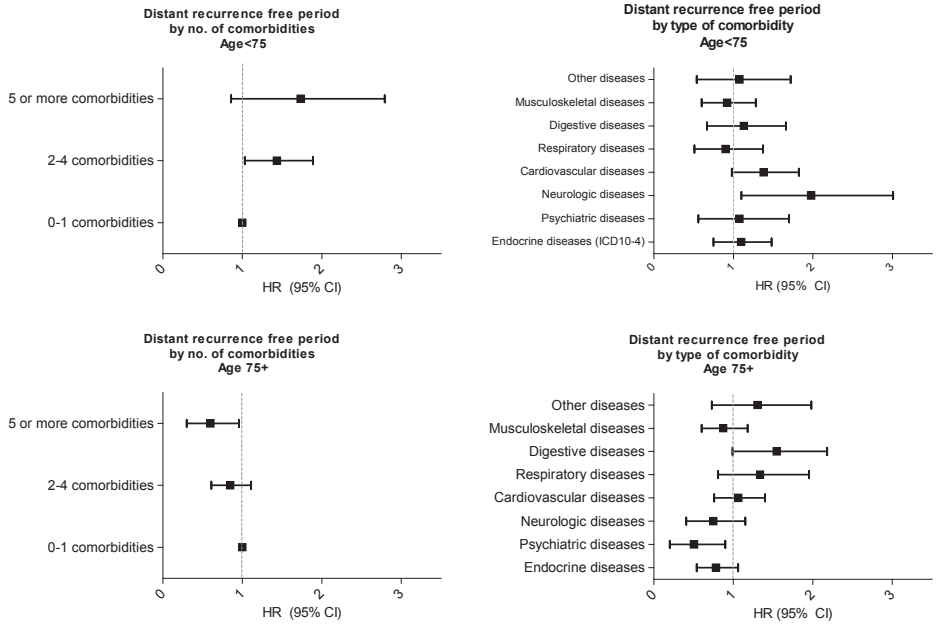

Figure 3. Distant recurrence free period, multivariable Cox regression analyses.

Table 2 - Comorbidity

	all patients		<75		≥75		
	N	%	N	%	N	%	p*
Number of comorbidities - mean (SD)	1.9 (1.8)		1.6 (1.7)		2.2 (1.9)		<0.001**
Endocrine diseases (ICD10-4)	983	26.8	447	25.6	536	27.8	0.13
hypercholesterolaemia	90	2.5	51	2.9	39	2.0	0.09
obesity	147	4.0	92	5.3	55	2.9	<0.001
diabetes	576	15.7	266	15.2	310	16.1	0.5
thyroid diseases	342	9.3	146	8.4	196	10.2	0.06
other endocrine diseases	13	0.4	4	0.2	9	0.5	0.3
Psychiatric diseases (ICD10-5)	354	9.6	127	7.3	230	11.9	<0.001
depression	109	3.0	49	2.8	60	3.1	0.6
severe psychiatric diseases	69	1.9	36	2.1	33	1.7	0.5
dementia/Alzheimer's	170	4.6	27	1.5	143	7.4	<0.001
other psychiatric diseases	48	1.3	27	1.5	21	1.1	0.2

Table 2 - Comorbidity (*continued*)

	all patients		<75		≥75		
	N	%	N	%	N	%	p*
Neurologic diseases (ICD10-6)	414	11.3	138	7.9	276	14.3	<0.001
Parkinson's disease	51	1.4	18	1.0	33	1.7	0.1
other neurologic diseases	366	10.0	120	6.9	246	12.8	<0.001
Cardiovascular diseases (ICD10-9)	1849	50.4	794	45.4	1055	54.8	<0.001
myocardial infarction	245	6.7	95	5.4	150	7.8	0.004
heart failure	190	5.2	37	2.1	153	7.9	<0.001
valve problems	159	4.3	52	3.0	107	5.6	<0.001
arrhythmia	426	11.6	137	7.8	289	15.0	<0.001
conduction disorder	60	1.6	13	0.7	47	2.4	<0.001
peripheral arterial occlusive disease	86	2.3	34	1.9	52	2.7	0.2
deep venous thrombosis	110	3.0	46	2.6	64	3.3	0.2
stroke	284	7.7	86	4.9	198	10.3	<0.001
hypertension	1177	32.1	561	32.1	616	32.0	0.9
other venous diseases	17	0.5	8	0.5	9	0.5	1.0
other cardiovascular diseases	79	2.2	33	1.9	46	2.4	0.6
Respiratory diseases (ICD10-10)	392	10.7	184	10.5	208	10.8	0.8
asthma	49	1.3	28	1.6	21	1.1	0.2
COPD	328	8.9	149	8.5	179	9.3	0.4
other respiratory diseases	23	0.6	11	0.6	12	0.6	1.0
Digestive diseases (ICD10-11)	469	12.8	194	11.1	275	14.3	0.004
ulcerative disease	142	3.9	50	2.9	92	4.8	0.003
diverticulosis	178	4.8	75	4.3	103	5.4	0.1
other digestive diseases	171	4.7	76	4.4	95	4.9	0.4
Musculoskeletal diseases (ICD10-13)	849	23.1	325	18.6	524	27.2	<0.001
arthrosis	564	15.4	206	11.8	358	18.6	<0.001
Sjogren's disease	6	0.2	3	0.2	3	0.2	1.0
rheumatoid arthritis	126	3.4	60	3.4	66	3.4	1.0
osteoporosis	175	4.8	65	3.7	110	5.7	0.005
other musculoskeletal diseases	101	2.8	44	2.5	57	3.0	0.4
Other diseases	306	8.3	133	7.6	173	9.0	0.1
blood/immune disease (ICD10-3)	37	1.0	20	1.1	17	0.9	0.5
ear/mastoid disease (ICD10-8)	18	0.5	9	0.5	9	0.5	1.0
genitourinary disease (ICD10-14)	226	6.2	95	5.4	131	6.8	0.06
other diseases not otherwise specified (ICD10-18)	30	0.8	13	0.7	17	0.9	0.7

*P for difference between age categories (Chi-square test). **unpaired T-test

DISCUSSION

The main finding of our present study is that comorbidity in older breast cancer patients has a major impact on all-cause mortality. This association is most pronounced among patients aged <75 years, but is also present in patients aged 75 years or older. Regarding breast cancer specific outcome, the risk to be diagnosed with distant breast cancer metastases decreases with an increasing number of comorbidities among patients aged ≥75, whereas comorbidity in patients <75 years is associated with a higher incidence of distant recurrences.

Several previous studies have shown that both younger and older breast cancer patients with comorbidity have increased all-cause mortality.[14-16] With the knowledge that there is a significant increase in the number and severity of comorbidities with increasing age[7,9,16], several studies reported on age-specific effects of comorbidity on outcome of older breast cancer patients.[7,14,17-24] But those results were not consistent across studies.

In the present study we found that although the presence and number of comorbidity is predictive for mortality irrespective of age, the impact of comorbidity on overall mortality decreases among the oldest old, although total mortality rates are almost three times higher in this oldest age group. A recent large population-based study performed in the US showed that the presence of comorbid conditions among older breast cancer patients is substantially associated with more all-cause mortality. Moreover, they showed that the impact of the investigated specific comorbidities decreased with increasing age.[14] Hence, our findings are fully consistent with these previous results, showing that the majority of specific comorbidities did not have a significant impact on all-cause mortality among the patients aged ≥75.[14] This finding indicates that there is an additional role of age (or age related factors) in the life expectancy, irrespective of the number or type of comorbidity. Probably, this can be explained by other factors that are associated with ageing, such as decreased physiologic reserves, functional status and cognition. The combination of these factors makes a patient more vulnerable to institutionalization and mortality.[25]

A remarkable outcome of our study that supports our hypothesis about the vulnerability of the oldest breast cancer patients, is the impact of psychiatric comorbidity on all-cause mortality. This probably reflects the effect of cognitive disorders, that are usually included in tools used in measuring frailty scores.[26] Unlike other specific comorbidities, psychiatric comorbidity is associated with higher hazards of all-cause mortality in the oldest group compared to their younger counterparts. In previous studies, dementia was shown to be associated with an increased risk of all-cause mortality in breast cancer patients[14,24,27-29], although the higher impact

among the oldest old found in our study was not previously described. Additionally, psychiatric diseases were associated with a lower risk on distant recurrences among the patients aged ≥75 in our study. This finding might reflect underreporting of recurrent disease in the oldest and most vulnerable patients rather than a true decrease in the incidence of distant recurrences. A recent study by Hamaker et al., showed that a substantial part of elderly care physicians working in nursing homes, do not refer patients with suspected (recurrent) breast cancer. The most important reason (accounting for 57% of all non-referrals) was end-stage dementia. By non-referral the patients will remain unregistered and will not be included in the cancer registry.[30] Nonetheless, our finding warrants further exploration.

In addition, we showed that an increasing number of comorbidities is associated with a lower risk on distant recurrences among patients aged ≥75, irrespective of tumor or treatment factors. To our knowledge, there are no previous studies assessing age-specific impact of comorbidity on breast cancer recurrence risk. The few studies assessing the impact of comorbidity on cancer-specific outcome use combined outcome measures like disease free survival or progression free survival, endpoints that in addition to recurrent disease, also include all-cause mortality in the endpoint.[31] This results in worse outcomes for patients with more comorbidity, but for the oldest patients, this is probably due to a higher risk on mortality and not on cancer recurrence. However, in the patients aged <75, after adjusting for breast cancer treatment, we found an increasing trend for distant recurrence incidence with an increasing number of comorbidities.

To our knowledge, the FOCUS cohort is the largest available cohort comprising detailed information about almost 3,700 older breast cancer patients. Additionally, the registration of all specific comorbidities, instead of the use of a comorbidity index or a predefined selection of specific comorbidities is a major strength of this paper. The volume of the cohort and the detailed registration of comorbidities makes this a robust analysis. A limitation of our study is the retrospective design, which only allowed us to assess qualitative comorbidity diagnoses and their predictive value on outcome. Future prospective studies should also assess other age-related factors that can influence patient related outcomes such as functional status and cognition. Furthermore, future prospective studies are needed in order to register the severity and treatment of comorbidity, and to study interactions of breast cancer itself and the cancer treatment with (the treatment of) comorbidity.

In conclusion, in our present study we showed an important negative impact of an increasing number of comorbid diseases and several specific comorbidities on the overall survival of older breast cancer patients, that cannot be explained by worse breast cancer specific outcome. However, the relative impact of the number of comorbidities on survival decreases with increasing age, indicating that clini-

cians should be aware of other factors that influence prognosis when treating older breast cancer patients.

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