Aus der Medizinischen Klinik und Poliklinik III der

Ludwig-Maximilians-Universität München

Direktor: Prof. Dr. med. W. Hiddemann

Overall Survival in Metastatic Breast Cancer Patients: A Single-Centre Analysis (2000-2005)

Dissertation

zum Erwerb des Doktorgrades der Medizin

an der Medizinische Fakultät der

Ludwig-Maximilians-Universität zu München

Vorgelegt von

Jitske Alida Cnossen

Aus Drachten, Niederlande

2011

Mit Genehmigung der Medizinischen Fakultät

der Universität München

Berichterstatter:	Prof. Dr. med. V. Heinemann
Mitberichterstatter:	Prof. Dr. D. Hölzel Priv. Doz. Dr. C. Scholz Prof. Dr. D. Nowak
Mitbetreuung durch den Promovierten Mitarbeiter:	Priv. Doz. Dr. med. H.J. Stemmler
Dekan:	Prof. Dr. med. Dr. h.c. M. Reiser, FACR, FRCR
Tag der mündlichen Prüfung:	30.06.2011

I a. ABSTRACT

Background: Recent epidemiological studies suggest that chemotherapy has not contributed to a marked improvement of patient outcome during the last decades. In most randomized trials which investigated the efficacy of a 1st-line schedule for metastatic breast cancer (MBC), the median survival ranged between 18 and 24 months. The goal of the present study was to analyse the survival of patients with MBC treated in a single university outpatient clinic.

Methods: Patients who had received their complete anti-cancer treatment for MBC in our outpatient clinic between 2000 and 2005 were analyzed for treatment and survival.

Results: 232 patients [median age of 53, range 27-87 yrs; ER and/or PgR positive (HR+) n=174 (75%); HER2 over-expression (HER2+) n=79 (34%)] were included in the analysis. Endocrine sensitive patients received 1-2 (58.6%), 3-4 (37.4%) and 5-6 (2.3%) hormonal regimens. Of all patients 53.4% received up to 3 cytostatic agents in palliative intent, 4-6 regimens were applied in 22.1% and 12.9% received more than 6 subsequent regimens during the course of their disease.

The median overall survival (OS) from time of diagnosis of metastatic disease was 44 months. Patients with HR positive tumours survived 46 months, whereas the survival of those with HR negative tumours was 34 months (p=0.07). HER2+ patients who received trastuzumab survived for a median of 44 months. Visceral involvement was associated with a shorter survival as compared to non-visceral disease (34 vs. 57 months, p<0.05). Thirty-one patients underwent loco-regional procedures as resection of metastases (n=14, 6.0%) or radiofrequency ablation (n=17, 7.3%).

Conclusion: These data show a selective patient population in a single-centre setting, that report improved survival rates. Whether innovative medicine, a step by

step escalation of all treatment modalities according to standard guidelines and individualized clinical requirements and a multidisciplinary treatment approach contribute to these good outcomes is debatable.

Key words: metastatic breast cancer, survival, chemotherapy, endocrine therapy, therapy sequences

I b. ZUSAMMENFASSUNG

Hintergrund: Jüngst veröffentlichte epidemiologische Studien zeigen, dass die Chemotherapie in den letzten Jahrzehnten nicht zu einer Verbesserung der Überlebenszeit beim metastasierten Mammakarzinom (MBC) beigetragen hat. In den meisten randomisierten Studien, welche die Effektivität einer systemischen “first-line” Therapie beim MBC untersucht haben, wird die mediane Überlebenszeit mit 18 bis 24 Monaten angegeben. Ziel dieser retrospektiven Studie war daher die Analyse der Überlebenszeit von MBC-Patientinnen, die in einer universitären Spezialambulanz behandelt wurden.

Methoden: Alle Patientinnen mit MBC, die im Zeitraum von 2000 – 2005 in unserer Spezialambulanz behandelt wurden, konnten bezüglich Therapiesequenz und Überlebenszeit ausgewertet werden.

Ergebnisse: 232 Patientinnen [medianes Alter 53 Jahre, Altersspanne 27-87 Jahre; ER und/oder PgR positiv (HR+) n=174 (75%); HER2 Überexpression (HER2+) n=79 (34%)] wurden in die Analyse aufgenommen. Als anti-hormonelle Therapie erhielten HR+ Patientinnen 1-2 (58.6%), 3-4 (37.4%) und 5-6 (2.3%) Therapiesequenzen. Dreiundfünfzig Prozent aller Patientinnen erhielten bis zu 3 Chemotherapiesequenzen in palliativer Intention, 4-6 Sequenzen wurden bei 22.1% verabreicht und 12.9% erhielten mehr als 6 verschiedene zytostatische Therapien im Verlauf der Erkrankung. Die mediane Überlebenszeit ab dem Zeitpunkt der Metastasierung betrug 44 Monate. Patientinnen mit HR positiven Tumoren überlebten ebenfalls 46 Monate, während Patientinnen mit HR negativen Tumoren Überlebenszeiten von 34 Monaten (p=0.07) zeigten. HER2+ Patientinnen, die Trastuzumab bekommen hatten, überlebten im Median 44 Monate. Die mediane Überlebenszeit bei viszeraler Metastasierung war im Vergleich zu nicht viszeraler

Erkrankung prognostisch ungünstiger (34 vs. 57 Monate, $p<0.05$). Einunddreißig Patientinnen wurden einer lokalen Therapie der Metastasen unterzogen [Metastasenresektion (n=14, 6,0%) oder Radiofrequenz-Ablation (n=17, 7.3%)]. **Schlussfolgerung**: Unsere Daten, die an einer selektiven Patientenkohorte in einem einzigen Klinikzentrum erhoben wurden, zeigen verbesserte Überlebensraten. Möglicherweise ist dies durch innovative Medizin, eine schrittweise Eskalation aller Therapiemodalitäten entsprechend standardisierten Therapieempfehlungen, individualisierte klinische Anforderungen und einen multidisziplinären Therapieansatz mit bedingt.

Schlüsselwörter: metastasiertes Mammakarzinom, Überlebensrate, Chemotherapie, hormonale Therapie, Therapiesequenzen.

II. CONTENTS

Ia. Abstract 1

Ib. Zusammenfassung 3

II. Contents 5

1. BREAST CANCER

1.1 Background 8

1.2 Prognoses 9

1.2.1 Risk Factors 9

1.2.2 Prognostic Factors 10

1.3 Systemic Treatment of Metastatic Breast Cancer 12

1.3.1 Endocrine Therapy 14

1.3.1.1 Tamoxifen 16

1.3.1.2 Aromatase Inhibitors 17

1.3.2 Chemotherapy 18

1.3.3 Immune Therapy 21

1.3.3.1 Trastuzumab 21

1.4 Bisphosphonates 22

1.5 Loco-regional Treatment Options 24

1.6 Survival of Metastatic Breast Cancer 25

1.7 Study Aims 27

2. MATERIALS AND METHODS

2.1 Study Focus 29

2.2 Study Design 29

2.3 Statistical Analyses 32

3. RESULTS

3.1 Patient Characteristics 33

3.2 Survival 37

3.2.1 Overall Survival 37

3.2.2 Tumor Characteristics and Survival 38

3.2.2.1 Tumor Size 38

3.2.2.2 Nodal Stage 39

3.2.2.3 M-Stage of Disease at Diagnosis 40

3.2.2.4 Grading 41

3.2.2.5 Hormone Receptor 42

3.2.2.6 Age at Diagnosis 47

3.2.3 Course of Disease and Survival 48

3.2.3.1 Number of Metastatic Sites 48

3.2.3.2 Local-Recurrence and Distant Metastasis 50

3.2.3.3 Visceral Metastasis 51

3.2.3.4 Singular Lung and Liver Metastasis 52

3.2.3.5 Bone Metastases 53

3.3 Uni- and Multivariate Analysis 55

3.4 Characteristics of Palliative Chemotherapy 58

3.4.1 Overview of Palliative Chemotherapy Treatment 58

3.4.2 Sequences of Palliative Chemotherapy Treatment and Survival 59

3.5 Characteristics of Endocrine Treatment and Survival 62

3.6 Systemic Treatment and Survival 65

4. DISCUSSION

4.1 General Overview 67

4.2 Patient- and Tumor Characteristics 68

4.3 Survival 69

4.4 Treatment of MBC 71

4.5 Limitations of the Study 74

4.6 Conclusion 76

V. Reference List 77

VI. Acknowledgements 83

VII. Curriculum Vitae 84

1. BREAST CANCER

1.1 BACKGROUND

In Germany, as in most other developed countries, breast cancer is the most common cancer observed in women. In Northern and Western Europe the incidence of breast cancer is 70-110/100.000. Overall, breast cancer will strike one of every 10 females in Western countries.

Despite advances in the treatment of breast cancer, approximately 30% of women initially diagnosed with earlier stages of breast cancer eventually develop recurrent, advanced or metastatic disease. As an initial presentation, metastatic breast cancer (MBC) is uncommon, occurring in only about 6-10% of newly diagnosed cases[1,2]. The prognosis of patients who develop metastases varies based on the site of metastases. Patients with local/regional or bone sites have a more favourable prognosis than patients who have visceral or central nervous system metastases. Studies have also shown that survival is inversely proportional to the number of anatomical sites of metastasis at the time of relapse[3].

Once metastases have been detected, goals of therapy are to ameliorate symptoms, delay disease progression, improve or at least maintain quality of life and prolong overall survival. For most women diagnosed with metastatic breast cancer, median survival time durations of 18 to 24 months after diagnosis are common[4,5]. Some retrospective studies report long-term survivors up to 35 months[6,7].

1.2. PROGNOSIS

1.2.1 RISK FACTORS

The tumor registry in Munich estimated the average lifetime risk (as noted above) of breast cancer in the female population of Western countries at birth is 10 percent. Many studies have evaluated risk factors for breast cancer. Some risk factors have been consistently associated with an increased risk and were reviewed by Armstrong *et al.* and Veronesi *et al.* (Table 1)[8,9].

Table 1. Established Risk Factors of Breast Cancer

Risk Factor	**Relative Risk**
Age (≥50 vs. <50 years)	6.5
Geographical location (developed countries)	5
Family history of breast cancer	1.4-13.6
First-degree relative	1.5-1.8
Second-degree relative	
Age at menarche (<12 vs. 14 years)	1.2-1.5
Age at menopause (≥55 vs. <55 years)	1.5-2.0
Age at first live birth (>30 vs. <20 years)	1.3-2.2
Benign breast disease	
Breast biopsy (any histologic finding)	1.5-1.8
Atypical hyperplasia	4.0-4.4
Hormone-replacement therapy	1.0-1.5

The association between breast cancer risk and breastfeeding or parity has been well established. Early age at first term birth is related to lifetime reduction in risk. Increased parity is associated with a long-term risk reduction. A nulli-parous woman has approximately the same risk as a woman with a first term birth at an age of about 30 years. Relative risk falls by 4.3% for every 12 months of breastfeeding in addition to a 7% reduction for every birth. The absence of short-lifetime duration of breastfeeding that is typical for women in developed countries substantially contributes to the high incidence of breast cancer in these areas[9]. Other risk factors

have been less consistently associated with breast cancer (such as diet, use of oral-contraceptives, lactation, and abortion) or are rare in the general population (such as radiation exposure), and are not included in currently used models to predict the risk of breast cancer[8].

Two major breast-cancer-susceptibility genes have been identified, *BRCA1* and *BRCA2*[10,11]. Women with mutations in either of these genes have a lifetime risk of breast cancer of 60 to 85 percent and a lifetime risk of ovarian cancer of 15 to 40 percent. The presence of certain major risk factors in a given family, or combinations of risk factors, has been proposed as a reasonable criterion for consideration of testing for *BRCA* mutations (Table 2)[8].

Table 2. Risk factors for carrying BRCA1 or BRCA2 mutation

Family-History Risk Factors for carrying a *BRCA1* or *BRCA2* mutation
• Known *BRCA1* or *BRCA2* mutation • Breast and ovarian cancer • Two or more family members under 50 years of age with breast cancer • Male breast cancer • One or more family members under 50 years of age with breast cancer plus Ashkenazi ancestry • Ovarian cancer plus Ashkenazi ancestry

For women without risk factors for a *BRCA* mutation, genetic testing is unlikely to provide useful information about breast-cancer risk. Women who test negative are at the same risk as women without a family history of breast cancer[8].

1.2.2 PROGNOSTIC FACTORS

Prognostic factors estimate prospectively the course of disease for an individual patient. Distinct from prognostic factors are predictive factors; these provide an indication of the response expected following therapy.

Standard predictive factors include hormone receptor status for selection of endocrine therapy and HER2 amplification and/or over-expression for selection of trastuzumab as a treatment modality in the metastatic setting[12]. Hormone receptor status is not only important for determining the potential effects of endocrine therapy, but newly reported data suggest that primary chemotherapy in endocrine unresponsive tumours is more effective[13-15].

Standard prognostic factors include clinical and pathological staging, especially lymph node status and tumor size, and further tumor grade, histologic type, estrogen, progestarone- and HER2/*neu* receptor status.

Recent attention has been focussed on a new classification system that uses the three common molecular markers, estrogen receptor (ER), progestarone receptor (PgR) and Her2/*neu,* and classifies patients into subtypes[16-18]*.* Luminal subtypes make up the hormone receptor positive tumours with a generally favourable prognosis. Most of the Her2 over-expressing tumours are hormone receptor negative and have specific gene expression patterns (HER2-subtype). The subtype of the basal-like tumours lacks both hormone receptor and HER2/*neu* expression, and has a poor prognosis.

More potential prognostic factors have been reported in the last decade[12]. Two of these are detection of bone marrow metastases and recognition of simultaneous multiple gene expression patterns, or “signatures”.

A Norwegian study reported that in addition to baseline bone marrow status, micro-metastases formed three to four years after primary therapy are associated with a high rate of recurrence during the following years. The presence or absence of micro-

metastases might not only improve the accuracy of staging but might also be helpful in stratifying breast cancer patients for different treatment modalities in the future[19].

With gene expression profiling, breast tumours can be classified into different subtypes, with significant difference in patient outcome[20,21]. Several groups have identified panels of gene expression markers with microarray-technology that appear to predict the likelihood of breast cancer recurrence in various populations of women with node negative disease[9,20]. A large proportion of these women would be disease-free at 10 years without systemic treatment or with tamoxifen alone. Consequently, many women with early breast cancer are probably over-treated, resulting in decreased quality of life for these patients as well as an increased economic burden of this disease on society.

1.3. SYSTEMIC TREATMENT OF METASTATIC BREAST CANCER

Systemic treatment has produced significant responses in patients with metastatic disease in the last decades. Many changes have been made in the mainstay of regimens, and as science is constantly advancing, many changes are still to come with a common goal: to improve the efficacy and tolerability of the individual treatment for each patient and with that prolongation of overall survival.

General treatment strategies for patients with MBC are summarized in the guidelines of the AGO ("*Arbeitsgemeinschaft für Gynaecologische Onkologie"*). These guidelines (2009) recommend for the treatment of MBC;

1) anti-endocrine treatment for hormonal positive disease,

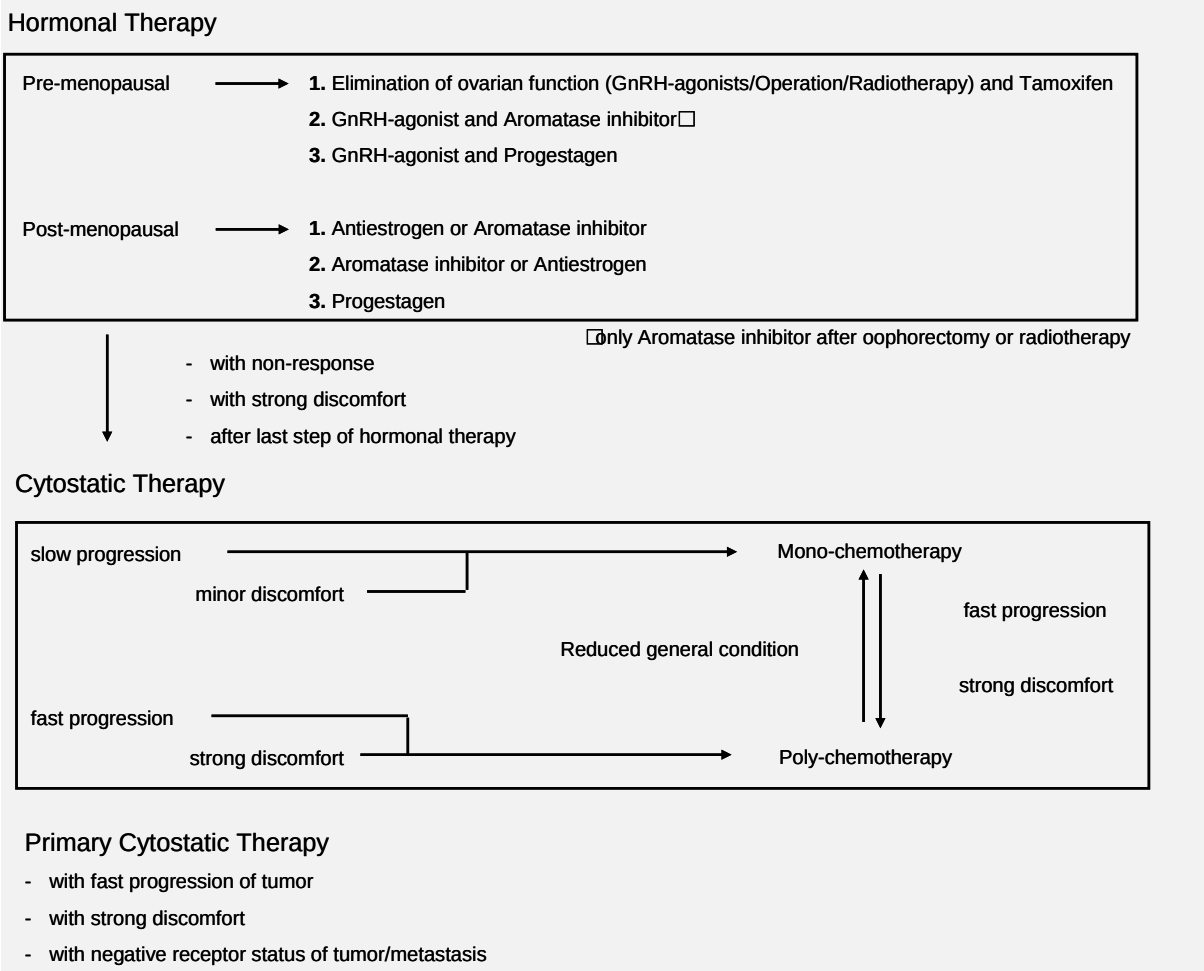
2) chemotherapy in hormone negative disease or visceral organ involvement,

3) single agent therapy is preferred before combination therapy and

4) the integration of targeted therapies with HER2 positive tumours.

Mono-chemotherapy is specifically indicated for the treatment of MBC in the case of slow, not life threatening progression and when the tumor is insensitive to or shows progression during endocrine treatment. Poly-chemotherapy is indicated to achieve a rapid remission in the case of extensive symptoms of MBC and imminent life-threatening metastases. The choice of the chemotherapeutic agent to be used depends on the aggressiveness of disease and localization of metastases, history of prior treatment and response rate, general health condition and age, and patients' preferences[15]. Figure 4. gives a flow-diagram of the treatment of MBC.

Figure 4. Therapy of MBC.



Source:TZM Manual Mammakarzinome, V.Heinemann, W. Abenhardt, G. Bastert et al.

1.3.1 ENDOCRINE THERAPY

Hormones have been demonstrated to play a very important role in breast cancer oncogenesis and progression. The roots of endocrine therapy lie in blocking the estrogen production by removing estrogen production organs (ablative therapy, like oophorectomy for premenopausal women and adrenalectomy in postmenopausal women), or by interfering at a cellular level with estrogen and its receptor (additive therapy), or additional hormonal axes.

Antiestrogenes or SERM´s, aromatase inhibitors, GnRH-agonists, estrogene receptor antagonists, and progestarones are endocrine treatment modalities for advanced or metastasized breast cancer and continuously in development. Table 6. gives an overview of endocrine treatment options. The SERM tamoxifen and the aromatase inhibitors are more specified below.

Table 6. Overview of endocrine therapies.

Antiestrogens	Tamoxifen (Novadex) Toremifen (Fareston)
Aromatase Inhibitors	Anastrozole (Arimidex) Letrozole (Femara) Exemestane (Aromasin)
GnRH-Analogues	Goserelin (Zoladex) Leuprorelin (Enantone-Gyn)
Estrogen receptor antagonists	Fulvestrant (Faslodex)
Gestagens	Medroxyprogesteronacetate (Clinovir) Megestrolacetate (Megestat)

Patients with MBC and a favourable prognosis; relapse >2 years from first diagnosis, no visceral metastasis and positive hormone receptor status (estrogen and/or progestarone) should, primarily, be treated with endocrine therapy[3], see Figure 4. Patients with a negative estrogen- and progestarone receptor status should not be treated with endocrine therapy, because a response rate of less than 10% is to be expected. The response rate to endocrine therapy is comparable with the response rate to mono-chemotherapy. On the other hand, the toxicity from cytostatic treatment is higher than that from endocrine treatment, with mono-chemotherapy having less toxicity than poly-chemotherapy. In contrast to endocrine therapy, a quicker response can be achieved with chemotherapy.

When the disease has metastasized, endocrine therapy should not be the first treatment of choice in the following situations:

a) fast disease progression,

b) symptomatic disease (outside bone-metastases, these can be treated with radiotherapy), and

c) a negative hormone receptor status[15].

1.3.1.1 TAMOXIFEN

The anti-estrogene tamoxifen has been the most widely used endocrine therapy for breast cancer for more than 30 years. Tamoxifen was meant to be an anti-estogenic drug, but later was found to have estrogenic stimulation effects in bone, liver and endometrial tissue. It is now called selective estrogene receptor modulator (SERM).

Tamoxifen is first-line endocrine therapy for premenopausal women with advanced breast cancer and positive hormone receptor status. It is a standard option for postmenopausal women as well, although more recent data suggest that aromatase inhibitors are a more effective choice than tamoxifen (see chapter 2 discussion on aromatase inhibitors). Tamoxifen is taken orally, at a dose of 20 mg daily. Between 50 and 60 percent of women whose breast cancers are ER and/or PR-positive will respond to tamoxifen therapy. In contrast, fewer than 10 percent of women with metastatic hormone receptor-negative breast cancers respond to tamoxifen[23]. The majority of breast cancers that initially respond remain sensitive to tamoxifen for at least 12 to 18 months, and some continue to respond for several years. Some ER/PR-positive breast cancers are primarily resistant to tamoxifen; secondary resistance and resistance after initial response, also may occur. Resistance to

tamoxifen does not necessarily imply resistance to other endocrine therapies, see Figure 4.

1.3.1.2 AROMATASE INHIBITORS

In postmenopausal women, estrogen is no longer produced in the ovaries but androgens (mainly from the adrenal glands) are converted into estrogens in peripheral tissue by the enzyme aromatase. Aromatase inhibitors (AIs) act systematically to inhibit estrogen synthesis in tissues. AIs are classified as either first, second or third generation. Aminoglutethimide was the first aromatase inhibitor in clinical use (first generation) and had a similar tumor-regressing effect to other endocrine treatments, which showed the potential of this alternative type of therapy, however it was poorly tolerated. Other AIs have since been developed and the third generation AI´s (anastrozole, exemestane and letrozole) is in current use. Mouridsen *et al.* showed in a Phase III clinical trial that letrozole was superior to tamoxifen use in time to progression (median, 9.4 v 6.0 months, respectively; P <.0001) and overall objective response rate (32% v 21%, respectively; P =.0002). Median overall survival (OS) was slightly prolonged, but showed no significance, with 34 months for the letrozole arm versus 30 months for the tamoxifen[22] treatment. Paridaens RJ *et al.* evaluated the efficacy of exemestane versus tamoxifen as first-line treatment for MBC in postmenopausal women until disease progression or unacceptable toxicity occurred. Exemestane showed a better overall response rate (46% v 31%; odds ratio = 1.85; 95% CI, 1.21 to 2.82; P=.005), and median progression-free survival (PFS) was longer than with tamoxifen (9.9 v 5.8 months) but no longer-term benefit was shown in PFS and OS between both study arms[23]. These studies, among others, led to the administration of anastrozole and letrozole as first-line treatment for MBC.

Exemestane is administered as second-line treatment. The question still remains whether OS is improved by treatment with AI´s.

1.3.2 CHEMOTHERAPY

In the primary therapy of MBC, mono-chemotherapy can achieve remission rates of 25-68%, which can be improved by poly-chemotherapy schedules to 35-80%. There are a number of agents with established single-agent activity, with antracyclines and taxanes generally considered the most active[1,24]

Table 7. Most commonly used poly-chemotherapeutic schedules.

Abbreviation	**Agents**	**Dosage**	**Repetition**
CMF	Cyclophosphamide Methotrexate Fluorouracil	600 mg/m^2 i.v. 40 mg/m^2 i.v. 600 mg/m^2 i.v.	Every third week
EC	Epirubicin Cyclophosphamide	60 mg/m^2 i.v. 600 mg/m^2 i.v.	Every fourth week
FEC	Fluorouracil Epirubicin Cyclophosphamide	500 mg/m^2 i.v. 75 mg/m^2 i.v. 500 mg/m^2 i.v.	Every third week
FAC	Fluorouracil Adriamycin Cyclophosphamide	500 mg/m^2 i.v. 50 mg/m^2 i.v. 500 mg/m^2 i.v.	Every third week
AC	Adriamycin Cyclophosphamide	60/50 mg/m^2 i.v. 600 mg/m^2 i.v.	Every third week
GemPac	Gemcitabine Paclitaxel	1250 mg/m^{2}i.v. Day 1/8 175 mg/m^2/3 hours i.v. Day 1	Every third week
ADoc	Adriamycin Docetaxel	50 mg/m^2 i.v. 75 mg/m^2/1 hour i.v.	Every third week
EDoc	Epirubicin Docetaxel	60 mg/m^2 i.v. 75 mg/m^2/1 hour i.v.	Every third week
CapDoc	Capecitabine Docetaxel	2x1250 mg/m^2 i.v. Day 1-1475 mg/m^2 i.v. Day 1	Every third week
VinMito	Vinorelbine Mitomycin C	25 mg/m^2 i.v. Day 1/8 8 mg/m^2 i.v.	Every fourth week
GemCis	Gemcitabine Cisplatin	750 mg/m^2 i.v. Day 1/8 30 mg/m^2 i.v. Day 1/8	Every third week

In addition, capecitabine (Xeloda), gemcitabine (Gemzar) and vinorelbine (Navelbine) have also demonstrated substantial activity in the metastatic setting[25]. Table 7. gives an overview of the different poly-chemotherapeutic schedules being given for MBC.

As the effect of taxanes on survival compared with other drugs was still unclear, Ghersi *et al*. published a review article describing taxane-containing regimens for MBC. This review concluded that despite the relative immaturity of many of the included studies, there was sufficient evidence that, on average, taxane-containing regimens were associated with a statistically significant improvement in overall survival (HR of 0.93 95% CI 0.86-1.00, P=0.05) compared with non-taxane-containing regimens. Further, the review concluded that docetaxel might be more effective than paclitaxel, given in three-weekly schedules[24]. This conclusion was supported by a phase III study where Jones *et al*. compared docetaxel with paclitaxel and found docetaxel superior to paclitaxel in time to progression, response duration and overall survival[26].

The use of poly-chemotherapy versus mono-chemotherapy or sequential single agents remains a subject of debate. Depending on the individual patient and specific treatment goals, either can be appropriate. Sequential single-agent therapy is frequently used for the management of asymptomatic patients with MBC. For patients with more extensive or symptomatic disease, oncologists prefer combination therapy [27]. Combination therapies generally result in higher overall response rates and times to disease progression than with sequential single agents, but usually at a cost of greater toxicity. In addition, the higher overall response rates with combination therapy versus sequential single agents may not necessarily translate into superior survival outcomes[1,27]. O'Shaugnessy showed in a review article that combination

therapies like doxorubicin + paclitaxel, doxorubicin + docetaxel and epirubicin + paclitaxel showed benefits in median response rates and median overall time to treatment failure but no improvement in overall survival rates[1].

Passardi *et al.* recently published a phase II study of gemcitabine, doxorubicin and paclitaxel (GAT) as first line chemotherapy for MBC. The study demonstrated that the addition of gemcitabine to doxorubicin and paclitaxel produced clinical results using low doses of the three drugs. Median response duration was 16.4 months. The median overall-survival time was 36.4 months[28]. Piccart-Gebhart *et al.* found that taxanes were significantly worse than single-agent anthracyclines in terms of PFS, but not in terms of response rates or survival. Taxane-based combinations were significantly better than anthracycline-based combinations in terms of response rates and PFS, but not in terms of survival[29].

The present ´*Arbeitsgemeinschaft Gynäkologische Onkologie*´ (AGO) guidelines recommend for first-line cytotoxic monotherapy agents for MBC: anthracyclines, taxanes, vinorelbine and nab-paclitaxel. First-line polychemotherapy options include: anthracycline plus taxane, and paclitaxel plus capecitabine. After adjuvant application of anthracyclines, docetaxel plus capecitabine, taxanes plus gemcitabine and CMF are recommended. Cytotoxic therapy recommendations after previous application of taxanes and anthracyclines include: capecitabine, peg-liposomal doxorubicin, vinorelbine, ixabepilone plus capecitabine and gemcitabine plus vinorelbine.

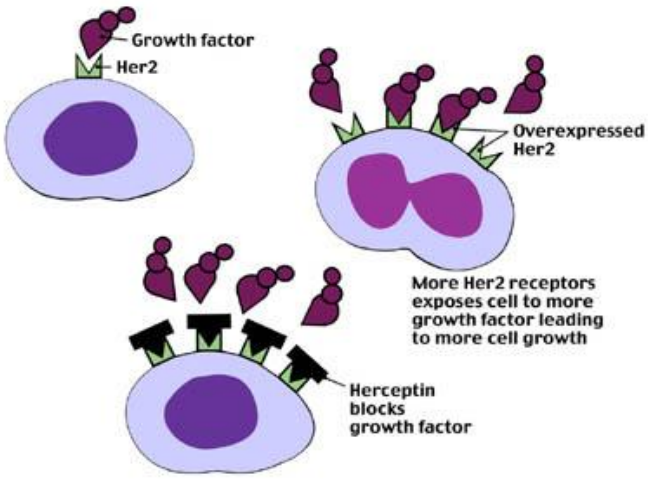
1.3.3 IMMUNE THERAPY

1.3.3.1 TRASTUZUMAB

Growth factors and their receptors play an important role in the pathogenesis of human cancer. The human epidermal growth factor receptor-2 (HER-2) encodes for a transmembrane receptor glycoprotein with tyrosine kinase activity. Normal epithelial cells contain two copies of the HER-2 gene and express 20.000-50.000 HER-2 receptors on the cell surface[30]. This receptor plays a central role in cellular growth. The consequence of HER-2 gene amplification is the over-expression of up to 2.000.000 receptors per cell (Figure 2.). This over-expression is seen in approximately 25-30% of all human breast cancers and is associated with clinically aggressive disease and a shorter survival time[30,31,32]. HER2 over-expression is determined by the immunohistochemical staining score (DAKO Hercep Test™) and a fluorescence *in-situ* hybridisation (FISH) gene amplification analysis.

In 2001 Slamon *et al*. found that a humanized monoclonal antibody (trastuzumab) (Figure 7) directed against the HER-2 receptor provided substantial clinical benefit to HER-2 positive metastatic breast cancer patients[30]. Two important phase III trials have evaluated the addition of trastuzumab to chemotherapy in women with HER-2 over expressing MBC[33,34]. Both studies found that the combination of chemotherapy and trastuzumab resulted in significantly higher overall response rates with a longer median time to disease progression and overall survival time than with chemotherapy alone (resp. 25.1 to 20.3 months and 31.2 to 22.7 months).

Figure 7. Functioning of the humanized monoclonal antibody trastuzumab.



Source: www.biotech.org.cn

Since May 2006 trastuzumab is approved for treatment of patients with metastatic breast cancer and HER2 over-expression, when at least two chemotherapy regimens have been given prior to the treatment. These chemotherapeutic regimens should include an anthracycline and a taxane, with the exception that those therapies have shown to be ineffective for the patient. For patients with an endocrine sensitive tumor, the endocrine therapy has to be shown to be ineffective or intolerated by the patient. In first-line therapy, trastuzumab is approved in combination with paclitaxel or docetaxel.

1.4 BISPHOSPHONATES

About 50-70% of women with metastatic breast cancer develop bone metastases during the course of the disease. These metastases are the source of severe pain, pathological fractures, hypercalcaemia and neurologic complications. Breast cancer bone metastases are predominantly osteolytic (50%) or mixed (40%), with only a small proportion (about 10%) being osteoblastic alone[35]. Osteoclasts account for bone resorption of lytic metastases, whether by direct activation through tumor cells or via tumor-secreted factors like cytokines. Bisphosphonates are potent inhibitors of

osteoclast bone resorption. The use of bisphosphonates is indicated for the treatment of osteoporotic disease, osteolytic bone metastases and cancer induced hypercalcaemia. Table 8. gives an overview of bisphosphonates in current use.

Table 8. Overview of bisphophonates in current use.

Clodronate	Bonefos®, Ostac®
Pamidronate	Aredia®
Zoledronic acid	Zometa®
Ibandronate	Bondronat®

Clodronate was the first oral bisphosphonate and was investigated by Paterson *et al*. in a double-blind, placebo-controlled trial in 1993. Clodronate showed a significant improvement in the reduction of hypercalcaemic events, vertebral fractures and vertebral deformities. A trend was seen in the reduction of pain[36]. In 1996 and 1998 Hortobagyi *et al.* published data about Pamidronate. The infusion of 90 mg pamidronate every month significantly reduced the median time to first skeletal complication (13.0 months for the pamidronate group and 7.0 months for the placebo group, $p<0.001$). The mean pain scores and reduction of performance status were significantly decreased in the pamidronate group. Survival time did not differ between the two groups[37,38]. The review by Allan Lipton describing bisphosphonate therapy concluded that zoledronate was as active against skeletal related events as pamidronate and showed better affectivity for zoledronate in preventing the need for radiation therapy of the bone[39]. The ASCO (American Society of Clinical Oncology) guidelines for clinical practice (2003) recommend for women with radiographic lytic bone metastases, zoledronic acid (4 mg over 15 minutes every three to four weeks)

or pamidronate (90 mg over two hours every three to four weeks). There is insufficient evidence to recommend one over the other, although zoledronic acid is more convenient because it can be administered over a shorter period of time.

1.5 LOCO-REGIONAL TREATMENT OPTIONS

Loco-regional treatment has gained acceptance in the treatment of metastases in the last few years. For hepatic lesions of colorectal cancer, hepatic resection is a well accepted and effective treatment option. Liver metastases of breast cancer are increasingly being treated in the same manner. Adam *et al.* reviewed 85 patients with breast cancer liver disease (BCLD) treated with hepatic resection and showed a median and 5-year overall survival of 32 months and 37%, compared to OS rates of 3-15 months for BCLD treated with the standard medical therapy methods[40]. The impressive data achieved by hepatic resection may in part be explained by patient selection.

The role of radiofrequency ablation (RFA) of BCLD has not yet been established. Lee *et al.* reviewed the role of hepatic resection and RFA for hepatic metastases of colorectal cancer. The hepatic resection group showed a significantly better cumulative 3-year and 5-year local recurrence free survival rate of 88.0% and 84.6%, compared with 53.3% and 42.6% for those in the RFA group (P=0.001).The 5-year OS rate was lower in the RFA group as compared with the hepatic resection group without statistical significance (5-year OS, 65.7% in the HR, 48.5% in the RFA group, P=0.227). Despite a higher local recurrence rate, RFA may be considered as a good therapeutic option for patients who are considered unsuitable for conventional surgical treatment[41]. Hoffmann *et al.* demonstrated that SIRT (selective internal radiation therapy) followed by RFA of the liver, for patients with hepatic lesion of

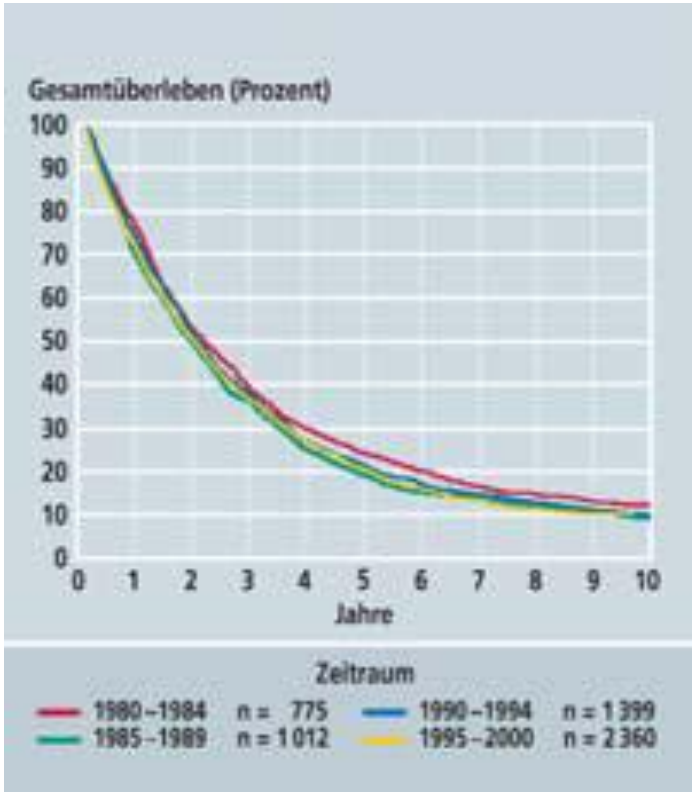
different tumor entities (16 of 46 patients had MBC), was successful in terms of complete ablation. In selected patients radio-embolization is able to downstage liver metastases to an extent making subsequent RFA effective thereby increasing the number of patients with a "complete response" after minimally invasive therapy[42].

The role of surgical resection of pulmonary metastases has to be defined. Welter *et al.* showed in a retrospective analysis that surgical resection of pulmonary metastases was associated with a OS time of 32 months, indicating that this approach might be of benefit for a small proportion of patients with resectable, singular pulmonary metastases[43].

1.6 Survival of Metastatic Breast Cancer

Overall survival rates of women with MBC have been the subject of intense investigation. The effectiveness of chemotherapy in improving the outcome of MBC patients has been demonstrated both in individual studies and in meta-analyses of published randomized trials. Schlesinger-Raab *et al*. recently published an epidemiologic research of survival rates based on data from the tumor registry centre in Munich, Germany, for a study period of 20 years (1978-2002)[44]. In summary, this study found that survival after metastases was related to age, grade, receptor status and survival time without metastasis. However, the outcomes were not influenced by time of diagnosis of the primary tumor or of the metastases or the hospital where the treatment occurred, see Figure 1.

Figure 1. Survival after diagnosis of first metastasis for four time intervals, (n = 5546).



Source: Deutsches Ärzteblatt Jg. 102 Heft 40 7. Oktober 2005

On the contrary, Giordano *et al.* found in 2003 that survival of women with recurrent breast cancer has been improving over the past decades. The median survival duration was 15 months, 17 months, 22 months, 27 months, and 58 months in the groups who developed recurrent disease during 1974-1979, 1980-1984, 1985-1989, 1990-1994 and 1995-2000. However, the more recent groups were confounded by more favourable profiles of prognostic factors[45]. Gennari *et al*. found as well a significant increase in overall-survival in recent cohorts. Median overall-survival was 18 months in 1983-1986 and 23.6 months in 1998-2001 (*p* for heterogeneity <0.0001)[6]. As described in chapter 1.3.3, Slamon *et al*. in 2001 found significant survival benefits in HER2-positive metastatic breast cancer patients treated with a combination of chemotherapy (anthracycline/ cyclophosphamide or paclitaxel) and

trastuzumab[33]. O'Shaughnessy reviewed in 2005 how the introduction of modern chemotherapeutic agents such as taxanes has helped improve survival time on the order of 3 months. Targeted biologic agents like trastuzumab in combination with traditional chemotherapeutics showed impressive response and survival benefits with improvements in overall survival ranging from 4 to 8 months[1].

1.7 STUDY AIMS

First-line studies for metastatic breast cancer have progression free survival (PFS) as primary endpoint. Overall survival is mostly reported as a secondary endpoint. As the treatment of MBC consists of many different agents over time, it is difficult to find out what the present overall survival time of MBC really is. There is a lack of studies describing whole treatment regimens during course of disease. Many published reports describe overall survival rates of MBC in time cohorts, end before 2000 or continue to 2002. As the administration of newer and more active chemotherapeutic agents (taxanes) and the targeted biologic agents like trastuzumab have been a part of treatment regimens since 2000, some of these reported time cohorts might not yet show the real benefits arising from use of these agents. Anecdotal clinical observations of specialized oncologists indicate that the overall survival of patients with MBC is improving over time. This study was started to investigate the current overall survival rates of women with MBC in a small clinical setting using all of the clinical date available out of the medical chart.

The aim of this retrospective analysis is to describe and define current overall survival rates of women with metastatic breast cancer, to whom treatment has been

given in the outpatient clinic of the oncology department of the university hospital Munich, Großhadern, between 2000 and the end of 2005, with respect to:

- patient characteristics
- tumour size, nodal status, grading, hormonal- and HER2 receptor state
- adjuvant chemotherapy and endocrine therapy given
- site of metastases and number of metastatic sites
- palliative systemic treatment, e.g. chemotherapy, endocrine treatment, targeted therapies and bisphosphonates given.
- loco-regional treatment given for metastatic lesions

2. MATERIALS AND METHODS

2.1 STUDY FOCUS

Subjects for this retrospective case study were women who came for treatment of metastatic breast cancer (MBC) to the outpatient clinic of the oncology department of the university hospital Munich Großhadern. Patients' recruitment was based on electronic review of the diagnostic database of the medical oncology department. Criteria for review were women with metastatic breast cancer treated in the outpatient clinic, between January 2000 and December 2005. The electronic review showed 669 women with "metastatic breast cancer" in the medical oncology department during this time period. Many patients came to our outpatient clinic for a second opinion concerning treatment options or for a short treatment of a critical condition. Other patients only had one or two therapies in our clinic and further treatment was continued somewhere else. All these patients were not included in the analyses. The study only included the women to whom the entire anti-cancer treatment was given in our outpatient clinic. In total the study identified 232 cases of women with MBC who satisfied the criteria.

2.2 STUDY DESIGN

The study employed a retrospective design, using all the medical documentation available for each patient who satisfied the entry criteria and was eligible for inclusion in the study.

Data that were collected about each case included:

- Date of birth

- Date of primary diagnosis
- Primary tumour size, nodal state, grading, hormonal receptor state and HER2-receptor state at first diagnosis
- Date of first metastasis, site of first metastasis.
- Other sites of metastases developed in course of disease and dates of diagnosis of these metastases
- Treatment given adjuvant and palliative (e.g. surgery, radiotherapy, loco-regional treatment, endocrine treatment, chemotherapy, bisphosphonates and targeted therapies given).
- Last date of a consultation with the medical oncologist in the university hospital (Follow-up)
- Date of death

Discrepancies in patient records related to diagnosis and treatment given were discussed with the nurses and medical oncologists of the department. Survival data were obtained from the medical chart. When information about the patients' deaths was unclear or not well documented, these patients were discussed with their general practitioner or with their family.

Hormonal receptor status was documented for both estrogen- and progestarone receptors, using the immune reactive score (Remelle score). Positive receptor stage was given to a score of 2 and more.

HER2 over-expression was determined by the immunohistochemical staining score (DAKO Hercep Test^{TM}) and a fluorescence in-situ hybridisation (FISH) gene

amplification analysis and was reported as positive after a test result of DAKO 3+ and DAKO 2+ together with a positive FISH test result.

Patient characteristics and tumour characteristics were verified retrospectively in the medical chart. Information regarding year of diagnosis, age, site of metastases, and medical treatments was also obtained directly from the medical chart. When no information describing tumour characteristics, estrogen and progestarone receptor status and HER2 receptor status was available in the medical chart, the missing data were verified with the tumor registry of Munich and with the department of pathology of the university hospital Munich, Großhadern. Missing data after this verification were coded as unknown.

A differentiation was made between visceral and non-visceral metastases. Patients presenting with soft tissue/lymph node involvement, bone involvement and/or cutaneous involvement at the exclusion of any other site were classified as having non-visceral metastases. Numbers of metastatic sites in course of treatment were analysed. One site was defined as one organ involved. A differentiation was also made between local-recurrence (e.g. local lymph node metastasis) and distant metastases.

Systemic treatment agents were analysed and a differentiation was made in; adjuvant chemotherapy and hormone therapy given, numbers of sequences of palliative chemotherapy given, numbers of sequences of palliative endocrine therapy given and the percentage of aromatase inhibitors given within, and bisphosphonate therapy given in course of treatment. Finally the total number of sequences of systemic treatments provided in palliative care was calculated and analysed. One

sequence of therapy (chemotherapeutical/endocrine therapy) was defined as one drug being given. When one drug was being given twice with other therapies being given in between, this drug was calculated as an extra sequence.

2.3 Statistical Analysis

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS version 16.0). Overall survival was measured from the initial diagnosis of systemic metastatic disease until death from any cause (intent-to-treat) or last visit to the medical oncology department.

Probability of survival was estimated by Kaplan-Meier analysis and compared using the log-rank test. Differences were considered statistically significant when $p<0.05$. A multivariate logistic regression model was used to calculate hazard ratios and 95 percent confidence intervals to investigate the relation between overall survival of metastatic breast cancer and the factors that were statistically significant in the univariate analysis. The proportional hazard assumption was tested by the global test of Grambsch and Therneau.

This study was performed as a retrospective analysis. All endpoints evaluated in this analysis are explorative in nature. Results obtained can therefore only serve the purpose of hypothesis-generation.

3. RESULTS

3.1 PATIENT CHARACTERISTICS

In total, the study identified 232 cases of women with MBC who received their entire anti-cancer treatment in our outpatient clinic. Table 9 shows a summary of patient characteristics. Patients were diagnosed with primary breast cancer at a median age of 49 years (range: 25-84) and 53 years (range: 27-87) for the diagnosis of metastatic disease. The median time of follow-up of the living study participants was 35.5 months. The greater part (76.2%) were diagnosed with a tumor smaller than 5 cm (T1 and T2 stage of tumor at diagnosis), with 14 % having a tumor of 5 cm at least at diagnosis. Approximately a quarter had a node negative tumor (n=64, 27.6%).

Of the 232 women who were analysed in this investigation, 32 (14.7%) had synchronous metastasis at the time of diagnosis. The majority of patients with node positive disease (n=142) received adjuvant chemotherapy 71.9% (n=102). The administration of anthracyclines (31.0%), the combination of CMF (30.3%), and the combination of anthracyclines and taxanes (14.8%), were the most frequently given adjuvant chemotherapies. Adjuvant endocrine therapy was administered to 42.2% of all patients. Invasive surgery was performed on 44.4% of the patients, they received a mastectomy. Almost half of the patients received adjuvant radiotherapy (46.2%).

The median time between primary diagnosis and metastatic disease was 35.5 months (range 0-18 yrs). Hormone receptor (HR) positive tumours were found in 174 patients (75%). Subdivided, 70% of the women (n=163) had an estrogen-receptor positive tumor and 65% (n=151) were progestarone-receptor positive. An over-expression of HER2 was detected in one third of patients (n=79, 34%). A triple negative tumor was diagnosed in 15 patients (6.5%).

Table 9. Patient characteristics of women with metastatic breast cancer.

Patient characteristics	**All patients; n (%)**
Patients	232 (100)
Median age at diagnosis of primary lesion [range;years]	49 [25-84]
Median age at diagnosis of metastases [range;years]	53 [27-87]
Median time between primary lesion and first metastasis [range;months]	35.5 [0-24]
Median time of follow up of metastatic disease [range;months]	33 [0-281]
Size of primary lesion	
Tis	2 (0.8)
T1	90 (38.8)
T2	85 (36.6)
T3	18 (7.8)
T4	15 (6.5)
Unknown	22 (9.5)
Nodal status of primary lesion	
N0	64 (27.6)
N1	122 (52.6)
N2	16 (6.9)
N3	4 (1.7)
Unknown	26 (11.2)
Metastases at time of primary lesion	
M0	198 (85.3)
M1	34 (14.7)
Grading of primary lesion	
G1	7 (3.0)
G2	99 (42.7)
G3	113 (48.7)
Unknown	13 (5.6)

Estrogen receptor status	
ER positive	163 (70.3)
ER negative	59 (25.4)
Unknown	10 (4.3)
Progestarone receptor status	
PR positive	151 (65.1)
PR negative	72 (31.0)
Unknown	9 (3.9)
HER2 receptor status	
HER2 positive [a]	79 (34.1)
HER2 negative	119 (51.3)
Unknown	34 (14.6)
Triple negative [e]	15 (6.5)
Site of first metastasis [b]	
Liver	72 (22.3)
Lung	60 (18.6)
Bone	88 (27.2)
Brain	10 (3.1)
Soft tissue [c]	80 (24.8)
Other [d]	13 (4.0)
Non-Visceral and Visceral metastasis	
non-Visceral	114 (49.1)
Visceral	118 (50.9)
Number of metastatic sites in the course of treatment	
1	83 (35.8)
2	82 (35.3)
≥3	67 (28.9)
Surgery of primary tumour	
Lumpectomy	14 (6.0)
Quadrantectomy	47 (20.3)
Mastectomy	103 (44.4)
Other	45 (19.4)
No Surgery	23 (9.9)
Adjuvant radiotherapy of primary tumour	
Yes	109 (46.2)
No	125 (53.8)
Adjuvant treatment of primary tumour:	
Chemotherapy of N positive patients [f]	
Anthracyclines	44 (31.0)
CMF	43 (30.3)
Anthracyclines + Taxanes	21 (14.8)
Taxanes	1 (1.4)
Other regimens	8 (5.6)
No Adj. Chemotherapy	40 (28.2)
Endocrine treatment of all patients	98 (42.2)

[a] HER2 positive = DAKO 2+ with FISH+ or DAKO 3+
[b] Patients were mentioned twice or more because of two or more metastatic sites (sum>100%).
[c] Includes axillary and supraclaviculary lymph nodes and local recurrence.
[d] Includes skin, orbita, ovarial, retina, pericard, thyroid, kidney and peritoneal metastases.
[e] Triple negative are patients with a negative estrogen receptor, a negative progestarone receptor and a negative HER2 receptor.
[f] Patients were mentioned twice because of combination therapies (sum>100%).

Regarding metastatic disease, visceral (solid organ) involvement was diagnosed in 118 patients (50.9%). The site of first metastases was (in descending order): Bone- (27.2%), soft tissue including lymph-nodes and skin- (24.8%), liver- (22.3%), lung- (18.6%), other (4.0%), and brain metastases (3.1%).

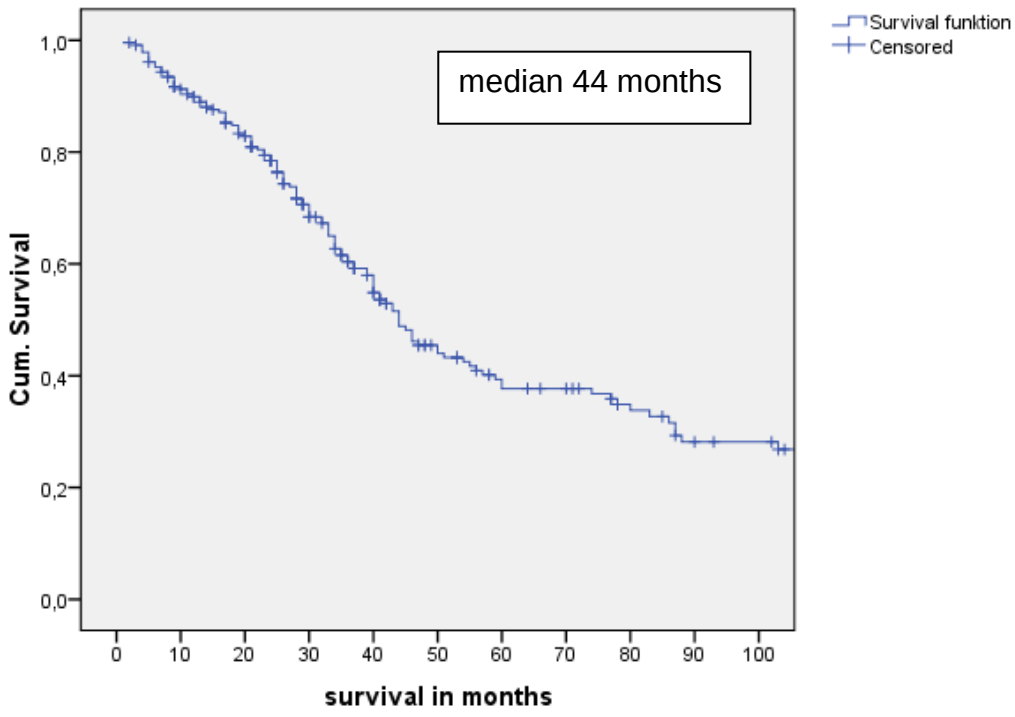
Considering the course of disease, almost one third (28.9%) developed more than three different sites of metastasis, whereas 70% developed two different sites or less. Patient characteristics of the whole study population are presented in Table 9.

3.2 SURVIVAL

3.2.1 OVERALL SURVIVAL

At the time of analysis, 126 women (60%) out of 232 had died because of metastatic disease. The median overall survival (OS) for all women included in this research was 44 months [95% CI; 39-49 months]. These results are shown in the Kaplan Meyer survival plot of the 232 women with MBC included in this analysis (Figure 8).

Figure 8. Kaplan-Meier estimate of OS of all patients.



No. at Risk:

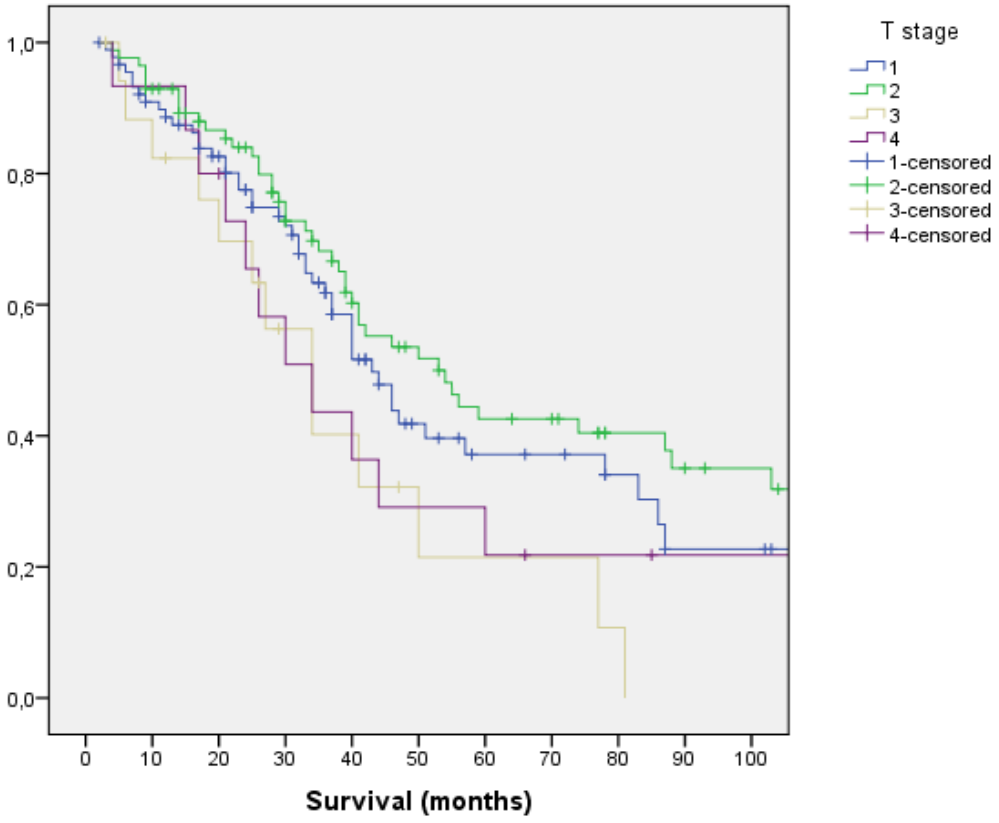
All patients	232	171	86	46	31

3.2.2. TUMOR CHARACTERISTICS AND SURVIVAL

3.2.2.1 TUMOR SIZE

Considering tumour size at primary diagnosis, women with tumours between 2 and 5 cm (pT2) had the longest median survival of 53 months [95% CI 37-69 months]. Women with pT3 and pT4 tumours at diagnosis had a median survival of 34 months, see Figure 9.

Figure 9. Kaplan-Meier estimate of overall survival by T stage of primary tumor.



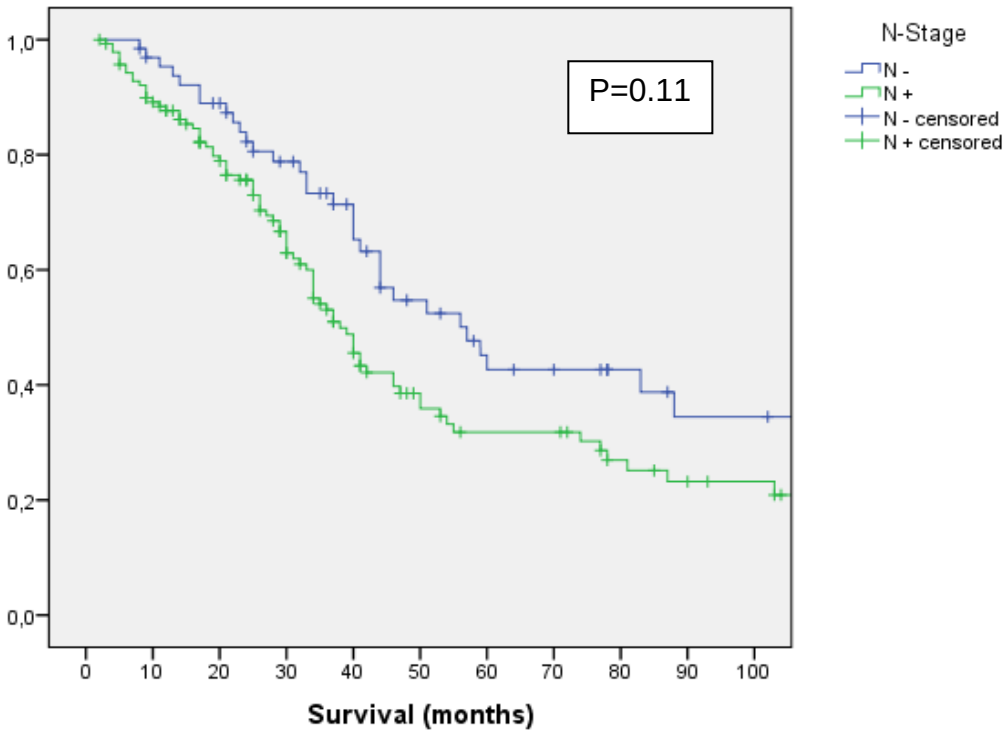
No. at Risk:

T1	88	66	30	14	9
T2	84	66	36	23	15
T3	16	11	5	2	1
T4	14	11	5	3	2

3.2.2.2 Nodal Stage

Of all patients 65 women had node negative tumours. With 57 months [95% CI 41-73 months], these women had better survival rates than those with node-positive tumours (n=141). They showed a median OS of 38 months [95% CI 32-44 months]. The distribution of overall survival rates of node-positive vs. node-negative patients reached the level of significance with p=0.037 (Figure 10A).

Figure 10A. Kaplan-Meier estimate of overall-survival by N-stage of primary tumor.

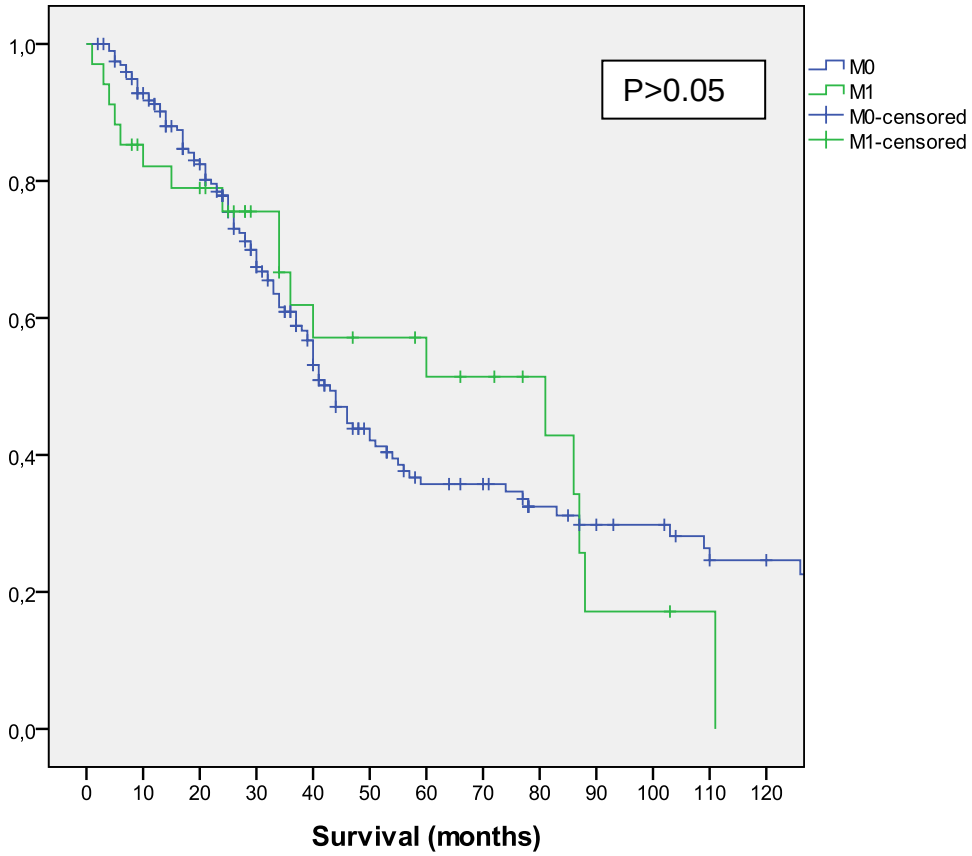


No. at Risk:					
N-negative	65	54	32	17	11
N-positive	141	96	41	22	15

3.2.2.3 M-STAGE OF DISEASE AT DIAGNOSIS

Thirty-four women (14.7%) had synchronous metastases at time of primary diagnosis. At time of analyses 18 women (53%) died. Median age at time of diagnosis of these women was 52 years. Of these women 27 (79.4%) had hormone receptor positive disease. A visceral metastases was diagnosed in 12 cases (35.3%) and 10 women (29.4%) had primary bone metastases. The distribution of overall survival rates of women with synchronous metastases (median OS of 81 months [95% CI 15-146]) versus women with metachronous metastases (median OS of 43 months [95% CI 38-47]) did not reach the level of significance (p>0.05) (Figure 10B)

Figure 10B. Kaplan-Meier estimate of overall-survival by M1-stage of primary tumor.



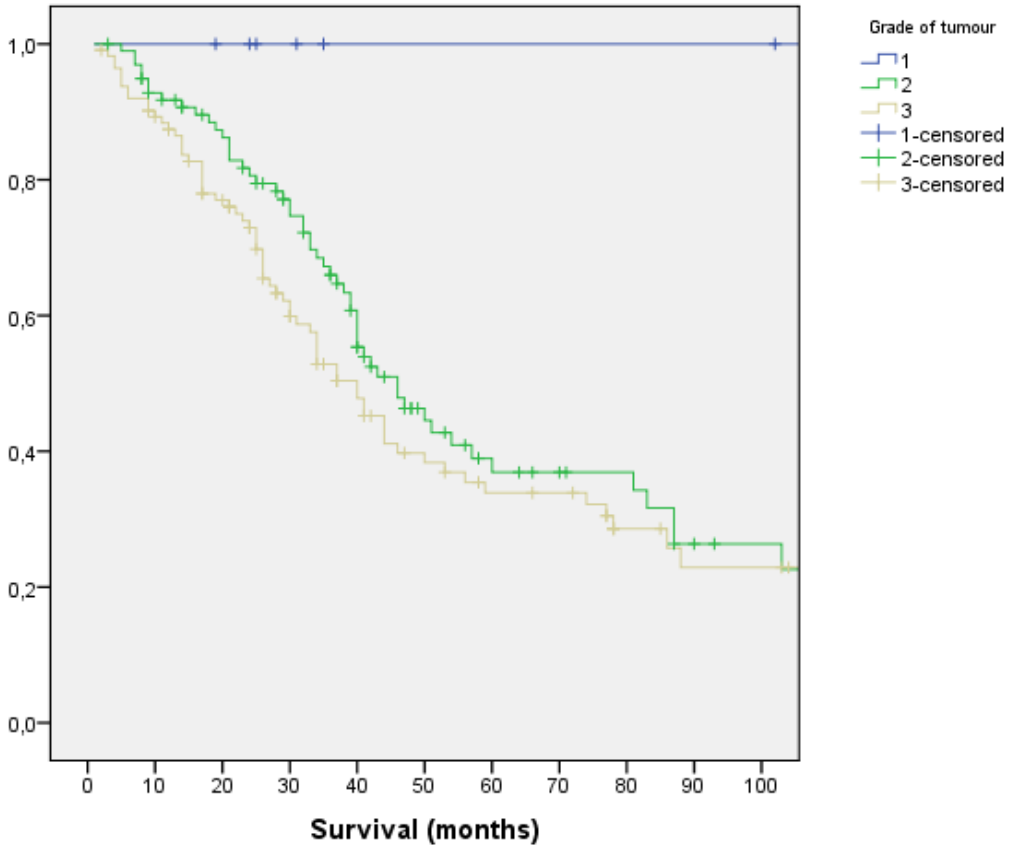
No. at Risk:

M0	195	146	78	36	24
M1	33	24	12	9	5

3.2.2.4 GRADING

Women with grade 3 tumours (n=113] had a median survival of 40 months [95% CI 33-47 months], compared to a median overall survival of 46 months [95% CI 36-56 months] for women with a grade 2 tumour. The 7 women with a grade 1 tumour at diagnosis all lived at the time of analysis. Therefore, we cannot report the survival rates for these women (Figure 11).

Figure 11. Kaplan-Meier of estimate of OS and grade of tumour at diagnosis.



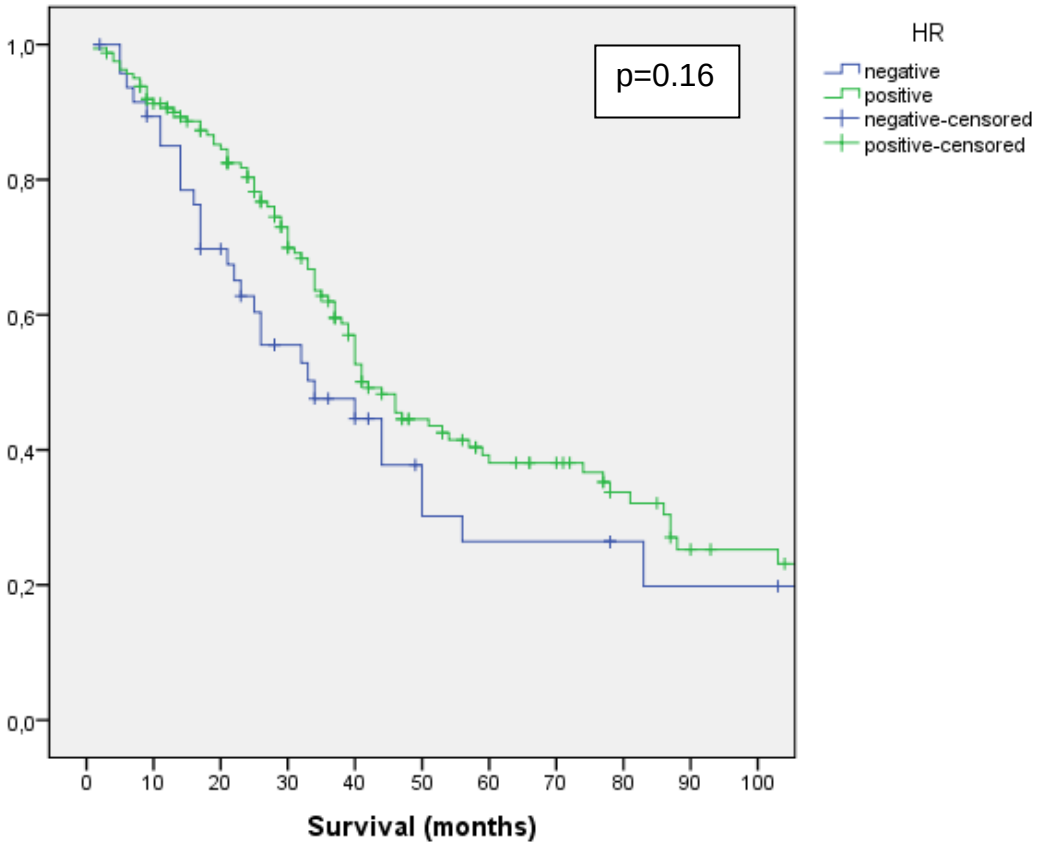
No. at Risk:

G1	7	7	7	7	7
G2	99	77	39	18	14
G3	113	78	37	22	11

3.2.2.5 HORMONE RECEPTOR

In total 49 patients were diagnosed with a hormone receptor negative tumor. Hormone receptor positive tumours were seen in 174 patients. Of nine patients the HR status was unknown. Women with HR-positive tumours showed a median survival of 46 months [95% CI 38-54 months], whereas the survival of those with HR-negative tumours was 34 months [95% CI 18-50 months]. Despite a median survival difference of 12 months, this difference does not reach the level of significance (p>0.05) (Figure 12).

Figure 12. Kaplan-Meier estimate of OS by HR.

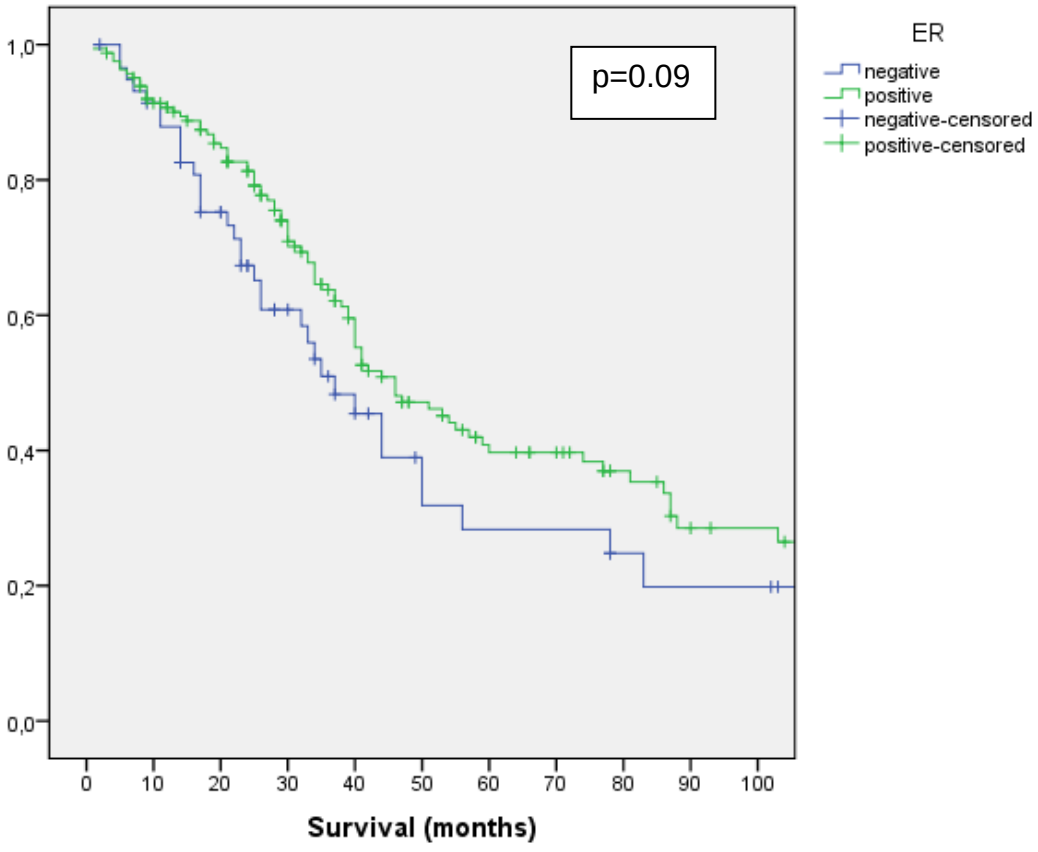


No. at Risk:

HR-	174	132	64	35	23
Hr+	49	31	7	8	5

Subdivision of hormone receptor-stage of disease showed a median survival of 37 months [95% CI 28-46] for estrogen negative disease (n=59), compared to 46 months [95% CI 35-57] for women with an estrogen positive tumour (n=164, p=0.091) (Figure 13) . Statistical significance was shown in median OS and progestarone receptor (PgR) stage of the tumour with a median OS of 40 months [95% CI 29-51] for PgR negative- (n= 72) and 44 months [95% CI 34-54] for PgR positive tumours (n=151) (p=0.044) (Figure 14).

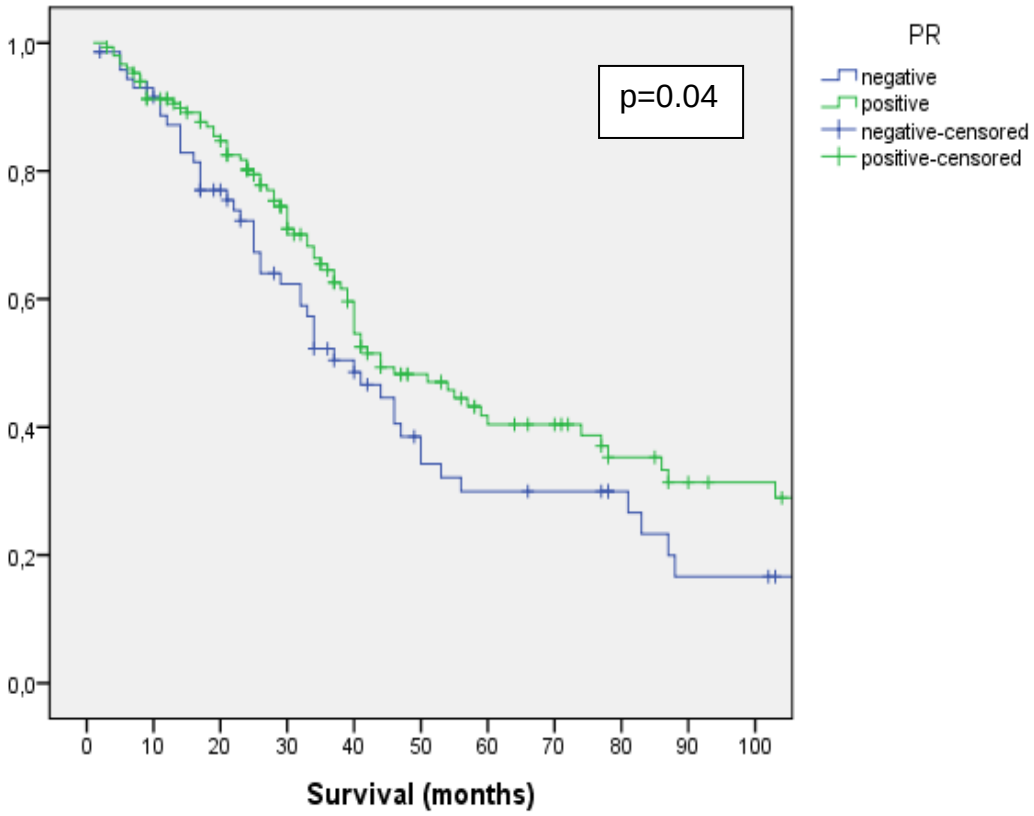
Figure 13. Kaplan-Meier estimate of OS by estrogen receptor stage of disease.



No. at Risk:

ER-	57	38	15	8	5
ER+	163	125	64	36	23

Figure 14. Kaplan-Meier estimate of OS by progestarone receptor stage of disease.

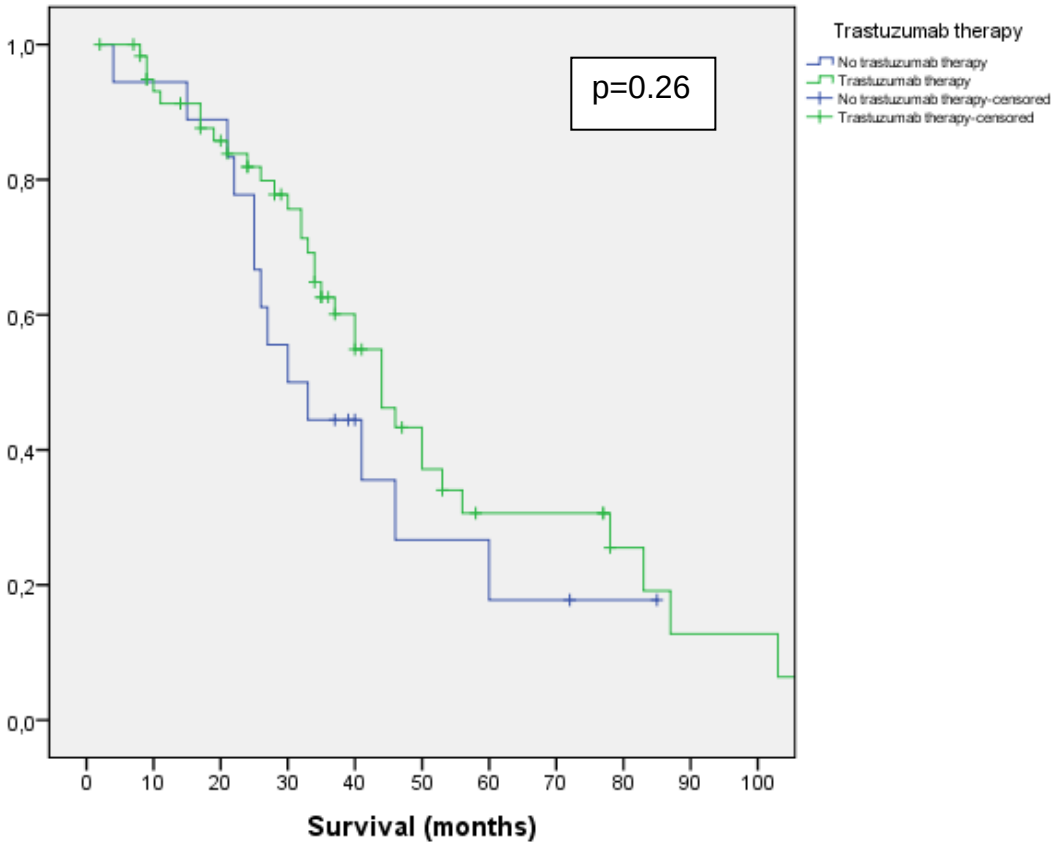


No. at Risk:

PR-	71	49	25	14	9
PR+	150	114	54	29	19

When HER2 over expression is considered, median overall survival did not demonstrate any significant difference, with 42 months [95% CI 32-52] for HER2 negative (n=119) and 41 months [95% CI 37-51] for HER2 positive tumours (n=79). Looking at the group of women with a HER2 positive tumour and the ones who received trastuzumab (n=61) as medication, a median OS of 44 months [95% 36-52] was shown, compared to 30 months [95% CI 18-42] for the ones who did not receive trastuzumab (n=18). Of the 79 patients with HER2 positive tumours, 61 received trastuzumab (77.2%) (Figure 15)

Figure 15. Kaplan-Meier estimate of OS by trastuzumab therapy for HER2 positive tumours.

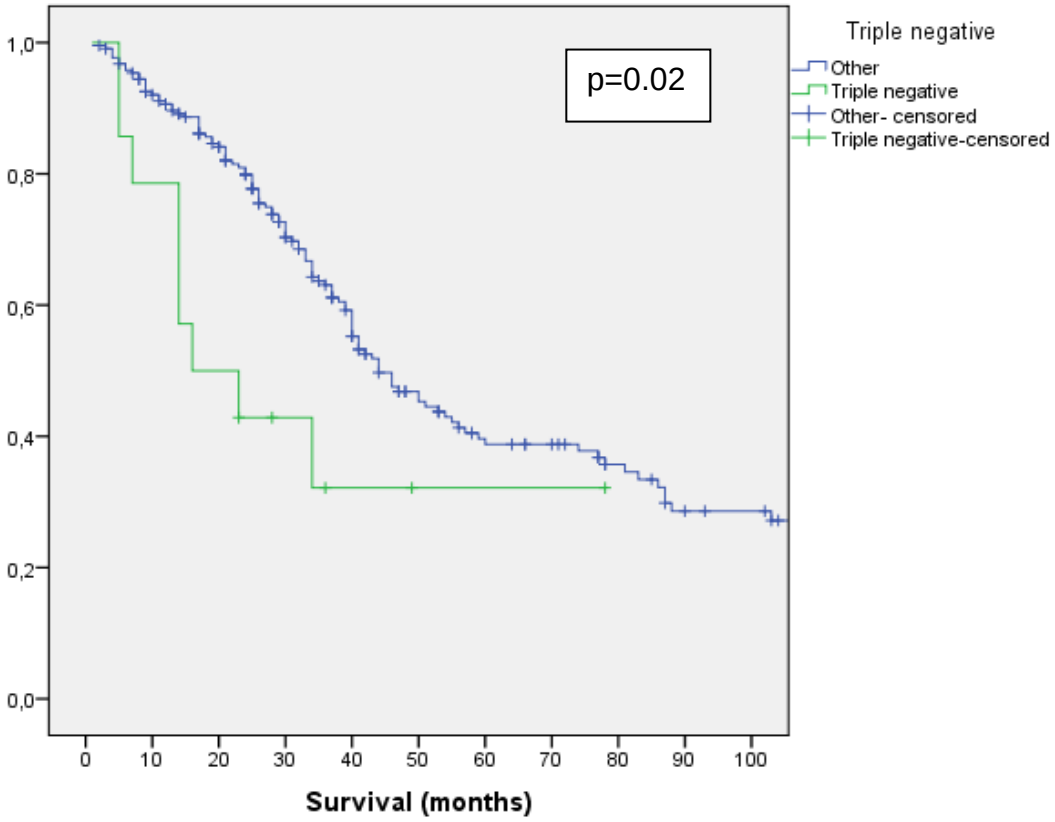


No. at Risk:

T-	17	16	6	2	1
T+	58	45	20	8	4

Triple negative disease was clearly related to a negative survival outcome. We identified 15 patients (6.5%) with triple negative disease. These 15 women had a median OS of 16 months [95% CI 7-25] (p=0.018). See figure 16 for the overall survival curve of these women.

Figure 16. Kaplan-Meier estimate of OS by triple negative disease.



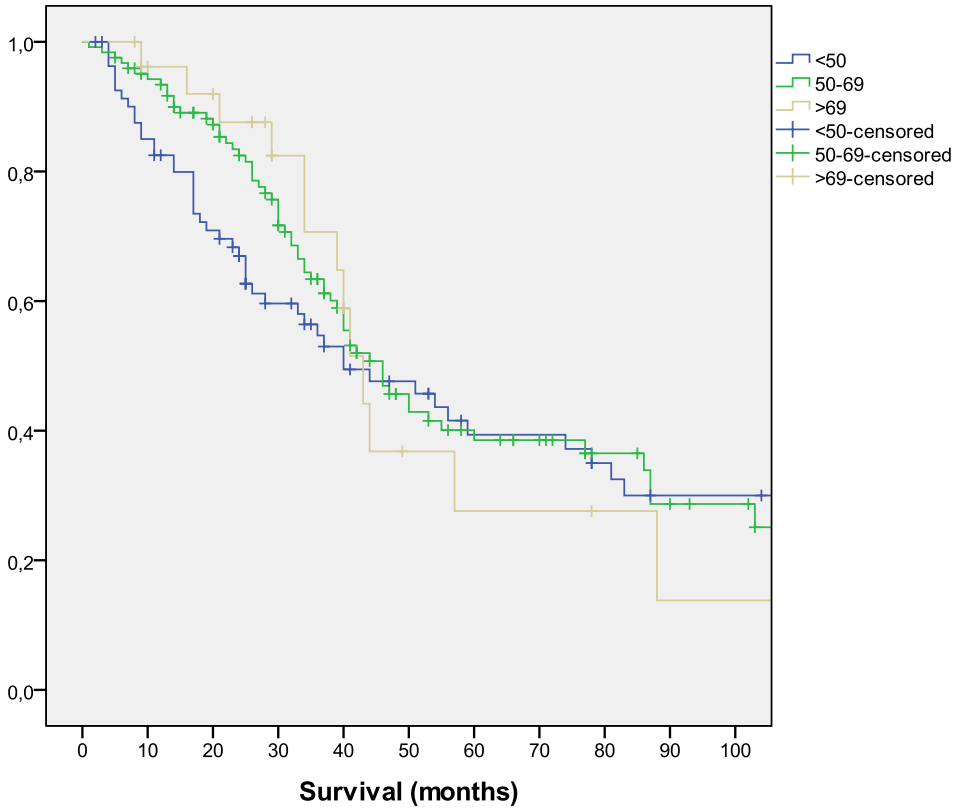
No. at Risk:

Other	217	163	83	46	31
Triple-	15	7	1	0	0

3.2.2.6 AGE AT DIAGNOSIS

A survival analysis was also made for the factor “age at diagnosis of metastatic disease”. This analysis was made in different age groups; >50, 50-69 and ≥ 70 years. Median age at diagnosis of metastatic disease was 53 years [range: 27-87]. Eighty-two women (35%) were younger than 50 years, 123 women (53%) were between 50 and 69 years and 27 women (12%) were ≥ 70 years at time of diagnosis. The median OS rates of three groups with ascending age category are 40 [95% CI 21-58], 46 [95% CI 38-54] and 44 months [95% CI 38-47] (Figure 17).

Figure 17. Kaplan-Meier estimate of OS by age at diagnosis



No. at Risk:					
<50	79	55	29	17	13
50-69	122	94	50	25	14
≥70	25	21	10	2	1

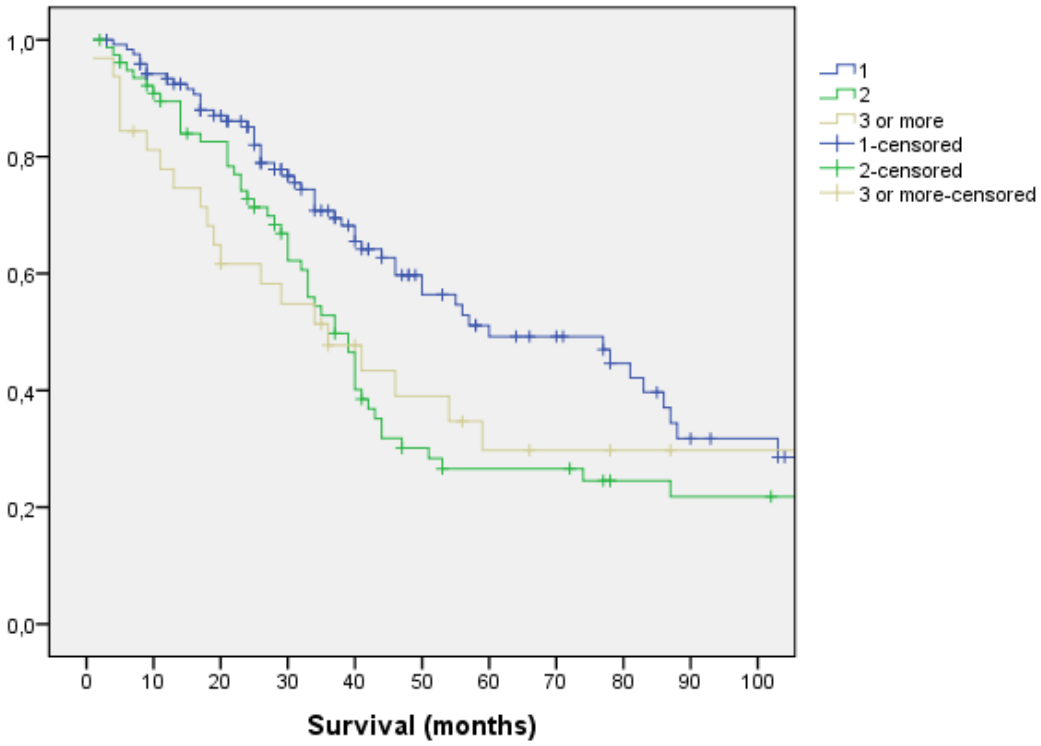
3.2.3. Course of Disease and Survival

To evaluate the influence of course of disease on survival, the number of metastatic sites developed, local recurrence versus distant relapse, the presence of visceral metastasis (recorded as yes or no), and single lung and single liver metastasis specifically were analysed.

3.2.3.1 Number of Metastatic Sites

This study considered 122 women who developed one metastatic site during the course of disease. These patients had a median OS of 60 months [95% CI 33-87]. Two metastatic sites were developed by 78 women and this group had a median OS of 37 months [95% CI 32-42]. Three or more sites in course of disease were shown by 32 women (median OS of 36 months, 96% CI 18-54). Figure 18 shows the survival curves for these patients.

Figure 18. Kaplan-Meier estimate of OS by number of metastatic sites developed during the course of disease.

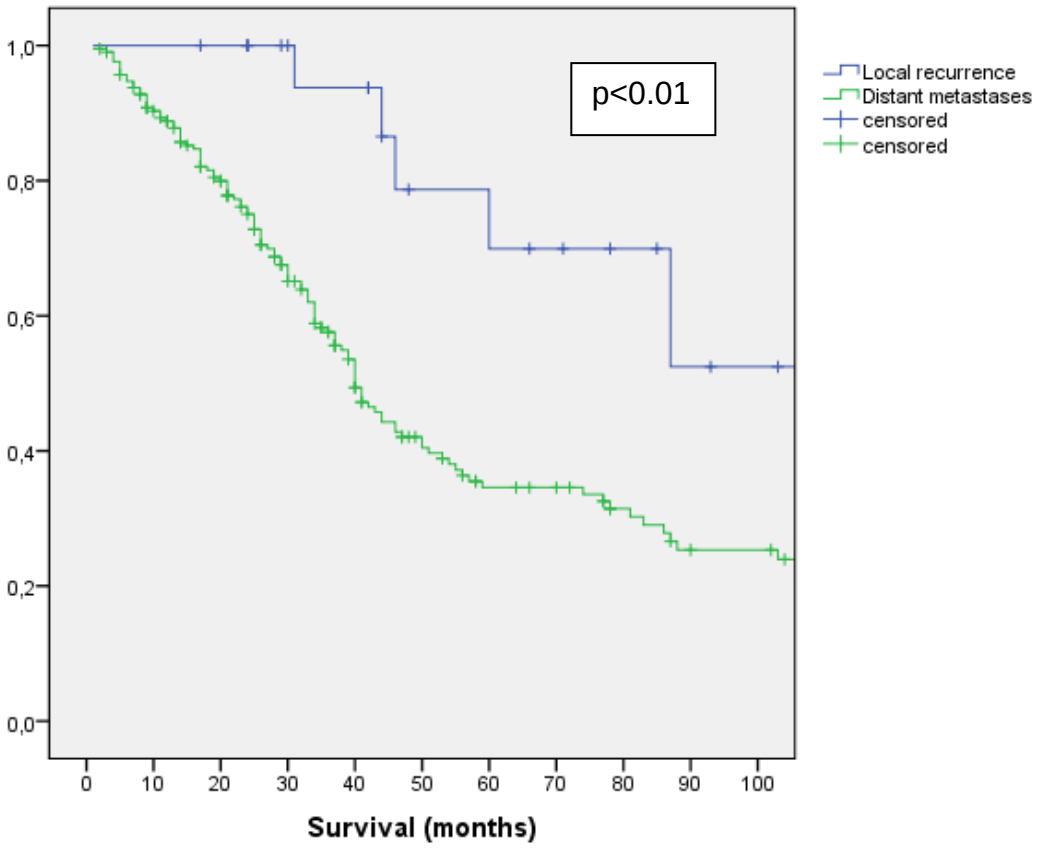


No. at Risk:					
1	122	92	48	26	18
2	78	59	25	14	9
3>	32	18	11	6	4

3.2.3.2 Local Recurrence and Distant Metastases

This study also differentiated between women who developed a local recurrence (n=22) (e.g. local lymph node recurrence) and women who had distant metastases during the course of disease. The group of women who developed a local recurrence did not reach the 50% cumulative survival line; as a consequence a median OS rate could not be estimated. The survival curve of these women showed a very good prognosis until study end. The women who developed distant metastases (n=210) showed an OS of 39 months [95% CI 34-44]. This distribution reached the level of significance ($P < 0.01$) (Figure 19).

Figure 19. Kaplan-Meier estimate of OS and distant metastases versus local recurrence of disease.



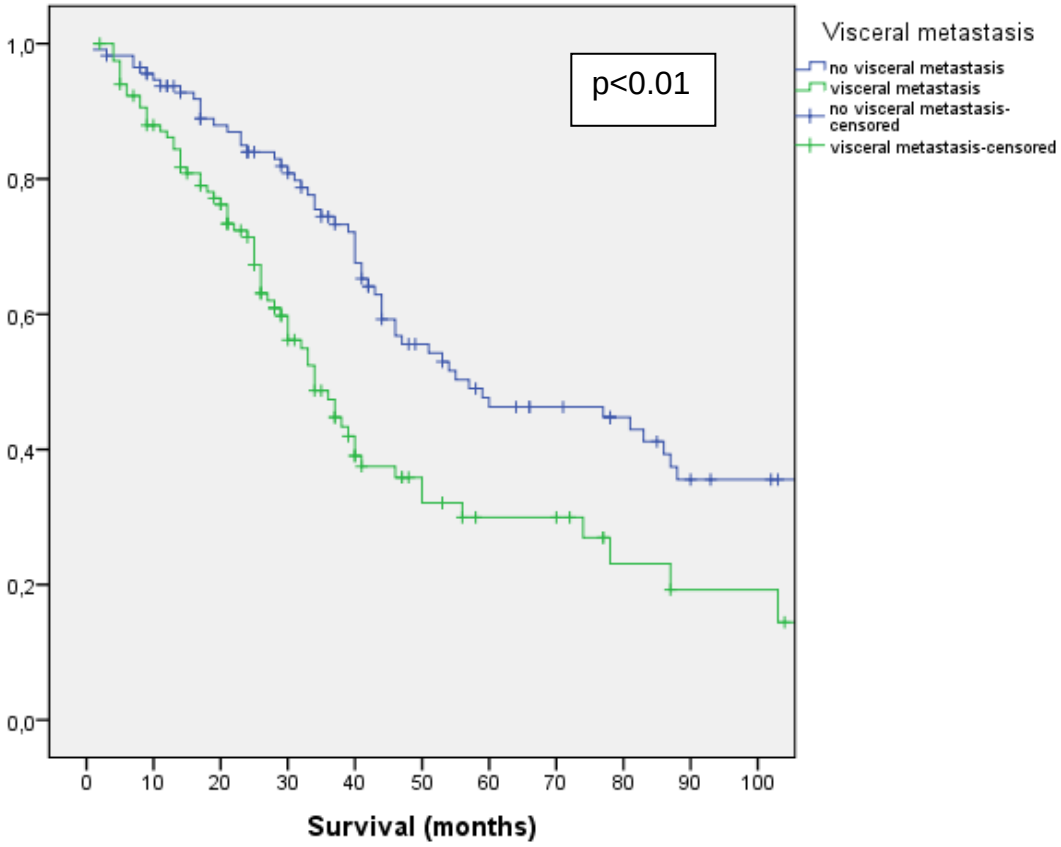
No. at Risk:

Local	15	15	15	9	5
Distant	209	148	69	38	26

3.2.3.3 VISCERAL METASTASIS

The negative prognostic outcome related to visceral involvement of metastatic disease was confirmed by the OS of this group of women in this study. Visceral organ involvement was documented for 118 women and showed a median OS of 34 months, compared to a median OS of 57 months for no visceral involvement in 114 women (P=0.001) (Figure 20).

Figure 20. Kaplan-Meier estimate of OS by visceral or non-visceral metastases.



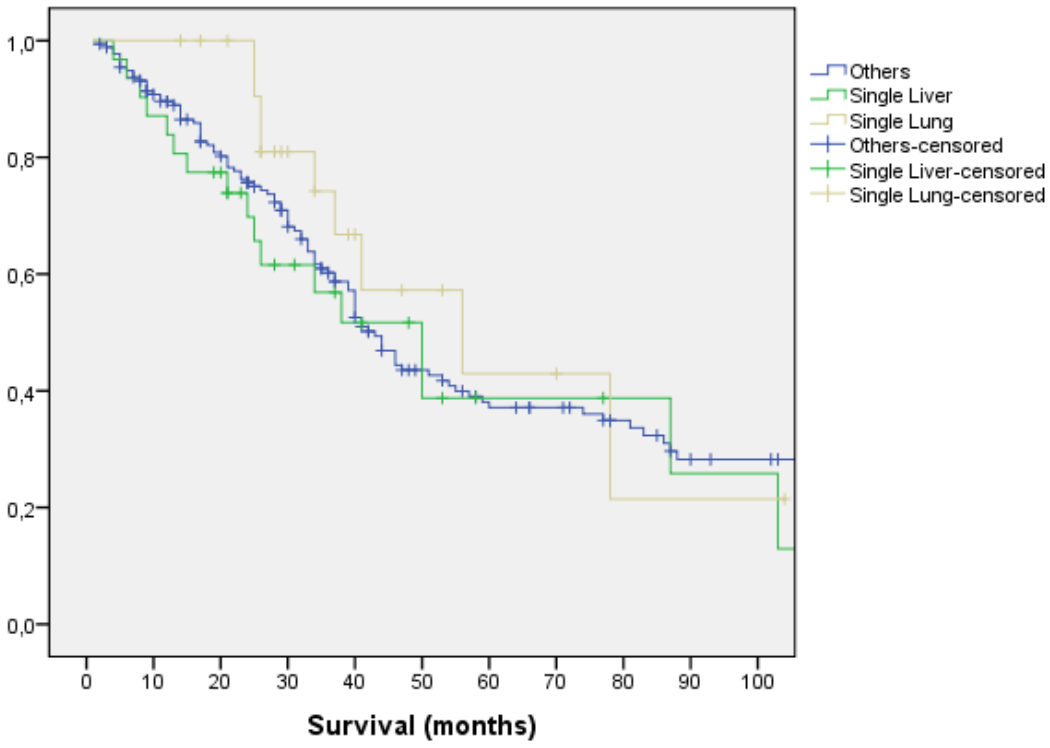
No. at Risk:					
No visc. met.	113	93	59	37	25
Visc. met.	116	80	25	12	6

3.2.3.4 Singular Lung and Liver Metastasis

As loco-regional treatment options of metastatic breast cancer are improving (e.g. surgical resection, RFA), women with these metastases were analysed specifically regarding survival.

Singular lung metastasis was shown in 24 women. Of this group, 9 women died because of MBC. The median OS rate for this group was 56 months (95% CI 23-89). Singular hepatic lesions were shown in 31 women; of these, 17 women died as a result of MBC. The median OS for this group of women was 50 months (95%CI 31-69) (Figure 21).

Figure 21. Kaplan-Meier estimate of OS by single liver and single lung metastases.



No. at Risk:					
Others	177	127	74	41	28
Liver	31	22	11	4	3
Lung	24	24	8	3	1

Loco-regional treatments for hepatic- and pulmonal metastases were given to 31 patients (13 patients received radiofrequency ablation (RFA), laser-induced thermo therapy (LITT) was given to three patients, one patient was treated with chemoembolisation of the liver, partial liver- or lung resection was performed on three and 11 patients).

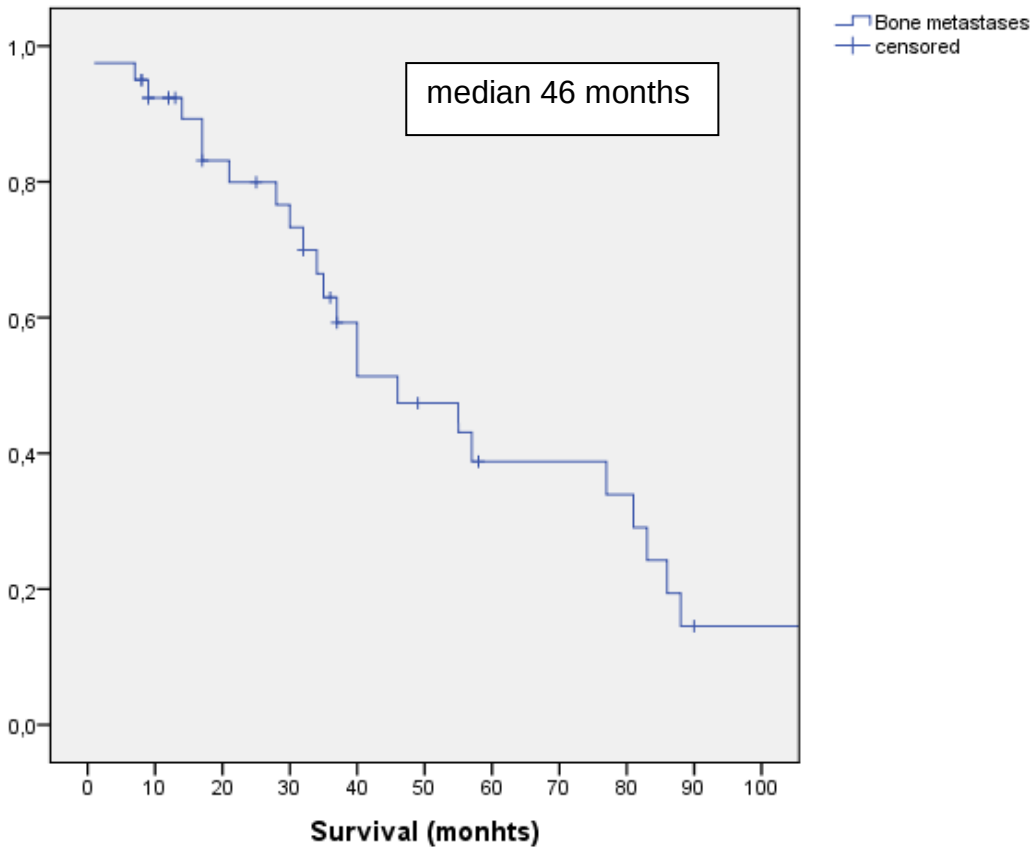
3.2.3.5 BONE METASTASES

Of all the patients studied, 91 women (39.2%) developed bone metastases in the course of disease. Treatment with bisphosphonates was given to 57 patients (63%) while the other patients received systemic treatment with endocrine-, targeted and/or chemotherapy regimens with or without radiotherapy. Bisphosphonate therapy was also given to 28 patients without bone metastases. Reasons for these women to receive a bisphosphonate therapy could be that they received an endocrine treatment (aromatase inhibitors) which led to osteoporosis and/or because patients were susceptible for osteoporosis because of age.

Hormonal-ablative therapies for breast cancer can cause marked and rapid reductions in circulating estrogen levels, resulting in significant effects on bone metabolism and cancer treatment-induced bone loss (CTIBL). Bisphosphonates have the potential to delay or prevent CTIBL in patients receiving hormonal therapies[46]. Among all patients, 40 women had only bone metastases. Of these patients 85% received bisphosphonate treatment.

The median OS of the women bone metastases was 46 months (Figure 22).

Figure 22. Kaplan-Meier estimate of OS by bone metastases.



No. at Risk:

Bone	40	26	16	10	8

3.3 UNI- AND MULTIVARIATE ANALYSIS

A univariate analysis was made to investigate the relation between the prognostic factors investigated in this study and the overall survival rates of MBC (Table 10). A P- value of global test was calculated for categorical variables.

Table 10. Univariate analysis of prognostic factors for overall survival.

	Overall Survival			
Characteristics	**Hazard Ratio**	**95% CI**	***P***	***P Value of global test for categorical variables***
Age at metastatic disease	1.00	0.98-1.01	0.60	
T Stage				0.16
T1	5.16	1.10-23.58	0.04	
T2	0.86	0.44-1.66	0.65	
T3	0.71	0.37-1.37	0.31	
T4	1.54	0.68-3.46	0.30	
N Stage				0.18
N1	1.28	0.18-9.37	0.81	
N2	1.98	0.27-14.23	0.50	
N3	1.97	0.25-15.56	0.52	
M Stage	0.98	0.60-1.62	0.94	
Grading				6.11
G1	0.00	0.00-8.55	0.95	
G2	0.84	0.59-1.19	0.32	
G3	-	-	-	
Estrogen receptor	0.72	0.49-1.06	0.09	
Progestarone receptor	0.70	0.49-1.06	0.09	
Hormone receptor	0.73	0.49-1.09	0.12	
Her2 receptor	1.25	0.85-1.83	0.26	
Triple negative disease	2.22	1.12-4.40	0.02	
Number of metastatic sites				0.01
1	0.61	0.37-1.01	0.06	
2	1.09	0.66-1.78	0.75	
≥3	-			
Visceral metastases	1.76	1.24-2.50	<0.01	
Distant metastases	3.68	1.50-9.02	<0.01	

David W. Hosner and Stanley Lemeshow wrote in Chapter 5 of their book about “applied survival analysis” that all significant variables at the 20-25 percent level ($p<0.2$) in the bivariate analysis should be selected for the multivariate analysis [68].

For this study the covariates T-Stage, N-Stage, estrogen receptor, progesterone receptor, hormone receptor, triple negative disease, number of metastatic sites, visceral metastases and distant metastases were therefore part of the multivariate logistic regression model. To avoid the problem of multicollinearity, this study took triple negative disease (most significant associated with OS, $p=0.02$) as a factor for the multivariate analyses and left estrogen receptor, progesterone receptor and hormone receptor out of the analysis. The final model included 199 patients. The proportional hazards assumption of the Cox regression model was reasonably fulfilled ($p=0.623$).

In the multivariable model T-stage (P-value of global test: <0.01), triple negative disease ($p=0.02$), number of metastatic sites ($p=0.02$) and visceral metastasis ($p<0.01$) were statistically significant associated with worse overall survival after adjusting for all factors in the table (Table 11).

Table 11. Multivariate analysis for overall survival.

	Overall Survival			
Characteristics	**Hazard Ratio**	**95% CI**	***P***	***P Value of global test for categorical variables***
T Stage				<0.01
T1	6.96	1.35-35.91	0.02	
T2	1.10	0.52-2.31	0.82	
T3	0.70	0.33-1.49	0.35	
T4	2.16	0.86-5.42	0.10	
N Stage				0.19
N1	2.83	0.37-21.37	0.31	
N2	3.81	0.51-28.34	0.19	
N3	5.31	0.65-43.61	0.12	
Triple negative disease	2.53	1.18-5.41	0.02	
Visceral metastasis	2.10	1.34-3.18	<0.01	
Number of metastatic sites				0.02
1	0.95	0.53- 1.71	0.86	
2	1.07	0.95-3.07	0.08	
≥3	-	-		
Distant metastasis	2.12	0.73-6.18	0.17	

3.4 CHARACTERISTICS OF PALLIATIVE CHEMOTHERAPY

3.4.1 OVERVIEW OF PALLIATIVE CHEMOTHERAPY TREATMENT

Following adjuvant treatment (see Table 9.), anthracyclines and taxanes were the most frequently given first-line palliative treatments, followed by capecitabine, navelbine and CMF. As second-line treatment, most patients received capecitabine, or gemcitabine in combination with cisplatin, or navelbine. As third-line treatment, most patients were treated with taxanes, capecitabine and other substances (e.g. bendamustin, mitoxantrone). Table 12 and Figure 23 give an overview of 1st, 2nd and 3rd-line cytostatic treatment of metastatic disease.

Table 12. Overview of chemotherapy given in palliative intent.

Palliative Treatment	**First-line (n)**	**Second-line (n)**	**Third-line (n)**
Anthracyclines	12	3	0
Anthracyclines and Taxanes	54	1	1
CMF	16	0	7
Taxanes	19	8	20
Capecitabine	19	24	20
Gemcitabine/Cisplatin	7	19	17
Navelbine	18	10	17
Others	23	14	30

Figures 23. Overview of the palliative regimens given to the patients (n)

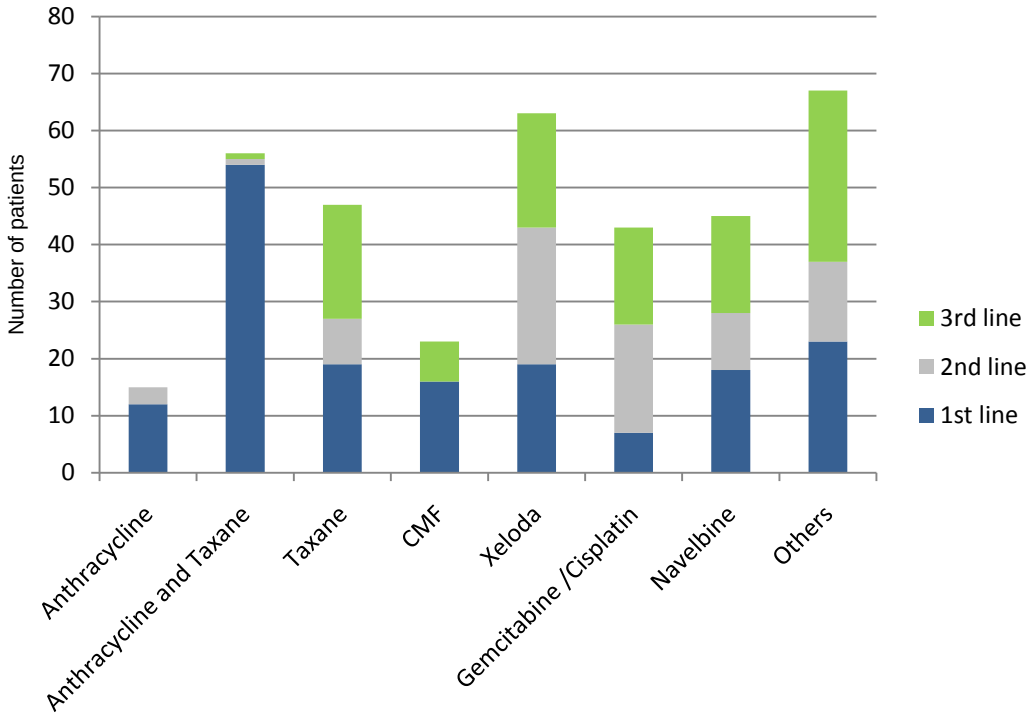


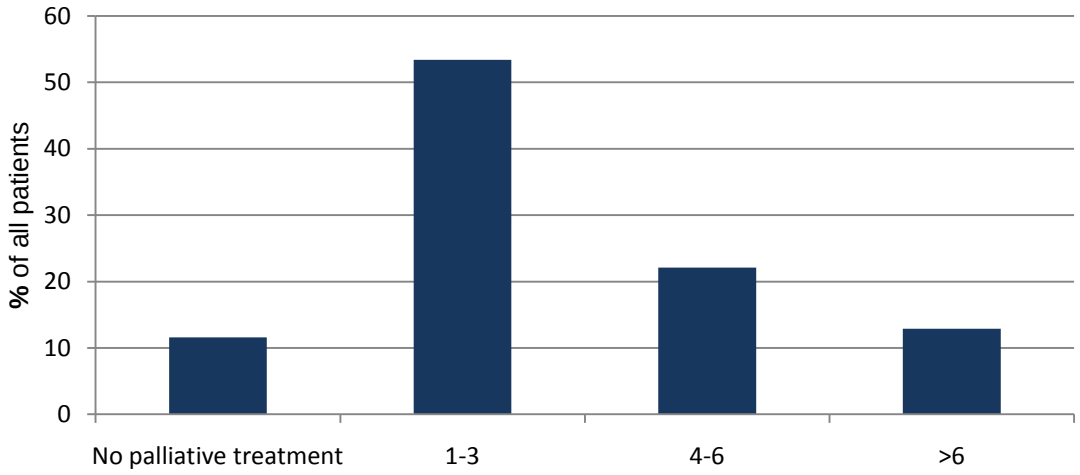
Figure 22 analyzed together with the adjuvant chemotherapy given, shows that most of the women received anthracycline and taxane treatment in course of disease. Capecitabine, navelbine, gemcitabine and cisplatin were also used frequently in the treatment of MBC.

3.4.2 Sequences of Palliative Chemotherapy Treatment and Survival

Data regarding systemic treatment of the women with MBC were used to calculate the total number of chemotherapy-sequences given to all patients during the course of treatment.

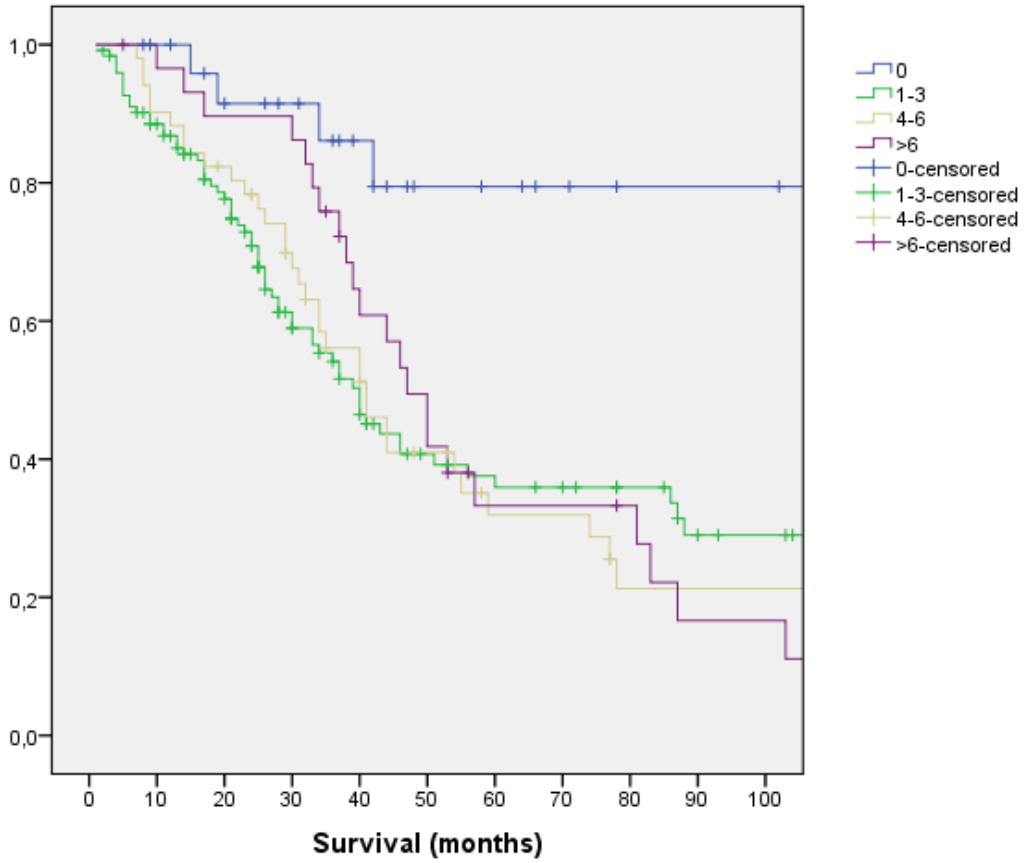
Of all women with MBC, 88.4% received chemotherapeutic therapy regimens. One to three sequences were given to 53.4%. Four to six sequences of treatment were given to 22.1% of all patients and 12.9% of all patients received more than 6 treatment sequences in the course of treatment for MBC (Figure 24).

Figure 24. Number of sequences of palliative chemotherapy given to the patients (% of all patients).



To see the effects of the step by step escalation of all the treatment modalities given in course of disease on survival, a Kaplan-Meier analysis was made for this factor (Figure 25). The survival-analysis showed the subgroup of women (blue line) who did not receive any chemotherapy treatment with an improved prognosis. These women had either HR-positive tumors and were well treated with endocrine therapy, had bone metastasis and were treated with bisphosphonates or had a loco-regional treatment (e.g. resection of lymph node recurrence and radiation therapy). Women with 1-3 sequential chemotherapies being given had a median OS of 40 [95% CI 32-48] months, patients being treated with 4-6 sequential chemotherapies showed an OS of 41 months [95% CI 32-50] and patients treated with more than 6 sequential palliative chemotherapies in the course of disease had a median OS of 47 months [95% CI 40-54].

Figure 25. Kaplan-Meier estimate of OS and sequential palliative chemotherapy given.



No. at Risk:

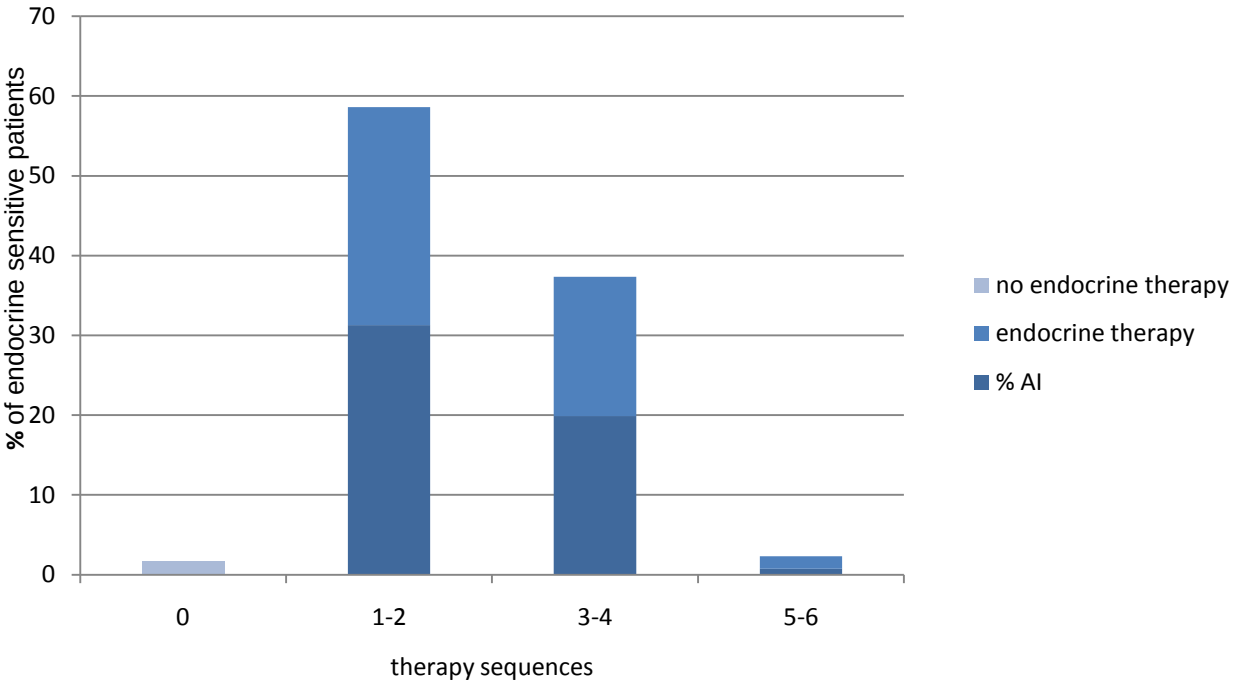
0	27	20	13	7	3
1-3	124	80	35	22	17
4-6	51	41	20	10	5
>6	30	26	16	7	6

3.5 CHARACTERISTICS OF ENDOCRINE TREATMENT AND SURVIVAL

Data about endocrine treatment was also used to calculate the endocrine sequences given in the course of metastatic disease. Of the 174 women with HR-positive disease 102 women (58.6%) received 1-2 hormone substances for MBC. Sixty-five women (37.4%) were treated with 3-4 different endocrine treatment modalities and 4 women received 5-6 (2.3%) endocrine agents in the course of disease. No endocrine therapy was given to 3 of the endocrine sensitive patients (1.7%).

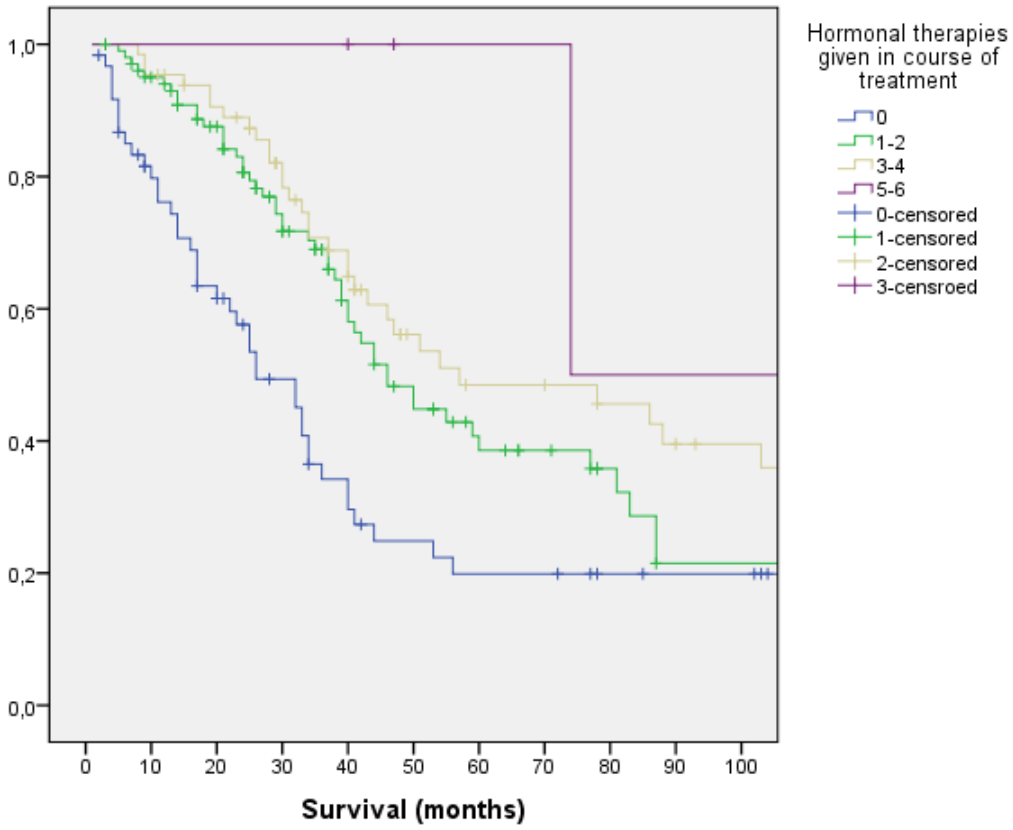
To evaluate the influence of new endocrine agents in the treatment of MBC, this study specifically looked at the percentage of aromatase inhibitors given. In the group of women treated with 1-2 endocrine agents (n=102), 53% of these endocrine treatments were aromatase inhibitors. In the group of patients treated with 3-4 endocrine sequences (n=65) and 5-6 (n=4), 53% and 33% of these sequences were aromatase inhibitors (Figure 26). These data show that the application of aromatase inhibitors is well incorporated in the endocrine treatment in our study population.

Figure 26. Overview of the endocrine sequences applied in endocrine sensitive patients (%), with percentage of aromatase inhibitors within each group.



To evaluate the influence of endocrine therapy modifications during MBC treatment on overall survival, a Kaplan Meier analysis was made for all the women (n=232). Differentiation was made in the frequency of endocrine treatment sequences; no endocrine treatment, 1-2 sequences, 3-4 sequences and 5-6 sequences (Figure 27). Women treated with 1-2, 3-4 and 5-6 had a median OS of 46 [95% CI 38-54], 57 months [95% CI 15-98] and 74 months. Of the group of women who did not receive any endocrine substances (n=61), 49 women had HR-negative disease (n=49) and had a worse prognosis from the beginning. The other 12 patients had an unknown HR-status, or were women with HR-positive disease who did not receive any endocrine therapy. They showed a median OS of 28 months [95% CI 19-37].

Figure 27. Kaplan-Meier estimate of OS by sequential endocrine therapy given.



No. at Risk:

0	61	33	13	8	5
1-2	102	77	36	18	10
3-4	65	57	34	18	15
5-6	4	4	4	4	1

3.6 SYSTEMIC TREATMENT AND SURVIVAL

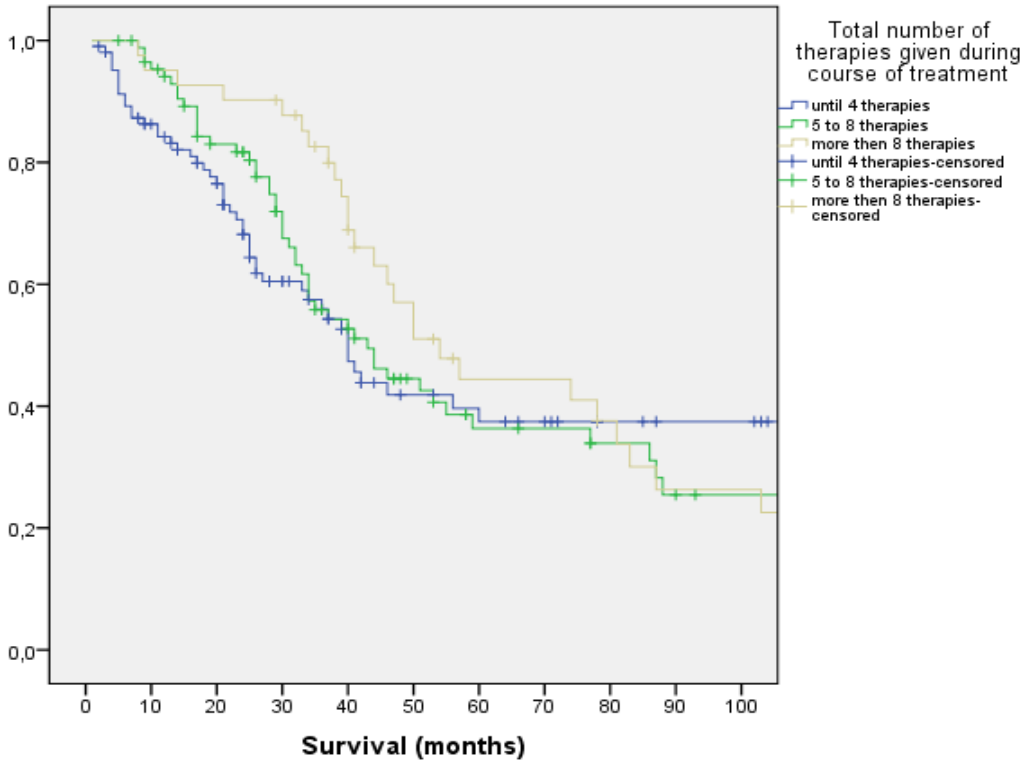
An analysis was also conducted for all treatment substances given; including chemotherapy, endocrine therapy, targeted therapy, and bisphosphonate treatment. Of the women in this study, 44.8% (n=104) received up to 4 therapy sequences, 37.5 % (n=87) received up to 8 sequences and 17.7% (n=41) received more than 8 treatment sequences for MBC (Table 13). Most of the women received more than 5 therapy sequences during the course of disease (55.2%).

Table 13. Overview of all therapy sequences given in course of disease

Total treatment sequences	**Percentage (n)**
1-4 sequences	44.8% (104)
5-8 sequences	37.5% (87)
> 8 sequences	17.7% (41)

A Kaplan-Meier survival analysis was made for this factor (Figure 28). Women with a treatment of 4 or less substances had a median OS of 40 months [95% CI 34-46], followed by 43 months [95% CI 31-54] for women treated with 5 to 8 therapies and 54 months [95% CI 41-67] for the women treated with more than 8 therapies.

Figure 28. Kaplan-Meier estimate of OS by all therapies given in course of treatment



No. at Risk:

<4	104	66	27	17	9
4-8	87	65	33	16	12
>8	41	38	27	13	10

4. DISCUSSION

4.1 GENERAL OVERVIEW

As breast cancer is the most common type of cancer in women and has an enormous impact on society, socially and economically, new and better treatment modalities are in continuous development. Advances have been made in the management of primary breast cancer by the introduction of screening methods, by better and less invasive surgical options followed by postoperative radiotherapy, by neo-adjuvant chemotherapy schedules for larger primary or multilocal tumours, and by better adjuvant hormonal- and chemotherapy options. In the treatment of metastatic breast cancer improvement is not only seen in supportive care as expressed by the wide use of bisphosphonates for bone metastases and pain management, but also by the introduction of new hormonal therapies like aromatase inhibitors and anticancer drugs such as taxanes and capecitabine.

Targeted therapeutic drugs like trastuzumab improved survival in women with HER2 over expressing breast cancer. The recombinant, humanised monoclonal antibody to vascular endothelial growth factor, bevacizumab, showed a promising improvement in progression free survival and objective response rate in combination with paclitaxel (64). Lapatinib in combination with capecitabine, paclitaxel or letrozole demonstrated an improvement in progression free survival (PFS) of HER2 positive BC when compared to single agent treatment with about 4 to 5 months[47,48].

Moreover, favourable advances have been made in the fields of surgery, radiotherapy and minimal invasive procedures as radiofrequency ablation of the liver or resection of single liver- or lung metastases[49-54].

4.2 PATIENT- AND TUMOR CHARACTERISTICS

Looking at the patient characteristics of this study, a relatively young patient cohort was diagnosed with MBC with a median age of 53 years. Other studies report a median age of 57-64 years [7,28,59,67]. Endocrine sensitive tumours were reported in 75% (ER+ or/and PgR+) of all cases, which is a high percentage compared to rates shown in other studies (33-67%)[6,28,59,67].

A synchronous metastasis was seen in 14.7% of all cases. Most studies report an incidence of synchronous metastases of 6-10% [1,2]. The median age of these women was 52 years which is relatively young in comparison to other studies. Andre et all.[7] reported a median age of 59 for women with synchronous metastases. In his research a positive hormone receptor was seen in 52% (1987-1993) and 56% (1994-2000) of all cases. The present study showed a positive hormone receptor in 80% of all women with synchronous metastases. These findings demonstrate that the group of women analysed in this study is difficult to compare with others (very young patient cohort and a high percentage of women with endocrine sensitive tumours). More about the difficulty to compare the outcomes of this project with others is written in the chapter about study limitations. HER2-positive status was reported for 34.1% of the study collective. Six percent were negative for all three markers.

About 51% presented with visceral sites of metastases. This percentage is comparable to results of visceral metastases described in other studies, 57% reported by Gennari *et al.*[6] and 54% reported by Andre *et al.*[7] More than three metastatic sites in course of disease were reported for almost one third of the patients, which is relatively high when compared to the 10-year follow-up study by Falkson *et al*. which reported 8-24% having more than three organs with cancer[55].

4.3 SURVIVAL

The median overall survival of the whole study population in this analysis was 44 months. As 22 women with local recurrence were included in the analyses, the overall survival for women with distant metastasis was 39 months. After adjusting for the significant factors in the univariate analysis, distant metastasis vs. local recurrence was no longer associated with worse survival outcome because of the low amount of women with loco-regional recurrence (n=22). T-Stage at diagnosis, triple negative disease, visceral metastasis and amount of metastatic sites were significant related to overall survival in the multivariate analysis.

In most randomized trials where the efficacy of a 1st-line schedule for MBC has been investigated, the median survival ranged between 18-24 months[4-6], although an increase in survival was reported in a small proportion of patients with median survival times of 30 months or longer [15,45,55-57]. The first-line studies have PFS as their primary endpoint and are therefore difficult to use for finding out the overall survival rates for the whole treatment area of MBC.

Most studies describing overall survival rates as primary endpoint differentiate time cohorts and lack in describing treatment data. S. Dawood *et al*.[67] investigated the trends in survival of 15.438 women with MBC between 1988 and 2003. The results showed an improvement in OS in the last two decades (1988-1993:16-, 1994-1998: 18- and 20 months between 1999 and 2003). The multivariate model indicated that over time women with endocrine sensitive tumours had a decreased of risk of death compared to women with hormone receptor-negative disease. A hypothesis this study puts forward is that new and more effective therapeutic agents and supportive measures might contribute to the survival improvement over time. But this study

doesn't show any data about treatments being given to these patients. Andre et al.[7] reported survival rates of 724 women diagnosed with breast cancer and synchronous metastases in a 14 years period of 1987 to 2000. The median overall survival rates also improved over time (23 months between 1987 and 1993, and 29 months for the period of 1994 to 2000). His study showed an OS of 45 months for women with HR positive tumours and 12 months for HR negative tumours diagnosed between 1994 and 2000. In his study only the application of taxanes was well documented. Trastuzumab and capecitabine were not analysed specifically. Gennari *et al.* also analysed the influence of time cohort on overall survival. This study concluded that survival did improve over time, with a survival of 23.6 months in 1998-2001 compared to 18 months of the patients treated between 1983 and 1986. Gennari et al. found that survival was related to taxane administration, but no information was provided about other sequential therapies given in course of disease, or about targeted therapy given[6]

The studies of Gennari *et al*. ,Andre *et al*. and S. Dawood *et al.,* [6,7,67] all investigate overall survival for different time cohorts. The present study investigated women treated in the outpatient clinic between 2000 and 2005, and is therefore difficult to compare with the other studies. As already noted in chapter 4.2, the patients characteristics of this research differ with others.

In particular, the wide use of trastuzumab in the management of HER2 overexpressing MBC has markedly improved the prognosis of this subset of patients when compared to the prognosis of these patients in the pre-trastuzumab era[31,33]. The median survival of 44 months in patients treated with trastuzumab because of HER2 overexpressing MBC in the present study underscores the advances which have been made in this subset of patients.

Analysis of the subgroup of patients with HR-positive tumours demonstrated a median survival time of 46 months which is in accordance with the median survival of this subset of patients in the study of Andre *et al*. (45 months)[7]. Andre *et al.* also reported that 39% of the women treated for synchronous metastases of breast cancer received new aromatase inhibitors. This is in accordance with the findings of the present study with respect to the percentage of aromatase inhibitors given for endocrine treatment of MBC (33-53% of endocrine therapies given were AI´s). Mouridsen *et al*.[22] showed in a phase III clinical trial that the median OS of women with advanced breast cancer treated with letrozole as first-line therapy was 34 months compared 30 months of the tamoxifen arm. There is a major importance of newer hormonal drugs in the actual treatment of MBC.

4.4 TREATMENT OF MBC

Data about palliative treatment were analysed to describe treatment given in this single-centre outpatient clinic. Following adjuvant treatment, 1st-line treatment for metastatic disease consisted mainly of the combination therapy of anthracyclines+ taxanes, followed by taxanes alone, capecitabine and vinorelbine. 2nd-line treatment that was given predominantly consisted of capecitabine followed by gemcitabine+cisplatin and vinorelbine. For patients pre-treated with anthracyclines and taxanes in the adjuvant setting, the AGO recommends capecitabine and vinorelbine as treatment. Capecitabine has been evaluated extensively. Large, multi-centre trials showed consistent efficacy and well tolerated treatment in women pre-treated with taxanes and anthracyclines[61-63].

In this study third-line palliative treatment consisted predominantly out of taxane,

capecitabine, gemicitabine+cisplatin and vinorelbine. As Figure 22 in paragraph 4.3.2 shows, taxanes were given more frequently in 3rd-line than 1st- and 2nd- line palliative treatment. This can be explained by the strategy of re-induction of chemotherapy agents. When a longer time has passed since an agent has been applied and this agent showed a positive tumour response in the past, application of this agent is an option under good clinical conditions. In the same manner re-induction might be applied with endocrine treatment as well during the course of treatment.

Our data were also used to calculate the total number of chemotherapeutic sequences given in course of disease. The 27 women is this analysis who did not receive any chemotherapeutic treatment had such a good prognosis because of HR positive disease which could be treated well with endocrine agents and had no visceral metastases, or had bone metastasis and were well treated with bisphosphonates.

Many patients were treated with more than four sequences (35%) of chemotherapy. Women with 1-3 sequential chemotherapies had a median OS of 40 [95% CI 32-48] months, patients with more than 6 sequential palliative chemotherapies in the course of disease had a median OS of 47 months [95% CI 40-54].

Analyses of endocrine treatment showed the influence of newer endocrine agents in the current treatment guidelines. The percentage of aromatase inhibitors given within the endocrine treatment was calculated (33-53% for the different groups).

Clinical trials of the third generation aromatase inhibitors; anastrozole, letrozol and exemestan, led to an improvement in the 1st-line treatment of MBC. These trials showed improvement in response rate, but did not show an advantage in OS[22,23].

This study was not designed to make any fix conclusions about the impact of treatment modalities on survival as the patient cohort is too small and too selective. Nevertheless some hypotheses could be put forward. The patients who received more cytostatic treatment sequences might have had favourable prognostic factors e.g. by slow progression due to tumorbiology which led to a higher number of treatment adjustments during course of disease. On the other side, improvement of survival might here be achieved by an accurate step by step escalation of many different treatment modalities by medical oncologists.

Further investigation of the optimal sequences of endocrine- and chemotherapeutic treatment on survival of MBC, taking in concern prognostic factors for MBC e.g. receptor stage, amount of metastases and site of metastases as well as disease free interval[64], is needed to support any conclusions about potential influence of these treatment regimens on overall survival.

Another question to ask is whether treatment in specialized centres contributes to survival improvement. Improvement in OS outcome of women treated in this university outpatient clinic could be due to the fact that treatment is given in a multidisciplinary setting. At weekly intervals surgeons, gynaecologists, pathologists, radiological oncologists, radiologist, psycho-oncologist and medical oncologist come together to discuss difficult decisions to be made about treatment of breast cancer patients, which results in the best optimal care of MBC patients.

This study was not developed to make any conclusion about this collaboration, however the evidence to date suggests that loco-regional treatment of metastatic disease, e.g. radiofrequency ablation or resection of metastasis, is improving over time[40,42,49,65]. In this study, 31 patients underwent local-regional procedures such as

resection of metastases (n=14, 6.0%) or radiofrequency ablation (n=17, 7.3%). Patients with single lung metastases showed an OS of 56 months and 50 months for women with singular hepatic lesions. Patients with these types of metastatic patterns might be seen more frequently in specialized centres offering more options in loco-regional treatment. Multidisciplinary treatment might contribute to improve survival in the same manner as newer and more powerful agents do.

Despite all advances in the management of MBC, there are still remaining problems as expressed by the dismal prognosis of those patients with triple negative tumours (16 months). The lack of any improvement of survival in this subgroup underscores the advances which have been undertaken in patients who are candidates for targeted immunotherapeutic strategies or anti-endocrine treatments.

4.5 LIMITATIONS OF THE STUDY

It is important to critically evaluate the results of this project. The present study has certain limitations concerning the study population and the good survival outcomes. The first limitation to note is the median age of 53 years at diagnosis of metastatic breast cancer. This relatively young patient cohort might be one of the reasons for good survival outcomes. The second limitation is that the median interval between primary tumor and metastatic relapse, which is one of the most important prognostic factors in MBC[60], amounts to 35.5 months. This relatively long disease-free interval probably induced a bias due to selection of patients with a better prognosis. The third limitation is the high percentage (75%) of endocrine sensitive tumours (ER+ or/and PgR+). Endocrine sensitive tumours have better prognostic outcomes. All these

study limitations induce a bias in the patient selection and contribute to the improved survival outcomes.

It is also critical to note that some patients (n=22) with locoregional metastases are a part of the study population. These women have a very good prognosis. Figure 18 shows the differences between this group and women with distant metastases. However, the 210 women with distant metastases had a median OS of 39 months, which shows as well the improvement in OS.

As already mentioned the patient population of this study only represents 1.6% of all breast cancer patients in the catchment area of the tumor centre of Munich. This makes it difficult to compare the outcomes with the outcomes noted in the study of Schlesinger-Raab *et al*. [44]

The present study is limited by a number of biases inherent with the retrospective design and all results are explorative. As all patients who were well documented and had all of the treatments in the outpatient clinic of the medical oncology department were included in this research without having clearly defined in- and exclusion criteria, these results are difficult to compare with other retrospective or prospective studies. Many papers report improvements in overall survival over time, as they compared time cohorts. A comparison with these studies is not possible because the present study did not indicate different time cohorts.

4.6 CONCLUSIONS

This retrospective single-centre analysis was made to investigate the overall survival rates in the outpatient clinic of the oncology department. The results of this study are all explorative and should be interpreted with caution. The study shows a small patient cohort with improved overall survival rates as seen in the last decades by others [7,57,66]. Reasons for these outcomes are difficult to investigate. A bias due to centre specific selection is given. It is reasonable to think that younger, more mobile and ambitious women will consult a university hospital for treatment. The median age of 53 years confirms this statement.

This study looked at the treatment being given in the outpatient clinic. These data are descriptive. They show a step by step escalation of all treatment modalities according to standard guidelines and individualized clinical requirements of MBC patients in a centre offering multidisciplinary treatment. Whether innovative medicine, multiple cycles of therapies and a multidisciplinary treatment approach contribute to these good outcomes is debatable. On the one hand is it obvious that women who survive longer with cancer receive more therapies, on the other hand it cannot be ruled out that a step by step escalation of all treatment modalities according to standard guidelines and individualized clinical requirements in a centre offering multidisciplinary treatment might contribute to the clearly improvement in survival outcome reported in this study.

V. REFERENCE LIST

1. O'Shaughnessy J: Extending survival with chemotherapy in metastatic breast cancer. Oncologist 10 Suppl 3:20-9, 2005

2. Mincey BA, Perez EA: Advances in screening, diagnosis, and treatment of breast cancer. Mayo Clin Proc 79:810-6, 2004

3. Chung CT, Carlson RW: Goals and objectives in the management of metastatic breast cancer. Oncologist 8:514-20, 2003

4. Norton L: Metastatic breast cancer. Length and quality of life. N Engl J Med 325:1370-1, 1991

5. Muss HB, Case LD, Richards F, 2nd, et al: Interrupted versus continuous chemotherapy in patients with metastatic breast cancer. The Piedmont Oncology Association. N Engl J Med 325:1342-8, 1991

6. Gennari A, Conte P, Rosso R, et al: Survival of metastatic breast carcinoma patients over a 20-year period: a retrospective analysis based on individual patient data from six consecutive studies. Cancer 104:1742-50, 2005

7. Andre F, Slimane K, Bachelot T, et al: Breast cancer with synchronous metastases: trends in survival during a 14-year period. J Clin Oncol 22:3302-8, 2004

8. Armstrong K, Eisen A, Weber B: Assessing the risk of breast cancer. N Engl J Med 342:564-71, 2000

9. Veronesi U, Boyle P, Goldhirsch A, et al: Breast cancer. Lancet 365:1727-41, 2005

10. Miki Y, Swensen J, Shattuck-Eidens D, et al: A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science 266:66-71, 1994

11. Wooster R, Bignell G, Lancaster J, et al: Identification of the breast cancer susceptibility gene BRCA2. Nature 378:789-92, 1995

12. Hayes DF: Prognostic and predictive factors revisited. Breast 14:493-9, 2005

13. Colleoni M, Bonetti M, Coates AS, et al: Early start of adjuvant chemotherapy may improve treatment outcome for premenopausal breast cancer patients with tumors not expressing estrogen receptors. The International Breast Cancer Study Group. J Clin Oncol 18:584-90, 2000

14. Colleoni M, Minchella I, Mazzarol G, et al: Response to primary chemotherapy in breast cancer patients with tumors not expressing estrogen and progestarone receptors. Ann Oncol 11:1057-9, 2000

15. V.Heinemann AA, T. Beinert et al.: Manual des Tumorzentrums München. Emppfelungen zur Diagnostik, Therapie und Nachsorge. Mammakarzinome, Prof. Dr. med. Hansjörg Sauer, 2005, pp 225-241

16. Jacquemier J, Ginestier C, Rougemont J, et al: Protein expression profiling identifies subclasses of breast cancer and predicts prognosis. Cancer Res 65:767-79, 2005

17. Matos I, Dufloth R, Alvarenga M, et al: p63, cytokeratin 5, and P-cadherin: three molecular markers to distinguish basal phenotype in breast carcinomas. Virchows Arch 447:688-94, 2005

18. Haffty BG, Yang Q, Reiss M, et al: Locoregional relapse and distant metastasis in conservatively managed triple negative early-stage breast cancer. J Clin Oncol 24:5652-7, 2006

19. Wiedswang G, Borgen E, Karesen R, et al: Detection of isolated tumor cells in bone marrow is an independent prognostic factor in breast cancer. J Clin Oncol 21:3469-78, 2003

20. van't Veer LJ, Paik S, Hayes DF: Gene expression profiling of breast cancer: a new tumor marker. J Clin Oncol 23:1631-5, 2005

21. Oh DS, Troester MA, Usary J, et al: Estrogen-regulated genes predict survival in hormone receptor-positive breast cancers. J Clin Oncol 24:1656-64, 2006

22. Mouridsen H, Gershanovich M, Sun Y, et al: Phase III study of letrozole versus tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: analysis of survival and update of efficacy from the International Letrozole Breast Cancer Group. J Clin Oncol 21:2101-9, 2003

23. Paridaens RJ, Dirix LY, Beex LV, et al: Phase III study comparing exemestane with tamoxifen as first-line endocrine treatment of metastatic breast cancer in postmenopausal women: the European Organisation for Research and Treatment of Cancer Breast Cancer Cooperative Group. J Clin Oncol 26:4883-90, 2008

24. Ghersi D, Wilcken N, Simes RJ: A systematic review of taxane-containing regimens for metastatic breast cancer. Br J Cancer 93:293-301, 2005

25. Gralow JR: Optimizing the treatment of metastatic breast cancer. Breast Cancer Res Treat 89 Suppl 1:S9-S15, 2005

26. Jones SE, Erban J, Overmoyer B, et al: Randomized phase III study of docetaxel compared with paclitaxel in metastatic breast cancer. J Clin Oncol 23:5542-51, 2005

27. Hamilton A, Hortobagyi G: Chemotherapy: what progress in the last 5 years? J Clin Oncol 23:1760-75, 2005

28. Passardi A, Massa I, Zoli W, et al: Phase II study of gemcitabine, doxorubicin and paclitaxel (GAT) as first-line chemotherapy for metastatic breast cancer: a translational research experience. BMC Cancer 6:76, 2006

29. Piccart-Gebhart MJ, Burzykowski T, Buyse M, et al: Taxanes alone or in combination with anthracyclines as first-line therapy of patients with metastatic breast cancer. J Clin Oncol 26:1980-6, 2008

30. Slamon D: Herceptin: increasing survival in metastatic breast cancer. Eur J Oncol Nurs 4:24-9, 2000

31. Stemmler HJ, Kahlert S, Siekiera W, et al: Prolonged survival of patients receiving trastuzumab beyond disease progression for HER2 overexpressing metastatic breast cancer (MBC). Onkologie 28:582-6, 2005

32. Burstein HJ, Kuter I, Campos SM, et al: Clinical activity of trastuzumab and vinorelbine in women with HER2-overexpressing metastatic breast cancer. J Clin Oncol 19:2722-30, 2001

33. Slamon DJ, Leyland-Jones B, Shak S, et al: Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 344:783-92, 2001

34. Marty M, Cognetti F, Maraninchi D, et al: Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group. J Clin Oncol 23:4265-74, 2005

35. Harvey HA: Issues concerning the role of chemotherapy and endocrine therapy of bone metastases from breast carcinoma. Cancer 80:1646-51, 1997

36. Paterson AH, Powles TJ, Kanis JA, et al: Double-blind controlled trial of oral clodronate in patients with bone metastases from breast cancer. J Clin Oncol 11:59-65, 1993

37. Hortobagyi GN, Theriault RL, Lipton A, et al: Long-term prevention of skeletal complications of metastatic breast cancer with pamidronate. Protocol 19 Aredia Breast Cancer Study Group. J Clin Oncol 16:2038-44, 1998

38. Hortobagyi GN, Theriault RL, Porter L, et al: Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases. Protocol 19 Aredia Breast Cancer Study Group. N Engl J Med 335:1785-91, 1996

39. Lipton A: Management of bone metastases in breast cancer. Curr Treat Options Oncol 6:161-71, 2005

40. Adam R, Aloia T, Krissat J, et al: Is liver resection justified for patients with hepatic metastases from breast cancer? Ann Surg 244:897-907; discussion 907-8, 2006

41. Lee WS, Yun SH, Chun HK, et al: Clinical outcomes of hepatic resection and radiofrequency ablation in patients with solitary colorectal liver metastasis. J Clin Gastroenterol 42:945-9, 2008

42. Hoffmann RT, Jakobs TF, Kubisch CH, et al: Radiofrequency ablation after selective internal radiation therapy with Yttrium90 microspheres in metastatic liver disease-Is it feasible? Eur J Radiol, 2009

43. Welter S, Jacobs J, Krbek T, et al: Pulmonary metastases of breast cancer. When is resection indicated? Eur J Cardiothorac Surg 34:1228-34, 2008

44. Schlesinger-Raab A, Eckel R, Engel Jea, et al: metastasiertes Mammakarzinom: keine Überlebensverlängerung seit 20 Jahren. Deutsches Ärzteblatt 40:2280-2285, 2005

45. Giordano SH, Buzdar AU, Smith TL, et al: Is breast cancer survival improving? Cancer 100:44-52, 2004

46. Brufsky AM: Cancer treatment-induced bone loss: pathophysiology and clinical perspectives. Oncologist 13:187-95, 2008

47. Geyer CE, Forster J, Lindquist D, et al: Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med 355:2733-43, 2006

48. Di Leo A, Gomez HL, Aziz Z, et al: Phase III, double-blind, randomized study comparing lapatinib plus paclitaxel with placebo plus paclitaxel as first-line treatment for metastatic breast cancer. J Clin Oncol 26:5544-52, 2008

49. Bangash AK, Atassi B, Kaklamani V, et al: 90Y radioembolization of metastatic breast cancer to the liver: toxicity, imaging response, survival. J Vasc Interv Radiol 18:621-8, 2007

50. Gunabushanam G, Sharma S, Thulkar S, et al: Radiofrequency ablation of liver metastases from breast cancer: results in 14 patients. J Vasc Interv Radiol 18:67-72, 2007

51. Helmberger T, Holzknecht N, Schopf U, et al: [Radiofrequency ablation of liver metastases. Technique and initial results]. Radiologe 41:69-76, 2001

52. Maksan SM, Lehnert T, Bastert G, et al: Curative liver resection for metastatic breast cancer. Eur J Surg Oncol 26:209-12, 2000

53. Manglani HH, Marco RA, Picciolo A, et al: Orthopedic emergencies in cancer patients. Semin Oncol 27:299-310, 2000

54. Vogl TJ, Weinhold N, Muller P, et al: [MR-controlled laser-induced thermotherapy (LITT) of liver metastases: clinical evaluation]. Rontgenpraxis 49:161-8, 1996

55. Falkson G, Holcroft C, Gelman RS, et al: Ten-year follow-up study of premenopausal women with metastatic breast cancer: an Eastern Cooperative Oncology Group study. J Clin Oncol 13:1453-8, 1995

56. Greenberg PA, Hortobagyi GN, Smith TL, et al: Long-term follow-up of patients with complete remission following combination chemotherapy for metastatic breast cancer. J Clin Oncol 14:2197-205, 1996

57. Block KI, Gyllenhaal C, Tripathy D, et al: Survival Impact of Integrative Cancer Care in Advanced Metastatic Breast Cancer. Breast J, 2009

58. Abrial C, Leheurteur M, Cabrespine A, et al: Does survival increase in metastatic breast cancer with recently available anticancer drugs? Oncol Res 15:431-9, 2006

59. Eichbaum MH, Gast AS, Schneeweiss A, et al: Activity and tolerability of a combined palliative chemotherapy with mitomycin C, folinate, and 5-Fluorouracil in patients with advanced breast cancer after intensive pretreatment: a retrospective analysis. Am J Clin Oncol 30:139-45, 2007

60. Chang J, Clark GM, Allred DC, et al: Survival of patients with metastatic breast carcinoma: importance of prognostic markers of the primary tumor. Cancer 97:545-53, 2003

61. Blum JL, Jones SE, Buzdar AU, et al: Multicenter phase II study of capecitabine in paclitaxel-refractory metastatic breast cancer. J Clin Oncol 17:485-93, 1999

62. Blum JL, Dieras V, Lo Russo PM, et al: Multicenter, Phase II study of capecitabine in taxane-pretreated metastatic breast carcinoma patients. Cancer 92:1759-68, 2001

63. Reichardt P, Von Minckwitz G, Thuss-Patience PC, et al: Multicenter phase II study of oral capecitabine (Xeloda(")) in patients with metastatic breast cancer relapsing after treatment with a taxane-containing therapy. Ann Oncol 14:1227-33, 2003

64. Largillier R, Ferrero JM, Doyen J, et al: Prognostic factors in 1,038 women with metastatic breast cancer. Ann Oncol 19:2012-9, 2008

65. Evrard S, Becouarn Y, Fonck M, et al: Surgical treatment of liver metastases by radiofrequency ablation, resection, or in combination. Eur J Surg Oncol 30:399-406, 2004

66. Falkson G, Tormey DC, Carey P, et al: Long-term survival of patients treated with combination chemotherapy for metastatic breast cancer. Eur J Cancer 27:973-7, 1991

67. Dawood S, Broglio K, Gonzalez-Angulo AM, et al: Trends in survival over the past two decades among white and black with newly diagnosed stage IV breast cancer.

68 David W. Hosmer and Stanley Lemeshow: Applied Survival Analysis, regression modelling of time to event data. Chapter 5: Model Development, page 159.

VI. ACKNOWLEDGEMENTS

I take the opportunity to thank Prof. Dr. med. V. Heinemann very much for giving me the possibility to start this project and for showing me the importance of scientific research in the clinical practise.

I thank PD Dr. med. H.J. Stemmler very much for his contributions to my understanding of this project and for helping me to finish this thesis.

Ms Kaiser thank you very much for sharing your knowledge of all the patients you have been supporting in the outpatient clinic and Ms Di Gioia for giving me insight in some of her data.

At last I want to thank all members of my family and friends, especially my husband Cornelius and my children Elisa and Bastian, my parents, Jelle and Adrie Cnossen, and my mother-in-law, Judith Stockmair, for always being there for me, constantly giving me the encouragement and support I needed throughout this project and for making me feel at home in Munich.

This work would have been impossible without the motivation that you all provided me with.

VII. CURRICULUM VITAE

Jitske Alida Cnossen

Geb. 22.02.1978 in Drachten, Niederlande

Verheiratet, 1 Tochter und 1 Sohn

SCHULAUSBILDUNG:

1990-1996 Liudger Gymnasium in Drachten, Niederlande

BERUFLICHE AUSBILDUNG:

1996-2004 Studium Humanmedizin an der Rijksuniversiteit van Groningen, Niederlande

ARBEITSERFAHRUNG:

2004-2005 Assistenzärztin in Innerer Medizin, Krankenhaus Nij Smellinghe, Drachten, Niederlande (Dr. Strijbos)

Seit 2006 Assistenzärztin in der Medizinischen Klinik III, Klinikum Großhadern, München, Deutschland (Direktor: Prof. Dr. W. Hiddemann)

POSTER/PUBLIKATION:

10/2007 Deutsche Gesellschaft für Hämatologie und Onkologie (DGHO). Poster: Überlebenszeit beim metastasiertem Mammakarzinom (MBC): Retrospektive Analyse eines Schwerpunktzentrums 2000-2005
J. Cnossen, H. J. Stemmler, D. Lässig und V. Heinemann

05/2008 American Society of Clinical Oncology (ASCO) abstract:
Long-term survival with metastatic breast cancer (MBC): Results of a retrospective, single-centre analysis from 2000-2005.
J. Cnossen, V. Heinemann, D. Lässig, H.J. Stemmler.
J Clin Oncol 26: 2008 (May 20 suppl; abstr 1128)

06/2011 Published Ahead-of-Print: Long-term follow-up of patients with metastatic breast cancer: results of a retrospective, single-center analysis from 2000 to 2005. Geiger, Sandra*; Cnossen, Jitske Alida*; Horster, Sophia; DiGioia, Dorit; Heinemann, Volker; Stemmler, Hans-Joachim. Anti-Cancer Drugs, June 2011