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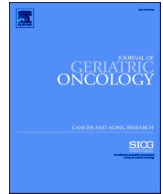
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Research Paper

A comparison of treatment allocation and survival between younger and older patients with HER2-overexpressing de novo metastatic breast cancer

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ABSTRACT

Introduction: There have been several developments in the treatment of HER2-overexpressing metastatic breast cancer. However, pivotal trials mainly included younger and healthier patients, resulting in a lack of information about the benefits and harms of treatment for most older patients. The aim of this study was to provide an overview of the differences in treatment allocation and survival outcomes over time between younger and older patients with HER2-overexpressing metastatic breast cancer.

Materials and Methods: All patients from the Netherlands Cancer Registry with de novo metastatic breast cancer between 2005 and 2021 were included. Patients were divided into three age groups: <65, 65–74, and ≥75 years. Changes in treatment allocation were graphically depicted over time. Cox proportional hazard models were used to calculate overall survival and Poisson models for relative survival.

Results: Overall, 2,722 patients were included. Between 2005 and 2021, the use of targeted therapy as first-line treatment increased for all age groups (<65 years from 33.8% to 90.6%, $p < 0.001$; 65–74 years from 29.2% to 86.5%, $p = 0.001$; ≥75 years from 4.3% to 55.8%, $p < 0.001$). Use of chemotherapy as first-line treatment also increased for all age groups (<65 years from 73.5% to 89.8%, $p < 0.001$; 65–74 years from 50.0% to 78.4%, $p = 0.01$; ≥75 years from 8.7% to 37.2%, $p = 0.04$). Although not statistically significant, the use of endocrine therapy, both as monotherapy and in combination with targeted therapy in the first line, decreased (<65 years 19.1% to 5.5%, $p < 0.001$; 65–74 years 25.0% to 13.5%, $p = 0.03$; ≥75 years 65.2% to 37.2%, $p = 0.16$). Changes in relative and overall survival were similar and improved in all age groups, but most in the youngest age group (relative excess risk [RER] 0.93, 95% confidence interval [CI] 0.91–0.94 per year, $p < 0.001$), and least in patients ≥75 (RER 0.96, 95% CI 0.93–0.98 per year, $p = 0.001$).

Discussion: The use of first-line chemotherapy and targeted therapy increased in all age groups, while the use of endocrine therapy decreased over time. Nevertheless, the uptake of chemotherapy and targeted therapies was substantially slower in the oldest age group. Overall survival and relative survival improved for all age groups, but these improvements were smaller in the older age groups.

1. Introduction

Breast cancer is the most frequently diagnosed malignancy in women and is increasingly common in women over 65 years of age [1]. Among older patients, about 4–9% have metastases at the time of diagnosis [2]. Although older patients generally have more favourable biological

tumour characteristics compared to younger patients, 10–15% of their tumours overexpress the human epidermal growth factor receptor 2 (HER2) protein [3]. The overexpression of HER2 is associated with a poor prognosis, because HER2 mediates cell growth, differentiation, and survival of cells [4]. However, since the registration of the anti-HER2 antibody trastuzumab two decades ago, and later other HER2-directed

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monoclonal antibodies, tyrosine kinase inhibitors, and antibody-drug conjugates, treatment of this aggressive subtype has improved considerably. The marketing authorisation of trastuzumab in Europe was issued in 2000 and included in Dutch guidelines from 2002 [5]. Unfortunately, the pivotal trials on this targeted therapy mainly included younger and healthier patients, which means that less is known about the benefits and harms of treatment for older patients [6–9]. This information is crucial, because this growing older population represents a heterogeneous group with large differences in fitness and frailty, potentially putting them at higher risk of side effects than younger patients [10]. As a result of this lack of evidence, older patients are often under- or overtreated but there are limited data on age-related differences in HER2-overexpressing metastatic breast cancer.

The aim of this study was therefore to provide an overview of the differences in treatment allocation and survival outcomes over time between younger and older patients with HER2-overexpressing de novo metastatic breast cancer.

2. Methods

All patients from the Netherlands Cancer Registry who were diagnosed with metastatic breast cancer between 2005 and 2021 were included [11]. For this registry, trained data managers collected data from medical records on patient, tumour, and treatment characteristics of all patients in the Netherlands with newly diagnosed breast cancer up to one year after diagnosis. Incident cases are identified through the national pathology archive and, since tumour data of patients are not updated, only information on patients with metastatic breast cancer at the time of diagnosis (i.e., de novo) is complete. Vital status and date of death are obtained by a yearly linkage of the Netherlands Cancer Registry to the municipal Personal Records Databases with the latest linkage on February 1, 2023.

If patients were diagnosed with bilateral breast cancer, the most aggressive tumour was used for the analyses. This was defined in the following order: tumour size, grade, or hormone receptor-negative disease.

The proportion of patients with undetermined or unknown HER2 status increased with age, ranging from 0% in patients aged 20–29 years up to 30.4% in patients aged 90–99 years (Supplemental Figs. 1 and 2). For the current analyses, only patients with known HER2 status and HER2 overexpression were included. A score of 3+ determined by immunohistochemistry and/or HER2 gene amplification detected by in situ hybridization or PCR was considered HER2 overexpression.

Patients were divided into three age groups: <65 years, 65–74 years, ≥75 years. Tumour morphology was divided into four categories (i.e., lobular, ductal, a combination of both, or unknown). Tumours were classified as hormone receptor-positive if the estrogen receptor (ER) and/or progesterone receptor (PR) expression was >10%. The number of metastatic sites was categorized into three groups: 1, 2, or 3 or more. Since the Netherlands Cancer Registry collected data until one year after diagnosis, information on second- or third-line systemic treatment may not be complete for every patient. Therefore, only first-line systemic treatment was used for the analyses. This was defined as the first systemic treatment given or, if another therapy was already given within two months (cut-off: 65 days) after initiation, the second therapy. Targeted therapy mainly includes trastuzumab, followed by pertuzumab. Lapatinib, trastuzumab emtansine, and tucatinib were all rarely prescribed in this time period as first-line treatment.

2.1. Statistical Analysis

Differences in tumour characteristics and treatment allocation between the age groups were assessed with the chi-square test, stratified for the hormone receptor status, and illustrated in bar graphs. Second, the percentage of patients receiving first-line systemic treatment (i.e., chemotherapy, endocrine therapy, and/or targeted therapy) was

graphically depicted over time as three-year moving means. Moreover, logistic regression models were used to assess changes in treatment patterns (chemotherapy, targeted therapy, and endocrine therapy) per year, stratified by age group. Next, median overall survival with inter-quartile ranges (IQR) and five-year overall survival rates by age group were estimated using the Kaplan-Meier method. Cox proportional hazard models were used to additionally adjust for [1] tumour characteristics (i.e., grade, morphology, hormone receptor status, number of metastatic sites) and [2] tumour characteristics and adjuvant systemic treatment (i.e., chemotherapy, endocrine therapy, and targeted therapy) to assess the additional effect of these variables on overall survival. Sensitivity analyses were performed to assess overall survival over time for all age groups and for the hormone receptor status.

Lastly, as older patients with breast cancer often die from other causes than breast cancer, the relative survival over time was calculated using the Ederer II method [12]. Relative survival is the observed survival of patients divided by the expected survival of the general population, matched by age, sex, and year of diagnosis. This ratio provides an estimate of survival if breast cancer were the only possible cause of death and is thereby a proxy for breast cancer-specific survival. This analysis can be performed under the assumption that the background mortality (i.e., the risk of dying if a patient would not have had breast cancer) of patients with metastatic breast cancer is similar to that of the general population. As the prevalence of most comorbidities is comparable among patients with breast cancer and the general population, relative survival is frequently used in this tumour type and is considered a valid method [13]. Relative excess risks (RER) were calculated with Poisson models and were adjusted for tumour characteristics (i.e., grade, morphology, hormone receptor status, and number of metastatic sites) and systemic treatment (i.e., chemotherapy, endocrine therapy, and targeted therapy).

The statistical tests were performed in SPSS version 29.0 (IBM, Armonk, New York, USA) and STATA version 16.1 (StataCorp, College Station, Texas, USA). All analyses were two-sided and a p -value of <0.05 was considered statistically significant.

3. Results

Between 2005 and 2021, 13,347 patients were diagnosed with de novo metastatic breast cancer. Of them, 2722 (20.4%) patients had HER2 overexpressing disease and were included in the current study (Table 1). Of patients <65 years, 26.3% of tumours had HER2 overexpression; of patients 65–74 years, 16.8%; and of patients ≥75 years, 12.3%.

4. Tumour Histology and Hormone Receptor Status

The tumour morphology differed between different age groups, with patients under 65 years of age having more ductal tumours than older patients, whereas older patients had relatively more lobular tumours (Table 1). Hormone receptor status did not significantly differ between age groups (<65 years: 56.6%, 65–74 years: 54.1%, ≥75 years: 60.2% of patients had ER and/or PR-positive breast cancer, $p = 0.41$). Irrespective of age, most tumours metastasized to bone, followed by the liver for the youngest and the middle age groups, and by the lung for those aged 75 years and older.

5. First-Line Treatment

Between 2005 and 2021, the use of chemotherapy and targeted therapy as first-line treatment gradually increased for patients under the age of 65 (chemotherapy use from 73.5% of patients in 2005 to 89.8% in 2021, $p < 0.001$; targeted therapy from 33.8% in 2005 to 90.6% in 2021, $p < 0.001$), while the use of first-line endocrine therapy, both as monotherapy or in combination with targeted therapy, decreased (19.1% in 2005 to 5.5% in 2021, $p < 0.001$) (Fig. 1, Supplemental Table 1). For the

Table 1
Patient and tumour characteristics.

	<65 years	65–74 years	≥75 years	p-value*
Number of patients	1801	458	463	
Median age (range)	52 (22–64)	69 (65–74)	82 (75–102)	
Year of inclusion				0.45
2005–2008	322 (17.9)	79 (17.2)	85 (18.4)	
2009–2012	388 (21.5)	78 (17.0)	98 (21.2)	
2013–2016	438 (24.3)	123 (26.9)	108 (23.3)	
2017–2021	653 (36.3)	178 (38.9)	172 (37.1)	
Morphology				<0.001
Lobular	73 (4.1)	34 (7.4)	37 (8.0)	
Ductal	1445 (80.2)	343 (74.9)	342 (73.9)	
Combination	29 (1.6)	7 (1.5)	2 (0.4)	
Other	254 (14.1)	74 (16.2)	82 (17.7)	
ER and/or PR status				0.41
Negative	769 (42.7)	206 (45.0)	180 (38.9)	
Positive	1020 (56.6)	248 (54.1)	279 (60.2)	
Unknown	12 (0.7)	4 (0.9)	4 (0.9)	
Number of metastatic sites				<0.001
1	962 (53.4)	207 (45.2)	262 (56.6)	
2	472 (26.2)	119 (26.0)	114 (24.6)	
≥3	367 (20.4)	132 (28.8)	87 (18.8)	
Metastatic site**				
Bone	1070 (59.4)	280 (61.1)	261 (56.4)	0.32
Lung	388 (21.5)	149 (32.5)	153 (33.0)	<0.001
Liver	840 (46.6)	178 (38.9)	146 (31.5)	<0.001
Brain	60 (3.3)	14 (3.1)	16 (3.5)	0.94
Distant lymph nodes	463 (25.7)	165 (36.0)	126 (27.2)	<0.001
Other/unknown	191 (10.6)	52 (11.4)	42 (9.1)	0.50

* A p-value of 0.05 was considered statistically significant.
** Higher total number as several patients had more than one metastatic site.

entire group of patients aged 65–74 years, the use of first-line chemotherapy increased from 50.0% of patients in 2005 to 78.4% in 2021 ($p = 0.01$), while the use of endocrine therapy decreased from 25.0% to 13.5% in that same period ($p = 0.03$) (Fig. 1). The prescription of targeted therapy increased from 29.2% of patients in 2005 to 86.5% in 2021 ($p < 0.001$). The use of chemotherapy and targeted therapy also increased for the oldest age group (from 8.7% of patients in 2005 to

37.2% of patients in 2021 ($p = 0.04$) and from 4.3% in 2005 to 55.8% of patients in 2021 ($p < 0.001$), respectively. Although not statistically significant, the use of endocrine therapy decreased numerically from 65.2% in 2005 to 37.2% in 2021 ($p = 0.16$). In total, 69.8% of patients aged <65 years, 51.2% aged 65–74 years, and 24.1% aged ≥75 years received chemotherapy in combination with targeted therapy (Supplemental Fig. 2).

5.1. Hormone Receptor-Negative Disease

For hormone receptor-negative disease, 13.1% of patients below 65 years of age received first-line chemotherapy as monotherapy and 78.2% of patients in combination with targeted therapy over the entire study period (Fig. 2A). The other patients either received no therapy (6.0%), targeted therapy only (2.1%), or endocrine therapy only (0.7%).

Of patients aged 65–74 years with hormone receptor-negative disease 79.1% were treated with first-line chemotherapy, 9.7% with monotherapy and 69.4% combined with targeted therapy (Fig. 2A). In the same age group, 16.0% of patients with hormone receptor-negative disease did not receive any first line systemic treatment. Very few patients received targeted therapy (2.4%) or endocrine therapy (1.9%) only.

Of patients aged 75 years and older with hormone receptor-negative disease, 42.2% of patients were treated with a first-line treatment combination of chemotherapy and targeted therapy (Fig. 2A). Also, 37.2% of patients did not receive any form of systemic therapy in the first line. Chemotherapy, endocrine therapy, and targeted therapy were given as monotherapy in 6.7%, 9.4%, and 4.4% of patients, respectively.

5.2. Hormone Receptor-Positive Disease

For those patients aged <65 years with hormone receptor-positive disease, 11.0% received first-line chemotherapy as monotherapy and 62.8% in combination with targeted therapy over the entire study period (Fig. 2B). Thirteen percent of this age group received endocrine therapy only, whereas 8.6% received endocrine therapy in combination with targeted therapy.

Of those patients aged 65–74 with hormone receptor-positive disease, 36.7% received a first-line treatment combination of chemotherapy and targeted therapy and 10.5% chemotherapy only (Fig. 2B). More than a quarter of patients (27.0%) received endocrine therapy only and 18.1% received endocrine therapy in combination with targeted therapy. No first-line systemic therapy was given to 6.5% of patients.

Nearly three-quarters of patients aged 75 years and older with hormone receptor-positive disease were treated with first-line endocrine therapy: 49.5% as monotherapy and 24.0% combined with targeted

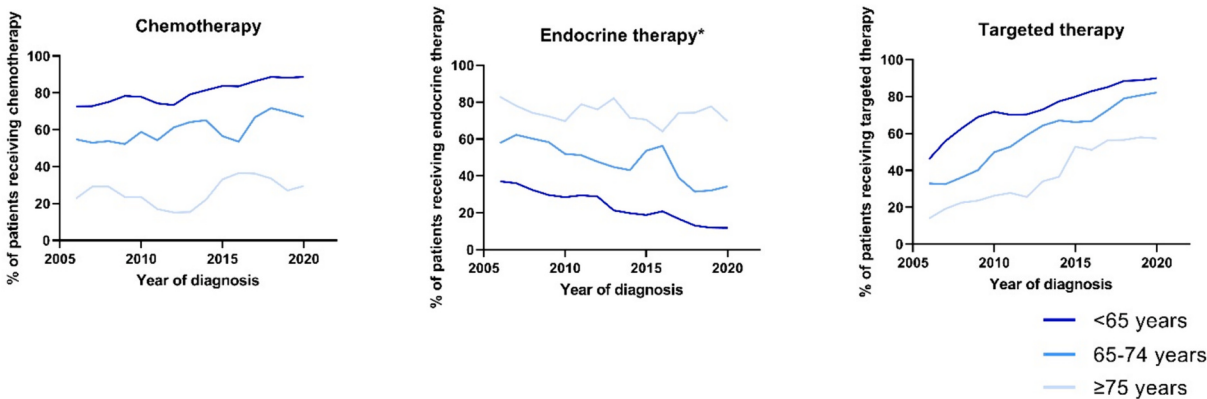


Fig. 1. First-line treatment allocation over time per age group. All figures are shown as three-year moving means.
*Only hormone receptor-positive tumours included.

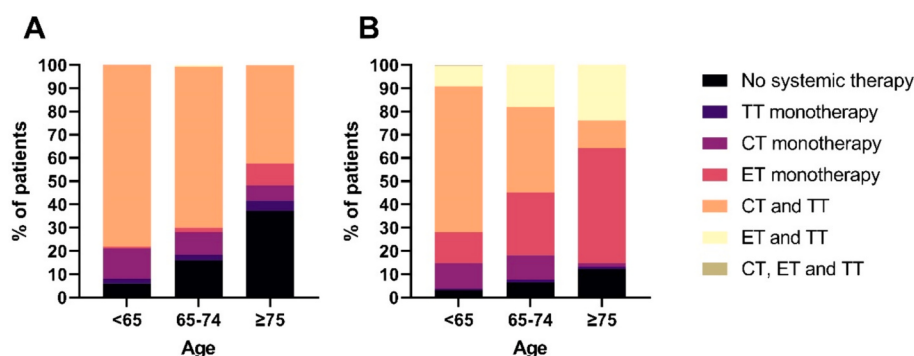


Fig. 2. First-line systemic treatment schedule per age group between 2005 and 2021 for patients with hormone receptor-negative (A) and hormone receptor-positive (B) disease.

Abbreviations: TT – Targeted Therapy; CT – Chemotherapy; ET – Endocrine Therapy

therapy (Fig. 2B). Chemotherapy in combination with targeted therapy was prescribed in 11.8% of patients, and 1.4% of patients received chemotherapy as monotherapy. Moreover, 12.2% of patients had no first-line systemic therapy.

6. Survival

6.1. Overall Survival

Median follow-up was 6.55 years (IQR 3.87–9.76). Median overall survival was 3.19 years (IQR 1.16–7.58) and was statistically significantly different per age group and after adjusting for tumour- and first-line systemic treatment characteristics (Table 2). Median overall survival was lowest for the oldest age group (1.30 [IQR 0.37–3.15] years), followed by patients between 65 and 74 years of age (2.04 [IQR 0.64–5.19] years) and was highest for the youngest age group (4.34 [IQR 1.83–10.23] years), $p < 0.001$. The overall survival of the whole cohort of patients improved statistically significantly over time (multivariable-adjusted hazard ratio [HR] 0.94, 95% confidence interval [CI] 0.93–0.95 per year, $p < 0.001$) (Fig. 3).

6.2. Relative Survival

The RER has improved over time for the entire cohort (multivariable-adjusted RER 0.93, 95% CI 0.92–0.94 per year, $p < 0.001$), indicating increased relative survival over the years of 7% (Fig. 4). The improvement was observed in all age groups, and was largest in the youngest age group (multivariable-adjusted RER 0.93, 95% CI 0.91–0.94 per year, $p < 0.001$) and patients aged 65–74 years of age (multivariable-adjusted RER 0.93, 95% CI 0.91–0.96 per year, $p < 0.001$), followed by patients over 75 (multivariable-adjusted RER 0.96, 95% CI 0.93–0.98 per year, $p = 0.001$).

Table 2

Comparison of unadjusted and adjusted overall mortality between the age groups.

	Crude HR (95% CI)	Adjusted HR (95% CI)*	Adjusted HR (95% CI)**
<65y	1 (reference)	1 (reference)	1 (reference)
65–74y	1.79 (1.58–2.03)	1.65 (1.46–1.87)	1.44 (1.27–1.63)
≥75y	2.70 (2.40–3.04)	2.74 (2.44–3.09)	1.75 (1.53–1.99)

HR: hazard ratio, CI: confidence interval.

* Adjusted for tumour characteristics: grade, morphology, hormone receptor-status, and number of metastatic sites.

** Adjusted for tumour- and first-line systemic treatment characteristics (i.e., chemotherapy, endocrine therapy, and targeted therapy).

7. Discussion

This population-based study showed that between 2005 and 2021, the use of first-line chemotherapy and targeted therapy for patients with HER2-overexpressing de novo metastatic breast cancer increased in all age groups, while the use of first-line endocrine therapy, both as monotherapy and in combination with targeted therapy, decreased. Over the same period, both overall survival and relative survival improved for every age group. Nevertheless, survival was still statistically significantly better for patients younger than 65 years of age than for those older than 65, and the greatest improvement over time was observed in the youngest age group.

Most guidelines recommend a combination of targeted therapy and chemotherapy as first-line treatment for patients with HER2-overexpressing metastatic breast cancer, except for those with congestive heart failure or a severely reduced left ventricular ejection fraction (LVEF), who should first undergo an individual risk evaluation [14–16]. Therefore, it seems plausible that older patients are less likely to receive targeted therapy because of an increased occurrence of congestive heart failure, a higher risk of reduced LVEF, and an increased risk of cardiac adverse events from targeted therapy with increasing age [6,17]. The lack of specific guidance for older patients due to the fact that most guidelines have been based on trials conducted in fit younger patients may further lead to treatment variation in the older population [18]. It is therefore not surprising that the overall percentage of patients receiving the preferred first-line treatment decreased with advancing age (<65 years: 69.4%, 65–74 years: 51.3%, ≥75 years: 23.5% of patients received a combination of targeted therapy and chemotherapy). Yet, the lower use of the preferential treatment in the middle and oldest age groups cannot be entirely attributed to heart failure or frailty, as the number of patients not treated with this therapy is higher than the prevalence of these conditions in the general older population [19,20]. Unfortunately, this late introduction of new therapies is often at the expense of potential survival gains for older patients. Moreover, some patients can continue targeted therapy despite a reduced LVEF [21–23].

Differences in treatment allocation in older versus younger patients with HER2-overexpressing breast cancer have also been investigated in other countries. In a recent French study by Annonay and colleagues, 89.1% of patients younger than 70 years compared to 65.0% of patients aged 70 years and older received targeted therapy in combination with chemotherapy [24]. These are much higher percentages than found in our study (<65 years: 69.4%, 65–74 years: 51.3%, ≥75 years: 23.5%). A combination of endocrine therapy and targeted therapy was rarely given in France: 1.5% of patients aged <70 and 7.7% of patients aged ≥70, while 63.0% versus 68.8% of patients had hormone receptor-positive tumours, respectively. The studies are, however, not completely comparable for several reasons: the French study only selected patients from 18 comprehensive cancer centers if patients had not received first-line

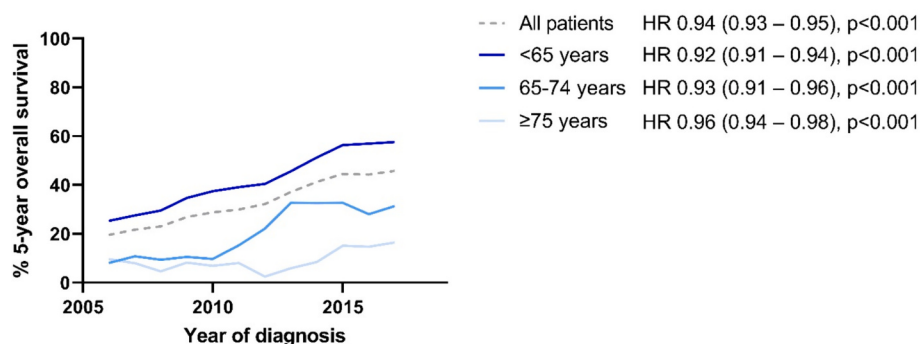


Fig. 3. Five-year overall survival over time per age group.

Data is shown as three-year moving means. The hazard ratios (HR) and 95% confidence intervals are adjusted for age at diagnosis, grade, morphology, hormone receptor-status, and number of metastatic sites.

HR – Hazard Ratio.

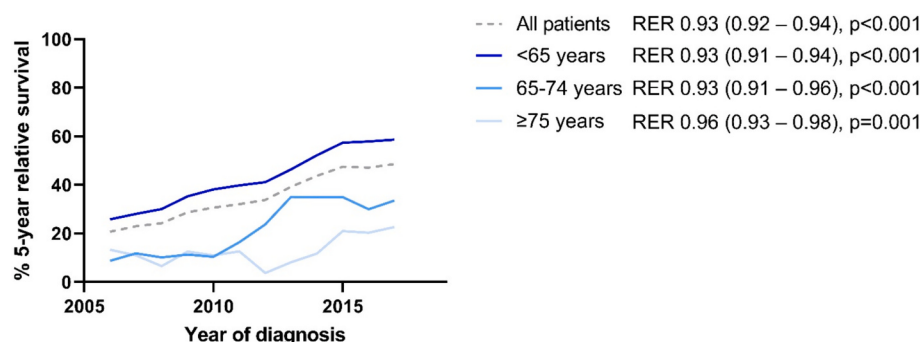


Fig. 4. Five-year relative survival over time per age group.

Data is shown as three-year moving means. The relative excess risks (RER) and 95% confidence intervals are adjusted for age at diagnosis, grade, morphology, hormone receptor-status, and number of metastatic sites.

RER – Relative Excess Risk.

treatment elsewhere, they used a different age cut-off, their time window was shorter (2008–2016), no distinction between hormone receptor-status was made, and they also included patients whose breast cancer had recurred after initial diagnosis and treatment. Another, observational study (registHER) from the United States that included patients with recurrent metastatic HER2-overexpressing breast cancer or de novo metastatic breast cancer diagnosed between 2003 and 2006 found that 57.2% of patients aged <65 years, 56.9% of patients aged 65–74, and 46.2% of patients aged ≥75 years received a combination of chemotherapy and targeted therapy [25]. These percentages are high for that period, but it may have to do with the fact that relatively healthy patients are included in these studies. Numbers were also very small, whereas our study addressed an unselected nationwide cohort of patients with only de novo metastatic breast cancer. However, it may be possible that Dutch clinicians are more reluctant to administer these types of therapy, for instance for fear of side effects.

Although no distinction in hormone receptor status was made in the aforementioned studies from France and the United States, endocrine therapy can be considered as a substitution of chemotherapy in patients with hormone receptor-positive disease, especially if patients have contraindications for chemotherapy or if the tumour is not rapidly progressive and without multiorgan metastases [18,26]. HER2-overexpressing tumours have previously been shown to be associated with a negative hormone receptor status [27]. Yet 57% of all patients included in the current study had hormone receptor-positive disease. Older patients are usually more likely to have hormone receptor-positive disease than younger patients, but, remarkably, the number of patients with a positive hormone receptor status did not differ between the age groups in the current study [28,29]. Nevertheless, endocrine therapy

was prescribed more frequently in the older population. Moreover, patients with hormone receptor-negative disease, which is generally considered a more aggressive form of breast cancer, were more often denied any type of first-line systemic therapy than patients with hormone receptor-positive disease.

In early-stage breast cancer, we have previously demonstrated that survival gains in older patients lag behind those of younger patients [30]. Also, in the entire Dutch cohort of older women with de novo metastatic disease, hardly any survival gain was achieved in older patients (with all types of breast cancer) between 1990 and 2012 [31]. In sharp contrast, we demonstrated an increase in survival for all age groups in patients with HER2-overexpressing breast cancer, even after adjusting for tumour and treatment characteristics. Most likely, this was a result of the increased availability of active agents and use of targeted therapy. The relatively lower survival gain for the older population may again be attributable to a delay in the introduction of the next line of anti-HER2 therapies, such as pertuzumab, trastuzumab-emtansine (TDM1), and tucatinib, especially because the survival in patients with metastatic breast cancer is likely to be dominated by breast cancer rather than competing risks [32]. Moreover, the median overall survival in the current study was worse than in the French study: 3.2 years compared to 4.1 years, respectively (<70: 4.5 years, ≥70: 2.9 years in French patients, compared to <65: 4.3 years, 65–74: 2.0 years, ≥75: 1.3 years in our study). Unfortunately, the breast cancer-specific survival was not analysed in that study. Again, the study design makes it difficult to draw firm conclusions about the differences between the two studies, but the increased use of targeted therapy in the French study could imply that the Netherlands may achieve further survival gain by prescribing “standard” therapy. However, this also largely depends on patient

characteristics, such as comorbidity and treatment preferences. To better individualise treatment, further research should focus on the effect of treatment in patients from specific subgroups (e.g., patients with comorbidity or frailty) and the impact of therapy on quality of life and independence [33,34]. Moreover, therapy is led by diagnostics and the available data revealed an increasing proportion of patients with undetermined or unknown HER2-status with advancing age (ranging from 0% in patients aged 20–29 years up to 30.4% in patients aged 90–99 years). Of note, in the early years of trastuzumab use, the side effect heart failure received a considerable amount of attention. Furthermore, HER2 diagnostics were still considered cumbersome and expensive and were therefore typically omitted in patients known to have heart failure, which is more common in older patients. This omission deserves attention, as it may only be justified in patients who are unsuitable for therapy or have other preferences, but it already seems to be improving as targeted therapy use continues.

The main strength of this study is the inclusion of all patients with HER2-overexpressing de novo metastatic breast cancer diagnosed in the Netherlands, resulting in many patients with detailed information on tumour and treatment characteristics over a long period of time collected by the quality-assured Netherlands Cancer Registry. The study also has its limitations. No detailed information was available on factors that particularly affect treatment decisions and outcomes in the older population, such as patient characteristics (e.g., comorbidity, polypharmacy, geriatric characteristics), patient preferences, or toxicity. Therefore, it was not possible to discuss whether patients should have been treated according to the guidelines. As the Netherlands Cancer Registry collected data until one year after diagnosis, we only included de novo metastatic breast cancer and the first-line treatment allocation. Inclusion of second-line therapies and patients whose breast cancer had recurred after initial diagnosis and treatment might have resulted in different treatment and survival rates compared to patients with recurrent metastatic disease [35,36]. Finally, we were unable to assess long-term progression-free survival and breast cancer-specific survival, because this information was not available and the cause of death was not recorded. However, we do believe that relative survival is a valid proxy for breast cancer-specific survival, especially for the older population in whom autopsies are often omitted [37,38].

In conclusion, the use of first-line chemotherapy and targeted therapy has increased in all age groups, while the use of endocrine therapy has decreased over time. The uptake of chemotherapy and targeted therapies, however, has been substantially slower in the oldest age groups, which may not be fully attributable to the prevalence of heart failure or frailty in these age groups. This study also showed that both overall survival and relative survival improved for every age group in patients with HER2-overexpressing metastatic breast cancer, albeit with the smallest improvements in the oldest age group.

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CRediT authorship contribution statement

Annelieke Lemij: Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Nienke de Glas:** Writing – review & editing, Writing – original draft, Supervision, Software, Methodology, Investigation, Conceptualization. **Judith Kroep:** Writing – review & editing, Supervision. **Sabine Siesling:** Writing – review & editing, Writing – original draft, Resources, Data curation. **Frederiek van den Bos:** Writing – review & editing, Writing – original draft, Supervision. **Esther Bastiaannet:** Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Formal analysis. **Gerrit Jan Liefers:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation. **Johanneke Portielje:** Writing

– review & editing, Writing – original draft, Supervision, Methodology, Investigation, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jgo.2024.101805>.

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