Metastatic breast cancer

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Metastatic breast cancer: understanding prognosis and treatment patterns in real-life

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Metastatic breast cancer: understanding prognosis and treatment patterns in real-life

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Contents

Chapter 1	Introduction and outline of the thesis	7
Chapter 2	Prognosis of metastatic breast cancer subtypes: the hormone receptor/HER2-positive subtype is associated with the most favorable outcome <i>Breast Cancer Res Treat 2013;141:507-514</i>	15
Chapter 3	Prognosis of metastatic breast cancer: are there differences between patients with <i>de novo</i> and recurrent metastatic breast cancer? <i>British Journal of Cancer 2015;112:1445-1451</i>	31
Chapter 4	The role of histological subtype in hormone receptor positive metastatic breast cancer: similar survival but different therapeutic approaches. A study of the Southeast Netherlands Breast Cancer Consortium <i>Oncotarget 2016;7:29412-29419</i>	47
Chapter 5	In real life, one-quarter of patients with hormone receptor- positive metastatic breast cancer receive chemotherapy as initial palliative therapy. A study of the Southeast Netherlands Breast Cancer Consortium <i>Annals of Oncology 2016;27:256-262</i>	61
Chapter 6	A real-world study on implementation of bevacizumab in a cohort of HER2-negative metastatic breast cancer patients. A study of the Southeast Netherlands Breast Cancer Consortium <i>Submitted</i>	75
Chapter 7	Real-world and trial based cost-effectiveness analysis of bevacizumab in HER2-negative metastatic breast cancer patients. A study of the Southeast Netherlands Breast Cancer Consortium <i>Submitted</i>	91
Chapter 8	Summary, conclusions and future perspectives	109
	Nederlandse samenvatting	127
	Valorisation	137
	List of publications	143
	Dankwoord	147
	Curriculum vitae	153

Chapter 1

Introduction and outline of the thesis

Introduction and outline of the thesis

Breast cancer is the most frequent cancer among women, with an estimated number of new cases of 1.67 million worldwide.¹ Although prognosis of patients with early stage disease has significantly improved during the last two decades, breast cancer is still the major cause of death among women in the age group of 40 to 60 years and over 500 000 patients die of the disease annually.¹ This illustrates that breast cancer remains a major global health issue. Around 20-30% of all breast cancer patients will develop a distant recurrence after prior treatment of early stage breast cancer, and around 5% of patients are found to have metastatic breast cancer already at initial diagnosis.² Once distant recurrence has occurred the disease is generally incurable and the patient has a median survival of 2 to 3 years.³

What is relevant to notice is that breast cancer is now recognized as a heterogeneous disease, in which different subtypes of breast cancer can be distinguished with variable outcome.^{4,5} Also in patients with metastatic breast cancer, the outcome can vary largely and about 20% of patients may have a very indolent disease course, surviving for many years in a generally excellent condition.

The assessment of breast cancer subtype is essential in every-day clinical practice, as the presence or absence of hormone receptor or human epidermal growth factor receptor 2 (HER2) amplification are known to be associated with different metastatic patterns, different treatment responses, and differences in long term outcome.⁶⁻⁸ Currently, for clinical practice, we identify four different breast cancer subgroups by the presence or absence of the hormone receptor and the HER2 status, each associated with different therapeutic strategies and a different outcome.^{9,10} Besides hormone and HER2 receptor status, other classifications of breast cancer subtypes can be used, for instance based on genetic profiles, histology or other prognostic biomarkers, such as Ki-67.

Approximately 75% of all breast cancers are estrogen and/or progesterone receptor positive, so called hormone receptor-positive breast cancer and thereby represent the largest breast cancer subgroup.¹¹ A positive hormone receptor status is a favorable prognostic factor for the outcome of metastatic breast cancer.⁹ Furthermore, hormone receptor-positivity is an important predictive factor for response to endocrine therapy. Targeting the estrogen pathway by receptor blockade or reducing circulating estrogen levels by suppression of estrogen synthesis are effective endocrine treatment strategies for patients with hormone receptor-positive breast cancer.¹² Since the approval of tamoxifen, a selective estrogen receptor modulator, by the US Food and Drug Administration (FDA) in 1977, several other therapeutic agents for the treatment of hormone receptor-positive breast cancer became available, including aromatase inhibitors and fulvestrant.

Amplification of HER2 is present in approximately 15% of breast cancer patients and is associated with a worse prognosis.^{13,14} In 1998, the FDA approved the first HER2-targeted therapy, named trastuzumab, for the treatment of patients with metastatic HER2-positive breast cancer. This was an important milestone, since the implementation and use of this targeted therapy resulted in a significant improvement of the prognosis of patients with HER2-positive metastatic breast cancer.¹⁵ After the introduction of trastuzumab, more and more HER2-targeted therapies became available, including lapatinib, trastuzumab-emtansine (T-DM1) and pertuzumab. These HER2-targeted therapies changed the unfavorable prognostic profile of HER2-positive breast cancer into a favorable one, as a result of its strong predictive value for response to these drugs.

In patients with hormone receptor- and HER2-negative breast cancer, so called triple-negative breast cancer, systemic treatment currently consists of chemotherapy alone, although new targeted agents, for instance poly (ADP-ribose) polymerase (PARP) inhibitors and immunotherapy, are being developed that may also lead to a significant change in breast cancer outcome for this patient group in the near future.¹⁶

Although metastatic breast cancer still remains incurable, it can be sensitive to systemic therapy and more and more therapeutic options for metastatic breast cancer are becoming available. These new drugs provide a huge variety of treatment options for patients with metastatic breast cancer and will profoundly change the landscape of metastatic breast cancer. Consequently, the large variety in new drugs makes the treatment of an individual patient a very complex process. The challenge is to incorporate the results obtained from randomized clinical trials into the treatment of patients with metastatic breast cancer. Even though it is not always a clear-cut case to translate the clinical trial data to the patients with metastatic breast cancer we see in every-day clinical practice.

Treatment decisions in metastatic breast cancer are not only based on the expected progression-free or overall survival benefit, but also on the toxicity profile of the various treatment options, taking age, comorbidities and co-medication, site and extensiveness of distant metastasis and expected disease course into account. To inform patients and guide the treatment-decision making process, knowledge on efficacy and toxicity data from trials, in combination with knowledge on real-world outcome based on correct patient selection, is essential.

In the end, the aim of treating patients with metastatic breast cancer should of course be prolonging survival, but improving quality of life by balancing the side effects of treatment with the improvement of disease-related symptoms is of equal importance. Apart from informing our patients on expected outcome and toxicity, at every treatment decision made these aims do play an important role.

Even so, in a recent survey among patients with metastatic breast cancer 55% of the patients felt in need of more accurate information on metastatic breast cancer.¹⁷

Having said this, we note that data on disease course and treatment patterns in real-life metastatic breast cancer are scarce.

This thesis is designed to provide the required information on real-life patients with metastatic breast cancer in a recent period in which new therapeutic options were implemented and available to all patients. Therefore we carried out an observational population-based cohort study including all consecutive breast cancer patients diagnosed with metastatic breast cancer between 2007-2009, from all hospitals participating in the Southeast Netherlands Breast Cancer Consortium.

In the first part of this thesis we focus on the total cohort of metastatic breast cancer. It was known from previous studies that outcome of patients with metastatic breast cancer was influenced by several prognostic factors, including age, performance status and site and number of distant metastases.^{9,18-21} However, nowadays metastatic breast cancer is no longer considered a single disease entity, but a heterogeneous group of cancers which can be divided in subtypes. In **chapter 2** we describe a model to investigate the prognostic impact of breast cancer subtypes in metastatic breast cancer, based on hormone receptor and HER2 status, after accounting for the other known prognostic factors.

Besides the prognostic impact of breast cancer subtypes, one of the strongest prognostic factors is the metastatic-free interval, which is the time between diagnosis of primary breast cancer and the development of distant metastasis.⁹ With that in mind, the patients diagnosed with distant metastasis at initial diagnosis, so called *de novo* metastatic breast cancer, can be viewed as a group with very short metastatic-free interval and is investigated as a distinct subgroup to determine their prognosis in **chapter 3**.

In early breast cancer, histology can also be used to determine breast cancer subtypes with known differences in outcome and response to therapy. **Chapter 4** focuses on the two largest histological subtypes, invasive ductal carcinoma and invasive lobular carcinoma, in metastatic breast cancer.

Prognostic information is needed in daily practice to inform patients on the expected course of their disease course but also to help guide treatment decisions in real-life. Systemic treatment in metastatic breast cancer is complex since decisions are dependent on many factors, including the continuous development and growing availability of new drugs. Real-life data provide the opportunity to investigate the implementation of these new drugs in real-life. Furthermore, when focusing on treatment in metastatic breast cancer, which currently remains to have a non-curative intent, quality of life and cost-efficacy are also important factors to consider.

Recently, globally and nationally costs of cancer care are more and more debated and the value of a new drug for the treatment of metastatic breast cancer is not only weighed by efficacy, but also by toxicity, improvement of quality of life and cost-effectiveness.

The second part of the thesis focuses more on these aspects of metastatic breast cancer.

In **chapter 5** treatment patterns in the largest subgroup of breast cancer, the patients with hormone receptor-positive metastatic disease, are presented. These data provide a unique insight in the real-life treatment of patients with metastatic breast cancer.

This real-life treatment is further explored in **chapter 6**, in which the implementation of bevacizumab, one of the new drugs available for the treatment of metastatic breast cancer, is studied. Since this drug is approved for treatment of metastatic HER2-negative breast cancer patients we focused on this subgroup from our total cohort.

Chapter 7 used the information on the use and efficacy of bevacizumab in real-life providing a cost-effectiveness model for this new drug in the real-world. We compared the real-life cost-effectiveness ratio with the cost-effectiveness based on the efficacy results of a randomized controlled trial.

Finally, in **chapter 8** we summarize the most important findings and draw a number of conclusions based on this thesis. Furthermore, we discuss the future development of new (targeted) therapies and the need of a more efficient allocation of current therapies, to improve effectiveness, to reduce toxicity and lower costs with the ultimate goal of improving survival and quality of care for patients with metastatic breast cancer.

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Chapter 2

Prognosis of metastatic breast cancer subtypes: the hormone receptor/HER2-positive subtype is associated with the most favorable outcome

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Breast Cancer Research and Treatment 2013;141:507-514

Abstract

Background

Contrary to the situation in early breast cancer, little is known about the prognostic relevance of the hormone receptor (HR) and human epidermal growth factor receptor 2 (HER2) in metastatic breast cancer. The objectives of this study were to present survival estimates and to determine the prognostic impact of breast cancer subtypes based on HR and HER2 status in a recent cohort of metastatic breast cancer patients, which is representative of current clinical practice.

Patients and methods

Patients diagnosed with metastatic breast cancer between 2007-2009 were included. Information regarding patient and tumor characteristics and treatment was collected. Patients were categorized in four subtypes based on the HR and HER2 status of the primary tumor; HR positive (+)/HER2 negative (-), HR+/HER2+, HR-/HER2+ and triple negative (TN). Survival was estimated using the Kaplan-Meier method. Cox proportional hazards model was used to determine the prognostic impact of breast cancer subtype, adjusted for possible confounders.

Results

Median follow up was 21.8 months for the 815 patients included; 66% of patients had the HR+/HER2- subtype, 8% the HR-/HER2+ subtype, 15% the TN subtype and 11% the HR+/HER2+ subtype. The longest survival was observed for the HR+/HER2+ subtype (median 34.4 months), compared to 24.8 months for the HR+/HER2- subtype, 19.8 months for the HR-/HER2+ subtype and 8.8 months for the TN subtype ($P < 0.0001$). In the multivariate analysis, subtype was an independent prognostic factor, as were initial site of metastases and metastatic-free interval.

Conclusion

The HR+/HER2+ subtype was associated with the longest survival after diagnosis of distant metastases.

Introduction

In early breast cancer, survival is predominantly estimated by primary tumor size, histological grade and nodal status.¹ However, these factors cannot account for the heterogeneity of the disease. It is known that different biological breast cancer subtypes have distinct epidemiology, response to therapy and prognosis.² Therefore, an expert panel at the 12th St Gallen International Meeting adopted a new approach for adjuvant treatment recommendations based on the biological subtypes of early breast cancer, distinguished by clinicopathological factors including hormone receptor (HR) and human epidermal growth factor receptor 2 (HER2) status.³

In metastatic breast cancer the prognostic relevance, disease course and outcome of breast cancer subtypes are less intensively studied and outcome of these studies varies considerably, even though, as for early breast cancer, this knowledge is essential in guiding treatment for metastatic breast cancer patients. Factors that have been reported as favorable in patients diagnosed with metastatic breast cancer are a good performance status, presence of metastases largely limited to bone and soft tissue, a low number of metastatic sites and a long metastatic-free interval.⁴⁻⁸

In a consensus paper on the treatment for metastatic breast cancer, HER2 overexpression was categorized as unfavorable, however, with the remark that the significance of HER2 has become less clear in the era of HER2-targeted therapies.⁹ In a recent study, breast cancer subtypes were shown to be associated with notable differences in survival after relapse.¹⁰ The HER2-positive subtypes (irrespective of HR status) had a significantly worse survival compared with patients with HR-positive/HER2-negative tumors. In this study, patients with early breast cancer diagnosed between 1986 and 1992 were included and followed for 14.8 years. Since most patients relapsed within the first five years from primary diagnosis, the results of this study largely represent outcome from the pre-HER2-targeted therapy era. Another study reported a better prognosis for HER2-positive metastatic breast cancer treated with trastuzumab compared with HER2-negative metastatic breast cancer.¹¹ The objectives of this study were to present survival estimates and to determine the prognostic impact of breast cancer subtypes based on HR and HER2 status in a recent cohort of metastatic breast cancer patients, in which diagnostics and treatment have remained largely unchanged over time and are representative of current clinical practice.

Patients and Methods

Patients

This observational study was conducted in eight hospitals in the southeast part of the Netherlands. In these hospitals, all patients diagnosed with metastatic breast cancer

between 2007 and 2009 were identified, including patients with primary metastatic disease. Patients were included irrespective of the date of diagnosis of the primary tumor with the exception of patients with a diagnosis of primary breast cancer before 1990, due to the limited available data on the primary tumor characteristics and the initial treatment.

Data collection

After obtaining approval from the Medical Research Ethics Committee of Maastricht University Medical Center, specially trained registration clerks collected data from the medical files in a central electronic database. Information was collected regarding patient and tumor characteristics, treatment information (surgery, radiotherapy and systemic treatment, both adjuvant and palliative), number and sites of distant metastases and overall survival time since diagnoses of metastatic breast cancer. Initial metastatic sites were registered as single or multiple and were categorized as bone, visceral (including lung, liver, pleural, peritoneal, pericardial and lymphangitic carcinomatosis), brain (including leptomeningeal and central nervous system), skin and lymph nodes and multiple metastases (more than one of the aforementioned metastatic sites). Tumors were characterized by the sixth edition of the TNM classification of malignant tumors¹² and Scarff-Bloom-Richardson (SBR) histological grading.¹³ Estrogen receptor (ER) and progesterone receptor (PR) positivity was defined as positive nuclear staining of $\geq 10\%$. HER2 positivity was defined as immunohistochemistry score of 3+ or 2+ with a positive fluorescence in situ hybridization (FISH) result.

Classification of patients

All included patients were classified in four clinical breast cancer subtypes, based on the HR and HER2 status of the primary tumor. HR positivity was defined as ER and/or PR positive. If there was no information on the primary tumor, we used the pathology results from the metastases. The following breast cancer subtypes were defined: HR positive/HER2 negative, HR positive/HER2 positive, HR negative/HER2 positive and triple negative (TN) (i.e., HR and HER2 negative).

Statistical analysis

The primary aim of our study was to assess median survival time of patients with distant metastases according to breast cancer subtype. Survival after distant metastasis was defined as time between date of first distant metastasis and date of death. All patients still alive at the time of the analysis were censored at the date of last follow-up. Survival was estimated using the Kaplan-Meier method and compared between the subtypes using log-rank test. Metastatic-free survival was defined as

time between date of diagnosis and date of first distant metastasis, and for the analyses divided into two categories: < 24 months or ≥ 24 months.

Secondary aim of our study was to assess the relative contribution of breast cancer subtypes and other factors to survival after diagnosis of metastatic breast cancer, using Cox proportional hazards models. First, we carried out separate analyses for each possible prognostic factor, with the subtype as covariate. Next, factors with a *P* value below 0.10 were included in multivariable analyses in a model resulting from forward selection (criteria for entry $P < 0.05$). Factors included in the models, besides cancer subtype, were the following: age (< 50 years vs. ≥ 50 years), menopausal status (postmenopausal vs premenopausal), pathological primary tumor status (T1 vs. T2 vs. T3 vs. T4), pathological lymph node status of the primary tumor (N0 vs N1 vs. N2 vs. N3), histological grade of the primary tumor (grade 1 vs. 2 vs. 3), prior use and type of adjuvant systemic therapy (yes vs no), metastatic-free interval (< 24 months vs ≥ 24 months) and number of initial metastatic sites (1 vs. >1) and initial site of metastases (bone vs visceral vs. brain vs. skin and lymph nodes vs. multiple). There were relatively large numbers of missing values for the factors such as primary tumor status, histological grade and lymph node status due to patients treated with neo-adjuvant systemic therapy or patients not undergoing surgery of the primary tumor. To evaluate the robustness of our result, we carried out analyses with and without the factors with large number of missing values. The missing value pattern did not influence the results.

Results

Patient characteristics

A total of 815 metastatic breast cancer patients were included in the study, of which 798 patients could be categorized in the four subtypes (based on HR and HER2 status of the primary tumor in 92.7% and on HR and HER2 status of metastatic lesion in 7.3%). Table 2.1 shows baseline characteristics of the included patients, of which 19% had primary metastatic disease. Median follow-up after diagnosis of metastatic disease was 21.8 months, with 300 patients (36.8%) being alive at the end of the follow-up period.

Table 2.1 Baseline characteristics of patients with metastatic breast cancer according to subtype

Characteristics	HR+/HER2- n=527		HR+/HER2+ n=84		HR-/HER2+ n=64		TN n=123		P
	n	%	n	%	n	%	n	%	
Age at primary diagnosis									
<50 years	138	26.2	29	34.5	22	34.4	43	35.0	0.10
≥50 years	389	73.8	55	65.5	42	65.6	80	65.0	
Menopausal status									
Premenopausal	140	29.1	27	37.5	22	37.3	44	39.6	0.09
Postmenopausal	341	70.9	45	62.5	37	62.7	67	60.4	
Primary tumor stage*									
T1	173	43.8	20	39.3	16	39.1	34	38.2	0.91
T2	187	47.3	29	56.9	21	51.2	48	53.9	
T3	22	5.6	1	1.9	3	7.3	4	4.5	
T4	13	3.3	1	1.9	1	2.4	3	3.4	
Unknown**	132		33		23		34		
Regional lymph node stage primary tumor*									
N0	170	42.6	16	30.8	16	38.1	31	34.8	0.12
N1	136	34.1	23	44.2	14	33.3	24	27.0	
N2	54	13.5	5	9.6	6	14.3	21	23.6	
N3	39	9.8	8	15.4	6	14.3	13	14.6	
Unknown**	128		32		22		34		
Histological grade of primary tumor									
SBR 1	55	15.7	5	9.1	0	0.0	2	2.0	<.0001
SBR 2	181	51.9	31	56.4	16	32.0	21	21.0	
SBR 3	113	32.4	19	34.5	34	68.0	77	77.0	
Unknown**	178		29		14		23		
Prior adjuvant chemotherapy									
Yes	152	28.8	30	35.7	23	35.9	48	39.0	0.10
No	375	71.2	54	64.3	41	64.1	75	61.0	
Prior adjuvant targeted therapy									
Yes	4	0.8	16	19.1	24	37.5	0	0.0	<.0001
No	523	99.2	68	80.9	40	62.5	123	100.0	
Prior adjuvant endocrine therapy									
Yes	271	51.4	45	53.6	8	12.5	9	7.3	<.0001
No	256	48.6	39	46.4	56	87.5	114	92.7	
Metastatic-free interval									
<24 months	180	34.2	38	45.2	30	46.9	77	62.6	<.0001
≥24 months	347	65.8	46	54.8	34	53.1	46	37.4	
No. of initial metastatic sites									
1	357	67.7	51	60.7	41	64.1	70	56.9	0.11
≥2	170	2.3	33	39.3	23	35.9	53	43.1	
Initial site of metastases									
Bone	209	39.6	18	21.5	8	12.5	20	16.3	<.0001
Visceral	130	24.7	28	33.3	24	37.5	41	33.3	0.03
Brain	9	1.7	3	3.6	7	10.9	7	5.7	0.0004
Skin and lymph nodes	29	5.5	7	8.3	7	10.9	11	8.9	0.23
Multiple	150	28.5	28	33.3	18	28.2	44	35.8	0.38
Palliative systemic therapy									
Chemotherapy	256	48.6	62	73.8	40	62.5	78	63.4	<.0001
Endocrine therapy	437	82.9	50	59.5	4	6.3	13	10.6	<.0001
Targeted therapy***	5	0.9	55	65.5	36	56.3	0	0.0	<.0001

HR hormone receptor, HER2 human epidermal growth factor receptor 2, TN triple negative, SBR Scarff-Bloom-Richardson. * Pathological TNM by the sixth edition of the TNM classification of malignant tumors;

** Missing pathological T and N stage and histological grade values include patients treated with neo-adjuvant systemic treatment and patients not undergoing surgery of the primary tumor; *** Including trastuzumab and lapatinib.

The largest subtype was the HR+/HER2- group comprising 66% of all patients; the HR-/HER2+ subtype consisted of 8% of all patients, the TN subtype of 15% of patients and the HR+/HER2+ subtype of 11% of all patients.

Median age at initial diagnosis was 59 years (range 25-93 years). At initial diagnosis, most of the HR+ tumors were grade 2, whereas most of the HR- tumors were grade 3, irrespective of HER2 status. The largest proportion of node-positive tumors at initial diagnosis was found in the HR+/HER2+ subtype (69.2%). Of all patients with HR+ tumors, 52% had received adjuvant endocrine therapy. A small proportion of patients with HR- tumors had received adjuvant endocrine therapy based on treatment recommendations at the time of the initial diagnosis.

Median metastatic-free survival was ≥ 24 months in all subtypes, with the exception of the patients with TN tumors with a median metastatic-free survival of < 24 months. The distribution of initial metastatic sites is significantly different between subtypes (Table 2.1). Bone was the most frequent initial site of metastases in HR+ breast cancer subtypes, whereas visceral and multiple metastases as initial site of distant recurrence were most frequently seen in HR- breast cancer subtypes.

Univariate analysis and survival estimates of metastatic breast cancer

The median survival of all patients since first diagnosis of distant metastases was 21.8 months. The median survival ranged from 8.8 months (95% CI 6.3-11.8 months) for patients in the TN subtype to 34.4 months (95% CI 25.6-46.6 months) for patients with the HR+/HER2+ subtype ($P < 0.0001$). Median survival was 24.8 months (95% CI 21.3-30.3 months) for patients with the HR+/HER2- subtype and 19.8 months (95% CI 14.6-33.1 months) for patients with the HR-/HER2+ subtype (Figure 2.1).

Figure 2.1 Survival after diagnosis of metastatic breast cancer per subtype in a cohort of 798 patients with metastatic breast cancer.

Figure 2.2 shows survival after distant metastasis per subtype according to initial metastatic site; bone (A), visceral (B) and multiple initial metastatic sites (C).

Figure 2.2 Survival after diagnosis of distant metastases per subtype according to initial metastatic site; bone (A), visceral (B), multiple (C).

Survival curves according to brain and skin and lymph nodes as initial metastatic sites were not further shown due to limited numbers per subtype. Irrespective of site of metastases, worst survival was seen in the TN subtype and best survival in the HR+/HER2+ subtype.

Besides subtype, age at primary breast cancer diagnosis, menopausal status, primary tumor stage, regional lymph node stage at initial diagnosis, histological grade of the primary tumor, metastatic-free interval and initial number and site of metastases all showed a statistically significant relationship with survival after distant metastasis when analyzed with the Kaplan-Meier method ($P < 0.05$).

Multivariate analyses of prognostic factors for survival

Also after adjustment for potential confounders in a Cox regression analysis, the HR+/HER2+ subtype appeared to be associated with a significantly better survival, as compared to the HR+/HER2- group, with a hazard ratio of 0.64 (95% CI 0.45-0.92, $P = 0.02$). The TN subtype appeared to be associated with a significantly worse survival, as compared to the HR+/HER2- group, with a hazard ratio of 2.15 (95% CI 1.65-2.80, $P < 0.0001$).

Age at initial diagnosis, metastatic-free interval and initial metastatic sites were statistically significant in a multivariate analysis with forward selection (Table 2.2). Older age at initial diagnosis (age > 50 years) was associated with worse survival after metastatic disease (hazard ratio 1.39, 95% CI 1.12-1.71, $P = 0.003$), whereas a metastatic-free interval of 24 months or longer demonstrated to be a favorable factor (hazard ratio 0.62, 95% CI 0.50-0.75, $P < 0.0001$).

The presence of visceral, brain and multiple metastases as initial sites of metastases as compared with bone metastases were associated with a shorter survival time after distant metastases.

The above results are based on analyses only including the prognostic factors that had relatively few missing values. Subsequent analyses including prognostic factors with many missing values led to the same results with almost similar hazard ratios (data not further shown).

Table 2.2 Multivariable analysis of prognostic factors for survival after metastatic breast cancer.

	Hazard ratio	95 % CI	P
Subtype			
HR+/HER2-	1		
HR+/HER2+	0.64	0.45-0.92	0.02
HR-/HER2+	1.35	0.96-1.92	0.09
TN	2.15	1.65-2.80	<0.0001
Age at initial diagnosis			
<50 years	1		
≥50 years	1.39	1.12-1.71	0.003
Adjuvant endocrine therapy			
No	1		
Yes	1.30	1.05-1.62	0.02
Metastatic-free interval			
<24 months	1		
≥24 months	0.62	0.50-0.75	<0.0001
No. of initial metastatic sites			
1	1		
>1	1.21	0.79-1.85	0.38
Initial site of metastases*			
Bone	1		
Visceral	1.82	1.41-2.35	<0.0001
Brain	2.58	1.55-4.30	0.0003
Multiple	1.90	1.18-3.07	0.009

HR hormone receptor, HER2 human epidermal growth factor receptor 2, TN triple negative, CI confidence interval. * Skin and lymph nodes as site of metastases did not meet the entry-criteria for multivariable analysis of $P < 0.05$.

Discussion

Contrary to the available knowledge on prognostic factors and the survival difference of breast cancer subtypes in early breast cancer, risk estimation of metastatic breast cancer subtypes is less well established. With this study, we present survival estimates and the prognostic impact of breast cancer subtypes on survival after diagnosis of metastatic breast cancer.

This study showed that the HR+/HER2+ subtype was associated with the best prognosis with a median survival after diagnosis of metastatic breast cancer of 34.4 months, even better than the HR+/HER2- subtype (hazard ratio 0.64, 95% CI 0.45-0.92, $P = 0.02$).

This observation was not demonstrated in a recent study on metastatic breast cancer subtypes.¹⁰ In that study, 3,726 patients with early-stage breast cancer diagnosed between 1986–1992 were followed for 14.8 years and divided into breast cancer subtypes based on retrospective assessment of ER, PR, HER2, Ki-67, EGRF and/or CK5/6. A total of 1,357 patients developed distant metastases and their survival was significantly different per subtype ($P < 0.001$). The luminal/HER2-positive and the HER2-

enriched subtypes had a significantly lower median survival compared with the luminal A and luminal B subtypes, thereby indicating that the overexpression of HER2 was unfavorable. However, for metastatic HER2-positive breast cancer trastuzumab was registered and rapidly implemented in the year 1998 and lapatinib in the year 2007. Taking into account that most patients relapsed within the first five years from primary diagnosis, the study of Kennecke et al.¹⁰, therefore, largely reflects outcome from a time that HER2-targeted therapy for metastatic breast cancer was not yet implemented.

In our study, we included patients diagnosed with metastatic breast cancer between 2007-2009, which is a recent cohort in which HER2-targeted therapy was available in treatment for metastatic breast cancer. Our result indicates that in the era of HER2-targeted therapy, the prognostic relevance of HER2 have shifted towards a more favorable influence on survival. This is supported by the results of a large single-institution study in which 2,091 patients with metastatic breast cancer were included and divided into three groups: HER2-negative disease, HER2-positive disease with no trastuzumab treatment for metastatic disease; and HER2-positive disease with trastuzumab treatment for metastatic disease.¹¹ Women with HER2-positive breast cancer treated with trastuzumab for metastatic disease had a better prognosis than those with HER2-positive disease not treated with trastuzumab and even a better prognosis than patients with HER2-negative disease (hazard ratio 0.56, 95% CI 0.45-0.69, $P < 0.0001$). In this study, none of the patients received adjuvant treatment with trastuzumab, whereas in our cohort, a proportion of patients, depending on timing of primary breast cancer diagnosis that ranged from 1990 to 2009, did receive adjuvant anti-HER2 therapy (38% of patients with HR-/HER2+ subtype and 19% of patients with HR+/HER2+ subtype).

Improved prognosis of HER2-positive breast cancer patients was also seen in an analysis of 756 metastatic breast cancer patients, in which patients with HER2-positive disease (based on the primary tumor) treated with trastuzumab had a comparable survival after diagnosis of metastatic disease as patients with HER2-negative disease.¹⁴

Besides breast cancer subtype, multivariable analysis showed age at primary breast cancer diagnosis, metastatic-free interval and initial site of metastases as significant prognostic factors. However, primary tumor characteristics such as histological grade, size of the primary tumor and nodal status proved to be of no prognostic significance. In 1998, a prognostic index for patients with metastatic breast cancer was presented including metastatic-free interval, site of initial metastasis, as well as the administration of adjuvant chemotherapy and level of serum lactate dehydrogenase.⁴ Primary tumor characteristics were not included since these factors were not found to be of prognostic significance for patients with metastatic breast cancer. Since then, several retrospective studies have been reported on the prognostic relevance of primary tumor characteristics on survival after diagnosis of metastatic breast cancer, all showing considerable variation.^{5,6,8,14,15}

In this study, breast cancer subtypes based on the HR and HER2 status of the primary tumor showed to be of prognostic relevance for survival after diagnosis of metastatic breast cancer, contrary to other primary tumor characteristics.

It is well known that HR and HER2 receptor conversion between primary tumor and metastases can occur; however, the impact on choice of systemic treatment and clinical outcome remains unclear.¹⁶ In a retrospective analysis, in which analytic variables were ruled out by using only whole section histological biopsies of non-bone metastases with standardized staining methods, a conversion rate of 10.3% for ER and 30% for PR was found.¹⁷ In that analysis, the conversion rate for HER2 of 5.2% was lower than the conversion rates found in other retrospective analyses (14 and 24%, respectively).^{18,19} In a prospective study evaluating the impact of receptor discordance on systemic treatment, conversion rates of ER, PR and HER2 were comparable to the retrospective analyses with, respectively, 16, 40 and 10%.²⁰ However, only in 14% of all included patients a change in management was seen after biopsy of metastatic lesions, which was confirmed in a pooled analysis.²¹ Even though receptor discordance between primary tumor and metastatic lesion has negative prognostic value,^{19,22,23} the effect of changing systemic therapy based on receptor status of metastatic sites on survival is yet unknown.

We categorized patients in subtypes based on primary tumors since not all included patients had histological biopsies of metastatic lesions. In a recent consensus guideline for advanced breast cancer, biopsy of metastatic lesion with re-evaluation of HR and HER2 is recommended for all patients diagnosed with metastatic breast cancer.²⁴ Further prospective analyses need to be undertaken to determine the impact of HR and HER2 re-assessment during the course of disease on the effectiveness of systemic treatment decision-making.

A limitation of this study is the use of subtypes based on the HR and HER2 status without incorporating other markers, such as Ki-67 or CK5/6. However, the assessment of these markers is not incorporated in the standard pathological assessment of breast cancer and is therefore not widely available in daily practice.

Further, according to Dutch guidelines, HR positivity was defined as 10% or more nuclear staining by immunohistochemistry, while recently the American Society of Clinical Oncology (ASCO) and American college for Pathology have recommended a 1% threshold value.²⁵ Even so, the distribution of subtypes in this cohort with 20% of included patients having a HER2-positive tumor and 50% of these also being HR-positive is comparable to previously published international studies on metastatic breast cancer subtypes.^{10,26,27}

With the inclusion of all diagnosed metastatic breast cancer patients, irrespective of treatment, from university and (non)-teaching hospitals in the Netherlands, this cohort is representative of the whole Dutch population of metastatic breast cancer patients.

In conclusion, this study demonstrates the relevance of breast cancer subtypes, based on HR and HER2 status, on the survival of patients with metastatic breast cancer. The

results are based on a recent cohort, representative of current clinical practice. We found that the HR+/HER2+ subtype was associated with the longest survival with a hazard ratio of 0.64 (95% CI 0.45-0.92, $P=0.02$) compared with the HR+/HER2- subtype. This knowledge is useful for the treatment of metastatic breast cancer patients in this era of individualized therapy.

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Chapter 3

Prognosis of metastatic breast cancer: are there differences between patients with *de novo* and recurrent metastatic breast cancer?

A study of the Southeast Netherlands Breast Cancer Consortium

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Abstract

Background

We aimed to determine the prognostic impact of time between primary breast cancer and diagnosis of distant metastasis (metastatic-free interval, MFI) on the survival of metastatic breast cancer patients.

Patients and methods

Consecutive patients diagnosed with metastatic breast cancer in 2007-2009 in eight hospitals in the Southeast of the Netherlands were included and categorized based on MFI. Survival curves were estimated using the Kaplan-Meier method. Cox proportional hazards model was used to determine the prognostic impact of *de novo* metastatic breast cancer versus recurrent metastatic breast cancer (MFI $\leq$ 24 months and $>$ 24 months), adjusted for age, hormone receptor and HER2 status, initial site of metastasis and use of prior (neo)adjuvant systemic therapy.

Results

815 patients were included and divided in 3 subgroups based on MFI; 154 patients with *de novo* metastatic breast cancer, 176 patients with MFI $<$ 24 months and 485 patients with MFI $>$ 24 months. Patients with *de novo* metastatic breast cancer had a prolonged survival compared with patients with recurrent metastatic breast cancer with MFI $<$ 24 months (median 29.4 versus 9.1 months, $P<0.0001$), but no difference in survival compared with patients with recurrent metastatic breast cancer with MFI $>$ 24 months (median, 29.4 versus 27.9 months, $P=0.73$). Adjusting for other prognostic factors, patients with MFI $<$ 24 months had increased mortality risk (hazard ratio 1.97, 95% CI 1.49-2.60, $P<0.0001$) compared with patients with *de novo* metastatic breast cancer. When comparing recurrent metastatic breast cancer with MFI $>$ 24 months with *de novo* metastatic breast cancer no significant difference in mortality risk was found. The association between MFI and survival was seen irrespective of use of (neo)adjuvant systemic therapy.

Conclusion

Patients with *de novo* metastatic breast cancer had a significantly better outcome when compared with patients with MFI $<$ 24 months, irrespective of the use of prior adjuvant systemic therapy in the latter group. However, compared with patients with MFI $>$ 24 months, patients with *de novo* metastatic breast cancer had similar outcome.

Introduction

Despite progress in the treatment of early breast cancer, 20-30% of the patients will develop a distant recurrence.¹ Once distant recurrence has occurred the disease remains largely incurable and median survival of patients with metastatic breast cancer ranges from 2 to 3 years.²

The outcome of patients with metastatic breast cancer depends on several prognostic factors. Biological breast cancer subtypes based on hormone receptor (HR) and human epidermal growth factor receptor 2 (HER2) status are associated with different outcomes once distant recurrence has occurred.^{3,4} Besides biological breast cancer subtype, other known prognostic factors are age, performance status and site and number of distant metastases.^{5,6}

Furthermore, the metastatic-free interval (MFI), which is defined as the time between primary breast cancer diagnosis and the development of distant recurrence, is a known strong prognostic factor for survival of patients with metastatic breast cancer. MFI < 24 months is associated with a worse prognosis, as shown in several population based studies of patients with metastatic breast cancer.⁶⁻⁸ The importance of MFI is stressed by the incorporation of this prognostic factor in clinically relevant and validated prognostic models for patients with metastatic breast cancer.^{5,9}

Acknowledging separate prognostic groups based on MFI, patients with distant metastasis at initial breast cancer diagnosis can also be viewed as a distinct prognostic subgroup. This subgroup, called *de novo* metastatic breast cancer, could on the one hand be suggested to represent a poor prognostic group with early distant metastasis as a sign of more aggressive disease. On the other hand, one could hypothesise that patients with *de novo* metastatic breast cancer have a better prognosis because their disease is therapy-naïve and thus less likely to show resistance to systemic therapy.

Indeed, in a large study on metastatic breast cancer diagnosed in the period 1992-2007, outcome of patients with *de novo* metastatic breast cancer was superior compared with patients with recurrent metastatic breast cancer.¹⁰ This favourable outcome was also demonstrated for patients with *de novo* HER2-positive metastatic breast cancer, as compared to those with recurrent HER2-positive metastatic breast cancer.¹¹ However, in another analysis on HER2-positive patients all treated with first-line palliative trastuzumab-based therapy no difference in outcome between *de novo* and recurrent metastatic breast cancer was found.¹²

This led to our study investigating the prognosis and prognostic factors, including HR and HER2 status, for patients with *de novo* metastatic breast cancer compared with patients with recurrent metastatic breast cancer in a large multi-centre study. All patients were diagnosed with metastatic breast cancer in the period 2007-2009 and were treated according to modern treatment strategies, including targeted therapy.

Patients and methods

Patients and data collection

All consecutive patients diagnosed with metastatic breast cancer in 2007-2009 in eight hospitals in the Southeast of the Netherlands were identified. Patients were included irrespective of the date of diagnosis of the primary tumour with the exception of patients with a diagnosis of primary breast cancer before 1990, due to the limited available data on the primary tumour characteristics and the initial treatment.

Data on all included patients was obtained from medical files by specially trained registration clerks, after approval from the Medical Research Ethics Committee of Maastricht University Medical Centre. Information was collected on patient and tumour characteristics, treatment information (surgery, radiotherapy and systemic treatment, both adjuvant and palliative), number and sites of distant metastases and survival time. Initial metastatic sites were registered as single or multiple and were categorized as: bone, visceral (including lung, liver, pleural, peritoneal, pericardial and lymphangitic carcinomatosis), brain (including leptomeningeal and central nervous system), skin and lymph nodes and multiple metastases (more than one of the aforementioned metastatic sites). Tumors were characterized by the sixth edition of the TNM classification of malignant tumors¹³ and Scarff Bloom Richardson (SBR) histological grading.¹⁴ We used pathological TNM also for the small amount of patients with neo-adjuvant systemic therapy (9% of all patients treated with (neo) adjuvant therapy). Oestrogen receptor and progesterone receptor positivity was defined as positive nuclear staining of $\geq 10\%$ and HR positivity was defined as oestrogen receptor- and/or progesterone receptor-positive breast cancer. HER2 positivity was defined as immunohistochemistry score of 3+, or 2+ with a positive fluorescence *in situ* hybridization result. In case of missing HER2 status a dedicated pathologist centrally reviewed missing data when material was available.

Data analysis

We categorized the total of 815 included metastatic breast cancer patients based on MFI. MFI was defined as time between date of diagnosis of primary breast cancer and date of diagnosis of first distant metastatic recurrence. Based on the cut-off points used in other studies and their demonstrated differential impact, patients were divided in three categories; patients with *de novo* metastatic breast cancer (MFI < 3 months), patients with recurrent metastatic breast cancer with MFI ≤ 24 months and patients with recurrent metastatic breast cancer with MFI of > 24 months. The primary aim of our study was to assess differences in survival of patients with *de novo* metastatic breast cancer compared with those with recurrent metastatic breast cancer. Survival of patients with distant metastasis was defined as time between date of diagnosis of first distant metastasis and date of death. All patients still alive were

censored at the date of last follow-up of each individual patient. Survival curves were obtained using the Kaplan-Meier method.

We selected prognostic factors based on clinical importance rather than by statistical significance and included the following factors in the model; age at metastatic breast cancer diagnosis, HR and HER2 status and initial number and site of metastases. First, a Cox proportional hazards model was used to assess whether the prognostic impact of these factors differed between the three subgroups based on MFI by statistical testing of the interaction between the prognostic factors and MFI with a likelihood ratio test. Second, the ratios of the hazard rates comparing *de novo* metastatic breast cancer with recurrent metastatic breast cancer were adjusted for these factors in a Cox regression model. To evaluate the effect of (neo)adjuvant therapy we repeated this model when excluding patients with (neo)adjuvant systemic therapy.

All reported *P*-values were two-sided and a *P*-value ≤ 0.05 was considered of statistical significance.

Results

Characteristics

A total of 815 metastatic breast cancer patients were included in the study, of which 154 patients (19%) were diagnosed with *de novo* metastatic breast cancer and 661 patients (81%) had recurrent metastatic breast cancer (Table 3.1). Of the patients with recurrent metastatic breast cancer, 176 patients (27%) had MFI<24 months and 485 patients (73%) had MFI>24 months.

Median age at diagnosis of metastatic breast cancer was 61 years (range 25-89 years) for patients with *de novo* metastatic breast cancer and 64 years (range 25-93 year) for patients with recurrent metastatic breast cancer, irrespective of MFI ($P=0.06$).

Pathological tumour and lymph node status was missing for the majority of patients with *de novo* metastatic breast cancer, as surgical removal of the primary tumour was not routinely performed after diagnosis of metastatic breast cancer (83% of patients with *de novo* metastatic breast cancer did not have surgery of the primary tumour).

HR-positive breast cancer was most frequently seen in patients with *de novo* metastatic breast cancer (81%) and recurrent metastatic breast cancer with MFI>24 months (83%), but less in patients with recurrent metastatic breast cancer with MFI<24 months (55%) ($P<0.0001$). HER2-positive status was not different between patients with *de novo* metastatic breast cancer (23%), recurrent metastatic breast cancer with MFI>24 months (18%) ($P=0.21$) and recurrent metastatic breast cancer with MFI<24 months (21%) ($P=0.76$).

Table 3.1 Baseline characteristics.

Characteristics	De Novo			Recurrent all			Recurrent with MFI≤24 months			Recurrent with MFI>24 months		
	n=154			n=661			n=176			n=485		
	No	%		No	%	P	No	%	P	No	%	P
Age at diagnosis of metastatic disease												
Median, (range)	61	25-89		64	25-93	0.06	62	25-93	0.40	64	32-90	0.04
<40 years	10	6		18	3		12	7		6	1	
40-70 years	100	65		408	62		98	56		310	64	
>70 years	44	29		235	35		66	37		169	35	
Primary tumour stage*												
T1	9	25.7		240	44		38	31		202	48	
T2	22	62.9		265	48		73	58		192	45	
T3	2	5.7		29	5		8	6		21	5	
T4	2	5.7		16	3		6	5		10	2	
Unknown	119			111			51			60		
Regional lymph node stage primary tumour*												
N0	6	17		230	41		46	37		184	43	
N1	13	37		187	34		32	25		155	36	
N2	6	17		82	15		26	21		56	13	
N3	10	29		57	10		22	17		35	8	
Unknown	119			105			50			55		
Histological grade of primary tumour												
SBR 1	8	11		55	11	0.26	10	6	0.01	45	14	0.59
SBR 2	39	53		212	44		57	37		155	47	
SBR 3	26	36		219	45		89	57		130	39	
Unknown	81			175			20			155		
Hormone receptor status												
Positive	121	81		490	76	0.21	96	55	<.0001	394	83	0.43
Negative	29	19		156	24		78	45		78	17	
Unknown	4			15			2			13		
HER2 status												
Positive	34	23		122	19	0.29	37	21	0.76	85	18	0.21
Negative	116	77		524	81		137	79		387	82	
Unknown	4			15			2			13		

Table 3.1 (continued)

Characteristics	De Novo		Recurrent all		P	Recurrent with MFI≤24 months n=176		Recurrent with MFI>24 months n=485		P
	n=154		n=661			n=176		n=485		
	No	%	No	%		No	%	No	%	
Prior (neo)adjuvant chemotherapy										
Yes	-		306	46		85	48	221	46	
No			355	54		91	52	264	54	
Prior (neo)adjuvant endocrine therapy										
Yes	-		339	51		64	36	275	57	
No			322	49		112	64	210	43	
Prior (neo)adjuvant anti-HER2 therapy										
Yes	-		44	7		17	10	27	6	
No			617	93		159	90	458	94	
No. of metastatic sites										
1	103	67	426	64	0.57	123	70	303	62	0.32
≥2	51	33	235	36		53	30	182	38	
Site of metastases										
Bone	60	39	202	31	0.04	41	23	161	33	0.19
Visceral	37	24	188	28	0.27	58	33	130	27	0.49
Brain	0	0	26	4	0.01	18	10	8	2	0.11
Skin and lymph nodes	9	6	46	7	0.62	16	9	30	6	0.88
Multiple	48	31	199	30	0.80	43	25	156	32	0.82
Any palliative chemotherapy										
Yes	88	57	350	53	0.35	84	48	266	55	0.62
No	66	43	311	47		92	52	219	45	
Any palliative endocrine therapy										
Yes	106	69	408	62	0.10	67	38	341	70	0.73
No	48	31	253	38		109	62	144	30	
Any palliative targeted therapy										
Yes	33	21	121	18	0.37	23	13	98	20	0.74
No	121	79	540	82		153	87	387	80	

SBR Scarff Bloom Richardson. * pathological TNM according to the sixth edition of the TNM classification of malignant tumors.

The percentage of patients with visceral or brain metastasis as initial metastatic site for recurrent metastatic breast cancer with MFI<24 months was, respectively, 33% and 10%. These percentages were lower for patients with *de novo* metastatic breast cancer (respectively, 24% and 0%) and for patients with recurrent metastatic breast cancer with MFI>24 months (respectively, 27% and 2%).

For all patients with recurrent metastatic breast cancer, 46% had received prior (neo)adjuvant chemotherapy and 51% prior (neo)adjuvant endocrine therapy.

Of patients with *de novo* metastatic breast cancer 57% received at least one line of palliative chemotherapy versus 53% of patients with recurrent metastatic breast cancer ($P=0.35$). Also the use of any palliative endocrine therapy was not different between *de novo* and recurrent metastatic breast cancer (respectively, 69% versus 62%) ($P=0.10$).

Survival and prognostic factors

Median follow-up after diagnosis of metastatic disease was 37.1 months (range 2.1-55.4), with 302 patients (37%) being alive at the end of the follow-up period.

The median survival of patients with *de novo* metastatic breast cancer was 29.4 months (95% CI 19.3-35.0 months) compared with 21.1 months (95% CI 18.7-24.4 months) for patients with recurrent metastatic breast cancer ($P=0.14$).

When looking at the patients with recurrent metastatic breast cancer stratified by MFI, survival of those with *de novo* metastatic breast cancer was significantly better than for patients with MFI<24 months (median, 29.4 versus 9.1 months, $P<0.0001$) (Figure 3.1). Survival of *de novo* metastatic breast cancer patients was not significantly different from the survival of recurrent metastatic breast cancer patients with MFI >24 months (median, 29.4 versus 27.9 months, $P=0.73$) (Figure 3.1).

Figure 3.1 Survival after diagnosis of metastatic breast cancer for patients with *de novo* metastatic breast cancer and recurrent metastatic breast cancer with MFI<24 months and recurrent metastatic breast cancer with MFI>24 months.

The prognostic impact of the prognostic factors did not differ significantly for the three MFI groups (test for interaction $P=0.98$). Therefore the results could be pooled to obtain the final Cox proportional hazards model (Table 3.2).

Adjusted for other prognostic factors, patients with MFI < 24 months had a significantly increased risk in mortality (hazard ratio 1.97; 95% CI 1.49-2.60) compared with patients with *de novo* metastatic cancer (Table 3.2). Recurrent metastatic breast cancer patients with MFI > 24 months had no increased risk in mortality compared with *de novo* metastatic breast cancer patients (hazard ratio of 0.89, 95% CI 0.70-1.14) (Table 3.2).

Older age at diagnosis of metastatic breast cancer, HR-negative breast cancer, HER2-negative breast cancer, multiple initial metastatic sites as well as brain or visceral metastases as initial site compared to bone metastases were all associated with a worse prognostic impact on outcome (Table 3.2).

Performing the multivariable analysis when excluding patients with (neo)adjuvant systemic therapy, thereby comparing the therapy-naïve patients with recurrent metastatic breast cancer and *de novo* metastatic breast cancer, the increased mortality risk for patients with MFI < 24 months compared with *de novo* metastatic breast cancer remained statistically significant (adjusted hazard ratio 1.69, 95% CI 1.11-2.58) (Table 3.2).

Discussion

We present survival and prognostic factors of patients with *de novo* metastatic breast cancer compared with patients with recurrent metastatic breast cancer in a multi-centre, unselected cohort of patients. As all patients were diagnosed with metastatic breast cancer between 2007-2009, this cohort reflects a time period in which HER2 status was routinely performed and treatment included targeted therapy.

There was no significant difference in prognosis between patients with *de novo* and recurrent metastatic breast cancer irrespective of MFI.

The median overall survival of 29 months for patients with *de novo* metastatic breast cancer in this cohort was comparable to the survival found in other cohort studies on patients with *de novo* metastatic breast cancer.^{10,15,16}

However, when stratifying patients with recurrent metastatic breast cancer according to the MFI differences in survival between *de novo* and recurrent metastatic breast cancer became apparent. Patients with *de novo* metastatic breast cancer had a similar outcome when compared with patients with late distant recurrent metastatic breast cancer. However, patients with *de novo* metastatic breast cancer had a significant better outcome when compared to patients with an early distant recurrence, also after exclusion of the patients receiving (neo)adjuvant systemic treatment.

We defined early distant recurrence as MFI shorter than 24 months, based on the cut-off points used in other studies and the demonstrated prognostic impact.⁵⁻⁹

Table 3.2 Multivariable analysis for survival after diagnosis of metastatic breast cancer.

	All patients <i>n</i> =815			Patients without (neo) adjuvant systemic therapy <i>n</i> =318		
	Hazard Ratio	95% CI	<i>P</i>	Hazard Ratio	95% CI	<i>P</i>
Recurrent with MFI < 24 months vs <i>de novo</i>	1.97	1.49-2.60	<.0001	1.69	1.11-2.58	0.015
Recurrent with MFI > 24 months vs <i>de novo</i>	0.89	0.70-1.14	0.358	0.89	0.64-1.24	0.498
Age at diagnosis of metastatic breast cancer	1.02	1.01-1.02	<.0001	1.02	1.00-1.03	0.008
Hormone receptor negative vs positive	1.74	1.40-2.17	<.0001	2.21	1.58-3.11	<.0001
HER2 negative vs positive	1.44	1.13-1.83	0.003	1.27	0.88-1.86	0.207
Visceral metastases as initial metastatic site vs bone	1.80	1.41-2.31	<.0001	1.56	1.03-2.36	0.037
Brain metastases as initial metastatic site vs bone	2.31	1.40-3.80	0.001	4.50	1.49-13.64	0.008
Skin/lymph nodes as initial metastatic site vs bone	1.06	0.71-1.59	0.783	1.37	0.71-2.67	0.350
Multiple initial metastatic sites vs 1 metastatic site	2.30	1.81-2.93	<.0001	2.66	1.83-3.87	<.0001

CI confidence interval, *MFI* metastatic-free interval, *vs.* versus.

When looking closer at this subgroup, patients with an early distant recurrence were more likely to have HR-negative breast cancer. It is known that breast cancer subtypes, based on HR and HER2 status, have different prognostic impact and different patterns of distant recurrence, with HR-negative subgroups having earlier recurrence and unfavourable prognosis compared with HR-positive subgroups.^{3,4} However, even when adjusting for HR-negative status, the difference in survival between *de novo* and early distant recurrent metastatic breast cancer remained present.

Another hypothesis explaining the better outcome of *de novo* metastatic breast cancer compared with early recurrent metastatic breast cancer is the use of adjuvant systemic therapy in patients with recurrent metastatic breast cancer. This could lead to more resistant metastatic disease compared with patients with therapy-naïve *de novo* metastatic breast cancer. But, when we excluded patients with recurrent metastatic breast cancer with (neo)adjuvant systemic therapy, the difference in survival between *de novo* and early distant recurrent metastatic breast cancer remained present. Hence, in our cohort there was no evidence that the administration of systemic therapy in early breast cancer could explain the better outcome of *de novo* metastatic breast cancer when compared with patients with an early distant recurrence.

The role of surgery of the primary breast tumour on the outcome of metastatic breast cancer patients remains controversial. Initial retrospective studies and meta-analyses of these data supported the idea that surgery of the primary tumour in *de novo* metastatic breast cancer could have a positive impact on outcome.¹⁷⁻¹⁹ However, data on randomised clinical trials could not show a survival advantage for surgery of the primary tumour and palliative systemic therapy compared with palliative systemic therapy alone.^{20,21} Furthermore, when looking at the current views on molecular models of metastasis and tumour dormancy, some hypothesise that surgery of the primary tumour can be the systemic event that interrupts the dormant state of metastatic cancer cells, and thereby even have an unfavourable effect on outcome.²²

The model of metastasis in breast cancer has evolved over the years and the knowledge gathered by genomic assays supports the idea that the capacity of metastasis is acquired early in the life of primary breast cancer.^{23,24} Therefore, the assessment of recurrence risk is not only dependent on classical clinicopathological factors, but also on detection of metastatic potential of the primary breast tumour. This also leads to newer insights into relevant prognostic factors in early breast cancer to determine risk of recurrence, amongst others gene expression profiling and the detection of disseminated tumour cells. However, once metastatic breast cancer is present, the need for clinical prognostic factors remains and is of importance to guide further treatment decision and to provide prognostic information to patients.

In this analyses, prognostic factors that influenced survival besides MFI were age at diagnosis of metastatic breast cancer, HR and HER2 status and initial site of metastases. This is in accordance with other studies investigating prognostic factors in

metastatic breast cancer.^{4,6,10,15} As expected, we found a favourable impact of HR-positive breast cancer, with a hazard ratio of 0.57 ($P < 0.0001$) compared with HR-negative breast cancer in our cohort, which is similar to that found in a large study on survival between *de novo* and recurrent metastatic breast cancer.¹⁰ HR-positivity is a known favourable prognostic factor as well as a predictive factor for response to endocrine therapy. The hazard ratio as calculated in our model is not only reflecting the favourable prognostic influence but also the strong predictive influence for response to endocrine therapy.

The strength of this study is the incorporation of HER2 status, due to a very low rate of missing results for HER2 status (only 2%) because all missing HER2 results were centrally determined whenever possible. Interestingly, HER2-positive breast cancer was found to have a favourable influence on outcome of metastatic breast cancer. Even though in the pre-trastuzumab era, the amplification of HER2 in breast cancer was demonstrated to be a strong unfavourable prognostic factor.²⁵ However, with the availability of anti-HER2 therapy this unfavourable prognostic factor has also become a favourable predictive factor for response to anti-HER2 therapy. And with the implementation of anti-HER2 therapy, outcome of HER2-positive breast cancer has changed to the extent that HER2-positive status is nowadays a prognostic factor associated with a favourable outcome in breast cancer.^{4,26} Numbers were too low to look at outcome of biological subtypes based on HR and HER2 in the three separate subgroups, but previous studies investigated differences in outcome between HER2-positive *de novo* metastatic breast cancer and HER2-positive recurrent metastatic breast cancer. In an unplanned analysis from the registHER observational study, a better survival was found for patients with HER2-positive *de novo* metastatic breast cancer compared to patients with HER2-positive recurrent metastatic breast cancer.¹¹ This difference in survival was seen regardless of adjuvant systemic therapy for patients with recurrent breast cancer. However, only 9% of patients with HER2-positive recurrent breast cancer had received anti-HER2 therapy in adjuvant setting. Another study investigating the outcome of patients with HER2-positive *de novo* metastatic breast cancer did not demonstrate a difference in outcome compared with patients with HER2-positive recurrent metastatic breast cancer.¹²

Besides low number of patients when dividing the total cohort according to biological breast cancer subtype, there are other limitations of this study owing to its retrospective nature. Lead-time bias due to improved imaging could be a confounder in this study. However, all patients were diagnosed with metastatic breast cancer (either *de novo* or recurrent) during the same recent and relatively short time period so the availability of imaging techniques was probably equal. Even so, with the inclusion of all patients with metastatic breast cancer diagnosed in eight different hospitals we feel this cohort is a good representation of the actual diagnosis and treatment of patients with metastatic breast cancer in the Netherlands. With the availability and implementation of more advanced and sensitive diagnostic techniques, for example positron emission tomography, the subgroup of patients with

de novo metastatic breast cancer will probably increase. Therefore, prognostic information on this subgroup is of relevance for oncology practice.

In conclusion, we confirm that MFI is a strong prognostic indicator for outcome of metastatic breast cancer patients, with a short MFI being prognostic unfavourable. However, *de novo* metastatic breast cancer, which can be considered as a group with a 'very short' MFI was not found to be a very poor prognostic subgroup. In real life, patients with *de novo* metastatic breast cancer had a clearly better outcome, similar to what was seen in patients with metastatic breast cancer with MFI>24 months, compared with patients with MFI < 24 months who had a nearly two-fold increased mortality risk.

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Chapter 4

The role of histological subtype in hormone receptor positive metastatic breast cancer: similar survival but different therapeutic approaches

A study of the Southeast Netherlands Breast Cancer Consortium

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Abstract

Introduction

This study describes the differences between the two largest histological breast cancer subtypes (invasive ductal carcinoma (IDC) and invasive (mixed) lobular carcinoma (ILC) with respect to patient and tumor characteristics, treatment-choices and outcome in metastatic breast cancer.

Patients and methods

We included 437 patients with hormone receptor-positive IDC and 131 patients with hormone receptor-positive ILC, all diagnosed with metastatic breast cancer between 2007-2009, irrespective of date of the primary diagnosis. Patient and tumor characteristics and data on treatment and outcome were collected. Survival curves were obtained using the Kaplan-Meier method.

Results

Patients with ILC were older at diagnosis of primary breast cancer and had more often initial bone metastasis (46.5% versus 34.8%, $P=0.01$) and less often multiple metastatic sites compared to IDC (23.7% versus 30.9%, $P=0.11$). Six months after diagnosis of metastatic breast cancer, 28.1% of patients with ILC and 39.8% of patients with IDC had received chemotherapy with a longer median time to first chemotherapy for those with ILC ($P=0.001$). After six months 84.8% of patients with ILC had received endocrine therapy versus 72.5% of patients with IDC ($P=0.0001$). Median overall survival was 29 months for ILC and 25 months for IDC ($P=0.53$).

Conclusion

Treatment strategies of hormone receptor-positive metastatic breast cancer were remarkably different for patients with ILC and IDC. Further research is required to understand tumor behavior and treatment-choices in real-life.

Introduction

The two most frequent histological subtypes of breast cancer are invasive ductal carcinoma (IDC) and invasive lobular carcinoma (ILC), with IDC comprising 75-80% and ILC 5-15% of all breast cancer cases. ILC is being associated with larger tumor size at presentation, more bilateral and multifocal involvement and with a different pattern of metastatic spread compared with IDC.^{1,2} Furthermore, ILC is more often HR-positive, HER2-negative, with lower S-phase fraction and less often positive for the tumor suppressor gene p53, compared with IDC.¹ Also, treatment response is known to be different. In a combined analysis on a number of retrospective series, the pathological complete response rate of neo-adjuvant chemotherapy was significantly lower in ILC (1.7%) than in IDC (11.6%).³ In the adjuvant setting, retrospective data suggest a higher efficacy of endocrine therapy for ILC than IDC.⁴ More recently, a large retrospective study strongly suggested that HR-positive breast cancer patients with ILC do not seem to benefit from adjuvant chemotherapy in addition to endocrine therapy.⁵

Whether these differences have a prognostic impact is controversial. Some studies found no effect of histology on survival,^{1,6,7} others found a better prognosis for patients with ILC compared to those with IDC,⁸⁻¹⁰ and some found a change in prognosis over time with a better prognosis for ILC during the first years of follow-up and a worse prognosis during later years.^{2,11}

So far, studies on histological subtypes consider early breast cancer and not metastatic breast cancer. The aim of this study was to describe the differences between IDC and ILC with respect to patient and tumor characteristics, treatment-choices and outcome in metastatic breast cancer. In order to account for the effect of the hormone receptor (HR) on outcome and treatment-decision making, we only included patients with HR-positive breast cancer.

Patients and methods

Patient selection

We identified all patients diagnosed with metastatic breast cancer between 2007-2009 in eight hospitals in the South-East of the Netherlands. All patients with metastatic breast cancer were selected irrespective of the date of primary breast cancer diagnosis (also including patients with *de novo* metastatic breast cancer; 18.5% of patients with IDC and 19.9% of patients with ILC), with the exception of patients with a diagnosis of primary breast cancer before 1990, due to limitations in the availability of data on the primary tumor and initial treatment.

Histology was classified according to the International Classification of Diseases for Oncology (ICD-O).¹² ILC and mixed histology were defined as code 8520 and 8522. IDC

was defined as code 8500. From the total of 815 metastatic breast cancer patients, we excluded 76 patients with either unknown histology or histological subtypes other than IDC or ILC. Of the remaining 739 metastatic breast cancer patients, we excluded 171 patients with HR-negative tumors (27% of patients with IDC and 8% of patients with ILC) in order to rule out the impact of HR status. In total, our study population consisted of 568 patients divided in two groups based on histology; one group of 437 patients with IDC and the other group of 131 patients with ILC.

Data collection

Information was collected on patient and tumor characteristics, treatment and outcome. Tumors were characterized by the sixth edition of the TNM classification of malignant tumors¹³ and Scarff Bloom Richardson (SBR) histological grading.¹⁴ Estrogen receptor (ER) and progesterone receptor (PR) positivity was defined as positive nuclear staining of $\geq 10\%$. HER2 positivity was defined as immunohistochemistry score of 3+ or 2+ with positive FISH. In case of missing HER2 status a dedicated pathologist centrally reviewed missing data when material was available. Initial sites of metastasis were categorized as: bone, visceral (including lung, liver, pleural, peritoneal, pericardial and lymphangitic carcinomatosis), brain (including leptomeningeal and CNS), skin and lymph nodes, and multiple metastases (more than one of the metastatic sites).

Statistical analysis

Baseline characteristics between the two histological groups were compared using chi-square tests for categorical variables and Wilcoxon rank sum tests for continuous variables.

Metastasis-free interval was defined as time between date of primary diagnosis and date of first distant metastasis. Overall survival after diagnosis of metastatic breast cancer was defined as time between date of first distant metastasis and date of death. Survival curves and time to first palliative systemic therapy (either chemotherapy or endocrine therapy) were estimated using the Kaplan-Meier method and compared using log-rank tests. All patients still alive were censored at the date of last follow-up of each individual patient. Patients who died without palliative therapy were censored at the date of death in the analysis of time to first palliative therapy.

To explore the association of palliative systemic therapy with the survival of patients with metastatic breast cancer for both histological subtypes a Cox proportional hazards model was performed with palliative chemotherapy and endocrine therapy as a time-dependent covariate, since the administration of treatment can change over time and is dependent on the time available for each patient to receive the treatment. We did not explore the association between palliative targeted therapy, such as trastuzumab and bevacizumab, and survival since the number of patients with IDC and ILC receiving targeted therapy was very low. Since all these patients received targeted

therapy with chemotherapy, these patients were included in the analysis on initial chemotherapy. In addition, the landmark method was used to estimate survival after a specific time-point, the so-called residual survival.¹⁵ As we were interested to learn about the obtained survival in relation to the initial palliative treatment choices, we chose six months after diagnosis of metastatic breast cancer as landmark. Consequently, patients who already died within 6 months were excluded for the residual survival curves.

All analyses were performed using SAS version 9.2. All reported P-values are two-sided and P-value ≤ 0.05 was considered statistically significant.

Results

Patient characteristics

Of the 568 patients with HR-positive metastatic breast cancer, 23% had (mixed type) ILC (131 patients), hereafter referred to as ILC and 77% had IDC (437 patients) (Table 4.1).

Metastatic breast cancer patients with ILC were older at the time of primary breast cancer diagnosis, compared with patients with IDC (median age at diagnosis 62 years for ILC versus 58 years for IDC, $P=0.03$). At initial presentation, patients with HR-positive ILC had larger tumors (T2-3, 62.5% versus 49.7%, $P=0.002$) and slightly more node-positive disease (66% versus 56.9%, $P=0.10$), but with less often a HER2 positive status (7.6% versus 15.3%, $P=0.02$) and lower grade (not significant) compared with patients with HR-positive IDC. No differences were seen in use of adjuvant chemotherapy or endocrine therapy between the histological subtypes.

Bone was the most common initial site of distant metastasis in both HR-positive histological subtypes, although bone metastasis as initial site was more frequently observed for patients with ILC compared to those with IDC (46.5% versus 34.8%, $P=0.01$). Fewer patients with ILC were diagnosed with multiple sites of distant metastasis compared to those with IDC (23.7% versus 30.9%, $P=0.11$).

Table 4.1 Baseline characteristics of HR+ metastatic breast cancer divided by histological subtype.

Characteristics	Invasive ductal carcinoma <i>n</i> =437		Invasive lobular and mixed carcinoma <i>n</i> =131		<i>P</i>
	No	%	No	%	
Age at primary diagnosis					
Median (range)	58 (25 - 91)		62 (36 - 89)		0.03
<50 years	124	28.4	28	21.4	0.11
≥50 years	313	71.6	103	78.6	
Histological grade of primary tumor					
SBR 1	41	13.4	17	19.8	0.11
SBR 2	157	51.5	48	55.8	
SBR 3	107	35.1	21	24.4	
Unknown	132		45		
Primary tumor stage					
T1	157	48.2	29	30.2	<0.001
T2	150	46.0	51	53.1	
T3	12	3.7	9	9.4	
T4	7	2.1	7	7.3	
Unknown	111		35		
Regional lymph node stage					
N0	141	43.1	34	34.0	0.005
N1	110	33.6	40	40.0	
N2	50	15.3	8	8.0	
N3	26	8.0	18	18.0	
Unknown	110		31		
HER2 status of primary tumor					
Positive	67	15.3	10	7.6	0.02
Negative	370	84.7	121	92.4	
Prior adjuvant endocrine therapy					
Yes	228	52.2	76	58.0	0.24
No	209	47.8	55	42.0	
Prior adjuvant chemotherapy					
Yes	135	30.9	40	30.5	0.94
No	302	69.1	91	69.5	
Prior adjuvant targeted therapy					
Yes	18	4.1	1	0.8	0.06
No	419	95.9	130	99.2	
Metastasis-free interval (MFI)					
Median (range), months	38.7 (0-234)		32.3 (0-321)		0.58
De novo	81	18.5	26	19.9	0.1
MFI ≤24 months	64	14.7	28	21.3	
MFI >24 months	292	66.8	77	58.8	
Initial site of metastasis					
Bone	152	34.8	61	46.5	0.01
Visceral	114	26.1	30	22.9	0.50
Brain	8	1.8	3	2.3	0.74
Skin and lymph nodes	28	6.4	6	4.6	0.44
Multiple*	135	30.9	31	23.7	0.11

HR+ hormone receptor positive, *n* number, SBR Scarff Bloom Richardson, MFI metastatic-free interval.

* ≥1 of the aforementioned initial sites of metastasis.

Palliative systemic treatment

Median follow-up after diagnosis of metastatic disease was 37.1 months (range 5.2-54.6) with 239 patients (42%) alive at the end of the follow-up period.

Time between diagnosis of HR-positive metastatic breast cancer and start of palliative chemotherapy was significantly longer for patients with ILC (median not yet reached) compared with IDC (median 16.9 months, 95% Confidence Interval (CI) 9.6-22.3, $P=0.001$) (Figure 4.1A). Six months after diagnosis of HR-positive metastatic breast cancer less patients with ILC had received palliative chemotherapy compared with IDC (28.1% versus 39.8% respectively).

Time between diagnosis of HR-positive metastatic breast cancer and start of palliative endocrine therapy was significantly shorter for patients with ILC (median, 0.6 months, 95% CI 0.5-0.8) compared with patients with IDC (median, 1.1 months, 95% CI 1.0-1.5, $P=0.0001$) (Figure 4.1B). Six months after diagnosis of metastatic breast cancer 84.8% of patients with ILC had received palliative endocrine therapy compared with 72.5% of patients with IDC.

Figure 4.1 Time to first palliative chemotherapy (A) and endocrine therapy (B) by histological subtype.

Outcome

Median overall survival was 29.4 months (95% CI 22.5-36.6) for patients with HR-positive ILC and 25.4 months (95% CI 21.8-31.7) for patients with HR-positive IDC ($P=0.53$).

In multivariable analysis for patients with ILC with palliative endocrine therapy and palliative chemotherapy as time-dependent covariates, early initiation of palliative chemotherapy was associated with an unfavorable survival (hazard ratio 2.8, 95% CI 1.7-4.6, $P<0.0001$) compared to no palliative chemotherapy during the observation period. Conversely, early initiation of palliative endocrine therapy was associated with a favorable survival (hazard ratio 0.4, 95% CI 0.2-0.8, $P=0.005$) compared to no palliative endocrine therapy during the observation period.

In multivariable analysis for patients with IDC, early initiation of palliative chemotherapy was associated with an unfavorable survival (hazard ratio 2.1, 95% CI 1.6-2.7, $P<0.0001$) when compared with no chemotherapy, whereas early treatment with palliative endocrine therapy was not associated with survival (hazard ratio 0.9, 95% CI 0.6-1.2, $P=0.4$).

Residual survival; six months after diagnosis

For ILC, the residual survival was significantly longer for patients not treated with palliative chemotherapy within the first six months after diagnosis of metastatic breast cancer (median 44.0 months, 95% CI 30.2-not yet reached) versus patients treated with palliative chemotherapy (median 15.2 months, 95% CI 7.8-19.2) (Figure 4.2A). For IDC, residual survival when not treated with palliative chemotherapy was 41.8 (95% CI 33.3-not yet reached) compared with 16.8 months (95% CI 13.6-22.5) for patients treated with palliative chemotherapy within the first six months after diagnosis of metastatic breast cancer (Figure 4.2B).

Figure 4.2 Residual survival for patients with HR-positive ILC (A) and HR-positive IDC (B) treated with or without any palliative chemotherapy during the first six months after diagnosis of metastatic breast cancer.

Reversely, for ILC-patients with palliative endocrine treatment within the first six months after diagnosis of metastatic breast cancer residual survival was 37.5 months (95% CI 26.9-not yet reached) compared with 11.2 months (95% CI 3.0-20.4) for patients with HR-positive metastatic ILC without palliative endocrine therapy before the first six months (Figure 4.3A). For patients with HR-positive metastatic IDC treated with palliative endocrine therapy during the first six months, residual survival was 33.5 months (95% CI 25.7-not yet reached) compared with 18.9 months (95% CI 14.0-

26.8) for patients with HR-positive metastatic IDC without palliative endocrine therapy in the first six months of metastatic disease (Figure 4.3B).

Figure 4.3 Residual survival for patients with HR-positive ILC (A) and HR-positive IDC (B) treated with or without any palliative endocrine therapy during the first six months after diagnosis of metastatic breast cancer.

Discussion

To our knowledge, the role of histological subtype in palliative systemic treatment of metastatic breast cancer has not been studied before. In a cohort of 568 HR-positive metastatic breast cancer patients, we showed that patients with HR-positive ILC had more often bone and less often multiple sites as initial site of distant metastasis compared to those with HR-positive IDC. Six months after metastatic diagnosis, patients with HR-positive ILC had received significantly less often chemotherapy (28% versus 40%) and more often endocrine therapy (85% versus 73%) as compared to patients with HR-positive IDC. Patients starting with palliative chemotherapy during the first six months had a significantly shorter median residual survival thereafter as compared to those who did not (15 months versus 44 months for ILC, and 17 and 42 months for IDC, respectively). Reversely, patients treated with endocrine therapy in the first six months had a longer median residual survival compared to those who did not (37 months versus 11 months for ILC and 33 and 19 months for IDC, respectively). Our results confirm that, in addition to HR-status, histology correlates with presentation of metastatic disease by number and type of distant metastatic sites, and thereby affects treatment-decision making in real-life.

The intriguing scientific question is to determine how histological subtype influences the metastatic spread in HR-positive breast cancer. It is hypothesized that the loss of E-cadherin, a cell-cell adhesion molecule, in ILC may result in less adhesiveness of the

tumor cells and therefore disseminate and infiltrate certain distant locations more easily.¹

In this HR-positive metastatic breast cancer cohort we also looked at the association of palliative systemic treatment with survival of patients with metastatic breast cancer for both histological subtypes. With the favorable presentation of distant metastasis by number and location of patients with HR-positive ILC as compared to HR-positive IDC, one would expect a more indolent disease course and a better outcome. However, we showed that for patients with HR-positive breast cancer, overall disease outcome was comparable irrespective of histology and irrespective of different treatment choices made in real-life, as discussed above. And interestingly, the efficacy of chemotherapy - once the treatment choice was made - was comparable irrespective of histology. However, treatment with palliative endocrine therapy was only associated with a favorable prognosis of patients with HR-positive ILC, whereas this was not seen in patients with HR-positive IDC, also suggesting the impact of histology over HR-status. This is in concordance with the early breast cancer setting, in which there is evidence suggesting differences in efficacy of systemic therapy between the two histological subtypes.^{3-5,16}

Although there is some proof that histology could be helpful in treatment decision-making,¹⁷⁻¹⁹ the current guidelines do not include histological subtype as an indicator for the use of systemic treatment in general, or of a specific regimen.^{20,21} Interestingly, in the adjuvant setting, histology has been shown to be of importance when deciding between the use of breast-conserving surgery or mastectomy after neo-adjuvant chemotherapy.²² The current study shows that histological subtype can be of predictive value for HR-positive metastatic breast cancer with regards to the effectiveness of early initiation of palliative endocrine therapy. It may be possible that in patients with HR-positive lobular breast cancer, the higher incidence of bone metastases as initial metastatic site partly accounts for the initial choice of endocrine therapy. It underlines the relevance of acknowledging a different metastatic pattern, and thereby different initial treatment choices, between breast cancer patients with ductal versus lobular histology.

Much more than in the adjuvant setting, treatment decisions in the metastatic setting are based on the observed and anticipated clinical course of the disease, which is not only determined by the tumor characteristics as described earlier. Also age, performance status, previous therapies and toxicities, comorbidity and patient and doctor preferences play a role. The complexity of this process, together with the retrospective design of our study make it impossible to identify and rule out confounding by indication. Furthermore, localization of the metastases (visceral versus bone metastasis for instance) could be related to symptomatology and thereby timing of detection, and could therefore have introduced lead time bias.

In this study patients with pure lobular carcinoma and mixed lobular carcinomas were combined for the analyses. In other studies on histological subtypes of breast cancer mixed and lobular carcinoma had similar outcome.^{18,23} Even with combining these

subgroups, the proportion of HER2-positive tumors was too low to further analyze anti-HER2 therapy. In the adjuvant treatment setting the magnitude of benefit from adjuvant trastuzumab between patients with ILC and IDC was shown not to be different.²⁴ Another limitation of our study is that patient numbers were too small to perform analysis on specific chemotherapy regimens. Microarray analysis have demonstrated that ILC and IDC can be distinguished on the basis of genomic and expression profiles.²⁵ The increasing knowledge on genomic differences between ILC and IDC can help to answer questions on in vivo chemosensitivity. For example, topoisomerase-II α gene amplification is a predictive biomarker for response to anthracyclines and in ILC this gene amplification is lacking, which could help understand the poor responsiveness of ILC to neo-adjuvant chemotherapy, including anthracyclines.²⁶ This genetic information can help guide further research and may eventually be useful in making treatment decisions for histological breast cancer subtypes.

In conclusion, to our knowledge, this is the first study that investigates the role of histological subtype in HR-positive metastatic breast cancer. Although survival was comparable for the two histological subtypes, this was achieved with different treatment strategies. As patients with HR-positive ILC were less likely to receive chemotherapy than those with HR-positive IDC, histology may be a relevant factor in treatment-decision making. For a more definite conclusion on the role of histology, we recommend to incorporate histological subtype as a stratification factor in future clinical trials.

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Chapter 5

In real life, one-quarter of patients with hormone receptor positive metastatic breast cancer receive chemotherapy as initial palliative therapy

A study of the Southeast Netherlands Breast Cancer Consortium

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Abstract

Background

The objective of this study was to present initial systemic treatment choices and outcome of hormone receptor positive (HR+) metastatic breast cancer.

Patients and methods

All 815 consecutive patients diagnosed with metastatic breast cancer in 2007-2009 in eight participating hospitals were identified. From the 611 patients with HR+ disease, a total of 520 patients with HER2 negative (HER2-) breast cancer was included. Initial palliative systemic treatment was registered. Progression-free survival (PFS) and overall survival (OS) per initial palliative systemic therapy was obtained using the Kaplan-Meier method and compared using the log-rank test.

Results

From the total of 520 patients with HR+/HER2- metastatic breast cancer, 482 patients (93%) received any palliative systemic therapy. Patients that received initial chemotherapy ($n=116$) were significantly younger, had less comorbidity, had received more prior adjuvant systemic therapy and were less likely to have bone metastasis only compared to patients that received initial endocrine therapy ($n=366$). Median PFS of initial palliative chemotherapy was 5.3 months (95% CI 4.2-6.2) and of initial endocrine therapy 13.3 months (95% CI 11.3-15.5), with a median OS of 16.1 and 36.9 months, respectively. Initial chemotherapy was also associated with worse outcome in terms of PFS and OS after adjustment for prognostic factors.

Conclusions

A high percentage of patients with HR+ disease received initial palliative chemotherapy, which was associated with worse outcome, even after adjustment of relevant prognostic factors.

Introduction

Metastatic breast cancer generally remains incurable and treatment has a palliative intent, despite the improvement in survival.^{1,2} Since patients with metastatic breast cancer form a heterogeneous population, treatment recommendations ought to be made on an individual basis, taking into account hormone receptor (HR) and human epidermal growth factor receptor 2 (HER2) status, metastasis-free interval, response to and cumulative doses of previous therapy, location and extend of metastases and symptoms.^{3,4}

Two thirds of breast cancer patients have HR-positive (HR+) tumors,⁵ for whom endocrine therapy is the preferred initial treatment for metastatic disease as recommended in the treatment guidelines, even in the presence of visceral metastases.^{4,6,7}

Recently, advances have been made in the treatment of HR+ metastatic breast cancer with dual blocking of the estrogen receptor (ER) pathway and several growth factor and cell-signaling pathways, leading to the introduction of everolimus.⁸

The availability of a growing number of treatment options makes treatment of patients with metastatic breast cancer in daily practice complex. Real-world knowledge of treatment patterns and outcome in metastatic breast cancer, outside the setting of clinical trials, is essential in improving every day treatment decisions. Therefore we present data on actual treatment patterns and outcome in a large, multicenter cohort of patients with HR+ metastatic breast cancer in the Netherlands.

The primary study objective was to assess the initial systemic treatment choices made in a real-world setting, taking impact of initial metastatic site into account. Secondary study objective was to determine the outcome in terms of progression-free survival (PFS) and overall survival (OS) according to initial systemic treatment choice.

Patients and methods

Patients and data collection

All patients diagnosed with metastatic breast cancer between 2007-2009 in eight hospitals in the South-East of the Netherlands were identified. Patients were selected irrespective of the date of diagnosis of the primary tumor with the exception of patients with a diagnosis of primary breast cancer before 1990, due to the limited available data on the primary tumor characteristics and initial treatment.

From a total of 815 patients with metastatic breast cancer, we excluded 204 patients with HR-negative breast cancer. From the 611 patients with HR+ (i.e. ER and/or progesterone receptor (PR) positive) breast cancer another 91 patients with HER2+ disease were excluded. Thus, the total cohort consisted of 520 patients with HR+/HER2- breast cancer.

Patient and tumor characteristics, comorbidity, treatment (surgery, radiotherapy and systemic treatment, both adjuvant and palliative) and outcomes (local, regional or distant recurrences of breast cancer and the occurrence of another malignant condition) were retrospectively collected by trained data managers based on extensive chart review.

Comorbidity was categorized as cardiovascular (including atherosclerosis, hypertension, myocardial infarction and/or heart failure), cerebrovascular disease (also including dementia), diabetes mellitus, lung disease (either asthma, chronic obstructive pulmonary disease or dyspnea without other diagnosis), other malignancy before date of primary breast cancer diagnosis and other (including kidney, liver or gastro-intestinal disease as well as auto-immune diseases or relevant infectious disease). Tumors were categorized according to the sixth edition of the TNM classification of malignant tumors⁹ and the Scarff Bloom Richardson (SBR) histological grading system.¹⁰ ER and PR positivity was defined as positive nuclear staining of $\geq 10\%$. HER2 negativity was defined as immunohistochemistry score of 0, 1+ or with a negative fluorescence in situ hybridization result. In case of missing HER2 results it was centrally determined by a dedicated breast cancer pathologist if tumor tissue could be obtained. Initial metastatic sites were registered as single or multiple and were categorized as follows: bone, visceral (including lung, liver, pleural, peritoneal, pericardial and lymphangitic carcinomatosis), brain (including leptomeningeal and CNS), skin and lymph nodes and multiple metastases (more than one of the aforementioned metastatic sites).

Statistical analysis

Primary study objective was to assess the initial systemic treatment choices made in a real-life setting within a HR+ metastatic breast cancer cohort. For this study objective, initial palliative systemic therapy was categorized as chemotherapy or endocrine therapy. Initial systemic therapy was defined as first-given systemic therapy for metastatic breast cancer. We analyzed initial systemic therapy for the total included cohort, and according to initial metastatic site. Baseline characteristics between patients with initial chemotherapy and initial endocrine therapy were compared using chi-square tests for categorical variables and Wilcoxon rank sum test for continuous variables.

Secondary study objective was to determine the outcome in terms of PFS and OS according to initial systemic treatment choice. PFS of initial palliative systemic treatment was defined as time from start of initial palliative systemic therapy until reported progression or death. In case of no information on response (mostly in case of bone metastases only) the start of a new therapy was defined as progression. However patients with initial chemotherapy without reported progression that started with endocrine therapy directly after chemotherapy, so called maintenance endocrine therapy, were censored at date of start of endocrine therapy (8% of

patients treated with initial chemotherapy). OS was defined as time from date of diagnosis of metastatic breast cancer to date of death and was determined according to initial systemic therapy. All patients still alive were censored at the date of last follow-up of each individual patient. For this study objective, survival curves were determined using the Kaplan-Meier method and tested for difference between the two groups with the log-rank test.

Furthermore, the difference in outcome (PFS and OS) between patients initially treated with chemotherapy and with endocrine therapy was adjusted for relevant prognostic factors by analyzing in a Cox proportional hazards model. The included prognostic factors in the model were age at diagnosis of metastatic breast cancer, adjuvant systemic therapy, comorbidity, metastasis-free interval (MFI) and site of distant metastases. All reported P-values are two-sided and P-value ≤ 0.05 was considered statistically significant.

Results

Characteristics of HR+ metastatic breast cancer cohort

During the follow-up period (median 37.1 months, range 5.2-54.6 months), 7.3% of all included patients with HR+ metastatic breast cancer did not receive any palliative systemic therapy. These patients had a median age of 68.5 years and 75% of these patients had one or more comorbidities. More than half of these patients had a MFI of less than 24 months and 46% of patients had received prior adjuvant systemic therapy.

From the 482 patients treated with palliative systemic therapy; 116 (24%) patients were treated with initial chemotherapy and 366 (76%) patients started initial therapy with endocrine therapy (Table 5.1). The patients that initiated systemic treatment with chemotherapy were younger at diagnosis of metastatic breast cancer than patients with initial endocrine therapy (respectively, median 52 versus 61 years, $P < 0.0001$). For both groups, cardiovascular comorbidity was most frequent (22% of patients with initial chemotherapy and 41% of patients with initial endocrine therapy). There were no statistically significant differences between the primary breast cancer characteristics size, lymph node status and histological grade. Adjuvant chemotherapy was administered in 52% of patients that were also treated with initial chemotherapy in metastatic disease setting, compared to 31% of patients that were treated with initial endocrine therapy in metastatic disease setting ($P = 0.0002$).

Table 5.1 Characteristics of patients with hormone receptor positive metastatic breast cancer, according to initial palliative systemic therapy.

Characteristics	Initial chemotherapy	Initial endocrine therapy	<i>P</i>
	<i>n</i> =116 <i>n</i> (%)	<i>n</i> =366 <i>n</i> (%)	
Age at diagnosis MBC			
Median in years (range)	52 (25-80)	61 (30-91)	<.0001
<50 years	45 (39)	84 (23)	0.0008
≥50 years	71 (61)	282 (77)	
Comorbidity			
Any	54 (47)	247 (68)	<.0001
Cardiovascular	25 (22)	151 (41)	0.0001
Diabetes	8 (7)	59 (16)	0.01
Lung disease	4 (3)	37 (10)	0.03
Cerebrovascular	5 (4)	21 (6)	0.55
Other malignancy	7 (6)	45 (12)	0.06
Other**	6 (5)	29 (8)	0.32
Primary tumor stage*			0.30
T1-2	85 (94)	252 (91)	
T3-4	5 (6)	25 (9)	
unknown	26	89	
Primary lymph node stage*			0.07
Node negative	31 (34)	125 (45)	
Node positive	60 (66)	154 (55)	
unknown	25	87	
Histological grade of primary tumor			0.15
Grade 1	10 (11)	41 (18)	
Grade 2	48 (51)	119 (52)	
Grade 3	36 (38)	68 (30)	
unknown	22	138	
Adjuvant therapy†			
None	18 (19)	102 (34)	0.003
Endocrine therapy	73 (75)	179 (60)	0.008
Chemotherapy	50 (52)	91 (31)	0.0002
Metastasis-free interval			0.65
Primary metastatic disease	19 (16)	69 (19)	
<24 months	19 (16)	49 (13)	
≥24 months	78 (68)	248 (68)	
Initial metastatic sites			0.02
Bone	17 (15)	181 (49)	
Visceral	42 (36)	73 (20)	
Brain	3 (2)	2 (1)	
Skin and lymph nodes	7 (6)	21 (6)	
Multiple	47 (41)	89 (24)	

n number, *HER2* human epidermal growth factor receptor 2. * pathological TNM by the sixth edition of the TNM classification of malignant tumors; ** including kidney, liver or gastro-intestinal disease, auto-immune disease or infectious disease; † excluding patients with primary metastatic disease.

Initial systemic therapy in daily practice for HR+ metastatic breast cancer, according to initial metastatic site

As reported in Table 5.1, there are differences in initial metastatic site between patients receiving initial palliative chemotherapy and initial palliative endocrine therapy. Almost half of patients treated with endocrine therapy had bone metastases as initial metastatic site, whereas this was only 15% of patients treated with initial chemotherapy.

When looking at HR+ metastatic breast cancer patients categorized by initial metastatic site, patients with visceral and multiple sites of metastases were more likely to receive initial chemotherapy compared to patients with bone metastasis only (35% and 37% versus 9% (both $P<0.0001$) (Figure 5.1).

Figure 5.1 Initial palliative systemic therapy per initial metastatic site for patients with HR+ metastatic breast cancer treated with palliative systemic therapy.

Outcome in daily practice for HR+ metastatic breast cancer

PFS and OS for the total included HR+ cohort was determined for initial palliative chemotherapy and initial palliative endocrine therapy. The median PFS of patients treated with initial chemotherapy was 5.3 months (95% CI 4.2-6.2) and the median PFS of those with initial endocrine therapy was 13.3 months (95% CI 11.3-15.5) ($P<0.0001$) (Figure 5.2A). The patients that were treated with chemotherapy as initial therapy had a median OS of 16.1 months (95% CI 13.7-19.7). This in contrast to the median survival of 36.9 months (95% CI 30.6-43.9) for patients that were treated with endocrine therapy as initial therapy ($P<0.0001$) (Figure 6.2B).

Figure 5.2 Progression-free survival (PFS) (A) and Overall Survival (OS) after diagnosis of metastatic breast cancer (B) for initial palliative systemic therapy in patients with HR-positive metastatic breast cancer treated with either palliative chemotherapy or palliative endocrine therapy.

Even after adjusting for known prognostic factors the outcome in terms of PFS and OS was significantly worse for patients starting with initial chemotherapy compared to initial endocrine therapy with a hazard ratio of 2.33 (95% CI 1.77-3.08, $P < 0.0001$) for PFS and a hazard ratio of 2.24 (95% CI 1.64-3.06, $P < 0.0001$) for OS. Apart from initial chemotherapy, MFI < 24 months and visceral or multiple initial metastatic sites were associated with worse outcome (Table 5.2).

Table 5.2 Multivariable analysis of outcome of hormone receptor positive metastatic breast cancer patients.

	Progression-free survival			Overall Survival		
	HR	95% CI	P	HR	95% CI	P
Initial systemic therapy						
Initial endocrine therapy	1			1		
Initial chemotherapy	2.33	1.77-3.08	<.0001	2.24	1.64-3.06	<.0001
Age at diagnosis of MBC						
<50 years	1			1		
≥50 years	1.15	0.875-1.52	0.34	1.31	0.96-1.80	0.09
Comorbidity						
No	1			1		
Any	0.98	0.75-1.27	0.86	1.26	0.94-1.69	0.13
Adjuvant systemic therapy						
No	1			1		
Yes	1.27	0.98-1.64	0.07	1.19	0.88-1.61	0.26
Metastasis-free interval						
≥24 months	1			1		
<24 months	1.75	1.29-2.37	0.0003	1.81	1.30-2.53	0.0005
Initial metastatic sites						
Bone	1			1		
Visceral	1.22	0.91-1.65	0.18	1.53	1.09-2.16	0.02
Brain	0.67	0.21-2.19	0.51	1.18	0.41-3.38	0.76
Skin and lymph nodes	0.78	0.45-1.356	0.38	0.86	0.45-1.68	0.67
Multiple	1.29	0.97-1.73	0.08	1.53	1.09-2.176	0.02

HR hazard ratio, 95% CI 95% Confidence Interval.

Discussion

Here we present data on patient characteristics, initial systemic treatment choice and outcome in daily practice for patients with HR+ metastatic breast cancer.

To our knowledge, this is the first cohort study that focused on the initial palliative systemic therapy for HR+ metastatic breast cancer. In our study all consecutive breast cancer patients were included, whereas other real-life data on treatment patterns are mostly based on a selection of metastatic breast cancer patients.¹¹⁻¹⁶ Population-based observational studies, such as our study, are a necessity in addition to clinical trials to provide information that can impact prognosis, treatment and quality of care for metastatic breast cancer.¹⁷

One of the examples of important information that can only be derived from observational studies is a possible difference between guideline recommendations and patterns of care. Our study demonstrated that up to a quarter of patients with HR+ metastatic breast cancer started with chemotherapy in real-life, consistent with high percentages of initial chemotherapy found in other real-life reports.^{15,16} This finding could be the reflection of the consensus statement published at the time of initial treatment of patients in our cohort (2007-2009) recommending the use of initial

endocrine therapy only for patients with low burden of disease.¹⁸ Even so, in our cohort 9% of patients with HR+ metastatic breast cancer with bone metastases only received initial chemotherapy.

Since initial chemotherapy has not found to be more effective compared to initial endocrine therapy and is associated with more toxicity,¹⁹ current guidelines recommend initial endocrine therapy for all HR+ metastatic breast cancer patients, with the exception of patients in need of immediate tumor reduction.^{4,6,7}

The high percentage of initial chemotherapy in this large real-life cohort is an important finding and continuous gathering of these data is essential. Not only to raise awareness to the treating physicians, but to study guideline adherence and determine predictive factors for non-adherence. This can help improve guideline implementation and thereby improve quality of care and outcome of patients with HR+ metastatic breast cancer.^{20,21}

For the HR+ metastatic breast cancer patients treated with initial chemotherapy, outcome in terms of PFS and OS was worse compared to the patients treated with initial endocrine therapy, even after adjusting for prognostic factors. This could be explained by the fact that patients with HR+ tumors have a lower response to chemotherapy than patients with HR- tumors, as known from early breast cancer studies.^{22,23} In a previous meta-analysis on the efficacy of chemotherapy versus endocrine therapy in metastatic breast cancer no difference was found in terms of survival.¹⁹ However, in the trials included in the meta-analysis many of the patients did not have a HR+ tumor, possibly resulting in an underestimation of the efficacy of endocrine treatment. Nowadays, with known HR status before commencing palliative systemic therapy endocrine therapy should remain treatment of choice for HR+ metastatic breast cancer.

The information on outcome by initial systemic therapy is not only relevant in treatment-decision making for future patients with HR+ metastatic breast cancer, it is also crucial when interpreting results of randomized clinical trials. When including patients with prior endocrine therapy for metastatic breast cancer in a trial on first-line chemotherapy, these patients will be more likely to have a good outcome compared to patients without prior palliative endocrine therapy. Initial therapy should therefore be a stratification factor in randomized trials on palliative systemic treatment regimens.

The results of our real-life study imply that initial endocrine therapy should remain treatment of choice for the palliative treatment of HR+ metastatic breast cancer, as stated by the current guidelines.^{4,6,7} Even so, treatment choices on endocrine therapy in metastatic breast cancer are complex. Even though palliative endocrine therapy will be impacted more and more by the increasing use of adjuvant tamoxifen and aromatase-inhibitors, still several options for endocrine treatment exist depending on type of adjuvant endocrine therapy and time between end of adjuvant endocrine therapy and distant relapse.²⁴ Furthermore, an important aspect of treatment of HR+ metastatic breast cancer is endocrine resistance. This could also have played a role in

the low use of initial palliative endocrine therapy we observed in our cohort, since we did not include type of adjuvant endocrine therapy and timing of distant relapse in our analysis. Progress in understanding mechanisms of the development of endocrine resistance is made and there are several trials investigating the efficacy of targeted therapy of several pathways involved in HR+ breast cancer.²⁵ Of on the examples of such a trial resulted in the approval of the mTOR inhibitor everolimus in combination with an aromatase inhibitor for HR+ metastatic breast cancer patients previously treated with non-steroidal aromatase inhibitors.⁸

Inherent to the retrospective nature of observation cohort studies and recognizing possible confounding by indication, our study has several limitations. In making clinical treatment-decisions not only tumor characteristics, age and comorbidity plays a role, also performance status, laboratory results and preferences of patient and doctor are taken into consideration. These factors are not accounted for in this study. Furthermore, new treatment options, such as high dose fulvestrant and everolimus were not available and used in our cohort of metastatic breast cancer patients diagnosed between 2007-2009. These new treatment options could alter the outcome of metastatic breast cancer patients treated today.

In conclusion, this real-life data provide a good overview of initial palliative treatment for HR+ metastatic breast cancer. In metastatic breast cancer, systemic palliative treatment choices are diverse and options are increasingly expanding. Therefore, continuous collection of real-life data is essential in evaluating every day clinical breast cancer care and optimizing treatment strategies and thereby outcome of metastatic breast cancer patients.

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Chapter 6

A real-world study on implementation of bevacizumab in a cohort of HER2-negative metastatic breast cancer patients

A study of the Southeast Netherlands Breast Cancer Consortium

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Abstract

Background

The objective of this study was to analyze real-world use and effectiveness of bevacizumab in combination with taxanes as first-line treatment in HER2-negative metastatic breast cancer. Furthermore, we aimed to gain detailed insight in first-line treatment choices, shortly before and after introduction of bevacizumab.

Patients and methods

Patients were diagnosed with HER2-negative metastatic breast cancer between 2007-2009. Data on patient and tumor characteristics, palliative treatment and outcome was collected. Progression-free (PFS) and overall survival (OS) curves were estimated with Kaplan-Meier method.

Results

From the included 650 HER2-negative metastatic breast cancer patients, 193 received first-line chemotherapy after introduction of bevacizumab of whom 33 (17%) received bevacizumab and taxane. Patients treated with bevacizumab-taxane were younger, had a trend towards less cardiovascular comorbidities, a longer metastasis-free survival and received more adjuvant chemo- and endocrine therapy as compared to patients treated with other first-line chemotherapy regimens. Twenty-four percent of patients receiving bevacizumab-taxane had no indication for bevacizumab or received this despite contraindication. Thirty-three (17%) of 193 patients could have received bevacizumab, but were treated with other first-line therapies, of whom 21 received bevacizumab in second line or beyond. Median PFS of first-line bevacizumab-taxane was 6.0 months (95% CI 4.8-13.1). Median OS was 28.4 months (95% CI 14-undetermined).

Conclusion

Bevacizumab was prescribed less frequently than expected, offered to a selected population and frequently outside guideline recommendations. Early field research on the implementation, use and effectiveness of new drugs in daily practice is necessary to guarantee effective implementation of these drugs.

Introduction

Metastatic breast cancer (MBC) is a major cause of death among women worldwide.¹ Over the last decade, progress in treatment of patients with MBC has been made due to introduction of new therapeutic drugs. Bevacizumab, a recombinant humanized IgG1 antibody inhibiting vascular endothelial growth factor (VEGF) induced effects, is one of these new drugs.

Bevacizumab was evaluated as first-line therapy in combination with weekly paclitaxel for HER2-negative MBC in the E2100 trial.² Progression-free survival (PFS) was significantly prolonged for bevacizumab-paclitaxel as compared to paclitaxel alone with a median 11.8 months versus 5.9 months (hazard ratio (HR) 0.60; 95% Confidence Interval (CI) 0.51- 0.70). However, this improvement was not reflected in a difference in overall survival (OS) (HR 0.88, $P = 0.16$). Shortly thereafter, two placebo-controlled studies were designed to validate the findings of E2100, and to explore different chemotherapy backbones combined with bevacizumab.^{3,4} Both of these trials showed improvement in PFS, but not in OS.

The E2100 trial led to the accelerated approval of bevacizumab for the treatment of MBC by the US Food and Drug administration (FDA) in 2008, followed by the approval by the European Medicines Agency (EMA). Based on the subsequent trial results the FDA decided to revoke the approval of bevacizumab for the treatment of MBC. In 2010, the CHMP committee of the EMA reassessed bevacizumab in combination with paclitaxel for the first line treatment of HER2-negative MBC. They concluded that the available data had convincingly shown to prolong PFS without a negative effect on overall survival (OS), i.e. that the benefits continue to outweigh the risks. Furthermore, in 2011 the EMA approved the use of capecitabine in combination with bevacizumab in this indication. As a result, in many other countries, including the Netherlands, bevacizumab in combination with either paclitaxel or capecitabine is approved as first-line treatment regimen for patients with HER2 negative MBC.

Therefore, bevacizumab was allowed for conditional reimbursement by the National Health Care Institute (CVZ). For unconditional reimbursement, the National Health Care Institute requested real-life data on use, effectiveness, costs and tolerability to be collected during the initial four years after approval.⁵

However, these real-life data are not only relevant for health care package. Real-world data also provide insight into patterns of care, the implementation of new therapeutic regimens and adherence to guidelines. In early breast cancer this information is known to improve quality of care and thereby outcome of breast cancer patients.⁶⁻⁸

The objective of this study was to analyze real-world use and effectiveness of bevacizumab in combination with taxanes as first-line treatment of HER2-negative MBC patients. Furthermore, we aimed to gain detailed insight in first-line treatment choices made within the Netherlands, shortly before and after the introduction of bevacizumab.

Patients and methods

Patients

We conducted an observational cohort study in eight hospitals in the South East of the Netherlands. Participating centers were one academic hospital, six teaching hospitals and one non-teaching hospital. All consecutive breast cancer patients diagnosed with distant metastases between January, 1st 2007 and December 31st, 2009 were identified ($n = 815$). All patients with a HER2-negative tumor were included ($n = 650$). The study was approved by the Medical Research Ethics Committee of Maastricht University Medical Center.

Data collection

Data from the medical files were collected by trained data clerks in an electronic case report form. Data lock was on August 1st, 2011. Patients were identified by a list of the hospital diagnosis-treatment combinations for each hospital. Also, the national cancer registry database was checked to guarantee a 100% data capture.

Statistical analyses

The primary study goals were to analyze the use of bevacizumab in combination with taxanes as first-line regimen for the treatment of HER2-negative MBC in a real-life setting with the following research questions; how often was bevacizumab in combination with taxanes used and was the use according to the then applicable guidelines (at the time of the treatment of patients in our cohort bevacizumab was registered in combination with both paclitaxel and docetaxel and not (yet) in combination with capecitabine); to whom bevacizumab-taxane was given and how did it compare to the patients included in the randomized clinical trials; what was the effectiveness of taxanes combined with bevacizumab in daily practice compared to the efficacy reported in the clinical trials (both E2100 and the AVADO trials, but not the RIBBON-1 trial, since that trial combined the taxane and anthracycline chemotherapy backbone with bevacizumab for the reported outcomes). The primary study goals above described were analyzed in all patients diagnosed with HER2-negative MBC after March 1st, 2008 (date of approval of bevacizumab combined with paclitaxel in the Netherlands).

Secondary study goals were to evaluate the types of chemotherapy regimens and their effectiveness in patients treated with first-line chemotherapy for HER2-negative MBC diagnosed before and after introduction of bevacizumab. The secondary study goals were assessed in all patients diagnosed with HER2-negative MBC between January 1st, 2007 and December 31st, 2009 and treated with first-line chemotherapy. We classified these patients in two groups: diagnosed before or after the introduction of bevacizumab (March 1st, 2008).

PFS and OS were estimated using the Kaplan-Meier method. PFS was defined as the time from starting first-line chemotherapy until reported progression or date of death. In case of no information on response (mostly in case of bone metastases only) the start of a new therapy was defined as progression. However patients with initial chemotherapy without reported progression that started with endocrine therapy directly after chemotherapy, so called maintenance endocrine therapy, were censored at date of start of endocrine therapy. For the PFS analyses, all patients without registered progression or death at the time of analysis were censored at the date of last follow-up. OS was defined as the time from date of first distant metastasis until date of death. For the OS analyses, all patients still alive at the time of analysis were censored at the date of last follow-up of each patient. Confidence intervals were set at 95%. All analyses were performed using SAS software version 9.2.

Results

First-line chemotherapy regimens before and after introduction of bevacizumab

A total of 650 patients with HER2-negative MBC were included, with a median follow-up of 36.5 months (range 2.1-54.6). Of these, 329 patients (51%) were treated with at least one line of chemotherapy for their MBC; 136 before the introduction of bevacizumab and 193 patients after introduction of bevacizumab. Characteristics of the patients treated with first-line chemotherapy before and after introduction of bevacizumab are presented in Table 6.1.

For patients treated with monotherapy taxane before the introduction of bevacizumab at least 28% of patients had one cardiovascular comorbidity, whereas after the introduction of bevacizumab this percentage was higher for patients treated with monotherapy taxane (41%) and lower for patients treated with taxane in combination with bevacizumab (21%). Of patients treated with monotherapy taxane before the introduction of bevacizumab 79% had received (neo-)adjuvant chemotherapy, compared to 69% of patients treated with monotherapy taxane after the introduction of bevacizumab and compared to 85% of patients treated with taxane in combination with bevacizumab.

For patients treated with first-line chemotherapy before introduction of bevacizumab, median PFS ranged from 5.8 months to 10.7 months and median OS from 15.6 months to 34.9 months, depending on type of first-line treatment (Figure 6.1).

Table 6.1 Characteristics of HER2-negative metastatic breast cancer patients treated with first-line chemotherapy, according to type of first-line chemotherapy.

Characteristics	Before introduction of bevacizumab					After introduction of bevacizumab					
	All first-line N=136	Taxane N=28	Antra- cyclines N=46	Cape- citabine N=33	Other N=29	All first-line N=193	Bevacizumab + Taxane N=33	Taxane N=29	Antra- cyclines N=77	Cape- citabine N=40	Other N=14
Median age range (years)	59 (25-88)	59 (29-76)	57 (39-77)	62 (40-78)	58 (25-88)	56 (33-83)	51 (38-77)	53 (34-74)	56 (33-82)	63 (38-83)	53 (37-81)
Age n (%)											
<40 years	3 (2)	1 (4)	1 (2)	0 (-)	1 (3)	10 (5)	1 (3)	2 (7)	4 (5)	2 (5)	1 (7)
40-70 years	110 (81)	26 (92)	37 (81)	23 (70)	24 (83)	149 (77)	30 (91)	22 (76)	63 (82)	24 (60)	10 (71)
≥70 years	23 (17)	1 (4)	8 (17)	10 (30)	4 (14)	34 (18)	2 (6)	5 (17)	10 (13)	14 (35)	3 (22)
Hormone receptor positive n (%)	104 (76)	25 (89)	38 (83)	24 (73)	17 (59)	151 (78)	27 (82)	21 (72)	62 (81)	30 (75)	11 (79)
Hormone receptor negative n (%)	32 (24)	3 (11)	8 (17)	9 (27)	12 (41)	42 (22)	6 (18)	8 (28)	15 (19)	10 (25)	3 (21)
Prior (neo)adjuvant chemotherapy n (%)	72 (53)	22 (79)	13 (28)	20 (61)	17 (59)	103 (53)	28 (85)	20 (69)	23 (30)	22 (55)	10 (71)
Prior (neo)adjuvant endocrine therapy n (%)	60 (44)	20 (71)	17 (37)	11 (33)	12 (41)	100 (52)	24 (73)	15 (52)	34 (44)	17 (43)	10 (71)
At least one cardiovascular comorbidity n (%)	43 (32)	8 (28)	11 (24)	15 (45)	9 (31)	63 (33)	7 (21)	12 (41)	22 (29)	18 (45)	4 (29)
Cardiovascular comorbidity n (%)											
Hypertension	35 (26)	5 (18)	10 (22)	14 (42)	6 (21)	47 (24)	7 (21)	7 (24)	15 (19)	15 (38)	3 (21)
Cardiac failure	0 (-)	-	-	-	-	3 (2)	1 (3)	1 (3)	1 (1)	0 (-)	0 (-)
Myocardial infarction	5 (4)	2 (7)	0 (-)	1 (3)	2 (7)	5 (3)	1 (3)	2 (7)	1 (1)	0 (-)	1 (7)
Diabetes	12 (9)	2 (7)	0 (-)	5 (15)	5 (17)	17 (9)	0 (-)	5 (17)	5 (6)	4 (10)	3 (21)
Cerebrovascular disease	5 (4)	2 (7)	1 (2)	2 (6)	0 (-)	9 (5)	0 (-)	2 (7)	4 (5)	3 (8)	0 (-)
Initial metastatic site n (%)											
Bone	50 (37)	10 (36)	19 (42)	14 (43)	7 (25)	46 (24)	6 (18)	3 (11)	19 (25)	14 (35)	4 (29)
Visceral	33 (24)	9 (32)	8 (17)	8 (24)	8 (28)	60 (31)	8 (25)	11 (38)	25 (32)	11 (27)	5 (36)
Brain	1 (1)	0 (-)	0 (-)	0 (-)	1 (3)	4 (2)	0 (-)	1 (3)	2 (3)	1 (3)	0 (-)
Skin and lymph nodes	6 (4)	1 (4)	1 (2)	3 (9)	1 (3)	16 (8)	5 (15)	2 (7)	5 (6)	2 (5)	2 (14)
Multiple metastatic sites	46 (34)	8 (28)	18 (39)	8 (24)	12 (41)	67 (35)	14 (42)	12 (41)	26 (34)	12 (30)	3 (21)
Prior endocrine therapy for metastatic disease n (%)	65 (48)	13 (46)	24 (52)	22 (67)	6 (21)	76 (39)	15 (45)	13 (45)	22 (29)	21 (53)	5 (36)

Figure 6.1 Progression-free survival (A) and overall survival (B) per type of chemotherapy regimen for 136 patients treated with first-line chemotherapy before introduction of bevacizumab.

For the patients treated with first-line chemotherapy after the introduction of bevacizumab median PFS ranged from 4.8 months to 7.1 months and median OS from 14.2 months to 30.9 months, again depending on type of first-line chemotherapy regimen (Figure 6.2).

Figure 6.2 Progression-free survival (A) and overall survival (B) per type of chemotherapy regimen for 193 patients treated with first-line chemotherapy after introduction of bevacizumab.

Patients treated with bevacizumab in combination with taxane in daily practice and compared to clinical trials

Of the 193 HER2-negative MBC patients who received first-line chemotherapy after introduction of bevacizumab, 33 actually received taxane chemotherapy in combination with bevacizumab (17%; 25 with paclitaxel, 8 with docetaxel). In 8 of the 33 patients (24%) bevacizumab was administered not according to the registered indication ($n=6$; all could have been treated with anthracyclines) or despite a (relative) contra-indication ($n=2$; 1 patient had surgery in the three weeks prior to bevacizumab

administration and 1 patient had a left ventricular ejection fraction of 40% at start of bevacizumab administration).

Thirty-three of 193 (17%) patients receiving first-line non-bevacizumab containing chemotherapy had no relative contra indications for taxane-bevacizumab therapy (Table 6.2).

Twenty-one of these 33 patients received second ($n=17$) or higher line ($n=4$) bevacizumab containing therapy.

Table 6.2 Comorbidity, prior anthracyclines and characteristics implying a contraindication for bevacizumab and anthracycline therapy for HER2 negative metastatic breast cancer patients treated with first-line chemotherapy after introduction of bevacizumab.

	Bevacizumab + Taxane $n=33$	Taxane $n=29$	Anthracycline $n=77$	Capecitabine $n=40$	Other $n=14$
Relative contraindications for treatment with bevacizumab					
Recent surgery	1	0	0	0	2
Hypertension	5	7	14	15	3
Cardiac failure	1	2	1	1	1
Cerebrovascular disease	0	2	4	3	0
Diabetes	0	5	5	4	3
Age > 65 year	5	8	23	18	4
Wound healing disorders	0	0	0	0	0
Prior treatment with anthracyclines					
Prior anthracycline therapy	27	9	15	12	9
Contraindication anthracycline therapy	1	4	0	1	0
Prior anthracyclines and no contraindications bevacizumab	25	9	8	12	4

Table 6.3 shows the characteristics of patients treated with first-line bevacizumab-taxane in the real-world setting compared to the characteristics of patients reported in the two placebo-controlled trials including the bevacizumab-taxane regimen: E2100 registration trial (bevacizumab-paclitaxel vs. paclitaxel monotherapy) and the AVADO trial (bevacizumab-docetaxel (15mg) vs. docetaxel monotherapy).

In our cohort, patients treated with first-line bevacizumab were slightly younger (median age 51 years, range 38-77) compared to patients in the E2100 (median age 56 years, range 29-84) and the AVADO trial (median age 55 years, range 27-76). Patients in our cohort treated with bevacizumab were more likely to be treated with prior (neo-)adjuvant chemotherapy and more likely to have a metastasis-free interval of ≥ 24 months compared with patients in the experimental arm in the E2100 trial. In the E2100 and AVADO trial, visceral metastases were more frequent than in our real-world cohort (respectively 80%, 93% and 67%).

Table 6.3 Characteristics of real world patients treated with bevacizumab-taxane and taxane monotherapy as first-line chemotherapy versus the patients treated in the randomized clinical trials (E2100 trial and the AVADO trial).

Characteristics	Real world cohort			E2100 trial		AVADO trial	
	Bevacizumab + Taxane	Taxane		Bevacizumab + Paclitaxel	Paclitaxel	Bevacizumab (15mg/kg) + Docetaxel	Docetaxel
	n=33	n=29		n=347	n=326	n=247	n=241
Age in years	51	53		56	55	55	55
median (range)	(38-77)	(34-74)		(29-84)	(27-85)	(27-76)	(29-83)
Hormone receptor positive n (%)	27 (82)	21 (72)		208 (60)	205 (63)	187 (76)	189 (78)
Prior (neo)adjuvant chemotherapy n (%)	28 (85)	20 (69)		226 (65)	212 (65)	167 (68)	165 (65)
Prior (neo)adjuvant endocrine therapy n (%)	24 (73)	15 (52)		NA	NA	120 (49)	135 (56)
Metastasis-free interval >= 24 months n (%)	25 (76)	59 (17)		203 (59)	193 (59)	NA	NA
Metastatic site at time of treatment n (%)							
Bone only	4 (14)	4 (12)		36 (10)	25 (8)	7 (3)	9 (4)
Visceral	22 (67)	20 (69)		276 (80)	284 (87)	229 (93)	211 (88)
At least three metastatic sites	5 (15)	3 (11)		149 (43)	151 (46)	NA	NA
Prior endocrine therapy metastatic disease n (%)	15 (45)	13 (45)		NA	NA	69 (28)	76 (32)
Efficacy endpoint PFS							
Median in months (95%- CI)	6.0 (4.8-13.1)	7.1 (3.0-13.5)		11.8 (NA)	5.9 (NA)	10.0 (NA)	8.1 (NA)

NA not available

Median duration of treatment with bevacizumab-taxane in our cohort was 7.3 months, compared to 7.1 months in the E2100 trial and 7.9 months in the AVADO trial (ranges not reported).

The effectiveness of addition of bevacizumab to taxane chemotherapy in daily practice and compared to clinical trials

The median PFS of patients treated with first line bevacizumab-taxane in the real-world cohort was 6.0 months (95% CI 4.8-13.1) (Figure 6.2A). The median PFS of patients treated with bevacizumab-paclitaxel in the E2100 trial was 11.8 months and the median PFS of patients treated with bevacizumab-docetaxel in the AVADO-trial was 10.0 months (Table 6.3).

Median OS with bevacizumab-taxane in the real-world cohort was 28.4 months (95% CI 14-undetermined) (Figure 6.2B). For patients treated with bevacizumab-taxane in the E2100 and AVADO trials median OS was respectively 26.7 months and 30.2 months.

Discussion

This real-world study describes implementation and use of bevacizumab in a HER2-negative MBC cohort. Furthermore, these data also provide detailed insight into first-line treatment choices in patients with HER2-negative MBC shortly before and after the introduction of bevacizumab in 2008.

In real-world practice, bevacizumab was administered less frequently than expected and potentially indicated. Actually 30% of patients (58 out of 193; Table 6.2) could have been treated with first-line paclitaxel/bevacizumab, considering prior use of adjuvant anthracyclines and absence of (relative) contra-indications for bevacizumab use. But in real-life only 17% of patients on first-line chemotherapy received bevacizumab-taxane. Moreover, bevacizumab-taxane was offered despite significant co-morbidity or (relative) contraindications in 24% of these patients treated with bevacizumab-taxane. Of the thirty-three (17%) patients that could have received bevacizumab-containing regimen but were treated with other first-line chemotherapy, 21 received bevacizumab in second or later lines of therapy. It is possible that the patients receiving bevacizumab after first-line therapy started their first-line chemotherapy regimen before official registration of bevacizumab and were considered 'suitable candidates' hereafter, even though it is off-label use of bevacizumab. The unexpected lower and off-label use of bevacizumab after approval in 2008 is an important observation, stating the importance of real world evaluation of drug implementation.

When comparing real-world selected patients treated with bevacizumab with patients included in the pivotal trials, real-world patients were slightly younger, the percentage

of patients with a metastasis-free interval ≥ 24 months was higher and adjuvant chemotherapy was more frequently administered than in the clinical trials. Nevertheless, despite real-world patients were slightly younger and had less comorbidity, median PFS was shorter (6.0 months) than the PFS reported in several clinical trials on first-line bevacizumab regimens; respectively 11.8 months in the E2100 trial¹, 10.1 months in the AVADO trial, 9.2 months in the RIBBON-1 trial, 9.5 months in the ATHENA trial and 8 months in a single-center analysis.^{2-4,9,10} The reported differences in age, metastasis-free interval, number of anthracycline and (palliative) endocrine pretreatment between real-world and trial populations and the fact that 24% of patients in real-world received bevacizumab despite of contraindications may partly explain this difference in PFS. Furthermore, in real-world only a small percentage of MBC patients participates in clinical trials.¹¹ When in real-world population patients are treated outside the strict eligibility criteria of the randomized trials, the reported trial results are not always directly translatable, as was recently shown in metastatic colon cancer.¹² Real-world data on the implementation, use and effectiveness and safety of a new drug in the treatment of MBC are therefore essential as an addition to the available trial data.¹³

Clearly, with the low number of patients treated with bevacizumab-taxane in first-line in our cohort caution should be taken when interpreting the effectiveness results. Even so, median OS in our study of patients treated with bevacizumab in first-line was 28.4 months, which is comparable to the OS found in the randomized trials.

Even though OS as endpoint in clinical trials of MBC remain the gold standard, the lack of gain in OS is not always indicative of lack of efficacy.^{14,15} Multiple lines of treatment after first-line progression and the cross-over effect of these different treatment regimens can explain the lack of difference in OS,¹⁴ despite improved PFS.¹⁶

This highlights the need to further identify the patients who benefit most from the use of the new regimen, such as bevacizumab. This was attempted by performing subgroup analyses of the randomized trials on first-line bevacizumab,^{17,18} as well by prospectively evaluating biomarkers for response, such as VEGF-A for bevacizumab.¹⁹ It is likely that when selecting the patients that derive most benefit from bevacizumab, this could also reflect in a gain in overall survival.

Our study has some limitations inherent to the retrospective nature of this study. An important factor was the lower than expected number of patients who received taxane-bevacizumab treatment in our large cohort of HER2-negative MBC patients. Of course we are well aware that this limits the conclusions regarding taxane-bevacizumab treatment that can be drawn from this study. In spite of the limitations, this study provides an unbiased view on the implementation of a new drug and helps to increase awareness of the importance of adequate prescription of a drug in order to guarantee effectiveness and tolerability in daily practice. Besides that, further research towards optimal use and implementation of bevacizumab in daily practice to establish not only effectiveness but also cost-effectiveness is needed. In contrast to

earlier cost-effectiveness studies on bevacizumab treatment adapted from clinical trials,^{20,21} an analysis based on data and health utilities from a real-world population will give insight in the real-world cost-effectiveness of bevacizumab treatment.

In conclusion, this study demonstrates that bevacizumab was less frequently administered than expected and potentially indicated. Furthermore, it was offered despite significant co-morbidity in a substantial number of patients. This study shows the importance of monitoring the use of new treatments, to optimize their implementation and to assess their real world effectiveness.

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Chapter 7

Real-world and trial based cost-effectiveness analysis of bevacizumab in HER2-negative metastatic breast cancer patients

A study of the Southeast Netherlands Breast Cancer Consortium

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Abstract

Introduction

The aim of our analysis was to assess the real-world cost-effectiveness of bevacizumab in addition to taxane treatment versus taxane monotherapy for HER2-negative metastatic breast cancer compared with the cost-effectiveness based on the efficacy results from a trial.

Methods

A state transition model was built to estimate costs, life years (LYs) and quality-adjusted life years (QALYs) for both treatments.

Two scenarios were examined: a real-world scenario and a trial-based scenario in which transition probabilities were primarily based on a real-world cohort study and the E2100 trial respectively. In both scenarios, costs and utility parameter estimates were extracted from the real-world cohort study. Moreover, the Dutch health care perspective was adopted.

Results

In both the real-world and trial scenarios bevacizumab-taxane is more expensive (incremental costs of €56,213 and €52,750 respectively) and more effective (incremental QALYs of 0.362 and 0.189 respectively) than taxane monotherapy. In the real-world scenario, bevacizumab-taxane compared to taxane monotherapy led to an ICER of €155,261 per QALY gained. In the trial scenario, the ICER amounted to €278,711 per QALY gained.

Conclusion

According to the Dutch informal threshold, bevacizumab in addition to taxane treatment was not considered cost-effective for HER2-negative metastatic breast cancer both in a real-world and in a trial scenario.

Introduction

With the availability and use of new and more effective systemic treatment options, the survival for metastatic breast cancer has improved.¹ One new treatment option is bevacizumab, a recombinant humanized IgG1 antibody that binds VEGF (vascular endothelial growth factor). Bevacizumab was approved by the US Food and Drug administration (FDA) and the European Medicines Agency (EMA) in 2008 based on the results of the E2100 trial, in which a significant improvement in progression-free survival (PFS) was found for bevacizumab and paclitaxel compared to paclitaxel alone.² However, no significant difference in overall survival (OS) was seen. Based on the subsequent trial results of bevacizumab in combination with different chemotherapy backbones, again showing improvement in PFS but not in OS, the FDA decided to revoke the approval.^{3,4} In many other countries, including the Netherlands, bevacizumab is still registered as first-line treatment option for patients with HER2-negative metastatic breast cancer.

Due to the introduction of new drugs in breast cancer, cancer treatment costs have increased rapidly during the past years and will continue to do so.⁵ Due to uncertainties with regard to the (cost-)effectiveness and/or appropriate use in daily practice, some drugs, including bevacizumab, are allowed for conditional reimbursement by the National Health Care Institute. One of the conditions requested by the National Health Care Institute for unconditional reimbursement is the collection of data on the use and cost-effectiveness in real-world after initial approval of the drug.⁶ So far cost-effectiveness analyses (CEA) for bevacizumab in the treatment of metastatic breast cancer have been based on trial data.⁷⁻⁹

In this context, we conducted a model-based study to assess the real-world cost-effectiveness of first-line bevacizumab added to taxane chemotherapy compared with taxane chemotherapy only in Dutch HER2-negative metastatic breast cancer patients.

Methods

Real-world versus trial scenario

Bevacizumab in addition to first-line taxane chemotherapy (bevacizumab-taxane) and first-line taxane chemotherapy alone (taxane monotherapy) were compared for the treatment of HER2-negative metastatic breast cancer. This comparison was performed using two scenarios: a real-world scenario and a trial scenario. These two scenarios differed with regards to the sources used to inform the transition probabilities for overall treatment time (OTT), PFS and OS.

For the real-world scenario OTT, PFS and OS were primarily based on a real-world cohort study including 650 consecutive patients diagnosed with HER2-negative metastatic breast cancer (irrespective of treatment received) between 2007-2009 in

eight Dutch hospitals.¹⁰ This cohort included 33 patients that received bevacizumab-taxane which was used to estimate OTT, PFS and OS for bevacizumab-taxane. The OTT for taxane monotherapy was based on 29 patients from the cohort that received first-line taxane monotherapy. In contrast, the relative effectiveness (taxane monotherapy versus bevacizumab-taxane), used to inform PFS and OS for taxane monotherapy in the real-world scenario, was retrieved from the E2100 trial.²

For the trial scenario, the E2100 trial was primarily used to inform OTT, PFS and OS for both treatment strategies.²

For both scenarios resource use to calculate the health state costs and health state utilities were retrieved from the cohort study (Table 7.1).

Table 7.1 Overview of sources for the input parameters.

Input parameter	Scenarios	
	Real-world	Trial
Resource use	Cohort	Cohort
Health state utility	Cohort	Cohort
OTT	Cohort	E2100 trial
PFS	Cohort	E2100 trial
PFS (relative effectiveness)	E2100 trial	E2100 trial and indirect comparison
OS	Cohort	E2100 trial ^a
OS (relative effectiveness)	E2100 trial ^{a,b}	NA ^c

OTT, Overall treatment time; PFS, progression free survival; OS, overall survival; NA, not applicable.

^a Paclitaxel and docetaxel are assumed to be equally effective for this input parameter; ^b Calculated based on OS from the trial scenario; ^c For the trial scenario no hazard ratio is used to calculate OS, rather baseline OS is used for both arms.

Model description

A state transition model was developed consisting of three health states: progression-free, progressed disease, and death (Figure 7.1).

Figure 7.1 Markov state transition model structure.

To compare the two competing treatment strategies, a state transition model aims to reflect the course of a disease through transiting a hypothetical cohort of patients between these mutually exclusive health states. Subsequently, the expected costs and effects are calculated and compared for both treatment strategies.¹¹

The present model considered HER2-negative metastatic breast cancer patients with a median age of 58 years. Moreover, it was assumed, based on the cohort study, that for taxane monotherapy 28% of the patients received paclitaxel, whereas 72% received docetaxel. For bevacizumab-taxane, 76% of the patients received paclitaxel, while 24% of the patients received docetaxel in addition to bevacizumab.¹⁰

A lifetime time horizon and a cycle time of 1 month were used. A half cycle correction was applied for both QALYs and costs. Future costs and effects were discounted by rates of 4.0% and 1.5% respectively according to the Dutch pharmacoeconomic guideline.¹²

Transition probabilities

For the real-world scenario, OTT was retrieved from the cohort study.¹⁰ For the trial scenario, a parametric survival model (Weibull distribution) was used to calculate OTT for bevacizumab and paclitaxel (with or without bevacizumab).² The OTT for docetaxel was estimated by multiplying the lambda of paclitaxel with a hazard ratio (HR) of 1.450 to calculate the lambda for docetaxel (Table 7.2).

For the real-world scenario, the monthly progression probability for bevacizumab-taxane was estimated to be 11.5% based on the cohort study.¹⁰ For taxane monotherapy this was calculated to be 20.3%, using a HR of 1.853 (based on the E2100 trial²). Equal PFS is assumed for docetaxel and paclitaxel. For the trial scenario a parametric survival model (Gompertz distribution) was used to calculate PFS for bevacizumab-taxane and taxane monotherapy with paclitaxel.² PFS for taxane monotherapy with docetaxel in the trial scenario was estimated by multiplying the lambda of bevacizumab-taxane with a HR of 1.805 (estimated using an indirect treatment comparison,^{2,13,14} see Appendix 7.1) to calculate the lambda for docetaxel.

For the real-world scenario, OS estimated from the cohort¹⁰ was used to calculate the monthly mortality probability of 2.6% for bevacizumab-taxane (constant over time). The monthly mortality probability for taxane monotherapy was calculated by applying HR's calculated from the Kaplan-Meier curves of the E2100 trial.² This resulted in mortality probability of 5.4% for months 0-6, 2.7% for months 6-12, 2.6% for months 12-24 and 2.9% afterwards. For the trial scenario, monthly mortality probabilities for both treatments were estimated based on the Kaplan-Meier curves of the E2100 trial.² Mortality probabilities for docetaxel and paclitaxel were assumed to be equal in both scenarios.

Table 7.2 Overall treatment time, progression free survival and overall survival.

	Estimate	Se	Distribution	Source
Overall treatment time real-world scenario				
<i>Bevacizumab-taxane</i>				
Months of bevacizumab	7.01	0.93	Gamma	[1]
Months of paclitaxel	5.04	0.33	Gamma	[1]
Months of docetaxel	7.76	2.13	Gamma	[1]
<i>Taxane monotherapy</i>				
Months of paclitaxel	4.41	0.48	Gamma	[1]
Months of docetaxel	3.81	0.59	Gamma	[1]
Overall treatment time trial scenario				
<i>Weibull model to calculate months of bevacizumab</i>				
Lambda bevacizumab (with BV)	0.060	0.009	Multivariate normal	[2]
Alpha	1.355	0.062	Multivariate normal	[2]
<i>Weibull model to calculate months of paclitaxel</i>				
Lambda paclitaxel (with bevacizumab)	0.112	0.011	Multivariate normal	[2]
Lambda paclitaxel (without bevacizumab)	0.074	0.008	Multivariate normal	[2]
Alpha	1.316	0.042	Multivariate normal	[2]
HR docetaxel vs paclitaxel	1.450		Fixed	Assumption
Progression free survival real-world scenario				
Monthly progression probability bevacizumab-taxane				
HR taxane monotherapy vs bevacizumab-taxane	0.115	0.020 _b	Beta	[1]
	1.853 ^a			[2]
Progression free survival trial scenario				
Gompertz model				
Lambda bevacizumab-taxane	-0.043	0.005	Multivariate normal	[2]
Lambda paclitaxel	-0.081	0.007	Multivariate normal	[2]
Lambda docetaxel	-0.078 ^c	0.017 ^c	Multivariate normal	[2]
Alpha	0.053	0.010	Multivariate normal	[2]

Table 7.2 (continued)

	Estimate	Se	Distribution	Source
<i>Overall survival</i>				
<i>Real-world scenario</i>				
Monthly mortality probability bevacizumab-taxane	0.026	0.003	Beta	[1]
HR taxane monotherapy vs bevacizumab-taxane (months 0-6)	2.142	^e		^d
HR taxane monotherapy vs bevacizumab-taxane (months 6-12)	1.068	^e		^d
HR taxane monotherapy vs bevacizumab-taxane (months 12-24)	1.003	^e		^d
HR taxane monotherapy vs bevacizumab-taxane (months 24+)	1.132	^e		^d
<i>Trial scenario</i>				
Monthly mortality probability bevacizumab-taxane (months 0-6)	0.010	0.002	Beta	[2]
Monthly mortality probability paclitaxel (months 0-6)	0.022	0.003	Beta	[2]
Monthly mortality probability docetaxel (months 0-6)	0.022	0.003	Beta	[2]
Monthly mortality probability bevacizumab-taxane (months 6-12)	0.023	0.002	Beta	[2]
Monthly mortality probability paclitaxel (months 6-12)	0.025	0.002	Beta	[2]
Monthly mortality probability docetaxel (months 6-12)	0.025	0.002	Beta	[2]
Monthly mortality probability bevacizumab-taxane (months 12-24)	0.032	0.002	Beta	[2]
Monthly mortality probability paclitaxel (months 12-24)	0.032	0.002	Beta	[2]
Monthly mortality probability docetaxel (months 12-24)	0.032	0.002	Beta	[2]
Monthly mortality probability bevacizumab-taxane (months 24+)	0.041	0.007	Beta	[2]
Monthly mortality probability paclitaxel (months 24+)	0.047	0.011	Beta	[2]
Monthly mortality probability docetaxel (months 24+)	0.047	0.011	Beta	[2]

Se, standard error; 95%CI, 95% confidence interval; HR, hazard ratio; ^a Calculated based on PFS from the trial scenario (i.e. the lambda of the Gompertz model); ^b Based on the multivariate normal distributions of the lambda parameters used to calculate this hazard ratio; ^c Calculated based on the lambda of bevacizumab and the HR of 1.805 retrieved from the indirect treatment comparison (see Appendix 7.1); ^d Calculated based on OS from the trial scenario; ^e Based on the beta distributions of the monthly mortality probabilities used to calculate this hazard ratio.

Each cycle, the total proportion of patients dying during that particular cycle is calculated by multiplying the proportion of patients in the progression-free and progressive disease health states with the monthly mortality probabilities described above. Subsequently, the proportion of patients transiting to the death health state from the progression free health state was calculated using Dutch all-cause age-dependent mortality for women. The remaining proportion of patients dying during the cycle were assumed to transit to the death health state from the progressive disease health state.

Health state utilities

In both scenarios, health state utilities were based on a cross-sectional survey among 96 HER2-negative metastatic breast cancer patients recruited in four Dutch hospitals. During regular outpatient visits, these patients (recruited irrespective of treatment or disease state) were asked to fill out the EQ-5D questionnaire once. In total 58 patients were progression-free and 38 had progressive disease at time of the questionnaire evaluation. The utility scores, calculated using the Dolan tariff,¹⁵ for the progression-free and progressive disease health states were estimated to be 0.66 and 0.55 (standard errors: 0.051 and 0.083) respectively.

Resource use and costs

Resource use to calculate first-line treatment and health state costs per month were equal for both scenarios (Table 7.3).

Table 7.3 Treatment and health state costs (equal for both scenarios).

Cost input parameters	Estimate	Se	Distribution	Source
Treatment costs (per month)				
Bevacizumab-taxane				
Bevacizumab	€5,962	-	Fixed ^a	[1, 2]
Paclitaxel	€2,008	-	Fixed ^a	[1, 2]
Docetaxel	€2,054	-	Fixed ^a	[1, 2]
Taxane monotherapy				
Paclitaxel	€1,789	-	Fixed ^a	[1, 2]
Docetaxel	€1,950	-	Fixed ^a	[1, 2]
Health state costs (per month)				
Bevacizumab-taxane				
Progression free	€1,567	€152	Gamma	[1-3]
Progressive disease	€2,233	€243	Gamma	[1-3]
Taxane monotherapy				
Progression free	€1,834	€311	Gamma	[1-3]
Progressive disease	€2,233	€243	Gamma	[1-3]

Se, standard error. ^atreatment costs were assumed to be fixed since differences in these costs are most likely a result of variability (not parameter uncertainty)

The actual number of vials used in the cohort study (retrieved from patient charts)¹⁰ and the unit costs per vial¹⁶ were used to calculate the first-line treatment costs per month. In the model, these monthly treatment costs were combined with the OTT to calculate the total first-line treatment costs. Treatment administration costs for first-line treatment were already incorporated in the progression-free health state costs and therefore not incorporated separately (to prevent double counting).

The health state costs were calculated based on the actual medical resources used in the cohort study (retrieved from patient charts).¹⁰ This included consults, diagnostics, surgery, hormonal therapy and chemotherapy (administered after the first-line). The progression-free health state costs were calculated separately for patients receiving bevacizumab-taxane and patients receiving taxane monotherapy. Progressive disease health state costs were assumed to be equal for both treatment strategies.

Unit prices for drugs were based on the Dutch reimbursement system for pharmaceuticals.¹⁶ All other unit costs were derived from the Dutch manual for cost research.¹⁷ Cost were calculated using the Dutch health care perspective and converted to the 2012 price level based on price indices from Statistics Netherlands.¹⁸

Analyses

Base case

Life years (LY) and quality adjusted life years (QALY) were estimated for both treatment strategies. Subsequently, the incremental cost-effectiveness ratio (ICER), representing the costs of an additional QALY gained when comparing two strategies, was calculated by dividing the incremental costs by the incremental QALYs. If the ICER is below the maximum amount society is willing to pay per gained QALY, the new treatment can be considered cost-effective. In the Netherlands an informal maximum threshold of €80,000 per gained QALY was proposed for high burden diseases and is thus adopted in this study.^{19,20}

One-way sensitivity analyses and exploratory subgroup analyses

One-way sensitivity analyses (deterministic) were performed for the proportion of patients treated with either paclitaxel or docetaxel, using treatment dependent medical costs for the progressive disease health state (€2,546 for bevacizumab-taxane and €1,920 for taxane monotherapy), and using health state utilities from the literature (0.715 and 0.433 for the progression-free and progressive disease health states).²¹

Exploratory subgroup analyses (deterministic) were performed to assess the impact of ER/PR status and age on the incremental cost effectiveness ratios in both scenarios. These subgroup analyses were performed by varying the relative effectiveness for PFS based on HR's retrieved from the E2100 trial.²²

Probabilistic sensitivity analyses and value of information analysis

Probabilistic sensitivity analyses were performed to reflect the uncertainty of the input parameters on the outcomes. Cost-effectiveness acceptability curves were used to present the results of the probabilistic sensitivity analyses. Moreover, the expected value of perfect information (EVPI) was calculated to examine the maximum amount that society should be willing to pay for further evidence to reduce available uncertainty.¹¹ The population EVPI was calculated by multiplying the EVPI per patient by the effective population in the next 10 years (the expected life span of the technology) and discounting this by a rate of 4%. The effective population was calculated based on a yearly incidence of 1,219 metastatic breast cancer in the Netherlands.²³ This incidence was obtained based on a total incidence of 3,250 metastatic breast cancer multiplied by the proportion of HER2-negative patients (75%) and the proportion of patients expected to be eligible for chemotherapy (50%).

Results

In both the real-world and trial scenarios bevacizumab-taxane is more expensive (incremental costs of €56,213 and €52,750 respectively) and more effective (incremental QALYs of 0.362 and 0.189 respectively) than taxane monotherapy. This resulted in ICERs of €155,261 and €278,711 per QALY gained for the real-world and trial scenario respectively (Table 7.4).

In both scenarios, the majority of the incremental costs could be attributed to the difference in first-line treatment costs. However, bevacizumab-taxane treatment costs (€52,917 versus €59,445) as well as the total incremental treatment costs (€45,376 versus €50,988) (costs real-world versus trial scenario respectively) were smaller in the real-world scenario as compared to the trial scenario due to differences in OTT between the scenarios (OTT for bevacizumab was shorter in the real world scenario). The incremental costs associated with the progressive disease health state were, however, larger in the real-world scenario (Table 7.4).

The incremental QALYs and LYs were larger for the real-world scenario compared with the trial scenario (0.362 and 0.628 versus 0.189 and 0.289). This was mainly due to the larger incremental LYs in the progressive disease health state (Table 7.4).

In the one-way sensitivity analyses the ICER ranged between €146,294 - €190,535 and €236,552 - €324,438 for the real-world and trial scenario analyses, respectively. For the explorative subgroup analyses these ranges were €146,184 - €176,136 and €254,615 - €319,081 respectively (Appendix 7.2).

Table 7.4 Base case results for real-world and trial scenario.

	Real-world scenario			Trial scenario		
	Costs (95% CI)	LYs (95% CI) ^a	QALYs (95% CI) ^a	Costs (95% CI)	LYs (95% CI) ^a	QALYs (95% CI) ^a
Bevacizumab-taxane						
Treatment	€52,917 (€42,730 - €64,517)			€59,445 (€55,927 - €63,206)		
Progression free	€13,687 (€9,362 - €19,851)	0.704 (0.491 - 1.010)	0.460 (0.307 - 0.671)	€20,313 (€16,586 - €25,191)	1.067 (0.963 - 1.183)	0.697 (0.573 - 0.825)
Progressive disease	€58,892 (€40,119 - €81,650)	2.538 (1.836 - 3.37)	1.318 (0.818 - 1.932)	€39,611 (€28,608 - €53,648)	1.665 (1.296 - 2.144)	0.876 (0.571 - 1.254)
Total	€125,496 (€104,870 - €150,355)	3.242 (2.599 - 4.029)	1.778 (1.292 - 2.372)	€119,369 (€107,416 - €133,962)	2.732 (2.384 - 3.198)	1.573 (1.25 - 1.954)
Taxane monotherapy						
Treatment	€7,541 (€5,962 - €9,346)			€8,456 (€7,832 - €9,116)		
Progression free	€9,272 (€5,573 - €14,865)	0.385 (0.251 - 0.578)	0.253 (0.160 - 0.387)	€16,221 (€11,132 - €23,230)	0.710 (0.579 - 0.868)	0.465 (0.357 - 0.593)
Progressive disease	€52,469 (€31,012 - €81,916)	2.229 (1.335 - 3.494)	1.164 (0.631 - 1.919)	€41,941 (€30,099 - €58,031)	1.733 (1.334 - 2.313)	0.918 (0.587 - 1.335)
Total	€69,282 (€47,735 - €98,285)	2.614 (1.747 - 3.867)	1.416 (0.889 - 2.156)	€66,619 (€53,909 - €82,948)	2.443 (2.082 - 2.999)	1.384 (1.054 - 1.799)
Increment						
Treatment	€45,376 (€34,966 - €57,008)			€50,988 (€47,441 - €54,787)		
Progression free	€4,415 (€-175 - €9,483)	0.319 (0.197 - 0.481)	0.208 (0.124 - 0.318)	€4,092 (€-3,670 - €10,846)	0.357 (0.204 - 0.498)	0.231 (0.131 - 0.332)
Progressive disease	€6,422 (€-13,806 - €22,927)	0.309 (-0.691 - 1.078)	0.154 (-0.338 - 0.567)	€-2,330 (€-16,825 - €11,476)	-0.068 (-0.748 - 0.563)	-0.042 (-0.396 - 0.282)
Total	€56,213 (€33,510 - €76,933)	0.628 (-0.377 - 1.383)	0.362 (-0.133 - 0.766)	€52,750 (€36,712 - €67,459)	0.289 (-0.368 - 0.897)	0.189 (-0.157 - 0.506)
ICER			€155,261			€278,711

ICER, incremental cost effectiveness ratio ^a Undiscounted.

At a threshold of €80,000 per QALY gained, the probability that the bevacizumab-taxane treatment strategy was cost-effective compared to taxane monotherapy as a first-line treatment in patients with HER2-negative metastatic breast cancer was 1% in the real-world scenario and < 1% in the trial scenario. The EVPI analysis showed that the maximum value of additional research amounted to €367,000 and €2,000 in the real-world and trial scenarios respectively.

Discussion

The real-world cost-effectiveness of bevacizumab added to taxane chemotherapy as first-line treatment of HER2-negative metastatic breast cancer was assessed in this study. Two scenarios were examined: a real-world scenario and a trial scenario. These analyses showed that bevacizumab-taxane therapy compared to taxane monotherapy led to ICERs of €155,261 and €278,711 per QALY gained for the real-world and trial scenario respectively. At a threshold of €80,000 per QALY gained the probability that bevacizumab-taxane therapy is cost-effective is nearly zero. As a result, further research into the cost-effectiveness of bevacizumab-taxane treatment strategy compared to taxane monotherapy as a first-line treatment in patients with HER2-negative metastatic breast cancer, to reduce available uncertainty, is unlikely to be worthwhile.

The real-world scenario analysis was hampered by the low number of patients in both treatment groups ($n = 29$ for bevacizumab-taxane, and $n = 33$ for taxane monotherapy), leading to uncertainty in the assessment of the survival and the health state costs of these patients. For that reason and to prevent confounding by indication, we based the relative efficacy of bevacizumab use on the E2100 trial results.² Conversely, the effects for the trial scenario were based on a large randomized clinical trial, including a more restricted patient population than in the real-world setting, but this additional analysis resulted in an even higher ICER for the addition of bevacizumab. This is probably due to different patient selection in a clinical trial versus the real world situation.

The results of the trial scenario were in line with previous cost-effectiveness analyses reported in the literature for Switzerland (ICER = €189,427 per QALY gained⁷), for the US (\$745,000 and \$232,720 per QALY gained^{8,9}) and for the UK (£117,803 per QALY gained versus paclitaxel monotherapy²⁴). Effectiveness in these cost-effectiveness analyses was based on the E2100 trial. None of the studies indicated that bevacizumab is cost-effective based on a threshold of €80,000 per QALY gained.^{20,25}

The relative (cost-)effectiveness of bevacizumab with taxane chemotherapy in patients with HER2-negative metastatic breast cancer patients could potentially be improved by prospective evaluation of biomarkers for response (such as VEGF-A) and better selection in real-life biological breast cancer subgroups.²⁶

Another element in the (financial) sustainability of cancer treatment in health care systems are the costs of the vastly increasing number of cancer treatments and drugs.²⁷ Besides that, recent evaluations of actual costs of cancer drugs noted substantial price differences in cancer drugs in several European countries.^{28,29} This could lead to an imbalance in costs and effectiveness and eventually the availability of promising new drugs in several countries. Performance-based risk sharing agreements, informed by real life effectiveness and cost-effectiveness evaluations, could be used to mitigate risk of financial sustainability and inequality in access to care.³⁰

In conclusion, this is the first report on cost-effectiveness of bevacizumab based on real-world data. Given that the cost-effectiveness estimates were robust in several scenarios, sensitivity and subgroup analyses, we concluded that the addition of bevacizumab is not cost-effective for metastatic breast cancer patients in daily practice in the Netherlands.

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Appendix 7.1

Indirect treatment comparison for progression free survival

	HR	Distribution	95%CI	Source
HR (BV-Pac q2w vs. Pac q1w)	0.483	LogNormal	0.385 - 0.607	[1]
HR (Pac q3w vs. Pac q1w)	1.430	LogNormal	0.600 - 0.815	[2]
HR (Pac q1w vs. Pac q3w)	0.699	LogNormal	1.330 - 2.020	[3]
HR (BV-Pac q2w vs. Doc q3w)	0.554			
HR (Doc q3w vs. BV-Pac q2w)	1.805			

HR, hazard ratio; 95%CI, 95% confidence interval; BV, bevacizumab; Pac, paclitaxel; Doc, docetaxel; vs., versus.

Appendix 7.2

Tornado diagrams for one-way sensitivity and explorative subgroup analyses (both deterministic)

Tornado diagram one-way sensitivity analyses for real-world scenario

Tornado diagram explorative subgroup analyses for real-world scenario

Tornado diagram one-way sensitivity analyses for trial scenario

Tornado diagram explorative subgroup analyses for trial scenario

Chapter 8

**Summary, general conclusions and
future perspectives**

Summary

Metastatic breast cancer is a major health issue and 500 000 patients die of the disease worldwide annually. Data on prognosis and treatment of real-life patients with metastatic breast cancer are needed to improve quality of care and to improve their outcome. However, most clinical breast cancer research relates to the early breast cancer setting rather than the metastatic disease setting. Moreover, most studies on management of metastatic breast cancer make use of results from intervention trials instead of addressing actually delivered treatment and outcome in the real-world breast cancer setting. This thesis focused on the treatment and prognosis of the metastatic breast cancer population in every-day clinical practice.

In **chapter 1**, an introduction on metastatic breast cancer and an outline of this thesis are provided.

The aim of the first part of the thesis was to determine the prognosis of breast cancer patients in real-life, classified by hormone receptor and human epidermal growth factor receptor 2 (HER2) status. In addition, the size and relevance of other prognostic factors, such as the metastatic-free interval and histology, were determined with regard to actual treatment choices and outcome.

The second part of the thesis focused on treatment of metastatic breast cancer. We were interested in treatment patterns in real-life, that is the first given palliative systemic therapy in patients with hormone receptor positive metastatic breast cancer. Further, we studied the implementation of a new agent, bevacizumab, for the treatment of metastatic breast cancer in the Netherlands, and we assessed the real-life cost-effectiveness of this agent.

In **chapter 2**, we present the survival outcome of patients with metastatic breast cancer per subtype, based on the hormone receptor and HER2 status.

All 815 patients consecutively diagnosed with metastatic breast cancer in the participating hospitals of the Southeast Netherlands Breast Cancer Consortium were categorized into four subtypes based on the hormone receptor and HER2 status of the primary tumor: 1. hormone receptor-positive (defined as estrogen and/or progesterone receptor positive)/HER2-negative, 2. hormone receptor-positive/HER2-positive, 3. hormone receptor-negative/HER2-positive and 4. hormone receptor-negative and HER2-negative, that is, triple negative. Primary study objective was the median survival time of patients with distant metastases according to breast cancer subtype. Overall survival was defined as survival from date of first distant metastasis. We used a Cox proportional hazards model to determine the prognostic impact of breast cancer subtypes and to adjust for potential confounders.

We found that patients with the hormone receptor-positive/HER2-positive subtype had the longest median survival (34.4 months), compared to 24.8 months for the hormone receptor-positive/HER2-negative subtype, 19.8 months for the hormone

receptor-negative/HER2-positive subtype and 8.8 months for the triple negative subtype ($P < 0.0001$). In the multivariable analysis, breast cancer subtype was an independent prognosticator for overall survival. The hormone receptor-positive/HER2-positive subtype was associated with the best outcome with a hazard ratio of 0.64 (95% CI 0.45-0.92), as compared to the hormone receptor-positive/HER2-negative subtype. A metastatic-free interval of ≥ 24 months was also associated with a significantly improved survival (hazard ratio of 0.62; 95% CI 0.50-0.75). Prior adjuvant systemic therapy and age at initial breast cancer diagnosis of ≥ 50 years were statistically significant unfavorable prognostic factors. Also initial metastatic site was an important prognostic factor, with visceral, brain or multiple metastatic sites being unfavorable as compared to bone as initial metastatic site.

We concluded that in metastatic breast cancer, in addition to previously reported factors, the breast cancer subtype significantly affects outcome, with the hormone receptor-positive/HER2-positive subtype nowadays being associated with the most favorable prognosis.

In **chapter 3**, the focus of the study is the prognostic impact of metastatic-free interval, which was defined as the time between primary breast cancer diagnosis and detection of distant metastasis.

All 815 patients consecutively diagnosed with metastatic breast cancer in the participating hospitals of the Southeast Netherlands Breast Cancer Consortium were included and classified by the metastatic-free interval into three categories: patients with *de novo* metastatic breast cancer (that is, diagnosis of distant metastasis at time of primary breast cancer diagnosis), patients with metastatic breast cancer diagnosed within 24 months after primary diagnosis and patients with a metastatic-free interval of more than 24 months. A Cox proportional hazards model was used to determine the prognostic impact of metastatic-free interval on survival, adjusted for age, hormone receptor and HER2 status, initial site of metastasis and use of prior (neo-) adjuvant systemic therapy.

Patients with *de novo* metastatic breast cancer ($n = 154$) had a significantly better outcome in terms of overall survival compared to patients with a metastatic-free interval of 24 months or less ($n = 176$) ($P < 0.0001$). Interestingly, survival of patients with *de novo* metastatic breast cancer was not different from those that had a metastatic-free interval of more than 24 months ($n = 485$) ($P = 0.73$). Also after adjusting for other prognostic factors as aforementioned, patients with *de novo* metastatic breast cancer (hazard ratio 1.97, 95% CI 1.49-2.60, $P < 0.0001$) had a better outcome as compared to patients with a metastatic-free interval of 24 months or less. The association between metastatic-free interval and survival was observed irrespective of use of (neo-)adjuvant systemic therapy.

So in conclusion, in real-life metastatic-free interval was strongly related to metastatic breast cancer outcome. Most important, *de novo* metastatic breast cancer was not found to be an unfavorable prognostic subgroup, in contrast to the subgroup that had

a short metastatic-free interval with a distant recurrence within 24 months after diagnosis and initial treatment.

In **chapter 4**, we report the results of a study on the role of histological subtype on the prognosis and treatment of metastatic breast cancer.

We selected all patients with hormone receptor-positive metastatic breast cancer diagnosed in the years 2007-2009 in the participating hospitals in the Southeast Netherlands Breast Cancer Consortium and classified them based on the histological breast cancer subtype, either invasive ductal carcinoma ($n = 437$) or (mixed) invasive lobular carcinoma ($n = 131$). We analyzed the outcome of these two histological breast cancer subtypes after a median follow-up of 37.1 months.

Patients with invasive lobular carcinoma were older at diagnosis of primary breast cancer, had larger primary tumors and were slightly more likely to have node-positive disease compared to patients with invasive ductal carcinoma.

Patients with invasive lobular carcinoma had more often initial bone metastasis (46.5% versus 34.8%, $P = 0.01$) and less often multiple metastatic sites compared to patients with invasive ductal carcinoma (23.7% versus 30.9%, $P = 0.11$). Despite these differences, overall survival after diagnosis of distant metastasis was not different for invasive lobular carcinoma versus invasive ductal carcinoma (median 29 and 25 months, respectively, $P = 0.53$). There were, however, differences in treatment patterns between patients with invasive lobular carcinoma and those with invasive ductal carcinoma. Six months after diagnosis of metastatic breast cancer, 28.1% of patients with hormone receptor-positive lobular carcinoma and 39.8% of patients with hormone receptor-positive ductal carcinoma had received chemotherapy with a longer median time to first palliative chemotherapy for those with lobular carcinoma ($P = 0.001$). After six months, 84.8% of patients with lobular carcinoma had received endocrine therapy compared to 72.5% of patients with invasive ductal carcinoma ($P = 0.0001$).

Our results confirmed that, in addition to hormone receptor status, histology correlates with presentation of metastatic disease by number and type of distant metastatic sites, and thereby affects treatment-decision making in real-life.

The study described in **chapter 5** assessed the initial palliative systemic treatment choices made in real-life for patients with hormone receptor-positive, HER2-negative metastatic breast cancer. Furthermore, progression-free and overall survival according to the initial systemic treatment choices - chemotherapy or endocrine therapy - was determined, after adjusting for known prognostic factors.

In total, 520 metastatic breast cancer patients with hormone receptor-positive, HER2-negative breast cancer were included. Ninety-three percent of these patients ($n = 482$) received any palliative systemic therapy during the observation period: 116 patients received palliative chemotherapy as first-given palliative systemic treatment and 366 patients received initial palliative endocrine therapy. The patients with initial

chemotherapy were significantly younger, had less comorbidity, had received more prior adjuvant systemic treatment and were less likely to have bone metastasis compared to patients with initial endocrine therapy. Median progression-free survival for patients treated with initial palliative chemotherapy was 5.3 months (95% CI 4.2-6.2 months) compared to a median progression-free survival for patients treated with initial endocrine therapy of 13.3 months (95% CI 11.3-15.5 months). Median overall survival for patients treated with initial chemotherapy was 16.1 months versus 36.9 months for patients treated with initial endocrine therapy. Also after adjustment for prognostic factors, initial chemotherapy was associated with a worse outcome in terms of progression-free survival (hazard ratio 2.33, 95% CI 1.77-3.08, $P < 0.0001$) and overall survival (hazard ratio of 2.24, 95% CI 1.64-3.06, $P < 0.0001$).

We concluded that a high percentage of patients with hormone receptor-positive metastatic breast cancer received chemotherapy as initial palliative therapy in real-life. Initial chemotherapy was associated with a worse outcome compared to initial endocrine therapy, although this does not necessarily indicate that chemotherapy is less effective.

In **chapter 6**, we described the real-world use and effectiveness of bevacizumab in combination with taxane chemotherapy as first-line treatment regimen for patients with HER2-negative metastatic breast cancer.

We included all HER2-negative metastatic breast cancer patients from the participating hospitals of the Southeast Netherlands Breast Cancer Consortium ($n = 650$) and focused on patients receiving first-line palliative chemotherapy ($n = 332$).

There were 193 patients treated with first-line chemotherapy after the introduction of bevacizumab in the Netherlands and 17% of these patients actually received bevacizumab. The patients receiving bevacizumab were younger, showed a trend towards having less cardiovascular comorbidities, had a longer metastatic-free survival and were more likely to have hormone receptor-positive breast cancer (82%) than patients not receiving bevacizumab. Further, patients who received first-line chemotherapy with bevacizumab more often had received prior (neo-) adjuvant systemic therapy and were more likely to have multiple initial metastatic sites compared to patients treated with other first-line chemotherapeutic regimens. Twenty-four percent of patients treated with bevacizumab had a (relative) contra-indication or did not confer with applicable registration indications for bevacizumab, such as no prior treatment with anthracyclines in the absence of contra-indications for anthracyclines. The median progression-free survival of patients treated with bevacizumab was 6.0 months (95% CI 4.8-13.1) and median overall survival was 28.4 months (95% CI 14-undetermined).

This study shows that bevacizumab was less frequently administered than expected and potentially indicated in this large Dutch real-world cohort. Progression-free survival of first-line bevacizumab in combination with taxane chemotherapy was shorter than the progression-free survival rates reported in the registration trials, but

overall survival was comparable between the real-life cohort and the registration trials.

In **chapter 7**, we presented a real-world cost-effectiveness analysis of bevacizumab in addition to taxane versus taxane monotherapy in HER2-negative metastatic breast cancer patients.

A state transition model was built to estimate costs, life years and quality-adjusted life years (QALYs) for both treatment options. Two scenarios were used; a real-world scenario and a trial-based scenario in which transition probabilities were primarily based on a real-world cohort study and the E2100 trial respectively. Costs and utility parameter estimates were extracted from the real-world cohort study for both scenarios. A health care perspective was adopted.

For both the real-world and trial-based scenario the addition of bevacizumab to taxane was more effective (incremental QALYs of 0.362 and 0.189 respectively), but also more expensive (incremental costs of €56,213 and €52,750 respectively). This led to an incremental cost-effectiveness ratio of €155,261 per QALY gained in the real-world scenario and an incremental cost-effectiveness ratio of €278,711 per QALY gained in the trial-based scenario. In the one-way sensitivity analyses the incremental cost-effectiveness ratio ranged from €146,294 to €190,535 for the real-world scenario and from €236,552 to €324,438 for the trial-based scenario.

We concluded that the addition of bevacizumab to taxane monotherapy for HER2-negative metastatic breast cancer is not cost-effective in daily practice in the Netherlands.

In **chapter 8** a summary on the thesis is provided, followed by the general concluding remarks and future perspectives on metastatic breast cancer.

General conclusions and future perspectives

In this thesis we provided detailed information on a real-world cohort of patients with metastatic breast cancer. We addressed real-life outcome and prognostic factors, treatment patterns, as well as the implementation and cost-effectiveness of a new treatment option. All the results presented in this thesis are derived from a large, multicenter database including all patients consecutively diagnosed with metastatic breast cancer between 2007 and 2009 in eight hospitals in the Southeast region of the Netherlands, which participate in the Southeast Netherlands Breast Cancer Consortium.

Population-based studies, such as the cohort study on which this thesis is based, are a valuable addition to clinical trial data.¹ Their added value is based on the fact that only a small percentage of all patients with metastatic breast cancer participate in intervention trials.² As a consequence, data from randomized clinical trials are based on a selection of patients and therefore the results are not directly transferable to the real-life metastatic breast cancer setting. Population-based cohort studies are thus essential in order to provide a complete view on prognosis and outcome, by also including those patients who are treated outside the framework of a clinical trial. Hence, large population-based studies provide information on use, effectiveness and toxicity of a treatment in daily practice, which can help in translating data from clinical trials to real-life patients and thereby in improving quality of care.³

As summarized above, our population-based cohort study addressed several important research questions on real-life management and outcome of metastatic breast cancer. Currently, our large dataset of Dutch metastatic breast cancer patients is expanded by the inclusion of more recent cohorts, as well as the addition of more participating hospitals in the Netherlands. This unique dataset provides many opportunities for future research. Not only will we continue to use the observational data to provide insight into the implementation and real-world use of new treatment options, but also we will focus more extensively on the breast cancer subgroups to determine new prognostic and predictive factors. Our future research will increasingly focus on the efficient allocation of treatments, reasons for variation in treatment patterns and consequences in terms of outcome for patients with metastatic breast cancer.

Our first study provided insight into the prognosis of patients with metastatic breast cancer, diagnosed and treated in every day clinical practice. This information is not only essential to help inform future patients, but accurate prognostic and predictive information is also helpful for clinicians to guide treatment decisions.

In early breast cancer, different prognostic factors are used to select patients with a high risk of recurrence who are most likely to benefit from adjuvant systemic therapy and to identify patients with a low risk of recurrence in whom potential toxic

treatment may be avoided. These prognostic factors, which include patient and tumor characteristics, are used in guidelines and clinical tools, such as New Adjuvant! Online, to estimate the risk of recurrence and estimate the benefit of adjuvant systemic treatment. More recently, genetic profiling techniques became available and data on multiple gene profiling assays, including the 70-gene signature and the 21-gene assay, have been demonstrated to provide additional information on risk of recurrence and to be of additional prognostic value in comparison with the classical clinicopathological factors and clinical tools.⁴⁻⁹

However, the question remains whether the genetic profile of a tumor can also predict response to treatment and could thus be helpful in guiding treatment decisions for individual breast cancer patients. Recently, a prospective study on the 21-gene expression assay showed that in patients with hormone receptor-positive, HER2-negative, lymph node negative early breast cancer low rates of recurrences were found when receiving endocrine therapy alone, despite the treatment guidelines of the American National Cancer Comprehensive Network (NCCN), recommending the use of adjuvant chemotherapy based on clinicopathological factors.¹⁰ The Dutch guideline on systemic treatment recommendations for early breast cancer is more restrictive compared to the American NCCN guideline, based on the recommendation that chemotherapy is only justified if an absolute risk reduction of around 4% of the 10-year mortality can be expected.¹¹ However, also the Dutch guideline recommends chemotherapy in patients with a high-risk profile based on clinicopathological factors. Prospective randomized trial results on the value of genetic profiling in selection of early breast cancer patients for adjuvant therapy are eagerly awaited, although it remains to be seen how these data translate to the Dutch situation. In the meantime, breast cancer classification based on nodal status, hormone receptor and HER2 status, histological grade or Ki-67 is being used in real-life clinical practice.¹²

In metastatic breast cancer less is known about the impact of breast cancer genetic profiling and subtypes. We showed that the breast cancer subtypes based on hormone receptor and HER2 status both have a prognostic and predictive impact in patients with metastatic breast cancer. Prognostic impact relates to the prognosis when not treated with a specific targeted therapy. Predictive impact relates to the effectiveness of targeted treatment: in patients with hormone receptor-positive disease endocrine treatment may be effective, whereas it is not effective in hormone receptor-negative disease. Similarly, in HER2-positive disease HER2-targeted therapy is of relevance, whereas HER2-targeted therapy is not effective in patients with HER2-negative disease.

Our study showed that patients with HER2-positive tumors that are also hormone receptor-positive nowadays have the longest median survival, compared to the other metastatic breast cancer subgroups. Actually, they have a much more favorable disease course than a decade or two ago, which could well be the reflection of improved treatment options. Hence, as was also shown in a study by Dawood *et al.*,

the outcome HER2-positive breast cancer has improved substantially in an era in which HER2-targeted therapy is widely available.¹³

There is an urgent need for additional predictive factors in order to better allocate systemic treatment to patients with metastatic breast cancer. However, despite the advances in genetic profiling, the hormone receptor and HER2 status of the tumor are still the only targetable options with prognostic and predictive value. Currently, more research is focusing on the identification of driver mutations in metastatic breast cancer, such as *TP53* and *PIK3CA* mutations. However, even if such driver mutations are established, many challenges still remain, and randomized clinical trials should be performed with targets for these mutations, taking into account the low incidence of these mutations and the need to screen multiple metastatic breast cancer patients.¹⁴ One of the ways forward is to create a dataset of molecular profiles of metastatic breast cancer. In the Netherlands, currently, genetic profiling of metastatic tumors is performed with next-generation DNA sequencing within the framework of the CPCT-02 study. It is expected that this will provide new predictive markers, to personalize treatment in the near future.

Besides breast cancer subtypes based on the hormone receptor and HER2 status, we investigated the prognostic impact of other clinical factors. One of the strongest prognostic factors we found was the metastatic-free interval, which is the time between primary breast cancer diagnosis and the detection of distant metastasis. In the Southeast Netherlands Breast Cancer Consortium cohort, patients with a metastatic-free interval of less than 24 months had a significantly worse outcome than patients with either *de novo* metastatic breast cancer (i.e. having distant metastasis at presentation of primary breast cancer) or patients with a metastatic-free interval of more than 24 months. The patients with a short metastatic-free interval, and thereby worse outcome, more often had histological grade 3 tumors and hormone receptor-negative tumors compared to patients with *de novo* metastatic breast cancer. Furthermore patients with a short metastatic-free interval initially had larger breast tumors (T2-T3) and were more likely to have axillary nodal involvement (N1-3) compared to patients with a metastatic-free interval of more than 24 months. Remarkably, the percentage of patients who previously had received (neo-) adjuvant chemotherapy was quite low (48%) in the group with a metastatic-free interval of less than 24 months. So, in hindsight, at least a percentage of these patients might have had a lower risk of distant recurrence if treated with systemic therapy. These patients had a primary diagnosis of breast cancer in the years 2005-2007. In the Dutch national breast cancer guidelines of 2002 and 2005 treatment recommendations were more conservative than nowadays.¹⁵ At least some of these patients would have been treated with adjuvant systemic therapy if diagnosed in 2016, and moreover, would have received more effective treatment. A large proportion of patients with early distant recurrence had triple-negative breast cancer for whom currently only chemotherapy is available as a treatment option. For patients with early stage, high

risk triple negative breast cancer with a known BRCA1/2 mutation one of the future treatment options could be the addition of poly(ADP-ribose)polymerase (PARP) inhibitors, as currently investigated in a phase III trial.¹⁶ So, future research should focus on developing more effective drugs for specific patient subgroups in order to prevent distant recurrences, in addition to a lower threshold for recommending (neo-) adjuvant chemotherapy. This requires improved identification of patients with primary breast cancer at risk for developing metastatic disease. Looking at the models of breast cancer metastatic spread, it is evident that the development of metastases is not only determined by clinicopathological factors but that the metastatic potential is also predicted by the molecular profile of the tumor cell, which is thought to be acquired early in the development of primary breast cancer.^{17,18} Furthermore, in animal models, genetic profiling can predict the risk of developing metastases in a specific organ.¹⁹ Knowledge on site-specific metastases may help provide new therapeutic targets and drugs in the future for prevention, but also on treatment strategies once distant recurrence has occurred. Future research within our large cohort will focus on gaining more insight in patterns of metastatic spread within the breast cancer subgroups.

Of further interest are patients with isolated and/or limited distant disease, for example patients with isolated liver metastases. In colorectal cancer studies, it has been shown that patients with isolated liver metastases treated with additional local treatments, such as surgical resection, have a median overall survival of 3.6 years.²⁰ Considering this favorable figure, resection of liver metastases is recommended in the current guidelines for a subset of patients with colorectal cancer.²¹ For breast cancer, evidence thus far also suggests a role for surgical resection of liver metastases in selected patients, although the number of suitable candidates is much smaller than in colorectal cancer.²² A future direction for improving outcome of patients with metastatic breast cancer may be to focus on this specific subgroup and to discuss the best treatment strategy in a multi-disciplinary dedicated team of breast cancer specialists. Ongoing collection of real-life data on metastatic breast cancer patients is essential for analyzing new treatment strategies.

The need for information on disease course and prognostic factors is important in the treatment-decision making process. Moreover, knowledge on the current use and effectiveness of available treatment options is also a key factor in making well-substantiated decisions about the optimal allocation of therapeutic agents and resources for patients with metastatic breast cancer in the future. One of the studies from this thesis focused on the initial palliative treatment for metastatic breast cancer and led to some interesting observations. Even in the presence of hormone receptor-positive disease, a large percentage of patients received initial chemotherapy for their metastatic disease. This is contrary to the guideline recommendations to start initial endocrine therapy for all patients with hormone-receptor positive disease, unless

immediate tumor reduction is needed.²³⁻²⁵ These patients did not only receive potentially more toxic treatment, their outcome was also worse compared to patients starting treatment with endocrine therapy, even after adjusting for known prognostic factors. Even though the presence of unidentified prognostic parameters could have had some influence as well, this may very well be the result of less than optimal use of available endocrine treatment options. This real-life information on treatment patterns stresses the need to raise awareness on the use of different treatment options in daily clinical practice. Furthermore, these data offer the opportunity to monitor implementation of guidelines and the adherence to them. From studies in early breast cancer it is known that proper adherence to guidelines is associated with a better outcome.^{26,27} Therefore, in our view this study shows that there is still room for improvement in the allocation of currently available treatments for patients with hormone-receptor positive metastatic breast cancer. And we also believe that spreading and discussing these results are essential if we want to improve the outcome of patients with metastatic breast cancer. Future research should focus more extensively on the implementation of guidelines and on the reasons for non-adherence.

The identification of other factors that play a role in deciding between available palliative systemic treatments is also one of the aims of our ongoing cohort study. One of the other interesting observations on treatment patterns was found in our study on histological subtype. Despite the fact that histological subtype is not taken into account in current breast cancer treatment guidelines, we found differences in treatment patterns between patients with invasive lobular and invasive ductal hormone-receptor positive metastatic breast cancer. Even though outcome was similar, patients with ductal carcinoma were more likely to receive chemotherapy and also more likely to receive chemotherapy earlier in the disease course. This could well be the reflection of differences in patient and tumor characteristics, such as age and metastatic site. But, interestingly, in early breast cancer more and more data are presented on the possible predictive role of tumor histology, with evidence of a lower response to chemotherapy and a higher efficacy of endocrine therapy for lobular carcinoma compared to ductal carcinoma.²⁸⁻³⁰ Since, there are no other data available on the role of tumor histology in metastatic breast cancer treatment, further research is needed in establishing if histology could be helpful as a predictive factor for the response to systemic treatment.

Our cohort study underlines the need for more guidance on treatment-decision making in metastatic breast cancer. Even though new advances in molecular profiling are promising, current treatment decisions in metastatic breast cancer are still largely based on classical clinicopathological features. One of the future research projects resulting from the cohort-based studies in this thesis is to develop a simple and effective clinical tool, such as a nomogram, to help inform our patients about their

prognosis and guide our treatment decisions. Another simple, but effective method to help guide treatment decisions is to discuss all metastatic breast cancer patients in a multidisciplinary tumor board with dedicated breast cancer specialists, which is currently standard of care for all early breast cancer patients in the Netherlands.

Besides prognostic and predictive factors, disease course, treatment patterns and guideline adherence, there should be more focus on other aspects of metastatic breast cancer in research. We addressed the implementation of a new treatment regimen, as well as the cost-effectiveness of this regimen in real-life. It is apparent that these data can only be generated from a population-based cohort, such as our metastatic breast cancer cohort. With the recent debate on the increasing costs of cancer care it is essential to gather information on real-world allocation, efficacy, toxicity, quality of life and cost-effectiveness of newly developed treatment regimens for metastatic breast cancer.

There is a need to determine health care value of cancer drugs, which is complicated by the rapidly increasing number of cancer treatment options, with the associated increase in health care costs. Recently, initiatives from the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were published to introduce methods to determine the clinical value and benefit of a cancer treatment regimen.^{31,32} Clinical value is not only determined by efficacy and toxicity, it is also determined by the costs of the treatment.

In the Netherlands, an algorithm is used with preset limits of clinical relevant gains, to help medical decision making in the evaluation of new drugs. The members of the Dutch Medical Oncology association developed the PASQUIL algorithm to determine the clinical relevance of a therapeutic drug, comprising specific criteria for **P**alliative treatment, **A**djuvant therapy, **S**ide effects, **Q**uality of life, **I**mpact of treatment and **L**evel of evidence and cost.³³ The criteria were recently revised in March 2016. According to the currently used criteria, for instance for palliative treatment, improvements in progression-free and overall survival of at least 3 months and/or a hazard ratio of <0.7 is preferable, taking into consideration the type of cancer and the expected survival as well as the number of treatment lines. For adjuvant treatment, a difference in 5-years survival of at least 5% and/or a hazard ratio of <0.7 compared with control was chosen as the minimal limit of benefit. Further, it was agreed that treatment-related mortality should not exceed 5%, that the incidence of grade 3-4 side effects should remain below 25% and that less than 10% of patients should have long lasting side effects with an impact on daily living. These set limits to determine relevant clinical gains of a therapeutic drug are compared to the current standard of care and also take into account the quality of the study investigating the therapeutic drug, indicating the level of evidence. Lastly, costs of the treatment regimen are reported. All these criteria may help us to discuss the health care value of this new drug. In contrast to the relative constant clinical benefit, the health care value may

differ between countries and health care systems since costs of drugs are known to differ between countries.³⁴

The goal for the future should be to make drugs with a clear clinical benefit available to all patients with metastatic breast cancer at acceptable costs; i.e. the costs of a new cancer treatment option should have relevance to the clinical benefit for the patients in terms of efficacy and quality of life. There are several steps which can help us to attain that goal.

First of all, pricing of the drugs should be made transparent and health care authorities, medical oncologists, researchers and the pharmaceutical industry should work together with the goal to develop new cancer drugs at an affordable cost price.

Furthermore, the development of new cancer drugs is rapidly changing in this era of personalized medicine, in which genomic alterations with actionable targets can provide the basis for targeted therapy.³⁵ This development can lead to the availability of more effective drugs and thereby may improve cost-effectiveness of treatment.

Currently, development of a new cancer drug is an extremely slow process and it takes around 8-10 years before a new drug is registered for approval. This process starts with a phase I trial to establish the maximum tolerated dose before moving to phase II and III trials to establish clinical efficacy. In breast cancer, large randomized trials with long follow-up are needed to establish efficacy, thereby preventing quick access of efficacious cancer drugs to the breast cancer patients. And if these large trials fail to establish efficacy, the high costs of the development of this drug poses an impact on the development of the next drug, even though the drug could be of value in a subset of patients or in combination with other drugs. On the other hand, if efficacy of a drug is established in a large trial and it becomes available for the treatment of metastatic breast cancer, it could well be that some patients do not experience the expected benefit, but are still exposed to a potentially toxic treatment which can lead to higher health care costs.³⁶ This clearly indicates the need to develop new trial designs based on the molecular basis of breast cancer to guarantee a more efficient allocation of the drug. When stratifying patients by targetable alterations a drug can be tested in a smaller population and in a shorter time, which could result into the conditional approval of the drug. When new drugs can be conditionally approved and thereby become available earlier, it is critical that we use them efficiently in daily practice, according to the registered indication, and that we establish if the use of the drug will benefit the patient at acceptable toxicity and costs. In order to study the implementation, use, efficacy, toxicity and costs in daily practice, our population-based cohort is a unique and essential addition to the trial results.

In conclusion, metastatic breast cancer is a heterogeneous disease and more awareness should be brought to this group of breast cancer patients focusing on the large pallet of relevant issues; prognosis, treatment, implementation and adherence, cost-effectiveness and more importantly quality of life.³⁷

We hope this thesis on real-life data of metastatic breast cancer patients will lead to more understanding of prognostic and predictive factors, treatment patterns, disease course and outcome in real-life and that this insight stimulates new developments. It is only by collaboration of dedicated breast cancer specialists, research groups and patients and their advocates that we can make progress in improving the prognosis of patients with metastatic breast cancer.

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Samenvatting

Samenvatting

Het mammacarcinoom is de meest voorkomende maligniteit bij vrouwen, met wereldwijd een jaarlijkse incidentie van 1,67 miljoen. De prognose van patiënten met een mammacarcinoom is in de afgelopen jaren verbeterd, maar desondanks is het de belangrijkste doodsoorzaak voor vrouwen tussen de 40 en 60 jaar. Ongeveer 20% van alle patiënten met een mammacarcinoom ontwikkelt metastasen op afstand en 5% van alle patiënten die de diagnose mammacarcinoom krijgt, heeft al metastasen op het moment van vaststellen van de diagnose. Zodra er metastasen op afstand zijn vastgesteld is er in principe geen kans op curatie en is de mediane overleving tussen de 2 en 3 jaar.

Om de kwaliteit van zorg voor de patiënten met gemetastaseerd mammacarcinoom te verbeteren is meer kennis nodig over de prognose en gegeven behandeling in de dagelijkse praktijk. Echter, het grootste deel van het observationele en experimentele klinisch onderzoek naar mammacarcinoom gaat over patiënten met een vroeg stadium mammacarcinoom en niet over patiënten met gemetastaseerde ziekte. Verder wordt de behandeling van gemetastaseerd mammacarcinoom met name gebaseerd op gerandomiseerd interventie onderzoek, terwijl bekend is dat in de dagelijkse praktijk maar een klein deel van de patiënten met gemetastaseerd mammacarcinoom participeert in deze onderzoeken. Meer inzicht in de gegeven behandeling en uitkomsten daarvan in de dagelijkse praktijk is dan ook nodig.

In dit proefschrift worden de resultaten beschreven van onderzoek naar de prognose en behandeling van patiënten met gemetastaseerd mammacarcinoom in de dagelijkse praktijk. Alle resultaten beschreven in dit proefschrift zijn gebaseerd op een groot multi-center cohortonderzoek waarin alle patiënten zijn geïnccludeerd die zijn gediagnosticeerd met gemetastaseerd mammacarcinoom tussen 2007 en 2009 in de acht deelnemende ziekenhuizen in de regio Zuidoost Nederland, het zogenoemde Zuidoost Nederlands Borstkanker Consortium.

In **hoofdstuk 1** wordt een introductie gegeven ten aanzien van dit proefschrift en wordt de opbouw van het proefschrift uitgelegd.

Het doel van het eerste deel van dit proefschrift is het bepalen van de prognose van patiënten met gemetastaseerd mammacarcinoom in de dagelijkse praktijk. Omdat we weten dat hormoonreceptor- en HER2-status prognostisch belangrijke kenmerken zijn, is de prognose bepaald per subgroep op basis van hormoonreceptor- en HER2-status. Daarnaast is er gekeken naar de relevantie van andere prognostische factoren, zoals het metastasevrij interval en het histologische subtype van de tumor, in relatie tot de gegeven systemische behandeling.

Het tweede deel van dit proefschrift focust op de behandeling van het gemetastaseerd mammacarcinoom. Hierbij hebben we gekeken naar de eerst

gegeven systemische therapie aan patiënten met een hormoonreceptor-positieve tumor.

Tevens hebben we de implementatie van een nieuw middel, bevacizumab, in de behandeling van gemetastaseerd mammacarcinoom onderzocht. Ook hebben we de kosteneffectiviteit van dit middel in de dagelijkse praktijk berekend.

In **hoofdstuk 2** tonen we de overleving van patiënten met gemetastaseerd mammacarcinoom per subgroep. Alle 815 patiënten die gediagnosticeerd zijn met gemetastaseerd mammacarcinoom in de deelnemende ziekenhuizen werden ingedeeld in 4 subgroepen gebaseerd op de hormoonreceptor- en HER2-receptor-status van de primaire tumor: 1. hormoonreceptor-positief (gedefinieerd als oestrogeen- en/of progesteronreceptor-positief)/HER2-negatief, 2. hormoonreceptor-positief/HER2-positief, 3. hormoonreceptor-negatief/HER2-positief en 4. hormoonreceptor-negatief en HER2-negatief (zogenoemde triple negatief mammacarcinoom). Het primaire onderzoeksdoel was om de mediane overleving per subgroep te onderzoeken. Overleving was gedefinieerd als tijd tussen datum van diagnose van metastasen op afstand tot overlijden. Middels een Cox proportional hazard model werd de prognostische impact van de subgroepen berekend en gecorrigeerd voor beïnvloedende factoren.

Dit onderzoek liet zien dat de hormoonreceptor-positief/HER2-positieve subgroep de langste mediane overleving had (34,4 maanden) in vergelijking met 24,8 maanden voor de hormoonreceptor-positief/HER2-negatieve subgroep, 19,8 maanden voor de hormoonreceptor-negatief/HER2-positieve subgroep en 8,8 maanden voor de triple negatieve subgroep ($P < 0,0001$).

In de multivariate analyse was de subgroep een onafhankelijke prognostische factor voor overleving van gemetastaseerd mammacarcinoom. De hormoonreceptor-positief/HER2-positieve subgroep was geassocieerd met de beste overleving met een hazard ratio van 0,64 (95% betrouwbaarheidsinterval van 0,45-0,92), in vergelijking met de hormoonreceptor-positieve/HER2-negatieve subgroep. Daarnaast was een metastasevrij interval van meer dan 24 maanden ook geassocieerd met een betere overleving (hazard ratio 0,62; 95% betrouwbaarheidsinterval 0,50-0,75). Eerdere adjuvante systemische therapie en een leeftijd ouder dan 50 jaar bij diagnose van mammacarcinoom waren geassocieerd met een slechtere prognose. Plaats van initiële metastasen op afstand is ook een belangrijke prognostische factor, met botmetastasen als gunstige prognostische factor in vergelijking met viscerale metastasen, hersenmetastasen of meerdere plaatsen van initiële metastasen.

Concluderend is de op hormoonreceptor- en HER2-status gebaseerde subgroep van het mammacarcinoom, naast de eerder genoemde factoren, een belangrijke prognostische factor voor patiënten met gemetastaseerd mammacarcinoom, waarbij de hormoonreceptor-positieve/HER2-positieve subgroep in de huidige tijd de beste prognose heeft.

In **hoofdstuk 3** ligt de focus op het metastasevrij interval als prognostische factor. Hierbij is het metastasevrij interval gedefinieerd als de tijd tussen de primaire diagnose van mammacarcinoom en het vaststellen van metastasen op afstand. Ook in deze studie werden alle 815 patiënten uit de deelnemende ziekenhuizen geïnccludeerd. Deze patiënten werden in drie categorieën ingedeeld op basis van het metastasevrij interval: patiënten met *de novo* gemetastaseerd mammacarcinoom (dat wil zeggen patiënten die bij stellen van de diagnose mammacarcinoom ook metastasen op afstand hadden), patiënten met een metastasevrij interval van 24 maanden of minder en patiënten met een metastasevrij interval van meer dan 24 maanden. Een Cox proportional hazard model werd gebruikt om de prognostische impact van het metastasevrij interval te berekenen, gecorrigeerd voor leeftijd, hormoonreceptor- en HER2-receptorstatus, plaats van initiële metastasen op afstand en eerdere (neo-) adjuvante systemische therapie.

Patiënten met *de novo* gemetastaseerd mammacarcinoom ($n=154$) hadden een significant betere overleving in vergelijking met patiënten met een metastasevrij interval van 24 maanden of minder ($n=176$) ($P<0,0001$). Er werd geen verschil gezien in overleving tussen patiënten met *de novo* gemetastaseerd mammacarcinoom en patiënten met een metastasevrij interval van meer dan 24 maanden ($n=485$) ($P=0,73$). Ook na het corrigeren voor de hierboven genoemde factoren hadden de patiënten met een metastasevrij interval van 24 maanden of minder een slechtere uitkomst in vergelijking met patiënten met *de novo* gemetastaseerd mammacarcinoom (hazard ratio van 1,97, 95% betrouwbaarheidsinterval 1,49-2,60, $P<0,0001$). De associatie tussen metastasevrij interval en overleving van het gemetastaseerd mammacarcinoom werd gezien onafhankelijk van eerder gebruik van (neo-) adjuvante systemische therapie.

Samengevat is het metastasevrij interval een belangrijke prognostische factor voor de overleving van patiënten met gemetastaseerd mammacarcinoom, waarbij patiënten met *de novo* gemetastaseerd mammacarcinoom geen slechtere uitkomst hadden, in tegenstelling tot de patiënten met een kort metastasevrij interval (≤ 24 maanden).

In **hoofdstuk 4** beschrijven we de resultaten van een studie naar de rol van het histologisch subtype op de prognose en behandeling van het gemetastaseerd mammacarcinoom. We hebben alle patiënten met een hormoonreceptor-positieve tumor geselecteerd en geclassificeerd op basis van histologisch subtype, ofwel invasief ductaal carcinoom ($n=437$) ofwel invasief lobulair carcinoom ($n=131$). We hebben de overleving van deze twee histologische subtypes van mammacarcinoom geanalyseerd met een mediane follow-up duur van 37,1 maanden.

Patiënten met een invasief lobulair carcinoom waren ouder ten tijde van de diagnose van het primair mammacarcinoom, hadden grotere primaire tumoren en iets vaker lymfeklierpositieve ziekte in vergelijking met patiënten met invasief ductaal carcinoom. Patiënten met invasief lobulair carcinoom hadden vaker initieel botmetastasen (46,5% versus 34,8%, $P=0,01$) en minder vaak multipale plaatsen van

initiële metastasen in vergelijking met patiënten met invasief ductaal carcinoom (23,7% versus 30,9%, $P=0,11$). Ondanks deze verschillen in metastaseringspatroon werd er geen verschil in overleving gezien tussen de twee histologische subtypes (mediaan 29 maanden voor invasief lobulair carcinoom en 25 maanden voor invasief ductaal carcinoom, $P=0,53$). Wel waren er verschillen in behandeling voor gemetastaseerd mammacarcinoom tussen de twee histologische subtypes. Zes maanden na de diagnose van gemetastaseerd mammacarcinoom was 28,1% van de patiënten met hormoonreceptor-positief lobulair carcinoom en 39,8% van de patiënten met hormoonreceptor-positief ductaal carcinoom behandeld met chemotherapie. De mediane tijd tot eerste behandeling met palliatieve chemotherapie was significant langer voor patiënten met lobulair carcinoom in vergelijking met patiënten met ductaal carcinoom ($P = 0,001$). Na zes maanden had 84,8% van de patiënten met lobulair carcinoom een behandeling met endocriene therapie gehad in vergelijking met 72,5% van de patiënten met ductaal carcinoom ($P=0,0001$).

Deze resultaten laten zien dat, naast hormoonreceptor status, histologisch subtype correleert met het metastaseringspatroon (aantal en plaats van initiële metastasen) en daardoor ook de gekozen behandeling in dagelijkse praktijk voor patiënten met gemetastaseerd mammacarcinoom beïnvloedt.

In **hoofdstuk 5** wordt de initiële palliatieve systemische behandeling beschreven die in de dagelijkse praktijk is gegeven aan patiënten met hormoonreceptor-negatief/HER2-negatief gemetastaseerd mammacarcinoom. Tevens wordt de progressievrije overleving en totale overleving per gekozen behandeling – chemotherapie of endocriene therapie – bepaald, gecorrigeerd voor de bekende prognostische factoren. In totaal werden 520 patiënten met hormoonreceptor-positief/HER2-negatief mammacarcinoom geïnccludeerd. Drieënnegentig (93) procent van deze patiënten ($n=482$) kreeg een vorm van palliatieve systemische behandeling gedurende de observatieperiode: 116 patiënten (24%) kreeg palliatieve chemotherapie als eerst gegeven behandeling voor gemetastaseerd mammacarcinoom en 366 patiënten (76%) kreeg palliatieve endocriene therapie als eerst gegeven systemische behandeling. De patiënten met initiële chemotherapie waren jonger, hadden minder vaak comorbiditeit, hadden vaker adjuvante systemische behandeling gehad en hadden minder vaak botmetastasen in vergelijking met patiënten die initiële endocriene therapie kregen. De mediane progressievrije overleving voor patiënten met initiële chemotherapie was 5,3 maanden (95% betrouwbaarheidsinterval 4,2-6,2 maanden) tegenover een progressievrije overleving van 13,3 maanden (95% betrouwbaarheidsinterval 11,3-15,5 maanden) voor patiënten met initiële endocriene therapie. De mediane overleving was 16,1 maanden voor patiënten met initiële chemotherapie versus 36,9 maanden voor patiënten met initiële endocriene therapie. Na correctie voor bekende prognostische factoren was initiële chemotherapie nog steeds geassocieerd met een slechtere progressievrije overleving (hazard ratio van

2,33, 95% betrouwbaarheidsinterval 1,77-3,08, $P < 0,0001$) en overleving (hazard ratio van 2,24, 95% betrouwbaarheidsinterval 1,64-3,06, $P < 0,0001$).

Geconcludeerd kan worden dat een groot deel van de patiënten met hormoon-receptor-positief gemetastaseerd mammacarcinoom initiële behandeling met palliatieve chemotherapie krijgt in de Nederlandse dagelijkse praktijk. Het starten van de behandeling met chemotherapie is geassocieerd met een ongunstiger beloop van de ziekte in vergelijking met het starten van de behandeling met palliatieve endocriene therapie, hoewel dit niet impliceert dat chemotherapie minder effectief is.

In **hoofdstuk 6** wordt het gebruik en de effectiviteit van bevacizumab in combinatie met taxaan bevattende chemotherapie als eerstelijns behandeling voor patiënten met HER2-negatief gemetastaseerd mammacarcinoom in de dagelijkse praktijk beschreven.

Alle patiënten met HER2-negatief mammacarcinoom gediagnosticeerd tussen 2007-2009 in de deelnemende ziekenhuizen werden geïnccludeerd ($n=650$) en daarbij zijn de 332 patiënten die eerstelijns chemotherapie hebben gekregen geselecteerd.

In totaal werden 193 patiënten behandeld met eerstelijns chemotherapie na de introductie van bevacizumab in Nederland, waarvan 17% daadwerkelijk een behandeling met bevacizumab heeft gekregen. De patiënten die bevacizumab kregen waren jonger, hadden een trend tot significant minder cardiovasculaire comorbiditeit, hadden een langer metastasevrij interval en hadden vaker hormoonreceptor-positief mammacarcinoom dan de patiënten die geen bevacizumab kregen. Verder hadden de patiënten die als eerstelijns behandeling chemotherapie en bevacizumab kregen vaker (neo-) adjuvante systemische therapie gehad en hadden ze vaker meerdere initiële lokalisaties van metastasen op afstand in vergelijking met patiënten die geen bevacizumab hadden gehad. Vierentwintig procent (24%) van de patiënten die als onderdeel van hun systemische behandeling bevacizumab kregen hadden een (relatieve) contra-indicatie voor het middel of voldeden niet aan de geldende registratiecriteria van het middel, zoals bijvoorbeeld patiënten die in de eerstelijns behandeld hadden kunnen worden met antracyclines. De mediane progressievrije overleving van patiënten behandeld met bevacizumab was 6,0 maanden (95% betrouwbaarheidsinterval 4,8-13,1) en de mediane overleving was 28,4 maanden (95% betrouwbaarheidsinterval 14-nog niet bereikt).

Deze studie laat zien dat bevacizumab minder vaak is voorgeschreven dan verwacht en mogelijk geïndiceerd in dit grote Nederlands cohort. De progressievrije overleving van eerstelijns behandeling met bevacizumab was lager dan de gerapporteerde progressievrije overleving in de registratie studies, maar de totale overleving was vergelijkbaar tussen de onderzoekspopulatie en het Nederlandse cohort.

In **hoofdstuk 7** presenteren we de kosteneffectiviteit van bevacizumab in de Nederlandse dagelijks praktijk en vergelijken deze met de kosteneffectiviteit van bevacizumab gebaseerd op de registratiestudie.

In beide scenario's (zowel de dagelijkse praktijk als die van de registratiestudie) leidde de toevoeging van bevacizumab tot meer effectiviteit (uitgedrukt in gewonnen levensjaren gecorrigeerd voor kwaliteit van leven, zogenaamde QALYs) met een toename van respectievelijk 0,362 en 0,189). De toevoeging van bevacizumab aan de eerstelijns behandeling met taxaan bevattende chemotherapie leidde ook in beide scenario's tot een toename van kosten, €56213 in de dagelijkse praktijk en €52750 voor het scenario gebaseerd op de registratie studie. De kosteneffectiviteits ratio is daarbij berekend op €155261 per gewonnen QALY in de dagelijkse praktijk en €278711 per gewonnen QALY in het scenario gebaseerd op de registratiestudie.

In Nederland zijn er referentiewaarden voor de bepaling of een interventie kosteneffectief is, waarbij de bovengrens van €80000 per gewonnen QALY informeel wordt gehanteerd om een middel als kosteneffectief te beschouwen. Daarmee is bevacizumab dus niet te beschouwen als een kosteneffectieve eerstelijns behandeling in combinatie met taxaan bevattende chemotherapie voor patiënten met HER2-negatief gemetastaseerd mammacarcinoom in de Nederlandse dagelijkse praktijk.

Hoofdstuk 8 beschrijft de samenvatting van dit proefschrift. Tevens worden er hier een algemene conclusie op basis van dit proefschrift getrokken en een toekomstperspectief beschreven.

De resultaten uit dit proefschrift laten zien dat de prognose van patiënten met gemetastaseerd mammacarcinoom in de dagelijkse praktijk wordt beïnvloedt door verschillende factoren, zoals hormoonreceptor- en HER2-receptorstatus en metastasevrij interval. Deze informatie is van belang voor de patiënten die we in de dagelijkse praktijk zien, omdat we zo betere informatie kunnen verstrekken over het ziektebeloop en de prognose. Maar deze informatie is ook van belang voor de behandelend artsen, omdat dit kan helpen bij het maken van de juiste behandelkeuzes. Niet alleen op individueel patiënniveau zal dit leiden tot een efficiëntere inzet van de beschikbare middelen, maar ook op macroniveau is deze informatie van cruciaal belang voor de plaatsbepaling van de geneesmiddelen die beschikbaar zijn voor de behandeling van het gemetastaseerd mammacarcinoom.

Het huidige cohort van patiënten gediagnosticeerd en behandeld in Zuidoost Nederland, waarop dit proefschrift is gebaseerd, geeft de zo nodige informatie over ziektebeloop, prognose, prognose beïnvloedende factoren en de in de dagelijkse praktijk gegeven behandelingen met de daarbij behorende uitkomsten. Een van de uitkomsten van het onderzoek was dat bijna een kwart van de patiënten met gemetastaseerd hormoonreceptor-positief mammacarcinoom initieel wordt behandeld met palliatieve chemotherapie, en dat deze patiënten, na correctie van belangrijke prognostische factoren, een slechtere uitkomst hadden in vergelijking met patiënten die initieel behandeld waren met palliatieve hormonale therapie. Zonder voorbij te gaan aan mogelijke 'confounding by indication', is dit een belangrijk onderzoeksresultaat met het oog op inzet van de huidige behandelingsmogelijkheden.

Deze informatie is tevens van belang om te weten hoe de implementatie van richtlijnen plaatsvindt in de dagelijkse praktijk.

Met het oog op de toenemende behandelingsmogelijkheden voor het mamma-carcinoom en de daarmee gepaard gaande groeiende zorgkosten is efficiënte implementatie van deze middelen, post-marketing onderzoek na implementatie en kosten-effectiviteitsanalyse van het middel in de dagelijkse praktijk van belang.

De cohortstudies hierboven beschreven hebben een aantal belangrijke onderwerpen in onderzoek naar gemetastaseerd mamma-carcinoom laten zien. Op dit moment wordt de grote dataset verder uitgebreid met meer deelnemende centra en vindt tevens uitbreiding van het cohort plaats met patiënten gediagnosticeerd met gemetastaseerd mamma-carcinoom na 2009. Het doel hiervan is om, door middel van continueren en uitbreiding van het onderzoek naar gemetastaseerd mamma-carcinoom in de dagelijkse praktijk, de kwaliteit van zorg voor patiënten met een gemetastaseerd mamma-carcinoom gunstig te beïnvloeden. Met als het ultieme doel de uitkomst van deze patiënten te verbeteren.

Valorisation

Valorisation

In this thesis several studies based on patients with metastatic breast cancer in every day clinical practice are presented. The results are not only relevant for scientific purposes, but are also of importance from a societal and economical perspective. Breast cancer is a major global health issue with over 500 000 deaths annually. In the Netherlands, almost 16 000 patients were diagnosed with invasive breast cancer in the year 2015. Around 20% of all breast cancer patients will develop a distant recurrence after prior treatment of early stage breast cancer, and around 5% of patients are found to have metastatic breast cancer at initial diagnosis. Once distant recurrence has occurred the disease is generally incurable.

In the first study described in this thesis, we determined the median survival of patients with metastatic breast cancer, according to subgroup based on HER2 and hormone receptor status. The subgroup with the most favorable prognosis, the hormone receptor-positive/HER2-positive subgroup, had a median survival of 34.4 months, with a range up to more than 46.6 months. This shows that, even though metastatic breast cancer remains incurable, there are patients with metastatic breast cancer who will live many years after the diagnosis of metastatic breast cancer. During those years, these patients are most likely treated with several lines of therapy. This period has major implications for the patient and their families, as well as for society. First of all, the diagnosis and the uncertainty on prognosis and disease course can lead to feelings of isolation, worries and even depression in a third of women with advanced breast cancer at diagnosis. And these patients feel the need to have more information available on metastatic breast cancer at diagnosis, as well as during the course of their disease and treatment.

With the impact of metastatic breast cancer diagnosis and treatment on the quality of life, it is essential that we translate our scientific data to useful and personalized information to the patients and their families in every day clinical practice.

One of the societal benefits from this thesis is the use of these data to help inform our patients with metastatic breast cancer in daily practice. Our data provide knowledge on anticipated disease course, which can help to make informed decisions on treatment and can prevent anxiety and uncertainty of the future once the diagnosis is determined.

Furthermore, more than half of patients with metastatic breast cancer experience a decline in income and, besides paid employment, many of the women with metastatic breast cancer participate in unpaid activities, such as cooking, household and taking care of children and/or relatives on which the disease has an impact as well. This so called 'grey economy' needs to be accounted for when examining the economic burden of metastatic breast cancer, in addition to the costs directly related to the disease, symptoms and treatment as well as costs related to loss of productivity.

This thesis is based on a large real-life cohort of patients in several hospitals in the Southeast part of the Netherlands. This is in contrast to most data on metastatic breast cancer, which are usually derived from randomized clinical trials. There is an added value of these real-life data, since in daily practice only a small percentage of metastatic breast cancer patients participate in randomized trials. Therefore, the objective of this thesis was to gather and analyze real-life data on disease course, prognostic factors and treatment allocation. Not only are these data needed to help inform patients and their treating physicians, but it can also help to determine efficacy, implementation and use of therapeutic regimens in real-life. This information has major implications for society, since it is needed to determine and improve the quality of care and estimate the cost-effectiveness of new drugs.

One of the future improvements should be the gathering of relevant real-life data in a way that is less time consuming and more integrated in every day clinical practice. In an era in which electronic medical records are commonly used in hospitals in the Netherlands and most Western Countries the possibilities of data collection and sharing are numerous. With less time and less costs involved in data collection, the results from these population-based studies should become available more quickly and could thus have a bigger impact on daily treatment, information provided to the patients with metastatic breast cancer and their quality of life.

Since there is such an added value of real-life data, not only for patients and their treating physicians, but also for pharmaceutical industries and governments deciding on reimbursement and health care budgets and controlling quality of care, the efficacy of collection of the relevant data should be a joined effort of all involved fields in breast cancer care.

One of the examples of the value of real-life data comes from the study of this thesis exploring the first given treatment for patients with hormone-receptor positive metastatic breast cancer. Our study showed that nearly a quarter of patients started palliative treatment with chemotherapy, although it is recommended in the guidelines to start with endocrine treatment provided that the disease is not (extremely) aggressive. Our study does not only show that in real-life different treatment choices are made, it also implicates that real-life treatment choices in metastatic breast cancer are complex and that many factors play a role in the treatment decision-making process. These data are relevant when informing our patients on treatment options, but may also help to improve future decision-making. Data from the real-life population based studies can also help to guide the design of the randomized clinical trials, thereby resulting in more appropriate and thereby more efficient trial designs.

Another example concerns the use of bevacizumab, which was registered and approved for the treatment of metastatic breast cancer in 2008 based on randomized

clinical trial data. One of the studies of this thesis describes the implementation of bevacizumab hereafter. It was shown that bevacizumab was administered less often than anticipated and potentially indicated. Moreover, almost a quarter of patients receiving bevacizumab-taxane had no indication for bevacizumab or received this despite (relative) contraindication in real-life in the Netherlands. This study shows the importance of monitoring the daily use of a new therapeutic drug in daily practice to help guide optimal implementation and use of a new drug in according to guideline recommendations. This is essential in controlling quality of the provided cancer care and thereby improving the quality of life and outcome of patients with metastatic breast cancer.

Besides the implementation and thereby directly influencing the patients and their doctors, these real-life data are also of importance from an economic perspective. These new cancer drugs impose a substantial burden on our health care budget. Due to the introduction of new cancer drugs, the costs will continue to increase over the years. From a societal view, it is essential that these new drugs are properly implemented, limited to the patients who are expected to benefit the most. We observed, that patients who were in real-life selected for first-line bevacizumab-taxane treatment had a median progression-free survival of 6.0 months (95% CI 4.8-13.1). As aforementioned, the selection of patients was suboptimal. The addition of bevacizumab to a taxane for the first-line treatment of HER2-negative metastatic breast cancer was associated with an increase in costs of €56,213. Even though there was also an increase in quality-adjusted life years with the addition of bevacizumab of 0.362, the cost-effectiveness ratio amounted to €155,261 per quality-adjusted life years gained, which is not considered cost-effective in the Netherlands. Such information is essential for decisions on reimbursement as well as for the ongoing debate on how to manage the increasing health care expenditure.

In conclusion, this thesis provides essential data on metastatic breast cancer in real-life. One of the main goals of this thesis is to increase awareness about this important group of patients. We hope the results of the studies in this thesis will lead to a better understanding of prognostic and predictive factors, treatment patterns, disease course and outcome in patients with metastatic breast cancer. Furthermore, we hope these results will help stimulate more appropriate allocation of existing treatment options, and can be a starting point of new developments of treatment regimens for patients with metastatic breast cancer in the future. All with the ultimate goal to improve quality of care and outcome for patients with metastatic breast cancer.

List of publications

List of publications

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Dankwoord

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Curriculum vitae

Curriculum vitae

Dorien Josina Albertina werd geboren op 23 mei 1985 in Woerden. Na het afronden van het VWO op het van Maerlantlyceum in Eindhoven in 2003 studeerde zij geneeskunde aan de Universiteit van Maastricht. Hier haalde zij in 2004 haar propedeutisch examen. Tijdens deze studie volgde zij in 2007 een keuze coschap kinderoncologie in het Starship Children's Hospital in Auckland, Nieuw-Zeeland. Na het behalen van haar doctoraal examen in 2008 volgde een afsluitende semi-arts stage binnen de Interne Geneeskunde met als aandachtsgebied Medische Oncologie in het Maastricht Universitair Medisch Centrum+. Het wetenschappelijk deel van de stage omvatte een literatuuronderzoek naar het internationale gebruik van kwaliteitsindicatoren voor zorg voor patiënten met een mammacarcinoom met begeleiding van prof. dr. V.C.G. Tjan-Heijnen en het klinische deel bestond uit zowel poliklinisch als klinische zorg voor oncologie patiënten met begeleiding van dr. R.I. Lalisang.

Na het behalen van haar artsexamen in 2009 was zij werkzaam als arts-assistent op de afdeling Interne Geneeskunde in het Máxima Medisch Centrum in Veldhoven. Van 2010 tot 2013 werkte zij aan het onderzoek waarvan dit proefschrift het resultaat is, onder begeleiding van prof. dr. V.C.G. Tjan-Heijnen (Maastricht Universitair Medisch Centrum+), dr. M.W. Dercksen (Máxima Medisch Centrum) en dr. A.C. Voogd (Maastricht Universitair Medisch Centrum+). Gedurende deze periode werden de taken als arts-onderzoeker gecombineerd met klinische werkzaamheden als escalatie-arts en arts-assistent op de afdeling Interne Geneeskunde in het Máxima Medisch Centrum. In 2013 startte zij daar met de opleiding tot internist (opleider: prof. dr. H.R. Haak, later dr. A.G. Lieveverse).

Dorien woont samen met haar partner Tom Bazelmans in Veldhoven en in februari 2017 verwachten zij hun eerste kind.