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Research Article

Risk Factors for Developing Brain Metastasis for Patients with HER2-Positive Breast Cancer

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Abstract

Background: The prognosis for patients with HER2-positive breast cancer has improved significantly; however, a large number of patients develop brain metastases (BM). **Aims**: To examine factors that increase the risk of BM or affect the time to development of BM in patients with HER2-positive metastatic BC and to assess the effect of adjuvant trastuzumab on recurrence-free survival (RFS) and overall survival (OS). **Material and methods:** Patients (n=599) with primary HER2 positive BC from 2006-2015 were included in this retrospective non-randomized investigation. Patients where curative intention surgery was performed were included in the analysis (n=551). Clinical and biological data were extracted from patient's charts. Recurrence-free survival (RFS) and overall survival (OS) were estimated. **Results:** Out of the 102 patients who presented with recurrence in the form of distant metastasis, 37 patients (36.3%) developed BM. BM was more common in patients <50 years compared to patients ≥ 50 years (58.3% and 29,5%; p=0.021) and in patients given adjuvant trastuzumab (p=0.030). BM developed faster in patients with HR-negativity and vascular invasion (p=0.015 and p=0,024, respectively). RFS and OS improved by adjuvant trastuzumab in univariate (p=<.0001 and OS p=<.0001) and in multivariate analysis (p=<.0001 and p=<.0001, respectively) adjusted for tumor size, nodal status and grade. **Conclusions:** CNS metastasis was common in patients who experience a recurrence of their disease in the form of distant metastasis, and the risk was higher in younger patients than previously described. Administration of adjuvant Trastuzumab clearly improved OS and RFS in patients with early HER2-positive BC.

Keywords: HER2-positive BC; Adjuvant therapy; CNS-metastasis; Survival.

Introduction

Breast cancer is globally the most common cancer in women, with about 1.7 million new cases per year [1]. Despite the fact that the prognosis for patients with early breast cancer has clearly improved in recent years, the diagnosis still constitutes the cause of death for 14% of malignant diseases globally1. After the discovery of HER2-positive breast cancer with a poor prognosis in the 80s, the prognosis for patients has significantly improved following the development of effective drugs for this subtype [2-4].

Despite the development of more effective treatment of early HER2-positive breast cancer, there are still patients who relapse into their disease in such a way that curative treatment is not possible. In addition, there are still patients who, in connection with their primary diagnosis of breast cancer, have developed metastatic disease, so-called de novo metastatic breast cancer [5].

The organs commonly affected by metastatic breast cancer are the bone, lung and liver, but the pattern differs in different subtypes of breast cancer [6]. Metastasis to the brain is usually a difficult condition in most forms of metastatic cancer, as systemic treatment with cancer drugs has difficulty penetrating the blood brain barrier [7,8]. Although lung cancer often causes brain metastases, 15-30% of breast carcinomas may give rise to brain metastases [9,10].

It is likely that the number of patients with brain metastases is higher than previously known, as radiological investigation is carried out almost exclusively in neurological symptoms and not in asymptomatic patients. An autopsy study in patients with advanced breast cancer showed that about 30% of patients had findings of brain metastases [11]. Young age, low differentiated tumor, negative hormone receptor status and node positivity were identified as risk factors for developing brain metastasis in breast cancer [12]. Concerning BC subgroups, patients with HER2-positive tumors as well as TNBC have a higher risk of developing brain metastasis compared to patients with luminal BC [6]. Despite the introduction of adjuvant Trastuzumab, a number of patients will have breast cancer recurrence and just over 30% of patients with metastatic HER2-positive breast cancer will develop brain metastases [13]. In most cases, brain metastasis comes later in the cancer process and often follows after metastasis found in the liver, lung and bones but brain metastases can sometimes occur early in the course and even at the primary diagnosis of breast cancer [14].

The purpose of this study was to investigate the prognosis and metastatic pattern of HER2-positive breast cancer with special regard to brain metastasis. We wanted to study potential risk factors for developing BM in patients with metastatic BC, but also to see if we could identify any factors that could affect the timing of when BM developed.

As secondary objectives, we also wanted to study the outcome regarding RFS and OS in patients who received treatment with Trastuzumab compared to those who did not receive the treatment in real world setting. We also aimed to study how many patients were able to complete 1 year of treatment with Trastuzumab and investigate reasons for early treatment discontinuation. In addition, we wanted to perform a comparison of risk factors between recurrent and de novo metastatic HER2-positive breast cancer.

Material and Methods

Patients

Information on patients diagnosed as HER2-positive breast cancer for the period from January 1 2006 through December 31 2015 was obtained from the Regional Cancer Center Sahlgrenska University Hospital, Gothenburg, Sweden (= 599). Data on standard breast cancer parameters (tumor size, nodal status, histopathological type and grade, hormone receptor status, HER2 status, proliferation index (Ki67), vascular invasion) were extracted from patients records. In addition, recommended adjuvant systemic treatment, adherence to treatment and reason for discontinuation, date of relapse, affected organs at the time of relapse and survival were documented. Reason for prematurely termination of recommended adjuvant systemic treatment was divided into the following groups; Cardiotoxicity; other toxicity; allergic reactions to treatment; participation in RCT:s with shorter treatment then 1 year and other reasons. We divided recurrence into locoregional recurrence or distant recurrence, where locoregional recurrence was defined as recurrence on chest wall, residual breast tissue or ipsilateral lymph node stations. The median follow-up time was 108,5 months (range 2-198 months).

Pathology

Data regarding tumor size, nodal involvement, histopathological type and grade, expression of estrogen receptor (ER), progesterone receptor (PgR), HER2 status, Ki67 and vascular invasion were collected from the original pathology report. Tumor markers were determined on formalin-fixed, paraffin embedded tumor tissue. Tumor paraffin block were stained for estrogen receptor (IR084, clone EP1; Dao, Carpentaria, CA), progesterone receptor (PgR; IR068, clone 636; Dao). When confirmation of vascular invasion was needed, immunostaining against the endothelial markers D2-40 (DAKO M3619, clone D2-40) and CD34 (DAKO M7165 clone QBEnd10) was performed with. HER2 protein was established with HER2 IHC (Hercep Test) (DAKO K5260, Copenhagen, Denmark), and gene amplification was established with HER2 FISH pharmDxTM (DAKO K5331, Copenhagen, Denmark) in accordance with the manufacturer's instructions between 2008-2010. After 2010, tests for gene amplification were performed with SISH using Ventana HER2 ISH assay (on a benchmark XT from Roche according to manufacture´s specifications). To be considered HER2 positive, the immunohistochemistry (IHC) staining score 2-3+ and amplification in situ hybridization (ISH) requirement was defined as ≥ 2.0 gene copies of the HER2 gene compared to the number of copies of chromosome 17.

Decision on recommended adjuvant systemic treatment

Decisions on the recommended adjuvant systemic treatment for each individual patient were made at a weekly multidisciplinary conference with participants from departments of breast surgery, oncology, imaging and pathology, as well as representatives from the clinical research units.

Statistical analyses

Continuous variables were described with means and standard deviations (SD) or medians and interquartile ranges or ranges. For comparison of dichotomous variables between two groups Fisher´s Exact test was used.

Survival outcomes were analyzed using a time to-event analysis method. The recurrence-free survival and overall survival according to trastuzumab treatment, BM at relapse and patients with de novo metastatic *vs* distant recurrent were analyzed using Kaplan-Meier survival curves and compared using logrank-test. The effect of treatment with transtuzumab on death was analyzed using Cox proportional hazard regression, while the effect of this treatment on relapse was by using a cause-specific Cox regression

analysis (i.e. with censoring at death). In these two analysis hazard ratio are presented with 95% confidence intervals (CIs), unadjusted and adjusted for T-stadium, Grade and Node . Risk factor for BM were analyzed using univariable cause-specific Cox regression analysis (i.e, with censoring at death) . The cumulative incidence of CNS was estimated using cumulative incidence function accounting for competing event (i.e.., death before CNS).

All tests were two-tailed and $p < 0.05$ was considered significant. All analysis were performed using SAS/STAT® Software, Version 9.4 of the SAS System for Windows (SAS Institute Inc., Cary, NC, USA).

Results

Patients

A total of 599 patients were diagnosed with primary HER2-positive BC from January 01, 2006 to December 31, 2015 out of which 40 patients had de novo metastatic disease. Eight patients were excluded as they were judged not to be able to tolerate any treatment including surgery and four patients, 3 patients who have undergone surgery and 1 patient with de novo mBC, are lost from follow-up leaving 548 patients for this study Figure 1. The last date for follow-up was April 30, 2022.

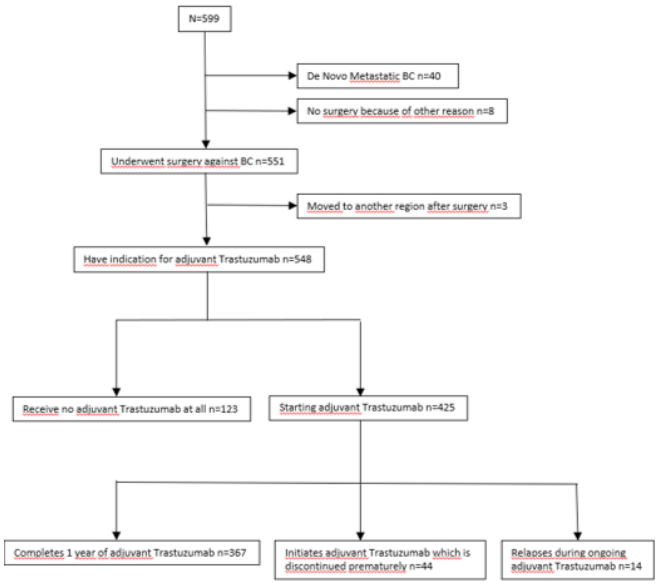


Figure 1: Patients diagnosed with HER2-Positive BC between 2006-2015.

Recurrence and survival – all patients

Treatment with trastuzumab was delivered to 425 patients, with the highest figures in patients ≤ 50 years (90.4%) and the lowest in patients > 80 years (6.9%). Figure 2. This was stastically significant when patients < 50 years were compared with patients ≥ 50 years (p=<.0001) Table 1.

Variable	Total (n=599)	< 50 (n=178)	>=50 (n=421)	p-value
Trast				
No	123 (22.4%)	16 (9.6%)	107 (28.0%)	
Yes	425 (77.6%)	150 (90.4%)	275 (72.0%)	<.0001
For categorical variables n (%) is presented. For comparison between groups Fisher´s Exact test (lowest 1-sided p-value multiplied by 2) was used for dichotomous variables.				

Table 1: Comparison of trastuzumab between age groups.

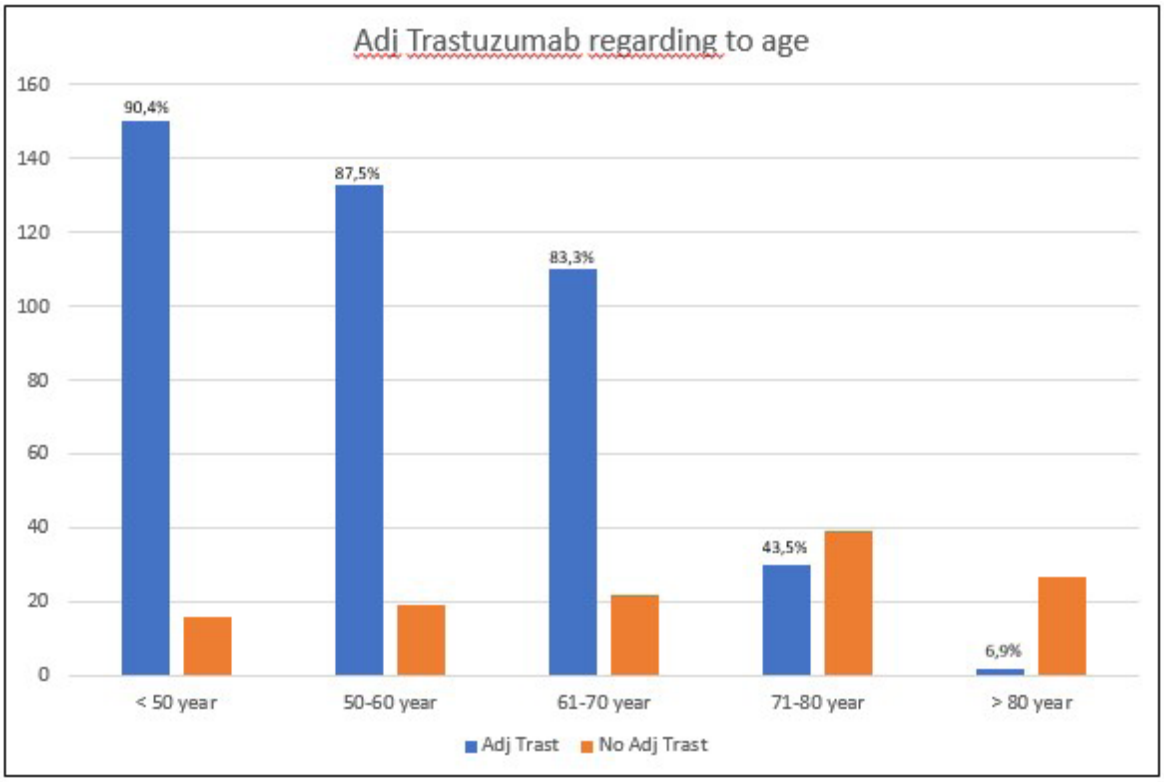


Figure 2: Adj Trastuzumab regarding to age.

A total of 367 patients (86%) completed one year of trastuzumab, 14 patients (3%) had a relapse during this year. The most common reason for discontinuation of treatment with Trastuzumab was cardiotoxicity in 13 patients (3%) Table 2.

Trastuzumab < 1 year	**(n=44)**
Cardiotoxicity	13
Participating in RCT	12
Other reason	11
Other toxicity	7
Allergic reaction	3

Table 2: Reason for discontinuation of Trastuzumab.

One hundred and sixteen patients (21,2%) had a relapse; 95 patients with distant metastases and 21 patients with local relapses. There was a statistically significant difference in recurrence-free survival (RFS) and overall survival (OS) according to trastuzumab treatment with a worse prognosis for the group where treatment was omitted; RFS ($p<0,0001$) and OS ($p<0,0001$) respectively Figures 3 and 4.

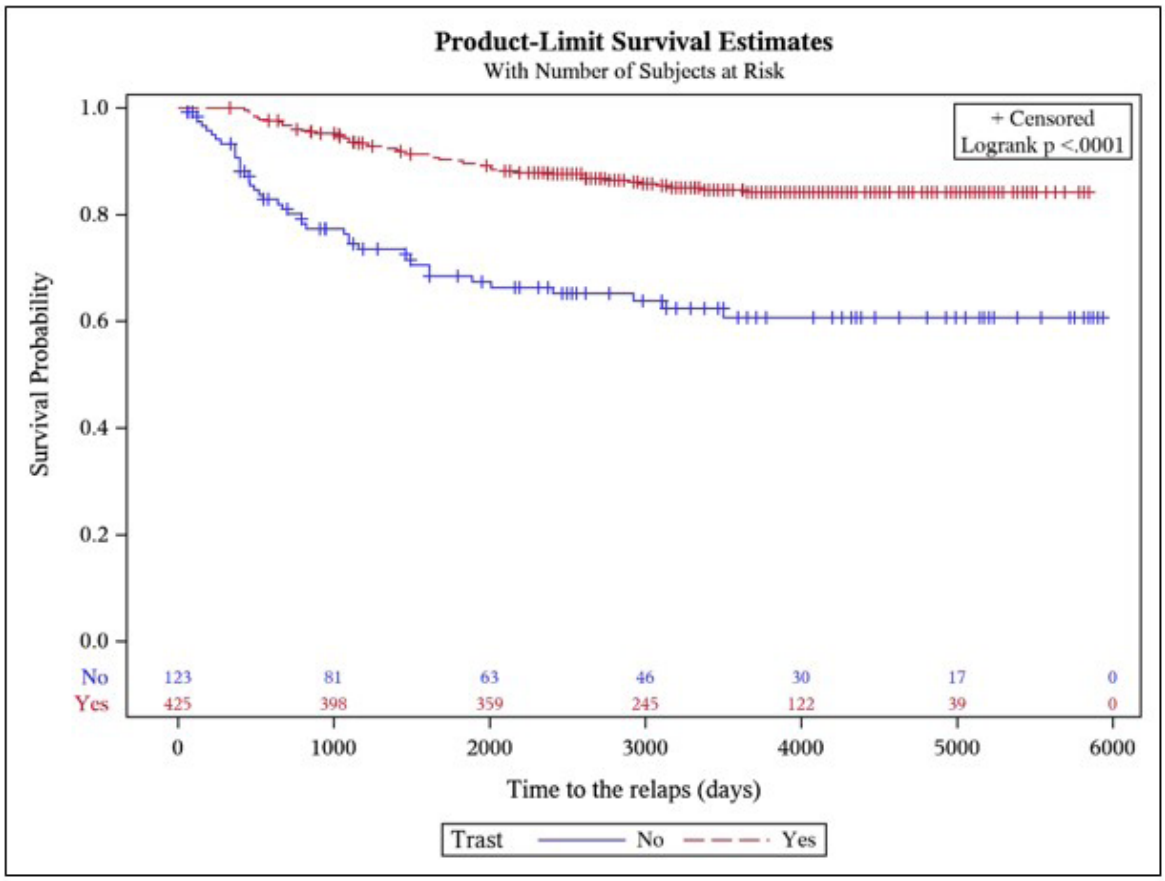


Figure 3: Kaplan-Meier curve for time to the event of relaps stratified by Trastuzumab.

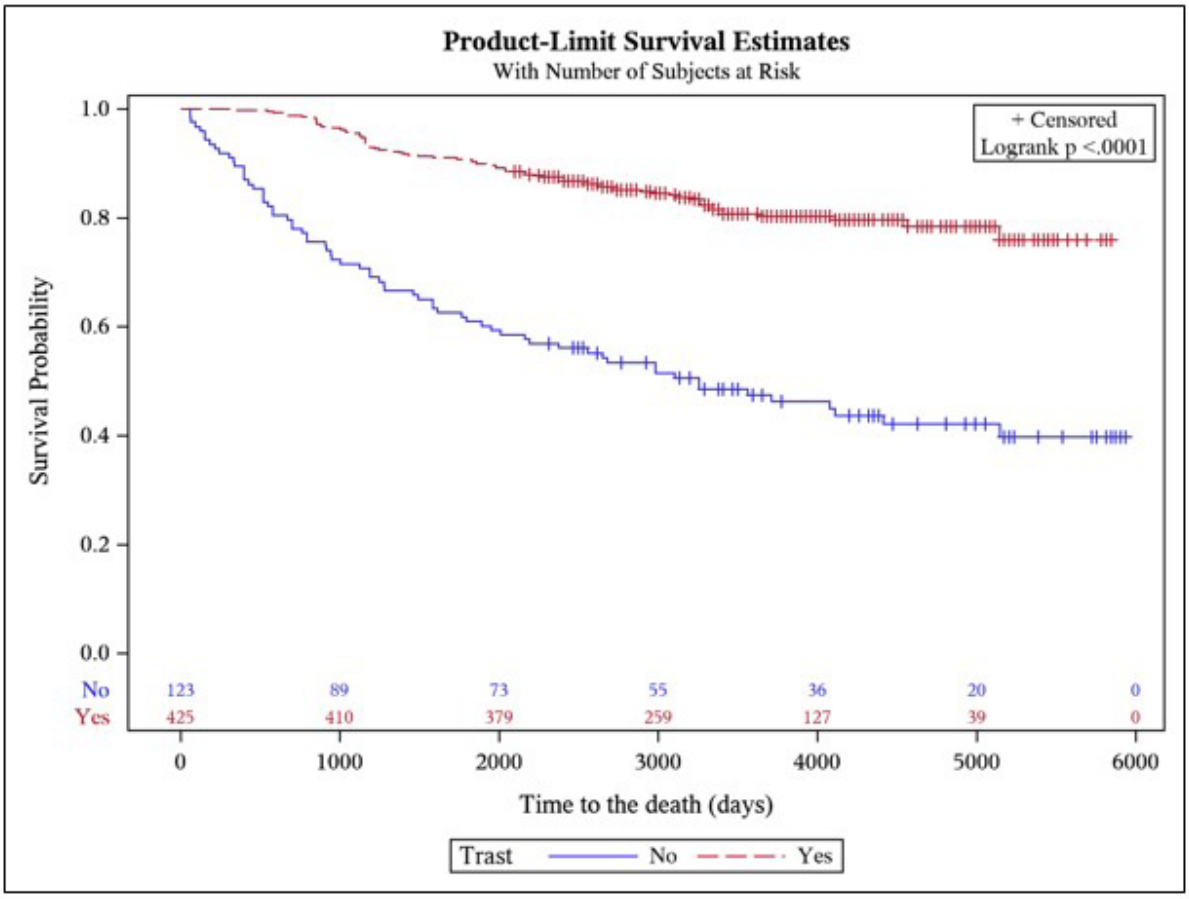


Figure 4: Kaplan-Meier curve for time to the event of death stratified by Trastuzumab.

This difference persisted in a multivariate assay adjusted for tumor size, nodal status and grade, RFS (HR 0,21(95%CI); p<0,0001) and OS (HR 0,19(95%CI); p<0,0001) Tables 3 and 4. Out of the 21 patients who experience a local recurrence and are treated with renewed surgery followed by new adjuvant treatment, 7 (33%) of these patients experience further recurrence in the form of distant metastasis, of which one with brain metastasis. Four of these seven patients belonged to the group of 14 patients who experienced recurrence during ongoing adjuvant trastuzumab. In summary, 102 patients developed distant metastasis.

					Unadjusted Cox model			Adjusted Cox model			
Outcome	Variable	Value	Events	Event rate (95% CI)	Number of missing observations in the model	Hazard Ratio (95% CI)	p-value	Number of missing observations in the model	Hazard Ratio (95% CI)	p-value	Adjusted for
Relaps_evt	Trast	No	41/123 (33.33%)	5.09 (3.65; 6.90)							
		Yes	61/411 (14.84%)	1.64 (1.26; 2.11)	3/537 (0.56%)	0.32 (0.21 - 0.47)	<.0001	27/537 (5.03%)	0.21 (0.14 - 0.32)	<.0001	T-stadium, Grade, Node

	Trast (Yes as reference)	Yes	61/411 (14.84%)	1.64 (1.26; 2.11)							
		No	41/123 (33.33%)	5.09 (3.65; 6.90)	3/537 (0.56%)	3.16 (2.12 - 4.69)	<.0001	27/537 (5.03%)	4.72 (3.10 - 7.20)	<.0001	T-stadium, Grade, Node
For each variable the hazard ratio with corresponding confidence interval and p-value are presented; All variables in the adjusted analysis have been adjusted for T-stadium, Grade and Node.											

Table 3: Univariable Cox model for time to the event of relaps adjusted by T-stadium, Grade and Node.

					Unadjusted Cox model			**Adjusted Cox model**			
Outcome	Variable	Value	Events	Event rate (95% CI)	Number of missing observations in the model	Hazard Ratio (95% CI)	p-value	Number of missing observations in the model	Hazard Ratio (95% CI)	p-value	Adjusted for
dead_evt	Trast	No	68/123 (55.28%)	7.47 (5.80; 9.47)							
		Yes	78/425 (18.35%)	2.00 (1.58; 2.50)	3/551 (0.54%)	0.26 (0.19 - 0.36)	<.0001	27/551 (4.90%)	0.19 (0.13 - 0.27)	<.0001	T-stadium, Grade, Node
	Trast (Yes as reference	Yes	78/425 (18.35%)	2.00 (1.58; 2.50)							
		No	68/123 (55.28%)	7.47 (5.80; 9.47)	3/551 (0.54%)	3.86 (2.78 - 5.35)	<.0001	27/551 (4.90%)	5.33 (3.74 - 7.60)	<.0001	T-stadium, Grade, Node
For each variable the hazard ratio with corresponding confidence interval and p-value are presented. All variables in the adjusted analysis have been adjusted for T-stadium, Grade and Node.											

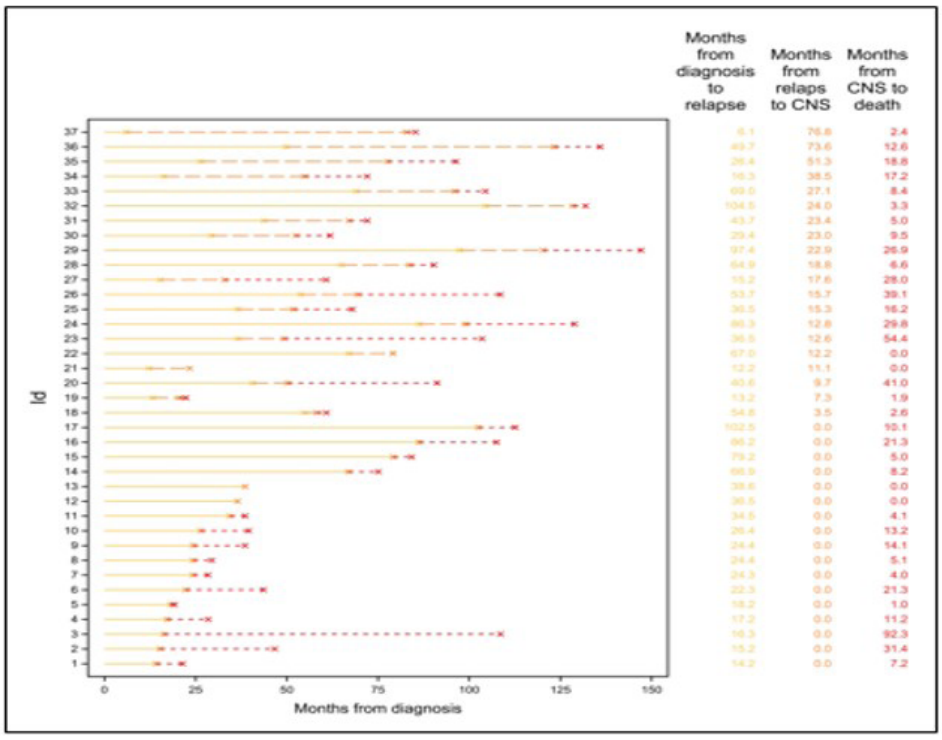
Table 4: Univariable Cox model for time to the event of death adjusted by T-stadium, Grade and Node.

Diagnoses of brain metastases (BM)

Thirty-seven patients (36.3%) of patients with distant metastasis were diagnosed with BM; either at the same time as the diagnoses of distant metastases (n=17), or later during progression of the disease (n=20). If divided into age groups at the primary diagnosis of BC, 58.3% of patients <50 years developed BM, while the corresponding figure for patients ≥50 years was 29.5%. Four of these patients were alive at last follow-up.

Survival in relation to time to diagnose of BM

We investigated the time periods from diagnose of primary BC to recurrent disease, from date of recurrence to diagnose of BM and from diagnose of BM to death. The median time from diagnose of recurrence to diagnose of BM was 7,3 months (range: 0-76,8 months). Figure 5. We found a statistically impaired OS (p=0,0031) from the date of relapse for patients diagnosed with BM at the time of first recurrence compared to patients diagnosed with relapse at another location first. Figure 6.



Variable	Label	N	Median	Minimum	Maximum
timeDiagRelapsM	Months from diagnosis to relapse	37	36.5000000	6.0666667	104.5333333
Relaps_to_CNSm	Months from relaps to CNS	37	7.3333333	0	76.7666667
TimeToDeath_daysm	Months from CNS to death	37	9.5333333	0	92.3000000

Figure 5: The time point when CNS metastasis occurs after the primary diagnosis; The 17 bottom patients develop CNS metastasis at the first recurrence, while the remaining 20 patients develop it later.

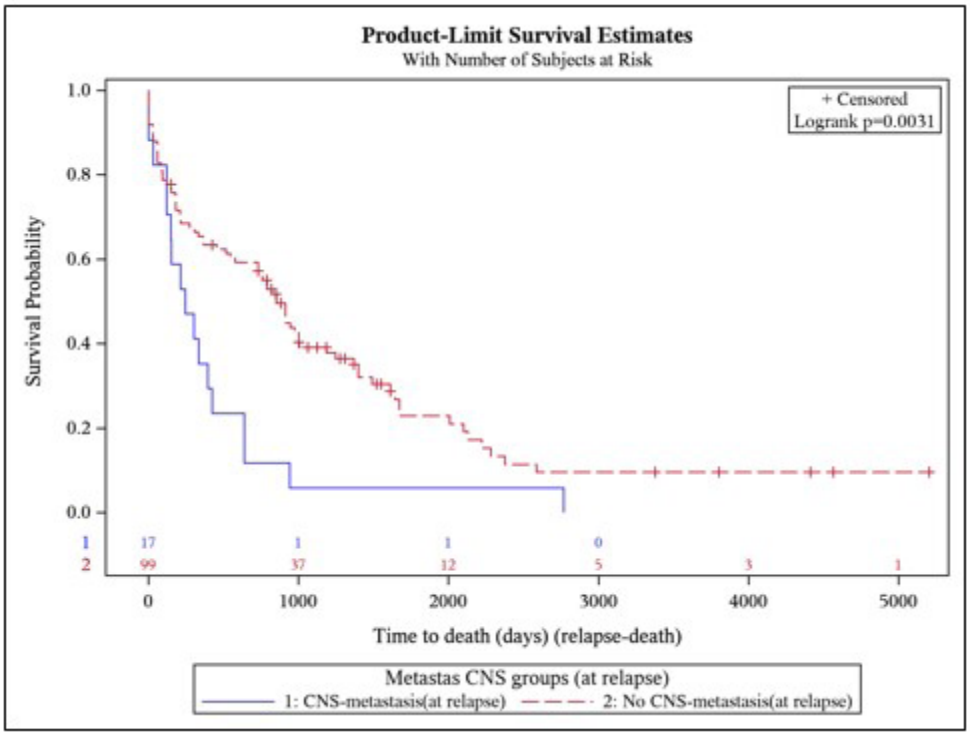


Figure 6: Kaplan-Meier curve for time to the event of death stratified by CNS-metastases at recurrence.

Clinical and biological markers of risk for development of BM

We compared patients with or without diagnose of BM among the 95 patients who debut with distant recurrences directly plus the 7 patients who experienced distant recurrence after first experiencing locoregional recurrence, and found that younger age defined as <50 years and delivery of trastuzumab as statistically significantly correlated with diagnose of BM; (p=0.021) (p=0.030) respectively. Tumor size, histological grade, ER status, vascular invasion, proliferation index, or nodal status were equal in the two groups. Out of the 102 patients who developed distant metastasis, 37 patients (36.3%) developed BM. Out of the 24 patients < 50 years at the diagnosis of BC who develop distant metastasis, 14 patients (58.3%) developed BM, the corresponding figure for patients ≥ 50 years is 23 out of 78 patients (29.5%) Table 5.

Variable	Total (n=102)	No CNS-metastasis (n=65)	CNS-metastasis (n=37)	p-value	Difference between groups Mean (95% CI)
Ålder ≥ 50					
No	24 (23.5%)	10 (15.4%)	14 (37.8%)		-22.5 (-42.5; -2.4)
Yes	78 (76.5%)	55 (84.6%)	23 (62.2%)	0.021	22.5 (2.4; 42.5)
T-stad ≥ 2					
No	5 (4.9%)	4 (6.2%)	1 (2.7%)		3.5 (-6.5; 13.4)
Yes	97 (95.1%)	61 (93.8%)	36 (97.3%)	0.80	-3.5 (-13.4; 6.5)
BRE 3					
No	22 (21.8%)	15 (23.4%)	7 (18.9%)		4.5 (-14.0; 23.0)
Yes	79 (78.2%)	49 (76.6%)	30 (81.1%)	0.79	-4.5 (-23.0; 14.0)
HR-positiv					
No	45 (44.1%)	26 (40.0%)	19 (51.4%)		-11.4 (-33.5; 10.8)
Yes	57 (55.9%)	39 (60.0%)	18 (48.6%)	0.37	11.4 (-10.8; 33.5)
VI					
No	45 (46.9%)	32 (52.5%)	13 (37.1%)		15.3 (-7.3; 37.9)
Yes	51 (53.1%)	29 (47.5%)	22 (62.9%)	0.22	-15.3 (-37.9; 7.3)
Ki-67%					
Neg	45 (44.1%)	29 (44.6%)	16 (43.2%)		1.4 (-20.8; 23.5)
Pos	57 (55.9%)	36 (55.4%)	21 (56.8%)	1.00	-1.4 (-23.5; 20.8)
Node-pos					
No	31 (31.3%)	21 (33.3%)	10 (27.8%)		5.6 (-15.3; 26.4)
Yes	68 (68.7%)	42 (66.7%)	26 (72.2%)	0.73	-5.6 (-26.4; 15.3)

For categorical variables n (%) is presented.
For comparison between groups Fisher´s Exact test (lowest 1-sided p-value multiplied by 2) was used for dichotomous variables. The confidence interval for dichotomous variables is the unconditional exact confidence limits. If no exact limits can be computed the asymptotic Wald confidence limits with continuity correction are calculated instead

Table 5: Comparison between patients with CNS-metastasis *vs* no CNS-metastasis.

Clinical and biological markers for time to diagnose of BM

We found that patients with ER/PR-negative BC were diagnosed with BM earlier compared with patients with hormone receptor positive BC (HR 0,44(95%CI); p=0.015), as well as, that patients with vascular invasion developed brain metastasis earlier than those without vascular invasion (HR 2,31 (95%CI); p=0.024). No difference was seen concerning age, stage, grade, proliferation index, nodal status, or treatment with Trastuzumab. Table 6 and Figure 7. Regarding age and treatment with Trastuzumab, there was no difference in the time aspect of developing brain metastasis Figure 8.

						Cox PH model	
Outcome	**Variable**	**Number of missing observations in the model**	**Value**	**Events**	**Events per 100 patient years**	**Hazard Ratio (95% CI)**	**p-value**
Metastas CNS groups	**Age**		**<50 years**	14/24 (58.33%)	333.7140		
		0/102 (0.00%)	**≥50 years**	23/78 (29.49%)	186.7663	0.58 (0.30 - 1.13)	0.1075
	T-stad ≥2		**No**	1/5 (20.00%)	80.1925		
		0/102 (0.00%)	**Yes**	36/97 (37.11%)	235.8636	3.09 (0.42 - 22.61)	0.2656
	BRE 3		**No**	7/22 (31.82%)	173.0847		
		1/102 (0.98%)	**Yes**	30/79 (37.97%)	248.3492	1.57 (0.69 - 3.59)	0.2822
	HR-pos		**No**	19/45 (42.22%)	321.4186		
		0/102 (0.00%)	**Yes**	18/57 (31.58%)	169.8311	0.50 (0.26 - 0.95)	0.0353
	VI		**No**	13/45 (28.89%)	154.1957		
		6/102 (5.88%)	**Yes**	22/51 (43.14%)	315.7781	2.38 (1.15 - 4.92)	0.0192
	Ki-67%		**Neg**	16/45 (35.56%)	190.8556		
		0/102 (0.00%)	**Pos**	21/57 (36.84%)	258.4055	1.58 (0.81 - 3.07)	0.1793
	Node-pos		**No**	10/31 (32.26%)	159.3911		
		3/102 (2.94%)	**Yes**	26/68 (38.24%)	258.6991	1.75 (0.83 - 3.67)	0.1385
	Trast		**No**	6/31 (19.35%)	134.4039		
		0/102 (0.00%)	**Yes**	31/71 (43.66%)	257.3489	1.86 (0.77 - 4.49)	0.1657
For each variable the hazard ratio with corresponding confidence interval and p-value are presented.							

Table 6: Univariable Cox model for time to CNS-metastasis for those with distance Recurrence.

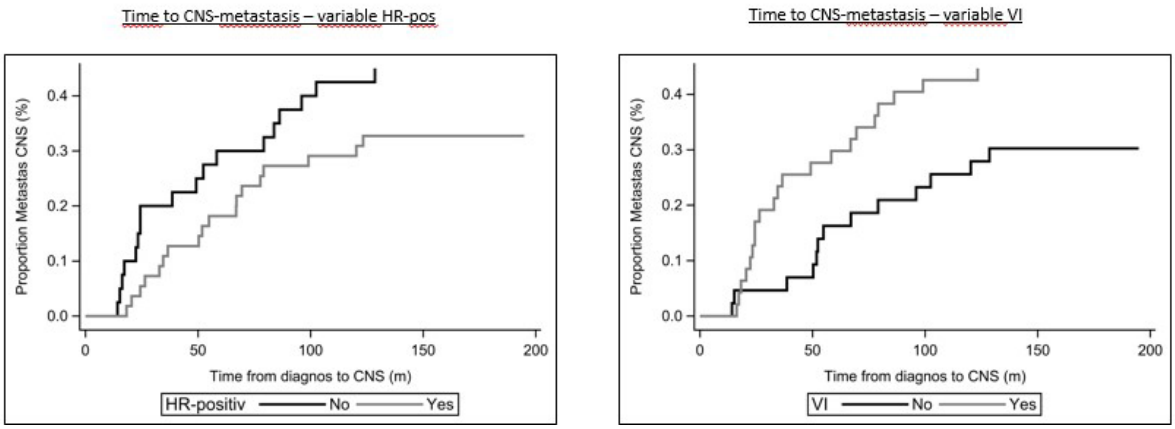


Figure 7: Time to CNS-metastasis-variable HR-pos; Time to CNS-metastasis-Variable VI.

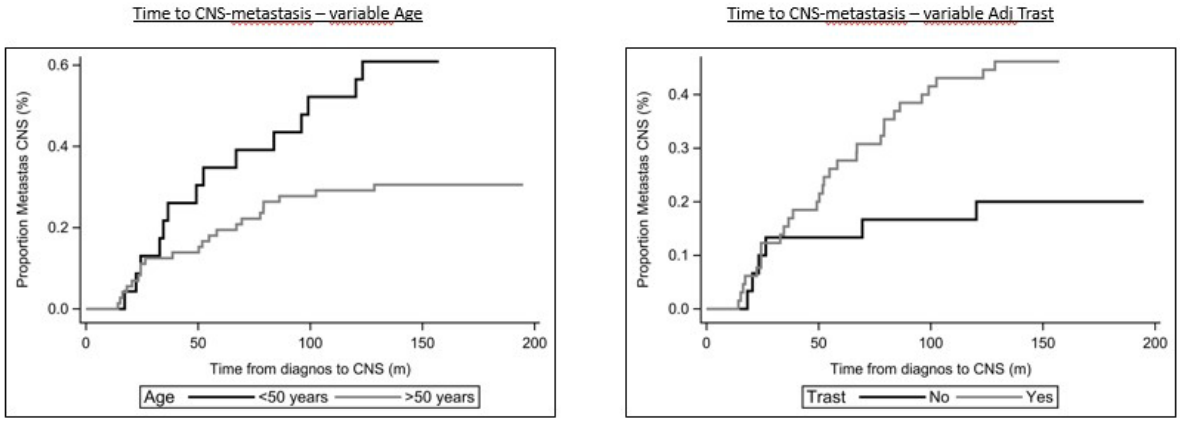


Figure 8: Time to CNS-metastasis-variable Age; Time to CNS-metastasis-Variable Adj Trast.

In order to compare the risk to get BM according to delivered trastuzumab or not, we performed an alternative analysis to compute the risk of brain metastasis with adjustment for the competing risk that the patient can die before they develop BM. In this analysis, it is observed that for those who did not receive adjuvant Trastuzumab i.e. elderly patients, most will die before developing brain metastasis, whereas the opposite is true for those who received trastuzumab, where there is no increased risk of death before the development of brain metastasis Figure 9.

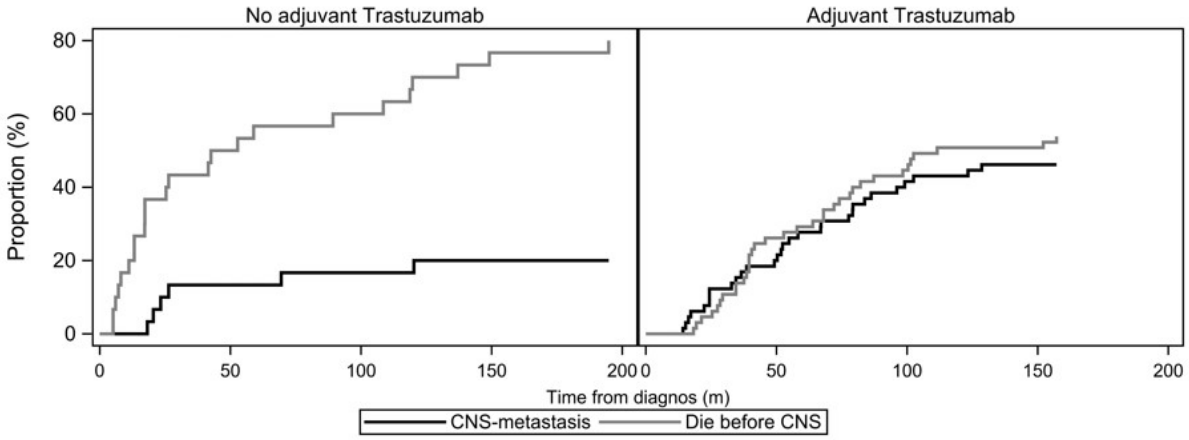


Figure 9: Risk of death in patients with adjuvant Trastuzumab *vs*. no Adjuvant Trastuzumab.

BM according to recurrent or de novo MBC

We compared patients with de novo metastatic BC (n=40) with patients with distant recurrent BC (n=102) concerning standard clinical and biological factors. We found a statistically significant difference in proliferation rate with higher figures for patients with de novo metastatic BC (p=0.0015), whilst other factors were equal in the two groups Table 7. There was a better survival for patients with de novo metastatic BC compared with recurrent BC (p=0.0127) Figure 10.

Variable	Total (n=142)	De Novo metastatic (n=40)	Relapse (n=102)	p-value	Difference between groups Mean (95% CI)
Age ≥50					
No	35 (24.6%)	11 (27.5%)	24 (23.5%)		4.0 (-13.9; 21.8)
Yes	107 (75.4%)	29 (72.5%)	78 (76.5%)	0.77	-4.0 (-21.8; 13.9)
T-stad ≥2					
No	8 (5.7%)	3 (7.5%)	5 (5.0%)		2.5 (-8.4; 13.5)
Yes	133 (94.3%)	37 (92.5%)	96 (95.0%)	0.81	-2.5 (-13.5; 8.4)
BRE 3					
No	37 (26.2%)	15 (37.5%)	22 (21.8%)		15.7 (-3.1; 34.5)
Yes	104 (73.8%)	25 (62.5%)	79 (78.2%)	0.093	-15.7 (-34.5; 3.1)
ER					
Negative	64 (45.1%)	19 (47.5%)	45 (44.1%)		3.4 (-16.6; 23.4)
Positive	78 (54.9%)	21 (52.5%)	57 (55.9%)	0.86	-3.4 (-23.4; 16.6)
Ki-67%					
Neg	51 (35.9%)	6 (15.0%)	45 (44.1%)		-29.1 (-45.5; -12.7)
Pos	91 (64.1%)	34 (85.0%)	57 (55.9%)	0.0015	29.1 (12.7; 45.5)
CNS-met					
No CNS-metastasis	91 (64.1%)	26 (65.0%)	65 (63.7%)		1.3 (-17.9; 20.5)
CNS-metastasis	51 (35.9%)	14 (35.0%)	37 (36.3%)	1.00	-1.3 (-20.5; 17.9)
Node-pos					

Variable	Total (n=142)	De Novo metastatic (n=40)	Relapse (n=102)	p-value	Difference between groups Mean (95% CI)
No	39 (31.7%)	8 (22.2%)	31 (35.6%)		-13.4 (-32.3; 5.5)
Yes	84 (68.3%)	28 (77.8%)	56 (64.4%)	0.21	13.4 (-5.5; 32.3)

For categorical variables n (%) is presented.
For comparison between groups Fisher´s Exact test (lowest 1-sided p-value multiplied by 2) was used for dichotomous variables. The confidence interval for dichotomous variables is the unconditional exact confidence limits. If no exact limits can be computed the asymptotic Wald confidence limits with continuity correction are calculated instead

Table 7: Comparison between de novo metastatic and relapse patients.

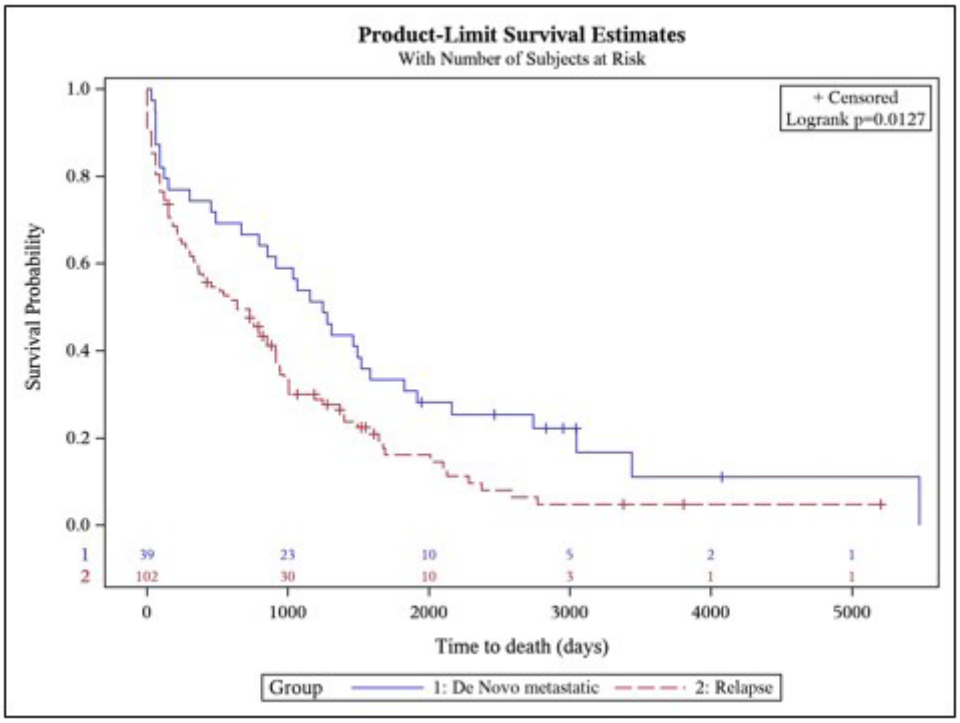


Figure 10: Kaplan-Meier curve for time to the event of death stratified between de novo metastatic and distant relapse.

Discussion

Out of the 102 patients with distant recurrence of their disease, about 36% develop BM, which is consistent with results from other studies [15]. About 15% of patients who relapse have BM as the first location, which agrees well with results in other studies [16]. We do not find it surprising that there is a statistically significant deterioration in OS for the 17 patients who debut with a relapse where BM occurs when it is well consistent with our clinical experience. Among the 102 patients with distant recurrence, we found that the only significant statistical associations that distinguished those who developed BM or not were age < 50 years and initiation of adjuvant trastuzumab. The fact that BM is more common in those who have received adjuvant Trastuzumab compared to controls has been described in meta-analyses of randomized trials with adjuvant trastuzumab, and one interpretation has been that this drug is effective in protecting against extracranial recurrence but has limitations in terms of penetrating the blood-brain barrier [16,17].

However, a problem with these studies is that they only consider recurrence of BM as the first DFS event and do not take into account whether patients develop BM later in the course of the disease. In a subsequent analysis of patients participating in the HERA study, where the risk of developing BM later in the disease progression was also taken into account, it could not be found that adjuvant trastuzumab increased the risk of BM [18]. Young age is described in previous studies as a risk factor itself for the risk of developing BM, but it is surprising that other tumor characteristics such as nodal positivity are not significantly correlated to the risk of developing CNS metastasis in our population [15]. Perhaps this may be because this patient material is too small to demonstrate statistical significance. When we investigated the time aspect of developing BM, we found that the only two variables that could significantly affect this were HR negativity and vascular invasion. The fact that patients with hormone receptor-positive breast cancer more often experience recurrence later compared to those with hormone receptor-negative breast cancer has been confirmed in previous studies [6]. We have not found that previous studies described the occurrence of vascular invasion leading to earlier development of BM, but we believe that this can be explained by the increased risk of hematogenous spread in the presence of vascular invasion, and this should be the only plausible route of spread to the CNS. When we examined the time aspect of developing BM in those who did not receive adjuvant trastuzumab, we found that the risk of death was higher in this group due to older age compared to the group receiving adjuvant treatment. Therefore, it could be that the risk of developing BM does not actually increase at a young age with given adjuvant trastuzumab but is instead explained by the fact that older patients, who less frequently received adjuvant trastuzumab, died from natural causes before they had a chance to develop BM. The fact that as many as >58% of patients who are <50 years of age at the time of their primary diagnosis of BC and who was diagnosed with distance recurrence develop BM is very serious and demonstrates the need for even more effective adjuvant therapy than Trastuzumab in this age group.

The vast majority of patients in this material have been treated with primary surgery followed by postoperative treatment with Trastuzumab and chemotherapy, which is different from the way we mainly treat patients with early HER2-positive breast cancer today [19]. Of the patients who started adjuvant Trastuzumab, over time, 8.7% of patients developed BM. This does not differ significantly from the results in the KATHERINE study where 6.1% of patients with postoperative T-DM1 and 5.4% of patients with postoperative Trastuzumab developed BM [20]. This suggests that we need to develop even better methods to prevent BM in patients with early HER2-positive breast cancer. Perhaps newer HER2-targeted drugs such as Tucatinib and T-Dxd can contribute to reduced incidence of BM in the future?

In this retrospective study of a larger patient population consisting of patients with early HER2-positive breast cancer, we find a statistically significant impaired RFS and OS in those patients who do not start adjuvant Trastuzumab. This difference persists even after performed multivariate analysis adjusted for tumor size, lymph node status and histological grade. These results are consistent with previous results at our department when we studied elderly patients with HER2-positive breast cancer, but also with results in the randomized trials that examined adjuvant Trastuzumab [2,21,22].

The most important explanation why some patients were not recommended adjuvant Trastuzumab was that the patient was not expected to tolerate treatment with chemotherapy and thus treatment with Trastuzumab was also excluded as we have no evidence to give it without concomitant chemotherapy. The difference regarding RFS and OS between the two groups is thus not only due to the absence of treatment with Trastuzumab, but also to the fact that the patients who did not receive Trastuzumab almost exclusively did not receive treatment with chemotherapy either.

We can state that the vast majority of people who start 1 year of planned treatment with Trastuzumab are able to complete the treatment without complications. Only 3% discontinue initiated adjuvant Trastuzumab due to cardiotoxicity, which is a result that is very consistent with the results published in the large, randomized trials investigating adjuvant Trastuzumab [23]. A small number of 14 patients are found to have recurrence during ongoing adjuvant Trastuzumab and in all these cases we have found that there were no radiological or clinical signs of disseminated or residual disease before the onset of adjuvant Trastuzumab. Thus, these 14 patients appear to have a different tumor biology that makes the disease largely refractory to anti HER2 treatment. Most likely, this is due to some known resistance mechanism to HER2 treatment, such as PIK3CA mutation [24].

We found that 7% of patients had de novo metastatic disease, which is well in line with previous studies that estimate this figure to be between 3-6% in high-income countries [5]. Somewhat surprisingly, we were unable to find any statistically significant differences in parameters such as T-stage or glandular positivity between the patients who had de novo metastatic disease compared to those who received relapse after previously started adjuvant Trastuzumab. After all, it was an improved survival statistically significant for those with de novo metastatic breast cancer compared to those who received distant recurrence after previously started adjuvant Trastuzumab. Several previous studies have previously investigated this and in most cases the results have shown improved survival in de novo metastatic BC compared to recurrent metastatic BC, but there are also studies that show the

opposite. One theory why de novo metastatic BC would have a better prognosis compared to recurrent metastatic BC is that the latter group could have developed resistant metastatic cell lines to previous adjuvant therapies.

Conclusion

We observed a higher prevalence of BM in patients with HER2-positive mBC than previously has been described. We are aware, however, that this is a relatively small patient sample, which means that these numbers must be interpreted with caution, as the number of patients with metastatic HER2-positive BC who develop BM could have been lower if we had a larger patient sample to study. Administration of adjuvant Trastuzumab clearly improved OS and RFS in patients with early HER2-positive BC in this retrospective study.

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Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki. The Sahlgrenska University Hospital Ethical Review Board, Gothenburg, Sweden, approved the study (460-09). Informed consent was waived by The Ethical Review Board for this retrospective study.

Conflict of interest

The authors have no conflict of interest.

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