clinical practice guidelines

Annals of Oncology 21 (Supplement 5): v9–v14, 2010
doi:10.1093/annonc/mdq159

Primary breast cancer: ESMO Clinical Practice Guidelines 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 an ageing population. There is a steep age gradient with about one-quarter of breast cancers occurring before age 50, and <5% before age 35. In some countries the mortality rate has decreased especially in middle-aged and younger age groups because of improved treatment and possibly earlier detection. However, breast cancer is still the leading cause of cancer-related death in European women.

diagnosis

The diagnosis is based on clinical, radiological and pathological examinations. Clinical examination includes bimanual palpation of the breasts and local regional lymph nodes. Radiological examinations include bilateral mammography and ultrasound of the breasts (and regional lymph nodes depending on local expertise). MRI of the breast is not needed as a routine procedure, but may be considered in cases involving diagnostic challenges arising, e.g. because of dense breast tissue especially in young women and in cases of familial breast cancer associated with BRCA mutations, or positive axillary lymph node status with occult primary tumour in the breast, or where multiple tumour foci are suspected. 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 operation. Final pathological diagnosis should be made according to the World Health Organization (WHO) classification and the tumour–node–metastases (TNM) staging system analysing all tissue removed.

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Approved by the ESMO Guidelines Working Group: August 2003, last update February 2010. This publication supercedes the previously published version–Ann Oncol 2009; 20 (Suppl 4): iv10–iv14.

Conflict of interest: Professor Aebi has reported that in the past 2 years he has received travel support from Bristol-Myers Squibb, AstraZeneca and Amgen. He is also a member of the advisory board of Novartis, Roche, Glaxo-Smith-Kline and Bristol-Myers Squibb. His department is currently conducting research in collaboration with Wyeth, AstraZeneca, Roche and Novartis; Dr Davidson, Dr Gruber and Professor Castiglione have reported no conflicts of interest.

staging and tumour biology 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 oestradiol and follicle-stimulating hormone (FSH) 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 determination of oestrogen receptor (ER), progesterone receptor (PgR) and HER2 receptor status by IHC or FISH/CISH test [III, B]. Alternatively, these markers can be assessed on the definitive surgical specimen if primary systemic therapy is not planned.

If preoperative (neoadjuvant) systemic therapy is planned, additional investigations such as chest X-ray, abdominal ultrasound and bone scintigraphy should be considered to exclude metastatic disease. These investigations are recommended also for patients with locally advanced disease (clinically positive axillary nodes, large tumours) or clinical signs, symptoms or laboratory values indicating the presence of metastases, even if preoperative systemic treatment is not planned [III, B]. Patients with early stage (e.g. N0) breast cancer do not profit from comprehensive radiological staging [III, B].

The postoperative pathological assessment of the surgical specimen should be made according to the pTNM system to include: number, location and maximum diameter of tumours removed, the total number of removed and number of positive lymph nodes, and the extent of metastases in the lymph nodes

[isolated tumour cells, micrometastases (0.2–2 mm), macrometastases]. Sentinel node biopsy is the recommended procedure for the surgical staging of the axilla for patients with clinically node-negative (cN0) breast cancer. The report should also include histological type and grade of the tumour (using a standard grading system), evaluation of the resection margins including the location and minimum distance of the margin, vascular and lymphovascular invasion; immunohistochemical evaluation of ER and PgR using a standardized assessment methodology (e.g. Allred or H-score), proliferation markers such as Ki67 labelling index, and immunohistochemical evaluation of HER2 receptor expression. HER2 gene amplification status may be determined directly from all tumours using *in situ* hybridization (FISH or CISH), repl2acing immunohistochemistry (IHC), or only from tumours with an ambiguous (2+) IHC [II, B].

Clinical parameters have been integrated into scores that allow the probability of recurrence and death from breast cancer to be accurately estimated; examples include the Nottingham prognostic index or Adjuvant (www.adjuvantonline.com). Gene expression profiles such as Mammaprint™ or Oncotype Dx Recurrence Score may be used to gain additional prognostic and/or predictive information to complement pathology assessment and to predict response to adjuvant chemotherapy, in particular in patients with ER-positive early breast cancer [II, A].

treatment plan

Multidisciplinary treatment planning involving a breast surgeon, radiologist, pathologist, medical and radiation oncologists, 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 counselling and testing of the patient [IV, D].

surgery

Arguably the major change in the surgical treatment of primary breast cancer has been the shift towards breast conservation treatment that started over 30 years ago. Currently in western Europe about two-thirds of newly diagnosed cancers are amenable to breast conservation (wide local excision and radiotherapy) but in the remaining third, mastectomy is still recommended because of tumour size (e.g. >4cm diameter), or tumour multifocality/multicentricity, prior radiation to the chest wall or breast.

breast conservation surgery

For patients undergoing wide local excision, greater emphasis is now placed on achieving acceptable cosmesis and breast surgeons are now trained to undertake glanduloplasty to reduce the local volume deficit with adjacent tissue displacement flaps. Newer oncoplastic procedures such as therapeutic mammoplasty (breast reduction at the same time as wide local tumour excision) can achieve better cosmetic outcomes in patients with large breasts. The role of breast MRI in assessing tumour multifocality and planning surgery is currently the subject of intense debate.

Careful histological assessment of resection margins is essential, and marking the tumour bed with clips can facilitate accurate siting of the radiation boost field where appropriate. Postoperative radiotherapy is strongly recommended after breast conserving surgery [I, A]. Acceptably low local recurrence rates remain the major quality assurance target and current guidelines recommend that local recurrence rates after wide excision and radiotherapy should be <1% per year and should not exceed 10% overall.

mastectomy

European treatment guidelines recommend that breast reconstruction should be available to those women requiring mastectomy. Immediate reconstruction in some women can make the prospect of losing a breast easier to accept, but not all women will be suitable for immediate reconstruction. Many women will decline or defer reconstruction because of personal preference and for oncological reasons; particularly when post-mastectomy radiation therapy is anticipated, some women will be advised against immediate reconstruction. Endoscopic breast surgery is an emerging technique that is currently being performed in the context of clinical trials.

For women undergoing breast reconstruction, whether immediate or delayed, a wide range of surgical options is available. Silicone gel implants are safe and effective components of the reconstructive armamentarium [III, A] and the moratorium against their use in the USA is now over. Advances in gel cross-linking have reduced silicone bleed and cohesive gel implants are likely to have fewer problems from extracapsular rupture.

Myocutaneous tissue flaps using the *latissimus dorsi* muscle from the back or transverse *rectus abdominis* muscle, or the free deep inferior epigastric perforator (DIEP) flap from the lower abdomen can replace relatively large volumes of breast tissue. There is no evidence that reconstruction makes detection of local recurrence more difficult and no basis for the outdated view that patients should wait 2 years after mastectomy before being offered reconstruction.

advances in axillary staging

Regional lymph node status remains the strongest predictor of long-term prognosis in primary breast cancer. Sentinel lymph node biopsy (SLNB) rather than full nodal clearance is now accepted as the standard of care for axillary staging in early breast cancer [II, A], unless axillary node involvement is suspected clinically or on ultrasound.

SLNB delivers less morbidity in terms of shoulder stiffness and arm swelling and allows for reduced hospital stay [I, A]. Training and quality assurance in SLNB have been rolled out to breast units across Europe in the last 10 years.

The presence of macrometastatic spread in the sentinel node mandates conventional axillary lymph node clearance. The optimal management of micrometastatic spread and isolated tumour cells is the subject of ongoing research.

surgery for *in situ* malignancy (intraepithelial neoplasia)

Ductal carcinoma *in situ* (DCIS, ductal intraepithelial neoplasia) may be treated with breast-conserving surgery (BCS)

providing clean healthy tissue margins can be achieved. There is no general consensus on what is regarded as a safe (negative) margin, however, margins <2 mm are considered inadequate. Adjuvant breast irradiation after BCS decreases the risk of local recurrence but has no effect on survival [I, A]. Total mastectomy with clear margins in DCIS is curative, and radiation therapy is not recommended. Lobular neoplasia (formerly called lobular carcinoma *in situ*, LCIS), unlike DCIS, is considered a non-obligate precursor to invasive cancer and is best regarded as a risk factor for future development of invasive cancer in both breasts (RR 5.4–12). The pleomorphic variant of lobular neoplasia may behave similarly to DCIS and should be treated accordingly.

risk-reducing mastectomy

Risk-reducing surgery with prophylactic mastectomy and reconstruction may be offered to women at very high risk, such as those with previous breast cancer or carrying the BRCA1 or BRCA2 gene mutations, or where invasive carcinoma is associated with widespread LCIS or hyperplasia with atypia in the surrounding breast tissue. Risk, both for subsequent breast cancer incidence and mortality, is reduced by ∼90%–95% but prevention of developing breast cancer in the future cannot be guaranteed [III, A]; careful genetic assessment and psychological counselling is mandatory before undertaking such surgery.

The increasing sophistication and knowledge of patients facing surgery, both for breast cancer treatment and for risk reduction, mean that the range of surgical options is now discussed in great depth by breast surgeons, clinicians and nurses. Despite the overall trend towards breast conservation over the last 30 years, breast specialists both in Europe and the USA are noting increasing numbers of younger women opting for bilateral mastectomy (incorporating contralateral risk-reducing surgery) in preference to breast conservation and mammographic surveillance of the irradiated breast.

radiation therapy

invasive carcinoma

Postoperative radiotherapy is strongly recommended after BCS [I, A]. Whole breast radiotherapy reduces the risk of local recurrence by two-thirds and an additional boost gives a further 50% risk reduction. Furthermore, radiotherapy has a beneficial effect on survival. In general, boost irradiation is indicated, too, in older patients [I, A], but optional in patients with a presumed low risk of local failure (wide margins, node-negative, no vessel invasion) [III, B]. In patients >70 years of age who have endocrine-reponsive invasive breast cancer with maximum stage pT1N0 and clear margins it may be possible to omit radiation therapy without compromising survival [II, B]. Partial breast irradiation (PBI) is currently not recommended outside a clinical trial.

Post-mastectomy radiotherapy is always recommended for patients with four or more positive axillary nodes [II, B], and indicated for patients with T3–T4 tumours independent of the nodal status [III, B]. Post-mastectomy radiotherapy may also be considered in patients with one to three positive axillary lymph nodes in the presence of additional risk factors, like young age, vessel invasion and low number of examined axillary lymph nodes; the worth of post-mastectomy radiation therapy in such patients is being investigated in clinical trials. Randomized trials have used large comprehensive fields encompassing the chest wall and all regional lymph nodes, but axillary relapses after axillary dissection and relapses in the mammary internal region are rare, and irradiation of these sites is not routinely recommended unless there is suspicious residual tumour.

Supraclavicular lymph nodes should be considered for inclusion into the target volume in case of extensive involvement of axillary and supraclavicular lymph nodes ($N \geq 2$); internal mammary lymph nodes should be included in the target volume in cases of metastatic spread to this area.

Adjuvant doses used for local and/or regional irradiation are 45–50 Gy in 25–28 fractions of 1.8–2.0 Gy. The typical boost dose is 10–16 Gy in 2 Gy single doses. As an option, shorter fractionation schemes (e.g. 16 fractions with 2.66 Gy single dose) have shown similar effectiveness and comparable side-effects [I, B], but caution is needed in young patients, patients with mastectomy and/or additional regional irradiation, as these patients were either not included or under-represented in these trials.

non-invasive carcinoma (intraepithelial neoplasia)

Adjuvant whole breast irradiation after BCS of DCIS decreases the risk of local recurrence but has no effect on survival [I, A]. Randomized data about additional dose to the tumour bed (boost) are lacking, but a boost can be considered for patients at higher risk for local failure, e.g. for young patients [III, B]. PBI only should only be performed within a clinical trial. The decrease in risk of local recurrence by radiotherapy is evident in all subtypes of DCIS. However, in some patients with low-risk DCIS (tumour 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. 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 to decrease the risk of contralateral breast cancer [II, B]. Lobular neoplasia (formerly called LCIS) is a risk factor for future development of invasive cancer in both breasts; radiotherapy is not warranted.

systemic therapy

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 tumours for reducing tumour size in order to possibly perform BCS [I, A]. Before primary systemic therapy, a core needle biopsy is essential; in addition, full clinical staging to rule out gross metastatic disease. Chemotherapy should be chosen based on predictive factors similar to adjuvant treatment; primary hormonal therapy may be useful but has not been investigated in

randomized controlled clinical trials. Trastuzumab should be added to primary chemotherapy in patients with HER2-positive tumours [II, B]; the concomitant use of anthracyclines and trastuzumab should be limited to clinical trials. Primary systemic therapy should be followed by both surgery and radiation therapy according to the principles outlined above. Postoperative systemic adjuvant treatment should be used if appropriate according to the following principles.

adjuvant systemic therapy

Treatment is recommended if a relevant reduction of the estimated risk of recurrence and death can be expected with an acceptable level of treatment-related adverse effects. ER and HER2 status are the most relevant predictive factors for the choice of treatment modality. Tumours with any detectable (≥1%) expression of ER and/or PgR are considered endocrine responsive. Tumours with no detectable expression of ER and PgR are considered endocrine non-responsive. Features indicative of uncertainty of endocrine responsiveness include low levels of steroid hormone receptor immunoreactivity, lack of PgR, poor differentiation (G3), high proliferation markers (Ki-67), HER2 overexpression and gene expression scores (e.g. Oncotype Dx, Mammaprint).

Patients with tumours of different degrees of endocrine responsiveness may receive endocrine treatment alone, or a combination of chemotherapy and endocrine therapy, the choice being determined by factors outlined in Table 1. Patients with tumours of uncertain endocrine responsiveness are usually treated with a combination of endocrine therapy and chemotherapy.

Patients with endocrine non-responsive tumours benefit from chemotherapy and should not receive endocrine therapy.

In addition to endocrine and chemotherapy, patients with tumours indicative of HER2 overexpression or amplification should be considered for adjuvant treatment with trastuzumab and chemotherapy (see below). For each individual, the choice of adjuvant therapy must take into account the potential benefit, 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 tumours considered of high or uncertain responsiveness (ER ≥ 1%) should be treated with endocrine therapy.

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) 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. Tamoxifen should not be used simultaneously with chemotherapy, whereas the best use of GnRHAs (concurrent or sequential with chemotherapy) is unknown.

In postmenopausal patients AIs are preferably used upfront for 5 years [I, A]. For patients who are being treated with tamoxifen a switch to an AI after 2–3 years of tamoxifen is recommended [I, A]. In postmenopausal patients 5 years of tamoxifen alone is still a viable option for certain patients at

Table 1. Threshold for treatment modalities according to the 2009 St Gallen Consensus Conference

	Relative indications for chemoendocrine therapy	Factors not useful for decision	Relative indications for endocrine therapy alone
Clinicopathological features			
ER and PgR	Lower ER and PgR level		Higher ER and PgR level
Histological grade	3	2	1
Proliferation	High[a]	Intermediate[a]	Low[a]
Nodes	Node positive (≥4 involved nodes)	Node positive (1–3 involved nodes)	Node negative
PVI	Presence of extensive PVI		Absence of extensive PVI
pT size	>5 cm	2.1–5 cm	≤2 cm
Patient preference	Use all available treatments		Avoid chemotherapy-related side-effects
Multigene assays			
Gene signature[b]	High score	Intermediate score	Low score

(Ann Oncol 2009, with permission).

[a]Conventional measurements of proliferation include assessment of Ki67 labelling index (e.g. low, ≤15%; intermediate, 16%–30%; high, >30%) and pathological description of the frequency of mitoses. The reliability of these measurements will vary in different geographical settings. First-generation genetic signatures contain genes sampling the ER, HER2 and proliferative pathways. Meta-analysis indicates that much of the prognostic information in these signatures resides in their sampling of proliferative genes, but their respective total scores may be the only form in which information is provided at present and could be used in this component of assessment of relative indications for chemotherapy.

[b]The Panel agreed that validated multigene tests, if readily available, could assist in deciding whether to add chemotherapy in cases where its use was uncertain after consideration of conventional markers.

ER, oestrogen receptor; PgR, progesterone receptor; PVI, peritumoural vascular invasion.

very low risk of recurrence. For patients who have completed 5 years of tamoxifen the addition of an AI for a further period of 2–5 years may be recommended especially in cases with node-positive disease [I, A]. The total duration of optimal adjuvant endocrine treatment is between 5 and 10 years. Sequential rather than concurrent administration of cytotoxic and endocrine therapies should be used [II, A] although it is unclear whether AIs may be started concurrently with chemotherapy or sequentially after chemotherapy.

bisphosphonate therapy. Women treated with AIs should receive sufficient vitamin D and calcium, if necessary as nutritional supplements; further, a dual energy X-ray absorption (DEXA) scan is recommended to allow early treatment of osteoporosis. A DEXA scan should also be performed for women experiencing premature menopause (e.g. <45 years of age).

Bisphosphonates prevent bone loss in patients with iatrogenic premature menopause and in postmenopausal patients treated with AIs [I, A].

Preliminary data indicate that adjuvant therapy with zoledronic acid and possibly other bisphosphonates may lower the risks of breast cancer recurrence in premenopausal patients treated with endocrine therapy and in postmenopausal patients treated with AIs. For patients who meet these selection criteria the use of adjuvant zoledronic acid may be justified [II, B]. There are no data supporting zoledronic acid for patients with ER-negative tumours or following chemotherapy.

chemotherapy. Adjuvant chemotherapy is recommended for patients with tumours of uncertain or absent endocrine responsiveness and for patients with HER2 overexpressing or amplified tumours. A multiplicity of chemotherapy regimens acceptable for adjuvant treatment exist (common examples are listed in Table 2). At present, the use of anthracyclines may be recommended for most patients and especially for patients with HER2-positive disease. However, anthracycline-free regimens with similar or superior efficacy to anthracycline-containing comparator regimens are being developed (e.g. DC). For some patients (elderly, cardiac contraindication, etc.), CMF may still be appropriate [I, A]. Some retrospective analyses suggest that taxanes may be particularly effective in patients with ER-negative or HER2-positive early breast cancer; other trials did not replicate these findings [II, C]. 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), in particular for patients with a higher risk of recurrence (e.g. node-positive disease). The use of dose-dense schedules with prophylactic G-CSF is controversial [II, B], whilst high-dose therapy requiring bone marrow progenitor cell support cannot be recommended at all.

trastuzumab. Patients with cancers that overexpress HER2 protein ($p185^{HER2}$, measured by IHC, e.g. 3+ using HercepTest DAKO) or have HER2 gene amplification (measured by FISH or CISH) benefit from adjuvant treatment with trastuzumab [I, A]. While randomized trials have excluded patients with small primaries of <1 cm, overexpression of HER2 confers a poor prognosis, and the use of trastuzumab should be discussed with women with small, node-negative breast cancers. Based on pharmacokinetic analyses a 3-weekly schedule (6 mg/kg) is considered equivalent to a weekly schedule (2 mg/kg). The optimum 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 outside the context of a clinical trial. Even when given after an anthracycline-containing regimen trastuzumab may have cardiotoxic effects and cardiac function should be routinely monitored. It is important to avoid trastuzumab in patients with low left ventricular ejection fraction (LVEF, <50%–55%) and in patients whose cardiac function deteriorates during therapy. The use of trastuzumab with endocrine therapy without chemotherapy is not supported by clinical trial evidence.

Table 2.

Regimen	No. of cycles	Duration of cycles (weeks)
AC	4	3
CMF	6	4
FEC_{100}	6	3
CEF	6	4
A(or E)→CMF	4→4 (–8)	3→4
AP→CMF	4→4	3→4
DC	4	3
AC→P qwk	4→4	3→3
AC→D	4→4	3→3
ddAC→ddP (G-CSF)	4→4	2→2
DAC	6	3
FEC_{100}→D	3→3	3→3

A, doxorubicin; C, cyclophosphamide; D, docetaxel; E, epirubicin; F, fluorouracil; G-CSF, granulocyte colony stimulating factor, e.g. filgrastim; M, methotrexate; P, paclitaxel; qwk, weekly; dd, dose-dense; →, followed by.

follow-up and survivor care

There is no evidence from randomized trials supporting any particular follow-up sequence or protocol. The aims of follow-up are to detect early in-breast and local recurrences or contralateral breast cancer, to evaluate and treat therapy-related complications (such as menopausal symptoms and osteoporosis), 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]. In asymptomatic patients, there are no data to indicate that other laboratory or imaging tests (e.g. blood counts, routine chemistry tests, chest X-rays, bone scans, liver ultrasound exams, CT scans or any tumour markers such as CA 15-3 or CEA) produces a survival benefit [I, A].

Weight gain affect prognosis adversely and should be discouraged; if necessary, nutritional counselling is recommended. Regular long-term moderate to strenuous

physical activity is associated with a favourable prognosis; aerobic training and weight lifting does not negatively affect the development of lymphoedema.

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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