



Survival of older patients with metastasised breast cancer lags behind despite evolving treatment strategies – A population-based study



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Abstract Background: Older women are more likely to be diagnosed with primary metastasised breast cancer than their younger counterparts. Evolving treatment strategies of metastasised breast cancer have resulted in improved survival in younger patients, but it remains unclear if this improvement has occurred in older patients as well. The aim of this study was to assess changes in treatment strategies over time in relation to overall and relative survival of older patients compared to younger patients with primary metastasised breast cancer.

Methods: All patients with a breast cancer diagnosis and distant metastases at first presentation (stage IV), between 1990 and 2012, were selected from the Netherlands Cancer Registry. Changes in treatment over time per age-group (<65 years, 65–75 years and >75 years) were assessed using logistic regression. Overall survival over time was calculated using Cox Regression Models and relative survival was assessed using the Ederer II method.

Results: Overall, 14,310 patients were included. Treatment strategies have strongly changed in the past twenty years; especially the use of chemotherapy has increased ($P < 0.001$ in all age-groups). Overall survival of patients <65 has significantly improved (Hazard Ratio (HR) per year 0.98, 95% Confidence Interval (CI) 0.98–0.99, $P < 0.001$), but the survival of older patients has not improved (HR 1.00, 95% CI 0.99–1.01, $P = 0.86$ for patients aged 65–75 and HR 1.00, 95% CI 1.00–1.01, $P = 0.46$ for patients aged >75). Similarly, relative survival has improved in patients <65 but not in women aged 65–75 and >75.

Conclusion: Overall and relative survival of older patients with metastasised breast cancer at first presentation have not improved in recent years in contrast with the survival of younger

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patients, despite increased treatment with chemotherapy for women of all ages. Future studies should focus on stratification models that can be used to predict which patients may benefit from specific treatment options.

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1. Introduction

Breast cancer is still the leading cause of cancer-related mortality in women worldwide [1]. About 5–10% of breast cancer patients present with distant metastases at diagnosis [2]. In recent years, treatment of metastatic breast cancer has evolved, especially due to the development of new endocrine therapies, novel chemotherapeutic regimens and targeted therapy including trastuzumab [3,4]. Several studies have shown that these improvements have led to an improvement of survival rates of metastasised breast cancer patients [3,5,6]. However, it is uncertain whether this improvement in survival has occurred in older patients with metastasised breast cancer as well. This is an important issue, as older patients are more likely to be diagnosed with advanced or metastasised breast cancer than their younger counterparts [2,7].

Since older patients are generally underrepresented in randomised clinical trials [8], current guidelines for treatment of older patients with metastasised breast cancer are mostly based on studies that were performed in younger populations [7,9]. In addition, older breast cancer patients who are included in clinical trials, have a more favourable prognosis than the general older breast cancer population [10]. It is well known that older breast cancer patients comprise a heterogeneous group due to large differences in comorbidity, functional status and geriatric syndromes between patients [11–13]. This large variation in phenotypes makes it difficult to extrapolate general guidelines to the individual older breast cancer patients. By studying observational data, we can gain better insight in outcomes after treatment of older breast cancer patients with metastasised breast cancer in the population.

The aim of this nationwide observational study was to assess changes in treatment strategies over time, in relation to overall and relative survival of older patients compared to younger patients with primary metastasised breast cancer.

2. Methods

All patients with metastasised (stage IV) breast cancer at time of the initial diagnosis, who were diagnosed between 1989 and 2012 were selected from the Netherlands Cancer Registry. The Netherlands Cancer Registry registers data of all patients who are diagnosed with cancer in the Netherlands. Patients are detected

through the central pathology database, after which trained personnel obtain patient, tumour and treatment characteristics from the patient charts. Follow-up status is available through linkage with municipal population registries, and was complete until December 31st, 2012.

Stage IV disease was defined as pathological stage at diagnosis according to the Tumour-Node-Metastasis (TNM)-stage that was used in the year of diagnosis. If pathological stage was missing, clinical stage was used. Oestrogen-receptor (ER) status and Progesteron-receptor (PR) status were available from the year 2005.

All patients were divided into three age-groups (<65, 65–75 and >75). Surgical treatment, axillary surgery, radiotherapy, first-line endocrine therapy and chemotherapy were available as binary variables since details about the specific therapies were lacking. The most extensive surgery and axillary surgery were used for the analyses.

2.1. Statistical analyses

All analyses were performed in IBM SPSS Statistics version 20.0 and STATA version 12.0. All statistical tests were two-sided, and a *P*-value smaller than 0.05 was considered as significant. If data were missing, patients were not excluded from the analyses, but analysed as a separate ‘unknown’ group within the same variable.

First, we graphically depicted the proportion of patients who received any of the specified treatments (surgery, radiotherapy, endocrine therapy and chemotherapy) per age-group. Differences between groups were assessed using Chi-square tests. Second, we depicted all treatment strategies over time, and assessed if the proportion of patients receiving specific treatments significantly changed over time using logistic regression models with the treatment as the outcome and the year of diagnosis as continuous variable.

Next, we calculated overall survival over time for all age-groups using Cox Regression Models. These analyses were additionally adjusted for age at diagnosis and tumour characteristics (grade, morphology, hormone receptor status and number of metastatic sites).

Finally, we assessed relative survival over time by calculating the relative excess risk (RER) using the Ederer II method. This method calculates the ratio of the survival observed among cancer patients divided by the survival of the corresponding general population (‘expected survival’), matched by age, sex and year of

diagnosis. National life tables were used to estimate the expected survival. Again, these analyses were adjusted for age at diagnosis and relevant tumour characteristics (grade, morphology, hormone receptor status and number of metastatic sites).

3. Results

Overall, 14,310 patients were included (7246 aged <65 years, 3,259 patients between the ages of 65 and 75 and 3805 patients aged >75 years, Table 1). Younger patients were more frequently diagnosed with tumours of ductal morphology than older patients (54.0% of patients aged <65, 46.9% of patients aged 65–75 and 46.1% of patients aged >75, $P < 0.001$). Younger patients had more metastatic sites than older patients ($P < 0.001$) and metastases were more often localised in bone and liver in younger patients (34.5% of patients aged <65 presented with bone metastases versus 31.8% of patients >75, $P < 0.001$ while 20.8% of patients <65 presented with liver metastases versus 10.1% of patients >75, $P < 0.001$).

Older patients received significantly less surgical treatment and radiotherapy for the primary tumour (32.3% of patients aged <65, 23.1% of patients aged 65–75 and 16.7% of patients aged >75 received surgical treatment, $P < 0.001$, while 17.7% of patients aged <65,

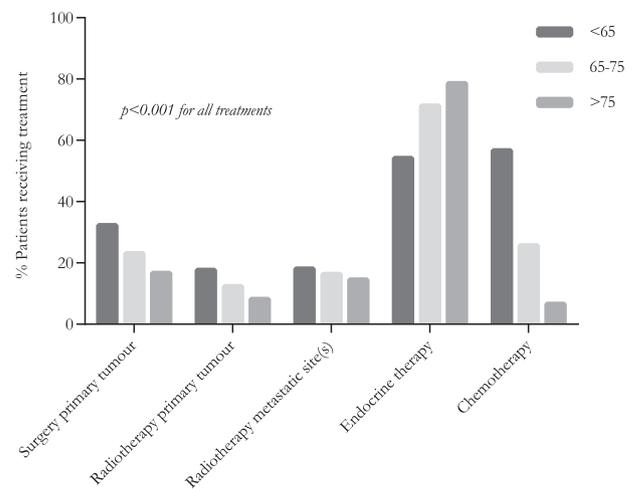


Fig. 1. Treatment per age-group.

12.4% of patients aged 65–75 and 8.2% of patients aged >75 received radiotherapy, $P < 0.001$). Furthermore, older patients were more likely to receive endocrine treatment and less likely to receive chemotherapy than their younger counterparts ($P < 0.001$ for both treatments, Fig. 1).

Treatment strategies of metastasised breast cancer have strongly changed over time (Fig. 2). The proportion of patients who were surgically treated increased

Table 1
Patient characteristics.

	All patients (N = 14,310)		Age <65 (N = 7246)		Age 65–75 (N = 3259)		Age >75 (N = 3805)		P-value
	N	%	N	%	N	%	N	%	
Grade									
I	326	(2.3)	157	(2.2)	70	(2.1)	99	(2.6)	<0.001
II	1762	(12.3)	969	(13.3)	412	(12.6)	381	(10.0)	
III	2988	(20.8)	1799	(24.8)	623	(19.1)	566	(14.9)	
Unknown	9265	(64.6)	4343	(59.8)	2157	(66.1)	2765	(72.6)	
Morphology									
Ductal	7209	(50.3)	3925	(54.0)	1529	(46.9)	1755	(46.1)	<0.001
Lobular	1887	(13.2)	910	(12.5)	491	(15.1)	486	(12.8)	
Other	5245	(36.6)	2433	(33.5)	1242	(38.1)	1570	(41.2)	
Oestrogen-receptor/progesteron-receptor (ER/PR) status^a									
Negative	1077	(7.5)	637	(8.8)	200	(6.1)	240	(6.3)	<0.001
Positive	4042	(28.2)	2117	(29.2)	814	(25.0)	1111	(29.2)	
Unknown	9191	(64.2)	4492	(62.0)	2245	(68.9)	2454	(64.5)	
Metastases localisation^b									
Bone	4687	(32.7)	2505	(34.5)	970	(29.7)	1212	(31.8)	<0.001
Lung	1458	(10.2)	680	(9.4)	320	(9.8)	458	(12.0)	<0.001
Liver	2270	(15.8)	1515	(20.8)	370	(11.3)	385	(10.1)	<0.001
Other	2447	(17.1)	1177	(16.3)	708	(18.6)	663	(17.4)	0.007
Unknown	5262	(36.7)	2479	(34.1)	1310	(40.2)	1473	(38.7)	<0.001
Number of metastatic sites									
1	10,733	(74.8)	5232	(72.0)	2489	(76.3)	3012	(79.0)	<0.001
2	2319	(16.2)	1252	(17.2)	504	(15.5)	563	(14.8)	
3 or more	1289	(9.0)	784	(10.8)	269	(8.2)	236	(6.2)	

^a Available from the year 2006.

^b More than one localisation possible.

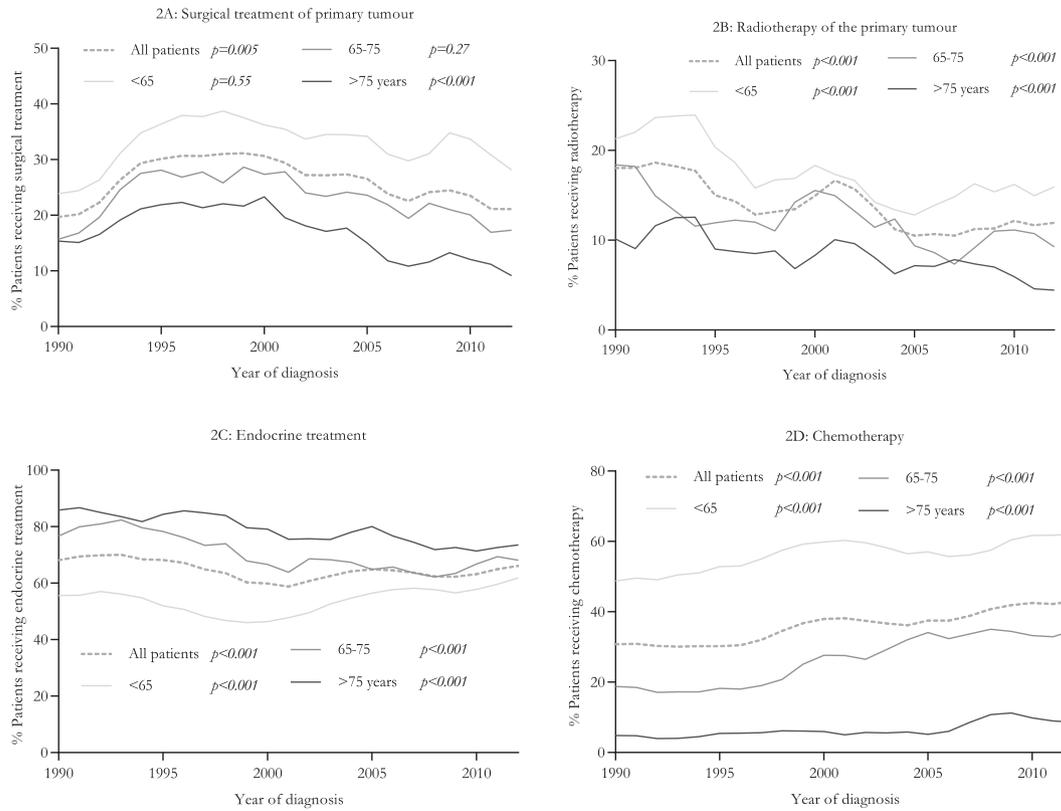


Fig. 2. Treatment modalities over time per age-group. All figures are presented as three-year moving means. *P*-values were calculated using logistic regression, and represent *p* for trend for year of diagnosis.

between 1990 and 1995 (21.7% of all patients in 1990 to 30.1% in 1995), but strongly decreased after 1998 in all age-groups (30.1% in 1995 to 20.5% of patients in 2012 were surgically treated *P* for trend over the whole time period (1990–2012) = 0.005). Also, use of radiotherapy significantly decreased in all age-groups between 1990 and 2012 (*P* for trend <0.001). In contrast, the use of first line endocrine treatment slightly increased in patients aged <65, but decreased in patients aged 65–75 and patients aged >75. Finally, the proportion of patients receiving chemotherapy significantly increased in all age-groups (*P* for trend <0.001 for all age-groups).

Median overall survival was 1.78 years in patients <65 years, inter quartile range (IQR) 0.72–3.47. In patients aged 65–75, median survival was 1.34 years, IQR 1.34–3.08, while median survival of patients >75 was 0.97 years, IQR 0.24–2.40 years. The overall survival of the whole cohort of patients has significantly improved in the past twenty years (multivariable adjusted Hazard Ratio (HR) 0.99, 95% Confidence Interval (CI) 0.99–1.00, *P* < 0.001, Fig. 3). This survival gain was fully explained by the improved survival of younger patients (multivariable adjusted HR 0.98, 95% CI 0.98–0.99 per year, *P* < 0.001), as the survival of

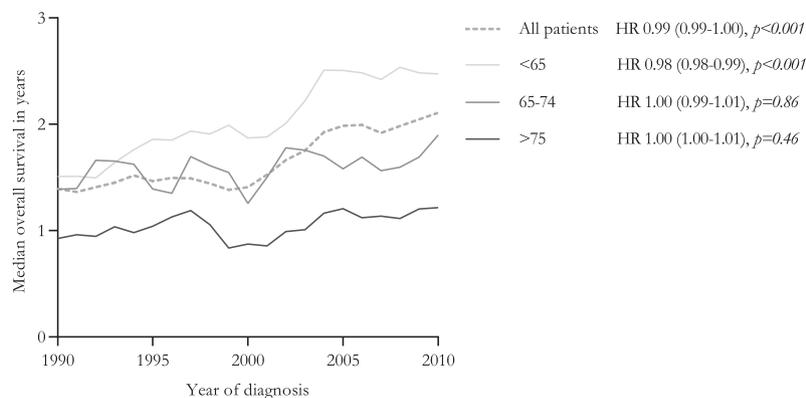


Fig. 3. Median overall survival over time per age-group. Data are presented as 3-year moving means. All presented Hazard Ratios (HRs) are adjusted for age at diagnosis, oestrogen-receptor/progesteron-receptor (ER/PR) status, morphology, grade and number of metastatic sites.

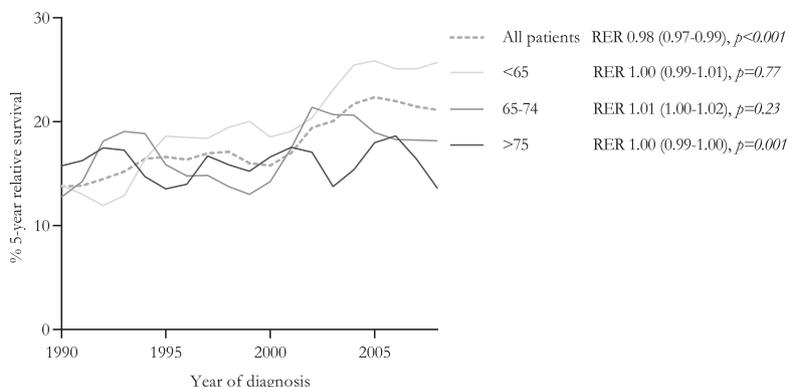


Fig. 4. 5-Year relative survival over time per age-group. Data are presented as 3-year moving means. All presented Relative Excess Risks (RERs) are adjusted for age at diagnosis, oestrogen-receptor/progesteron-receptor (ER/PR) status, morphology, grade and number of metastatic sites.

older patients has not improved in these years (multivariable adjusted HR 1.00, 95% CI 0.99–1.01 per year, $P = 0.86$ for patients aged 65–75 and multivariable adjusted HR 1.00, 95% CI 1.00–1.01 per year, $P = 0.46$ for patients aged >75).

Similarly, relative survival has improved for the whole cohort (multivariable adjusted RER 0.98, 95% CI 0.98–0.99 per year, $P < 0.001$, Fig. 4). Again, this improvement of relative survival was fully explained by a survival gain in younger patients (multivariable adjusted RER 0.98, 95% CI 0.97–0.99 per year, $P < 0.001$ for patients <65 years). Relative survival did not improve in patients older than 65 years (multivariable adjusted RER 1.00, 95% CI 0.99–1.01 per year, $P = 0.77$ for patients aged 65–75 and multivariable adjusted RER 1.01, 95% CI 1.00–1.02 per year, $P = 0.23$ for patients aged 75 years and older).

4. Discussion

This study shows that treatment strategies for both older and younger patients with metastasised breast cancer have drastically changed in the past twenty years. However, these changes have only resulted in improved overall and relative survival rates in younger women with metastasised breast cancer, while survival of older patients with metastasised breast cancer has not improved.

Around 80% of older women with breast cancer have hormone-receptor positive disease [9], which explains the high prescription rate of endocrine treatment in older women in our data. In the early nineties, tamoxifen was the first line endocrine treatment. After 2002, third generation aromatase inhibitors were incorporated as first line treatment of metastasised ER-positive breast cancer in the Dutch national guideline [14], as they were shown to be superior as compared to tamoxifen in postmenopausal women with advanced breast cancer [15]. Of note, we observed almost no changes in the percentage of older women who received endocrine treatment,

but it is likely that an increasing proportion of patients was treated with aromatase inhibitors after 2002.

Also, we have shown that an increasing proportion of patients over the age of 65 was treated with chemotherapy in more recent years. Several chemotherapeutic regimens have become available that are well tolerated by older women such as capecitabine and liposomal doxorubicin [9]. In older patients, monotherapy with chemotherapeutic drugs with low toxicity profiles is generally preferred to combined chemotherapy regimens, although strong evidence in older patients is lacking [7,9]. In addition, treatment with bisphosphonates for patients with bone metastases has been advised since the late 1990s to all women with bone metastases [14], but it is unlikely that this has attributed to changes in survival rates, as no survival benefit for treatment with bisphosphonates has been proven in patients with metastasised breast cancer [14,16].

Despite these evolving palliative treatments, we have shown that survival of older patients with metastasised breast cancer lacks behind compared to survival of younger patients. These findings are in line with previous studies that were performed in patients with non-metastasised breast cancer [17]. The increasing survival gap may be explained by both undertreatment and overtreatment of older patients. Possibly, there are patients who would benefit from palliative chemotherapy and targeted therapy, but who do not receive it due to age discrimination. On the other hand, frail elderly women may suffer decreased survival due to unanticipated toxicity of chemotherapy or hormonal therapy.

An important consideration in treating older patients with metastasised breast cancer, is to determine the goals of treatment. In patients with metastasised breast cancer, the main treatment goals should be to maintain quality of life, to minimise disease symptoms and to prolong survival without causing toxicity of treatment [7,9,18]. Balancing survival gain and toxicity is especially challenging in older patients, since older breast cancer patients are at increased risk of adverse outcomes of surgical treatment, chemotherapy and endocrine therapy

[19–21]. This requires good selection of patients for specific treatments [18]. A possible tool for this purpose may be the geriatric assessment [18]. Several studies have shown that a geriatric assessment can predict the risk of early mortality as well as toxicity of treatments in the adjuvant setting [22–24] and this might also apply to palliative treatment of metastasised breast cancer. A recent study by van de Water et al. suggested that treatment of older patients, in an oncogeriatric care programme may result in an improved overall survival of older patients [25]. In this programme, treatment choices were guided by a comprehensive geriatric assessment [25], thereby improving individualised treatment. However, this study included only a small number of patients, and it remains unclear if an improved selection of older patients truly improves the clinical outcome of older breast cancer patients.

Unfortunately, few studies have specifically investigated breast cancer treatment in older patients, especially in metastasised breast cancer. Older patients are generally underrepresented in clinical trials [7] and older women who participate in trials tend to have more favourable prognostic patient and tumour characteristics than patients in the general population [8,10]. Consequently, trial results cannot be extrapolated to the general older breast cancer population. Furthermore, currently ongoing trials rarely incorporate end-points that are relevant for older patients such as functional status or quality of life [26]. This is not different for clinical trials in patients with metastasised breast cancer. Therefore, studying observational data will be essential in order to improve our knowledge in the treatment of older breast cancer patients in the near future. Recently, we have initiated a prospective observational study in metastasised older breast cancer patients. In this study, we will perform a geriatric assessment at the time of diagnosis, after which we will prospectively register functional, cognitive and psychological decline as well as quality of life of these patients.

4.1. Strengths and limitations

The main strength of this study is the large number of included patients from the Netherlands Cancer Registry with well-registered, quality assured data. Also, this study provides new insights in the poor outcome of older patients with metastasised breast cancer.

Of course, this study also has its limitations. Importantly, we were not able to incorporate specific patient characteristics such as comorbidity in our analyses, as these data are not registered in the Netherlands Cancer Registry. Also, specific details of the prescribed therapies were not available. In addition, the data of the Netherlands Cancer Registry are gathered between six months and one year after diagnosis of patients, and follow-up is provided by linkage to municipal systems. This means that mainly treatments that are prescribed as the

first line of treatment are registered in the Netherlands Cancer Registry, which may lead to an underestimation of the proportion of patients who receive chemotherapy and/or endocrine therapy. Finally, one could argue that the fact that we did not assess breast cancer specific survival is a limitation of the study. However, by using relative survival, we believe that we have used a reasonable alternative, as it has been shown that relative survival can be used as a valid proxy for cancer specific survival [27]. Furthermore, estimation of the cause of death is especially difficult in older patients [28], which makes relative survival a more reliable end-point [27].

In conclusion, despite evolving treatment strategies, overall and relative survival of older patients with metastasised breast cancer have not improved in recent years in contrast with the survival of younger patients, thereby increasing the survival gap between young and older patients with metastasised breast cancer. In order to individualise care of older breast cancer patients with metastasised breast cancer, future studies should focus on stratification methods that can be used to decide which patients should receive certain treatments and that can predict specific outcomes that are especially of interest for older breast cancer patients, such as functional status and quality of life.

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Conflict of interest statement

None declared.

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