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, the mortality was 38.4/100 000 women/year. 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 6% of breast cancers are metastatic at diagnosis with a 5-year survival rate of 21%. Depending on prognostic factors, in the worst 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); 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 hormonal receptors and HER2 status, should be evaluated in the metastatic lesion whenever possible. Potential exceptions are (a) situations where the biopsy procedure is too risky, (b) the time elapsed between the primary tumour and the metastatic disease diagnosis is relatively short or (c) 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 patients. However, the available data are from a time when neither biological therapy nor efficacious (in terms of local control) and less invasive loco-regional techniques, such as radiosurgery for central nervous system (CNS) metastases or radiofrequency for liver metastases, were available. Additionally, new techniques are now available, such as magnetic resonance imaging (MRI), PET scan, PET–CT, circulating tumour cells and others, that may allow for 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.

The occurrence of loco-regional recurrence is often associated with distant spread and such patients should undergo full staging procedures before undergoing local treatments.

staging and risk assessment

- Complete history, including:
  - (i) menopausal status and co-morbidities;
  - (ii) detailed history of the primary tumour, 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).
- 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 tumour markers has not been well proven; however, their use may be of value to assess the

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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
Tumour 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

efficacy of treatment particularly in patients with non-measurable disease.
- Chest X-ray or computed tomography (CT), 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 an isolated metastatic lesion, since this subset of patients may benefit from a more aggressive multidisciplinary approach.
- Estrogen and progesterone receptors, HER2 receptors and proliferation markers of the metastatic lesion should be obtained, if possible, and particularly if not available on the primary tumour.
- Cardiac assessments, in particular in HER2(+) patients.
- Circulating tumour cells is still an experimental technique and should not be used outside a clinical trial.

treatment

local–regional recurrence

Isolated local–regional recurrence should be treated like a new primary with a curative intent. If feasible, complete excision of recurrent tumour is recommended. In patients not exposed to postoperative irradiation, radical radiotherapy to chest wall and (in most cases) 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 radiation-free period, intensity of post-radiotherapy changes and the risk of local–regional relapse. Inoperable patients can, if 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 tumour 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 'secondary or pseudo-adjuvant' chemotherapy is a subject of ongoing randomized studies [II, B].

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.
- There are few proven standards of care in MBC management, therefore well-designed, independent, prospective randomized trials are a priority.
- 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 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 need to be facilitated by a specialist breast care nurse or key worker.
- Systemic treatment options for MBC are endocrine therapy, chemotherapy and biological agents such as trastuzumab, bevacizumab and lapatinib [I, A] (see Table 1).
- The choice of therapy should be made after consideration of factors such as: previous therapies and response to them, disease-free interval, endocrine responsiveness, HER2 status, tumour burden (defined as number and site of metastases), menopausal status, biological age and co-morbidities (including organ dysfunction), performance status, need for rapid disease/symptom control, socio-economic and psychological factors, patient's preference and available therapies in the patient's country.
- Patients' preferences should always be taken into account not only about treatment options but also methods of treatment administration (i.v. 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 that are painful or carry a risk of fractures and/or neurological complications (radiotherapy options include 'limited field' external beam irradiation, hemi-body irradiation and application of radioactive 'bone-seeking' isotopes);

- Brain metastases (several series have shown that, in patients with single or a few metastatic foci, stereotactic radiosurgery can be used with equally good local control and less side-effects than whole brain radiotherapy);
- Painful or fungating soft tissue masses.

- For limited metastatic presentations surgery or radical radiotherapy may be considered.
- Bisphosphonates should be used for the treatment of hypercalcaemia and clinically evident bone metastases (to palliate symptoms and decrease risk of bone events) [I, A]. The timing and optimal duration of bisphosphonates are unknown. The choice of drugs, their timing, optimal duration, methods of administration and side-effects have significant consequences for a patient's life-style especially in terms of their ability to adhere to treatment. Monitoring of acceptability and adherence is crucial, and choice where possible should be offered.

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

- Endocrine therapy is the preferred option except when clinically aggressive disease mandates a quicker response or if there are doubts regarding the endocrine responsiveness of the tumour. Available endocrine agents are listed in Table 2.
- The choice of endocrine agent should be individualized according to the safety profile, patient's co-morbidities and tumour biology.
- Apart from combination of tamoxifen with ovarian suppression in premenopausal patients there is no rationale for the 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.

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 analogues	Goserelin; leuprorelin
Third-generation aromatase inhibitors	
Non-steroidal	Anastrozole, letrozole
Steroidal	Exemestane
Progestins	Medroxyprogesterone acetate; megestrol acetate
Androgens	
Anabolic steroids	Nandrolone decanoa

- In the case of HER2 overexpression/amplification, addition of anti-HER2 therapies to hormonal treatment is beneficial.

premenopausal patients

If no prior adjuvant tamoxifen or if discontinued for >12 months: tamoxifen with ovarian ablation (luteinizing hormone releasing hormone analogue 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 had 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, exemestane) or if discontinued for >12 months these are the preferred options 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.

Tamoxifen remains an acceptable first-line therapy. Patients given tamoxifen should be instructed to avoid use of drugs modulating the activity of CYP2D6, such as some selective serotonin reuptake inhibitor antidepressants (paroxetine, fluoxetine).

Second-line 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 particularly, 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.

patients with 'triple negative' breast cancer (hormone receptor-negative and HER2-non-overexpressed/ non-amplified breast cancer)

- Patients having hormone receptor-negative tumours 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 are 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 single cytotoxic agents. However, very few randomized clinical trials have correctly addressed this question

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

Non-anthracycline-containing
Cyclophosphamide/methotrexate/5-fluorouracil (CMF)
Platinum-based combinations (e.g. cisplatin + 5-fluorouracil)
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 or epirubicin/cyclophosphamide
Liposomal doxorubicin with or without cyclophosphamide
5-fluorouracil/doxorubicin/cyclophosphamide
5-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
Ixabepilone
Abraxane (nab-paclitaxel)

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.
- There is no standard approach for patients requiring second- or further-line treatment since there are no 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 may be justified in patients with good performance status and response to previous chemotherapy.
- High-dose chemotherapy should not be proposed.

- The role of bevacizumab will be discussed in the section on other biological agents.

patients with HER2-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 the phase III randomized Trial Beyond Progression show that continuing trastuzumab after the first disease progression, associated with a different chemotherapy regimen is superior to the discontinuation of this agent. With the approval of lapatinib for the treatment of MBC, the question of continuing trastuzumab or changing to lapatinib at the time of first progression remains open.
- Lapatinib has shown a significant increase in time to progression in combination with capecitabine in patients progressing after trastuzumab.
- Addition of anti-HER2 agents (trastuzumab and lapatinib) to endocrine therapy allows for prolongation of progression-free survival (PFS) and may be a viable option in patients with ER/PgR-positive and HER2-positive tumours.
- Other anti-HER2 or pan-anti-HER agents, such as pertuzumab 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 anti-angiogenic agent, has been approved by the FDA and the 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. However, in two other randomized phase III trials, the AVADO and RIBBON studies, the benefit of bevacizumab in an unselected breast cancer population was of 1 month in PFS with no significant benefit in overall survival. Efforts must continue to be made to clearly identify which patients may benefit from this expensive therapy.
- Several 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 measurements. 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.
- Serum tumour markers (CA 15-3) 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.
- 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. 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 local–regional 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.
- Finally 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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