Breast Cancer Res Treat (2013) 138:561–569
DOI 10.1007/s10549-013-2462-9

EPIDEMIOLOGY

Postoperative complications and survival of elderly breast cancer patients: a FOCUS study analysis

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Received: 30 January 2013 / Accepted: 18 February 2013 / Published online: 28 February 2013

Abstract Old age is associated with comorbidity and decreased functioning which influences treatment decisions in elderly breast cancer patients. The purpose of this study was to identify risk factors for complications after breast cancer surgery in elderly patients, and to assess mortality in patients with postoperative complications. The FOCUS cohort is a detailed retrospective cohort of all breast cancer patients aged 65 years and older who were diagnosed between 1997 and 2004 in the South-West of the Netherlands. Risk factors for postoperative complications were assessed using univariable and multivariable logistic regression models. One-year survival and overall survival were calculated using univariable and multivariable Cox Regression models, and relative survival was calculated according to the Ederer II method. 3179 patients received surgery, of whom 19 % ($n = 618$) developed 1 or more postoperative complication(s). The odds ratio of having postoperative complications increased with age [OR 1.85 (95 % confidence interval (CI) 1.37–2.50, $p = 0.001$) in patients >85 years] and number of concomitant diseases [OR 1.71 (95 % CI 1.30–2.24, $p \leq 0.001$) for 4 or more concomitant diseases]. One-year overall survival, overall survival, and relative survival were worse in patients with postoperative complications [multivariable HR 1.49 (95 % CI 1.05–2.11), $p = 0.025$. HR 1.21, (95 % CI 1.07–1.36), $p = 0.002$ and RER 1.19 (95 % CI 1.05–1.34), $p = 0.006$ respectively]. Stratified for comorbidity, relative survival was lower in patients without comorbidity only. Increasing number of concomitant disease increased the risk of postoperative complications. Although elderly patients with comorbidity did have a higher risk of postoperative complications, relative mortality was not higher in this group. This suggests that postoperative complications in itself did not lead to higher relative mortality, but that the high relative mortality was most likely due to geriatric parameters such as comorbidity or poor physical function.

Keywords Breast cancer · Elderly · Breast surgery · Postoperative complications · Comorbidity · Geriatric oncology

Introduction

In developed countries, 40 % of breast cancer patients are older than 65 years of age at diagnosis and this percentage is increasing [1]. Old age is predictive for comorbidity and decreased functioning [2, 3]. Therefore, these factors might influence treatment decisions in elderly breast cancer patients. Previous studies have shown that elderly breast cancer patients receive less aggressive treatment [4] and have a higher disease-specific mortality, even with 65 % of breast cancer patients above 75 years dying from other causes than breast cancer [5].

The most recent guideline of the International Society of Geriatric Oncology and the European Society of Breast Cancer Specialists (EUSOMA) advises breast conserving surgery with whole-breast radiotherapy, or mastectomy followed by postoperative radiotherapy in selected patients

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as standard care for elderly breast cancer patients [6]. However, the National Comprehensive Cancer Network guideline states that omission of radiotherapy may be considered in patients of 70 years or older with stage I estrogen receptor-positive breast cancer who undergo a lumpectomy with negative margins and are receiving endocrine therapy [7]. This shows that there is still no consensus on how to treat elderly breast cancer patients. Also, elderly patients are often not treated according to guidelines [8, 9]. Comorbid conditions and frailty are, besides age and patient and physician's preference, important reasons to deviate from the guidelines [10, 11]. Besides, treatment strategies for elderly breast cancer patients are mostly not evidence based because elderly are often not included in clinical trials due to age restrictions or comorbidity [12].

Breast surgery is generally considered as low-morbidity surgery [13]. However, a variety of complications can occur with serious consequences. For example, surgical site infections can lead to increased morbidity, additional costs and delay of postoperative adjuvant therapies [13].

In order to develop evidence-based guidelines for tailored care of breast cancer in the elderly, it is important to investigate the occurrence of complications of therapy in this specific group. Only few studies concerning postoperative complications in elderly breast cancer patients have been performed, often with a limited number of patients [11, 14, 15]. Therefore, the objective of this study was to identify risk factors for postoperative complications in elderly breast cancer patients, and to evaluate overall survival and relative survival in patients with postoperative complications compared with patients without postoperative complications.

Methods

Patients were selected from the FOCUS cohort study (Female breast cancer in the elderly; Optimizing Clinical guidelines USing clinico-pathologocial & molecular data). This cohort is based on the National Cancer Registry in the Netherlands, which contains data of all newly diagnosed malignancies.

The FOCUS-database contains information of 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 specific treatments, comorbidity according to the ICD-10 classification, adverse events, geriatric parameters, body mass index (BMI), smoking and recurrence. 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 who were treated with breast conserving surgery, mastectomy, or both were included. If patients received breast-conserving surgery (BCS) followed by mastectomy, the most extensive surgery was used for analyses. Stage was described using the pathological tumor-node-metastasis (TNM) classification, as valid in the year of diagnosis. If the pathological stage was missing, clinical stage was used. Hormone receptor status was analyzed in dichotomized variables for estrogen receptor status and progesterone receptor status. Axillary surgery was defined as a sentinel node procedure or an axillary lymph node dissection. Again, the most extensive axillary surgery was used for the analyses.

To compare different age groups, patients were categorized into five groups: 65–69, 70–74, 75–79, 80–84, and 85 years or older. Number of concomitant diseases was categorized in five groups: no concomitant disease, 1 concomitant disease, 2 concomitant diseases, 3 concomitant diseases, and 4 or more concomitant diseases. Specific groups of comorbid disease were defined according to the ICD-10 classification [16]. The clinically most important subgroups of the ICD-10 were separately analyzed, and the remaining comorbidities were defined as a category "other comorbidity." BMI was analyzed in three groups: <20, 20–25, and >25. In case of missing data, patients were not excluded in the analyses, but analyzed in a separate group.

Postoperative complications were defined before collection of the data. Only complications that needed any specific treatment within 30 days after surgery were registered. The possible postoperative complications were wound infections (including abscesses), bleeding, hematoma, seroma, anemia, delirium, cardiovascular complications (such as arrhythmias), thrombo-embolisms, systemic infections, and other complications that were separated into two groups: other wound-related complications (for instance poor wound healing) and other complications that were not wound-related. The primary outcome was defined as having one or more of these complications.

Statistical analyses

All analyses were performed in IBM SPSS Statistics version 20.0, except for relative survival, which was performed in STATA SE 10.0. All statistical analyses were two-sided. A p value smaller than 0.05 was considered as significant.

The following risk factors for having at least one postoperative complication were assessed in univariable logistic regression models: age (in groups per 5 years),

stage according to the TNM-classification, most extensive surgery, most extensive axillary surgery, number of comorbid conditions, specific comorbid conditions, polypharmacy (5 or more types of drugs per day), neoadjuvant treatment, BMI, and smoking at time of surgery. Also, specific subgroups of the ICD-10 classification for comorbidity were analyzed in univariable analyses.

Tests for interaction between stage and age, stage and type of surgery, comorbidity and polypharmacy, age and comorbidity, age and polypharmacy, most extensive axillary surgery and stage, and most extensive axillary surgery and age were performed using interaction terms in a multivariable logistic regression model. The primary outcome was no versus one or more postoperative complications.

Multivariable analyses were performed for age-groups, number of concomitant diseases, polypharmacy, and specified concomitant diseases, with adjustment for the significant univariable terms ($p < 0.05$), and for TNM-stage and age (when applicable).

Analyses for overall survival and 1-year survival were performed using univariable and multivariable Cox regression models. Additional multivariable survival analyses using Cox regression models were performed in stratified groups for each number of comorbid diseases. Relative survival was calculated by the Ederer II method, which calculates the ratio of the survival observed among the cancer patients compared to the survival that would have been expected based on the corresponding general population (based on age, sex, and year of diagnosis). National life tables were used to estimate expected survival. All multivariable survival analyses were adjusted for age, number of concomitant diseases, stage, grade, hormone receptor status, radiotherapy, hormonal therapy, chemotherapy, most extensive surgery, and most extensive axillary surgery.

Results

Patient characteristics

Overall, 3,672 patients of 65 years and older with invasive and in situ breast cancer were identified. A total number of 3,179 patients underwent BCS, mastectomy or both (for example in case of irradicality) and were included for analyses. Patient characteristics are shown in Table 1.

Most patients (62.4 %) were treated with mastectomy. The majority of patients (74.9 %) had at least one concomitant disease. Few patients (6.4 %) received neoadjuvant treatment. Thirteen and a half percent of the patients used 5 or more types of drugs per day. BMI values were missing in 1347 patients (42.4 %), and data about smoking were missing in 1,204 patients (37.9 %). Median follow up was 7.2 years (range 0.01–14.0).

Table 1 Patients characteristics

Median age (range)	74.0	(65.0–98.0)
	n	%
Age		
65–69	836	26.3
70–74	803	25.2
75–79	651	20.5
80–84	514	16.2
85+	375	11.8
Nr of concomitant disease		
0	798	25.1
1	750	23.6
2	632	19.9
3	404	12.7
4 or more	595	18.7
Stage		
0	198	6.2
I	1,058	33.3
II	1,435	45.1
III	322	10.1
IV	43	1.4
Unknown	123	3.9
Neoadjuvant treatment		
No neoadjuvant treatment	2,976	93.6
Neoadjuvant hormonal therapy and/or chemotherapy	203	6.4
Most extensive surgery		
Breast conserving surgery	1,194	37.6
Mastectomy	1,985	62.4
Most extensive axillary surgery		
No axillary surgery	578	18.2
Sentinal node procedure	780	24.5
Axillary lymph node dissection	1,821	57.3
BMI		
<20	97	3.0
20–25	651	20.5
>25	1,084	34.1
Unknown	1,347	42.4
Polypharmacy[a]		
No	2,751	86.5
Yes	428	13.5
Smoking at time of diagnosis		
No	1,648	51.8
Yes	327	10.3
Unknown	1,204	37.9

[a] 5 or more different types of medication

Postoperative complications

Overall, 19 % of patients developed 1 or more postoperative complications (Table 2). The most frequent complications

Table 2 Type of complications in different age groups

	Total	65–69	70–74	75–79	80–84	85+	*p* value
All complications *n* (%)	618 (19.4)	128 (15.3)	150 (18.7)	136 (20.9)	110 (21.4)	94 (25.1)	0.001
Wound infection	154 (4.8)	36 (4.3)	37 (4.6)	30 (4.6)	26 (5.1)	25 (6.7)	0.485
Bleeding	157 (4.9)	32 (3.8)	34 (4.2)	36 (5.5)	30 (5.8)	25 (6.7)	0.147
Hematoma	101 (3.2)	17 (2.0)	33 (4.1)	21(3.2)	14 (2.7)	16 (4.3)	0.107
Seroma	128 (4.0)	29 (3.5)	28 (3.5)	30 (4.6)	24 (4.7)	17 (4.5)	0.619
Anemia	37 (1.1)	3 (0.4)	9 (1.1)	11 (1.7)	8 (1.6)	6 (1.6)	0.108
Delirium	10 (0.3)	0 (0.0)	1 (0.1)	3 (0.5)	3 (0.6)	3 (1.1)	0.091
Cardiovascular complication	23 (0.7)	5 (0.6)	3 (0.4)	5 (0.8)	7 (1.4)	3 (1.1)	0.341
Thrombo-embolism	4 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	2 (0.4)	1 (0.4)	0.258
Systemic infection	19 (0.7)	2 (0.2)	4 (0.5)	4 (0.6)	3 (0.6)	0.4 (0.4)	0.082
Other wound-related complication	47 (1.2)	12 (1.4)	7 (0.9)	11 (1.7)	9 (1.8)	8 (2.1)	0.097
Other complication not wound-related	17 (0.5)	8 (1.0)	3 (0.4)	3 (0.5)	2 (0.4)	1.0 (0.4)	0.41

were wound infections ($n = 154$) and bleeding ($n = 157$). As shown in Table 3, the odds ratio (OR) for developing a postoperative complication increased with age (OR for patients aged >85 years was 1.85 [95 % confidence interval (CI) 1.37–2.50, $p = 0.001$] in a univariable logistic regression model. A higher number of concomitant diseases was associated with a higher risk of postoperative complications [patients without concomitant disease functioned as a reference; OR was 1.32 (95 % CI 1.01–1.72); 1.32 (95 % CI 1.00–1.75); 1.81 (95 % CI 1.34–2.44) and 1.71 (95 % CI 1.30–2.24) in patients with 1; 2; 3; 4 or more concomitant diseases, respectively ($p < 0.001$)]. Similarly, polypharmacy was strongly associated with risk of complications [OR 1.84 (95 % CI 1.46–2.32), $p < 0.001$]. Furthermore, patients who received a mastectomy and patients who underwent axillary lymph node dissection had more complications than patients who were treated with breast conserving surgery and less extensive axillary surgery. Also, neoadjuvant treatment was related to developing postoperative complications [OR 1.43 (95 % CI 1.03–1.98), $p = 0.035$]. Stage of disease was related to the risk of complications ($p < 0.001$). Smoking increased the odds for developing a complication with an OR of 1.41 (95 % CI 1.0–1.86, $p = 0.039$). There was no significant association between BMI and postoperative complications ($p = 0.327$).

None of the evaluated interaction terms were significant in the multivariable logistic regression (data not shown). Results of multivariable logistic regression analyses are shown in Table 4. Number of concomitant diseases and presence of polypharmacy were independently related to postoperative complications [OR 1.86 (95 % CI 1.20–2.09, $p = 0.003$) for 4 or more concomitant diseases and OR 1.76 (95 % CI 1.39–2.23, $p < 0.001$) for polypharmacy respectively].

To gain insight in concomitant disease, additional analyses were performed, in which specific diseases were included in the multivariable adjusted model separately (Table 4). A significant association was observed for musculoskeletal and connective tissue disease [OR 1.06 (95 % CI 1.01–1.12), $p = 0.023$] and endocrine disease [OR 1.08 (95 % CI 1.02–1.14), $p = 0.011$]. Cardiovascular disease, respiratory disease, gastrointestinal disease, disease of the nervous system, psychiatric disease, and other comorbidity were not associated with postoperative complications.

Survival analyses

Univariable analyses showed that patients with postoperative complications had a similar overall survival as patients without complications; 5-year survival was 67 versus 58 % (patients without complications functioned as a reference, hazard ratio (HR) for patients with postoperative complications was 1.06 [95 % CI 0.93–1.21), $p = 0.401$] (Table 5). However, in multivariable analyses the HR for patients with postoperative complications was 1.21 [(95 % CI 1.07–1.36), $p = 0.002$]. One-year survival was lower in patients with postoperative complications in both univariable analyses (HR 1.39, 95 % CI 1.23–1.56, $p < 0.001$) and multivariable analyses (HR 1.49, 95 % CI 1.05–2.11, $p = 0.025$). To investigate whether the observed difference in overall survival between patients with and without complications may be influenced by the number of concomitant disease, additional analyses were performed. Stratified by number of concomitant disease, only patients without concomitant diseases who developed a postoperative complications had a significantly lower overall survival [HR 1.41 (95 % CI 1.05–1.89), $p = 0.022$] (Table 6).

Relative survival was also lower for patients with one or more complications compared to patients without complications [multivariable relative excess risk 1.19 (95 % CI 1.05–1.34), $p = 0.006$]. Additional sensitivity analyses stratified for age groups showed a similar relative survival

Table 3 Association between patient and tumor characteristics and treatment and occurrence of postoperative complications, univariable logistic regression analysis

	Univariable			
	N patients with complication(s) (%)	OR	95 % CI	*p* value
Age				
65–69	128 (15.3)	Ref		0.001
70–74	150 (18.7)	1.27	(0.98–1.65)	
75–79	136 (20.9)	1.46	(1.12–1.91)	
80–84	110 (21.4)	1.51	(1.14–2.00)	
85+	94 (25.1)	1.85	(1.37–2.50)	
Nr of concomitant diseases				
0	120 (15.0)	Ref		<0.001
1	142 (18.9)	1.32	(1.01–1.72)	
2	120 (19.0)	1.32	(1.00–1.75)	
3	98 (24.3)	1.81	(1.34–2.44)	
4 or more	138 (23.2)	1.71	(1.30–2.24)	
Specified concomitant disease[a]				
Cardiovascular disease	347 (21.2)	1.26	(1.06–1.51)	0.009
Respiratory disease	68 (19.9)	1.03	(0.78–1.37)	0.827
Gastrointestinal disease	98 (23.2)	1.30	(1.02–1.66)	0.035
Musculoskeletal and connective tissue disease	173 (22,6)	1.30	(1.06–1.58)	0.010
Disease of nervous system	89 (25.7)	1.51	(1.16–1.95)	0.002
Endocrine disease	192 (21.8)	1.23	(1.01–1.48)	0.038
Psychiatric disease	69 (24.2)	1.36	(1.03–1.82)	0.034
Other	53 (19.7)	1.02	(0.74–1.39)	0.909
Polypharmacy				
No	495 (18.0)	Ref		<0.001
Yes	123 (28.7)	1.84	(1.46–2.32)	
Most extensive surgery				
BCT	172 (14.4)	Ref		<0.001
Mastectomy	446 (22.5)	1.72	(1.42–2.09)	
Most extensive axillary surgery				
No axillary surgery	84 (14.5)	Ref		<0.001
Sentinal node procedure	115 (14.7)	1.08	(0.75–1.38)	
Axillary lymph node dissection	419 (23.0)	1.76	(1.36–2.27)	
Neoadjuvant treatment				
No neoadjuvant treatment	567 (19.1)	Ref		0.035
Neoadjuvant hormonal therapy and/or chemotherapy	51 (25.1)	1.43	(1.03–1.98)	
TNM stage				
In situ	27 (13.6)	Ref		<0.001
I	196 (18.5)	1.44	(0.93–2.22)	
II	281 (19.6)	1.54	(1.01–2.36)	
III	90 (28.0)	2.46	(1.53–3.94)	
IV	8 (18.6)	1.45	(0.61–3.45)	
Unknown	16 (13.0)	0.95	(0.49-1.84)	
BMI				
20–25	139 (21.4)	Ref		0.327
<20	16 (16.5)	0.73	(0.41–1.28)	
>25	196 (18.1)	0.81	(0.64–1.04)	

Table 3 continued

	Univariable			
	N patients with complication(s) (%)	OR	95 % CI	*p* value
Unknown	267 (19.8)	0.91	(0.72–1.15)	
Smoking at time of diagnosis				
No	312 (18.9)	Ref		0.039
Yes	81 (24.8)	1.41	(1.07–1.86)	
Unknown	225 (18.7)	0.98	(0.81–1.19)	

[a] Reference category: absence of the specified concomitant disease

Table 4 Association between patient and tumor characteristics and occurrence of postoperative complications, multivariable logistic regression analysis

	Multivariable			
	N of patients with postoperative complication(s) (%)	OR	95 % CI	*p* value
Age[a]				
65–69	128 (15.3)	Ref		0.102
70–74	150 (18.7)	1.19	(0.91–1.55)	
75–79	136 (20.9)	1.22	(0.92–1.61)	
80–84	110 (21.4)	1.18	(0.87–1.59)	
85+	94 (25.1)	1.58	(1.14–2.16)	
Nr of concomitant disease[b]				
0	120 (15.0)	Ref		0.003
1	142 (18.9)	1.29	(0.98–1.68)	
2	120 (19.0)	1.24	(0.96–1.65)	
3	98 (24.3)	1.72	(1.27–2.32)	
4 or more	138 (23.2)	1.86	(1.20–2.09)	
Polypharmacy[b]				
No	495 (18.0)	Ref		<0.001
Yes	123 (28.7)	1.76	(1.39–2.23)	
Specified concomitant disease[c]				
Cardiovascular disease	347 (21.2)	1.12	(0.93–1.36)	0.222
Respiratory disease	68 (19.9)	1.01	(0.76–1.34)	0.952
Gastrointestinal disease	98 (23.2)	1.24	(0.97–1.60)	0.093
Musculoskeletal and connective tissue disease	173 (22.6)	1.06	(1.01–1.12)	0.023
Disease of nervous system	89 (25.7)	1.28	(0.97–1.69)	0.081
Endocrine disease	192 (21.8)	1.08	(1.02–1.14)	0.011
Psychiatric disease	69 (24.2)	1.24	(0.92–1.66)	0.158
Other	53 (19.7)	0.94	(0.68–1.30)	0.697

[a] Adjusted for stage, type of surgery, axillary surgery, neoadjuvant treatment, and nr of concomitant disease

[b] Adjusted for age (as continuous variable), stage, type of surgery, most extensive axillary surgery, and neoadjuvant treatment

[c] Adjusted for age (as continuous variable), stage, type of surgery, most extensive axillary surgery, neoadjuvant treatment, and number of concomitant diseases without the specified disease

for patients with postoperative complications in the eldest groups (75–79, 80–85 and > 85 years) (data not shown).

Discussion

This study shows that the number of concomitant diseases and polypharmacy are strongly related to the occurrence of postoperative complications in elderly breast cancer patients. Patients treated with mastectomy had more complications than patients who received breast conserving surgery. Elderly patients had complications more often, but after adjustment for tumor stage, comorbidity, and treatment, only a trend for increasing risk of complications in higher age groups was observed. One-year survival, overall survival and relative survival were worse in patients with

Table 5 Survival analyses for one or more postoperative complications versus no postoperative complications

	Univariable					Multivariable[a]		
	Events (*n*)	5-year survival (%)	HR	95 % CI	*p* value	HR	95 % CI	*p* value
Overall survival	1,586	65						
No postoperative complications	1,225	67	Ref		0.401	Ref		0.002
Postoperative complications	361	58	1.06	(0.93–1.21)		1.21	(1.07–1.36)	
1-year survival	165							
No postoperative complications	120		Ref		<0.001	Ref		0.025
Postoperative complications	45		1.39	(1.23–1.56)		1.49	(1.05–2.11)	
Relative survival			RER			RER		
No postoperative complications		71	Ref		<0.001	Ref		0.006
Postoperative complications		63	1.37	(1.22–1.55)		1.19	(1.05–1.34)	

[a] Adjusted for age, number of concomitant diseases, stage, grade, ER/PR status, radiotherapy, hormonal therapy, chemotherapy, most extensive surgery, most extensive axillary surgery

Table 6 overall survival analyses stratified for number of comorbidities

	Multivariable[a]				
	Events (n)	5-year survival (%)	HR	95 % CI	*p* value
No comorbidity	314	74			
No postoperative complications	253	75	Ref		0.022
Postoperative complications	61	65	1.41	(1.05–1.89)	
1 comorbidity	325	69			
No postoperative complications	248	70	Ref		0.179
Postoperative complications	77	61	1.20	(0.92–1.58)	
2 comorbidities	343	62			
No postoperative complications	268	63	Ref		0.145
Postoperative complications	75	57	1.22	(0.93–1.59)	
3 comorbidities	209	61			
No postoperative complications	159	64	Ref		0.748
Postoperative complications	50	64	1.06	(0.76–1.48)	
4 or more comorbidities	395	54			
No postoperative complications	297	53	Ref		0.087
Postoperative complications	98	48	1.23	(0.97–1.56)	

[a] Adjusted for age, number of concomitant diseases, stage, grade, ER/PR status, radiotherapy, hormonal therapy, chemotherapy, most extensive surgery, most extensive axillary surgery

one or more postoperative complications. However, when stratified for number of concomitant diseases, only patients without concomitant disease who developed a postoperative complication had a significantly lower overall survival.

These findings suggest that the increased risk for early and late overall mortality is not due to the complications in itself, but can be explained by the frail state of the patients who develop postoperative complications, since comorbidity in itself increases the risk of mortality in elderly breast cancer patients [17]. Although the multivariable models were adjusted for comorbidity and age, there may have been several other factors (unregistered confounders) that made these patients more at increased risk for mortality, such as poor physical function, since it has been shown that poor physical function increases the risk of dying, independent of age [3].

When using relative survival, the background mortality of the general population is used [18]. However, we showed that the number of comorbid diseases was strongly associated with developing a postoperative complication. Therefore, the background file with mortality that was used for the analyses underestimates the actual mortality of the group with postoperative complications, while this background file overestimates the actual mortality in patients without postoperative complications. Therefore, the excess mortality is most likely not due to breast cancer death, but to comorbidity or other confounders that were not registered, such as poor physical function. Sensitivity analyses

stratified by age were performed, and showed that in the age group over 75 years the RER in patients with postoperative complications compared to no postoperative complications was no longer significantly worse, which strengthens this theory. The fact that stratification by number of comorbid diseases showed that only patients without comorbid disease who developed a complication had a significantly lower overall survival endorses this assumption. Apparently, postoperative complications do not lead to a lower survival in patients with comorbidity, which implies that the worse survival that was observed for the whole group is most likely due to comorbidity in itself and not due to postoperative complications.

Concerning the impact of comorbidity on developing postoperative complications, Houterman et al. [15] concluded from an observational study that comorbidity and age did not influence the occurrence of complications after treatment. The study included only 154 patients aged 70 years or older, and investigated complications of all types of therapy in the first year after diagnosis. Also, patients who did not receive surgery were included in this study. Therefore, this study differs considerably from the current study, which might explain the differences in outcome. Another study by Janssen-Heijnen et al. [14] also found no association between comorbidity and postoperative complications. Again, this study included only 490 patients with breast cancer, of whom only 192 were older than 65. Since the impact of comorbid disease is the highest in the eldest elderly, this might explain the differences with the current study.

A recent Danish study [19] found that older age and mastectomy increases the risk of re-operation due to bleeding in breast cancer surgery. These results were confirmed in the current study. Another study [20] found that BMI > 25 kg/m^2, diabetes, and smoking were predictors of wound complications. In the current study, BMI was not related to risk of postoperative complications, which might be explained by missing values in about 50 % of patients, since BMI registration in a chart may not be missing at random.

The main strength of this study is the large number of patients in this study with detailed information. To our knowledge, the FOCUS cohort is the largest cohort with detailed information of all consecutive elderly patients in a certain area. Since elderly patients are rarely included in clinical trials [12], large cohort studies are of great importance in this population. These studies are a good way of studying complications of treatment, since data are unbiased and the studies generally contain more patients [21].

This study also has some limitations. Due to the retrospectively collection of data, there might have been an underestimation of the number of complications. However, in these data, 19 % of patients developed at least one complication, and this is even higher than a recent study in a large cohort in the U.S. [20] which reported a 30-day morbidity rate for all breast cancer procedures of 5.6 %. The most common complications were wound infections, which were confirmed in the current study. Therefore, these data seem to accurately reflect general practice and correspond with previous studies.

Second, causes of death were not registered. Therefore, relative survival was used to estimate cancer-specific survival. This method has been shown to be a valid proxy for cancer specific survival [18].

A Cochrane meta-analysis has confirmed that hormonal treatment as monotherapy is inferior to surgery (with or without hormonal treatment) for the local control and progression-free survival of breast cancer in medically fit older women [22]. However, in the Netherlands, elderly patients receive less surgery and more hormonal therapy as monotherapy than younger patients, even in lower stages of disease [4]. This suggests that patients might be undertreated due to fear of morbidity and mortality in breast cancer surgery. Although elderly patients with comorbidity do have a higher risk of postoperative complications, relative mortality was not higher in this group and therefore suggests that omitting surgery because of fear for treatment-related mortality is only justified in vulnerable elderly patients. The question remains how to identify this specific group. Therefore, future prospective studies are needed to identify patients at risk for postoperative complications, and to develop tailored care for elderly breast cancer patients.

Acknowledgments This work was supported by the Dutch Cancer Foundation (KWF 2007-3968). The authors would like to thank the Comprehensive Cancer Centre Netherlands (Leiden region), all participating hospitals and M. Murk-Jansen for data collection.

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards Data collection complies with the current laws of the Netherlands.

References

1. Wildiers H, Kunkler I, Biganzoli L, Fracheboud J, Vlastos G, Bernard-Marty C, Hurria A, Extermann M, Girre V, Brain E, Audisio RA, Bartelink H, Barton M, Giordano SH, Muss H, Aapro M (2007) Management of breast cancer in elderly individuals: recommendations of the international society of geriatric oncology. Lancet Oncol 8:1101–1115
2. Guralnik JM (1996) Assessing the impact of comorbidity in the older population. Ann Epidemiol 6:376–380
3. Braithwaite D, Satariano WA, Sternfeld B, Hiatt RA, Ganz PA, Kerlikowske K, Moore DH, Slattery ML, Tammemagi M, Castillo A, Melisko M, Esserman L, Weltzien EK, Caan BJ (2010) Long-term prognostic role of functional limitations among women with breast cancer. J Natl Cancer Inst 102:1468–1477

4. Bastiaannet E, Liefers GJ, de Craen AJ, Kuppen PJ, van de Water W, Portielje JE, van der Geest LG, Janssen-Heijnen ML, Dekkers OM, van de Velde CJ, Westendorp RG (2010) Breast cancer in elderly compared to younger patients in the Netherlands: stage at diagnosis, treatment and survival in 127,805 unselected patients. Breast Cancer Res Treat 124:801–807
5. van de Water W, Markopoulos C, van de Velde CJ, Seynaeve C, Hasenburg A, Rea D, Putter H, Nortier JW, de Craen AJ, Hille ET, Bastiaannet E, Hadji P, Westendorp RG, Liefers GJ, Jones SE (2012) Association between age at diagnosis and disease-specific mortality among postmenopausal women with hormone receptor-positive breast cancer. JAMA 307:590–597
6. Biganzoli L, Wildiers H, Oakman C, Marotti L, Loibl S, Kunkler I, Reed M, Ciatto S, Voogd AC, Brain E, Cutuli B, Terret C, Gosney M, Aapro M, Audisio R (2012) Management of elderly patients with breast cancer: updated recommendations of the international society of geriatric oncology (SIOG) and European society of breast cancer specialists (EUSOMA). Lancet Oncol 13:e148–e160
7. National Comprehensive Cancer Network (NCCN) (2013) NCCN Guidelines Version 1.2013; Senior Adult Oncology. http://www.nccn.org/professionals/physician_gls/pdf/senior.pdf. Accessed 4 Feb 2013
8. van de Water W, Bastiaannet E, Dekkers OM, de Craen AJ, Westendorp RG, Voogd AC, van de Velde CJ, Liefers GJ (2012) Adherence to treatment guidelines and survival in patients with early-stage breast cancer by age at diagnosis. Br J Surg 99:813–820
9. Lavelle K, Todd C, Moran A, Howell A, Bundred N, Campbell M (2007) Non-standard management of breast cancer increases with age in the UK: a population based cohort of women > or = 65 years. Br J Cancer 96:1197–1203
10. Louwman WJ, Janssen-Heijnen ML, Houterman S, Voogd AC, van der Sangen MJ, Nieuwenhuijzen GA, Coebergh JW (2005) Less extensive treatment and inferior prognosis for breast cancer patient with comorbidity: a population-based study. Eur J Cancer 41:779–785
11. Land LH, Dalton SO, Jensen MB, Ewertz M (2012) Impact of comorbidity on mortality: a cohort study of 62,591 Danish women diagnosed with early breast cancer, 1990–2008. Breast Cancer Res Treat 131:1013–1020
12. Zulman DM, Sussman JB, Chen X, Cigolle CT, Blaum CS, Hayward RA (2011) Examining the evidence: a systematic review of the inclusion and analysis of older adults in randomized controlled trials. J Gen Intern Med 26:783–790
13. Vitug AF, Newman LA (2007) Complications in breast surgery. Surg Clin N Am 87:431–451
14. Janssen-Heijnen ML, Maas HA, Houterman S, Lemmens VE, Rutten HJ, Coebergh JW (2007) Comorbidity in older surgical cancer patients: influence on patient care and outcome. Eur J Cancer 43:2179–2193
15. Houterman S, Janssen-Heijnen ML, Verheij CD, Louwman WJ, Vreugdenhil G, van der Sangen MJ, Coebergh JW (2004) Comorbidity has negligible impact on treatment and complications but influences survival in breast cancer patients. Br J Cancer 90:2332–2337
16. World Health Organization (1992) The ICD-10 classification of mental and behavioural disorders. WHO, Geneva, pp 1–267
17. Patnaik JL, Byers T, Diguiseppi C, Denberg TD, Dabelea D (2011) The influence of comorbidities on overall survival among older women diagnosed with breast cancer. J Natl Cancer Inst 103:1101–1111
18. Dignam JJ, Huang L, Ries L, Reichman M, Mariotto A, Feuer E (2009) Estimating breast cancer-specific and other-cause mortality in clinical trial and population-based cancer registry cohorts. Cancer 115:5272–5283
19. Winther LL, Cronin-Fenton D, Garne JP, Kroman N, Silliman R, Lash TL (2012) Predictors of re-operation due to post-surgical bleeding in breast cancer patients: a Danish population-based cohort study. Eur J Surg Oncol 38:407–412
20. de BC, Ogunleye AA, Momoh AO, Colakoglu S, Tobias AM, Sharma R, Houlihan MJ, Lee BT (2012) High body mass index and smoking predict morbidity in breast cancer surgery: a multivariate analysis of 26,988 patients from the national surgical quality improvement program database. Ann Surg 255:551–555
21. Vandenbroucke JP (2004) When are observational studies as credible as randomised trials? Lancet 363:1728–1731
22. Hind D, Wyld L, Reed MW (2007) Surgery, with or without tamoxifen, vs tamoxifen alone for older women with operable breast cancer: cochrane review. Br J Cancer 96:1025–1029