Early and locally advanced breast cancer:

diagnosis and treatment

This guideline updates and replaces NICE technology appraisal guidance 109 (docetaxel), 108 (paclitaxel) and 107 (trastuzumab)

This guideline was partially updated in July 2018. The sections that are no longer current are marked as 'Updated 2018' and grey shaded.

Further updates were made in 2023 to sections on arm and shoulder mobility and dose fractionation for external beam radiotherapy, and in 2024 to the section on further surgery after breast-conserving surgery. For the most up to date guidance and evidence reviews, please see https://www.nice.org.uk/guidance/ng101.

Full Guideline
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Foreword

Breast cancer is the most common cancer in women and its management often presents patients and their healthcare professionals with difficult decisions about the most appropriate treatment. For all those affected by breast cancer (including family and carers) it is important to recognise the impact of this diagnosis, the complexity of treatment options and the wide ranging needs and support required throughout this period of care and beyond. We hope that this document will provide helpful and appropriate guidance to both healthcare professionals and patients on the diagnosis and subsequent management of early and locally advanced breast cancer.

The management of breast cancer is such a large topic that it has been necessary to divide it into two separate guidelines: 'Early and locally advanced breast cancer: diagnosis and treatment' and Advanced breast cancer: diagnosis and treatment' (www.nice.org.uk/CG81) which were developed at the same time. It should be appreciated that this guideline is not intended to be an exhaustive textbook of early and locally advanced breast cancer. In addition it has been impossible to cover every aspect of the patient pathway but instead we have concentrated on those areas where it was felt uncertainty or variation in practice exists. We hope that those who use the guideline will find it helpful and informative in decision making and management.

We are very grateful for all the hard work, commitment and common sense of the members of the GDG, particularly the patient and carer members, whose views helped significantly in shaping the document. We would also like to thank the staff at the NCC-C for their considerable support and hard work during the development of this guideline.

Mr James Smallwood
Chair

Dr Adrian Harnett
Clinical Lead

Key priorities

1. Offer MRI of the breast to patients with invasive breast cancer:
   - if there is discrepancy regarding the extent of disease from clinical examination, mammography and ultrasound assessment for planning treatment
   - if breast density precludes accurate mammographic assessment
   - to assess the tumour size if breast conserving surgery is being considered for invasive lobular cancer.

2. Pretreatment ultrasound evaluation of the axilla should be performed for all patients being investigated for early invasive breast cancer and, if morphologically abnormal lymph nodes are identified, ultrasound-guided needle sampling should be offered.

3. Minimal surgery, rather than lymph node clearance, should be performed to stage the axilla for patients with early invasive breast cancer and no evidence of lymph node involvement on ultrasound or a negative ultrasound-guided needle biopsy. SLNB is the preferred technique.

4. Discuss immediate breast reconstruction with all patients who are being advised to have a mastectomy, and offer it except where significant comorbidity or (the need for) adjuvant therapy may preclude this option. All appropriate breast reconstruction options should be offered and discussed with patients, irrespective of whether they are all available locally.

5. Start adjuvant chemotherapy or radiotherapy as soon as clinically possible within 31 days of completion of surgery[1] in patients with early breast cancer having these treatments.

6. Postmenopausal women with ER-positive early invasive breast cancer who are not considered to be at low risk[2] should be offered an aromatase inhibitor, either anastrozole or letrozole, as their initial adjuvant therapy. Offer tamoxifen if an aromatase inhibitor is not tolerated or contraindicated.

7. Patients with early invasive breast cancer should have a baseline dual energy X-ray absorptiometry (DEXA) scan to assess bone mineral density if they:
   - are starting adjuvant aromatase inhibitor treatment
   - have treatment-induced menopause
   - are starting ovarian ablation/suppression therapy.

8. Treat patients with early invasive breast cancer, irrespective of age, with surgery and appropriate systemic therapy, rather than endocrine therapy alone, unless significant comorbidity precludes surgery.

9. Offer annual mammography to all patients with early breast cancer, including DCIS, until they enter the NHSBSP/BTWSP. Patients diagnosed with early breast cancer who are already eligible for screening should have annual mammography for 5 years.

[1] Department of Health (2007). Cancer reform strategy. London: Department of Health. (At present no equivalent target has been set by the Welsh Assembly Government.)

[2] Low-risk patients are those in the EPG or GPG groups in the Nottingham Prognostic Index (NPI) who have a 10 year predictive survival of 96% and 93% respectively. They would have a similar prediction using Adjuvant! Online. High-risk patients are those in groups PPG with 53% or VPG with 39%.

10. Patients treated for breast cancer should have an agreed, written care plan, which should be recorded by a named healthcare professional (or professionals), a copy sent to the GP and a personal copy given to the patient. This plan should include:
    - designated named healthcare professionals
    - dates for review of any adjuvant therapy
    - details of surveillance mammography
    - signs and symptoms to look for and seek advice on
    - contact details for immediate referral to specialist care, and
    - contact details for support services, for example support for patients with lymphoedema.

Key research recommendations

1. What is the effectiveness of cognitive behavioural therapy compared with other psychological interventions for breast cancer patients?

   There is currently a variation in the provision and quality of psychological approaches and services offered to patients with breast cancer. As a consequence of the diagnosis of breast cancer at least a quarter of patients report anxiety and depression and a third report sexual problems.

   Cognitive behavioural therapy (CBT) is one form of psychotherapy that has been proven to treat and reduce depression in many patients including cancer patients. It is a time-limited, structured and direct form of therapy that is well suited to patients with breast cancer. Unfortunately there are no studies that compare CBT in breast cancer patients alone with other forms of intervention. Other forms of psychotherapy include psychodynamic counselling, Gestalt therapy or any other psychological intervention. The comparison group could include support from the breast care nurse specialist, telephone support or pure counselling.

2. In the absence of good data about differences in clinical outcome between axillary radiotherapy and completion axillary lymph node dissection (ALND), entry into appropriate clinical trials, e.g. AMAROS, is recommended for early breast cancer patients when the axilla has been found by sentinel lymph node biopsy (SLNB) to contain metastasis.

   Optimum treatment of the axilla, in patients with early breast cancer, when SLNB has shown tumour positive lymph nodes remains unresolved: completion ALND or axillary radiotherapy both have significant but differing morbidities. Studies, including AMAROS, are needed to determine effectiveness of local control and overall survival, side effects and quality of life, cost effectiveness, and whether the additional information of the total number of involved lymph nodes obtained by ALND is relevant for optimum management. These alternative management strategies would have significant impact on service delivery in the UK. The piecemeal introduction of intraoperative sentinel lymph node assessment with immediate ALND for a positive sentinel lymph node may make such research difficult in the near future.

3. How effective is trastuzumab in patients with invasive breast cancer: (a) as adjuvant therapy without chemotherapy, (b) in terms of scheduling and duration of treatment in patients who are also receiving or who have completed chemotherapy, and (c) as primary systemic treatment in terms of quality of life, side effects, disease recurrence rates, disease-free survival and overall survival?

   In patients with human epidermal growth receptor 2 (HER2)-positive invasive breast cancer trastuzumab is a routine adjuvant therapy, where appropriate, following surgery, chemotherapy and radiotherapy. The recommended scheduling at present is 3-weekly treatment for 1 year but there may be more effective and cost effective regimens. Studies such as PERSEPHONE and HERA 2 year treatment duration study arm have been designed to address these issues. There are few studies assessing the role of trastuzumab as a primary systemic treatment and even fewer using it in endocrine receptor-positive patients treated with endocrine therapy alone and no chemotherapy.

Studies are needed to resolve the questions of scheduling and duration, the place of trastuzumab with endocrine therapy in the absence of adjuvant chemotherapy and its role in primary systemic therapy.

4. What is the effectiveness in patients with early invasive breast cancer of: (a) different hypofractionation radiotherapy regimens (b) partial breast radiotherapy and (c) newer radiotherapy techniques (including intensity modulated radiotherapy), in terms of long term outcomes such as, quality of life, side effects, disease recurrence rates, disease-free survival and overall survival?

   Following breast conservation surgery for invasive breast cancer the international standard radiotherapy practice is to treat the whole breast, giving 50 Gy in 25 fractions of 2 Gy fractions over 5 weeks. A 3-week schedule of 40 Gy in 15 fractions has been used in many centres in the UK for years and this has been supported by the recent publication of the UK Standardisation of Breast Radiotherapy (START) Trial. Further studies may show that it may be possible to use even more hypofractionated regimens, which would be far more convenient for patients and more cost effective if they are equally effective. In addition, with technical advances in radiotherapy treatment planning and delivery, it is possible to give partial breast radiotherapy or dose gradients across the breast in selected patients.

5. For patients who have been treated for early invasive breast cancer or ductal carcinoma in situ (DCIS), what is the optimal frequency and length of surveillance of follow-up mammography?

   There is little evidence that routine follow-up of patients treated for early breast cancer to detect recurrence early, or new primary disease, is either effective or offers any mortality benefit. However, it remains routine practice in virtually all breast units in the UK to provide post-treatment follow-up with regular clinical examination and mammography for at least 5 years. This routine follow-up is usually provided in the secondary care setting and requires significant resources. The consensus of those providing breast cancer treatment is that routine follow-up is beneficial for patient welfare and for monitoring effectiveness of treatment. There are few data on which to base guidelines on the most effective methods of providing follow-up, how frequently and for how long. Prospective randomised comparative studies are required to ascertain the most effective methods for detecting recurrence and new primary disease, and should include:
   - how (by clinical examination and/or imaging and/or serum tumour markers)
   - different patient populations, depending on their risks and toxicities from treatment
   - where (in primary care and/or secondary care) and by whom (by patients, nurses or doctors) these should be provided, and
   - whether such care provides any benefits (such as reduced mortality, morbidity and treatment costs).

Recommendations

Chapter 2: Referral, diagnosis, preoperative assessment and psychological support

Preoperative assessment of the breast and axilla

The routine use of magnetic resonance imaging (MRI) of the breast is not recommended in the preoperative assessment of patients with biopsy-proven invasive breast cancer or ductal carcinoma in situ (DCIS).

Offer MRI of the breast to patients with invasive breast cancer:

- if there is discrepancy regarding the extent of disease from clinical examination, mammography and ultrasound assessment for planning treatment
- if breast density precludes accurate mammographic assessment
- to assess the tumour size if breast conserving surgery is being considered for invasive lobular cancer.

Preoperative staging of the axilla

Pretreatment ultrasound evaluation of the axilla should be performed for all patients being investigated for early invasive breast cancer and, if morphologically abnormal lymph nodes are identified, ultrasound-guided needle sampling should be offered.

Providing information and psychological support

All members of the breast cancer clinical team should have completed an accredited communication skills training programme.

All patients with breast cancer should be assigned to a named breast care nurse specialist who will support them throughout diagnosis, treatment and follow-up.

All patients with breast cancer should be offered prompt access to specialist psychological support, and where appropriate psychiatric services.

Chapter 3: Surgery for early breast cancer

Surgery to the breast

DCIS

For all patients treated with breast conserving surgery for DCIS a minimum of 2 mm radial margin of excision is recommended with pathological examination to NHS Breast Screening Programme reporting standards.

Re-excision should be considered if the margin is less than 2 mm after discussion of the risks and benefits with the patient.

Enter patients with screen-detected DCIS into the Sloane Project[1] (UK DCIS audit).

All breast units should audit their recurrence rates after treatment for DCIS.

[1] www.sloaneproject.co.uk

Paget's disease

Offer breast conserving surgery with removal of the nipple-areolar complex as an alternative to mastectomy for patients with Paget's disease of the nipple, that has been assessed as localised. Offer oncoplastic repair techniques to maximise cosmesis.

Surgery to the axilla

Invasive breast cancer

Minimal surgery, rather than lymph node clearance, should be performed to stage the axilla for patients with early invasive breast cancer and no evidence of lymph node involvement on ultrasound or a negative ultrasound-guided needle biopsy. Sentinel lymph node biopsy (SLNB) is the preferred technique.

SLNB should only be performed by a team that is validated in the use of the technique, as identified in the New Start training programme[2].

Perform SLNB using the dual technique with isotope and blue dye.

Breast units should audit their axillary recurrence rates.

DCIS

Do not perform SLNB routinely in patients with a preoperative diagnosis of DCIS who are having breast conserving surgery, unless they are considered to be at a high risk of invasive disease[3].

Offer SLNB to all patients who are having a mastectomy for DCIS.

Evaluation and management of a positive sentinel lymph node

Offer further axillary treatment to patients with early invasive breast cancer who:

- have macrometastases or micrometastases shown in a sentinel lymph node
- have a preoperative ultrasound guided needle biopsy with histologically proven metastatic cancer.

The preferred technique is axillary lymph node dissection (ALND) because it gives additional staging information.

Do not offer further axillary treatment to patients found to have only isolated tumour cells in their sentinel lymph nodes. These patients should be regarded as lymph node-negative.

Breast reconstruction

Discuss immediate breast reconstruction with all patients who are being advised to have a mastectomy, and offer it except where significant comorbidity or (the need for) adjuvant therapy may preclude this option. All appropriate breast reconstruction options should be offered and discussed with patients, irrespective of whether they are all available locally.

Chapter 4: Postoperative assessment and adjuvant treatment planning

Predictive factors

Assess oestrogen receptor (ER) status of all invasive breast cancers, using immunohistochemistry with a standardised and qualitatively assured methodology, and report the results quantitatively.

Do not routinely assess progesterone receptor status of tumours in patients with invasive breast cancer.

[2] NEW START Sentinel Lymph Node Biopsy Training Programme, Raven Department of Education, Royal College of Surgeons, England.

[3] Patients considered at high risk of invasive disease include those with a palpable mass or extensive microcalcifications.

Test human epidermal growth receptor 2 (HER2) status of all invasive breast cancers, using a standardised and qualitatively assured methodology.

Ensure that the results of ER and HER2 assessments are available and recorded at the multidisciplinary team meeting when guidance about systemic treatment is made.

Adjuvant treatment planning

Consider adjuvant therapy for all patients with early invasive breast cancer after surgery at the multidisciplinary team meeting and ensure that decisions are recorded.

Decisions about adjuvant therapy should be made based on assessment of the prognostic and predictive factors, the potential benefits and side effects of the treatment. Decisions should be made following discussion of these factors with the patient.

Consider using Adjuvant! Online[4] to support estimations of individual prognosis and the absolute benefit of adjuvant treatment for patients with early invasive breast cancer.

Timing of adjuvant treatment

Start adjuvant chemotherapy or radiotherapy as soon as clinically possible within 31 days of completion of surgery[5] in patients with early breast cancer having these treatments.

Chapter 5: Adjuvant systemic therapy

Endocrine therapy for invasive disease

Ovarian suppression/ablation

Do not offer adjuvant ovarian ablation/suppression to premenopausal women with ER-positive early invasive breast cancer who are being treated with tamoxifen and, if indicated, chemotherapy.

Offer adjuvant ovarian ablation/suppression in addition to tamoxifen to premenopausal women with ER-positive early invasive breast cancer who have been offered chemotherapy but have chosen not to have it.

Aromatase inhibitors

Postmenopausal women with ER-positive early invasive breast cancer who are not considered to be at low-risk[6] should be offered an aromatase inhibitor, either anastrozole or letrozole, as their initial adjuvant therapy. Offer tamoxifen if an aromatase inhibitor is not tolerated or contraindicated.

Offer an aromatase inhibitor, either exemestane or anastrozole instead of tamoxifen to postmenopausal women with ER-positive early invasive breast cancer who are not low-risk[7] and who have been treated with tamoxifen for 2-3 years.

Offer additional treatment with the aromatase inhibitor letrozole for 2-3 years to postmenopausal women with lymph node-positive ER-positive early invasive breast cancer who have been treated with tamoxifen for 5 years.

[4] www.adjuvantonline.com

[5] Department of Health (2007). Cancer reform strategy. London: Department of Health. (At present no equivalent target has been set by the Welsh Assembly Government.)

[6] Low-risk patients are those in the EPG or GPG groups in the Nottingham Prognostic Index (NPI) who have a 10 year predictive survival of 96% and 93% respectively. They would have a similar prediction using Adjuvant! Online. High risk are patients in groups PPG with 53% or VPG with 39%.

[7] Low-risk patients are those in the EPG or GPG groups in the Nottingham Prognostic Index (NPI) who have a 10 year predictive survival of 96% and 93% respectively. They would have a similar prediction using Adjuvant! Online. High risk are patients in groups PPG with 53% or VPG with 39%.

The aromatase inhibitors anastrozole, exemestane and letrozole, within their licensed indications, are recommended as options for the adjuvant treatment of early ER-positive invasive breast cancer in postmenopausal women.[8]

The choice of treatment should be made after discussion between the responsible clinician and the woman about the risks and benefits of each option. Factors to consider when making the choice include whether the woman has received tamoxifen before, the licensed indications and side-effect profiles of the individual drugs and, in particular, the assessed risk of recurrence.[9]

Endocrine therapy for DCIS

Do not offer adjuvant tamoxifen after breast conserving surgery to patients with DCIS.

Chemotherapy

Offer docetaxel to patients with lymph node-positive breast cancer patients as part of an adjuvant chemotherapy regimen.

Do not offer paclitaxel as an adjuvant treatment for lymph node-positive breast cancer.

Biological therapy

Offer trastuzumab, given at 3-week intervals for 1 year or until disease recurrence (whichever is the shorter period), as an adjuvant treatment to women with HER2-positive early invasive breast cancer following surgery, chemotherapy, and radiotherapy when applicable.

Assess cardiac function before starting treatment with trastuzumab. Do not offer trastuzumab treatment to women who have any of the following:

- a left ventricular ejection fraction (LVEF) of 55% or less
- a history of documented congestive heart failure
- high risk uncontrolled arrhythmias
- angina pectoris requiring medication
- clinically significant valvular disease
- evidence of transmural infarction on electrocardiograph (ECG)
- poorly controlled hypertension.

Repeat cardiac functional assessments every 3 months during trastuzumab treatment. If the LVEF drops by 10 percentage (ejection) points or more from baseline and to below 50% then trastuzumab treatment should be suspended. Restart trastuzumab therapy only after further cardiac assessment and a fully informed discussion of the risks and benefits with the woman.

Assessment and treatment for bone loss

Bone mineral density

Patients with early invasive breast cancer should have a baseline dual energy X-ray absorptiometry (DEXA) scan to assess bone mineral density if they:

- are starting adjuvant aromatase inhibitor treatment
- have treatment-induced menopause
- are starting ovarian ablation/suppression therapy.

Do not offer a DEXA scan to patients with early invasive breast cancer who are receiving tamoxifen alone, regardless of pretreatment menopausal status.

Bisphosphonates

Offer bisphosphonates to patients identified by algorithms 1 and 2 in 'Guidance for the management of breast cancer treatment-induced bone loss: A consensus position statement from a UK expert group (2008) (see Appendix 2).

[8] This recommendation is from 'Breast cancer (early) – hormonal treatments', NICE technology appraisal guidance 112.

[9] This recommendation is from 'Breast cancer (early) – hormonal treatments', NICE technology appraisal guidance 112.

Chapter 6: Adjuvant radiotherapy

Breast conserving surgery and radiotherapy

Patients with early invasive breast cancer who have had breast conserving surgery with clear margins should have breast radiotherapy.

Offer adjuvant radiotherapy to patients with DCIS following adequate breast conserving surgery[10] and discuss with them the potential benefits and risks.

Post-mastectomy radiotherapy

Offer adjuvant chest wall radiotherapy to patients with early invasive breast cancer who have had a mastectomy and are at a high risk of local recurrence. Patients at a high risk of local recurrence include those with four or more positive axillary lymph nodes or involved resection margins.

Consider entering patients who have had a mastectomy for early invasive breast cancer and who are at an intermediate risk of local recurrence, into the current UK trial (SUPREMO) assessing the value of postoperative radiotherapy. Patients at an intermediate risk of local recurrence include those with one to three lymph nodes involved, lympho-vascular invasion, histological grade 3 tumours, ER-negative tumours, and those aged under 40 years.

Do not offer radiotherapy following mastectomy to patients with early invasive breast cancer who are at low risk of local recurrence (for example, most patients who are lymph node-negative).

Dose fractionation

Use external beam radiotherapy giving 40 Gy in 15 fractions as standard practice for patients with early invasive breast cancer after breast conserving surgery or mastectomy.

Breast boost

Offer an external beam boost to the site of local excision to patients with early invasive breast cancer who have a high risk of local recurrence following breast conserving surgery, with clear margins, and whole breast radiotherapy.

If an external beam boost to the site of local excision following breast conservation is being considered in patients with early invasive breast cancer inform the patient of the side effects associated with this intervention, including poor cosmesis particularly in women with larger breasts.

Radiotherapy to nodal areas

Do not offer adjuvant radiotherapy to the axilla or supraclavicular fossa to patients with early breast cancer who have been shown to be histologically lymph node-negative.

Do not offer adjuvant radiotherapy to the axilla after ALND for early breast cancer.

If ALND is not possible following a positive axillary SLNB or 4-node sample, offer adjuvant radiotherapy to the axilla to patients with early breast cancer[11].

Offer adjuvant radiotherapy to the supraclavicular fossa in patients with early breast cancer and four or more involved axillary lymph nodes.

Offer adjuvant radiotherapy to the supraclavicular fossa to patients with early breast cancer and one to three positive lymph nodes if they have other poor prognostic factors (for example, T3 and/or histological grade 3 tumours, with good performance status).

Do not offer adjuvant radiotherapy to the internal mammary chain to patients with early breast cancer who have had breast surgery.

[10] See recommendation on DCIS margins in Chapter 3.

[11] See recommendation in Chapter 3.

Chapter 7: Primary systemic therapy

Early breast cancer

Treat patients with early invasive breast cancer, irrespective of age, with surgery and appropriate systemic therapy, rather than endocrine therapy alone, unless significant comorbidity precludes surgery.

Preoperative systemic therapy can be offered to patients with early invasive breast cancer who are considering breast conserving surgery that is not advisable at presentation. However, the increased risk of local recurrence with breast conserving surgery and radiotherapy rather than mastectomy after systemic therapy should be discussed with the patient.

Locally advanced or inflammatory breast cancer

Offer patients with locally advanced or inflammatory breast cancer, who have been treated with chemotherapy, local treatment by mastectomy (or in exceptional cases, breast conserving surgery) followed by radiotherapy.

Chapter 8: Complications of local treatment and menopausal symptoms

Complications of local treatment

Lymphoedema

Inform all patients with early breast cancer about the risk of developing lymphoedema and give them relevant written information before treatment with surgery and radiotherapy.

Give advice on how to prevent infection or trauma that may cause or exacerbate lymphoedema to patients treated for early breast cancer.

Ensure that all patients with early breast cancer who develop lymphoedema have rapid access to a specialist lymphoedema service.

Arm mobility

All breast units should have written local guidelines agreed with the physiotherapy department for postoperative physiotherapy regimens.

Identify breast cancer patients with pre-existing shoulder conditions preoperatively as this may inform further decisions on treatment.

Give instructions on functional exercises, which should start the day after surgery, to all breast cancer patients undergoing axillary surgery. This should include relevant written information from a member of the breast or physiotherapy team.

Refer patients to the physiotherapy department if they report a persistent reduction in arm and shoulder mobility after breast cancer treatment.

Menopausal symptoms

Discontinue hormone replacement therapy (HRT) in women who are diagnosed with breast cancer.

Do not offer HRT (including oestrogen/progestogen combination) routinely to women with menopausal symptoms and a history of breast cancer. HRT[12] may, in exceptional cases, be offered to women with severe menopausal symptoms and with whom the associated risks have been discussed.

[12] The summaries of product characteristics state that HRT is contraindicated in women with known, past or suspected breast cancer. Informed consent should be obtained and documented.

Offer information and counselling for all women about the possibility of early menopause and menopausal symptoms associated with breast cancer treatment.

Tibolone or progestogens are not recommended for women with menopausal symptoms who have breast cancer.

The selective serotonin re-uptake inhibitor antidepressants paroxetine[13] and fluoxetine[14] may be offered to women with breast cancer for relieving menopausal symptoms, particularly hot flushes, but not to those taking tamoxifen.

Clonidine, venlafaxine[15] and gabapentin[16] should only be offered to treat hot flushes in women with breast cancer after they have been fully informed of the significant side effects.

Soy (isoflavone), red clover, black cohosh, vitamin E and magnetic devices are not recommended for the treatment of menopausal symptoms in women with breast cancer.

Chapter 9: Complications of local treatment and menopausal symptoms

Follow-up

Follow-up imaging

Offer annual mammography to all patients with early breast cancer, including DCIS until they enter the NHS Breast Screening Programme (NHSBSP)/Breast Test Wales Screening Programme (BTWSP). Patients diagnosed with early breast cancer who are already eligible for screening should have annual mammography for 5 years.

On reaching the NHSBSP/BTWSP screening age or after 5 years of annual mammography follow-up we recommend the NHSBSP/BTWSP stratify screening frequency in line with patient risk category.

Do not offer mammography of the ipsilateral soft tissues after mastectomy.

Do not offer ultrasound or MRI for routine post-treatment surveillance in patients who have been treated for early invasive breast cancer or DCIS.

Clinical follow-up

After completion of adjuvant treatment (including chemotherapy, and/or radiotherapy where indicated) for early breast cancer, discuss with patients where they would like follow-up to be undertaken. They may choose to receive follow-up care in primary, secondary, or shared care.

Patients treated for breast cancer should have an agreed, written care plan, which should be recorded by a named healthcare professional (or professionals), a copy sent to the GP and a personal copy given to the patient. This plan should include:

- designated named healthcare professionals
- dates for review of any adjuvant therapy
- details of surveillance mammography
- signs and symptoms to look for and seek advice on
- contact details for immediate referral to specialist care, and
- contact details for support services, for example support for patients with lymphoedema.

[13] These drugs are not licensed for the stated use. Informed consent should be obtained and documented.
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Methodology

Introduction

What is a clinical guideline?

Guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances – from prevention and self-care through to primary and secondary care and onto more specialised services. NICE clinical guidelines are based on the best available evidence of clinical and cost effectiveness, and are produced to help healthcare professionals and patients make informed choices about appropriate healthcare. While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills.

Clinical guidelines for the NHS in England, Wales and Northern Ireland are produced as a response to a request from the Department of Health (DH). They approve topics for guideline development and before deciding whether to refer a particular topic to the National Institute for Health and Clinical Excellence (NICE) they consult with the relevant patient bodies, professional organisations and companies. Once a topic is referred, NICE then commissions one of seven National Collaborating Centres (NCCs) to produce a guideline. The Collaborating Centres are independent of government and comprise partnerships between a variety of academic institutions, health profession bodies and patient groups. The National Collaborating Centre for Cancer (NCC-C) was referred the topic of breast cancer in October 2003 as part of NICE's ninth wave work programme. Because of the size of this topic, the NCC-C used 2 guideline slots (early breast cancer and advanced breast cancer) to fulfil this remit. However the guideline development process began officially on 10 April 2006 when sufficient capacity became available at the NCC-C.

Who is the guideline intended for?

This guideline does not include recommendations covering every detail of the diagnosis and treatment of early breast cancer. Instead we have tried to focus on those areas of clinical practice that are (i) known to be controversial or uncertain; (ii) where there is identifiable practice variation; (iii) where there is a lack of high-quality evidence; or (iv) where NICE guidelines are likely to have most impact. More detail on how this was achieved is presented later in the section on 'Developing Clinical Evidence Based Questions'.

This guideline is relevant to all healthcare professionals who come into contact with patients with early breast cancer, as well as to the patients themselves and their carers. It is also expected that the guideline will be of value to those involved in clinical governance in both primary and secondary care to help ensure that arrangements are in place to deliver appropriate care to this group of patients.

The remit of the guideline

Guideline topics selected by the DH identify the main areas to be covered by the guideline in a specific remit. The following remit for this guideline was received as part of NICE's ninth wave programme of work:

'To prepare a guideline for the NHS in England and Wales on the clinical management of breast cancer, to supplement existing service guidance. The guideline should cover:

- *the key diagnostic and staging procedures*
- *the main treatment modalities including hormonal treatments*
- *the role of tumour-specific bisphosphonates.'*

What the guideline covers - the scope

The remit was then translated into a scope document by the Guideline Development Group (GDG) Chair and Lead Clinician and staff at the NCC-C. The purpose of the scope was to:

- provide an overview of what the guideline would include and exclude
- identify the key aspects of care that must be included
- set the boundaries of the development work and provide a clear framework to enable work to stay within the priorities agreed by NICE and the NCC-C and the remit
- inform the development of the clinical questions and search strategy
- inform professionals and the public about the expected content of the guideline.

Prior to the commencement of the guideline development process, the scope was subject to a four week stakeholder consultation in accordance with processes established by NICE in the 'NICE guidelines manual' (NICE, 2005, NICE 2006, NICE 2007). The full scope is shown in Appendix 6. During the consultation period, the scope was posted on the NICE website (www.nice.org.uk). Comments were invited from registered stakeholder organisations and the NICE Guideline Review Panel (GRP). Further information about the GRP can also be found on the NICE website. The NCC-C and NICE reviewed the scope in light of comments received, and the revised scope was reviewed by the GRP, signed off by NICE and posted on the NICE website.

Involvement of stakeholders

Key to the development of all NICE guidelines are the relevant professional and patient/carer organisations that register as stakeholders. Details of this process can be found on the NICE website or in the 'NICE guidelines manual' (NICE 2007). In brief, their contribution involves commenting on the draft scope, submitting relevant evidence and commenting on the draft version of the guideline during the end consultation period. A full list of all stakeholder organisations who registered for the early breast cancer guideline can be found in Appendix 8.2.

Needs assessment

As part of the guideline development process the NCC-C invited specialist registrars to undertake a needs assessment. The needs assessment aims to describe the burden of disease and current service provision for patients with breast cancer in England and Wales, which informed the development of the guideline. This document forms a supplement to the full guideline and also appears on the accompanying CD-ROM to this guideline.

Assessment of the effectiveness of interventions is not included in the needs assessment, and was undertaken separately by researchers in the NCC-C as part of the guideline development process.

The information included in the needs assessment document was presented to the GDG. Most of the information was presented in the early stages of guideline development, and other information was included to meet the evolving information needs of the GDG during the course of guideline development.

The Process of Guideline Development – Who Develops the Guideline?

Overview

The development of this guideline was based upon methods outlined by the 'NICE guidelines manual'. A team of health professionals, lay representatives and technical experts known as the

GDG (see Appendix 8.1), with support from the NCC-C staff, undertook the development of this clinical guideline. The basic steps in the process of developing a guideline are listed and discussed below:

- using the remit, define the scope which sets the parameters of the guideline
- forming the guideline development group
- developing clinical questions
- systematically searching for the evidence
- critically appraising the evidence
- incorporating health economic evidence
- distilling and synthesising the evidence and writing recommendations
- agreeing the recommendations
- structuring and writing the guideline
- updating the guideline.

The Guideline Development Group (GDG)

The Early Breast Cancer GDG was recruited in line with the existing NICE protocol as set out in the 'NICE guidelines manual'. The first step was to appoint a Chair and a Lead Clinician. Advertisements were placed for both posts and candidates were informally interviewed prior to being offered the role. The NCC-C Director, GDG Chair and Lead Clinician identified a list of specialties that needed to be represented on the GDG. Requests for nominations were sent to the main stakeholder organisations and patient organisations/charities (see Appendix 8.2). Individual GDG members were selected by the NCC-C Director, GDG Chair and Lead Clinician, based on their application forms, following nomination from their respective stakeholder organisation. The guideline development process was supported by staff from the NCC-C, who undertook the clinical and health economics literature searches, reviewed and presented the evidence to the GDG, managed the process and contributed to drafting the guideline. At the start of the guideline development process all GDG members' interests were recorded on a standard declaration form that covered consultancies, fee-paid work, share-holdings, fellowships and support from the healthcare industry. At all subsequent GDG meetings, members declared new, arising conflicts of interest which were always recorded (see Appendix 8.1).

Guideline Development Group meetings

Fifteen GDG meetings were held between 10-11 April 2006 and 19-20 June 2008. During each GDG meeting (either held over one or two days) clinical questions and clinical and economic evidence were reviewed, assessed and recommendations formulated. At each meeting patient/carer and service-user concerns were routinely discussed as part of a standing agenda item.

NCC-C project managers divided the GDG workload by allocating specific clinical questions, relevant to their area of clinical practice, to small sub-groups of the GDG in order to simplify and speed up the guideline development process. These groups considered the evidence, as reviewed by the researcher, and synthesised it into draft recommendations prior to presenting it to the GDG as a whole. Each clinical question was led by a GDG member with expert knowledge of the clinical area (usually one of the healthcare professionals). The GDG subgroups often helped refine the clinical questions and the clinical definitions of treatments. They also assisted the NCC-C team in drafting the section of the guideline relevant to their specific topic.

Patient/carer members

Individuals with direct experience of early breast cancer services gave an integral user focus to the GDG and the guideline development process. The GDG included three patient/carer members. They contributed as full GDG members to writing the clinical questions, helping to ensure that the evidence addressed their views and preferences, highlighting sensitive issues and terminology relevant to the guideline and bringing service-user research to the attention of the GDG.

Developing Clinical Evidence-Based Questions

Background

The scope, as described in Appendix 6, needs to be very clear about which patient groups are included and which areas of clinical care should be considered. But within these boundaries it does not usually specify which topics are considered a priority.

It was recognised by the NCC-C at an early stage that in order to complete the guideline development work to an appropriate standard the GDG needed to restrict its work to approximately 30 clinical questions. Previously this prioritisation would have been carried out by the GDG at its first two meetings but it was clear from some guidelines already published that this approach had resulted in a much larger number of questions than 30 being addressed.

Clinical guidelines should be aimed at changing clinical practice and should avoid ending up as 'evidence-based textbooks' or making recommendations on topics where there is already agreed clinical practice. It was therefore felt important that the 30 clinical questions should be prioritised into areas that were known to be controversial or uncertain, where there was identifiable practice variation, or where NICE guidelines were likely to have most impact.

Method

An extensive list of potential topics for the guideline to investigate was compiled by the NCC-C Director and GDG Chair and Lead Clinician in consultation with a small number of breast cancer multidisciplinary teams across England and Wales.

This list was incorporated into a questionnaire which asked respondents to rate each topic as low, medium or high clinical priority as well as low or high economic priority. It was made clear that respondents would be rating the priority for each topic to be included in a clinical guideline to be published in two years' time. The questionnaire also asked respondents to suggest any additional topics they would like to see included with an equivalent assessment of their priority.

Questionnaires were subsequently sent to the Breast Cancer Advisory Groups of all 37 cancer networks in England and Wales with a request for a 4-week turnaround. (A list of all cancer networks can be found on the Cancer Action Team website at the DH). Questionnaires were also sent via the Patient and Public Involvement Programme (PPIP) at NICE to all relevant patient/carer stakeholder organisations.

The scores from each completed questionnaire were aggregated by NCC-C staff and ranked. These results together with information on identifiable practice variation (see needs assessment) were presented to the GDG at its first meeting. The list of prioritised topics produced via the questionnaire survey was in no way definitive and the GDG used these results to agree their final priorities for the clinical questions.

For clinical questions about interventions, the PICO framework was used. This structured approach divides each question into four components: the patients (the population under study – P), the interventions (what is being done - I), the comparisons (other main treatment options – C) and the outcomes (the measures of how effective the interventions have been – O). Where appropriate, the clinical questions were refined once the evidence had been searched and, where necessary, sub-questions were generated.

The final list of clinical questions can be found in Appendix 7.

Care Pathway

Early in the development process the GDG drafted an outline care pathway (or algorithm) in order to explore how patients with early breast cancer might access and be dealt with by the NHS.

Review of Clinical Literature

At the beginning of the development phase, initial scoping searches were carried out to identify any relevant guidelines (local, national or international) produced by other groups or institutions.

Additionally, stakeholder organisations were invited to submit evidence for consideration by the GDG, provided it was relevant to the agreed list of clinical questions.

In order to answer each question the NCC-C information specialist developed a search strategy to identify relevant published evidence for both clinical and cost effectiveness. Key words and terms for the search were agreed in collaboration with the GDG. When required, the health economist searched for supplementary papers to inform detailed health economic work, for example modelling (see section on 'Incorporating Health Economic Evidence').

Papers that were published or accepted for publication in peer-reviewed journals were considered as evidence. Search filters, such as those to identify systematic reviews (SRs) and randomised controlled trials (RCTs) were applied to the search strategies when there was a wealth of these types of studies. No language restrictions were applied to the search; however, foreign language papers were not requested or reviewed (unless of particular importance to that question).

The following databases were included in the literature search:

- The Cochrane Library
- Medline and Premedline 1950 onwards
- Excerpta Medica (Embase) 1980 onwards
- Cumulative Index to Nursing and Allied Health Literature (Cinahl) 1982 onwards
- Allied & Complementary Medicine (AMED) 1985 onwards
- British Nursing Index (BNI) 1994 onwards
- Psychinfo 1806 onwards
- Web of Science 1970 onwards. [specifically Science Citation Index Expanded
- (SCI-EXPANDED) and Social Sciences Citation Index (SSCI)]
- System for Information on Grey Literature In Europe (SIGLE) 1980–2005
- Biomed Central 1997 onwards
- National Research Register (NRR)
- Current Controlled Trials.

From this list the information specialist sifted and removed any irrelevant material based on the title or abstract before passing to the researcher. All the remaining articles were then stored in a Reference Manager electronic library.

Searches were updated and re-run 6–8 weeks before the stakeholder consultation, thereby ensuring that the latest relevant published evidence was included in the database. Any evidence published after this date was not included. For the purposes of updating this guideline, July 2008 should be considered the starting point for searching for new evidence.

Further details of the search strategies, including the methodological filters used, are provided in the evidence review (and appear on the accompanying CD-ROM to this guideline).

Critical Appraisal and Evidence Grading

Following the literature search one researcher independently scanned the titles and abstracts of every article for each question, and full publications were obtained for any studies considered relevant or where there was insufficient information from the title and abstract to make a decision. The researcher then individually applied the inclusion/exclusion criteria to determine which studies would be relevant for inclusion and subsequent appraisal. Lists of excluded papers were generated for each question and the rationale for the exclusion was presented to the GDG when required.

The researcher then critically appraised the full papers. Critical appraisal checklists were compiled for each paper and one researcher undertook the critical appraisal and data extraction.

The researcher assessed the quality of eligible studies by referring to the SIGN criteria for systematic reviews/meta-analyses and randomised control trials (Table A). Evidence relating to clinical effectiveness was classified using this established hierarchical system. However this checklist is less appropriate for studies reporting diagnostic tests of accuracy. In the absence of a validated hierarchy for this type of test, NICE suggests levels of evidence that take into account the factors likely to affect the validity of these studies.

Level	Source 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, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2−	Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	Non-analytical studies (for example case reports, case series)
4	Expert opinion, formal consensus

Table A. Levels of evidence for intervention studies. Data source: 'NICE guidelines manual' (NICE 2007).

For all the relevant appraised studies for a particular question, data on the type of population, intervention, comparator and outcomes (PICO) was recorded in evidence tables and an accompanying evidence summary prepared for the GDG (see evidence review). All the evidence was considered carefully by the GDG for accuracy and completeness.

All procedures were fully compliant with NICE methodology as detailed in the 'NICE guidelines manual'.

In general, no formal contact was made with authors; however, there were ad hoc occasions when this was required in order to clarify specific details.

Incorporating Health Economics Evidence

The aim of the economic input into the guideline was to inform the GDG of potential economic issues relating to early breast cancer. It is important to investigate whether health services are both clinically effective and cost effective, i.e. are they 'value for money'.

The health economist helped the GDG by identifying priority topics within the guideline that might benefit from economic analysis, reviewing the available economic evidence and, where necessary, conducting economic analysis. Where published economic evaluation studies were identified that addressed the economic issues for a clinical question, these are presented alongside the clinical evidence wherever possible.

In order to assess the cost effectiveness of each priority topic, a comprehensive systematic review of the economic literature was conducted. For those clinical areas reviewed, the information specialists used a similar search strategy as used for the review of clinical evidence but with the inclusion of a health economics and quality of life filter.

Each search strategy was designed to find any applied study estimating the cost or cost effectiveness of the topic under consideration. A health economist reviewed abstracts and relevant papers were ordered for appraisal.

Published economic evidence was obtained from a variety of sources:

- Medline 1966 onwards
- Embase 1980 onwards
- NHS Economic Evaluations Database (NHS EED)
- EconLit 1969 onwards.

Economic Modelling

In addition to the review of the relevant clinical evidence, the GDG were required to determine whether or not the cost effectiveness of each of the individual clinical questions should be investigated. After the clinical questions were decided, the GDG agreed which topics were an 'economic priority' for modelling. These 'economic priorities' were chosen on the basis of the following criteria, in broad accordance with the 'NICE guidelines manual:

Overall Relevance of the Topic

- *The number of patients affected*: interventions affecting relatively large numbers of patients were given a higher economic priority than those affecting fewer patients
- *The health benefits to the patient:* interventions that that were considered to have a potentially significant impact on both survival and quality of life were given a higher economic priority
- *The per patient cost:* interventions with potentially high financial (cost/savings) implications were given high priority compared to interventions expected to have lower financial implications
- *Likelihood of changing clinical practice:* priority was given to topics that were considered likely to represent a significant change to existing clinical practice.

Uncertainty

- *High level of existing uncertainty*: higher economic priority was given to clinical questions in which further economic analysis was considered likely to reduce current uncertainty over cost effectiveness. Low priority was given to clinical questions when the current literature implied a clearly 'attractive' or 'unattractive' incremental cost effectiveness ratio, which was regarded as generalisable to a UK healthcare setting
- *Likelihood of reducing uncertainty with further analyses (feasibility issues):* when there was poor evidence for the clinical effectiveness of an intervention, then there was considered to be less justification for an economic analysis to be undertaken.

Once the economic priority clinical questions had been chosen, the next task was to perform a systematic review of the cost effectiveness literature. When relevant published evidence was identified and considered to be of sufficient quality, this information was used to inform the recommendation for that specific clinical question. When no relevant cost effectiveness evidence was identified, or when it was not considered to be of reasonable quality, consideration was given to building a de novo economic model. This decision was made by the GDG based on an assessment of the available evidence required to populate a potential economic model.

For those clinical questions where an economic model was required, the information specialist performed supplemental literature searches to obtain additional data for modelling. Assumptions and designs of the models were explained to and agreed by the GDG members during meetings, and they commented on subsequent revisions.

The clinical question in this guideline selected for modelling was chosen because at the time it was considered likely that the recommendations under consideration could substantially change clinical practice in the NHS and have important consequences for resource use. The details of the model are presented in the evidence review and Appendix 3. During the modelling process the following general principles were adhered to:

- the GDG Chair and Clinical Lead were consulted during the construction and interpretation of the model
- the model was based on the best evidence from the systematic review
- model assumptions were reported fully and transparently
- the results were subject to thorough sensitivity analysis and limitations discussed
- costs were calculated from a health services perspective.

Linking to NICE technology appraisals

When this guideline was commissioned there were several published technology appraisals (TAs) and some TAs in development which were relevant to the guideline. Two methodological approaches were taken to link to these pieces of guidance.

1. Technology appraisals in development

   Once the TA had been published, its recommendations were reproduced unchanged in the most appropriate section of the guideline. To ensure accurate exchange of information between the GDG and the appraisals team, a representative from the GDG attended all Appraisal Committee meetings.

2. Published technology appraisals

   Published TAs are periodically reviewed to determine if they need to be updated. If the decision was taken by NICE, after consultation with stakeholders, that a TA should be updated within this guideline the GDG determined whether any new evidence had become available since the publication of the appraisal which meant the original recommendations needed to be changed. Changes to recommendations needed to be supported by cost-effectiveness analysis. Those TAs which were updated into this guideline were subject to the same methodology as all other clinical questions.

   For published TAs which were not due for review during the development of this guideline, their recommendations were reproduced unchanged in the most appropriate section.

Agreeing the Recommendations

For each clinical question the GDG were presented with a summary of the clinical evidence, and where appropriate economic evidence, derived from the studies reviewed and appraised. From this information the GDG were able to derive the guideline recommendations. The link between the evidence and the view of the GDG in making each recommendation is made explicit in the accompanying qualifying statement.

Qualifying Statements

As clinical guidelines are currently formatted, there is limited scope for expressing how and why a GDG made a particular recommendation from the evidence of clinical and cost effectiveness. To make this process more transparent to the reader, the NCC-C felt the need for an explicit, easily understood and consistent way of expressing the reasons for making each recommendation.

The way we have chosen to do this is by writing a 'qualifying statement' to accompany every recommendation and will usually cover:

- the strength of evidence about benefits and harms for the intervention being considered
- the degree of consensus within the GDG
- the costs and cost effectiveness (if formally assessed by the health economics team).

Where evidence was weak or lacking the GDG agreed the final recommendations through informal consensus. Shortly before the consultation period, ten key priorities and five key research recommendations were selected by the GDG for implementation and the patient algorithm were agreed (see page xxvi for algorithm). To avoid giving the impression that higher grade recommendations are of higher priority for implementation, NICE no longer assigns grades to recommendations.

Consultation and Validation of the Guideline

The draft of the guideline was prepared by NCC-C staff in partnership with the GDG Chair and Lead Clinician. This was then discussed and agreed with the GDG and subsequently forwarded to NICE for consultation with stakeholders.

Registered stakeholders (see Appendix 8.2) had one opportunity to comment on the draft guideline and this was posted on the NICE website between 13 August 2008 and 8 October 2008. The GRP also reviewed the guideline and checked that stakeholder comments had been addressed.

Following the consultation period the GDG finalised the recommendations and the NCC-C produced the final document. This was then submitted to NICE for approval and publication on their website. The other versions of the guideline (see below) were also discussed and approved by the GDG and published at the same time.

Other Versions of the Guideline

This full version of the guideline is available to download free of charge from the NICE website (www.nice.org.uk) and the NCC-C website (www.wales.nhs.uk/nccc).

NICE also produces three versions of the early breast cancer guideline which are available from the NICE website:

- the NICE guideline, which is a shorter version of this guideline, containing the key priorities, key research recommendations and all other recommendations
- the Quick Reference Guide (QRG), which is a summary of the main recommendations in the NICE guideline. This is available in hard copy via NICE publications (phone 0845 003 7783)
- Understanding NICE Guidance (UNG), which describes the guideline using non-technical language. It is written chiefly for patients with early breast cancer but may also be useful for family members, advocates or those who care for patients with early breast cancer. This is available in hard copy via NICE publications (phone 0845 003 7783).

Updating the Guideline

Literature searches were repeated for all of the clinical questions at the end of the GDG development process, allowing any relevant papers published before July 2008 to be considered. Future guideline updates will consider evidence published from this cut-off date.

Two years after publication of the guideline, NICE will commission a National Collaborating Centre to determine whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an early update. If not, the guideline will be updated approximately 4 years after publication.

Funding

The National Collaborating Centre for Cancer was commissioned by NICE to develop this guideline. Health economic analysis for this guideline was provided by the London School of Hygiene and Tropical Medicine and funded by the National Collaborating Centre for Cancer.

Disclaimer

The GDG assumes that healthcare professionals will use clinical judgment, knowledge and expertise when deciding whether it is appropriate to apply these guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by the practitioner in light of individual patient circumstances, the wishes of the patient and clinical expertise.

The NCC-C disclaims any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines.

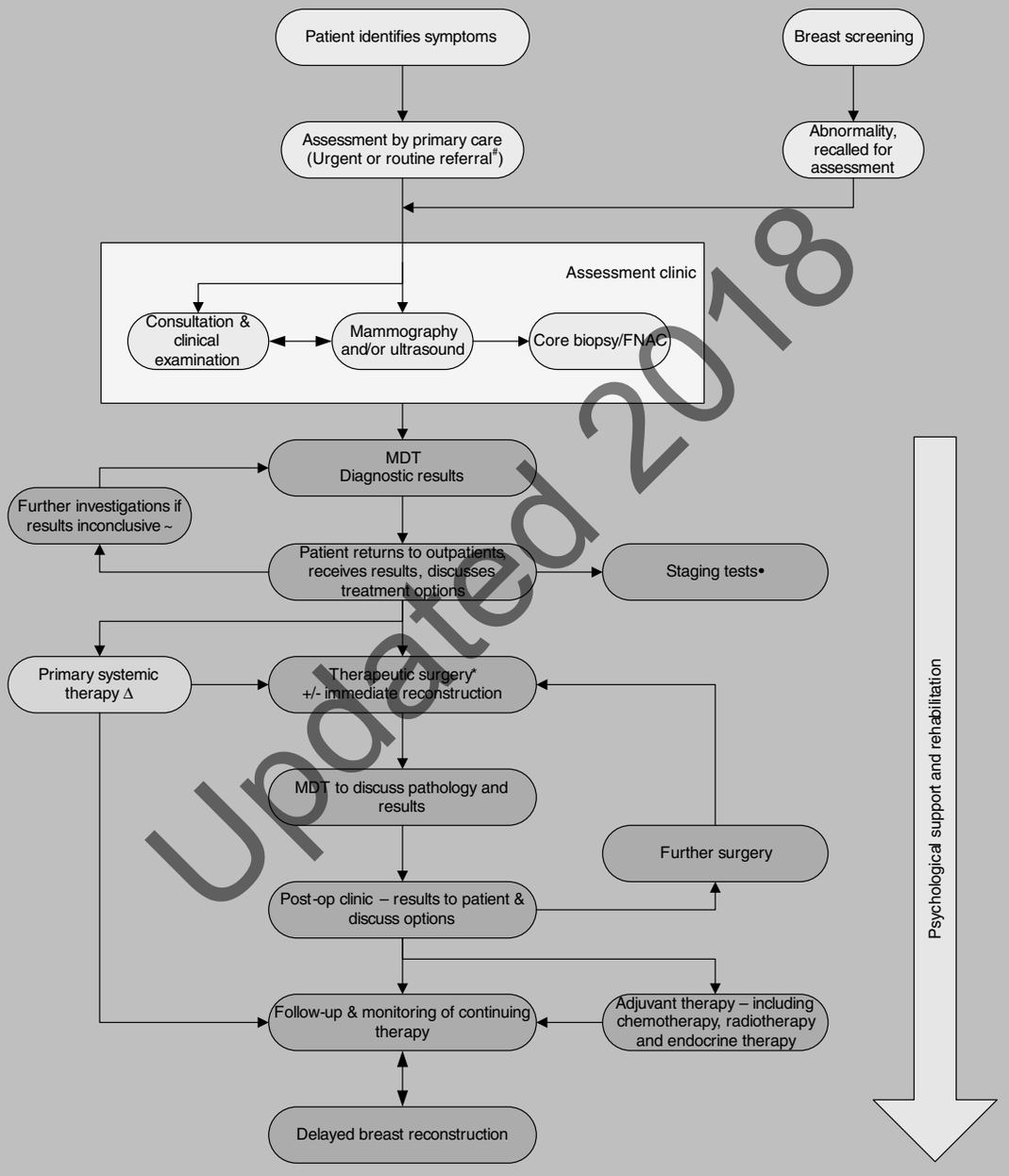
References

National Institute for Health and Clinical Excellence (2005) The guidelines manual. London: National Institute for Health and Clinical Excellence.

National Institute for Health and Clinical Excellence (2006) The guidelines manual. London: National Institute for Health and Clinical Excellence.

National Institute for Health and Clinical Excellence (2007) The guidelines manual. London: National Institute for Health and Clinical Excellence.

Algorithm



Key:

~ Include repeat core biopsy/open biopsy/MRI etc.

* Could include breast conservation (WLE), mastectomy & axillary staging (SLNB, sampling or clearance)

Δ For elderly or unfit patients, surgery may not be appropriate For locally advanced but non metastatic, primary systemic therapy precedes therapeutic surgery in order to reduce size of tumour

• Not all patients will require staging: Scottish Intercollegiate Guidelines Network (2005) Management of breast cancer in women: A national clinical guideline . SIGN Publication No. 84. Edinburgh: SIGN, 2005. ISBN: 1 899893 34 2.

Following the publication of the Cancer Reform Strategy (Department of Health, 2007), by December 2009 all patients presenting with breast problems referred by their GP to a specialist should be seen within two weeks, in England.

1 Epidemiology

1.1 Introduction

The following chapter provides a summary of the full needs assessment that was carried out as part of the evidence review for this guideline and includes current information available regarding the epidemiology of breast cancer regionally, nationally and internationally. Its purpose is to provide the context for this guideline, providing an overview of the size of the problem and disease burden, and assessing whether variation exists. The full needs assessment, which covers both early and advanced breast cancer, appears on the CD-ROM that accompanies this guideline.

1.2 Incidence

Breast cancer is the most commonly occurring cancer in the UK. In 2005 there were 45,947 new cases (Office for National Statistics (ONS), 2008; Welsh Cancer Intelligence and Surveillance Unit, 2008; Information and Statistics Division NHS Scotland, 2008 and Northern Ireland Cancer Registry, 2008) (Table 1.1), which was almost a third of all newly diagnosed cancers. It equates to a crude incidence rate[1] of 76.3 per 100,000 persons. However, all except 287 of these cases were found in women, amongst whom the crude incidence rate was 148.5 per 100,000. The European age-standardised rate[2] of incidence amongst women was 122.5 per 100,000. Amongst men the European age-standardised rate was less than 1 per 100,000. Except where specifically indicated to the contrary, the following data in this chapter describe the epidemiology of breast cancer in women.

[1] Crude incidence rate - the number of new cases of breast cancer over the total population without considering age or other factors, usually expressed as a rate per 100,000 persons per year.

[2] European age-standardised rate - the rate that would have been found if the population had the same age-composition (proportion of total population in each five year age class) as a hypothetical European population, usually expressed per 100,000 persons per year.

	England	Wales	Scotland	N.Ireland	UK
Cases					
Males	250	12	20	5	287
Females	38,212	2,375	3,998	1,075	45,660
Persons	38,462	2,387	4,018	1,080	45,947
Crude rate per 100,000 population					
Males	1.0	0.8	0.8	0.6	1.0
Females	148.6	156.8	151.5	122.1	148.5
Persons	76.2	80.8	78.9	62.6	76.3
Age-standardised rate (European) per 100,000 population					
Males	0.9	0.6	0.7	0.6	0.8
CI 95%	*0.8 1.0*	*0.3 1.0*	*0.4 1.0*	*0.1 1.2*	*0.7 0.9*
Females	123.2	122.2	119.8	110.1	122.5
CI 95%	*122.0 124.4*	*117.3 127.1*	*116.1 123.5*	*103.5 116.7*	*121.4 123.6*
Persons	64.9	64.5	64.5	58.6	64.7
CI 95%	*64.2 65.5*	*61.9 67.0*	*62.5 66.5*	*55.1 62.1*	*64.1 65.3*

Table 1.1 Incidence and incidence rates of new cases of breast cancer in the UK, 2005. Data source: ONS, 2008; Welsh Cancer Intelligence and Surveillance Unit, 2008; Information and Statistics Division NHS Scotland, 2008; and Northern Ireland Cancer Registry, 2008. Reproduced with permission of Cancer Research UK.

Amongst women, the rate of new diagnoses increase rapidly amongst those aged over 40 years, rising from about 1 per 100,000 in young adults to just over 400 per 100,000 in those aged over 85 years (Figure 1.1). Although the highest rate of breast cancer is seen in the eldest age group, the highest numbers of cases are seen in the screened age groups.

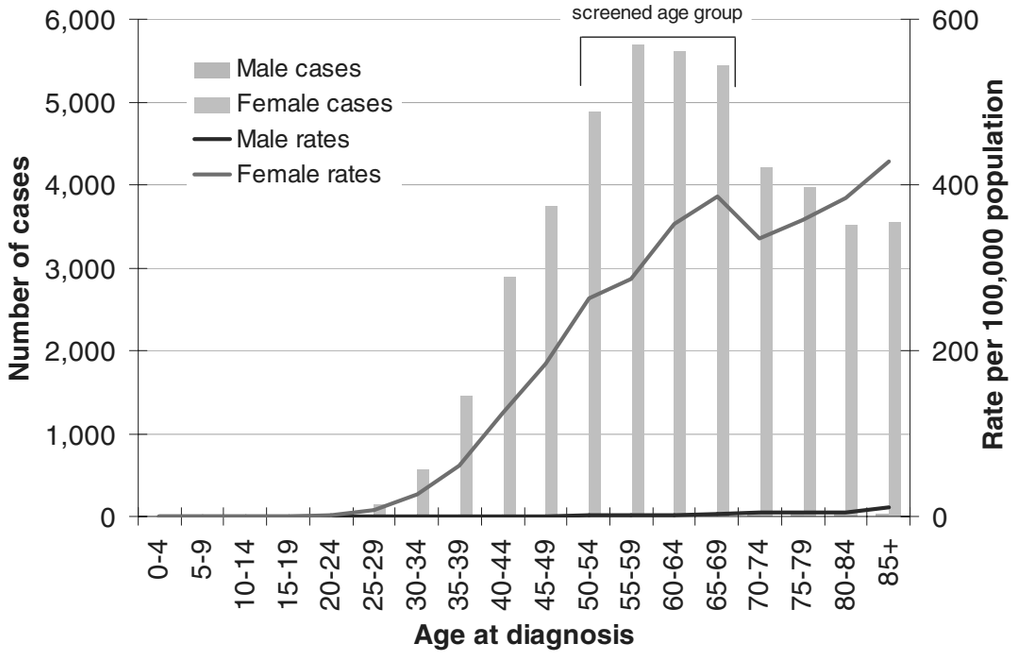


Figure 1.1 Age specific incidence and incidence rates of new cases of breast cancer in the UK, 2005. Data source: ONS, 2008; Welsh Cancer Intelligence and Surveillance Unit, 2008; Information and Statistics Division NHS Scotland, 2008; and Northern Ireland Cancer Registry, 2008. Reproduced with permission of Cancer Research UK.

Studies show that women in lower socioeconomic groups are less likely to develop breast cancer (Garvican and Littlejohns 1998; Faggiano *et al.,* 1997 and Smith *et al.,* 1996). This pattern is opposite to that expected when examining the effect of socioeconomic status on other aspects of health.

There is a slight variation in breast cancer incidence rates between the four countries within the UK (Quinn *et al.,* 2005) but these are not statistically significant in a single year of data after allowing for the different demographic profiles of each country (see Table 1.1). Looking beyond the UK, estimated age-adjusted incidence rates of diagnosed breast cancer in Europe varies by a factor of 2. Countries with the lowest rates comprise Eastern European and Baltic states. Those with highest rates comprise northern European countries including the UK (Ferlay *et al.,* 2007) (Figure 1.2). At a global level, the variation in incidence rates is greater still: rates in developed countries including the UK are 4-5 times higher than many countries in Africa and Asia (Ferlay *et al.,* 2004).

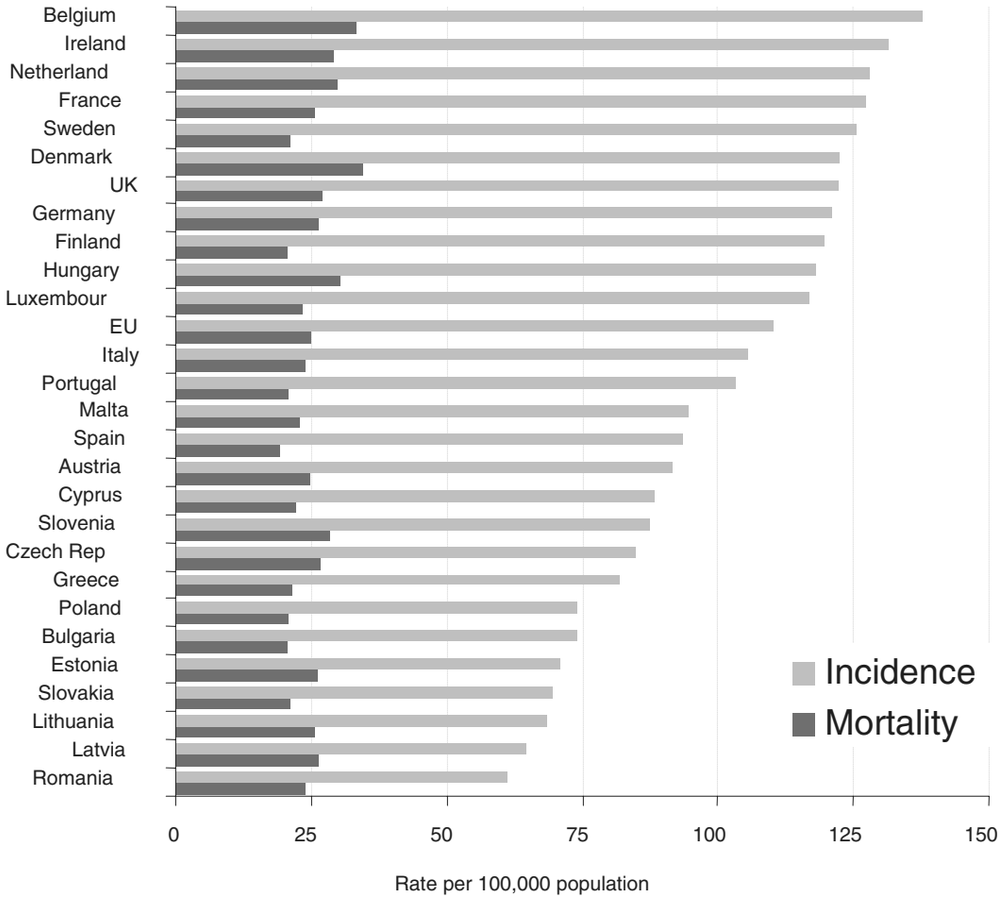


Figure1.2 Age-standardised rates of incidence and mortality in Europe, 2006 estimates. Data source: Ferlay *et al.* 2007. Reproduced with permission of Cancer Research UK.

Studies of UK and Australian residents have shown that the incidence rate of breast cancer for immigrants lies between the rate from their country of birth and their country of residence (dos Santos Silva *et al.,* 2003; Grulich *et al.,* 1995 and Adelstein *et al.,* 1979). For every age group South Asian women and men have a lower incidence than the rest of the UK population (Farooq and Coleman 2005; dos Santos Silva *et al.,* 2003 and Winter *et al.,* 1999).

Trend

Within the UK, the age-standardised incidence rates for England, Wales, Scotland and Northern Ireland increased by about 12% between 1993 and 2004 (ONS, 2008; Welsh Cancer

Intelligence and Surveillance Unit, 2008; Information and Statistics Division NHS Scotland, 2008 and Northern Ireland Cancer Registry, 2008). The effect of the introduction of the National Health Service Breast Screening Programme (NHSBSP) in England was to increase detection and so increase the age specific rates amongst the screened groups (Figure 1.3). This explains only some of the observed increase, and only towards the start of this period. The underlying increase predates national screening and is strongest in older age groups (Coleman, 2000). There is some evidence that the underlying incidence rate of breast cancer may be stabilising (Sant *et al.,* 2006).

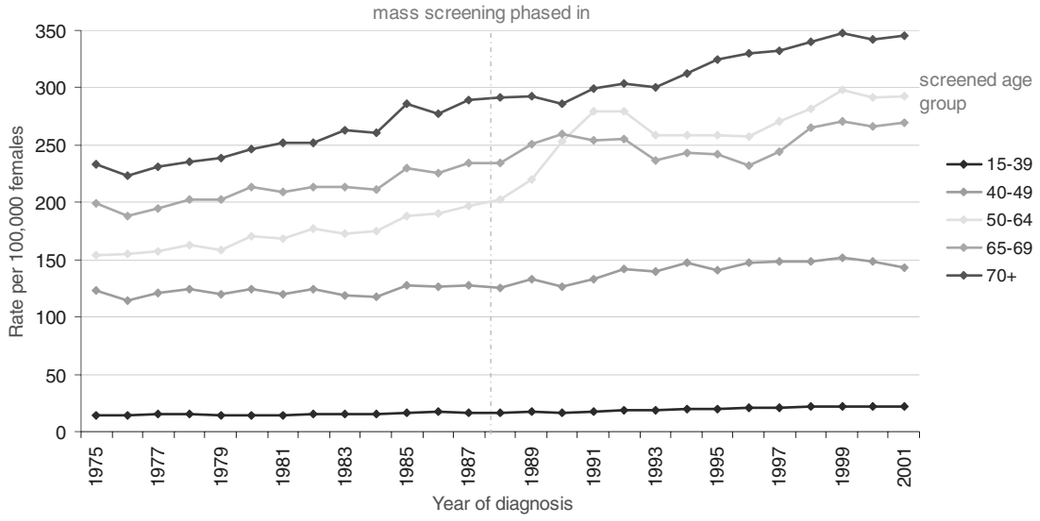


Figure1.3 Trend in age-specific incidence rate of breast cancer in the UK. Data source: ONS 2008; Welsh Cancer Intelligence and Surveillance Unit, 2008; Information and Statistics Division NHS Scotland, 2008; and Northern Ireland Cancer Registry, 2008. Reproduced with permission of Cancer Research UK.

1.3 Prognosis[3]

Breast Cancer Clinical Outcome Measures' (BCCOM) audit (2007) of more than 16,000 cancers diagnosed in 2004 found that the majority of symptomatic cancers were invasive. Where Nottingham Prognostic Index was known tumours were classified into 6 prognostic groups. 51% fell into the three most favourable prognostic groups (excellent, good or moderate). This contrasts with 83% of screen detected tumours that fall into the same three groups.

1.4 Mortality[4]

In 2006 there were 12,392 deaths in the UK caused by breast cancer of which all but 73 were amongst women. Overall these account for more than 1 in 6 of all cancer deaths in women, making it the second most frequent cause of cancer death in women (after lung cancer). Across the UK the European age-standardised mortality rate[5] is 27.7 per 100,000. Female age-specific mortality rates[6] increase sharply after the age of 40 years, peaking at almost 300 per 100,000 in those aged over 85 years (ONS, 2008; Welsh Cancer Intelligence and Surveillance Unit, 2008; Information and Statistics Division NHS Scotland, 2008; Northern Ireland Cancer Registry, 2008).

[3] Prognosis - a prediction of the probable course and outcome of a disease.

[4] Mortality - the number of deaths attributed to breast cancer in a specified period of time in a defined population.

[5] European age-standardised mortality rate - the rate that would have been found if the population had the same age-composition (proportion of total population in each five year age class) as a hypothetical European population, usually expressed per 100,000 persons per year.

[6] Age-specific mortality rate - The number of deaths from breast cancer per 100,000 persons per year for a specific age group. Five-year age groups are commonly used.

Trend

The recent trend in age-standardised breast cancer mortality in the UK has been downward. Since the late 1980s, the rate has reduced by about one third (ONS, 2008; Welsh Cancer Intelligence and Surveillance Unit, 2008; Information and Statistics Division NHS Scotland, 2008; Northern Ireland Cancer Registry, 2008). Reductions in mortality have been greatest in women aged 40-49 (39%), with progressively smaller reductions realised in older age groups (Figure 1.4).

This trend towards decreased mortality is accompanied by a levelling off in incidence and a marked increase in survival. This has been jointly attributed to the introduction of national screening and by improvements in treatment arising from the 1984-85 overview of systemic therapy (Sant *et al.,* 2006).

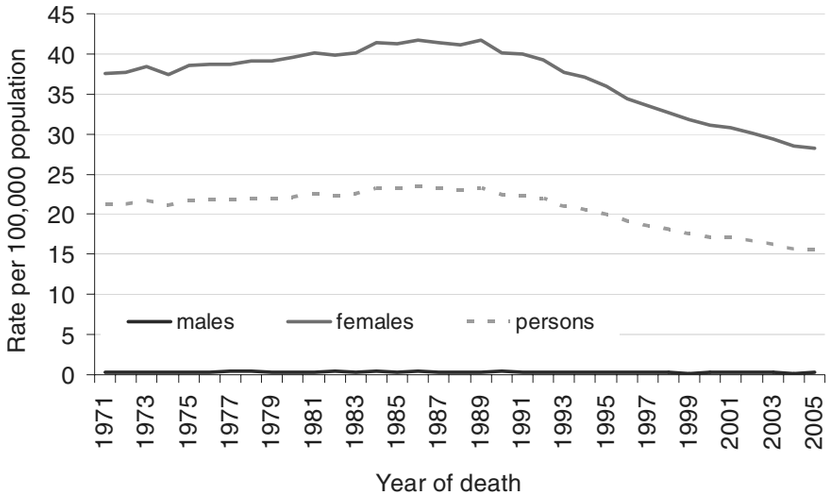


Figure 1.4 Age-standardised rates for breast cancer mortality in the UK, 1971-2005. Data source: ONS, 2008; Welsh Cancer Intelligence and Surveillance Unit, 2008; Information and Statistics Division NHS Scotland, 2008; and Northern Ireland Cancer Registry, 2008. Reproduced with permission of Cancer Research UK.

Recent projections of breast cancer mortality for 2006 by country (Ferlay *et al.,* 2007) show that the UK still has a higher rate (27.3 per 100,000) compared to that of many other European counties (range 16.9 – 34.5 per 100,000). Variations within the UK are smaller, with less than 10% variation between the regions with highest and lowest breast cancer mortality (Quinn *et al.,* 2005).

Mortality from breast cancer follows the same socioeconomic gradient as incidence (Gage *et al.,* 1997 and Faggiano *et al.,* 1997). Women in higher socioeconomic groups are more likely to have breast cancer recorded as their cause of death than those in lower socioeconomic groups. However, the survival in more deprived groups is worse at every stage of the disease (Coleman *et al.,* 2001). Studies have shown that women from lower socioeconomic backgrounds are more likely to be diagnosed with more advanced disease (Downing *et al.,* 2007), with differences more pronounced in the 50-69 age group (Schrijvers *et al.,* 1995). They are also more likely to have a poorer prognosis than affluent women (Garvican and Littlejohns, 1998). This relates to the fact that women from deprived groups are less likely to have their breast tumours diagnosed by screening (Robinson *et al.,* 2006).

Studies using country of birth as a factor have found consistent results that, in UK residents, those born outside the UK have a lower mortality from breast cancer than those born within the UK (Adelstein *et al.,* 1979). This has also been found for other cancers including colon, lung, lymphoma and leukaemia (Winter *et al.,* 1999). Studies of UK and Australian residents have shown that the mortality rate from breast cancer for immigrants lies between the rate from their

country of birth and their country of residence (dos Santos Silva *et al.,* 2003; Grulich *et al.,* 1995 and Adelstein *et al.,* 1979).

1.5 Survival

Estimated five-year relative survival[7] for women aged 50-69 years diagnosed with breast cancer between 2001-03 was over 80% (Coleman *et al.,* 2004). Twenty-year survival (based on projections) for this group is better than 70%. Amongst younger women survival is slightly lower (Figure 1.5). In women aged 70 or over at diagnosis, five-year survival is 70% and twenty-year survival is projected to be about 60%.

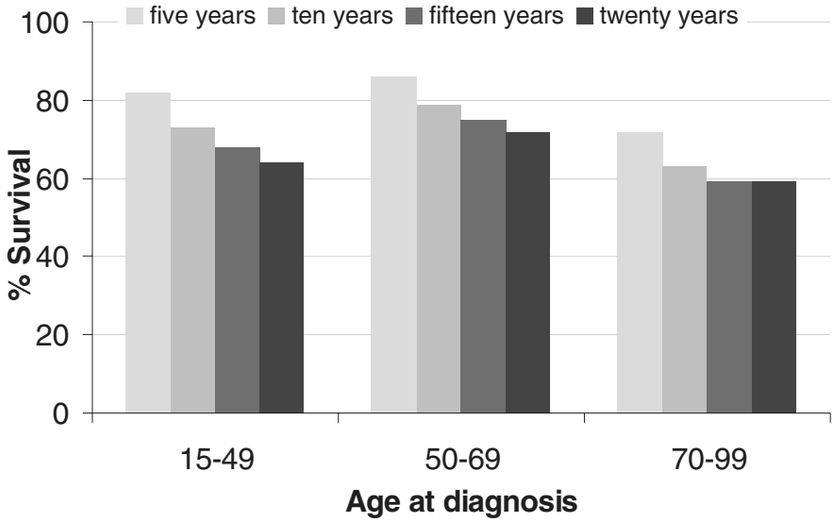


Figure 1.5 Breast cancer five-, ten-, fifteen- and twenty-year relative survival in England and Wales by age at diagnosis, 2001-2003. Data source: Coleman *et al.* 2004. Reproduced with permission of Cancer Research UK.

These rates of survival represent significant increases on historical rates. For example, whereas the overall five-year survival for women diagnosed in 2001-2003 was 80%, as recently as the early 1990s it was less than 70%. In the late 1970s five-year survival was less than 60%. This trend is attributed to the recommendations arising from the 1984-85 world overview of systemic therapy (Early Breast Cancer Triallists' Collaborative Group, 2005).

Survival also varies by staging at time of diagnosis. For women in the West Midlands diagnosed in the late 1980s, actual ten-year survival varied from almost 80% for stage I tumours to less than 5% for stage IV (Cancer Research UK, 2007).

In an international comparison of women diagnosed between 1990-1994, five year survival rates for England and Wales and Scotland were significantly lower than the European average. More advanced stage of disease at diagnosis is argued to be a key explanation for the lower survival rates found in Western Europe, including England, Scotland and Wales amongst people diagnosed in the early 1990s (Coleman, 2003).

There are inequalities in survival for most cancers, including breast cancer, with poorer survival in the lower socioeconomic groups (Pollock and Vickers 1997; Sloggett *et al.,* 2007; Coleman *et al.,* 2001; Garvican and Littlejohns 1998; Coleman *et al.,* 2004; Woods *et al.,* 2005; Schrijvers and Mackenbach, 1994 and Mackenbach *et al.,* 2003). This persists even after allowing for higher premature all cause mortality in the lower than the higher socioeconomic groups (Coleman *et al.,* 2001). Breast cancer survival has improved (Coleman *et al.,* 2001) but

[7] Relative survival - the proportion of people diagnosed with breast cancer who are living at the end of a defined period of time (for example after five or ten years) when compared to similar people of the same age who do not have breast cancer. This measure takes into account deaths from other causes.

the gap in survival between the women resident in the most and least deprived census wards has remained constant (Coleman *et al.,* 2004). This pattern is mirrored in other Western European countries (Mackenbach *et al.,* 2003). For many other cancers this gap in survival widened over this time period (Coleman *et al.,* 2004 and Faggiano *et al.,* 1997).

There is no evidence to support the theory that women, with symptomatic tumours, from higher socioeconomic groups present earlier to services (Garvican and Littlejohns 1998), or that their referral to hospital is more timely (Macleod *et al.,* 2000). Nor is there evidence that differences are due to losses in registration (Coleman *et al.,* 2004).

Women from lower socioeconomic backgrounds, at any age, were more likely to be diagnosed with more advanced disease (Downing *et al.,* 2007), although differences were more pronounced in the 65-99 age group (Schrijvers *et al.,* 1995). However, differences in survival have been found to persist even after adjusting for the stage of disease at diagnosis (Coleman *et al.,* 2001 and Schrijvers *et al.,* 1995) with survival being poorer at every stage of the disease (Garvican and Littlejohns, 1998). Women in the more deprived groups appear to have greater contact with their GP and more unrelated hospital admissions (Macleod *et al.,* 2000). Poorer survival in the most deprived group may be due to higher levels of comorbidity (Macleod *et al.,* 2000) including obesity (Garvican and Littlejohns, 1998).

South Asian women with breast cancer tend to be younger and live in more deprived areas than non-South Asian women in England and Wales (Farooq and Coleman, 2005; Walton *et al.,* 2006; dos Santos Silva *et al.,* 2003 and Velikova *et al.,* 2004). Despite this their survival has been found to be better than others in the UK with similar levels of deprivation (Farooq and Coleman, 2005). Black women have also been found to be younger at diagnosis (Bowen *et al.,* 2008), and to have more aggressive tumour types and poorer survival.

Women from higher socioeconomic groups are more likely to attend for breast screening (Garvican and Littlejohns, 1998) and women with tumours detected by screening have a better prognosis (Garvican and Littlejohns, 1998). Detection by screening may lead to earlier treatment and so improve survival. Women from the South Asian population are also less likely than the non-South Asian population to have screen detected tumours (Walton *et al.,* 2006). Women from the lowest deprivation groups are more likely to have a diagnosis with a poorer prognosis than affluent women (Garvican and Littlejohns, 1998).

1.6 Prevalence[8]

Based on numbers of women diagnosed up to the end of 1992, and historical survival patterns, it has been estimated that in 2003 there were approximately 172,000 women in the UK who have a history of breast cancer. This number is likely to be an underestimate in view of the increases in incidence and survival experienced in the UK since the early 1990s. The proportion of these living with secondary breast cancer is not known (Micheli *et al.,* 2002).

1.7 Treatment

The information available on breast cancer treatment in the UK is more open to interpretation than the preceding epidemiological data. It falls broadly into three types; data recorded to monitor activity, specially collected audit data and published research. The activity data is particularly useful to provide an estimate of the impact of breast cancer on healthcare services and can provide some indication of variation across the country. Activity data cannot currently allow us to assess the number of individuals receiving treatment or reveal patients' journeys through the healthcare system. This may be possible in the future when it is linked to the robust registry data. This will allow the relation of the date of diagnosis, and the registry diagnosis itself, to admissions and procedure data. There is currently no way of examining treatment by stage of disease and the indication for treatment is not recorded, so we cannot say which interventions are intended as treatments and which as palliation.

[8] Prevalence – the number of cases of a disease amongst a defined population at a set point in time.

Hospital Activity

The HES (Hospital Episode Statistics) for England are recorded by hospitals at the time of a patient's episode of care. These include day cases but do not include outpatient episodes so we do not know the level of activity in that setting. A similar system, PEDW (Patient Episode Database Wales), is used in Wales and analysis of this data is also included. These data were obtained from Dr Brian Cottier at NATCANSAT.

Activity over time in England and Wales

Procedures were analysed for hospital admissions associated with a first diagnosis of 'breast neoplasm' from 1997 to 2004. Procedures fall into three groups; 'mastectomy', 'biopsy' or 'other excision' which refers to procedures such as wide local excision or quadrantectomy. The data show that in England there has been an increasing trend in 'mastectomy' and 'other excision' over time, with a decrease in 'biopsy' which may reflect a change in practice or a move to procedures being performed in outpatients. In Wales there is less evidence of a trend. In both countries 'other excision' is performed more frequently than 'mastectomy'. The percentage of procedures related to benign and malignant diagnoses has remained fairly static over the time period, although the absolute numbers have been increasing. Day case procedures are more common than other admissions. The general increase over time appears to have been greatest in the group between 55 and 85 years of age, with the largest absolute numbers falling within the 50 to 65 year age group, the range for the breast screening programme during that time period.

English Data - 2005/06

Further analysis was performed for the English HES data for the single financial year 2005 to 2006, the latest year available, to examine differences by region and length of stay. A single year was chosen to ensure stability when comparing areas such as cancer networks or strategic health authorities (SHAs). Procedures undertaken under general surgery are included for the length of stay analysis to eliminate differences found with the small number of procedures conducted under plastic surgeons; patients that died or were transferred between hospitals were excluded from the analysis.

In 2005/06 the majority of day case procedures (62%) were performed for benign disease and the majority of inpatient procedures (78%) were for malignant disease. The most common procedure performed in either setting is 'other excision' (day case 84.4%, inpatient 58.5%). 83% of all procedures performed were on an inpatient basis. Male patients account for 3.2% of breast procedures, but only 0.5% of those related to a tumour diagnosis. The type of procedure performed varies by the SHA area in which individuals live, illustrated in Figure 1.6.

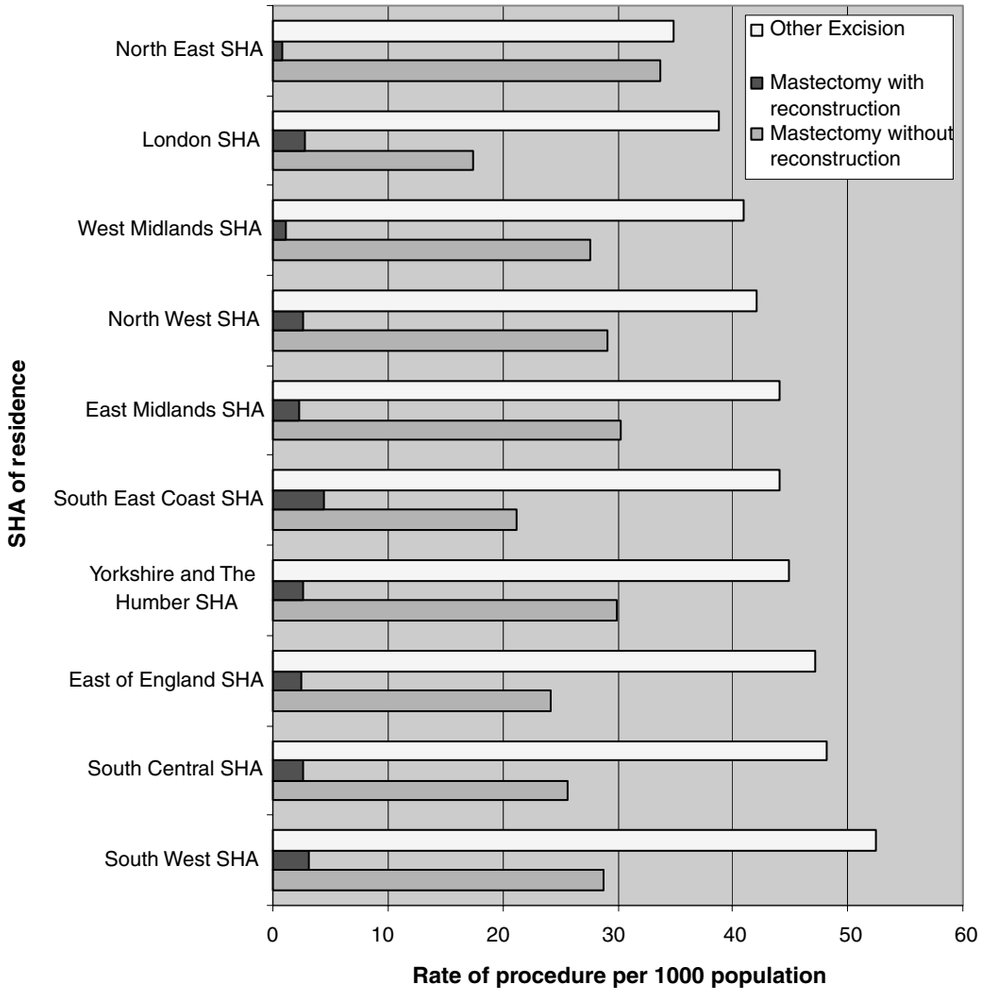


Figure 1.6 Rate of the three main procedure types by English SHA of residence of the patient, 2005/06. Data source: NATCANSAT.

Variation in surgical procedure occurs across England. There are similar rates of 'other excision' and 'mastectomy without reconstruction' in the North East, whereas in London and South Central the rates of 'other excision' are around twice that of 'mastectomy without reconstruction'. The data also shows that South East Coast has double the rate of 'mastectomy with reconstruction' compared with the North East and the West Midlands. This difference may be related to how episodes are coded or to actual differences in clinical practice. The first report of BCCOM (2006) confirmed that mastectomy rates for symptomatic breast cancer varied by region (36.4% to 53.2%) and also by surgeon (19% to 92%).

The type of procedure performed has consequences for the individuals and for the health service. Figure 1.7 illustrates that for those admitted for 'other excision' in 2005/6 the median length of stay was 2 days, compared to the median length of stay of 5 days for mastectomy.

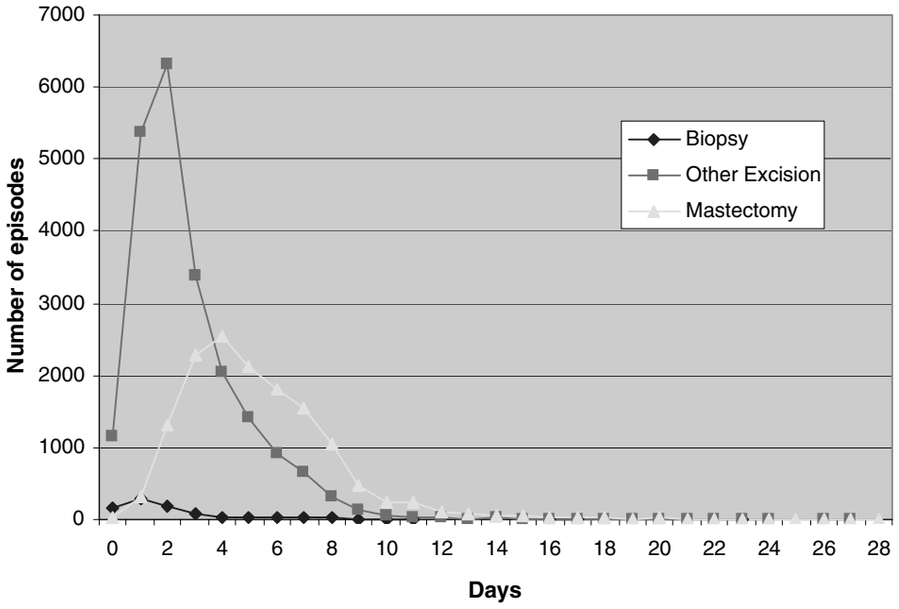


Figure 1.7 Length of stay for three main procedures, 2005/06. Data source: NATCANSAT.

The average length of stay for all procedures has been reducing over the past nine years. Over this period 8.2% of the mastectomy episodes included reconstruction, for 2005/06 alone this percentage was 9.8%. In 2005/06 the median length of stay for mastectomy without reconstruction was 5 days, and with reconstruction was 7 days.

There is a wide variation in the length of stay for procedures across England. This information is summarised by cancer network, as practices may be more similar in trusts within a particular network (Figure 1.8).

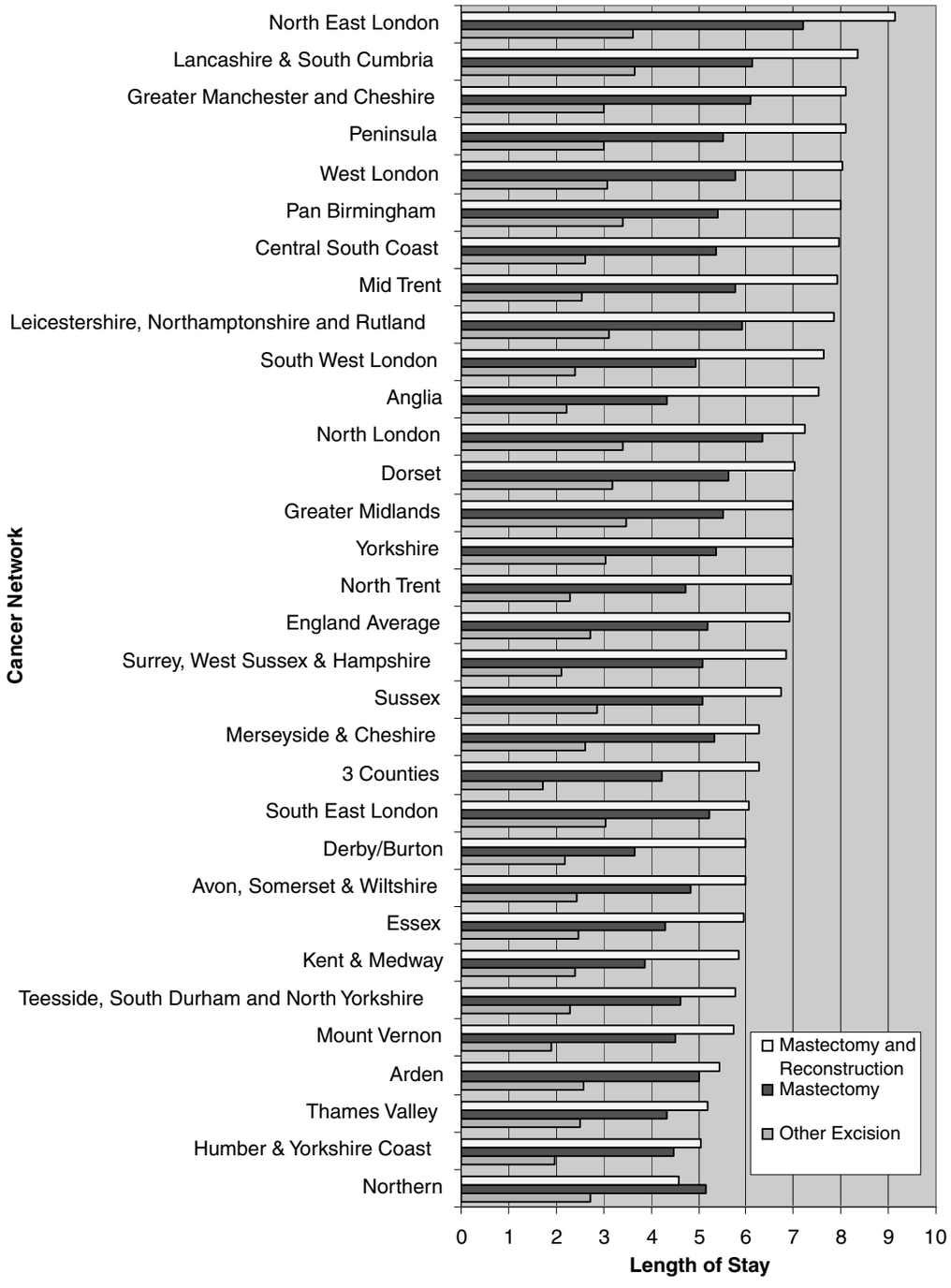


Figure 1.8 Length of stay for three main procedures by cancer network of provider, 2005/06. Data source: NATCANSAT.

All networks have a longer average length of stay for mastectomy with reconstruction than without, except Northern. This difference may be related to coding errors or to patient selection. 'Other excision' consistently has around half the length of stay of 'mastectomy' which has implications for the patient and the NHS.

In 2005/06 there were 427 surgical consultants recorded as performing mastectomies in the HES data. The Association of Breast Surgery (BASO, 2005) advises that only specialist teams should manage breast cancers, and that each surgeon should see between 30 and 150 new patients per year. We know from the data that approximately one third of breast surgical

procedures are mastectomies. From this we can infer that consultants treating 30 new patients per year should be performing around 10 mastectomies per year, the other 20 patients receiving other excisions or biopsies. In 2005/06 the 427 surgeons performed between 1 to 120 mastectomies each. 57 of the 427 consultants, 13.3%, performed fewer than 10 mastectomies in that year. The first BCCOM audit (2006) found that 40 patients, out of 16,407 with symptomatic breast cancer, were treated by surgeons treating fewer than 10 symptomatic cancers in the year.

Primary Care Activity

Primary care provides a great deal of healthcare to individuals with a current diagnosis or past history of breast cancer. This will include contacts for physical problems associated with the cancer and its treatment, plus social and psychological support. Primary care data is not recorded or compiled in a way that allows analysis of the workload within primary care, but survey estimates are available. The RCGP Annual Prevalence Report (2007) reveals that an average practice of 10,000 patients will have around 23 registered patients who consult their GP regarding their breast cancer each year.

Adjuvant Treatment

There is limited data available on the use of adjuvant therapy in breast cancer. The audit of the use of NICE approved cancer drugs by the National Cancer Director (2006) included the use of trastuzumab. Although there was a nearly three-fold difference in the level of its use by acute trusts across England in 2005, this had reduced from an over four fold variation in 2003. A similar pattern was seen for the other cancer drugs reviewed.

Other Variations in Treatment

The BCCOM audit data (2007) covers approximately 46,000 cases of symptomatic breast cancer diagnosed from 2002 to 2004. This has shown variation in treatment modalities by age. A lower percentage of those over 80 years received radiotherapy or chemotherapy compared to those less than 50 years. The opposite was seen in the use of hormonal therapy.

Contradictory results have been found when examining treatments received by socioeconomic groups. One study found no difference (Macleod *et al.,* 2000). Others have found that those living in less affluent areas were less likely to have surgery, receive radiotherapy or have breast conserving surgery (Downing *et al.,* 2007) and may be less likely to receive day case treatment (Pollock *et al.,* 1998).

Radiotherapy

Distance from radiotherapy centres is a significant factor in the equity of provision of radiotherapy services. The impact upon patients in early breast cancer is greater than on those with advanced disease as early breast cancer patients are often required to travel daily for treatment. Patients in rural areas are likely to be furthest by road from radiotherapy centres, for example around the Wash, West Wales, the rural north of England and the rural South West. Pure distance does not capture all the variables which affect equity of access but gives one method of assessing the access. 7% of the population of England and Wales live more than 50km from their local radiotherapy centre (Figure 1.9) but 15% of the catchment population of the three Welsh centres live more than 50km away.

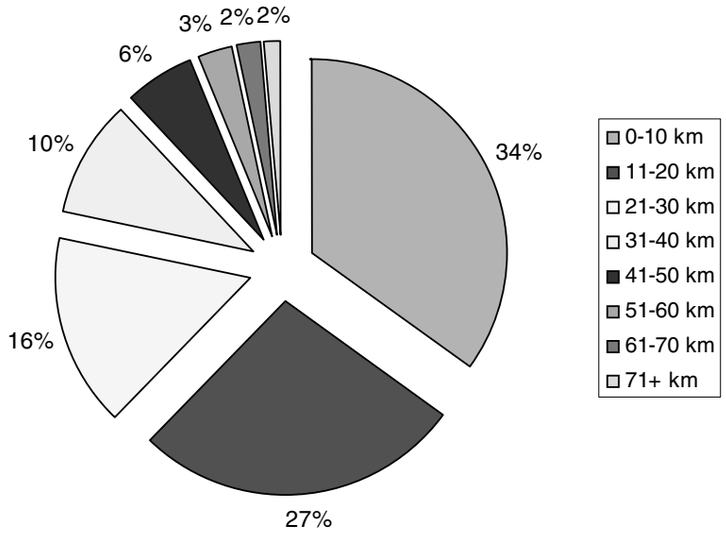


Figure 1.9 Distance by road of the population of England and Wales from their local radiotherapy centre. Data source: NATCANSAT.

Data has been collected by NATCANSAT from radiotherapy centres for diagnosis, dose delivered and the number of fractions in each course. Returns have been on a voluntary basis and are variable in quality and completeness. A review of the current data does not reveal any apparent variation between centres for breast cancer treatment but the quality of the data is not sufficient for any further analysis.

1.8 Summary

Breast cancer is the most commonly occurring cancer in women accounting for 46,000 new cases in 2005. In 2003 there were an estimated 172,000 women living in the UK with a history of breast cancer. The rates have been steadily increasing over the past 10-15 years but they may now be stabilising. Only a small number of cases, less than 1% of the total, occur in men. The numbers of cases of breast cancer are highest in the screened age group, 50 to 69 years, but the rates are highest in those aged over 85 years. There is little geographical variation in the incidence rates across the country but rates are highest in those in higher socioeconomic groups. The incidence in the UK is higher than other countries, in particular those in Eastern Europe and the risk of developing breast cancer appears to increase in those who move from a lower incidence country to the UK.

Breast cancer accounts for 1 in 6 female cancer deaths. It is the most frequent cancer in women but lung cancer is a commoner cause of death. Mortality from breast cancer increases with age and is highest in those over 85 years of age. Mortality is also highest in those from higher socioeconomic groups. Despite the increasing incidence of breast cancer, mortality has been on a downward trend since 1990 due to improved survival. There is little variation in mortality across the UK, but it is higher than many other European countries.

Women aged 50 to 69 diagnosed with breast cancer between 2001 and 2003 had an over 80% chance of surviving 5 years, and are predicted to have a 70% chance of surviving 20 years. Survival has improved in all socioeconomic groups in society but remains poorer in those in the lowest groups, despite their lower risk of developing breast cancer. The reason for this is uncertain but may be related to screening uptake or higher levels of co-morbidity. Survival rates are better than average in women of South Asian ethnic origin despite some evidence that they tend to present with larger tumours. Survival rates in the UK remain lower than the rest of Western Europe.

The secondary care workload associated with breast cancer has been increasing over time. This increase is particularly associated with malignant disease and those in the screened age group. It is not possible to asses the change in workload in primary care due to a lack of national data.

Variation in treatment occurs across the country. The types and rates of procedures performed vary by geography and by clinician. The length of time patients are in hospital for these procedures also varies. Around 13% of consultants undertaking mastectomies were performing 10 or fewer procedures in 2005/06.

Inequality in treatment also exists. Those in the older age groups are less likely to receive surgical treatment than younger women. Audit and research has shown that treatments vary according to the patient's age and socioeconomic status, although the reasons for this are not known. Physical access to services is also inequitable with 7% of the population of England and Wales living over 50km from their local radiotherapy centre.

1.9 Summary of findings from breast cancer teams peer review in England 2004–2007

Following the publication of the updated NICE guidance on 'Improving outcomes in breast cancer' (NICE 2002) a process was put in place in England (as for other cancer sites covered by service guidance from NICE or the Department of Health) to monitor progress made in implementing the changes in service organisation and delivery which had been recommended.

Breast cancer care was the first to be managed by multidisciplinary teams (MDTs), starting in the early 1990s. All these MDTs were reviewed in the first round of cancer peer review carried out in 2001 and many had been reviewed in predecessor systems too.

Between November 2004 and May 2007 each cancer network in England and all the designated breast cancer MDTs were reviewed by a team of clinical peers. A total of 174 breast cancer MDTs were included as part of this 2004-2007 peer review round. Of these, 88% had a full core team membership in place (a figure exceeded only by specialist urology cancer teams) although only half of the teams met the updated guidance requirement (NICE 2002) to have two core members in all the key disciplines.

For breast cancer teams alone, core members are required to spend at least half of their clinical time on breast cancer management. Only half of the teams reviewed complied with this measure, the most frequent source of non-compliance being histopathologists.

Compliance to attend MDT meetings (at the 50% minimum attendance level) was high at 77% and exceeded only by specialist teams in gynaecological and urological cancer.

The extant NICE Guidance (2002) requires hospital-based follow-up (after treatment of early breast cancer) to be limited to a maximum of three years. A total of 40% of cancer networks did not consent to this and several others, despite having guidelines to that effect, did not expect them to be followed. The 2002 guidance also seeks movement towards harmonisation and alignment of screening services with symptomatic services. Less than half of the cancer networks had carried out the required review and only a third had actually developed an action plan.

There is high compliance with patient experience measures (e.g. patient surveys) in most breast cancer teams but only 69% of teams were allocated a key worker.

As many as 16 (9%) of the breast cancer teams had workload volumes of less than 100 patients a year. Most of these teams had low overall compliance levels to all breast cancer measures.

Overall compliance to all cancer measures by breast cancer teams was 77% which is amongst the highest for all cancer sites (exceeded only by specialist gynaecological cancer teams). However, 5% of teams had total compliance levels of under 50%.

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2 Referral, diagnosis, preoperative assessment and psychological support

2.1 Introduction to Breast Cancer

Early breast cancer is sub-divided into two major categories, *in situ* disease in the form of ductal carcinoma in situ (DCIS), or invasive cancer. Both are heterogeneous processes with very variable appearances, biology and clinical behaviour. For recommendations on advanced breast cancer see the NICE guideline on 'Advanced breast cancer: diagnosis and treatment' NICE 2008.

DCIS is predominantly detected by breast screening as microcalcifications on mammography and is not commonly palpable. DCIS grows within a single duct system of the breast but it can vary in size and is sometimes extensive. However, DCIS, by definition, has not spread outside the boundaries of the normal structures of the breast and therefore cannot have metastasised. In the absence of invasive disease it is sometimes referred to as pure DCIS. Characterisation of DCIS is based on the cytonuclear features of the cells, into low, intermediate or high cytonuclear grade. High grade DCIS is a more inherently high-risk disease in terms of progression into invasive breast cancer and development of local recurrence after surgical excision.

Unlike DCIS, invasive breast cancer infiltrates into the breast stroma and thus has the potential to spread to lympho-vascular spaces and to metastasise. Not all invasive breast cancers are the same; some are more aggressive and some may spread earlier to distant sites. There are a variety of methods for classifying invasive breast cancer; most are based on the architectural microscopic pattern and nature of the cancerous cells. The most important of these is histological grading, which identifies tumours as being of histological grade 1 (least aggressive), grade 2 or grade 3 (most aggressive). Other systems more recently described, use genetic profiles/signatures of the cancer cells but this is not routinely assessed at present.

All such methods for classifying invasive breast cancer aim to identify tumours with differing clinical behaviours and prognoses. One such system defines histological tumour sub-type, the most common being invasive ductal carcinoma which is now known as 'cancer of no special type' (NST). Other types, such as invasive lobular cancers have particular clinical features and behaviours. There are a number of microscopic features which are reported in a defined 'minimum dataset'[1] including the histological grade and size of the tumour and the presence of lympho-vascular invasion. It is essential to confirm microscopically that surgically excised disease has been completely removed and to measure the distance to clear margins. Involved or close margins are associated with a higher risk of local recurrence than wider margins for both DCIS and invasive cancer.

[1] http://www.cancerscreening.nhs.uk/breastscreen/publications/nhsbsp58.html.

The assessment of lymph nodes in the axilla is crucial to staging and prognosis of patients with operable breast cancer, which requires surgical excision and microscopic examination. For small deposits of metastatic tumour in lymph nodes it is important to record the size of the metastasis as macrometastases (> 2mm), micrometastases or isolated tumour cells (see Chapter 3).

Markers of the likelihood of response for some specific treatments are also assessed histologically. These predictive markers for invasive breast cancer include oestrogen receptor alpha (ER) and human epidermal growth factor receptor 2 (HER2) status (see Chapter 4).

Using a combination of prognostic factors, to select whether systemic treatment is required, and predictive markers, to select the optimal therapy for the individual's tumour, individualised patient treatment is becoming a more realistic aim.

2.2 Referral and Diagnosis

Patients with symptoms that could be due to breast cancer are referred by their general practitioner (GP) to designated breast clinics in local hospitals (NICE Guidance on 'Referral guidelines for suspected cancer' NICE 2005). In addition, women between 50 and 70 years of age are invited for 3 yearly screening mammography through the National Health Service Breast Screening Programme (NHSBSP) in England or the Breast Test Wales Screening Programme (BTWSP) in Wales. In most cases, whether suspected at breast screening or through presentation to the GP, diagnosis in the breast clinic is made by triple assessment (clinical assessment, mammography and/or ultrasound imaging with core biopsy and/or fine needle aspiration cytology). It is best practice to carry these assessments out at the same visit (NICE Guidance on 'Improving outcomes in breast cancer – manual update' NICE 2002) and the results should be conveyed to the patient and GP as soon as possible. The results of all tests are reviewed and discussed at the multidisciplinary team (MDT) meeting. When the cancer diagnosis has been pathologically confirmed a treatment plan is suggested. The diagnosis and proposed plan are discussed with the patient in the presence of a breast care nurse specialist.

Recommendations on patient care plans can be found in Chapter 9.

2.3 Preoperative Assessment of the Breast and Axilla

The breast

For patients with early breast cancer accurate preoperative assessment of the size and extent of the primary tumour is essential for deciding whether wide local excision is an alternative option to mastectomy. For approximately 25% of patients breast conserving surgery is not appropriate. However, when the initial treatment has been wide local excision, further surgery is needed in about 20% of patients because the histology shows tumour at, or close to, the surgical margins. In many cases this will be due to unsuspected DCIS.

DCIS

The majority of cases of DCIS are detected through screening and 90% are identified as microcalcifications found on mammography. Mammographic extent alone will underestimate size of the disease extent in approximately 40% of cases. Ultrasound and magnetic resonance imaging (MRI) are unreliable for assessing the extent of DCIS but may be useful in detecting unsuspected associated invasive disease. MRI may also over-estimate the extent of DCIS.

Invasive breast cancer

Routine methods for assessing the extent of disease in the breast are clinical examination, mammography and ultrasound. In a significant number of cases the true extent of disease is underestimated, particularly with invasive lobular cancer.

MRI is more accurate for assessing the size of invasive tumour, for detecting the presence of multiple invasive foci in the ipsilateral breast and concurrent contralateral breast cancer. However, MRI identifies a significant number of false positive abnormalities that then require further investigation. The incidence of multifocal tumour shown on MRI is much higher than

the observed local recurrence rates following breast conserving surgery and radiotherapy, suggesting that mastectomy may not always be necessary in this situation. Nevertheless, preoperative MRI is increasingly being used.

In the majority of patients with early invasive ductal carcinoma or NST, the size and extent of disease in the breast can be accurately assessed on the basis of clinical examination, mammography and ultrasound and a decision made on whether breast conserving surgery can be considered. Invasive lobular cancer is difficult to size accurately using the same methods and MRI has been shown to be more accurate when assessing the size in this type of invasive breast cancer.

Recommendations

- The routine use of MRI of the breast is not recommended in the preoperative assessment of patients with biopsy-proven invasive breast cancer or DCIS.

Qualifying statement: There is insufficient evidence (a) to recommend the routine use of preoperative MRI in invasive breast cancer and no evidence that detection with MRI makes a difference to outcomes, and (b) on which to base any recommendation on the use of MRI in the assessment of the breast with a diagnosis of pure DCIS.

- Offer MRI of the breast to patients with invasive breast cancer:
  - if there is discrepancy regarding the extent of disease from clinical examination, mammography and ultrasound assessment for planning treatment
  - if breast density precludes accurate mammographic assessment
  - to assess the tumour size if breast conserving surgery is being considered for invasive lobular cancer.

Qualifying statement: There is good quality evidence that MRI is effective at detecting size and multifocality. There is some published evidence and GDG consensus, based on the difficulties of assessing and treating lobular cancer, to support this recommendation. There is no satisfactory health economic evidence to assist in this recommendation.

Clinical Evidence

MRI for detecting DCIS

Outcome data was identified from two case control studies and four case series, with a relatively high degree of consistency in results. However, data need to be interpreted with caution because of the limitations of the studies, low evidence levels and small sample sizes.

There is good evidence from retrospective case control studies that MRI can complement mammography in guiding surgical treatment of DCIS by providing better assessment to the extent of the lesion. 26/30 (86.7% sensitivity) lesions were detected by MRI as well as 8 lesions without mammographically detected microcalcification. In 7/30 cases MRI showed tumour extent accurately compared with mammography, and the combined diagnosis improved the accuracy of evaluating tumour extent. (Shiraishi, 2003).

The sensitivity of MRI for detecting DCIS is lower than that achieved for invasive breast cancer. However, contrast enhanced MRI can show foci of DCIS that are mammographically occult. The MRI technique is of complementary value for a better description of tumour size and detection of additional malignant lesions (Francescutti, 2002).

There is some evidence from case series that MRI is significantly more sensitive than mammography in DCIS detection. In women with known or suspected DCIS, MRI may have an important role in assessing the extent of disease in the breast (Menell, 2005).

Clinical Evidence (cont.)

MRI for detecting invasive breast cancer

The outcome data was identified from one systematic review, nine case control studies and 11 case series, with a relatively high degree of consistency in results.

Data need to be interpreted with caution because of the limitations of the studies, low evidence levels and small sample sizes.

Studies consistently demonstrate moderate to high sensitivity (75-100%) and specificity (82-100%) for breast MRI in detecting multicentric tumour foci in fibroglandular or dense breasts (Blue Cross/Blue Shield-TEC Review, 2004 and Del *et al.,* 2007). MRI will detect additional mammogram-occult foci greater than 2 cm from the index cancer in approximately 10% of women. These additional foci are similar to those detected by mammography and are therefore likely to be associated with an increased risk of local recurrence for breast conserving surgery (Schnall *et al.,* 2005). In patients eligible for breast conserving surgery, MRI is more accurate than conventional imaging in the assessment of tumour extent in one out of four patients (23%) and had a significantly higher yield than mammography of confirmed invasive lobular cancers (Deurloo *et al.,* 2006).

Patients who are likely to benefit from MRI are those with dense breasts on mammography, lobular carcinoma and occult primary tumour. In non-fatty breasts ultrasound and MRI were more sensitive than mammography for invasive cancer, but both MRI and ultrasound involved a risk of overestimation of tumour extent. Contrast enhanced MRI has the lowest false-negative rate in detecting invasive lobular carcinoma and has the highest accuracy in measuring the size of the invasive lobular carcinoma (Boetes *et al.,* 2004). MRI has been shown to detect occult invasive breast cancers with the sensitivity of 97%-100%. However, intraductal component of breast cancer is more accurately detected by ultrasound than MRI. MRI provided superior correlation between tumour size and pathology. Combined mammography, clinical examination and MRI was more sensitive than any other individual test or routine triad (Chung *et al.,* 2005).

Axillary lymph nodes can be evaluated as part of an MRI-mammography study without substantial increase in examination time, and provide information about the localisation of possible metastatic lymph nodes. Using dynamic contrast enhanced imaging an 83% sensitivity and a 90% specificity for the presence of lymph node metastases was found with the chosen threshold of abnormal signal intensity increase. There was a poor correlation with metastases (sensitivity 63% and specificity 80%) when the size and shape of the axillary lymph nodes in MRI were used as criteria. These results are comparable to computerised tomography (CT) examinations of the axilla but are poorer than the results from ultrasound examination. Axillary lymph nodes showed contrast enhancement in both axillary lymph node dissection (ALND)-positive and ALND-negative patients, but enhancement was stronger and more rapid in patients with metastases (Kvistad *et al.,* 2004).

The evidence about when the decision to change treatment (which was based on MRI/rates of mastectomy/procedures initiated by MRI investigation) reported that between 2% and 15% of patients otherwise eligible for breast conserving surgery who have had an MRI as part of their staging workup, would have a multicentric tumour not found by conventional preoperative staging workups. These percentages may be higher for patients with DCIS or invasive lobular cancer. Patients' treatment was changed to mastectomy based on MRI findings in 7% of the patients. In anticipation of breast conserving surgery or no surgery after mammography and clinical examination in 96 breasts, additional tumour was found by MRI in 30 cases (Blue Cross/Blue Shield-TEC Review, 2004; Bremner *et al.,* 2007 and Del *et al.,* 2007).

Breast MRI is accurate in staging extent of disease in the breasts of patients with histological grade 3 tumours. In 10 patients with histological grade 1 tumours, the MRI findings overestimated their disease. In 11/115 patients, the primary tumour or a second tumour was only seen by MRI. In 170 patients MRI detected 96% multifocal disease and 95% of multicentric disease, whereas mammography detected 37% and 18% respectively and ultrasound detected

Clinical Evidence (cont.)

41% and 9% respectively. All bilateral breast cancers were seen on MRI. Both mammography and ultrasound detected 56%. Additional malignant foci detected on MRI identified unsuspected multifocal, multicentric or bilateral breast cancer resulting in necessary changes in treatment (Schelfout *et al.,* 2004).

The evidence about tumour recurrence showed that preoperative MRI of the breast is effective in patients with histopathologically verified breast cancer, for local staging. The ipsilateral breast tumour recurrence is significantly higher in women with breast conserving surgery and no staging with MRI. Metachronous contralateral carcinoma has occurred significantly more in patients without preoperative MRI staging (Fischer *et al.,* 2004).

Health Economic Evaluation

A single literature review was performed to assess the cost effectiveness of breast MRI in the preoperative staging of patients with invasive breast cancer and DCIS. From 100 references initially identified through the search, 25 were considered further, although only 9 papers were finally retrieved. Only 1 study was finally included in the systematic review (Esserman *et al.,* 1999). The study was conducted in USA and investigated the usefulness of conducting contrast-enhanced MRI compared to mammography to assess the extent of cancer in the breast before surgery. It was a partial economic evaluation since only the cost assessment of MRI was conducted, but not that of mammography. The study sample included patients with invasive breast cancer, DCIS, Paget's disease and others; therefore, there seemed to be considerably heterogeneity in terms of the type of patients considered at analysis. A small patient sample was evaluated (57 patients in total, with only 45 patients having MRI and mammography at the same time). The usefulness of MRI was assessed prospectively in the diagnostic study, while the accuracy of mammography was retrospectively reviewed. The authors concluded that MRI was better than mammography for both identification of malignancy (98% versus 84%; $p = 0.03$) and concordance on extent (98% versus 55%; $p < 0.001$), and that it could lead to cost savings. Overall, there were relevant limitations in terms of both the clinical and the cost analysis. Moreover, it is not clear whether the study sample, the clinical practice and the unit costs used in the study would be representative of those from a UK setting. Therefore, the usefulness of this study was very limited and uncertainty remains about whether MRI is a cost effective strategy in the preoperative staging of early breast cancer patients.

2.4 Preoperative Staging of the Axilla

For patients with early invasive breast cancer, staging of the ipsilateral axilla is essential for deciding what local and systemic treatments are subsequently required. The axilla can be staged using limited axillary surgery (sentinel lymph node biopsy (SLNB) or four node sampling (4N-S)) carried out at the same time as the initial breast surgery but a second operation may be required if nodal disease is found. A preoperative diagnosis of nodal disease enables definitive treatment of the axilla at the time of initial breast surgery.

The majority of patients with axillary lymph node disease do not have clinically obvious lymph node involvement but imaging of the axilla can detect lymph nodes that may contain metastatic disease. Imaging alone is insufficiently accurate as a basis for treatment but if it suggests nodal involvement (> 2mm cortical thickness and/or abnormal morphology), ultrasound guided needle sampling[2] of abnormal lymph nodes detects 40-50% of patients with axillary node metastases.

Recommendations on surgery to the axilla can be found in Chapter 3.

[2] Either fine needle aspiration cytology (FNAC) or core biopsy.

Recommendation

- Pretreatment ultrasound evaluation of the axilla should be performed for all patients being investigated for early invasive breast cancer and, if morphologically abnormal lymph nodes are identified, ultrasound-guided needle sampling should be offered.

Qualifying statement: These recommendations are based on good evidence, including from a meta-analysis, of clinical effectiveness in reducing the number of patients who undergo SLNB and then need further axillary surgery, and reasonable evidence of cost effectiveness.

Clinical Evidence

The evidence for this topic comes from case series studies and one meta-analysis which pooled estimates.

Eight studies reported the proportion of cases in whom it was possible to visualise axillary lymph nodes on ultrasound. This proportion had a mean of 76% and median 81% but varied widely, with a range 35% to 99%. The remaining proportion represents patients for whom ultrasound does not add any information. (Altinyollar *et al.,* 2005; Brancato *et al.,* 2004; Damera *et al.,* 2003; Deurloo *et al.,* 2003; Dixon *et al.,* 1992; Esen *et al.,* 2005; Nori *et al.,* 2005 and Podkrajsek *et al.,* 2005).

The systematic review by Alvarez *et al.* (2006) performed a meta-analysis of staging outcomes for 'grey scale' axillary ultrasound based upon 16 case series studies. The meta-analysis provided pooled estimates of staging outcomes. When patients with palpable and non-palpable axillary lymph nodes were combined, lymph nodes that were suspicious on ultrasound based on their size (> 5mm); sensitivity was 69.2% and specificity was 75.2%. If lymph nodes were suspicious on ultrasound based on their morphology the sensitivity was 71.0% and specificity was 86.2%. Considering only studies of patients with non-palpable lymph nodes, ultrasound had reduced sensitivity (using the morphologic criterion for nodal involvement) and there was little change in specificity. When a meta-analysis including only patients in whom it was possible to obtain biopsy material by ultrasound were considered, the pooled sensitivity was 75.0% and the pooled specificity was 98.3%. In a meta-analysis of patients in whom ultrasound-guided biopsy was planned, and defining failure to find a lymph node on ultrasound or failure to collect biopsy material as a negative screen was conducted, the effect of these classifications was to reduce the sensitivity of ultrasound compared to earlier values, with little change in its specificity.

From case series studies the staging performance of 'grey scale' ultrasound alone showed a mean sensitivity of 62%, a mean specificity of 87%, a positive predictive value of 86% and a negative predictive value of 71%. (Altinyollar *et al.,* 2005; Bartonkova *et al.,* 2006; Brancato *et al.,* 2004; Chandawarkar and Shinde, 1997; Esen *et al.,* 2005; Heusinger *et al.,* 2005; Lee *et al.,* 1996; Hergan *et al.,* 1996; Sato *et al.,* 2004 and Van Rijk *et al.,* 2006).

The staging performance of 'grey scale' ultrasound plus colour doppler ultrasound showed a mean sensitivity of 65%; a mean specificity of 89% a positive predictive value of 78% and a negative predictive value of 81%. (Couto *et al.,* 2004; Dixon *et al.,* 1992; Esen *et al.,* 2005; Lee *et al.,* 1996;, Nori *et al.,* 2005; Perre *et al.,* 1996; Podkrajsek *et al.,* 2005 and Walsh *et al.,* 1994).

The staging performance of ultrasound guided fine needle aspiration cytology (FNAC) showed a mean sensitivity of 43%, a mean specificity of 100%, a positive predictive value of 99% and a negative predictive value of 72%. (Brancato *et al.,* 2004; Damera *et al.,* 2003; De Kanter *et al.,* 2006; Deurloo *et al.,* 2003; Lemos *et al.,* 2005; Podkrajsek *et al.,* 2005; Stewart *et al.,* 2006 and Van Rijk *et al.,* 2006). Ciatto *et al.* (2007) reported an overall sensitivity of 72.6% and specificity of 95.6% with a negative predictive value of 67.2% and a positive predictive value 96.6% when excluding inadequate results from analysis; including inadequate results as a negative gave a sensitivity of 64.6%, specificity of 95.7%,

Clinical Evidence (cont.)

negative predictive value of 61.3% and a positive predictive value of 96.6%. Sahoo *et al.* (2007) reported an overall sensitvity of 96% and specificity of 93%. Somasunder *et al.* (2006) reported an increase in sensitivity from T1 (35%) to T3/4 (78%) and specificity from T1 (96%) to T3/4 (100%). The likelihood of lymph node FNAC being positive was linked with tumour stage (Ciatto *et al.,* 2007 and Somasunder *et al.,* 2006). Ciatto *et al.* (2007) also reported a significant association with histological grade and number of lymph nodes involved. Sahoo *et al.* (2007) reported that 40 (70%) patients with positive ultrasound FNAC were spared the additional step of SLNB while Somasunder *et al.* (2006) reported that 79 (47%) patients with positive ultrasound FNAC were spared SLNB.

Health Economic Evaluation (see also Appendix 3)

Ultrasound-guided needle biopsy (ultrasound and needle biopsy) of abnormal lymph nodes using FNAC or core biopsy has the potential to provide the required definitive cytological or histological proof of a positive result on which to base treatment decisions. Ultrasound and ultrasound-guided needle sampling are routinely available in diagnostic breast clinics and can be used for preoperative staging of the axilla. By offering axillary dissection to those patients with early breast cancer, proven preoperatively to have nodal metastases, secondary surgery to the axilla either by SLNB and/or by 4-NS can be avoided in a significant number of patients. However, because of the low negative predictive values of these techniques, patients with no ultrasound evidence of abnormal lymph nodes or with negative ultrasound-guided needle sampling require surgical staging with SLNB as part of their initial surgical treatment.

A systematic review of the evidence about the cost effectiveness of pretreatment ultrasound-guided needle biopsy in staging the axilla of patients with early breast cancer, identified three relevant studies; one full economic evaluation (Brancato *et al.,* 2004) and two partial economic evaluations (Genta *et al.,* 2007 and Davies *et al.,* 2006). Two of these studies were conducted in Italy (Brancato *et al.,* 2004 and Genta *et al.,* 2007) and the third one in USA (Davies *et al.,* 2006). None of these studies was likely to be applicable to the UK context given that considerable variations exist in the costs of the different staging procedures across countries. Therefore an economic evaluation was conducted to assess the cost effectiveness of using ultrasound-guided needle biopsy (needle biopsy conducted by either FNAC or core biopsy) to stage the axilla of early breast cancer patients, compared to SLNB for all early breast cancer patients undergoing staging, in terms of the cost per patient avoiding SLNB with ultrasound-guided needle biopsy. The perspective adopted was that of the UK National Health Services (NHS). Other secondary health outcomes assessed were the number of patients with axillary metastasis that would be wrongly identified as having negative lymph nodes and therefore would remain undertreated because of inaccuracies of the staging procedures, and the number of patients whose nodal status would be accurately identified with either ultrasound-guided needle biopsy or SLNB.

A decision tree was constructed to represent the staging strategies considered at analysis, and the subsequent immediate consequences following them. The clinical evidence required to populate the model was mainly obtained from the systematic reviews conducted for this guideline. The studies identified from the systematic review of the clinical evidence on pretreatment ultrasound were again reviewed to select those assessing ultrasound-guided needle biopsy for which the patients who had undergone needle biopsy (either FNAC or core biopsy), after being identified as having suspected lymph nodes with ultrasound, were reported. A meta-analysis was conducted to synthesise the data from the included studies. The costs considered at analysis were those relevant to the NHS, and included the costs of the staging procedures undertaken (ultrasound, needle biopsy and SLNB, depending on the strategy considered); the costs of any additional secondary staging procedure required (i.e. SLNB) in case of negative results with ultrasound-guided needle biopsy, or in case lymph nodes could not be visualised with pretreatment ultrasound; and the costs of axillary lymph node clearance, when applicable. Costs were estimated based on the National Reference Costs and using 2006-2007 prices. Discounting was not conducted (since the time horizon of the decision model comprised only the period of staging and was definitively shorter than

Health Economic Evaluation (cont.)

one year). One-way and multi-way (deterministic) sensitivity analyses were conducted to assess the robustness of the study results when the values of relevant parameters were modified in order to identify those variables contributing the most to uncertainty.

The results of the base-case analysis showed that each patient avoiding SLNB with the ultrasound-guided needle biopsy strategy would cost an extra £285 when compared to the SLNB staging strategy. According to the results of the sensitivity analyses, the most favourable incremental cost effectiveness ratios (ICERs) would be obtained when the sensitivities and specificities of ultrasound-guided needle biopsy and SLNB are higher, and with higher prevalence rates of axillary metastasis. Moreover, there is the potential to achieve cost-savings by using ultrasound-guided needle biopsy if the unit cost per ultrasound test undertaken was lower than £15, which may not be the case in a typical UK cancer centre. The quality adjusted life years (QALY) gain required per patient for ultrasound-guided needle biopsy to be cost effective ranged between 0.0002 and 0.0037 depending on the type of parameter values considered. The GDG believed this health gain is attainable because both the reduction in the number of patients undergoing SLNB and the fact that, overall, ultrasound-guided needle biopsy is a less invasive staging procedure when compared to SLNB, can translate in gains in quality of life.

The GDG recognised that there was considerable uncertainty about the time cost of various procedures, especially of the cost of day care SLNB. They felt that it was likely that this uncertainty would if anything decrease the cost differential between the treatment options and improve the cost effectiveness of ultrasound-guided needle biopsy.

2.5 Providing Information and Psychological Support

Between 22 and 47% of patients diagnosed with breast cancer may suffer from an episode of significant anxiety and depression and 33% from sexual difficulties that require intervention. Although psychological care has been given much more attention by healthcare professionals in the past ten years, there is still a wide variation in assessment and treatment across the country. Prior identification of patients with a previous psychiatric background is particularly important. Early assessment of psychological problems and referral for appropriate intervention may reduce the psychological morbidity associated with the diagnosis of breast cancer.

Information giving, support from patient groups and support from breast care nurse specialists, have shown a reduction in psychological morbidity. Excellent communications skills are paramount, as breaking bad news and the manner in which it is imparted greatly influence the distress a patient may suffer.

Recommendations

- All members of the breast cancer clinical team should have completed an accredited communication skills training programme.
- All patients with breast cancer should be assigned to a named breast care nurse specialist who will support them throughout diagnosis, treatment and follow-up.
- All patients with breast cancer should be offered prompt access to specialist psychological support, and, where appropriate, psychiatric services.

Qualifying statement: There is evidence from good quality RCTs to support making these recommendations

Clinical Evidence

The evidence base for this topic comprises 24 papers: three systematic reviews (Tatrow and Montgomery, 2006, Bantum *et al.,* 2007 and Zimmermann *et al.,* 2007) 20 RCTs (Allard, 2007, Allen *et al.,* 2002, Andersen *et al.,* 2004, Antoni *et al.,* 2006, Badger *et al,*. 2007,

Clinical Evidence (cont.)

Burton *et al.,* 1995, Cohen and Fried, 2007, Dey *et al.,* 2002, Gotay *et al.,* 2007, McArdle *et al.,* 1996, Mutrie *et al.,* 2007, Ritz *et al.,* 2000, Samarel *et al.,* 2002, Sandgren and McCaul, 2003, Sandgren and McCaul, 2007, Stanton *et al.,* 2005, Manne *et al.*, 2007, Classen *et al.*, 2008, Vos *et al.*, 2007 and Meneses *et al.*, 2007) and two prospective comparative studies (Mock *et al.,* 1997 and Ambler *et al.,* 1999). The quality of papers was generally good and most study designs compared the effects of one or more interventions with one or more controls measured at two or more time points, the maximum follow-up being one year.

Cognitive behavioural therapy (CBT)

A high-quality systematic review of RCTs found that CBT interventions had a low effect size compared with controls. There was RCT evidence of no significant difference between CBT and guided imagery in reducing psychological stress or the perception of stress, although both interventions were significantly better than non-interventional controls.

Good quality evidence from two RCTs suggested that group therapy with non-CBT counselling or a group therapy intervention comprising CBT and several other psychosocial elements significantly reduced subjective levels of emotional distress whilst objective assessments of anxiety were not significantly different from controls.

Group therapy

A moderate quality systematic review found that group interventions provided significant improvements in emotional well-being when compared with individual interventions. The provision of multiple treatment elements was more useful than targeted clinical services. Only self help and information/education as single interventions had significant effects on emotional well-being.

RCT data showed that those who derived benefit from a couple-focused group intervention were women who naturally selected an emotional coping strategy to having breast cancer and women with unsupportive partners who attempted to understand and express their emotional reactions.

A multi-centre RCT showed that, compared with education, there was no evidence that psychological distress was alleviated by brief supportive-expressive group therapy. Neither was therapist training and experience associated with any treatment effect. It was thought that perhaps women with early breast cancer may be more likely to have pragmatic, rather than existentialist, concerns.

A small RCT compared group psychotherapy with group social support, neither of which was effective in improving psychosocial adjustment to breast cancer. Generally, body image improved significantly over time, particularly in women who had received breast-conserving surgery, and the limitations of breast cancer on recreation were also reduced.

Other interventions

Several, generally good quality, RCTs demonstrated that a variety of interventions including preoperative interview, attention focus and symptom management, telephone interpersonal counselling and structured exercise programs alleviated anxiety for variable lengths of time whilst not significantly improving depression, negative affect or general quality of life.

Intervention providers

A systematic review and meta-analysis found that psychologists were better qualified to deliver CBT to a woman with breast cancer either after the diagnosis, surgery or much later but not during other medical treatment. Nursing staff were better in delivering education to women with early stage disease, either individuals or in groups, preferably after diagnosis or surgery.

Clinical Evidence (cont.)

Moderate quality evidence suggested that adding the services of an advanced practice care nurse to standard care significantly reduced uncertainty, complexity, inconsistency and unpredictability without influencing quality of life or mood. Other studies found that support from a breast care nurse specialist following cancer surgery alleviated depression over time but made no significant difference to anxiety. However, receiving support from the breast care nurse specialist before and after receiving a pre-surgical diagnosis significantly lowered clinical relevant anxiety when measured two weeks after surgery, regardless of eventual diagnosis.

RCT evidence also showed that a psychoeducational intervention, delivered by a specialist nurse, demonstrated effectiveness amongst women with breast cancer after primary treatment thus providing a 'safe passage' from treatment to survivorship.

Health Economic Evaluation

The GDG did not consider this topic as a health economic priority; therefore the cost effectiveness literature on this topic has not been reviewed.

Research recommendation

- What is the effectiveness of cognitive behavioural therapy compared with other psychological interventions for breast cancer patients?

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3 Surgery for early breast cancer

3.1 Surgery to the Breast

Surgery is the mainstay of treatment for ductal carcinoma in situ (DCIS) and invasive breast cancer and is usually used as the first treatment option. With earlier detection and diagnosis of the disease, breast conservation surgery with local excision of the tumour has been more frequently performed rather than mastectomy. Similarly, lesser axillary surgery has been possible, especially with the advent of sentinel lymph node (SLN) techniques, reducing the morbidity of axillary clearance, but without losing valuable information about nodal involvement which helps guide the choice of adjuvant therapy. Where mastectomy is still necessary, routine management increasingly includes breast reconstruction, performed at the time of primary surgery when possible.

DCIS

Until the introduction of the National Health Service Breast Screening Programme (NHSBSP)/Breast Test Wales Screening Programme (BTWSP) in 1988, DCIS was uncommonly diagnosed. The introduction of breast screening has led to an increase in the detection of DCIS, accounting for approximately 22% of screen detected breast cancers (Association of Breast Surgery at British Association of Surgical Oncology (ABS at BASO) publications for 2007).

Traditional management for DCIS was mastectomy but breast conservation has become a more common method of treatment for apparently localised DCIS. However there is a 25% risk of local recurrence over 10 years without further therapy and half of these recurrences will be of invasive cancer.

Randomised clinical trials have evaluated the additional potential benefit of breast radiotherapy and endocrine therapy. However there has been much debate about what surgical margin of excision is optimum. Obviously the wider the margin, the more breast tissue is removed and therefore the greater detrimental effect on cosmesis. However, residual disease is present in up to 60% of cases when further surgery (re-excision or mastectomy) is performed after wide local excision with a 1 mm margin or less. Even when the surgical margin of a wide local excision is 1-2 mm, 31-64% of patients have histological proven residual disease. In addition, narrow margins are associated with high local recurrence rates; crude local recurrence rates of 20-38% are reported for margins 1 mm or less and rates of 13-34% are seen with margins 2 mm or less. Whilst crude local recurrence rates at the lower end of this range (13-19%) are obtained with the addition of radiotherapy to 1-2 mm margins, when margins of 2 mm or more are achieved, local recurrence rates of 2% (with radiotherapy) to 11% (without radiotherapy) are reported. The skin (superficial/anterior) and fascial (deep/posterior) margins are not included in these examinations when all the breast tissue has been excised to these aspects; clearly in this situation it is impossible to obtain a 2mm clearance.

DCIS has a long natural history and for patients treated by local excision long-term follow-up is required (see Chapter 9). Local recurrence rates are generally considered to be the best indicator of adequate excision with or without radiotherapy. Factors such as the grade of DCIS and total size of the lesion are also relevant.

Recommendations on radiotherapy following breast conserving surgery for DCIS can be found in Chapter 6.

Recommendations

- For all patients treated with breast conserving surgery for DCIS a minimum of 2 mm radial margin of excision is recommended with pathological examination to NHSBSP reporting standards. Re-excision should be considered if the margin is less than 2 mm after discussion of the risks and benefits with the patient.
- Enter patients with screen-detected DCIS into the Sloane Project (UK DCIS audit).
- All breast units should audit their recurrence rates after treatment for DCIS.

Qualifying statement: The evidence is from observational studies shows that there is no single size of clear margin that is the optimum for reduced local recurrence rate. These recommendations are based on GDG consensus.

Clinical Evidence

The best available evidence for this question was drawn from observational studies (Bijker *et al.,* 2001; Boland *et al.,* 2001 and 2003; Boyages *et al.,* 1999; Cabioglu *et al.,* 2007; Chan *et al.,* 2001; Cheng *et al.,* 1997; Denoux *et al.,* 2001; Dillon *et al.,* 2007; Goldstein *et al.,* 1999; Goldstein *et al.,* 2000; Goldstein *et al.,* 1998; Hetelekidis *et al.,* 1999; Holland *et al.,* 1998; Kell and Morrow 2005; Macdonald *et al.,* 2005 and 2006; Neuschatz *et al.,* 2001 and 2002; Ratanawichitrasin *et al.,* 1999; Rodrigues *et al.,* 2002; Sahoo *et al.,* 2005; Sigal-Zafrani *et al.,* 2004; Silverstein *et al.,* 1994, 1997 and 1999; Silverstein and Buchanan 2003; Solin *et al.,* 2005; Tunon-de-Lara *et al.,* 2001; Vargas *et al.,* 2005; Vicini *et al.,* 2001; Wong *et al.,* 2006; Yau *et al.,* 2006). There is no consistency regarding the optimal tumour-free tissue margin. Most existing studies agree that margins containing tumour cells are associated with local recurrence or bear the risk of residual cancer. There is consistency that the risk of local recurrence is reduced with very wide margins, e.g. more than 10 mm of tumour-free tissue. Several studies reported a linear correlation between margin widths and recurrence. There is conflicting evidence regarding whether wide margins can and whether they should replace radiotherapy. There is also disagreement regarding which of the two should most be avoided. The included studies varied in more than the factor margin widths (i.e. co-treatment, lengths of follow-up) and results are therefore difficult to compare. Studies varied in their definition of 'wide'.

Health Economic Evaluation

The GDG did not consider this topic as a health economic priority; therefore the cost effectiveness literature on this topic has not been reviewed.

Early invasive breast cancer

Following diagnosis of early invasive breast cancer surgery is normally the first definitive treatment. If disease has been assessed as unifocal, wide excision is an option for patients as an alternative to mastectomy, although the total tumour size compared to size of breast precludes this in some patients. The optimum clear margin has yet to be defined and was not a topic identified for this guideline. If poor cosmesis might occur, local oncoplastic reconstruction may be required. For those patients where conservation is not possible who are being advised to have a mastectomy, immediate breast reconstruction is a consideration (see recommendations

on breast reconstruction below). These treatment options need discussing with the patient in conjunction with a breast care nurse specialist.

Paget's disease

Paget's disease of the nipple is a malignant condition that affects the nipple/areola complex from where it may spread to the surrounding skin. Patients present with a thickened, reddened, weeping or crusted area on the nipple. Nipple discharge and ulceration may sometimes occur, and there may be an associated palpable breast lump. Microscopic examination shows intra-epithelial infiltration by malignant cells which, in most cases, originate from an underlying in situ or invasive cancer. The latter is usually located centrally (within 2 cm of the areola) but may occasionally be more peripheral and multifocal. In 5-10% of cases, Paget's disease is the only manifestation of breast cancer and no other underlying tumour can be found.

The treatment of Paget's disease of the nipple has traditionally been by mastectomy. Increasingly breast conservation surgery with nipple removal is being offered for central localised lesions, particularly now that oncoplastic repair techniques are available, but there have been no randomised trials comparing these treatments.

Comprehensive breast imaging by mammography, ultrasound and, when appropriate, magnetic resonance imaging (MRI) is indicated to avoid missing extensive or multifocal disease.

Recommendation

- Offer breast conserving surgery with removal of the nipple-areolar complex as an alternative to mastectomy for patients with Paget's disease of the nipple that has been assessed as localised. Offer oncoplastic repair techniques to maximise cosmesis.

Qualifying statement: This recommendation was based on observational studies which provided no strong evidence that survival of these patients would be adversely affected by having breast conserving surgery rather than mastectomy.

Clinical Evidence

There is a small volume of literature relating to Paget's disease of the nipple, with evidence comprising of mostly small retrospective, non-comparitive case series.

11 observational studies provide data on breast cancer recurrence in patients treated with mastectomy or breast conserving surgery for Paget's disease (Sutton *et al.,* 1999; Bijker *et al.,* 2001; Dixon *et al.,* 1991; Duff *et al.,*1998; Howard *et al.,* 1989; Nicolosai *et al.,* 1996; Polgar *et al.,* 2002; Zurrida *et al.,* 1993; Estabrook *et al.,* 1996 and Marshal *et al.,* 2003). These data appear to show higher rates of recurrence following breast conserving surgery compared to mastectomy, but no study provided a statistical analysis.

In 3 out of 4 studies in which survival data were reported for both mastectomy and breast conserving surgery, post-mastectomy breast cancer-specific survival was superior (Dixon *et al.,* 1991; Howard *et al.,* 1989; Polgar *et al.,* 2002 and Sutton *et al.,* 1999).

A single study statistically compared survival following mastectomy or breast conserving surgery and found no statistical difference in breast cancer-specific survival at 15 years following treatment (Chen *et al.,* 2006).

Cosmesis was assessed in one study only (Marshall *et al.,* 2003). The treating radiation oncologist assessed cosmesis in 31 patients. These were rated as: excellent, 10 (32%; 4 patients underwent nipple reconstruction); good, 18 (58%); fair, 3 (10%). No data was identified for quality of life, based on assessment with a specific instrument, as an outcome in patients treated for Paget's disease by mastectomy or breast conserving surgery.

Health Economic Evaluation

The GDG did not consider this topic as a health economic priority; therefore the cost effectiveness literature on this topic has not been reviewed.

3.2 Surgery to the Axilla

Invasive breast cancer

For patients with invasive breast cancer, one of the most important prognostic indicators is whether the tumour has spread to the axillary lymph nodes and this is essential in determining subsequent treatment. Current guidelines[1] advise that histological lymph node status should be obtained for all operable invasive breast cancers.

The main lymphatic drainage from the breast is to the axillary lymph nodes and the first draining lymph node is known as the sentinel lymph node (SLN). Although there is also drainage to the internal mammary lymph nodes, this rarely adds information to that obtained from the axillary lymph nodes.

Axillary lymph node dissection (ALND, also known as axillary clearance) has been considered the 'gold standard' procedure to stage the axilla in patients with invasive breast cancer. However it is associated with significant complications, such as problems with shoulder movement and lymphoedema. ALND is a defined surgical block dissection to remove all the lymph node tissue in the axilla, which is then examined by a pathologist to determine whether cancer cells are present. Typically 10–15 lymph nodes are retrieved and at least one section from each assessed by standard haematoxylin and eosin (H&E) staining. It is possible however for small metastases to be missed by this technique.

Sentinel lymph node biopsy (SLNB) and four node sampling (4-NS) are less invasive axillary staging techniques than ALND and have been shown to reduce the complication rate. SLNB is a targeted technique to identify and remove the SLN, causing minimal disruption to the axilla. There are currently three techniques in use to identify SLNs: combined isotope and blue dye, isotope or blue dye alone. When isotope is used, preoperative scintiscanning may also be added as well as intra-operative detection with a hand-held probe. The rate of identification of the SLN improves with the dual technique. The procedure has been shown to be effective in most situations including multifocal tumours and after primary chemotherapy or open diagnostic biopsy. 4-NS involves a more random identification and surgical removal of a minimum of four lymph nodes from the lower axilla which may be assisted by the use of blue dye.

The benefit of reduced complications following SLNB will be gained in those patients whose removed lymph nodes are tumour free, since further axillary treatment is avoided. Techniques to identify tumour positive lymph nodes intra-operatively are being evaluated and may avoid a second operation to clear the axilla. It is therefore advisable to identify those patients who can be shown to have involved lymph nodes by preoperative testing whenever possible (recommendations on ultrasound and ultrasound-guided needle biopsy sampling can be found in Chapter 2).

Because of the variation in the methodology of SLNB and 4-NS techniques in the reported literature, comparison of the clinical outcomes of these procedures to the 'gold standard' ALND is difficult and long term follow-up data are not yet available in many cases.

Although there are no absolute contraindications to SLNB for patients with invasive breast cancer, the risk of needing further axillary treatment is obviously higher in some groups than others. Nevertheless patients should not be denied the opportunity for a limited axillary staging procedure if there is a possibility that the lymph nodes may be tumour free; estimates of the risks of further surgery will need to be part of the discussion with the patient.

[1] NHS Breast Screening Programme Quality assurance guidelines for surgeons in breast cancer screening. Association of Breast Surgery (BASO) Guidelines for the management of symptomatic breast disease.

Recommendations

- Minimal surgery, rather than lymph node clearance, should be performed to stage the axilla for patients with early invasive breast cancer and no evidence of lymph node involvement on ultrasound or a negative ultrasound-guided needle biopsy. SLNB is the preferred technique.
- SLNB should only be performed by a team that is validated in the use of the technique, as identified in the New Start training programme[1].
- Perform SLNB using the dual technique with isotope and blue dye.
- Breast units should audit their axillary recurrence rates.

Qualifying statement: These recommendations are based on evidence from a meta-analysis of the results of observational studies and RCTs confirming the accuracy of SLNB in staging the axilla, RCT evidence of less morbidity with SLNB compared to axillary clearance and limited evidence that SLNB does not result in poorer overall or disease-free survival. Published health economic evidence is difficult to interpret in the UK context.

Clinical Evidence

Invasive breast cancer SLNB versus axillary clearance or axillary sampling

There is a large volume of evidence on SLNB both from RCTs and case series studies (Agarwal *et al.,* 2005; Blanchard *et al.,* 2003; BMJ Clinical Evidence 2005; Carlo *et al.,* 2005; Clarke *et al.,* 2004; Cody *et al.,* 1999; Cox. *et al.,* 2000; Cserni *et al.,* 2002; Fleissig *et al.,* 2006; Giuliano *et al.,* 1997; Haid *et al.,* 2002; Imoto *et al.,* 2004; Julian *et al.,* 2004; Katz *et al.,* 2006; Kim *et al.,* 2006; Kokke *et al.,*2005; Krag *et al.,* 2001 and 2007; Langer *et al.,* 2004; Langer *et al.,* 2005; Leidenius 2004; Lucci *et al.,* 2007; Mansel *et al.,* 2006; Naik *et al.,* 2004; Purushotham *et al.,* 2005; Reitsamer *et al.,* 2004; Rietman *et al.,* 2003; Ung *et al.,* 2004; Veronesi *et al.,* 2003 and 2006 and Zavagno *et al.,* 2005 a and b and 2008).

A well conducted systematic review and meta-analysis of 69 studies (of mixed study design) was undertaken by Kim, Giuliano and Lyman (2006) with data from over 8,000 patients. The overall sentinal lymph node localisation rate was 96.4%, the pooled estimate of false negative rate was 7.0%, the mean proportion of patients with positive sentinal lymph nodes was 42% and the post test probability negative was 4.6%. From other studies, the sentinal lymph node localisation rate ranged from 81.4% to 100% (mean 94.0% and median 94.9%) (Agarwal *et al.,* 2005; Carlo *et al.,* 2005; Clarke *et al.,* 2004; Cody *et al.,* 1999; Cox. *et al.,* 2000; Cserni *et al.,* 2002; Giuliano *et al.,* 1997; Haid *et al.,* 2002; Imoto *et al.,* 2004; Julian *et al.,* 2004; Krag *et al.,* 2001; Langer *et al.,* 2004; Langer *et al.,* 2005; Naik *et al.,* 2004; Reitsamer *et al.,* 2004; Ung *et al.,* 2004 and Veronesi *et al.,* 2003).

The false negative rate of SLNB ranges from 0% to 10.7% (mean 5.8%, median 5.9%) (Agarwal *et al.,* 2005; Clarke *et al.,* 2004; Cody *et al.,* 1999; Cox *et al.,* 2000; Cserni *et al.,* 2002; Giuliano *et al.,* 1997; Julian *et al.,* 2004; Krag *et al.,* 2001; Langer *et al.,* 2004; Ung *et al.,* 2004 and Veronesi *et al.,* 2003). The accuracy of SLNB ranges from 94.6% to 100% (mean 97.7% with a median of 98.3%) (Agarwal *et al.,* 2005; Clarke *et al.,* 2004; Cody *et al.,* 1999; Cserni *et al.,* 2002; Giuliano *et al.,* 1997; Krag *et al.,* 2001; Langer *et al.,* 2004; Ung *et al.,* 2004; Veronesi *et al.,* 2003 and Cox *et al.,* 2000.). The prevalence of axillary disease has a mean of 39.1%, median 35.4% and a range from 28.8% to 57.6% (Agarwal *et al.,* 2005; Clarke *et al.,* 2004; Cody *et al.,* 1999; Cserni *et al.,* 2002; Giuliano *et al.,* 1997; Krag *et al.,* 2001, Langer *et al.,* 2004; Leidenius *et al.,* 2004; Ung *et al.,* 2004; Veronesi *et al.,* 2003 and 2006 and Cox *et al.,* 2000.).

The evidence on morbidity, including lymphoedema, favours SLNB over axillary clearance (Mansel *et al.,* 2006; Fleissig *et al.,* 2006; Purushotham *et al.,* 2005; Lucci *et al.,* 2007 and Zavagno *et al.,* 2008). The ALMANAC RCT (reported by Mansel *et al.,* 2006 and Fleissig

Clinical Evidence (cont.)

et al., 2006) and the RCT by Purushotham *et al.* (2005) found little evidence, by intention to treat, that a difference exists in psychological morbidity between patients treated by SLNB compared to axillary clearance.

The follow-up periods in the studies ranged from a mean of 24 months from surgery (Blanchard *et al.,* 2003) to a median of 60 months by Carlo *et al.* (2005) and up to 78 months as reported by Veronesi *et al.* (2006). The extent of follow-up is therefore immature and results should be interpreted with caution. However, findings showed that patients treated by SLNB do not appear to have poorer rates of disease-free survival or overall survival, or of axillary recurrence in the short term, compared to patients treated by axillary clearance.

The retrospective review conducted by Katz *et al.* (2006) of SLNB procedures in 1,133 patients, the majority of whom had invasive disease, identified the following factors as risk factors for involvement of the sentinal lymph node: younger age; mastectomy as definitive surgery; larger tumour size; invasive histology; and tumour lymphovascular invasion. In the same study in patients with involved sentinal lymph nodes, the following factors were found to be risk factors for further axillary node involvement revealed by axillary clearance: tumour lymphovascular invasion; higher number of positive sentinal lymph nodes; larger sentinal lymph node deposits; and lower number of uninvolved sentinal lymph nodes. A RCT by Lucci *et al.* (2007) reported that the use of SLNB plus ALND resulted in more wound infections, axillary seromas, and paresthesias than SLNB alone. Lymphoedema was more common after SLNB plus ALND but was significantly different only by subjective report. The use of SLNB alone resulted in fewer complications. Zavagno *et al.* (2008) reported that the analysis of the Psychological General Well Being Index questionnaire showed a statistically more positive outcome in the anxiety domain and in the general index for the sentinal lymph node group.

Axillary sampling as staging surgery

In addition to SLNB, a literature search was performed to identify studies which evaluated axillary sampling as staging surgery in early breast cancer. 15 studies were identified: two RCTs (Chetty *et al.,* 2000 and Forrest *et al.,* 1995) and 13 case series studies (Hadjiminas and Burke, 1994; Rampaul *et al.,* 2004; Tanaka *et al.,* 2006; Thompson *et al.,* 1995; Mathew *et al.,* 2006; Sato *et al.,* 2001; Ishikawa *et al.,* 2005; Narredy *et al.,* 2006; Macmillan *et al.,* 2001; Hoar and Stonelake, 2003; Gui *et al.,* 2005; Cserni, 1999 and Kingsmore *et al.,* 2003).

Staging performance: staging data for axillary sampling were identified in five case series studies, most of which were very small in size. From these limited data, axillary sampling appears to have a median false negative rate of 3.6% (range 0%-6.5%) and a median accuracy of 98.5% (range 98%-100%). Although these values appear favourable to those of SLNB[2] they should be interpreted with caution due to the small volume of low-quality evidence. However the studies present no evidence that axillary sampling is inferior to SLNB in terms of detecting axillary disease.

Physical morbidity: evidence from one RCT is suggestive of reduced morbidity from axillary sample over axillary clearance or axillary sample plus radiotherapy, expressed as greater arm flexion at six months from surgery and smaller forearm circumference at three years from surgery. There were no other significant differences in morbidity outcomes, including upper arm circumference and other arm movements. Evidence from three observational studies comparing axillary sampling with axillary clearance favours axillary sample in terms of arm volume increase. Two of these studies suggest that radiotherapy, when used after axillary sampling in patients with disease-positive lymph nodes, has an adverse effect on shoulder mobility and arm volume.

[2] A meta-analysis by Kim, Giuliano & Lyman (2006) provided a pooled estimate of FNR for SLNB as 7.0% [95% CI 5.2%-8.8%]. In studies of SLNB reviewed for this guideline, the accuracy of SLNB had median 98.3% (range 94.6% to 100%), based on 10 series of patients (three series were within RCTs). The FNR of SLNB had median 5.9% (range 0% to 10.7%) based upon 11 series of patients (four series were within RCTs).

Clinical Evidence (cont.)

Recurrence and survival: two RCTs comparing axillary sampling with axillary clearance found no significant difference in terms of survival or recurrence. One retrospective analysis of a large series of patients who were treated in the pre-SLNB era, concluded that survival is significantly improved if four or more lymph nodes are sampled, compared to sampling fewer than four lymph nodes. This effect was demonstrated for patients with metastatic axillary lymph nodes and for patients with no detectable nodal metastases. A second observational study was suggestive of an inverse relationship between survival and the number of positive lymph nodes, with the best survival in patients with no detectable nodal disease.

Predictive factors for axillary metastases

Evidence on the risk factors for axillary metastases in patients with early invasive breast cancer was identified in 16 retrospective analyses. Although some studies represented large series of patients, the retrospective design constitutes poor quality evidence (Anan *et al.,* 2000; Barth *et al.,* 1997; Brenin *et al.,* 2001; Cao *et al.,* 2005; Chen *et al.,* 2002; Cutuli *et al.,* 2001; Giuliano *et al.,* 1996; Grube *et al.,* 2002; Houvenaeghel *et al.,* 2003; Katz *et al.,* 2006; Peters-Engl *et al.,* 2004; Rivadeneira *et al.,* 2000; Specht *et al.,* 2005; Tan, Tan *et al.,* 2005; Tan, Wu *et al.,* 2005 and Velanovich and Szymanski 1998).

The overall risk of axillary metastases in each of 13 studies had a median value of 27%. The most commonly reported risk factors for axillary metastases in 12 studies that performed multivariate analyses were larger tumour size (11 studies), presence of lympho-vascular invasion (8 studies), higher histological grade (5 studies) and younger patient age (5 studies), although other risk factors were reported.

The poor quality evidence from these studies does not permit definition of a distinct patient group with risk factors that indicate avoidance of SLNB in favour of axillary clearance.

Health Economic Evaluation

See health economic evaluation summary on page 36.

DCIS

Current guidelines advise that ALND should not be carried out in patients with DCIS[3]. For patients having a simple mastectomy SLNB restricts unnecessary encroachment into the axilla. Furthermore if unsuspected invasive disease is identified at mastectomy subsequent SLNB is impossible.

When breast reconstruction is being carried out in patients with invasive breast cancer or DCIS, it may be appropriate to carry out SLNB as an initial separate procedure.

Recommendations

- Do not perform SLNB routinely in patients with a preoperative diagnosis of DCIS who are having breast conserving surgery, unless they are considered to be at a high risk of invasive disease[1].

Qualifying statement: There was insufficient evidence to support the routine use of SLNB in patients with DCIS. There was GDG consensus that patients at a high risk of having unsuspected invasive disease would benefit from SLNB.

- Offer SLNB to all patients who are having a mastectomy for DCIS.

Qualifying statement: This recommendation was based on GDG consensus.

[3] NHS Breast Screenign Programme Quality assurance guidelines for surgeons in breast cancer screening.

Clinical Evidence

A limited volume of case series studies which address SLNB in patients with DCIS were identified. Ansari *et al.* (2008) conducted a meta-analysis (of observational studies) of the reported data on the incidence of sentinel lymph node metastasis in patients with DCIS. This analysis reported SLNB results in patients with the diagnosis of DCIS. The analysis showed the frequency of sentinel lymph node positivity in patients with a preoperative diagnosis of DCIS ranged from 0 to 16.7%. With an overall positivity incidence of 7·4%. Postoperative overall positivity incidence was 3.7%. The overall frequencies of nodal metastasis between the two groups (preoperative versus definitive diagnosis) were significantly different. Evidence on a subset of patients with a biopsy diagnosis of DCIS who were at high risk of an invasive component was reviewed and suggested that a palpable mass, a mammographic mass, a high-grade DCIS and a large size were associated with a significant risk of invasive disease in the final resection specimen.

In the other case series studies there was general consistency in differentiating between true DCIS, DCIS with microinvasion (DCISm) and invasive disease, usually based upon the definition of DCISm by the American Joint Committee on Cancer (i.e. invasive focus < 1mm in size on definitive histology). The overall rate of sentinel lymph node involvement for true DCIS was 1.8% (Veronesi *et al.,* 2005) and 5% (Wilke *et al.,* 2005). This evidence was drawn from observational studies which reported rates of detection of positive sentinel lymph nodes in patients with DCIS (with no detectable microinvasion) as 1.8% (Veronesi *et al.,* 2005). The median value from 12 included observational studies was 5.4% (range 0% to 22%). Overall rate of sentinel lymph node involvement for DCISm from an observational study by Wilke *et al.* (2005) showed that the subgroup of patients with DCISm represented only 51 individuals. Among these, the rate of detection of positive sentinal lymph nodes was 14%. The median value from 7 included observational studies is 11.1% (range 9.5% to 29.4%). From all other 16 case series studies the summary statistics for the rate of sentinal lymph node involvement in patients with DCIS (which represent patients with only true DCIS, only DCISm, or either of DCIS/DCISm) were: mean 7.6%; median 6.8%, range 0% to 22%. (Camp *et al.,* 2005; Cox *et al.,* 1998; Cserni *et al.,* 2002; Farkas *et al.,* 2004; Intra *et al.,* 2003; Katz *et al.,* 2006; Kelly *et al.,* 2003; Klauber-DeMore *et al.,* 2000; Liu, Yang and Chen, 2003; Mittendorf *et al.,* 2005; Pendas *et al.,* 2000; Trisal, Qian and Wagman, 2004; Veronesi *et al.,* 2005; Wilkie *et al.,* 2005; Zavagno *et al.,* a2005 and b and Zavotsky *et al.,* 1999).

There was no evidence to suggest that a pattern exists between the rate of positive sentinal lymph nodes and DCIS grade. There was no evidence to suggest that a pattern exists between the rate of positive sentinal lymph nodes and DCIS tumour size. It was not possible to reliably estimate the proportion of patients with DCIS and positive sentinal lymph nodes who have further axillary nodal involvement from the studies identified, because of small numbers of patients in the series.

None of the selected studies (all retrospective) reported changes to treatment plans as a result of staging by SLNB, and all studies were retrospective in nature. However five studies provided data on patients who were upstaged from the stage attributed by primary tumour biopsy, in the light of final, primary tumour histology from definitive surgery: a retrospective case series study (Wilkie *et al.,* 2005) provides evidence that 10% of patients staged by biopsy as having DCIS (including DCISm) and who undergo SLNB are found to have invasive disease by primary tumour histology revealed by definitive surgery.

Health Economic Evaluation

A joint systematic review of the evidence was conducted to assess the cost effectiveness of using SLNB as the staging procedure for patients with invasive breast cancer (compared to ALND or axillary node sampling), and of using SLNB for patients with DCIS; comparing SLNB to either ALND or no ALND. The volume of economic evidence identified was limited and referred to patients with invasive breast cancer only. From a total of 80 references obtained from the search, six studies were identified that were related in some way to the cost effectiveness of SLNB in patients with invasive breast cancer: one of these studies was a

Health Economic Evaluation (cont.)

full economic evaluation (Jeruss *et al.,* 2006), two of them were partial economic evaluations (Fortunato *et al.,* 2004 and Ronka *et al.,* 2004), and three of them were cost studies (Chirikos *et al.,* 2001, Gemignani *et al.,* 2000 and Perrier *et al.,* 2004).

The only full economic evaluation identified (Jeruss *et al.,* 2006) was conducted in USA and assessed two alternative ways of conducting SLNB: intra-operatively and postoperatively. The study used a decision tree to assess which of these two SLNB procedures was more cost effective in terms of quality-adjusted life years (QALYs) gained and costs incurred. The authors concluded that intra-operative SLNB seemed to be cost effective when compared to postoperative SLNB independent of the type of tumour (with an incremental cost effectiveness ratio of $13,731 per QALY gained for patients with T1 tumours, and $7,103 for T2 tumours, and higher QALYs gained at a lower cost for tumours T3 and T4). The results were sensitive to the utilities used to estimate QALYs. The cost analysis of this study was based on a very small sample (five patients), which may limit the internal and the external validity of the study results. Moreover, the study compared two SLNB staging procedures rather than comparing SLNB with ALND or axillary node sampling.

The partial economic evaluation by Fortunato *et al.* (2004) was conducted in Italy and assessed the accuracy of SLNB and the savings for the Italian Health System associated with avoiding deferred ALND by conducting intra-operative SLNB. SLNB resulted in a false negative rate of 13.7% and a false positive rate of 3.7%, and the authors concluded that intra-operative SLNB would result in significant cost savings derived from avoiding a delayed ALND on a subgroup of patients (those found with positive lymph nodes by intra-operative SLNB). On the other hand, the partial economic evaluation by Ronka *et al.* (2004) was conducted in Finland and compared three ways of conducting SLNB with ALND. A false negative rate of 13.24% was found for SLNB, and ALND was found to be the least costly staging strategy in terms of hospital costs. The authors mentioned that the benefits of intra-operative SLNB are likely to be found in the long-term (i.e. decreased arm morbidity) and that SLNB may be worth the relatively low false negative rates because it avoids secondary surgery (i.e. delayed ALND) in patients undergoing staging.

None of the identified cost studies were conducted in the UK. Two of these cost studies were conducted in the USA (Chirikos *et al.,* 2001, and Gemignani *et al.,* 2000) and considered billing charges rather than estimation of the costs related to SLNB (which may not be representative of the true costs of the intervention within the UK context). The other study was conducted in France (Perrier *et al.,* 2004). It was unclear whether SLNB was more or less expensive compared to ALNC: Perrier *et al.* (2004) concluded that SLNB seemed to be less expensive than ALND; according to Gemignani *et al.* (2000), SLNB did not seem to result in significantly higher hospital-related charges compared to ALND. Chirikos *et al.* (2001) highlighted that, although SLNB appeared to be a more expensive procedure than ALND according to the results of their study, the potential cost-savings from SLNB are likely to be observed in the long term. None of these studies considered the costs of postoperative complications, whose inclusion would have been required for an accurate cost assessment.

Overall, the identified studies have limitations, both methodological and in the applicability of their results to the UK. The evidence identified was not good enough to inform whether SLNB is cost effective compared to ALND as a staging procedure.

3.3 Evaluation and Management of a Positive Sentinel Lymph Node

Sentinel lymph nodes and ALND specimens are generally not examined in an equivalent manner in the pathology laboratory. The receipt of fewer lymph nodes in a sentinel lymph node procedure encourages more thorough histological examination, for example by means of assessment of additional H&E levels and/or by immunohistochemistry for epithelial/cytokeratin markers. The use of such techniques increases the chance of the pathologist identifying smaller foci of tumour cells. ALNDs are generally also examined more thoroughly than in the past.

A standard for reporting breast cancer cells in axillary lymph nodes is now used, such that disease is reported as macrometastatic (> 2mm), micrometastatic or as isolated tumour cells (ITCs), according to national and international guidelines[4]. However, the significance of small metastatic deposits in axillary lymph nodes is uncertain with regard to prediction of (a) the likelihood of additional metastatic disease in higher echelon lymph nodes in the axilla and (b) overall patient prognosis, and thus so for guiding clinical management.

Patients with macrometastases or micrometastases are classified as lymph node-positive, whilst those with ITCs are regarded as lymph node-negative. Multidisciplinary teams need to use data systems that allow identification of breast cancer patients with macrometastases, micrometastases or ITCs for subsequent audit and research.

There is an increasing likelihood of additional non-sentinel lymph node axillary nodal metastases with increasing size of the sentinel lymph node deposit and the larger the sentinel lymph node deposit the higher chance of non-sentinel lymph nodes containing metastatic disease.

Radiotherapy to the axilla is covered in Chapter 6.

Recommendations

- Offer further axillary treatment to patients with early invasive breast cancer who:
  - have macrometastases or micrometastases shown in a sentinel lymph node
  - have a preoperative ultrasound-guided needle biopsy with histologically proven metastatic cancer.

The preferred technique is ALND because it gives additional staging information.

- Do not offer further axillary treatment to patients found to have only isolated tumour cells in their sentinel lymph nodes. These patients should be regarded as lymph node-negative.

Qualifying statement: These recommendations are based on a large body of mainly observational evidence showing that increasing size of metastasis in the sentinel lymph node is associated with increasing likelihood of further, non- sentinel lymph node, metastases.

Clinical Evidence

From RCT evidence there were no significant differences in overall survival between groups given axillary dissection or axillary sampling with regional lymph node radiotherapy for lymph node-positive patients (Chetty *et al.,* 2000, Forrest *et al.,* 1995); similarly there was no significant difference in overall survival between the groups receiving SLNB and axillary dissection and SLNB or axillary dissection only in SLNB-positive patients (Veronesi 2003). Finally there were no differences between these groups for locoregional recurrences or axillary recurrences (Chetty *et al.,* 2000, Forrest *et al.,* 1995 and Veronesi *et al.,*2003). There were conflicting views from observational studies on whether patients with micrometastases can be spared axillary surgery. The majority of patients with macrometastases in observational studies were given axillary clearance, unless there were clinical reasons not to, or refusal (Chagpar and McMasters, 2006; EORTC Intergroup Study, 2007; Ganaraj *et al.,* 2003; Giard *et al.,* 2004; Gipponi *et al.,* 2006; Guenther *et al.,* 2003; Katz *et al.,* 2006; Langer *et al.,* 2005; Lyman *et al.,* 2005; Naik *et al.,* 2004; Park *et al.,*2007; Pinkney *et al.,* 2007 and Viale

[4] Pathology reporting of breast disease. A Joint Document Incorporating the Third Edition of the NHS Breast Screening Programme's Guidelines for Pathology Reporting in Breast Cancer Screening and the Second Edition of The Royal College of Pathologists' Minimum Dataset for Breast Cancer Histopathology. NHS BSP Publications No 58. 2005.

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Clinical Evidence (cont.)

et al., 2001). A retrospective case series by Samoilova *et al.* (2007) reported that the variable that most reliably separated N1a from N2-3 patients was the size of the tumour deposits in the sentinel lymph node. All patients with sentinel lymph node tumour deposits ≤ 5 mm had three or fewer positive lymph nodes; 95% were sentinel lymph node-positive only, and 91% had single lymph node involvement. The presence of lymphvascular invasion in the primary tumour was statistically significantly different between N1a and N2-3 patients and the presence of extracapsular extension of tumour in the sentinel lymph node was also statistically significantly different between N1a and N2-3 patients. The role of radiotherapy in reducing regional recurrence was unclear.

Five observational studies report the proportion of patients who undergo ALND after the finding of metastatic sentinel lymph nodes is made by SLNB, out of all patients with metastatic sentinel lymph nodes. The range of values is 63.2%-95.2% with the highest rate reported by a small, prospective study (de Widt-Levert *et al.,* 2003) and the remainder of values from larger, but retrospective, studies.

Eight observational studies indicate a trend whereby larger size of the metastasis in the sentinel lymph node is associated with higher rates of non-sentinel lymph node metastases. The mean proportion of patients with metastatic non-sentinel lymph nodes is 10% for sentinel lymph node isolated tumour cells, 17.7% for sentinel lymph node micrometastases and 53.2% for sentinel lymph node macrometastases (de Widt-Levert *et al.,* 2003; Goyal *et al.,* 1990; Bolster *et al.,* 2007; Calhoun *et al.,* 2005; Houvenaeghel *et al.,* 2006; Katz *et al.,* 2006a; van Rijk *et al.,* 2006 and Viale *et al.,* 2005). From two systematic reviews (Cserni *et al.,* 2004 and Degnim *et al.,* 2003) the pooled estimate for the rate metastatic non-sentinel lymph nodes in patients with sentinel lymph node metastases of size 2 mm or less was 20.2% (95% CI 15.5%-24.9%) when the sentinel lymph node metastases are detected by H&E staining, and 9.4% (95% CI 6.2%-12.6%) when the sentinel lymph node metastases are detected by immunohistochemistry techniques.

Evidence from observational studies suggests that size of the sentinel lymph node metastasis was frequently a statistically significant independent predictive factor along with several other tumour/treatment related variables (Goyal *et al.,* 2004; Bolster *et al.,* 2007; Degnim *et al.,* 2005; Houvenaeghel *et al.,* 2006; Katz *et al.,* 2006a and Viale *et al.,* 2005).

From four studies reporting on the size of metastasis in non-sentinel lymph nodes in patients with metastatic sentinel lymph nodes who then undergo ALND (Bolster *et al.,* 2007; Calhoun *et al.,* 2005; van Rijk *et al.,* 2006 and Viale *et al.,* 2005) (see Tables 5-7 of full evidence review for this topic on the accompanying CD-ROM) the data indicate that patients with sentinel lymph node isolated tumour cells (< 0.2mm in size) and those with sentinel lymph node micrometastases (of size 0.2-2 mm in size) may be found to have larger non-sentinel lymph node metastases when ALND is performed, and at potentially high rates, although due to small numbers, estimates of rates are unreliable.

Of the included studies only one (Calhoun *et al.,* 2005) provides data for recurrence and survival. All patients were alive at a mean follow-up of 80.5 months (6 years, 8 months).

Health Economic Evaluation

The GDG did not consider this topic as a health economic priority; therefore the cost effectiveness literature on this topic has not been reviewed.

Research recommendation

- In the absence of good data about differences in clinical outcome between axillary radiotherapy and completion ALND, entry into appropriate clinical trials, e.g. AMAROS, is recommended for early breast cancer patients when the axilla has been found by SLNB to contain metastasis.

3.4 Breast Reconstruction

Breast reconstruction can be carried out at the same time as mastectomy (immediate) or at any point in the future (delayed). Breast reconstruction is not associated with a higher risk of recurrence. Immediate reconstruction has the advantage, to those patients for whom loss of body image is a concern, of having one primary breast procedure and offering the possibility for limited skin removal. The advantage of immediate breast reconstruction, where it is possible, is that fewer operations are required in order to obtain the definitive shape. However, a large quantity of information about reconstruction has to be discussed with patients for them to make informed decisions and this can be difficult when at the same time absorbing the diagnosis of breast cancer. Furthermore, all methods of reconstruction have potential complications which might delay subsequent adjuvant therapy. Chest wall radiotherapy may significantly reduce the cosmetic outcomes of reconstruction.

Methods of reconstruction include sub-pectoral tissue expansion, pedicled flaps and free tissue transfers. There are pros and cons of each method which need to be combined with other patient characteristics when deciding which approach is best for each individual. This requires knowledge of the techniques available and well-defined referral pathways to be in place where not all methods can be carried out locally. Good practice in supporting patients could include, where possible, providing photographs of previous reconstructions or access to peer support.

Recommendation

- Discuss immediate breast reconstruction with all patients who are being advised to have a mastectomy, and offer it except where significant comorbidity or (the need for) adjuvant therapy may preclude this option. All appropriate breast reconstruction options should be offered and discussed with patients, irrespective of whether they are all available locally.

Qualifying statement: These recommendations are based on limited clinical evidence from observational studies and on GDG consensus that immediate reconstruction is an acceptable procedure that does not disadvantage patients compared to delayed reconstruction.

Clinical Evidence

A moderate volume of observational studies exists for breast reconstruction following mastectomy for breast cancer. There are few direct comparisons of immediate reconstruction versus delayed reconstruction.

With respect to psychological outcomes one systematic review of observational studies suggests that better psychological outcomes arise in patients treated with immediate reconstruction compared to delayed reconstruction (Fischbacher, 2002). Subsequently published observational studies suggest that psychological outcomes are generally good following immediate reconstruction (Drucker-Zertuche and Robles-Vidal 2007 and Gendy *et al.,* 2003).

There is high heterogeneity with regard to assessment of cosmetic outcome between the studies. No evidence was identified from one systematic review of observational studies and subsequent observational studies to suggest superiority of immediate versus delayed reconstruction in terms of cosmetic result. The majority of the observational studies report high rates of acceptable cosmetic results between 80% and 96% (Anderson *et al.,* 2004; Drucker-Zertuche and Robles-Vidal, 2007; Gendy *et al.,* 2003; Cordeiro *et al.,* 2004 and Vandeweyer *et al.,* 2003) whereas in one study the reported rate is only 20% (Knottenbelt *et al.,* 2004).

Clinical Evidence (cont.)

Two systematic reviews of observational studies suggest that immediate reconstruction may be associated with a higher rate of complications compared to delayed reconstruction (Fischbacher, 2002 and Javaid *et al.,* 2006). A third less rigorous review found similar rates of capsular contraction between immediate and delayed reconstruction with implants, but with a trend for unfavourable results with immediate autologous tissue reconstruction (Taylor *et al.,* 2005). Apart from radiotherapy, studies that examined potential risk factors for complications following reconstruction did not consistently identify any other factors (Anderson *et al.,* 2004 and Woerdeman *et al.,* 2006).

No reliable evidence was identified on whether immediate breast reconstruction following mastectomy delays the start of adjuvant chemotherapy or radiotherapy. Whilst a minority of observational studies included in an expert review (Taylor and Kumar, 2005) indicated that such delays occur after immediate reconstruction, the review's authors concluded that the evidence was inconclusive. Subsequently published observational studies have demonstrated little difference in the interval from surgery to adjuvant therapy in patients treated with immediate reconstruction compared to those for whom reconstruction is delayed, or those who do not receive reconstruction (Gouy *et al.,* 2005; Taylor and Kumar, 2005; Wilson *et al.,* 2004 and Rey *et al.,* 2005).

No reliable evidence was identified to suggest that recurrence or survival differs in patients treated with immediate reconstruction compared to those who receive delayed reconstruction. One systematic review citing observational studies reported no difference in recurrence and survival following mastectomy with immediate reconstruction compared to mastectomy with no reconstruction. One expert review (Taylor *et al.,* 2005), summarised the rate of local recurrence with a median value of 5%, drawn from observational studies of patients treated with mastectomy and immediate reconstruction. The rate of distant metastasis in 16 studies of similarly treated patients had a median value 10.5%.

Evidence from observational studies suggests that in general, patients are satisfied with their reconstructed breasts following either immediate reconstruction, or delayed reconstruction. However some patients are not satisfied with their reconstructions and the impact of this is not further explored by the identified studies (Tykka *et al.,* 2002; Ascherman *et al.,* 2006; Cordeiro *et al.,* 2004 and Vandeweyer *et al.,* 2003). Very little direct evidence for women's preference for immediate versus delayed breast reconstruction was identified.

Health Economic Evaluation

The GDG did not consider this topic as a health economic priority; therefore the cost effectiveness literature on this topic has not been reviewed.

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4 Postoperative assessment and adjuvant treatment planning

4.1 Introduction

Following surgery, further information is obtained by histological examination, which provides prognostic information including histological grade, nodal status and tumour size. Factors predicting response to specific targeted therapies including hormone receptor and human epidermal growth factor receptor 2 (HER2) status are also evaluated. These prognostic and predictive factors, together with patient characteristics, enable subsequent treatment planning to be undertaken by the breast cancer multidisciplinary team (MDT).

4.2 Predictive Factors

Hormone receptors

Approximately 70% of invasive breast cancers are oestrogen receptor alpha (ER) positive and the level of ER assessed immunohistochemically provides useful predictive information regarding efficacy of endocrine therapy. ER status therefore forms part of the UK minimum dataset for histopathology reporting of invasive breast cancer[1]. ER status is routinely determined on all invasive breast cancers and reported using a standardised technique (such as the Allred scoring system[2]).

The prediction of likelihood of response of a breast cancer to endocrine therapies using ER assessment is not, however, precise; some patients with ER-positive disease will not respond to endocrine therapies. Further discriminatory markers, such as progesterone receptor (PR) to predict response to endocrine agents with greater accuracy are required. PR status does not appear to add useful information in ER-positive tumours. Divergent ER and PR status is uncommon (for example < 5% of cases are ER-negative but PR-positive) and the value of the addition of PR status in this situation in predicting likelihood of response to endocrine therapy is also unclear. Nevertheless, PR examination is routinely performed on all invasive tumours by some laboratories.

HER2 status

The clinical importance of amplification of the human epidermal growth factor receptor gene HER2 in breast cancer was recognised in 1987 and an association with poorer patient outcome was subsequently reported. HER2 positivity (protein overexpression or gene amplification) is

[1] Pathology reporting of breast disease. A Joint Document Incorporating the Third Edition of the NHS Breast Screening Programme's Guidelines for Pathology Reporting in Breast Cancer Screening and the Second Edition of The Royal College of Pathologists' Minimum Dataset for Breast Cancer Histopathology. NHS BSP Publication 58. January 2005.

[2] Estrogen receptor status by immunohistochemistry is superior to the ligand-binding assay for predicting response to adjuvant endocrine therapy in breast cancer. JM Harvey, GM Clark, CK Osborne, DC Allred. J Clin Oncol 17:1474-1481.

seen in approximately 15% of early invasive breast cancer. Women whose breast cancers are HER2-positive may benefit from trastuzumab therapy. Therefore the HER2 status of an invasive breast cancer has become an essential part of selection of this therapy.

Diagnostic tests for HER2 over-expression and gene amplification include immunohistochemistry (IHC) and in situ hybridisation (ISH). A standardised and quality assured methodology for these needs to be used as per the updated UK recommendations for HER2 testing[3]. Breast cancers are reported as HER2-negative or HER2-positive according to these guidelines (i.e. those scoring 3+ by IHC, or 2+ and ISH amplified, as positive).

Recommendations

- Assess ER status of all invasive breast cancers, using immunohistochemistry with a standardised and qualitatively assured methodology, and report the results quantitatively.
- Do not routinely assess progesterone receptor status of tumours in patients with invasive breast cancer.
- Test HER2 status of all invasive breast cancers, using a standardised and qualitatively assured methodology.
- Ensure that the results of ER and HER2 assessments are available and recorded at the multidisciplinary team meeting when guidance about systemic treatment is made.

Qualifying statement: These recommendations are based on evidence from observational studies that ER status is a useful predictor of survival and response to tamoxifen but that there is no strong evidence for the usefulness of measuring PR status.

Clinical Evidence

Four retrospective studies addressed the relative contribution of progesterone receptor (PR) status to the choice and outcomes of endocrine therapy. Ponzone *et al*. (2006) examined the effects of various endocrine therapies. Two moderate quality cohort studies compared tamoxifen with a non-intervention control (Dowsett *et al*., 2006 and Stendahl *et al*., 2006) and a third study re-examined tissue from a trial which had compared tamoxifen with anastrozole versus both in combination (Dowsett *et al*., 2008). All groups used immunohistochemistry to visualise the presence of hormone receptors but the criteria used to assign negative and positive status was not consistent.

Positive hormone receptor status (either estrogen or progesterone) was associated with significantly longer relapse-free survival compared with negative receptor expression. Weak evidence suggested that the ER+ve/PR-ve sub-group experienced a significant relapse-free survival benefit with tamoxifen therapy compared with controls whilst those with ER-ve status had a poorer relapse-free survival (Dowsett *et al.,* 2006).

Low levels of either ER or PR correlated with a shorter time to recurrence but hormone status did not predict the superiority of anastrazole over tamoxifen that had been found in a large multi-centre RCT (Dowsett *et al.,* 2008).

Tamoxifen therapy was significantly better than control treatment with respect to RFS when either ER or PR were labelled in > 75% of cells at which point PR was also independently associated with favourable overall survival (Stendahl *et al*., 2006).

Compared with the other three sub-groups, ER-positive/PR-negative status was initially associated with superior prognosis with respect to disease-free survival but after 8 years this advantage was lost and the prognosis was reversed (Ponzone *et al*., 2006).

[3] HER2 Testing in the UK: Further Update to Recommendations. RA Walker, JM Bartlett, M Dowsett, IO Ellis, AM Hanby, B Jasani, K Miller, SE Pinder. J Clin Pathol. 2008; 61; 818-824).

Clinical Evidence (cont.)

There was no strong evidence to support PR being predictive of a response to endocrine therapy despite being independently prognostic for relapse-free survival and/or overall survival. The benefits of PR status appeared to change with time and with the degree of scellular expression. There were no prospective studies comparing the response to a specific endocrine therapy of ER/PR sub-groups and no evidence with regard to treatment decisions based on hormone receptor status.

Health Economic Evaluation

The GDG did not consider this topic as a health economic priority; therefore the cost effectiveness literature on this topic has not been reviewed.

4.3 Adjuvant Treatment Planning

Planning adjuvant treatment is complex and incorporates a variety of prognostic and predictive factors. There are a number of tools to help the MDT with decisions on adjuvant treatment planning which assess prognosis and estimate potential treatment benefit. One of these tools is Adjuvant! Online[4] which has about 3,000 registered users in the UK.

The Adjuvant! Online computer programme is designed to help inform the discussion between healthcare professionals and patients with early stage breast cancer about the benefits of adjuvant endocrine therapy and chemotherapy. A version of Adjuvant! Online that will include HER2 status and the potential benefit of trastuzumab is in development. The current version (version 8) may underestimate the risk of mortality and the benefit of trastuzumab in HER2-positive patients. Patient and tumour characteristics are entered and provide an estimate of the baseline risk of mortality or relapse for patients without adjuvant therapy. Information about the efficacy of different therapy options are derived from Early Breast Cancer Trialists Collaborative Group (EBCTCG) meta-analyses in order to provide estimates of reduction in risk at 10 years of breast cancer related death or relapse for selected treatments. Results may be displayed and printed in graphical form to aid shared decision-making.

Recommendations

- Consider adjuvant therapy for all patients with early invasive breast cancer after surgery at the multidisciplinary team meeting and ensure that decisions are recorded.
- Decisions about adjuvant therapy should be made based on assessment of the prognostic and predictive factors, the potential benefits and side effects of the treatment. Decisions should be made following discussion of these factors with the patient.
- Consider using Adjuvant! Online[5] to support estimations of individual prognosis and the absolute benefit of adjuvant treatment for patients with early invasive breast cancer.

Qualifying statement: These recommendations are based on GDG consensus and an expert position paper on Adjuvant! Online.

Clinical Evidence

Researchers were unable to define this question specifically enough to enable it to be appraised. The GDG commissioned an expert position paper to assess the validity of Adjuvant! Online as a tool to assist with clinical decisions, about adjuvant therapy in patients with early invasive breast cancer (see Appendix 1).

[4] www.adjuvantonline.com
[5] www.adjuvantonline.com

Health Economic Evaluation

The GDG did not consider this topic as a health economic priority; therefore the cost effectiveness literature on this topic has not been reviewed.

4.4 Timing of Adjuvant Treatment

Most patients with early breast cancer will require adjuvant therapy using radiotherapy, chemotherapy or endocrine therapy and many will require a combination of these.

The factors governing the interval between surgery and adjuvant therapy are variable and include postoperative recovery and availability of resources. However, the interval between surgery and adjuvant therapy that affects outcome has not been defined. Nevertheless, it is appropriate to start these therapies as soon as possible. Whether these treatments should be given concurrently or sequentially and if sequentially in what order, is unclear.

Concurrent radiotherapy and chemotherapy is not used because of increased acute and late local toxicity resulting in a poor cosmetic result. Data from retrospective studies have demonstrated a small increase in local recurrence rate in patients who have chemotherapy prior to radiotherapy and an increase in distant recurrence rates in those given radiotherapy prior to chemotherapy.

There is no good evidence that concurrent radiotherapy and endocrine therapy is detrimental. However, concurrent chemotherapy and tamoxifen compromises survival.

Recommendation

- Start adjuvant chemotherapy or radiotherapy as soon as clinically possible within 31 days of completion of surgery[6] in patients with early breast cancer having these treatments.

Qualifying Statement: This recommendation is based on GDG consensus in the absence of good quality evidence.

Clinical Evidence

Sequencing of adjuvant therapies

Concurrent adjuvant chemotherapy/radiotherapy versus chemotherapy followed by radiotherapy: there is high-quality evidence from RCTs (Hickey *et al.,* 2006; Calais *et al.,* 2005 and Toledano *et al.,* 2007) that suggest there is no advantage arising from concurrent adjuvant chemotherapy/radiotherapy versus sequential chemotherapy followed by radiotherapy in terms of local recurrence, distant metastases and overall survival. RCT evidence on acute toxicity for this comparison is not consistent, since there is no difference with regard to some toxic effects, whereas other toxic effects are more common following either concurrent therapy, or sequential therapy. RCT evidence suggests that late toxic effects are more common following concurrent therapy than sequential therapy and that in the subgroup of lymph node-positive patients local recurrence-free survival is higher following concurrent therapy than sequential therapy.

Radiotherapy followed by chemotherapy versus chemotherapy followed by radiotherapy: further RCT evidence (Hickey *et al.,* 2006 and Huang *et al.,* 2003) suggests there is no advantage arising from radiotherapy followed by chemotherapy versus chemotherapy followed by radiotherapy in terms of distant metastases and overall survival. RCT evidence is suggestive of a higher rate of neutropenic sepsis in patients who receive radiotherapy

[6] Department of Health (2007). Cancer reform strategy. London: Department of Health. (At present no equivalent target has been set by the Welsh Assembly Government.)

Clinical Evidence (cont.)

before chemotherapy but with no difference for other toxicity outcomes. One meta-analysis of data from observational studies suggests that loco-regional recurrence is higher where chemotherapy precedes radiotherapy, compared to radiotherapy then chemotherapy.

Early versus late chemotherapy: RCT evidence from the International Breast Cancer Study Group (1997) suggests there is no difference in 5-year disease-free survival or overall survival arising from early chemotherapy given over the first three months following surgery versus delayed chemotherapy given between 9 and 15 months following surgery.

Interval between surgery and start of adjuvant therapy

Interval from surgery to radiotherapy: there is considerable high-quality evidence that addresses this clinical issue (Huang *et al.,* 2003; Whelan *et al.,* 2003 and Hershman *et al.,* 2006a). Evidence from a meta-analysis of data from observational studies suggests that loco-regional recurrence is more likely if radiotherapy is delayed more than 8 weeks following surgery. Other observational studies do not consistently indicate that a longer interval to start of radiotherapy is associated with greater likelihood of locoregional recurrence, but these studies consider different lengths of interval. Evidence from a meta-analysis of data from observational studies suggests there is no difference in the rate of distant metastases arising from an interval to radiotherapy of 8 weeks or more, compared to an interval of less than 8 weeks. Authors of a Canadian guideline based upon a systematic review conclude that evidence does not support the definition of an optimal interval between surgery and radiotherapy (Whelan *et al.,* 2003). One retrospective cohort study (Hershman *et al.,* 2006a) suggests that in elderly patients who receive radiotherapy and no chemotherapy, higher mortality is observed where radiotherapy is given 3 months or more following surgery, compared to within 3 months of surgery. In the same study numerous demographic and tumour-related variables were also associated with mortality outcomes, making interpretation difficult.

Other observational studies found that disease-free and overall survival were not adversely affected by increasing delay to the start of radiotherapy in the first three months after surgery (Benchalal *et al.,* 2005; Jobsen *et al.,* 2006 and Mikeljevic *et al.,* 2004). A large UK cohort study of 7800 women found that overall survival was adversely affected only in those whose radiotherapy was delayed for at least 5 to 6 months after surgery (Mikeljevic *et al.,* 2004).

Interval from surgery to chemotherapy: One retrospective cohort study (Hershman *et al.,* 2006b) suggests that in elderly patients who receive chemotherapy with no radiotherapy prior to chemotherapy, higher mortality is observed where chemotherapy is given 3 months or more following surgery, compared to within 3 months of surgery. In the same study numerous demographic and tumour-related variables were also associated with mortality outcomes, making interpretation difficult.

Other cohort studies found increasing delay to the start of adjuvant chemotherapy in the first 3 months after surgery was not associated with poorer disease-free or overall survival (Cold *et al.,* 2005; Colleoni *et al.,* 2000; Lohrisch *et al.,* 2006; Sanchez *et al.,* 2007 and Shannon *et al.,* 2003). Colleoni *et al.* (2000) reported that disease-free survival was adversely affected by delays of three or more weeks in the sub-group of women with ER-negative disease. Another study reported that disease-free and overall survival were adversely affected only when the start of chemotherapy was delayed until at least three to six months after surgery (Lohrisch *et al.,* 2006).

Health Economic Evaluation

The GDG did not consider this topic as a health economic priority; therefore the cost effectiveness literature on this topic has not been reviewed.

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5 Adjuvant systemic therapy

5.1 Introduction

A proportion of patients with early invasive breast cancer will have occult metastatic disease at the time of diagnosis and will relapse at a later date. The purpose of adjuvant systemic treatment is to reduce this risk. Adjuvant therapy options include endocrine treatments, chemotherapy and targeted biological agents (such as trastuzumab, please see page 63); the selection of these is based on tumour and patient characteristics (see Chapter 4). Endocrine therapies include direct treatments such as tamoxifen and aromatase inhibitors and indirect treatments such as radiation menopause, medical oophorectomy by luteinising hormone-releasing hormone agonists (LHRHa) and ovarian ablation by surgery. Endocrine therapy with tamoxifen or an aromatase inhibitor should only be considered in patients with hormone receptor-positive tumours. The potential benefits of treatments have been assessed by the Early Breast Cancer Trialists Collaborative Group (EBCTCG), which is updated every 5 years.

5.2 Endocrine Therapy for Invasive Disease

Ovarian suppression/ablation

Data from the EBCTCG (2005) indicate that patients whose tumours are potentially responsive to endocrine therapy achieve a reduction in risk of relapse and death from breast cancer from treatment strategies that reduce the levels, or block the action, of circulating oestrogens. In premenopausal women with oestrogen receptor alpha (ER) positive tumours, ovarian ablation or suppression is associated with a reduction in risk of relapse and death from breast cancer. Whether younger women, not rendered menopausal as a consequence of adjuvant chemotherapy gain additional benefit from ovarian suppression remains a subject of continuing research. Similarly, the therapeutic 'equivalence' of ovarian ablation/suppression and adjuvant chemotherapy in premenopausal women with hormone receptor-positive tumours remains contentious.

Menopausal symptoms following ovarian ablation/suppression are worse than after chemotherapy. Recommendations on menopausal symptoms can be found in Chapter 8.

Recommendations

- Do not offer adjuvant ovarian ablation/suppression to premenopausal women with ER-positive early invasive breast cancer who are being treated with tamoxifen and, if indicated, chemotherapy.
- Offer adjuvant ovarian ablation/suppression in addition to tamoxifen to premenopausal women with ER-positive early invasive breast cancer who have been offered chemotherapy but have chosen not to have it.

Qualifying statement: There is conflicting evidence and GDG consensus to support these recommendations.

Clinical Evidence

There is a large volume of RCTs of ovarian ablation and ovarian suppression in women with early breast cancer, and numerous high-quality systematic reviews are also available. Broadly, the literature describes two types of intervention: either ovarian ablation (by surgery or radiotherapy) or ovarian suppression using luteinising hormone releasing hormone agonist (LHRHa), each used adjuvant to surgery to the breast.

Evidence from systematic reviews of RCTs, meta-analyses of individual patient data from RCTs and further published RCTs is suggestive of the following effects of ovarian ablation (by oophorectomy or radiotherapy) or suppression (by LHRHa).

Ovarian ablation or suppression versus none: in premenopausal women with breast cancer that is ER-positive or with unknown ER status, ovarian ablation or suppression is beneficial compared to no ovarian treatment in terms of recurrence (respective rates 47% and 52%, $p<0.0001$) and breast cancer mortality (respective rates 40% and 44%, $p<0.004$), both assessed at 15 years follow-up (Early Breast Cancer Trialists' Collaborative Group, 2005).

Ovarian ablation and the role of chemotherapy: the most recent evidence from a meta-analysis of individual patient data suggests that ovarian ablation has a benefit in terms of recurrence and survival over no ablation in premenopausal women, with or without chemotherapy (EBCTCG, 2005). An earlier meta-analysis performed by the same group found that this benefit exists in the absence of chemotherapy, but not where adjuvant chemotherapy is given (EBCTCG, 1998). RCTs that were not included in these reviews have demonstrated equivalence in terms of 10 year recurrence and survival between ovarian ablation and chemotherapy, with tamoxifen used in some randomised arms (Nomura *et al.,* 1999 and Thomson *et al.,* 2002). A RCT was able to show no advantage of additional goserelin after a risk-adapted chemotherapy with respect to event free survival in hormone receptor-negative patients (Kaufmann *et al.,* 2007a).

LHRHa versus no systemic therapy: a relatively small meta-analysis (n=338) found no difference in recurrence or survival, comparing LHRHa with no systemic therapy (Cuzick *et al.,* 2007). From a well conducted RCT, premenopausal women with operable breast cancer showed a 5 and 10 year disease-free survival and overall survival rates were significantly improved following adjuvant oophorectomy and tamoxifen (Love *et al.,* 2008).

LHRHa versus chemotherapy: a larger meta-analysis (n=3184) in the same study found LHRHa to be equivalent to chemotherapy in terms of recurrence and survival (Cuzick *et al.,* 2007).

LHRHa plus tamoxifen versus LHRH alone or tamoxifen alone: a Cochrane Review indicates that recurrence and mortality are reduced in premenopausal women treated with a LHRHa combined with tamoxifen compared to women treated with either drug alone (Sharma *et al.,* 2007). In contrast a meta-analysis of individual patient data found no difference in recurrence or death following recurrence arising from treatment with LHRHa plus tamoxifen versus tamoxifen alone (Cuzick *et al.,* 2007).

LHRHa with or without tamoxifen in addition to chemotherapy: evidence from a narrative Cochrane Review and meta-analysis of RCTs indicates that recurrence and mortality are reduced in premenopausal women with ER-positive tumours who are treated with a LHRHa, with or without tamoxifen, in addition to chemotherapy (Sharma *et al.,* 2007 and Cuzick *et al.,* 2007).

LHRHa with or without tamoxifen versus chemotherapy: evidence from a narrative Cochrane Review and meta-analysis of randomised trials indicates that LHRHa, with or without tamoxifen, are as effective as chemotherapy for premenopausal women with ER-positive tumours, in terms of recurrence and mortality (Cuzick *et al.,* 2007 and Sharma *et al.,* 2007)

Side effects and quality of life: evidence from RCTs suggests that ovarian ablation, ovarian suppression and chemotherapy each have adverse side effects and each can induce menopausal symptoms, including amenorrhoea (Brunt *et al.,* 2004a; Groenvold *et al.,* 2006; Schmid *et al.,* 2007; Love *et al.,* 1999; Sharma *et al.,* 2007 and Celio *et al.,* 2002).

Clinical Evidence (cont.)

A randomised comparison of oophorectomy and tamoxifen versus observation in Vietnamese women found that menopausal symptoms resulted from oophorectomy and tamoxifen within the first 12 months from start of treatment (Love *et al.,* 1999). A Cochrane Review cited trials which found that side effects are more severe following LHRHa plus tamoxifen compared to tamoxifen alone (Sharma *et al.,* 2007). Health-related quality of life tends to favour ovarian ablation or suppression over chemotherapy, whereas acute adverse effects appear to be worse following chemotherapy. In contrast, menopausal symptoms (for example hot flushes) appear to be worse following ablation or suppression, than following chemotherapy, and with earlier onset. Amenorhoea can be longer lasting following chemotherapy compared with LHRHa *(*Brunt *et al., 2004a;* Groenvold *et al., 2006;* Sharma *et al. 2007* and Schmid *et al.* 2007). In one study a self assessment of tolerability by patients favoured LHRHa over CMF chemotherapy during the first 6 months, but with comparable tolerability at two years (Schmid *et al.,* 2007).

Health Economic Evaluation

The GDG did not consider this topic as a health economic priority; therefore the cost effectiveness literature on this topic has not been reviewed.

Aromatase inhibitors

Tamoxifen has a long established role in the adjuvant therapy of invasive breast cancer. There is a reduction in local and distant recurrence, a reduced risk of cancer in the contralateral breast and improved overall survival in patients with ER-positive tumours treated with tamoxifen. The Nottingham Prognostic Index[1] can be used to identify groups namely, excellent (EPG), good (GPG), moderate (MPG), poor (PPG) and very poor (VPG) prognostic group of patients, which can guide the healthcare professional concerning adjuvant treatment. Current practice is to give low-risk patients tamoxifen for five years.

The aromatase inhibitors (anastrozole, exemestane and letrozole), are alternative options to tamoxifen for ER-positive invasive breast cancer in postmenopausal women. The sequencing either after tamoxifen, or replacing it, will be defined more clearly as the results of large international randomised studies mature (for example ATAC, ARNO, IES).

The choice of specific adjuvant endocrine therapy will depend upon consultation between the clinician and patient and will include weighing up the benefits and side effects of each treatment. The value, if any, in assessing additional biomarkers to ER (for example human epidermal growth factor receptor 2 (HER2) or progesterone receptor (PR)) to predict response to different endocrine agents, is controversial and there is no good evidence.

The benefit from endocrine therapy with tamoxifen or an aromatase inhibitor in low-risk breast cancer (for example small tumours < 2 cm, grade 1, lymph node-negative) is very small and needs to be weighed with the effects on quality of life (and indeed whether the patient reliably takes the medication). Lymph node-negative patients with other poor prognostic indicators (for example grade 3 tumours) may have greater benefit with an aromatase inhibitor than tamoxifen.

It is appropriate to use an aromatase inhibitor for patients in whom tamoxifen is contraindicated or who are intolerant of tamoxifen.

[1] Survival of invasive breast cancer according to the Nottingham Prognostic Index in cases diagnosed in 1990-1999. Blamey RW, Ellis IO, Pinder SE, Lee AH, Macmillan RD, Morgan DA, Robertson JF, Mitchell MJ, Ball GR, Haybittle JL, Elston CW. Eur J Cancer. 2007;43:1548-55.

Recommendations

2
- Postmenopausal women with ER-positive early invasive breast cancer who are not considered to be at low risk[2] should be offered an aromatase inhibitor, either anastrozole or letrozole, as their initial adjuvant therapy. Offer tamoxifen if an aromatase inhibitor is not tolerated or contraindicated.

3
- Offer an aromatase inhibitor, either exemestane or anastrozole instead of tamoxifen to postmenopausal women with ER-positive early invasive breast cancer who are not low-risk[3] and who have been treated with tamoxifen for 2–3 years.
- Offer additional treatment with the aromatase inhibitor letrozole for 2–3 years to postmenopausal women with lymph node-positive ER-positive early invasive breast cancer who have been treated with tamoxifen for 5 years.

Qualifying statement: These recommendations are based on high-quality RCTs.

Clinical Evidence

There are several high-quality RCTs and systematic reviews of RCTs that report the role of aromatase inhibitors (AIs) as adjuvant therapy in postmenopausal women with hormone receptor-positive breast cancer.

Anastrazole

Disease-free survival is significantly increased with anastrazole compared to tamoxifen either as first line adjuvant treatment or after tamoxifen. Prior chemotherapy (CMF, anthracyclines or taxanes) reduces the disease-free survival advantage of anastrozole (Boccardo *et al.,* 2005; Buzdar *et al.,* 2006; Buzdar and Cuzick, 2006; Dowsett *et al.,* 2005; Forbes *et al.,* 2008; Hind *et al,.* 2007; Howell *et al.,* 2005; Jakesz *et al.,* 2005 and Kaufmann *et al.,* 2007b). For hormone receptor-positive patients disease-free survival favoured the anastrozole group and in the hormone receptor-negative subgroup there was no difference (Forbes *et al.,* 2008).

There is no difference in overall survival either as first adjuvant treatment or after tamoxifen (Boccardo *et al.,* 2005; Buzdar *et al.,* 2006; Dowsett *et al.,* 2005; Forbes *et al.,* 2008; Hind *et al.,* 2007; Howell *et al,.* 2005 and Jakesz *et al.,* 2005). However in contrast, Kaufmann *et al.* (2007b) showed a significant improvement in survival for patients in the anastrozole group when the benefits of switching to anastrozole after 2 years of tamoxifen treatment were compared with continuing on tamoxifen for 5 years.

The risk of disease recurrence is significantly reduced with anastrozole and is reported to be independent of nodal status, tumour size or prior chemotherapy. All ER-positive patients showed a benefit but there was no statistical difference between the progesterone receptor (PR)-positive or PR-negative subgroup (Boccardo *et al.,* 2005; Buzdar *et al.,* 2006; Dowsett *et al.,* 2005; Forbes *et al.,* 2008; Hind *et al.,* 2007; Howell *et al.,* 2005; Jakesz *et al.,* 2005 and Kaufmann *et al.,* 2007b). When patients who were disease-free at the end of receiving 5 years of adjuvant tamoxifen (with or without the aromatase inhibitor, amino-glutethimide, for the first 2 years of therapy) were randomly assigned to receive either 3 years of anastrozole or no further treatment; the disease-free survival was statistically improved with significantly fewer recurrences. The risk of contralateral breast cancer is significantly reduced only if anastrozole is given as first line adjuvant treatment; it is not significantly different if given after tamoxifen (Boccardo *et al.,* 2005; Buzdar *et al.,* 2006; Dowsett *et al,.* 2005; Forbes *et al.,* 2008; Hind *et al.,* 2007; Howell *et al.,* 2005; Jakesz *et al.,* 2005 and Kaufmann *et al.,* 2007b).

[2] Low-risk patients are those in the EPG or GPG groups in the Nottingham Prognostic Index (NPI) who have a 10 year predictive survival of 96% and 93% respectively. They would have a similar prediction using Adjuvant! Online. High-risk patients are those in groups PPG with 53% or VPG with 39%.

[3] Low-risk patients are those in the EPG or GPG groups in the Nottingham Prognostic Index (NPI) who have a 10 year predictive survival of 96% and 93% respectively. They would have a similar prediction using Adjuvant! Online. High-risk patients are those in groups PPG with 53% or VPG with 39%.

Clinical Evidence (cont.)

Time to progression was significantly increased for ER-positive/PR-negative tumours. The data for ER-positive/PR-positive tumours were significantly different from ER-positive/PR-negative tumours (non-overlapping confidence intervals). There is no statistical significant difference in the risk of distant disease. Forbes et al. (2008) and Kaufmann et al. (2007b) both showed that statistically fewer patients on anastrozole experienced distant disease recurrence.

There were statistically significant adverse events, with a significant increased in risk of bone fracture with anastrazole compared to tamoxifen. However women treated with tamoxifen were at significantly increased risk of endometrial cancer, deep venous and venous thromboembolic events and ischaemic cerebrovascular events compared to anastrozole.

Letrozole

The BIG 1-98 trial (Crivellari *et al.,* 2008: Coates *et al.,* 2007; Hind *et al.,* 2007; Thurlimann *et al.,* 2005 and Rasmussen *et al.,* 2008) compared letrozole versus tamoxifen in the initial adjuvant setting; and the MA-17 trial (Goss *et al.,* 2005 and 2007; Hind *et al.,* 2007; Ingle *et al.,* 2006 and Muss *et al.,* 2008) compared letrozole versus placebo in the extended adjuvant setting following standard adjuvant treatment with tamoxifen. For the monotherapy arm of the BIG 1 98 trial and the MA-17 trial, disease-free survival was significantly improved with letrozole compared to tamoxifen for lymph node-positive tumours (Crivellari *et al.,* 2008; Coates *et al.,* 2007; Goss *et al.,* 2005, 2007 and 2008; Hind *et al.,* 2007; Ingle *et al.,* 2006; Muss *et al.,* 2008; Thurlimann *et al.,* 2005 and Rasmussen *et al.,* 2008).

When letrozole was compared to placebo disease-free survival showed a significant improvement with letrozole. Over time (6 months to 4 years) the difference in the risk of progression significantly increased in the letrozole group compared to the placebo group (Goss *et al.,* 2005 and 2007; Hind *et al.,* 2007; Ingle *et al.,* 2006 and Muss *et al.,* 2008). When patients in the placebo arm of the MA-17 trial were subsequently offered letrozole and then compared to those who did not take the letrozole (placebo arm), disease-free survival was improved (Goss *et al.,* 2008).

Overall survival was not statistically different between letrozole and tamoxifen (Crivellari *et al.,* 2008; Coates *et al.,* 2007; Hind *et al.,* 2007; Thurlimann *et al.,* 2005 and Rasmussen *et al.,* 2008). Overall survival was not statistically different between letrozole and the placebo groups (Goss *et al.,* 2005 and 2007; Hind *et al.,* 2007; Ingle *et al.,* 2006 and Muss *et al.,* 2008). Over time any difference in risk (significant or not) disappears. When patients in the placebo arm of the MA-17 trial were subsequently offered letrozole and then compared to those who did not take the letrozole (placebo arm), the overall survival adjusted hazard ratio was 0.30 for the letrozole arm.

Risk of contralateral breast cancer did not report statistically significant results; letrozole vs tamoxifen: 0.4% vs 0.7% (Crivellari *et al.,* 2008; Coates *et al.,* 2007; Hind *et al.,* 2007; Thurlimann *et al.,* 2005 and Rasmussen *et al.,* 2008). Risk of contralateral breast cancer when letrozole was compared to placebo showed no difference for time to recurrence (Goss *et al.,* 2005 and 2007; Hind *et al.,* 2007; Ingle *et al.,* 2006and Muss *et al.,* 2008). There was a reduction in contralateral breast cancer in the letrozole arm of the Goss *et al.* (2008) trial.

There were fewer thromboembolic events with letrozole compared with tamoxifen but there was a significantly higher risk of bone fracture and some cardiac events with letrozole (Crivellari *et al.,* 2008; Coates *et al.,* 2007; Hind *et al.,* 2007; Thurlimann *et al.,* 2005 and Rasmussen *et al.,* 2008). The incidence of bone fractures, observed more often in the letrozole group, did not differ by age. In elderly patients, letrozole had a significantly higher incidence of any grade 3 to 5 non-fracture adverse event compared with tamoxifen. Incidence of bone fractures was higher among patients treated with letrozole. Differences were not significant for thromboembolic or cardiac adverse events (Crivellari *et al.,* 2008).

Clinical Evidence (cont.)

There was a significantly higher incidence of osteoporosis but no difference in the fracture rate with letrozole compared to placebo (Goss *et al.,* 2005 and 2007; Hind *et al.,* 2007; Ingle *et al.,* 2006 and Muss *et al.,* 2008). There were statistically significantly more self-reported new diagnoses of osteoporosis with letrozole compared with placebo. There were significantly more clinical fractures in the women who took letrozole and there was a non-significant difference in the number of cardiac events occurring between the groups. Thromboembolic events occurred rarely in both groups (Goss *et al.,* 2008).

The time to any disease recurrence was significantly decreased with letrozole compared to tamoxifen or placebo (Crivellari *et al.,* 2008; Coates *et al.,* 2007; Goss *et al.,* 2005, 2007 and 2008; Hind *et al.,* 2007; Ingle *et al.,* 2006; Muss *et al.,* 2008; Thurlimann *et al.,* 2005 and Rasmussen *et al.,* 2008).

There was no significant difference between letrozole and tamoxifen with respect to quality of life (Crivellari *et al.,* 2008; Coates *et al.,* 2007; Hind *et al.,* 2007; Thurlimann *et al.,* 2005 andRasmussen *et al.,* 2008).

When letrozole was compared to placebo the disease-free survival for ER-positive/PR-positive tumours was significantly increased with letrozole. For ER-positive/PR-negative tumours the reported data had very wide confidence intervals spanning the line of no effect as well as that of the ER-positive/PR-positive tumours (Goss *et al.,* 2005 and Muss *et al.,* 2008). When letrozole was compared to placebo, lymph node-positive and lymph node-negative women had significantly improved disease-free survival (Goss *et al.,* 2005). Goss *et al.* (2007) demonstrated a significant benefit in disease-free survival in this subgroup and significant benefits were also observed for distant disease-free survival and overall survival versus placebo. When letrozole was compared to tamoxifen the lymph node-negative tumour data also had very wide confidence intervals which spanned a line of no effect as well as that for the lymph node-positive data (Crivellari *et al.,* 2008; Coates *et al.,* 2007; Hind *et al.,* 2007 and Thurlimann *et al.,* 2005). These findings make it very difficult to interpret nodal status outcomes. Letrozole significantly improved disease-free survival compared with placebo for both lymph node-negative and lymph node-positive patients younger than 60 years and for patients with negative lymph nodes ≥ 70 years old (Muss *et al.,* 2008). When letrozole was compared with placebo in lymph node-positive patients the results indicated a significant improvement in distance disease-free survival in those aged 60 to 69 years and a significant improvement in overall survival for those aged ≥ 70 years (Muss *et al.,* 2008).

Exemestane

Disease-free survival was significantly increased with exemestane compared with tamoxifen, and nodal status did not affect outcome. (Coombes *et al.,* 2004 and 2007; Eisen *et al.,* 2008 and Hind *et al.,* 2007).

Overall survival was not significantly different between exemestane or tamoxifen or between exemestane and placebo (Coombes *et al.,* 2004; Eisen *et al.,* 2008 and Hind *et al.,* 2007). A modest improvement in overall survival was reported for patients who switch to exemestane after 2–3 years on tamoxifen (Coombes *et al.,* 2007).

There was a significant increase in bone fractures with exemestane (Coombes *et al.,* 2004; Eisen *et al.,* 2008 and Hind *et al.,* 2007).

The risk of contralateral breast cancer was significantly decreased with exemestane. Endocrine events decreased for all women with no difference between exemestane or tamoxifen. Disease-free survival was significantly increased for women with ER-positive histology regardless of PR status (Coombes *et al.,* 2004; Hind *et al.,* 2007). Significant improvements in overall survival were reported in the update Coombes *et al.* (2007) study when receptor-negative patients were excluded. There is difficulty with interpretation of results in order to determine the outcomes for ER/PR status (Coombes *et al.,* 2004 and Hind *et al.,* 2007).

Clinical Evidence (cont.)

A decision modelling exercise found that women with ER-positive/PR-positive tumours gained more benefit from over 10 years by starting with tamoxifen then crossing over to an aromatase inhibitor whereas women with ER-positive/PR-negative gained benefit from initial treatment with an aromatase inhibitor (Coombes *et al.,* 2004 and Hind *et al.,* 2007).

Health Economic Evaluation

The GDG did not consider this topic as a health economic priority; therefore the cost effectiveness literature on this topic has not been reviewed.

The following recommendations are from 'Hormonal therapies for the adjuvant treatment of early oestrogen-receptor-positive breast cancer', NICE technology appraisal guidance 112 (NICE 2006d). It has been incorporated into this guideline in line with NICE procedures for developing clinical guidelines.

Recommendations

- The aromatase inhibitors anastrozole, exemestane and letrozole, within their licensed indications, are recommended as options for the adjuvant treatment of early ER-positive invasive breast cancer in postmenopausal women.
- The choice of treatment should be made after discussion between the responsible clinician and the woman about the risks and benefits of each option. Factors to consider when making the choice include whether the woman has received tamoxifen before, the licensed indications and side-effect profiles of the individual drugs and, in particular, the assessed risk of recurrence.

Guidance was issued by NICE on the use of the aromatase inhibitors anastrozole, exemestane and letrozole (within the marketing authorisations for each drug at the time of the appraisal), for the treatment of ER-positive early breast cancer:

- anastrozole for primary adjuvant therapy
- exemestane for adjuvant therapy following 2–3 years of adjuvant tamoxifen therapy
- letrozole for primary adjuvant therapy and extended adjuvant therapy following standard tamoxifen therapy.

5.3 Endocrine Therapy for DCIS

Tamoxifen has a long established role in the adjuvant therapy of invasive breast cancer. Studies in invasive disease have demonstrated reductions in local and distant recurrence, a reduced risk of cancer in the contralateral breast and improved overall survival in appropriately selected patient groups. Whether tamoxifen treatment in DCIS has a similar role is uncertain. Supporting trials e.g. IBIS II may help further establish the role of endocrine therapy in DCIS.

Recommendation

- Do not offer adjuvant tamoxifen after breast conserving surgery to patients with DCIS.

Qualifying statement: There is conflicting evidence to support the use of tamoxifen in reducing local recurrence particularly when surgery is adequate (although the GDG recognises that there is a small reduction in the incidence of contralateral breast cancers).

Clinical Evidence

There is evidence from one placebo controlled RCT that in patients treated for DCIS with lumpectomy and adjuvant radiotherapy, adjuvant tamoxifen reduces the risk of ipsilateral local recurrence by 30% and contralateral breast cancer by 50%. The risk at 5 years of any breast cancer event in the tamoxifen arm was 8% and in the placebo arm, 13% (NSABP B-24 trial-Fisher *et al.,* 1999). One subsequent RCT with a less rigorous design found no similar benefit arising from tamoxifen (UKCCCR trial-Houghton *et al.,* 2003).

The NSABP B-24 trial found that Tamoxifen and radiotherapy improved disease-free survival at 5 years (87%) compared to placebo and radiotherapy (83%), but with no difference between groups for overall survival.

The UKCCCR trial examined the use of tamoxifen versus no adjuvant therapy following complete local excision of DCIS (without radiotherapy) and found no benefit arising from tamoxifen, except in terms of subsequent DCIS in either breast: this risk was reduced by 30%. The risk of any breast event in the tamoxifen arm at 56 months was 12% (UKCCCR) and in the control arm, 15%.

Health Economic Evaluation

The GDG did not consider this topic as a health economic priority; therefore the cost effectiveness literature on this topic has not been reviewed.

5.4 Chemotherapy

Meta-analyses of randomised clinical trials by the EBCTCG have indicated that the use of adjuvant chemotherapy is associated with a reduction in the risk of relapse and death in women with early stage breast cancer (EBCTCG, 2005). The reduction in risk of relapse and death attributable to adjuvant chemotherapy is dependent on age at diagnosis but is independent of prognosis. The absolute benefit of chemotherapy therefore varies according to both patient age and underlying prognosis. Estimates of the benefits of adjuvant chemotherapy are therefore made on the basis of patient age and prognosis derived from pathological features. Tools such as Adjuvant! Online (see Chapter 4) allow an estimate of prognosis from which attributable benefits of chemotherapy may be estimated from the reductions in risk of relapse and death derived from the EBCTCG meta-analyses.

Anthracycline containing regimens have been used routinely in the adjuvant setting. Clinical trials evaluating a different class of drug, the taxanes, led to the recommendation of docetaxel, when given concurrently with doxorubicin and cyclophosphamide, for the adjuvant treatment of early lymph node-positive breast cancer (NICE 2006c). Some subsequent studies have demonstrated improvements in disease-free and overall survival for the sequential use of taxanes. The use of weekly paclitaxel has been shown to have similar efficacy to that of docetaxel.

Recommendations

- Offer docetaxel to patients with lymph node-positive breast cancer as part of an adjuvant chemotherapy regimen.
- Do not offer paclitaxel as an adjuvant treatment for lymph node-positive breast cancer.

Qualifying statement: These recommendations were based on a systematic review which found no new evidence to change the health economic analysis carried out for TA 108 (NICE 2006b). The GDG considered the data from the TACT trial but, because it had not been fully published and it was at variance with a large body of other RCT evidence showing that the addition of docetaxel improved outcomes, they did not believe it should change the recommendation. They were also aware of the data from Sparano *et al.* (2008) showing that in terms of overall survival weekly paclitaxel was

Recommendations (cont.)

more effective than 3 weekly paclitaxel. This trial also showed no difference in overall survival between 3 weekly docetaxel and 3 weekly paclitaxel. Because this trial was only found when updating the evidence searches, it was not possible to start a *de novo* health economic analysis. Given the current significantly reduced acquisition cost of pacitaxel for the NHS, it is possible that a regimen including paclitaxel may be appropriate.

Clinical Evidence

There is a considerable volume of high-quality evidence that evaluates the clinical and cost effectiveness of docetaxel and paclitaxel for the adjuvant treatment of early breast cancer. The evidence includes a Cochrane review (Ferguson *et al.,* 2007); a HTA report (Ward *et al.,* 2007); a meta-analysis (De Laurentiis *et al.,* 2008); a pooled analysis (Bria *et al.,* 2006); 2 RCTs (Kummel *et al.,* 2006; Piedbois *et al.,* 2007) and 1 RCT from an abstract (Ellis *et al.,* 2007).

The studies which reported overall survival (Ferguson *et al.,* 2007; Ward *et al.,* 2007) showed improved overall survival with use of the taxanes. The meta-analysis and pooled analysis (De Laurentiis *et al.,* 2008 and Bria *et al.,* 2006) also showed significant improvements in overall survival with the taxanes compared with the control treatments. The TACT (taxotere as adjuvant chemotherapy) abstract (Ellis *et al.,* 2007) showed a non-significant difference between those given docetaxel and the control chemotherapy arm.

Disease-free survival showed improvement with the taxanes (Ferguson *et al.,* 2007 and Ward *et al.,* 2007). The meta-analysis and pooled analysis (De Laurentiis *et al.,* 2008 and Bria *et al.,* 2006) also showed significant differences with the taxanes compared with the control treatments in disease-free survival. The TACT study (Ellis *et al.,* 2007) found a non-significant difference in disease-free survival with those in the docetaxel group and those in the control group.

Neutropenia and febrile neutropenia were identified as occurring more frequently in those in the docetaxel groups than in the control groups. Where quality of life was reported the reductions in quality of life associated with treatment were higher with docetaxel than in the control groups, with paclitaxel there was no significant difference compared with controls.

The HTA report (Ward *et al.,* 2007) noted that the comparators used in most trials restrict the generalisibility of results as they do not conform to current standards of care in the UK for reasons such as too few cycles of chemotherapy or using doxorubicin instead of the more widely used epirubicin.

One further study has been published which compared the efficacy of paclitaxel and docetaxel given weekly or every 3 weeks in the adjuvant treatment of breast cancer (Sparano *et al.,* 2008). All received 4 cycles of IV doxorubicin and cyclophosphamide, with each of four groups then followed this with paclitaxel or docetaxel (175mg/m^2) at 3-week intervals for 4 cycles, or at 1-week intervals for 12 cycles (80mg/m^2). For disease-free survival, compared with those receiving paclitaxel every 3 weeks there was significantly higher survival with weekly paclitaxel and with docetaxel every 3 weeks and no significant difference with weekly docetaxel.[4] For overall survival, compared with those receiving paclitaxel every 3 weeks there was significantly higher survival with weekly paclitaxel and no significant difference with weekly docetaxel or 3-weekly docetaxel. Those with HER2-negative disease who had weekly paclitaxel had improved disease-free survival and overall survival. No significant difference was seen with other groups.

[4] Results were similar where the definition of end point did not include contralateral breast cancer or contralateral breast cancer and second nonbreast cancer.

Health Economic Evaluation

A full systematic review and economic evaluation of taxanes for the adjuvant treatment of early breast cancer (Ward *et al.,* 2007) and two further economic evaluations (Limwattananon *et al.,* 2006; Wolowacz *et al.,* 2008) have been published since the publication of TA 108 and TA 109.

These studies address questions already posed within the TA 108 and TA 109. Ward *et al.* (2007) also carried out an indirect comparison to determine the estimated clinical and cost effectiveness of docetaxel and paclitaxel versus standard UK comparators in the absence of head to head clinical trials. The authors advise that results from this indirect comparison should be viewed with caution as the analysis was carried out by combining data from several trials. Each of these trials differed slightly in terms of trial populations enrolled and the exact doses and timings of the regimens. The results of the indirect comparison and subsequent economic analysis presented in Ward *et al.* (2007) shows that docetaxel versus FEC for six weeks has a very wide range of cost effectiveness and that there are only very few occasions when paclitaxel may be considered cost effective compared with E-CMF and FEC. Overall, the review of the evidence by Ward *et al.* (2007) showed considerable uncertainty in the benefits of taxane containing regimens when compared with standard regimens used in the UK.

Given the evidence from the GDG on the current use of taxanes in the NHS and the uncertainty surrounding estimates of cost effectiveness on the use of docetaxel, recommendations made following the review of the clinical evidence are appropriate and supported by the available economic evidence. There was no further evidence to support the cost effectiveness of paclitaxel against relevant UK comparators.

No further economic analysis was undertaken as it was thought that no further clinical evidence to support the economic evaluation of taxanes against UK standard comparators was available.

5.5 Biological Therapy

The HER2 receptor is one member of the family of human epidermal growth factor receptors that is present at high levels in about 15% of early stage invasive breast cancers (see recommendations on HER2 testing in Chapter 4). Overexpression is associated with a poor prognosis. The humanised monoclonal antibody trastuzumab targets the extracellular domain of HER2 and its use in the adjuvant therapy of HER2-positive breast cancer reduces the risk of relapse by about 50% and the risk of death by about 30%.

Recommendations

- Offer trastuzumab, given at 3-week intervals for 1 year or until disease recurrence (whichever is the shorter period), as an adjuvant treatment to women with HER2-positive early invasive breast cancer following surgery, chemotherapy, and radiotherapy when applicable.
- Assess cardiac function before starting treatment with trastuzumab. Do not offer trastuzumab treatment to women who have any of the following:
  - a left ventricular ejection fraction (LVEF) of 55% or less
  - a history of documented congestive heart failure
  - high-risk uncontrolled arrhythmias
  - angina pectoris requiring medication
  - clinically significant valvular disease
  - evidence of transmural infarction on electrocardiograph (ECG)
  - poorly controlled hypertension.

Recommendations (cont.)

– Repeat cardiac functional assessments every 3 months during trastuzumab treatment. If the LVEF drops by 10 percentage (ejection) points or more from baseline and to below 50% then trastuzumab treatment should be suspended. Restart trastuzumab therapy only after further cardiac assessment and a fully informed discussion of the risks and benefits with the woman.

Qualifying statement: These recommendations are based on good clinical evidence and cost effective analysis.

Clinical Evidence

Two papers reporting from the HERA trial (Herceptin Adjuvant) trial (Smith *et al.,* 2007 and Suter *et al.,* 2007), one joint-analysis of the NSABP B-31 trial (National Surgical Adjuvant Breast and Bowel Project), B-31 trial and the NCCTG N9831 trial (North Central Cancer Treatment Group) (Romond *et al.,* 2005), two papers which considered cardiac dysfunction in the NSABP B-31 (Tan-Chiu *et al.,* 2005) and NCCTG N9831 (Perez *et al.,* 2008), a meta-analysis of cardiotoxicity and brain metastases with adjuvant trastuzumab (Bria*,* 2008), a paper from the FinHer trial (Joensuu *et al.,* 2006) and an abstract from the E2198 trial (Budzar *et al.,* 2007) were identified which considered the adjuvant treatment of early breast cancer with trastuzumab. One small trial (Buzdar *et al.,* 2007) was identified which considered the primary systemic treatment of early breast cancer with trastuzumab.

Sequential chemotherapy

The HERA trial results at 1-year follow-up were included in the TA 107 (NICE 2006a), the 2-year follow-up of those who received 1-year treatment with trastuzumab showed improved overall survival and distant recurrence event-free survival benefit for trastuzumab compared with the control group (Smith *et al.,* 2007). A further study considered the trastuzumab-associated cardiac adverse events from HERA, this identified a higher incidence of cardiac end points (severe congestive heart failure (CHF), symptomatic CHF and confirmed left ventricular ejection fraction (LVEF) drop) in the trastuzumab group compared with the control group.

Concurrent chemotherapy

The joint analysis of the NSABP B-31 and NCCTG N9831 trials identified improved disease-free survival, overall survival and distant metastases as a first distant recurrence with trastuzumab compared with the control group. Cardiac dysfunction in the NSABP B-31 identified a higher relative risk of a cardiac event with trastuzumab compared with control, with no significant difference between the groups in the cumulative incidence of cardiac events (Tan-Chiu *et al.,* 2005).

Meta-analysis

A safety and efficacy meta-analysis identified an increased risk of grade III-IV CHF, asymptomatic LVEF and brain metastases with trastuzuamb compared with controls, along with prolonged disease-free survival, prolonged distant disease-free survival and prolonged overall survival with trastuzumab (Bria*,* 2008).

Shorter duration

The FinHer trial showed improvements in recurrence (or died without recurrence) and distant recurrence for the trastuzumab arm (9 week duration) compared with the control group. There was no significant difference between the groups for overall survival or in adverse events (Joensuu *et al.,* 2006).

Clinical Evidence (cont.)

The E2198 trial[5] did not identify a significant advantage for prolonged trastuzumab administration (10 weeks compared with 52 weeks).

Primary systemic therapy

One small study identified improved disease-free survival with primary systemic 24-week chemotherapy and trastuzumab regimen compared with chemotherapy alone (Budzar *et al.,* 2007).

Health Economic Evaluation

A large volume of economic evidence was identified on the cost effectiveness of trastuzumab in the adjuvant setting. Ten economic evaluations were reviewed in detail (Garrison *et al.,* 2007; Kurian *et al.,* 2007; Lidgren *et al.,* 2007; Liberato *et al.,* 2007; Millar and Millward 2007; Dedes *et al.,* 2007; Neyt *et al.,* 2006; Neyt *et al.,* 2008; Norum *et al.,* 2007 and Shiroiwa *et al.,* 2008). Two regulatory submissions have also been published not including TA 107 (the New Zealand PHARMAC evaluation and the Belgian KCE report) and were included in the review.

Cost utility studies

Five cost utility studies were identified and were undertaken by constructing Markov models, using the results of RCTs to inform the efficacy of trastuzumab. Expected life years and quality adjusted life years (QALYs) were used to measure treatment benefits. There were two USA studies, two European studies and one Australian study. One study considered both the 12 month and 9 week regimens. The majority of the studies based their efficacy data on the NSABP-B31 and NCCTG N983 trials (and subsequent joint analysis) and the HERA trial. One study based its effectiveness on the BCIRG 006 trial. The main comparison was doxorubicin and cyclophosphamide followed by paclitaxel (AC->P) with AC->P plus trastuzumab (AC->PT). The studies varied as to whether or not they considered that trastuzumab may be given to patients who had progressed to metastatic cancer who had already received trastuzumab in the adjuvant stage. Most of the studies examined this aspect in some way either as their base case analysis or in their sensitivity analysis. Two of the studies included the costs of HER2 testing in the model. The benefits of trastuzumab were accounted for in all models as the relative risk of recurrence. The majority of studies derived relative risks of recurrence from clinical trials. Three of the studies assumed that there was no added or diminished benefit due to trastuzumab following the trial duration and benefits were assumed to be the same over the lifetime of the patient. The overall quality of these evaluations was judged to be good. No study reported a base case incremental cost effectiveness ratio (ICER) above £30,000 per QALY despite variations in:

- treatment regimens considered
- modelling approaches
- assumptions regarding the efficacy of trastuzumab beyond the trial period
- the inclusion or otherwise of HER2 testing
- considering the use of trastuzumab in the metastatic setting, and
- the inclusion or otherwise of cardiac toxicity due to trastuzumab.

Cost effectiveness analyses

Five cost effectiveness analyses were identified: there were four European studies and one from Japan. These were developed using decision analytic models. Three of the studies were based on the 12 month trastuzumab regimen and two studies considered both the 12 month and 9 week regimens. The two studies that considered the 12 month and 9 week

[5] Not designed or powered to test the question of trastuzumab duration.

Health Economic Evaluation (cont.)

regimens based their efficacy data on the HERA and FinHer trials. One study (Shiroiwa *et al.,* 2008) based its efficacy data on the 2 year follow up of the HERA trial and the other studies based efficacy data on the NSABP-B31 and NCCTG N983 trials and the BCIRG 006 trial. All of the studies considered trastuzumab in patients who had progressed to metastatic cancer. However, in some of the studies it was unclear whether the efficacy of trastuzumab in this setting was taken into account. The costs of HER2 testing were included in the majority of the studies. Some methodological issues meant these papers were not judged to be as good quality as the cost-utility studies. In the study that examined the 2 year follow up data from the HERA trial, the ICER did not exceed £30,000 per life year gained. The cost effectiveness studies were generally supportive of the cost effectiveness of 1 year of trastuzumab treatment.

Shorter treatment duration

The FinHer regimen represents an unlicensed use of trastuzumab with respect to both treatment duration (9 weeks versus 12 months) and treatment schedule, that is, trastuzumab given concurrently with vinorelbine or docetaxel versus a sequential approach in the HERA trial. The studies examining the 9 week trastuzumab regimen concluded that the cost per QALY/life year was very low and could therefore be considered cost effective. A careful assessment of the internal and external validity of the FinHer trial was considered by the GDG. No further economic evaluation was undertaken as the GDG considered that there was not enough clinical evidence on the effectiveness of the 9 week regimen to accurately assess cost effectiveness.

Summary

Overall the review of the evidence showed that despite uncertainty surrounding long-term outcomes and variation in the regimens used, the 12 month trastuzumab regimen can generally be considered cost effective in the adjuvant setting. No further economic analysis was undertaken due to the large volume of existing economic evaluations examining various methods of modelling the cost effectiveness of trastuzumab.

Research Recommendation

- How effective is trastuzumab in patients with invasive breast cancer: (a) as adjuvant therapy without chemotherapy, (b) in terms of scheduling and duration of treatment in patients who are also receiving or who have completed chemotherapy, and (c) as primary systemic treatment in terms of quality of life, side effects, disease recurrence rates, disease-free survival and overall survival?

5.6 Assessment and Treatment for Bone Loss

Bone Mineral Density (BMD)

Adjuvant endocrine therapy is associated with changes in BMD.

In premenopausal women ovarian suppression as a therapeutic strategy in itself or as a consequence of adjuvant chemotherapy leads to accelerated bone loss due to induction of menopause.

In premenopausal women, tamoxifen leads to a decrease in BMD whereas it has the opposite effect in postmenopausal women.

As a consequence of a reduction in circulating oestrogen levels, the use of aromatase inhibitors in the adjuvant endocrine therapy of postmenopausal women is associated with an increased risk of bone fractures. With the increasing use of aromatase inhibitors, bone health is becoming a significant clinical issue. Other risk factors, for example family history, smoking, previous history of fracture, may need to be assessed when prescribing preventative therapy.

There is an increased risk of bone fractures due to osteoporosis associated with aromatase inhibitors and with chemotherapy induced premature menopause. Tamoxifen is also associated with increased bone loss in premenopausal patients, although not so severe. BMD measurements have shown considerable bone loss and identified those at a higher risk of fracture and treatment related morbidity.

A recent consensus position statement from a UK expert group provides guidance on the management of breast cancer treatment-induced bone loss (Reid *et al.,* 2008) (see algorithms 1 and 2 in Appendix 2). This gives recommendations on when BMD should be measured and when repeated.

Recommendations

- Patients with early invasive breast cancer should have a baseline dual energy X-ray absorptiometry (DEXA) scan to assess bone mineral density if they:
  - are starting adjuvant aromatase inhibitor treatment
  - have treatment-induced menopause
  - are starting ovarian ablation/suppression therapy.
- Do not offer a DEXA scan to patients with early invasive breast cancer who are receiving tamoxifen alone, regardless of pretreatment menopausal status.

Qualifying Statement: These recommendations are based on guidance produced by Reid *et al.* (2008) and GDG consensus.

Clinical Evidence

The following evidence based guideline was used to inform the recommendation for management of bone loss after breast cancer treatment; Guidance for the management of breast cancer treatment induced bone loss: A consensus position statement from a UK Expert Group. Cancer Treatment Reviews (2008). This guideline was appraised using the AGREE Instrument and rated as high-quality. The evidence based approach was clearly conducted.

Health Economic Evaluation

A systematic review was conducted to assess the cost effectiveness of undertaking measurements of BMD in patients with invasive breast cancer who are on adjuvant endocrine therapy to assess bone health. The initial search identified 207 papers, from which 205 were excluded on the basis of the title and the abstract. Two papers were obtained for appraisal (Boyc *et al.,* 2004 and Yeh *et al.,* 1995). One of the studies (Boyc *et al.,* 2004) was excluded because it was not relevant for the study question: it assessed healthcare resources used and costs of treatment patterns for cancer therapy induced bone loss. The other study (Yeh *et al.,* 1995) was finally excluded on the grounds that it did not assess the patient population considered in the PICO question (it was not clear that patients in this study were on endocrine treatment; in addition, some patients with stage 4 breast cancer were also included). Therefore, no economic evaluations were identified from the systematic review and there is uncertainty concerning the cost effectiveness of undertaking BMD measurements in patients with invasive breast cancer who are on adjuvant endocrine therapy.

Bisphosphonates

Bisphosphonates belong to a class of drugs which affect bone metabolism and have an established role in the management of osteoporosis and Paget's disease of bone.

The main reason for using bisphosphonates in patients with early invasive breast cancer is in the prevention of treatment induced osteoporosis. They may also have a role in the prevention of metastatic disease, which is the subject of large randomised trials.

Health Economic Evaluation (cont.)

Evidence from trials for the role of bisphosphonates (particularly zoledronate) in the adjuvant setting in reducing the risk of developing skeletal metastases is imminently awaited. Alendronate, risedronate, pamidronate or zoledronate can all be used to protect the skeleton. The choice is directed by the adjuvant treatment given.

Recommendation

- Offer bisphosphonates to patients identified by algorithms 1 and 2 in 'Guidance for the management of breast cancer treatment-induced bone loss: a consensus position statement from a UK expert group' (2008) (see Appendix 2).

Qualifying statement: This recommendation is based on evidence from RCTs and guidance produced by Reid *et al.* (2008).

Clinical Evidence

There is considerable, high-quality evidence from systematic reviews and meta-analyses of RCTs that have indicated the effectiveness of bisphosphonates for specific groups of breast cancer patients:

Evidence from RCTs (Brufsky, 2006 and Bundred *et al.,* 2008) have indicated that in women who were receiving adjuvant letrozole; immediate treatment with zoledronate compared to delayed may prevent loss of BMD at both lumbar spine and total hip. There is evidence that immediate treatment with zoledronic acid maintains the baseline osteopenia status of patients compared with delayed treatment at 12 months. Furthermore, Bundred *et al.* (2008) showed no evidence to suggest a difference in the occurrence of fractures in immediate versus delayed treatment with zoledronate and that there was no difference in breast cancer recurrence when comparing immediate and delayed treatment with zoledronate. There are no significant acute adverse effects with zoledronate.

A systematic review of RCTs of bisphosphonates showed no statistically significant reduction in the risk of developing skeletal metastases (Wu, 2007). Fuleihan (2005) has shown that pamidronate prevents chemotherapy induced bone loss compared with placebo. A RCT by Greenspan *et al.* (2007) compared risedronate with placebo and showed that in postmenopausal women with breast cancer with or without aromastase inhibitors therapy, once-weekly oral risedronate was beneficial for spine and hip BMD and reduced bone turnover. There were no significant acute adverse effects with risedronate.

Saarto *et al.* (2004) showed that there was no difference in bone metastases or overall survival in women with lymph node-positive disease who were treated with chemotherapy or endocrine therapy and received clodronate or a control. Disease-free survival was poorer in the clodronate group which may be attributed to visceral metastases. When IV clodronate was compared to a control during adjuvant chemotherapy there was no statistically significant difference in chemotherapy induced bone loss at 6 months or 12 months. (Vehmanen *et al.,* 2004)

A meta-analysis of RCTs (Ha and Li, 2007) compared clodronate with placebo and found no statistically significant difference in overall survival skeletal metastasis or non-skeletal metastases. A Cochrane systematic review by Pavlakis *et al.* (2006) compared adjuvant oral clodronate with placebo and found no significant difference with skeletal metastases but overall survival was significantly improved with clodronate.

Gnant *et al.* (2007) conducted a four-arm trial comparing tamoxifen and goserelin +/- zoledronate versus anastrozole and goserelin +/- zoledronate for 3 years in premenopausal women with hormone-responsive breast cancer. Overall bone loss was significantly more severe in patients receiving anastrozole/goserelin compared with patients receiving tamoxifen and goserelin. Conversely, BMD remained stable in zoledronate treated patients

Clinical Evidence (cont.)

compared with endocrine therapy alone. Brufsky (2006) compared letrozole with early versus delayed zoledronate and found at 12 months BMD was higher in the 'early' group versus 'delayed', both in the spine and hip. Mystakidou *et al*. (2005) conducted a RCT comparing zoledronate with a control and found that the median bone metastases-free interval for zoledronate was significantly higher than with the control. Furthermore, there was a significant difference in favour of zoledronate in the bone-metastases-free interval at the 18 month follow-up.

The following evidence based guideline was also used to inform the recommendation for the role of bisphosphanates 'Guidance for the management of breast cancer treatment induced bone loss: A consensus position statement from a UK Expert Group' Cancer Treatment Revies (2008). This guideline was appraised using the AGREE Instrument and rated as high-quality. The evidence based approach was clearly conducted.

Health Economic Evaluation

The GDG did not consider this topic as a health economic priority; therefore the cost effectiveness literature on this topic has not been reviewed.

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6 Adjuvant radiotherapy

6.1 Introduction

Radiotherapy is given to the breast after conservation surgery and may be given to the chest wall after mastectomy to complete local treatment. The nodal areas, particularly supraclavicular fossa (SCF) and axilla, may also be treated in patients considered to be at higher risk of regional relapse. Radiotherapy is frequently given daily (Monday to Friday) over 5 weeks, which is the international standard, although shorter fractionation schedules have been used for many years in the UK. This is followed by a boost to the tumour bed over a further 1-2 weeks in some patients who have had breast conservation.

6.2 Breast Conserving Surgery and Radiotherapy

Whole breast radiotherapy after wide local excision for small invasive breast cancers is necessary to maintain acceptable local recurrence rates and is routinely given. It has been shown to be equivalent, and an alternative, to mastectomy which can therefore be avoided. The question of whether it can be omitted in good prognostic tumours has been addressed but, even in these low-risk patients, radiotherapy has a significant role in reducing local recurrence (UK BASO II trial[1]). Randomised controlled trials have also shown the value of radiotherapy after breast conserving surgery for DCIS, particularly as 50% of these recurrences are invasive.

NICE has issued interventional procedure guidance on 'Brachytherapy as the sole method of adjuvant radiotherapy for breast cancer after local excision'[2]. This says it should only be used in research.

Recommendations on DCIS and the Sloane project can be found in Chapter 3.

Recommendations

- Patients with early invasive breast cancer who have had breast conserving surgery with clear margins should have breast radiotherapy.
- Offer adjuvant radiotherapy to patients with DCIS following adequate breast conserving surgery[3] and discuss with them the potential benefits and risks.

Qualifying statement: There is good quality randomised controlled trial evidence that radiotherapy reduces absolute risk of further recurrence. There was GDG consensus that there may be a subgroup of patients with DCIS who have a lowrisk of recurrence and thus for whom the addition of radiotherapy may not be justified, namely patients with small and low grade DCIS.

[1] Houghton *et al.* 2003.

[2] National Institute for Health and Clinical Excellence (2008) Brachytherapy as the sole method of adjuvant radiotherapy for breast cancer after local excision. NICE interventional procedure guidance 268. London: National Institute for Health and Clinical Excellence.

[3] See recommendation on DCIS margins in Chapter 3.

Clinical Evidence

Invasive breast cancer

The strongest overview was the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) (Clarke *et al.,* 2005) who conducted a systematic review of individual patient data (IPD) from the relevant trials, and provided data up to the year 2000 with 15 years of follow-up. A heterogeneous group of studies were assessed of patients receiving breast conserving surgery with and without radiotherapy. A range of participants were included, for example patients with tumours of less than 1 cm and elderly patients. Some of the studies provided an additional boost of radiotherapy to the tumour bed. A number of associated reviews were not as strong as the EBCTCG review and these have been included where additional data was provided (Liljegren, 2002; Rutqvist *et al.,* 2003 and Vinh-Hung and Verschraegen, 2004). One recent RCT (Ford *et al* 2006) from the St George's study (with earlier IPD reported in Clarke, 2005) and another retrospective cohort study from the US SEER database (Vinh-Hung *et al.,* 2003) were also included.

Two systematic reviews reported cosmetic outcomes (Liljegren, 2002 and Mul *et al.,* 2007). These were also reported in one RCT (Johansen *et al.,* 2002) and one non-randomised study (Duetsch and Flickinger, 2003). Four studies reported quality of life outcomes using five different instruments. Three were recruited from RCTs (Lee *et al.,* 2008; Rayan *et al.,* 2003 and Whelan *et al.,* 2000a) and the fourth was a survey (Back *et al.,* 2005).

Three reviews (one narrative, Kuerer *et al.,* 2004, and two systematic reviews Cuncins-Hearn *et al.,* 2004 and Sarin, 2005) of non-randomised studies assessed a range of accelerated partial breast irradiation (APBI) techniques including intra-operative and postoperative brachytherapy. Another review (Kunkler *et al.,* 2006) discussed whether radiotherapy could be omitted after surgery.

Four guidelines were included, two Canadian (Shelley and Trudeau, 2002 and Whelan *et al.,* 2003), one American (Morrow *et al.,* 2002) and one recent German DEGRO guideline (Sautter-Bihl *et al.,* 2007).

Most studies from RCTs and well conducted meta-analyses/systematic reviews were consistent in the finding that postoperative radiation decreased the risk of local recurrence. The EBCTCG meta-analysis of breast conserving surgery trials showed a moderate reduction in breast cancer deaths and overall mortality after 15 years. Subgroup analyses by age, tumour characteristics and nodal status in the EBCTCG revealed further treatment effects of radiotherapy. Quality of life was generally high among patients receiving radiotherapy. Patient satisfaction with breast conserving surgery was also high.

Health Economic Evaluation

See health economic evaluation summary on page 79.

Clinical Evidence

DCIS

When radiotherapy is compared to no radiotherapy following breast conserving surgery for DCIS there are RCTs that provide strong evidence that radiotherapy after breast conserving surgery to treat patients with DCIS is associated with a lower rate of ipsilateral breast recurrence compared to breast conserving surgery alone, and reduces the risk of such recurrence by approximately half (Bijker *et al.,* 2006; Emdin *et al.,* 2006; Fisher *et al.,* 1998; Bijker *et al.,* 2006; Emdin *et al.,* 2006; Fisher *et al.,* 1998; Houghton *et al.,* 2003; Holmberg *et al.,* 2008 and Houghton *et al.,* 2003).

Evidence from three systematic reviews of mixed primary study designs and two large retrospective analyses, (Boyages *et al.*, 1999; Fonseca *et al.*, 1997; Shelley *et al.,* 2006; Baxter *et al.,* 2005 and Smith *et al.,* 2006a) provide evidence that the addition of radiotherapy to breast conserving surgery reduces the risk of local recurrence.

Clinical Evidence (cont.)

There is strong evidence that the use of radiotherapy following breast conserving surgery to treat patients with DCIS is associated with longer disease-free survival than breast conserving surgery alone (Bijker *et al.,* 2006; Emdin *et al.,* 2006 and Fisher *et al.,* 1998). Evidence from two RCTs suggest no difference in overall survival between in patients with DCIS treated with breast conserving surgery plus radiotherapy versus breast conserving surgery alone (Fisher *et al.,* 1998 and Bijker *et al.,* 2006). One retrospective study found no statistically significant difference in 10-year overall survival between patients treated for DCIS with local excision alone, local excision plus radiotherapy and local excision plus radiotherapy plus boost (Omlin *et al.,* 2006).

There is evidence that small lesion size (< 2cm), widely clear surgical margins (≥ 1cm), low nuclear grade and the absence of necrosis are favourable risk factors with a risk of breast cancer recurrence after 10 years of 4%-10% in patients with all four factors, and with a very small absolute risk reduction arising from radiotherapy. Guidelines associated with these two systematic reviews concluded that the evidence does not support identification of a group of patients with DCIS who can be treated routinely with breast conserving surgery without radiotherapy.

Health Economic Evaluation

The GDG did not consider this topic as a health economic priority; therefore the cost effectiveness literature on this topic has not been reviewed.

6.3 Post-Mastectomy Radiotherapy

Although many patients with early breast cancer are suitable for breast conserving surgery a significant number undergo mastectomy. Local chest wall recurrence can occur many years later, which may cause increased psychological morbidity and affect breast cancer mortality. Post-mastectomy radiotherapy is effective in reducing the risk of recurrence by around two-thirds and consequently reduces mortality. The risk of local recurrence varies between patient groups. There have been many randomised trials to identify factors associated with an increased risk of local recurrence. These include increasing tumour size, axillary nodal involvement, extensive lympho-vascular involvement and positive resection margins. Post-mastectomy radiotherapy may be offered to patients with these factors in an effort to reduce the likelihood of local recurrence in the chest wall or nodal region.

Recommendations

- Offer adjuvant chest wall radiotherapy to patients with early invasive breast cancer who have had a mastectomy and are at a high risk of local recurrence. Patients at a high risk of local recurrence include those with four or more positive axillary lymph nodes or involved resection margins.
- Consider entering patients who have had a mastectomy for early invasive breast cancer and who are at an intermediate risk of local recurrence into the current UK trial (SUPREMO) assessing the value of postoperative radiotherapy. Patients at an intermediate risk of local recurrence include those with one to three lymph nodes involved, lymphovascular invasion, histological grade 3 tumours, ER-negative tumours, and those aged under 40 years.
- Do not offer radiotherapy following mastectomy to patients with early invasive breast cancer who are at low risk of local recurrence (for example, most patients who are lymph node-negative).

Qualifying statement: These recommendations are based on strong evidence from RCTs.

Clinical Evidence

A large volume of high-quality evidence was available examining both post-mastectomy and breast conserving surgery with adjuvant radiotherapy. Several meta-analyses of RCTs were available including a recent analysis from the EBCTCG (Clarke *et al.,* 2005), two additional meta-analyses were reviewed that included some of the same studies as the EBCTCG, as well as additional RCTs (Gebski *et al.,* 2006; Killander *et al.,* 2007, Kyndi *et al.,* 2008 and Whelan *et al.,* 2000b). Some analyses were conducted in specified subgroups of the Danish Breast Cancer Cooperative Group (Nielsen *et al.,* 2006 and Overgaard *et al.,* 2007), and another used all trials from the EBCTCG (Van de Steene *et al.,* 2000). Evidence from other studies included Bartelink, 2000; Bellon *et al.,* 2006; Fisher *et al.,* 2002; Gustavsson *et al.,* 1999; Hojris *et al.,* 2000; Hojris *et al.,* 1999; Recht *et al.,* 2001; *et al.,* Smith 2006b and *et al.,* Truong 2004.

There was general consistency that radiotherapy reduced locoregional recurrence. The effects of radiotherapy on overall survival were of benefit for women of all ages with positive lymph nodes, but of less benefit for women with negative lymph nodes.

Loco-regional recurrence

Clarke (2005) reported that radiotherapy after mastectomy with axillary clearance significantly reduced locoregional recurrence. The absolute reduction in local recurrence was greater in lymph node-positive than lymph node-negative disease (17% versus 4%). Whelan *et al.* (2000b) included some of the trials from the EBCTCG and found a large reduction in locoregional recurrence and for any recurrence after post-mastectomy radiotherapy. A 25 year follow-up of a RCT (Fisher *et al.,* 2002) reported no significant differences between the three groups of women with negative lymph nodes or between the two groups of women with positive lymph nodes for disease-free survival, relapse-free survival, distant-disease-free survival, or overall survival. A subgroup analysis of the DBCG 82 b and c trials was performed to evaluate the loco-regional recurrence rate in relation to number of positive lymph nodes (1-3 or 4 or more) (Overgaard *et al.,* 2007). The risk of loco-regional recurrence was most pronounced in patients with 4+ positive lymph nodes. Another subgroup analysis of the DBCG 82 b and c trials by Nielsen *et al.* (2006) found the frequency of locoregional recurrence was 30% among patients randomised to no radiotherapy and 5% for patients randomised to radiotherapy.

Mortality

The EBCTCG (Clarke *et al.,* 2005) reported that in trials of radiotherapy after mastectomy with axillary clearance there was a reduction in 15 year all cause mortality of 4.2% with radiotherapy for lymph node-negative disease and in lymph node-positive disease, the reduction in 15-year all-cause mortality in the radiotherapy group was 4·4%. In a meta-analysis by Gebski *et al.* (2006) studies were categorised according to how the radiotherapy dose was delivered. Category 1 studies were defined as delivering optimal radiation therapy doses in the range of 40-60 Gy in 2-Gy fractions or as a biologically equivalent dose to the chest wall, axillary lymph nodes, and the supraclavicular fossa with or without the internal mammary lymph nodes. At a follow-up of 5 years category 1 studies gave a statistically significant 13% relative survival advantage associated with radiation therapy, compared with no radiation therapy. This equates to an absolute 2.9% increase in survival. At a follow-up of 10 years, category 1 studies gave a statistically significant 22% increase in relative survival associated with radiation therapy compared with no radiation therapy. This corresponds to an absolute 6.4% increase in survival. In trials of high-risk patients (patients with lymph node-positive disease) a separate analysis found that an absolute 5.2% increase in survival (52 per 1000) at 10-year follow-up was associated with adjuvant radiation therapy compared with no radiation therapy. In the analysis by Whelan *et al.* (2000) radiation was shown to significantly reduce mortality. The DBCCG (2006) reported that with 18 years follow-up the probability of loco-regional recurrences (with or without distant metastases) or loco-regional recurrences alone was significantly lower in the post-mastectomy radiotherapy group than the no radiotherapy group. It also showed that overall fewer patients have distant metastases. Killander *et al.* (2007) reported that post-mastectomy radiotherapy

Clinical Evidence (cont.)

significantly reduced loco-regional recurrences, but overall survival was not improved. At 20 years, a lower mortality was recorded for non-irradiated patients treated with tamoxifen. A survival benefit was found for lymph node 1-3 and lymph node 4+ patients in the analysis of high risk patients by Overgaard *et al.* (2007) from the DBCCG trials only. A further analysis comparing locoregional reccurrence and survival in patients with 1-3 positive lymph nodes and 4+ positive lymph nodes showed that the values were almost identical irrespective of the number of positive lymph nodes. Another analysis of the same trials by Nielsen *et al.* (2006) assessed the independent prognostic factors for survival after locoregional recurrence from multivariate analysis. Significant factors reducing survival were a large tumour size (larger than 21 mm), number of involved lymph nodes, extra-capsular invasion, and site of local recurrence. The meta-analysis of the EBCTCG reported no significant reduction in 15 year breast cancer mortality with radiotherapy. Kyndi *et al.* (2008) reported that there were significantly smaller improvements in locoregional recurrence control after post-mastectomy radiotherapy were found for ER-negative and PR-negative tumours compared with the ER-positive and PR-positive tumours and for the triple-negative, and the ER-negative and PR-negative/human epidermal growth factor receptor 2 (HER2)-postive subtypes compared with the ER-positive PR-positive /HER2-negative subtype.

Health Economic Evaluation

The GDG did not consider this topic as a health economic priority; therefore the cost effectiveness literature on this topic has not been reviewed.

6.4 Dose Fractionation

Radiotherapy fractionation schedules have been developed over many years based on radiobiological data, clinical experience and resource availability. For breast cancer patients having primary breast conservation surgery or mastectomy, the commonest schedule used internationally involves 25, 2 Gy fractions given over a period of 33 days. In the UK shorter overall treatment times using higher doses per fraction have been extensively used.

Current studies are examining hypofractionation schedules and partial breast irradiation using intensity modulated radiotherapy (IMRT) in early invasive breast cancer. Radiobiological modelling has established dose fractionation regimens that are equivalent to 50 Gy in 25 fractions. Large randomised trials have been reported comparing the internationally accepted 50 Gy in 25 fractions with biologically equivalent doses using fewer fractions (hypofractionated schedules). Thus equivalent rates of local recurrence and similar cosmetic outcomes can be obtained when a schedule of 42.5 Gy in 16 fractions is compared to the above international standard. A UK study has produced similar results, but with short follow-up, using 40 Gy in 15 fractions (START trial[4]). Treatment given on 2 or 3 days per week when compared with daily treatment also gives equivalent results and further trials of less frequent fractions are ongoing.

Careful treatment planning is required for all patients to avoid potential hotspots in the breast but this may be particularly important with hypofractionated schedules. Patients with breast reconstruction/augmentation or large breast size may have a better cosmetic result using conventional dose radiotherapy of 50 Gy in 25 fractions, (lower dose per fraction), although 3D radiotherapy planning may make hypofractionated regimens equivalent.

The use of hypofractionated regimes should result in considerable saving of resources both human and financial.

[4] The START Trialists' Group (2008) The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet Oncol,* 9(4): 331-41.

The START Trialists' Group (2008) The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet,* 371 (9618): 1098-1107.

Recommendation

- Use external beam radiotherapy giving 40 Gy in 15 fractions as standard practice for patients with early invasive breast cancer after breast conserving surgery or mastectomy.

Qualifying statement: This recommendation is based on RCT evidence of clinical effectiveness and the GDG agreeing that a regimen using fewer fractions would probably be cost effective.

Clinical Evidence

Two systematic reviews of high-quality were identified that compared hypofractionated radiotherapy with no radiotherapy (EBCTCG 2002 and Gebski *et al.,* 2006). The strongest evidence was from RCT (Owen *et al.,* 2006; START A and B 2008; Whelan *et al.,* 2002 and Yarnold *et al.,* 2005). An earlier trial by Bates (1998) did not use the conventional 50 Gy in 25 fractions radiotherapy dose as comparator. The remaining two trials were small and of lower quality (Goel *et al.,* 2000 and Taher *et al.,* 2004).

Side effects or cosmesis were assessed in five RCTs (Bates, 1988; Goel *et al.,* 2000; Taher *et al.,* 2005; Whelan *et al.,* 2002 and Yarnold *et al.*, 2005) two cohort studies (Olivotto *et al.,* 1996 and Marhin *et al.,* 2007) and four non-randomised (NRS) studies (Marcenaro *et al.,* 2004; Mladenovic, 2001; Wallace *et al.,* 1993 and Yamada *et al.,* 1999). One NRS focused on women aged 65 years or over (Mladenovic, 2001). Two guidelines originating in Canada were included (Cancer Care Ontario Practice Guidelines Initiative 2002 and Whelan *et al.,* 2003).

Rates of local recurrence were not significantly different between conventional 50 Gy fractions and hypofractionated schedules (Owen *et al.,* 2006; Whelan *et al.,* 2002; Dewar *et al.,* 2007; Bates, 1988; Goel *et al.,* 2000; Mladenovic, 2001; START A 2008 and Yamada *et al.,* 1999). Distant relapse was lower in the hypofractionated arm of the START B (2008) trial and this improved the rates of disease-free survival and overall survival. Assessments of cosmetic outcomes were less consistent, and depended on the comparisons made. One strong RCT (Whelan *et al.,* 2002) reported no significant difference between the 50 Gy and 42.5 Gy arms, whilst another (Yarnold *et al.,* 2005) reported a significantly poorer cosmetic outcome in the 42.9 Gy arm when compared to the 39 Gy arm. The hazard ratio for no change in breast appearance was significantly improved in the 39 Gy arm of the START A trial compared to 50 Gy; whilst there was no difference between the 50 Gy and 41.6 Gy arms in START A or between 50 Gy and 40 Gy in START B.

Global cosmetic outcomes were also less consistent since effects were reported at different times and between different fractionation doses. Breast oedema, fibrosis, lymphedema and telangiectasia were reported in few studies. Only one study reported on quality of life in terms of daily living (Wallace *et al.,* 1993).

The START trials reported late normal tissue effects on cardiac and lung morbidity, however the follow-up period was too short to allow the assessment of all potential late effects.

Health Economic Evaluation

The GDG did not consider this topic as a health economic priority; although there are likely to be cost savings with hypofractionated schedules.

Research recommendation

- What is the effectiveness in patients with early invasive breast cancer of: (a) different hypofractionation radiotherapy regimens (b) partial breast radiotherapy and (c) newer radiotherapy techniques (including intensity modulated radiotherapy), in terms of long term outcomes such as, quality of life, side effects, disease recurrence rates, disease-free survival and overall survival?

6.5 Breast Boost

Whole breast radiotherapy after breast conservation surgery has become the standard of care for patients with invasive breast cancer, reducing local recurrence significantly. Despite this approach, breast recurrence will develop in between 3 and 30% of patients, depending on the length of follow-up. A variety of factors increase the risk of local recurrence and include young patient age (under 40 years of age), histological grade 3 disease and lymph node negativity. Studies have shown that an additional boost dose of radiation to the tumour bed is effective in reducing local recurrence rates.

Recommendations

- Offer an external beam boost to the site of local excision to patients with early invasive breast cancer and a high risk of local recurrence, following breast conserving surgery with clear margins and whole breast radiotherapy.
- If an external beam boost to the site of local excision following breast conserving surgery is being considered in patients with early invasive breast cancer, inform the patient of the side effects associated with this intervention, including poor cosmesis, particularly in women with larger breasts.

Qualifying statement: These recommendations are based on good RCT evidence and GDG consensus.

Clinical Evidence

Data from RCTs and non-randomised studies were included for this topic. The most frequent study reported was the boost versus no boost EORTC 22881-10882 randomised trial. RCT data were consistent in the finding that a boost dose to the tumour bed reduced local recurrence but had little effect on overall survival. However most of the data were from the EORTC trial. One RCT compared the effects of the boost technique on local recurrence (Poortmans *et al.,* 2004) and found no difference between the three techniques. Most RCTs reported an association of local failure with age. The absolute failure rates and difference in failure rates between treatment groups decreased as age increased. Other factors associated with local failure were: no boost dose, high histological grade of tumour, size of the tumour, excision volume and adjuvant systemic therapy.

Non-randomised studies reported that young age (≤ 45 years), lower T status, and close final margin status (≤ 2mm) were the strongest predictors of local recurrence.

A range of cosmetic outcomes were reported and these were assessed by clinicians, patients, panels and digitizer measurements. Global cosmetic results following surgery were excellent or good (Vrieling *et al.,* 1999), however fibrosis and telangiectasia tended to be worse in the boost group (Bartelink *et al.,* 2007 and Romestaing *et al.,* 1997).

Health Economic Evaluation

A joint systematic review of the evidence regarding the cost effectiveness of radiotherapy after breast conserving surgery, and the cost effectiveness of adding an external beam radiotherapy boost to the site of local excision after breast conserving surgery in patients with invasive breast cancer was conducted. From 958 initially identified references, four economic

Health Economic Evaluation (cont.)

evaluations relevant to radiotherapy after breast conserving surgery and one economic evaluation relevant to radiotherapy boost after breast conserving surgery were included in the review.

Three of the four studies that assessed the cost effectiveness of radiotherapy after breast conserving surgery were full economic evaluations: one of them had been conducted in UK (Prescott *et al.,* 2007), one in the USA (Hayman *et al.,* 1998) and one in Sweden (Liljegren *et al.,* 1997). The other study had been published as two congress abstracts (Alvegard *et al.,* 2005 and Persson *et al.,* 2005) and was conducted in Sweden. Most of the studies had focused on a specific subgroup of the early breast cancer population and therefore their results may be generalisable only to similar populations (in terms of age, tumour stage, etc.). Overall, the studies seemed to have been appropriately conducted for their corresponding study setting; they had used some kind of modelling, either to conduct the economic evaluation and/or to perform sensitivity analyses. Although these studies presented some limitations (which were considered to be minor), their results seemed to be valid.

There was some controversy regarding the cost effectiveness of using radiotherapy after breast conserving surgery. Two studies (Prescott *et al.,* 2007; Liljegren *et al.,* 1997), including the RCT conducted in UK (Prescott *et al.,* 2007), identified radiotherapy after breast conserving surgery as a non cost effective strategy for specific groups of patients, specifically those older and at lower risk of local recurrence. One study (Hayman *et al.,* 2000) identified radiotherapy after breast conserving surgery as being cost effective for 60 year-old, early breast cancer patients with clinical stage 1 or 2 tumours. The final studies (Alvegard *et al.,* 2005 and Persson *et al.,* 2005) concluded that radiotherapy after breast conserving surgery was cost effective in pre- and postmenopausal women with breast cancer with stage I and II tumours only as an adjunction to no medical adjuvant treatments, while it would be cost effective only for patients at high risk of local recurrence if it were used as an adjunct to novel adjuvant medical treatment. Based on these results, radiotherapy after breast conserving surgery may not be a cost effective intervention among those patient groups older and at low risk of developing local recurrence, since the health benefits obtained in terms of recurrences avoided seemed to be too low to compensate for the high costs of administering the radiotherapy regimes after breast conserving surgery.

The only identified economic evaluation that assessed the cost effectiveness of a radiotherapy boost after breast conserving surgery (Hayman *et al.,* 2000) was conducted in USA and considered early breast cancer patients with stage 1 or 2 tumours who had undergone breast conserving surgery in combination with radiotherapy. The study appeared to have been appropriately conducted, although it presented some minor limitations. The authors concluded that the addition of a radiotherapy boost after breast conserving surgery and radiotherapy on early breast cancer patients with stage 1 and 2 tumours and negative margins does not seem to be cost effective, unless the patients place an unexpectedly large utility value on small reductions in the likelihood of local recurrence, or unless the cost of the radiotherapy boost decreases considerably (less than one half its actual USA cost), conditions that do not seem likely to be met in clinical practice. As the authors reported, omitting radiotherapy boost among early breast cancer patients with negative margins after breast conserving surgery would lead to very important savings.

6.6 Radiotherapy to Nodal Areas

Radiotherapy to the supraclavicular fossa (SCF), internal mammary chain (IMC) and axilla after breast conservation or mastectomy is considered separately to radiotherapy to the breast or chest wall. The increase in screen-detected breast cancer and the decrease in locally advanced breast cancer has resulted in a reduction in the involvement of the internal mammary chain, which is technically difficult to irradiate accurately.

Options for surgical staging of the axilla include sentinel lymph node biopsy (SLNB), 4-node sample and, historically, axillary lymph node dissection (ALND). Recommendations on a positive SLN can be found in Chapter 3. Radiotherapy to the axilla does not improve local control

or mortality after ALND (performed as an initial procedure or after a positive SLN), but increases morbidity. Where there are four or more positive axillary lymph nodes there is increased risk of recurrence in the SCF.

Recommendations

- Do not offer adjuvant radiotherapy to the axilla or supraclavicular fossa to patients with early breast cancer who have been shown to be histologically lymph node-negative.
- Do not offer adjuvant radiotherapy to the axilla after ALND for early breast cancer.
- If ALND is not possible following a positive axillary SLNB or four-node sample, offer adjuvant radiotherapy to the axilla to patients with early breast cancer[5].
- Offer adjuvant radiotherapy to the supraclavicular fossa in patients with early breast cancer and four or more involved axillary lymph nodes.
- Offer adjuvant radiotherapy to the supraclavicular fossa to patients with early breast cancer and one to three positive lymph nodes if they have other poor prognostic factors (for example, T3 and/or histological grade 3 tumours) and good performance status.
- Do not offer adjuvant radiotherapy to the internal mammary chain to patients with early breast cancer who have had breast surgery.

Qualifying statement: These recommendations are based on evidence from randomised control trials and GDG consensus.

Clinical Evidence

Since there were few studies that directly addressed this question the available literature was grouped into those studies comparing surgery and regional lymph node irradiation with mastectomy and axillary dissection or mastectomy only (Fisher *et al.,* 2002; Overgaard *et al.,* 1999; Ragaz *et al.,* 2005 and Wallgren *et al.,* 1986); studies comparing breast conserving surgery with or without axillary dissection or axillary radiotherapy (Louis-Sylvestre *et al.,* 2004; Pejavar *et al.,* 2006, and Veronesi *et al.,* 2005); studies applying radiation to the internal mammary lymph nodes (Arriagada *et al.,* 1988; Grabenbauer 2004; Kaija and Maunu 1995; Obedian and Haffty 1999; Vinod and Pendlebury, 1999); one retrospective cohort of patients receiving breast conserving surgery with axillary dissection and no regional lymph node irradiation (Livi *et al.,* 2006); a retrospective study of predictors of regional nodal failure where only a small proportion of patients received regional radiotherapy (Grills *et al.,* 2003); and two retrospective studies of lymph node ratios as prognostic factors (Fortin *et al.,* 2006 and Tai *et al.,* 2007).

The evidence from four strong RCTs delivering regional nodal irradiation (axilla, supraclavicular and internal mammary lymph nodes) after mastectomy found a reduction in local and regional recurrence rates in the radiotherapy group in both lymph node-positive and negative women. An exception occurred in one trial of lymph node-positive women where no difference in recurrence rates was found in the RT group (Fisher *et al.,* 2002). Overall survival was improved in the RT arm from two of these trials (Overgaard *et al.,* 1999 and Ragaz *et al.,* 2005), however no difference in overall survival was reported in the remaining two trials (Fisher *et al.,* 2002 and Wallgren *et al.,* 1986).

The evidence from two well conducted RCTs including women with clinically negative lymph nodes in which the the interventions were breast conserving surgery and breast radiotherapy with or without radiotherapy to the axilla (Veronesi *et al.,* 2005), or BCS and breast radiotherapy followed by axillary dissection or axillary radiotherapy (Louis-Sylvestre *et al.,* 2004) reported no difference between arms for disease-free survival. The incidence of axillary metastases was not significantly different in the study by Veronesi *et al.* (2005), but

[5] See recommendations in Chapter 3.

Clinical Evidence (cont.)

was significantly increased in the axillary radiotherapy arm compared to axillary dissection in the trial by Louis-Sylvestre *et al.* (2004). Evidence comparing axillary dissection and axillary radiotherapy after breast conserving surgery and radiotherapy to the breast in lymph node-positive and negative women found no difference between groups in lymph node recurrence (Pejavar *et al.* 2006).

Radiation to the internal mammary chain lymph nodes was assessed in one RCT (Kaija and Maunu, 1995) after breast conserving surgery with axillary dissection and breast radiotherapy. No significant differences in local and distant relapse rates were reported, however, the follow-up time was short (2.7 years). A systematic review also suggested that the short observation time was not sufficient to allow any conclusions as to the value of internal mammary chain irradiation (Vinod and Pendlebury, 1999).

Evidence from observational studies reported conflicting findings for distant metastases and survival with or without internal mammary chain lymph node irradiation. Arriagada *et al.* (1988) found a benefit of internal mammary chain irradiation in these outcomes to patients with medial tumours, whilst Obedian and Haffty (1999) found no difference regardless of tumour location. In another cohort of patients (Grabenbauer, 2004) overall survival and systemic disease-free survival were comparable when patients were treated with radiotherapy to the IMN for medial tumours, but radiotherapy was omitted for lateral tumours.

A large cohort study that did not treat the regional lymph nodes of patients with radiotherapy (Livi *et al.,* 2006) assessed locoregional and lymph node relapses (axilla, internal mammary chain or supraclavicular fossa) over a median of 8 years. Most patients were lymph node-negative at diagnosis. Multivariate analyses showed that lymph node relapse were more likely in women with more than three positive lymph nodes, pathological T2 tumours and angiolymphatic invasion. Locoregional recurrences were also associated with these characteristics as well as younger age groups.

A further observational study determined the incidence and risk factors for regional nodal failure in a cohort of patients receiving breast conserving surgery, axillary dissection and radiotherapy to the breast alone, a proportion of these (13%) also received radiotherapy to the regional lymph nodes (Grills *et al.,* 2003). A subgroup analysis found that axillary failure was significantly higher in patients with 4 or more positive lymph nodes who did not receive regional lymph node irradiation; however supraclavicular failure was significantly higher in patients with 1-3 positive lymph nodes who did receive regional lymph node irradiation. However, rates of failure for lymph node-negative and all lymph node-positive patients were not significantly different between those receiving regional lymph node irradiation and no regional lymph node irradiation. Overall survival and distant metastases free survival were lowest in patients with positive lymph nodes who received regional lymph node irradiation compared with those not receiving regional lymph node irradiation. lymph node-negative patients receiving regional lymph node irradiation also had lower overall survival and distant metastases free survival rates. A multivariate analysis of all patients found that the only significant independent predictor of RNF was the maximal size of the nodal metastasis.

Two observational studies assessed the percentage (Fortin *et al.,* 2006) or ratio (Tai *et al.,* 2007) of involved lymph nodes. Fortin *et al.* (2006) assessed the effects on regional lymph node failure, and Tai *et al.* (2007) assessed the effects on survival. Regional radiotherapy was found to be more effective in patients with medium to high lymph node ratios than low lymph node ratios in both studies.

Health Economic Evaluation

The GDG did not consider this topic as a health economic priority; therefore the cost effectiveness literature on this topic has not been reviewed.

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7 Primary systemic therapy

7.1 Early Breast Cancer

Optimal management of breast cancer includes local control in the breast and the prevention of metastatic spread. Some patients will have developed occult metastatic spread before clinical or radiological detection of the primary tumour. There are also patients whose tumours at presentation are too large to be considered appropriate for breast conservation. Primary systemic therapy of invasive breast cancer may be offered in an attempt to enable breast conserving treatment and subsequent surgery (mastectomy or wide local excision). Radiotherapy may then be offered according to similar criteria to those patients presenting *de novo*. Primary systemic treatment involves the use of systemic therapy, either chemotherapy or endocrine therapy, after diagnosis but before definitive surgery. Primary systemic therapy (also referred to as neoadjuvant therapy) can be successfully used to shrink the size of the primary tumour such that breast conservation may be achieved with a good cosmetic result but with a slightly higher risk of local recurrence compared to mastectomy. Primary systemic therapy can also identify the efficacy of the systemic treatment regimen since the primary tumour is available to monitor response to the therapy. This option is of course not available if the primary tumour has been removed surgically. The use of primary systemic treatment allows targeting of occult metastatic tumour deposits at an earlier stage than the conventional approach of postoperative chemotherapy. Randomised trials of primary systemic therapy have failed to show a significant survival benefit, but more recent studies using current chemotherapy regimens have been able to identify subgroups of patients, such as those achieving complete pathological response at surgery, that have a survival advantage.

Recommendations

- Treat patients with early invasive breast cancer, irrespective of age, with surgery and appropriate systemic therapy, rather than endocrine therapy alone, unless significant comorbidity precludes surgery.

Qualifying statement: This recommendation is based on a Cochrane review of RCTs with small patient numbers.

- Preoperative systemic therapy can be offered to patients with early invasive breast cancer who are considering breast conserving surgery that is not advisable at presentation. However, the increased risk of local recurrence with breast conserving surgery and radiotherapy rather than mastectomy after systemic therapy should be discussed with the patient.

Qualifying statement: This recommendation is based on the results of a Cochrane review of RCTs of good quality.

Clinical Evidence

The evidence that describes the role of primary systemic treatment in patients with early, invasive breast cancer has been drawn from three systematic reviews (Hind *et al.,* 2006; Mieog *et al.,* 2007 and Trudeau *et al,*. 2005) and a review providing updated results of two RCTs (Rastogi *et al.,* 2008). This research question lists two comparisons of interest; the first comparison is related to primary endocrine therapy versus primary surgery in elderly patients while the second comparison relates to primary chemotherapy versus surgery as primary treatment for patients with breast cancer.

Primary endocrine therapy

A systematic review of RCTs provides the most applicable data for the use of endocrine therapy as initial treatment in patients > 70 years and reported no significant difference in overall survival between surgery and primary endocrine treatment (Hind *et al.,* 2006). There was evidence of a non-significant trend in favour of surgery plus endocrine therapy over primary endocrine therapy (Hind *et al.,* 2006). There is a statistically significant effect in favour of surgery plus endocrine therapy over endocrine therapy for breast cancer specific survival (Hind *et al.,* 2006).

Primary chemotherapy

A systematic review (Mieog *et al.,* 2007) and a subsequently published review (Rastogi *et al.,* 2008) reported no significant difference in overall survival or disease-free survival between preoperative and postoperative chemotherapy. A statistically significant difference in rate of mastectomy in favour of preoperative chemotherapy was observed based on pooled estimates from good quality RCTs (Mieog *et al.,* 2007).

Health Economic Evaluation

The GDG did not consider this topic as a health economic priority; therefore the cost effectiveness literature on this topic has not been reviewed.

7.2 Locally Advanced or Inflammatory Breast Cancer

In cases of locally advanced or inflammatory breast cancer treated by primary chemotherapy, adequate long-term local control by surgery and/or radiotherapy is still essential, although there remains a high risk of developing late metastatic disease. This includes those patients with complete clinical response. Inflammatory breast cancer is an aggressive disease, presenting with usually a short history of breast swelling, redness, discomfort and pain and characterised by an oedematous, indurated and erythematous breast.

Recommendation

- Offer local treatment by mastectomy (or in exceptional cases, breast conserving surgery) followed by radiotherapy to patients with locally advanced or inflammatory breast cancer who have been treated with chemotherapy,.

Qualifying statement: This recommendation is based on evidence from a RCT and retrospective studies and GDG consensus.

Clinical Evidence

There is a considerable body of high-quality evidence on the role of primary chemotherapy in patients with locally advanced breast cancer, inflammatory breast cancer, or operable breast cancer. Patients also received loco-regional treatment, the effect of which was not the main focus of the study resulting in little direct evidence on the individual effects of surgery or radiotherapy following primary chemotherapy.

Clinical Evidence (cont.)

In patients with locally advanced breast cancer who receive primary chemotherapy, findings from a Cochrane review and two systematic reviews suggest that better tumour response is associated with better outcomes (Mieog *et al.,* 2007; Shenkier *et al.,* 2004 and; Pouillart *et al.,* 1981). The applicability of this evidence is limited however because the majority of patients had operable breast cancer of stage I-II.

No difference in overall survival was observed when comparing different radiotherapy regimens (Bucholz *et al.,* 2006 and Shenkier *et al.,* 2004), however there was also evidence of a higher rate of loco-regional recurrence in patients who received radiotherapy without surgery after primary chemotherapy (Mieog *et al.,* 2007 and Mauri *et al.,* 2005). Veyret *et al.* (2006) evaluated the outcomes after primary chemotherapy. Some patients underwent surgery or received radiotherapy. The univariate analysis conducted in this study showed the following factors were statistically significantly associated with recurrence: no surgery, no overall pathological complete response, no breast pathological complete response, no lymph node pathological complete response and diffuse inflammatory signs. However no variable remained statistically significant in multivariate analysis and the use of radiotherapy was not included in the model. A retrospective study by Huang *et al.* (2004) examined the effect of radiotherapy on outcomes in patients treated for locally advanced breast cancer with primary chemotherapy and mastectomy. Radiotherapy was found to reduce loco-regional recurrence and improve survival for patients. Another retrospective study by McGuire *et al.* (2007) investigated the role of post-mastectomy radiotherapy in women with breast cancer who achieved a pathologic complete response to neo-adjuvant chemotherapy. In patients initially presenting with stage III disease; those receiving radiotherapy had statistically significantly lower rates of locoregional response; higher distant metastatic survival rates; higher cause specific survival rates and higher overall survival rates.

Health Economic Evaluation

The GDG did not consider this topic as a health economic priority; therefore the cost effectiveness literature on this topic has not been reviewed.

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8 Complications of local treatment and menopausal symptoms

8.1 Introduction

Previous chapters have discussed in detail surgical management, adjuvant systemic treatment including biological therapy, postoperative radiotherapy and lastly primary systemic treatment. The common local side effects of lymphoedema and problems with arm mobility are addressed in this chapter, followed by the very frequent and difficult to manage complaint of menopausal symptoms. The importance of psychological support of the patient is the last topic in this section.

8.2 Complications of Local Treatment

Lymphoedema

Patients diagnosed with early breast cancer may develop lymphoedema as a consequence of breast cancer surgery and/or radiotherapy.

Lymphoedema is a chronic condition that may result in significant physical and psychological morbidity including arm or breast swelling, pain, numbness and decreased functional ability affecting quality of life. Lymphoedema diagnosis is confirmed by an increase in circumference or volume of the affected upper limb or visually in the case of breast oedema.

Lymphoedema is associated with skin and subcutaneous tissue changes, distorted shape, increased risk of cellulitis and psychological morbidity.

Treatment options for patients with lymphoedema include skin care, exercises, use of compression garments and lymphatic drainage massage which are designed to reduce swelling. The Lymphoedema Support Network produces literature that may be accessed by patients. The British Lymphology Society also produces information documents suitable for healthcare professionals. Please see recommendations on the management of lymphoedema in the NICE clinical guideline on 'Advanced breast cancer: diagnosis and treatment' NICE 2008.

The NICE guidance on 'Improving outcomes in breast cancer manual update' (NICE 2002) recommended that 'networks should agree guidelines for identification and management of lymphoedema' and that 'a lymphoedema service, staffed by trained nurses and physiotherapists, should be available for all patients who experience arm swelling or discomfort'. Although there is an expectation of delivery of these services for breast cancer patients, current provision of lymphoedema services is variable.

Recommendations

- Inform all patients with early breast cancer about the risk of developing lymphoedema and give them relevant written information before treatment with surgery and radiotherapy.
- Give advice on how to prevent infection or trauma that may cause or exacerbate lymphoedema to patients treated for early breast cancer.
- Ensure that all patients with early breast cancer who develop lymphoedema have rapid access to a specialist lymphoedema service.

Qualifying statement: There was GDG consensus to support making these recommendations which also support the NICE guidance on ''Improving outcomes in breast cancer manual update' NICE 2002.

Clinical Evidence

The quality of the evidence for this question is varied, including few RCTs and several observational studies. There appear to be few studies of interventions aimed to prevent lymphoedema in the population of patients with breast cancer (including patients who have received surgery and adjuvant treatment) who are at risk of developing the condition.

Evidence from recent RCTs suggests that arm or shoulder exercise interventions after surgery for breast cancer do not affect subsequent rates of lymphoedema and that their effect upon shoulder mobility is inconsistent. An earlier systematic review of studies with mixed design found that shoulder exercise therapy does improve shoulder mobility. It should be noted that there is high heterogeneity across the studies: the interventions investigated differed considerably in their design, time of commencement and intensity. Control groups were also treated differently across studies. (Bendz and Fagevik, 2002; Box *et al.,* 2002a and 2002b; Cave and Jones, 2006 and Cheema *et al.,* 2008).

Evidence from one RCT and a systematic review supports the role of aerobic exercise in patients treated for breast cancer, with some demonstrable benefit in terms of shoulder mobility and quality of life, but not consistently. Evidence from observational studies suggests that aerobic exercise is beneficial both physically and in terms of psychological well being (Karki *et al.,* 2001; Lane 2005 and Sandel *et al.,* 2005).

There was very limited evidence for the effectiveness of cognitive-behavioural interventions and arm massage. A poor quality RCT by Forchuk *et al*. (2004) found that an intervention whereby patients' partners were instructed to perform distal-to-proximal circular arm massage had no demonstrable effect on shoulder range of motion at four months postoperatively. The intervention group experienced significantly greater arm swelling than the control group at 14 weeks and four month postoperatively. A RCT by Braden and Badger (2000) found that patients who received an intervention designed to help them manage uncertainty arising from breast cancer reported better coping with arm swelling than patients in the control group, over a seven month period of follow-up. This result should be interpreted with caution as full trial details are not currently available.

Observational evidence suggests that where information is provided to patients on lymphoedema, it is done so by different healthcare professionals, with no apparent dominant group. (Cordero *et al*., 2003; Coward, 1999; Karki *et al.,* 2004 and Yik *et al.,* 2001).

Health Economic Evaluation

A systematic review was conducted to assess the cost effectiveness of strategies used to prevent arm lymphoedema. The initial search identified 159 articles, from which 153 papers were excluded on the basis of the title and the abstract. Six papers were obtained for appraisal, and all of them were excluded: 4 of them because they were not relevant for the study question or were not economic evaluations (Forchuk *et al.,* 2004; Morgan *et al.,* 2005; Norman *et al.,* 2001 and Orr *et al.,* 1999), and one study was rejected because, although it

Health Economic Evaluation (cont.)

compared the effectiveness and costs of Australian rehabilitation programs for breast cancer patients, lymphoedema was not assessed in the study (Gordon *et al.,* 2005b). Therefore, no economic evaluations were identified from the systematic review. The GDG considered there to be insufficient clinical information available to enable robust economic modelling.

Arm mobility

Reduced arm and shoulder mobility are frequent complications of the treatment of breast cancer, particularly after axillary lymph node dissection (ALND). Other side effects include pain, decreased muscle strength, altered sensation and diminished functional ability. Physiotherapy and exercise are used to minimise these side effects.

Although physiotherapy is widely accepted as beneficial there is variation as to which regimen to use. There is variation in protocols across breast units and in some areas there is no physiotherapy provision at all. Referral to physiotherapy tends to be reactive rather than proactive, especially when limited movement interferes with radiotherapy planning.

Recommendations

- All breast units should have written local guidelines agreed with the physiotherapy department for postoperative physiotherapy regimens.
- Identify breast cancer patients with pre-existing shoulder conditions preoperatively as this may inform further decisions on treatment.
- Give instructions on functional exercises, which should start the day after surgery, to all breast cancer patients undergoing axillary surgery. This should include relevant written information from a member of the breast or physiotherapy team.
- Refer patients to the physiotherapy department if they report a persistent reduction in arm and shoulder mobility after breast cancer treatment.

Qualifying statement: These recommendations are based on GDG consensus and evidence from several randomised control trials on the effects of postoperative physiotherapy.

Clinical Evidence

There is a considerable body of high-quality evidence that evaluates strategies to reduce arm and shoulder mobility problems after breast cancer treatement.

RCT evidence suggests that physiotherapy or exercise interventions can improve arm and shoulder function in patients who have received surgery for breast cancer. However the RCTs do not consistently show such improvements for all outcome measures. There is no evidence from RCTs of higher rates of long term complications following physiotherapy or exercise interventions (Bendz and Fagevik, 2002; Dawson *et al.,* 1989; Gordon *et al.,* 2005a; Johannsson, 2005; Kilbreath *et al.,* 2006; Lauridsen *et al.,* 2005; Le Vu *et al.,* 1997; Sandel *et al.,* 2005 and Wingate *et al.,* 1989). One poor quality RCT suggests that commencing exercise on the 1st postoperative day may increase short term complications (Dawson *et al.,* 1989)

Data from two RCTs suggest that the addition of stretching exercise to physiotherapy has no benefit in terms of arm/shoulder function, quality of life, muscular strength or rate of adverse effects. However in one RCT data were reported unclearly and the other RCT studied only 22 patients (Kilbreath *et al.,* 2006; Lee *et al.,* 2007). Data from two RCTs suggest that massage can bring benefit in terms of arm function in the short term. However the trials did not consistently find massage to be advantageous for all outcome measures (Forchuk *et al.,* 2004 and Le Vu *et al.,* 1997).

Clinical Evidence (cont.)

RCT evidence suggests that the timing of physiotherapy within the first two postoperative weeks does not affect outcomes that are assessed one month or later from the date of surgery. RCT evidence suggests that physiotherapy given in the first postoperative week to patients with surgical drains in situ is associated with a larger drainage volume, compared to delayed physiotherapy, or compared to other interventions (for example, massage). (Bendz and Fagevik, 2002; Chen and Chen, 1999; Jansen *et al.,* 1990; Johansson *et al.,* 2001; Le Vu *et al.,* 1997 and Van der Horst *et al.,* 1985). RCT evidence suggests that for exercise interventions that commence between 6 weeks and 26 weeks from the time of surgery, the precise timing of the exercises does not influence outcomes (Sandel *et al.,* 2005).

RCT evidence suggests that instructed physiotherapy or instructed exercise interventions are associated with improved patient compliance, a better range of arm movement and lower rates of lymphoedema compared to control arms in which patients receive booklets or other education for unsupervised exercise (Beurskens *et al.,* 2007; Box *et al.,* 2002a; Cinar *et al.,* 2008; Gerber *et al.,* 1992; Lauridsen *et al.,* 2005; Na *et al*., 1999 and Wang *et al*., 2005). Data from one RCT suggest that patients treated with zaltoprofen have improved range of shoulder movement during physiotherapy compared to patients in a control group (Hase *et al.,* 2006).

Health Economic Evaluation

The GDG did not consider this topic as a health economic priority; therefore the cost effectiveness literature on this topic has not been reviewed.

8.3 Menopausal Symptoms

Approximately a quarter of patients diagnosed with early breast cancer will be pre- or perimenopausal. Treatment strategies for these patients include chemotherapy, ovarian ablation or suppression, and adjuvant endocrine therapy, all of which may result in premature menopause and in some cases an impact on fertility. Chemotherapy induced menopause occurs in up to 50% of women under 40 years of age and up to 90% in those over 40.

The average age of normal menopause in the UK is 52. Menopausal symptoms may begin up to 10 years before the menopause and continue for several years after. Symptoms include vasomotor-flushes and night sweats, urogenital - vaginal dryness, urinary frequency, loss of libido, mood swings, depression and loss of concentration. Postmenopausal status confers increased risk of osteoporosis and cardiovascular disease. Menopausal symptoms for patients with breast cancer may be more sudden and severe due to the effect of treatment on the ovaries.

Hormone replacement therapy (HRT) is the treatment of choice for menopausal symptoms, but is rarely used in patients with breast cancer because of concerns regarding tumour stimulation and interference with adjuvant endocrine treatments. The Million Women Study and The Women's Health Initiative confirmed that all types of HRT cause a duration dependent increase in the diagnosis of breast cancer. Until recently there was no evidence that HRT use was associated with an increased recurrence risk among breast cancer patients, but a recent trial in Sweden was stopped early as results indicated that HRT increased the risk of another breast cancer event.

Alternative drug therapy for women in general with vasomotor symptoms include:

- Progestogens – for example megestrol acetate
- Tibolone, a synthetic steroid
- Clonidine
- Venlafaxine (an antidepressant)
- Selective serotonin re-uptake inhibitors (SSRIs) antidepressants (fluoxetine and paroxetine).

However, there is a concern about using some of these drugs in patients who have breast cancer because of possible drug interactions or influences on other biochemical pathways. Tamoxifen is metabolised to the potent anti-oestrogen endoxifen by the cytochrome P450 CYP 2D6 enzyme.

The CYP2D6 gene is highly polymorphic, resulting in four phenotypes (poor, intermediate, extensive and ultrarapid metabolisers). This affects the levels of endoxifen, and as a result possibly the effectiveness of tamoxifen and its associated side effects. The co-prescription of SSRIs, which are CYP2D6 inhibitors, for the treatment of depression or hot flushes significantly decreases endoxifen concentrations and may reduce the effectiveness of tamoxifen.

There are a range of non-pharmacological interventions that may have a place in treatment of menopausal symptoms. Most are unproven and have not been sufficiently evaluated by rigorous clinical trials. The most widely used are plant phytoestrogens, soy, black cohosh and red clover.

Complementary therapies including acupuncture, hypnosis, cognitive behaviour therapy (CBT) and relaxation techniques may all ameliorate some menopausal symptoms. Their value may reflect the personalised treatment and time spent with the patient.

Recommendations

- Discontinue HRT in women who are diagnosed with breast cancer.
- Do not offer HRT (including oestrogen/progestogen combination) routinely to women with menopausal symptoms and a history of breast cancer. HRT[1] may, in exceptional cases, be offered to women with severe menopausal symptoms and with whom the associated risks have been discussed.
- Offer information and counselling for all women about the possibility of early menopause and menopausal symptoms associated with breast cancer treatment.

Qualifying statement: This recommendation is based on GDG consensus and concerns about long term safety.

- The selective serotonin re-uptake inhibitor antidepressants paroxetine[2] and fluoxetine[3] may be offered to women with breast cancer for relieving menopausal symptoms, particularly hot flushes, but not to those taking tamoxifen.

Qualifying statement: This recommendation is based on RCT evidence, although there is some evidence that these drugs may be effective they inhibit the metabolism of tamoxifen to the active drug.

- Clonidine, venlafaxine[4] and gabapentin[5] should only be offered to treat hot flushes in women with breast cancer after they have been fully informed of the significant side effects.

Qualifying statement: This recommendation is based on evidence from RCTs and comparative studies.

- Soy (isoflavone), red clover, black cohosh, vitamin E and magnetic devices are not recommended for the treatment of menopausal symptoms in women with breast cancer.

Qualifying statement: The evidence on the effectiveness of these interventions is limited and conflicting and there was GDG consensus that it does not support their widespread use.

[1] The summaries of product characteristics state that HRT is contraindicated in women with known, past or suspected breast cancer. Informed consent should be obtained and documented.

[2] These drugs are not licensed for the stated use. Informed consent should be obtained and documented.

[3] These drugs are not licensed for the stated use. Informed consent should be obtained and documented.

[4] These drugs are not licensed for the stated use. Informed consent should be obtained and documented.

[5] These drugs are not licensed for the stated use. Informed consent should be obtained and documented.

Clinical Evidence

Many different types of intervention were identified including pharmacological (for example, endocrine therapies), alternatives to endocrine therapies, (for example antidepressants and other prescribed medications), complementary therapies, (for example, isoflavones and herbal remedies), psychological support and group activities, (for example, relaxation and exercise). The majority of the evidence was drawn from systematic reviews some of which included studies of women without breast cancer (Antoine *et al.,* 2007; Bordeleau *et al.,* 2007; Carpenter *et al,.* 2007; Col *et al.,* 2005; Deng *et al.,* 2007; Ganz *et al.,* 2000; Goodwin *et al.,* 2008; Hickey *et al.,* 2005; Kenemans *et al.,* 2005; Kimmick *et al.,* 2006; Kroiss *et al.,* 2005; Loprinzi *et al.,* 2007; MacLennan *et al.,* 2004; Modelska *et al.,* 2002; Mom *et al.,* 2006; Nedrow *et al.,* 2006; Nelson *et al.,* 2006; Pritchard *et al.,* 2002; Royal College of Obstetricians and Gynaecologists *et al.,* 2006; Thompson *et al.,* 2008; Tremblay *et al.,* 2008; von Schoultz *et al.,* 2005 and Walji *et al.,* 2007).

There was inconsistency in the findings of RCTs of HRT and progestational agents regarding breast cancer recurrence, several trials were ongoing. All RCTs of SSRIs and selective norepinephrine/noradrenaline reuptake inhibitors (SNRIs) were consistent in reporting a moderate effect in reducing hot flush frequency and severity. A reduction in menopausal symptoms was also reported from RCTs of clonidine and gabapentin, although the latter was only effective at high doses. A comparison of venlafaxine with clonidine found that daily hot flush frequency was reduced more effectively by venlafaxine than clonidine. The synthetic steroid, tibolone, produced a reduction in hot flushes comparable to HRT, improved sexual function and possibly mood. However there were longer term safety considerations since the drug increased blood lipids and clotting factors. There was no effect of red clover on menopausal symptoms however there were no studies of women with breast cancer. Soy extracts provided conflicting effects with a possible weak effect for women without breast cancer. There were no significant effects on hot flushes for black cohosh, vitamin E or magnetic therapy in women with breast cancer. There may be a risk of hepatic disorders with black cohosh and its safety remains under review by the Medicines and Healthcare products Regulatroy Agency (MHRA). A comprehensive menopausal assessment programme found significant improvements in the menopausal symptom scale with reduced symptoms in the intervention group and an improvement in sexual functioning. Another systematic review found some effect of relaxation on hot flushes for women with breast cancer however the study quality was poor. There was no significant effect on hot flush frequency of acupuncture for women with breast cancer from one RCT.

Health Economic Evaluation

The GDG did not consider this topic as a health economic priority; therefore the cost effectiveness literature on this topic has not been reviewed.

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9 Follow-up

9.1 Introduction

Follow-up of patients after treatment for early breast cancer includes clinical and radiological options for assessment of both the treated and the contralateral breast. It incorporates supervision of ongoing adjuvant treatment and potential side effects, and review of patients who are in clinical trials. Follow-up should also include advice on general health, diet and exercise. Further demand for follow-up of patients with early invasive breast cancer has been created by the increasing duration and sequencing of adjuvant therapy.

How follow-up should be carried out has been the subject of controversy and there is variation in England and Wales as to who should undertake this, and where this should be performed. This has led to pressures on service provision.

9.2 Follow-up Imaging

Invasive breast cancer

Patients treated for early invasive breast cancer are at risk of developing local recurrence and are also at increased risk of developing a further new primary breast cancer. It is currently common practice for women being followed-up after treatment for early breast cancer to return to the National Health Service Breast Screening Programme (NHSBSP)/Breast Test Wales Screening Programme (BTWSP) after five years of follow-up or when they reach 50 years of age. The NHSBSP/BTWSP invites women between 50 and 70 years of age for mammographic screening every three years (7 screening events over 21 years). Younger women are only eligible for screening if they have a significant increased risk, in which case they are usually offered annual mammography between 40 and 50 years of age. Women over 70 years of age are not invited for screening mammography but can attend by self-referral every three years. The NHSBSP will extend the age of invitation from 47 to 73 years of age (two additional screening events – 9 screening events over 27 years) to be fully implemented by 2012 in England. The screening interval will remain at three years but there is concern about whether this interval is appropriate for extended surveillance (i.e. after 5 years) in patients treated for breast cancer.

Local recurrence

The rationale for early detection of local recurrence is that treatment may be more effective and there may be a survival benefit. The risk of local recurrence is determined by the prognostic factors of the primary tumour and the type of treatment given. Overall the risk of local recurrence in the treated breast is between 0.5% and 1% per annum when new primaries are included (and is lifelong). Local recurrence can be detected by regular surveillance, (clinical examination and breast imaging) or, most commonly, by the patient presenting with new symptoms or signs between scheduled follow-up visits. It is currently routine practice for all patients treated for early breast cancer to be offered regular surveillance, although the method, duration and frequency is variable. Patients who have had breast reconstruction may have particular follow-up requirements.

Mammography is widely used as part of surveillance and up to a third of local recurrences are detected by mammography alone. It is most likely to detect recurrence in the conserved breast. The recurrence usually has similar mammographic features to the original primary disease. It is not effective in detecting superficial and skin recurrence either in the conserved breast or

on the chest wall following mastectomy. Mammography may detect recurrence with better prognostic factors than clinical examination.

Surveillance ultrasound may detect some recurrences that are not detectable on mammography, particularly in the dense breast or when the primary tumour was occult on mammography. Magnetic resonance imaging (MRI) can be expected to have significantly higher sensitivity for recurrence than other imaging techniques but is also likely to have a high false positive rate with a high proportion of benign biopsies. MRI is not currently recommended for routine surveillance but is used for further assessment and problem solving when other investigations have equivocal findings. Both mammography and MRI are more likely to result in false positive findings in the conserved breast in the first 18 months after radiotherapy.

Contralateral breast cancer

Patients treated for early breast cancer are also at increased risk of developing a cancer in the other breast, compared to women without breast cancer. The risk is estimated to be in the region of just under three per thousand per annum. The current rationale for offering regular mammography to all women treated with breast cancer at least up to the age at which population screening is routinely available, is that earlier diagnosis of a second breast cancer may result in more effective treatment and possibly improved survival. Mammography is the most effective modality for detecting contralateral breast cancers. Ultrasound and MRI are not currently used for routine contralateral breast surveillance.

Ductal Carcinoma in Situ (DCIS)

Patients treated for DCIS are at risk of local recurrence and also at increased risk of developing a new primary invasive breast cancer in either breast. The risk of local recurrence is determined by factors including the grade of the DCIS and the use of radiotherapy, following breast conserving surgery. Mammography is the most effective modality for detecting DCIS. Ultrasound is not effective for detection of DCIS and MRI is currently not used for routine surveillance after treatment for DCIS.

Recommendations

- Offer annual mammography to all patients with early breast cancer, including DCIS, until they enter the NHSBSP/BTWSP. Patients diagnosed with early breast cancer who are already eligible for screening should have annual mammography for 5 years.

Qualifying statement: This recommendation is based on evidence from observational studies and GDG consensus.

- On reaching the NHSBSP/BTWSP screening age or after 5 years of annual mammography follow-up we recommend the NHSBSP/BTWSP stratify screening frequency in line with patient risk category.

Qualifying statement: This recommendation is based on evidence from observational studies, and GDG consensus that these patients are at a risk of recurrence and at higher risk of new primaries than other patients in the NHSBSP/BTWSP, and of at least equivalent risk as patients at a higher risk as a result of their family history.

- Do not offer mammography of the ipsilateral soft tissues after mastectomy.

Qualifying statement: This recommendation is based on evidence from observational studies

- Do not offer ultrasound or MRI for routine post-treatment surveillance in patients who have been treated for early invasive breast cancer or DCIS.

Qualifying statement: There is insufficient evidence to support the routine use of ultrasound or MRI imaging modalities in post-treatment surveillance.

Clinical Evidence

Invasive breast cancer

Evidence from three systematic reviews of observational studies does not confirm that routine follow-up mammography directly improves survival in patients treated for breast cancer, even though one included observational study is suggestive of improved 5 year survival for patients in whom ipsilateral recurrence is detected by mammography (McGahan and Noorani, 2000; Temple *et al.,* 1999; Grunfeld *et al,.* 2002 and Montogomery *et al.,* 2007).

Evidence from one RCT suggests that in the first 18 months of follow-up, further tests prompted by mammography are more frequent in patients treated initially with breast conserving surgery plus radiotherapy compared to patients who received breast conserving surgery alone (Holli *et al.,* 1998).

Estimates of the proportion of cases of recurrent breast cancer that are detected first by follow-up mammography come from observational studies, but there is wide variation. Two systematic reviews of observational studies summarise this proportion. For ipsilateral local recurrence, the proportion detected first by follow-up mammography had a range of 8%-50% (Grunfeld *et al.,* 2002 and McGahan and Noorani 2000) and median values of 26% (McGahan and Noorani, 2000) and 27% (Grunfeld *et al.,* 2002). For contralateral breast cancer, the proportion detected first by follow-up mammography had a range of 8%-80% (Grunfeld *et al.,* 2002 and McGahan and Noorani, 2000) and median values of 36% (McGahan and Noorani, 2000) and 45% (Grunfeld *et al.,* 2002).

Evidence from a systematic review of observational studies suggests that the sensitivity of mammography in detecting ipsilateral local recurrence has a range of 38%-74% and a specificity of 39%-60%. Sensitivity and specificity for the detection of contralateral breast cancer was provided for physical examination plus mammography combined, with sensitivity (range) 81%-88% and specificity (range) 96.5%-99.9% (Temple *et al.,* 1999).

Evidence on the role of MRI in the follow-up of patients treated for breast cancer comes from observational studies and suggests that the sensitivity and specificity of MRI in detecting locally recurrent breast cancer are potentially high. In severn diagnostic studies of follow-up MRI, sensitivity had a range of 85.7%-100%. Specificity had a range of 82%-100% (Aichinger *et al.,* 2002; Bone *et al.,* 1995; Buthiau *et al.,* 1995; Coulthard *et al.,* 1999; Heywangkobrunner *et al.,* 1993; Preda *et al.,* 2006 and Viehweg *et al.,* 1998). Follow-up MRI can detect multifocal tumours, multicentric tumours and DCIS (Bone *et al.,* 1995) and also incidental breast cancer tumours in the contralateral breast in patients treated for breast cancer but in whom the contralateral is clinically and mammographically asymptomatic (Liberman *et al.,* 2003). There is some evidence that follow-up MRI has higher diagnostic performance when the interval from radiotherapy to MRI is longer (Heywangkobrunner *et al.,* 1993 and Viehweg *et al.,* 1998).

Evidence on the role of ultrasound in the follow-up of patients treated for breast cancer comes from observational studies and shows the sensitivity of ultrasound in detecting locally recurrent breast cancer had a range of 70.6%-90.9% and specificity had a range of 82%-98.3%.

DCIS

A very small volume of poor quality evidence was identified on follow-up mammography in patients treated initially for DCIS, in two retrospective studies (Liberman *et al.,* 1997 and Weng *et al.,* 2000). These two studies suggest that follow-up mammography is able to detect locally recurrent breast cancer in some patients treated initially for DCIS.

Health Economic Evaluation

A joint literature review was conducted to assess (a) the cost effectiveness of breast imaging modalities (mammography, ultrasound, MRI, mammoscintigraphy positron emission tomography (PET) and CT) in the follow-up of patients with invasive breast cancer, and (b), to assess

Health Economic Evaluation (cont.)

the cost effectiveness of mammography, ultrasound and MRI in the follow-up of patients with DCIS. From 347 references initially identified through the search, 333 were excluded on the grounds of the title and abstract, and 14 references were considered further. All the retrieved papers were finally excluded: 4 studies did not include an economic analysis (Emens *et al.,* 2003; Grilli, 1995; Khandekar, 1996; Sakorafas *et al.,* 2000), 1 did not consider the relevant PICO question (Mould, 2004), 3 did not consider the relevant PICO interventions (Coleman *et al.,* 1990; Mapelli *et al.,* 1995 and Schapira *et al.,* 1991), 1 did not consider the relevant PICO comparator (Mandelblatt *et al.,* 2006) and 1 was written in a foreign language (Lamy *et al.,* 2005). Therefore, no evidence was available to assess the cost effectiveness of breast imaging modalities in the follow-up of invasive breast cancer patients and in patients with DCIS, so no further economic modelling was undertaken.

Research recommendation

- For patients who have been treated for early invasive breast cancer or ductal carcinoma in situ (DCIS), what is the optimal frequency and length of surveillance of follow-up mammography?

9.3 Clinical Follow-up

Currently not all patients have the choice of where their clinical follow-up takes place. Given choice, some women will opt for follow-up in primary care, others for follow-up in secondary care, or even a shared system. It is important that choice, as with other treatment decisions, is explored and patient preferences respected.

Clinical follow-up (hospital based)

The follow-up of breast cancer patients has been a topic of controversy for many years and each breast unit has had to formally develop follow-up policies as part of cancer guidance. These policies will have been agreed with primary care in some cases but all will have been agreed across cancer networks. Although, as noted above, the rationale for early detection of local recurrence is that treatment may be more effective and there may be a survival benefit, there is no robust evidence that follow-up in any specific setting reduces the rate of recurrence or improves survival.

In the hospital setting patients are able to undergo clinical and radiological review, prosthetic follow-up, supportive care and review of treatment plans particularly where adjuvant therapies are prolonged or sequential.

Where breast care nurse specialists are now holding breast care clinics patients also have the advantage of seeing the same person. Some patients may gain considerable reassurance from being reviewed in a specialist setting with healthcare professionals who have been responsible for their care from the beginning.

Clinical follow-up (General Practice (GP) based)

An average practice of 10,000 patients will have around 23 registered patients who consult their GP regarding their breast cancer each year. Most GPs wish to provide follow-up for their patients with breast cancer if their concerns about increased workload can be met, if clear guidelines for follow-up can be given, and if assurances are given that patients will be seen urgently by the specialist on an open access basis. The quality outcome framework [QOF] part of the GP contract 2003[1] requires GPs to produce a register of cancer patients and to document a review of patients within 6 months of confirmed diagnosis. The review includes an assessment of support needs and co-ordination of arrangements with secondary care. Fully computerised problem based records are almost universal in primary care and greatly facilitate this process.

[1] www.rcgp.org.uk

GP follow-up of women with breast cancer in remission is not associated with increase in time to diagnosis of recurrence, increase in anxiety, or deterioration in health related quality of life. Most recurrences are detected by women as interval events and present to the GP,irrespective of continuing hospital follow-up. GPs should be well placed to provide continuity of care within the patients' socioeconomic background and taking account of other comorbidities.

Studies have shown no difference in outcome of patients followed up in GP practice or in the hospital setting. NICE guidance (NICE 2002) advised that breast cancer patients should be followed up in hospital setting for a minimum of 3 years. Some units, however, according to local policy continue to review patients in the hospital-based setting, after this time for clinical and mammographic surveillance.

Recommendations

- After completion of adjuvant treatment (including chemotherapy, and/or radiotherapy where indicated) for early breast cancer, discuss with patients where they would like follow-up to be undertaken. They may choose to receive follow-up care in primary, secondary, or shared care.
- Patients treated for breast cancer should have an agreed, written care plan, which should be recorded by a named healthcare professional (or professionals), a copy sent to the GP and a personal copy given to the patient. This plan should include:
  - designated named healthcare professionals
  - dates for review of any adjuvant therapy
  - details of surveillance mammography
  - signs and symptoms to look for and seek advice on
  - contact details for immediate referral to specialist care, and
  - contact details for support services, for example support for patients with lymphoedema.

Qualifying statement: These recommendations are based on GDG consensus in the absence of any good quality data

Clinical Evidence

There is a reasonable volume of evidence available that is related to follow-up of patients with breast cancer. A systematic review of mixed study design (Collins *et al.,* 2004) found that most patients expressed a preference for attending regular follow-up sessions, even when asymptomatic. Although patients reported that the anticipation of attending these routine sessions provoked anxiety, reduced fear of recurrence and less physical and psychological distress was experienced after attending their routine visit. A report on follow-up of a UK breast cancer charity focus group (Breakthrough Breast Cancer, 2007) concluded that patients should be given the information and support they need if they want to consider opting out of follow-up care.

With respect to optimal frequency of follow-up, one systematic review of RCTs concluded that the available trials are unable to indicate an ideal frequency of follow-up (Montgomery *et al.,* 2007). However the review cited trials that suggest detection of recurrence is not affected by 3 monthly versus 6 monthly follow up, nor by scheduled follow-up versus that available to patients on demand.

A Cochrane review (Rojas *et al.,* 2000) found no statistically significant difference in 5 year overall survival arising from routine follow-up versus intensive (increased frequency and testing) follow-up regimens.

Clinical Evidence (cont.)

With respect to evidence about where follow-up should take place and who should perform follow-up, one systematic reviews of RCTs concluded that traditional routine clinic visits are an inefficient method of safeguarding against recurrent disease. No difference in either total recurrences detected in hospital, versus by the GP was reported, or in serious clinical events, or total number of deaths (Montgomery *et al.,* 2007). There was also no evidence for a difference in either the total number of recurrences detected, or overall survival, when follow-up is performed by a doctor, compared to a breast care nurse specialist (Montgomery *et al.,* 2007). RCT evidence indicated that satisfaction is higher in patients followed up by nurses than in those followed up by doctors, but that quality of life is similar.

Evidence from qualiatative studies also provided insight into the topic of effective follow-up care for patients who had been treated for breast cancer. These studies broadly described that checking for recurrence offering reassurance and providing information were key elements required in follow up care (Adewuyi-Dalton *et al.,* 1998; Beaver *et al.,* 2005; Jiwa *et al.,* 2006; Kelly *et al.,* 2006; Renton *et al.,* 2002 and Vanhuyse *et al.,* 2007).

Health Economic Evaluation

The GDG did not consider this topic as a health economic priority; therefore the cost effectiveness literature on this topic has not been reviewed.

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Appendix 1

Adjuvant! Online: review of evidence concerning its validity, and other considerations relating to its use in the NHS

A report by Jonathan Gribbin & Robyn Dewis

Introduction

The Guideline Development Group (GDG) for early and locally advanced breast cancer proposed a piece of work to assess the validity of Adjuvant! Online as a tool to assist with clinical decisions, about adjuvant therapy, in patients with early invasive breast cancer. This document summarises the methodology used to assess this, and the key findings including a description of the Adjuvant! Online product, the methods used to develop it, and commercial issues associated with recommending its use.

Adjuvant! Online can be accessed at www.adjuvantonline.com. It is a tool for assessing the risks of an individual patient developing recurrent disease and/or dying within 10 years, when receiving specific treatment (on the basis of well validated factors such as age, menopausal status, oestrogen receptor (ER) status, number of involved axillary lymph nodes etc.). Doctor and patient can use the tool together to decide on the most appropriate adjuvant treatment regimen (chemotherapy, endocrine therapy, or none). Adjuvant! Online is a decision aid and does not direct towards a specific treatment regimen.

This appraisal has been proposed as an alternative to a question that had been framed in the PICO question 'What are the indications for adjuvant chemotherapy in patients with early invasive breast cancer?'. The GDG agreed that this PICO question covered huge topic areas and would need to be addressed using a very long list of search terms which the group were unable to specify satisfactorily.

Noting that Adjuvant! Online is already in use in the UK and is designed to incorporate the Oxford Overview meta-analyses, an alternative, pragmatic approach was proposed, namely of undertaking an appraisal of evidence about the validity of Adjuvant! Online. Two SpR/SpTs providing support to the GDG were asked to undertake this appraisal by reviewing what is known about the tool. The following represents their understanding of the research question, and the approach they took in addressing it.

Research question

The primary purpose of the appraisal was to summarise and critique what is known about Adjuvant! Online, and its validity as a tool for supporting clinical decisions about adjuvant chemotherapy, in UK patients, with early invasive breast cancer. Where it exists, evidence regarding its usefulness is also included.

This is a narrative report incorporating a formally referenced review of the published literature, together with other information provided by Adjuvant!. It addresses:

- A description of Adjuvant! Online: its intended purpose and use
- Current usage in the NHS
- Methodology underpinning Adjuvant! Online, including how it was developed and how it is updated.
- Any caveats/issues/known shortcomings highlighted to Adjuvant! Online users

- An appraisal of published evidence about Adjuvant! Online's validity
- An appraisal of any published evidence regarding its usefulness
- General assumptions/issues/uncertainties in applying this tool based on USA data to NHS patients
- Commercial considerations – implications for Adjuvant! Online's validity and/or practical use
- Licensing considerations – implications for unrestricted access to Adjuvant! Online
- Any other practical considerations relating to Adjuvant! Online's use in the NHS.

Specific questions raised by GDG members that were included within the appraisal

1. To what extent does the SEER database on which the tool is based consider adverse reactions?
2. What is the applicability of the USA data in the SEER database to UK patients in the NHS?
3. What commercial relationships underpin the design and maintenance of the system?
4. Are there any current/future licensing considerations for NHS users?
5. What are the key practical considerations relating to its use?

Excluded from the appraisal

The decision about which chemotherapy or endocrine therapy regimen to recommend are separate questions, which fall outside the scope of this appraisal. This appraisal focuses on the validity of the Adjuvant! Online tool itself.

This approach highlights issues relating to major assumptions inherent in the methodology which are apparent from a consideration of Adjuvant! Online's methodology and the published literature. However, it does not provide a systematic, exhaustive breakdown of all the individual factors, algorithms and statistical models on which the Adjuvant! Online model may be based (except where these are appraised in the published literature). Similarly, this relatively short piece of work is not intended to be a critical appraisal of the Oxford Overviews (whose meta-analyses are fundamental to Adjuvant! Online).

Search strategy

Sources

The Ovid search engine was used to interrogate MEDLINE database (1950 to October 2007) and EMBASE. A subsequent search was also made against SIGLE for relevant grey literature.

Search parameters

A pilot search experimented with a number of synonyms for Adjuvant! Online. The final definitive search was executed using the following search criteria (Table A1.1) and the above source.

Search	Criteria applied	Date run	Result
1	Breast neoplasm$ or breast cancer$ And (decision making or computer assisted or computer$ or decision support or decision support systems or software or decision support techniques) And (adjuvant$)	15/10/07	615 papers

Table A1.1 Parameters and logic used in the automated search

Further screening and supplementary information

The results of the automated search were manually screened, by reading the abstracts, in order to identify relevant articles and to exclude all other papers that were not reporting research into Adjuvant! Online or similar decision support tools.

Adjuvant Inc. was invited to respond directly to specific questions that the literature does not address. These responses are incorporated in the findings.

Search results

Executing the automated search strategy resulted in the identification of 615 papers satisfying the search parameters. Manual screening of abstracts resulted in the exclusion of all but 9 of these papers. Excluded papers included studies of specific treatments, risk communication and other methods of displaying outcomes for example prognostic tables.

Findings

Adjuvant! Online tool

The purpose of Adjuvant! Online is to assist healthcare professionals and patients with early stage breast cancer to discuss the risks and benefits of adjuvant therapy after surgery. It does this by presenting estimates of the risk of cancer-related mortality or relapse, which can be used in consultations. It is intended to be operated and interpreted by oncologists and suitably qualified healthcare professionals. It is not intended to replace clinical judgement and is not designed to be used by patients alone.

Conceptual design

The concept behind Adjuvant! Online is that the quality of decision-making about adjuvant therapy is enhanced in consultations where clinicians can communicate to patients the net benefit of various adjuvant therapies (Ravdin *et al.,* 2001). Therefore Adjuvant! Online is designed to:

1. Estimate the 'baseline' risk of mortality or relapse for patients without adjuvant therapy
2. Estimate the proportion of negative events that given therapies are known to prevent
3. Epply this effect to the baseline risk so that direct comparisons can be made of the estimated risks of mortality or relapse between treatments and with no treatment.

User functionality

The current version of Adjuvant! is version 8. User functionality comprises facilities to:

1. Enter patient information including age, comorbidities plus tumour information including size, oestrogen receptor status and number of involved lymph nodes. This is used to estimate risk at 10 years of breast cancer related death or relapse without additional therapy
2. Display information about the efficacy of different therapy options, with the option of over-riding the estimated efficacies
3. Derive estimates of risk at 10 years of breast cancer related death or relapse for the treatments selected by the user
4. Print results, access on-line help and links to sources of evidence.

Underlying this user functionality there are tables and algorithms, which aim to encapsulate evidence of effectiveness according to the Oxford Overviews. These are maintained by Adjuvant! Inc. User access to these is limited to that described above.

User access to Adjuvant! Online is controlled via a logon screen requiring a username and password. Registration for a username and password is open to users willing to sign a license agreement. In doing so they agree that they are a suitably qualified medical professional. There is no additional authentication of this at registration.

Technological implementation

Users access Adjuvant! Online via a desktop browser with an Internet connection to www.adjuvantonline.com. User functionality is implemented in a Java-based program which is only present for the duration of the user's session. Some functionality also requires Adobe Acrobat and/or a printer. The server functionality runs under a Unix operating system. No patient identifiers are entered into Adjuvant! Online, thereby avoiding any risk or concern relating to patient confidentiality.

Further evaluation of the physical implementation is beyond the scope of this study.

There are also versions of Adjuvant! Online designed to run on Palmtop or PocketPC. These are also beyond the scope of this study.

Control and licensing

Adjuvant! Online is owned by a US-based company called Adjuvant Inc. Adjuvant Inc. and all IP rights in the Adjuvant! Online tool are owned by Dr Ravdin, who has created and developed the tool over a period of more than 10 years. Dr Ravdin's stated motivation is academic; the venture has not been for the purpose of realising financial profit (Ravdin, 2008).

Over the years, funding has been secured from government, industry and research foundations. None of these sources of funding exercise editorial purview over the content of releases. Adjuvant! Online carries no advertising and there are no other sources of revenue.

Licenses to use Adjuvant! Online are free of charge. Dr Ravdin states they will remain free of charge indefinitely; there is no plan to charge a license fee either now or in the long term (Ravdin, 2008).

Maintenance and development

Maintenance of functionality in the current version of the tool is undertaken by Adjuvant! Inc., which secures part-time or occasional assistance from a small group of relevant specialists.

Help files are updated to reflect the current literature. The user functionality and underlying methodology is updated less frequently; recent versions of the tool have incorporated only minor changes.

The direction and timing of these developments is determined by Dr Ravdin, according to the publication of new evidence, requests from users, and the availability of personnel to implement the changes. In the past, new versions have been released around the time of major research meetings, for example ASCO, San Antonio Breast Cancer Symposium.

Currently efforts are focussed on developing the next major release of Adjuvant! Online, which will incorporate recent trial evidence relating to human epidermal growth factor receptor 2 (HER2) and trastuzumab. Beyond this, there is no formally documented plan describing the development path for the product.

Users are not required to undertake any maintenance.

Current usage in the NHS

Dr Ravdin reports that there were 2,978 registered active users in the UK as at July 2007 (which represents about 7% of the total registered user base of more than 42,000). This is based on information supplied at registration which is not authenticated.

Estimates of frequency of usage are derived from the number of Adjuvant! Online sessions that ran in a given period of time. In the first six months of 2007 the Adjuvant! Online platform delivered 110,800 user sessions. Based on the crude assumption that frequency of usage is the same across all users, this represents an estimated 8,000 user sessions in the same period for users registered in the UK. It is not possible to determine how many of these sessions supported actual consultations with NHS patients.

A survey of usage amongst oncologists in the UK is planned but will not report before July 2008 at the earliest (Agarwal, 2008).

Underlying methodology - derivation of baseline risk estimate

Population

The data used for the baseline risk estimate was derived from the SEER database (Surveillance, Epidemiology and End Results Program in the USA) (US National Cancer Institute). Adjuvant! Online was based upon database 9 which covered 14% of the US population (Warren *et al.,* 2002). Detailed information was not available on the breakdown for the SEER 9 population but studies have assessed its similarity to the US population:

1. The SEER population is similar to the US population in terms of age and sex distribution. The US population has a larger percentage of the population in the under 55 age groups and fewer in the over 55 age groups, when compared to the population of England and Wales (Office of National Statistics).
2. The SEER population over represents certain ethnic groups, for example Native American/ Hawaiian and some South East Asian groups compared to the US population. This is related to the States that are included in the database e.g. Alaska and Hawaii (US National Cancer Institute).
3. The ethnic mix of the US population differs from that of England and Wales. Only broad categories can be considered due to differences in categorising ethnicity, but broadly speaking in the US there are lower percentages of white and mixed races, with higher percentages of black and other races (US National Cancer Institute)
4. Socioeconomic data in the SEER database is of poor quality.
5. Date and cause of death are recorded. Date of death is considered robust, however cause of death is of poor quality (Warren et al., 2002).

As survival is analysed in terms of age group the differences in the age of the population is unlikely to affect the generaliseability of the data. The difference in ethnicity, however, is likely to affect this. The incidence of breast cancer is highest in the white population, but mortality is highest in the black population. A program based on this data, that does not take ethnicity into account, will tend to overestimate survival in the black population and underestimate in the white. It is difficult to assess what effect this would have on other ethnic groups or to know if survival differs in these ethnic groups in the United Kingdom.

Selection

Ravdin *et al.* (2001) selected a population from the SEER database for the development of Adjuvant!. Women who met the following criteria were included in the calculations of baseline risk:

1. Had invasive, unilateral and non-inflammatory breast cancer
2. Had received definitive surgery and axillary staging with at least 6 lymph nodes
3. Had data on tumour size, number of lymph nodes sampled and the number of positive lymph nodes.

Women were specifically excluded from the calculations of baseline risk for the following reasons:

1. Those aged under 35 years. This group of young women were observed to have a worse prognosis than the other age groups. (A correction applied to allow for this group of women is described below.)
2. Those aged over 59 years. This group of women was believed to be healthier and have better access to health care. Analysis of this group revealed that women with breast cancer appeared to have better survival than the general US population of the same age.

Survival

The SEER data were then used to calculate survival. This was observed survival for 5 years that was then extrapolated to 10 years, as the data were insufficient to cover this period. Relative survival was used, which makes an adjustment for age specific death rates from other causes.

This survival estimate is based upon the tumour size, the number of positive lymph nodes and the oestrogen receptor status of the tumour. There are some assumptions made in calculating survival for Adjuvant! Online.

1. Impact of ER status. There were data issues around ER status that led to estimates inconsistent with what would be expected from the literature. For this reason a relative risk of 1.3 was applied to predict survival in ER-positive and negative individuals (based on evidence from long-term studies of lymph node-negative patients).
2. The effect of stage of tumour and adjuvant therapy received. An assumption was made that a percentage of the population would have received adjuvant therapy. In order to find the 'baseline risk', the survival without the use of adjuvant therapy, it was assumed that at stage one the adjuvant therapy would have improved outcomes by 15% and at all other stages by 30%.
3. Constant hazard. Survival calculations assume that the risk of death/recurrence remain constant throughout the study period considered.

Relapse

The SEER database does not hold information on relapse of disease. An assumption is made that, on average, individuals survive for three years after relapse of breast cancer in order to calculate the risk of relapse.

Other issues with UK/US comparisons

Other differences between the US and UK population were also considered. There is a lack of universal access to healthcare in the US, which may affect the survival of certain groups within the US. However, individuals' data were only entered into the study when they had received initial surgery and staging and so should not affect applicability to the UK population. There are also differences in attitudes towards healthcare between the two countries, for example the UK population tend to choose less radical surgery than the US population (Locker *et al.,* 2004). Although this may lead to differences in decisions made when using the tool it does not affects its validity for the UK.

Estimating negative outcomes averted

Adjuvant! Online applies an estimation of negative outcomes averted to the baseline survival to give an estimation of survival following one or more adjuvant therapies (Ravdin *et al.,* 2001). Estimation of negative outcomes averted is quantified in terms of the proportion risk reduction (PRR), i.e. the proportion of the baseline risk, which is reduced by each therapy.

PRR for specific therapies are derived from the Overviews. They are incorporated into Adjuvant! Online to derive estimates of breast cancer specific mortality. To avoid the possibility of gross error in estimating the breast cancer specific mortality of over 70 year olds (in which group most mortality is probably non-breast cancer specific), Adjuvant! applies the PRR for 50-69 years for women 70 years or older. When the operator is using the tool to model outcomes for patients over 70 years of age, Adjuvant! Online warns the user about the possible effect of this simplifying assumption.

To model the relative value of various chemotherapy regimens Adjuvant! Online groups treatments into three distinct "generations", based on their perceived efficacy and toxicity. Prompts appear on screen at relevant points in the user session with details of the basis on which this grouping has been done. The prompts also outline the key inferences that Adjuvant! Online makes to estimate relative efficacy (for example of a third generation regimen compared to none) and points the user to further information contained in the Help files.

Applying calculation to previous baseline

The Oxford Overviews report the results of clinical trials. Few trials for cancer therapy consider the effect of one treatment against placebo/no treatment. The majority report the risk reduction of using one treatment over another. According to Ravdin *et al.* (2001), the Overviews suggest that treatment effects are independent of other treatment used. Adjuvant! uses this assumption,

through the following formula, to calculate the proportionate risk reduction achieved by the use of a specific adjuvant therapy:

PRR combined therapy = 1– [(1 – PRR therapy 1) x (1 – PRR therapy 2)]

Validation

Since Ravdin *et al.'s* 2001 paper describing the tool and its methodology, there have been two further published studies that assess the validity of the Adjuvant! Online tool. The tool is currently being compared against two further European registers (Ravdin, 2008).

Prospective population-based validation

Olivotto *et al.* (Olivotto *et al.,* 2005) set out to independently validate Adjuvant! Online by comparing the observed 10 year outcome of each of 4083 patients with stage 1 and 2 breast cancer on a British Columbian register with the outcome predicted by Adjuvant! Online.

Taking the cohort as a whole, they found a high degree of agreement between the predicted and observed overall survival and breast cancer specific survival. They also analysed the differences between observed and predicted outcomes for specific subgroups which in most cases were within 2% or not significantly different (at P>0.05).

For patients younger than 35 years of age or with lymphatic or vascular invasion (LVI) Adjuvant! over-estimated the survival. After the operators applied their judgement to adjust for LVI using the prognostic factor impact calculator tool within Adjuvant! (PFIC), the 10 year predictions were no longer significantly different.

The strength of this study is that it provides validation of Adjuvant! Online predictions using an external reference population. The strength of evidence it provides in this assessment is limited by the following factors:

- The study was undertaken on version 5 of Adjuvant! Online
- It is implicit that the operators were very familiar with the tool, and may have included its author. It is not clear whether an "average" operator would achieve the same level of agreement when making adjustments using the prognostic factor impact calculator (PFIC).

In summary, the study provides independent validation of an earlier version of Adjuvant! Online. For women aged 30 to 59 years of age whose adverse prognostic factors are automatically accounted for within the tool, Adjuvant! Online provides reliable predictions of the benefits of adjuvant therapy. The reliability of predictions for other groups depends in part on the knowledge and judgement of the operator in making adjustments using the PFIC.

It should be noted that more recent versions of Adjuvant! Online incorporate an adjustment to "correct" the overestimation of survival for young ER-positive patients (Ravdin, 2008).

Clinician-based validation

Loprinzi *et al.* (2001) describe the development of an algorithm to calculate 10-year outcomes for breast cancer patients. As part of this, they asked 11 US oncologists for their estimates of 10-year disease-free survival. The mean of these estimates were compared to predictions generated by Adjuvant! Online. The degree of correlation was not measured formally; the graphical representation of the correlation suggests a reasonable degree of agreement.

These published data provides weak evidence for the validity of Adjuvant! Online. However, the fact that the predictions of oncologists vary supports the rationale that there is a need for a tool, which provides evidence-based predictions in an understandable format.

Impact and usefulness

The purpose of Adjuvant! Online is to provide predictions of risk that support dialogue between clinician and patient about the most appropriate adjuvant therapies for that patient. There is little published literature evaluating the impact of Adjuvant! on these interactions, nor on the degree to which clinicians correctly handle the tool or what meaning patients ascribe to the predictions. A USA study (Siminoff *et al.,* 2006) of the effects on treatment choices of

Adjuvant! Online compared to well presented information pamphlets did not find statistically significant differences between the groups. After adjusting for disease-related and socio-demographic confounders, they found that those who used Adjuvant! Online were less likely to choose adjuvant treatment (OR 0.32 95%CI 0.12-0.84). This is broadly consistent with the findings of an apparently related study (Peele *et al.,* 2005).

A study of 102 treatment management decisions in a Hong Kong oncology centre (Epstein *et al.,* 2006) found that clinicians changed their decision in 13 instances after taking into consideration the predictions made by Adjuvant! Online. Based on analysis of this decision-making, Adjuvant! Online's impact was attributed to: the distinction it makes between the marginal benefits of intervention compared to prognosis per se, the deeper consideration of therapeutic goals and costs for individuals which it enables, a comparison of the relative benefits of different treatments, the quantification of iatrogenic risks. The study found that treatment decisions continued to be strongly influenced by factors *omitted* from the version of Adjuvant! Online used in the study (for example lymphovascular invasion and HER2 expression). Clinicians in this study tended to ignore the adjustments to risk recommended by the programme on the basis of low tumour grade when these adjustments were perceived to conflict with other indicators such as lymph node-positivity. Clinicians' attitudes to the utility of Adjuvant! Online were varied but the study authors formed the impression that, in the context of case discussions, the tool enabled groups to achieve consensus more quickly.

There is a body of literature concerning the impact of *other* decision tools on a range of patient-clinician interactions. For example, a systematic review (O'Connor *et al.,* 1999) of 17 RCTs did not show a consistent impact on patient knowledge and satisfaction. More recently, there has been at least one trial to evaluate the effect of a decision support tool on the knowledge and satisfaction of breast cancer patients in particular (Whelan *et al.,* 2003). A full review of this literature is beyond the scope of this assessment.

Summary/Conclusions

The predictions made by Adjuvant! Online are based on a published methodology, which has been updated periodically as evidence of treatment effectiveness and data on risk factors becomes available.

Help files and published descriptions of the tool make clear some of the assumptions and limitations that underpin the methodology. The impact of these individual assumptions is difficult to assess, and beyond the scope of this paper. Adjuvant! Online deals with key uncertainties by alerting the user to them at relevant points.

Survival estimates are derived from a US population. Quantifying the impact on survival of socio-economic background and of ethnic differences between the US and UK populations is difficult.

The strongest evidence of Adjuvant! Online's validity for the UK is derived from comparisons between its predictions and observed outcomes using a Canadian population. This study found its predictions to be reliable for most groups. Since that study, an adjustment has been applied to 'correct' the predictions made for a subset of younger patients.

Further validation is under way using European populations. Dr Ravdin would welcome similar validation against a UK population.

Weaker evidence for its validity includes comparisons of its predictions with the predictions of clinicians. The development path for Adjuvant! Online appears to be consistent with a product which intends to remain evidence-based.

Dr Ravdin's stated intention is that license to use Adjuvant! Online will remain free of charge. This together with its web-based design means that the cost to users of using Adjuvant! Online should remain very low.

There are only two trials assessing the impact of Adjuvant! Online in patient and clinician interactions. These indicate that in a USA setting patients considering adjuvant treatment were less likely to select adjuvant treatment if their consultation involved use of Adjuvant! Online

instead of an information pamphlet. A third study of 102 clinician decisions about patient management found that using Adjuvant! Online resulted in a change of decision in 13 cases, and that clinicians' views of the tool's utility were varied.

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Appendix 2

Algorithms taken from 'Guidance for the management of breast cancer treatment-induced bone loss: A consensus position statement from a UK expert group (2008)'[1]

Algorithm 1: Women who experience premature menopause

The development of a treatment-induced menopause or planned ovarian suppression treatment before the age of 45 years are indications for evaluation of BMD by DXA.

BMD assessments should be done at the lumbar spine and at one or both total hip sites. There is no requirement to obtain a DXA before starting treatment, but a baseline assessment should be obtained within 3 months of commencing ovarian suppression therapy or oophorectomy and within 12 months of developing postchemotherapy amenorrhoea.

Monitoring and treatment thereafter depends on the baseline BMD and the type of any concomitant endocrine treatment. Owing to the very rapid bone loss observed with the use of ovarian suppression therapy plus an aromatase inhibitor, a different threshold for follow-up, monitoring and intervention is recommended.

Any patient with a documented vertebral fragility fracture or previous low trauma hip fracture should receive prophylactic bisphosphonate treatment irrespective of baseline BMD.

For patients who are not receiving a concomitant aromatase inhibitor, three groups of patients are defined based on baseline BMD:

High-Risk Group: Patients with a baseline T-score of <−2 at the lumbar spine or either hip site or whose BMD falls below this threshold should receive bisphosphonate therapy at osteoporosis doses in addition to lifestyle advice, calcium and vitamin D supplementation.

- The choice of bisphosphonate should be based on local protocols and funding arrangements. Weekly oral alendronate 70 mg or risedronate 35 mg, monthly oral ibandronate 150 mg, 3-monthly intravenous ibandronate 3 mg, or 6-monthly intravenous zoledronic acid 4 mg are all considered appropriate.
- Bisphosphonates are contraindicated in patients with a low glomerular filtration rate (<30 ml/min/1.73m²) or hypocalcaemia. Such patients who require bone sparing therapy should be referred to the local bone service. Oral bisphosphonates must be used with caution in patients with oesophageal disease, although intravenous bisphosphonates will usually be appropriate in such patients.
- Follow-up of patients requiring bisphosphonate treatment should include a repeat DXA after 24 months and/or measurement of a bone resorption marker, if desired, as an aid to judging compliance and response. If there is bone loss associated with bisphosphonate therapy, first check that the compliance with instructions is correct, then re-evaluate for secondary osteoporosis. Poor compliance and secondary osteoporosis explain most cases of poor response. However, some patients may be true non-responders and a switch of therapy, for example to an intravenous bisphosphonate, or a referral to the local bone service should be considered in these patients.

Medium-Risk Group: For those patients with a T-score between −1 and −2, lifestyle advice plus calcium (1 g/day) and vitamin D (400–800 IU) supplementation are recommended unless dietary intake of calcium exceeds 1 g/day and serum 25-hydroxyvitamin D is known to be >20 μg/L.

- A follow-up DXA scan should be performed at 24 month intervals to exclude a clinically significant reduction in BMD (T-score of <−2 or >4% per annum decline in BMD at either the spine or hip [the forearm is not suitable for repeat assessments within such timeframes]).
- Patients who exceed these limits should commence bone protection therapy as described in the high-risk group.

Low-Risk Group: For those patients with normal BMD (T-score of >−1), the risk of developing osteoporosis over a 5-year treatment and follow-up period is very low. Advice on lifestyle (diet, weight-bearing exercise, reduced alcohol consumption and cessation of smoking) is sufficient and no specific intervention or follow-up assessment of BMD is required.

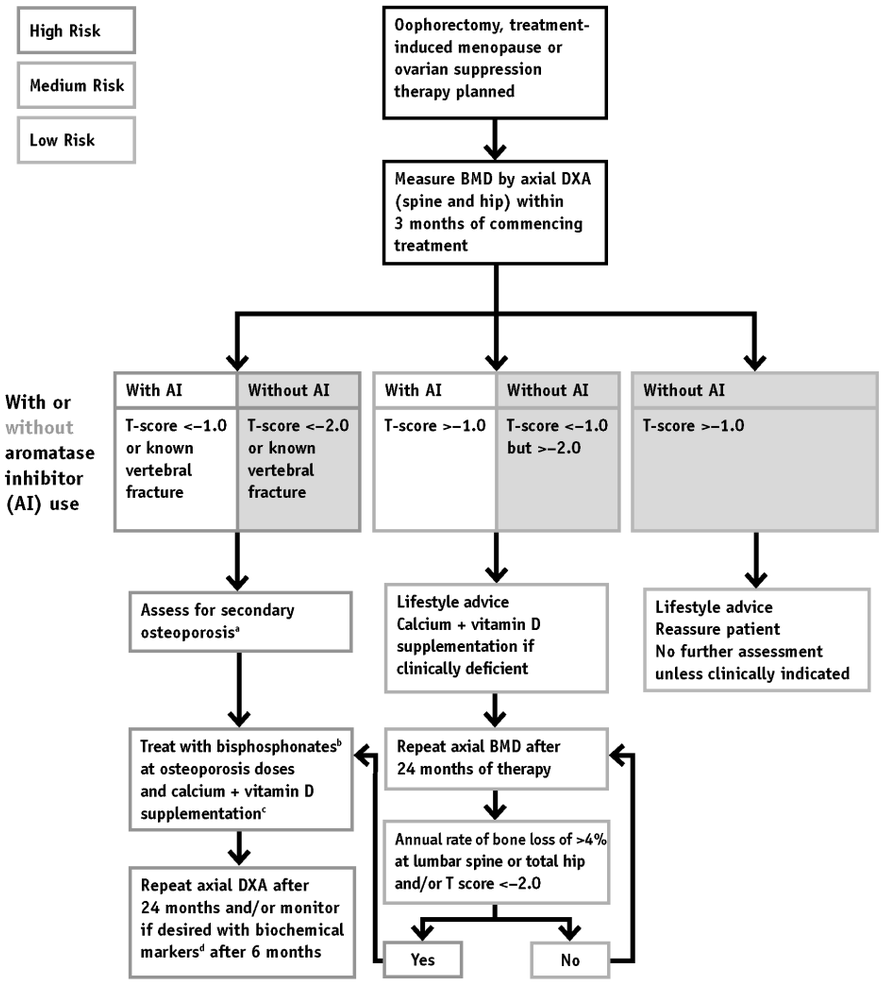
For patients receiving a concomitant aromatase inhibitor, only two groups are defined:

High-Risk Group: Those patients with a T-score of <−1 should receive bone protection therapy with a bisphosphonate as described above.

Medium-Risk Group: Those patients with a T-score of >−1 should be monitored as indicated for all medium-risk groups.

[1] Reprinted from: Cancer Treatment Reviews. Volume 34, Supplement 1. David M. Reid, Julie Doughty, Richard Eastell, Steven D. Heys, Anthony Howell, Eugene V. McCloskey, Trevor Powles, Peter Selby, Robert E. Coleman. Guidance for the management of breast cancer treatment-induced bone-loss: A consensus position statement from a UK Expert Group. Pages S3-S18, Copyright 2008 with permission from Elsevier.

Algorithm 1: Adjuvant treatment associated with ovarian suppression/failure with or without concomitant aromatase inhibitor use in women who experience premature menopause



a ESR, FBC, bone and liver function (calcium, phosphate, alkaline phosphatase, albumin, AST / γGT), serum creatinine, endomysial antibodies, serum thyroid-stimulating hormone

b Alendronate 70 mg per week, risedronate 35 mg per week, ibandronate (150 mg po monthly or 3 mg iv 3-monthly), zoledronic acid 4 mg iv 6-monthly

c To be given as ≥1 g of calcium + ≥800 IU of vitamin D

d Biochemical markers such as serum C-terminal telopeptide of type I collagen or urinary N-telopeptide of type I collagen

Algorithm 2: Postmenopausal women

The use of an aromatase inhibitor (steroidal or non-steroidal) is an indication for evaluation of BMD by DXA.

BMD assessments should be done at the lumbar spine and at one or both total hip sites. There is no requirement to obtain a DXA before starting treatment, but a baseline assessment should be obtained within 3 months of commencing an aromatase inhibitor.

Monitoring and treatment thereafter depends on the baseline BMD, age, and presence of any major risk factors for osteoporotic fracture. These are defined as:

- previous fragility fracture above the age of 50 years;
- parental history of fracture;
- a body mass index (BMI) of <22;
- alcohol consumption of 4 or more units per day;
- diseases known to increase fracture risk such as premature menopause, rheumatoid arthritis;
- ankylosing spondylitis, immobility, and Crohn's disease; and
- prior oral corticosteroid use for more than 6 months.

For women over the age of 75 years with one or more major risk factors, bone protection therapy with a bisphosphonate is recommended irrespective of baseline BMD.

For women aged under 75 years or without major risk factors, three groups of patients are defined based on baseline BMD:

High-Risk Group: Patients with a baseline T-score of <–2 at the lumbar spine or either hip site or whose BMD falls below this threshold should receive bisphosphonate therapy at osteoporosis doses in addition to lifestyle advice, calcium and vitamin D supplementation.

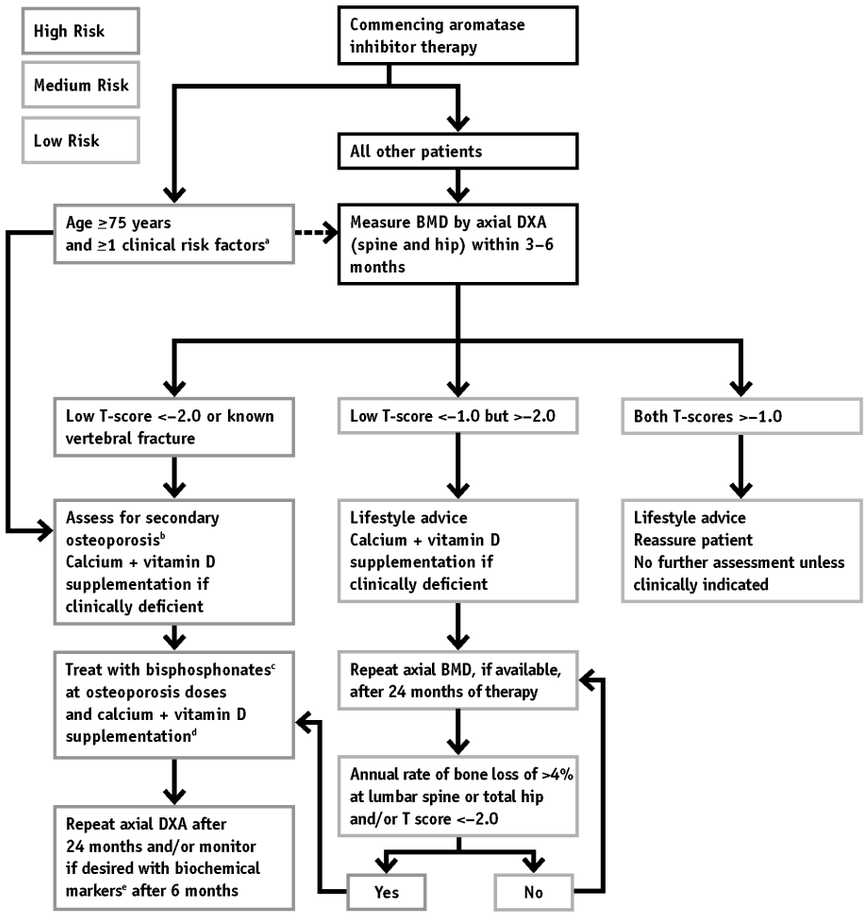
- The choice of bisphosphonate should be based on local protocols and funding arrangements. Weekly oral alendronate 70 mg or risedronate 35 mg, monthly oral ibandronate 150 mg, 3-monthly intravenous ibandronate 3 mg, or 6-monthly intravenous zoledronic acid 4 mg are all considered appropriate.
- Bisphosphonates are contraindicated in patients with a low glomerular filtration rate (<30 ml/min/1.73m²) or hypocalcaemia. Such patients who require bone sparing therapy should be referred to the local bone service. Oral bisphosphonates must be used with caution in patients with oesophageal disease, although intravenous bisphosphonates will usually be appropriate in such patients.
- Follow-up of patients requiring bisphosphonate treatment should include a repeat DXA after 24 months and/or measurement of a bone resorption marker, if desired, as an aid to judging compliance and response. If there is bone loss associated with bisphosphonate therapy, first check that the compliance with instructions is correct, then re-evaluate for secondary osteoporosis. Poor compliance and secondary osteoporosis explain most cases of poor response. However, some patients may be true non-responders and a switch of therapy, for example to an intravenous bisphosphonate, or a referral to the local bone service should be considered in these patients.

Medium-Risk Group: For those patients with a T-score between –1 and –2, lifestyle advice plus calcium (1 g/day) and vitamin D (400–800 IU) supplementation are recommended unless dietary intake of calcium exceeds 1 g/day and serum 25-hydroxyvitamin D is known to be >20 µg/L.

- A follow-up DXA scan should be performed at 24 month intervals to exclude a clinically significant reduction in BMD (T-score of <–2 or >4% per annum decline in BMD at either the spine or hip [the forearm is not suitable for repeat assessments within such timeframes]).
- Patients who exceed these limits should commence bone protection therapy as described in the high-risk group.

Low-Risk Group: For those patients with normal BMD (T-score >–1), the risk of developing osteoporosis over a 5-year treatment period is very low. Advice on lifestyle (diet, weight-bearing exercise, reduced alcohol consumption and cessation of smoking) is sufficient and no specific intervention or follow-up assessment of BMD is required.

Algorithm 2: Postmenopausal adjuvant treatment with aromatase inhibitors



a Previous low-trauma fracture after age 50, parental history of hip fracture, alcohol intake of ≥4 units/day, diseases associated with secondary osteoporosis, prior corticosteroids for >6 months, low BMI (<22)

b ESR, FBC, bone and liver function (calcium, phosphate, alkaline phosphatase, albumin, AST / γGT), serum creatinine, endomysial antibodies, serum thyroid stimulating hormone

c Alendronate 70 mg per week, risedronate 35 mg per week, ibandronate (150 mg po monthly or 3 mg iv 3-monthly), zoledronic acid 4 mg iv 6-monthly

d To be given as ≥1 g of calcium + ≥800 IU of vitamin D

e Biochemical markers such as serum C-terminal telopeptide of type I collagen or urinary N-telopeptide of type I collagen

Appendix 3

A cost effectiveness analysis of pretreatment ultrasound for the staging of the axilla in early breast cancer patients

Introduction

Staging of the ipsilateral axilla of early breast cancer patients to identify the axillary nodal status is essential for deciding what local and systemic treatments are subsequently required. Axillary lymph node dissection (ALND) (also known as axillary node clearance (ANC)) is considered the 'gold standard' procedure to stage the axilla for invasive breast cancer, but is associated with significant complications such as problems with shoulder movement and lymphoedema. Sentinel lymph node biopsy (SLNB) and 4-node sampling (4-NS) are less invasive axillary staging techniques than ANC and have been shown to reduce the complication rate when the lymph nodes are tumour free. For both techniques, the benefit in reduced complications is gained by those patients whose removed lymph nodes are tumour free since further axillary treatment is avoided. However, if the lymph nodes are positive, then further treatment including full axillary lymph node dissection and/or radiotherapy is usually required. At present, there is no entirely reliable technique to identify tumour positive lymph nodes intra-operatively and a second operation on the axilla may be required. It is therefore advisable to identify those patients who can be shown to have involved lymph nodes by preoperative testing wherever possible.

The majority of patients with axillary lymph node disease do not have clinically obvious disease and imaging of the axilla may detect potentially abnormal lymph nodes containing metastatic disease. There is no evidence that axillary findings on imaging alone (ultrasound, computed tomography (CT), scintigraphy, magnetic resonance imaging (MRI) or positron emission tomography (PET)) can be used as the basis for treatment because of significant false negative and false positive results. However, for those patients where imaging suggests nodal involvement, ultrasound-guided needle sampling of abnormal lymph nodes (using fine needle aspiration cytology (FNAC) or core biopsy) has the potential to provide the required definitive cytological or histological proof of a positive result on which to base treatment decisions. Ultrasound and ultrasound-guided needle sampling are routinely available in diagnostic breast clinics and can be used for preoperative staging of the axilla. By offering axillary dissection to those proven preoperatively to have nodal metastases, secondary surgery to the axilla (i.e. SLNB or 4-NS) can be avoided in a significant number of patients. However, because of the low negative predictive values of these techniques, patients with no ultrasound evidence of abnormal lymph nodes or with negative ultrasound-guided needle sampling require surgical staging with SLNB as part of their initial surgical treatment.

Existing Economic Evidence

A systematic review of the evidence regarding the cost effectiveness of pretreatment ultrasound plus needle biopsy in staging early breast cancer patients identified three relevant studies, one full economic evaluation (Brancato *et al.,* 2004) and two partial economic evaluations (Genta *et al.,* 2007 and Davies *et al.,* 2006). Two of these studies were conducted in Italy (Brancato *et al.,* 2004 and Genta *et al.,* 2007) and the third one in USA (Davies *et al.,* 2006). All these studies were cost-consequences analysis, since they reported several health benefit outcomes measured as natural units, mainly the accuracy of the staging procedures and the number of patients avoiding secondary staging with ultrasound plus needle biopsy (among other outcomes). None of the studies estimated the number of quality adjusted life years (QALYs)

gained with each of the staging strategies. The costs associated with the different staging procedures were estimated and reported, either from the perspective of the hospital (Davies *et al.,* 2006), of the healthcare provider (Brancato *et al.,* 2004), or both (Genta *et al.,* 2007). However, no price year was reported in any of the studies. In all the studies some sort of extrapolation and/or assumptions were used to obtain the clinical effectiveness of one or more of the staging procedures compared. All studies concluded that ultrasound plus needle biopsy seemed to be a cost effective staging strategy when compared to SLNB, although none of them stated on what basis they considered cost effectiveness. All three studies identified the potential of ultrasound plus needle biopsy to lead to cost-savings under specific scenarios. As the study by Brancato *et al.* (2004) highlighted, considerable variations exist regarding the costs of the different staging procedures across countries; therefore, it is difficult to generalise the results from country to country. This was confirmed by the differences in the unit costs observed across studies: in the study by Davies et al. (2006) the cost of SLNB was much higher than that of ANC, i.e. $6,300 (£3,895) and $3,700 (£2,287), respectively; on the other hand, the study by Brancato et al. (2007) reported a unit cost of €216 (£156) for SLNB and €1,550 (£1,119) for ANC.

Aim

The aim of this analysis was to assess the cost effectiveness of using pretreatment ultrasound in combination with needle biopsy (i.e. either FNA or core biopsy) when compared to not using pretreatment ultrasound (i.e. SLNB for all early breast cancer patients undergoing staging), to prevent unnecessary surgery (i.e. to reduce the number of early breast cancer patients with positive lymph nodes who would otherwise undergo staging by SLNB) when staging the axilla in early breast cancer patients. The perspective adopted was that of the UK National Health Services (NHS). Other secondary health outcomes were assessed, such as the number of patients with axillary metastasis that would be wrongly identified as having negative lymph nodes and therefore would remain undertreated due to inaccuracies of the staging procedure.

Methods

Study population

The study population considered in the analysis included women with early invasive breast cancer requiring staging of the axilla to identify the appropriate management strategy. Women with locally advanced disease or inflammatory disease, and those having primary systemic therapy were excluded from the analysis.

Interventions

The main intervention of interest was the use of pretreatment ultrasound in combination with needle biopsy, either core biopsy or FNAC, for staging the axilla of early breast cancer patients. The usefulness of pretreatment ultrasound rests on its ability to identify axillary lymph node metastatic involvement at the time of first presentation. Patients shown to have lymph node metastatic disease can then be offered definitive axillary surgery and avoid having two surgical procedures (i.e. SLNB followed by the necessary ANC). If the results of the axillary ultrasound are normal (i.e. do not show axillary involvement) or no lymph nodes are visualised by ultrasound, the patient would be recommended to have further axillary staging, either with SLNB or with 4-NS. If axillary ultrasound is abnormal and biopsy (either by core biopsy or FNAC) confirms malignancy, then the patient would be offered definitive surgery to the axilla, i.e. ANC. The use of this type of staging strategy is rather recent.

Pretreatment ultrasound was compared was SLNB, which is a targeted technique to identify and surgically remove the true sentinel lymph node (SLN), causing minimal disruption to the axillary structures. There are currently 3 techniques in use to identify SLNs: isotope, blue dye and combined isotope and blue dye. When isotope is used, preoperative scintiscanning may also be added as well as intra-operative detection with a hand held probe. The rate of identification of the SLN improves with the dual technique and preoperative scintiscanning and typically exceeds 95% by appropriately trained surgical teams. According to the results of a survey recently conducted in the UK, among those surgeons using SLNB as the type of early breast cancer staging procedure, almost 65% of them chose the combination of blue dye and

radioisotope to perform SLNB (Mansfield *et al.,* 2007). If the SLN cannot be identified the breast team's standard axillary procedure is performed, which is usually 4-NS immediately after SLNB. After SLNB, ANC would be conducted only on those patients with evidence of lymph node involvement based on SLNB results, while patients with negative lymph nodes would not undergo further axillary staging.

Following recommendations of the Guideline Development Group (GDG), palpation alone (as the basis to stage the axilla) was not considered as an alternative comparator for this analysis since palpation is not, in any case, recommended clinical practice. As it has been mentioned before, 'clinical staging alone is insufficient to identify patients at high risk of relapse' (i.e. those with lymph node involvement; Glynne-Jones *et al.,* 1990), since an important percentage of patients with metastatic lymph nodes are inadequately staged (between 25% and 65%; Genta *et al.,* 2007). Similarly, ultrasound alone was not included in the cost effectiveness assessment as it was not considered good clinical practice since the management of the axilla is largely dependent on histological findings in support of imaging and clinical examination.

Structure of the model

The proposed structure for the economic model is presented in Figure A3.1. A decision tree was constructed to represent the staging strategies considered at analysis, and the subsequent immediate consequences following them. The model starts by considering patients with early breast cancer requiring staging of the axilla. As previously reported, there are two staging strategies assessed, which start by undertaking either initial ultrasound or SLNB for all the patients. Independently of the type of staging procedure initially undertaken, patients may actually have axillary metastasis or not. This way of structuring the model allowed using the information about prevalence of nodal metastasis and accuracy of the staging procedures as reported in the systematic reviews of the clinical evidence related to the use of ultrasound plus needle biopsy and SLNB (in terms of their sensitivity and specificity values; Hunink and Glasziou, 2001).

Under the ultrasound plus needle biopsy staging strategy, all patients start by undergoing ultrasound. Patients identified as having suspected metastasis with ultrasound are further investigated with needle biopsy, while those patients that do not have suspected lymph nodes with ultrasound and those with non-visualised lymph nodes with ultrasound will not be further assessed with needle biopsy but will undergo SLNB. After undergoing needle biopsy, patients may be identified as having either positive or negative lymph nodes (i.e. needle biopsy(+) or needle biopsy(-) result). If the needle biopsy result is positive, then the patient undergoes ANC, which is an appropriate procedure if the patient actually has axillary metastasis, although it would be an unnecessary procedure if the patient is truly lymph node-negative. Patients identified as not having suspicious lymph nodes with ultrasound, those with non-visualised lymph nodes and those with a negative result after needle biopsy undergo SLNB (which has been highlighted in the corresponding decision tree arm with an asterisk: *). The results of this further staging procedure can be either positive, in which case the patient undergoes ANC, or negative, in which case no further staging procedure is undertaken. Again, ANC is a necessary procedure if the patient is truly lymph node-positive, while it would be an unnecessary procedure if they do not have nodal metastasis (i.e. truly lymph node-negative). It may also happen that a patient with nodal metastasis is wrongly identified as having negative lymph nodes and therefore no ANC would be undertaken, in which case the patient would remain undertreated.

In the case of the SLNB staging strategy, all patients initially undergo SLNB. SLNB results can be either positive, in which case the patient undergoes ANC, or negative, in which case no further staging procedures is undertaken. Due to the inaccuracy of SLNB, in a few cases some patients with positive lymph nodes may be wrongly identified as lymph node-negative and would remain undertreated. On average, sentinel lymph nodes may not be identified in 3.6% of SLNBs conducted (as identified by the systematic review of the clinical evidence related to SLNB). In these cases, 4-NS would be conducted as part of the same intervention. Given that performing 4-NS under these circumstances will take only a few additional minutes the added cost would be minimal, and it was decided not to differentiate between those SLNB cases with identified sentinel nodes from those who required further 4-NS.

The base-case analysis considered a situation for which the number of false positive patients with needle biopsy and with SLNB was null, although further sensitivity analysis investigated how the results were influenced in case either needle biopsy and/or SLNB lead to few false positive patients (as reported by some studies, such as Podkrajsek *et al.* 2005). Complications related to the staging procedures were excluded from the model. In the case of ultrasound plus needle biopsy, studies report no complications related to this staging procedure (Damera *et al.,* 2003; Nori *et al.,* 2007; Sapino *et al.,* 2003 and van Rijk *et al.,* 2006). In the case of SLNB, although some studies report SLNB-related lymphoedema rates (Mansel *et al.,* 2006), the GDG suggested that the type of complications usually related to SLNB are minor, the rate is small, and the costs incurred to treat them are negligible; consequently they were considered irrelevant for this economic analysis.

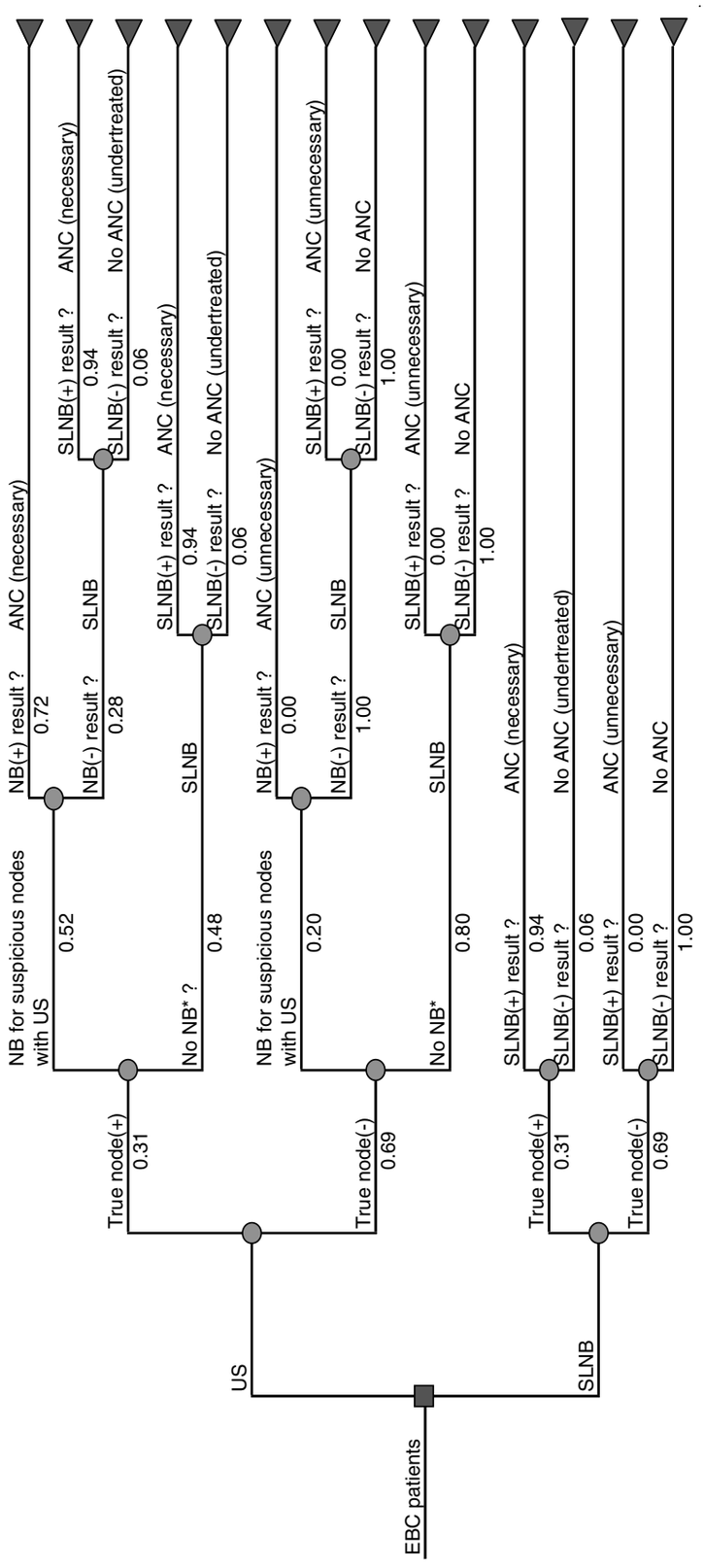


Figure A3.1 Model structure for the cost effectiveness analysis of pretreatment ultrasound plus FNAC compared to SLNB for the staging of the axilla in early breast cancer patients.

Clinical evidence

The clinical evidence required to populate the model was mainly obtained from the systematic reviews conducted within the early breast cancer guideline. A prevalence of axillary metastasis of 31.4% was considered in the model (see Table A3.1). This prevalence included both patients with palpable and with non-palpable lymph nodes, as reported by the systematic review of the clinical evidence on this topic. Further sensitivity analyses considered prevalence values of 25% (corresponding to the prevalence of axillary metastasis among early breast cancer patients identified through screening in UK), 40% (corresponding to the prevalence of axillary metastasis among early breast cancer patients detected clinically for being symptomatic) and a value of 35% (which reflects an approximate average prevalence for axillary metastasis among the patients with early breast cancer in UK, since one third of them are identified through screening and the other two thirds are clinically identified for being symptomatic), as suggested by the GDG.

Mean	Median	Range		Source
31.4	27	18	59	13 studies, including a series of patients with palpable axillary lymph nodes (systematic review of the clinical evidence for SLNB).

Table A3.1 Overall risk of axillary metastasis (%)

The data reported by the systematic review for pretreatment ultrasound identified the sensitivities/false negative rates and the specificities for ultrasound combined with FNAC (altogether) and for SLNB. However, to populate the model as previously explained, accuracy data were required on the proportion of patients identified by ultrasound as having suspicious lymph nodes and the proportion of them that underwent consequently needle biopsy. For this, the studies included in the systematic review of the clinical evidence were again reviewed to identify those assessing the use of ultrasound in combination with FNAC/core biopsy for which the patients who had undergone needle biopsy (either FNAC or core biopsy after being identified as having suspected lymph nodes with ultrasound) were reported. Only studies that considered ultrasound in combination with FNAC/core biopsy were included in this new review. Studies were included if needle biopsy had been conducted only in patients for whom ultrasound had detected a suspicious lesion. Studies were excluded if needle biopsy had been conducted before ultrasound and not afterwards (Dixon *et al.,* 1992 and Walsh *et al.,* 1994) or if needle biopsy had been conducted for all patients, independently of whether a suspicious lesion was detected with ultrasound. A total of five studies were finally included that assessed the accuracy of ultrasound followed by needle biopsy on patients with suspected lymph nodes (Bedrosian *et al.,* 2003; Brancato *et al.,* 2004; Damera *et al.,* 2003; Deurloo *et al.,* 2003 and Podkrajsek *et al.,* 2005). In all the studies a combination of ANC and SLNB (depending on whether the patient had been identified as positive or negative lymph nodes with ultrasound plus FNAC/core biopsy) were used as gold standard. Two of these studies (Brancato *et al.,* 2004 and Damera *et al.,* 2003) included both patients with clinically positive and clinically negative axillary lymph nodes, while the other three studies (Bedrosian *et al.,* 2003; Deurloo *et al.,* 2003 and Podkrajsek *et al.,* 2005) included only patients with clinically negative axillary lymph nodes.

In order to synthesise the data from the studies reporting accuracy of ultrasound and of needle biopsy the latter for patients that had suspected lymph nodes as identified with ultrasound), a meta-analysis was conducted. A simple analysis was undertaken by pooling the estimates of the sensitivity and specificity separately across studies according to the corresponding study sample size by assuming that there was no variation in terms of the diagnostic threshold used across studies (Egger *et al.,* 2001; pg 267). As recommended, the Spearman's test was conducted to test whether the true positive rate and the false positive rate were positively correlated (in which case the method of the weighted averages could not have been used). This test was statistically no significant (Spearman's rho = 0.7000; p = 0.1881), therefore evidence against the null hypothesis that true positive rate and false positive rate were independent was very weak and the pooling of sensitivities and specificities using weighted averages was

considered to be appropriate. The estimated pooled sensitivity and pooled specificity were estimated as follows:

$p = \Sigma y_i / \Sigma n_i$

where *p* represents either the pooled sensitivity or pooled specificity for all the studies,

Σy_i represents the sum of all true positives in the case of the sensitivity or the sum of all true negatives in the case of the specificity, and Σn_i represents either the total number of patients with the disease (if the pooled sensitivity is calculated) or the total number of patients without the disease (if the specificity is the proportion to be pooled). The standard error for the pooled proportion was estimated as follows:

$se(p) = [\, p\,(1-p) / \Sigma n_i \,] \wedge 0.5$

therefore, the 95% confidence intervals (95% CI) were calculated as:

$$(p^-, p^+) \equiv \left(\hat{p} - z\sqrt{\frac{\hat{p}(1-\hat{p})}{n}}, \hat{p} + z\sqrt{\frac{\hat{p}(1-\hat{p})}{n}} \right)$$

The results of the review and the pooled analysis are reported below. From Figure A3.2 to Figure A3.5 and Table A3.2 to Table A3.3 it can be observed that the studies by Bedrosian *et al.* 2003 and Brancato *et al.* (2004) show sensitivities and specificities for ultrasound that seemed to differ considerably when compared to the other three studies. Additionally, the study by Bedrosian *et al.* (2003) also showed a very low sensitivity of FNAC when compared to the other four studies included in the meta-analysis. Therefore, mean and 95% confidence intervals of the pooled results were estimated by including initially all the studies, and excluding these two studies (Bedrosian *et al.,* 2003 and Brancato *et al.,* 2004) in further analysis, either one by one and both together.

The specificity of SLNB was considered to be 100%, following the results of the systematic review of the clinical evidence for this topic, which meant that no false positive rate was identified within the included studies. Sensitivity analyses were conducted to test for specificities lower than 100% for SLNB. On the other hand, SLNB was not 100% accurate in detecting nodal status among those patients with axillary metastasis since around 5.8% of these patients are wrongly identified as being lymph node-negative (i.e. since: sensitivity = 1 – false negative rate (FNR), and FNR = 5.8%, then sensitivity = 94.2%; see 4).

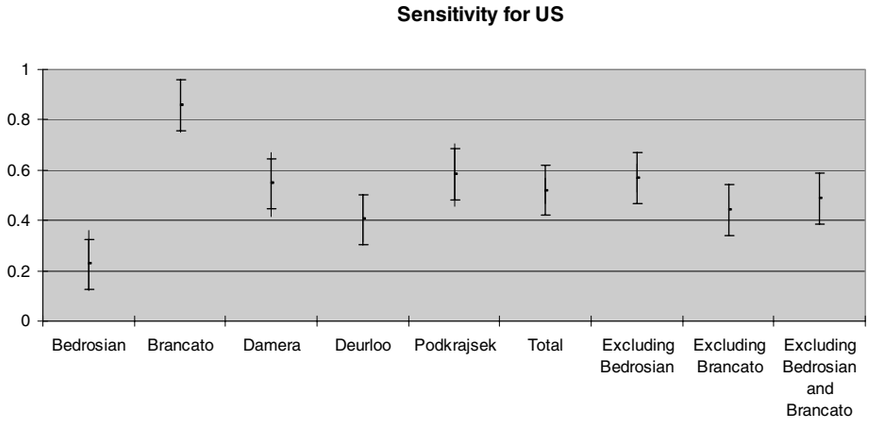


Figure A3.2 Estimates of the sensitivities of US

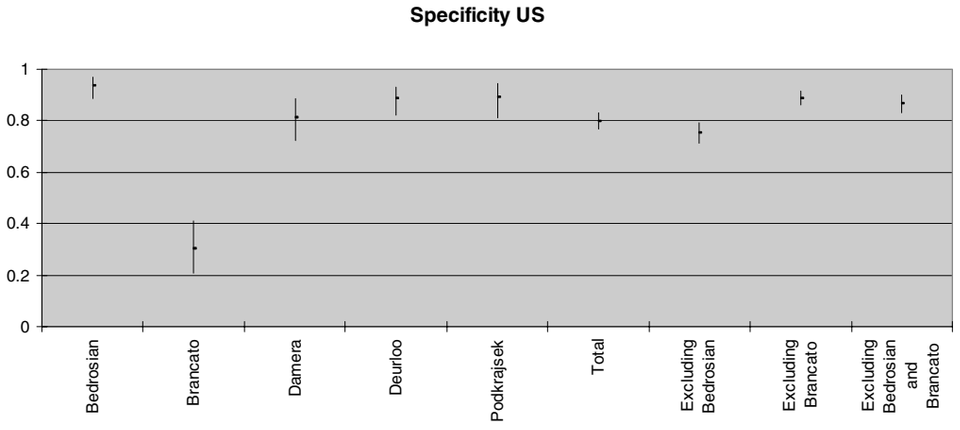


Figure A3.3 Estimates of the specificities of US

	Sensitivity				Specificity			
	Mean	**se**	**95% CI**		**Mean**	**se**	**95% CI**	
Bedrosian	0.2264	0.0290	0.1228	0.3621	0.9355	0.0170	0.8846	0.9686
Brancato	0.8571	0.0278	0.7529	0.9293	0.3034	0.0365	0.2103	0.4099
Damera	0.5469	0.0386	0.4175	0.6718	0.8137	0.0302	0.7245	0.8840
Deurloo	0.4050	0.0300	0.3167	0.4980	0.8844	0.0195	0.8213	0.9312
Podkrajsek	0.5846	0.0384	0.4556	0.7056	0.8900	0.0244	0.8117	0.9438
Total	0.5201	0.0259	0.4694	0.5708	0.7993	0.0164	0.7671	0.8316
Total excluding Bedrosian	0.5688	0.0277	0.5145	0.6230	0.7511	0.0207	0.7106	0.7916
Total excluding Brancato	0.4422	0.0285	0.3863	0.4982	0.8869	0.0141	0.8592	0.9145
Total excluding Bedrosian and Brancato	0.4880	0.0316	0.4260	0.5500	0.8653	0.0183	0.8295	0.9011

se = standard error; 95% CI = 95% confidence interval

Table A3.2 Sensitivities and specificities of US: individual studies and pooled estimates

	Sensitivity				Specificity			
	Mean	se	95% CI		Mean	se	95% CI	
Bedrosian	0.2500	0.0300	0.0549	0.5719	1	-	0.6915	1
Brancato	0.6833	0.0369	0.5504	0.7974	1	-	0.9422	1
Damera	0.7714	0.0326	0.5986	0.8958	1	-	0.8235	1
Deurloo	0.7551	0.0263	0.6113	0.8666	1	-	0.8049	1
Podkrajsek	0.8421	0.0284	0.6875	0.9398	0.9091	0.0224	0.5872	0.9977
Total	0.7216	0.0322	0.6586	0.7847	0.9916	0.0084	0.9752	1
Excluding Bedrosian	0.7527	0.0320	0.6901	0.8154	0.9908	0.0091	0.9729	1
Excluding Brancato	0.7388	0.0379	0.6644	0.8132	0.9825	0.0174	0.9484	1
Excluding Bedrosian and Brancato	0.7869	0.0371	0.7142	0.8596	0.9787	0.0210	0.9375	1

se = standard error; 95% CI = 95% confidence interval

Table A3.3 Sensitivities and specificities of FNA for early breast cancer patients having suspected lymph nodes with US: individual studies and pooled estimates

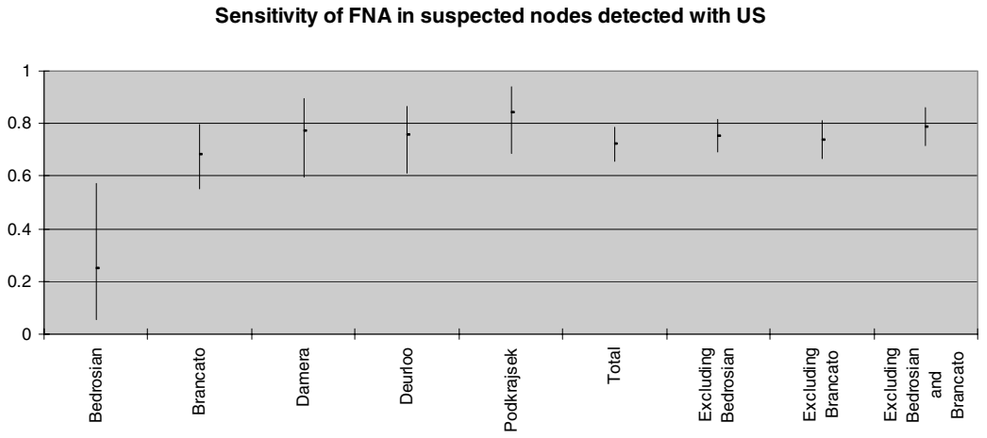


Figure A3.4 Estimates of the sensitivities of FNA for patients having suspicious lymph nodes with US

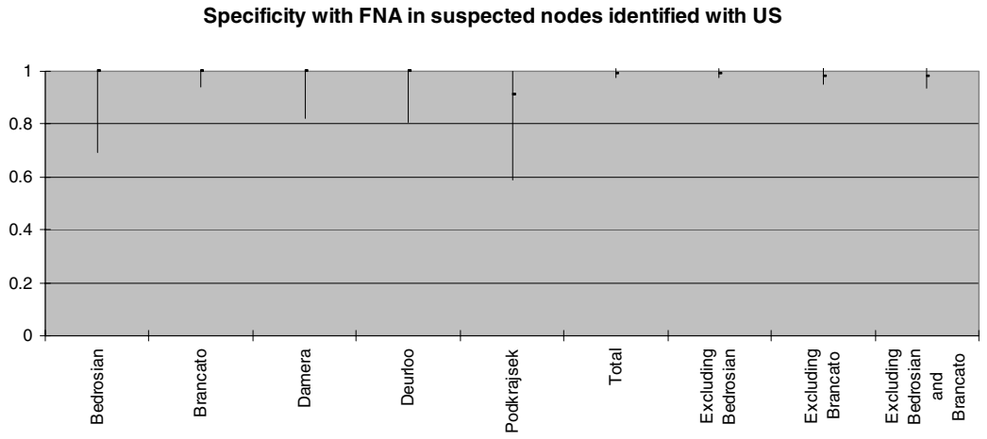


Figure A3.5 Estimates of the specificities of FNA for patients having suspicious lymph nodes with US

	Mean	Median	Range		Source
SLNB FNR (%)	5.8	5.9	0.00	10.70	11 series of patients, 4 were RCTs. Systematic review of SLNB

Table A3.4 Staging performance of SLNB: false negative rates (FNR; %)

A table summarising the probabilities related to the accuracy of the staging procedures that were used in the model is presented below (Table A3.5).

	Mean
US:	
Sensitivity	0.5201
Specificity	0.7993
FNA for suspected lymph nodes with US:	
Sensitivity	0.7216
Specificity	1*
SLNB:	
Sensitivity	0.9420
Specificity	1

* This value was assumed to be one since only one false positive was identified across all the studies included in the review of the accuracy of US+FNA

Table A3.5 Staging performance: probabilities used in the model

No complications were observed in the studies associated with US+FNA/CB (Damera *et al.,* 2003; Nori *et al.,* 2007; Sapino *et al.,* 2003 and van Rijk *et al.,* 2006).

Health benefits

The main health outcome estimated in the analysis was the number of patients that would avoid a secondary staging surgery (i.e. SLNB) by undertaking ultrasound plus needle biopsy as the initial staging strategy. In addition, other secondary health outcomes were estimated for both staging strategies (ultrasound plus needle biopsy and SLNB):

- The number of patients with axillary metastasis that would undergo necessary ANC
- The number of patients with axillary metastasis that would be left undertreated (i.e. who would not undergo ANC) for been misidentified as having negative lymph nodes
- The number of patients with negative lymph nodes that would undergo unnecessary ANC (this variable was mainly estimated for the sensitivity analyses since the specificity values considered in the base-case analysis were equal to 1, which means that all patients with negative lymph nodes would be identified correctly and therefore would not undergo ANC)
- The total number of patients that would be accurately identified with each of the staging procedures.

Life expectancy following either ultrasound plus needle biopsy versus SLNB was not estimated since the time horizon considered in the model was limited to the period of staging, following the recommendations of the GDG members. No utilities related to undergoing ultrasound plus needle biopsy versus SLNB were found; therefore, the number of QALYs gained with each of the staging procedures could not be calculated.

Cost estimation

According to the perspective adopted, the costs considered at analysis were those relevant to the NHS. Costs were estimated based on 2006-2007 prices. The categories of costs included were:

- The costs of the staging procedures undertaken (ultrasound, needle biopsy and SLNB, depending on the strategy considered)
- The costs of any secondary staging procedure required (i.e. SLNB) in case of negative results with ultrasound plus needle biopsy, or in case lymph nodes could not be visualised with pretreatment ultrasound
- The costs of ANC, when applicable.

The costs of complications related to the staging procedures were excluded since the only staging procedure with some related complications was SLNB, and the GDG members believed these complications were minor and with insignificant associated costs of treatment.

The unit costs considered at analysis were estimated by mapping the Classification of Surgical Operations and Procedures from the Office of Population, Censuses and Survey (OPCS-4) into Health Related Groups (HRGs) and by identifying the relevant unit cost as reported in the NHS Reference Costs for the specific HRGs (Tables 6 and 7). The OPCS-4 codes for FNAC, SLNB and ANC were provided by the Bolton Breast Unit. For the case of US, an appropriate OPCS-4 code could not be identified, and its unit cost could not be mapped in the same way. The NHS Reference Cost finally used was £49, which was obtained from the Outpatient Radiology Services (corresponding to 'Ultrasound Scan less than 20 minutes').

	Average Unit Cost	Lower Quartile	Upper Quartile	Source
US	49	34	65	Radiology Services - Outpatient
FNA	243	115	252	Outpatient Procedures
SLNB	883	540	1062	Day Cases HRG Data
ANC	2343	1662	2934	Elective Inpatient HRG Data

Table A3.6 Unit costs for the staging procedures and ANC obtained from the NHS Reference Costs 2006-2007 (in £)

From the model, the number of procedures undertaken with ultrasound plus needle biopsy (in terms of the number of ultrasounds, needle biopsies, SLNBs and ANCs) were estimated and compared to the number of procedures undertaken with SLNB (i.e. number of SLNBs and number of ANCs).

It has been reported by one of the GDG members that in the estimation of the cost for SLNB, the 25% of cost of the breast surgery undertaken (i.e. either wide local excision or mastectomy) can be considered as representative of the cost for SLNB. Therefore, further sensitivity analyses took into account this alternative cost for SLNB based on the total cost of a mastectomy (£1,098, based on the HRG code JA06Z, 'Major Breast Procedures Category 3') or of a wide local excision (WLE: £1003, based on JA07B, 'Major Breast Procedures Category 2 with intermediate complications', as reported in the NHS Reference Costs).

The costs of the breast surgery (i.e. either wide local excision or mastectomy), which was conducted at the same time as the staging procedure but was not an intervention to stage the axilla, were excluded from the analysis since these costs would have been the same, independently of the type of staging procedure undertaken, therefore their exclusion is justified on the grounds that they would not have an impact on the results of the comparative analysis (Drummond *et al.,* 2005).

Discounting

Discounting is an adjustment conducted in economic evaluations to take account of the fact that individuals have a preference for experiencing benefits (in this case, health benefits) as soon as possible, while when it comes to payments, money not spent today (lets say in health care) but invested in a more profitable way, may yield a higher monetary benefit in the future (Drummond *et al.,* 2005 and Hunink and Glasziou, 2001). This type of adjustment needs to be considered when the analysis covers a period longer than 1 or 2 years, in which case the adjustment should be conducted for both the estimated costs and health benefits using a discount rate which should reflect this time preference within the context of analysis (i.e. 3.5% for both health benefits and costs in a UK context, as stated in the Guide to the Methods of Technology Appraisal published by the National Institute of Health and Clinical Excellence (NICE); www.nice.org.uk: reference N0515).

Since the time horizon of the decision model comprised only the period of staging and was definitively shorter than one year, discounting was not necessary and therefore it was not conducted.

Table A3.7 Mapping OCPS-4 codes into HRG4 codes and identifying corresponding National Reference Costs (£2006-07)

	OCPS4		HRG4		HRG3.5		National Reference Cost	
	Code	Description	HRG1 flag	HRG2 flag			HRG	Description
NB	B32.2	Biopsy of lesion of breast NEC	JA11 a		JA07 a		JA11A	Minor Breast Procedures Category 1 with Major CC
	Y20.4	Fine needle aspiration NOC	UZ05 a				JA11B	Minor Breast Procedures Category 1 with Intermediate CC
							JA11C	Minor Breast Procedures Category 1 without CC
SLNB	T91.1	Biopsy of sentinel lymph node NEC	JA09 a				JA09A	Intermediate Breast Procedures with CC
	T87.8	Procedures on the Lymphatic System w/o cc			Q10a		JA09B	Intermediate Breast Procedures without CC
ANC	T85.2	Block dissection of axillary lymph nodes	JA07 a		J11a		JA07A	Major Breast Procedures Category 2 with Major CC
							JA07B	Major Breast Procedures Category 2 with Intermediate CC
							JA07C	Major Breast Procedures Category 2 without CC
Mastectomy	B27.1	Total mastect & excis both pect muscles & part chest wall	JA07 a	JA06 c	J46	J47	JA06Z	Major Breast Procedures Category 3
	B27.2	Total mastectomy and excision of both pectoral muscles nec	JA07 a	JA06 c	J46	J47	JA07A	Major Breast Procedures Category 2 with Major CC
	B27.3	Total mastectomy and excision of pectoralis minor muscle	JA07 a	JA06 c	J46	J47	JA07B	Major Breast Procedures Category 2 with Intermediate CC
	B27.4	Total mastectomy nec	JA07 a	JA06 c	J46	J47	JA07C	Major Breast Procedures Category 2 without CC
	B27.5	Subcutaneous mastectomy	JA07 a	JA06 c	J46	J47		
	B27.8	Total excision of breast OS	JA07 a	JA06 c	J46	J47		

	OCPS4		HRG4		HRG3.5		National Reference Cost	
	Code	Description	HRG1 flag	HRG2 flag			HRG	Description
	B27.9	Total excision of breast unspecified	JA07 a	JA06 c	J46	J47		
		Total mastectomy wo/cc	J47					
		Partial/Subtotal Mastectomy w/o cc	J49					
WLE	B28.1	Quadrantectomy of breast	JA07 a	JA06 c			JA07A	Major Breast Procedures Category 2 with Major CC
	B28.2	Partial excision of breast NEC	JA07 a	JA06 c			JA07B	Major Breast Procedures Category 2 with Intermediate CC
							JA07C	Major Breast Procedures Category 2 without CC
	B28.3	Excision of lesion of breast	JA09 a				JA09A	Intermediate Breast Procedures with CC
							JA09B	Intermediate Breast Procedures without CC
US							RA22Z	Ultrasound Scan, non-imaging Procedures
							RA23Z	Ultrasound Scan less than 20 minutes
							RA24Z	Ultrasound Scan more than 20 minutes
							RA25Z	Ultrasound Mobile Scan / Intraoperative Procedures less than 20 minutes
							RA26Z	Ultrasound Mobile Scan / Intraoperative Procedures 20 to 40 minutes
							RA27Z	Ultrasound Mobile Scan / Intraoperative Procedures more than 40 minutes

Type of economic evaluation

A cost effectiveness analysis was performed given that the type of health outcome estimated was the number of patients avoiding SLNB with ultrasound/FNAC. Specifically, the analysis was a cost-consequences analysis, since there were other measures of health benefit, also measured in natural units (i.e. the number of patients with axillary metastasis that would undergo necessary ANC, the number of patients with negative lymph nodes that would undergo unnecessary ANC, the number of patients with axillary lymph nodes that would be left undertreated and the total number of patients accurately identified with each of the staging procedures) that were estimated and should also be taken into account when making recommendations about the best staging procedure to choose between ultrasound plus needle biopsy and SLNB.

The usual way of expressing the cost effectiveness of an intervention is by using what is called the incremental cost effectiveness ratio (ICER) (see Figure A3.6), which is a ratio that compares interventions where one of them is more effective but at the same time more costly than its alternative. In this case, the difference in costs and the difference in effectiveness between both interventions are compared to identify how much it should be spent with the most effective, most costly intervention to obtain each additional unit of health benefit (which in the particular case of this economic analysis would be determined by the number of patients avoiding SLNB with ultrasound plus needle biopsy). Since it was expected that ultrasound plus needle biopsy would lead to patients avoiding SLNB at a higher cost per patient compared to SLNB as initial staging procedure, an ICER was to be calculated as the additional cost incurred to avoid one patient undergoing SLNB with ultrasound plus needle biopsy, when compared to SLNB (for which no patients avoided SLNB since this staging procedure was conducted in all patients).

$$\text{ICER} = \frac{\text{COST most costly - COST least costly}}{\text{HB most effective - HB least effective}}$$

Figure A3.6 Calculation of the ICER

NICE highlights in its Social Value Judgements document that no ICER "has never [been] identified […] above which interventions should not be recommended and below which they should. However, NICE presumes that interventions with an ICER of less than £20,000 per QALY gained are cost effective. There must be increasingly strong reasons for recommending interventions with an ICER of more than £20,000 per QALY gained, and even stronger reasons where the ICER is more than £30,000 per QALY gained". As it was mentioned above, for the purposes of this study the number of QALYs could not be estimated since utilities related to undergoing ultrasound plus needle biopsy versus SLNB were not found. Given the absence of a QALY estimation in the analysis, the interpretation of the ICERs in terms of the cost per patient avoiding SLNB with ultrasound plus needle biopsy was difficult. Therefore, an attempt was made to identify the QALY gain necessary to make ultrasound plus needle biopsy cost effective (compared to SLNB) at thresholds of £20,000 and £30,000 per QALY.

Sensitivity analysis

One-way and multi-way (deterministic) sensitivity analyses were conducted to assess the robustness of the study results when the values of relevant parameters were modified in order to identify those variables contributing the more to uncertainty. The following sensitivity analyses were conducted:

- Modifications in the sensitivities and specificities of US, NB and SLNB. A specificity lower to one was considered for either NB and/or SLNB to take account of the possibility that few false positive patients could result from these tests (Podkrajsek *et al.,* 2005). In addition, the lower and upper values of the 95% confidence intervals (as estimated after pooling the results of the independent studies) were taken into account, as well as those obtained from excluding those studies thought to differ from the rest in terms of the overall accuracy reported (i.e. Bedrosian, 2003 and Brancato, 2004).

- Changes in prevalence, considering a range between 25% and 40%, and including 35% as the representative prevalence for UK patients with early breast cancer, as identified by the GDG members.
- Variations in the costs of the staging procedures, by considering:
  - The upper and lower quartiles of the unit costs as reported in the National Reference Costs.
  - A null cost for ultrasound, based on the fact that some of the GDG members highlighted that, in some UK cancer centres, ultrasound is conducted in all early breast cancer women; the additional cost of adding ultrasound to the axilla seems to be minimal in those cases. Therefore, a sensitivity analysis considering a null cost for ultrasound could shed light on the comparison of ultrasound plus needle biopsy versus SLNB under those circumstances.
  - A cost for SLNB equal to 25% of the breast surgery cost, which would be £586 in case wide local excision was conducted, or £683 if mastectomy was performed (see Table A3.8), and the corresponding lower and upper quartiles as reported in the National Reference Costs.

Type of breast surgery	NHS Reference Costs 2006-07			Unit cost of SLNB as 25% of breast surgery cost		
	Average Unit Cost	Lower Quartile	Upper Quartile	Average Unit Cost	Lower Quartile	Upper Quartile
Mastectomy	2731	2159	3836	683	540	959
WLE	2343	1662	2934	586	415	733

Table A3.8. Unit cost of SLNB as 25% of breast surgery cost

Results

Base-case results

The results are reported for a hypothetical cohort of 1,000 early breast cancer patients undergoing axillary staging. The base-case results showed that US plus NB would avoid SLNB in 118 patients per 1,000 early breast cancer patients staged, at a total cost of £1,609,140, compared to £1,575,569 needed to conduct SLNB in all patients (see Table A3.9). Therefore, the average cost per patient staged with US plus NB would be £1,609, and that per patient staged with SLNB would be £1,576. The results of the incremental analysis showed that for each additional patient avoiding SLNB with the US plus NB strategy, the extra-cost incurred would be £285, when compared to the SLNB staging strategy.

	US+NB	SLNB
Secondary SLNB avoided with US+NB	118	0
Δ Effectiveness: avoided SLNB	118	–
Total costs	1,609,140	1,575,569
Δ Costs	33,572	–
ICER	285	–

ICER = Incremental Cost Effectiveness Ratio;
ICER = Δ Costs / Δ Effectiveness
Results reported for a hypothetical cohort of 1,000 patients

Table A3.9 Incremental cost effectiveness for the base-case analysis

Under the base-case analysis, 303 necessary ANC would be performed if the staging strategy were ultrasound plus needle biopsy, compared to 296 for SLNB. No patient would undergo unnecessary ANC. A total of 11 patients would remain undertreated with the ultrasound plus needle biopsy staging strategy, compared to 18 patients with SLNB. The number of patients that would have their nodal status accurately identified through the axillary staging strategy would be 989 with ultrasound plus needle biopsy and 982 with SLNB (see Table A3.10). The average health gain that would make ultrasound plus needle biopsy cost effective at a £20,000 per QALY threshold would be 0.0017 QALYs per patient. In terms of the number of procedures undertaken, 1,000 ultrasounds, 301 needle biopsies, 882 SLNBs and 303 ANCs would be undertaken per 1,000 early breast cancer patients if the ultrasound plus needle biopsy staging strategy was implemented, compared to 1,000 SLNBs and 296 ANCs under the SLNB staging strategy (see Table A3.10).

	US+NB	**SLNB**
Secondary health outcomes:		
Necessary ANCs conducted	303	296
Unnecessary ANCs conducted	0	0
Patients undertreated	11	18
Patients with nodal status accurately identified	989	982
Number of procedures undertaken:		
Number of US undertaken	1000	0
Number of NB undertaken	301	0
Number of SLNB undertaken	882	1000
Number of ANC undertaken	303	296

Table A3.10 Results for the secondary outcomes and number of procedures undergone under each staging strategy for the base-case analysis

Sensitivity analysis

The results of the sensitivity analyses showed that the higher the accuracy of US plus NB and SLNB, the lower the incremental cost per additional patient avoiding SLNB would be with the ultrasound plus needle biopsy staging strategy when compared to the SLNB stating strategy, and vice versa. For example, when the sensitivity for SLNB was considered to be 0.893 (which was the lowest sensitivity observed from the systematic review of this topic), the extra-cost incurred per patient avoiding SLNB with the ultrasound plus needle biopsy strategy would be £400 when compared to the SLNB staging strategy; under these circumstances, at least 0.0024 QALYs should be gained per patient avoiding SLNB to make ultrasound plus needle biopsy cost effective at a £20,000 per QALY threshold. However, if SLNB was assumed to be 100% sensitive, then the incremental cost would be reduced to £149 per additional patient avoiding SLNB, and the health gain should be, at least, 0.0009 QALYs to make ultrasound plus needle biopsy cost effective at this same threshold. If NB and SLNB were 100% accurate, ultrasound plus needle biopsy would lead to 163 patients avoiding SLNB, at a reduced cost, resulting in a saving of £22,566 for a cohort of 1,000 early breast cancer patients when compared to the SLNB strategy.

Overall, the exclusion of the two papers showing accuracies that are more dissimilar for US (Bedrosian 2003 and Brancato 2005) led to more favourable ICERs when compared to those obtained when pooling all the five studies together. For example, when these two studies were excluded and a prevalence of axillary metastasis of 35% was considered, the ICER obtained was £101, which was less than half that observed when all studies were included (i.e. £212).

As the prevalence of nodal metastasis increased, lower ICERs were observed, which means that the higher the number of patients with positive lymph nodes, the more cost effective ultrasound plus needle biopsy would be. Therefore, the higher the number of patients with positive lymph nodes, the greater the potential of ultrasound plus needle biopsy to identify them and avoid in these patients further staging (i.e. SLNB). When the prevalence is 40% the extra cost that should be paid per additional patient avoiding SLNB with ultrasound plus needle biopsy (when compared to SLNB staging) would be £117 (which is less than half of that observed for the base-case analysis, for which a prevalence of nodal metastasis of 31.5% was assumed). The opposite is also observed: with lower prevalence values, the ICER increases considerably, reaching £516 per additional patient avoiding SLNB with ultrasound plus needle biopsy when the prevalence of axillary metastasis was 25%.

In terms of the secondary health outcomes considered at analysis, specificities for needle biopsy or SLNB lower than 100% would result in some patients undertaking unnecessary ANC. For example, if the specificity of needle biopsy was 0.9916 (which was the value obtained from pooling the results of all the studies reporting the accuracy of ultrasound plus needle biopsy), there would be 1 patient out of 1000 that would undergo unnecessary ANC. On the other hand, if the specificity of SLNB was 0.98 (for a specificity of NB = 1), there would be 14 patients out of a 1,000, under each staging procedure, who would undergo unnecessary ANC for being wrongly identified as having axillary metastasis.

Consideration of the lower quartiles for the unit costs of ultrasound, needle biopsy, SLNB and ANC, as reported in the National Reference Costs, led to an ICER equal to £141, while the upper quartiles resulted in an incremental cost per additional patient avoiding SLNB with US plus NB equal to £303. Under the hypothetical situation that the costs of US were null, there would be a cost reduction of £15,028 with ultrasound plus needle biopsy when compared to the SLNB strategy. This saving would be reduced to £2,878 per cohort of 1,000 early breast cancer patients if only 25% of the total cost of US was considered. Any cost of US higher than £15 would make the ultrasound plus needle biopsy strategy more expensive than the SLNB strategy. When the cost for SLNB procedure was considered to be equal to 25% of the breast surgery cost, the extra-cost incurred per additional patient avoiding SLNB with US plus NB was £485 if the patient underwent mastectomy, and £582 if the patient underwent WLE (with required QALY gains of 0.0029 and 0.0034 per patient, respectively, in order to make ultrasound plus needle biopsy cost effective compared to SLNB. These results suggest that that the lower the cost of SLNB, the higher the relative weight of the cost of US plus NB, which leads to higher values for the ICER of the ultrasound plus needle biopsy staging strategy when compared to the SLNB strategy.

In terms of the overall number of procedures undertaken, the higher the prevalence of axillary metastasis, the more ANCs would be conducted, while the number of NBs and SLNBs for the ultrasound plus needle biopsy staging strategy would depend on the accuracy of US and NB to identify accurately patients with positive lymph nodes in the first instance. For example, for a prevalence of nodal metastasis of 40%, the number of procedures undertaken would be: 1000 ultrasounds, 328 needle biopsies, 849 SLNBs and 387 ANCs with ultrasound plus needle biopsy; and: 1000 SLNBs and 377 ANCs with the SLNB strategy. On the other hand, for a prevalence of nodal metastasis equal to 25%, the number of procedures undertaken would be: 1000 ultrasounds, 281 needle biopsies, 905 SLNBs and 242 ANCs with ultrasound plus needle biopsy; and: 1000 SLNBs and 236 ANCs with the SLNB strategy.

Discussion

The aim of this study was to assess the cost effectiveness of using pretreatment US plus NB to avoid unnecessary further axillary staging in early breast cancer patients with positive lymph nodes, compared to SLNB for all patients, from an UK NHS perspective. For this, a cost effectiveness analysis was undertaken to estimate the incremental cost per patient avoiding SLNB with the ultrasound plus needle biopsy staging strategy when compared to SLNB. The results of the base-case analysis showed that each additional patient avoiding SLNB with the ultrasound plus needle biopsy strategy would cost an extra £285 when compared to the SLNB staging strategy. The exclusion of the two papers showing accuracies that were more dissimilar for ultrasound

plus needle biopsy (Bedrosian, 2003 and Brancato, 2005) led to more favourable ICERs when compared to those obtained when pooling all the five studies together. The results of the sensitivity analyses showed that the most favourable ICERs were obtained when the sensitivities and specificities of ultrasound plus needle biopsy and SLNB and the prevalence rates of axillary metastasis were higher. Additionally, the lower the cost of SLNB, the higher values were observed for the ICERs since the relative cost of ultrasound plus needle biopsy increases when compared to the SLNB strategy. Logically, more favourable ICERs were obtained when the cost of ultrasound was excluded from the analysis, or when it was considered to be just a proportion of the total cost of the US procedure.

A systematic review of the evidence regarding the cost effectiveness of pretreatment ultrasound plus needle biopsy in staging early breast cancer patients identified three relevant studies: one full economic evaluation (Brancato *et al.,* 2004) and two partial economic evaluations (Davies *et al.,* 2006 and Genta *et al.,* 2007). Two of these studies were conducted in Italy (Brancato et al. 2004; Genta et al. 2007) and the third one in USA (Davies *et al.,* 2006). All these studies were cost-consequences analysis, similar to the one here conducted. None of them estimated the number of QALYs gained with each of the staging strategies, but the accuracy of the staging procedures, the number of patients avoiding secondary staging with ultrasound plus needle biopsy (among other outcomes) and the costs associated with the different staging procedures. All studies concluded that ultrasound plus needle biopsy seemed to be a cost effective staging strategy when compared to SLNB, although none of them stated on what basis they considered cost effectiveness. All three studies identified the potential of ultrasound plus needle biopsy to lead to cost-savings under specific scenarios. This is consistent with the results here obtained: it was observed that if the cost of ultrasound was lower than £15, then potential cost-savings could be realised by conducting ultrasound plus needle biopsy. The marginal cost of undergoing ultrasound in some of the breast cancer units have been reported by one of the GDG members to be very low, since some breast cancer units already do an ultrasound when diagnosing patients with early breast cancer. This would mean that no significant, additional cost would be associated with conducting ultrasound for the ultrasound plus needle biopsy staging strategy. However, this may not be true across all UK centres. It should be noted as well that the unit cost of ultrasound for this analysis was £49, which is a much higher cost than that identified as potentially leading to cost-savings (i.e. £15 or less per ultrasound). As the study by Brancato *et al.* (2007) highlighted, considerable variations exist regarding the costs of the different staging procedures across countries; therefore, it is difficult to generalise the results from country to country. This was confirmed by the differences in the unit costs observed across studies: in the study by Davies *et al.* (2006) the cost of SLNB was much higher than that of ANC, i.e. $6,300 (£3,895) and $3,700 (£2,287), respectively; on the other hand, the study by Brancato et al. (2007) reported a unit cost of €216 (£156) for SLNB and €1,550 (£1,119) for ANC. From our model, we identified that for any cost of SLNB higher than £1,168, ultrasound plus needle biopsy would lead to cost savings when compared to the SLNB staging strategy. However, this is an unlikely cost to be encountered in UK clinical practice, as it has been mentioned by the GDG members, who believed that the actual unit cost of SLNB was much lower than that reported by the National Reference Costs.

In addition, the GDG members highlighted the difficulties of undertaking any cost analysis of the staging procedures: since these staging procedures are conducted as part of the major breast surgery undergone by the early breast cancer patient (either WLE or mastectomy), the cost to be considered at analysis for the staging procedure should be its marginal cost (on the top of the major breast surgery cost), and not the total cost of the procedure (either for ultrasound plus needle biopsy or for SLNB), as obtained from the National Reference Costs. Given the difficulties to identify these marginal costs, the base-case analysis took into consideration total costs of procedures as reported by the National Reference Costs (following recommendations from NICE). The suggestion of using the 25% of the cost of major surgery as representative of the unit cost of the SLNB procedure was considered in the sensitivity analysis. The lower the unit cost considered for SLNB, the higher the incremental cost per each additional patient avoiding SLNB with ultrasound plus needle biopsy was, given the fact that the cost of ultrasound plus needle biopsy acquired a more relevant weight in the cost effectiveness comparisons, and consequently the total cost of the SLNB staging strategy would be much lower when

compared to the total costs of the ultrasound plus needle biopsy strategy, increasing the numerator of the ICER.

Other issue to highlight is the fact that SLNB may be unsuccessful in identifying sentinel lymph nodes for some of the patients (according to the results of the systematic review for SLNB, between 4% and 6% of early breast cancer patients will not have a sentinel lymph node identified with SLNB). In this situation, the surgeon would undergo 4-NS immediately, and the cost of doing so will be basically the same because the procedure is very similar; it may take some minutes more, but the additional cost of conducting it on the top of an unsuccessful SLNB is considered to be insignificant. Therefore, the model structure was simplified and did not take into account the possibility of unsuccessfully identified sentinel lymph nodes with SLNB.

Complications were excluded from the analysis. According to the GDG members, there is no evidence that undergoing SLNB on a second operation (in case ultrasound plus needle biopsy fails to identify patients with axillary metastasis that should undergo ANC, in which case SLNB would be conducted), would result in worst outcomes when compared to early breast cancer patients with positive lymph nodes that are accurately identified by ultrasound plus needle biopsy and undertake ANC at the same time as the initial major breast surgery.

An additional limitation from this study was that the evidence on the accuracy of ultrasound plus needle biopsy and SLNB was not collected from studies comparing directly these two staging procedures, but from two different systematic reviews, one for ultrasound plus needle biopsy and the other one for SLNB. Moreover, in most of the studies included in the review of ultrasound plus needle biopsy, SLNB was used as the gold standard for some of the patients. Therefore, there may be some bias associated with the accuracy of these two staging procedures as reported by the estimates used to populate the model. Extensive sensitivity analyses were conducted to take account of a range of possible values for the sensitivities and specificities of ultrasound plus needle biopsy and SLNB. It has been already mentioned that none of the staging procedures identifies with complete accuracy patients with nodal metastasis; consequently, some patients with metastasis in the axilla may be missed and will remain undertreated. This can represent a potential risk for the patient, although its impact on patients' outcomes is still under investigation (Genta *et al.,* 2007).

NICE has established that its preferred measure of health benefit is the QALY, since it is an outcome measure that takes into account not only the increased life expectancy from an intervention, but also the quality of the increased life. According to NICE, interventions presenting an ICER lower than £20,000 per QALY gained are presumed to be cost effective, while there should be strong reasons for recommending health care interventions with ICERs higher than £20,000, and even stronger reasons if the ICER exceeds £30,000 (Social Value Judgements 2008). For the purposes of this study, the number of QALYs could not be estimated since utilities related to undergoing US plus NB versus SLNB were not found. An attempt was made to estimate the QALY gain necessary to make ultrasound + needle biopsy cost effective compared to SLNB at thresholds of £20,000 and £30,000 per QALY. The QALY gain required per patient for ultrasound plus needle biopsy to be cost effective ranged between 0.0002 and 0.0037 depending on the type of parameter values considered. The GDG members believed that because of the reduction in the number of patients undergoing SLNB, and given that, overall, ultrasound plus needle biopsy is a less invasive procedure when compared to SLNB, ultrasound plus needle biopsy will translate in sufficient QALY gains as to make this staging strategy cost effective compared to SLNB.

Conclusion

The results of the base-case analysis showed that each patient avoiding SLNB with the ultrasound plus needle biopsy strategy would cost an extra £285 when compared to the SLNB staging strategy. According to the results of the sensitivity analyses, the most favourable ICERs would be obtained when the sensitivities and specificities of ultrasound plus needle biopsy and SLNB are higher, and with higher prevalence rates of axillary metastasis. Moreover, there is the potential to achieve cost-savings by using ultrasound plus needle biopsy if the unit cost per ultrasound test undertaken was lower than £15, which may not be the case in a typical UK cancer centre. The QALY gain required per patient for ultrasound plus needle biopsy to be cost

effective ranged between 0.0002 and 0.0037 depending on the type of parameter values considered. The GDG members believed this health gain is attainable because both the reduction in the number of patients undergoing SLNB and the fact that, overall, ultrasound plus needle biopsy is a less invasive staging procedure when compared to SLNB, can translate in sufficient gains in quality of life.

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Appendix 4

Abbreviations

4-NS	4-node sampling
ABS at BASO	Association of Breast Surgery at British Association of Surgical Oncology
AIs	Aromatase Inhibitors
ALND	Axillary lymph node dissection
ANS	Axillary node sampling
BMD	Bone mineral density
BTWSP	Breast Test Wales Screening Programme
CBT	Cognitive behavioural therapy
CT	Computed tomography
DCIS	Ductal carcinoma in situ
DCISm	DCIS with microinvasion
DEXA	Dual energy X-ray absorptiometry
EBCTCG	Early Breast Cancer Trialists Cancer Group
ER	Oestrogen receptor
FNAC	Fine needle aspiration cytology
GP	General Practitioner
HER2	Human epidermal growth factor receptor 2
HRT	Hormone replacement therapy
ICER	Incremental cost effectiveness ratio
IHC	Immunohistochemistry
IMC	Internal mammary chain
IMRT	Intensity modulated radiotherapy
ISH	In situ hybridisation
LHRHa	Luteinising hormone-releasing hormone agonists
MDT	Multidisciplinary team
MRI	Magnetic resonance imaging
NHS	National Health Service
NHSBSP	National Health Service Breast Screening Programme

PR	Progesterone receptor
QALYs	Quality adjusted life years
QoL	Quality of life
SCF	Supraclavicular fossa
SLN	Sentinel lymph node
SLNB	Sentinel lymph node biopsy
SLND	Sentinel lymph node dissection
SSRIs	Selective serotonin re-uptake inhibitors

Appendix 5

Glossary

Acupuncture

A technique of inserting and manipulating fine needles into specific points on the body with the aim of relieving pain and for therapeutic purposes.

Adjuvant therapy

Treatment given after surgery, generally designed to remove any microscopic traces of tumour which may have been left behind.

Ameliorate

To make or become better, more bearable or more satisfactory.

Amenorrhoea

Absence of regular periods.

Antidepressants

Drugs that work by affecting the levels of one or more chemicals within the brain to help lift mood.

Areola complex

The coloured area of skin around the nipple.

Aromatase inhibitors

Drugs that reduce the blood levels of oestrogen in postmenopausal women by blocking aromatase, a key enzyme which helps to form oestrogen from other steroids.

Augmentation

Cosmetic surgery to increase the size of the breast.

Axilla

The armpit.

Axillary lymph node dissection/axillary node sampling

Surgery to remove some, or all of, the lymph nodes with surrounding fat from the armpit. It can be done either at the same time as breast surgery or as a separate operation.

Bilateral breast cancer

Cancer that occurs in both breasts.

Biopsy

Removal of a sample of tissue from the body to assist in diagnosis of a disease.

Bisphosphonates

A group of drugs used to treat or prevent osteoporosis and to treat the bone pain caused by some types of cancer.

Bone mineral density

A term for the amount of calcium present in bone. Bone mineral density measurement is used to identify people at risk of osteoporosis, fracture and treatment related morbidity.

Boost dose

An additional dose (boost) of radiotherapy given to just the part of the breast where the cancer was identified before surgical removal.

Breast conserving surgery

Surgery in which the cancer is removed, together with a margin of normal breast tissue. The whole breast is not removed.

Breast density

Density of breast tissue, usually referring to mammographic appearance.

Breast care nurse specialist

A nurse with specialist knowledge of breast cancer and skills in communication as defined by the Manual of Cancer Services 2004 (www.dh.gov.uk/en/ Healthcare/ NationalServiceFrameworks/ Cancer/DH_4135595).

Breast reconstruction

The formation of a breast shape after a total mastectomy, using a synthetic implant or tissue from the woman's body.

Breast stroma

The supportive framework of the breast composed of connective tissue of fat and fibrous material.

Carcinoma

Cancer of the lining tissue that covers all the body organs.

Cellulitis

An acute spreading bacterial infection below the surface of the skin characterised by warmth, redness, pain and swelling.

Chemotherapy

The use of medication (drugs) that are toxic to cancer cells, given with the aim of killing the cells or preventing or slowing their growth.

Chest wall radiotherapy

Radiotherapy to the chest wall after mastectomy.

Clinical examination/assessment

Examination by a healthcare professional, by touch, of breast tissue and the lymph glands under arms and in the neck.

Cognitive behaviour therapy

Type of therapy usually based in talking and practicing specific types of voluntary activity.

Comorbidities

The presence of more than one disease or health condition in an individual at a given time.

Compression garment

Items of clothing which provide mild compression in order to increase the flow of blood to and from specific muscle groups.

Computerised tomography

A diagnostic imaging technique that uses X-rays in conjunction with a special computer to produce a detailed picture of a cross section of the body.

Contraindicated

A situation in which a medication or treatment should not be administered.

Contralateral breast cancer

Cancer in the opposite breast.

Core biopsy

The removal of a tissue sample with a needle for laboratory examination. This test uses a slightly larger needle than the one used for fine needle aspiration (a few mm thick) and is done under local anaesthetic.

Cosmesis

Body beauty or self image.

Counselling

Counselling takes place when a counsellor sees a client in a confidential setting to explore a difficulty the client is having, or distress they may be experiencing.

Cytonuclear

Pertaining to the relationship between the nucleus of the cell and the cytoplasm.

Dual energy x-ray absorptiometry (DEXA)

An imaging technique for quantifying bone mineral density.

Ductal carcinoma in situ (DCIS)

The commonest form of preinvasive breast cancer, which is confined to normal breast structures and has not infiltrated into the supporting breast tissue and thus cannot have spread to other sites in the body.

Endocrine

Having to do with glandular tissues that secrete hormones directly into the blood stream.

Endocrine therapy

Treatment of cancer by removing and/or blocking the effects of hormones which stimulate the growth of cancer cells.

Excision

The act of surgically removing or 'cutting out' tissue from the body.

Fibroglandular

The breast is composed of fat and fibroglandular tissue. Fibroglandular tissue is the denser of the two and makes up the supporting structure of the breast.

Fibrosis

An increase in fibrous tissue, which may make an area seem harder than adjacent normal structures.

Fine needle aspiration cytology

The sampling of cells, rather than pieces of tissue, from breast tissue for examination by a pathologist.

Foci

A small group of cells or area of disease. Pleural of focus is *foci*.

Fractionation

Radiotherapy is usually given over several weeks. The dose delivered each day is known as a fraction.

Free tissue transfers

A section of tissue detached from its blood vessels moved to another part of the body and attached by microsurgery to another blood supply.

Gene amplification

Excessive amounts of the gene are present, above the 2 copies of each which are present in normal tissue

Grading

The degree of aggressiveness of a malignant tumour, assessed by its appearance under the microscope.

Histology

An examination of the cellular characteristics of a tissue using a microscope.

Hormone receptor

Proteins with a cell that bind to specific hormones

Hormone replacement therapy

Supplements to replace the female hormone oestrogen which falls during the menopause.

Hotspots

An area that represents an abnormally high absorption of radiation.

Human epidermal growth factor receptor

A molecule on the surface of a cell which interacts with a specific growth factor and helps to control how rapidly the cells grow.

Hypnosis

An altered state of consciousness brought about by a trained specialist to help change or differently control behaviour, emotions or the state of one's physical appearance.

Hypofractionated schedules

Radiotherapy given with fewer, larger doses.

Immediate reconstruction

The reconstruction of the breast at the time of mastectomy.

Immunohistochemistry

A technique that uses antibodies to identify specific molecules in tissues which are examined and scored by a pathologist down a microscope.

Inflammatory breast cancer

A type of breast cancer characterised by skin oedema, thickness and pinkness.

In situ hybridisation

A technique for assessment of the number of copies of a gene using a microscope.

Intensity modulated radiotherapy

Specialised form of conformal radiation therapy where the radiation can be adjusted to vary the doses given to different parts of an organ.

Invasive breast cancer

Breast cancer where the malignant cells have broken through the lining layer of the normal tissues and extend into the fat and fibrous tissue of the breast.

Invasive lobular carcinoma

A special type of invasive breast cancer with particular microscopic appearances.

Ipsilateral

On, or affecting, the same side.

Irradiation

Treatment with, or exposure to, any form of irradiation.

Isolated tumour cells

Single cells or tiny clusters of cells, generally referring to metastatic malignant cells within a lymph node that are usually detected by immunohistochemistry.

Local recurrence

Return of the cancer in the affected breast.

Local treatment/control

Treatment that is directed at tumour cells.

Locoregional recurrence

Recurrence limited to a localised area, as contrasted to systemic or metastatic, e.g. spread of pathological change into the same area as the original disease (local) or just beyond the site of origin but only into the nearby region (regional).

Lumpectomy

Surgical removal of a lump from the breast.

Luteinising hormone-releasing hormone agonists

Hormonal drugs that inhibit the production of the hormones that control the production of sex hormones in men and women.

Lymph nodes

Small structures which act as filters of the lymphatic system. Lymph nodes close to the primary tumour are generally the first site to which cancer spreads.

Lymphatic drainage

A one-way drainage system to transport excess fluid from body tissues into the blood system.

Lymphoedema

Swelling of the arm or breast because of a collection of lymphatic fluid.

Macrometastases

Metastases in the lymph glands which are more than 2mm in size, as assessed using a microscope.

Magnetic resonance imaging

A diagnostic imaging technique that uses powerful electromagnets, radio waves and a computer to produce well-defined images of the body's internal structures.

Malignant

Cancerous cells which can invade into nearby tissue and spread to other parts of the body.

Mammography

The process of taking a mammogram – a soft tissue x-ray of the breast which may be used to evaluate a lump or which may be used as a screening test in women with no signs or symptoms of breast cancer.

Margins

The edge of the tissue removed.

Markers

Substances found in increased amounts in the blood, other body fluids or tissues which suggest that a certain type of cancer may be in the body.

Mastectomy

Surgical removal of the breast.

Medical oophorectomy

Endocrine therapy to stop the functioning of the ovaries (see ovarian ablation).

Menopause

The end of menstruation; this usually occurs naturally around the age of 50.

Metachronous

At different times.

Metastases

Deposits of cancer elsewhere in the body.

Metastasis

Spread of cancer away from the primary site to elsewhere in the body via the bloodstream or the lymphatic system.

Microcalcifications

Pieces of calcium, often about the size of a pinhead or less, which can form in the breast tissue and which can be seen on a mammogram.

Micrometastases

Very small clusters of malignant cells (less than 2mm in size but larger than isolated tumour cells) which have spread to the lymph nodes.

Morbidity

A diseased condition or state.

Morphological

Pertaining to morphology, which is the science of the form and structures of tissues.

Multidisciplinary team

A team with members from different healthcare professions (including for example, oncology, pathology, radiology, nursing).

Necrosis

The death of a group of cells within tissue.

Needle biopsy

The removal of tissue or fluid through a needle for examination under a microscope.

Neutropenic sepsis

Life threatening infection made more severe by the patient's having a very low level of white blood cells.

Nottingham Prognostic Index

A formula based on assessment of microscopic tumour features and the spread of disease to lymph nodes, to help predict the patient's likely outcome/cure.

Occult

Hidden, or difficult to observe directly.

Oedema

The medical name for excess fluid collection or swelling.

Oestrogen

A female sex hormone.

Oestrogen receptor alpha

A protein within breast cancer cells that binds to oestrogens. It indicates that the tumour may respond to endocrine therapies. Tumours rich in oestrogen receptors have a better prognosis than those which are not.

Oncologist

A doctor who specialises in treating cancer.

Oncoplastic

Cancer specific reconstructive surgery.

Osteoporosis

The loss of bony tissue resulting in bones that are brittle and liable to fracture.

Ovarian ablation/Ovarian suppression

Surgery, radiation therapy or drug treatment which stops the functioning of the ovaries and significantly reduces oestrogen levels in the blood.

Overexpression

An increase in the amount (and activity) of a molecule in a cell, for example of a gene or growth factor receptor such as HER2.

Paget's disease of the nipple

Paget's disease of the breast is an eczema-like change in the skin of the nipple, almost always caused by an underlying breast cancer (either DCIS or invasive cancer).

Palpable

A mass that can be felt by the doctor.

Pathologist

A doctor who examines tissues and cells using a microscope. The pathologist assesses the appearances of the breast cancer and provides information on prognostic and predictive markers, such as histological grade and oestrogen receptor status.

Pathology

A branch of medicine concerned with the study of disease, especially its structure and its functional effects on the body.

Pedicled flaps

Flap of fat and overlying skin from elsewhere in the body moved to create a new breast shape during reconstruction.

Positron emission tomography

A diagnostic imaging technique using a radio-active tracer which shows increased tissue metabolism.

Predictive values/markers

A molecule that is assessed to predict the likely response to a specific treatment, for example oestrogen receptor to predict the likely response to endocrine therapy.

Preoperative assessment

The assessment and management of the patient before surgery, e.g. imaging, diagnosis and preparation for surgery.

Primary care

Services provided in a community setting, outside secondary care, with which patients usually have first contact.

Primary systemic therapy

Systemic therapy given before surgery or radiotherapy.

Progesterone receptor

A protein within cells that binds to progesterones.

Prognosis

A prediction of the likely outcome or course of a disease; the chance of recovery, recurrence or death.

Prognostic factors

Disease characteristics that influence the course of the disease and which are used to predict the likely outcome.

Prosthesis

Fabricated substitute for a diseased or missing part of a body. A breast prosthesis usually consists of a silicone envelope containing normal saline or silicone gel.

Psychological

Adjective of psychology, which is the scientific study of behaviour and its related mental process. Psychology is concerned with such matters as memory, rational and irrational thought, intelligence, learning, personality, perceptions and emotions and their relationship to behaviour.

Psychosocial

Concerned with psychological influences on social behaviour.

Radiotherapy

A treatment for cancer that uses high energy ionising radiation (usually X-rays) to prevent cell growth.

Reconstruction

See breast reconstruction.

Regimen

A plan or regulated course of treatment.

Resection margins

Margins of tissue removed by surgery around a cancer.

Scintiscanning

A diagnostic method. A radioactive tracer is injected into the body. The radiation it sends out produces flashes of light on a scintillator (instrument used to detect radioactivity), and they are recorded.

Secondary care

Services provided by multidisciplinary team in the hospital, as opposed to the General Practitioner and the primary care team.

Sentinel lymph node

The sentinel lymph node is the first lymph node that filters fluid from the breast. This is usually found in the lower part of the armpit.

Sentinel lymph node biopsy/sentinel lymph node dissection

A surgical removal of the sentinel lymph node(s). This is less extensive than axillary clearance/dissection, which removes multiple lymph nodes from the axilla.

Staging

Clinical description of the size and spread of a patient's tumour, allocated by internationally agreed categories.

Subcutaneous

Beneath the skin.

Supraclavicular fossa

The indentation immediately above the clavicle (collar bone).

Systemic therapy/treatment

Medicine, usually given by mouth or injection, to treat the whole body rather than targeting one specific area.

Telangiectasia

Permanent dilation if groups of superficial blood vessels.

Thromboembolic disease

Obstruction of a blood vessel with a blood clot which may be carried in the blood stream from the site of origin to plug another blood vessel.

Tumour bed

The area surrounding the site from which a cancer has be surgically removed.

Ultrasound

An imaging method in which high-frequency sound waves are used to outline a part of the body.

Vasomotor flushes

Hot flushes and sweats.

Wide local excision

The complete removal of a tumour with a surrounding margin of normal breast tissue.

Appendix 6

Guideline scope

Guideline title

Early and locally advanced breast cancer: diagnosis and treatment

Short title

Early and locally advanced breast cancer

Background

a. The National Institute for Health and Clinical Excellence ('NICE' or 'the Institute') has commissioned the National Collaborating Centre for Cancer to develop a clinical guideline on the diagnosis and treatment of breast cancer for use in the NHS in England and Wales. This follows referral of the topic by the Department of Health and Welsh Assembly Government. Recommendations on early and advanced breast cancer will be developed in parallel. This document is the scope for the recommendations on early breast cancer. The guideline will provide recommendations for good practice that are based on the best available evidence of clinical and cost effectiveness.
b. The Institute's clinical guidelines will support the implementation of National Service Frameworks (NSFs) in those aspects of care where a Framework has been published. The statements in each NSF reflect the evidence that was used at the time the Framework was prepared. The clinical guidelines and technology appraisals published by the Institute after an NSF has been issued will have the effect of updating the Framework.
c. This guideline will support current national initiatives outlined in the 'NHS Cancer Plan', the 'Calman-Hine Report', the 'Cameron Report', the 'Manual of Cancer Service Standards for England' and the 'Wales Cancer Standards'. The guidelines will also refer to the NICE service guidance 'Improving outcomes in breast cancer' and 'Improving supportive and palliative care for adults with cancer' and the clinical guideline 'Referral guidelines for suspected cancer'.
d. NICE clinical guidelines support the role of healthcare professionals in providing care in partnership with patients, taking account of their individual needs and preferences, and ensuring that patients (and their carers and families, where appropriate) can make informed decisions about their care and treatment.

Clinical need for the guideline

Breast cancer is the most common cancer for women in England and Wales, with about 37,000 new cases diagnosed[1,2] and 11,000 deaths[3] recorded in England and Wales each year. In men

[1] Office for National Statistics, Cancer Statistics Registrations: Registrations of cancer diagnosed in 2002, England. Series MB1 number 33. 2005, National Statistics: London.
[2] Welsh Cancer Intelligence and Surveillance Unit (2005) Cancer incidence in Wales 1992–2002. Welsh Cancer Intelligence and Surveillance Unit: Cardiff.
[3] Office for National Statistics, Mortality Statistics: Cause. England and Wales 2003. The Stationery Office: London.

breast cancer is rare, with about 270 cases diagnosed[4,5] and 70 deaths[6] in England and Wales each year. Of these new cases in women and men, around 90% of those diagnosed are in the early stages before the tumour has spread significantly within the breast or to other organs of the body. Over recent years there have been significant new developments in the investigation and surgical management of these patients and also in the indications for and use of adjuvant chemotherapy and hormone therapy. There is some evidence of practice variation across the country and of patchy availability of certain treatments and procedures. A clinical guideline will help to address these issues and offer guidance on best practice.

The guideline

a. The guideline development process is described in detail in two publications which are available from the NICE website (see 'Further information'). 'The guideline development process: an overview for stakeholders, the public and the NHS' describes how organisations can become involved in the development of a guideline. 'Guideline development methods: information for national collaborating centres and guideline developers' provides advice on the technical aspects of guideline development.
b. This document is the scope. It defines exactly what this guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health and Welsh Assembly Government.
c. The scope forms the basis on which the work of a guideline development group (GDG) is planned and should be very clear about which patient groups are included and which areas of clinical care will be considered.
d. The areas that will be addressed by the guideline are described in the following sections.

Population

Groups that will be covered

a. Women with newly diagnosed invasive adenocarcinoma of the breast of clinical stages 1 and 2. This is where the primary tumour is less than 5 cm in maximum diameter and there is no sign of spread beyond the breast and axillary lymph nodes.
b. Women with invasive adenocarcinoma of the breast of clinical stage 3. This includes primary tumours which may be larger than 5 cm in diameter (and includes inflammatory carcinoma).
c. Men with newly diagnosed invasive adenocarcinoma of the breast of clinical stages 1, 2 and 3.
d. Women with newly diagnosed ductal carcinoma in situ.
e. Women with Paget's disease of the breast.

Groups that will not be covered

a. Women and men with invasive adenocarcinoma of the breast of clinical stage 4 (this will be covered by 'Advanced breast cancer: diagnosis and treatment' NICE clinical guideline 81 (2009)).
b. Women and men with rare breast tumours (for example, angiosarcoma, lymphoma).
c. Women and men with benign breast tumours (for example, fibroadenoma, phyllodes tumour).
d. Women with lobular carcinoma in situ (LCIS).
e. Women with an increased risk of breast cancer due to family history. This population is covered by the published NICE 'Clinical guidelines for the classification and care of women at risk of familial breast cancer in primary, secondary and tertiary care'. *NICE clinical guideline* no. 14 (2004). Available from: www.nice.org.uk/CG014.

[4] Office for National Statistics, Cancer Statistics Registrations: Registrations of cancer diagnosed in 2002, England. Series MB1 number 33. 2005, National Statistics: London.

[5] Welsh Cancer Intelligence and Surveillance Unit (2005) Cancer incidence in Wales 1992–2002. Welsh Cancer Intelligence and Surveillance Unit: Cardiff.

[6] Office for National Statistics, Mortality Statistics: Cause. England and Wales 2003. The Stationery Office: London.

Healthcare setting

Primary care – excluding population-based and opportunistic screening.

Secondary care.

Tertiary care by specialist breast cancer teams.

Clinical management

a. Diagnostic investigation.
b. Staging investigation.
c. Pathological investigation including receptor analysis.
d. Surgical management, including plastic surgery for breast reconstruction.
e. Neo-adjuvant therapy (primary medical therapy)
f. Radiotherapy – external beam and brachytherapy.
g. Post operative rehabilitation.
h. Prevention of lymphoedema.
i. Adjuvant systemic therapy (including hormone therapy, chemotherapy, biological therapy and bisphosphonates).
j. Follow-up.
k. Management of menopausal symptoms.
l. Patient information, support and communication.

Status

Scope

This is the final version of the scope.

Guideline

The development of the guideline recommendations will begin in April 2006.

Further information

Related NICE guidance

Published guidance

The following guidance will be cross referred to in the early breast cancer guideline as appropriate:

- Referral guidelines for suspected cancer. *NICE clinical guideline* no. 27 (2005). Available from: www.nice.org.uk/CG027
- Familial breast cancer: the classification and care of women at risk of familial breast cancer in primary, secondary and tertiary care (partial update of NICE clinical guideline 14). *NICE clinical guideline* no. 41 (2006). Available from: www.nice.org.uk/CG041
- Improving supportive and palliative care for adults with cancer. Cancer service guidance (2004). Available from: www.nice.org.uk/csgsp
- Improving outcomes in breast cancer – manual update. Cancer service guidance (2002). Available from: www.nice.org.uk/csgbc
- Bisphosphonates (alendronate, etidronate, risedronate), selective oestrogen receptor modulators (raloxifene) and parathyroid hormone (teriparatide) for the secondary prevention of osteoporotic fragility fractures in postmenopausal women. NICE technology appraisal no. 87 (2005). Available from http://www.nice.org.uk/TA087
- Interstitial laser therapy for breast cancer. NICE interventional procedure guidance no. 89 (2004). Available from http://www.nice.org.uk/IPG089

- Endoscopic axillary lymph node retrieval for breast cancer. NICE interventional procedure guidance no. 147 (2005). Available from www.nice.org.uk/IPG147.

Guidance in development

NICE is in the process of developing the following Technology Appraisals (details available from www.nice.org.uk). Recommendations from these Technology Appraisals will be incorporated in the early breast cancer guideline.

- Docetaxel for the treatment of early breast cancer. NICE single technology appraisal. (Publication expected July 2006).
- Paclitaxel for the treatment of early breast cancer. NICE single technology appraisal. (Publication expected July 2006).
- Trastuzumab as adjuvant therapy for early stage breast cancer. NICE single technology appraisal. (Publication expected October 2006).
- Hormonal therapies for the adjuvant treatment of early breast cancer. NICE technology *appraisal*. (Publication expected November 2006).

NICE is also in the process of developing the following guidance (details available from www.nice.org.uk) and these will be cross referred to in the early breast cancer guideline as appropriate.

- Advanced breast cancer: diagnosis and treatment. NICE clinical guideline. (Publication date to be confirmed.)
- Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk. NICE clinical guideline. (Publication date to be confirmed.)
- Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women. NICE technology appraisal. (Publication date to be confirmed.)
- Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women (update of NICE technology appraisal 87). NICE technology appraisal. (Publication date to be confirmed.)

Guideline development process

Information on the guideline development process is provided in:

- 'The guideline development process: an overview for stakeholders, the public and the NHS'
- 'Guideline Development Methods: information for National Collaborating Centres and guideline developers'.

These booklets are available as PDF files from the NICE website (www.nice.org.uk/guidelinesprocess). Information on the progress of the guideline will also be available from the website.

Referral from the Department of Health

The Department of Health and Welsh Assembly Government asked the Institute:

'To prepare a guideline for the NHS in England and Wales on the clinical management of breast cancer, to supplement existing service guidance. The guideline should cover:

- the key diagnostic and staging procedures
- the main treatment modalities including hormonal treatments
- the role of tumour specific bisphosphonates'.

Appendix 7

List of topics covered by each chapter

Chapter 2 – Referral, diagnosis, preoperative assessment and psychological support

- What is the role of breast magnetic resonance imaging (MRI) in the preoperative staging of patients with biopsy-proven ductal carcinoma in situ (DCIS) or invasive breast cancer?
- What is the role of pretreatment ultrasound assessment in staging the axilla?
- What are the effective strategies to prevent and manage psychological distress in patients with early stage breast cancer?

Chapter 3 – Surgery for early breast cancer

- What is the optimal tumour-free tissue margin to achieve in patients who undergo wide local excision for (DCIS)?
- What is the role of mastectomy in patients with localised Pagets disease of the nipple?
- In patients with invasive breast cancer or DCIS when is sentinel lymph node biopsy justified as a staging procedure?
- What are the indications for completion axillary clearance when the axilla has been found by biopsy to contain metastasis?
- What is the prognostic significance of small metastatic deposits in sentinel nodes?
- When is it appropriate to perform immediate breast reconstructive surgery?

Chapter 4 – Postoperative assessment and adjuvant treatment planning

- Does progesterone receptor status add further, useful information to that of oestrogen receptor status in patients with invasive breast cancer?
- What are the indications for adjuvant chemotherapy in patients with early invasive breast cancer?
- What is the optimal time interval from completion of definitive surgery to commencement of adjuvant therapy?

Chapter 5 – Adjuvant systemic therapy

- In premenopausal breast cancer patients, what are the benefits of ovarian suppression versus tamoxifen?
- What is the best timing/ sequencing of aromatase inhibitors and the duration of treatment as adjuvant therapy in postmenopausal women with hormone receptor-positive breast cancer?
- Breast cancer (early) - hormonal treatments, (taken from the NICE technology appraisal guidance 112 (2006))
- Is there an indication for the use of tamoxifen after excision of pure DCIS?
- Update of NICE technology appraisal 109 - docetaxel for the adjuvant treatment of early node-positive breast cancer.
- Update of NICE technology appraisal 108 – paclitaxel for the adjuvant treatment of early node-positive breast cancer.
- Update of NICE technology appraisal 107 - trastuzumab for the adjuvant treatment of early-stage HER2-positive breast cancer.

- What are the indications for the measurement of bone mineral density in patients with invasive breast cancer who are on adjuvant endocrine therapy?
- What are the indications (if any) for the use of bisphosphonates in patients with early breast cancer?

Chapter 6 – Adjuvant radiotherapy

- What are the indications for radiotherapy after breast conserving surgery?
- When should patients with DCIS who have undergone complete excision or wide local excision be given radiotherapy?
- Which groups of patients should receive chest wall radiotherapy after mastectomy?
- What is the most effective radiotherapy dose fractionation regimen for patients undergoing external beam radiotherapy after surgical excision of breast cancer?
- What are the indications for an external beam radiotherapy boost to the site of local excision after breast conserving surgery?
- What are the indications for radiotherapy to the supraclavicular fossa, internal mammary chain and axilla?

Chapter 7 – Primary systemic therapy

- What is the role of primary systemic treatment in patients with early, invasive breast cancer?
- For patients treated with primary systemic therapy for breast cancer, including inflammatory or locally advanced disease, what is the role of surgery and/or radiotherapy?

Chapter 8 – Complications of local treatment and menopausal symptoms

- In patients with breast cancer which strategies are effective in preventing arm lymphoedema?
- What strategies are effective in reducing arm and shoulder mobility problems after breast cancer surgery?
- What treatments are effective and safe for use to treat patients with menopausal symptoms and invasive breast cancer or DCIS?

Chapter 9 – Follow-up

- What is the role of breast imaging modalities in the follow-up of patients with invasive breast cancer or DCIS?
- What is the best setting for clinical follow up of patients treated for breast cancer?

Appendix 8

People and organisations involved in production of the guideline

8.1. Members of the Guideline Development Group
8.2. Organisations invited to comment on guideline development
8.3. Individuals carrying out literature reviews and complementary work
8.4. Members of the Guideline Review Panel

Appendix 8.1

Members of the Guideline Development Group (GDG)

GDG Chair

Mr James Smallwood	Consultant Surgeon, Southampton University Hospital NHS Trust

GDG Lead Clinician

Dr Adrian Harnett	Consultant in Clinical Oncology, Norfolk & Norwich University Hospital NHS Foundation Trust

Group Members

Claire Borrelli	Head of Education & Training and Senior Lecturer & Lead Clinical Trainer, St George's National Breast Screening Training Centre, London
Nancy Cooper[1]	Patient/Carer Member
Dr Jane Halpin	Director of Public Health/Deputy CEO, East & North Hertfordshire Primary Care Trust and West Hertfordshire Primary Care Trust
Dr Hilary Harris	General Practitioner, Manchester
Marie Kirk	Patient/Carer Member
Melanie Lewis	Lead Macmillan Lymphoedema Physiotherapist Specialist, Singleton Hospital, Swansea
Dr David Miles	Consultant Medical Oncologist, Mount Vernon Cancer Centre, Middlesex
Mr Ian Monypenny	Consultant Breast Surgeon, University Hospital of Wales & Breast Test Wales, Cardiff
Prof Sarah Pinder	Professor of Breast Pathology, Kings College London, Guy's and St Thomas' Hospitals
Miss Elaine Sassoon	Consultant Plastic Surgeon, Norfolk & Norwich University Hospital NHS Foundation Trust
Dr Alan Stewart[2]	Consultant Clinical Oncologist, Christie Hospital, Manchester
Ursula van Mann	Patient/Carer Member
Nicola West	Consultant Nurse, University Hospital of Wales
Dr Robin Wilson	Consultant Radiologist, King's College Hospital and Guy's and St Thomas' Hospital, London

[1] From March 2006 to February 2008.
[2] From March 2006 to April 2008.

Declarations of Interest

The Guideline Development Group were asked to declare any possible conflicts of interest which could interfere with their work on the guideline.

GDG Member	Interest Declared	Type of Interest	Decisions Taken
Adrian Harnett (Lead Clinician)	Honorarium plus expenses from Roche to lecture about fluropyrimidines at the Annual Malaysian Oncological Society meeting, Feb 2007	Personal pecuniary, specific	Declare and chairperson action to be asked questions on chemotherapy
	Honorarium from Roche diagnostics to advise on tamoxifen metabolisers, Aug 2007	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics as presentation was not on the drug tamoxifen specifically
	Received expenses from Roche to go to San Antonio Breast Cancer Conference, Dec 2007	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics as the expenses were not beyond reasonable amounts
	Department received educational grant from Astra Zeneca for updating electronic library, Aug 2007	Non-personal pecuniary, non-specific	Declare and can participate in discussions on all topics
	Received expenses from Astra Zenca to go to ASCO, May 2008	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics as the expenses were not beyond reasonable amounts
Claire Borelli	Received expenses from University of Salford for being an external examiner and subject specialist in mammography, current and ongoing Mar 2006	Personal pecuniary, specific	Declare and can participate in discussions on all topics as not healthcare industry related
David Miles	Honorarium from Roche to present on avastin at Symposia, March 06	Personal pecuniary, specific	Declare and chairperson action to be asked questions on monoclonal antibodies
	Honorarium from Roche to advise on herceptin, March 2006	Personal pecuniary, specific	Declare and must withdraw from discussions of any topics that include herceptin
	Honorarium from Astra Zeneca to advise on aromatase inhibitors, March 2006	Personal pecuniary, specific	Declare and must withdraw from discussions of any topics that include aromatase inhibitors
	Honorarium from Roche to advise on avastin, March 2006	Personal pecuniary, specific	Declare and chairperson action to be asked questions on monoclonal antibodies
	Department received educational grant from Astra Zeneca to summarise the state of art in aromatase inhibitors, Aug 2007	Non-personal pecuniary, specific	Declare and can participate in discussions on all topics
	Honorarium from Astra Zeneca to present on avastin at ASCO with expenses received from Roche, June 06	Personal pecuniary, specific	Declare and chairperson action to be asked questions on monoclonal antibodies
	Received expenses from Roche to go to ASCO, May 2008	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics as the expenses were not beyond reasonable amounts

GDG Member	Interest Declared	Type of Interest	Decisions Taken
Ian Monypenny	Received expenses from Astra Zeneca to go to San Antonio Breast Cancer Conference, Dec 2005	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics as the expenses were not beyond reasonable amounts
	Received expenses from Pfizer to go to European Breast Cancer Conference, April 2007	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics as the expenses were not beyond reasonable amounts
	Received expenses from Astra Zeneca to go to San Antonio Breast Cancer Conference, Dec 2006	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics as the expenses were not beyond reasonable amounts
	Received expenses from Astra Zeneca to go to San Antonio Breast Cancer Conference, Dec 2007	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics as the expenses were not beyond reasonable amounts
	Receiving expenses from Astra Zeneca to go to San Antonio Breast Cancer Conference, Dec 2008	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics as the expenses were not beyond reasonable amounts
Sarah Pinder	Received funding from Roche for a biomedical scientist for HER2 testing in West Anglia Cancer Network and cost of kits for IHC and FISH for 6 months, March 2006	Non-personal pecuniary, non-specific	Declare and can participate in discussions on all topics
	Honorarium from Roche to lecture about HER2 testing, Feb 2006	Personal pecuniary, specific	Declare and must withdraw from discussions of any topics that include HER2 testing
	Received expenses from Pfizer to go to Controversies in Breast Cancer meeting, Sep 2007	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics as the expenses were not beyond reasonable amounts
	Honorarium from Roche to advise on HER2, Nov 2007	Personal pecuniary, specific	Declare and must withdraw from discussions of any topics that include HER2
	Honorarium from Roche to lecture about HER2 testing, Aug 2007	Personal pecuniary, specific	Declare and must withdraw from discussions of any topics that include HER2 testing
Alan Stewart	Has a shareholding in Astra Zeneca, current and ongoing Mar 2006	Personal pecuniary, specific	Declare and must withdraw from discussions of any topics that include Astra Zeneca interventions
	Honorarium from Cambridge Labs, CJ Corp & Helsinn Pharma to present about antiemetics, current and ongoing Mar 2006	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics as the interventions presented are not being investigated by the guideline
	Honorarium from Roche to lecture about herceptin and bisphosphonates, current and ongoing Mar 2006	Personal pecuniary, specific	Declare and must withdraw from discussions of any topics that include herceptin and bisphosphonates

GDG Member	Interest Declared	Type of Interest	Decisions Taken
	Received expenses from Roche to go to ASCO, June 2007	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics as the expenses were not beyond reasonable amounts
	Received expenses from GlaxoSmith-Kline to go to ECCO, Sep 2007	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics as the expenses were not beyond reasonable amounts
	Honorarium from Schering Plough Mexico to lecture about antiemetics and endocrine therapy, Oct 2007	Personal pecuniary, specific	Declare and must withdraw from discussions of any topics that include endocrine therapy
	Honorarium from Roche to advise on herceptin, Dec 2007	Personal pecuniary, specific	Declare and must withdraw from discussions of any topics that include herceptin
	Has a shareholding in GlaxoSmith-Kline, current and ongoing Dec 2007	Personal pecuniary, specific	Declare and must withdraw from discussions of any topics that include GlaxoS-mithKline interventions
	Honorarium from GlaxoSmithKline to advise on lapatanib, Nov 2007	Personal pecuniary, specific	Declare and must withdraw from discussions of any topics that include lapatanib
	Honorarium from Roche to advise on bisphosphonates, April 2008	Personal pecuniary, specific	Declare and must withdraw from discussions of any topics that include bisphosphonates
Elaine Sassoon	Chairperson of Breast Special Interest Group of British Association of Plastic Aesthetic & Reconstructive Surgeons, current and ongoing Mar 2006	Personal non-pecuniary	Declare and can participate in discussions on all topics
	BAPRAS representative to the BAPRAS/BASO special interfaces group, current and ongoing Mar 2006	Personal non-pecuniary	Declare and can participate in discussions on all topics
Robin Wilson	Chairperson of Radiology Breast Screening Coordinating Committee DoH, current and ongoing Mar 2006	Personal non-pecuniary	Declare and can participate in discussions on all topics
Fergus Macbeth	Principle investigator for FRAGMATIC trial in lung cancer patients, current and ongoing Mar 2006	Non-personal pecuniary, non-specific	Declare and can participate in discussions on all topics as the interventions included in the trial are not being investi-gated by the guideline

Appendix 8.2

Organisations Invited to Comment on Guideline Development

The following stakeholders registered with NICE and were invited to comment on the scope and the draft version of this guideline

3 Countries Cancer Network Palliative Care Lead Clinicians Group

Abbott Laboratories Ltd (BASF/Knoll)

Abbott Molecular

Abraxis Oncology

Afiya Trust, The

Age Concern Cymru

Age Concern England

Airedale NHS Trust

All About Nocturnal Enuresis Team

Almac Diagnostics

Amgen UK Ltd

Anglesey Local Health Board

Anglia Cancer Network

Arden Cancer Network

Association of Breast Surgery at BASO

Association of Chartered Physiotherapists in Oncology and Palliative Care

Association of Surgeons of Great Britain and Ireland

Association of the British Pharmaceuticals Industry (ABPI)

AstraZeneca UK Ltd

Bard Ltd

Barnsley Acute Trust

Barnsley PCT

Bath and North East Somerset PCT

Baxter Healthcare Ltd

Bayer Healthcare PLC

Bedfordshire & Hertfordshire NHS Strategic Health Authority

Bedfordshire PCT

Birmingham Cancer Network

Birmingham Clinical Trials Unit

Birmingham Heartlands & Solihull NHS Trust

Blaenau Gwent Local Health Board

Boehringer Ingelheim Ltd

Bournemouth and Poole PCT

Bradford & Airdale PCT

Breakthrough Breast Cancer

Breast Cancer Care

Bristol-Myers Squibb Pharmaceuticals Ltd

British Association for Behavioural & Cognitive Psychotherapies (BABCP)

British Association for Counselling and Psychotherapy

British Association of Art Therapists - 2nd contact

British Association of Plastic Surgeons

British Dietetic Association

British Geriatrics Society

British Homeopathic Association

British Lymphology Society

British Menopause Society

British Nuclear Medicine Society

British Oncological Association

British Oncology Pharmacy Association

British Psychological Society, The

British Society for Cancer Genetics

Bromley PCT

BUPA

Calderdale PCT

Cambridge University Hospitals NHS Foundation Trust

Cancer Network Pharmacists Forum

Cancer Research UK

Cancer Services Collaborative

CancerBACUP

Cancer Black Care

Cancer Voices

CASPE

Central Liverpool PCT

Cephalon UK Ltd

Chartered Society of Physiotherapy

CIS'ters

Clatterbridge Centre for Oncology NHS Trust

Clinical Knowledge Summaries (CKS)

Clinovia Ltd

College of Occupational Therapists

Commission for Social Care Inspection

Connecting for Health

Conwy & Denbighshire NHS Trust

Co-operative Pharmacy Association

Countess of Chester Hospital NHS Foundation Trust

Craven, Harrogate & Rural District PCT

Cytyc UK Ltd

DakoCytomation Ltd

David Lewis Centre, The

Department of Health

Derby-Burton Cancer Network

Doncaster PCT

Eisai Ltd

Eli Lilly and Company Ltd

Essex Cancer Network

Faculty of Public Health

General Practice and Primary Care

GlaxoSmithKline UK

Gloucestershire Hospitals NHS Trust

Good Hope NHS Trust

Greater Manchester & Cheshire Cancer Network

Guerbet Laboratories Ltd

Guys & St Thomas NHS Trust

Hampshire & Isle of Wight Strategic Health Authority

Harrogate and District NHS Foundation Trust

Healthcare Commission

Help the Hospices

Humber and Yorkshire Coast Cancer Network

Imaging Equipment Ltd

Independent Healthcare Advisory Service

Intra-Tech Healthcare Ltd

Johnson & Johnson Medical

King's College Hospital NHS Trust

Kirklees PCT

L'Arche UK

Launch Diagnostics Ltd

Leeds PCT

Leeds Teaching Hospitals NHS Trust

Leicestershire Northamptonshire and Rutland Cancer Network

Liverpool Women's Hospital NHS Trust

Long Term Medical Conditions Alliance

Luton and Dunstable Hospital NHS Trust

Macclesfield District General Hospital

Macmillan Cancer Relief

Maidstone and Tunbridge Wells NHS Trust

Marie Curie Cancer Care

Medeus Pharma Ltd

Medical Device Innovations Ltd

Medical Solutions

Medicines and Healthcare Products Regulatory Agency

Merck Pharmaceuticals

Mid Staffordshire General Hospitals NHS Trust

Milton Keynes PCT

National Association of Assistants in Surgical Practice

National Audit Office

National Cancer Network Clinical Directors Group

National Cancer Research Institute (NCRI) Clinical Studies Group

National Childbirth Trust

National Council for Disabled People, Black, Minority and Ethnic Community (Equalities)

National Council for Palliative Care

National Osteoporosis Society

National Patient Safety Agency

National Public Health Service – Wales

Newcastle PCT

Newham PCT

NCCHTA

NHS Cancer Screening Programme

NHS Clinical Knowledge Summaries Service

NHS Direct

NHS Health and Social Care Information Centre

North Bradford PCT

North East London Cancer Network

North East London Strategic Health Authority

North Eastern Derbyshire PCT

North Lincolnshire PCT

North Sheffield PCT

North Tees PCT

North Trent Cancer network

North Yorkshire and York PCT

Northwest London Hospitals NHS Trust

Northumbria Healthcare NHS Trust

Nottingham City Hospital

Nottingham University Hospitals NHS Trust

Novartis Pharmaceuticals UK Ltd

Nucletron B.V.

Nutrition Society

Organon Laboratories Ltd

Ortho Biotech

Ovarian Cancer Action

Oxford Nutrition Ltd

Peach

Peninsula Clinical Genetics Service

PERIGON Healthcare Ltd

Pfizer Ltd

Pierre Fabre Ltd

Primary Care Pharmacists' Association

Princess Alexandra Hospital NHS Trust

Queen Elizabeth Hospital NHS Trust

Queen Victoria Hospital NHS Foundation Trust

Regional Public Health Group – London

Roche Diagnostics

Roche Ltd

Rotherham General Hospitals NHS Trust

Rotherham PCT

Royal Bolton Hospitals NHS Trust

Royal College of General Practitioners

Royal College of General Practitioners Wales

Royal College of Midwives

Royal College of Nursing (RCN)

Royal College of Obstetricians & Gynaecologists

Royal College of Pathologists

Royal College of Physicians of London

Royal College of Psychiatrists

Royal College of Radiologists

Royal Society of Medicine

Royal United Hospital Bath NHS Trust

Royal West Sussex Trust, The

Salford PCT

Sandwell & West Birmingham Hospitals NHS Trust

Sandwell PCT

Sanofi-aventis

Schering-Plough Ltd

Scotland Cancer Network

Scottish Executive Health Department

Shropshire County and Telford & Wrekin PCT

Sheffield South West PCT

Sheffield Teaching Hospitals NHS Foundation Trust

Siemens Medical Solutions Diagnostics

Sigvaris Britain Ltd

Society and College of Radiographers

Society for Academic Primary Care

South & Central Huddersfield PCT

South East Sheffield PCT

South West Kent PCT

South West London SHA

South East Wales Cancer Network

Staffordshire Moorlans PCT

Stockport PCT

Sussex Cancer Network

Tameside and Glossop Acute Services NHS Trust

Tameside and Glossop PCT

Taunton Road Medical Centre

Thames Valley Cancer Network

Thames Valley Strategic Health Authority

Trafford PCT

UCLH NHS Foundation Trust

UK Anaemia

UK National Screening Committee

University College London Hospital NHS Trust

University Hospital Birmingham NHS Foundation Trust

University Hospitals Coventry & Warwickshire NHS Trust

University of Birmingham, Department of Primary Care & General Practice

Velindre NHS Trust

Walsall Teaching PCT

Welsh Assembly Government

Welsh Scientific Advisory Committee (WSAC)

Wessex Cancer Trust

West London Cancer Network

Western Cheshire PCT

Wets Herfordshire Hospitals Trust

World Cancer Research Fund International

Wyeth Laboratories

Wyeth Pharmaceuticals

York NHS Trust

Yorkshire and the Humber Specialised Commissioning Group

Appendix 8.3

Individuals Carrying out Literature Reviews and Complementary Work

Overall Co-ordinators

Dr Fergus Macbeth[1]	Director, National Collaborating Centre for Cancer, Cardiff
Dr Andrew Champion	Centre Manager, National Collaborating Centre for Cancer, Cardiff

Project Managers

Dr Nansi Swain[2]	National Collaborating Centre for Cancer, Cardiff
Victoria Titshall[3]	National Collaborating Centre for Cancer, Cardiff

Senior Researcher

Angela Melder	National Collaborating Centre for Cancer, Cardiff

Researchers

Margaret Astin[4]	National Collaborating Centre for Cancer, Cardiff
Dr Nathan Bromham	National Collaborating Centre for Cancer, Cardiff
Andrew Cleves[5]	National Collaborating Centre for Cancer, Cardiff
Dr Andrew Cuthbert[6]	National Collaborating Centre for Cancer, Cardiff
Dr Karen Francis	National Collaborating Centre for Cancer, Cardiff
Dr Susan O'Connell[7]	National Collaborating Centre for Cancer, Cardiff
Roberta Richey[8]	National Institute for Health and Clinical Excellence
Dr Rossela Stoicescu	External Researcher
Dr Susanne Hempel	External researcher

[1] From November 2005 to September 2008.
[2] From November 2005 to January 2007.
[3] From January 2007.
[4] From February 2007 to June 2008.
[5] From November 2005 to March 2008.
[6] From February 2007 to May 2007.
[7] From May 2008.
[8] From October 2007.

Information Specialists

Sabine Berendse	National Collaborating Centre for Cancer, Cardiff
Elise Collins	National Collaborating Centre for Cancer, Cardiff

Health Economists

Raquel Aguiar-Ibáñez[9]	Research Fellow in Health Economics, London School of Hygiene and Tropical Medicine
Ruth McAlister[10]	National Institute for Health and Clinical Excellence
Dr Neill Calvert[11]	Lecturer in Health Economics, London School of Hygiene and Tropical Medicine
Sarah Willis[12]	Research Assistant, London School of Hygiene and Tropical Medicine
Dr Dyfrig Hughes[13]	Director, Centre for the Economics and Policy in Health, University of Wales, Bangor
Dr Rhiannon Tudor Edwards[14]	Director, Centre for the Economics and Policy in Health, University of Wales, Bangor
Pat Link[15]	Research Officer, Centre for the Economics and Policy in Health, University of Wales, Bangor

Needs Assessment

Dr Robyn Dewis	Specialist Registrar in Public Health, Derby City Primary Care Trust
Mr Jonathan Gribbin	Directorate of Public Health, Derbyshire County Primary Care Trust
Prof Mark Baker[16]	Medical Director for Oncology and Surgery and Lead Cancer Clinician, Leeds Teaching Hospitals, Leeds

[9] From January 2007 to July 2008
[10] From October 2007.
[11] From August 2006 to May 2007.
[12] From August 2006.
[13] From November 2005 to July 2006.
[14] From November 2005 to July 2006.
[15] From November 2005 to July 2006.
[16] July 2008.

Appendix 8.4

Members of the Guideline Review Panel

The Guideline Review Panel is an independent Panel that overseas the development of the guideline and takes responsibility for monitoring its quality. The members of the Guideline Review Panel were as follows:

Dr John Hyslop – Chair

Consultant Radiologist, Royal Cornwall Hospital NHS Trust

Dr Ash Paul

Deputy Medical Director, Health Commission Wales

Professor Liam Smeeth

Professor of Clinical Epidemiology, London School of Hygiene and Tropical Medicine

Mr Peter Gosling

Lay member

Mr Jonathan Hopper

Medical Director (Northern Europe), ConvaTec Ltd.