Management of elderly patients with breast cancer : towards evidence based medicine

Water, W. van de

Chapter 4

Adherence to treatment guidelines and survival by age at diagnosis in patients with early stage breast cancer

Willemien van de Water
Esther Bastiaannet
Olaf M. Dekkers
Anton J.M. de Craen
Rudi G.J. Westendorp
Adri C. Voogd
Cornelis J.H. van de Velde
Gerrit-Jan Liefers

British Journal of Surgery 2012 Jun;99(6):813-20

Abstract

Background

Elderly patients with breast cancer are underrepresented in clinical studies. Therefore, it is unknown whether treatment guidelines, based on clinical trials, can be extrapolated to this population. The aim of this study was to assess adherence to treatment guidelines by age at diagnosis, and to examine age-specific survival in relation to guideline adherence.

Methods

Patients with early stage breast cancer aged younger than 65 years, or 75 years or older, diagnosed between 2005 and 2008, were identified from the Netherlands Cancer Registry. Adherence to treatment guidelines for breast and axillary surgery, radiotherapy, chemotherapy and endocrine therapy was determined. Nonadherence to the guidelines was defined as overtreatment or undertreatment. The primary endpoint was overall survival, assessed by means of an instrumental variable, the comprehensive cancer center region.

Results

Overall, 24,959 patients younger than 65 years and 6,561 patients aged 75 years or older were included. Median follow-up was 2.8 years. Compared with patients younger than 65 years, those aged 75 years or older were less frequently treated in concordance with guidelines: 62.0% (15,487 patients) versus 55.6% (3,647 patients) ($p<0.001$). In both age groups, most patients received at least three out of five treatment modalities in concordance with guidelines: 98.8% (24,652 patients) and 93.8% (6,152 patients) respectively. Survival analysis using the instrumental variable showed that adherence to guidelines was not associated with overall survival in patients younger than 65 years ($p=0.601$) or those aged 75 years or older ($p=0.190$).

Conclusions

Adherence to treatment guidelines was affected by age at diagnosis. However, adherence to the guidelines was not associated with overall survival in either age group.

Introduction

The first national multidisciplinary guideline 'Breast Cancer Treatment', initiated by the Dutch Institute of Health Care Improvement CBO and the Dutch National Breast Cancer Society[1], was implemented in the Netherlands in 2002. The aim was to improve breast cancer care and cure by providing consensus and evidence based recommendations for treatment[1]. Deviation from the guidelines is possible, but reasons should be documented. Since 2002, regular revisions have ensured that information and recommendations are updated.

In 2008 in the Netherlands, almost 20% of breast cancer patients was 75 years or older at time of diagnosis[2]. Elderly patients differ from younger patients in many respects. The presence of comorbidities and concomitant medication may interact with treatment or survival from breast cancer[3-6]. In addition, there is evidence of different tumor biology in elderly breast cancer patients[7]. Moreover, a recent study showed that, in contrast to younger patients, survival of elderly breast cancer patients has not improved significantly in recent years[8].

Despite comprising a large proportion of those with breast cancer, elderly breast cancer patients have been underrepresented in trials[7]; it has been estimated that only 1 to 2% of the elderly participates in clinical trials[9]. Therefore, adherence to guidelines may not necessarily improve breast cancer cure and care in the elderly as it is expected in the younger population.

The aim of this study was to assess adherence to national breast cancer treatment guidelines by age at diagnosis, and to evaluate age specific survival in relation to adherence to the guidelines. Previous studies have investigated the association between guideline adherence and survival in an observational setting[10;11]. However, these studies all suffer from confounding by indication[12] and so alternative methods were applied in the present analysis.

Methods

Subjects

Female patients with incident early stage breast cancer, diagnosed between 2005 and 2008, were identified from the Netherlands Cancer Registry database. Early stage breast cancer was defined as T012, N01, M0 breast cancer, i.e. a tumor size smaller than five centimeters, with either no axillary metastases, or one or more metastases in movable ipsilateral level I or II axillary lymph nodes, without distant metastasis. PALGA (Pathologisch-Anatomisch Landelijk Geautomatiseerd Archief), the nationwide Dutch network and registry of histo- and cytopathology, regularly submits reports of all diagnosed malignancies to the regional cancer registries. The national hospital discharge databank, which receives discharge diagnoses of admitted patients from all Dutch hospitals, completes case ascertainment. Registry personnel collects data on diagnosis, staging, and treatment from the medical records, including

pathology and surgery reports, by using the registration and coding manual of the Dutch Association of Comprehensive Cancer Centers. All data from the regional cancer registries are merged into the Netherlands Cancer Registry.

Patients were categorized in age groups as discussed at the meeting of the International Society of Geriatric Oncology (SIOG) in 2009[13]. Inclusion was restricted to patients aged younger than 65 years and patients aged 75 years or older, since patients aged younger than 65 years at diagnosis are frequently included in trials upon which guidelines are based, while patients aged 75 years or older are included sporadically[9]. Primary endpoint was overall survival, which was defined as time from diagnosis to death from any cause. Relative survival, which takes into account the risk of dying from other causes than breast cancer, was also evaluated.

Guideline adherence

Supplementary table 1 shows guideline recommendations with regards to breast and axillary surgery, radiotherapy, chemotherapy and endocrine therapy. Breast surgery and axillary surgery was recommended for all patients. Radiotherapy was recommended after a wide local excision, and after a mastectomy in case of non-radical surgery, involvement of the pectoral muscle, or positive axillary nodes at the apex. Chemotherapy was recommended in patients with nodal involvement, and in node negative patients with other unfavorable tumor characteristics. In patients aged 70 years or older, no general recommendations were given. With few exceptions, endocrine therapy was recommended in patients with estrogen and/or progesterone positive tumors.

Patients were adherent if they received treatment in concordance with guideline recommendations. Nonadherence was defined as undertreatment (omission of treatment despite recommendation), or overtreatment (administration of treatment despite no recommendation). The definitions of undertreatment and overtreatment were based on guidelines at time of diagnosis, and did not include reasons for treatment decisions. Adherence was assessed for all treatment modalities, summed, and then dichotomized in 100% adherence versus less than 100% adherence. As data on non-radicality, and localization of positive lymph nodes were not available, adherence with radiotherapy after a mastectomy could not be assessed and may therefore slightly differ from true adherence. Chemotherapy recommendations in some patients depend on general health. As these data were not available, adherence could not be assessed in these patients, and calculated adherence may again slightly differ from true adherence.

Statistical analysis

SPSS 17.0 and STATA/SE 10.0 were used for statistical analyses. Descriptive statistics comprised median and interquartile range (i.q.r) and numbers (%). Pearson chi square test was used to compare differences in guideline adherence between age groups. A Cox proportional hazard model was used to assess overall survival, and reported with 95% confidence interval (CI). Relative survival was calculated by the Hakulinen method as the ratio of the observed

survival among the cancer patients and the survival that would have been expected based on the corresponding (age, sex and year) general population. National life tables were used to estimate expected survival. Relative Excess Risks of death (RER) were estimated using a multivariable generalized linear model with a Poisson distribution, based on collapsed relative survival data, using exact survival times.

Survival was assessed for patients who were treated 100% adherent and patients who were treated less than 100% adherent. As observational studies suffer from confounding by indication, additional survival analyses by means of an instrumental variable were performed. An instrumental variable may serve as a substitute for randomization in non-randomized studies, and may reduce confounding by indication under the assumptions that the instrumental variable is 1) associated with the exposure, 2) unrelated to the confounders (exclusion restriction), and 3) has no direct association with the outcome other than through the exposure (independence assumption)[14;15]. The geographically defined comprehensive cancer center regions (CCCRs) were used as an instrumental variable. CCCRs thus represented different proportions of patients who were treated 100% adherent, and were used as a substitute for randomization; the place of residence determines a patient's allocation to a CCCR and thereby to a probability of being treated 100% adherent. Analyses were performed to explore potential differences in tumor characteristics among CCCRs, although no large differences were expected a priori. Both multivariable and stratified analyses were performed. Covariates were included in the multivariable model if they were judged to be clinically relevant, and comprised histological grade (G1; G2; G3,4), T stage (T0,1; T2), nodal stage (negative; positive), estrogen receptor status (negative; positive), progesterone receptor status (negative; positive) and age (continuous). All statistical tests were two-sided. P values <0.05 were considered to be statistically significant.

Data were analyzed as intention to treat analyses; patients were categorized by theoretical allocation to CCCR based on postal code, which did coincide with CCCR of treatment in more than 95% of the patients. For survival analyses, CCCRs were ranked based on decreasing proportion of patients who were treated 100% adherent.

Results

Between 2005 and 2008, 36,459 women, who were younger than 65 years or 75 years or older, were diagnosed with early stage breast cancer. Overall, 4,267 patients were excluded because of carcinoma in situ, or missing data regarding invasiveness, 649 patients because of missing data on estrogen and progesterone receptor status, and 23 patients because of missing data regarding therapy. This resulted in a study population of 31,520 patients, of whom 24,959 were younger than 65 years (median 52.3 years) and 6,561 were 75 years or older (median 82.5 years). Median follow-up (i.q.r) was 2.8 (1.8 to 3.9) years for all patients, 2.9 (1.9 to 3.9) years for patients younger than 65 years and 2.5 (1.5 to 3.5) years for patients aged 75 years or older.

Table 1. Treatment characteristics by age at diagnosis.

	<65 years (n=24,959)		≥75 years (n=6,561)		p
	n	%	n	%	
Most extensive surgery					<0.001
Mastectomy	9,037	36.2	3,473	52.9	
Wide local excision	15,805	63.3	1,677	25.6	
No resection	117	0.5	1,411	21.5	
Most extensive AS					<0.001
ALND	9,699	38.9	2,211	33.7	
SLN	14,864	59.6	2,665	40.6	
None	396	1.6	1,685	25.7	
Radiotherapy					<0.001
Yes	16,931	67.8	1,649	25.1	
No	8,028	32.2	4,912	74.9	
Chemotherapy					<0.001
Yes	12,22	49.0	27	0.4	
No	12,739	51.0	6,534	99.6	
Endocrine therapy					<0.001
Yes	10,547	42.3	3,776	57.6	
No	14,412	57.7	2,785	42.4	

AS: axillary surgery; ALND: axillary lymph node dissection; SLNB: sentinel lymph node biopsy.

Patients aged 75 years or older more often presented with an unknown histological grade and unknown nodal status, with larger tumors and a positive estrogen receptor status (all p values <0.001). Table 1 shows treatment characteristics by age. Patients aged 75 or older less often underwent breast and axillary surgery, and had a lower probability of receiving radiotherapy and chemotherapy, while endocrine therapy was administered more frequently.

As shown in Table 2, the proportion of patients who received all five treatment modalities in concordance with guidelines was significantly lower in patients aged 75 years or older; 15,487 (62.0%) patients versus 3,647 (55.6%) patients, respectively. In both age groups, the majority of patients received at least three out of five treatment modalities in concordance with guidelines; 24,652 (98.7%) patients and 6,152 (93.8%) patients, respectively.

Table 2. Number of treatments in concordance with guidelines, by age at diagnosis.

	<65 years (n=24,959)		≥75 years (n=6,561)		p
	n	%	n	%	
Number of treatments					<0.001
5 (100%)	15,487	62.0	3,647	55.6	
4 (80%)	5,722	22.9	1,266	19.3	
3 (60%)	3,443	13.8	1,239	18.9	
<3 (<60%)	304	1.3	409	6.2	

Figure 1 shows the distribution of patients who were treated adherent, overtreated and undertreated for all treatment modalities according to the guidelines, by age at diagnosis. Patients aged 75 years or older had a marked lower adherence to surgical therapy recommendations as compared with patients who were younger than 65 years (breast surgery 99.5% (n=24,842) versus 78.5% (n=5,150), p<0.001; axillary surgery 98.4% (n=24,563) versus 74.3% (n=4,876), p<0.001). As surgical resection is recommended for all patients with early stage breast cancer, nonadherence to surgical therapy recommendations was fully explained by undertreatment. Adherence with endocrine therapy recommendations was slightly lower in patients aged 75 years or older (80.8% (n=20,167) versus 79.2% (n=5,194), p=0.003). In case of nonadherence, patients aged 75 years or older were overtreated more often as compared with patients younger than 65 years. Most patients aged 75 years or older were adherent with chemotherapy recommendations (73.9% (n=18,452) versus 99.6% (n=6,534), p<0.001), because specific chemotherapy recommendations for patients aged 70 years or older were not given.

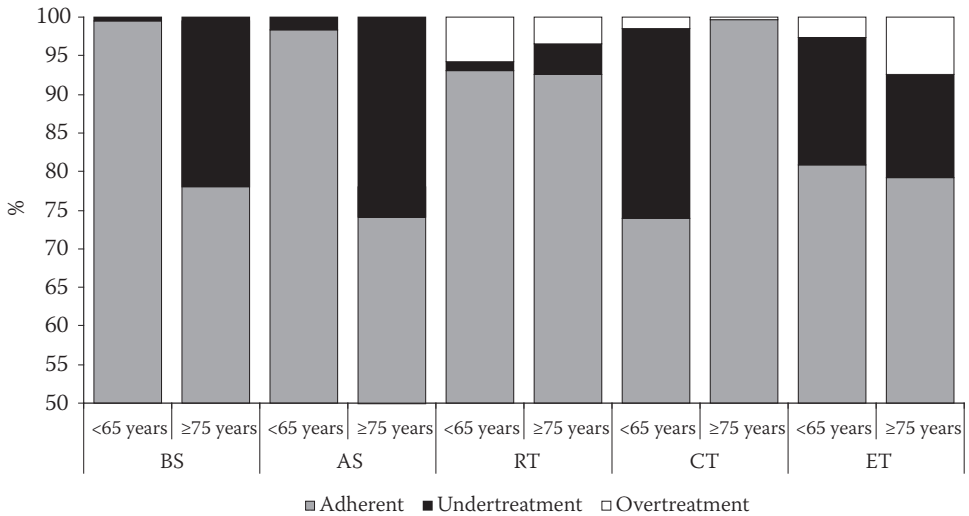

Figure 1. Adherence to guidelines, undertreatment and overtreatment per treatment, by age at diagnosis.

Number of deaths was 762 (3.1%) in patients younger than 65 years and 1,547 (23.6%) in patients aged 75 years or older. By conventional survival analyses, in patients younger than 65 years, overall survival was lower in patients who were treated less than 100% adherent as compared with those who were treated 100% adherent (patients who were treated 100% adherent functioned as reference category, univariate hazard ratio (HR) for patients who were treated less than 100% adherent was 1.68 (95% CI 1.46-1.94), p<0.001). In patients aged 75 years or older, these results were even more pronounced; HR 2.56 (95% CI 2.31-2.84), p<0.001. To account for unequal distribution of tumor characteristics and age, multivariable analyses were performed, which revealed comparable results (Table 3).

Table 3. Overall survival by adherence to guidelines and tumour characteristics, by age at diagnosis.

	<65 years			≥75 years		
	5-years survival (%)	HR (95% CI)*	p	5-years survival (%)	HR (95% CI)*	p
Adherence			**<0.001**			**<0.001**
100%	95	1 (reference)		71	1 (reference)	
<100%	92	1.75 (1.50-2.05)		48	1.62 (1.41-1.85)	
Histological grade			**<0.001**			**0.004**
G1 (well)	98	1 (reference)		76	1 (reference)	
G2 (moderate)	96	1.14 (0.86-1.50)		68	1.13 (0.95-1.36)	
G3, G4 (poor)	89	1.83 (1.38-2.43)		59	1.39 (1.13-1.71)	
T stage			**<0.001**			**0.001**
T0	88	1 (reference)		51	1 (reference)	
T1	95	1.06 (0.26-4.28)		68	0.79 (0.69-0.91)	
T2	91	1.69 (1.34-1.83)		56	1.25 (1.09-1.44)	
N stage			**<0.001**			**0.002**
Negative	95	1 (reference)		64	1 (reference)	
Positive	92	1.57 (1.34-1.83)		56	1.25 (1.09-1.44)	
ER			**<0.001**			**0.001**
Positive	96	1 (reference)		63	1 (reference)	
Negative	86	2.82 (2.25-3.54)		52	1.40 (1.14-1.72)	
PR			**0.014**			**0.002**
Positive	96	1 (reference)		65	1 (reference)	
Negative	89	1.32 (1.06-1.64)		55	1.30 (1.10-1.53)	
Age (years)	-	1.02 (1.01-1.03)	**<0.001**	-	1.09 (1.07-1.10)	**<0.001**

* Hazard ratios adjusted for all variables included in the model. HR: hazard ratio; CI: confidence interval; ER: estrogen receptor status; PR: progesterone receptor status.

In addition, survival was assessed by CCCR. The proportion of breast cancer patients who were treated 100% adherent varied among CCCRs in both age categories (in patients younger than 65 years 55.4% to 66.2%, p<0.001; in patients aged 75 years or older 50.0% to 59.8%, p=0.001). In both age groups, CCCR was not associated with overall survival (p=0.732; p=0.905 respectively). Multivariable analyses were performed to adjust for unequal distribution of tumor characteristics, which did not alter the results (Table 4). Analyses were stratified by T stage, N stage and histological grade, and adjusted for estrogen and progesterone receptor status. Again, results remained similar (data not shown). It was also studied whether CCCR was associated with relative survival (Supplementary table 2). Both in univariate and multivariable analyses the excess risk of death was similar among CCCRs.

Additional analyses restricted to the CCCR with the lowest and highest proportion of patients who were treated 100% in concordance with guidelines, did not alter the results. In patients younger than 65 years, the HR for the region with the lowest proportion of patients who were treated 100% adherent was 0.93 (95% CI. 0.69-1.26), p=0.657; in patients aged 75 years or older, HR was 0.87 (95% CI 0.60-1.11), p=0.262. Analyses were also stratified by year of diagnosis.

With a maximum median follow-up of 4.5 and 3.7 years respectively, similar results were observed (p=0.588 and p=0.335 respectively).

Since general recommendations for chemotherapy were not available for patients aged 75 years or older, survival analyses in this age group were repeated, in which 100% adherence was calculated without adherence to chemotherapy recommendations. Results were similar. Finally, an alternative definition of adherence was used, in which non adherence to guideline recommendations was defined as undertreatment only. In both age categories, again no difference in overall survival was observed among CCCRs (data not shown).

Table 4. Overall survival by Comprehensive Cancer Center Region, by age at diagnosis.

	<65 years			≥75 years		
	5-years survival (%)	HR (95% CI)*	p	5-years survival (%)	HR (95% CI)*	p
CCCR**			0.601			0.190
1 (highest)	93	1 (reference)		60	1 (reference)	
2	93	0.84 (0.61-1.15)		62	0.65 (0.49-0.88)	
3	95	0.81 (0.55-1.18)		60	0.80 (0.59-1.08)	
4	94	1.01 (0.73-1.41)		62	0.79 (0.58-1.09)	
5	95	0.93 (0.66-1.32)		60	0.87 (0.63-1.20)	
6	93	1.01 (0.74-1.38)		60	0.78 (0.59-1.03)	
7	95	0.87 (0.62-1.22)		63	0.84 (0.63-1.13)	
8 (lowest)	93	1.09 (0.73-1.61)		63	0.77 (0.57-1.05)	
Histological grade			**<0.001**			**0.003**
G1 (well)	98	1 (reference)		76	1 (reference)	
G2 (moderate)	96	1.31 (0.99-1.72)		68	1.19 (0.90-1.42)	
G3, G4 (poor)	89	2.07 (1.55-2.75)		59	1.43 (1.16-1.76)	
T stage			**<0.001**			**0.004**
T0	88	1 (reference)		51	-	
T1	95	0.89 (0.22-3.58)		68	1 (reference)	
T2	91	1.35 (0.33-5.44)		56	1.23 (1.07-1.41)	
N stage			**<0.001**			**0.006**
Negative	95	1 (reference)		64	1 (reference)	
Positive	92	1.57 (1.34-1.84)		56	1.22 (1.06-1.40)	
ER			**<0.001**			**0.004**
Positive	96	1 (reference)		63	1 (reference)	
Negative	86	2.62 (2.08-3.30)		52	1.36 (1.10-1.67)	
PR			**0.017**			**0.008**
Positive	96	1 (reference)		65	1 (reference)	
Negative	89	1.31 (1.05-1.64)		55	1.26 (1.06-1.49)	
Age (years)	-	1.02 (1.01-1.03)	**<0.001**	-	1.10 (1.08-1.11)	**<0.001**

* Hazard ratios adjusted for all variables included in the model. ** CCCR is ranked from highest to lowest proportion of patients who were treated 100% adherent. HR: hazard ratio; CI: confidence interval; ER: estrogen receptor status; PR: progesterone receptor status.

Discussion

Overall adherence with breast cancer guidelines, and in particular adherence with surgical therapy recommendations, was lower in patients aged 75 years or older. By using an instrumental variable to reduce confounding by indication, comprehensive cancer center regions, representing a different proportion of patients who were treated 100% adherent, were not associated with overall survival nor with relative survival in both age categories.

A considerable number of papers have been published on adherence to breast cancer guidelines, in which most define nonadherence as undertreatment only[16-20]. Few studied guideline adherence by age at diagnosis. Most studies observed that increasing age was associated with nonadherence to either surgical treatment[18;20-22], radiotherapy[19;22], chemotherapy[18;19] or endocrine therapy[18]. Some studies have assessed the association between guideline adherence and survival in an observational setting. However, these studies all suffer from confounding by indication[12]; frailty status, age, tumor characteristics or presence of comorbidity may all affect both adherence as well as survival. Most studies showed that adherence with guideline recommendations was associated with worse breast cancer outcome[10;11;23;24]. The authors did acknowledge the risk of confounding by indication, and adjusted for multiple variables. By conventional survival analyses, this study confirmed in both age groups a higher overall survival for patients who were treated 100% adherent as compared with patients who were treated less than 100% adherent. Even after adjustment for confounders, the results from the multivariable model may suffer from residual confounding by indication. Therefore, a conventional survival analysis may yield insufficient results in this particular field of study.

The use of an instrumental variable may improve the quality of analyses by minimizing confounding by indication[15;25], provided certain assumptions are met. An association was observed between CCCR and the proportion of patients who were treated 100% adherent. Further, tumor characteristics were slightly different among CCCRs. Therefore, both multivariable and stratified analyses were performed, which did not alter the results. Regional differences in background mortality may affect survival by region in another way than through guideline adherence. However, no major differences in background mortality, or remaining life expectancy among regions have been observed in elderly patients[26]. Since treatment allocation of more than 95% of the patients coincided with allocated CCCR, effect modification by cross-over is unlikely. There seems to be reasonable ground to justify the use of CCCR as an instrumental variable. Using an instrumental variable, guideline adherence was not associated with survival in both age groups.

It was expected that in patients younger than 65 years, guideline adherence would be associated with an improved survival. The results from the present study did not confirm this hypothesis. The current study evaluated outcome of patients who received five treatment modalities in concordance with guideline recommendations, compared with patients who did not, which

may not be representative for outcomes of a single randomized clinical trial; most trials study one particular treatment at once.

This study has some critical limitations. The proportion of patients who were treated 100% adherent differed 10 to 11% among regions, which might have been too small to result in survival differences. Virtually all patients who were treated less than 100% adherent, received three or more treatment modalities in concordance with guidelines. Consequently, the difference between adherent and nonadherent patients may have been too small to detect substantial survival differences. Although additional analyses stratified by year of diagnosis were performed, the limited follow-up time may have reduced the statistical power of the analyses.

Supplementary table 1. Guideline recommendations early stage breast cancer* in The Netherlands.

Breast surgery	Guideline 2005 – 2007: All. Guideline 2008: No change.
Axillary surgery	Guideline 2005 – 2007: All. Guideline 2008: No change.
Radiotherapy	Guideline 2005, 2006: Always after a wide local excision; radiotherapy may be considered after a mastectomy in case of a non-radical resection, involvement of pectoral muscle, or a positive axillary top. Guideline 2008: No change.
Chemotherapy	Guideline 2005 – 2007: <70 years, node positive #; ≤35 years (except <1cm, BR I); >35<70 years, N0, >3cm#; >35<70 years, N0, 2-3cm, BR II#; >35<70 years, N0, >1cm, BR III#. In patients aged 70 years or older with nodal involvement, general recommendations cannot be given. Chemotherapy may be considered for those with unfavorable tumor characteristics. Guideline 2008: <70, node positive; <35 years (except ≤ 1cm BR I); ≥35<70 years, N0, 1,1-2 cm, BR II/III; ≥35<70 years, N0, >2 cm. In patients aged 70 years or older, benefit of chemotherapy may be limited. It is advised to use AdjuvantOnline to calculate the expected benefit in individual cases.
Endocrine therapy$	Guideline 2005 – 2007: Node positive; ≤35 years (except <1cm, BR I); >35 years, N0, ≥3cm; >35 years, N0, 2-3cm, BR II; >35 years, N0, >1cm, BR III. Guideline 2008: Node positive; <35 years (except ≤ 1cm BRI); ≥ 35 years, N0, 1,1-2 cm, BR II/III; ≥ 35 years, N0, >2cm.

BR: Histological grade according to Bloom Richardson. * Early stage breast cancer was defined as T0-2, N0-1, M0 breast cancer, i.e. a tumor size smaller than five centimeters, with either no axillary metastases, or one or more metastases in movable ipsilateral level I or II axillary lymph nodes, without distant metastasis. # Patients aged 50 to 59 years in good physical state with an estrogen receptor and/or progesterone receptor positive tumor, and patients aged 60 to 69 years with an unfavorable prognosis. $ Patients with estrogen and/or progresterone receptor positive tumors only.

Supplementary table 2. Relative survival by Comprehensive Cancer Center Region, by age at diagnosis.

	5-years RS (95% CI)	Univariate RER (95% CI)	p	Multivariable* RER (95% CI)	p
< 65 years			0.726		0.639
CCCR1 (66.2)**	95.4 (93.0-97.2)	1 (reference)		1 (reference)	
CCCR2 (64.8%)	95.2 (92.7-97.0)	1.4 (0.8-2.4)		1.2 (0.7-2.1)	
CCCR3 (64.2%)	96.8 (95.3-98.0)	0.9 (0.5-1.5)		0.8 (0.5-1.3)	
CCCR4 (64.0%)	95.7 (94.3-96.9)	1.0 (0.6-1.7)		1.0 (0.6-1.6)	
CCCR5 (63.4%)	96.5 (94.9-97.8)	1.1 (0.6-1.8)		0.9 (0.6-1.5)	
CCCR6 (62.7%)	95.3 (93.5-96.7)	1.1 (0.7-1.8)		1.2 (0.7-1.9)	
CCCR7 (59.6%)	96.6 (94.7-98.0)	0.9 (0.5-1.6)		1.0 (0.6-1.7)	
CCCR8 (55.4%)	95.2 (93.5-96.6)	0.9 (0.5-1.5)		0.9 (0.6-1.4)	
≥ 75 years			0.873		0.820
CCCR1 (59.7%)**	91.0 (76.4-100)	1 (reference)		1 (reference)	
CCCR2 (58.7%)	97.5 (86.5-100)	0.3 (0.0-2.4)		0.5 (0.1-1.7)	
CCCR3 (58.2%)	94.3 (85.1-100)	0.6 (0.2-2.1)		0.6 (0.2-1.7)	
CCCR4 (56.4%)	95.9 (89.0-100)	0.5 (0.2-1.6)		0.9 (0.3-2.2)	
CCCR5 (56.1%)	91.5 (79.0-100)	0.6 (0.2-2.4)		0.8 (0.2-2.5)	
CCCR6 (55.7%)	92.1 (80.2-100)	0.5 (0.1-2.3)		0.8 (0.3-2.2)	
CCCR7 (54.2%)	94.7 (85.8-100)	0.6 (0.2-1.9)		0.9 (0.3-2.5)	
CCCR8 (49.9%)	98.1 (89.7-100)	0.3 (0.1-1.7)		0.5 (0.1-1.4)	

*Hazard ratios adjusted for histological grade, T stage, nodal stage, estrogen receptor, and progesterone receptor.
** Percentage of patients treated 100% adherent. RS: relative survival; RER: relative excess risk of death.

Reference List

(1) Dutch national breast cancer guidelines. 2011. 1-4-2011. Ref Type: Online Source

(2) VIKC. 2011. 12-8-2011. Ref Type: Online Source

(3) Pallis AG, Fortpied C, Wedding U et al. EORTC elderly task force position paper: approach to the older cancer patient. *Eur J Cancer* 2010;46:1502-1513.

(4) Bastiaannet E, Liefers GJ, de Craen AJ et al. 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* 2010;124:801-807.

(5) Louwman WJ, Janssen-Heijnen ML, Houterman S et al. Less extensive treatment and inferior prognosis for breast cancer patient with comorbidity: a population-based study. *Eur J Cancer* 2005;41:779-785.

(6) Houterman S, Janssen-Heijnen ML, Verheij CD et al. Comorbidity has negligible impact on treatment and complications but influences survival in breast cancer patients. *Br J Cancer* 2004;90:2332-2337.

(7) Wildiers H, Kunkler I, Biganzoli L et al. Management of breast cancer in elderly individuals: recommendations of the International Society of Geriatric Oncology. *Lancet Oncol* 2007;8:1101-1115.

(8) Bastiaannet E, Portielje JE, van de Velde CJ et al. Lack of survival gain for elderly women with breast cancer. *Oncologist* 2011;16:415-423.

(9) Hillner BE, Mandelblatt J. Caring for older women with breast cancer: can observational research fill the clinical trial gap? *J Natl Cancer Inst* 2006;98:660-661.

(10) Bouchardy C, Rapiti E, Fioretta G et al. Undertreatment strongly decreases prognosis of breast cancer in elderly women. *J Clin Oncol* 2003;21:3580-3587.

(11) Wockel A, Kurzeder C, Geyer V et al. Effects of guideline adherence in primary breast cancer--a 5-year multi-center cohort study of 3976 patients. *Breast* 2010;19:120-127.

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

(13) International Society of Geriatric Oncology. 2011. Ref Type: Online Source

(14) Greenland S. An introduction to instrumental variables for epidemiologists. *Int J Epidemiol* 2000;29:722-729.

(15) Rassen JA, Brookhart MA, Glynn RJ, Mittleman MA, Schneeweiss S. Instrumental variables I: instrumental variables exploit natural variation in nonexperimental data to estimate causal relationships. *J Clin Epidemiol* 2009;62:1226-1232.

(16) Silliman RA, Troyan SL, Guadagnoli E, Kaplan SH, Greenfield S. The impact of age, marital status, and physician-patient interactions on the care of older women with breast carcinoma. *Cancer* 1997;80:1326-1334.

(17) Goodwin JS, Hunt WC, Samet JM. Determinants of cancer therapy in elderly patients. *Cancer* 1993;72:594-601.

(18) Giordano SH, Hortobagyi GN, Kau SW, Theriault RL, Bondy ML. Breast cancer treatment guidelines in older women. *J Clin Oncol* 2005;23:783-791.

(19) Eisinger F, Ronda I, Puig B, Camerlo J, Giovannini MH, Bardou VJ. Breast cancer guidelines--Physicians' intentions and behaviors. *Int J Cancer* 2007;120:1136-1140.

(20) Yancik R, Wesley MN, Ries LA, Havlik RJ, Edwards BK, Yates JW. Effect of age and comorbidity in postmenopausal breast cancer patients aged 55 years and older. *JAMA* 2001;285:885-892.

(21) Allemani C, Storm H, Voogd AC et al. Variation in 'standard care' for breast cancer across Europe: a EUROCARE-3 high resolution study. *Eur J Cancer* 2010;46:1528-1536.

(22) White J, Morrow M, Moughan J et al. Compliance with breast-conservation standards for patients with early-stage breast carcinoma. *Cancer* 2003;97:893-904.

(23) Varga D, Wischnewsky M, Atassi Z et al. Does guideline-adherent therapy improve the outcome for early-onset breast cancer patients? *Oncology* 2010;78:189-195.

(24) Wockel A, Varga D, Atassi Z et al. Impact of guideline conformity on breast cancer therapy: results of a 13-year retrospective cohort study. *Onkologie* 2010;33:21-28.

(25) Brookhart MA, Rassen JA, Schneeweiss S. Instrumental variable methods in comparative safety and effectiveness research. *Pharmacoepidemiol Drug Saf* 2010;19:537-554.

(26) Statistics Netherlands. 2011. Ref Type: Internet Communication