Incidence
The crude incidence of breast cancer in the European Union is 109.8/100 000, the mortality is 38.4/100 000 women/year. After primary treatment with breast-conserving surgery and radiotherapy, 2–20% of patients will have local recurrence in the breast within 10 years. After radical surgery and postoperative radiotherapy local–regional recurrences occur in <10%.
Distant metastases are diagnosed within 10 years in 10–70% of patients treated with surgery/radiotherapy and systemic therapy depending on prognostic factors.

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: complete blood count, liver and renal function tests, alkaline phosphatase, calcium, markers (CA 15-3, CEA).
- Chest X-ray or computed tomography (CT), abdominal ultrasound or CT should be used to identify visceral disease.
- Bone scintigraphy (with confirmation of lesions by CT/magnetic resonance imaging (MRI)).
- CT and/or MRI of the central nervous system should be symptom driven.

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

<table>
<thead>
<tr>
<th>Factor</th>
<th>Prognosis</th>
</tr>
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<tbody>
<tr>
<td>Long disease-free interval (&gt;1–2 years)</td>
<td></td>
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<tr>
<td>Extent of metastatic involvement (limited metastatic sites, no bulky disease)</td>
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<tr>
<td>Localization of metastases (no visceral involvement)</td>
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</tbody>
</table>

- Estrogen and progesterone receptor and HER2 expression of the metastases, if possible, and particularly 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 as appropriate [II, B].
- Treatment for systemic disease is palliative. Goals of treatment include improving and maintaining quality of life and prolongation of survival [I, A].
- Treatment of metastatic breast cancer usually involves hormone therapy or chemotherapy with or without trastuzumab.
- Radiation therapy is an integral part of palliative treatment.
- For limited metastatic presentations surgery may be considered.
- Bisphosphonates are effective in hypercalcemia and palliate symptoms and decrease risk for pathological fractures from clinically evident bone metastases [I, A]. The timing and optimal duration of administration of bisphosphonates are unknown.

Patients with hormone receptor-positive tumor
Patients should start with endocrine therapy (Table 2) except if a clinically aggressive disease mandates a quicker response.

Premenopausal patients
If no prior adjuvant tamoxifen or if discontinued for >12 months: tamoxifen with ovarian ablation (luteinizing
hormone releasing hormone analogue, surgery or radiation) [I, B]. Otherwise, third-generation aromatase inhibitors may be considered after or concomitantly with ovarian ablation.

postmenopausal patients

- Third-generation aromatase inhibitors (anastrozole, letrozole, exemestane) are superior to tamoxifen in first-line therapy in terms of response rate and time to progression [II, A]. Hormonal therapy should be individualized according to patient’s safety profile, and tamoxifen remains an acceptable first-line therapy in selected cases.
- Second-line hormone therapy may include tamoxifen, anastrozole, letrozole, exemestane, fulvestrant, megestrol acetate and androgens.
- No definitive recommendation can be given for endocrine treatment cascade.
- Patients with evidence of endocrine resistance should be offered chemotherapy.
- Concomitant chemohormonal therapy is not recommended.

patients with hormone receptor-negative tumor

Patients having hormone receptor-negative tumors and/or having progressed on hormone therapy are candidates for cytotoxic chemotherapy (Table 3). The selection of the regimen should be on the basis of the tumor and patient characteristics (e.g. symptoms, performance status, extent of metastatic disease, 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. Chemotherapy can be polychemotherapy or agents can be used in sequence. Prolonged treatment may result in improved quality of life and time to progression, but there is no evidence for survival advantage [I, A].

Selection of commonly used chemotherapeutic regimens is shown in Table 3. Anthracyclines, taxanes, capecitabine, vinorelbine, fluorouracil as continuous infusion and gemcitabine are examples of commonly used single agents.

There is no standard approach for patients requiring second- or further-line treatment. 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.

patients with overexpression of HER2/neu

Patients with metastatic breast cancer with overexpression of HER2/neu in IHC and/or in situ hybridization with FISH or CISH should be treated with trastuzumab with or without non-anthraclycline-containing chemotherapy [II, B]. Cardiac monitoring should be performed before and while on trastuzumab therapy. Discontinuation of trastuzumab after disease progression is standard care, although some benefit from the treatment beyond disease progression has been reported with changing chemotherapy regimen.

Lapatinib has shown a significant increase in time to progression in combination with capecitabine in patients progressing after trastuzumab.

response evaluation

Response evaluation is recommended after 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 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 carried out as for primary breast cancer. Patients must be...
seen frequently 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.

**literature**

1. Rosen PP, Groshen S, Saigo PE et al. Pathological prognostic factors in stage I (T1N0M0) and stage II (T1N1M0) breast carcinoma: a study of 644 patients with median follow-up of 18 years. J Clin Oncol 1989; 7: 1239–1251.


