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Less extensive treatment and inferior prognosis for breast cancer patient with comorbidity: A population-based study

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Abstract

The prevalence of coexistent diseases in addition to breast cancer becomes increasingly important in an ageing population. However, the clinical implications are unclear. The age-specific prevalence of serious comorbidity among all new breast cancer patients diagnosed from 1995 to 2001 ($n = 8966$) in the South of the Netherlands was analysed in relation to age, stage and treatment. Independent prognostic effects of age and comorbidity were evaluated (follow-up was continued until 1 January 2004). The prevalence of comorbidity increased from 9% for those aged <50 years to 56% for patients aged 80+ years. The most frequent conditions were cardiovascular disease (7%), diabetes mellitus (7%), and previous cancer (6%). In the presence of comorbidity, fewer patients received radiotherapy (51% vs. 66%, $P < 0.0001$) and fewer patients who underwent breast-conserving surgery also had axillary dissection ($P < 0.0001$). Relative 5-year survival rates for patients without comorbidity (87%) were significantly higher ($P < 0.01$) than those for patients with previous cancer (77%), diabetes mellitus (78%), and for patients with 2+ coexistent diseases (59%). Relative survival of patients without comorbidity increased with age to 93% for patients older than 70 years. Comorbidity negatively affected prognosis, independent of age, stage of disease, and treatment (Hazard Ratio (HR) = 1.3, $P = 0.0001$ for one coexistent disease and HR = 1.4, $P = 0.0001$ for 2+ coexistent diseases). The most important effects were found for previous cancer (HR = 1.4, $P = 0.003$), cerebrovascular disease (HR = 1.6, $P < 0.004$) or dementia (HR = 2.3, $P < 0.0001$). Elderly breast cancer patients can be divided in those without other diseases, who have a relatively good prognosis, and those who have at least one other serious coexistent disease and significantly poorer prognosis.

Keywords: Breast cancer; Comorbidity; Treatment; Long-term prognosis; Elderly

1. Introduction

Breast cancer is the most common type of cancer among women in the Netherlands, as in many other Western countries [1], and 51% of all new patients are 60 years or older [2]. With increasing age, the prevalence of coexistent diseases increases [3]. Previously, we found that approximately 50% of all breast cancer patients aged 60 years and older have one or more serious coexistent diseases [4]. Clinical trials that focus on treatment evaluation often exclude older patients and those with pre-existing serious diseases, so that optimal treatment

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for these patients is still uncertain. Elderly patients often do not receive any treatment and are less likely to undergo a combination of therapeutic modalities [5]. Often, patients with comorbidity are not treated according to guidelines [6,7], although this may be the effect of advanced age instead of comorbidity. In addition to the influence on treatment, comorbidity has also been demonstrated to lower 3-year survival rates, independent of age, stage of disease, and type of treatment [8].

Since 1993, the Eindhoven Cancer Registry has routinely collected data on serious coexistent diseases in all newly diagnosed cancer patients in the southeastern part of the Netherlands [9]. This provides us with the unique opportunity to study its prognostic implications in a population-based setting.

In an increasingly ageing population, comorbid conditions will become to play an even more important role in clinical decision-making and outcome. The presence of these coexistent diseases warrants care programmes with adapted treatment guidelines.

In the present study, we describe the prevalence of serious comorbidity for all consecutive breast cancer patients since 1995 with follow-up until January 1st, 2004. We investigated the impact of comorbidity on treatment and its effect on prognosis, independent of the patient's age and stage of the disease.

2. Patients and methods

Data were derived from the population-based Eindhoven Cancer Registry, which collects data on all new cancer cases in southeastern Netherlands since 1955. The registry covers a population of approximately 2.3 million inhabitants and is embedded in the Comprehensive Cancer Centre South, where all cancer patients are discussed in multi-disciplinary meetings. The area offers good access to specialised medical care supplied in 12 general hospitals and two large radiotherapy institutes. Trained registry personnel actively collect data on diagnosis, staging, and treatment from the medical records after notification by pathologists and medical registration offices. Data on type of treatment (surgery, radiotherapy, chemotherapy or hormonal therapy) were recorded as well as details on the type of surgical procedure (such as breast-conserving surgery, mastectomy and axillary dissection).

Since 1993, the registry also records comorbidity according to a slight adaptation of the list of serious diseases drawn up by Charlson and colleagues [10]. In short, the following important conditions were recorded: chronic obstructive pulmonary diseases (COPD), cardiovascular and cerebrovascular diseases, other malignancies (excluding basal cell carcinoma of the skin), and diabetes mellitus. Connective tissue diseases, rheumatoid arthritis, kidney, bowel, and liver diseases, dementia, tuberculosis and other chronic infections were also recorded [9].

Between 1995 and 2001, a total of 9123 patients with invasive breast cancer were diagnosed. A previous malignancy was diagnosed in 658 patients, for which the localisation could be traced in 71% of the cases. Patients who had been diagnosed with breast cancer (invasive or *in situ*) before 1995 and developed a second breast tumour during 1995–2001, were excluded from the analyses ($n = 164$). After the exclusion, the most frequent previous tumours were gynaecological tumours (25%) and colorectal cancer (23%).

Information on the vital status of all patients was obtained initially from the municipal registries and since 1998 from the Central Bureau for Genealogy. These registers provide virtually complete coverage of all deceased Dutch citizens. Patients who moved outside of the Netherlands were lost to follow-up; the estimated proportion was 0.2%. Follow-up lasted until January 1st, 2004.

The prevalence of comorbidity was analysed according to age (<50 years, 50–69 years, 70–79 years, and $\geqslant$80 years); sometimes combining the patients aged 70–79 years and 80+ years because of the small numbers. Differences in treatment between patients with and without comorbidity were analysed according to age group, and tested with the χ^2 test. Crude survival analyses were performed separately for the first year of follow-up and for the following period, and were stratified according to age at diagnosis. The log-rank test was performed to evaluate significant differences between survival curves in univariate analyses. We used Cox regression models to compute multivariate rates. The independent prognostic effect of comorbidity (in general and specific diseases) was investigated, adjusting for age, stage of disease, and treatment of the patient.

Relative survival (the ratio of the observed to the expected rates) is an estimation of disease-specific survival, which reflects survival of cancer patients adjusted for survival in a background population with the same age structure [11]. Expected survival rates were calculated from life-tables for regional male and female populations with the same 5-year age distribution.

3. Results

The proportion of patients with one or more serious coexistent disease at the time of diagnosis of breast cancer increased from 9% for patients younger than 50 years to 55% for patients aged 80 years and older (Table 1).

The most frequent coexistent diseases were cardiovascular disease (7%), diabetes mellitus (7%), and previous cancer (6%), for all age groups (Table 1).

Treatment of patients without comorbidity was less extensive in the older age groups (Fig. 1). The presence of comorbidity affected treatment in all age groups, but

Table 1
Number of serious concomitant conditions and type of comorbidity by age of consecutive breast cancer patients diagnosed 1995–2001 in southeastern Netherlands

	Age at diagnosis (years)				All ages
	<50	50–69	70–79	⩾80	
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Number of concomitant conditions					
0	1816 (79)	2804 (67)	826 (50)	283 (35)	5729 (64)
1	184 (8)	686 (16)	458 (27)	268 (34)	1596 (18)
⩾2	23 (1)	174 (4)	228 (14)	175 (22)	600 (7)
Unknown	290 (13)	521 (12)	156 (9)	74 (9)	1041 (12)
Type of concomitant condition[a]					
Previous cancer	52 (2)	212 (5)	136 (8)	93 (12)	493 (6)
Cardiovascular disease	17 (1)	197 (5)	240 (14)	170 (21)	624 (7)
COPD	57 (2)	174 (4)	114 (7)	58 (7)	403 (4)
Diabetes mellitus	18 (1)	245 (6)	241 (14)	133 (17)	637 (7)
Cerebrovascular	10 (0)	54 (1)	81 (5)	62 (8)	207 (2)
Tuberculosis	8 (0)	36 (1)	37 (2)	19 (2)	100 (1)
Dementia	0 (0)	3 (0)	24 (1)	43 (5)	70 (1)
Digestive tract	27 (1)	50 (1)	34 (2)	32 (4)	143 (2)
Other[b]	33 (1)	54 (1)	31 (2)	20 (3)	138 (2)
Total	2313	4185	1668	800	8966

COPD, chronic obstructive pulmonary diseases.
[a] Patients may suffer from more than one concomitant condition.
[b] Connective tissue diseases, rheumatoid arthritis, kidney diseases.

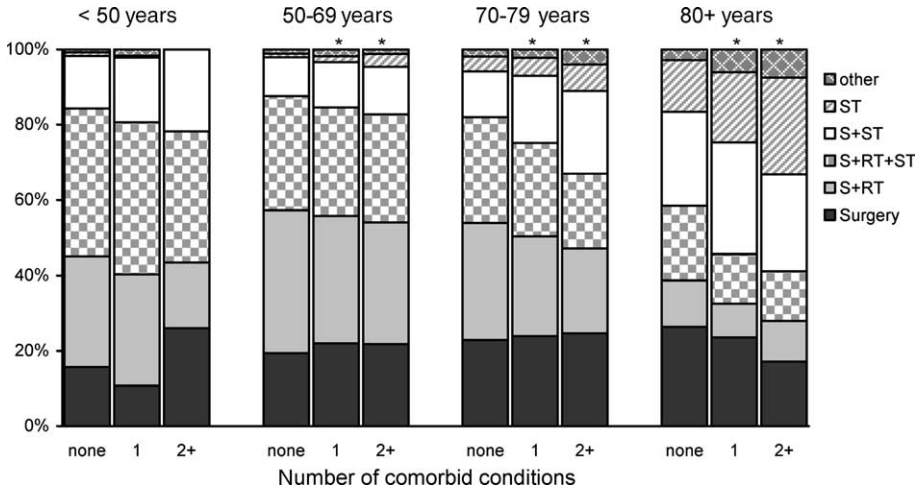

Fig. 1. Primary treatment (%) of consecutive breast cancer patients diagnosed in southeastern Netherlands, 1995–2001, according to age and number of comorbid conditions. S, surgery; RT, radiotherapy; ST, systemic therapy. *$P \leqslant 0.01$. ST was mainly chemotherapy (93%) in age <50 years, and mainly hormonal treatment (78%, 96% and 100%) in age groups 50–69 years, 70–79 years and 80+ years, respectively.

these effects were much smaller before age 70 years. Patients with at least one serious coexistent disease received less radiotherapy (51% vs. 66%, $P < 0.0001$) and more systemic therapy (tamoxifen 44% vs. 30%, $P < 0.0001$) compared with those without comorbidity (all ages combined). The effect of comorbidity on treatment was most clear for patients aged 80 years and older, when the proportion treated with surgery alone was lower for those with comorbidity (21% vs. 26%, $P = 0.09$), and treatment with tamoxifen only was higher (21% vs. 14%, $P = 0.01$). Surgical procedures were less extensive for patients with comorbidity. The standard breast-conserving treatment consists of lumpectomy, axillary dissection and radiotherapy. Among all patients who underwent lumpectomy ($n = 3138$), axillary dissection was performed in 78% of the patients with at least two other serious diseases, compared with 97% of those without comorbidity ($P < 0.0001$) (Fig. 2). Radiotherapy was administered to 94% of the patients without comorbidity who underwent lumpectomy, compared with 87% of patients with one coexistent disease and 78% of patients with two or more comorbid conditions

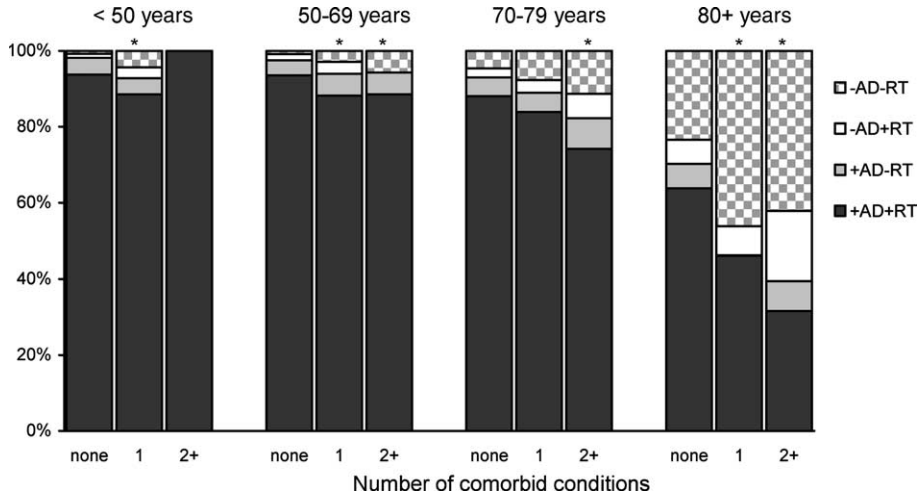

Fig. 2. Proportion axillary dissection and radiotherapy among breast cancer patients who underwent lumpectomy in southeastern Netherlands, 1995–2001, according to age and number of comorbid conditions. AD, axillary dissection; RT, radiotherapy. *$P \leqslant 0.01$.

($P < 0.0001$). This effect was strongest among patients aged over 80 years at diagnosis. The proportion who underwent axillary dissection combined with lumpectomy decreased from 70% in those without coexistent disease to 46% and 40% in those with one and two or more coexistent diseases, respectively ($P = 0.009$). The proportion that received radiotherapy in this patient group decreased from 70% in those without comorbidity to 54% and 50% of patients with one and two or more coexistent diseases, respectively ($P = 0.12$) (Fig. 2).

Crude 5-year survival rates for patients who suffered from comorbidity were significantly lower than for patients without coexistent diseases (Table 2). Among patients aged 50–69 years, both 1 and 5-year survival rates were significantly lower in the presence of previous cancer ($P < 0.01$). Crude survival of patients aged 70+ with cardiovascular disease, diabetes mellitus, cerebrovascular disease, dementia or other comorbidity cancer was significantly lower ($P < 0.01$). Survival adjusted for background mortality (relative survival) yielded similar results (Table 2).

Relative 5-year survival for patients without comorbidity (all ages combined) was 87% (95% Confidence Interval (CI): 86–88), which was significantly higher than that for patients with a previous cancer (77% (95% CI: 71–83)), or diabetes mellitus (78% (95% CI: 72–84)). Patients with only one comorbid condition experienced 80% 5-year relative survival, patients with

Table 2
Overall survival (% and SE) of consecutive breast cancer patients diagnosed in southeastern Netherlands, 1995–2001, according to age and concomitant disease

Age:	<50 years			50–69 years			70 years			All ages combined
	Survival			Survival			Survival			Survival
	Crude		Relative	Crude		Relative	Crude		Relative	Relative
Time since diagnosis:	1 year	5 year	5 year	1 year	5 year	5 year	1 year	5 year	5 year	5 year
No comorbidity	98 (0.3)	84 (1.0)	84 (1.0)	98 (0.3)	84 (0.7)	87 (0.8)	93 (0.8)	68 (1.6)	93 (2.1)	87 (0.6)
One concomitant disease:										
Previous cancer	96 (2.9)	77 (7.2)	78 (7.2)	**92 (2.2)**	**73 (3.8)**	**76 (3.9)**	89 (2.8)	59 (4.9)	78 (6.5)	**77 (3.2)**
Cardiovascular disease	100 (0.0)	–[a]	–	98 (1.2)	83 (4.0)	88 (4.1)	**93 (2.0)**	**56 (4.4)**	**77 (6.0)**	83 (3.8)
COPD	100 (0.0)	74 (6.9)	75 (7.0)	98 (1.4)	84 (3.7)	88 (3.9)	94 (2.9)	62 (6.8)	88 (10)	84 (3.5)
Diabetes mellitus	93 (6.9)	–	–	96 (1.5)	84 (3.1)	88 (3.3)	**87 (2.6)**	**53 (4.4)**	**69 (5.8)**	**78 (3.2)**
Cerebrovascular	–	–	–	94 (6.1)	–	–	**80 (4.8)**	**48 (6.6)**	75 (10)	76 (8.4)
Tuberculosis	–	–	–	100 (0.0)	87 (6.9)	91 (7.2)	96 (3.6)	–	–	84 (7.1)
Dementia	–	–	–	–	–	–	**83 (6.2)**	**27 (8.8)**	–	–
Digestive tract	96 (4.2)	83 (9.5)	–	95 (3.7)	87 (6.1)	91 (6.3)	89 (5.9)	60 (10)	–	94 (6.2)
Other	96 (3.5)	81 (7.9)	81 (8.0)	97 (3.1)	84 (7.8)	86 (8.0)	**84 (7.3)**	**54 (10)**	–	85 (6.4)
Two or more concomitant diseases	96 (4.3)	72 (9.6)	73 (9.7)	**92 (2.1)**	**65 (4.3)**	**68 (4.4)**	**81 (2.0)**	**35 (2.8)**	**53 (4.2)**	**59 (3.1)**

Bold: Survival significantly different from patients without comorbidity ($P < 0.01$).
SE, standard error.
[a] –, number of patients at risk too small for reliable survival estimate (SE > 10%).

Table 3
Multivariate survival of consecutive breast cancer patients diagnosed in southeastern Netherlands, 1995–2001

	n	(%)	HR	(95% CI)	*P* value
Concomitant disease					
No comorbidity	5729	(64)	1.00		
One concomitant disease					
Previous cancer	493	(6)	1.37	(1.2–1.7)	0.003
Cardiovascular disease	624	(7)	1.34	(1.1–1.7)	0.009
COPD	403	(4)	1.13	(0.9–1.5)	0.4
Diabetes mellitus	637	(7)	1.33	(1.1–1.6)	0.004
Cerebrovascular	207	(2)	1.63	(1.2–2.3)	0.004
Tuberculosis	100	(1)	1.02	(0.6–1.7)	1.0
Dementia	70	(1)	2.34	(1.6–3.5)	0.0001
Digestive tract	143	(2)	1.18	(0.8–1.8)	0.5
Other	138	(2)	1.27	(0.8–1.9)	0.2
Two or more concomitant diseases	600	(7)	1.44	(1.3–1.5)	0.0001
Stage					
I	2490	(28)	1.00		
II	3680	(41)	1.93	(1.6–2.3)	0.0001
III/IV	1105	(12)	3.82	(3.2–4.6)	0.0001
Unknown[a]	1691	(19)	1.82	(1.5–2.2)	0.0001
Treatment					
S	1850	(21)	1.00		
S + RT	2733	(30)	0.70	(0.6–0.8)	0.0001
S + RT + ST	2656	(30)	1.05	(0.9–1.2)	0.5
S + ST	1245	(14)	1.29	(1.1–1.5)	0.001
ST	310	(3)	2.99	(2.5–3.6)	0.0001
Other	172	(2)	3.62	(2.9–4.6)	0.0001
Age (years)					
<50	2313	(26)	1.00		
50–69	4185	(47)	0.97	(0.9–1.1)	0.7
70–79	1668	(19)	1.47	(1.3–1.7)	0.0001
80+	800	(9)	2.42	(2.1–2.8)	0.0001

HR, Hazard Ratio; 95% CI, 95% Confidence Interval.
[a] Patients with a negative sentinel node without complete axillary clearance were coded as stage unknown by the cancer registry.

two or more conditions only 59% (95% CI: 53–65). Comparing patients without comorbidity by age group showed that patients without coexistent disease above age 70 years had higher relative 5-year survival rates than those below age 50 years (93% (95% CI: 89–97) vs. 84% (95% CI: 82–86)).

In a multivariate survival analysis, the presence of any comorbidity yielded a prognostic effect, after adjustment for age, stage of disease, and treatment (HR = 1.3, $P = 0.0001$ for one coexistent disease and HR = 1.4, $P = 0.0001$ for 2+ coexistent diseases) (Table 3). The most important effects on survival were found for previous cancer (HR = 1.4, $P = 0.003$), cerebrovascular disease (HR = 1.6, $P < 0.004$), and dementia (HR = 2.3, $P < 0.0001$).

4. Discussion

Primary treatment of breast cancer patients with serious comorbidity was less extensive than treatment of those without comorbidity. Adjuvant radiotherapy was administered less often, being replaced by either another surgical procedure (mastectomy instead of breast-conserving surgery) or adjuvant hormonal treatment. Axillary dissection was omitted in a large portion of the (older) patients with serious comorbidity. Independent of age, stage and treatment, survival was significantly worse for breast cancer patients who suffered from a previous cancer, cardiovascular disease, diabetes mellitus, cerebrovascular disease, or dementia, compared with those without these coexistent diseases. The discrepancy in survival between those patients with only breast cancer and those who also suffered from other chronic diseases increased.

The Charlson's list was used to score prognostic comorbidity in the present study, without subdivision according to severity, because this was too complex for the registrars. Misclassification of comorbidity is limited, because the comorbid diseases are recorded routinely by trained registry personnel and data are collected directly from the medical records of the patients. A validation study among breast cancer patients showed some under-registration, mainly for

cardiovascular diseases [12]. This means that the real effects of comorbidity on treatment choice and survival are probably even stronger than those described here.

Other studies also reported less extensive treatment of older breast cancer patients [13,14], although they could not attribute this to either advanced age or the presence of comorbidity. We found that treatment was affected much more among the patients aged 70 years and older than in the younger patients. Approximately 10% of elderly patients were not treated according to guidelines [6,7,14]. More specifically, elderly patients did not receive radiotherapy [6,13] and surgical procedures were less extensive [7,13], especially with respect to axillary lymph node dissection [7]. In the western part of the Netherlands, the proportion receiving non-standard treatment was higher among patient aged 75 years and older, the highest for patients with severe comorbidity [6]. We also found that older patients received less radiotherapy and less extensive surgery. The presence of comorbid conditions clearly altered the therapeutic regimen, independent of the patient's age and stage.

The question is whether this is good clinical practice. Treatment of patients with coexistent conditions according to current guidelines may cause more complications and thus lower survival rates. However, these patients could also be 'understaged' and/or 'undertreated'. The omission of radiotherapy has been shown to have adverse effects on recurrence rates and overall mortality [15–17]. Furthermore, axillary node dissection contributes to prolonged survival [18]. In contrast, we found no relationship between the number of post-surgical complications and severity of comorbidity in a random sample of approximately 500 patients, but we did find an increase of the severity of comorbidity with age [19]. This could explain the increased contrast in survival between patients with and without comorbidity in the older age groups.

Obviously, breast cancer patients are at risk of dying from breast cancer as well as from other causes. However, it seems likely that serious comorbidity affects survival, either due to mortality as a result of the comorbid disease or because of 'undertreatment'. Recently, Yancik and colleagues [7] showed that diabetes and previous cancer predicted early mortality. The death of only approximately 50% of the patients who died within 30 months after diagnosis was due to breast cancer. Schairer and colleagues [20] found that white patients older than 70 years with localised, regional or unknown stage at diagnosis had a higher probability of dying from other causes than breast cancer 5 years after diagnosis. The probability of death from other causes at the end of follow-up (27.9 years) exceeded that from breast cancer for patients with localised disease aged >50 years, and patients with regional disease aged >60 years. Unfortunately, we do not have individual data on the cause of death, so we used relative survival to estimate disease-specific survival (this means we adjusted for survival for the background population with the same age structure). This showed significantly lower 5-year survival rates for most of the recorded coexistent diseases, with rates up to 50% lower. Furthermore, Hazard Ratios were still significantly elevated after adjustment for age, stage and treatment. Thus, an independent effect of the presence of comorbidity on survival was demonstrated.

We also observed an independent prognostic effect of age. This implies that other prognostic factors may play a role, such as an inferior performance status, decreased organ reserves, a diminished mental condition, and unfavourable social factors [21,22].

To our knowledge, this is the first time that the effect of comorbidity in breast cancer patients has been investigated in a population-based setting with a population of this size and such a long follow-up period. We could disentangle the prognostic effect of the coexistent disease itself from the effect of the altered treatment of patients with comorbidity.

In an increasingly ageing population comorbid conditions will play an even more important role in clinical decision-making and outcome. We demonstrated that elderly breast cancer patients can be divided in to those without other diseases, with a relatively good prognosis, and those who have at least one other serious coexistent disease with a significantly poorer prognosis. The presence of these coexistent diseases warrants care programmes with adapted treatment guidelines.

Conflict of interest statement

None declared.

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