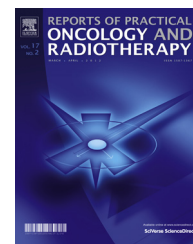


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Review

Prognostic factors and survival in metastatic breast cancer: A single institution experience

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ABSTRACT

Background: The current retrospective study aims to identify some determinants of survival in metastatic breast cancer.

Methods: The study concerned 332 patients with synchronous (SM) or metachronous (MM) metastatic breast cancer treated between January 2000 and December 2007. Statistical comparison between subgroups of patients concerning survival was carried out employing log-rank test for the invariable analysis and Cox model for the multivariable analysis. Factors included: age group (≤ 50 years vs. >50 ; ≤ 70 years vs. >70 ; ≤ 35 years vs. >35), menopausal status, presentation of metastatic disease (SM vs. MM), disease free interval (DFI) (≤ 24 months vs. >24 months; ≤ 60 months vs. >60 months), performance status at diagnosis of metastatic disease (PS) (0–1 vs. >1), hormone receptors (HR), number of metastatic sites (1 site vs. >1), nature of the metastatic site (visceral vs. non visceral), first line therapy, surgery of the primary tumor (SPT), locoregional radiotherapy (LRRT) and use or not of bisphosphonates.

Results: Overall survival at 5 years was 12%. Positive prognostic factors in univariate analysis were: age ≤ 70 years, hormono-dependence of the tumor, good PS (PS 0–1), less than two metastatic sites, no visceral metastases, DFI ≥ 24 months, SPT or LRRT. In multivariate analysis, favorable independent prognostic factors included: good PS (PS 0–1), absence of visceral metastases (liver, lung, brain) and age ≤ 70 years.

Conclusion: Many of the prognostic factors in metastatic breast cancer found in our study are known in the literature but some of them, like the application of locoregional treatment (radiotherapy or surgery) and the use of bisphosphonates, need to be further investigated in randomized clinical trials.

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1. Background

Breast cancer is the most common malignant disease among women in the world.¹ Despite the advances in

the diagnosis and in the treatment of breast cancer, 6–10% of affected patients present metastatic breast cancer at diagnosis and 30–40% will develop metastasis during the evolution of their disease.^{2,3} The peak of relapses is seen between 2 and 3 years.² The onset of metastases,

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Table 1 – Distribution of metastatic location.

Metastatic locations	Numbers	(%)
Bone		
Bone and others	225	(67.6)
Only bone	85	(38)
Liver		
Liver and others	116	(35)
Only liver	31	(27)
Lung		
Lung and others	103	(31)
Only lung	28	(27)
Node	56	(16.8)
Brain		
Brain and others	37	(11.1)
Only brain	6	(16)
Skin	25	(7.5)
Ovarian	5	(1.5)

as a sign of incurability, constitutes a major problem of care.⁴

The emergence of new drugs and recent therapeutic strategies have not only helped to extend the median survival time (around 30 months now) but also to improve the quality of patients' lives.⁵

The aim of this retrospective study is to identify the prognostic factors influencing the survival of patients affected with metastatic breast cancer taken over in the south of Tunisia.

2. Materials and methods

This study included 332 patients with histologically proven breast cancer with synchronous (SM) or metachronous (MM) metastasis (MTS). The study was conducted over eight years (from January 2000 to December 2007). Data were updated on January 2010. We collected, for each patient, the epidemiological and clinical data, the therapeutic modalities and the evolution. The treatment of the primary tumor consisted, according to the operability and the response to chemotherapy (CT), in the surgery (mastectomy or tumorectomy with or without axillary lymph nodes dissection) and/or radiotherapy (RT) at a dose of 36 Gy in 12 sessions. The metastasectomy and/or the RT had been indicated for solitary metastasis. The RT had been, also, used for painful bone metastasis, in case of spinal cord compression, for consolidation of threatening bone lesions and/or in case of cerebral metastasis with a dose of 30 Gy in 10 sessions. The first line systemic treatment for metastatic relapse consisting in hormone therapy (HT) or chemotherapy (CT) depends on the disease free interval (DFI) between the end of the adjuvant treatment and the metastatic relapse, of the positivity of hormonal receptors (HR), characteristics of metastasis and the patient PS based on the WHO classification. Bisphosphonates (Pamidronate, Zoledronate or Ibandronate) were prescribed in cases of bone metastases.

The OS was defined as the time between the date of diagnosis and the date of death or last visit for the group of patients presenting SM and as the time between the date of relapse and the date of death or last visit for patients with MM using the Kaplan–Meier. The OS was analyzed in relation to different prognostic factors: the age (≤ 50 years vs. >50 ; ≤ 70 years vs. >70 ; ≤ 35 years vs. >35), the menopausal status (premenopausal

vs. postmenopausal); the presentation of metastatic disease (SM vs. MM), the disease free interval (DFI) (≤ 24 months vs. >24 , ≤ 60 months vs. >60), the performance status (PS) (0–1 vs. >1), the estrogen receptor (ER) (ER+ vs. ER–); the hormone receptors for progesterone (PR) (PR+ vs. PR–); the number of metastatic sites (1 site vs. >1 site); the nature of the metastatic site (visceral vs. non visceral), the type of the first line medical treatment (CT vs. HT), the surgery of the primitive tumor (SPT) vs. no SPT, the loco regional RT (LRRT) vs. no LRRT and the use of biphosphonates (biphosphonates vs. no biphosphonates). The study of survival based on prognostic factors was performed using the log-rank test for univariate analysis and Cox model for multivariate analysis.

3. Results

3.1. Characteristics of patients and of the disease

There were 129 cases of SM (39%) and 203 cases of MM (61%). The median age was 50.5 years (range: 25–85 years). The PS was 0–1 in 72% of cases. Fifty-five percent of our patients were premenopausal at diagnosis. The anatomopathological examination concluded to an invasive ductal carcinoma in 82% of the cases, a II or III histological grade in 98% of cases and a positive HRs in 56% of the cases. Her2 status was determined by immunohistochemistry for 3 patients, this marker was over expressed in one of them. The rate of CA15-3 was increased in 72% of the specified cases. The median time of relapse in MM cases was 31 months (2–248 months). The distribution of the metastatic locations is detailed in Table 1. One hundred and fifty-seven patients (47.3%) had a single metastatic site.

3.2. Treatment

3.2.1. Surgery

Two hundred and ninety-eight patients were treated. Fifty-two patients were treated by surgery for their primitive tumor: 39 underwent a mastectomy with axillary node dissection, eleven had a mastectomy without axillary node dissection and two had a lumpectomy with axillary node dissection. Twelve patients had surgeries of secondary localizations: Hepatic metastasectomy (two patients), cerebral metastasectomy (two patients), bilateral annexectomy (one patient), spinal lymph node dissection (one patient) and bone consolidating surgery (six patients).

3.2.2. Medical treatment

Amongst the 298 treated patients, 283 patients (94.6%) received a first line medical treatment consisting in CT (258 patients) or HT (25 patients). The untreated patients were lost to follow up at diagnosis of metastases or had a poor PS preventing treatment. Among the 265 patients who received CT (in first line or after first line HT), 119 (44.9%) were treated with second line CT and 47 (17.7%) with 3 lines of CT or more.

The first line CT was anthracycline-based in 137 cases (51.6%), taxane-based in 88 cases (33.2%), vinorelbine-based in 48 cases (18.2%) and platinum-based in 19 cases (7.3%). Fifteen patients had a combination of anthracycline with taxane

Table 2 – Prognostic factors in univariate analysis.

Prognostic factors	3 years OS	5 years OS	p
Age (years)			
<35 vs. >35	25% vs. 31%	15% vs. 12%	0.2
<50 vs. >50	34% vs. 27%	12.4% vs. 11.7%	0.3
<70 vs. >70	32.2% vs. 15.4%	12.8% vs. 3.8%	0.006
Menopausal status			
Postmenopausal vs. premenopausal	25.4% vs. 35%	11.3% vs. 13%	0.25
DFI (Months)			
<24 vs. >24	21.7% vs. 37%	6.8% vs. 14.9%	0.004
<60 vs. >60	26% vs. 58%	8.7% vs. 25.8%	0.008
PS			
(0–1) vs. ≥1	39.3% vs. 9.3%	15.2% vs. 4.6%	<0.00001
HR			
ER (+) vs. ER (–)	41.5% vs. 21.4%	19% vs. 5%	<0.00001
PR (+) vs. PR (–)	42.4% vs. 22.3%	18% vs. 6.5%	<0.00001
MTS			
SM vs. MM	34% vs. 29%	16.4% vs. 10.3%	0.25
Visceral vs. non visceral	26% vs. 43.5%	8% vs. 25%	<0.00001
1 site vs. >1 site	41% vs. 21%	15% vs. 9%	<0.001
Medical treatment			
CT vs. HT	21% vs. 52%	4% vs. 11.5%	<0.01
Anthracyclines vs. no anthracyclines	43% vs. 23%	21% vs. 5%	0.004
Taxanes vs. anthracycline	28% vs. 43%	–	0.03
Biphosphonates vs. no biphosphonates	49% vs. 19%	23% vs. 8%	0.0003
Local treatment in SM			
SPT vs. no SPT	48% vs. 24%	21% vs. 11%	0.0003
RT vs. no RT	49% vs. 29%	25% vs. 11%	0.02

Abbreviations – DFI: disease free interval; PS: performance status; HR: hormonal receptors; ER: estrogen receptor; PR: progesterone receptor; MTS: metastasis; SM: synchronous metastasis; MM: metachronous metastasis; SPT: surgery of the primitive tumor; RT: radiotherapy; CT: chemotherapy; HT: hormonotherapy.

according to a sequential schedule in 5 cases (1.9%) and concomitant schedule in 8 cases (3%).

After receiving the first line CT, the objective response rate was 65% and the median time for progression was 9 months.

One hundred and eight patients were treated with HT (immediately to the diagnosis of the metastatic disease in 25 cases, a relay after a response to the first line CT in 73 cases or after the failure of a first line CT in 10 cases). Forty-one percent of these patients underwent second-line HT and thirteen percent had at least three lines.

Out of 225 patients with bone metastases, only 94 patients (41.7%) received bisphosphonates. Pamidronate was the most widely used molecule. The average duration of the prescription of bisphosphonates was 18.6 months (1–96 months).

3.2.3. Radiotherapy

One hundred and fifty-five patients underwent RT, 15 of them had only a palliative RT without systemic treatment. It was brain RT (54 cases), bone RT (78 cases) and/or locoregional RT (23 cases). The response (tumor size reduction) to the LRRT was observed in 67% of cases. The response to the palliative RT was variable depending on location. Seventy-one percent of patients with brain metastases showed a disappearance of intracranial hypertension symptoms after RT. The relief of the spinal cord compression was observed in 69% of irradiated patients. The effectiveness of RT for pain management was observed in 90% of cases. The average duration of analgesic response to radiotherapy was 26 weeks.

3.3. Survival and prognostic factors

In our study, the OS was respectively 63%, 42%, 26% and 12% at 1, 2, 3 and 5 years (Fig. 1).

The median survival of patients who received treatments was 18 months. It was 23.3 months, 29.3 months, 18 months, 15 months and 11 months, respectively, in case of only: bone, lymph node, hepatic, lung or brain MTS.

In patients with single bone MTS, the 5 years OS was 36% and it was 23% for those with only lymph node metastasis.

The median survival for patients who underwent metastasis resection was 83 months.

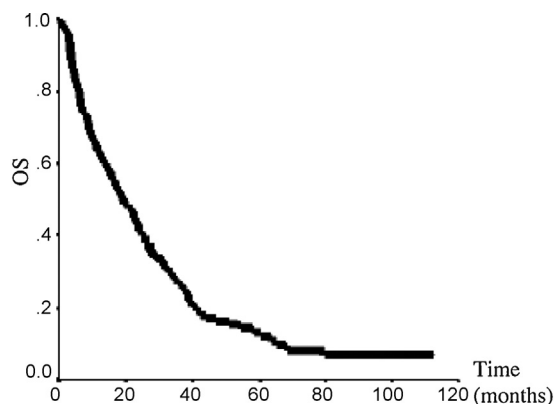


Fig. 1 – Kaplan-Meier curve for overall survival.

Table 3 – Prognostic factors in multivariate analysis.

Prognostic factors	Hazard ratio (95%)	p
General state		
PS (0–1) vs. >1	2.59 (1.94–3.46)	<0.0001
MTS		
Visceral vs. no visceral	1.63 (1.07–2.48)	0.021
Age (years)		
<70 vs. >70	1.67 (1.24–2.25)	0.001

Abbreviations – PS: performance status; MTS: metastasis.

3.3.1. Univariate analysis

Using univariate analysis, the following prognostic factors were found to influence positively the survival: Age \leq 70 years, good PS (0–1), positive ER, positive PR, single metastatic site, non visceral MTS, using HT in first line metastatic treatment, locoregional treatment (RT or/and surgery) in case of SM and the use of bisphosphonates (Table 2).

3.3.2. Multivariate analysis

In case of multivariate analysis, improved survival was associated significantly with good PS (1–2), non visceral MTS and age \leq 70 years (Table 3).

4. Discussion

In our study, the median survival of SM and MM breast cancer patients who received treatment was 18 months and the 5 years OS was 12%. Our results were similar to those reported in many previous studies in which the median survival ranged between 16 and 34 months and the 5 years OS varied from 4% to 28%.^{6–10}

For many authors, age at diagnosis is acknowledged as a prognostic factor affecting the survival. Dawood et al. did not find age to be a prognostic factor for predicting survival.² However, according to the study of Largillier et al., poor prognosis was reported with age over 50 years.¹¹ In our material, we studied survival according to differing age groups (\leq or $>$ 35 years); (\leq or $>$ 50 years) and (\leq or $>$ 70 years). We identify that the age of more than 70 years was a pejorative factor influencing significantly the survival in univariate and multivariate analysis.

Some studies have shown that premenopausal women have a better prognosis than postmenopausal patients.² This finding was not confirmed in our study and the influence of the menopausal status on survival was not significant.

Several studies have shown that the more altered the PS is, the worst the prognosis.^{12–15} Our study confirmed this finding in univariate and multivariate analysis.

Many previous studies have shown that the DFI is an important prognostic factor.^{2,14,16–21} Vogel et al. reported in a series of 433 patients with recurrent breast cancer a median survival from first relapse of 26 months for patients with DFI $<$ 24 months and 44 months for patients with DFI $>$ 24 months ($p <$ 0.01).²⁰ Our study confirmed these findings; relapse after 2 years of adjuvant therapy was a good prognostic factor.

Dawood et al. found that the median survival in women with SM was 12 months longer than women with MM, the difference was statistically significant in univariate and

multivariate analysis.² Our study did not confirm these data and the difference in survival between these two groups was not statistically significant.

The non visceral localizations (skin, soft tissue and bone) have a better prognosis than visceral sites. The most pejorative visceral sites are the brain, liver and lung.^{12,21} Our study confirmed these results as well in univariate or multivariate analysis.

In our study, the 5 years OS and the median survival with single bone MTS were respectively 36% and 23.3 months. In other previous studies, median survival ranged between 24 and 48 months and the 5 years OS achieved 20%.^{22–24} In a study conducted by Coleman and Rubens concerning patients whose cancers were diagnosed in the 1970s and 1980s, the median survival was 24 months in patients with first recurrence in the skeleton compared with 3 months after first relapse in the liver ($p <$ 0.01).²⁵

Hepatic metastases are generally associated with a poor prognosis. Pentheroudakis et al. reported in a retrospective study of 500 liver metastasis breast cancer cases a median survival of 16.4 months and 5 years OS of 8.5%.²⁶ Reported median survivals in a phase III EORTC trial which investigated the first line CT in metastatic breast cancer were respectively 27.1 months and 16.8 months in patients with liver MTS alone and with liver with other sites of MTS.⁴ In our study, median survival was 17.7 months in cases of hepatic MTS only. Long survival (83 months) was obtained in one patient who underwent surgical resection of liver MTS.

The median survival for patients with only lung MTS ranges from 6 to 15 months as noted in previous studies.^{24,27} In our study it was 14.6 months.

The majority of patients with cerebral MTS died in 40% of cases because of non control of the latter.²⁸ The median survival depends on the application of treatment: if not treated, this median is 1 month; and 2 months for patients who had received corticosteroids only, while it grows to 3–6 months if the whole brain RT is carried out.²⁸ In our study this median was 11.2 months.

The median survival in case of ovarian and/or peritoneal metastases, according to previous studies, ranges from 6.4 months to 23 months. However, long term survival reaching more than 12 years has been reported particularly in cases of metastatic breast cancer with positive hormonal receptors.^{29,30}

Many retrospective recent studies have shown that the surgical treatment of the primitive tumor improve the OS rate for patients presenting breast cancer with SM.^{31–33} This was confirmed by our study.

The Le Scodan et al.³³ retrospectively reviewed a mono centric study of 581 treated patients for an SM breast cancer. Of that number, 320-patients had a loco regional treatment (exclusive RT for 78% of them, a surgery followed by a RT for 13% and exclusive surgery for 9%), in addition to systemic treatment against 261 patients who received systemic treatment only. After a median follow-up of 39 months, the 3-year OS was 43.4% for patients who underwent a local therapy, against 26.7% for patients who had only systemic treatment ($p <$ 0.02). Our study showed the benefit provided by a local therapy (RT and/or surgery) on OS for patients with synchronous metastases of breast cancer.

The use of biphosphonates in case of bone MTS reduced the skeletal-related events (SREs) rate, delayed the time to SREs and prolonged the time in developing bone pain, but it do not appear to affect survival.³⁴ However, in our study we noticed that the use of biphosphonates improves the overall survival.

5. Conclusion

Our therapeutic results in terms of survival were correlated with those of previous studies. Our study confirmed the positive impact, influencing independently the duration of survival in metastatic breast cancer, of the good general state, of the age ≤ 70 years, and of the absence of visceral metastasis.

Conflict of interest

No conflict of interest.

Financial disclosure

Not applicable.

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