Position Paper

Guidelines on endocrine therapy of breast cancer EUSOMA

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Portait of George Beatson.
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1. Introduction

It was in 1896 in Glasgow that George Beatson published his famous paper showing that removal of the ovaries had reduced the size of a primary breast cancer. As the first description of any systemic therapy that affected any malignant tumour it was a brilliant discovery but it rates even higher, for the idea followed from the line of Beatson's research. An aspiring surgeon, in his MD thesis on the control of lactation he showed that the ovaries controlled the persistence of lactation and said, "It pointed to one organ holding the control over the secretion of another and separate organ"—suggesting endocrine action.

Removal or irradiation ablation of the ovaries were initially slow to achieve widespread acceptance. Other hormonal methods came into use, stilbestrol in the 1930s (Haddow), adrenalectomy in the 1940s (Huggins), androgenic steroids in the 1950s, hypophysectomy or ablation (Forrest) in the 1960s, tamoxifen in the 1970s, aminoglutethimide and goserelin in the 1980s, new generation aromatase inhibitors in the 1990s and total oestrogen receptor blockers may be the next.

All these were used in the treatment of advanced disease but, in the 1940s and 1950s, two trials of ovarian ablation used in early breast cancer were established: in Manchester by Ralston Patterson and in Norway by Nissen-Meyer. Cole reported from the Manchester trial that ovarian ablation prolonged the disease-free interval, but did not improve survival. However, two later UK trials of adjuvant tamoxifen gave encouraging results. It was use of meta-analysis of worldwide trials by Peto that really highlighted the role of tamoxifen in improving case survival.

At the same time, an understanding of the mechanism of action of endocrine therapy and together with that a means of predicting response, were provided by the work of Elwood Jensen in the recognition of the oestrogen receptor (ER).

During the 1960s, cytotoxic agents were being introduced. The use of combinations of these agents gave startling results in the haematological malignancies and on some solid tumours. Chemotherapy was rapidly introduced into breast cancer, giving promising response rates in advanced disease and prolongation of the disease-free interval when applied in early disease. Although the response duration was generally short cytotoxic therapy achieved predominance over endocrine therapy, especially in the Americas, and combination chemotherapy became the accepted adjuvant treatment for young women.

Nevertheless, tamoxifen became the agent of choice for adjuvant therapy in older women and in particular for ER-positive tumours. Results in new clinical trials, together with confirmation by the 1995 meta-analysis of the Early Breast Cancer Trialists Collaborative Group, show a comparable result is obtained by ovarian suppression to combination cytotoxic therapy in premenopausal women with ER-positive tumours. With increasing recognition of the importance of ER as a predictive factor, with the introduction of the newer agents and trials of the use of endocrine agents in prevention, carcinoma *in situ* and primary medical therapy, interest in hormonal therapies has been rekindled.

Whilst cytotoxic and hormonal therapies are complementary, each with specific roles, hormonal therapy has several advantages:

1. ER gives a prediction of effect, so that endocrine therapy does not have to be given against tumours that will be unresponsive. This means that cytotoxic therapies and not hormonal, are indicated in ER-negative tumours.
2. Side-effects are more tolerable, long-term fertility is not threatened, serious adverse events are less and quality of life is better. These considerations are particularly important in situations 5–7 below.
3. In advanced disease, although the response rate to endocrine therapies in an unselected population is lower than chemotherapy, response duration is longer. The best chance a woman has of being alive 5 years after the appearance of symptomatic distant disease is to have an endocrine responsive tumour.
4. Adjuvant systemic endocrine therapy is the preferred treatment in postmenopausal women with ER-positive tumours; in premenopausal women with ER-positive tumours it equals the effect of cytotoxic therapy.
5. Endocrine agents have a marked effect on diminishing the rate of contra-lateral breast cancer in the short-term and for that reason, endocrine agents are being tested as preventatives in women at high risk of developing breast cancer and have demonstrated an apparent lowering of the incidence of breast cancer in the short term, the fall being dependent upon a lower incidence of ER-positive tumours.
6. Following surgical removal of ductal carcinoma *in situ*, endocrine therapy further diminishes the rate of local recurrence (although not at present recommended as standard therapy).
7. For primary tumours diagnosed in patients unfit for surgery, in whom the side-effects of cytotoxic therapy also forbid that as an option, primary endocrine therapy can give very long periods of disease control.

It is therefore a most appropriate moment to determine how to maximise in clinical practice the benefits of endocrine therapy and that is the intention of European Society of Mastology (EUSOMA) in producing these Guidelines.

Modern Breast Cancer Units must provide a high quality of clinical care and service provision and to ensure this there must be a quality assurance system. The Outcome Measures in these Guidelines may be used for an audit programme; in general, each Outcome Measure should be met in 90% of cases. This leaves room for some exceptions, but if it cannot be met, the quality of care has to be questioned.

2. For which tumour types should endocrine therapy be restricted?

2.1. Rationale

1. Many endocrine agents have been designed to interfere with oestrogen action, an event that is critically dependent upon the presence of ER. Not surprisingly, therefore, pre-clinical studies overwhelmingly show that the major growth inhibitory effects of such agents occur specifically within ER-positive breast cancer cell lines in both *in vitro* and *in vivo* model systems. Moreover, clinical studies in advanced disease demonstrate that the benefits associated with many forms of endocrine therapy are primarily restricted to ER-positive patients, with only 5–10% of women with ER-negative disease being responsive. Similarly, in the adjuvant setting, only ER-positive patients benefited, with no significant effect in ER-poor or -negative disease [1].

2. With regard to the most appropriate lower cut-off point to define ER status for each of the assay types, values of 10 and 20 fmol/mg protein are generally recommended for the ligand binding- and enzyme immuno-assays, respectively [2]. In reporting the results of immunohistochemistry, simple scoring systems have been shown to work best [3–5]. These are based on either a direct count of the proportion of epithelial nuclei that take up the stain or a simple combination of the proportion of cells staining plus a measure of intensity of stain (H-score). Lower cut-off points to define ER status by immunohistochemistry, equivalent to approximately 10% of cells positive, have been widely used.

Upper cut-off values (higher ER values enrich for endocrine response predicting response rates of 75% or more) are generally set at ER values of > 100 fmol/mg protein for the ligand binding- and enzyme immuno-assays and 30–100% ER-positive epithelial nuclei with intense immuno-staining for the immuno-histochemical assay or an H-score of 100 out of 300.

3. Although ER status is the single best predictor of endocrine responsive and unresponsive tumours, high Progesterone Receptor (PgR) levels in an ER-negative tumour may indicate a chance of endocrine response. However, a negative PgR measurement alone is not informative, approximately 30% of ER-positive–PgR-negative tumours will respond to first-line endocrine therapy [6].

4. ER negativity is highly predictive of endocrine non-responsiveness. However, the relationship between ER-positivity and response is not perfect and even high ER-positive tumours fail to respond in approximately 25% of cases. Several other biological factors have been suggested to be associated with endocrine response, e.g. protein expression may be induced by oestrogens, such as pS2 [7,8] or correlation with endocrine failure; e.g. positive growth factor receptors epidermal growth factor (EGF)-receptor, c-erbB-2 [9–11]. None has found its way into routine clinical practice since their predictive value does not add to ER in multivariate analysis. Thus EGF-receptor and c-erbB-2-positive tumours are mainly ER-negative and pS2-positive tumours are invariably ER-positive. Additionally, well-differentiated tumours, which are also more likely to be ER-positive, are associated with increased response to endocrine therapies, as are those with low proliferative indices. These additional factors are not routinely employed to select patients for endocrine measures.

5. Any assay that is used in a clinical setting must have a good quality assurance (QA) programme associated with it. Excellent QA schemes for the ER and PgR ligand binding- and enzyme immuno-assays were set up in the 1980s in Europe [12] and are still running today. For immunohistochemical methods, the UK-based NEQAS-ICC (Scheme organisers, K. Miller and T. Rhodes, Department of Histopathology, University College London Medical School, London WC2E 6JJ, UK) has over 150 participating laboratories and is designed to provide unstained breast cancer sections of known ER content that are then assayed by the participating laboratories. Such slides are subject to review by an expert panel to ensure acceptable staining of ER [3]. EUSOMA recommends the adoption of this QA scheme in those European laboratories undertaking the routine assessment of steroid hormone receptors in breast cancer specimens.

6. In advanced disease, the primary tumour is usually the sole source of material for the assessment of the ER status. At least 80% of tumours retain their receptor status from primary to metastatic disease [13]. However, if metastatic tissue is easily available and of suitable quality, additional assay should be performed before commencing endocrine therapy [14].

Quality objective	Outcome measure
To identify those patients who are likely to benefit/fail to benefit from endocrine therapy	An ER assay must be performed in every case on the primary tumour tissue, prior to decisions regarding systemic therapy.

7. Whilst all the above assays are amenable to routine use, immunohistochemical assays allow direct correlation with routine histology to be made.

Quality objective	Outcome measure
To standardise the assessment of ER across Europe and facilitate QA	Laboratories that are newly-establishing ER assays should use an immunohistochemistry method.
To provide the best information for clinical use	1. All primary breast cancers must be assayed for ER using a ligand binding procedure, an enzyme immunoassay or an immunohistochemical assay (see above).
	2. Upper and lower cut-off points must be assigned to each of the ER assays that will allow sub-groups of patients to be identified at high and low probability of obtaining a response to endocrine therapy (see below).
	3. Additional PgR assays should be performed in order to identify those tumours, which are ER-low or negative, yet may be responsive to endocrine measures.
	4. ER and PgR assays must only be performed by laboratories working within internal and external quality assessment schemes, in which the consistency and quality of receptor measurements is assured.

2.2. Levels determining ER positivity

Within the multicentre ZEBRA trial [2], an analysis of ER data was undertaken by R. Nicholson (data not shown). The following cut-off points for ER-positivity were identified based on literature search, expert opinion and the assays of the laboratories involved in the study.

Ligand-binding assay	$\geqslant 10$ fmol/mg protein
Enzyme immunoassay	$\geqslant 20$ fmol/mg protein
Immunohistochemical	
assay, either	$\geqslant 2$ IRS
or	$\geqslant 20$ H-score
or	$\geqslant 10\%$ of cells staining positive

References

1. Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomised trials. *Lancet* 1998, **351**, 1451–1467.
2. Kaufmann M. Zoladex (goserelin) versus CMF as adjuvant therapy in pre-/perimenopausal node positive early breast cancer: preliminary efficacy results from the ZEBRA study. *Breast* 2001, **10**(Suppl. 1), S30 (abstr P53).
3. Rhodes A, Jasani B, Balaton AJ, Miller KD. Immunohistochemical demonstration of ER and PR: correlation of standards achieved on in-house tumours with that achieved on external quality assessment material in over 150 laboratories from 26 countries. *J Clin Pathol* 2000, **53**, 292–301.
4. Barnes DM, Millis RR, Beex LV, Thorpe SM, Leake RE. Increased use of immunohistochemistry for oestrogen receptor measurement in mammary carcinoma: the need for quality assurance. *Eur J Cancer* 1998, **34**, 1677–1682.
5. Leake R, Barnes D, Pinder S, *et al.* Immunohistochemical detection of steroid receptors in breast cancer: a working protocol. *J Clin Path* 2000, **53**, 634–635.
6. McGuire WL, Chamness GC, Fuqua SA. Estrogen receptor variants in clinical breast cancer. *Mol Endocrinol* 1991, **5**, 1571–1577.
7. Henry JA, Piggott NH, Mallick UK, *et al.* pNR-2/pS2 immunohistochemical staining in breast cancer: correlation with prognostic factors and endocrine response. *Br J Cancer* 1991, **63**, 615–622.

8. Schwartz LH, Koemer FC, Edgerton SM, *et al.* pS2 expression and response to hormonal therapy in patients with advanced breast cancer. *Cancer Res* 1991, **51**, 624–628.
9. Nicholson RI, McClelland RA, Gee JM, *et al.* Epidermal growth factor receptor expression in breast cancer: association with response to endocrine therapy. *Breast Cancer Res Treat* 1994, **29**, 117–125.
10. Carlomagno C, Perrone F, Gallo C, *et al.* C-erbB-2 overexpression decreases the benefit of adjuvant tamoxifen in early stage breast cancer without axillary lymph node metastases. *J Clin Oncol* 1996, **14**, 2702–2708.
11. Elledge RM, Green S, Ciocca D, *et al.* HER-2 expression and response to tamoxifen in estrogen receptor positive breast cancer: a Southwest Oncology Group study. *Clin Cancer Res* 1998, **4**, 7–12.
12. Koenders A, Thorpe SM. Standardization of steroid receptor assays in human breast cancer-II. Samples with low receptor content. *Eur J Cancer Clin Oncol* 1983, **19**, 1467–1472.
13. Robertson JF. Oestrogen receptor: a stable phenotype in breast cancer. *Br J Cancer* 1996, **73**, 5–12.
14. Kuukasjärvi T, Kononen J, Heikki H, Holli K, Jorma I. Loss of oestrogen receptor in recurrent breast cancers associated with poor response to endocrine therapy. *J Clin Oncol* 1996, **14**, 2584–2589.

3. Endocrine therapy in primary breast cancer

3.1. Selection of suitable cases for adjuvant endocrine therapy

3.1.1. Rationale

As discussed above, there is convincing evidence that the benefit in lowering the risk of disease recurrence with adjuvant endocrine therapies is related to the steroid hormone receptor content of the primary tumour. In patients whose primary tumour is classified as receptor negative the benefit with adjuvant endocrine therapy is unlikely to be clinically meaningful [1,2]. In addition, since the reduction in mortality is constant [1,2], patients with a low risk of recurrence derive little benefit from adjuvant endocrine therapy.

The potential of adjuvant endocrine therapy to prevent or delay the appearance of a contralateral primary breast cancer is not in itself sufficient as an indication for routine treatment, given that the prognosis is usually dictated by the first tumour, the risk of adverse side-effects and uncertainty as to the effect on overall survival.

Quality objective	Outcome measure
To obtain adequate information for the allocation of systemic treatment	To obtain (in addition to hormone receptor status) histopathological lymph node status, tumour size and tumour grade in all operable cases of early-stage breast cancer and to integrate these to estimate the prognosis e.g. by the Nottingham Prognostic Index (see below) or by using the St Gallen Consensus Guidelines [3].

3.2. Side-effects of hormone therapy

The most frequent side-effects associated with luteinising hormone-releasing hormone (LH-RH) agonists in pre-menopausal patients are similar to those of a natural menopause, such as hot flushes, mood changes and problems related to sexuality. LH-RH agonists may also decrease bone mineral density, although this effect appears to be reversible after cessation of treatment, and may be prevented by concomitant use of tamoxifen. Physical exercise should be encouraged since epidemiological data suggest that it may help to prevent bone demineralisation.

In postmenopausal patients, the most frequent side-effect of tamoxifen is hot flushes. Several methods have been tested to alleviate such symptoms including non-hormonal therapies such as clonidine methyl-dopa, serotonin re-uptake inhibitors, belladonna analogues and vitamin E, and complementary therapies such as phyto-oestrogens, acupuncture, bioflavonoids, herbs and physical exercise. So far, there is evidence for the use of serotonin re-uptake inhibitors [4] and vitamin E [5].

Long-term tamoxifen after the menopause prevents the natural loss of bone mineral density and decreases serum cholesterol. The effect on long-term cardiovascular mortality, however, remains controversial.

Tamoxifen has been associated with an increased risk of endometrial cancer. However, given the low absolute risk, and relatively favourable outcome of tamoxifen-associated endometrial cancers diagnosed because of clinical symptoms, routine screening for endometrial abnormalities during long-term tamoxifen therapy is not indicated.

In both pre- and postmenopausal patients, tamoxifen increases the risk of thromboembolic events, particularly when given concurrently with cytotoxic chemotherapy. It is therefore recommended that if chemotherapy is considered indicated, it be given sequentially with tamoxifen rather that concurrently.

3.3. Agents and methods to be used in different settings

3.3.1. Rationale

Adjuvant tamoxifen results in clinically significant treatment benefits and is at present established as the agent of choice for ER-positive tumours in postmenopausal patients [1]. For premenopausal women with ER-positive tumours, some form of ovarian suppression is considered the preferred therapy.

3.3.1.1. Post menopausal women. In postmenopausal women, the optimal duration of tamoxifen appears to be 5 years [1]. In postmenopausal women, there is currently insufficient evidence to support the routine use of other endocrine agents than tamoxifen in the adjuvant setting. Findings from the ATAC trial (which includes more than 9000 patients) at a median follow-up of 34 months have shown superiority for the aromatase inhibitor anastrozole over tamoxifen in terms of event-free survival, with a hazard ratio of a most encouraging 83.7% in hormone-receptor (HR)-positive women. These data must be considered preliminary at present. (Data presented at the San Antonio Breast Cancer Conference, December 2001) [6]. In addition, there is no evidence to support the use of tamoxifen in combination with other endocrine agents.

3.3.1.2. Pre menopausal women. In premenopausal patients, ovarian suppression alone (through surgery, radiation or treatment with LH-RH agonists) results in clinically significant treatment benefits [2]. Comparative studies indicate that in ER-positive tumours the outcome with LH-RH agonist treatment is comparable to that achieved with cyclophamide, methstrexate, 5-fluorouracil (CMF) [7–9].

The large (*n* = 1640) ZEBRA trial showed equivalence of 2 years goserelin treatment to CMF for ER-positive tumours [7]. Three trials—initiated by the Italian GROCTA, the French GFEA and the Austrian ABCSG—have compared combination cytotoxic therapy with combination endocrine treatments using an LH-RH agonist plus tamoxifen for ER-positive tumours. The Italian GROCTA-2 trial (*n* = 244) indicated an identical prognosis in both groups, the comparison being between goserelin plus tamoxifen and CMF [8]. Using an anthracycline-containing regimen, Roche and collaborators in France showed a 9% difference in favour of combination endocrine treatment (non-significant) [10]. Results from 1064 patients in the Austrian ABCSG-5 trial comparing CMF with combination endocrine (goserelin plus tamoxifen) treatment demonstrated a significant improvement in relapse-free survival in favour of the endocrine treatment [9].

In both the ZEBRA and ABCSG-5 trials, a major part of the effect of CMF on disease-free survival was shown to be in those patients in whom amenorrhoea was induced (65% of those treated). In the ZEBRA trial, by 3 years after therapy had commenced (i.e. 1 year after completion of endocrine therapy), hormonal side-effects were recorded in larger numbers of women who had received CMF than in those who had received endocrine therapy.

In advanced disease, a meta-analysis of four trials showed that the combination of an LH-RH agonist (goserelin in 90%, buserelin in the fourth trial) and tamoxifen produces a higher response rate and an improved overall survival compared with treatment with the LH-RH agonist alone [11]. In the adjuvant setting, the combination also appears to give a better quality of life [12] and the addition of tamoxifen may prevent the loss of bone density. There is also some evidence from the adjuvant setting showing superiority of the addition of the combination to chemotherapy over the addition of an LH-RH agonist alone [9].

The optimal duration of LH-RH agonist treatment is unknown, but at present almost all of the evidence from clinical trials (above) is based on 2 years prescription.

Methods of ovarian suppression appear equivalent in their adjuvant effects; ovarian radiotherapeutic ablation has an equivalent effect to chemotherapy in ER-positive tumours [13,14]. The use of an LH-RH agonist is the only non-invasive method; side-effects are associated with both surgery (wound complications, adhesions, deep vein thrombosis and anaesthetic problems) and radiotherapy (uncertain effect requiring follow-up with hormone levels, pelvic adhesions); only LH-RH agonist usage gives a reversible state, correcting long-term hormonal side-effects [7], reversing the fall in bone density [7] and preserving fertility.

Quality objective	Outcome measure
To offer endocrine therapy to all patients with invasive disease who have a clinically significant chance of absolute risk reduction	• All patients with ER-receptor positive invasive disease should be offered endocrine therapy, with the exception of those at low risk and an expectation of survival close to that of an age-matched population.

Quality objective	Outcome measure
To offer the best therapy taking note of menopausal status (postmenopausal status is taken as no menstruation for 6 months or an follicle stimulating hormone (FSH) of 50 units in women who have undergone a hysterectomy)	• Postmenopausal patients should be offered 5 years of adjuvant tamoxifen therapy. • Premenopausal patients should be offered treatment with an LH-RH agonist for 2 years, with or without tamoxifen for 5 years as an alternative to adjuvant cytotoxic chemotherapy. • To recommend such treatment to premenopausal women treated with chemotherapy whose menses return or who fail to achieve castrate levels of oestrogens or FSH, after completion of chemotherapy. • In patients in whom the intent is to treat with both hormonal and chemotherapy, these treatments should be used sequentially rather than in combination.

3.4. Pregnancy after diagnosis of breast cancer

Several recent studies [15,16] have shown that pregnancy after the diagnosis of breast cancer does not affect the prognosis of the underlying disease. Those patients who desire to attempt a natural pregnancy can be reassured, although it is acknowledged that the exact relationship between the endocrine and immunological effects of pregnancy and breast cancer survival is not known.

3.5. The use of hormone replacement therapy (HRT) in women during breast cancer follow-up

The theoretical risks of HRT usage by breast cancer patients are stimulation of growth of residual tumour tissue, higher risk of a second breast cancer, increased density of breast tissue to mammographical surveillance for local recurrence. However, there is no firm evidence to support these arguments.

The application of HRT when hormone therapies are being actively applied seems contradictory and is not routinely recommended. However, when women are not receiving such therapy, because they have a very good prognosis (little chance of distant spread being present) or because they have ER-negative tumours (unresponsive to hormonal influences) or because they have completed their hormonal treatment, there seems no reason to advise against HRT.

Quality objective	Outcome measure
To maintain therapy in the face of side effects	• To offer conselling to those women who experience side-effects, including information about the possible methods to alleviate these (see above and Section 6). • Post menopausal patients who discontinue tamoxifen before 5 years because of thrombosis, vaginal bleeding or endometrial hyperplasia should be offered the opportunity to switch to an aromatase inhibitor. • In premenopausal women, the main side-effects are those associated with the menopause. ○ Women at a relatively low risk should be re-advised on a cancer-risk to quality-of-life benefit basis and may prefer to stop therapy to restore quality of life. ○ Women at a higher risk who have completed two years of therapy may be told that there is no firm evidence that 2 years of therapy is suboptimal and that (in parallel with the postmenopausal situation) the gains of an extra 3 years of therapy are relatively modest. Again patients may wish to cease therapy on a quality-of-life basis.

3.6. Estimation of absolute benefit to the individual

As described above, selection for adjuvant systemic therapy depends upon the magnitude of absolute benefit to the individual: this may be calculated [17,18] by applying the reduction in mortality as demonstrated by the EBCTCG Overviews [1,2] to the prognosis of the individual.

3.6.1. Accurate estimation of prognosis

Accurate estimation of prognosis relies upon the integration of prognostic factors. This may be carried out by several methods (NPI, St Gallen). The Nottingham Prognostic Index (NPI) [19,20] is the only intra- [21] and inter-centre [22,23] prospectively validated, integrated index published to date.

| Lymph node (LN) stage (1–3) | + | Grade (1–3) | + | (Size in cm×0.2) | = | NPI |

The higher the NPI, the greater the risk of recurrence and of death from breast cancer.
The range is 2.1 (0.5 cm, Grade I, LN−ve) to 7.0 (5 cm, Grade III, more than 3LNs +ve).
Survival is now normally given in five prognostic groups (Table 1).

Table 1

NPI score	NPI group	Breast cancer-specific survival without the use of adjuvant systemic therapy (%)		
		5 years	10 years	15 years
⩽2.4	Excellent (EPG)	97	87	78
2.41–3.4	Good (GPG)	90	76	60
3.41–4.4	Moderate I (MPG I)	79	59	50
4.41–5.39	Moderate II (MPG II)	65	44	36
⩾5.4	Poor (PPG)	27	14	10

3.6.2. Extra women alive from therapy at 10 years

By applying the relative risk reductions shown in the EBCTCG overviews, the absolute reduction may be calculated for each prognostic group [18].

The risk reduction for tamoxifen in women aged 50+ with ER+ve tumours is 29% [1]. The reduction for ovarian ablation (and ovarian suppression is equivalent) is 19% [2]; by allowing for 65% being ER+ve, this raises to 29% in women with ER+ve tumours. Hormonal manipulation therefore appears to confer the same benefit in pre- as in postmenopausal women, although brought about by different agents, as is also apparent in advanced disease. Separate calculations therefore do not have to be made for tamoxifen in postmenopausal women and LH-RH agonists in pre-menopausal women, but rather a single calculation can be used for hormonal therapy at either age (see Table 2).

The calculation for the effect of hormonal therapy in women aged 50–60 years is shown in Tables 2 and 3, which follow. Because of mortality from other causes, the extra numbers surviving are enhanced by 6% for women under 45 years at receipt of therapy and are reduced by 40% for women aged 65 years at receipt of therapy.

3.6.3. Benefit by 10 years expressed as prolongation of life

The above expression of benefit assumes that a minority are 'cured' and the remainder are unaffected by treatment. An alternative expression of benefit is that of prolongation of life rather than 'cure'. By calculating the total women-

Table 2

NPI Group	Survival at 10 years (%)		
	Without therapy	With therapy	
		Extra	Overall
EPG	87	4	91
GPG	76	7	83
MPG I	59	9	68
MPG II	44	16	60
PPG	14	25	39

Table 3

NPI Group	Total w-y gained by 100 in group	Years gained per woman treated	% dead by 10 years	
EPG	20	0.20	9	
GPG	35	0.35	17	Average gain
MPG I	45	0.45	32	2 years for
MPG II	80	0.80	40	each death
PPG	120	1.25	61	

years (w-y) saved in each group by 10 years, the benefits may be expressed as prolonged survival. Over the succeeding 10 years (i.e. years 10–20 of follow-up) more women will die from breast cancer and the numbers of women benefiting from prolongation of life will further rise.

If gain is calculated taking into account quality of life [24], then on the basis of quality years gained, overall women receiving therapy in the top three NPI groups lose rather than gain quality time (time without symptoms of tumour or toxicity (TWIST).

References

1. Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomised trials. *Lancet* 1998, **351**, 1451–1467.
2. Early Breast Cancer Trialists' Collaborative Group. Ovarian ablation in early breast cancer: overview of the randomised trials. *Lancet* 1996, **348**, 1189–1196.
3. Goldhirsch A, Glick JH, Gelber RD, *et al.* Meeting highlights: International consensus panel on the treatment of primary breast cancer. *J Clin Oncol* 2001, **19**, 3817–3827.
4. Loprinzi CL, Kugler JW, Sloan JA, *et al.* Venlafaxine in management of hot flashes in survivors of breast cancer: a randomised controlled trial. *Lancet* 2000, **16**, 2059–2063.
5. Barton DL, Loprinzi CL, Quella SK, *et al.* Prospective evaluation of vitamin E for hot flashes in breast cancer survivors. *J Clin Oncol* 1998, **16**, 495–500.
6. Baum M, on behalf of the ATAC Trialists' Group. The ATAC (Arimidex, Tamoxifen, alone or in combination) adjuvant breast cancer trial in postmenopausal women. *Breast Cancer Res Treat* 2001, **69**, 210 (abstr 8).
7. Kaufmann M. Zoladex (goserelin) versus CMF as adjuvant therapy in pre-/perimenopausal node positive early breast cancer: preliminary efficacy results from the ZEBRA study. *Breast* 2001, **10**(Suppl. 1), S30 (abstr P53).
8. Boccardo P, Rubagotti A, Amaroso D, *et al.* Cyclophosphamide, methotrexate and fluorouracil versus tamoxifen plus ovarian suppression as adjuvant treatment of estrogen receptor-positive pre-/perimenopausal breast cancer patients: results from the Italian Breast Cancer Adjuvant Study Group 02 randomized trial. *J Clin Oncol* 2000, **18**, 2718–2727.
9. Jakesz R, Hausmaninger H, Samonigg H, *et al.* Comparison of adjuvant therapy with tamoxifen and goserelin vs. CMF in premenopausal stage I and II hormone-responsive breast cancer patients: four-year results of Austrian Breast Cancer Study Group (ABCSG) Trial 5. *Proc Am Soc Clin Oncol* 1999, **18**, 67a abstr 250.
10. Roche HH, Kerbrat P, Bonneterre J, *et al.* Complete hormonal blockade versus chemotherapy in premenopausal early-stage breast cancer patients with positive hormone-receptor (HR+) and 1–3 node-positive (N+) tumor: results of the FASG 06 trial. *Proc Am Soc Clin Oncol* 2000, **19**, 72a (abstr 277).
11. Klijn JGM, Blamey RW, Boccardo F, *et al.* Combined tamoxifen and luteinizing hormone-releasing hormone (LHRH) agonist versus LHRH agonist alone in premenopausal advanced breast cancer: a meta-analysis of four randomized trials. *J Clin Oncol* 2001, **19**, 343–353.
12. Nystedl M, Berglund G, Bolund C, Brandberg Y, Fornander T, Rutquist LE. Randomized trial of adjuvant tamoxifen and/or goserelin in premenopausal breast cancer—self-rated physiological effects and symptoms. *Acta Oncol* 2000, **39**, 959–968.
13. Scottish Cancer Trials Breast Group and ICRF breast unit, London. Adjuvant ovarian ablation versus CMF chemotherapy in premenopausal women with pathological stage II breast carcinoma: the Scottish trial. *Lancet* 1993, **341**, 1293–1298.
14. Eljertsen B, Dombernowsky P, Mouridsen HT, *et al.* Comparable effect of ovarian ablation and CMF chemotherapy in premenopausal hormone receptor positive breast cancer patients. *Proc ASCO* 1999, **18**, 66a (abstr. 248) [GD Lit Search full paper].
15. Gelber S, Coates AS, Goldhirsch A, *et al.* Effect of pregnancy on overall survival after the diagnosis of early-stage breast cancer. *J Clin Oncol* 2001, **19**, 1671–1675.
16. Surbone A, Petrek JA. Pregnancy after breast cancer: the relationship of pregnancy to breast cancer development and progression. *Crit Rev Oncol Hematol* 1998, **27**, 169–178.
17. Blamey RW, Morgan DAL, Mitchell M, *et al.* Tables of anticipated benefit from adjuvant therapy for the individual. *Eur J Cancer* 2001, **37**, Suppl. 5, (abstr 014).
18. Ravdin PM, Siminoff LA, Davis GJ, Mercer MB, Hewlett J, Gerson N, Parker HL. Computer program to assist in making decisions about adjuvant therapy for women with early breast cancer. *J Clin Oncol* 2001, **19**, 980–991.
19. Haybittle JL, Blamey RW, Elston CW, Johnson J, Doyle P. A prognostic index in primary breast cancer. *Br J Cancer* 1982, **45**, 361–366.
20. Blamey RW. The design and clinical use of the Nottingham Prognostic Index in breast cancer. *Breast* 1996, **5**, 156–157.
21. Todd JH, Dowle C, Williams MR, *et al.* Confirmation of a prognostic index in primary breast cancer. *Br J Cancer* 1987, **56**, 489–492.
22. Balslev I, Axelsson CK, Zedeler Z, Rasmussen BB. The Nottingham Prognostic Index applied to 9149 patients from the studies of the Danish Breast Cancer Cooperative Group (DBCG). *Breast Cancer Res Treat* 1994, **32**, 281–290.

23. D'Eredita G, Martellotta M, Natale T, Ferrarese F. Prognostic factors in breast cancer: the predictive value of the Nottingham Prognostic Index on patients with a long term follow-up and treated in a single institution. *Eur J Cancer* 2001, **37**, 591–596.

24. Cole BF, Gelber RD, Gelber S, Coates AS, Goldhirsch A. Polychemotherapy for early breast cancer: an overview of the randomized clinical trials with quality-adjusted survival analysis. *Lancet* 2001, **358**, 277–286.

4. Endocrine therapy for advanced breast cancer

4.1. Background

1. Cytotoxic and endocrine therapy are important parts of the management of most women with breast cancer. The aims of systemic treatment of metastatic disease are control of disease progression with relief of symptoms and with the least toxicity; treatment may also prolong survival.

The use of chemotherapy and endocrine therapy in the management of advanced breast cancer have recently been analysed by Stockler and co-workers [1] and whether to use chemotherapy alone or endocrine therapy as the first option for the treatment of advanced breast cancer has been analysed in a Cochrane review [2]. These analyses reviewed the results from nine identified trials. The conclusion was that in general response rates were higher for chemotherapy treated patients not selected on the basis of steroid receptors compared with those treated with endocrine therapy. However, there was a tendency for prolonged survival in favour of those treated firstly with endocrine therapies.

Many trials have revealed that in HR-positive patients, those treated with endocrine therapy have comparable response rates and longer times to progression, duration of response and survival to those patients treated with cytotoxic drugs.

The systemic therapy to be used for the treatment of advanced breast cancer must be selected on the basis of steroid receptor (HR) determination (see Section 2).

2. The anti-oestrogen tamoxifen has until recently been considered the drug of choice for first-line endocrine therapy in postmenopausal women, due to its efficacy and low toxicity. The introduction of specific aromatase inhibitors [3] has renewed interest in newer forms of endocrine therapy. Data from large randomised trials have demonstrated a slight superiority in terms of response rate and time to progression in favour of these specific aromatase inhibitors (A.I.s) compared with tamoxifen, even in patients not previously treated with adjuvant tamoxifen [4,5]. These agents are also well tolerated and do not induce thrombotic events nor endometrial bleeding.

Tamoxifen is given as 20 mg orally daily. There is no advantage to higher doses [6] or to a loading dose. Third generation aromatase inhibitors are: anastrozole 1 mg daily; letrozole 2.5 mg daily; exemestane 25 mg daily.

3. In premenopausal women (defined here as currently menstruating or with FSH levels in the premenopausal range), ovarian ablation or removal was for a long time the only therapy. LH-RH agonists provide a non-invasive alternative method [7] of ovarian suppression, which is reversible, sparing women who fail to respond the menopausal side-effects.

Goserelin is given as a 3.6 mg 4-weekly subcutaneous injection; other LH-RH agonists including leuprolide, triptorelin and buserelin are available for the treatment of breast cancer in certain countries.

4. A meta-analysis of four randomised trials [8] has demonstrated superiority for the use of combined therapy with a LH-RH agonist plus tamoxifen over a LH-RH agonist alone, in response rate and particularly in response duration and survival from the time of diagnosis of advanced disease.

Quality objective	Outcome measure
To determine the optimal first-line systemic therapy for advanced breast cancer in pre- and postmenopausal patients	• All ER-positive patients at first appearance of advanced breast cancer should receive endocrine therapy as part of the first-line systemic therapy. • Patients with dyspnoea due to metastases in the lung parenchyma may be given a course of cytotoxic chemotherapy for symptom relief prior to the application of endocrine treatment. A similar approach should be taken in the face of massive liver involvement.

Quality objective	Outcome measure
To use the optimal first-line endocrine therapy according to menopausal status	• Premenopausal women should receive a combination of LH-RH agonist plus tamoxifen. • Postmenopausal women should receive either a new generation aromatase inhibitor or a peripheral antioestrogen such as tamoxifen. • An A.I. is the mandatory choice if there is a past history of a thrombotic event. • An A.I. should be strongly considered if the patient received tamoxifen as adjuvant therapy (and vice versa).

4. An interesting aspect of advanced breast cancer is the possibility of obtaining a further response by applying another form of endocrine therapy following progression of disease on the original therapy.

Quality objective	Outcome measure
To select patients for second-line endocrine therapy for advanced breast cancer	All patients who responded complete response (CR), partial response (PR) or static disease for at least 6 months) to first-line endocrine therapy should, on relapse, be offered second-line endocrine therapy rather than cytotoxic therapy. It follows that evidence of response to the first-line treatment must be documented (see below).

5. The preference for a specific (third generation) A.I. as second-line endocrine therapy after tamoxifen has been substantiated in several trials in comparison to progestins. Both lower toxicity and a trend for higher efficacy than with the progestins favour the use of aromatase inhibitors [9–11]. Trials have demonstrated improved survival times with third-generation A.I.s over megestrol acetate [10,11].

6. Patient's perception of side-effects is, for obvious reasons, different in advanced disease than during treatment for early disease. The side-effects are usually mild and only 2–3% of the patients want to terminate because of toxicities. The management of side-effects like nausea, thromboembolic disease and gastrointestinal disturbance is symptomatic. Hot flushes can be alleviated by serotonin re-uptake inhibitors [12] and vaginal dryness treated with local oestrogens (e.g. Vagifem).

Quality objective	Outcome measure
The optimal second-line endocrine therapy according to menopausal status	The treatment of choice for premenopausal patients initially treated with combined endocrine therapy (LH-RH agonist plus tamoxifen) should be to continue ovarian suppression with an LH-RH agonist and replace tamoxifen with a specific aromatase inhibitor. Post-menopausal patients with a previous response to either tamoxifen or a specific aromatase inhibitor should be treated with the crossover therapy.

7. Third-line endocrine therapy offers response rates of 20–25% in previous endocrine therapy responders.

Quality objective	Outcome measure
To select patients for third-line endocrine therapy for advanced breast cancer	All patients with a response (objectively measured with a minimum duration of 6 months) to second-line endocrine therapy should be offered further endocrine therapy with either a progestin or a pure anti-oestrogen, in preference to cytotoxic therapy.

4.2. Possible agents for third-line therapy

Pure anti-oestrogens are: 182 780/fulvestrant (Faslodex), 250 mg administered as a monthly intramuscular injection.

Progestins are megestrol acetate, best used at 160 mg daily to avoid excessive weight gain, and medroxyprogesterone acetate given orally at 300–1000 mg/day.

An androgen such as fluoxymesterone 5 mg daily and an oestrogen in the form of diethylstilbestrol 5 mg three times daily are also used.

4.3. The assessment of response in patients receiving endocrine therapy

1.

Quality objective	Outcome measure
To ensure the correct application of systemic therapies in advanced disease	• A complete work-up (including all relevant imaging, the taking of serum tumour markers and other relevant biochemistry) (see below) must be performed at treatment start and at disease progression. • Representative metastatic lesions with which to assess response to a systemic treatment in advanced breast cancer must be identified at the start of treatment. • These must be re-assessed if there are clinically significant symptoms indicating progression. • The diagnosis of progression should be followed by a change of systemic therapy. An endocrine therapy is otherwise maintained, unless it is causing serious adverse effects. • Side-effects must be assessed regularly (see Section 6)

2.

Quality objective	Outcome measure

To ensure the best method of measuring response or progression	• In the absence of symptoms of progression, evidence of progression or response should be sought at 3 months, looking at:
	  ○ the representative lesions identified for imaging at the start of therapy.
	  ○ serum markers
	  ○ other previously abnormal blood tests (e.g. LFTs)
	• A predefined set of criteria, such as World Health Organization (WHO) or RECIST [13, 14] should be employed to evaluate response.
	• The most reliable techniques should be used to evaluate tumour measurements (RECIST guidelines)[13].
	• Ultrasound examinations of the liver may be used to assess response or progression, although less reliable than computed tomography (CT) scans or magnetic resonance imaging (MRI).

To interpret changes in tumour marker measurements	• Tumour markers alone (Ca15.3 or carcinoembryonic antigen (CEA)) or in combination (Ca15.3, CEA and ESR) should not be used in isolation to assess response or progression if the tumour is assessable by other means.

- If markers are initially above the upper normal limit, they must return to normal levels for a patient to be considered in complete clinical response when all assessable lesions have disappeared.
- In the absence of evaluable disease, increase in a tumour marker accompanied by an increase in symptoms (e.g. bone pain) should be taken as indicating disease progression.
- An increase in serum markers without symptoms of progression should prompt a complete work-up to investigate for progression of known disease sites or appearance of new sites.
- In the absence of evaluable disease, and without symptom change, significant increases in serum markers on serial consecutive measurements over several weeks or months should be regarded as progressive disease and lead to a change in therapy.

4.3.1. Assessment of bone lesions

Bone lesions are difficult to measure. Blastic lesions are generally considered non-evaluable for response. Recalcification of lytic lesions is considered a sign of response to treatment, but it is generally difficult to quantify the amount of calcification. Lesions that have been irradiated cannot be used to assess response. An additional problem is the common use of bisphosphonates in patients with lytic bone lesions; bone lesions in patients receiving bisphosphonates can be evaluated only for progression.

4.4. Concurrent therapies and change of therapy

Where lesions are assessable, a change of therapy should only be made on disease progression, which is assessed objectively or by a significant rise in serum tumour markers [15] (see above). However, where there is no assessable lesion and tumour markers lie in the normal range, treatment may occasionally have to be changed on symptomatic grounds.

Concurrent palliative therapies may be used in addition to systemic hormonal therapy, e.g. radiotherapy or bisphosphonates for bone pain, orthopaedic surgery, blood transfusions, pain relief, pleural drainage or pleurodecis, surgery for local or regional disease, control of hypercalcaemia.

References

1. Stockler M, Wilcken NR, Ghersi D, Simes RJ. Systematic reviews of chemotherapy and endocrine therapy in metastatic breast cancer. *Cancer Treat Rev* 2000, **26**, 151–168.
2. *Issue 4*. Oxford, Cochrane Library, 2000.
3. Harper-Wynne C, Dowsett M. Recent advances in the clinical application of aromatase inhibitors. *J Steroid Biochem Mol Biol* 2001, **76**, 179–186.
4. Bonneterre J, Buzdar A, Nabholtz J-MA, *et al.* Anastrozole is superior to tamoxifen as first-line therapy in hormone receptor positive advanced breast carcinoma: results of two randomized trials designed for combined analysis. *Cancer* 2001, **92**, 2247–2258.
5. Mouridsen H, Gershanovitch M, Sun Y, *et al.* Superior efficacy of letrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer: results of a Phase III study of the International Letrozole Breast Cancer Group. *J Clin Oncol* 2001, **19**, 2596–2606.
6. Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomised trials. *Lancet* 1998, **351**, 1451–1467.
7. Taylor CW, Green S, Dalton WS, *et al.* Multicenter randomized clinical trial of goserelin versus surgical ovariectomy in premenopausal patients with receptor-positive metastatic breast cancer: an Intergroup Study. *L Clin Oncol* 1998, **16**, 994–999.
8. Klijn JGM, Blamey RW, Boccardo F, *et al.* Combined tamoxifen and luteinizing hormone-releasing hormone (LHRH) agonist versus LHRH agonist alone in premenopausal advanced breast cancer: a meta-analysis of four randomized trials. *J Clin Oncol* 2001, **19**, 343–353.
9. Dombernowsky P, Smith I, Falkson G, *et al.* Letrozole, a new oral aromatase inhibitor for advanced breast cancer: double-blind randomized trial showing a dose effect and improved efficacy and tolerability compared with megestrol acetate. *J Clin Oncol* 1998, **16**, 453–461.
10. Buzdar AU, Jonat W, Howell A, *et al.* Anastrozole versus megestrol acetate in the treatment of postmenopausal women with advanced breast carcinoma. Results of a survival update based on a combined analysis of data from two mature Phase III trials. *Cancer* 1998, **83**, 1142–1152.
11. Kaufmann M, Bajetta E, Dirix LY, *et al.* Exemestane is superior to megestrol acetate after tamoxifen failure in postmenopausal women with advanced breast cancer: results of a Phase III randomized double-blind trial. *J Clin Oncol* 2000, **18**, 1399–1411.
12. Loprinzi CL, Kugler JW, Sloan JA, *et al.* Venlafaxine in management of hot flashes in survivors of breast cancer: a randomised controlled trial. *Lancet* 2000, **16**, 2059–2063.

13. Therasse P, Arbuck SG, Eisenhauer EA, *et al.* New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000, **92**, 205–216.

14. Standard Chapter and Guidelines for EORTC Protocols: implementation of the RECIST criteria for Phase II Trials. Brussels, EORTC Data Center.

15. Robertson JFR, Jaeger W, Syzmendera JJ, *et al*, on behalf of the European Group for Serum Tumour Markers in Breast Cancer. The objective measurement of remission and progression in metastatic breast cancer by use of serum tumour markers. *Eur J Cancer* 1999, **35**, 47–53.

5. Other indications for endocrine therapy

5.1. Ductal carcinoma in situ

5.1.1. Rationale

Two trials have been conducted assessing the value of adjuvant tamoxifen in reducing breast relapse after breast conservation treatment in Ductal carcinoma *in situ* (DCIS): the National Surgical Adjuvant Breast Project (NSABP) B-24 trial and the (UK DCIS) trial.

Published data are available from the B-24 trial [1,2]. In this study, 1804 patients were randomly assigned to lumpectomy plus radiation therapy (50 Gray) and placebo ($n = 902$) or lumpectomy plus radiotherapy and tamoxifen (20 mg daily for 5 years, $n = 902$). Involved margins after lumpectomy (16% in both groups) were allowed. After a median follow-up of 74 months (57–93 months), women in the tamoxifen group had significantly fewer breast cancer events (and particularly local recurrences) at 5 years compared with those in the placebo group (8.2% versus 13%, $P = 0.009$). The authors stated that the combination of a lumpectomy, radiotherapy and tamoxifen was effective in the prevention of invasive breast cancer in patients with DCIS.

No width of margin clearance on histology was required in this trial and this is likely to explain the high recurrence rate in both arms; the UK trial is likely to give a similar result for the same reason. This trial has raised a number of questions of interpretation.

1. The trial results are from a relatively short-term follow-up. In invasive carcinomas, tamoxifen-resistance develops with time and it seems likely to do so in DCIS.

2. Over 80% of patients had DCIS lesions less than 1 cm. Patients for this study appear to have been selected in contributory centres for smaller lesions, as in population-based series screen-detected DCIS are, on average, of larger size. Despite over 805 of the patients having lesions smaller than 1 cm, the incidence of invasive ipsilateral breast recurrences after 5 years was 9.3 and 6.1%, in the placebo and tamoxifen groups, respectively, which must be judged unacceptably high rates. This has been ascribed to insufficient attention to margin clearance.

3. The effect of tamoxifen is particularly seen in patients with known risk factors for breast relapse: younger age ($\leqslant 49$ years), positive margins, the presence of comedo necroses and tumours detected by clinical examination (usually larger lesions). This raises the question of the magnitude of the absolute effect of tamoxifen in patients with a low risk of relapse.

4. At a median of 4 years, the 902 patients treated with tamoxifen had 29 fewer invasive breast cancers and 17 fewer *in-situ* carcinomas, but eight extra thromboembolic events and five extra endometrial cancers [3].

5. Tamoxifen must not be relied upon to compensate for inadequate local treatment.

Quality objective	Outcome measure
In patients treated by wide local excision (WLE) and intact breast irradiation (RT), to keep local (in-breast) recurrence to an acceptable minimum	• In-breast relapse rates must be below 15% at 10 years. • Routine prescription of tamoxifen following WLE + RT is not recommended (outside of clinical trials).

Quality objective	Outcome measure
To avoid over-treatment of those at low risk of recurrence (low grade and smaller tumours with widely-clear histological margins)	Tamoxifen should not be added to WLE + RT in those patients judged to be at low risk of recurrence.

Quality objective	Outcome measure
To lower the recurrence rate where there is a high risk of local recurrence, e.g. patient desires breast conserving surgery but clear margins cannot be achieved.	• Tamoxifen may be prescribed for 5 years in patients with ER-positive tumours. • The patient must be told that the risk of recurrence is higher than that achieved by mastectomy • Explanation in terms of absolute risk-reduction over time must be given. • The patient must be told that the only information available at present on the use of hormonal therapy in DCIS relates to the reduction of risk in the short term. • The patient must be advised of the risk of serious adverse effects.

5.2. Breast cancer risk reduction

Among women who are at an increased risk of developing breast cancer there is evidence that prolonged treatment with tamoxifen may substantially reduce this risk in the short term [4]. However, there is no evidence that such treatment reduces long-term risk or that it reduces the risk of dying from the disease.

The treatment is associated with clinically significant adverse side-effects including endometrial cancer and thromboembolic disease, as well as symptoms of hormonal deprivation.

The uncertainty as to the balance between benefits and risks with tamoxifen is such that no recommendation can be made for the routine use of tamoxifen for breast cancer chemoprevention in healthy women.

There is, at present, insufficient evidence concerning the chemopreventive efficacy of other endocrine agents.

Quality objective	Outcome measure
To advise women at increased risk of contracting breast cancer on risk reduction	Endocrine measures should not be recommended outside clinical trials.

5.3. Primary medical therapy

5.3.1. Background

Primary medical therapy using chemotherapy has recently excited interest and in many units has been accepted as the standard for larger tumours. The possible advantages were thought to be increased survival and decreased mastectomy rates.

From the trials reported so far [5,6], the former does not appear to have been achieved. Although a higher proportion of cases among those, receiving preoperative cytotoxic therapy underwent breast-conserving surgery, this has only been achieved at the expense of a high rate of local recurrence.

A. Trials of treatment of primary tumours *in the elderly* ($\geqslant 70$ years) [7,8,12] with tamoxifen have shown a high response rate in ER + ve disease and a long duration of response. Although local control is, as expected, much better with surgery or surgery plus endocrine therapy, 50% of women in one study [7] escaped having to undergo surgery. Complete responses of more than 15 years were seen and 80% of women with ER-positive tumours had responses of 5 years or more [7]. Although survival was better in the groups undergoing mastectomy [8] than in those maintained on endocrine therapy without operation until progression, the advantage is small in this group of women with short natural life expectancy. Priorities may change with age so that prolongation of life is viewed by some as of less importance than quality of life and given informed choice; a significant proportion of elderly patients may elect primary endocrine therapy.

Quality objective	Outcome measure
To treat the patients with primary breast cancer who are in poor medical or psychological health	Primary medical therapy with endocrine agents should be used in patients with ER positive tumours who are unfit for or refuse even limited surgery.

Quality objective	Outcome measure
To offer the choice of non-operative therapy to elderly women with ER-positive primary breast cancer	Elderly women who are not fully generally well, with ER-positive primary tumours, must receive an explanation of both the advantages offered by surgery and of what primary medical therapy may achieve in the context of their natural life expectancy.

Quality objective	Outcome measure
To ensure early treatment of re growth of the primary tumour	Patients who opt for primary medical therapy must be closely followed by clinical and ultrasound assessment of the primary tumour and on evidence of progression advised surgery for the primary tumour.

B. Tamoxifen has been evaluated as the primary therapy for *locally advanced or large tumours* [10] and shown to give objective responses (a reduction in tumour size) or disease stasis in over 80% of ER + ve tumours, and was found to have no survival disadvantage against the initial use of irradiation. Another series [13] showed an objective response rate of 50% in patients treated with an aromatase inhibitor (letrozole).

There has recently been a return to major surgery for this situation, preceded by cytotoxic therapy to reduce tumour size. Since the latter can also be achieved using endocrine therapy, it seems reasonable to first attempt a reduction of the tumour size by-endocrine therapy in ER-positive cases. One study [11] has shown no disadvantage to primary treatment with tamoxifen, against CMF.

A study of 108 cases given primary therapy with aromatase inhibitors to reduce tumour size and then treated with breast conserving surgery showed only five local recurrences at a median follow up of 4 years [14].

Since one of the advantages of the primary medical therapy approach is to be able to determine to which agents the tumour is responsive, the use of endocrine therapy together with chemotherapy is undesirable.

Quality objective	Outcome measure
To reduce the size of large primary tumours prior to surgery	When primary medical therapy is to be applied in ER positive tumours, the use of endocrine therapy should be considered.

References

1. Fisher B, Dignam J, Wolmark N, *et al*. Tamoxifen in treatment of intraductal breast cancer: National Surgical Breast and Bowel Project B-24 randomised controlled trial. *Lancet* 1999, **353**, 1993–2000.
2. Wilcken NRC. Tamoxifen hits the target in situ (Commentary). *Lancet* 1999, **353**, 1986–1987.
3. Dignam J, Fisher B. Occurrence of stroke and tamoxifen in NSABP B-24 (Letter). *Lancet* 2000, **355**, 848.
4. Fisher B, Costantino JP, Wickerham DL, *et al*. Tamoxifen for prevention of breast cancer: report of the National Surgical Breast and Bowel Project P-1 study. *J Natl Cancer Inst* 1998, **90**, 1371–1388.
5. Fisher B, Bryant J, Wolmark N, *et al*. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. *J Clin Oncol* 1998, **16**, 2672–2685.
6. Mauriac L, MacGrogan G, Avril A, *et al*. Neoadjuvant chemotherapy for operable breast carcinoma larger than 3 cm: a unicentre randomised trial with a 124-month median follow-up. *Ann Oncol* 1999, **10**, 47–52.
7. Willsher PC, Robertson JFR, Jackson L, Al-Hilaly M, Blamey RW. Investigation of primary tamoxifen therapy for elderly patients with operable breast cancer. *Breast* 1997, **6**, 150–154.
8. Bates T, Fennessy M, Riley DR, Baum M, Houghton J, MacRae K. *Eur J Cancer* 2001, **37**(Suppl. 5) 7 (abstr).
10. Willsher PC, Robertson JFR, Armitage N, Morgan DAL, Nicholson RI, Blamey RW. Locally advanced breast cancer: long term results of a randomised trial comparing primary treatment with tamoxifen or radiotherapy. *Eur J Surg Oncol* 1996, **22**, 34–37.
11. Willsher PC, Robertson JFR, Chan SY, Jackson L, Blamey RW. Locally advanced breast cancer: randomised trial of multimodal therapy versus initial hormone therapy. *Eur J Cancer* 1997, **33**, 45–49.
12. Kenny FS, Robertson JFR, Ellis IO, Elston CW, Blamey RW. Long-term follow-up of elderly patients randomized to primary tamoxifen or wedge mastectomy as initial therapy for operable breast cancer. *Breast* 1998, **7**, 335–339.
13. Dixon JM, Love CD, Bellamy CO, Cameron DA, Leonard RC, Smith H, Miller WR. Letrozole as primary medical therapy for locally advanced and large operable breast cancer. *Breast Cancer Res Treat* 2001, **66**, 191–199.
14. Dixon JM, Renshaw L, Iqbal S, Sahni S, Miller WR. Evaluation of long-term recurrence rate following breast-conserving surgery after neoadjuvant endocrine therapy. *Eur J Cancer* 2001, **37**(Suppl. 5), 7 (abstr 018).

6. Quality of life issues in endocrine therapy

6.1. Consensus in different treatment conditions

6.1.1. Rationale
Endocrine therapy is applied in the very different preventative, adjuvant and palliative settings. Different disease characteristics are at stake in these conditions and therefore weighing the pros and cons of treatment, good decision-making and adequate supportive care are relevant for all.

6.2. Chemoprevention

In the NSABP P-1 study [1], comparing tamoxifen and placebo groups, it was found that the use of endocrine treatment did not result in excess psychological or physical distress. However, the women treated with tamoxifen experienced side-effects such as cold sweats, vaginal discharge and bleeding, night sweats, hot flushes, genital itching, lost bladder control and weight gain. In addition, sexuality was impaired: they reported a lack of sexual interest, difficulty becoming aroused and having an orgasm, as well as pain during intercourse [2].

Women at risk considering entry into a clinical trial of chemoprevention must be informed about these side-effects (in addition to the increased risk of endometrial cancer and cardiovascular disease) and understand alternative treatment options so as to reach an informed choice regarding preventive treatment [3]. If needed, supportive care should be provided.

Quality objective	Outcome measure
To provide adequate information for women prior to choice of entering a clinical trial of chemoprevention	The woman must be • informed about the 'pros and cons' of chemoprevention: 1. absolute risk reduction, 2. specific symptoms such as weight gain, hot flushes, hot/cold sweats, vaginal discharge, lost bladder control and 3. effects on sexuality.

Quality objective	Outcome measure
To achieve good decision-making	Ensure that • The woman's understanding is checked • Patient's preference is asked for and taken into account.

Quality objective	Outcome measure
To provide good supportive care	After 3 months of therapy: • the woman is asked systematically (e.g. on the basis of a checklist—see example in Appendix) about: 1. side-effects 2. (problems in) treatment adherence 3. maintenance of treatment preference 4. need for support • if needed, the woman is offered: 1. emotional support 2. sexual counselling.

6.3. Adjuvant therapy

A meta-analysis of treatment for postmenopausal breast cancer indicated that chemoendocrine treatment did not provide more quality-adjusted survival than tamoxifen alone for women of 50 years and older with node-positive breast cancer [4]. Studies investigating hormonal treatments; tamoxifen or goserelin, have shown the side-effects that are to be expected are endometrial bleeding, muscle weakness, vasomotor symptoms (such as feeling warm, sweating,

hot flashes), weight gain, vaginal dryness and loss of libido [5–7]. Patients must be informed about these effects and should consider them when choosing to undergo endocrine treatment. Effective interventions have also been reported. Ganz and colleagues found supportive care to be helpful in relieving menopausal symptoms, as well as sexual dysfunction in patients undergoing endocrine therapy [8].

Quality objectives	Outcome measure
To provide adequate information prior to therapy	The woman is informed about: 1. survival gain on the basis of her chance of absolute risk reduction (see Tables 1 and 2, Section 3) 2. hormonal symptoms like weight gain, hot flushes and other possible side-effects (see above) 3. effects on sexuality.

Quality objectives	Outcome measure
To achieve good decision-making	Ensure that: • the woman is informed about 'pros and cons' of therapy (see above) • the woman is informed about alternative treatment options • the woman's understanding is checked • the woman's preference is asked for and taken into account.

Quality objective	Outcome measure
To provide good supportive care	After 3 months on therapy: the woman is asked systematically (e.g. on the basis of a checklist: see Appendix) about: 1. side-effects 2. (problems in) treatment adherence 3. maintenance of treatment preference 4. need for support • if needed the woman is offered: 1. emotional support 2. sexual counselling.

6.4. Treatment in advanced disease

Several authors have studied the toxicity of hormonal treatment in advanced breast cancer patients. Side-effects are likely to occur. Fallowfield [6] found no difference in side-effects as experienced by patients with early and advanced disease undergoing hormonal treatment. However, the perceptions of their importance and of the need for receiving therapy are likely to differ in the two situations.

In advanced disease, responders to endocrine therapy were found to have a better quality of life, i.e. better physical well-being, mood, coping, appetite and less dizziness, than those patients not responding to treatment [9]. Responders to megestrol acetate, which has more side-effects at high doses [10], also had better quality of life (better physical well-being, mood, coping, appetite and less dizziness) than non-responders [11,12]. These studies emphasise that quality of life (Q.O.L.) in advanced disease is dictated more by the effect of therapy on the disease than by side-effects; however, the alleviation of side-effects remains a worthwhile objective.

In advanced breast cancer, physicians have often been found to be uncomfortable in discussing problems under these circumstances. Such discussion is needed, however, to provide good decision-making and supportive care. At the same time, one should realise that some patients may wish their doctor to take the decisions rather than being responsible themselves.

Quality objective	Outcome measure
To provide adequate information	• the patient's preference for information is checked • the patient is informed about:

1. prognosis
2. hormonal symptoms, e.g. weight gain, hot flushes (see above)
3. effects on sexuality
- understanding is checked.

Quality objective	Outcome measure
To achieve good-decision making	• the woman's preference for decision-making is checked • the woman is informed about 'pros and cons' of therapy (side-effects and prognosis) • the woman is informed about alternative or concurrent palliative treatment options • patient's preference is asked for and taken into consideration.

Quality objective	Outcome measure
To provide good supportive care	After 3 months on therapy • the woman is asked systematically (e.g. on the basis of a checklist) about: 1. side-effects 2. (problems with) treatment adherence 3. maintenance of treatment preference 4. need for support • if needed the woman is offered emotional support.

Appendix A. Checklist symptoms and adherence in endocrine therapy

Have you, lately, been bothered by	
- Hot flushes	no/yes; if yes, to what extent?
- Weight gain	no/yes; if yes, to what extent?
- Sweats	no/yes; if yes, to what extent?
- Menstrual changes	no/yes; if yes, to what extent?
- Fatigue	no/yes; if yes, to what extent?
- Decreased sexual interest	no/yes; if yes, to what extent?
- Mood swings/changes	no/yes; if yes, to what extent?
- Vaginal dryness	no/yes; if yes, to what extent?
- Bony pain / achy joints	no/yes; if yes, to what extent?
- Fluid retention	no/yes; if yes, to what extent?
Have you been able to take your drugs as indicated?	
	yes/no; if not, what were the obstacles?

[a]Derived from Fellowes and colleagues [9].

References

1. Fisher B, Costantino JP, Wickerham DL, *et al*. Tamoxifen for the prevention of breast cancer: a report from the NSABP. P-1 study. *J Natl Cancer Inst* 1998, **90**, 1371–1388.
2. Day R, Ganz PA, Costantino JP, Cronin WM, Wickerham DL, Fisher B. Health-related quality of life and tamoxifen in breast cancer prevention: a report from the National Surgical Adjuvant Breast and Bowel Project P-1 study. *J Clin Oncol* 1999, **17**, 2659–2669.
3. Garber J. A 40-year old woman with a strong family history of breast cancer. *JAMA* 1999, **282**, 1953–1960.
4. Gelber RD, Cole BF, Goldhirsch A, *et al*. Adjuvant chemotherapy plus tamoxifen compared with tamoxifen alone for postmenopausal breast cancer: meta-analysis of quality-adjusted survival. *Lancet* 1996, **347**, 1066–1071.
5. Nystedt M, Berglund G, Bolund C, Brandberg Y, Fornander T, Rutqvist LE. Randomized trial of adjuvant tamoxifen and/or goserelin in premenopausal breast cancer—self-rated physiological effects and symptoms. *Acta Oncol* 2000, **39**, 959–968.

6. Fallowfield LJ, Leaity SK, Howell A, Benson S, Cella D. Assessment of quality of life in women undergoing hormonal therapy for breast cancer: validation of an endocrine symptom subscale for the FACT-B. *Breast Cancer Res Treat* 1999, **55**, 189–199.

7. de Haes H, Olschewski M, Schumacher M, Kaufmann M, Jonat W. Early benefits in quality of life observed in Zoladex-treated versus CMF-treated pre/perimenopausal patients with node positive early breast cancer. *Proc ASCO* 2001, **20**, 35a (abstr 138).

8. Ganz PA, Greendale GA, Petersen L, Zibecchi L, Kahn B, Belin TR. Managing menopausal symptoms in breast cancer survivors: results of a randomized controlled trial. *J Natl Cancer Inst* 2000, **92**, 1054–1064.

9. Fellowes D, Fallowfield LJ, Saunders CM, Houghton J. Tolerability of hormone therapies for breast cancer: how informative are documented symptom profiles in medical notes for 'well-tolerated' treatments? *Br Cancer Res Treat* 2001, **66**, 73–81.

10. Kornblith AB, Hollis DR, Zuckerman E, *et al*. Effect of megestrol acetate on quality of life in a dose response trial in women with advanced breast cancer. *J Clin Oncol* 1993, **11**, 2081–2089.

11. Bernhard J, Castiglione-Gertsch M, Schmitz SF, *et al*. Quality of life in postmenopausal patients with breast cancer after failure of tamoxifen: formestane versus megestrol acetate as second line hormonal treatment. Swiss Group for Clinical Cancer Research (SAKK). *Eur J Cancer* 1999, **35**, 913–920.

12. Bernhard J, Thurlimann B, Schmitz SF, *et al*. Defining clinical benefit in postmenopausal patients with breast cancer under second line endocrine treatment: does quality of life matter? *J Clin Oncol* 1999, **17**, 1672–1679.

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