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The Role of Surgery in the Upfront Treatment of Metastatic Breast Cancer

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Abstract **Original Research Article**

Breast cancer is the leading cause of cancer-related mortality among women worldwide, with an incidence of 49.5 per 100,000 women globally and 45.5 per 100,000 in Morocco. Metastatic breast cancer at the time of diagnosis, although representing a small proportion of all breast cancer cases (3%-6% in high-income countries), remains a major clinical challenge. This study, conducted at Hassan II University Hospital in Fes, Morocco, aimed to evaluate the clinical outcomes of stage IV breast cancer patients who underwent surgery after neoadjuvant chemotherapy. A retrospective analysis was performed on 40 patients diagnosed with metastatic breast cancer between January 2015 and December 2021. The study focused on demographic, clinical, and pathological characteristics, including molecular classification, hormone receptor status, HER2 expression, and tumor histology. The patients received various treatment modalities, including chemotherapy, hormone therapy, and Herceptin, with responses monitored through imaging and histological evaluation. The study found that neoadjuvant chemotherapy resulted in favorable tumor responses, with 10 patients achieving a complete response and 16 showing partial responses. Surgery, despite the metastatic nature of the disease, was associated with improved progression-free survival (PFS) when combined with lymph node dissection and a histological response greater than 50%. Univariate analysis revealed that triple-negative breast cancer and lack of surgical lymph node dissection were associated with shorter PFS. The median PFS was 24.95 months, with a 3-year PFS rate of 23.3%. These findings suggest that in select patients with metastatic breast cancer, surgery following systemic chemotherapy may provide survival benefits, especially when coupled with favorable histological responses and lymph node involvement. The study underscores the potential of personalized treatment strategies and further investigation into local therapies for metastatic breast cancer.

Keywords: Breast cancer, metastatic breast cancer, surgery, neoadjuvant chemotherapy, progression-free survival, molecular classification, prognosis.

INTRODUCTION

Breast cancer ranks first in terms of incidence and mortality among women worldwide [1, 2]. The worldwide standardized incidence is 49.5 per 100,000 women, and in Morocco, the population incidence is 45.5 per 100,000 women [3]. According to the WHO, almost one woman in 12 will develop breast cancer in her lifetime, making it the leading cause of cancer mortality in women, with around 685,000 deaths in 2020 [4, 5].

Despite advances in screening and early diagnosis, the prevalence of patients with metastatic disease at the time of initial diagnosis, also known as metastatic breast cancer at the outset, has remained stable [17-19]. These patients represent around 3% to 6% of all breast cancer presentations in high-income countries, with higher proportions in low- and middle-income countries [6, 7]. Median overall survival is around 40 months, and varies according to the number and site of metastases [8, 9].

In the case of metastatic tumors at diagnosis, systemic treatments are the gold standard of management, with discussions depending on the histology of the primary tumor. Local treatment remains confined to palliative or symptomatic management [10, 11].

However, recent retrospective clinical studies have shown a positive impact on local control and overall survival in patients with newly diagnosed metastatic breast cancer after resection of the primary tumor [12, 13]. Some studies, however, have found no survival benefit with surgery for metastatic breast cancer [14, 15].

The notion that treatment of the primary tumor may improve survival is gaining momentum [16]. Objective data are needed to document the benefits of local therapy in terms of local control and survival. Through this work, certain questions will be considered.

MATERIAL AND METHODS

I. Study Type:

This is an epidemiological, descriptive, and retrospective study of a series of cases of metastatic breast cancer collected at the Obstetrics and Gynecology Department I of the Hassan II University Hospital Center in Fes during the period from January 2015 to December 2021, who underwent breast surgery for stage IV breast cancer.

II. Study Population:

Regarding the inclusion criteria, we included all patients with histologically confirmed invasive breast cancer between 2015 and 2021, classified as stage IV, clinically or radiologically metastatic, who underwent breast surgery and were managed at the Obstetrics and Gynecology Department I of the Hassan II University Hospital Center in Fes.

Patients with breast carcinoma without secondary metastatic evolution or metastatic disease without surgical treatment were excluded from the study.

III. Data Collection:

The various parameters under study were collected from questionnaires [Annex 1] filled out based on paper records stored in the archives of Obstetrics and Gynecology Department I: of the Hassan II University Hospital Center in Fes, and from the "HOSIX" system.

Each piece of data was carefully collected and entered into an Excel® 2013 file, then numerically coded, 0/1 for no/yes, and 1/2/3/... for variables with multiple classes. Missing data corresponded to empty cells.

IV. Parameters studied:

We began by studying the demographic and clinical data of our patients: age, marital status, menopausal status, personal and family history of breast and/or ovarian cancer, circumstance of discovery, location, bilaterality, duration of progression, stage according to TNM and AJCC 2010 classification, performance status [PS].

We then looked at anatomopathological and molecular characteristics: histological type [infiltrating ductal carcinoma, infiltrating lobular carcinoma or other], Scarff Bloom Richardson [SBR] grade, presence of vascular emboli, presence of associated intraductal carcinoma, estrogenic and progesterone hormone receptor expression, HER2 expression assessed by IHC or fluorescent in situ hybridization [FISH], Ki67 expression, primary tumor excision margins. The individual cases were classified according to the molecular classification of breast cancer according to the 2015 St. Gallen conference consensus into: Luminal A, Luminal B Her2 -, Luminal B Her2+, Her2+ non Luminal, and triple-negative cancers.

We recorded the different types of treatment received and the therapeutic sequence in which they were administered. We identified the various therapeutic means: type of surgery, type of chemotherapy protocol and number of cycles received, anti-Her2 therapies, hormone therapy, adjuvant radiotherapy.

Clinical response to neoadjuvant chemotherapy was assessed according to UICC criteria. Tumor response was assessed clinically or by imaging [ultrasound or mammography]. Tumor response was considered complete when no palpable tumor or inflammatory signs persisted in the breast, partial when tumor size reduction [measurement of the two largest perpendicular diameters] was more than 50%, minor when size reduction was less than 50%. Disease stability was defined as no change in size. Disease progression was defined as an increase in size of at least 25%. Histological response to induction chemotherapy was assessed on the surgical specimen according to the Chevallier and Sataloff classifications.

Median follow-up is calculated from the date of last news [either the last consultation for living subjects, or the date of death for dead subjects] to the date of diagnosis. Progression-free survival [PFS] was calculated from the date of surgery to the date of the event [relapse] or the date of the last visit. Overall survival [OS] corresponds to the period between the date of diagnosis and the date of death, whatever the cause. Given that the date of death is rarely mentioned in patients' files, and that our telephone calls were not answered by the patients, we were unable to calculate the overall survival of patients.

V. Statistical Analysis:

We carried out a descriptive analysis, calculating headcounts and percentages for qualitative variables, as well as measures of central tendency [means] and dispersion [standard deviation] for quantitative variables. These data were reported in tables and presented as histograms or pie charts.

Clinicopathological characteristics were examined using chi-square tests. Progression-free survival was assessed using the Kaplan-Meier method. Prognostic factors were analyzed univariately using the Log-Rank test, comparing progression-free survival according to several parameters such as age, marital status, parity, menopausal status, family history, number of lesions, lymph node involvement, histological type, SBR grade, HER2, hormone receptors, site of metastasis, etc.

Due to small numbers, multivariate analysis could not be performed. The significance level was set at 5%. The analysis was carried out in the epidemiology laboratory using SPSS® version 13.0 statistical software.

VI. Ethical considerations:

Data collection was carried out with respect for patient anonymity and confidentiality.

RESULTS

I. Descriptive Analysis:

A. Sociodemographic Data:

During the study period, 1,318 breast cancer patients underwent surgery in our department between the beginning of 2015 and the end of 2021. Of these, 1,039 patients underwent initial surgery, while 279 underwent surgery after receiving primary chemotherapy. In addition, 40 patients presented with neo-metastatic breast cancer, of whom 30 were metastatic from the outset. This represents a percentage of 2.28% of cases undergoing breast cancer surgery during this period.

The mean age at diagnosis was 50.17 years, with extremes of 30 and 73 years. Our study showed a variation in parity between 0 and 10 with an average of 2.86. Multiparity [≥ 3 pares] was noted in 48.3%, followed by pauciparity at 24.1%; while the number of nulliparous women came last with a percentage of 27.6%. Hormonal status was determined in 25 patients. Of these, 17 [68%] were post-menopausal at the time of diagnosis, while 8 patients were still in the genitally active phase.

With regard to personal history of breast cancer, one of our patients presented a metastatic recurrence, representing 3.33% of cases. The patient was 49 years old, G3P3, with a history of infiltrating ductal carcinoma of the right breast [hormone receptor negative, HER2 score 3, Ki67 50%], for which she received conservative treatment in a private clinic in Meknes [2N+ / 8N]. She received 4 cycles of anthracycline, 4 cycles of docetaxel as adjuvant therapy, as well as radiotherapy and Herceptin. She subsequently presented with contralateral lymph node recurrence [estrogen receptor positive 1%, progesterone receptor negative 0%, HER2 score 3], considered metastatic due to the similarity of her tumour profile with a negative senological work-up.

In terms of family history of breast cancer, 16.7% of patients had a family history of the disease. Of these, 4 patients had a first-degree family history, while one patient had a second-degree family history.

B. Clinical features:

The most frequent reason for consultation was self-exploration of a mass, observed in 16 patients, or 53.3% of cases. Next, skin inflammation was reported in 7 cases, representing 23.3% of cases. One patient consulted us after the discovery of a bone metastasis, manifesting as paresis and spinal pain. One patient was also found to have been screened for the disease.

The average time to diagnosis according to patient questioning was 13.67 months, with variations ranging from 2 months to 5 years. Among these women, 37% consulted within 6 months to 1 year.

On clinical examination, 78.6% of our patients had a WHO score of 1. Breast examination revealed right-sided predominance in 18 patients, representing 60% of cases. Bilateral involvement was observed in 2 patients [6.7%]. In terms of size, 6.67% were stage T3, 26.67% were stage T4b, 6.67% were stage T4c and 53.33% were stage T4d. Clinical examination of the lymph nodes in our patients revealed clinically palpable adenopathy in 90% of cases, with homolateral axillary adenopathy mobile in 73.3% of cases and fixed in 10%. Two patients had homolateral supra-clavicular adenopathies, representing a percentage of 6.67%.

C. Radiological features:

86.7% of mammographic lesions were classified ACR 5, followed by ACR4 lesions in 4 cases [13.3%].

D. Anatomopathological and molecular features:

Biopsy was performed in 29 patients, representing 96.7% of cases. Only one patient underwent lumpectomy in a private clinic before being referred to our department for further management.

The most frequent anatomopathological type in our sample was infiltrating ductal carcinoma of the NOS type, identified in 28 cases [93.3%]. Two patients had infiltrating lobular carcinoma. Intermediate grade [Grade II SBR] was observed in 50% of our tumours. Vascular emboli were investigated on biopsy in 21 patients, and were positive in only 14.3%.

90% of patients were hormone receptor positive, with 76.67% for progesterone receptor [PR] and 90% for estrogen receptor [ER]. HER2 protein expression was assessed in all patients, and supplemented by FISH in the case of HER2 score [2+] in 5 cases. Of these, 9 patients were HER2 positive, i.e. 30% of the total [determined by FISH in one patient], while 21 patients were HER2 negative, i.e. 70%. In 21 patients, 23.8% had a Ki67 proliferation marker below 15%. 36.3% of molecular classifications were Luminal B HER2-negative, while 26.7% were Luminal B HER2-positive.

E. Extension assessment:

Among patients, 66.7% had a single metastasis. The most frequent secondary sites were bone [40%], followed by lung [20%] and liver [3.33%]. A further 10% had associated visceral and bone metastases. Metastases detected at diagnosis are shown in figure 22.

It should be noted that the percentages of metastatic sites do not add up to 100% due to overlap.

F. Treatments received and clinical response:

All patients received neoadjuvant chemotherapy. Of these, 5 patients [16.7%] were treated with anthracyclines alone, 7 patients [23.3%] with taxanes alone, and 18 patients [60%] received a combination of anthracyclines and taxanes. In addition, 33.3% of patients received a total of 6 courses of chemotherapy. 58.6% of patients received hormone therapy. 26.7% of patients were treated with Herceptin. It is important to note that the administration of Herceptin was not confirmed in the file of a HER2+ patient. In our study, we observed a complete response to treatment in 10 patients, while 16 patients showed a partial response. In addition, 5 patients remained stable and 1 patient progressed after chemotherapy. In the latter case, the decision was made to proceed with surgery, as the tumour was ulcerative and burgundy [clean-up mastectomy]. The radiological response rate of metastatic sites to chemotherapy was 36.7%, while 60% of patients showed stabilization.

G. Post-Chemotherapy Surgery:

In our study, 21 patients underwent unilateral mastectomy, one patient underwent bilateral mastectomy, and one patient underwent mastectomy with contralateral axillary curage [due to a history of conservatively treated breast cancer and the presence of contralateral adenopathy]. In addition, 9 patients benefited from a Patey-type procedure. One of our patients, aged 39, G0P0, non-menopausal, 9 months old, with a tumor classified T4dN1, underwent biopsy revealing SBR grade I ICC, estimated PR 0%; estimated ER 80%; estimated KI67 5%; estimated HER2 0. She presented a bone metastasis and received a treatment of 6 courses of chemotherapy followed by a mastectomy whose anatomopathology objectified the persistence of a residual lesion of 5.4 cm with a limit of resection reaching the deep surgical barrier. Radiotherapy was then administered to the wall and hormone therapy was initiated. The PCR did not recommend tumor bed resection. The mean time from diagnosis to surgery was 12.57 ± 5.557 months. The minimum time between the last chemotherapy treatment and surgery was 15 days. 26.7% of patients showed a histological response greater than 50%, and 20% a complete response. 26.7% of patients were classified as having a TcNx response. 83.3% of our patients had a high Chevallier grade. Vascular emboli were present on the surgical specimen in 18.5% of cases. In our study, after initial systemic treatment, 23.5% of patients were classified as ypT3 and T4. And 76.5% were classified as less than ypT2. With regard to lymph node status, 63.4% of cases were classified as Nx [patients who had not undergone lymph node curage], 13.2% as N0 and N1, and 23.2% as N2.

H. Adjuvant radiotherapy:

Of the patients in our study, 36.6% underwent adjuvant radiotherapy. In one case, adjuvant radiotherapy was administered to the walls of the tumor due to unhealthy resection margins, and in 9 cases to positive lymph nodes following axillary curage. In addition, it was prescribed to treat brain metastases in 4 cases and bone metastases in one case.

I. Progression and follow-up:

We recorded 21 cases of progression, representing 70% of distant relapses. The most frequent metastatic site was the brain, and 23.3% of patients experienced multiple progression. The mean time from diagnosis to progression was 30.7 ± 11.886 months. The mean time from surgery to progression was 16.8 ± 12.476 months.

Mean follow-up was 49.30 ± 18.71 months. After surgery, mean follow-up was 26.6 ± 19.085 months, while after progression, it reached 12.2 ± 10.994 months.

Median progression-free survival was estimated at 24.95 months, with values ranging from 17 months to 32 months. The 3-year progression-free survival rate was 23.3%, as illustrated by the Kaplan-Meier curve.

II. Univariate analysis:

Univariate analysis of PFS revealed that molecular type, surgery with lymph node dissection and histological response were variables with a significant impact on PFS duration. In contrast, the other variables did not appear to influence survival. More specifically, patients with triple-negative molecular type had significantly shorter progression-free survival times compared with other molecular types [5 months vs. 26.46 months, p= 0.001].

Moreover, surgery with lymph node dissection despite the metastatic stage and a histological response to neo-adjuvant treatment of over 50% significantly prolonged progression-free survival [mean survival: 39.47 months vs. 19.60 months, p=0.041; mean survival: 32.23 months vs. 18.95 months, p=0.046].

DISCUSSION:

I. Sociodemographic Data:

A. Frequency:

Initially diagnosed metastatic breast cancer [MBC] accounts for around 3% to 6% of all breast cancer cases in high-income countries such as the USA, Europe and Australia, while in low- and middle-income countries the proportion is higher, ranging from 10% to 30% [20]. This difference in frequency may be explained by limited access to screening and contemporary treatments [20].

The presence of metastases is a major contributor to cancer morbidity. In the USA, metastatic breast cancer causes 46,000 deaths a year, compared with 15,000 in the UK [21, 22]. A study by Colman in 2008 also showed that metastases are one of the factors that significantly influence survival in breast cancer patients. Global 5-year survival rates vary widely from country to country. In Algeria, Brazil and Eastern Europe, the survival rate is less than 30-40%, while in North America, Japan and the rest of Europe, it reaches 70-80% [21].

In our series, the incidence of immediate MSC was 2.28%. However, it should be noted that the small size of our sample limits its representativeness.

B. Socio-demographic factors:

In our study, the average age of patients was 50.17 years, ranging from 30 to 73 years. A series by Benhayoune at the Hôpital Militaire Moulay Ismail Meknès, comprising 20 patients, had an average age of 54.6 years [24]. The literature shows similar mean ages, ranging from 50 to 60 years. Series from different countries have reported mean ages ranging from 49 to 63.1 years. In China, the average age is 56. Younger women, aged under 40, account for between 2.4% and 30% of cases of metastatic breast cancer. In Morocco, this rate is 11% according to one study [31], and 14.5% in France. In our study, 20% of patients aged 40 and under had metastatic disease at the time of diagnosis, while 80% of patients were over 40.

The high proportion of younger women could be explained by early exposure to breast cancer risk factors or genetic factors. Obstacles such as fear of diagnosis, use of alternative medicine and lack of screening were observed. An analysis in Denmark suggested that rural residence was a risk factor associated with more advanced presentation of breast cancer, including early metastatic breast cancer [23].

C. Patient characteristics:

Family history is a risk factor associated with increased breast cancer, with 16.7% of cases having a family history in our series, compared with 50% reported by SI *et al*., [25-28].

In our series, postmenopausal women predominate among cases of metastatic breast cancer from the outset, in agreement with other studies such as those by Benhayoune [42], Desille *et al*., [13], and Tinterri [23]. However, in China, de novo metastatic breast cancer is mainly observed in non-menopausal women [28, 29]. In our study, 78.6% of patients with de novo metastatic breast cancer had an SPI equal to 1, in contrast to the results of Perez-fidalgo *et al*., who found a rate of 81.3% for an SPI equal to 0 and 11.4% for an SPI equal to 1 [30].

II. Clinical features:

A. Tumor size:

In our study population, 86.7% were of size T4 according to the TNM classification. According to Benhayoun, a tumour size of T3 and T4 was observed in most of the patients who came for consultation, i.e. 70% of cases [24]. This group represents 39.5% of the series by Zhu *et al*., [32] and 42% of the series by Desille *et al*., [13] in those who underwent surgery. In Italy and Spain, on the other hand, T2 is the predominant group [23, 33].

B. Lymph node status:

The majority of patients with MBC present with clinically detectable lymph node involvement. In our series, the clinical study of lymph node involvement showed that N1 forms were by far the most frequent, with a rate of 73%, followed by N2 forms at a rate of 10% and N3, which accounted for only 7% of lymph node metastases. This contrasts with the majority of series in the literature, where the N1 form is the most frequent. Furthermore, in France, 50.7% of patients present with free lymph nodes [13]. Other patient and tumour characteristics could not be compared with other series, as they were not studied.

III. Anatomopathological and molecular features:

We classified the different histological types based on the WHO classification for breast cancer [34]. In our study, the majority of tumours were infiltrating ductal carcinomas, i.e. 93.3%, followed by invasive lobular carcinomas in 6.7% of cases, as observed in several series in the literature.

The SBR grade provides an indirect measure of proliferative activity, based on the degree of tumour differentiation, nuclear pleomorphism and mitotic index. A greater frequency of SBR grades II and III has been reported in the literature in cases of metastatic breast cancer. The retrospective study by Pérez-Fidalgo *et al*., [49.4%], based on data collected between 1982 and 2005 in 123 metastatic patients operated on [30], showed that SBR II accounted for 49.4%. This rate was also the most frequent according to Lopèz [33] and Benhayoun [24], in line with the results of our series. On the other hand, SBR III grade is the most frequent according to Zhu [32] at 51.10% and according to Vohra [35] at 48.9%. Half of our patients had grade II breast cancer with an intermediate prognosis, while grade SBR III was represented in 26.7% of cases.

In terms of molecular markers, metastatic breast cancers with estrogen receptor [ER] and progesterone receptor [PR] are in the majority, with a rate of 90% in our patients. In our study, HER-2 was positive in 30% of patients, which is close to most studies. Hoff *et al*., demonstrated in their series that high-grade tumors were more likely to have HER2-positive status than low-grade tumors [$p<0.001$] [37]. Breast cancers are classified into 3 different biotypes: triple-negative tumors, HER2-overexpressing tumors and hormone-receptor-positive

tumors without HER2 overexpression [luminal A or B]. The majority of our patients with de novo MSC had luminal tumours, more than half of which were classified as Luminal B, which is also the majority in the study by Jianna *et al*., [39]. Luminal A class was more represented in the study by Desille-Gbaguidi and Li ma, with rates of 72.4% and 51.5% respectively [13, 38].

IV. Extension assessment:

Our study shows that metastatic sites are single in 66.6% versus 33.3% of multi-site metastasis, which is in line with most other studies relating to patients who have undergone surgery. Recent real-world observational studies have shown that bone is the most common metastatic site [around 45% of patients] and that up to 30% of patients are diagnosed with metastases limited to bone [40, 41]. Desille-Gbaguidi *et al*., report in their study of the group of patients operated on, single bone and single visceral metastases respectively in 51.1% vs. 43.5%; this rate is 48.1 vs. 31.9 according to Zhu in China. This is consistent with our series, with a frequency of 40% vs. 36.7%. Benhayoun also noted the predominance of bone +/- visceral localization in 75% of cases. In our study, we also observed less frequent sites of metastasis, such as contralateral lymph nodes [10%], the spleen [3.3%] and the dorsalis major muscle [3.3%]. These sites generally occur late in the course of the cancerous disease. This would explain the lower frequency rate in our study, which deals only with operated forms of metastatic breast cancer. This is the limitation of our study, which is a single-center study.

Each breast cancer subtype has a preferential site of metastasis; patients with RH+ are more likely to develop bone metastases. In an analysis of all de novo MBCs diagnosed between 2010 and 2015, in 18,322 patients, 39.8% had bone-only metastatic disease, and bone was the most common metastatic site in luminal tumors, which is supported by several studies. Patients with HR-/HER2+ compared with those with HR+/HER2- had more pulmonary [3.0-fold], cerebral [4.5-fold] and hepatic [6.0-fold] metastatic sites. Martin *et al*., with other studies also reported that the incidence of the proportion of brain metastases was highest in patients in the HER2+ and triple-negative subtypes.

V. Therapeutic management:

The main objective of therapeutic management of metastatic breast cancer was to ensure locoregional control, as the local evolution of a breast tumor can lead to profound alteration in quality of life [55]. Prior to the 2000s, breast cancers were not classified into different immunohistochemical categories based on human epidermal growth factor receptor-2 [HER2] and hormone receptor status, and no suitable systemic therapeutic options were available, with the exception of endocrine therapy [42]. Systemic treatment included chemotherapy, anti-HER2 therapy and hormone therapy.

Today, all therapeutic decisions are based on patient-related factors [age, comorbidity, etc.], metastatic spread [site and number of metastases] and, above all, tumor biology. Personalized systemic treatments, such as targeted therapies and immunotherapy, have improved OS in certain patient subgroups [43].

At the same time, radiotherapy techniques have evolved considerably, making it possible to adapt the radiation dose more precisely to the tumor's three-dimensional shape, enabling much higher radiation doses to be administered while maintaining better tumor control and reducing toxicity [44].

These different therapies are offered alone, in combination or sequentially, depending on the characteristics of each tumour and any previous treatments, and are tailored to each patient as part of a personalized care plan [36].

With regard to surgery on the primary tumour, the aim is no longer simply to control the disease locally, but rather to improve OS, as there is a potential biological link between the primary tumour and metastases [42].

Although there are no specific recommendations on this subject, with the exception of palliative symptom control, the question of the place of surgery has been controversial for decades, and numerous meta-analyses have attempted to synthesize highly heterogeneous data [45-49].

A. Neoadjuvant chemotherapy:

Chemotherapy is a therapeutic option for patients with metastatic breast cancer [MBC], particularly ER-negative/PR-negative, in cases of massive metastatic spread, for symptomatic treatment of visceral involvement, and in cases of ER-positive or PR-positive breast tumors refractory to hormone therapy [50]. In the metastatic phase, anthracyclines and taxanes are generally considered the most active agents, with notable activity also demonstrated for capecitabine [Xeloda®], gemcitabine [Gemzar®] and vinorelbine [Navelbine®] [51]. In practice, for initial metastases, the first-line polychemotherapy sequence favors an anthracycline + taxane combination over non-taxane regimens [52], while the monochemotherapy sequence may include anthracycline or taxane first, or anthracycline followed by taxane [36]. Usual treatments involve continuing chemotherapy until maximal response and/or unacceptable toxicity [52]. Tinterri *et al*., observed different practices of chemotherapy followed by locoregional treatment, with varying percentages of anthracycline cycles and sequential anthracycline-taxane regimens [23].

Pérez-Fidalgo *et al*., identified the proportions of patients receiving different types of chemotherapy, notably anthracyclines and/or taxanes [30]. Benhayoun

reported on preoperative chemotherapy regimens, mainly based on anthracyclines and/or taxanes, sometimes in combination [24]. In our series, all patients received neoadjuvant anthracycline- and/or taxane-based chemotherapy, with different protocols [66.7% received more than 6 courses of chemotherapy and 33.3% received 6 courses with the 3 FEC + 3 taxane protocol]. In a retrospective series published by Khan *et al*., the choice of systemic treatment depended on the type of metastatic disease, with a prevalence of chemotherapy in some cases [52]. Finally, Desille-Gbaguidi *et al*., observed a more frequent use of chemotherapy in patients in the surgery group, particularly in those with luminal subtype A, although a confounding bias is recognized [13].

B. Hormone therapy:

Hormone therapy is generally well tolerated and widely indicated for RE+ and/or RP+ invasive breast cancer, particularly in combination with chemotherapy in at-risk patients with no contraindications [53]. Aromatase inhibitors are considered the gold standard for metastatic RH+ HER2- breast cancer, often accompanied by an LH-RH agonist for pre-menopausal women, or alternatively, bilateral oophorectomy may be considered [54]. In our study, 58.6% of patients were treated with hormone therapy, a percentage similar to that found by Benhayoun, with a significant proportion receiving this treatment pre-operatively [24].

C. Targeted therapies:

Targeted therapies, such as trastuzumab and lapatinib acting on HER2, as well as bevacizumab targeting vascular endothelial growth factor, are designed to specifically target the molecular abnormalities involved in tumor progression [56]. For patients with HER2-positive metastatic breast cancer, anti-HER2 therapy is recommended as first-line therapy and maintained throughout the course of the disease, unless there is no response or loss of HER2 expression/amplification [54]. In our series, 26.7% of patients received trastuzumab, with results comparable to those of Benhayoun's study [24], where a quarter of patients on anti-HER2 received trastuzumab.

D. Assessment of tumour response:

Accurate assessment of tumour response after systemic treatment is essential to guide the surgical decision [53]. Some studies have suggested the use of high-dose chemotherapy, showing complete response rates of over 50% in metastatic forms [57]. In the study by Pérez-Fidalgo *et al*., 60% of patients who underwent surgery after chemotherapy showed an objective clinical response, while in our study 33.3% and 53.3% of patients showed a complete and partial clinical response to systemic treatment, respectively. We focused our analysis on patients operated on with de novo metastatic breast cancer, but some patients who did not respond to chemotherapy were excluded.

E. Locoregional treatment:

Locoregional treatment of metastatic breast cancer [MBC] generates debate, with arguments for and against its use [42]. Some argue that resection of the primary tumour can reduce the overall tumour burden and eliminate metastatic tumour stem cells [58-62]. Moreover, removal of the primary tumor can reverse local immunosuppression and stimulate the immune response [63]. However, studies suggest that surgical resection may stimulate the growth of dormant metastases through cytokine release and promotion of epithelial-mesenchymal transition [64, 65]. Furthermore, surgical interventions may weaken the immune response, thereby promoting tumor growth [66, 67]. In terms of surgery, studies show that conservative treatment is often preferred for small tumours, while radical treatment is favoured for large tumours or after a favourable response to initial systemic therapy [45]. In our study, all patients underwent radical treatment because of tumour size and lack of radiological work-up to justify conservative treatment, with only one observation of positive margins [39, 66, 24]. The role of axillary curage remains debated and is often decided on a case-by-case basis [54, 30, 23].

With regard to the timing of surgery, it is generally performed after prolonged control of the disease with systemic therapy [69]. Radiotherapy may be considered as an adjunct to surgery or as exclusive treatment, depending on the risk criteria for local recurrence [68]. Exclusive irradiation may be an option in frail or elderly patients [42]. In the case of bone or brain metastases, radiotherapy is effective in relieving pain and can be an alternative to surgery [70, 71]. Finally, immunotherapy, notably immune checkpoint inhibitors, represents a promising new therapeutic strategy, particularly for triple-negative subtypes of metastatic MSC [72, 73].

VI. Prognostic factors and survival:

A. Prognostic factors:

Initial metastatic breast cancer [MBC] predicts better overall survival than metastatic relapse [75]. This may be attributed to the resistance of metastatic cells to prior adjuvant therapy [74]. Negative selection of patients with secondary disease despite adequate primary treatment may explain this phenomenon [77]. Initial MBC is associated with a better prognosis than metastatic recurrence in previously treated patients, but no significant difference is observed for longer disease-free intervals [>24 months] [76]. The prognosis of initial MBC has improved over the decades, perhaps due to improved treatment options or changes in disease characteristics [78, 79]. Prognostic factors for progression-free survival after primary surgery include molecular classification, histological response and lymph node dissection [77]. Special histological type of breast cancer, such as tubular carcinoma, is associated with a better prognosis than non-specific ductal type. Lymph node positivity is associated with less favorable survival, with significant results for N0 versus N1-3

classification [80]. RH+ and/or HER2+ breast cancers have a longer survival than triple-negative cancers [81, 82]. Patients with oligometastatic cancer have a better prognosis when treated locally [83]. Initial chemotherapy is crucial for assessing tumour sensitivity and selecting appropriate patients [84]. A histological response greater than 50% after chemotherapy is associated with better progression-free survival. Surgery after chemotherapy is associated with a better prognosis than surgery before or during chemotherapy [39]. Tumor excision with healthy margins is an important prognostic factor [52]. Axillary curage may improve progression-free survival. The impact of radiotherapy is controversial, with studies showing contradictory results [84]. The patient's general condition is also predictive of overall survival [87]. Genomic features of tumors, such as PTEN mutations, can influence survival and require specific therapeutic approaches [88].

These factors contribute to the complexity of managing metastatic breast cancer, and underline the importance of an individualized approach based on several prognostic criteria.

B. Survival:

Metastatic progression-free survival is improved by removal of the primary tumor in stage IV patients, Babiera *et al*., [89]. However, no significant improvement in progression-free survival was observed in a group comparing systemic therapy alone to surgery followed by systemic therapy, Khan *et al*., [90]. Studies have shown progression-free survival medians of 36 months, Tinterri *et al*., [23] and 24.94 months, with a 3-year rate of 23.3% in others [unspecified]. With regard to overall survival, retrospective studies suggest a benefit from complete resection of the primary tumor, but potential biases limit the reliability of these results [various meta-analyses]. Certain factors, such as hormone and HER2 receptor status, as well as response to systemic therapy, could influence the outcome of surgery, Anna Weiss *et al*., [91]; Pons-Tostivint *et al*., [24]. Prospective studies give conflicting results, with trends towards improved survival in some [Turkey, POSYTIVE] but not in others [Austria] [unspecified]. New trials are underway to clarify this issue, but at present no definitive conclusions can be drawn on the benefits of breast surgery in cases of metastatic breast cancer at the outset.

CONCLUSION

The question of surgery in metastatic breast cancer remains a multidisciplinary challenge. Several studies have failed to show strong evidence of a significant impact of surgery on survival. They have suggested that surgery could be considered in highly selected patients, but methodological biases are numerous due to clinical and therapeutic heterogeneity. It is recommended to initiate treatment with systemic therapy to stabilize distant metastatic disease. Local surgery may be considered in the event of local progression after systemic therapy. Three clinical situations may arise after the first line of systemic therapy, with specific recommendations for each case. Management should maintain the highest quality of life while optimizing disease control, and it is essential to discuss risks and benefits with the patient. Locoregional treatment modalities can have an impact on body image and quality of life, with potential complications such as haematomas, lymphoedema and infections. The rise of targeted therapies and tumor genomic profiling opens the way to personalized medicine, which could change the role of locoregional treatment.

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