

ESMO Minimum Clinical Recommendations for diagnosis, treatment and follow-up of locally recurrent or metastatic breast cancer (MBC)

Incidence

- The crude incidence of breast cancer in the European Union is 109.8/100 000 women/year, the mortality is 38.4/100 000 women/year. After primary treatment with curative intent, recurrence occurs in 10–30% in 10 years in stage I and in 40–50% in five years in stage II. Up to 85% of the recurrences occur within five years from the diagnosis. After postoperative radiotherapy local-regional recurrences occur in <10%.

Diagnosis

- Clinical suspicion should be confirmed by radiologic and/or scintigraphic examinations and blood tests.
- Histopathological or cytopathological confirmation should be obtained whenever possible.

Staging and risk assessment

- Complete history, especially relating to the primary tumor, its management, and menopausal status (Table 1).
- Physical examination, performance status.
- Blood tests: full blood count, liver and renal function tests, calcium.
- Chest X-ray, abdominal ultrasound or CT-scans should be used to identify visceral disease.
- Bone scintigraphy or CT and/or MRI of the CNS should be symptom driven.
- Estrogen and progesterone receptor and HER2 expression on the metastases at least, if not available on the primary tumor.

Treatment

- Isolated local-regional recurrence should be treated like a new primary with a curative intent including adjuvant treatment modalities.
- Treatment for systemic disease is palliative. Goals of treatment include improving quality of life and prolongation of survival [I, A]. Treatment of metastatic breast cancer usually involves hormone therapy and/or chemotherapy with or without trastuzumab. Radiation therapy is an integral part of palliative treatment.
- Bisphosphonates are effective in hypercalcemia and palliate symptoms from lytic bone metastases [I, A]. The timing

and optimal duration of administration of bisphosphonates is unknown.

Patients with hormone-receptor positive tumor

- Patients should start with endocrine therapy (Table 2) except if biologically aggressive disease mandates a quicker response.

Premenopausal patients

- If no prior adjuvant tamoxifen or discontinued for more than 12 months:
- Tamoxifen with ovarian ablation (LHRH analogs or surgery) [I, B]. Otherwise: Third generation aromatase inhibitors can be considered after or concomitantly with ovarian ablation.

Postmenopausal patients:

- Aromatase inhibitors or tamoxifen. Third generation aromatase inhibitors are superior to tamoxifen in first line therapy regarding response and time to progression but not for overall survival [II, A].
- Second-line hormone therapy in postmenopausal women include selective aromatase inhibitors, such as anastrozole, letrozole, or exemestane (there is some evidence of incomplete cross-resistance between steroidal and non-steroidal aromatase inhibitors), megestrol acetate, fulvestrant, androgens.
- Patients with evidence of endocrine resistance should be offered chemotherapy.
- Concomitant chemohormonal therapy is not recommended.

Patients with hormone-receptor negative tumor

- Patients whose tumors are hormone-receptor negative and/or have progressed on hormone therapy are candidates for cytotoxic chemotherapy (Table 3). The selection of the regimen should be based on tumor and patients characteristics (e.g., rate of disease progression, presence or absence of comorbid medical conditions, previous adjuvant systemic therapy) and patient/physician preferences. At this time, there are no data supporting the superiority of any particular regimen. The optimal treatment duration for patients with responsive or stable disease is unknown. In randomized trials, improved quality of life and time to progression was

Table 1. Factors associated with favorable prognosis in metastatic breast cancer

ER/PR positive tumor
Long disease free interval (>1–2 year)
No visceral involvement
Limited metastatic sites, no bulky disease
HER2 negative tumor

Table 2. Commonly used endocrine therapies in MBC

Selective estrogen receptor modulators (SERMs)	Luteinizing hormone-releasing hormone (LHRH) analogs
Tamoxifen, toremifene	Goserelin, leuprorelin, triptorelin, buserelin
Third generation aromatase inhibitors	Progestins
Non-steroidal: anastrozole, letrozole	Medroxyprogesterone acetate, megestrol acetate
Steroidal: exemestane	
Androgens	Estrogen receptor (ER) antagonist
Fluoxymesterone	Fulvestrant

observed for prolonged treatment, but there was no evidence for survival advantage.

- Selection of commonly used chemotherapy regimens are shown in Table 3. Anthracyclines, taxanes, capecitabine, vinorelbine, fluorouracil as continuous infusion, gemcitabine are examples of commonly used single agents. There is no standard approach for patients requiring second- or further line treatment.
- Patients with metastatic breast cancer with substantial over-expression of HER2/neu (3+ immunohistochemistry, positive in-situ hybridisation with FISH or CISH) are candidates for treatment with the combination of trastuzumab and chemotherapy (not anthracycline) [II, B].
- Continuing beyond third line chemotherapy may be justified in patients with good performance status and response to previous chemotherapy.
- There is no evidence of an advantage in terms of overall or relapse-free survival for patients receiving high-dose chemotherapy.

Response evaluation

- Response evaluation is recommended after 3 months of endocrine therapy and after 2 or 3 cycles of chemotherapy by clinical evaluation, subjective symptom evaluation, blood tests, and repeating the initially abnormal radiologic examinations. Serum tumor markers (CA 15.3) may be helpful in monitoring response of not easily measurable disease but should not be used as the only determinant for treatment decision.

Follow-up

- Follow-up after the treatment of local-regional recurrence may be done as for primary breast cancer. Patients must be

Table 3. Selection of commonly used chemotherapy regimens

Non-anthracycline containing:

Cyclophosphamide/methotrexate/fluorouracil (CMF)

Anthracycline containing:

Doxorubicin/cyclophosphamide (AC)

Fluorouracil/doxorubicin /cyclophosphamide (FAC)

Fluorouracil/epirubicin/cyclophosphamide (FEC)

Taxane containing:

Doxorubicin/taxane (AT) (paclitaxel or docetaxel)

Epirubicin/taxane (ET) (paclitaxel or docetaxel)

Docetaxel/capecitabine

seen often enough to provide best possible palliation of symptoms and quality of life.

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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