



## 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

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