clinical practice guidelines

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Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

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incidence

Breast cancer is the most common cancer in women in many countries, including developing countries. In 2006, the crude incidence in the European Union was 109.8/100 000, and the mortality was 38.4/100 000 women/year. In 2008, 1.38 million new cases and 458 000 breast cancer deaths were noted in the world. Since 1990 the incidence rate has increased 1.5% annually. Due to advances both in early detection and in adjuvant treatment, mortality rates from breast cancer have been decreasing steadily in most Western countries since the early 1990s. However, it is still the leading cause of cancer mortality in women. Approximately 4–6% of breast cancers are metastatic at diagnosis; of those approximately one-fifth will survive 5 years. Depending on prognostic factors, in the worst-case scenario, up to 30% of node-negative and up to 70% of node-positive breast cancers will relapse. The prevalence of metastatic disease is high because many women live with the disease for several years.

diagnosis

Clinical suspicion must be confirmed by imaging (including functional imaging such as positron emission tomography-computed tomography (PET-CT) or dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI); additional information may be provided by laboratory tests.

Efforts should be made to obtain histopathological confirmation particularly in the situation of an isolated metastatic lesion. Biological markers important for treatment decisions, such as hormone receptor (HR) and HER2 status, should be evaluated in the metastatic lesion whenever possible. Although there are no data to support the choice of therapy in the case of discordance in HR/HER2 status between primary and metastatic tumor, retrospective data suggest an inferior outcome in 'discordant' patients (possibly due to inappropriate treatment, not adjusted for biomarker changes). Biopsy may potentially be avoided (i) in situations where the procedure is too risky; (ii) in cases where the time elapsed between the primary tumor and the metastatic disease diagnosis is relatively short (<1–2 years); (iii) or when the results of the biopsy are unlikely to change the therapeutic attitude (e.g. pre-existent contraindications for the use of chemotherapy or anti-HER2 therapies).

There is no proven value of routine diagnostic tests 'screening' for metastatic disease in asymptomatic early breast cancer patients. However, the available data are from a time when neither biological therapy nor efficacious (in terms of local control) and less invasive (in terms of quality of life and side effects) locoregional techniques, such as radiosurgery for central nervous system (CNS) metastases or radiofrequency ablation for liver metastases, were available. Additionally, new techniques are now available, such as MRI, PET-scan, PET-CT, circulating tumor cells and others, that may allow the detection of very early metastatic disease. Therefore, new studies are needed to evaluate the role of early diagnosis of metastatic disease in this new context.

Locoregional recurrence is often associated with distant spread, and such patients should undergo full staging procedures before undergoing local treatments.

staging and prognosis assessment

- Complete history, including
  - (i) menopausal status and co-morbidities;
  - (ii) detailed history of the primary tumor, its biology, management and status at last follow-up;
  - (iii) history of recurrent/metastatic disease including duration, previous sites of involvement, previous treatments and their effect;
  - (iv) current symptoms, performance status, socio-economic background and preferences (Table 1).

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- Detailed physical examination.
- Blood tests: complete blood count, liver and renal function tests, alkaline phosphatase, calcium and, if applicable, specific tests required for particular treatments such as urinary protein. The clinical value of tumor markers has not been proven. However, they may assist in evaluating response to treatment particularly in patients with non-measurable disease.
- Chest X-ray or CT, or abdominal ultrasound, CT or MRI should be used to identify visceral disease.
- Bone scintigraphy, with confirmation of lesions by X-ray/CT/MRI.
- CT and/or MRI of the CNS should be symptom driven.
- PET/PET-CT may be useful for identifying the site of relapse, particularly when traditional imaging methods are equivocal or conflicting. It may also be helpful to identify or confirm the situation of an isolated locoregional relapse or metastatic lesion, since this subset of patients may benefit from a more aggressive multidisciplinary approach.
- Estrogen receptor (ER), progesterone receptor (PgR), HER2 receptors and proliferation markers of the metastatic lesion should be obtained, if possible, and particularly if not available on the primary tumor.
- Cardiac assessments, in particular in HER2+ patients and patients eligible for anthracycline-based chemotherapy.
- Circulating tumor cells is still an experimental technique and should not be used outside a clinical trial.
- In the case of lesions inaccessible for biopsy, functional imaging such as PET-CT or DCE-MRI may be helpful to confirm their malignant character.

treatment—general statements:

locoregional recurrence

- Isolated locoregional recurrence should be treated like a new primary with a curative intent. If feasible, complete excision of recurrent tumor is recommended. In patients previously treated with breast-conserving surgery, a mastectomy should be performed when feasible. In patients not exposed to postoperative irradiation, full dose radiotherapy to the chest wall and (when indicated) regional lymph node areas should be given. In those previously irradiated, the value of re-irradiation is not proven; however, re-irradiation to limited areas in the chest wall may be applied, after a careful benefit–risk balance, taking into consideration the duration of the radiation-free period, intensity of postradiotherapy changes and the risk of additional locoregional relapse. Inoperable patients can, if it is feasible, undergo radical radiotherapy to chest wall and regional lymph node areas with boost to macroscopic disease sites. However, in these patients, primary systemic therapy to decrease the size of the tumor and render it operable should be the first choice.
- The value of 'secondary or pseudo-adjuvant' systemic treatment is not well proven. The role of chemotherapy in this setting is a subject of ongoing randomized studies [II, B]. These studies have been very hard to run due to poor accrual, and this question might therefore remain unanswered. Factors such as tumor aggressiveness, previous adjuvant systemic therapy received, the patient's co-morbidities and preferences should all be taken into account when deciding to propose or not 'pseudo-adjuvant' chemotherapy (expert opinion). Although unproven, 'pseudo-adjuvant' endocrine therapy is a common practice in the case of HR+ tumors and is acceptable in view of its predicted benefit and low toxicity (expert opinion). 'Pseudo-adjuvant' trastuzumab therapy is also acceptable in cases where adjuvant trastuzumab was not prescribed due to unavailability at the time of initial diagnosis and if no contraindications exist (expert opinion).

Table 1. Factors to consider in risk assessment and treatment decision making for MBC

Disease-related factors	Patient-related factors
Disease-free interval	Patient's preferences
Previous therapies and response	Biological age
Biological factors (hormonal receptors, HER2)	Menopausal status
Tumor burden (number and site of metastases)	Co-morbidities and performance status
Need for rapid disease/symptom control	Socio-economic and psychological factors
	Available therapies in the patient's country

metastatic disease

- The management of metastatic breast cancer (MBC) should involve all appropriate specialties in a multi-/interdisciplinary team (medical, radiation, surgical and imaging oncologists, palliative care specialist, psychosocial support), and patients should be offered personalized appropriate psychosocial, supportive and symptom-related interventions as a routine part of their care. Specialist breast nurses can provide crucial support to patients with advanced breast cancer and should be available to all patients. Countries in which this nurse subspecialty does not yet exist should make every effort to establish it.
- There are few proven standards of care in MBC management; therefore, well-designed, independent, prospective randomized trials are a priority. Additionally, participation in such clinical trials should be offered to all eligible patients, whenever available.
- The vast majority of MBC is incurable, and hence the main treatment goal is palliation, with the aim of maintaining/improving quality of life, and possibly improving survival.
- The realistic treatment goals should be discussed with the patient and her/his family from the beginning and the patient should be encouraged to actively participate in all decisions. Patients' preferences should always be taken into account.

- Co-ordination and continuity of care may be facilitated by a specialist breast care nurse or equivalent.
- Systemic treatment options for MBC are endocrine therapy, chemotherapy and biological agents such as trastuzumab, bevacizumab and lapatinib [I, A].
- The choice of therapy should be made after consideration of the factors listed in Table 1
- Patients' preferences should always be taken into account not only about treatment options but also methods of treatment administration (intravenous or oral).
- For the majority of patients, overall survival outcomes from sequential use of single cytotoxic drugs are equivalent to combination chemotherapy. The choice between both these options should primarily take into account the need for a rapid and significant response and quality of life.
- Duration of each regimen and number of regimens should be tailored to each individual patient.
- Radiation therapy is an integral part of palliative treatment. The most common indications for palliative radiotherapy include:
  - bone metastases which are painful or carry a risk of fracture and/or neurological complications (radiotherapy options include 'limited field' external beam irradiation, hemi-body irradiation and application of radioactive 'bone-seeking' isotopes);
  - brain metastases. In patients with single or few metastatic foci, stereotactic radiosurgery can be used as an alternative to surgical resection, with improvement in local control and fewer side effects than whole brain radiotherapy;
  - painful or fungating soft tissue masses.
- For limited metastatic presentations, surgery or radical radiotherapy may be considered. Although no randomized data exist, the bulk of retrospective data suggests a significant survival benefit from the removal of the primary tumor in patients with metastatic disease. Prospective randomized trials addressing this question are currently ongoing.
- Bisphosphonates should be used for the treatment of hypercalcemia and clinically evident bone metastases (to palliate symptoms and decrease risk of bone events) [I, A]. Bisphosphonates should start following a diagnosis of bone metastases. Although the timing and optimal duration of bisphosphonate treatment are unknown and the benefit of duration beyond 2 years has not yet been demonstrated in clinical trials, ongoing risk of skeletal events persists, especially at times of disease progression, and long-term treatment seems wise. The impact of bisphosphonate-associated side effects (including osteonecrosis of the jaw and nephrotoxicity) is minor, and for the vast majority of patients the benefit of treatment outweighs the risks. Recent studies demonstrated superior activity and a favorable toxicity profile of the RANK-ligand antibody denosumab in breast cancer-related bone disease and hopefully this compound will become generally available for this indication soon.
- The choice of drugs, their timing, optimal duration, methods of administration and side effects should be considered individually, taking into account predicted treatment acceptability and adherence. Availability and reimbursement issues must also be taken into account.

treatment—specific breast cancer subtypes

patients with luminal-type breast cancer (HR-positive breast cancer, irrespective of HER2 status)

- Endocrine therapy is the preferred option except if clinically aggressive disease mandates a quicker response or if there are doubts regarding the endocrine responsiveness of the tumor. Available endocrine agents are listed in Table 2.
- The choice of endocrine agent should be individualized according to the drug safety profile, co-morbidities, tumor biology and agents received in the adjuvant setting.
- Apart from combination with ovarian suppression in premenopausal patients, there is no rationale for use of combination hormonal therapies.
- The value of maintenance with hormonal treatment after chemotherapy has not been confirmed by controlled clinical studies, but is a reasonable approach.
- Concomitant chemo-hormonal therapy is discouraged.
- In the case of HER2 overexpression/amplification addition of anti-HER2 therapies to hormonal treatment is beneficial.

premenopausal patients. If no prior adjuvant tamoxifen was given or if it has been discontinued for >12 months: tamoxifen with ovarian ablation (luteinizing hormone-releasing hormone analog or surgery) is the preferred option [I, B]. Otherwise, third-generation aromatase inhibitors may be considered after or concomitantly with ovarian ablation. Further treatment lines (in patients who have undergone ovarian ablation/suppression) do not differ from those used in the postmenopausal population (as described below).

postmenopausal patients. If no prior adjuvant third-generation aromatase inhibitors (anastrozole, letrozole or exemestane)

Table 2. Available endocrine therapies for MBC

Class of agent	
Selective estrogen receptor modulators	Tamoxifen; toremifene
Estrogen receptor down-regulator	Fulvestrant
Luteinizing hormone-releasing hormone analogs	Goserelin; leuprorelin
Third-generation aromatase inhibitors	
Non-steroidal	Anastrozole, letrozole
Steroidal	Exemestane
Progestins	Medroxyprogesterone acetate; megestrol acetate
Anabolic steroids	Nandrolone decanoat

were given or if they have been discontinued for >12 months these are the preferred option since they have consistently shown superior results to tamoxifen as first-line therapy in terms of response rate, time to progression and, for letrozole, in 2-year overall survival [II, A]. Caution should be given to the risk of accelerated bone loss in these patients, and calcium and vitamin D supplements are recommended.

Tamoxifen remains an acceptable first-line therapy. Albeit definitive data are still needed, it seems reasonable to advise patients under tamoxifen to avoid, whenever possible, the use of drugs modulating the activity of CYP2D6, such as some selective serotonin reuptake inhibitor antidepressants (paroxetine, fluoxetine). Fulvestrant has also shown value as first-line therapy after progression on adjuvant aromatase inhibitors.

Second- and further lines of hormone therapy may include tamoxifen, third-generation aromatase inhibitors (if not previously used), fulvestrant, megestrol acetate and androgens. No definitive recommendation can be given for endocrine treatment cascade and, in particular, the best option after progression on a third-generation aromatase inhibitor is currently unknown.

Patients with clear evidence of endocrine resistance should be offered chemotherapy or participation in clinical trials. No overall recommendation can be made regarding the number of lines of endocrine therapy which should be given before switching to chemotherapy since this is highly variable and dependent on various factors such as intensity and duration of response to previous endocrine therapies, presence or absence of symptoms and/or rapidly progressive or life-threatening disease, patient performance status and estimated capacity to tolerate chemotherapy, among others

Table 3. Selection of available chemotherapy agents/regimens for MBC

Non-anthracycline-containing
Cyclophosphamide/methotrexate/fluorouracil (CMF)
Platinum-based combinations (e.g. cisplatinum + 5-fluorouracil; carboplatin + gemcitabine)
Capecitabine
Vinorelbine
Gemcitabine
Capecitabine + vinorelbine
Vinorelbine ± gemcitabine
Oral cyclophosphamide with or without methotrexate (metronomic chemotherapy)
Anthracycline-containing
Doxorubicin or epirubicin monotherapy (weekly or 3-weekly)
Doxorubicin/cyclophosphamide or epirubicin/cyclophosphamide
Liposomal doxorubicin with or without cyclophosphamide
Fluorouracil/doxorubicin/cyclophosphamide
Fluorouracil/epirubicin/cyclophosphamide
Taxane-containing
Paclitaxel monotherapy weekly
Docetaxel monotherapy 3-weekly or weekly
Doxorubicin/taxane (paclitaxel or docetaxel)
Epirubicin/taxane (paclitaxel or docetaxel)
Docetaxel/capecitabine
Paclitaxel/gemcitabine
Paclitaxel/vinorelbine
Paclitaxel/carboplatin
New cytotoxic agents
Eribulin
Ixabepilone
Abraxane (nab-paclitaxel)

patients with 'triple negative' breast cancer (HR-negative and HER2-non-overexpresed/ non-amplified breast cancer)

- Patients having HR-negative tumors are candidates for cytotoxic chemotherapy. Available agents/regimens are listed in Table 3.
- The only standard of care with level 1 evidence is the use of a taxane-based regimen as first-line therapy in patients progressing after adjuvant anthracycline-based chemotherapy [I, A]. The selection of the best agent/regimen should be individualized and should take into account the factors listed in Table 1.
- For the majority of patients, overall survival outcomes from the sequential use of single cytotoxic drugs is equivalent to that of combination chemotherapy, with less associated toxicity and better quality of life. Therefore, in the absence of the need for a rapid and significant response for symptom control or life-threatening disease, preference should be given to the sequential use of a sequential single cytotoxic agent approach. However, very few randomized clinical trials have correctly addressed this question and there is an urgent need for a well-designed, prospective randomized trial to compare sequential single-agent with combination chemotherapy as first-line therapy of MBC. In triple negative disease, because of frequent visceral involvement, aggressive course and risk of rapid patient deterioration, combination chemotherapy is often required. Notwithstanding the above, all factors should be taken into account, and triple negative biology on its own does not always require combination chemotherapy as shown by data from trials where patients with this subtype of breast cancer, but without extensive or life-threatening disease, were treated successfully with single agent chemotherapy.
- There is no standard approach for patients requiring second- or further line treatment since there are few data supporting the superiority of any particular regimen.
- Duration of each regimen and number of regimens should be tailored to each individual patient. Continuing beyond third-line treatment may be justified in patients with good performance status and response to previous chemotherapy.
- High-dose chemotherapy should not be proposed.

patients with HER-2-positive (overexpressed/ amplified) breast cancer

- Patients should be treated with trastuzumab with or without chemotherapy [II, B].

- Trastuzumab should be offered early to all HER2-positive MBC patients.
- Cardiac monitoring should be performed before and while on trastuzumab therapy.
- The bulk of retrospective data and results of a phase III randomized trial show that continuing trastuzumab, associated with a different chemotherapy regimen, after the first disease progression is superior to the discontinuation of this agent. The benefit of continuing anti-HER2 therapy beyond first progression is based on fewer data, but available evidence points to the continuation of anti-HER2 therapy for as long as possible.
- Lapatinib has shown a significant increase in time to progression in combination with capecitabine in patients progressing after trastuzumab, anthracyclines and taxanes. The question of continuing trastuzumab or changing to lapatinib at the time of first progression remains open.
- Combination of trastuzumab and lapatinib seems to be superior to lapatinib monotherapy in patients progressing on anthracyclines, taxanes and trastuzumab, albeit not yet approved.
- Addition of anti-HER2 agents (trastuzumab or lapatinib) to endocrine therapy allows for prolongation of progression-free survival (PFS) and may be a viable option for some patients with ER/PgR-positive and HER2-positive tumors who are evaluated as not needing or not being able to tolerate chemotherapy with anti-HER2 therapy. The potential side effects of the available combinations of endocrine agents and anti-HER-2 agents should be discussed with the patient.
- Other anti-HER-2 or pan-anti-HER agents, such as pertuzumab, trastuzumab-DM1 and HKI-272, are currently under investigation, as are combinations of trastuzumab with other biological agents with or without chemotherapy to tackle the problem of resistance to trastuzumab.

other biological agents

- Bevacizumab, an antiangiogenic agent, has been approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) for use in combination with paclitaxel as first-line treatment of MBC after showing a benefit of 6 months in PFS in the ECOG 2100 study. In two other randomized phase III trials, the AVADO and RIBBON studies, and in a meta-analysis of phase III randomized trials, the benefit of bevacizumab in an unselected breast cancer population was of 1 month in PFS at the cost of increased toxicity and with no significant benefit in overall survival. For this reason, the FDA recommended removing the breast cancer indication for bevacizumab because of an unfavorable efficacy–safety profile. In Europe, however, bevacizumab remains approved, only as first-line therapy and only in combination with paclitaxel, and may be considered for carefully selected patients with limited treatment options, requiring a well thought out balance between side effects, benefits and costs.
- Sunitinib, another antiangiogenic agent, both as single agent and in combination with chemotherapy, failed to show a significant benefit in unselected MBC populations and should not be used outside clinical trials. Additionally, certain tyrosine kinase inhibitors (i.e. gefitinib and erlotinib) have also not yielded significant benefit for MBC.
- Efforts must continue to be made to identify which patients may benefit from the antiangiogenic approach.
- PARP [poly (ADP-ribose) polymerase] inhibitors have shown promising results, in phase II trials, as single agents in BRCA-mutated MBC and in combination with carboplatin and gemcitabine in unselected triple negative MBC patients. However, a large phase III trial evaluating iniparib in combination with carboplatin and gemcitabine in unselected triple negative MBC failed to show the expected benefit. Other PARP inhibitors and other combinations are still under evaluation in clinical trials.
- Several other biological or targeted agents are currently under active investigation as single agents or in combination.

response evaluation

- Response evaluation is routinely recommended after 2–3 months of endocrine therapy and after two or three cycles of chemotherapy by clinical evaluation, subjective symptom evaluation, blood tests and repeating the initially abnormal radiological examinations with comparative measures. However, the interval between assessments should be tailored to the clinical needs of the patient and to the aggressiveness of the disease. In the case of clinical suspicion of progressive disease, appropriate tests (imaging and laboratory) should be performed irrespective of scheduled examinations, if necessary including areas not imaged in previous tests.
- Bone scans should be used with extreme caution and only if other imaging tests are unavailble to assess response in bone due to the potential for a flare response being confused with progression.
- Serum tumor markers (such as CA 15-3 and/or CEA) may be helpful in monitoring response, particularly in the case of not easily measurable disease, but should not be used as the only determinant for treatment decision.
- The role of PET/PET-CT in response assessment is still under investigation, but it may be used to determine disease progression.
- Maintenance of a good quality of life is paramount and can best be achieved with prompt amelioration of symptoms and side effects of treatment. Psychometrically sound, well-validated questionnaires are available to measure patient-reported outcomes (PROs). These should be employed regularly to help assess the impact of treatment and to monitor symptoms that demand supportive intervention promptly.

follow-up

- Follow-up after the treatment of locoregional recurrence may be carried out as for primary breast cancer.

- Patients with MBC must be seen frequently enough to provide best possible palliation of symptoms and quality of life, which means on average every 2–3 months if on endocrine therapy and every one or two cycles of chemotherapy. If progression is suspected (due to aggravation or appearance of new signs/symptoms and/or significant increase in the levels of tumor markers), response evaluation should be done immediately.
- There is no defined optimal visit schedule for MBC patients in disease remission and no active treatment; however, apart from scheduled visits these patients should be instructed to contact their physician immediately in case of symptoms suggestive of progressive disease or treatment complications.
- Patients need good quality information and a care plan outlining all aspects of treatment and care, clarification of the purpose of different treatments, their side effects and potential impact on functional, emotional and social well-being.

note

Levels of evidence [I–V] and grades of recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.

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