

1 **Original paper**

2 **Chemotherapy for metastatic breast cancer. Comparison of clinical practice**
3 **and cost of drugs in two cohorts of patients: 1994-1998 and 2003-2006**

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20 **Short title**

21 MBC patients treated by chemotherapy

22

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24

1 **Abstract**

2 **Purpose:** Although new chemotherapeutic drugs for metastatic breast cancer (MBC)
3 have been approved over the past decade, it is unclear whether this has changed the
4 overall outcome of patients. This study assessed the clinical and economic impacts
5 of these drugs. **Methods:** We retrospectively studied MBC patients receiving
6 chemotherapy in our institution over two time periods, 1994-1998 and 2003-2006.
7 Patient characteristics and outcomes, and treatment characteristics and costs (€,
8 2008) were compared. **Results:** Three hundred and one patients were identified, 149
9 patients in the first cohort and 152 in second one. The median number of lines was
10 similar in the two cohorts (3 lines). The median costs of chemotherapy per patient
11 nearly doubled over time, from 6,272 € in the 1994-1998 cohort to 13,035 € in the
12 2003-2006 cohort ($P<0.001$). No survival difference was observed between the two
13 groups, with a 3-years survival rate estimated to 41% in the 1994-1998 cohort and
14 44% in the 2003-2006 cohort ($P=0.52$). In multivariate analysis, prognostic factors
15 associated with longer OS were single metastatic site (HR 0.48; $p<10^{-3}$), bone
16 metastases (HR=0.67; $P=0.007$) and positive hormone receptors (HR 0.56;
17 $P=0.0002$). **Conclusions:** New chemotherapeutic agents induced a significant cost
18 increase over time. The limited size and heterogeneity of our cohort do not allow any
19 conclusion concerning their impact on survival.

20 **Key-words**

21 Metastatic breast cancer, chemotherapy, survival, costs, medico-economic study

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1 **Introduction**

2 Despite recent advances in early detection and treatment, breast cancer remains the
3 leading cause of death by cancer in women. At metastatic stages, there is no single
4 standard of care for the patients, as treatment plans require an individualized
5 approach based on multiple factors including specific tumor biology, presence of
6 visceral metastases, history of prior therapy and response, and patient preference.

7 Metastatic breast cancer (MBC) remains an incurable disease, and treatments are
8 aimed to improve patient quality of life and possibly to prolong survival without
9 excessive toxicity. The average survival time is no longer than 2 years [1].

10 Because of the chemosensitivity of the disease, the large majority of MBC patients
11 are candidates for chemotherapy, either upfront or after failure of hormonal
12 treatments. Over the last decade, new chemotherapy drugs, including capecitabine,
13 gemcitabine and liposomal doxorubicin, have been developed and approved in this
14 setting. In addition, targeted biologic agents, such as trastuzumab, bevacizumab and
15 lapatinib, combined with traditional chemotherapies appear to offer new treatment
16 opportunities. These molecules have been approved based on the results of
17 hundreds of randomized trials comparing chemotherapy drugs, doses, combinations,
18 sequences and durations. But it is important to note that only eight of these trials
19 have shown improved survival in MBC patients [2, 3]. Furthermore, most published
20 clinical trials have focused on first-line chemotherapies and few have evaluated the
21 cost-efficacy of new drugs [4]. In the context of current health policy, with a majority
22 of governments trying to limit the escalation of health care expenditures, such
23 analysis may contribute to the on-going debate about the dissemination of innovative
24 cancer drugs.

1 In this retrospective study, we examined temporal trends in the use of
2 chemotherapeutic agents for the treatment of MBC in the context of clinical practice
3 and their costs. We also performed a study of the survival rates of MBC patients over
4 time.

5

6 **Materials and Methods**

7 ***Patient selection***

8 The patients included in this retrospective study were selected among MBC patients
9 treated by chemotherapy at Léon Bérard Cancer Center (CLB), Lyon, France.
10 Inclusion criteria included histological or cytological evidence of breast cancer, but a
11 biopsy of the metastasis was not required. Based on the timing of the development
12 and dissemination of anti-MBC chemotherapeutic agents, we defined two time
13 cohorts, 1994-1998 (group 1) and 2003-2006 (group 2). Any patient diagnosed with
14 MBC (either primary tumor or first recurrence of distant metastases) and treated with
15 chemotherapy could be included in these time cohorts. Patients in group 1 must have
16 received their first cure of chemotherapy between January 1st 1994 and December
17 31st 1998. Patients in group 2 must have received their first cure of chemotherapy
18 between January 1, 2003 and December 31, 2006. Group 1 was used as the
19 baseline comparator and corresponded to the introduction of taxanes (paclitaxel and
20 docetaxel). Group 2 corresponded to the period when trastuzumab and capecitabine
21 became available. Prior endocrine therapy for metastatic disease was allowed. The
22 institutional review board approved the acquisition and report of the data from these
23 patients.

24 The extent of metastatic involvement was determined by physical examination and
25 routine imaging procedures including chest x-ray, liver ultrasound and bone scan

1 before initiation of medical treatment. Information regarding date of diagnosis, patient
2 age, Scarff-Bloom and Richardson (SBR) grade and TNM stage [5] of the initial
3 tumor, performance status (PS), disease-free interval from initial diagnosis, number
4 and sites of metastases, hormone receptor (HR) status, HER-2 status and medical
5 treatments in the adjuvant and metastatic settings was obtained from original patient
6 records. A treatment was considered delivered when at least one dose of the drug
7 was received by the patient. The data were last updated in April 2008.

8

9 ***Chemotherapy drugs***

10 The patients identified from the CLB breast cancer database were cross-referenced
11 with the pharmacy database to collect information on the chemotherapeutic drugs
12 used for their treatment. The pharmacy database records the date, the type and dose
13 of all systemic agents administered in the hospital or at home and indications for their
14 use in the treatment of a specific cancer in a given patient. For oral chemotherapy
15 drugs purchased from local retail pharmacies, information was retrieved from original
16 patient records and prescriptions. The line of chemotherapy (LOC) was defined as
17 the interval from the date of the beginning of a treatment to the date of progression.

18

19 ***Cost analysis***

20 The cost analysis was limited to the direct costs of chemotherapy drugs, thus
21 excluding the costs of drug preparation and administration, hospitalization and
22 transportation. The respective costs of chemotherapy agents were calculated from
23 the beginning of treatment to death or end of the study. They were estimated in
24 Euros (€, 2008) from the perspective of the French health care system. For
25 treatments administered in the hospital, we determined the exact number of

1 milligrams per prescription and per patient, and then we multiplied this quantity by the
2 purchase price of each drug as nationally negotiated by the federation of French
3 cancer centers (FNCLCC) with which the CLB is affiliated. The treatments
4 administered at home were identified by examination of the follow-up records of the
5 patients. We determined the number of vials per prescription and per patient, and we
6 calculated the total cost of the treatment, assuming that every vial opened at home
7 was used (unused drug in opened vials was discarded). For oral chemotherapy drugs
8 purchased from local pharmacies, the number of milligrams per prescription was
9 determined and valued using prices fixed by the French public health authorities.

11 ***Statistical analysis***

12 The characteristics of the patients were compared using Pearson's Chi-square test
13 (or Fisher's exact test, if necessary) and Student's *t* test. Overall survival (OS) was
14 defined as the time from diagnosis of metastasis to date of death or date of last
15 follow-up for patients alive at last contact. Survival distributions were estimated by
16 the Kaplan-Meier method [6]. To evaluate the relationship between survival and
17 biological and/or clinical factors known to be relevant in MBC, all potential prognostic
18 factors were included in univariate Cox proportional hazard regression models [7].
19 Candidate prognostic factors with a 0.05 level of significance in univariate analysis
20 were then selected for inclusion in the multivariate analysis. Independent prognostic
21 variables of survival were identified by a Cox regression analysis using a backward
22 selection procedure to adjust the time cohort effect on patient's characteristics. All
23 statistical analyses were performed using SAS software v.9.1 (Cary). All P values for
24 two-tailed tests were considered significant when $P < 0.05$.

1 **Results**

2 ***Patient characteristics***

3 In total, 301 of 957 MBC patients of treated in our institution between 1994 and 2006
4 fulfilled the study criteria. Group 1 included 149 patients treated with chemotherapy
5 between 1994 and 1998, and group 2 included 152 patients treated between 2003
6 and 2006. The median follow-up for surviving patients was 3.87 years for the entire
7 cohort. Patient characteristics are listed in table 1. Overall, missing data were more
8 frequent in group 1. Patient characteristics did not statistically differ between groups,
9 except for age; patients of group 1 were younger than those of group 2. HR and
10 HER-2 status were more frequently known in group 2. All patients of group 1 with
11 positive HR status received adjuvant hormone therapy, compared to only 64 patients
12 (53.8%) in group 2 ($P<0.001$). Similarly, a greater proportion of patients in group 1
13 received hormone therapy for MBC (table 1) and this did not correlate with HR status.
14 Thus, 27 patients (81%) with negative HR status received hormone therapy in group
15 1, compared to only 12 patients (21.4%) in group 2 ($P<0.001$).

16 The majority of patients from both groups received adjuvant chemotherapy, in
17 particular anthracyclines (Table 1). Only one patient from group 1 received taxanes in
18 the adjuvant setting, compared to 18 patients (15.1%) from group 2 ($p<0.001$).

19

20 ***Chemotherapy drugs administered for MBC***

21 The various chemotherapeutic agents used for the treatment of MBC in the patients
22 of the two time groups are outlined in table 2. Overall, there was no significant
23 difference between groups in the median number of LOC ($n=3$). There was a trend
24 toward a reduction in the use of anthracyclines over time. The quasi-totality of group
25 1 patients (93.3%) received anthracyclines, most of them in first line (77.2%),

1 compared to only 50% of group 2 patients. The lower use of anthracyclines in the
2 metastatic setting in group 2 was correlated with an increased use in the adjuvant
3 setting. Taxanes, trastuzumab and capecitabine were more frequently administered
4 to patients from the later time cohort. The majority of patients in group 2 received
5 taxanes (84.9%), compared to 71.8% in group 1 ($P<0.01$). Most patients in group 2
6 received taxanes in first line (67.8%), compared to only 16.8% in group 1 ($p<0.001$).
7 Trastuzumab was administered to all HER-2 positive patients from either group. But,
8 as HER-2 status was more frequently known in group 2, the number of patients
9 treated with trastuzumab was also much higher ($n=38$) than in group 1 ($n=3$) (Table
10 2). Capecitabine was administered to 69% patients in group 2, compared to only
11 4.7% in group 1 ($P<0.001$). Finally, 27 patients (18.1%) of group 1 received high-
12 dose chemotherapy with stem cell transplantation (HDCSCT) and their median age
13 was 37 years, whereas none of group 2 patients received HDCSCT.
14 All patients of the entire cohort received at least one cure of chemotherapy in the
15 hospital. We observed a significant increase in the use of oral chemotherapy (71.7%
16 vs. 9.3%; $P<0.001$) and systemic treatments at home (32.2% vs. 2%; $P<0.001$) over
17 time.

18

19 **Costs of chemotherapy drugs**

20 Not surprisingly, the total costs of chemotherapy nearly tripled over time. The overall
21 costs of chemotherapy drugs for the entire cohort ($n=301$) were estimated to be
22 5,209,771 €, breaking down into 1,321,023 € for group 1 and 3,848,748 € for group
23 2. Thus, the median costs of chemotherapy drugs per patient increased from 6,272 €
24 in group 1 to 13,035 € in group 2 ($P<0.001$; Table 4).

25 Up to progression, the median cost of metastatic breast cancer chemotherapy per

1 patient and per year was 3,167 €. It appeared to be higher in group 2 (4,864 €) than
2 in group 1 (2,273€). As regards costs according to the LOC, the median cost of a
3 LOC was significantly higher in group 2 (3,306 €) than in group 1 (1,005 €; $P<0.001$)
4 (table 5).

5 Trastuzumab, docetaxel and paclitaxel were responsible for 66.7% of the total costs
6 of chemotherapy (Table 6). As expected, trastuzumab was the most expensive drug,
7 with a total of 1,800,007 €, corresponding to 36.35% of the overall costs. With only
8 43 patients treated with trastuzumab in the entire cohort, the median cost per patient
9 was 43,721 €. The second most expensive molecule was docetaxel, with a total cost
10 of 1,193,386 €, corresponding to 22.9% of the total expenditures. The median cost of
11 docetaxel per patient was 6,521 €. The third most expensive molecule was paclitaxel,
12 with a total cost of 402,163 €, corresponding to 7.7% of the total expenditures. The
13 median cost of paclitaxel per patient was 4,278 €.

14

15 ***Survival of metastatic breast cancer patients treated by chemotherapy***

16 The median OS of the entire cohort was 2.75 years. The survival of MBC patients
17 treated by chemotherapy did not change between the two cohorts (Figure 1A), with a
18 3-years OS rate estimated to 41% in the 1994-1998 group and 44% in the 2003-2006
19 group ($P=0.52$). Interestingly, we observed higher 5-years survival rate in the second
20 group (28%) in comparison to the first one (16%). Most of long surviving patients (> 5
21 years) in group 2 had hormone receptor positive tumors (73%) and only two of them
22 were HER-2 positive.

23 Univariate analysis of survival showed that the presence of HR, a progression-free
24 interval >2 years, bone metastases and the administration of anthracyclines in first
25 line were associated with improved OS. In contrast, multiple metastases, soft tissue

1 metastases, visceral metastases and performance status >1 were associated with
2 poor outcome (Table 3).

3 All patients with a positive HER-2 status (n=41) received at least one line of
4 chemotherapy with trastuzumab used alone or combined with other drugs.
5 Interestingly, for patients with known HER-2 status (n=131), positivity was not
6 associated with worse survival (HR=0.99, $P=0.99$; Figure 2). When only patients with
7 HR-positive tumors were considered (n=172), the median OS was 3.15 years in
8 patients treated by chemotherapy between 2003 and 2006 and 2.54 years for those
9 treated between 1994 and 1998, but this difference was not statistically significant
10 ($P=0.13$, Figure 3). As expected, a multivariate analysis adjusted on the patient
11 cohort showed that single metastatic site, bone metastases and HR were prognostic
12 factors for survival (Table 4).

13

14

1 **Discussion**

2 Although clinical trials suggest that some advances have been made in the
3 management of MBC over the last two decades, it is not clear whether the survival of
4 these patients has improved in the context of daily practice. The major new
5 chemotherapy drugs were approved after 1994 and this date became a turning point
6 in cancer treatment. One of the objectives of our work was to study the evolution of
7 clinical practice in the treatment of MBC with chemotherapy during the last 15 years.
8 The first period (1994-1998) was chosen because it corresponds to the introduction
9 of taxanes in MBC.; paclitaxel was approved in France in 1994 and docetaxel in
10 1998. The second period (2003-2006) corresponds to the routine use of trastuzumab
11 and capecitabine, respectively approved in 2000 and 2002.

12 Patient's characteristics were not balanced in terms of age,
13 hormonal receptor status, HER-2 status and prior exposure to major
14 chemotherapeutic agents. Age difference is probably due to two principal causes.
15 First, the majority of old patients (older than 70 years) with MBC did not receive
16 chemotherapy in the early 1990's because of the poor tolerability of available drugs
17 and the lack of supportive therapies. Most of these patients received hormone
18 therapies when indicated or palliative care. Second, in the 1990's, several clinical
19 trials testing HDCSCT were ongoing at the Centre Léon Bérard [8-10] and these
20 trials included only young patients (younger than 50 years). In our study, 27 patients
21 treated in group 1 received HDCSCT and their median age was 37 years.

22 HER-2 status was virtually unknown in the quasi-totality of the first group patients.
23 This analysis was generalized in the early 2000's with the generalization of
24 administration of trastuzumab to patients with positive HER-2 status. Similarly,
25 hormone receptors (HR) status was more frequently known in group 2 than group 1

1 whereas hormone therapies in the metastatic setting was prescribed to the majority
2 of patients of group 1, including some patients with negative HR. Until the end of the
3 1990's, hormone therapies could be administered to patients independently of HR
4 status [11]. The publication of a meta-analysis of clinical trials evaluating tamoxifen
5 [12] showed that positive HR is a predictive factor of response and changed clinical
6 practice.

7 Recent studies have investigated the costs of expensive drugs like trastuzumab [13-
8 15] and taxanes [16] or the total costs of chemotherapy [17] but, to our knowledge,
9 this is the first study describing the evolution of expenditures associated with all the
10 chemotherapy drugs prescribed in the context of daily clinical practice. Our study was
11 motivated by the fact that the costs of chemotherapeutic drugs have one of the
12 highest growth rates. In France, the French drug agency (AFSSAPS) estimated this
13 increase to be 23% per year in 2006 [18]. Overall, we observed an increase in the
14 administration of expensive drugs such as trastuzumab, taxanes and capecitabine,
15 and a significant reduction in the administration of "old drugs", i.e. anthracyclines and
16 vinorelbine, to MBC patients. Consequently, the total costs of chemotherapy nearly
17 tripled while the median number of lines of chemotherapy remained stable. This
18 increase in costs was mainly due to the two molecules described above, trastuzumab
19 and docetaxel, which were responsible for more than half of expenditures. Our
20 observations are in accordance with those reported by the French drug agency since
21 these two molecules were the most important cost drivers for hospital pharmacies in
22 2006 in France [18]. Although trastuzumab is responsible for 36% of the total costs of
23 chemotherapy, in our cohort it beneficially altered the natural history of women with
24 HER-2 positive MBC by leveling out outcome differences with women with HER-2
25 negative disease.

1 Our study has revealed no significant difference in overall survival rate at 3 years
2 between the two periods of time. Nevertheless, it is important to note that this
3 survival was longer than reported in most published series [19, 20]. Recent
4 retrospective studies have shown a trend toward improved survival in MBC patients
5 [19-22] but none has clearly demonstrated a relationship with new chemotherapeutic
6 drugs. Herein, we observed a tendency toward increased survival rate at 5 years in
7 group 2 patients' and most of these long-surviving patients had hormone positive
8 tumors, suggesting a benefit from new hormonal therapies.

9 Several hypotheses could explain the absence of survival improvement in our study.
10 First, the median number of lines of chemotherapy was similar and equal to three in
11 the two groups, which is higher than reported in the literature [20]. Second, we
12 observed similarities between the two major chemotherapeutic drugs used in MBC,
13 i.e. anthracyclines and taxanes, which were administered to the majority of patients
14 in the two groups. Thus taxanes were extensively used in both cohorts, all lines
15 included. Data showing improvement of OS with the use of taxanes in advanced
16 breast cancer came from trials comparing populations with exposure to taxanes to
17 those with limited exposure (limited cross-over)[23]. As a consequence, this fact does
18 not allow entertaining any potential impact of taxanes on OS between the 2 cohorts.
19 Third, the major difference between the two periods of time was the introduction of
20 trastuzumab and capecitabine. Trastuzumab was given only to the sub-group of
21 patients with positive HER-2 status, who represent no more than 25% of all MBC
22 patients [24]. The benefit of this drug is expected to be limited to this population [25].
23 In our study, the sub-group of HER-2 positive patients treated with trastuzumab
24 actually benefited from this drug since their survival was equal to that of patients with
25 negative HER-2 status, a cohort historically considered to be associated with better

1 prognosis. These observations are in accordance with recent reports [26]. Thus,
2 trastuzumab has definitively an effect on OS of patients with positive HER-2 status,
3 but this beneficial impact is diluted in our study due to the small percentage of these
4 patients among total MBC population. Capecitabine has only a modest potential
5 benefit in terms of overall survival, as shown in the registration trial [27]. Moreover,
6 the compliance of patients to this oral agent is certainly an issue to be addressed in
7 the context of potential impact on OS.

8 Interestingly, we observed a trend toward improved survival over time in patients with
9 HR-positive tumors. This is probably related to the use of new hormonal therapies
10 approved for MBC patients during the last decade such as aromatase inhibitors [28]
11 and LH-RH agonists combined with tamoxifen [29, 30]; these drugs have
12 demonstrated a significant survival benefit over other endocrine therapies.

13 Our study has many limitations. It is a retrospective study conducted in a tertiary care
14 institution with biases that do not allow drawing any general reliable conclusions on
15 the impact of modern chemotherapies and trastuzumab on survival of MBC patients.
16 The two cohorts are small and consequently lack statistical power. This small sample
17 size introduces some concerns in the context of an extremely heterogeneous
18 malignancy like breast carcinoma.

19 Our medico-economic study also has many limitations. First, we only evaluated the
20 costs of MBC chemotherapy drugs, and we did not explore other direct and indirect
21 costs, principally hospitalization costs which probably decreased with the extensive
22 use of outpatient hospitalization and the development of cancer supportive
23 treatments like biphosphonates and G-CSF. Indeed, 18% of group 1 patients
24 received HDCSCT. In this case, the costs of chemotherapy drugs were clearly
25 negligible compared to the total costs of the procedure [31]. Second, we used 2008

1 prices, not the prices in effect when the drugs were administered. As the prices of
2 certain drugs like taxanes and trastuzumab have changed over the last decade, this
3 could have an impact on the calculation of total costs. Third, we did not evaluate the
4 quality of life of the patients included in our cohort, because the study was
5 retrospective. Nevertheless, our results confirm the important increase over time of
6 expenditures related to chemotherapy drugs [32]. In MBC, the part of chemotherapy
7 in the total pharmaceutical costs has grown from 10% to 26% between 1988 and
8 2000 [33] and this evolution has probably accelerated since the approval of new
9 expensive targeted therapies such as trastuzumab, lapatinib and bevacizumab.

10 There is a growing consensus worldwide that cost-effectiveness considerations
11 should be taken into account when making private or public health insurance
12 decisions regarding the coverage of innovative and costly medical procedures [34].
13 As the median survival of MBC patients does not exceed 3 years, a cost-utility study
14 evaluating both the costs of treatment and patient quality of life in a large prospective
15 and multicentric study, i.e. the French federation of cancer centers, with control of
16 major outcome predictors could be useful in order to draw the appropriate
17 conclusions.

18

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1 **Tables and Figures**

2

3 **Table 1: Baseline demographics of the two time groups.** SCT: stem cell
4 transplantation

5 **Table 2: Lines of chemotherapy (LOC) administered in the metastatic setting**

6 **Table 3: Univariate analysis of overall survival (OS).** CI: Confidence Interval, HR:
7 Hazard Ratio, SBR: Scarff Bloom and Richardson score.

8 **Table 4: Multivariate analysis of overall survival adjusted to the group of**
9 **patients.** HR: Hazard Ratio; 95% CI: 95% Confidence Interval

10 **Table 5: Costs of lines of chemotherapy according to patient group.*:** patient
11 included in a clinical trial

12 **Table 6: Costs of the three most expensive chemotherapy drugs according to**
13 **patient group.**

14 **Figure 1: Overall survival of metastatic breast cancer patients according to the**
15 **period of treatment.**

16 **Figure 2: Overall survival of metastatic breast cancer patients according to**
17 **HER-2 status.**

18 **Figure 3: Overall survival of metastatic breast cancer patients with positive**
19 **hormone receptors according to the group.**

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	Group 1 (1994-1998)		Group 2 (2003-2006)		P
	n=149		n=152		
Median age at diagnosis of MBC, years	49		55		
≤ 50	82	(55%)	51	(35.6%)	<0.001
> 50	67	(67%)	101	(66.5%)	
Median disease-free interval, years	2.29		2.14		
≤2	67	(45%)	70	(46%)	NS
>2	82	(55%)	82	(54%)	
Number of metastatic sites					
1	88	(59%)	86	(57.3%)	NS
≥ 2	61	(41%)	66	(42.7%)	
Sites of metastases					
Bone	86	(57.7%)	85	(56%)	NS
Viscera	84	(56.4%)	86	(56.6%)	
Soft tissue	35	(23.5%)	29	(19.1%)	
Other	7	(4.7%)	9	(6%)	
Performance status					
0-1	147	(98.7%)	147	(96.7%)	NS
≥ 2	2	(1.3%)	4	(2.6%)	
Unknown	0		1	(0.7%)	
Hormone receptor status					
Positive	84	(56.4%)	88	(57.9%)	<0.001
Negative	33	(22.1%)	56	(36.8%)	
Unknown	32	(21.5%)	8	(5.3%)	
HER-2 status					
Positive	2	(25%)	39	(25.7%)	NS
Negative	6	(75%)	84	(68.3%)	
Unknown	141		29		
Synchronous metastases					
Yes	29	(19.5%)	33	(21.7%)	NS
No	120	(79.5%)	119	(78.3%)	
Adjuvant chemotherapy					
Yes	88	(73.3%)	91	(76.5%)	NS
No	32	(26.7%)	28	(23.5%)	
Type of adjuvant chemotherapy					
Anthracyclines					
Yes	77	(64.2%)	87	(72.5%)	NS
No	43	(35.8%)	32	(27.5%)	
Taxanes					
Yes	1	(0.8%)	18	(15.1%)	<0.001
No	119	(99.2%)	101	(84.9%)	
Adjuvant hormone therapy					
Yes	84	(70%)	64	(53.8%)	<0.001
No	29	(24.2%)	54	(45%)	
Unknown	7	(5.8%)	1	(8.3%)	
Hormone therapy at metastatic stage					
Yes	135	(90.6%)	93	(61.2%)	<0.001
No	12	(8%)	59	(38.8%)	
Unknown	2	(1.4%)	0		
High-dose chemotherapy with SCT at metastatic stage					
Yes	27	(18.1%)	0		<0.001
No	122	(81.9%)	152	(100%)	

2 **Table 1**

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	Group 1(1994-1998)	Group 2 (2003-2006)	<i>P</i>
	<i>n</i>	<i>n</i>	
Number of LOC			
Median	3	3	
Minimum	1	1	NS
Maximum	11	11	
Anthracyclines			
1st line	115 (77.2%)	52 (34.2%)	<0.001
All lines	139 (93.3%)	76 (50%)	<0.001
Taxanes			
1st line	25 (16.8%)	103 (67.8%)	<0.001
All lines	107 (71.8%)	129 (84.9%)	<0.01
Capecitabine			
1st line	0	26 (17.1%)	<0.001
All lines	7 (4.7%)	105 (69%)	<0.001
Vinorelbine			
1st line	14 (9.4%)	7 (4.6%)	NS
All lines	112 (75.2%)	84 (55.3%)	<0.001
Trastuzumab			
1st line	0	32 (21%)	<0.001
All lines	3 (100% of HER-2+)	38 (100% of HER-2+)	NS

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Table 2

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OS adjusted on group of patients				
Variable	n	HR	95% CI	P
Primary tumor size				
T1	70	1	-	
≥T2	133	1.25	0.97-1.61	0.09
SBR grade				
1	13	1	-	
2	104	1.23	0.64-2.38	
3	103	1.64	0.85-3.15	0.10
Number of involved nodes				
0	67	1	-	
≥1	182	0.95	0.70-1.28	0.72
Hormone receptors				
No	89	1	-	
Yes	172	0.55	0.42-0.73	<0.0001
HER-2 expression				
No	90	1	-	
Yes	41	0.99	0.64-1.55	0.99
Adjuvant chemotherapy				
No	57	1	-	
Yes	179	1.02	0.75-1.40	0.89
Adjuvant hormone therapy				
No	83	1	-	
Yes	148	0.77	0.57-1.03	0.08
Adjuvant radiotherapy				
No	19	1	-	
Yes	213	0.97	0.58-1.63	0.91
Age at diagnosis of metastases				
≤50	133	1	-	
>50	168	0.85	0.66-1.09	0.20
Progression-free interval				
≤2 years	137	1	-	
>2 years	164	0.78	0.61-0.99	0.04
Number of metastatic sites				
1	174	1	-	
≥2	125	1.74	1.36-2.24	<0.0001
Bone metastases				
No	130	1	-	
Yes	171	0.76	0.59-0.97	0.03
Soft tissue metastases				
No	237	1	-	
Yes	64	1.64	1.22-2.21	0.001
Visceral metastases				
No	131	1	-	
Yes	170	1.56	1.21-2.00	0.0001
Performance status				
0-1	294	1	-	

>1	6	3.55	1.45-8.66	0.006
1st line chemotherapy with anthracyclines				
No	128	1	-	
Yes	172	0.72	0.55-0.94	0.02
1st line chemotherapy with taxanes				
No	173	1	-	
Yes	128	0.99	0.73-1.35	0.95

1 **Table 3**

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Variables	HR	95% CI	P
Single metastatic site	0.48	0.36-0.64	<0.0001
Bone metastases	0.67	0.50-0.90	0.007
Positive hormone receptors	0.56	0.42-0.77	0.0002
Group	1.04	0.70-1.55	0.83

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Table 4

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	Group 1 (1994-1998) (n=149)			Group 2 (2003-2006) (n=152)			<i>p</i>
	Median	Minimum	Maximum	Median	Minimum	Maximum	
Total cost of chemotherapy drugs per patient (€)	6,272	20	189,923	13,035	11	162,960	<0.001
Cost of 1 st line (€)	1,269	1.50	12,994	5,744	11	137,074	<0.001
Cost of 2 nd line (€)	1,421	0*	18,900	2,625	0*	53,564	<0.001
Cost of 3 rd line (€)	1,074	0.40	14,484	2,315	0*	30,509	<0.001

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4 **Table 5**

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	Group 1 (1994-1998)			Group 2 (2003-2006)		
	Number of patients (%)	Total costs (€)	% of costs	Number of patients (%)	Total costs (€)	% of costs
Trastuzumab	3 (2%)	153,037	11.6	40 (26.3%)	1,726,970	44.8
Docetaxel	94 (63%)	623,840	47.2	89 (58.6%)	569,546	14.7
Paclitaxel	22 (14.7%)	103,891	7.8	72 (47.4%)	298,273	7.7

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3 **Table 6**

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Figure 1

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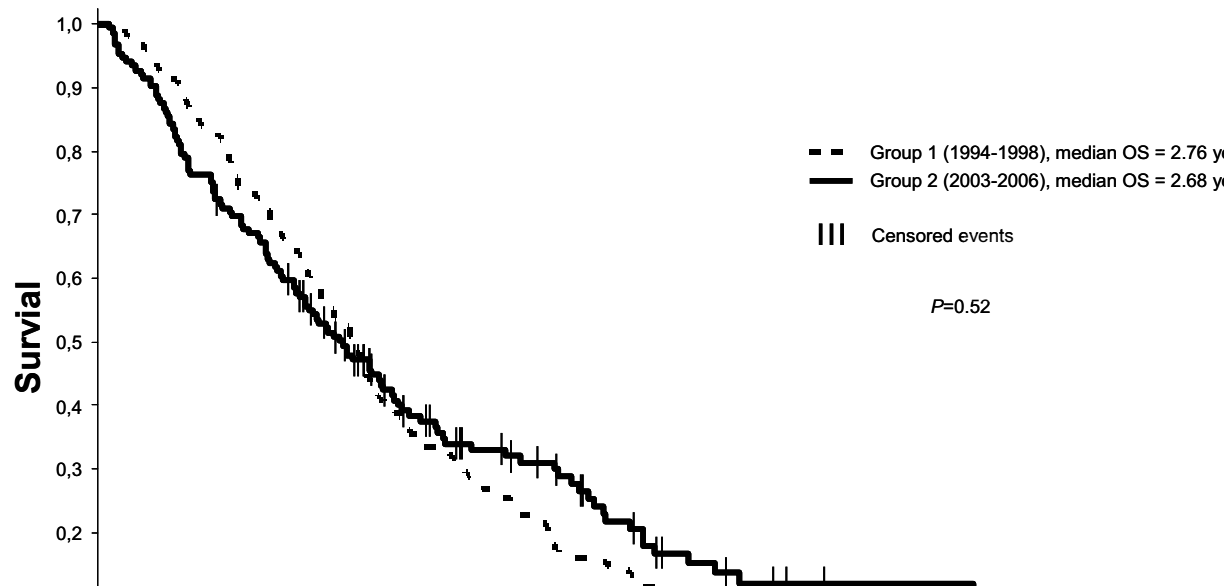


Figure 2

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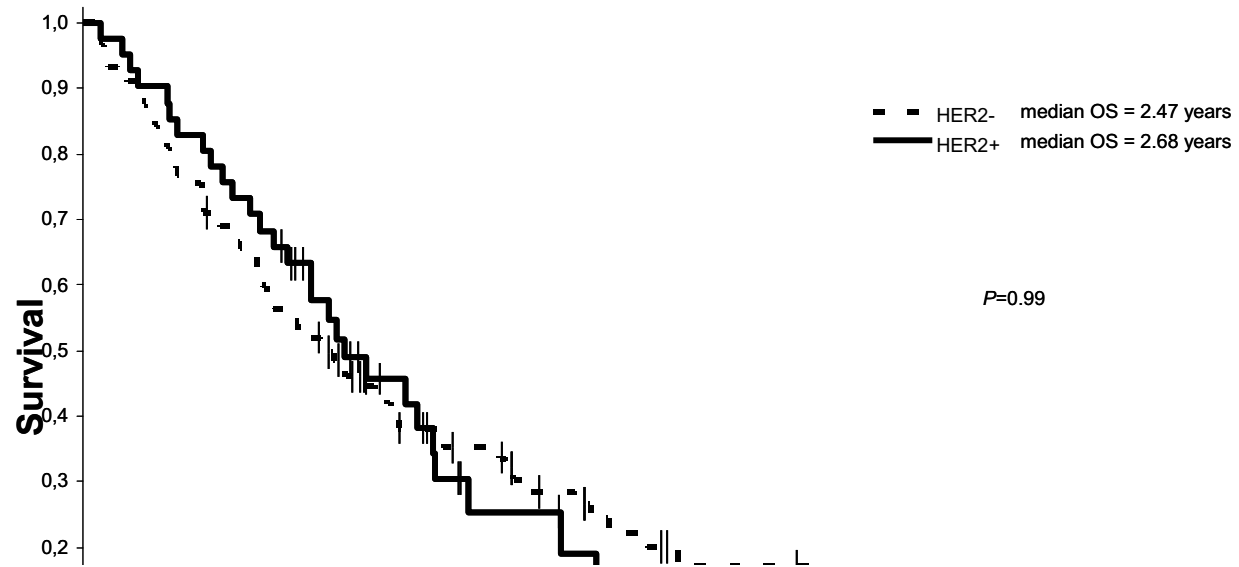


Figure 3

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