

# Long Survival of Metastatic Breast Cancer in center of Tunisia, about 34 cases

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## Abstract

Breast cancer is the most common cancer for women. Survivals protruding 5 years are rare.

Our retrospective study was about 34 patients with metastatic breast cancer surviving more than 5 years who were supported at the department of medical oncology in Farhat Hached Hospital between January 1994 and December 2011. The aim of our study was to identify clinic pathologic characteristics, treatment and prognostic factors for long survival of women with metastatic breast cancer. The average age at diagnosis of metastases was 53ans.

The tumor was classified as T3-T4 in 64.6% of cases. Infiltrating ductal carcinoma was found in 85.3% of cases. Nearly 80% of tumors were grade II or III SBR. Hormone receptors were positive in 88.2% of the cases.

Thirteen patients had metachronous metastases (38.2%) and 21 had synchronous metastases (61.8%). Bone metastases were the most frequent (82.3%). The recurrence-free interval was 51.5 months.

Twelve patients (92%) with metachronous metastases and 21 patients with synchronous metastases underwent palliative chemotherapy with a median time to progression of 6 to 25 months. 30 patients underwent palliative hormone therapy (20 in the case of synchronous metastases and 10 cases of metachronous metastases) with a median time to progression of 13 to 35 months.

The median overall survival was 100 months. The median survival was 75 months metastatic. Prognostic factors for survival were a long clinical size of the tumor (T1 and T2) and hormone receptor negative.

In recent years, new treatments associated with the evaluation of new strategies, show significant improvement in survival in metastatic breast cancer.

## Introduction

Breast cancer is the leading cancer for women worldwide [1]. In Tunisia, according to three registers in the country (north, center and south), it ranks first cancers woman with respective frequencies of 30%, 31% and 31% [2]. It remains a public health problem.

Although recent advances have led to improved prognosis of this cancer, thanks to advances in screening and adjuvant therapy, some forms mainly metastatic disease remain poor in prognosis. Indeed, 6-10% of patients present with synchronous metastases and 30% of patients initially nonmetastatic develop metachronous metastases during the course of their disease with a maximum peak of relapses which is between 2 and 3 years [3].

Metastatic breast cancer remains an incurable disease in the majority of cases. Therapeutic progress, both in terms of chemotherapy targeted therapies have certainly prolonged the survival of these patients, but the long survivals are rare. In this work, we present a series of 34 patients with metastatic breast cancer and surviving more than 5 years.

The objectives of this work are to clarify clinical, pathological and therapeutic features and to identify prognostic factors in this series

## Patients and methods

Our retrospective study over a period of 17 years (January 1994-September 2011). It involved 34 patients with breast cancer diagnosed and histologically proven.

These patients presented either synchronous metastases (MS) [at the time of initial diagnosis] or metachronous metastases (MM) occurred at any time after the initial treatment.

Overall survival over five years from the initial diagnosis of secondary locations. The dependent variables studied were survival and duration of response.

Survival was calculated from the date of diagnosis of metastases to the date of last news for patients with synchronous metastases and from the date of metastatic relapse up to date with the latest news for patients' metachronous metastases.

The duration of response was calculated from the date of the beginning of the treatment of metastatic disease to the date of progress or death of patients.

The study of survival is calculated according to the Kaplan-Meier method and comparison of different rates of survival by log-rank test, a value of  $p \leq 0.05$  was considered statistically significant.

## Results

### Clinical and pathological characteristics

The age of our patients was between 30 and 79 years with an average of 53 years. The tumor was classified as T4 in 16 cases (47%), T3 in 6 cases (17.6%), T2 in 9 cases (26.6%) and T1 in three remaining cases (8.8%). The clinical nodal involvement was observed in 53% of cases.

The histological type was the most common invasive ductal carcinoma in 85.3% of cases. The SBR histologic grade was high (II or III) in 79.4% of cases.

Hormone receptors were positive (ER + and / or PR +) in 88.2% of cases.

HER2 status was performed in 2 patients by immunohistochemistry and was not expressed in the two cases.

Thirteen patients had metachronous metastases (38.2%) and 21 had synchronous metastases (61.8%).

The mean time to relapse was 51.5 months with a range of 17 to 132 months.

Relapse had occurred after the first 2 years in 92.3% of cases.

Relapse diagnosis was made before clinical symptoms for 9 of our patients.

Bone pains were the most frequent presenting symptoms synchronous metastases (42.8%) and metachronous metastases (53.8%).

Bone metastases were more frequent in patients with synchronous metastases (90%) and in patients with metachronous metastases (69.2%), followed by lung and liver secondary

Six patients with synchronous locations.

### Therapeutic results

All patients with metachronous metastases had undergone surgery for their primary tumor. It was Patey type in 69.2% of cases and conservative in 23.1% of cases. Metastases underwent surgery of their primary tumor. It was Patey type in 4 cases (after correct answer metastases palliative chemotherapy in one patient and before complete staging by bone scintigraphy in the other 3 patients) and mastectomy clean in two remaining cases.

Two patients had received surgery for osseous metastases secondary. The first patient had a consolidation surgery of the bone after a pathologic fracture and the second patient had a spinal surgery (laminectomy) for spinal cord compression.

The first-line chemotherapy was essentially based on anthracyclines in 27 cases (81.8%), taxane in 2 cases (6%) and based CMF (cyclophosphamide-methotrexate-endoxan) in 3 cases (9%). After the first line palliative chemotherapy, the objective response rate, all protocols together for synchronous and metachronous metastases were 57.8% and the average duration of response was 11.9 months.

Twenty-three patients underwent palliative chemotherapy second-line. This was taxane in 11 cases (47.8%), based on vinorelbine in 10 cases (43.6%), based on platinum in 1 (4.3%) and base mitomycin-vinblastine in the remaining case (4.3%). The objective response rate, all combined protocols for synchronous and metachronous metastases were 47.8% and the average duration of response was 13.6 months.

Thirteen patients underwent palliative chemotherapy third line. This was based on vinorelbine in 6 cases (46.1%), taxane in 6 cases (46.1%) and based capecitabine in the remaining case (7.8%). The objective response rate after chemotherapy, all protocols combined was 30.7%.

Six patients underwent palliative chemotherapy fourth line. She was based in 3 cases capecitabine and CMF-based in three remaining cases. The objective response rate after chemotherapy, all protocols combined was 16.7%.

Thirty patients underwent palliative first-line hormone therapy, either immediately at diagnosis of metastases after failure of either relay or response to palliative chemotherapy. It was essentially based on tamoxifen in the majority

of cases (70%). The objective response rate in the first-line metastatic hormone of all types, was 50%. While the average duration of response was 23 months in the case of synchronous metastases and 35 months for metachronous metastases. Hormone palliative second line was used in 20 of our patients. It was based on anti-aromatase such 2nd generation steroidal or non-steroidal in most cases (85%). The objective response rate to hormone palliative second line of all types was 55%. While the average duration of response was 11.3 months.

Of the 28 patients who presented with bone metastases, 21 had bisphosphonates (75%). The median duration of bisphosphonate prescription was 49 months for metachronous metastases and 22.5 months in the case of synchronous metastases. Radiotherapy was bone analgesic in 14 cases, for decompressed spinal cord compression in 1 case, after loco regional palliative surgery of the primary tumor in 2 cases and loco regional recurrence in cervical lymph node metastasis in 2 cases.

### Study of survival

The median overall survival was 100 months, with a range from 60 to 221 months (Fig 1) and the median survival from diagnosis of metastases was 75 months, with a range from 60 to 162 months (Fig 2).

Patients classified as T1 and T2, TNM malignant tumors (UICC / AJCC) had a better survival than patients classified as T3 and T4. The difference was statistically significant with  $p = 0.05$  (Fig 3). The median survival of patients classified as T1 or T2 was 162 months versus 68 months for patients classified as T3 or T4.

Other factors influencing survival were not statistically significant: age, menopausal status, clinical nodal involvement, histological type, grade SBR, Nature metastatic site, the chronology of metastasis and response to palliative chemotherapy.

### Evolution

Of the 34 patients in our series and date update medical records (01 September 2011):

- Twenty-three patients died due to progression of metastatic disease.
- Ten patients are still alive:
  - Two of them are in complete response.
  - Five women are stable.
  - Three women are in metastatic progression.
- One patient was out of sight, she was in complete remission at the time of her latest news.

### Discussion

Breast cancer is the most common cancer for women. It is a major problem of public health. Its incidence increases significantly over the past three decades in the United States and Western Europe [4]. Moreover, it's the most common cause of death from cancer for women.

In Tunisia, breast cancer is the most common cancer for women. It represents about 30% of female cancers. Unfortunately, the diagnosis is still at a late stage. In Tunisia, the frequency of metastatic breast cancer at diagnosis in a series of Tunisian center until the year 1996 was 15.4%. The rate was 13.1% in the north of Tunisia until 2004 according to the study Maalej et al [5] However, in southern Tunisia, the incidence was 9.6% until 2007.

In Western countries, this rate varies between 6% and 10% [6].

The proportion of patients who will develop metastases secondary is around 30% [3].

Currently, the median survival of metastatic breast cancer is between 18 and

30 months [7]. The notion of long-term survival is not clearly defined in the literature. Our choice of 5 years followed after the diagnosis of metastases was arbitrary.

Several studies have focused on analyzing the prognostic impact of patient age of diagnosis of metastases on survival.

Long survival beyond 5 years are more common in young women, as proved by the series of German Cnossen [8] and the Danish series Ryberg [9].

In our series, the survival of patients whose age was <50 years was slightly better than that of other patients, but the difference was not statistically significant.

Dawood et al [3] showed that long-term survival rate was higher in premenopausal women with a median survival of 45 months (range: 37-64) against 38 months in postmenopausal women (range: 33-42).

In our series, the survival of premenopausal women was better than postmenopausal but the difference was not statistically significant.

Cnossen et al [8] showed that long-term survival rate was higher in tumors classified as pT1 or pT2 with a median survival of 53 months (range 37-69) months against 34 tumors classified pT3 or pT4.

In our study, the clinical size was a prognostic factor determining the long-term survival ( $p = 0.05$ ).

In the German series of Cnossen et al [8], women without lymph node involvement (N-) with a longer survival (median survival 57 months, with a range from 41 to 73 months) compared to the population N+ (median survival 38 months, with a range from 32 to 44 months).

In our series, survival between the 2 groups in clinical N0 and N+ was almost identical. The difference was not statistically significant.

Histological type did not influence survival in metastatic. Long survivals are described for both the CLI ITC [10].

In the Danish series of Hietanen et al [11], the rate of long-term survival beyond 5 years was higher in patients with SBR grade I (24%) compared with patients with a high grade SBR (12%).

In our series, patients with SBR grade I had a better survival than those with a high grade (II or III), but the difference was not statistically significant.

It is clearly recognized that the expression of hormone receptors by the tumor is associated with longer survival [12]. The estrogen receptor and / or progesterone were expressed in 88.2% of our patients. This frequency was similar to that described in a retrospective study German [19], focusing on the long survival in metastatic breast cancer where the rate of RH+ was high (78%).

According to the literature, 20% of patients with breast cancer have HER2 overexpression status [3]. It was sought only in 2 of our patients and was not expressed in the two cases. Its overexpression is a poor prognostic factor [13,14]. The time of relapse is a prognostic factor and predictive of longer survival. In the Danish series Hietanen et al [11], the rate of long-term survival beyond 5 years was higher in patients with relapsed within > 2 years (21%) compared with patients with a short delay < 2 years (15%).

Some studies have shown that the prognosis of synchronous metastases is better than metachronous metastases. Dawood et al [3] found that the median survival of women with MS was 12 months longer than women in relapse of their disease. The rate of long-term survival beyond 5 years was higher in case of synchronous metastases: 32% versus 22% for metachronous metastases.

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

Survival in breast cancer with bone metastases is generally longer than for other metastatic sites: median survival is between 24 and 48 months [15, 16]. Long survivals are also common with 20% surviving beyond 5 years [16].

Several recent studies have shown that surgical treatment of the primary tumor significantly improves overall survival of patients with metastases. Three of

them have shown the benefits of this treatment on long survival beyond 5 years [17, 18], such as the series of Ruitkamp et al [19] where the rate of long-term survival with surgery of the primary tumor was 24.5%.

Long survival in metastatic breast cancer, described through literature, are obtained after an objective response (complete or partial response) to several lines of chemotherapy and / or hormone therapy if the tumor is hormone [19, 20]. This was the case in our series. Long survival beyond 5 years caused by a single line of chemotherapy or hormone therapy are extremely rare [21].

In a prospective study internationally, the rate of long-term survival (beyond 5 years) was 16% among women who were treated with anthracyclines Protocol (FAC) against 5% when using the CMF protocol [22]

In our series, these protocols (FAC or FEC) used in first-line metastatic gave an average rate of objective response of 59%, a complete remission rate of about 11% and a median time to progression of 10.7 months.

Taxanes are often used either as mono therapy or in combination with other cytotoxic agents in the treatment of metastatic breast cancer. A review of 21 randomized trials in 2005 showed the superiority of chemotherapy regimens containing taxanes compared to other types of chemotherapy, in terms of objective response rate and overall survival [23]. As for HRT, several trials randomized showed that RNs are more effective than tamoxifen in first-line metastatic with objective response rates higher and longer response times ranging from 8.2 to 11.1 months as against 5.6 to 8 months tamoxifen [24,25].

Trastuzumab can extend survival in metastatic breast cancer over expressing HER2, as shown in a recent French study [26] where the rate of long survival beyond 7 years in patients treated with trastuzumab in the first line metastatic in combination with chemotherapy was 17%.

Few studies in the literature have examined the impact of palliative loco regional radiotherapy on overall survival of patients with breast cancer metastatic immediately. Scodan et al [27] showed the benefit of local therapy (which was essentially an exclusive irradiation therapy in 78% of cases associated with surgery in 13% of cases), overall survival at 3 years without any real benefit in the long survival beyond 5 years.

## Conclusion

Metastatic breast cancer is incurable at present. The disease progresses by successive bouts and remissions are shorter and shorter as and measurement of exhaust treatment. But in recent years, advances in treatment because of new treatments associated with the evaluation of new strategies, show significant improvement in survival. The long-term survival in metastatic breast cancer necessarily entails progress in the field of palliative care. Palliative care and support are multidisciplinary physicians, nurses, psychologists, physiotherapists, social and educational assistants are particularly called upon to intervene and coordination is essential. They cater to the patient as a person, and his family, at home or in an institution.

## Figures

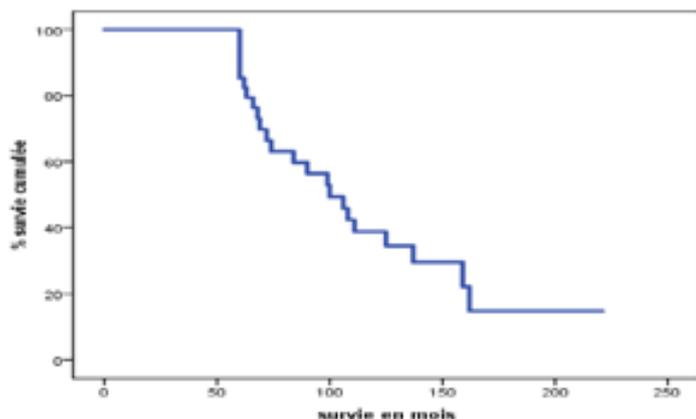


Fig 1. Overall survival according to Kaplan-Meier

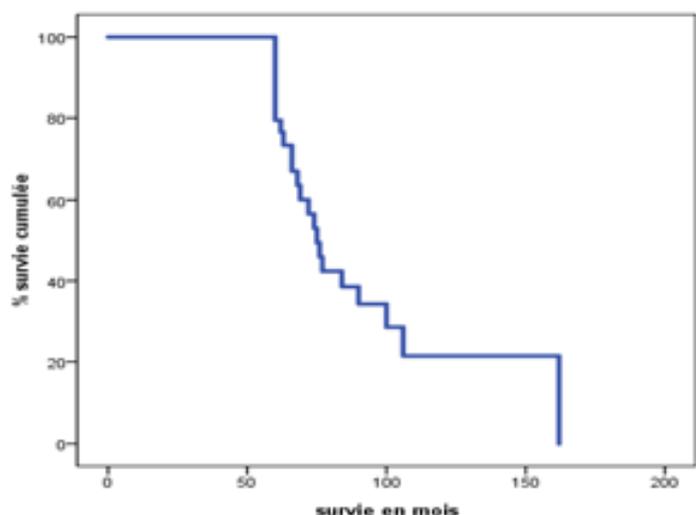


Fig 2. Survival from diagnosis of metastases

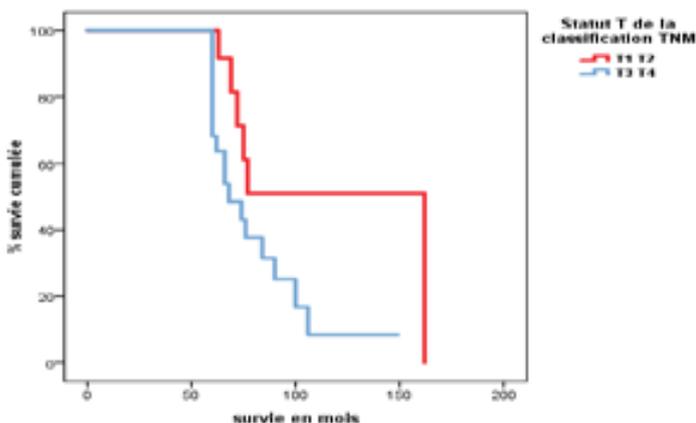


Fig 3. Survival according to clinical size

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