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CONSENSUS

Mexican breast cancer consensus. Management of advanced breast cancer

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Abstract

Breast cancer is the most common neoplasia, with the highest mortality in women worldwide. The 10th update of the Mexican Consensus on Diagnosis and Treatment of Breast Cancer (2023) is published by its authors in different articles. This article includes the management of advanced breast cancer, the adjuvant systemic treatment, the role of surgery and radiotherapy in metastatic disease, and follow-up after treatment with curative intent. The dissemination of this consensus contributes to the updating and homogeneity of breast cancer management of advanced stages.

Keywords: *Breast cancer. Metastatic. Consensus.*

Consenso mexicano de cáncer mamario. Manejo del cáncer de mama avanzado

Resumen

El cáncer de mama es la neoplasia más frecuente y con mayor mortalidad en mujeres en todo el mundo. La décima actualización del Consenso Mexicano Sobre Diagnóstico y Tratamiento del Cáncer Mamario (2023) es publicada por sus autores en diferentes artículos. El presente artículo incluye el manejo de cáncer de mama avanzado, el tratamiento sistémico adyuvante, el papel de la cirugía y la radioterapia en enfermedad metastásica y el seguimiento posterior al tratamiento con intención curativa. La difusión de este consenso contribuye a la actualización y homogeneidad de criterios de manejo del cáncer mamario en etapas avanzadas.

Palabras clave: *Cáncer de mama. Metástasis. Consenso.*

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Introduction

Metastatic breast cancer is a heterogeneous disease with variable clinical manifestations, the treatment of which depends on the site and number of metastases, patient characteristics, tumor immunophenotype, and sensitivity or resistance to previous anticancer medical treatments[1].

At this stage of the disease, a significant improvement in median survival has been observed, with highly variable ranges, depending on the immunophenotype[2-4].

The goals of metastatic breast cancer treatment are:

- To prolong progression-free interval and overall survival (OS)
- To palliate disease-related symptoms
- To maintain an adequate quality of life with a good performance status
- The most important clinicopathological factors to decide the best therapeutic strategy are[1,3]:
- Age
- Disease-related symptoms and performance status
- Concomitant diseases
- Disease-free interval
- Number and location of metastases
- Previous treatment and response to it
- Hormone receptors (HR), *HER2* neu, *BRCA* 1 and 2 mutations, and programmed death ligand 1 (PD-L1) expression (only in triple-negative disease)
- Patient preferences.

In patients with stages I to III and who subsequently present with tumor recurrence, metastatic disease extent evaluation is recommended, including performing a biopsy of a metastatic site to confirm the diagnosis and determine HR and *HER2* status, since up to 30% of cases have been shown to change their immunophenotype[5]. Assessing for the presence of *BRCA* 1 and 2 germline mutations and PD-L1 expression (only in triple-negative disease) is also recommended in view of the availability of approved therapeutic options[6,7]. Evaluation of other biomarkers is not recommended.

Treatment is established according to the breast cancer subtype:

- Metastatic/recurrent breast cancer with positive HR and negative *HER2* status
- Metastatic/recurrent breast cancer with positive HR and positive *HER2* status
- Metastatic/recurrent breast cancer with negative HR and positive *HER2* status
- Triple-negative or HR-positive, *HER2*-negative metastatic/recurrent breast cancer is not a candidate for hormone therapy (BRCA positive/negative).

Systemic treatment

Metastatic breast cancer with positive hormone receptors and negative HER2 neu status

Endocrine therapy plus a CDK4/6 inhibitor is the treatment of choice, given that it has been shown to increase OS in both first and second lines of treatment[8], in addition to improving other efficacy parameters, such as progression-free survival (PFS) and response rates, including patients with visceral disease. However, in patients with significant symptoms and/or rapidly progressing visceral metastases (visceral crisis)[1], chemotherapy is recommended as an option given that it produces higher response rates. Visceral crisis is a serious organ dysfunction that is identified by symptoms and signs, laboratory tests, and rapidly progressive disease. Visceral crisis does not exclusively refer to the presence of visceral metastases but rather implies significant visceral involvement that requires effective and rapid-acting treatment, particularly if another treatment option is not possible after further progression.

For therapeutic decision-making in this section, it is important to take the following concepts into consideration[1]:

- Primary endocrine resistance. Considered in patients with recurrence within the first 2 years of adjuvant endocrine therapy or disease progression within the first 6 months of first line for metastatic disease
- Secondary endocrine resistance. Defined as recurrence during adjuvant endocrine therapy, after the first 2 years, recurrence 12 months after having completed adjuvant hormone therapy, or disease progression in the context of metastatic disease, 6 months after having started the first line.

Hormone treatment in pre-menopausal patients

Owing to the benefits of endocrine therapy + other targeted therapies in post-menopausal patients, medical, or surgical ovarian ablation is recommended in pre-menopausal patients, and treating them as if they were post-menopausal[1].

An aromatase inhibitor (AI) plus ribociclib, with ovarian ablation or suppression, is indicated as a first-line treatment in pre-menopausal patients[9].

Tamoxifen as monotherapy is an option for patients who do not accept ovarian suppression or ablation.

Hormone treatment in post-menopausal patients

First line

In patients with *de novo* metastatic or recurrent disease with secondary endocrine resistance, the standard treatment is an AI + a CDK4/6 inhibitor[10-13]. At present, palbociclib, ribociclib, and abemaciclib are available in Mexico; ribociclib is the only CDK4/6 inhibitor that has so far shown to increase OS[10-14]. However, the choice of treatment must also consider age, performance status, comorbidities, toxicity profile, availability, and patient preferences.

An AI is also an option in patients for whom CDK4/6 inhibitors are not available[15].

Another additional first-line possibility is fulvestrant, mainly in patients with no visceral metastases[16].

Second line

If patients have already received a non-steroidal AI (anastrozole/letrozole) or show progression during adjuvant treatment with a non-steroidal AI, the first treatment option is:

- Fulvestrant plus CDK4/6 inhibitor (palbociclib, ribociclib, or abemaciclib), as long as the latter has not been used at first line[14-20]
- Other options include:
- Exemestane plus everolimus[21,22]
- Exemestane[22,23]
- Fulvestrant[24]
- Fulvestrant plus everolimus[25].

Third line

The third line will depend on previously received first and second lines. So far, there is no standard sequence.

Abemaciclib monotherapy is a third-line treatment option for patients who have not received a CDK4/6 inhibitor in previous lines, either with endocrine treatment or chemotherapy[26].

If available, trastuzumab/deruxtecan is a third-line option for patients with positive HR and low *HER2* neu (defined with a scale of 1 + or 2 ++ by immunohistochemistry and with negative *in situ* hybridization)[27].

In patients with a response or clear initial clinical benefit with hormone therapy and who progress with a first line, a second, third, and even fourth hormonal lines should be tried, depending on the previously used drug, given that a new tumor response is often obtained, which means the possibility of chemotherapy-free survival with better quality of life. In case of proven resistance to hormonal management, switching to chemotherapy should be carried out.

For patients with positive receptors who have received chemotherapy to maximum benefit, continuing with maintenance hormone therapy is suggested, and the selected drug should be administered until progression[1].

Metastatic/recurrent breast cancer with positive hormone receptors and positive *HER2* neu status (triple positive)

The recommended treatment is chemotherapy associated with anti-*HER2* therapy due to the demonstrated OS increase (see section on Metastatic/recurrent breast cancer with negative hormone receptors and positive *HER2* neu status)[1,28].

In patients with a complete response and/or who exhibit dose-limiting toxicity, it is possible to discontinue chemotherapy and continue with anti-*HER2* blockade in combination with endocrine monotherapy[1].

In post-menopausal patients who are not candidates for chemotherapy, with high HR expression, *de novo* disease, or with a long disease-free period and absence of visceral disease, double anti-*HER2* blockade (trastuzumab/lapatinib or pertuzumab/trastuzumab) could be used in combination with a non-steroidal AI. This strategy demonstrated a benefit in PFS, but not in OS. Anti-*HER2* therapy (trastuzumab or lapatinib) with endocrine therapy is another alternative, having in mind that it has an inferior median PFS[29-32].

Metastatic/recurrent breast cancer with negative hormone receptors and positive *HER2* neu status

To decide the type of management, it is important for patients to be stratified based on previous exposure to anti-*HER2* therapies and the time elapsed between the last dose of anti-*HER2* therapy and disease recurrence or progression[28].

First line

Standard treatment for patients at *de novo* stage IV or exposed to anti-*HER2* therapy in the neo/adjuvant

Table 1. Triple-negative or hormone receptor-positive, *HER2* neu-negative metastatic breast cancer not candidate for hormone therapy

	Adjuvant setting			
	Did not receive	**With taxane + anthracycline**	**With taxane**	**With anthracycline**
1st line	Regimen based on – Anthracycline – Taxane*	– Capecitabine – Eribulin – Gemcitabine – Vinorelbine – Platinum salts†	Regimen based on – Anthracycline	Taxane* ± – Capecitabine – Gemcitabine
2nd line	According to previously-used treatment			
3rd line	According to previously-used treatment			

*Including docetaxel, paclitaxel, and nab-paclitaxel.
†Only in case of triple-negative tumors.

setting and with more than 12 months of DFS, is docetaxel or paclitaxel in combination with double anti-*HER2* blockade based on trastuzumab and pertuzumab, since it has demonstrated benefit in OS, PFS and response rate[33,34].

In patients who cannot receive pertuzumab, the combination of trastuzumab plus taxane or vinorelbine should be considered an alternative[35,36].

If a patient exposed to anti-*HER2* therapy in the neo/adjuvant setting experiences disease progression during treatment or within a period of < 6 months after having received the last dose, it is advisable to use trastuzumab/deruxtecan or, if not available, pertuzumab and trastuzumab emtansine (T-DM1)[37,38].

Second and subsequent lines

The use of pertuzumab is not recommended beyond progression to a first line of treatment[39].

In patients previously treated with a trastuzumab-based regimen and with disease progression, the indicated treatment is trastuzumab/deruxtecan or, if not available, T-DM1[37,38].

In patients who cannot receive trastuzumab/deruxtecan or T-DM1, the option of continuing trastuzumab in combination with a chemotherapy agent should be considered. The previously-mentioned regimens and double blockade with trastuzumab/lapatinib can be interchangeably used at third and subsequent lines[39,40].

In all patients, maintaining the blockade with anti-*HER2* therapy during all phases of antineoplastic treatment is recommended, except in cases where it is contraindicated since its impact on disease control has been demonstrated[28,41-43].

Triple-negative or hormone receptor-positive, *HER2*-negative metastatic/recurrent (*BRCA*-positive/negative)

In all patients with triple-negative breast cancer, *BRCA* germline pathogenic variants, as well as PD-L1, should be systematically determined[44].

The choice of treatment should take previous adjuvant therapy (Table 1) and recurrence-free interval into account. In patients with an interval longer than 1 year, it is possible for drug reinduction to be evaluated. For patients with triple-negative tumors, one treatment option is chemotherapy, although currently, it is not possible for a specific regimen or sequence to be recommended[1,44,45]. Studies that evaluated the use of pembrolizumab plus chemotherapy or sacituzumab/govitecan demonstrated higher efficacy and OS increase vs. chemotherapy[46,47].

First-line chemotherapy: in combination or sequential?

Polychemotherapy is not recommended as a standard of care. Treatment with drugs as monotherapy and sequentially is preferred due to better tolerance and less quality of life deterioration. The use of polychemotherapy can be considered in patients with good performance status in whom a rapid response or symptom palliation is sought, and/or in case of visceral crisis and/or in cases in which life expectancy is deemed to allow only one treatment opportunity[1,38,48,49].

The cornerstone of first-line chemotherapy is based on anthracyclines and taxanes. In previously-exposed patients, treatment options include capecitabine, gemcitabine, vinorelbine, or eribulin (Table 1).

In case a combination is chosen, a taxane (paclitaxel or docetaxel) plus capecitabine or gemcitabine is recommended. Both regimens have been associated with higher response rates and superior progression-free interval versus taxane monotherapy[49-55]. The efficacy of both regimens is similar, and the choice will depend on patient individual characteristics and available resources.

Nab-paclitaxel is indicated for patients with failure to a previous chemotherapy line in the context of metastatic disease or contraindication to paclitaxel. In case paclitaxel is chosen, weekly administration is recommended[56,57]. Nab-paclitaxel is indicated in patients who have failed to a previous chemotherapy regimen in the context of metastatic disease or patients with contraindication to paclitaxel[58]. Eribulin is the only drug that has demonstrated an impact on OS in patients previously treated with taxanes/anthracyclines in the population with triple-negative tumors[59,60].

The choice of treatment depends on patients' characteristics, tolerance, and response to previous treatments, as well as on availability[1,44].

Platinum salts

There are studies that show the effectiveness of platinum and its derivatives in triple-negative tumors[59-62]. The TNT study, a phase III trial, evaluated the use of docetaxel versus carboplatin and failed to show superiority of the platinum salt in a triple-negative unselected population (*BRCA* germline mutation vs. mutated *BRCA*); however, in the population with *BRCA* germline mutation present, a superiority in PFS was observed in favor of carboplatin[62]. Although platinum salts are not recommended as first-line therapy in unselected populations, they may represent an option for the population with germline *BRCA* mutations[61-63].

Bevacizumab

The use of bevacizumab plus a chemotherapy agent increases disease control and PFS, but it does not impact OS as first-line therapy in metastatic breast cancer[64-69]. Bevacizumab plus taxane is a treatment option for patients with triple-negative tumors or those with positive hormone receptors who experience a clinically aggressive evolution and are considered candidates for first-line chemotherapy.

Immunotherapy

In patients with advanced triple-negative breast cancer that expresses PD-L1 (combined positive score > 10%/clone on IHC 22C3 pharmDx assay), pembrolizumab plus chemotherapy (paclitaxel, nab-paclitaxel, or gemcitabine plus carboplatin) as first-line therapy, was shown to be superior versus chemotherapy in terms of OS and PFS[7,46].

Poly(ADP)-ribose polymerase (PARP) inhibitors

In patients with breast cancer and *BRCA* germline pathogenic variants, olaparib and talazoparib demonstrated an impact on PFS, and thus, they can be regarded as a treatment option[70-72].

Conjugated antibodies

Sacituzumab/govitecan

In treatment-experienced patients with metastatic breast cancer, the use of sacituzumab/govitecan increased PFS and OS, which is why it should be considered a treatment option[47].

Trastuzumab/deruxtecan

The use of trastuzumab/deruxtecan is indicated in patients with previously treated metastatic breast cancer with low *HER2* expression and negative HRs[27].

Treatment duration

The treatment duration has not been fully defined. Several studies have shown that continuing chemotherapy can increase progression-free interval, but without survival being prolonged[73,74].

In clinical practice, continuing chemotherapy until progression or toxicity is recommended, depending on the administered drug (intravenous vs. oral), maximum cumulative doses, and the impact on patients' quality of life.

Bisphosphonates and receptor activator of nuclear factor κB ligand (RANKL) inhibitors in bone metastases

Both bisphosphonates and receptor activators of nuclear factor κB ligand (RANKL) inhibitors allow for

improving the results in the management of bone metastases, malignant hypercalcemia, and bone health by reducing systemic treatment-secondary osteopenia or osteoporosis[73-77].

Patients with radiographic evidence of bone metastases should be treated either with denosumab (120 mg subcutaneously every 4 weeks)[79] or zoledronic acid (4 mg intravenously over 15 min) every 3-4 weeks[78-81].

- The total duration of treatment with bisphosphonates should be up to 2 years
- Zoledronic acid can be administered every 3-4 weeks or every 3 months, since the beginning[82]
- After 1 year of treatment, and in case of stable disease, administering zoledronic acid every 12 weeks is recommended during the 2nd year[83], and then reconsider its use depending on bone metastatic activity
- Denosumab treatment's optimal duration is not known.

General recommendations for the use of bisphosphonates and RANKL inhibitors are the same as for the adjuvant setting.

Role of surgery in metastatic disease

Standard treatment of stage IV breast cancer focuses, in all possible scenarios, on the palliative field, which includes chemotherapy, radiotherapy, hormone therapy, immunotherapy, and targeted therapies, with the role of surgery being left only to prevention or treatment of local symptoms[84]; however, over the past 20 years, various centers around the world have published series of patients with metastatic breast cancer who underwent resection at different sites (liver, brain, and lung), with favorable results being reported[85], mainly in those cases with metastases at diagnosis. In fact, the median OS for metastatic breast cancer has almost tripled, from 13 months in 1985 to 33 months in 2016, thanks to multimodal treatment[86,87]. In contrast, in 2022, the results of protocol NCT02364557 trial were published, which showed that the addition of local therapies to systemic management did not improve disease-free period or OS in patients with metastatic disease, even with oligometastatic pathology[88].

Metastatic disease resection

Liver metastases

The liver, as the only site with distant metastases, accounts for only 10% of cases, and for this reason, liver resection has had a limited role in treatment, since breast cancer is most often accompanied by metastases at another level[89]. The 5-year survival rate after surgical resection of liver metastases, combined with systemic therapy, has been reported to range between 40 and 61%. The current surgical techniques allow resection to have a post-operative mortality of < 6% and morbidity between 0.8 and 5.4% in referral centers[90]. Another valid option is metastases ablation with radiofrequency or laser-induced interstitial thermotherapy, by means of which a mean survival of 30-60 months and 5-year survival of 27-41% are reported[90].

As regards prognostic factors, most studies emphasize the importance of R0 resection, since positive margins are an adverse factor for survival[91]. Other adverse predictors for survival that has been identified are lesion size (> 5 cm), HR-negative status, poor response to chemotherapy, vascular invasion, the number of metastases, and a disease-free interval of < 1 year after primary breast cancer resection[92].

Lung metastases

Metastatic disease is usually generalized and rarely is it only localized at the pulmonary level. In a series of 13,502 breast cancer patients at the Mayo Clinic, only 60 (0.4%) were found to have isolated lung metastases, out of whom 40 underwent surgery[93].

Lung metastases complete surgical resection can be carried out with low morbidity and mortality, either by thoracotomy or video-assisted thoracoscopic surgery. Case series analyses have established the following well-accepted surgical selection criteria:

- Primary disease is under control
- Metastases are limited to the lung and pleura
- Ability to completely remove metastatic disease (R0)
- Lung physiological reserve to tolerate the planned procedure[94]

A common finding in most studies that have assessed the role of lung metastases resection is that the disease-free interval between primary tumor initial management and the appearance of lung metastases has a highly significant impact on survival. A disease-free interval of more than 36 months at recurrence has achieved 5-year survival rates of up to 75% in single lesions undergoing resection and systemic treatment[95].

Other factors that have been associated with survival improvement are positive HR, *HER2* neu-positive status, and solitary metastases. As in the case of liver

metastases, patients with single lesions and a prolonged disease-free interval should be considered candidates for pulmonary metastasectomy.

Brain metastases

Breast cancer represents the second cause of metastatic lesions in the brain, and generally, they are associated with HR-negative/*HER2*-positive tumors in pre-menopausal patients with lung and/or liver metastatic disease[96]. Patients who do not receive any type of treatment have a survival prognosis of 1-2 months, which increases up to 6 months in those who receive radiotherapy, and when surgery is indicated, it can even reach up to 16 months[97].

Indications for surgery are limited, with this approach being a reasonable option for single lesions of < 5 cm in size, with the absence of extracranial metastases, and especially in patients with adequate performance status. Palliative resection of these lesions is indicated for improving patient symptoms or as an emergency procedure to preserve patient life.

Other metastatic sites

This group is less investigated and, in general, no survival benefit has been observed. An example is bone metastases: according to several reports, surgical resection has not shown prognostic improvement in these patients[98], with radiotherapy being the palliative modality of choice. On the other hand, some studies have reported that resection of sternum or rib cage metastases is associated with a survival increase[99]. Even less investigated due to their low frequency are adrenal, ovarian, and gastrointestinal metastases; in these cases, resection is not recommended, except for situations of symptom palliation.

Primary tumor resection in metastatic disease

This is a clinical scenario where controversies are even bigger, since the vast majority of currently available data originate from retrospective trials. The conclusions of some meta-analyses and other publications point to an OS benefit associated with primary tumor resection in *de novo* metastatic breast cancer. In these studies, the women who were offered primary tumor resection were predominantly younger, had better performance status, and had less metastatic burden, which introduced the risk of selection bias[100-105]. However, other studies, also retrospective, have not shown any benefit deriving from primary tumor resection in this context[106-108].

So far, there is information available from four prospective randomized studies. One of them (Protocol MF07-01), which randomly assigned patients to primary surgery versus no surgery at the time of presentation, initially reported no survival difference at 3 years; however, with a longer follow-up of 5 years, median survival did significantly improve in patients who received local therapy[108]. In 2021, a 10-year follow-up update was published, with a median survival of 46 months being reported for the surgery group versus 35 months for the systemic therapy alone group. The controversies aroused by this trial were an imbalance between arms since the group proposed for surgery included younger patients, more frequently with ER-positive and *HER2*-negative status, and with single bone metastases, which are factors that might have had an impact on the outcome. The other three studies have failed to demonstrate any impact on OS derived from primary tumor local management in metastatic breast cancer[109-112].

In addition to the above-mentioned four studies, in 2021, the prospective study BOMET MF1401 was published, in which the performance or not of primary tumor surgery was segmented before the medical management of choice in patients with oligometastatic bone disease, with locoregional management being found to prolong OS and decrease locoregional recurrence in a 3-year follow-up evaluation[113,114].

A retrospective study was recently published in which, using a recursive partitioning analysis, patients were divided into three properly balanced groups according to their prognostic factors. All patients were observed to benefit from surgery, with a median OS with surgery versus no surgery of 72.7 versus 42.9 months, 47.3 versus 30.4 months, and 23.8 versus 4.4 months (all $p < 0.001$) in the subdivision by groups I, II, and III, respectively[114]. Therefore, it appears to be a reasonable alternative that can be discussed with those patients with favorable clinical characteristics such as good general condition, younger than 55 years, HR-positive/*HER2* neu-negative disease, limited tumor volume, predominantly with bone metastases, without brain metastases, and in whom obtaining negative margins is considered possible regardless of the type of surgery performed, which should necessarily include control of the primary tumor and axilla; in addition, the use of locoregional radiotherapy after surgery, and even breast reconstruction, whether immediate or deferred, should be evaluated, with the case being individualized

and all these points being discussed in a multidisciplinary group and with the patient[115-119].

In a retrospective study, Wang et al. evaluated the added benefit of radiotherapy in *de novo* stage IV patients also undergoing mastectomy, where they included 1,458 women who were analyzed and divided into two adequately balanced groups, where the group with added radiotherapy had an improvement in cancer-specific survival prognosis and OS (hazard ratio [Hr]: 0.739, 95% confidence interval [CI]: 0.619-0.884, p = 0.001 and Hr: 0.744, 95% CI: 0.628-0.8810, p = 0.001, respectively)[120].

Primary tumor palliative resection in metastatic disease

In this clinical scenario, there is no controversy: surgery is indicated in patients with a fungating, ulcerated, or hemorrhagic tumor and has the purpose to improve quality of life, without an impact on survival being expected. In the case of unresectable primary tumors, palliative radiotherapy may be considered[121].

Radiotherapy in metastatic disease

The treatment of metastatic disease distinguishes three groups, according to different characteristics: (a) patients with good general conditions, controlled primary tumor and disease confined to three sites or less; (b) poor performance status or extensive metastatic dissemination, in whom palliation of symptoms such as bleeding, infection, pain or compression is required, and (c) those who require local control for bleeding, infection or pain.

Thoracic radiotherapy in patients with de novo metastatic disease

Improvements in local control and PFS have been reported in patients who undergo radiotherapy with or without surgery and who are younger than 55 years, who have HR-positive *HER2*-negative, HR-positive *HER2*-positive molecular subtypes, with limited bone and liver metastases, low-grade tumors, good performance status and partial or complete response to systemic treatment[122,123].

Bone metastases in polymetastatic disease

In patients with high-risk asymptomatic metastases (> 2 cm, disease involving hip or sacroiliac joint, disease in long bones involving > 1/3 of cortical thickness, junctional spine at C7-T1, T12-L1, L5-S1, or posterior spinal element disease), prophylactic irradiation with conventional regimens has been shown to improve OS with a decrease in skeletal events in phase II trials[124]. Commonly used regimens are 30 Gy in 10 sessions, 20 Gy in five sessions, and, ideally, 8 Gy in a single dose. Re-irradiation may be considered in case of symptom persistence[125].

In cases of complicated bone metastases (spinal cord compression or cauda equina syndrome), a single dose of 8-10 Gy is preferred in patients who are not candidates for surgery, whereas longer regimens should be used after surgical decompression[126].

Brain metastases

In patients with single brain metastases, primary tumor controlled at extracranial level and good performance status, treatment options include surgical resection with radiosurgery to the cavity, intracranial radiosurgery single dose of 20-24 Gy in lesions < 2 cm, 18 Gy for 2-3 cm or hypofractionated stereotactic radiotherapy in lesions > 3 cm in case these techniques are available, or whole brain radiotherapy with or without hippocampal preservation and with or without memantine[127,128].

In the setting of limited brain disease, radiosurgery is an option in cases of < 5 lesions < 2 cm in diameter with < 15-cc tumor volume[129].

In case of > 5 lesions, whole-brain radiotherapy with or without hippocampal preservation is used at doses of 30 Gy in 10 fractions, with or without memantine[130].

Stereotactic body radiation therapy (SBRT) in oligometastatic disease

Defined as the presence of 1-5 lesions detectable by imaging[130]. In breast cancer, bone, lung, and liver metastases are the most common[131].

SBRT for bone and vertebral metastases

The indications for SBRT to the spine are Karnofsky Performance Status > 60, single or multiple lesions (≤ 2 consecutive vertebrae or up to three non-contiguous sites), no data consistent with spinal cord compression or pathological fracture, residual or recurrent tumor after surgery, and a disease-free interval longer than 6 months in cases of re-irradiation[132].

In the case of non-spine bone metastases, SBRT could be useful in pre-menopausal women with controlled primary tumor, satisfactory response to systemic treatment, disease-free interval > 12 months, painful metastases, and high-risk molecular subtypes but not for HR-positive and *HER2*-negative disease[89,133].

SBRT for liver metastases

Indicated in patients who are not candidates for surgical management or who refuse surgery. The criteria for offering this technique include adequate liver function, Eastern Cooperative Oncology Group performance status score 0-2, stable or absent extrahepatic disease, 1-5 lesions with a maximum added-up diameter of 10 cm, and healthy liver volume > 700 cc. Chemotherapy should be interrupted at least 3 weeks before the procedure and be restarted 2 weeks after its performance[134,135].

SBRT for lung metastases

It is indicated for small lesions with a volume < 11 cc, with a biological equivalent dose (BED) ≥ 100 Gy being reached with adequate respiratory function[136].

Radiotherapy for symptom control

It is offered with hypofractionated schedules in cases of pain, foul-smelling discharge and bulky disease, tumor bleeding, oncological emergencies, and meningeal carcinomatosis[137].

Evaluation and management of locoregional recurrence

Recurrent disease exclusively in the breast or ipsilateral axilla is an event that is observed with a frequency of < 10%, which can occur after conservative surgery or mastectomy, with or without ipsilateral axillary treatment, followed or not by total radiotherapy to the breast[138]. Initially, the extent of recurrence should be established, i.e., whether there is a distant disease or not. The distinction between purely recurrent disease and second primary lesions takes into account classic factors such as those indicated by Warren, in addition to considering the lesion quadrant, hormone expression, and even genetic, profile, which can be modified by previous treatment[139].

Mammography/ultrasound and extent of disease evaluation (only local, regional, and/or distant) should be carried out. In the case of distant disease, the recommendations for metastatic disease are to be followed. The studies to rule out distant disease are positron-emission tomography, bone scan, or computed tomography.

The management of recurrent disease must consider that this event is by itself a predictor of distant disease and an adverse prognostic factor, which is why systemic treatment should be considered in any of its forms.

Surgical management

A multidisciplinary approach to the management of locoregional recurrence, according to the initial treatment of the primary tumor, is essential.

Patients with prior mastectomy and chest wall recurrences can undergo local resection. Most recurrences occur on the skin and subcutaneous tissue, although recurrence to the chest wall can occur in about 59% of cases[140]. Resectability will depend on the extension to the skin, the possibility of soft tissue coverage, and bone structure involvement. In cases of isolated local recurrences that are considered operable, primary simple closure or use of advancement flaps after wide resection is preferable; when this is not possible, the use of skin grafts or autologous tissue transfer is recommended, always considering that reconstructions in a previously irradiated field are associated with a higher rate of complications[141].

On the other hand, in patients previously treated with breast-conserving surgery who present with local recurrence, although mastectomy is accepted as standard management for breast cancer ipsilateral recurrence, in selected cases, when recurrences are small and breast: tumor ratio allows for it, a second conservative surgery can be considered, as long as reirradiation administration is possible. The NRG Oncology/RTOG 1014 trial, which included patients with local recurrences of 3 cm or less occurring 1 year or more after initial conservative treatment, with disease confirmed as being unicentric by pre-operative magnetic resonance imaging, demonstrated that a second conservative surgery with partial reirradiation to the breast allows preservation of the breast with low rates of locoregional recurrence (5.2% at 5 years). Recurrences located in a different quadrant or outside the initial surgical bed or with a different histology may represent a new primary lesion[142].

Axillary recurrences usually involve the remaining lymph nodes and may also appear within axillary fat or connective tissue. Determining previous lymph node involvement and the extent of previous axillary surgery is the key to subsequent management. If axillary dissection

Table 2. Recommendations for follow-up

Procedure	Frequency
Instruction of the patient on the symptoms and signs of recurrence	At radical treatment conclusion
Physical examination	First 2 years every 3-4 months. 3rd-4th year every 6 months. From 4th year on, annually
Breast self-examination	Monthly
Mammogram	Annually
Tumor markers	Not recommended
Chest, abdominal CT, PET, bone scintigraphy, and liver enzymes	Only if there are specific symptoms
Screening for other tumors (cervical, colorectal, ovarian, endometrial, etc.)	Follow early detection guidelines
Instructions to the patient on exercise, physical activity, and weight control. Evaluate and promote adherence to endocrine therapy and monitor/treat its possible adverse events. Emphasize the use of contraceptive methods (barrier or definitive)	At each appointment

CT: computed tomography; PET: positron-emission tomography.

was initially performed, then the surgery will have recurrent tumor resection as the only purpose; on the contrary, if sentinel lymph node (SLN) biopsy or limited lymphadenectomy (< 6-8 lymph nodes) was carried out, then complete axillary dissection will be indicated, having in mind that it may increase the probability of lymphedema, with axillary restaging with level I and II dissection being the standard management in this scenario. However, performing a SLN procedure after previous axillary surgery is possible, with the identification rate being observed to range from 66 to 71%[4] and non-axillary SLN localization increasing to 43%[142], although the rate of positive SLN appears to be low (8%). The false-negative rate is 9.4%, and the accuracy of the procedure is 97.1%. Using more than one identification technique (dye, radiotracer, magnetic tracer, etc.) and considering possible extra-axillary drainage are suggested. Reverse lymphatic mapping has been described as an alternative means for identifying and preserving the lymphatic vessels and lymph nodes that drain from the arm in this type of patients[142].

Management with radiotherapy

The decision to offer reirradiation to patients with locoregional recurrence must be multidisciplinary, taking into account the extent of the disease and prior management of the area. In these cases, there is information that favors the performance of a second conservative surgery with accelerated partial breast radiotherapy as a reirradiation method[143].

Systemic management

In women with local recurrence, and once complete resection of the disease has been carried out, adjuvant treatment administration has shown an improvement in disease-free and OS in all patients, with greater benefit in the group of women with negative hormone receptors[144]. As in distant recurrence, if possible, obtaining a reevaluation of the tumor subtype is recommended to determine the best recommended systemic treatment, according to previous management, time to recurrence, and patient characteristics.

Follow-up after treatment with curative intent and in metastatic disease

Follow-up after treatment with curative intent

At the conclusion of primary treatment for breast cancer, usually with surgery, chemotherapy, and radiotherapy, the surveillance and control stage known as follow-up begins. The goals of follow-up are to detect recurrences and contralateral breast cancer, to evaluate and treat treatment-related complications (e.g., osteoporosis and second primary tumors), to motivate the patient to continue endocrine therapy, and to treat its side effects.

Table 2 describes internationally accepted recommendations for the follow-up of these patients. It is

Table 3. Follow-up of patients with metastatic disease

Evaluation	Baseline	Chemotherapy	Endocrine therapy
Symptom evaluation	Yes	Before each cycle	Every 1-3 months
Physical examination	Yes	Before each cycle	Every 1-3 months
BC+LFT, BCh	Yes	Every 2-4 cycles	Every 2-6 months
Chest-abdominal CT	Yes	Every 4 cycles	Every 4-6 months
Pelvic CT	Optional	Optional	Optional

BC: blood count; BCh: blood chemistry; CT: computed tomography; LFT: liver function tests.

important to highlight that the appearance of metastases after adequate primary treatment is unrelated to medical action; in addition, anticipating the diagnosis of relapse does not increase survival or quality of life.

Follow-up of patients with metastatic disease

The purpose is to detect disease progression, avoid toxicity or use of an inefficacious treatment, as well as resource optimization. Patient re-evaluation is also indicated if there is deterioration, increased symptoms, or appearance of new signs, regardless of the interval elapsed since the previous control (Table 3).

Conclusions

Significant advances have been made in the management of metastatic breast cancer. One of the most important is a better knowledge of tumor biology, which creates new specific treatment paradigms according to each biological subtype. It is imperative to test biomarkers in all patients, with the purpose to make the best therapeutic decision on an individualized basis. Although the cornerstone is systemic therapy, management must be multidisciplinary, which is an essential requirement for optimal treatment, which should rely on locoregional therapies and early supportive treatments. Metastatic breast cancer is an incurable disease; however, with appropriate strategies, it has been possible to increase progression-free and OS with quality of life.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were carried out on humans or animals for this investigation.

Confidentiality of data. The authors declare that no patient data appear in this article. Furthermore, the authors have recognized and followed the recommendations according to the SAGER guidelines depending on the type and nature of the study.

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