clinical recommendations

doi:10.1093/annonc/mdp114

Primary breast cancer: ESMO Clinical Recommendations for diagnosis, treatment and follow-up

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incidence

In 2006 the estimated age-adjusted annual incidence of breast cancer in the European Union (25 countries) was 110.3/100 000 and the mortality 25.0/100 000. The incidence is increasing due to mammographic screening and aging population. The mortality rate has decreased especially in younger age groups because of earlier detection and improved treatment. However, breast cancer is still the leading cause of cancer-related deaths in European women.

diagnosis

The diagnosis is based on the triad of clinical, radiological and pathological examinations. Clinical examination includes bi-manual palpation of the breasts and local regional lymph nodes. Radiological examinations include bilateral mammography of the breasts and ultrasound of the breasts and local regional lymph nodes. MRI of the breasts is not a routine procedure, but may be considered in cases involving diagnostic challenges arising, for example, because of dense breast tissue or positive axillary lymph node status with occult primary tumor in the breast. Pathological diagnosis should be based on core needle biopsy obtained by manual, or preferably by ultrasound or stereotactic guidance. A core needle biopsy, or if that is not possible, at least a fine needle aspiration indicating carcinoma should be obtained before any surgical operations. Final pathological diagnosis should be made according to the World Health Organization (WHO) classification and the tumor–node–metastases (TNM) staging system analyzing all tissue removed.

staging and risk assessment

Patient-related staging examinations include complete personal medical history, family history relating to breast/ovarian and other cancers, physical examination, performance status, full blood count, liver and renal function tests, alkaline phosphatase and calcium. Assessing the menopausal status is imperative, if in doubt, by measuring serum hormone levels.

Preoperative disease-related staging includes clinical TNM staging, pathological examination of the core needle biopsy with a pathologist's report on histologic type and grade, and providing there is sufficient tissue available, determination of estrogen receptor (ER), progesterone receptor (PgR) and HER2 receptor status by IHC or FISH/CISH test [III, B].

If preoperative (neoadjuvant) systemic therapy is planned, additional investigations such as thorax X-ray, abdominal ultrasound and bone scintigraphy should be considered to exclude metastatic disease. These investigations are recommended also for patients with clinically advanced disease (clinically positive axillary nodes, large tumors) or with laboratory values or clinical signs or symptoms indicating the presence of metastases, even if preoperative systemic treatment is not planned [III, B].

Postoperatively the pathologist's report should include: number of tumors in the tissue removed, the maximum diameter of the largest tumor (T), histologic type and grade of the tumor, evaluation of the resection margins including the minimum margin in millimetres and its anatomical direction; total number of removed lymph nodes, number of positive lymph nodes, extent of metastases in the lymph nodes (ITC, micrometastatic, metastatic), i.e. N-status. Performing sentinel node biopsy is recommended in the surgical staging of the axilla for patients with clinical stage I or stage II breast cancer. The report should also include immunohistochemical evaluation of ER and PgR using a standardized assessment methodology, e.g. Allred or H score, and immunohistochemical evaluation of HER2 receptor expression. HER2 gene amplification status may be determined directly from all tumors using *in situ* hybridization (FISH or CISH) or only from tumors with an ambiguous (2+) immunohistochemistry. Vascular and lymphovascular invasion should also be reported.

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Approved by the ESMO Guidelines Working Group: August 2003, last update October 2008. This publication supercedes the previously published version—Ann Oncol 2008; 19 (Suppl 2): ii7–ii10.

Conflict of interest: The authors have reported no conflicts of interest.

Risk stratification currently includes three categories: low, intermediate and high risk, based on calculated risk of recurrence involving age, tumor size, histopathological grade, vascular invasion, axillary lymph node involvement, ER/PgR status and HER2 status (Table 1).

The place of gene/molecular profiling shows promise but requires prospective validation before routine use.

treatment plan

Multidisciplinary discussion involving an oncologist, breast surgeon, radiologist, radiation oncologist and pathologist leading to treatment planning should be used to integrate local and systemic therapies and their sequence [III, B]. The possibility of hereditary cancer should be explored and, if needed, prophylactic procedures discussed following adequate genetic counseling and testing of the patient [IV, D].

local therapy

non-invasive carcinoma

Intraductal carcinoma (ductal carcinoma *in situ*, DCIS) may be treated with breast-conserving surgery (BCS) providing healthy tissue margins can be reached. There is no general consensus on what is regarded as a safe (negative) margin. However, margins >10 mm are adequate and margins <1 mm are inadequate. Adjuvant breast irradiation after BCS decreases the risk of local recurrence but has no effect on survival [I, A]. This decrease in risk of local recurrence is evident in all subtypes of DCIS. However, in some patients with low-risk DCIS (tumor size <10 mm, low/intermediate nuclear grade, adequate surgical margins), the risk of local recurrence following excision only is so low that omitting radiation may be an option. Especially in ER-positive DCIS tamoxifen may be considered following BCS (with or without adjuvant radiation) [II, A]. Total mastectomy with clear margins in DCIS is curative, and radiation therapy is not recommended. In this group of patients tamoxifen may also be considered as a risk reduction therapy to decrease the risk of contralateral breast cancer [II,B]. Lobular carcinoma *in situ* (LCIS) is a risk factor for future development of invasive cancer in both breasts (RR 5.4–12).

invasive carcinoma

Invasive breast cancer is operated by using BCS or mastectomy, both combined with sentinel node biopsy (SNB) alone, SNB followed by axillary dissection or axillary dissection without SNB, depending on clinical situation. SNB should not be performed in cases of palpable axillary node(s), in large (>3 cm) T2–T4 tumors, multicentric tumors, prior axillary surgery or large biopsies, after breast reconstruction or implantation of a prosthesis, during pregnancy or lactation, and after neoadjuvant systemic treatment outside clinical trials. Contraindications to BCS include multicentric tumors, large tumors (>3–4 cm) in small breasts especially when no neo-adjuvant therapy is planned, positive margins after resection, inflammatory breast cancer and patient's own wish. Postoperative radiotherapy is strongly recommended after BCS [I, A]. Radiotherapy reduces the risk of local recurrence by two-thirds and has a beneficial effect on survival. In patients >70 years of age who have receptor-positive invasive breast cancer with maximum stage pT1N0 and clear postoperative margins it may be possible to use adjuvant tamoxifen instead of radiation therapy [II, B].

Table 1. Risk categories for patients with operated breast cancer

Low risk	Node-negative and all of the following features	Estimated risk of recurrence in 10 years (%)
	pT ≤ 2 cm Grade 1 Absence of extensive peritumoral vascular invasion ER and/or PgR expressed HER2 gene neither overexpressed nor amplified Age ≥ 35 years	<10
Intermediate risk	Node-negative and at least one of the following features	
	pT > 2 cm Grade 2–3 Presence of extensive peritumoral vascular invasion ER and PgR absent HER2 gene overexpressed or amplified Age < 35 years OR Node-positive (1–3 involved nodes) AND ER and/or PgR expressed AND HER2 gene neither overexpressed nor amplified	10–50
High risk	Node-positive (1–3 involved nodes) AND	
	ER and PgR absent OR HER2 gene overexpressed or amplified OR Node-positive (4 or more involved nodes)	>50

Post-mastectomy radiotherapy is always recommended for patients with four or more positive axillary nodes [II, B], and indicated for patients with T3–T4 tumors independent of the nodal status [III, B]. Post-mastectomy radiotherapy may also be considered in cases of at least T1 tumor with 1–3 positive axillary lymph nodes, particularly if young, and in cases of T2 or greater medially located tumors which show signs of biological aggressiveness (receptor-negative, grade 3, HER2-positive, high proliferation activity, e.g. Ki-67).

primary (neo-adjuvant) systemic therapy

Primary systemic therapy is indicated for locally advanced breast cancer (stages IIIA–B) including inflammatory breast cancer [III, B] and for large operable tumors for reducing tumor size in order to possibly perform BCS [I, A]. Before primary systemic therapy a biopsy for histopathology and analyses of predictive factors should be performed. In addition, for these high-risk patients full clinical staging to rule out metastatic disease is necessary. It may employ chemo- or endocrine therapy based on predictive factors similar to adjuvant treatment. Trastuzumab should be considered in the treatment protocol in HER2-positive tumors. It should be followed by both surgery and radiotherapy and postoperative systemic adjuvant treatment.

adjuvant systemic therapy

Treatment is initiated providing that there is a relevant reduction of (calculated) risk of recurrence which can be reached with an acceptable level of treatment-related adverse effects. Hormone receptor and HER2 status are the most relevant predictive factors for the choice of treatment modality. Tumors with an incomplete (some expression) or high degree of expression of ER and/or PgR are considered endocrine responsive. Patients with no detectable expression of ER and PgR in their tumors are considered endocrine non-responsive. Features indicative of uncertainty of endocrine responsiveness include low levels of steroid hormone receptor immunoreactivity, lack of PgR, G3, high proliferation markers (Ki-67), HER2 overexpression and possibly uPA and PAI-1.

Patients with tumors considered endocrine responsive may receive endocrine treatment alone (Table 2), or a combination of endocrine therapy and chemotherapy. Patients with tumors of uncertain endocrine responsiveness are usually treated with a combination of endocrine therapy and chemotherapy. Patients with endocrine non-responsive tumors derive greater benefit from chemotherapy and should not receive endocrine therapy. In addition to endocrine and chemotherapy, patients with HER2 overexpression or amplification should be considered for adjuvant treatment with trastuzumab (see below). For each individual, the choice of adjuvant therapy must take into account the potential benefits, possible side-effects and patient preference. Several decision-making tools have been developed to help doctor–patient communication for adjuvant treatment decisions.

endocrine therapy

Patients with tumors considered uncertainly or highly endocrine responsive should be treated with endocrine therapy (Table 2).

In premenopausal patients tamoxifen alone (20 mg daily for 5 years) or the combination of ovarian function ablation with tamoxifen are standard therapies. Ovarian function ablation may be achieved by bilateral oophorectomy which leads to irreversible ablation of ovarian function. Gonadotropin-releasing hormone analogues (GnRHAs) generally lead to reversible ovarian suppression sufficient for therapeutic activity. GnRHAs should be given for at least 2 years, although optimal duration for this treatment has not been established [III, D]. Combining GnRHAs and aromatase inhibitors (AIs) in premenopausal patients is not indicated, as is the use of AIs alone. In premenopausal patients GnRHAs may be started concurrently with chemotherapy, leading to rapid amenorrhea.

In postmenopausal patients 5 years of tamoxifen alone is still a viable option for certain patient categories. For the use of AIs a switch from tamoxifen to an AI after 2–3 years of tamoxifen or initial use of an AI for 5 years are most commonly accepted strategies [I, A]. Initial use of an AI is the preferred option in patients at higher risk of relapse (large tumor size, node positivity, HER2-positive disease). For patients who have completed 5 years of tamoxifen the addition of an AI for a further period of 2–3 years may be recommended in cases with node-positive disease [I, A]. The total duration of optimal adjuvant endocrine treatment is between 5 and 10 years, 5 years for tamoxifen alone being standard. Sequential rather than concurrent administration of cytotoxic and endocrine therapies should be used [II, A]. It is unclear whether AIs should be started concurrently with chemotherapy (CT + ET) or sequentially after chemotherapy (CT/ET).

The long-term skeletal adverse effects associated with AIs are an issue of concern. Women treated with AIs should receive

Table 2. Choice of treatment modalities according to St Gallen Consensus 2007 (Goldhirsch A et al., 2007)

HER2 status	Highly endocrine responsive	Incompletely endocrine responsive	Endocrine non-responsive
Negative	ET[a] (consider adding CT according to risk)[b]	ET[a] (consider adding CT according to risk)[b]	CT
Positive	ET + Trastuzumab + CT	ET + Trastuzumab + CT	Trastuzumab + CT

[a]Endocrine therapy is effective for prevention and ductal carcinoma *in situ* and therefore might be considered even for very low-risk invasive breast cancer.
[b]Within the highly and incompletely endocrine-responsive categories, addition of chemotherapy may be based on degree of steroid hormone receptor expression and level of risk.
ET, endocrine therapy; CT, chemotherapy.

vitamin D and calcium supplements. There is no clear evidence for the concomitant use of bisphosphonates with AI in the adjuvant setting. However, several randomized controlled trials are ongoing with pending final results. Before commencing AI treatment, women should have BMD assessed by DEXA with a low threshold, and receive bisphosphonate if T-score is less than −2,5 SD, which equals to osteoporosis.

chemotherapy

Adjuvant chemotherapy is generally recommended for intermediate- or high-risk patients. A multiplicity of chemotherapy regimens acceptable for adjuvant treatment exist (Table 3). The use of anthracyclines for all patients and especially for patients with HER2-positive disease may be recommended. However, for some patients (elderly, cardiac contraindication, etc.) non-anthracycline-containing regimes (CMF) may still be appropriate [I, A]. The optimal duration of the treatment is not known. However, at least four cycles (12–16 weeks) should be administered, generally aiming for six to eight cycles (18–24 weeks). The use of taxanes may be limited to high-risk patients. The use of dose-dense schedules with prophylactic G-CSF is controversial, whilst high-dose therapy requiring peripheral blood stem cell support cannot be recommended at all. A shorter duration of chemotherapy (12–16 weeks) may be suitable for elderly patients, for whom the role of chemotherapy remains uncertain. Premenopausal women may benefit from 3- to 6-monthly bisphosphonate infusions during the first year to prevent bone loss associated with temporary or permanent hormonal changes during adjuvant chemotherapy [II, B].

trastuzumab

Patients with HER2 receptor IHC overexpression (3+) or *HER2* gene amplification benefit from adjuvant treatment with trastuzumab. There are no relevant data to support the use of trastuzumab as a standard treatment in women with a primary tumor <1 cm in size and with no axillary node involvement, especially in endocrine-responsive disease. Based on pharmacokinetic analyses a 3-weekly schedule (6 mg/kg) is considered equivalent to a weekly schedule (2 mg/kg). The standard duration of adjuvant trastuzumab has not yet been established but for the time being 1 year is recommended.

Trastuzumab may be started in parallel with a taxane, but it should not be given concurrently with an anthracycline. Even when given after an anthracycline-containing regimen trastuzumab may have cardiotoxic effects and cardiac function should be routinely monitored. To administer trastuzumab with endocrine therapy without chemotherapy is not supported by clinical trial evidence. It is important to avoid trastuzumab in patients with low left ventricular ejection fraction (LVEF) (<50%).

Table 3. Selected adjuvant chemotherapy regimens

Regimen	No. of cycles	Duration of cycle (weeks)
CMF	6	4
A–CMF	4–4 (–8)	3–4
CEF	6	4
CAF	6	4
AC–T	4–4	3–3
AC–T (G-CSF)	4–4	2–2
DAC	6	3
FEC–D	3–3	3–3
FEC100	6	3
A–D–CMF	3–3–3	3–3–4
DC	4	3

A, doxorubicin; C, cyclophosphamide; D, docetaxel; E, epirubicin; F, fluorouracil; G-CSF, filgrastim; M, methotrexate; T, paclitaxel.

follow-up

There is no evidence from randomized trials supporting any particular follow-up sequence or protocol. The aims of follow-up are to find early possible local recurrences or contralateral breast cancer, to evaluate possible treatment-related complications (such as menopausal symptoms and osteoporosis) and to treat them, and to provide psychological support and information in order to enhance returning to normal life after breast cancer. Whatever the follow-up protocol and the frequency of visits, every visit should include history taking, eliciting of symptoms and physical examination. Ipsilateral (after BCS) and contralateral clinical mammography is recommended yearly for premenopausal women and every 1–2 years for postmenopausal women [D]. There are no data to indicate that performing blood counts, chemistry, chest X-ray, bone scan, liver ultrasound, CT scans of chest and abdomen or any tumor markers such as CA 15-3 or CEA on asymptomatic patients produces a survival benefit [I, A].

A DEXA scan should be performed for women experiencing a premature menopause (<45 years of age), those on an AI with a baseline T score of less than –1 SD and repeated every 2 years.

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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