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Management of breast cancer in women

A national clinical guideline

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December 2005

KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS

LEVELS OF EVIDENCE

- 1⁺⁺ High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias
- 1⁺ Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
- 1⁻ Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
- 2⁺⁺ High quality systematic reviews of case control or cohort studies
High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
- 2⁺ Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
- 2⁻ Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
- 3 Non-analytic studies, eg case reports, case series
- 4 Expert opinion

GRADES OF RECOMMENDATION

Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

- A** At least one meta-analysis, systematic review of RCTs, or RCT rated as 1⁺⁺ and directly applicable to the target population; *or*
A body of evidence consisting principally of studies rated as 1⁺, directly applicable to the target population, and demonstrating overall consistency of results
- B** A body of evidence including studies rated as 2⁺⁺, directly applicable to the target population, and demonstrating overall consistency of results; *or*
Extrapolated evidence from studies rated as 1⁺⁺ or 1⁺
- C** A body of evidence including studies rated as 2⁺, directly applicable to the target population and demonstrating overall consistency of results; *or*
Extrapolated evidence from studies rated as 2⁺⁺
- D** Evidence level 3 or 4; *or*
Extrapolated evidence from studies rated as 2⁺

SIGN 29 Verbatim extract from SIGN 29 published in 1998. This material covers areas that were not updated in the current version of the guideline.

GOOD PRACTICE POINTS

- ☒ Recommended best practice based on the clinical experience of the guideline development group

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Scottish Intercollegiate Guidelines Network, 28 Thistle Street, Edinburgh EH2 1EN • www.sign.ac.uk

1 Introduction

1.1 THE NEED FOR A GUIDELINE

Breast cancer in women represents a significant health problem because of the numbers of individuals affected by this disease. Thirty percent of all cancers in women occur in the breast making it the most commonly diagnosed female cancer. Five year incidence in Scotland is 116 per 100,000 in women, with over 3,600 women newly diagnosed with breast cancer in 2002.¹ 80% of breast cancers occur in postmenopausal women. Despite the fact that breast cancer is one of the best-researched areas in medicine, there remain significant gaps in the published evidence to yield answers to the questions that are important to patients and health professionals.

1.2 REMIT OF THE GUIDELINE

Since the publication of Breast Cancer in Women, SIGN guideline 29, in 1998² there have been new data published to update recommendations in several areas such as psychological issues, surgery, radiotherapy techniques, and systemic treatments. This new guideline, which replaces SIGN 29, focuses attention on the evidence to support practices in the more controversial areas (see section 1.5), as it is often in these that there is the greatest variation in practice.

1.3 KEY QUESTIONS

The information in this guideline was obtained from literature searches conducted to answer “key questions” in line with current SIGN methodology.³ The key questions used in this guideline are listed in annex 1. The method of evidence searching meant that not all the topics from the last breast cancer guideline, SIGN 29, could be reviewed. Salient recommendations from SIGN 29 have been included, to provide a document that is useful to those who want guidance on a wide range of aspects of breast cancer treatment.

1.4 STATEMENT OF INTENT

This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. However, it is advised that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient’s case notes at the time the relevant decision is taken.

1.5 REVIEW AND UPDATING

This guideline was issued in 2005 and will be considered for review in three years. Any updates to the guideline in the interim period will be noted on the SIGN website: www.sign.ac.uk

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Older recommendations taken directly from SIGN 29 are clearly marked with a SIGN 29 symbol and a green font. It should be remembered that these older recommendations have not been developed with the rigour of current SIGN methodology and the evidence on which they are based may have been superseded.

2 Diagnosis, referral and investigation

2.1 INTRODUCTION

This section addresses the specific triggers which should prompt referral to a breast clinic (*section 2.2.1*); delays from diagnosis to treatment which may affect patient outcome (*section 2.2.2*) and evidence for the most effective method of diagnosing symptomatic breast cancer (*section 2.3*).

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Women aged 50–70 years are invited every three years for screening through the NHS Breast Screening Programme (NHSBSP).⁴ Women over the age of 70 years are encouraged to continue to attend every three years although they are not routinely invited. **Women should be encouraged by the primary care team to participate in the programme.**⁵

The management of individuals at an increased genetic risk of suffering from breast cancer has been addressed by the NICE guideline on familial breast cancer.⁶ Evidence relating to the increased risk of breast cancer in women treated with radiotherapy for Hodgkin's Disease is available in the SIGN guideline on long term follow up of survivors of childhood cancer.⁷

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There is evidence that breast self examination does not reduce morbidity or mortality from breast cancer.^{8,9} **However, since the majority of breast cancers are found by women themselves, self examination optimises the chances of a woman finding a change from normal.**¹⁰

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C Women should be encouraged to become aware of the feel and shape of their breasts, so that they are familiar with what is normal for them.

C Women should be encouraged to report any change from normal to their general practitioner.

2.1.1 STAFFING

SIGN 29 Radiographers

Radiographers performing mammography should have undertaken the postgraduate level course on mammography, and should attend regular courses for updates on the technique.

Radiologists

Radiologists with appropriate training,¹¹ a special interest in breast disease and an appropriate workload should be part of the multidisciplinary team.

Radiologists should be performing at least one session of breast work per week and reporting at least 500 mammograms per year and, ideally, should be involved in both screening and symptomatic services. They should also be able to perform breast ultrasound and breast intervention procedures.

Screening radiologists should read approximately 5,000 mammograms per year, participate in assessment clinics and have their work regularly audited.¹¹

2.1.2 RADIATION RISK FROM MAMMOGRAPHY

It is thought that ionising radiation increases the risk of breast cancer development after a latent period of 10 years, that the risk is cumulative, and that the risk is greatest for adolescent exposure and decreases with increasing age at exposure.¹² In those aged over 50, the risk of cancer induction is, very approximately, 1:100,000 per single view examination.¹³⁻¹⁷ The average dose per examination (single view per breast) is approximately 2 mGy, the dose being dependent on breast thickness and exposure factors used.¹⁶

2.2 DIAGNOSING BREAST CANCER

2.2.1 TRIGGERS FOR PROMPT REFERRAL TO A BREAST CLINIC

There is limited published evidence on the signs and symptoms most likely to be associated with the diagnosis of breast cancer.^{18,19}

The Scottish Cancer Group has produced guidance²⁰ on criteria for referral, based on the Guidelines for Referral of Patients with Breast Problems¹⁸ and incorporating work done by the NHS Breast Screening Programme and the Cancer Research Campaign (see *Table 1*). 4

Some women with breast symptoms can be managed initially by their general practitioner (GP), as listed in *Table 1*.

- ▣ Referral from primary to specialist care should be made in accordance with the Scottish Cancer Group referral guideline.

Table 1: Scottish Cancer Group Referral Guideline

Urgency of referral	Sign or symptom
Urgent referrals	▣ patients with a discrete lump in the appropriate age group (eg age >30) ▣ signs which are highly suggestive of cancer such as: ▣ ulceration ▣ skin nodule ▣ skin distortion ▣ nipple eczema ▣ recent nipple retraction or distortion (< 3 months)
Early referrals	▣ lump ▣ discrete lump in a younger woman (eg age < 30 years) ▣ asymmetrical nodularity that persists at review after menstruation ▣ abscess ▣ persistently refilling or recurring cyst ▣ pain ▣ intractable pain not responding to reassurance and simple measures such as wearing a well supporting bra, caffeine avoidance and common drugs ▣ nipple discharge ▣ age < 50 years with bilateral discharge sufficient to stain clothes ▣ age < 50 years with bloodstained discharge ▣ age > 50 years with any nipple discharge
Conditions that can be managed in primary care initially	▣ premenopausal women or women on HRT with tender lumpy breasts ▣ postmenopausal women with symmetrical nodularity provided in they have no localised abnormality ▣ women with minor and moderate degrees of breast pain who do not have a discrete palpable lesion ▣ women aged less than 50 years who have nipple discharge that is from more than one duct or is intermittent and is neither bloodstained nor troublesome.

2.2.2 EFFECT OF DELAYS FROM DIAGNOSIS TO TREATMENT

No evidence was identified that delays of less than three months have an effect on survival.

There is some evidence for an adverse effect of delays in referral of between three to six months. This evidence includes delays from first symptoms to treatment as well as delays from seeing a professional to treatment.²¹

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2.3 INVESTIGATION OF SYMPTOMATIC BREAST CANCER

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Methods of assessment of a breast abnormality include clinical examination, imaging and sampling the lesion with a needle for cytological/histological assessment (fine needle aspirate cytology; FNAC, or core biopsy). These three investigations collectively comprise triple assessment.

There is evidence that triple assessment provides more accurate diagnoses than a smaller number of tests.²²

2⁺⁺

B

All patients should have a full clinical examination.

B

Where a localised abnormality is present, patients should have imaging usually followed by fine needle aspirate cytology or core biopsy.

B

A lesion considered malignant following clinical examination, imaging or cytology alone should, where possible, have histopathological confirmation of malignancy before any definitive surgical procedure takes place (eg mastectomy or axillary clearance).

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There is evidence that a one-stop symptomatic breast clinic provides an accurate and effective means of establishing a correct diagnosis in women referred with breast symptoms. A one-stop, multidisciplinary clinic will usually involve breast clinicians, radiologists and cytologists.²³

3

D

Patients should be seen at a one-stop, multidisciplinary clinic involving breast clinicians, radiologists and cytology.

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Patients attending for diagnostic purposes should be seen by a clinician with special training in breast diseases (consultant surgeon, breast physician or staff grade surgeon with special training in breast diseases) or a senior trainee in breast surgery. Higher surgical trainees should only give unsupervised opinions in breast diagnostic clinics when judged competent to do so by the supervising consultant.

Breast care nurses with appropriate training are part of the clinical team. Good communication between the hospital and primary care teams is essential. The GP should be informed of the management plan after the initial visit, and at the time of discharge should be sent data based on the immediate discharge document issued by SIGN.²⁴

4

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C

Clear lines of communication should be maintained between the primary care team and staff in the breast unit.

C

The GP should be made aware of the information given to the patient and relatives.

There is some evidence that women diagnosed with breast cancer at a one-stop clinic are at greater risk of adverse psychological sequelae than women attending more than once. One study demonstrated this effect only in women with confirmed malignant disease eight weeks after diagnosis,²⁵ and a second study showed a similar delayed effect but did not present data by malignant or benign diagnosis.²⁶

1⁺

A

Psychological support should be available to women diagnosed with breast cancer at the clinic.

It is considered good practice for patients, under the management of breast physicians and their colleagues, to have their case discussed at a multidisciplinary clinico-pathological meeting

- Patients in whom the triple assessment has not excluded cancer should have their case discussed at a multidisciplinary meeting involving specialists from surgery, nursing, pathology, oncology and imaging.

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Units normally seeing at least 100 new cases of cancer per annum should be able to maintain their expertise. In areas where the density of population is low and hence the number of new cancers seen is low, formal collaborative links with adjacent larger units/centres should give patients access to all necessary facilities as well as helping to maintain expertise in the smaller unit.

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- C Centres and units should develop an integrated network of cancer care using common clinical guidelines, management protocols and strategies of care.

2.3.1 IMAGING OF SYMPTOMATIC DISEASE

Magnetic resonance imaging (MRI) has been shown to be helpful in patients with breast implants who have developed symptoms where ultrasound has not been diagnostic. Patients with suspected recurrent disease in the conserved breast may benefit from MRI if mammography, ultrasound and cytology have been unhelpful.²⁷⁻²⁹ MRI may also be helpful in women with metastatic deposits in axillary nodes where no primary cancer has been identified.³⁰⁻³³

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Table 2: Summary of investigations

Investigation	
Mammography	Must be performed as a part of triple assessment - cannot be used alone to exclude breast cancer. Mammography is not recommended under the age of 35 unless there is a strong clinical suspicion of carcinoma. ³⁴⁻³⁹
Ultrasound	May provide additional information to mammography. Can be useful for focal breast disease in women under 35 years. ⁴⁰
Magnetic Resonance Imaging (MRI)	Helpful in symptomatic patients with implants, where ultrasound results have not been diagnostic. May be helpful in women with metastatic deposits in axillary nodes where no primary cancer has been identified. ²⁷⁻²⁹

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- B In patients with symptomatic disease two-view mammography should be performed as part of triple assessment (*clinical assessment, imaging and tissue sampling*) in a designated breast clinic.

- B Mammography is not recommended in women under the age of 35 years unless there is a strong suspicion of carcinoma.

- C Magnetic resonance imaging should be considered in specific clinical situations where other imaging modalities are not reliable, or have been inconclusive, and where there are indications that MRI is useful.

2.3.2 STAGING OF BREAST CANCER

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In early operable breast cancer (T1-2, N0-1; see *annex 2*), there is no current evidence to support routine screening for metastatic disease in asymptomatic women. Patients with symptoms suggestive of metastases at a particular site do require appropriate investigation. The incidence of asymptomatic metastases increases as the T and N stage of the locoregional cancer increases. If it will affect treatment, patients with more advanced but operable disease (T3, N1-2), may require staging to exclude distant metastases.

2.3.3 PATHOLOGICAL EXAMINATION OF THE BIOPSY

The use of specimen radiographs is necessary in the pathology department to allow histological examination of the appropriate portion of the biopsy specimen and to confirm excision of the mammographic lesion.⁴¹

3 Surgery

3.1 CONSERVATION SURGERY VERSUS MASTECTOMY

There are two well established surgical procedures for local treatment of invasive breast cancer:

- conservation surgery which involves removal of the tumour with a rim of surrounding normal breast tissue with retention of the breast
- mastectomy

All cases of invasive breast cancer should have an axillary procedure (see section 3.3).

One robust evidence based guideline recommends:⁴²

- women with primary operable invasive breast cancer, who are candidates for conservation surgery should be offered the choice of breast conservation surgery or modified radical mastectomy;
- the choice is an individual one for the patient. Patients should be fully informed of the options including the risks and benefits of each procedure, that breast irradiation is part of the procedure for breast conserving surgery, and should be aware of the potential need for further surgery if the margins are positive.

4

The updated Milan conservation trial compared the efficacy of radical mastectomy with that of breast conservation surgery plus radiotherapy in 701 women (349 mastectomy, 352 conservation) over 20 years.⁴³ The results showed an increase in local recurrence in the conservation group (crude cumulative incidence of 8.8% versus 2.3% after 20 years). There was no difference in the long term survival between the two groups. At a median follow up of 20 years death from all causes was 41.7% in the conserved group versus 41.2% in the mastectomy group. Death from breast cancer was 26.1% and 24.3% respectively. The study concludes that breast-conserving surgery is the treatment of choice in women with relatively small breast cancers.

1++

A trial conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP) Group⁴⁴ compared the efficacy of mastectomy against conservation with or without radiotherapy. The trial, involving 1851 women, noted an increase in local recurrence if radiotherapy was omitted following conservation. There was no significant difference between disease-free survival, distant disease-free survival and overall survival between the three groups. Radiation therapy was associated with a slight decrease in deaths due to breast cancer. This was offset by an increase in deaths from other causes. This increase may have been the result of use of older radiotherapy techniques. The study concluded that lumpectomy and irradiation is an appropriate therapy for women with breast cancer, provided that the margins of the resected specimen are free from tumour and an acceptable cosmetic result can be obtained.

1++

The European Organisation for Research and Treatment of Cancer (EORTC) trial⁴⁵ compared modified radical mastectomy with breast conserving surgery and compared quality of life between the two groups, with 278 patients completing quality of life questionnaires at two years. The conservation group showed a significant benefit in body image and satisfaction. There was no significant difference with respect to fear of recurrence.

1++

Several randomised controlled trials (RCTs) have compared the addition/omission of radiotherapy following conservation surgery. The Milan group concluded that radiotherapy is necessary in all women up to the age of 55, optional in women aged 55-65 with negative nodes and may be avoided in women over 65 years.⁴⁶ The findings relate to quadrantectomy where the risks of local recurrence are lower, reflecting the much larger margin of normal tissue resected. Most UK surgeons perform much more conservative surgery with narrower margins. Another study advised that radiotherapy is necessary in all cases, even when there are favourable prognostic features.⁴⁷ An update of the NSABP B-06 trial concluded that no clinical or pathological features allow for the omission of radiotherapy following conservation surgery.⁴⁸

1+

Breast conserving surgery requires the complete excision of the tumour with clear margins and an acceptable cosmetic result following excision and radiotherapy.

- A** All women with early stage invasive breast cancer who are candidates for breast conserving surgery should be offered the choice of breast conserving surgery (*excision of tumour with clear margins*) or modified radical mastectomy.
- A** The choice of surgery must be tailored to the individual patient, who should be fully informed of the options and who should be aware that breast irradiation is required following conservation and that further surgery may be required if the margins are positive.
- C** Breast conserving surgery is contraindicated if:
- the ratio of the size of the tumour to the size of the breast would not result in acceptable cosmesis
 - there is multifocal disease or extensive malignant microcalcification on mammogram
 - there is a contraindication to local radiotherapy (*eg previous radiotherapy at this site, connective tissue disease, severe heart and lung disease, pregnancy*).
- C** Central situation of the tumour is not a contraindication to conservation, although it may require excision of the nipple and areola, which may compromise cosmesis.

3.2 BREAST RECONSTRUCTION AFTER MASTECTOMY

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Breast reconstruction does not appear to be associated with an increase in the rate of local cancer recurrence, nor to impede the ability to detect recurrence if it develops⁴⁹ and can yield psychological benefit.⁵⁰

Breast reconstruction may be performed either at the time of mastectomy or as a delayed procedure. Immediate reconstruction has been reported to produce better cosmetic results.⁵¹ The psychosocial effects of breast reconstruction, and the relative merits of immediate and delayed surgery, have not been adequately studied.

The choice of operation for an individual patient depends on several factors including breast size, the adequacy of skin flaps and whether radiotherapy is planned or has been previously used. Surgery to the opposite breast may be required to achieve symmetry. Techniques for reconstruction of the nipple/areola complex have been described.^{49,52,53} Alternatively acceptable nipple prostheses may be made by taking a mould from the existing nipple.⁵³

Silicone implants are currently licensed in the United Kingdom for breast reconstruction. Despite some adverse publicity there is no evidence that silicone prostheses are associated with significant systemic problems.⁵⁴

The surgeon performing the reconstruction should be fully trained in all the appropriate techniques and in most units, will be a plastic surgeon. Patients who are being prepared for a mastectomy should be informed of the option of reconstruction and, if appropriate, should discuss the options with a surgeon trained in reconstructive techniques, prior to their surgery.

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- C** The possibility of breast reconstruction should be discussed with all patients prior to mastectomy.

3.3 SURGICAL MANAGEMENT OF THE AXILLA

Spread of metastatic disease to axillary nodes is the most significant prognostic indicator and is used as one of the major determinants of appropriate systemic adjuvant therapy.^{55,56} Axillary surgery is necessary for adequate staging and treatment of invasive breast carcinoma. Axillary clearance also serves to treat metastatic disease by surgically removing it from the involved axilla.

2+

There is some morbidity associated with surgery which is well documented by trials and guidelines. One Scottish study showed no difference in the axillary recurrence rate between a level 3 clearance and a four node lower axillary node sample with a selective policy of axillary irradiation in node positive patients. There was some increased morbidity associated with clearance.⁵⁷

1++

A Axillary surgery should be performed in all patients with invasive breast cancer.

There is no consensus regarding the best way to manage the axilla in patients with invasive breast cancer. Table 3 describes the procedures in current practice.

An RCT comparing 232 patients undergoing axillary node clearance with 234 patients who received axillary sample plus radiotherapy for node positive, at a median follow up of 4.1 years, found that there was no significant difference in local or distant recurrence (14 versus 15 patients and 8 versus 7 patients). There was no reported difference in five year survival rates (82.1% vs 88.6%; $p = 0.20$) or in disease-free survival (79.1% versus 76%; $p = 0.68$). Axillary clearance was associated with significant lymphoedema of the upper limb when compared to axillary sample. Sampling with radiotherapy was associated with a significant reduction in range of shoulder movement at three years.⁵⁷ Axillary surgery may reduce the risk of axillary recurrence.⁵⁸

1++

No published RCTs were identified comparing sentinel node biopsy with formal axillary dissection. The former procedure has been associated with technical difficulties and a significant learning curve. It is associated with a false negative rate of 5-7% in experienced hands.⁴² At present it is not possible to recommend sentinel node biopsy, unless undertaken as part of a randomised controlled trial or following an evaluated training programme. Any such trials must consider the clinical significance of micrometastatic disease.

4

□ Sentinel node biopsy is only recommended as part of a randomised controlled trial or following an evaluated training programme.

Table 3: Surgical management of the axilla

Procedure	
Axillary node sample	picks out a minimum of four individual lymph nodes from the axillary fat. Suitable for staging only.
Axillary node clearance	block dissection of the axillary contents □ level 1 - up to the lateral border of pectoralis minor □ level 2 - up to the medial border of pectoralis minor □ level 3 - up to the apex of the axilla
Sentinel node biopsy	selective removal of the first draining nodes

3.3.1 SUMMARY OF EXISTING SURGICAL GUIDELINES

Several guidelines and RCTs have considered the relative merits of the different surgical approaches to the axilla.

The Cancer Care Ontario guideline recommends axillary dissection (level 1 and 2 with pathological examination) as the standard of care in women with stage 1 and 2 breast cancer.⁴² The guideline reports that there is insufficient evidence to support sentinel node biopsy alone, but encourages the participation of patients in relevant clinical trials, as the procedure appears to be promising. The guideline bases its conclusions on the results of six RCTs summarised in a single meta-analyses.

4

The National Health and Medical Research Council clinical practice guideline on the management of early breast cancer recommends that management of the axilla should be decided following multidisciplinary team discussion involving the patient, but that a minimum of level 1/2 axillary node dissection should be offered as the standard procedure.⁵⁹

4

Further guidance is also offered:⁵⁹

- ▣ Treatment of the axilla by either dissection or irradiation will reduce rates of axillary recurrence. In practice, most women will be offered axillary dissection as the first choice since this will also provide information to assist in staging and in contributing to decisions about systemic and locoregional adjuvant treatment. Axillary irradiation will be the preferred treatment method in some patients
- ▣ For some women, irradiation rather than dissection will be the preferred method of axillary control. This includes selected women in whom the result of axillary dissection would be unlikely to influence the decisions about systemic adjuvant therapy. Other women may not wish to have further surgery, and any decision should involve consultation with appropriate members of the multidisciplinary team
- ▣ Some women at high risk of axillary recurrence will require both axillary dissection and axillary irradiation. In particular, this will include those women who have remaining axillary disease following dissection
- ▣ There should be national coordination of trials of sentinel node biopsy.

4

3.4 MANAGEMENT OF DUCTAL CARCINOMA IN SITU

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Ductal carcinoma in situ (DCIS) covers a heterogeneous group of lesions and is classified by histological type, grade, and the presence of necrosis.⁶⁰

3.4.1 CHOICE OF MASTECTOMY OR BREAST CONSERVING SURGERY

Patients with ductal carcinoma in situ may be surgically managed by either mastectomy or breast conserving lumpectomy. No randomised studies which were designed to directly compare the outcomes of these forms of surgery were identified. Patients with DCIS in the NSABP B-06 trial of breast conserving surgery in patients with early stage invasive breast cancer were allocated to the three treatment arms: total mastectomy, lumpectomy only, and lumpectomy with postoperative radiation. A subgroup analysis of the trial showed the rate of ipsilateral breast cancer recurrence was 43% (9/21) in the lumpectomy only group, and 7% (2/27) in the lumpectomy and radiation group ($p = 0.01$); there were no local failures in the mastectomy group (0/28).⁶¹

2⁺

One meta-analysis of cohort studies of patients with DCIS who were treated by mastectomy or breast conserving surgery also included the above NSABP B-06 trial.⁶² The reported rates of local recurrence at five years were higher for patients treated by breast conserving surgery, with or without radiation, (21.5%; 95% confidence interval [CI], 14.0% to 30.7%) versus those treated by mastectomy (4.6%; 95% CI, 2.3% to 7.6%). In studies reporting on patients treated by breast conserving surgery plus radiation, the risk of local recurrence did not appear to be increased compared with mastectomy (10.6%; 95% CI, 5.6% to 16.9% for breast conserving surgery plus radiation versus 7.3%; 95% CI, 2.7% to 14.1% for mastectomy). Mortality rates at five years were similar for patients treated by breast conserving surgery or mastectomy (4.2%; 95% CI, 1.4% to 8.5% and 3.9%; 95% CI, 1.7% to 6.8%, respectively). The interpretation of this data is limited to a large extent by cross study comparisons, lack of randomisation, lack of comparison groups in some studies and potential cohort effect.

2⁺⁺

B

Women with ductal carcinoma in situ who are candidates for breast surgery should be offered the choice of lumpectomy or mastectomy.

3.4.2 IRRADIATION FOLLOWING BREAST CONSERVING SURGERY

Three large randomised trials, detected a significant benefit for ipsilateral breast irradiation following breast conserving surgery (BCS) in reducing the risk of invasive and non-invasive breast recurrence in the ipsilateral breast. The trials reported an increased risk of developing contralateral breast cancer in those who received radiotherapy. If this was due to radiotherapy, then the new primary cancers would be expected to be predominantly located medially, which is not the case.

In the NSABP B-17 trial, 818 women with DCIS treated by lumpectomy with clear resection margins were randomised to one of two arms: breast irradiation (5,000 cGy in 25 fractions over five weeks) or observation only.⁶³ At a follow up of 12 years, there was a significant reduction in ipsilateral breast tumour recurrence with radiation (16.4% versus 7%, $p < 0.001$). There was a significant reduction in the five-year rate of non-invasive local recurrence from 14.1% to 7.8% ($p = 0.001$). No significant difference was observed in overall survival (87% in the surgery with radiotherapy group versus 86% in the surgery alone group, $p = 0.80$). Contralateral breast cancers occurred in 4.5% of patients in the lumpectomy alone group and in 7.3% of patients in the lumpectomy plus radiotherapy group at 12 year follow-up (not significant; NS).

1++

The EORTC 10853 trial explored the role of radiotherapy in BCS for patients with DCIS.⁶⁴ Women with DCIS measuring less than or equal to 5 cm were treated by local excision and were randomised to no further treatment ($n = 503$), or to radiotherapy ($n = 507$) on an intention-to-treat basis. The four year local relapse-free rate for patients receiving no further treatment was 84% as compared to 91% of patients in the radiotherapy group (log rank $p = 0.005$; hazard ratio = 0.62). The radiotherapy group, relative to the no further treatment group, had a reduced risk of invasive recurrence from 8% to 4% (hazard ratio = 0.60, CI 0.37 to 0.97) and non-invasive recurrence from 8% to 5% (hazard ratio 0.65, CI 0.41 to 1.03). There were no significant differences in distant metastasis, death, or event free survival.

1++

The UK DCIS trial compared the efficacy of wide local excision alone, with excision followed by radiotherapy, or excision followed by tamoxifen, for five years, or both, in reducing the incidence of ipsilateral recurrent DCIS or invasive breast cancer.⁶⁵ The trial supports the finding that radiotherapy does reduce recurrent DCIS and invasive disease.^{63,64}

1+

One guideline addresses the toxicity of radiation specifically for invasive disease, but given similar technical issues it is reasonable to predict acute and chronic toxicity in non-invasive disease comparable to radiation treatment for invasive disease.⁶⁶ While the risk of tumours developing in the opposite breast is greater in patients who receive radiotherapy, it must be weighed against the greater benefit of a lower risk of recurrence in the ipsilateral breast for those patients who receive radiotherapy. Radiotherapy for breast cancer contributes little to the already high risk of a second cancer in the opposite breast.

4

A Women who have undergone breast conserving surgery should be offered postoperative breast irradiation.

No trials were identified that randomised patients at low risk of local recurrence to observation versus adjuvant radiation to determine if any patients may be treated without adjuvant radiation therapy. One retrospective analysis reported the pathological results for 439 women with DCIS, 213 who received radiotherapy after BCS and 256 who received no further treatment. For patients with margins > 10 mm, there was no benefit to radiation therapy in terms of rates of recurrence at eight years (relative risk; 1.14; CI 0.10 to 12.64, $p = 0.92$). For patients with margins ranging from 1 to < 10 mm there was no reported benefit from radiotherapy (RR, 1.49; CI, 0.76 to 2.90, $p = 0.24$); however, radiation therapy had significant benefit to patients with margins < 1 mm (RR, 2.54; CI, 1.25 to 5.18, $p = 0.01$).⁶⁷

2+

Patients with small (< 2.5 cm), well-differentiated tumours with histologically assessed clear margins (> 10 mm) may have a sufficiently low risk of recurrence to forgo breast irradiation. Further trials are required in this area to establish the benefit.

3.4.3 THE ROLE OF TAMOXIFEN IN DCIS

One randomised trial has reported that the use of tamoxifen in women with DCIS is associated with a lower disease recurrence, particularly in women less than 50 years or with receptor positive disease.⁶⁸ On this basis, it has been recommended that women should be informed of the option of five years of tamoxifen therapy and of the harms and benefits associated with tamoxifen use, but that the absolute benefit is small.⁶⁹ Tamoxifen is not licensed for the treatment of DCIS outwith a trial setting. 1+
4

The UK DCIS trial does not show advantage in preventing recurrence of DCIS or development of invasive cancer. The use of tamoxifen should only be considered in the context of a clinical trial, even in oestrogen receptor positive patients.⁶⁵ 1+

□ The benefits and harms of hormonal therapy should be discussed with women with ductal carcinoma in situ and treatment decisions made based on individual circumstances.

4 Radiotherapy

4.1 INTRODUCTION

Adjuvant radiotherapy continues to have an important role in the management of breast cancer. More patients are treated now with postmastectomy radiotherapy (PMRT) than was the case 10 years ago.⁷⁰ The scheduling of radiotherapy is an important issue and is addressed in this section.

4.2 ADJUVANT RADIOTHERAPY

The addition of radiotherapy to surgery and adjuvant systemic treatment reduces the risk of any recurrence of breast cancer by 30%, mainly as a result of an increase in locoregional control.⁷¹ A large meta-analysis estimates that the risk of locoregional recurrence is reduced by two thirds following adjuvant radiotherapy.⁷² The effect was seen to be largely independent of the type of patient or type of radiotherapy (8.8% vs 27.2% local recurrence by year 10). As a result of improved local control breast cancer mortality was reduced ($p=0.0001$) but other, particularly vascular, mortality was increased ($p=0.0003$), and overall 20-year survival was 37.1% in patients receiving radiotherapy versus 35.9% in patients in the control arm ($p=0.06$).

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4.2.1 RADIOTHERAPY FOLLOWING MASTECTOMY

The effect of PMRT on mortality is variable. A systematic review (involving 34 RCTs) comparing mastectomy with mastectomy followed by radiotherapy to the chest wall found that radiotherapy did not reduce all-cause mortality or breast cancer mortality after mastectomy alone or mastectomy plus axillary clearance. Radiotherapy did reduce all cause mortality and breast cancer mortality after mastectomy plus axillary sampling.⁷³ In the review, radiotherapy may have been associated with late adverse effects, which are rare, including pneumonitis, pericarditis, arm oedema, brachial plexopathy, and radionecrotic rib fracture, mainly due to outdated radiotherapy techniques which are no longer in use.

This study examined approximately 20,000 women entered into randomised trials of adjuvant radiotherapy before 1990. The radiotherapy techniques and doses used in the studies are less advanced than those of the present day. In addition, the patient population is different from those presenting currently, with an under-representation of patients with screen-detected tumours and of those who received tamoxifen for five years. For example, most of the studies included in this review were of trials of irradiation of chest, axilla, supraclavicular fossa, and internal mammary node chain – a minority (7%) of patients received radiotherapy to the breast only. This may explain the moderate, but significant, increase in non-cancer related deaths, such as vascular deaths. Excess vascular deaths are also evident from two years after radiotherapy, but are particularly significant if more than 10 years have elapsed after adjuvant radiotherapy. Current, and perhaps conservative, estimates are that if long term treatment-related side effects are avoided, then adjuvant radiotherapy may offer a 1% improvement in mortality rate for low risk women (eg those with small screen-detected cancers or with no evidence of nodal involvement after mastectomy with axillary clearance) and 2-4% improvement in those at high risk.⁷³

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4.2.2 RADIOTHERAPY FOLLOWING BREAST CONSERVING SURGERY

One systematic review⁷³ and a subsequent RCT⁷⁴ found that adding radiotherapy to breast conserving surgery reduced the risk of local recurrence compared with breast conserving surgery alone. The review found that postoperative radiotherapy significantly reduced the annual risk of breast cancer mortality compared with no radiotherapy, but found no significant difference between treatments in the annual risk of all cause mortality (odds ratio (OR) for breast cancer mortality 0.86; $p=0.04$; OR for all cause mortality 0.94; $p>0.1$). The review found that postoperative radiotherapy significantly decreased the annual risk of isolated local recurrence compared with no postoperative radiotherapy (OR 0.32; $p<0.00001$). It also indicated that radiotherapy increased the annual rate of non-breast cancer deaths compared with no radiotherapy, this increase was of borderline significance (OR 1.34; $p=0.05$).

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A subsequent RCT involving 1187 women with stage I–II invasive node negative breast cancer found no significant difference in overall survival between adjuvant radiotherapy and no adjuvant radiotherapy, but found that adjuvant radiotherapy significantly reduced ipsilateral breast recurrence compared with no adjuvant radiotherapy at five years (overall survival at five years: (RR) 1.16, 95% (CI) 0.81 to 1.65; ipsilateral breast recurrence at five years: absolute risk 14% without radiotherapy v 4% with radiotherapy; RR 3.33, 95% CI 2.13 to 5.19).⁷⁴

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One systematic review⁷⁵ and one additional RCT⁷⁶ were identified which compared radiotherapy after breast conserving surgery versus simple or modified radical mastectomy in women with invasive breast cancer. The review found no significant difference in annual risk of death over 10 years (OR 1.02; $p = 0.7$), or annual risk of any recurrence or local recurrence (overall OR for any recurrence: mastectomy vs breast conservation plus radiotherapy 0.96, 95% CI 0.88 to 1.04; absolute risk; AR for local recurrence: 6.2% with radiotherapy after breast conserving surgery vs 5.9% with radical mastectomy; not significant).

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Radiotherapy should be given following mastectomy or breast conserving surgery to reduce local recurrence where the benefit to the individual is likely to outweigh risks of radiation related morbidity.

4.3 SELECTING THE APPROPRIATE SITE

4.3.1 CHEST WALL AND SUPRACLAVICULAR FOSSA RADIO THERAPY

The question of whether adjuvant radiotherapy should be given to the chest wall and supraclavicular fossa has been addressed in another guideline.⁷⁷ Fewer data are available which discuss the benefit of PMRT in subgroups of patients with specific numbers of positive axillary nodes. Supraclavicular nodal failures are more common in unirradiated patients with four or more positive axillary nodes.

In one series, supraclavicular nodal failure appeared in 17% of unirradiated or inadequately irradiated patients (17 of 102), compared with 2% of 56 irradiated patients.⁷⁸ In another series, the risk of supraclavicular failure was 13% (six of 46) among unirradiated patients with four or more positive nodes, compared with 4% (two of 52) for those irradiated.⁷⁹

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An RCT showed improvements in risk of loco-regional failure (LRF) in irradiated patients in the subgroups with either one to three or four or more positive nodes.⁸⁰ The difference in crude LRF rates for patients with one to three positive nodes was of borderline significance between the arms (20% in the control arm and 8% in the irradiated arm, $p = 0.066$), while the difference between the arms for patients with four or more positive nodes remained highly significant (LRF rates of 51% and 17% in the two arms, respectively, $p = 0.004$).

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In another trial, patients with one to three positive nodes and those with four or more positive nodes had statistically significant improvements in disease-free survival when given PMRT in addition to chemotherapy, but only patients with four or more involved nodes derived a significant advantage in cancer-specific survival from the addition of PMRT.⁸¹

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The supraclavicular field should be irradiated in all patients with four or more positive axillary nodes.

4.3.2 AXILLARY RADIOOTHERAPY

The American Society of Clinical Oncology recommends that after adequate surgery by a complete or level I/II axillary dissection, routine adjuvant axillary radiotherapy is not necessary and may add to morbidity.⁷⁷

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4.3.3 INTERNAL MAMMARY NODE CHAIN RADIOOTHERAPY

There are studies that address whether radiotherapy to the internal mammary node chain (IMC) is of benefit. The evidence for IMC is conflicting.

Two trials showed no improvement in survival in patients who underwent internal mammary node dissection in addition to standard radical mastectomy.^{82,83}

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A trial of 150 patients with internal mammary node involvement randomised individuals to either radical resection of the internal mammary supraclavicular chain, irradiation of the supraclavicular and internal mammary nodes, or no further surgery or deliberate irradiation of these areas. The five-year disease-free survival rates were similar in the three arms (57%, 53%, and 51%, respectively), although the risk of supraclavicular and/or internal mammary recurrence was lowest in the irradiated group (12%, 0%, and 16%, respectively).⁸⁴

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One overview of case series and randomised controlled trials showed no benefit of IMC radiotherapy.⁸⁵ Studies reviewed included patient data from 1938 onwards, raising the possibility that the side effects of antiquated treatments may have influenced the results against IMC irradiation. There is no evidence that IMC irradiation should be performed routinely in any patient group.^{77,85} The number of screen-detected cancers is increasing and, together with the fact that fewer patients present with locally advanced cancers, should result in a reduction in IMC involvement.

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4.4 SCHEDULING OF RADIOOTHERAPY

The optimal timing of adjuvant radiotherapy following surgery has not been established in a randomised trial. In one large RCT, 244 patients were randomised to receive either chemotherapy first or radiotherapy first following conservative breast surgery. There were no significant differences between the chemotherapy first and radiotherapy first arms in time to any event, distant metastasis, or death. The study concludes that there is no advantage to giving radiotherapy before adjuvant chemotherapy. However, this study does not have enough statistical power to rule out a clinically important survival benefit for either sequence.⁸⁶ It is usual for trial eligibility criteria that radiotherapy is commenced within at least 12 weeks of surgery unless receiving adjuvant chemotherapy.⁸⁷ Evidence for this is described in a guideline which included patients who had breast-conserving surgery, but it is not unreasonable to extrapolate this also to patients who have undergone mastectomy. Access to radiotherapy within four weeks is a current political target,⁸⁸ and a minimum of 95% of patients receiving radiotherapy to the breast after conservation for invasive cancer is a desirable criterion within four weeks of final operation/chemotherapy dose.⁸⁹ There is insufficient evidence to recommend the ideal sequencing of PMRT and systemic therapy.

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4.5 DOSE FRACTIONATION

A systematic review suggests that local recurrence may be higher below certain biologically effective doses.⁹⁰ Current evidence is not able to identify an optimal dose/fractionation for postoperative radiotherapy.^{87,91} It is therefore reasonable to treat patients with currently accepted regimens such as 50Gy in 25 daily fractions over 5 weeks, 45Gy in 20 fractions, or 40 Gy in 15 or 16 fractions. Results of ongoing trials investigating fractionation are awaited.

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5 Systemic therapy

5.1 ADJUVANT CHEMOTHERAPY

The ability of postoperative adjuvant chemotherapy to reduce the risk of recurrence and death from breast cancer has been established by a series of meta-analyses of many clinical trials.⁹² The concept of adjuvant chemotherapy is a difficult one for many patients. It is often hard to convey the reasons for giving a toxic treatment that only cures a minority of those who receive it, whereas the proportion having some benefit will depend on the overall risk of recurrence. Helping patients make correct choices about treatment is important, as chemotherapy usually impairs the patient's short term quality of life.

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There is no clear consensus on how individual chemotherapy drugs should be sequenced. Drugs are often combined, and there is limited evidence that block sequential administration may be better,⁹³ and if given with granulocyte-colony stimulating factor (G-CSF) support, more "dose-dense" regimens can be given which may improve disease-free survival.^{94,95} G-CSF is available in a pegylated (slow-release depot) preparation, given only once per chemotherapy cycle, which may be as effective as the standard preparation, and may be better at preventing neutropenic fever.⁹⁶ The results of further trials are awaited. Biological markers to predict risk of relapse have been shown to be effective⁹⁷ although the difficulty in recruiting patients to such trials suggests that simpler more reliable tests are still needed.⁹⁸

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In women over the age of 70 years there is a paucity of data on the benefit of adjuvant chemotherapy, with no clear evidence for or against its use.

There are data to suggest that the degree of benefit may be reduced with increasing age.⁹² There is evidence that the use of a structured visual aid can improve patient satisfaction and understanding of the rationale of adjuvant chemotherapy.⁹⁹

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The decision regarding which patients should be offered adjuvant chemotherapy is based on a risk-benefit analysis made on the basis of their tumour details, including whether or not the cancer was screen-detected; age; and type of therapy offered. In determining prognosis, there are a number of tools available, from guidelines to biological analyses and simple and complex mathematical/computer models, but none have been validated in a prospective randomised trial. Chemotherapy has a negative effect on patients' sexuality that does not resolve following cessation of treatment. The addition of hormonal therapy to chemotherapy does not impair sexuality further (although the use of hormonal therapies alone impairs sexual function).¹⁰⁰

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All women under the age of 70 years, with early breast cancer should be considered for adjuvant chemotherapy.

Some of the beneficial effects of adjuvant chemotherapy may be mediated by ovarian suppression. Those who become amenorrhoeic during chemotherapy have fewer relapses.¹⁰¹ Endocrine therapy alone (ovarian suppression with or without tamoxifen), in premenopausal women over 35 years with moderate or high risk oestrogen receptor (ER) positive tumours, is as effective as cyclophosphamide, methotrexate and 5-fluorouracil (CMF) chemotherapy alone^{102,103} and may be superior.¹⁰⁴ Other studies have found the addition of CMF chemotherapy to tamoxifen to be beneficial to premenopausal women with less than four axillary lymph glands involved.¹⁰⁵

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There is a paucity of data on the addition of tamoxifen to chemotherapy in premenopausal women, although there is no evidence that it is not of additional benefit. Similarly, there are no clear data on the benefit of additional ovarian suppression to women with hormone receptor positive tumours already receiving chemotherapy and tamoxifen.

Breast cancer patients aged less than 35 years have a lower survival and higher relapse rate than older patients. In a study where most patients did not get additional endocrine therapy, younger patients with oestrogen receptor positive disease had lower survival rates than those with oestrogen receptor negative disease.¹⁰⁶ Omission of hormonal therapy in younger patients may be especially detrimental to their outcome.

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C Women with oestrogen receptor-positive tumours who receive chemotherapy should be considered for additional endocrine therapy, especially if they are under 35 years.

5.2 NEOADJUVANT CHEMOTHERAPY

There is good quality evidence that there is no difference in long term survival if the same chemotherapy is given before rather than after surgery for patients with operable breast cancers, with the added benefit that neoadjuvant chemotherapy appears to be associated with a reduction in requirement for mastectomy.¹⁰⁷⁻¹⁰⁹ It is often offered to facilitate surgery in women with either large T3 tumours in whom mastectomy may be difficult, or with large T2–T3 tumours where breast conservation is not possible at presentation, but would be appropriate if the tumour were smaller. There is some evidence to show that the type of chemotherapy given may affect the numbers of complete pathological responses seen¹¹⁰ although the difference between regimens is not always apparent.¹¹¹

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A Neoadjuvant chemotherapy should be considered for women with large cancers as it improves the rate of breast conservation and is not detrimental to long term outcome.

5.3 ANTHRACYCLINE AND TAXANE THERAPY

In the adjuvant setting there is evidence that anthracyclines offer superior survival benefits compared with non-anthracyclines regimens (such as CMF).^{92,112} They are more toxic, with higher rates of myelodysplasia (bone marrow abnormalities) and neutropenic sepsis in some studies.¹¹² They are also associated with a modest risk of cardiac damage.¹¹⁴

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Taxanes are active in the adjuvant setting, but although they have been shown to improve upon some adriamycin-based regimens,¹¹³ there are not yet any published data that they offer additional survival benefits over optimal anthracyclines regimens.

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5.3.1 ADVANCED DISEASE

Epirubicin

Randomised controlled trials in advanced breast cancer have shown that epirubicin and doxorubicin have equivalent efficacy when measured by response rates or survival. In a pooled analysis of six trials comparing equal doses of these drugs, alone or as part of combination therapy, response rates were equivalent (RR, 1.04; 95% CI, 0.92 to 1.18; $p=0.51$). In doses equal to doxorubicin, epirubicin had less cardiotoxicity (electrocardiogram changes, decrease in ventricular ejection fraction, increase in pre-ejection period/left ventricular pre-ejection period ratio), (RR, 0.43; 95% CI, 0.24 to 0.77; $p=0.0044$) and fewer episodes of congestive heart failure. Response rates are higher with escalating doses of epirubicin but survival the same, although toxicities are more common with increasing dose.¹¹⁴ The British National Formulary recommends a maximum cumulative dose of 0.9–1 g/m² to help avoid cardiotoxicity.¹¹⁵ The Scottish Medicines Consortium has advised (December 2003) that the pegylated liposomal preparation of doxorubicin is not recommended for metastatic breast cancer.¹¹⁶ It has been shown that the use of anthracycline based chemotherapy in advanced disease is associated with a modest survival advantage.¹¹⁷

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A Anthracyclines should be prescribed in preference to non-anthracycline regimens in the adjuvant setting, as they offer additional benefits. Epirubicin may be preferred as it causes less cardiac adverse effects.

Taxanes

A meta-analysis of four trials of paclitaxel, single-agent for first line treatment, has shown a 25-34% overall response rate with time to progression (TTP) five months.¹¹⁸ Most patients relapse within 12 months and median survival is 17-22 months. When using paclitaxel in combination with other agents for first line treatment, neutropenia is seen in 40-68% of cases although it is unclear if combining with anthracyclines makes this worse. Thrombocytopenia (a decrease in the number of blood platelets) is more common when paclitaxel is used in combination, a 10% peripheral neuropathy rate is seen, and alopecia occurs in three-quarters of patients, but with no significant difference in quality of life when paclitaxel added (four studies, n = 1545). The improved response rate and survival advantage have been replicated in other trials.^{119,120}

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Taxanes should be considered in patients with advanced disease.

5.4 BIOLOGICAL THERAPIES

5.4.1 TRASTUZUMAB MONOTHERAPY

A systematic review¹²¹ of trastuzumab as monotherapy found some anti-tumour effects in terms of overall response (partial and complete) ranging from 12% to 24%.¹²²⁻¹²⁴ The review included one randomised trial which compared two regimens of trastuzumab as a single agent in women with metastatic breast cancer who had not previously received chemotherapy.¹²⁴ The objective response rate was 24% (95% CI, 18.0 to 34.3%) among 111 evaluable patients. Median duration of survival was 24.4 months. A retrospective analysis evaluating the response to trastuzumab according to over-expression of the human epidermal growth factor receptor 2 (HER2) demonstrated by fluorescence in situ hybridization (FISH), found that patients with FISH-positive tumours (n = 79) had a response rate of 34% (95% CI, 23.9% to 45.7%) compared to 7% (95% CI, 0.8% to 22.8%) in 29 women with tumours that were FISH-negative. The response rate in such patients is comparable to some other systemic therapies when used as first-line therapy for metastatic breast cancer, such as tamoxifen (20-45% response rate), letrozole (30%), doxorubicin (32%) and doxorubicin plus vinorelbine (39%).^{125,126}

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Trastuzumab should be reserved for those patients whose tumours have HER2 over-expression.

5.4.2 ADJUVANT TRASTUZUMAB THERAPY

Several large international trials are being conducted to test the benefit of this agent in early breast cancer, and preliminary reports from some indicate that one years' treatment provides a significant benefit.

The HERA trial randomised women who had completed locoregional therapy and adjuvant chemotherapy to either one year of three weekly trastuzumab therapy, two years of trastuzumab therapy or observation.¹²⁷ Interim results are available for the comparison between observation and one year of therapy. A total of 127 first events were reported in the one-year trastuzumab group and 220 in the observation group. The unadjusted hazard ratio in the one-year trastuzumab group as compared with the observation group was 0.54 (95% confidence interval, 0.43 to 0.67; p < 0.0001) which corresponded to an absolute disease-free survival benefit of 8.4% at two years. Approximately two thirds of reported first events were distant metastases. The hazard ratio for time to a distant recurrence in the one-year trastuzumab group compared with the observation group was 0.49 (95% confidence interval, 0.38 to 0.63; p < 0.0001).

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Two trials which compared adjuvant chemotherapy with or without concurrent trastuzumab in women with surgically removed HER2-positive breast cancer have published combined results.¹²⁸

The National Surgical Adjuvant Breast and Bowel Project trial B-31 compared doxorubicin and cyclophosphamide followed by paclitaxel every three weeks (group 1) with the same regimen plus 52 weeks of trastuzumab given concurrently with paclitaxel (group 2). The North Central Cancer Treatment Group trial N9831 compared doxorubicin and cyclophosphamide followed by weekly paclitaxel (group A), with the same regimen plus 52 weeks of trastuzumab initiated concomitantly with paclitaxel (group C). The studies were amended to include a joint analysis comparing groups 1 and A (the control group, n = 1679) with groups 2 and C (the trastuzumab group, n = 1672). At interim analysis the trastuzumab group was associated with around half of the number of events (cancer recurrence, second primary cancer, or death before recurrence) of the control group; (261 vs 133 events; hazard ratio, 0.48; 95 % CI, 0.39 to 0.59, p < 0.0001).

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There were approximately one third fewer deaths in the trastuzumab group than the control group (92 vs 62; hazard ratio 0.67 95 % CI 0.48 to 0.93; p = 0.015). Time to distant recurrence in the trastuzumab group was around half of that in the control group (193 vs 96 patients with recurrence; hazard ratio 0.47 95 % CI, 0.37 to 0.61; p < 0.0001).

There is currently insufficient long term outcome evidence available to assess the toxicity-benefit balance for different patient groups or treatment regimens. Preliminary results are encouraging, but until there is medium term evidence of benefit and freedom from adverse cardiac effects it is not possible to make any clear recommendation for or against the use of this agent in the adjuvant setting. This research is currently in progress. Any updates relating to the use of trastuzumab will be noted on the SIGN website.

5.4.3 TRASTUZUMAB COMBINATION THERAPY

Trastuzumab added to paclitaxel or adriamycin/cyclophosphamide (a combination associated with a high incidence of cardiac dysfunction)¹²⁹ gave a better time to progression (seven versus five months), better overall response rate (50% versus 32%), and greater one-year survival (median survival 25 versus 20 months) than the same chemotherapy alone.¹³⁰ The combination of chemotherapy plus trastuzumab was not associated with any significant difference in quality of life. One phase 2 study of trastuzumab with cisplatin showed a 24% response rate and five months average TTP.¹³¹ In a second phase 2 study of weekly paclitaxel/trastuzumab combination therapy the response rate was 61%.¹³² Patients with HER2-negative tumours were included in the trial, but responded less often, suggesting that the addition of trastuzumab was of no benefit in these tumours. The median response duration was seven months. The cardiac dysfunction rate was similar to doxorubicin-based chemotherapy (any 7%, severe 5%) but higher if trastuzumab was combined with any anthracycline (any 28, severe 19%).¹³³ One RCT showed that weekly trastuzumab plus docetaxel (100 mg/m² every three weeks) proved superior to the same dose of single-agent docetaxel in all end points including overall response rate (61% v 34%; p = 0.0002), overall survival (median, 31.2 v 22.7 months; p = 0.0325), time to disease progression (median, 11.7 v 6.1 months; p = 0.0001), time to treatment failure (median, 9.8 v 5.3 months; p = 0.0001), and duration of response (median, 11.7 v 5.7 months; p = 0.009).¹³⁴

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Combination therapy of trastuzumab with a taxane is recommended in women with metastatic breast cancer.

5.4.4 DURATION OF THERAPY

No randomised trial data were identified which address the question of duration of therapy. In the RCT of trastuzumab identified in section 5.4.3 treatment was continued until progression.¹³⁰ No randomised data were identified to address the question of whether to discontinue trastuzumab therapy after progression.

5.5 VINORELBINE AND CAPECITABINE THERAPY

No evidence was identified to support the use of these agents in the adjuvant setting, although there are ongoing studies which will address their role. Two systematic reviews report the following evidence in patients with metastatic disease.^{135,136}

5.5.1 VINORELBINE

A single RCT was identified which compared single agent vinorelbine to melphalan in patients who failed to respond to anthracycline-containing chemotherapy (n = 179).¹³⁷ The study showed a survival benefit for vinorelbine (p = 0.034). The median survival time was 35 versus 31 weeks, with improved quality of life. A phase 2 study of vinorelbine/ vinorelbine plus 5-fluorouracil (5FU) plus leucovorin and mitoxantrone plus 5FU plus leucovorin (n = 99) showed equivalent objective response rates and survival times in all three groups (RR 21-30%).¹³⁸ An RCT examining vinorelbine versus vinorelbine plus doxorubicin (n = 289 assessable), showed no difference in response, duration of response, or survival. Toxicity was mainly haematological and alopecia was seen in 12%.¹³⁹

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Vinorelbine is an active drug in the treatment of advanced disease, but its optimum position within a treatment algorithm is unclear due to a paucity of randomised trials.

5.5.2 CAPECITABINE

A phase 2 study of capecitabine versus paclitaxel for patients who had not responded to anthracycline treatment was discontinued early because of strong patient preferences for capecitabine with results showing similar efficacy. Capecitabine showed 8/22 responses of which three were complete, (36%, CI 17-59%) and paclitaxel 4/20, with no complete responses, (21%; 6-46%). Median TTP was the same at just over 90 days. Adverse events, typically neutropenia and neuropathy, were more common with paclitaxel.¹⁴⁰

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A phase 2 study of capecitabine in patients with paclitaxel-resistant metastatic cancer showed a 20% response rate, three complete responses, median duration of response of eight months, median survival of 13 months, median TTP of three months, and a one year survival of 52%. There was a 30% response rate in patients considered to be both anthracycline and paclitaxel-resistant. Adverse events noted were diarrhoea, fatigue, stomatitis, nausea, and neutropenia in 3%.¹⁴¹

3

As first line treatment in metastatic disease, a phase 2 study comparing capecitabine with CMF showed 25% RR for capecitabine and 16% RR for CMF (n = 95). The median time to progression was 132 days for capecitabine and 92 for CMF.¹⁴²

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A randomised phase 3 trial of docetaxel with or without capecitabine in patients who had previously undergone anthracycline treatment showed that the response rate was higher with the combination (42% versus 30%).¹⁴³ Median survival was 14 months with the combination and 11 months with docetaxel alone. The median TTP was six months for the combination and four months for capecitabine, however, patients were not assigned to receive capecitabine upon progression in the single agent docetaxol arm.

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Capecitabine appears to be effective as a first line and second line treatment of advanced disease, even after anthracyclines and taxanes. It is not possible to make a firm recommendation about its precise place in the treatment of advanced breast cancer given the paucity of randomised trials.

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Either capecitabine or vinorelbine should be considered for patients with advanced breast cancer.

5.6 ROLE OF BISPHOSPHONATES

5.6.1 BISPHOSPHONATES IN ADJUVANT THERAPY

The evidence for the effectiveness of bisphosphonates in reducing bone metastases in patients with high risk early breast cancer is conflicting.^{91,144} The largest trial (n = 1,069) showed that although the observed incidence of bone metastases was lower in the clodronate group (12% vs 15% with placebo), the difference between clodronate and placebo over the five-year follow-up period was not statistically significant (hazard ratio, 0.77; 95% CI, 0.56 to 1.08; p = 0.127).¹⁴⁵ When the analysis was restricted to the two-year treatment period, the hazard ratio was 0.44 (95% CI, 0.22 to 0.86; p = 0.016). These data were reported as the final analysis for a trial that was designed to have the power to detect a 50% reduction in the incidence of bone metastases at three years and a 25% reduction at five years.

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5.6.2 BISPHOSPHONATES AND METASTATIC DISEASE

The role of bisphosphonates in advanced disease has been extensively investigated. Three systematic reviews and an evidence based guideline have addressed the effectiveness of these drugs in patients with metastatic disease.^{91,144,146,147} Bisphosphonates have a beneficial effect on bone pain, and reduce the rate of skeletal events in patients with metastatic bone disease. The optimal duration of therapy is unclear although the benefits are largely based on trials using two years' therapy. There was no clear benefit from bisphosphonate therapy in advanced disease without bone metastases, as defined by development of bone metastases, in the groups treated with bisphosphonate compared with placebo or no additional treatment. Using indirect comparisons, the third generation bisphosphonate ibandronate is similar to pamidronate and may be used as an alternative.⁹¹ The third generation bisphosphonate zoledronate has shown 20% superiority over pamidronate in a randomised controlled trial.¹⁴⁸

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There is evidence for a low level of renal toxicity, particularly with some intravenous bisphosphonates, which must be borne in mind during their use in patients with advanced breast cancer.¹⁴⁸

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A Bisphosphonates should be routinely used in combination with other systemic therapy in patients with metastatic breast cancer with symptomatic bone metastases. The choice of agent for an individual patient depends on individual circumstances.

5.7 ENDOCRINE THERAPY

5.7.1 PREMENOPAUSAL WOMEN

Ovarian suppression and tamoxifen as adjuvant treatment have been shown to improve five year survival, even when given to a population for whom oestrogen-receptor status is not known.¹⁴⁹ There are data to confirm that it is of no benefit in patients whose tumours do not express hormonal receptors, it is standard practice to measure the hormonal status of a patient with breast cancer.¹⁵⁰ Ovarian suppression has been shown to be as effective as CMF chemotherapy alone and, when given in combination with tamoxifen, to be more effective.¹⁵¹⁻¹⁵³ Endocrine therapy alone has never been compared with anthracycline or taxane-based regimens that are now seen as standard.

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As there are no clear data to suggest that the benefit of tamoxifen added to chemotherapy seen in postmenopausal women is not also seen in premenopausal women although this has not been formally evaluated.

In advanced breast cancer, the addition of tamoxifen to ovarian suppression with luteinizing hormone-releasing hormone (LHRH) agonists improves response rate and overall survival.¹⁵⁴

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A Premenopausal women whose tumours are not shown to have absent oestrogen or progesterone receptors should be considered for adjuvant endocrine therapy.

A In premenopausal women with advanced disease, the combination of tamoxifen plus ovarian ablation should be offered before tamoxifen therapy alone.

5.7.2 POSTMENOPAUSAL WOMEN

Tamoxifen given to patients with advanced disease, over a five year period in the adjuvant setting significantly reduces breast cancer recurrence, development of second breast cancers and improves overall survival.¹⁵⁰ Nevertheless patients may still relapse despite its use, and it is associated with toxicities including thrombo-embolic disease and endometrial thickening, atypia, and rarely cancer.¹⁵⁵ These changes can be prevented by the use of intra-uterine progestagen-releasing devices, although these may not be acceptable to all women. The use of an aromatase inhibitor, which is not associated with such uterine effects, is an alternative in susceptible women.¹⁵⁶

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1+**Adjuvant therapy**

The only group of women who do not benefit from tamoxifen are those with oestrogen receptor negative tumours.¹⁵⁰ For postmenopausal women who are candidates for adjuvant endocrine therapy five years of tamoxifen therapy is not the optimal regimen in terms of short/medium term disease-free survival, with superiority being shown for either five years of anastrozole, five years of tamoxifen followed by a median of two and a half years of letrozole, or two to three years of tamoxifen followed by two to three years of exemestane or anastrozole. Some of these alternatives have yet to show convincing overall survival benefit, although it has recently been reported in a subgroup of patients. The MA17 trial, investigated whether extended adjuvant therapy with the aromatase inhibitor letrozole after tamoxifen reduced the risk of late recurrences and showed that letrozole improved disease-free survival (HR) for recurrence or contralateral breast cancer = 0.58, 95% CI = 0.45 to 0.76; $p < 0.001$).¹⁵⁷ Overall survival was the same in both arms (HR for death from any cause = 0.82, 95% CI = 0.57 to 1.19; $p = 0.3$). Among lymph node-positive patients, overall survival was statistically significantly improved with letrozole (HR = 0.61, 95% CI = 0.38 to 0.98; $p = 0.04$). In addition, there is a different profile of side effects, with fewer gynaecological and thrombotic events, but more musculoskeletal disorders, including fractures.¹⁵⁵

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Neo-adjuvant therapy

There is no evidence that the use of a few weeks or months of endocrine therapy before loco-regional surgery has any long-term beneficial or detrimental effects. It may, as with neo-adjuvant chemotherapy, facilitate surgical options but there are no data to confirm this. Four months' letrozole offers a higher response rate than tamoxifen for the same duration.¹⁵⁸

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Advanced disease

There is no clear evidence that any particular sequence of endocrine agents offers an overall survival advantage over another. The third generation aromatase inhibitors show evidence of superiority in clinically meaningful endpoints, including response rate and TTP as compared to tamoxifen, irrespective of the prior use of adjuvant tamoxifen.¹⁵⁰ There is good evidence that in patients who do not respond to tamoxifen the third generation aromatase inhibitors are superior to megestrol acetate.¹⁵⁰

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A In postmenopausal women with breast cancer tamoxifen remains the treatment of choice as initial therapy in the adjuvant setting. If there are relative contraindications to its use (*high risk of thromboembolism or endometrial abnormalities*) or intolerance, an aromatase inhibitor can be used in its place.

A Postmenopausal patients should be considered for a switch to an aromatase inhibitor after either two to three years or after five years of tamoxifen therapy.

A In postmenopausal women with advanced disease, third generation aromatase inhibitors should be considered before either tamoxifen or megestrol acetate.

5.8 TIMING OF SURGERY AND CHEMOTHERAPY

No evidence was identified to support a recommendation to delay surgery pending systemic therapy. Delaying radiotherapy for adjuvant chemotherapy may increase the rate of local recurrence, whereas delaying chemotherapy for the radiotherapy may have some detrimental impact in terms of systemic recurrence.¹⁵⁹

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There is conflicting evidence regarding the effect of delaying chemotherapy following surgery in women with ER negative tumours. One meta-analysis showed that the 10-year disease free survival rate in women who commenced chemotherapy within 21 days was significantly higher than in those who commenced chemotherapy at 21-86 days following surgery (60% vs 34%; (HR), 0.49; 95% (CI), 0.33 to 0.72; $p=0.0003$).¹⁶⁰ 1 +

A retrospective analysis of a similar cohort of 1161 patients found no significant difference in disease free survival between those women who had received chemotherapy within 21 days of surgery and those who had started chemotherapy at a later time.¹⁶¹ 3

C All treatments for patients with early breast cancer should be started as soon as is practical. Young women with oestrogen receptor negative tumours may benefit particularly from early initiation of chemotherapy following surgery.

5.9 MANAGEMENT OF MENOPAUSAL SYMPTOMS

There is good evidence that both low dose megestrol acetate and depot intramuscular medroxyprogesterone acetate can reduce the frequency of hot flushes in postmenopausal women with breast cancer.¹⁶² There are fewer data on whether these agents affect the outcome of the breast cancer treatment. There are no clear data as to whether the use of conventional HRT alleviates these symptoms or alters outcome in women with breast cancer treated with endocrine agents.¹⁶³ Current use of HRT is associated with an increased risk of incident and fatal breast cancer; the effect is substantially greater for oestrogen-progestagen combinations than for other types of HRT.¹⁶⁴ Clonidine appears to have some effect on the control of hot flushes, but there is some evidence that it does not improve quality of life.¹⁶⁵ 1 + +
1 +
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B Megestrol acetate or depot intramuscular medroxyprogesterone acetate may be considered to control the severity of hot flushes in women with breast cancer.

6 Psychological care

6.1 INTRODUCTION

This section discusses the role of the specialist breast care nurse (*section 6.2*) and psychological distress in breast cancer patients (*section 6.3*). It also explores the most effective techniques of psychosocial support for breast cancer patients and/or their carers and families (*section 6.4*) and examines the communication methods that have been shown to be most effective in improving patient satisfaction or psychosocial morbidity (*section 6.5*).

6.2 THE ROLE OF THE BREAST CARE NURSE

The role of the breast care nurse specialist is well established within the multidisciplinary team and has developed and expanded to reflect local circumstances and the diversity of Scotland and its population. Women have complex needs at diagnosis and throughout their experience of the disease, requiring the input from many members of the team. Although there is limited research in this field, supporting women from diagnosis is acknowledged as an important intervention valued by women.^{166,167}

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Using a structured approach to the management of psychological care allows breast care nurse specialists to improve the continuity of care, information and support women received from diagnosis through to follow up.¹⁶⁷

3

C All women with a potential or known diagnosis of breast cancer should have access to a breast care nurse specialist for information and support at every stage of diagnosis and treatment.

D Contact details and information about the role of the breast care nurse should be available to the patients, their families and all the members of the multidisciplinary team including the primary care team.

6.2.1 EDUCATION

Breast care nurse specialists are working within a specialised nursing role and should be appropriately experienced and educated. Opportunities for continual professional development should be available for nurses working at this level. The Royal College of Nursing framework for adult cancer nursing provides recommendations on educational expectations.¹⁶⁸

4

D Breast care nurse specialists should have appropriate education and experience.

6.3 IDENTIFYING DISTRESS

SIGN 29

A number of studies have examined the incidence of psychological and psychiatric morbidity in women with breast cancer. They have shown a high risk of clinically significant levels of anxiety and/or depression, severe sexual difficulties and other problems related to body image.^{169,170} This is in addition to the normal reactions of women to the diagnosis of a potentially life threatening illness and the side effects of treatment.

Clinical staff frequently fail to identify psychological problems, for various reasons. When clinicians identify clinically significant distress, they may not offer treatment because they see the distress as being a 'normal' reaction to the diagnosis, treatment side effects, or prognosis.

Significant levels of psychological distress are commonly associated with experiences associated with the diagnosis of and treatment for breast cancer. In a study of 303 women entering a randomised controlled trial, up to 45% of the participants were found to have clinically significant levels of psychological distress using standardised criteria.¹⁷¹

3

Identifying distress is a significant task for the multi-professional team caring for patients with breast cancer. Distress can be the result of a range of factors and is not always a manifestation of an emotional or psychological problem. Many patients with high levels of distress are not recognised.

4

Routine screening for distress among people with cancer has been recommended by the US National Comprehensive Cancer Network.¹⁷² The National Health and Medical Research Council of Australia¹⁷³ recommends an approach to screening for significant psychological problems that includes advice to document risk factors for the presence of distress (see *Table 4*).

Although there have been many studies that have used a range of reliable and valid assessment measures to examine psychosocial aspects of breast cancer, there are few studies that specifically compare the utility of assessment methods.

A number of measures have been used in an attempt to screen for psychological symptoms in women with breast cancer. The Hospital Anxiety and Depression (HAD) scale is a reliable and valid questionnaire to screen for the presence of psychological symptoms and distress in the clinical setting.¹⁷⁴ The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) also has good reliability and validity as an assessment of important quality of life dimensions in research and the clinical settings.¹⁷⁵

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A large systematic review of the evidence relating to screening for distress in a general hospital setting indicated that the routine administration of questionnaires in screening for distress is a costly exercise with little bearing on psychological outcomes.¹⁷⁶ This is supported by research examining the utility of the HAD in detecting diagnosable mental disorders among women with breast cancer.¹⁷⁷

2++

Decisions to use these questionnaires should be taken when assessment reveals the presence of risk factors for severe psychological problems (see *Table 4*). Distress is often a manifestation of a physical, social, financial or spiritual concern and it should not be assumed that the presence of distress is always the result of an emotional or psychological problem.

B **The measurement of the presence of psychological symptoms in women with breast cancer should be tailored to the individual circumstances of the patient** (eg presence of high level of distress or risk factors for problems).

B **Routinely administered questionnaires are not recommended for the detection of clinically significant psychological symptoms in women with breast cancer who do not have specific risk factors for severe anxiety or distress.**

- D**
 - ▢ Breast cancer services should routinely screen for the presence of distress and risk factors for very high levels of distress from the point of diagnosis onwards (including during follow up review phases)
 - ▢ Multidisciplinary teams should have agreed protocols for distress assessment and management. These should include recommendations for referral and care pathways.

Table 4: Factors associated with increased risk of psychosocial problems

Characteristics of the individual
Younger
Single, separated, divorced or widowed
Living alone
Children younger than 21 years
Economic adversity
Lack of social support, perceived poor social support
Poor marital or family functioning
History of psychiatric problems
Cumulative stressful life events
History of alcohol or other substance abuse
Characteristics/stages of disease and treatment
At the time of diagnosis and recurrence
During advanced stage of the disease
Poorer prognosis
More treatment side effects
Greater functional impairment and disease burden
Experiencing lymphodema
Experiencing chronic pain
Fatigue

Source: Clinical Practice Guidelines for Psychosocial Care of Adults with Cancer¹⁷³

6.4 PSYCHOLOGICAL SUPPORT FOR WOMEN WITH BREAST CANCER AND THEIR FAMILIES

6.4.1 GROUP BASED PSYCHOLOGICAL INTERVENTIONS

Most of the studies evaluating a psychological intervention that has been delivered in a group format have evaluated supportive expressive therapy, cognitive behavioural group therapy or psycho-education in a group format.

Supportive-expressive psychotherapy has been shown to have positive effects in reducing traumatic stress symptoms,¹⁷⁸ mood disturbance and pain perception among women with advanced breast cancer.¹⁷⁹ This has not been shown in every study.¹⁸⁰ Supportive expressive therapy appears to have no effect on survival for women with advanced breast cancer.¹⁷⁹ Cognitive behaviourally focused group therapy in patients with localised breast cancer has been shown to be associated with a reduction in depression, mood disturbance, and with enhanced quality of life.¹⁸¹ These benefits have also been found in women with advanced breast cancer, where enhanced self esteem was also reported.¹⁸² The sustainability of these benefits is not yet proven, with studies reporting varying results with regard to maintenance of gains.¹⁸¹⁻¹⁸³ Although patients expressed high levels of satisfaction with their experiences of cognitive existential group psychotherapy (a therapy that combines elements of supportive expressive and cognitive behavioural therapies) an RCT has not shown beneficial psychosocial outcomes.¹⁸⁴ Discussion forums where women share their experiences offer short term benefit in maintaining patient hope.¹⁸⁵

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- A**
 - **Group psychological interventions should be available to women with breast cancer who feel it would suit their needs.**
 - **Supportive expressive therapy is recommended for patients with advanced cancer and cognitive behavioural therapy for patients with localised, locoregional or advanced disease.**
- Choice of psychological treatment modality in advanced breast cancer should be based on patient preference.

6.4.2 INDIVIDUAL INTERVENTIONS

Individual psychological interventions that have a psycho-educational or cognitive behavioural emphasis produce significant improvements in mood, coping and distress.¹⁸⁶⁻¹⁸⁹ They also have potential to ameliorate the specific side effects of cytotoxic chemotherapy.^{190,191} Problem solving, one-to-one approaches to psychosocial support can reduce distress in younger women with breast cancer and have a role in diminishing unreported need. These effects are not sustained once the intervention has finished.¹⁹² The provision of computers and limited training can aid information and patient confidence, but appears to have no effect on quality of life in general. Effects on confidence and knowledge are short term.¹⁹³ The benefit of computer-based support over more usual means of support is only marginal.¹⁹⁴ Where telephone therapy has been tried it has been widely acceptable but offers little benefit.¹⁹⁵ There is evidence from one RCT that a psychological intervention implemented by clinical psychologists resulted in improved outcomes for participating patients, when compared with the same intervention delivered by other professionals.¹⁸⁴

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The limited evidence available for the different forms of therapy and support available is in part due to the different standards and ways in which the interventions were used in the research setting.¹⁹⁶

- A** **Cognitive behavioural therapy (in group or individual format according to preference and availability) should be offered to selected patients with anxiety and depressive disorders.**
- A** **Computer and telephone-based interventions should not routinely be offered to patients.**
- Psychological interventions should be implemented according to the validated protocols and procedures used in the trials that have reported benefits within the literature and in consultation with local specialist psychological services.

6.5 COMMUNICATION METHODS

Effective communication with breast cancer patients is a cornerstone of good practice. The preference for, and ability to cope with, information varies between patients and discrepancies between the need for and actual communication of information can result in psychosocial problems.¹⁹⁷

Facilitating patient choice about treatment decisions benefits psychological morbidity.¹⁹⁸ Communication is enhanced by the provision of either tapes of consultations that contain information on diagnosis, management or prognosis, or of follow up letters.¹⁹⁹ Not all women want to make or share decision making.²⁰⁰ Following a written agenda at consultations significantly improves the experience for breast cancer patients.²⁰¹ Prompt sheets aid satisfaction with outpatient encounters.²⁰² Decision aids for chemotherapy improve patient knowledge and satisfaction.²⁰³

1++
1+

Communication skills training delivered by expert facilitators has been shown to result in demonstrable improvements in communication behaviours of participating senior clinicians.²⁰⁴

1++

- A** Women with breast cancer should be offered audiotapes or follow up summary letters of important consultations.
- A** Clinical encounters with women with breast cancer should facilitate patient choice about treatment decisions (*assuming patients wish to participate in the decision making process*).
- A** Written agendas, prompt sheets and decisions aids should be used to improve communication with women with breast cancer.
- A** Clinicians should be encouraged to attend validated training in communication skills.
- Communication skills training programmes should be implemented in accordance with empirically validated protocols, ensuring that attention is paid to the transfer and maintenance of new communication behaviours within clinical settings.

7 Follow up

7.1 IMPROVING OUTCOMES

Follow up for breast cancer patients following their primary treatment is an important aspect of care. Traditionally it has been carried out in hospitals by breast cancer teams.

Follow up surveillance is multifaceted in nature and fulfils a number of purposes, it:

- ▢ provides patients with support and counselling
- ▢ detects potentially curable local recurrence in the treated and opposite breast
- ▢ provides care for patients who develop metastases
- ▢ provides accurate data on morbidity and outcomes.

There is very little evidence linked to outcomes to suggest the effectiveness of long term follow up or to indicate the optimal follow up regimen.⁸⁸ One systematic review of RCTs suggested that regular hospital based review has no survival benefit over GP follow up.²⁰⁵ This review looked at follow up strategies for women treated with early breast cancer and reported one RCT involving 296 women which compared follow up by hospital-based specialists to follow up performed by general practitioners and found no significant differences in the time to detection of the recurrence and patient quality of life.²⁰⁶ Another RCT involving 196 women compared regular scheduled follow up, restricting it to the time of mammography and found no significant differences to interim use of telephone and frequency of GP consultations.²⁰⁷

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7.1.1 PATIENTS WITHOUT RECURRENCE

Improvements in survival have meant there are thousands of women who have completed primary treatment and are disease free and eligible for long-term follow up. It has become a challenge to offer effective follow up strategies. There are a number of different ways to provide follow up including patient initiated,²⁰⁸ GP and nurse-led follow up.⁸⁸ The evidence to determine the frequency of follow up is very limited and follow up practices are not always consistent.

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4

Detection of local recurrence

Clinical examination is the best method for detecting recurrence in the chest wall or axilla.²⁰⁹

2 +

Detection of recurrence in the treated breast and new primary in the contralateral breast

Relapses in the treated breast are detected clinically or mammographically. Mammography is the gold standard method of imaging for cancer detection²¹⁰ but no evidence was identified to suggest the optimal frequency of this procedure with this group of women. Current practice offers this one to twice yearly within the first five years.

3

C Mammography should be used to detect recurrence in patients who have undergone previous treatment for breast cancer.

7.1.2 PATIENTS WITH RECURRENCE

No evidence on the frequency of follow up of patients who have recurrence was available. This should be organised relating to patient need. The involvement of the palliative care team at this stage is important to ensure patients receive optimum management.

7.2 IDENTIFYING PATIENTS WITH METASTATIC DISEASE

7.2.1 DETECTION OF DISTANT METASTASES

The presentation of distant metastasis may occur at any time and not necessarily at routine follow up clinics. Patients will contact the breast care nurse, local GP or a member of the primary care team if they are concerned about symptoms. There is evidence that performing diagnostic tests such as X-rays, blood tests and scans on this group of women does not improve survival.^{205,209,210}

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2+
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B Routine diagnostic tests to screen for distant metastases in asymptomatic women should not be performed.

I Patients and primary care teams should have procedures in place for prompt re-referral to a person with responsibility for follow up and access to support services. They should be encouraged to report new, persistent symptoms promptly without waiting for the next scheduled appointment.

7.3 SPECIALIST PALLIATIVE CARE

Specialist palliative care has an integral place in the care of women with breast cancer whose disease is not amenable to cure. This requires a careful multidisciplinary approach with input where necessary from specialist palliative care teams. All those involved in the care of women with advanced disease require basic palliative care skills appropriate to their profession. There are agreed national standards in place for the provision of palliative care.²¹¹

Women with advanced breast cancer may have complex needs related to the psychosocial impact of disease, lymphoedema and symptoms, especially pain, fatigue and breathlessness. The control of pain in cancer patients is covered in detail in SIGN guideline 44.²¹²

The involvement of specialist palliative care teams has resulted in modest positive outcomes including symptom control, patient and carer satisfaction and chosen place of death.²¹³

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There is no evidence for the best point at which specialist palliative care should become involved in care, but a significant proportion of referrals arrive too late to give optimal benefit to patients.²¹⁴

B Patients with breast cancer should have access to input from a specialist palliative care team.

8 Information for discussion with patients and carers

8.1 GATHERING VIEWS FROM PATIENTS WITH BREAST CANCER

Patients and carers want information to help them understand and cope with the diagnosis of breast cancer, the treatment options available and the care they can expect from the health professionals they meet.

A literature search of patient views and experiences was carried out to inform the development of this guideline. One of the major themes that emerged was concern that the information needs of cancer patients are not met during their journey of care.

A one day workshop, on the broad issues of information needs and resources relating to any aspect of the disease, was held to gather views and suggestions from a group of women who all have direct experience of treatment for breast cancer. This was attended by 29 women from eight different health board areas in Scotland. Their age at diagnosis varied as follows: 30-39 years (n = 1); 40-49 (n = 10); 50-59 years (n = 12); 60-69 years (n = 5); not specified (n = 1).

Patients were asked to consider the information they have received throughout their journey of care, and the information they would have liked to have received. Five common themes emerged:

- ▢ delivery of information
- ▢ results of investigations
- ▢ side effects of treatment
- ▢ information for carers
- ▢ home care/follow up

8.1.1 DELIVERY OF INFORMATION

The manner in which important information was provided appeared to impact on both the relationship between the clinical staff and the patient and the patients' ability to understand and absorb it. The most effective "care partnerships" were those where the patients' individual wishes regarding information and involvement were acknowledged by their clinicians and determined the nature of their communications.

A need for clear, accurate information given face to face was identified. Decisions given over the telephone, conflicting or mislaid information from clinicians and poor communication across the different health settings (primary, secondary and tertiary) created increased anxiety for patients. Information was required about both NHS organisations and cancer charities that can offer further information in a verbal, written and visual format.

Frequently asked questions:

- ▢ Where can my family and I find further information?
- ▢ What are my treatment options?
- ▢ Could you write down my treatment plan?
- ▢ Is there someone I could see before my next appointment?
- ▢ Will my GP know my results?

8.1.2 RESULTS OF INVESTIGATIONS

A rapid referral from primary to secondary care was considered important to psychological well-being but this was sometimes delayed, as women were not always aware that a likelihood of breast cancer was being considered by the GP. There was no consistent approach to providing information about the triple assessment and many women were unaware of what to expect as they moved from primary to secondary and tertiary care. GPs, consultants and breast care nurses were considered gatekeepers to information about results and their approach to patients was very important.

Frequently asked questions:

- ▣ To the GP – what are you looking for?
- ▣ How long will I wait for an appointment?
- ▣ Will I be seen at my local hospital?
- ▣ What is the name of the doctor who will see me?
- ▣ What will happen at the hospital?
- ▣ Could you write this down for me?
- ▣ Is there any information that I could read?
- ▣ When will I get the results?
- ▣ Who will give me the results?

8.1.3 SIDE EFFECTS OF TREATMENT

There were a number of treatments that were believed to cause significant side effects including surgery, chemotherapy and radiotherapy. The common theme was that the quantity and quality of information about side effects was insufficient and, at times, given in an ad hoc manner. The majority of participants had not received written information or taped consultations, and there appeared to be no consistent approach to updating and adding to the information given or the use of published materials. There was some very positive feedback about using a record book while undergoing chemotherapy to record the different side effects experienced.

Frequently asked questions:

- ▣ What does the surgery involve?
- ▣ Are there any side effects of surgery?
- ▣ How long will I need to stay off work?
- ▣ What does the scar look like?
- ▣ What are the side effects of chemotherapy?
- ▣ Can I have information on the specific chemotherapy drugs I am on?
- ▣ Can I have information about radiotherapy; zoladex; tamoxifen; arimidex or the name of the drug you are on?
- ▣ Who will be in charge of my care?
- ▣ Who do I contact if I have a particular concern?

8.1.4 INFORMATION FOR CARERS

Information for the patient's personal support networks i.e. family, carers and friends, was very important. They also need to be involved in consultations when considered appropriate by the patient. Specific issues were identified that addressed different age groups of women.

Younger women raised concerns about the impact of the diagnosis on young children, relationships and employment.

Ethnic minorities had limited access to written information that is both culturally appropriate and in the correct language.

Women or their carers who had poor reading skills, were visually impaired or deaf needed to be able to access a range of information other than written material. This may include tapes, video material including British sign language signing and modified pictorial information.

Frequently asked questions:

- ▣ Can my partner, carer, friend come into the room with me?
- ▣ Are there places for my carer to access support?
- ▣ Is there someone we can get advice about benefits?

8.1.5 HOME CARE / FOLLOW UP

There were significant variations between women's experiences of aftercare. Some found their GP and breast care nurse a great source of support while others felt abandoned and isolated without knowing whom to contact. Women had a number of concerns about recurrence, practical support including wigs and prosthesis, psychological support and ongoing follow up care.

Frequently asked questions:

- ▣ Who fits my prosthesis?
- ▣ How often can it be replaced?
- ▣ Do I have to pay for it?
- ▣ Who do I contact when my treatment is finished in the hospital?
- ▣ Does my GP know what treatment I have had?
- ▣ How often will I be followed up?
- ▣ Who will do the follow up?
- ▣ Will they do additional tests?
- ▣ How will I know if the cancer is back?
- ▣ Are there any support groups I can attend?

8.2 SOURCES OF FURTHER INFORMATION FOR PATIENTS AND CARERS

Breast Cancer Care

4th floor, 40 St Enoch Square

Glasgow G1 4DH

Tel: 0845 077 1892 • Fax: 0141 221 9499

Email: sco@breastcancercare.org.uk • www.breastcancercare.org.uk

Breast Cancer Care provides information, practical assistance and emotional support for anyone affected by breast cancer.

CancerBACUP Scotland

Suite 2, 3rd Floor, Cranston House, 104-114 Argyle Street

Glasgow G2 8BH

Tel: 0141 223 7676 • Fax: 0141 248 8422

Freephone help line: 0808 800 1234, Monday to Friday 9am to 7pm

www.cancerbacup.org.uk

Offers a free cancer information service staffed by qualified and experienced cancer nurses. There are a growing number of CancerBACUP centres in hospitals and a freephone information service on all types of cancer, staffed by specialist cancer nurses. Produces over 50 booklets and 'CancerBACUP News' three times a year.

Cancer Research UK

PO Box 123, 61 Lincoln's Inn Fields

London WC2A 3PX

Tel: 020 7242 0200 • Fax: 020 7269 3100

www.cancerresearchuk.org

Macmillan Cancer Relief Scotland

Osbourne House, 1-5 Osbourne Terrace

Edinburgh EH12 5HG

Tel: 0131 346 5346 • Fax: 0131 346 5347

Helpline: 0808 808 2020, Monday to Friday 9am to 6pm

www.macmillan.org.uk

A UK charity supporting people with cancer and their families with specialist information, treatment and care.

Maggie's Centres Scotland

The Stables, Western General Hospital
Edinburgh EH4 2XU
Tel: 0131 537 3131 • Fax: 0131 537 3130

The Gatehouse, Western Infirmary, 10 Dumbarton Road
Glasgow G11 6PA
Tel: 0141 330 3311 • Fax: 0141 330 3363
Email: maggies.centre@ed.ac.uk • www.maggiescentres.org

The goal of Maggie's is to keep people who have cancer as healthy in mind and body as is possible, by enabling them to participate actively in the treatment of their disease.

Tak Tent Cancer Support Scotland

Flat 5, 30 Shelley Court, Gartnavel Complex
Glasgow G12 0YN
Tel: 0141 211 0122 • Fax: 0141 211 3988
Email: tak.tent@care4free.net • www.taktent.org.uk

Promotes the care of cancer patients, their families, friends and the staff involved professionally in cancer care by providing practical and emotional support, information, counselling and therapies as required. Network of local support groups throughout Scotland.

9 Development of the guideline

9.1 INTRODUCTION

SIGN is a collaborative network of clinicians and other healthcare professionals, funded by NHS Quality Improvement Scotland. SIGN guidelines are developed by multidisciplinary groups of practising clinicians using a standard methodology based on a systematic review of the evidence. Further details about SIGN and the guideline development methodology are contained in "SIGN 50; A Guideline Developer's Handbook", available at www.sign.ac.uk

9.2 THE GUIDELINE DEVELOPMENT GROUP

Dr Douglas Adamson (Chair)	<i>Consultant Clinical Oncologist, Ninewells Hospital, Dundee</i>
Dr David Cameron	<i>Senior Lecturer in Medical Oncology, Western General Hospital, Edinburgh</i>
Ms Kathy Clarke	<i>National Cancer Audit Coordinator, Scottish Cancer Therapy Network, Edinburgh</i>
Ms Sue Cruickshank	<i>Lecturer in Cancer Nursing, Napier University, Edinburgh</i>
Ms Lorraine Dallas	<i>National Manager, Breast Cancer Care, Glasgow</i>
Dr John Donald	<i>Referrals Adviser, Lothian Primary Care Trust, Edinburgh</i>
Dr Jane Edgecombe	<i>Consultant in Palliative Medicine, Beatson Oncology Centre, Glasgow</i>
Ms Carla Forte	<i>Principal Pharmacist, Beatson Oncology Centre, Glasgow</i>
Professor Neva Haites	<i>Professor of Medical Genetics, University of Aberdeen</i>
Dr Adrian Harnett	<i>Consultant in Clinical Oncology and Radiology, Norfolk and Norwich University Hospital</i>
Dr Paul Keeley	<i>Consultant in Palliative Medicine, Glasgow Royal Infirmary</i>
Ms Gillian Little	<i>Macmillan Specialist Nurse, Ninewells Hospital, Dundee</i>
Dr Elizabeth Mallon	<i>Consultant Pathologist, Western Infirmary, Glasgow</i>
Mr Michael McKirdy	<i>Consultant Breast Surgeon, Royal Alexandra Hospital, Paisley</i>
Dr Moray Nairn	<i>Programme Manager, SIGN</i>
Dr Russell Pickard	<i>Consultant Radiologist, West of Scotland Breast Screening Programme, Glasgow</i>
Mr Duncan Service	<i>Senior Information Officer, SIGN</i>
Dr James Tuckerman	<i>General Practitioner, Buckie</i>
Mr Patrick Walsh	<i>Consultant Surgeon, Raigmore Hospital, Inverness</i>
Dr Craig White	<i>Macmillan Consultant in Psychosocial Oncology, Ayrshire Central Hospital</i>

The membership of the guideline development group was confirmed following consultation with the member organisations of SIGN. All members of the guideline development group made declarations of interest and further details of these are available on request from the SIGN Executive. Guideline development and literature review expertise, support and facilitation were provided by the SIGN Executive.

9.3 SYSTEMATIC LITERATURE REVIEW

Literature searches were initially conducted in Medline, Embase, Cinahl, and the Cochrane Library using the year range 1998-2002. The literature search was updated to cover the period up to December 2003. Key websites on the Internet were also used, such as the National Guidelines Clearinghouse. These searches were supplemented by the reference lists of relevant papers and group members' own files. The Medline version of the main search strategies can be found on the SIGN website.

9.4 CONSULTATION AND PEER REVIEW

9.4.1 NATIONAL OPEN MEETING

A national open meeting is the main consultative phase of SIGN guideline development, at which the guideline development group presents its draft recommendations for the first time. The national open meeting for this guideline held on 1 October 2003 was attended by 157 representatives of all the key specialties relevant to the guideline. The draft guideline was also available on the SIGN website for a limited period at this stage to allow those unable to attend the meeting to contribute to the development of the guideline.

9.4.2 SPECIALIST REVIEW

The guideline has been reviewed in draft form by a panel of independent expert referees, who have commented on the comprehensiveness and accuracy of interpretation of the evidence base supporting the recommendations in the guideline. SIGN is very grateful to all of these experts for their contribution to this guideline.

Ms Christine Akilade	<i>Senior Nurse Cancer Support Service, Cancer BACUP Scotland</i>
Miss Elaine Anderson	<i>Consultant Surgeon, Western General Hospital, Edinburgh</i>
Mrs Margo Biggs	<i>Lay Representative</i>
Professor Rob Coleman	<i>Professor of Medical Oncology, Weston Park Hospital, Sheffield</i>
Dr John Dewar	<i>Consultant Radiotherapist and Oncologist, Ninewells Hospital, Dundee,</i>
Mr Mike Dixon	<i>Consultant Surgeon, Western General Hospital, Edinburgh</i>
Dr John Dorward	<i>General Practitioner, Eyemouth</i>
Dr Peter Harvey	<i>Lead Consultant Clinical Psychologist (Cancer), St James University Hospital, Leeds</i>
Dr Margaret Kenicer	<i>Consultant in Public Health, Tayside NHS Board, Dundee</i>
Dr Ian Kunkler	<i>Consultant Clinical Oncologist, Western General Hospital, Edinburgh</i>
Mr John Martin	<i>Senior Assistant Editor, British National Formulary, London</i>
Miss Pauline McIlroy	<i>Breast Care Nurse Specialist, Beatson Oncology Centre, Glasgow</i>
Ms Gillian Rafferty	<i>Lay Representative</i>
Mr Richard Sainsbury	<i>Senior Lecturer and Consultant Surgeon, University College, London</i>
Dr Maggie Watson	<i>Head of Department of Psychological Medicine, Royal Marsden Hospital, London</i>
Professor John Yarnold	<i>Professor and Honorary Consultant in Clinical Oncology, Royal Marsden Hospital, London</i>
Ms Susan Watt	<i>Education and Clinical Effectiveness Advisor, Royal College of Nursing</i>

9.4.3 SIGN EDITORIAL GROUP

As a final quality control check, the guideline was reviewed by an editorial group comprising the relevant specialty representatives on SIGN Council to ensure that the specialist reviewers' comments have been addressed adequately and that any risk of bias in the guideline development process as a whole has been minimised. The editorial group for this guideline was as follows.

Professor Robert Carachi	<i>Royal College of Physicians and Surgeons of Glasgow</i>
Dr Hugh Gilmour	<i>Royal College of Pathologists</i>
Dr Grahame Howard	<i>Royal College of Radiologists</i>
Professor Derek Johnston	<i>British Psychological Society</i>
Professor Gordon Lowe	<i>Chairman of SIGN; Co-editor</i>
Dr Safia Qureshi	<i>SIGN Programme Director; Co-editor</i>
Dr Sara Twaddle	<i>Director of SIGN; Co-editor</i>

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Dr Jeremy Keen	<i>Consultant in Palliative Medicine, Highland Hospice, Inverness</i>
Ms Lorraine McColl	<i>Lay Representative</i>
Dr Ann Cull Smyth	<i>Clinical Psychologist, Western General Hospital, Edinburgh</i>
Dr Lesley Wilkie	<i>Director of Public Health, NHS Argyll and Clyde</i>
Dr Rachael Wood	<i>Specialist Registrar in Public Health Medicine, NHS Lothian</i>

10 Implementation and audit

10.1 LOCAL IMPLEMENTATION

Implementation of national clinical guidelines is the responsibility of each NHS Board and is an essential part of clinical governance. It is acknowledged that every Board cannot implement every guideline immediately on publication, but mechanisms should be in place to ensure that the care provided is reviewed against the guideline recommendations and the reasons for any differences assessed and, where appropriate, addressed. These discussions should involve both clinical staff and management. Local arrangements may then be made to implement the national guideline in individual hospitals, units and practices, and to monitor compliance. This may be done by a variety of means including patient-specific reminders, continuing education and training, and clinical audit.

10.2 RECOMMENDATIONS FOR RESEARCH

- ▣ Efficacy of telephone and computer based individual support therapies for alleviating psychosocial distress
- ▣ Optimal duration of biological therapies
- ▣ Role of sentinel node biopsy
- ▣ Optimal sequencing of post mastectomy radiotherapy with systemic therapy
- ▣ Optimal role of adjuvant taxanes
- ▣ Defining the role of capecitabine and vinorelbine in advanced disease
- ▣ Identifying sub-groups of patients who get most benefit from adjuvant therapy: which patients need a taxane, which ones anthracyclines, which ones aromatase inhibitors and which ones benefit from trastuzumab?
- ▣ Identifying patients more at risk of certain toxicities such as cardiac damage from anthracyclines or trastuzumab
- ▣ Optimal pharmaceutical and non-pharmaceutical management of postmenopausal symptoms in women with breast cancer
- ▣ Optimal frequency and method of follow up in different groups of patients.

10.3 KEY POINTS FOR AUDIT

- ▣ The presence and content of distress screening protocols
- ▣ Assessment of staff knowledge and skill regarding the occurrence and management of distress
- ▣ Availability of the named psychological interventions and training needs audits with regard to the delivery of these interventions
- ▣ The number of clinicians offering patients audio tapes and/or summary letters of important consultations
- ▣ Audits of recommendations facilitating patient choice about treatment decisions and/or the use of written agendas, prompt sheets and decision aids
- ▣ Numbers of clinicians who have attended validated communication skills training courses and the presence of mechanisms to ensure skill maintenance
- ▣ Audit of patient related outcomes regarding communication encounters with key clinicians.

10.4 RESOURCE IMPLICATIONS

This section is based on discussions with the guideline development group regarding current resource use in Scotland and the likely impact of implementation of the recommendations of the guideline. Where current practice will not change as a result of the recommendations, it is unlikely that there will be resource implications.

The following table shows recommendations that are likely to have significant resource implications if implemented across Scotland. This does not consider the resource implications associated with good practice points, although that it is recognised that these may be significant.

Guideline section		Recommendation	Current situation	Likely Resource implications of implementing recommendation
2.3	D	Patients should be seen at a one-stop, multidisciplinary clinic involving breast clinicians, radiologists and cytology.	Not being achieved everywhere for organisational rather than resource reasons. Some radiology sessions remain unfilled.	Organisational change only •
5.8	C	For young women with oestrogen receptor negative tumours chemotherapy should be started as soon as possible and within three weeks.	Not being achieved everywhere for organisational rather than resource reasons	Organisational change only
6.2	C	All women with a potential or known diagnosis of breast cancer should have access to a breast care nurse specialist for information and support at every stage of diagnosis and treatment.	Breast cancer nurses are available in all areas, but there is variable access for women with advanced disease due to limited numbers in some regions.	An increase in the number of BCNs to deal with all women with breast cancer requires investment in staff training and support facilities.
6.2.1	D	Breast care nurse specialists should have appropriate education and experience	Specific education is very limited throughout the UK, no specific courses in Scotland	
2.3	A	Psychological support should be available to women diagnosed with breast cancer at the clinic.	Psychological support is provided by a range of people, not necessarily psychologists	An increase in the number of clinical psychologists to provide support and psychological interventions. This requires investment in staff, training and support facilities. This is likely to be area with significant resource implications
6.4.1	A	Group psychosocial interventions should be available to women with breast cancer who feel it would suit their needs.	Access to psychological therapies is very patchy throughout Scotland. There is access to CBT for some women, though	
6.4.2	A	Cognitive behavioural therapy (in group or individual format according to preference and availability) should be offered to selected patients with anxiety and depressive disorders.	an urgent need to ensure that there are more clinicians able to provide this for women with breast cancer who also have anxiety or mood disorders	
6.5	A	Clinicians should be encouraged to attend validated training in communication skills.	Most NHS Board areas have clinicians that have attended validated training in communication skills training. There is no centralised record of who has attended.	This would require investment in the training itself, providing of cover for staff attending the training and resources required to ensure the maintenance of communication skills following attendance at a course.

Abbreviations

5-FU	Fluorouracil
AR	Absolute risk
BCS	Breast conserving surgery
CI	Confidence interval
CMF	Cyclophosphamide, methotrexate and 5-fluorouracil
CT	Chemotherapy
DCIS	Ductal carcinoma <i>in situ</i>
ECG	Electrocardiogram
EORTC	European Organisation for Research and Treatment of Cancer
ER	Oestrogen receptor
FISH	Fluorescence in situ hybridization
FNAC	Fine needle aspirate cytology
G-CSF	Granulocyte colony stimulating factor
GP	General practitioner
Gy	Gray
HAD	Hospital anxiety and depression scale
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
HRT	Hormone replacement therapy
IMC	Internal mammary (node) chain
LHRH	Luteinizing hormone-releasing hormone
LRF	Loco-regional failure
MRI	Magnetic resonance imaging
NHSBSP	NHS Breast Screening Programme
NICE	National Institute for Health and Clinical Excellence
NS	Not significant
NSABP	National Surgical Adjuvant Breast and Bowel Project
OR	Odds ratio
PMRT	Postmastectomy radiotherapy
QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
RCT	Randomised controlled trial
RR	Relative risk
RT	Radiotherapy
SIGN	Scottish Intercollegiate Guidelines Network
TTP	Time to progression

Annex 1

KEY QUESTIONS USED TO DEVELOP THE GUIDELINE

Diagnosis and referral

1. Is there any evidence that identifies specific symptoms as triggers that should prompt referral to a breast clinic?
2. What evidence is there that delays from diagnosis to treatment affect patient outcome?
3. What is the evidence for the most effective method of diagnosing symptomatic breast cancer?

Systemic Therapy

4. What evidence is there to help identify the circumstances in which the use of adjuvant chemotherapy will improve patient outcomes?
5. What evidence is there of specific indications of when anthracycline or taxane therapy is appropriate?
6. What evidence is there of specific indications of when biological therapies such as the use of herceptin are appropriate?
7. What evidence is there of specific indications of when vinorelbine or capecitabine therapy is appropriate?
8. What evidence is there to support a role for bisphosphonates in adjuvant therapy and the treatment of metastatic disease?
9. What evidence is there to support a role for endocrine therapy in either pre- or post-menopausal women?
10. Is there any evidence to suggest there is an optimum time lapse between surgery and chemotherapy that has an influence on patient outcome?
11. Is there evidence to support the optimal management of menopausal symptoms in women with a diagnosis of breast cancer?

Radiotherapy

12. What evidence is there to support the use of radiotherapy techniques to the axilla and chest wall?
13. Is there any evidence to suggest there is an optimum time scale for the use of radiotherapy for the treatment of breast cancer that will have an influence on patient outcome?

Surgery

14. Is there any evidence that surgical technique in the axilla influences overall outcome?
15. Is there any evidence that carrying out breast reconstruction immediately is more or less effective than delayed reconstruction?
16. What evidence is there that prophylactic mastectomy is effective?
17. What evidence is there for the relative effectiveness of conservation surgery and mastectomy for invasive breast carcinoma in relation to mortality, maximising quality of life and patient preference?

Follow up

18. What evidence is there to show which management strategies are most effective in improving outcome for patients with or without recurrence in the breast or axilla?
19. What evidence is there to show which management strategies are most effective in identifying patients with metastatic disease?
20. Is there any evidence to show which imaging technique(s) are most effective in identifying recurrence of breast cancer?

Psychosocial issues

21. What techniques have been shown to be useful in establishing the level of psychological distress in breast cancer patients, and in identifying the level at which intervention becomes appropriate?
22. What evidence is there that identifies effective techniques for psychosocial support for breast cancer patients and/or their carers and families?
23. What communication methods have been shown to be most effective in improving patient satisfaction or psychosocial morbidity, and what skills are required of those delivering information to patients?
24. Is there any evidence to support the introduction of specialist palliative care at any particular stage in the development of the disease?

Ductal carcinoma in situ

25. What evidence is there to identify effective treatments for ductal carcinoma in situ?

Additional questions

26. What evidence is there that supports a specific role for the primary care team in the overall care of breast cancer patients?
27. What evidence is there that supports a specific role for breast cancer nurses in the overall care of breast cancer patients?
28. What evidence is there to suggest that multidisciplinary teams or specialist cancer centres improve patient outcomes?
29. Is there any evidence to suggest that a different approach to breast cancer in elderly patients will bring about an improvement in outcome?

Annex 2

TNM STAGING

T - PRIMARY TUMOUR

- TX Primary tumour cannot be assessed
- T0 No evidence of primary tumour
- Tis Carcinoma in situ: intraductal carcinoma, or lobular carcinoma in situ, or Paget disease of the nipple with no tumour¹
- T1 Tumour 2cm or less in greatest dimension²
- T1mic Microinvasion 0.1cm or less in greatest dimension
- T1a More than 0.1cm but not more than 0.5cm in greatest dimension
- T1b More than 0.5cm but not more than 1cm in greatest dimension
- T1c More than 1cm but not more than 2cm in greatest dimension
- T2 Tumour more than 2cm but not more than 5cm in greatest dimension
- T3 Tumour more than 5cm in greatest dimension
- T4 Tumour of any size with direct extension to chest wall³ or skin
- T4a Extension to chest wall
- T4b Oedema (including peau d'orange), or ulceration of the skin of the breast, or satellite skin nodules confined to the same breast
- T4c Both 4a and 4b, above
- T4d Inflammatory carcinoma⁴

N - REGIONAL LYMPH NODES

- NX Regional lymph nodes cannot be assessed (eg previously removed)
- N0 No regional lymph node metastasis
- N1 Metastasis to movable ipsilateral axillary node(s)
- N2 Metastasis to ipsilateral axillary node(s) fixed to one another or to other structures
- N3 Metastasis to ipsilateral internal mammary lymph node(s)

M - DISTANT METASTASIS

- MX Distant metastasis cannot be assessed
- M0 No distant metastasis
- M1 Distant metastasis

Notes:

1. Paget disease associated with a tumour is classified according to the size of the tumour
2. Microinvasion is the extension of cancer cells beyond the basement membrane into the adjacent tissues with no focus more than 0.1cm in greatest dimension. When there are multiple foci of microinvasion, the size of only the largest focus is used to classify the microinvasion. (Do not use the sum of all the individual foci.). The presence of multiple foci of microinvasion should be noted, as it is with multiple larger invasive carcinomas.
3. Chest wall includes ribs, intercostal muscles, and serratus anterior muscle but not pectoral muscle
4. Inflammatory carcinoma of the breast is characterized by diffuse, brawny induration of the skin with an erysipeloid edge, usually with no underlying mass. If the skin biopsy is negative and there is no localized measurable primary cancer, the T category is pTX when pathologically staging a clinical inflammatory carcinoma (T4d). Dimpling of the skin, nipple retraction, or other skin changes, except those in T4b and T4d, may occur in T1, T2, or T3 without affecting the classification.

Source: International Union Against Cancer (UICC). *TNM Classification of malignant tumours*. Edited by L.H. Sobin and Ch. Wittekind.. 5th ed. New York: Wiley-Liss; 1997.

References

- 1 Information and Statistics Division Scotland. Information and Statistics. Cancer Breast. Overview. [cited 3 October 2005] Available from url: [http://www.isdscotland.org/isd/cancer_definition.jsp?ContentID=1420&p_applic=CCC&p_service=Contentshow&ScottishIntercollegiateGuidelinesNetwork\(SIGN\).Breastcancerinwomen.Edinburgh:SIGN;1998.\(SIGNpublicationno.29\).](http://www.isdscotland.org/isd/cancer_definition.jsp?ContentID=1420&p_applic=CCC&p_service=Contentshow&ScottishIntercollegiateGuidelinesNetwork(SIGN).Breastcancerinwomen.Edinburgh:SIGN;1998.(SIGNpublicationno.29).)
- 2 Scottish Intercollegiate Guidelines Network (SIGN). Breast cancer in women. Edinburgh: SIGN; 1998. (SIGN publication no. 29).
- 3 Scottish Intercollegiate Guidelines Network (SIGN). A guideline developer's handbook. Edinburgh: SIGN; 2004 (SIGN publication no. 50). [cited 1 September 2005]. Available from url: <http://www.sign.ac.uk>
- 4 NHS Breast Screening Programme. Breast screening: a pocket guide. Sheffield: The Programme; 2002. [cited 13 Jun 2005]. Available from url: <http://www.cancerscreening.nhs.uk/breastscreen/publications/ia-01.html>
- 5 Chiu LF. Straight talking: communicating breast screening information in primary care. Leeds: Nuffield Institute for Health; 2002. [cited 13 Jun 2005]. Available from url: <http://www.cancerscreening.nhs.uk/breastscreen/publications/pc-06.html>
- 6 McIntosh A, Shaw C, Evans G, Turnbull N, Bahar N, Barclay M, et al. Clinical guidelines and evidence review for the classification and care of women at risk of familial breast cancer. London: National Collaborating Centre for Primary Care/University of Sheffield; 2004. [cited 14 Jun 2005] Available from url: <http://www.nice.org.uk/page.aspx?o=203183>
- 7 Scottish Intercollegiate Guidelines Network (SIGN). Long term follow up of survivors of childhood cancer. Edinburgh: SIGN; 2004. (SIGN publication no. 76).
- 8 Thomas DB, Gao DL, Ray RM, Wang WW, Allison CJ, Chen FL. Randomized trial of breast self-examination in Shanghai: final results. *J Natl Cancer Inst* 2002;94(19):1445-57.
- 9 Kösters JP, Göttsche PC. Regular self-examination or clinical examination for early detection of breast cancer (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2004. Chichester, UK: John Wiley & Sons, Ltd.
- 10 Austoker J. Screening and self examination for breast cancer. In: *Cancer prevention in primary care*. London: BMJ Publishing Group; 1995. p. 75-94.
- 11 NHS Breast Screening Programme. Quality assurance guidelines for radiologists. Sheffield: The Programme; 1997. (NHSBSP publication no. 15).
- 12 Stokell PJ, Robb JD. SPIDER-1 Software for evaluating the detriment associated with radiation exposure. Chilton: National Radiological Protection Board; 1993.
- 13 Royal College of Radiologists. NHS Breast Screening Programme. London: The College; 1997.
- 14 Law J. Risk and benefit associated with radiation dose in breast screening programmes-an update. *Br J Radiol* 1995;68:870-6.
- 15 Young KC, Ramsdale ML, Rust A. Mammographic dose and image quality in the UK Breast Screening Programme. Sheffield: NHS Breast Screening Programme; 1995. (NHSBSP publication no. 35).
- 16 Young KC, Ramsdale ML, Rust A. National survey of mammographic image quality and dose in the UK Breast Screening Programme. Sheffield: NHS Breast Screening Programme; 1998. (NHSBSP publication no. 37).
- 17 Burch A, Goodman DA. A pilot survey of radiation doses received in the United Kingdom Breast Screening Programme. *Br J Radiol* 1998;71:517-27.
- 18 Austoker J, Mansel R, Baum M, Sainsbury R, Hobbs R. Guidelines for referral of patients with breast problems. 2nd revised ed. Sheffield: NHS Cancer Screening Programmes; 2003. [cited 21 June 2005]. Available from url: <http://www.cancerscreening.nhs.uk/breastscreen/publications/pc-rgfw-01.html>
- 19 Dixon JM, Mansel RE. Symptoms, assessment and guidelines for referral. In: Dixon JM, editor. *ABC of breast diseases*. London: BMJ Publishing Group; 1995. p. 1-5.
- 20 Scottish Executive. Scottish referral guidelines for suspected cancer. Edinburgh: The Executive; 2002. [cited 2 June 2004]. Available from url: <http://www.scotland.gov.uk/library/5/health/rgsc.pdf>
- 21 Richards, M. A., Westcombe, A. M., Love, S. B., Littlejohns, P. and Ramirez, A. J. Influence of delay on survival in patients with breast cancer: A systematic review. *Lancet* 1999;353;1119-1126.
- 22 Morris KT, Pommier RF, Morris A, Schmidt WA, Beagle G, Alexander PW, et al. Usefulness of the triple test score for palpable breast masses. *Arch Surg*. 2001;136:1008-13.
- 23 Eltahir A, Jibril JA, Squair J, Heys SD, Ah-See AK, Needham G, et al. The accuracy of "one-stop" diagnosis for 1,110 patients presenting to a symptomatic clinic. *J R Coll Surg Edinb* 1999;44:226-30.
- 24 Scottish Intercollegiate Guidelines Network (SIGN). The Immediate Discharge Document. Edinburgh: SIGN; 2003. (SIGN publication no. 65). [cited 2 June 2004]. Available from url: <http://www.sign.ac.uk/>
- 25 Harcourt D, Ambler N, Rumsey N, Cawthorn SJ. Evaluation of a one-stop breast lump clinic: a randomized controlled trial. *Breast* 1998;7(6):314-9.
- 26 Dey P, Bundred N, Gibbs A, Hopwood P, Baildam A, Boggis C., et al. Costs and benefits of a one stop clinic compared with a dedicated breast clinic: randomised controlled trial. *BMJ* 2002;324(7336):507.
- 27 Harms SE, Flamig DP. MR imaging of the breast. *J Magn Reson Imaging* 1993;3:277-83.
- 28 Stelling CB. MR imaging of the breast for cancer evaluation. Current status and future direction. *Radiolog Clin North Am* 1995;33:1187-204.
- 29 Weinreb JC, Newstead G. MR imaging of the breast. *Radiology* 1995;196:593-610.
- 30 Khatri VP, Stuppino JJ, Espinosa MH, Pollack MS. Improved accuracy in differentiating malignant from benign mammographic abnormalities. *Cancer* 2001;92: 471-8.
- 31 Kristoffersen Wiberg M, Aspelin P, Perbeck L, Bone B. Value of MR Imaging in Clinical Evaluation of Breast Lesions. *Acta Radiologica* 2002;43:275-81.
- 32 Drew PJ, Turnbull LW, Chatterjee S, Read J, Carleton PJ, Fox JN, et al. Prospective comparison of standard triple assessment and dynamic magnetic resonance imaging of the breast for the evaluation of symptomatic breast lesions. *Ann Surg* 1999;230:680-5.
- 33 International Consensus Conference – Image-detected breast cancer: state of the art diagnosis and treatment. *Breast J*. 2002;8(2):70-6.
- 34 Azzarelli A, Guzzon A, Pilotti S, Quagliuolo V, Bono A, Di Pietro S. Accuracy of breast cancer diagnosis by physical, radiologic and cytologic combined examinations. *Tumori* 1983; 69: 137-41.
- 35 Dixon JM, Anderson TJ, Lamb J, Nixon SJ, Forrest AP. Fine needle aspiration cytology in relationship to clinical examination and mammography in the diagnosis of a solid breast mass. *Br J Surg* 1984; 71: 593-6
- 36 Di Pietro S, Fariselli G, Bandieramonte G, Lepera P, Coopmans de Yoldi G, Viganotti G, et al. Diagnostic efficacy of the clinical-radiological-cytological triad in solid breast lumps: results of a second prospective study on 631 patients. *Eur J Surg Oncol* 1987; 13: 335-40.
- 37 Hermansen C, Skovgaard Poulsen H, Jensen J, Langfeldt B, Steenskov V, Frederiksen P, et al. Diagnostic reliability of combined physical examination, mammography and fine-needle puncture ("triple-test") in breast tumours. A prospective study. *Cancer* 1987; 60: 1866-71.
- 38 Butler JA, Vargas HI, Worthen N, Wilson SE. Accuracy of combined clinical-mammographic-cytologic diagnosis of dominant breast masses. A prospective study. *Arch Surg* 1990; 125: 893-6.
- 39 Martelli G, Pilotti S, Coopmans de Yoldi G, Viganotti G, Fariselli G, Lepera P, et al. Diagnostic efficacy of physical examination, mammography, fine needle aspiration cytology (triple-test) in solid breast lumps: an analysis of 1708 consecutive cases. *Tumori* 1990; 76: 476-9.
- 40 Bassett LW, Ysrael M, Gold RH, Ysrael C. Usefulness of mammography and sonography in women less than 35 years of age. *Radiology* 1991; 180: 831-5.
- 41 Breast Surgeons Group of the British Association of Surgical Oncology. Guidelines for surgeons in the management of symptomatic breast disease in the United Kingdom. *Eur J Surg Oncol* 1995; 21 (Suppl A): 1-13.
- 42 Cancer Care Ontario. Breast Cancer Disease Site Group. Surgical management of early stage invasive breast cancer. 2003. Toronto: Cancer Care Ontario: 2003. (Practice Guideline Report #1-1 Version 2) [cited 12 July 2005]. Available from URL: <http://www.cancercare.on.ca/pdf/pebc1-1f.pdf>
- 43 Veronesi U, Cascinelli N, Mariani L, Greco M, Saccoccio R, Luini A, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med* 2002;347(16):1227-32.
- 44 Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med*. 2002;347(16):1233-41.
- 45 Curran D, van Dongen JP, Aaronson NK, Kiebert G, Fentiman IS, Mignolet F, et al. Quality of life of early-stage breast cancer patients treated with radical mastectomy or breast-conserving procedures: results of EORTC Trial 10801. The European Organization for Research and Treatment of Cancer (EORTC), Breast Cancer Co-operative Group (BCCG). *Eur J Cancer*. 1998;34(3):307-14.
- 46 Veronesi U, Marubini E, Mariani L, Galimberti V, Luini A, Veronesi P, et al. Radiotherapy after breast-conserving surgery in small breast carcinoma: long-term results of a randomized trial. *Ann Oncol*. 2001;12(7):997-1003.
- 47 Holli K, Saaristo R, Isola J, Joensuu H, Hakama M. Lumpectomy with or without postoperative radiotherapy for breast cancer with favourable prognostic features: results of a randomized study. *Br J Cancer*. 2001;84(2):164-9.
- 48 Fisher ER, Anderson S, Tan-Chiu E, Fisher B, Eaton L, Wolmark N. Fifteen-year prognostic discriminants for invasive breast carcinoma: National Surgical Adjuvant Breast and Bowel Project Protocol-06. *Cancer* 2001;91(8 Suppl):1679-87.
- 49 Codner A, Bostwick J. A review of breast reconstruction after mastectomy. *Breast* 1995;4:4-10.
- 50 Thomas PR, Ford HT, Gazet JC. Use of silicone implants after wide local excision of the breast. *Br J Surg* 1993;80:868-70.
- 51 Abbes M, Huss M. Breast and chest wall reconstruction by latissimus dorsi myocutaneous flap (238 cases). *Breast* 1995;4:33-9.
- 52 Lempereur G, Nievergelt J, Park F. Nipple-areola reconstruction. In: *Plastic and reconstructive breast surgery - an atlas*. Berlin: Springer; 1991. p. 141-55.
- 53 Watson JD, Sainsbury JR, Dixon JM. ABC of breast diseases. Breast reconstruction after surgery. *BMJ* 1995;310:117-21.

- 54 Malata CM, Sharpe DT. On the safety of breast implants. *Breast* 1992;1:62-75.
- 55 Veronesi U, Luini A, Galimberti V, Marchini S, Sacchini V, Rilke F. Extent of metastatic axillary involvement in 1446 cases of breast cancer. *Eur J Surg Oncol* 1990;16:127-33.
- 56 Veronesi U, Galimberti V, Zurrada S, Merson M, Greco M, Luini A. Prognostic significance of number and level of axillary node metastases in breast cancer. *The Breast* 1993;2:224-8.
- 57 Chetty U, Jack W, Prescott RJ, Tyler C, Rodger A. Management of the axilla in operable breast cancer treated by breast conservation: a randomized clinical trial. *Edinburgh Breast Unit. Br J Surg.* 2000;87(2):163-9.
- 58 Fisher B, Redmond C, Fisher ER, Bauer M, Wolmark N, Wickerham DL, et al. Ten-year results of a randomized clinical trial comparing radical mastectomy and total mastectomy with or without radiation. *N Engl J Med.* 1985;312(11):674-81.
- 59 Australia. National Health and Medical Research Council. Clinical practice guidelines for the management of early breast cancer. 2nd ed. Canberra: The Council; 2001. (Guideline CP74). [cited 12 July 2005]. Available from URL: <http://www.nhmrc.gov.au/publications/synopses/cp74syn.htm>
- 60 NHS Breast Screening Programme. Pathology reporting in breast cancer screening. 2nd ed. Sheffield: The Programme; 1997 Feb. NHSBSP Publication No. 3.
- 61 Fisher ER, Leeming R, Anderson S, Redmond C, Fisher B. Conservative management of intraductal carcinoma (DCIS) of the breast. Collaborating NSABP investigators. *J Surg Oncol.* 1991;47(3):139-47.
- 62 Yin XP, Li XQ, Neuhauser D, Evans JT. Assessment of surgical operations for ductal carcinoma in situ of the breast. *Int J Technol Assess Health Care.* 1997;13(3):420-9.
- 63 Fisher B, Dignam J, Wolmark N, Mamounas E, Costantino J, Poller W, et al. Lumpectomy and radiation therapy for the treatment of intraductal breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-17. *J Clin Oncol.* 1998;16(2):441-52.
- 64 Julien JP, Bijker N, Fentiman IS, Peterse JL, Delledonne V, Rouanet P, et al. Radiotherapy in breast-conserving treatment for ductal carcinoma in situ: first results of the EORTC randomised phase III trial 10853. *EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. Lancet.* 2000;355(9203):528-33.
- 65 Houghton J, George WD, Cuzick J, Duggan C, Fentiman IS, Spittle M; UK Coordinating Committee on Cancer Research; Ductal Carcinoma in situ Working Party; DCIS trialists in the UK, Australia, and New Zealand. Radiotherapy and tamoxifen in women with completely excised ductal carcinoma in situ of the breast in the UK, Australia, and New Zealand: randomised controlled trial. *Lancet.* 2003;362(9378):95-102.
- 66 Whelan TJ, Lada BM, Laukkanen E, Perera FE, Shelley WE, Levine MN, and the Provincial Breast Disease Site Group. Breast irradiation in women with early stage invasive breast cancer following breast conservation surgery. *Cancer Prevention & Control* 1997;3:228-240.
- 67 Silverstein MJ, Lagios MD, Groshen S, Waisman JR, Lewinsky BS, Martino S, et al. The influence of margin width on local control of ductal carcinoma in situ of the breast. *N Engl J Med.* 1999;340(19):1455-61.
- 68 Fisher B, Dignam J, Wolmark N, Wickerham DL, Fisher ER, Mamounas E, et al. Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial. *Lancet.* 1999;353:1993-2000.
- 69 Cancer Care Ontario. Breast Cancer Disease Site Group. Management of ductal carcinoma in situ of the breast: Toronto; Cancer Care Ontario; 2003. (Practice Guideline Report #1-10). [cited 12 July 2005]. Available from URL: http://www.cancercare.on.ca/pdf/full1_10.pdf
- 70 Chua B, Olivetto IA, Weir L, Kwan W, Truong P, Ragaz J. Increased use of adjuvant regional radiotherapy for node-positive breast cancer in British Columbia. *Breast J.* 2004;10(1):38-44.
- 71 Whelan TJ, Julian J, Wright J, Jadad AR, Levine ML. Does locoregional radiation therapy improve survival in breast cancer? A meta-analysis. *J Clin Oncol* 2000;18(6):1220-9.
- 72 Early Breast Cancer Trialists' Collaborative Group. Radiotherapy for early breast cancer (Cochrane Review). In: The Cochrane Library, Issue 2, 2002. Oxford: Update Software.
- 73 Early Breast Cancer Trialists' Collaborative Group. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. *Lancet.* 2000; 355(9217): 1757-70.
- 74 Malmstrom P, Holmberg L, Anderson H, Mattsson J, Jonsson PE, Tennvall-Nittby L, et al. Breast conservation surgery, with and without radiotherapy, in women with lymph node-negative breast cancer: a randomised clinical trial in a population with access to public mammography screening. *Eur J Cancer* 2003;39:1690-7.
- 75 Early Breast Cancer Trialists' Collaborative Group. Effects of radiotherapy and surgery in early breast cancer: an overview of the randomised trials. *N Engl J Med* 1995;333:1444-1455.
- 76 Lee HD, Yoon DS, Koo JY, Suh CO, Jung WH, Oh KK. Breast conserving therapy in stage I & II breast cancer in Korea. *Breast Cancer Res Treat* 1997;44:193-9.
- 77 Recht A, Edge SB, Solin LJ, Robinson DS, Estabrook A, Fine RE, et al. Postmastectomy radiotherapy: clinical practice guidelines of the American Society of Clinical Oncology. *J Clin Oncol* 2001;19(5):1539-69.
- 78 Kuske RR, Hayden D, Bischoff R, et al. The impact of extracapsular axillary nodal extension (ECE) with and without irradiation on patterns of failure and survival from breast cancer. *Int J Radiat Oncol Biol Phys* 36:277, 1996 (suppl 1, abstr).
- 79 Ewers SB, Attewell R, Baldetorp B, Borg A, Ferno M, Langstrom E, et al. Flow cytometry DNA analysis and prediction of loco-regional recurrences after mastectomy in breast cancer. *Acta Oncol.* 1992;31(7):733-40.
- 80 Ragaz J, Jackson SM, Le N, Plenderleith IH, Spinelli JJ, Basco VE, et al. Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. *N Engl J Med.* 1997;337(14):956-62.
- 81 McArdle CS, Crawford D, Dykes EH, Calman KC, Hole D, Russell AR, et al. Adjuvant radiotherapy and chemotherapy in breast cancer. *Br J Surg.* 1986;73(4):264-6.
- 82 Lacour J, Le M, Caceres E, Koszarowski T, Veronesi U, Hill C. Radical mastectomy versus radical mastectomy plus internal mammary dissection. Ten year results of an international cooperative trial in breast cancer. *Cancer.* 1983;51(10):1941-3.
- 83 Veronesi U, Marubini E, Mariani L, Valagussa P, Zucali R. The dissection of internal mammary nodes does not improve the survival of breast cancer patients. 30-year results of a randomised trial. *Eur J Cancer.* 1999;35(9):1320-5.
- 84 Yamashita T, Hurukawa M, Sekiguchi K, et al. Efficacy of loco-regional lymph nodes irradiation after mastectomy for breast cancer with biopsy proven lymph nodes metastases: A randomized study. *Int J Radiat Oncol Biol Phys* 36:277, 1996 (suppl 1, abstr).
- 85 Freedman GM, Fowble BL, Nicolaou N, Sigurdson ER, Torosian MH, Boraas MC, et al. Should internal mammary lymph nodes in breast cancer be a target for the radiation oncologist? *Int J Radiat Oncol Biol Phys.* 2000;46(4):805-14.
- 86 Bellon JR, Come SE, Gelman RS, Henderson IC, Shulman LN, Silver BJ, et al. Sequencing of chemotherapy and radiation therapy in early-stage breast cancer: updated results of a prospective randomized trial. *J Clin Oncol.* 2005;23(9):1934-40.
- 87 Whelan TJ, Lada BM, Laukkanen E, Perera FE, Shelley WE, Levine MN. Breast irradiation in women with early stage invasive breast cancer following breast conservation surgery. *Provincial Breast Disease Site Group. Cancer Prev Control.* 1997;1(3):228-40.
- 88 National Institute for Clinical Excellence. Improving outcomes for breast cancer: research evidence for the manual update. York; NHS Centre for Reviews and Dissemination; 2002.
- 89 NHS Quality Improvement Scotland. Breast cancer services: national overview. Edinburgh: NHSQIS; 2003. [cited 12 July 2005]. Available from URL: http://www.nhshealthquality.org/nhsqis/files/breast_overview.pdf
- 90 Yamada Y, Ackerman I, Franssen E, MacKenzie RG, Thomas G. Does the dose fractionation schedule influence local control of adjuvant radiotherapy for early stage breast cancer? *Int J Radiat Oncol Biol Phys.* 1999;44(1):99-104.
- 91 Cancer Care Ontario. Breast Cancer Disease Site Group. Use of Bisphosphonates in women with breast cancer. Toronto; Cancer Care Ontario; 2004. (Practice Guideline Report #1-11 Version 2.2002). [cited 2 June 2004]. Available from URL: <http://www.cancercare.on.ca/pdf/pebc1-11f.pdf>
- 92 Polychemotherapy for early breast cancer: an overview of the randomised trials. *Early Breast Cancer Trialists' Collaborative Group. Lancet.* 1998;352(9132):930-42.
- 93 Bonadonna G, Zambetti M, Valagussa P. Sequential or alternating doxorubicin and CMF regimens in breast cancer with more than three positive nodes. Ten-year results *JAMA* 1995;273:542-47.
- 94 Citron ML, Berry DA, Cirincione C, Hudis C, Winer EP, Gradishar WJ, et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. *J Clin Oncol* 2003;21(8):1431-39.
- 95 Fomier MN, Seidman AD, Theodoulou M, Moynahan ME, Currie V, Moasser M, et al. Doxorubicin followed by sequential paclitaxel and cyclophosphamide versus concurrent paclitaxel and cyclophosphamide: 5-year results of a phase II randomized trial of adjuvant dose-dense chemotherapy for women with node-positive breast carcinoma. *Clin Cancer Res* 2001;7(12):3934-41.
- 96 Holmes FA, O'Shaughnessy JA, Vukelja S, Jones SE, Shogan J, Savin M, et al. Blinded, randomized, multicenter study to evaluate single administration pegfilgrastim once per cycle versus daily filgrastim as an adjunct to chemotherapy in patients with high-risk stage II or stage III/IV breast cancer. *J Clin Oncol.* 2002;20(3):727-31.
- 97 Janicke F, Prechtel A, Thomssen C, Harbeck N, Meisner C, Untch M, et al. Randomized adjuvant chemotherapy trial in high-risk, lymph node-negative breast cancer patients identified by urokinase-type plasminogen activator and plasminogen activator inhibitor type 1. *J Natl Cancer Inst* 2001;93(12):913-20.
- 98 Amadori D, Nanni O, Marangolo M, Pacini P, Ravaioli A, Rossi A, et al. Disease-free survival advantage of adjuvant cyclophosphamide, methotrexate, and fluorouracil in patients with node-negative, rapidly proliferating breast cancer: a randomized multicenter study. *J Clin Oncol* 2000;18(17):3125-34.

- 99 Whelan T, Sawka C, Levine M, Gafni A, Reyno L, Willan A, et al. Helping patients make informed choice. *J Natl Cancer Inst* 2003; 95(8): 581-7.
- 100 Berglund G, Nystedt M, Bolund C, Sjoden PO, Rutquist LE. Effect of endocrine treatment on sexuality in premenopausal breast cancer patients: a prospective randomized study. *J Clin Oncol* 2001; 19(11): 2788-96.
- 101 Boccardo F, Rubagotti A, Amoroso D, Mesiti M, Romeo D, Sismondi P, et al. Cyclophosphamide, methotrexate, and fluorouracil versus tamoxifen plus ovarian suppression as adjuvant treatment of estrogen receptor-positive pre-/perimenopausal breast cancer patients: results of the Italian Breast Cancer Adjuvant Study Group 02 randomized trial. *J Clin Oncol* 2000; 18(14): 2718-27.
- 102 Jonat W, Kaufmann M, Sauerbrei W, Blamey R, Cuzick J, Namer M, et al. Goserelin versus cyclophosphamide, methotrexate, and fluorouracil as adjuvant therapy in premenopausal patients with node-positive breast cancer: The Zoladex Early Breast Cancer Research Association Study. *J Clin Oncol* 2002; 20(24): 4628-35.
- 103 Schmid P, Untch M, Wallwiener D, Kosse V, Bondar G, Vassiljev L, et al. Cyclophosphamide, methotrexate and fluorouracil (CMF) versus hormonal ablation with leuporelin acetate as adjuvant treatment of node-positive, premenopausal breast cancer patients: preliminary results of the TABLE-study (Takeda Adjuvant Breast cancer study with Leuporelin Acetate). *Anticancer Res* 2002; 22(4): 2325-32.
- 104 Jakesz R, Hausmaninger H, Kubista E, Gnant M, Menzel C, Bauernhofer T, et al. Randomized adjuvant trial of tamoxifen and goserelin versus cyclophosphamide, methotrexate, and fluorouracil: evidence for the superiority of treatment with endocrine blockade in premenopausal patients with hormone-responsive breast cancer—Austrian Breast and Colorectal Cancer Study Group Trial 5. *J Clin Oncol* 2002; 20(24): 4621-7.
- 105 Vorgias G, Koukouras D, Tzoracoeleftherakis E, Paleogianni V, Androulakis J. Adjuvant tamoxifen versus tamoxifen plus CMF in the treatment of early breast cancer in Greece. Fifteen-year results of a randomised prospective trial and the potential risks of the antioestrogen. *Anticancer Res* 2000; 20(5C): 3849-54.
- 106 Aebi S, Gelber S, Castiglione-Gertsch M, Gelber RD, Collins J, Thurlimann B, et al. Is chemotherapy alone adequate for young women with oestrogen-receptor-positive breast cancer? *Lancet* 2000; 355:1869-74.
- 107 Powles TJ, Hickish TF, Makris A, Ashley SE, O'Brien ME, Tidy VA, et al. Randomized trial of chemoendocrine therapy started before or after surgery for treatment of primary breast cancer. *J Clin Oncol*. 1995; 13(3):547-52.
- 108 van der Hage JA, van de Velde CJ, Julien JP, Tubiana-Hulin M, Vandervelden C, Duchateau L. Preoperative chemotherapy in primary operable breast cancer: results from the European Organization for Research and Treatment of Cancer trial 10902. *J Clin Oncol*. 2001; 19(22):4224-37.
- 109 Deo SV, Bhutani M, Shukla NK, Raina V, Rath GK, Purkayasth J. Randomized trial comparing neo-adjuvant versus adjuvant chemotherapy in operable locally advanced breast cancer (T4b N0-2 M0). *J Surg Oncol*. 2003; 84(4):192-7.
- 110 Heys SD, Hutcheon AW, Sarkar TK, Ogston KN, Miller ID, Payne S, et al. Neoadjuvant docetaxel in breast cancer: 3-year survival results from the Aberdeen trial. *Clin Breast Cancer* 2002; 3(Suppl 2):S69-S74.
- 111 Cocconi G, Di Blasio B, Boni C, Bisagni G, Ceci G, Rondini E, et al. Randomized trial comparing cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) with rotational CMF, epirubicin and vincristine as primary chemotherapy in operable breast carcinoma. *Cancer* 2002; 95(2): 228-35.
- 112 Levine MN, Bramwell VH, Pritchard KI, Norris BD, Shepherd LE, Abu-Zahra H, et al. Randomized trial of intensive cyclophosphamide, epirubicin, and fluorouracil chemotherapy compared with cyclophosphamide, methotrexate, and fluorouracil in premenopausal women with node-positive breast cancer. National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 1998; 16(8):2651-58.
- 113 Henderson IC, Berry DA, Demetri GD, Cirincione CT, Goldstein LJ, Martino S, et al. Improved outcomes from adding sequential Paclitaxel but not from escalating Doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. *J Clin Oncol*. 2003; 21(6):976-83.
- 114 Cancer Care Ontario. Breast Cancer Disease Site Group and Systemic Treatment Disease Site Group. Epirubicin, as a single agent or in combination, for metastatic breast cancer. Toronto; Cancer Care Ontario:2002. (Practice Guideline report #1-6.) [cited 12 July 2005] Available from URL: <http://www.cancercare.on.ca/pdf/pebc1-6f.pdf>
- 115 British Medical Association. Royal Pharmaceutical Society of Great Britain. British National Formulary No. 48. London; BMA:2004. [cited 15 July 2005] Available from URL: <http://www.bnf.org>
- 116 Scottish Medicines Consortium. Pegylated liposomal doxorubicin (Caelyx). Schering-Plough Ltd. Indication: metastatic breast cancer. Glasgow; SMC:2004. [cited on 12 July 2005] Available from URL: <http://www.scottishmedicines.org.uk/updocs/Pegylated%20Liposomal%20Doxorubicin%20HCl.pdf>
- 117 Fossati R, Confalonieri C, Torri V, Ghislandi E, Penna A, Pistotti V, et al. Cytotoxic and hormonal treatment for metastatic breast cancer: a systematic review of published randomized trials involving 31,510 women. *J Clin Oncol*. 1998; 16(10):3439-60.
- 118 Lister-Sharp D, McDonagh MS, Khan KS, Kleijnen J. A rapid and systematic review of the effectiveness and cost-effectiveness of the taxanes used in the treatment of advanced breast and ovarian cancer. *Health Technol Assess* 2000; 4(17):1-113.
- 119 Nabholz JM, Senn HJ, Bezwoda WR, Melnychuk D, Deschenes L, Douma J, et al. Prospective randomized trial of docetaxel versus mitomycin plus vinblastine in patients with metastatic breast cancer progressing despite previous anthracycline-containing chemotherapy. 304 Study Group. *J Clin Oncol*. 1999; 17(5):1413-24.
- 120 Chan S, Friedrichs K, Noel D, Pinter T, Van Belle S, Vorobiof D, et al. Prospective randomized trial of docetaxel versus doxorubicin in patients with metastatic breast cancer. *J Clin Oncol*. 1999; 17(8):2341-54.
- 121 Lewis R, Bagnall AM, Forbes C, Shiran E, Duffy S, Kleijnen J, et al. The clinical effectiveness of trastuzumab for breast cancer. *Health Technol Assess* 2002; 6(13):1-71.
- 122 Baselga J, Tripathy D, Mendelsohn J, Baughman S, Benz CC, Dantis L, et al. Phase II study of weekly intravenous recombinant humanized anti-p185(HER2) monoclonal antibody in patients with HER2/neu-overexpressing metastatic breast cancer. *J Clin Oncol* 1996; 14(3):737-744.
- 123 Cobleigh MA, Vogel CL, Tripathy D, Robert NJ, Scholl S, Fehrenbacher L, et al. Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. *J Clin Oncol* 1999; 17(9):2639-2648.
- 124 Vogel CL, Cobleigh MA, Tripathy D, Gutheil JC, Harris LN, Fehrenbacher L, et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. *J Clin Oncol* 2002; 20(3): 719-26.
- 125 Taylor SG 4th, Gelman RS, Falkson G, Cummings FJ. Combination chemotherapy compared to tamoxifen as initial therapy for stage IV breast cancer in elderly women. *Ann Intern Med* 1986; 104:455-61.
- 126 Mouridsen H, Gershonovich M, Sun Y, Pérez-Carrión R, Boni C, Monnier A, 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.
- 127 Piccart-Gebhart MJ, Procter M, Lelyand-Jones B, Goldhirsch A, Untch M, Smith I et al. Trastuzumab after Adjuvant Chemotherapy in HER2-Positive Breast Cancer. *N Engl J Med* 2005; 353:1659-72.
- 128 Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE, Davidson NE, et al. Trastuzumab plus Adjuvant Chemotherapy for Operable HER2-Positive Breast Cancer. *N Engl J Med* 2005; 353:1673-84.
- 129 Feldman AM, Lorell BH, Reis SE. Trastuzumab in the treatment of metastatic breast cancer: anticancer therapy versus cardiotoxicity. *Circulation* 2000; 102(3):272-4.
- 130 Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med*. 2001; 344(11):783-92.
- 131 Pegram MD, Lipton A, Hayes DF, Weber BL, Baselga JM, Tripathy D, et al. Phase II study of receptor-enhanced chemosensitivity using recombinant humanized anti-p185^{HER2/neu} monoclonal antibody plus cisplatin in patients with HER2/neu-overexpressing metastatic breast cancer refractory to chemotherapy treatment. *J Clin Oncol* 1998; 16:2659-71.
- 132 Fomier MN, Seidman AD, Theodoulou M, Moynahan ME, Currie V, Moasser M, et al. Doxorubicin followed by sequential paclitaxel and cyclophosphamide versus concurrent paclitaxel and cyclophosphamide: 5-Year results of a phase II randomized trial of adjuvant dose-dense chemotherapy for women with node-positive breast carcinoma. *Clin Canc Res* 2001; 7(12):3934-41.
- 133 Cancer Care Ontario. Breast Cancer Disease Site Group. Use of Trastuzumab (Herceptin) in metastatic breast cancer. Toronto; Cancer Care Ontario:2002. (Evidence Summary Report #1-15). [cited on 12 July 2005] Available from URL: <http://www.cancercare.on.ca/pdf/pebc1-11f.pdf>
- 134 Marty M, Cognetti F, Maraninchi D, Snyder R, Mauriac L, Tubiana-Hulin M, et al. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group. *J Clin Oncol*. 2005; 23(19):4265-74.
- 135 Cancer Care Ontario. Breast Cancer Disease Site Group. Capecitabine in Stage IV breast cancer. Toronto; Cancer Care Ontario:2003. (Practice Guideline Report #1-16). [cited on 2 June 2004]. Available from URL: <http://www.cancercare.on.ca/pdf/pebc1-16f.pdf>
- 136 Cancer Care Ontario. Breast Cancer Disease Site Group. Vinorelbine in stage IV breast cancer. Toronto; Cancer Care Ontario:2003. (Evidence Summary #1-4). [cited on 12 July 2005]. Available from URL: <http://www.cancercare.on.ca/pdf/pebc1-4f.pdf>
- 137 Jones S, Winer E, Vogel C, Laufman L, Hutchins L, O'Rourke M et al. Randomized comparison of vinorelbine and melphalan in anthracycline-refractory advanced breast cancer. *J Clin Oncol* 1995; 13:2567-74.
- 138 Venturino A, Comandini D, Simoni C, Merlini L, Naso C, Palumbo R, et al. Is salvage chemotherapy for metastatic breast cancer always effective and well tolerated? A phase II randomized trial of vinorelbine versus 5-fluorouracil plus leucovorin versus combination of mitoxantrone, 5-fluorouracil plus leucovorin. *Breast Cancer Res Treat* 2000; 60:195-200

- 139 Norris B, Pritchard KI, James K, Myles J, Bennett K, Marlin S, et al. Phase III comparative study of vinorelbine combined with doxorubicin versus doxorubicin alone in disseminated metastatic/recurrent breast cancer: National Cancer Institute of Canada Clinical Trials Group Study MA8. *J Clin Oncol* 2000;18:2385-94.
- 140 Talbot DC, Moiseyenko V, Van Belle S, O'Reilly SM, Alba Conejo E, Ackland S, et al. Randomised, phase II trial comparing oral capecitabine (Xeloda) with paclitaxel in patients with metastatic/advanced breast cancer pretreated with anthracyclines. *Br J Cancer* 2002;86:1367-72.
- 141 Blum JL, Jones SE, Buzdar AU, LoRusso PM, Kuter I, Vogel C, et al. Multicenter phase II study of capecitabine in paclitaxel-refractory metastatic breast cancer. *J Clin Oncol* 1999;17:485-93.
- 142 O'Shaughnessy JA, Blum J, Moiseyenko V, Jones SE, Miles D, Bell D, et al. Randomized, open-label, phase II trial of oral capecitabine (Xeloda) vs. a reference arm of intravenous CMF (cyclophosphamide, methotrexate and 5-fluorouracil) as first-line therapy for advanced/metastatic breast cancer. *Ann Oncol* 2001;12:1247-54.
- 143 O'Shaughnessy J, Miles D, Vukelja S, Moiseyenko V, Ayoub JP, Cervantes G, et al. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. *J Clin Oncol* 2002;20:2812-23.
- 144 Pavlakis N, Stockler M. Bisphosphonates for breast cancer (Cochrane Review). In: *The Cochrane Library*, Issue 2, 2002. Oxford: Update Software. 2002.
- 145 Powles T, Paterson S, Kanis JA, McCloskey E, Ashley S, Tidy A, et al. Randomized, placebo-controlled trial of clodronate in patients with primary operable breast cancer. *J Clin Oncol* 2002;20:3219-24.
- 146 Bloomfield DJ. Should bisphosphonates be part of the standard therapy of patients with multiple myeloma or bone metastases from other cancers? An evidence-based review. *J Clin Oncol* 1998;16(3):1218-25.
- 147 Cancer Care Ontario. Breast Cancer Disease Site Group. Adjuvant systemic therapy for node-negative breast cancer. Toronto; Cancer Care Ontario:2002. (Practice Guideline Report #1-8). [cited 12 July 2005]. Available from URL: http://www.ccopecb.ca/guidelines/bre/cpg1_8.html
- 148 Rosen LS, Gordon DH, Dugan W Jr, Major P, Eisenberg PD, Provencher L, et al. Zoledronic acid is superior to pamidronate for the treatment of bone metastases in breast carcinoma patients with at least one osteolytic lesion. *Cancer*. 2004;100(1):36-43.
- 149 Love RR, Duc NB, Allred DC, Binh NC, Dinh NV, Kha NN, et al. Oophorectomy and tamoxifen adjuvant therapy in premenopausal Vietnamese and Chinese women with operable breast cancer. *J Clin Oncol* 2002;20:2559-66.
- 150 Tamoxifen for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. *Lancet*. 1998;351(9114):1451-67.
- 151 Anonymous. Adjuvant ovarian ablation versus CMF chemotherapy in premenopausal women with pathological stage II breast carcinoma: the Scottish trial. Scottish Cancer Trials Breast Group and ICRF Breast Unit, Guy's Hospital, London. *Lancet*. 1993;341(8856):1293-8.
- 152 Kaufmann M, Jonat W, Blamey R, Cuzick J, Namer M, Fogelman I, et al. Survival analyses from the ZEBRA study. goserelin (Zoladex) versus CMF in premenopausal women with node-positive breast cancer. *Eur J Cancer*. 2003;39(12):1711-7.
- 153 Jakesz R, Hausmaninger H, Kubista E, Gnant M, Menzel C, Bauernhofer T, et al. Randomized adjuvant trial of tamoxifen and goserelin versus cyclophosphamide, methotrexate, and fluorouracil: evidence for the superiority of treatment with endocrine blockade in premenopausal patients with hormone-responsive breast cancer—Austrian Breast and Colorectal Cancer Study Group Trial 5. *J Clin Oncol*. 2002;20(24):4621-7.
- 154 Klijn JG, Blamey RW, Boccardo F, Tominaga T, Duchateau L, Sylvester R; Combined Hormone Agents Trialists' Group and the European Organization for Research and Treatment of Cancer. 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(2):343-53.
- 155 Gardner FJ, Konje JC, Abrams KR, Brown LJ, Khanna S, Al-Azzawi F, et al. Endometrial protection from tamoxifen-stimulated changes by a levonorgestrel-releasing intrauterine system: a randomised controlled trial. *Lancet*. 2000;356(9243):1711-7.
- 156 Baum M, Buzdar AU, Cuzick J, Forbes J, Houghton JH, Klijn JG, et al. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. *Lancet*. 2002;359(9324):2131-9.
- 157 Goss PE, Ingle JN, Martino S, Robert NJ, Muss HB, Piccart MJ, et al. Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. *J Natl Cancer Inst*. 2005;97(17):1262-71.
- 158 Eiermann W, Paepke S, Appfelstaedt J, Llombart-Cussac A, Eremin J, Vinholes J, et al. Preoperative treatment of postmenopausal breast cancer patients with letrozole: A randomized double-blind multicenter study. *Ann Oncol*. 2001;12(11):1527-32.
- 159 Recht A, Come SE, Henderson IC, Gelman RS, Silver B, Hayes DF, et al. The sequencing of chemotherapy and radiation therapy after conservative surgery for early-stage breast cancer. *N Engl J Med*. 1996;334(21):1356-61.
- 160 Colleoni M, Bonetti M, Coates AS, Castiglione-Gertsch M, Gelber RD, Price K, et al. Early start of adjuvant chemotherapy may improve treatment outcome for premenopausal breast cancer patients with tumors not expressing estrogen receptors. The International Breast Cancer Study Group. *J Clin Oncol*. 2000;18(3):584-90.
- 161 Shannon C, Ashley S, Smith IE. Does timing of adjuvant chemotherapy for early breast cancer influence survival? *J Clin Oncol*. 2003;21(20):3792-7.
- 162 Bertelli G, Venturini M, Del Mastro L, Bergaglio M, Sismondi P, Biglia N, et al. Intramuscular depot medroxyprogesterone versus oral megestrol for the control of postmenopausal hot flashes in breast cancer patients: a randomized study. *Ann Oncol* 2002;13(6): 883-8.
- 163 Col NF, Hirota LK, Orr RK. Hormone replacement therapy after breast cancer: a systemic review and quantitative assessment of risk. *J Clin Oncol* 2001;19:2357-63.
- 164 Beral V; Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet*. 2003;362(9382):419-27.
- 165 Pritchard, K. I., Khan, H., Levine, M. Steering Committee on Clinical Practice Guidelines for the care and treatment of breast cancer. Clinical practice guidelines for the care and treatment of breast cancer: 14. The role of hormone replacement therapy in women with a previous diagnosis of breast cancer. *CMAJ* 2002. 16;166(8):1017-22.
- 166 Ambler N, Rumsey N, Harcourt D, Khan F, Cawthorn S, Barker J. Specialist nurse counsellor interventions at the time of diagnosis of breast cancer: comparing 'advocacy' with a conventional approach. *J Adv Nurs*. 1999;29(2):445-53.
- 167 Liebert B, Parle M, Roberts C, Redman S, Carrick S, Gallagher J, et al. An evidence-based specialist breast nurse role in practice: a multicentre implementation study. *Eur J Cancer Care (Engl)* 2003;12(1):91-7.
- 168 Royal College of Nursing. A framework for adult cancer nursing. London; The College:2003. [cited 12 July 2005] Available from URL: <http://www.rcn.org.uk/members/downloads/RCNCancerFrameworkAug2003.pdf>
- 169 Maguire GP, Lee EG, Bevington DJ, Kuchemann CS, Crabtree RJ, Cornell CE. Psychiatric problems in the first year after mastectomy. *BMJ* 1978;1:963-5.
- 170 Irvine RN, Brown B, Crooks D, Roberts J, Browne G. Psychosocial adjustment in women with breast cancer. *Cancer* 1991;67:1097-117.
- 171 Kissane DW, Clarke DM, Ikin J, Bloch S, Smith GC, Vitetta L, et al. Psychological morbidity and quality of life in Australian women with early-stage breast cancer: a cross-sectional survey. *Med J Aust* 1998;169(4):192-6.
- 172 National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Guidelines for Supportive Care. Distress Management. [cited 28 September 2005]. Available from url: http://www.nccn.org/professionals/physician_gls/PDF/distress.pdf
- 173 Australia. National Breast Cancer Centre and National Cancer Control Initiative. Clinical practice guidelines for the psychosocial care of adults with cancer. Camperdown; National Breast Cancer Centre:2003.
- 174 Morasso G, Costantini M, Viterbori P, Bonci F, Del Mastro L, Musso M, et al. Predicting mood disorders in breast cancer patients. *Eur J Canc* 2001;37:216-23.
- 175 McLachlan SA, Devins GM, Goodwin PJ. Validation of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (QLQ-C30) as a measure of psychosocial function in Breast cancer patients. *Eur J Cancer* 1998;34(4):510-7.
- 176 Gilbody SM, House AO, Sheldon TA. Routinely administered questionnaires for depression and anxiety: systematic review. *BMJ* 2001;322(7283):406-9.
- 177 Love AW, Kissane DW, Bloch S, Clarke D. Diagnostic efficiency of the Hospital Anxiety and Depression Scale in Women with early stage breast cancer. *Aust N Z J Psychiatry* 2002;36:246-50.
- 178 Classen C, Butler LD, Koopman C, Miller E, DiMiceli S, Giese-Davis J, et al. Supportive-expressive group therapy and distress in patients with metastatic breast cancer: A randomized clinical intervention trial. *Arch Gen Psychiatry* 2001;58(5):494-501.
- 179 Goodwin PJ, Leszcz M, Ennis M, Koopmans J, Vincent L, Guthrie H, et al. The effect of group psychosocial support on survival in metastatic breast cancer. *N Engl J Med* 2001;345(24):1719-26.
- 180 Edmonds CV, Lockwood GA, Cunningham AJ. Psychological response to long-term group therapy: a randomized trial with metastatic breast cancer patients. *Psychooncology*. 1999;8(1):74-91.
- 181 Simpson JS, Carlson LE, Trew ME. Effect of group therapy for breast cancer on healthcare utilization. *Cancer Pract*. 2001;9(1):19-26.
- 182 Edelman S, Bell DR, Kidman AD. Group CBT versus supportive therapy with patients who have primary breast cancer. *J Cognitive Psychother* 1999;13(3):189-202.
- 183 Edelman S, Bell DR, Kidman AD. A group Cognitive Behaviour Therapy programme with metastatic breast cancer patients. *Psychooncology* 1999;8(4):295-305.
- 184 Kissane DW, Bloch S, Smith GC, Miach P, Clarke DM, Ikin J. Cognitive-Existential Group Psychotherapy for women with primary breast cancer: a randomised controlled trial. *Psychooncology*, 2003;12(6):532-46
- 185 Rustoen T, Wiklund I, Hanestad BR, Moum T. Nursing intervention to increase hope and quality of life in newly diagnosed cancer patients. *Cancer Nurs*. 1998;21(4):235-45.

- 186 Meyer TJ, Mark, MM. Effects of psychosocial interventions with adult cancer patients: a meta-analysis of randomized controlled experiments. *Health Psychol.* 1995;14:101-8.
- 187 Greer S, Moorey S, Baruch JD, Watson M, Robertson BM, Mason A, et al. Adjuvant psychological therapy for patients with cancer: a prospective randomized trial. 1992;BMJ, 304: 675-80.
- 188 Devine EC, Westlake SK. The effects of psychoeducational interventions provided to adults with cancer: Meta analysis of 116 studies. *Oncol Nurs Forum* 1995;22(9):1369-81.
- 189 Nezu AM, Nezu CM, Felgoise SH, McClure KS, Houts PS. Project Genesis: assessing the efficacy of problem-solving therapy for distressed adult cancer patients. *J Consult Clin Psychol* 2003;71:1036-48.
- 190 Morrow GR, Dobkin PL. Anticipatory nausea and vomiting in cancer patients undergoing chemotherapy treatment: prevalence, etiology and behavioural interventions. *Clin Psychol Rev* 1988;5:17-56.
- 191 Burish TG, Snyder, SL, Jenkins RA. Preparing patients for cancer chemotherapy: effect of coping preparation and relaxation interventions. *Jf Consult Clin Psychol* 1991;59:518-25.
- 192 Allen SM, Shah AC, Nezu AM, Nezu CM, Ciambone D, Hogan J, et al. A problem-solving approach to stress reduction among younger women with breast carcinoma: randomized controlled trial. *Cancer* 2002;94(12): 3089-100.
- 193 Gustafson DH, Hawkins R, Pingree S, McTavish F, Arora NK, Mendenhall J, et al. Effect of computer support on younger women with breast cancer. *J Gen Intern Med.* 2001;16(7):435-45.
- 194 Rawl SM, Given BA, Given CW, Champion VL, Kozachik SL, Kozachik SL, et al. Intervention to improve psychological functioning for newly diagnosed patients with cancer. *Oncol Nurs Forum.* 2002;29(6):967-75.
- 195 Sandgren AK, McCaul KD, King B, O'Donnell S, Foreman G. Telephone therapy for patients with breast cancer. *Oncol Nurs Forum.* 2000;27(4):683-8.
- 196 Newell SA, Sanson-Fisher RW, Savolainen NJ. Systematic review of psychological therapies for cancer patients: overview and recommendations for future research. *J Natl Cancer Inst.* 2002;94(8):558-84.
- 197 McPherson CJ, Higginson IJ, Hearn J. Effective methods of giving information in cancer" a systematic literature review of randomized controlled trials. *J Public Health Med.* 2001;23(3):227-34.
- 198 Deadman JM, Leinster SJ, Owens RG, Dewey ME, Slade PD. Taking responsibility for cancer treatment. *Soc Sci Med.* 2001;53(5):669-77.
- 199 Kissane DW, Burke S. Psychosocial support for breast cancer patients provided by members of the treatment team: a summary of the literature 1976-1996. King's Cross(NSW);NHMRC National Breast Cancer Centre:1996. [cited 12 July 2005] Available from URL: http://www.nbcc.org.au/bestpractice/resources/MTT_psychosocialsupport.pdf
- 200 Fallowfield LJ, Hall A, Maguire P, Baum M, A'Hern RP. A question of choice: results of a prospective 3 year follow up study of women with breast cancer. *Breast* 1994;3(4):202-8.
- 201 Sepucha KR, Belkora JK, Mutchnick S, Esserman LJ. Consultation planning to help breast cancer patients prepare for medical consultations: effect on communication and satisfaction for patients and physicians. *J Clin Oncol.* 2002;20(11):2695-700.
- 202 Bruera E, Sweeney C, Willey J, Palmer JL, Tolley S, Rosales M, et al. Breast cancer patient perception of the helpfulness of a prompt sheet versus a general information sheet during outpatient consultation: A randomized, controlled trial *J Pain Symptom Manage.* 2003;25(5):412-9.
- 203 Whelan T, Sawka C, Levine M, Gafni A, Reyno L, Willan A, et al. Helping patients make informed choices: a randomized trial of a decision aid for adjuvant chemotherapy in lymph node-negative breast cancer.[comment]. *J Natl Cancer Inst.* 2003;16;95(8):581-7.
- 204 Fellows D, Wilkinson S, Moore P. Communication skills training for health care professionals working with cancer patients, their families and/or carers (Cochrane Review). In: *The Cochrane Library*, Issue 2, 2003. Oxford;Update Software.
- 205 Rojas MP, Telaro E, Russo A, Moschetti I, Coe L, Fossati R, et al. Follow-up strategies for women treated for early breast cancer (Cochrane Review). In: *The Cochrane Library*, Issue 4, 2004. Oxford, Update Software.
- 206 Grunfeld E, Mant D, Yudkin P, Adewuyi-Dalton R, Cole D, Stewart J, Fitzpatrick R, Vessey M. Routine follow up of breast cancer in primary care: randomised trial. *British Medical Journal* 1996;313(7058):665-9.
- 207 Gulliford T, Opomo M, Wilson E, Hanham I, Epstein R. Popularity of less frequent follow-up for breast cancer in randomised study: initial findings from the hotline study. *British Medical Journal* 1997;314:171-7.
- 208 Brown L, Payne S, Royle G. Patient initiated follow up of breast cancer. *Psychooncology* 2002;11:346-55.
- 209 Grunfeld E, Noorani H, McGahan L, Paszat L, Coyle D, van Walraven C, et al. Surveillance mammography after treatment of primary breast cancer: a systematic review. *Breast* 2002;11(3):228-35.
- 210 Flobbe K, van der Linden ES, Kessels AG, van Engelshoven JM. Diagnostic value of radiological breast imaging in a non-screening population. *Int J Cancer.* 2001;92(4):616-8.
- 211 Clinical Standards Board for Scotland. Clinical Standards: Specialist Palliative Care. Rev ed. Edinburgh;Clinical Standards Board for Scotland:2002. [cited 12 July 2005] Available from URL: <http://www.nhshealthquality.org/nhsqis/files/SPC.pdf>
- 212 Scottish Intercollegiate Guidelines Network (SIGN) Control of pain in patients with cancer. Edinburgh:SIGN; 2000. (SIGN guideline no.44). [cited 12 July 2005] Available from URL: <http://www.sign.ac.uk/pdf/sign44.pdf>
- 213 Hearn J, Higginson IJ. Do specialist palliative care teams improve outcomes for cancer patients? A systematic literature review. *Palliat Med.* 1998;12(5): 317-32.
- 214 Homs J, Walsh D, Nelson KA, LeGrand SB, Davis M, Khawam E, et al. The impact of a palliative medicine consultation service in medical oncology. *Support Care Cancer.* 2002;10(4):337-42.

Update to printed guideline

18 Jan 2006

Back cover of Guideline and Quick Reference Guide section on Endocrine therapy recommendation 2 paragraph 3 changed from -

In postmenopausal women with advanced disease, tamoxifen and third generation aromatase inhibitors should be considered before either tamoxifen or megestrol acetate.

to

In postmenopausal women with advanced disease, third generation aromatase inhibitors should be considered before either tamoxifen or megestrol acetate.

RADIOTHERAPY

ADJUVANT RADIOTHERAPY

A Radiotherapy should be given following mastectomy or breast conserving surgery to reduce local recurrence where the benefit to the individual is likely to outweigh risks of radiation related morbidity.

D The supradavicular field should be irradiated in all patients with four or more positive axillary nodes.

PSYCHOLOGICAL CARE

THE ROLE OF THE BREAST CARE NURSE

C All women with a potential or known diagnosis of breast cancer should have access to a breast care nurse specialist for information and support at every stage of diagnosis and treatment.

☒ Contact details and information about the role of the breast care nurse should be available to the patients, their families and all the members of the multidisciplinary team including the primary care team.

IDENTIFYING DISTRESS

B The measurement of the presence of psychological symptoms in women with breast cancer should be tailored to the individual circumstances of the patient (eg presence of high level of distress or risk factors for problems).

B Routinely administered questionnaires are not recommended for the detection of clinically significant psychological symptoms in women with breast cancer who do not have risk factors for severe anxiety or distress.

☒

- Breast cancer services should routinely screen for the presence of distress and risk factors for very high levels of distress from the point of diagnosis onwards (including during follow up review phases).
- Multidisciplinary teams should have agreed protocols for distress assessment and management. These should include recommendations for referral and care pathways.

PSYCHOLOGICAL SUPPORT FOR WOMEN WITH BREAST CANCER AND THEIR FAMILIES

A Group psychological interventions should be available to women with breast cancer who feel it would suit their needs. Supportive expressive therapy has been shown to be effective in advanced cancer and cognitive behavioural therapy for localised, locoregional or advanced disease.

A Cognitive behavioural therapy (in group or individual format according to preference and availability) should be offered to selected patients with anxiety and depressive disorders.

A Computer and telephone-based interventions should not routinely be offered to patients.

COMMUNICATION METHODS

A

- Women with breast cancer should be offered audiotapes or follow up summary letters of important consultations.
- Clinical encounters with women with breast cancer should facilitate patient choice about treatment decisions (assuming patients wish to participate in the decision making process).
- Written agendas, prompt sheets & decisions aids should be used to improve communication with women with breast cancer.
- Clinicians should be encouraged to attend validated training in communication skills.

FOLLOW UP AND PALLIATIVE CARE

C Mammography should be used to detect recurrence in patients who have undergone previous treatment for breast cancer.

B Routine diagnostic tests to screen for distant metastases in asymptomatic women should not be performed.

B Patients with breast cancer should have access to input from a specialist palliative care team.

DIAGNOSIS AND INVESTIGATION

▶ DIAGNOSIS

C Women should be encouraged to become aware of the feel and shape of their breasts, so that they are familiar with what is normal for them.

C Women should be encouraged to report any change from normal to their general practitioner.

A Psychological support should be available to women diagnosed with breast cancer at the clinic.

☒ Referral from primary to specialist care should be made in accordance with the Scottish Cancer Group referral guideline.

▶ INVESTIGATION

B All patients should have a full clinical examination.

B Where a localised abnormality is present, patients should have imaging usually followed by fine needle aspirate cytology or core biopsy.

B A lesion considered malignant following clinical examination, imaging or cytology alone should, where possible, have histopathological confirmation of malignancy before any definitive surgical procedure takes place (eg *mastectomy or axillary clearance*).

D Patients should be seen at a one-stop, multidisciplinary clinic involving breast clinicians, radiologists and cytology.

B In patients with symptomatic disease two-view mammography should be performed as part of triple assessment (*clinical assessment, imaging and tissue sampling*) in a designated breast clinic.

B Mammography is not recommended in women under the age of 35 years unless there is a strong suspicion of carcinoma.

C Magnetic resonance imaging should be considered in specific clinical situations where other imaging modalities are not reliable, or have been inconclusive, and where there are indications that MRI is useful.

SYSTEMIC THERAPY

▶ ADJUVANT CHEMOTHERAPY

A All women under the age of 70 years, with early breast cancer should be considered for adjuvant chemotherapy.

C Women with ER-positive tumours who receive chemotherapy should be considered for additional endocrine therapy, especially if they are under 35 years.

SYSTEMIC THERAPY (CONTD.)

▶ ANTHRACYCLINE AND TAXANE THERAPY

Taxanes are active in the adjuvant setting, but although they have been shown to improve upon some adriamycin-based regimens, there are not yet any published data that they offer additional survival benefits over optimal anthracyclines regimens.

A Anthracyclines should be prescribed in preference to non-anthracycline regimens in the adjuvant setting, as they offer additional benefits. Epirubicin may be preferred as it causes less cardiac adverse effects.

A Taxanes should be considered in patients with advanced disease.

▶ BIOLOGICAL THERAPIES

C Trastuzumab should be reserved for those patients whose tumours have HER2 over-expression.

A Combination therapy of trastuzumab with a taxane is recommended in women with metastatic breast cancer as it is associated with a survival advantage compared to taxane therapy alone.

▶ BISPHOSPHONATES

A Bisphosphonates should be routinely used in combination with other systemic therapy in patients with metastatic breast cancer with bone metastases. The choice of agent for an individual patient depends on individual circumstances.

▶ ENDOCRINE THERAPY

A Premenopausal women whose tumours are not shown to have absent oestrogen or progesterone receptors should be considered for adjuvant endocrine therapy.

A

- In postmenopausal women with breast cancer tamoxifen remains the treatment of choice as initial therapy in the adjuvant setting. If there are relative contraindications to its use (*high risk of thromboembolism or endometrial abnormalities*) or intolerance, an aromatase inhibitor can be used in its place.
- Postmenopausal patients should be considered for a switch to an aromatase inhibitor after either two to three years or after five years of tamoxifen therapy.
- In postmenopausal women with advanced disease, third generation aromatase inhibitors should be considered before either tamoxifen or megestrol acetate.

A In advanced disease, the combination of tamoxifen plus ovarian ablation should be offered ahead of tamoxifen therapy alone.

SURGERY

▶ CONSERVATION SURGERY VERSUS MASTECTOMY

A

- All women with early stage invasive breast cancer who are candidates for breast conserving surgery should be offered the choice of breast conserving surgery (*excision of tumour with clear margins*) or modified radical mastectomy.
- The choice of surgery must be tailored to the individual patient, who should be fully informed of the options and who should be aware that breast irradiation is required following conservation and that further surgery may be required if the margins are positive.

C Breast conserving surgery is contraindicated if:

- the ratio of the size of the tumour to the size of the breast would not result in acceptable cosmesis
- there is multifocal disease or extensive malignant microcalcification on mammogram

- there is a contraindication to local radiotherapy (eg *previous radiotherapy at this site, connective tissue disease, severe heart and lung disease, pregnancy*).

C The possibility of breast reconstruction should be discussed with all patients prior to mastectomy.

▶ SURGICAL MANAGEMENT OF THE AXILLA

A Axillary surgery should be performed in all patients with invasive breast cancer.

▶ MANAGEMENT OF DUCTAL CARCINOMA IN SITU

B Women with ductal carcinoma in situ who are candidates for breast surgery should be offered the choice of lumpectomy or mastectomy.

A Women who have undergone breast conserving surgery should be offered postoperative breast irradiation.

☒ The benefits and harms of hormonal therapy should be discussed with women with ductal carcinoma in situ and treatment decisions made based on individual circumstances.

▶ TIMING OF SURGERY AND CHEMOTHERAPY

C All treatments for patients with early breast cancer should be started as soon as is practical. Young women with oestrogen receptor negative tumours may benefit particularly from early initiation of chemotherapy following surgery.

▶ MANAGEMENT OF MENOPAUSAL SYMPTOMS

B Megestrol acetate or depot intramuscular medroxyprogesterone acetate may be considered to control the severity of hot flushes in women with breast cancer.