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SIGN 134 • Treatment of primary breast cancer

A national clinical guideline

September 2013

KEY TO EVIDENCE STATEMENTS AND RECOMMENDATIONS

LEVELS OF EVIDENCE

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

PRESENTING RECOMMENDATIONS

In this guideline SIGN is piloting new methodology, based on the principles of Grading of Recommendations Assessment, Development and Evaluation (GRADE). Further details are available at www.sign.ac.uk/pdf/gradeprincipals.pdf

The most apparent difference to other SIGN guidelines is the absence of grades of recommendation. The wording of the recommendation reflects how strongly the guideline development group believes following the recommendation will achieve the expected benefits.

Recommendations are denoted by an **R**. Good practice points on the clinical experience of the guideline development group are denoted by a ✓.



NHS Evidence has accredited the process used by **Scottish Intercollegiate Guidelines Network** to produce guidelines. Accreditation is applicable to guidance produced using the processes described in SIGN 50: a guideline developer's handbook, 2008 edition (www.sign.ac.uk/guidelines/fulltext/50/index.html). More information on accreditation can be viewed at www.evidence.nhs.uk

Healthcare Improvement Scotland (HIS) is committed to equality and diversity and assesses all its publications for likely impact on the six equality groups defined by age, disability, gender, race, religion/belief and sexual orientation.

SIGN guidelines are produced using a standard methodology that has been **equality impact assessed** to ensure that these equality aims are addressed in every guideline. This methodology is set out in the current version of SIGN 50, our guideline manual, which can be found at www.sign.ac.uk/guidelines/fulltext/50/index.html.

The EQIA assessment of the manual can be seen at www.sign.ac.uk/pdf/sign50eqia.pdf.

The full report in paper form and/or alternative format is available on request from the Healthcare Improvement Scotland Equality and Diversity Officer.

Every care is taken to ensure that this publication is correct in every detail at the time of publication. However, in the event of errors or omissions corrections will be published in the web version of this document, which is the definitive version at all times. This version can be found on our web site www.sign.ac.uk.



Scottish Intercollegiate Guidelines Network

Treatment of primary breast cancer

A national clinical guideline



September 2013

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1 Introduction

1.1 THE NEED FOR A GUIDELINE

Breast cancer is the most common cancer in women in Scotland and the second commonest cancer overall after lung cancer. The incidence has been increasing and over the last 10 years has risen by approximately 12%.¹ In Scotland in 2010 there were 4,457 newly diagnosed cases of breast cancer in women and 23 in men.¹ Although the five year relative survival has been improved over the last decade, from 61% for those diagnosed and treated in 1983-1987 to 81% in 2003-2007, there is still evidence of variation in the treatment patients with breast cancer receive.^{2,3}

With the continuing development of new therapies, ensuring that there is optimisation of available treatments for all patients is important. There are still gaps in the evidence base required to provide answers to the questions asked by both patients and health professionals in the management of patients with breast cancer.

This guideline replaces SIGN 84: Management of breast cancer in women.

1.2 REMIT OF THE GUIDELINE

1.2.1 OVERALL OBJECTIVES

This guideline provides recommendations based on current evidence for best practice in the treatment of patients with operable early breast cancer. It includes recommendations on surgery, chemotherapy, radiotherapy, endocrine therapy and other therapies, for example biological therapy. It excludes diagnosis, staging, follow up, and management of patients with metastatic disease.

The use of complementary therapies and lifestyle management, including diet are not addressed. Sources of information on these areas are included in section 8. Guidance on pregnancy and breast cancer is covered by Royal College of Obstetricians and Gynaecologists guidelines.⁴

TNM classification for breast cancer is included in Annex 2.

The search strategies for all key questions included men with breast cancer but no trials or data on this patient group were found (*see section 7 and Annex 1*).

1.2.2 TARGET USERS OF THE GUIDELINE

This guideline will be of interest to all members of the multidisciplinary team (MDT) treating patients with breast cancer, including surgeons, oncologists, pathologists, radiologists, therapy and diagnostic radiographers and nurses. This guideline will be of particular interest to these professionals, as well as to patients and carers, managers and policy makers.

1.3 STATEMENT OF INTENT

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

1.3.1 PRESCRIBING OF LICENSED MEDICINES OUTWITH THEIR MARKETING AUTHORISATION

Recommendations within this guideline are based on the best clinical evidence. Some recommendations may be for medicines prescribed outwith the marketing authorisation (MA) also known as product licence. This is known as 'off label' use.

Medicines may be prescribed off label in the following circumstances:

- for an indication not specified within the marketing authorisation
- for administration via a different route
- for administration of a different dose
- for a different patient population.

An unlicensed medicine is a medicine which does not have MA for medicinal use in humans.

Generally the off label use of medicines becomes necessary if the clinical need cannot be met by licensed medicines within the marketing authorisation. Such use should be supported by appropriate evidence and experience.⁵

"Prescribing medicines outside the conditions of their marketing authorisation alters (and probably increases) the prescribers' professional responsibility and potential liability".⁵

The General Medical Council (GMC) recommends that when prescribing a medicine off label, doctors should:

- be satisfied that such use would better serve the patient's needs than an authorised alternative (if one exists)
- be satisfied that there is sufficient evidence/experience of using the medicines to show its safety and efficacy, seeking the necessary information from appropriate sources
- record in the patient's clinical notes the medicine prescribed and, when not following common practice, the reasons for the choice
- take responsibility for prescribing the medicine and for overseeing the patient's care, including monitoring the effects of the medicine.

Non-medical prescribers should ensure that they are familiar with the legislative framework and their own professional prescribing standards.

Prior to any prescribing, the licensing status of a medication should be checked in the current version of the British National Formulary (BNF).⁵ The prescriber must be competent, operate within the professional code of ethics of their statutory bodies and the prescribing practices of their employers.⁶

1.3.2 ADDITIONAL ADVICE TO NHSSCOTLAND FROM HEALTHCARE IMPROVEMENT SCOTLAND AND THE SCOTTISH MEDICINES CONSORTIUM

Healthcare Improvement Scotland processes multiple technology appraisals (MTAs) for NHSScotland that have been produced by the National Institute for Health and Care Excellence (NICE) in England and Wales.

The Scottish Medicines Consortium (SMC) provides advice to NHS Boards and their Area Drug and Therapeutics Committees about the status of all newly licensed medicines and any major new indications for established products.

SMC advice relevant to this guideline is summarised in section 9.4.

2 Key recommendations

The following recommendations were highlighted by the guideline development group as the key clinical recommendations that should be prioritised for implementation.

2.1 SURGERY

- ✓ The choice of surgery must be tailored to the individual patient, who should be fully informed of the options and made aware that breast irradiation is required following conservation, and that further surgery may be required if the margins are not clear of tumour.
- R** If there is proven axillary lymph node disease preoperatively axillary lymph node clearance should be undertaken; if there is no proven disease the optimal axillary procedure is a sentinel lymph node biopsy (or if not available axillary node sample is an alternative).

2.2 RADIOTHERAPY

- R** Postoperative external beam radiotherapy to the conserved breast should be considered for all patients undergoing conservation surgery for early breast cancer.
 Post-mastectomy radiotherapy should be considered in patients with lymph node-positive breast cancer if they have high risk of recurrence (≥ 4 positive lymph nodes and T3/4 tumours).
 Post-mastectomy radiotherapy may be considered in patients with intermediate risk of recurrence (high-risk node negative tumours or one to three positive axillary lymph nodes).
 All patients with ductal carcinoma in situ should be considered for breast radiotherapy following breast conservation surgery.

2.3 ADJUVANT SYSTEMIC THERAPY

- R** Adjuvant chemotherapy should be considered for all patients with breast cancer where benefit outweighs risk.
 Adjuvant anthracycline-taxane combination chemotherapy should be considered for all patients with breast cancer where the additional benefit outweighs the risk.
 Primary prophylaxis with granulocyte colony stimulating factors should be considered where the risk of febrile neutropenia exceeds 20%.
 Adjuvant trastuzumab should be considered in all patients with HER-2 positive breast cancer who receive adjuvant chemotherapy.
 Adjuvant trastuzumab should not be given concurrently with anthracyclines but may be given either concurrently with taxane based regimens or sequentially.

2.4 ADJUVANT ENDOCRINE THERAPY

- R** Pre-menopausal women with ER positive invasive breast cancer should be treated with tamoxifen for at least five years, to a total of ten years, unless there are contraindications or side effects.
- Postmenopausal women with ER positive early breast cancer should be considered for treatment with aromatase inhibitors as an alternative to tamoxifen, either:
- as an upfront aromatase inhibitor for five years, or
 - by switching to an aromatase inhibitor after two to three years of tamoxifen for a total of five years.

2.5 NEOADJUVANT SYSTEMIC THERAPY

- R** Neoadjuvant chemotherapy should be considered for all patients with breast cancer whose disease is either:
- inoperable (locally advanced or inflammatory) but localised to the breast/locoregional lymph node groups, or
 - the only surgical option is mastectomy and downstaging might offer the patient the opportunity for breast conservation.

2.6 NEOADJUVANT ENDOCRINE THERAPY

- R** Aromatase inhibitor is recommended for ER positive postmenopausal women receiving neoadjuvant endocrine therapy.

3 Surgery

3.1 BREAST CONSERVATION SURGERY

Two well established surgical procedures for the local treatment of invasive or in situ breast cancer for disease in the breast itself are:

- conservation surgery, which involves removal of the tumour together with a rim of surrounding normal breast tissue with retention of the breast
- mastectomy, involving removal of the whole breast.

All patients with invasive breast cancer should have surgical management of the axilla (*see section 3.3*).

3.1.1 INVASIVE BREAST CANCER

Meta-analysis of six randomised controlled trials (RCTs) found that breast conservation surgery and radiotherapy to the breast resulted in similar long term mortality rates compared with mastectomy in patients with operable invasive breast cancer (pooled odds ratio (OR) 1.070; 95% confidence interval (CI) 0.935 to 1.224; $p=0.33$).⁷ Only one trial showed that mastectomy significantly reduced mortality. In four of the six trials mastectomy significantly reduced the risk of locoregional recurrence compared to breast conservation surgery (OR 1.561, 95% CI 1.289 to 1.890).⁷

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A meta-analysis of 21 observational studies reported that after breast conservation the lowest risk of ipsilateral recurrence of the tumour was associated with negative margins (greater than or equal to 1 mm).⁸ There was weak evidence that there is a reduction in the risk of ipsilateral recurrence as the width of margin free from tumour increased. Interpretation of the data was difficult due to confounders which may have affected local tumour recurrence, in particular the use of adjuvant therapies.⁸

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R Women with invasive breast cancer who are undergoing breast surgery should be offered the choice of either breast conservation surgery or mastectomy.

✓ The choice of surgery must be tailored to the individual patient, who should be fully informed of the options and made aware that breast irradiation is required following conservation, and that further surgery may be required if the margins are not clear of tumour.

R In patients undergoing breast conservation surgery the radial tumour margins must be clear (≥ 1 mm).

Section 4 covers which patients should be considered for adjuvant radiotherapy.

3.1.2 DUCTAL CARCINOMA IN SITU

No RCTs comparing breast conservation surgery with mastectomy in the treatment of patients with ductal carcinoma in situ (DCIS) were identified. A meta-analysis of cohort studies of patients with DCIS who were treated by mastectomy or breast conservation surgery showed that local recurrence rates at five years were higher for patients treated by breast conservation surgery with or without radiotherapy (21.5%, 95% CI 14.0 to 30.7%) when compared with mastectomy (4.6%, 95% CI 2.3% to 7.6%).⁹ In studies reporting on patients treated by breast conservation surgery plus radiotherapy, the risk of local recurrence did not increase when compared with mastectomy (10.6%, 95% CI 5.6% to 16.9% for breast conservation surgery plus radiation versus 7.3%, 95% CI 2.7 to 14.1% for mastectomy). There were no differences in mortality but data interpretation is difficult due to inconsistencies in studies, for example lack of randomisation and cohort effects.

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Defining the optimal radial margin on local recurrence after breast conservation surgery has not been investigated in RCTs. A systematic review of 20 studies identified that a negative margin was associated with the lowest risk of tumour recurrence after breast conservation surgery (OR 0.36, 95% CI 0.27 to 0.47).¹⁰ A margin of 2 mm was associated with less risk of ipsilateral recurrence than a narrower margin (OR 0.53, 95% CI 0.26 to 0.96) but the effect of wider margins remains unclear.¹⁰

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R Women with DCIS who are undergoing breast surgery should be offered the choice of breast conservation surgery or mastectomy.

In women with DCIS undergoing conservation surgery the radial margins must be clear (≥ 1 mm).

See section 4 for which patients should be considered for adjuvant radiotherapy.

3.1.3 THE ROLE OF ONCOPLASTIC THERAPEUTIC MAMMOPLASTY

The role of oncoplastic therapeutic mammoplasty compared with breast conservation surgery for invasive breast cancer or DCIS remains to be fully defined and RCTs have not yet been reported. Retrospective case series of patients treated with a variety of oncoplastic techniques, and which have included patients with tumours larger than have been treated previously with conservation surgery, have indicated tumour local recurrence rates of 0% to 7%. Follow up of some studies, particularly those with the lowest recurrences has been relatively short at a median of 30 months. Complications following surgery appear higher than with standard breast conservation surgery and up to six per cent of patients experience delays in receiving adjuvant treatment due to these complications.^{11,12} Further guidance on oncoplastic breast reconstruction has been published by the Association of Breast Surgery and British Association of Plastic, Reconstructive and Aesthetic Surgeons.¹

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R Patients with larger tumours may be considered for oncoplastic surgery instead of mastectomy.

3.2 RISK OF CONTRALATERAL CANCER

No definitive evidence was identified to determine which patients should undergo bilateral mastectomy due to risk of contralateral cancer.

✓ Patients with a family history of breast cancer or other cancer types should be referred to the local genetics service for a risk assessment for cancer arising in the contralateral breast, according to local guidelines.

3.3 MANAGEMENT OF THE AXILLA

Spread of metastatic disease to axillary nodes is the most significant prognostic indicator and is used as one of the major determinants of appropriate systemic adjuvant therapy.^{14,15} Axillary surgery is necessary for adequate staging and treatment of invasive breast carcinoma. Axillary clearance (level 3 axillary lymph node dissection) also serves to treat metastatic disease in the axilla by surgical removal.

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There is no consensus as to the best way to manage the axilla in patients with invasive breast cancer. Table 1 describes the procedures in current practice.

Table 1: Surgical management of the axilla

Procedure	
Axillary node sample	picks out a minimum of four individual lymph nodes from the axillary fat
Axillary node clearance (axillary lymph node dissection)	block dissection of the axillary contents <ul style="list-style-type: none"> level 1 - up to the lateral border of pectoralis minor level 2 - up to the medial border of pectoralis minor level 3 - up to the apex of the axilla
Sentinel node biopsy	selective removal of the first tumour-draining node(s)

3.3.1 SENTINEL LYMPH NODE BIOPSY

In an attempt to minimise damage to the axilla and subsequent axillary complications where possible, sentinel lymph node biopsy (SLNB) can be applied to those patients in whom the axillary lymph node status is negative on preoperative evaluation or is unknown prior to surgery.

Sentinel lymph node biopsy has a high detection rate for identifying the sentinel node, in particular when the combined detection technique of blue dye and radioisotope is used.¹⁶ In the first 2,000 patients in the AMAROS trial of patients with T1, T2 breast cancers that were clinically node negative, the sentinel was detected in 97% of cases.¹⁷ A meta-analysis of seven RCTs of 9,608 patients showed that there were no significant differences in the rate of axillary node positivity in clinically node-negative patients who underwent SLNB or axillary lymph node dissection (ALND).¹⁸ In a systematic review of 14,959 sentinel node-negative patients the rate of axillary recurrence was 0.3% but with a relatively short median follow up of 34 months.¹⁹ In a meta-analysis of eight RCTs there was no statistical difference in overall survival, disease-free survival nor regional lymph node recurrence between the SLNB and ALND groups.²⁰ Postoperative morbidity is significantly reduced in patients undergoing SLNB rather than ALND.^{18, 20, 21}

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3.3.2 TREATMENT OF PATIENTS WITH A POSITIVE SLNB

The management of the axilla after a positive sentinel lymph node biopsy is a controversial and evolving area of clinical practice. Axillary metastases are limited to the sentinel node in 40-60% of cases with the remainder of the axillary nodes being clear of tumour.²² A variety of predictive factors have been employed to try to identify those patients who have further disease in the axilla after a positive SLNB. In a meta-analysis of 56 studies, the most significant factor for prediction of further non-sentinel lymph node metastases was the mode of detection, which is associated with the size of metastasis detected by hematoxylin and eosin staining.²²

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As the presence of further axillary metastases cannot be predicted with certainty, axillary clearance will remove all further disease, but will show no further evidence of lymph node disease in up to 60% of patients.²² Regional radiotherapy has been used as an alternative in patients with a positive SLNB (*see section 3.3.3*).

Results are awaited from the AMAROS trial, which is evaluating the use of radiotherapy as an alternative to axillary dissection in women with involved lymph nodes after SLNB. In this trial patients with positive sentinel lymph nodes (any number and any tumour size), including those undergoing conservation surgery or mastectomy, are being randomised to have either axillary clearance or radiotherapy.

A meta-analysis of four randomised trials found a higher rate of axillary recurrence (1.5%-3%) in the absence of ALND or radiotherapy. There was no difference in overall survival, metastases or ipsilateral breast recurrence.²³ The AZ0011 RCT of 813 patients with T1 or T2 and clinically node-negative breast cancers who had one to two positive nodes at SLNB and were undergoing breast conservation surgery and breast irradiation without an axillary field, showed there were no differences in axillary relapse (0.5% v 0.9%), overall locoregional recurrence (4.1% v 2.8%) or survival (91.9% v 92.5%) at 6.3 years follow up when comparing ALND (clearance) to no further treatment.^{20, 24}

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3.3.3 TREATMENT OF PATIENTS UNDERGOING AN AXILLARY SAMPLE

An RCT comparing 232 patients undergoing axillary node clearance with 234 patients who received axillary sample plus radiotherapy for node-positive disease, at a median follow up of 4.1 years, found that there was no significant difference in local or distant recurrence (14 v 15 patients and 8 v 7 patients).²⁵ There was no reported difference in five year survival rates (82.1% v 88.6%; p=0.20) or in disease-free survival (79.1% v 76%; p=0.68). Axillary clearance was associated with significant lymphoedema of the upper limb when compared to axillary sample.²⁵ Sampling followed by radiotherapy was associated with a significant reduction in range of shoulder movement at three years.²⁵ There was some increased morbidity associated with clearance when compared with those who had undergone sample.²⁵

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3.3.4 IMPACT OF SLNB AND RADIOTHERAPY VERSUS AXILLARY CLEARANCE TO DETERMINE THE EXTENT OF NODAL INVOLVEMENT ON ADJUVANT TREATMENT

The impact of whether additional information on the number of nodes that were involved by tumour on adjuvant treatment planning was considered in the AMAROS trial. Five hundred and sixty-six of 2,000 patients had a positive sentinel node and were randomised to receive either radiotherapy or axillary clearance. One hundred and seventy-five of 300 in the clearance arm and 162 of 266 in the radiotherapy arm received adjuvant chemotherapy. Information on the number of positive lymph nodes in the clearance arm did not affect adjuvant treatment.²⁶

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3.3.5 TIMING OF SLNB IN PATIENTS UNDERGOING NEOADJUVANT CHEMOTHERAPY

Sentinel lymph node biopsy may be performed before neoadjuvant chemotherapy with a plan for ALND if the patient is node positive. Disadvantages of this approach are the need for two procedures and the possibility that ALND will be performed when all disease has been eradicated by chemotherapy.

For SLNB after neoadjuvant chemotherapy two meta-analyses of 2,148 and 1,799 node-negative patients have shown identification rates of 90.9% and 89.6%, respectively, and false-negative rate of 10.5% and 8.4%, respectively.^{27,28} The impact on axillary recurrence is unknown.

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R All patients with invasive breast cancer who are operable should have axillary surgery.

If there is proven axillary lymph node disease preoperatively axillary lymph node clearance should be undertaken; if there is no proven disease the optimal axillary procedure is a sentinel lymph node biopsy (or if not available axillary node sample is an alternative).

If the sentinel lymph node biopsy contains tumour, further treatment to the axilla, either axillary lymph node dissection or radiotherapy, should be given. Patients undergoing breast conservation surgery and radiotherapy for T1 or T2 and clinically node-negative breast cancer and who have one or two positive nodes at sentinel lymph node biopsy may be considered for no further treatment to the axilla.

3.4 TIMING OF RECONSTRUCTION

Systematic reviews of studies comparing immediate with delayed reconstruction found trials were of poor quality and had conflicting outcomes.^{29,30}

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A prospective longitudinal study reported that one year postoperatively, women undergoing either mastectomy alone, immediate or delayed reconstruction all showed similar levels of psychosocial morbidity and continuing support may be required in all patients.³¹ A further cross-sectional study suggested that women seeking immediate breast reconstruction have higher levels of distress at presentation compared to those seeking delayed reconstruction.³²

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Several observational studies suggest that if postoperative radiotherapy is likely, immediate reconstruction is still an option.³³⁻³⁵ Autologous flap should be considered rather than implant based reconstruction but there is an increased risk of postoperative complications which should be explained to the patient.³³ Immediate reconstruction may cause a delay in the delivery of adjuvant chemotherapy in up to five per cent of patients.³⁶ Neoadjuvant chemotherapy may be considered before surgery to obviate this delay.

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Overall, the evidence was too inconsistent to support a recommendation. Expert guidance is available from the Association of Breast Surgery and British Association of Plastic, Reconstructive and Aesthetic Surgeons.¹³

4 Radiotherapy

4.1 RADIOTHERAPY FOLLOWING BREAST CONSERVATION SURGERY FOR INVASIVE BREAST CANCER

Two meta-analyses of individual patient data have shown significant reduction in breast cancer recurrence with radiotherapy given after breast conservation surgery.^{37,38} The rate of recurrence is approximately halved at 10 years from 35% to 19.3% (absolute reduction 15.7%, 95% CI 13.7 to 17.7, $p < 0.00001$). Radiotherapy also reduced 15-year risk of breast cancer death from 25.2% to 21.4% (absolute reduction 3.8%, 95% CI 1.6 to 6.0, $p = 0.00005$). Overall, about one breast cancer death was avoided by year 15 for every four recurrences avoided by year 10. 1⁺⁺

Radiotherapy regimens using unconventional fractionation schedules (>2 Gy per fraction, eg 4,005 cGy in 15 fractions over three weeks) do not result in increased local recurrences when compared to regimens using standard fractionation (2 Gy per fraction, eg 5,000 cGy in 25 fractions over five weeks).³⁹ There was no difference in local recurrence risk with relative risk (RR) 0.97 (95% CI 0.76 to 1.22, $p = 0.78$). There was no difference in breast appearance or survival at five years. Acute skin toxicity was decreased with shorter fractionation regimens, RR 0.21 (95% CI 0.07 to 0.64, $p = 0.007$). Trials of even shorter fractionation schedules (FAST, FAST FORWARD) are ongoing. 1⁺⁺

A systematic review and meta-analysis showed a significantly lower axillary recurrence rate with breast radiotherapy after negative sentinel node biopsy ($p < 0.001$).⁴⁰ 2⁺

No difference was shown in overall survival, distant metastases or supraclavicular recurrences with partial breast irradiation (PBI) when compared to whole breast irradiation in a meta-analysis. There was statistically significant increased local and axillary recurrence with PBI. Local recurrence had pooled OR 2.15 (95% CI 1.396 to 3.312; $p = 0.001$).⁴¹ 1⁺⁺

An RCT comparing intraoperative radiotherapy (IORT) with external beam radiotherapy (EBRT) showed no significant increase in local recurrence after four years. Difference in recurrence between the two groups was 0.25%, 95% CI -1.04 to 1.54; $p = 0.41$.⁴² Longer follow up is required before recommendations can be made for the routine use of IORT. 1⁺⁺

Two RCTs comparing tamoxifen and EBRT with tamoxifen alone showed reduction in local recurrences in age groups >50 years and >70 years in the EBRT and tamoxifen group.^{43,44} However, there may be very low-risk patients in whom EBRT can safely be avoided. This is being assessed in the ongoing PRIME clinical trial. 1⁺⁺

There is a slight increased risk of lymphoedema and shoulder restriction after radiotherapy. Radiation that excludes the axilla does not adversely affect upper limb function.²¹ 2⁺⁺

A systematic review of cardiac toxicity after radiotherapy showed that older radiotherapy trials (larger fraction size, wide fields and orthovoltage energy) with >10 years follow up had an excess of cardiac toxicity. Whilst current published data on modern radiotherapy regimens have not reported an increase in cardiotoxicity, follow up is relatively short and so it cannot yet be concluded that they avoid all cardiac risk. Radiotherapy poses a cardiac risk and cardiac exposure should always be minimised as much as possible.⁴⁵ The risks of treatment are however outweighed by the reduction in breast cancer recurrence. 1⁺

R Postoperative external beam radiotherapy to the conserved breast should be considered for all patients undergoing conservation surgery for early breast cancer.

Shorter fractionation schedules (eg 4,005 cGy in 15 fractions over three weeks) should be considered in early breast cancer.

4.2 RADIOTHERAPY BOOST

Risk of local recurrence after standard radiotherapy can be reduced by the addition of a boost (16 Gy in eight fractions) to the tumour bed (hazard ratio (HR) of local recurrence 0.59 (0.46 to 0.76) in favour of the boost.⁴⁶ Relative benefit in reducing risk exists in all age groups. Absolute benefit is highest in patients aged <50 years, with a reduction in local recurrence from 19.4% to 11.4% (p=0.0046; HR 0.51).⁴⁷ For all patients with high grade invasive ductal carcinoma, boost reduced recurrence from 18.9% to 8.6% (p=0.01; HR 0.42).⁴⁷

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There was an increased risk of moderate to severe fibrosis from 13% to 27% in patients who received the boost (some of which may be accountable to older techniques).⁴⁸ These patients received 16 Gy in eight fractions as the boost dose to the tumour bed. A shorter biologically equivalent fractionation regimen may now be preferred.

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R Radiotherapy boost is recommended in all patients aged 50 years or under at diagnosis.

Radiotherapy boost should be considered in patients over 50 years at diagnosis, especially those with high-grade cancer.

4.3 POST-MASTECTOMY RADIOTHERAPY

In patients with node-positive disease, chest wall radiotherapy was associated with a 17% reduction in five-year local recurrence (23% to 6%), a 15 year breast cancer mortality risk reduction from 60.1% to 54.7% (absolute reduction of 5.4%, p=0.0002) and an absolute mortality reduction of 4.4% (p=0.0009). All patients with node-positive disease benefited from post-mastectomy radiotherapy (PMRT), however the benefit was greater in those patients with ≥ 4 positive nodes compared with those with one to three positive nodes. In these two groups the five-year risk of local recurrence with the addition of PMRT was reduced from 26% to 12% and 16% to 4% respectively. There were also significant reductions in local recurrence in patients with tumours >50 mm (T3 tumours) or those invading local structures (T4). Here the local recurrence rate was reduced from 36% to 8%.³⁷

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Post-mastectomy radiotherapy with biological effective dose (BED) of 40-60 Gy in 2 Gy fractions was associated with a 6.4% absolute increase in survival at ten years (OR for death 0.78, 95% CI 0.70 to 0.85; p<0.001) compared with those who had no radiotherapy.⁴⁹

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In patients with high risk node-negative disease, PMRT is associated with an 83% relative reduction in locoregional recurrence (p<0.00001) and a 14% improvement in survival (p=0.16). Baseline risk of local recurrence is increased with lymphovascular invasion, grade 3 tumour, tumours >2 cm and age <50 years.⁵⁰ This group of patients is currently being recruited for an ongoing clinical trial (SUPREMO).

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Meta-analysis of individual patient data using older radiotherapy regimens showed a significant excess in the incidence of contralateral breast cancer (rate ratio 1.18, standard error (SE) 0.06, p=0.002) and a significant increase in non-breast cancer mortality in women who received radiotherapy (rate ratio 1.12, SE 0.04, p=0.0001). The excess mortality was mainly from heart disease and lung cancer.³⁷ In cardiac sparing chest wall radiation techniques the risk of cardiovascular death was 0.8% versus 0.9% with and without chest wall radiotherapy at 12 years of follow up.⁵¹

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R Post-mastectomy radiotherapy should be considered in patients with lymph node-positive breast cancer if they have high risk of recurrence (≥ 4 positive lymph nodes or T3/4 tumours).

Post-mastectomy radiotherapy may be considered in patients with intermediate risk of recurrence (high-risk node-negative tumours or one to three positive axillary lymph nodes).

✓ Participation in clinical trials is strongly recommended.

4.4 DUCTAL CARCINOMA IN SITU FOLLOWING BREAST CONSERVATION SURGERY FOR INVASIVE BREAST CANCER

A systematic review of four large RCTs demonstrated that the addition of radiotherapy following breast conservation surgery reduced the risk of recurrence in all patients with ductal carcinoma in situ by 51% (HR 0.49, 95% CI 0.41 to 0.58, $p < 0.00001$), reducing both ipsilateral invasive recurrence (HR 0.50; 95% CI 0.32 to 0.76, $p = 0.001$) and ipsilateral DCIS recurrence (HR 0.61; 95% CI 0.39 to 0.95, $p = 0.03$).⁵²

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Radiotherapy reduced the absolute 10-year risk of any ipsilateral breast event (either recurrent DCIS or invasive cancer) by 15.2% (SE 1.6%, 12.9% v 28.1% $p < 0.00001$) regardless of age at diagnosis, extent of breast conservation surgery, use of tamoxifen, method of DCIS detection, margin status, focality, grade, comedonecrosis, architecture, or tumour size. The proportional reduction in ipsilateral breast events was greater in older women than in younger women ($p < 0.0004$ for the difference between proportional reductions; 10-year absolute risks: 18.5% v 29.1% at ages < 50 years, 10.8% v 27.8% at ages ≥ 50 years) but did not differ significantly according to any other factor. For women with negative margins and small low-grade tumours, the absolute reduction in the 10-year risk of ipsilateral breast events was 18% (SE 5.5, 12% v 30%, $p = 0.002$).⁵³ Ten-year follow up from four large RCTs showed no significant effect on breast cancer mortality, mortality from causes other than breast cancer, or all-cause mortality.⁵³

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There was no evidence of excess deaths attributable to the addition of radiotherapy, either due to vascular disease, pulmonary toxicity, or second malignancies, and no evidence of increased risk of contralateral breast events.⁵²

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R | All patients with ductal carcinoma in situ should be considered for breast radiotherapy following breast conservation surgery.

4.5 TREATMENT TO THE SUPRACLAVICULAR FOSSA

No RCTs were identified to guide the use of supraclavicular fossa radiotherapy after axillary clearance in patients with positive lymph node involvement. Retrospective observational data suggest that it may be of benefit in patients with ≥ 4 positive lymph nodes.⁵⁴⁻⁵⁶ Participation in clinical trials should be encouraged.

3

5 Adjuvant systemic therapy

5.1 SCHEDULING OF ADJUVANT THERAPY

There is no clear evidence to recommend the optimum sequencing of adjuvant treatment to improve overall survival. Concurrent chemotherapy and radiotherapy, and concurrent chemotherapy and tamoxifen are potentially more toxic, but there is no evidence that concurrent radiotherapy and endocrine treatment have additional toxicity.

Retrospective and observational studies indicate that delaying radiotherapy beyond eight weeks has a detrimental effect on local recurrence.^{57,58} 2⁺⁺
2⁺

Delaying chemotherapy beyond three months after surgery may have a detrimental outcome in older patients (over 65 years), but the evidence for this association is weak.⁵⁹ 2⁺

5.2 ADJUVANT CHEMOTHERAPY

A meta-analysis of over 100,000 patients showed overall mortality is reduced in patients receiving chemotherapy compared to those receiving no chemotherapy.⁶⁰ Overall, the two-year recurrence rate is halved for patients receiving six four-weekly cycles of CMF (cyclophosphamide 100 mg/m² × 14, methotrexate 40 mg/m² × 2, 5-fluorouracil 500 mg/m² × 2), or four three-weekly cycles of AC (adriamycin 60 mg/m² and cyclophosphamide 600 mg/m²) compared to those receiving no chemotherapy. The eight-year recurrence rate is reduced by one third and breast cancer mortality rate is reduced by about one quarter. This is largely independent of measured tumour characteristics or age. Most historical trials excluded patients over the age of 70 years so this group is under-represented, however, no evidence was identified to suggest that patients older than 70 years derive less benefit. 1⁺⁺

5.2.1 ANTHRACYCLINES

In a meta-analysis, four cycles of AC is equivalent to standard CMF (RR 0.98, SE 0.05, p=0.67).⁶⁰ Anthracycline-based chemotherapy with higher cumulative doses, such as six four-weekly cycles of FAC (cyclophosphamide 100 mg/m², adriamycin 30 mg/m² × 2, 5-fluorouracil 500 mg/m² × 2), or six four-weekly cycles of FEC (cyclophosphamide 75 mg/m² × 14, epirubicin 60 mg/m² × 2, 5-fluorouracil 500 mg/m² × 2), is associated with a significant reduction in disease recurrence (RR 0.89, 95% CI 0.82 to 0.96, p=0.003), breast cancer mortality (RR 0.80 CI 0.72 to 0.88, p=0.00001), and overall mortality (RR 0.84, 95% CI 0.76 to 0.92, p=0.0002) compared with non-anthracycline, non-taxane-based regimens (such as CMF).⁶⁰ The greatest benefit was in patients receiving higher dose anthracyclines compared to lower dose anthracyclines or CMF (RR 0.64, SE 0.09, p<0.0001 for FAC; RR 0.78, SE 0.09, p=0.01 for AC; RR 0.76, SE 0.05, p<0.0001 for CMF).⁶⁰ 1⁺⁺

Anthracyclines increase the risk of cardiotoxicity, particularly congestive cardiac failure, in a dose-dependent manner. In a large meta-analysis anthracyclines increased the risk of any cardiotoxicity (OR 2.27, 95% CI 1.50 to 3.43, p<0.0001) and the risk of cardiac death (OR 4.94, 95% CI 1.23 to 19.87, p=0.025) compared with non-anthracycline regimens.⁶¹ The relative risk of cardiotoxicity, while higher, was not statistically significant (95% CI 0.93 to 19.38; p= 0.08). This meta-analysis included patients (adults and children) with multiple different tumour types. It only identified eight studies where an anthracycline-based treatment was compared with a non-anthracycline-based regimen in women with breast cancer and the majority of breast cancer patients included had metastatic breast cancer. Different definitions of cardiotoxic event were used and there was significant heterogeneity between the studies. A more recent review of adjuvant chemotherapy in breast cancer suggests that the absolute risk is low, if the cumulative dose of anthracyclines does not exceed maximum levels (450 mg/m² for adriamycin and 720 mg/m² for epirubicin).⁶² 1⁺⁺
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R Adjuvant chemotherapy should be considered for all patients with breast cancer where benefit outweighs risk.

Higher dose anthracycline-based chemotherapy (ie six cycles of FAC or FEC or equivalent) is recommended rather than six cycles of CMF or four cycles of AC.

5.2.2 ANTHRACYCLINE-TAXANE COMBINATIONS

The dosage and scheduling of chemotherapy, particularly taxane-based regimens, is not clearly defined.

Use of anthracycline-taxane combinations or higher dose anthracycline-based regimens result in reduced mortality compared to older, lower dose anthracycline or CMF-type regimens.⁶⁰ This benefit is consistent across different pathological cancer subtypes and tumour grade/stage. Docetaxel-containing regimens have been studied in more patients than paclitaxel-containing regimens but the benefit appears consistent with both drugs.

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A large meta-analysis that compared the addition of four cycles of a taxane to a standard anthracycline-based control treatment (ie longer duration treatment) demonstrated improved breast cancer mortality (RR 0.86, SE 0.04, $p=0.0005$).⁶⁰ Other large meta-analyses (including over 15,000 patients) have demonstrated similar benefit with the addition of taxane-based chemotherapy compared to standard anthracycline-based chemotherapy, with improved overall survival (OS) (RR 0.87, 95% CI 0.81 to 0.93, $p<0.0001$),⁶³ HR 0.85, 95% CI 0.79 to 0.91⁶⁴ and disease-free survival (DFS) (RR 0.86, 95% CI 0.81 to 0.90, $p<0.00001$),⁶³ HR 0.83, 95% CI 0.79 to 0.87).^{64,65} Anthracycline-taxane regimens provided benefit regardless of oestrogen receptor (ER) status, nodal status, age, menopausal status and human epidermal growth factor receptor 2 (HER-2) status. In the largest meta-analysis, when longer duration treatment with an anthracycline-taxane combination was compared with regimens including extra cycles of anthracycline, there was, however, no significant difference in breast cancer mortality (RR 0.94, SE 0.06, $p=0.33$).⁶⁰

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There is an emerging consensus that, in some patients with strongly ER positive, HER-2 negative disease, the additional benefits of adjuvant chemotherapy over endocrine treatment are small and are probably outweighed by the risks. How best to identify these patients is the subject of ongoing research. The Nottingham Prognostic Index (NPI) and the algorithm Adjuvant! Online are tools to aid treatment recommendations for adjuvant chemotherapy.⁶⁶ Prognostic tests have been developed to correlate expression of certain genes or proteins with prognosis and chemosensitivity and these tests may aid in adjuvant treatment recommendation for patients with certain subtypes of breast cancer.⁶⁷ Evidence to support their routine use is limited and the results of several trials (MINDACT, TAILORx, RxPONDER) are awaited to further validate these tests.

The use of higher dose chemotherapy combinations increases the risk of haematological side effects, particularly neutropenic sepsis. In a Cochrane review the risk of febrile neutropenia was highest with taxane-containing regimens (OR 2.51, 95% CI 1.11 to 5.66),⁶⁵ and particularly with regimens where taxane is administered concurrently with an anthracycline (OR 6.80, 95% CI 1.91 to 24.15) rather than sequentially (OR 1.57, 95% CI 0.48 to 5.17). There was, however, no statistically significant increase in treatment-related deaths when taxane and non-taxane regimens were compared. Consideration of the relative benefits and risks of these regimens should be made when recommending a chemotherapy combination. Febrile neutropenia rates may be reduced with the use of granulocyte colony stimulating factors. European Organisation for Research and Treatment of Cancer (EORTC) guidelines recommend that primary prophylaxis with granulocyte-colony stimulating factors should be considered in patients undergoing chemotherapy with a greater than 20% risk of febrile neutropenia (such as FEC100, FEC-docetaxel).⁶⁸

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5.2.3 DURATION OF THERAPY

A large meta-analysis reported that chemotherapy regimens containing more chemotherapy than the four standard cycles of AC (4AC) or standard six cycles of CMF are more effective, giving a further reduction of 15-20% in breast cancer mortality rates. This was consistent across regimens such as FAC, FEC or 4AC plus four cycles of taxane.⁶⁰

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There is a paucity of data on dose-dense chemotherapy compared with conventional, similar chemotherapy regimens. A meta-analysis of 3,337 patients in three trials, where dose-dense chemotherapy regimens with growth factor support were compared with conventional chemotherapy regimens using similar drugs, showed benefit of dose-dense chemotherapy in women with oestrogen receptor negative breast cancer. This was seen both in improved OS (HR = 0.84, 95% CI 0.72 to 0.98, $p=0.03$ and improved DFS (HR 0.83, 95% CI 0.73 to 0.94, $p=0.005$). There was no reported benefit in patients with ER positive tumours.⁶⁹ Further studies in this area are ongoing. Currently the use of dose-dense chemotherapy is not recommended other than as part of a clinical trial.

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R Adjuvant anthracycline-taxane combination chemotherapy should be considered for all patients with breast cancer where the additional benefit outweighs risk.

Primary prophylaxis with granulocyte colony stimulating factors should be considered where the risk of febrile neutropenia exceeds 20%.

5.2.4 TRASTUZUMAB

Large meta-analyses confirm a clear benefit of trastuzumab in patients with HER-2 positive breast cancer (defined as 3+ on immunohistochemistry (IHC) or 2+ on IHC and fluorescence in situ hybridisation (FISH) amplified). A meta-analysis of 13,493 women in five RCTs with HER-2 positive breast cancer demonstrated improved DFS in patients treated with a trastuzumab and chemotherapy regimen compared to chemotherapy alone (RR 0.62, 95% CI 0.56 to 0.68, $p < 0.0001$), improved OS (RR 0.66, 95% CI 0.57 to 0.77, $p < 0.0001$), lower locoregional recurrence rate (RR 0.58, 95% CI 0.43 to 0.77, $p = 0.0002$) and lower distant recurrence rate (RR 0.60, 95% CI 0.53 to 0.68, $p < 0.0001$).⁷⁰ The majority of these trials used one year of trastuzumab (either weekly or three weekly infusions).⁷⁰

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A Cochrane meta-analysis of 11,991 women with HER-2 positive breast cancer demonstrated improvement in DFS and OS with the addition of trastuzumab to standard chemotherapy (DFS HR 0.6, 95% CI 0.50 to 0.71, $p < 0.00001$; OS HR 0.66, 95% CI 0.57 to 0.77, $p < 0.00001$).⁷¹ Another meta-analysis demonstrated reduction in risk of death from any cause (OR=0.78, 95% CI 0.69 to 0.88, $p = 0.001$); reduction in locoregional recurrence, (OR=0.53, 95% CI 0.44 to 0.65, $p = 0.001$); and reduction in distant recurrence, (OR=0.62, 95% CI 0.55 to 0.69, $p = 0.001$).⁷² There was a lower risk of mortality when trastuzumab was given concurrently, compared with sequential treatment.⁷²

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Trials are ongoing to determine whether one year is the optimum duration of trastuzumab treatment. Results from the HERA trial suggest no additional benefit for two years trastuzumab.⁷³ The PHARE trial, which included shorter duration trastuzumab, suggests that six months of treatment is not inferior to one year.⁷⁴ The results of these trials have been presented in abstract form and final results are awaited.

There is a lack of RCT evidence to support or refute the use of trastuzumab in patients with tumours <1 cm in size (T1a or T1b), as these patients were not included in the published trials. Results are awaited from ongoing trastuzumab trials which do include this patient group.

The addition of trastuzumab to chemotherapy (particularly anthracycline-based treatment) in one trial increased the risk of cardiac dysfunction.⁷⁵ This finding has been confirmed by a meta-analysis of 11,882 patients with early and advanced breast cancer, which showed that the incidence of left ventricular ejection fraction (LVEF) decrease was 7.5% (95% CI 4.2% to 13.1%) and incidence of congestive heart failure (CHF) was 1.9% (95% CI 1.0% to 3.8%) for those patients receiving trastuzumab.⁷⁶ The subgroup who received anthracyclines with trastuzumab had an incidence of CHF of 3.0% (95% CI 2.5% to 3.5%), while for non-anthracycline containing chemotherapy it was 1.5% (95% CI 0.5% to 4.3%). When trastuzumab and anthracyclines were administered sequentially, the incidence of CHF was 1.7% (95% CI 1.4% to 2.1%), whereas the incidence was significantly higher 13.9% (95% CI 9.4% to 20.0%) when trastuzumab and anthracyclines were administered concurrently. In a Cochrane review, patients receiving trastuzumab in addition to adjuvant chemotherapy had a fivefold increase in the risk of CHF, with a significantly increased risk of CHF when trastuzumab and anthracyclines were administered concurrently, rather than sequentially.⁷¹

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A consensus statement for the assessment and management of cardiac function in patients receiving trastuzumab highlights that:⁷⁷

- cardiac assessment, including LVEF measurement, should be performed before any chemotherapy.
- heart function measurement should be referenced to the local normal range for the modality used.
- management of cardiac risk factors including hypertension should occur before the first cycle of chemotherapy.
- reassessment of LVEF should occur after completing chemotherapy and before starting trastuzumab. repeat measurements should be performed after four and eight months of trastuzumab treatment.

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The consensus statement also makes recommendations on interrupting and restarting trastuzumab treatment, gives clear advice on initiating an angiotensin converting enzyme (ACE) inhibitor and when to consult a cardiologist.

The standard duration of treatment with trastuzumab is currently one year.

R Adjuvant trastuzumab should be considered in all patients with HER-2 positive breast cancer who receive adjuvant chemotherapy.

Adjuvant trastuzumab should not be given concurrently with anthracyclines but may be given either concurrently with taxane-based regimens or sequentially.

Cardiac function should be monitored in patients being treated with anthracyclines and/or trastuzumab.

Trastuzumab should be used with caution in patients with significant cardiac comorbidity. The benefits of adjuvant chemotherapy with or without trastuzumab may be outweighed by the potential harms in these patients, and treatment should only be recommended after careful consideration.

5.3 ADJUVANT ENDOCRINE THERAPY

The goal of adjuvant endocrine therapy is to reduce the availability of oestrogen to the cancer cells. This can be achieved by blocking oestrogen receptors with drugs such as tamoxifen, suppression of ovarian oestrogen synthesis by luteinising hormone releasing hormone (LHRH) agonists or surgical ovarian ablation. Aromatase inhibitors, used in postmenopausal women with no ovarian oestrogen synthesis or pre-menopausal women with concurrent suppression of oestrogen synthesis, prevent the synthesis of oestrogen from androgens.⁷⁸

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5.3.1 TAMOXIFEN

In a large meta-analysis of patients with ER positive (ER+) invasive disease, use of tamoxifen for five years substantially reduced recurrence rates throughout the first 10 years (RR 0.53 up to four years and RR 0.68 during years five to nine, $p < 0.00001$). This RR was independent of progesterone receptor status (or level), age, nodal status, or use of chemotherapy. Even in patients with marginally ER+ disease the recurrence reduction was substantial (RR 0.67, SE 0.08). Use of tamoxifen in patients with ER+ disease also reduced breast cancer mortality by about a third throughout the first 15 years (RR 0.71 up to four years, 0.66 during years five to nine, and 0.68 SE 0.08 during years 10 to 14; $p < 0.0001$ for extra mortality reduction during each separate time period).⁷⁹ Five years duration of tamoxifen was significantly more effective than one to two years ($p < 0.00001$).⁸⁰

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For women with ER+ invasive disease, continuing tamoxifen for 10 years rather than stopping at five years results in a further reduction in recurrence and mortality, particularly after year 10.⁸¹ These results, together with results from previous trials of five years of tamoxifen treatment compared to none, suggest that 10 years of tamoxifen treatment can approximately halve breast cancer mortality during the second decade after diagnosis.⁸¹ The cumulative risk of recurrence during years five to 14 was 21.4% for women allocated to continue compared to 25.1% for controls; breast cancer mortality during years five to 14 was 12.2% for women allocated to continue compared to 15.0% for controls (absolute mortality reduction 2.8%). The cumulative risk of endometrial cancer during years five to 14 was 3.1% (mortality 0.4%) for 10 years of tamoxifen compared

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to 1.6% (mortality 0.2%) for five years (absolute mortality increase 0.2%). Relative risk of pulmonary embolus 1.87 (95% CI 1.13 to 3.07, $p=0.01$) for 10 years compared to five years tamoxifen.⁸¹ | 1+

In women with ER negative disease use of tamoxifen had little or no effect on breast cancer recurrence or mortality.⁷⁹ | 1++

R | **Pre-menopausal women with ER positive invasive breast cancer should be treated with tamoxifen for at least five years, to a total of ten years, unless there are contraindications or side effects.**

5.3.2 LUTEINISING HORMONE RELEASING HORMONE AGONISTS

Luteinising hormone releasing hormone agonists, for example goserelin, provide effective ovarian suppression in pre-menopausal women and are an effective alternative to oophorectomy. They induce a menopausal status that is usually reversible upon cessation of therapy. LHRH agonists act by binding to pituitary LHRH receptors, resulting in down regulation of receptors and subsequent suppression of luteinising hormone and oestradiol.⁸² | 1++

A Cochrane review concluded that LHRH agonists have a similar effect to older chemotherapy protocols (for example CMF) in terms of recurrence-free and overall survival in pre-menopausal patients with ER+ breast cancer. There are insufficient data to compare the addition of LHRH agonists to the current standard chemotherapy regimens.⁷⁸ |

There were insufficient data to compare LHRH agonist alone or in combination with anti-oestrogen therapy, to treatment with tamoxifen alone. Results comparing LHRH agonists and aromatase inhibitors to LHRH and tamoxifen are inconclusive.⁷⁸ | 1++

There is a trend towards improved recurrence-free and overall survival in patients who received an LHRH agonist with tamoxifen plus chemotherapy combination in comparison to chemotherapy alone.⁷⁸ One trial showed that patients randomised to goserelin (3.6 mg depot every 28 days for two years) had significantly better recurrence-free survival (73%) and OS (86%) than those allocated to no goserelin (68% and 83% respectively). | 1++

None of the trials in the Cochrane review contained a control arm of a modern chemotherapy regimen and tamoxifen, which is the current standard of care. There is therefore insufficient data to fully assess the role of LHRH agonists in practice.

5.3.3 AROMATASE INHIBITORS

The aromatase inhibitors (AIs), anastrozole, exemestane and letrozole, are alternative options to tamoxifen for postmenopausal women with ER+ invasive breast cancer.

Disease-free survival is significantly increased with anastrozole compared to tamoxifen as first line adjuvant treatment over five years (HR 0.89, 95% CI 0.83 to 0.96). There is no difference in overall survival with anastrozole compared with tamoxifen as first adjuvant treatment (HR 0.94, 95% CI 0.82 to 1.08).⁸³⁻⁸⁵ The risk of disease recurrence is significantly reduced with anastrozole and is independent of nodal status, tumour size or prior chemotherapy. The risk of contralateral breast cancer is significantly reduced with anastrozole as first line adjuvant treatment. | 1++

One trial of letrozole versus tamoxifen as first line therapy showed improvement in disease-free survival in patients with lymph node positive tumours.^{83,85} Disease-free survival was also improved by the use of letrozole compared to placebo following standard adjuvant treatment with tamoxifen (HR 0.68, 95% CI 0.55 to 0.83, $p=0.0001$).⁸³⁻⁸⁵ Overall survival was not statistically different between letrozole and tamoxifen, nor letrozole and placebo. The time to any disease recurrence was significantly increased with letrozole compared to tamoxifen or placebo. | 1++

A trial randomising patients after five years of tamoxifen to either five years of letrozole or placebo, revealed a significantly longer disease-free survival in patients receiving letrozole (HR 0.58, 95% CI 0.45 to 0.75) at 30 months follow up. A pre-specified subgroup analysis showed an overall survival benefit with letrozole in the node-positive group (HR 0.56, 95% CI 0.38 to 0.98).⁸⁶ | 1++

A study compared sequenced therapy with tamoxifen for between two and three years followed by exemestane for five years in total, versus tamoxifen on its own. It resulted in a non-significant difference in OS (HR 0.83, 95% CI 0.67 to 1.02) but a significantly improved DFS (HR 0.73, 95% CI 0.62 to 0.86, $p=0.0001$). The switching strategy also resulted in a significant decrease in breast cancer recurrence (HR 0.70, 95% CI 0.58 to 0.83, $p=0.00005$).⁸³⁻⁸⁵ 1⁺⁺

Use of AIs increases the risk of bone density loss and osteoporosis associated fractures, as well as musculoskeletal disorders such as joint stiffness.⁸⁷ 1⁺⁺

R Postmenopausal women with ER positive early breast cancer should be considered for treatment with aromatase inhibitors as an alternative to tamoxifen, either:

- as an upfront aromatase inhibitor for five years, or
- by switching to an aromatase inhibitor after two to three years of tamoxifen for a total of five years.

Patients who are postmenopausal and have completed five years of tamoxifen may be considered for extended (five years) treatment with letrozole.

✓ The choice and sequencing of specific adjuvant endocrine therapy should be agreed following consideration of benefits and side effects for each treatment.

5.4 BISPSPHONATES

A Cochrane review shows a clear benefit of bisphosphonates in reducing skeletal events in patients with metastatic breast cancer with bone secondaries, but there is insufficient evidence to show benefit from use of bisphosphonates as a disease modifying agent in reducing recurrences in early breast cancer.⁸⁸ 1⁺⁺

A consensus statement on the guidance for the management of breast cancer treatment induced bone loss highlights that:⁸⁹

- adjuvant endocrine therapy whether tamoxifen or aromatase inhibitors is associated with changes in bone mineral density (BMD).
- in pre-menopausal women, ovarian suppression leads to accelerated bone loss due to the induction of menopause. In pre-menopausal women, tamoxifen leads to a decrease in BMD whereas it has the opposite effect in postmenopausal women. 4
- adjuvant aromatase inhibitors in postmenopausal women are associated with an increased risk of bone fractures. Other risk factors such as family history, smoking and previous history of fracture, should also be taken into account.
- there is an increased risk of bone fractures due to osteoporosis associated with aromatase inhibitors and with chemotherapy-induced premature menopause.

Algorithms 1 and 2 provide recommendations on when BMD should be measured (*see Annexes 3 and 4*). The consensus statement recommends:⁸⁹

R 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 inhibitors
- have treatment-induced menopause
- are starting ovarian suppression therapy.

A DEXA scan is not routinely needed in those who are receiving tamoxifen alone, regardless of pre-treatment menopausal status.

Offer bisphosphonates to patients identified by algorithms 1 and 2.

6 Neoadjuvant systemic therapy

6.1 NEOADJUVANT CHEMOTHERAPY

Neoadjuvant chemotherapy is widely recommended as part of a multimodal treatment approach for patients with inoperable (locally advanced or inflammatory) breast cancer.⁹⁰ 1⁺⁺

Neoadjuvant chemotherapy is associated with higher rates of breast conservation than adjuvant chemotherapy, with equivalent rates of overall survival and locoregional recurrence, providing surgery is part of the treatment pathway. A Cochrane review concluded that overall survival is equivalent for preoperative chemotherapy compared to adjuvant chemotherapy (HR 0.98, 95% CI 0.87 to 1.09, p=0.67).⁹⁰ Increased breast conservation rates were observed in patients who received neoadjuvant chemotherapy (RR 0.82 (95% CI, 0.76 to 0.89; p<0.00001). No significant increase in locoregional recurrence rates was observed (HR 1.12, 95% CI 0.92 to 1.37, p=0.25) with neoadjuvant chemotherapy compared to adjuvant chemotherapy. Patients who achieve pathological complete response (pCR) show improved survival, compared with patients with residual disease (HR 0.48, 95% CI 0.33 to 0.69, p=0.0001).⁹⁰ 1⁺⁺

There are no significant differences between adjuvant and neoadjuvant chemotherapy for postoperative complications, nausea/vomiting or alopecia. Events of leucopenia and infections (RR 0.69, 95% CI 0.56 to 0.84, p=0.0003) were significantly lower with neoadjuvant chemotherapy.⁹⁰ 1⁺⁺

R Neoadjuvant chemotherapy should be considered for all patients with breast cancer whose disease is either:

- inoperable (locally advanced or inflammatory) but localised to the breast/locoregional lymph node groups, or
- the only surgical option is mastectomy and downstaging might offer the patient the opportunity for breast conservation.

6.1.1 DURATION OF THERAPY

Three RCTs have shown that six cycles of epirubicin and docetaxel compared to three or four cycles results in higher pCR and a trend towards increased breast conservation.⁹¹⁻⁹³ Reported rates of toxicities were similar for each group.^{91, 93} 1⁺ 1⁺⁺

6.1.2 ANTHRACYCLINE-TAXANE COMBINATIONS

Breast conservation rates and rates of pCR are higher in patients treated with a combination of anthracycline and taxane-based neoadjuvant chemotherapy, compared with non-taxane based chemotherapy.^{94,95} Breast conservation surgery rates were higher with a taxane (absolute difference (AD) 3.4%, p=0.12). There was a trend to higher pCR in patients treated with taxanes, which reached statistical significance in patients receiving sequential anthracyclines/taxanes (AD 2.4%, p=0.013).⁹⁶ Pooled analysis of seven trials indicated higher pCR in patients receiving a taxane (29% v 15% in ER negative patients, p<0.001 and 8.8% v 2.0% in ER+ patients, p<0.001) compared to no taxane.⁹⁷ 1⁺ 1⁺⁺ 2^{*}

R Anthracycline-taxane-based chemotherapy combinations should be considered for all patients receiving neoadjuvant chemotherapy.

6.1.3 TRASTUZUMAB

In patients with HER-2 positive disease, adjuvant or neoadjuvant trastuzumab leads to improved DFS (HR 0.60, 95% CI 0.50 to 0.71, $p < 0.00001$) and OS (HR 0.66, 95% CI 0.57 to 0.77, $p < 0.00001$) with no heterogeneity of effect between adjuvant and neoadjuvant administration of trastuzumab.⁷¹ A meta-analysis has shown that use of neoadjuvant trastuzumab also improves pCR rates (RR 1.85, 95% CI 1.39 to 2.46, $p < 0.001$), although no difference was seen in the rate of breast conservation surgery (OR 0.98, 95% CI 0.80 to 1.19, $p = 0.82$).⁹⁸ A higher rate of breast conservation surgery has been reported in one trial of patients with locally advanced breast cancer receiving neoadjuvant trastuzumab in addition to chemotherapy (23% v 13%).⁹⁹

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A combined analysis of neoadjuvant and adjuvant trials reported a significantly increased risk of congestive heart failure (RR 5.11, 90% CI 3.00 to 8.72, $p < 0.00001$) and LVEF decline (RR 1.83, 90% CI 1.36 to 2.47, $p = 0.0008$) when trastuzumab is added to chemotherapy.⁷¹ There was no difference in haematological toxicities.

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R Patients with HER-2 positive breast cancer, receiving neoadjuvant chemotherapy, should receive trastuzumab, either as adjuvant treatment or with non-anthracycline-based neoadjuvant chemotherapy.

Cardiac function should be monitored in patients being treated with anthracyclines and/or trastuzumab.

Trastuzumab should be used with caution in patients with significant cardiac comorbidity. The benefits of adjuvant chemotherapy with or without trastuzumab may be outweighed by the potential harms in these patients, and treatment should only be recommended after careful consideration.

6.1.4 SUBTYPES

Two RCTs have demonstrated that the best predictor of response for pCR following neoadjuvant therapy is ER and progesterone receptor (PR) negativity (OR 3.08, 95% CI 2.32 to 4.09, $p < 0.001$).^{100, 101} In most breast cancer subtypes pCR is associated with improved DFS and OS in comparison to those patients where pCR is not observed.¹⁰² However, in patients with lower grade ER-positive tumours it is unusual to achieve pCR and failure to do so does not appear to be predictive of poorer outcomes.¹⁰²

1++
1+

6.2 NEOADJUVANT ENDOCRINE THERAPY

A meta-analysis of trials conducted in postmenopausal women concluded that an aromatase inhibitor is associated with higher clinical response rate, RR 1.29 (95% CI 1.14 to 1.47) and radiological (ultrasound) response rate, (RR 1.29, 95% CI 1.10 to 1.51) when compared with tamoxifen.¹⁰³ Aromatase inhibitor is also associated with a higher rate of breast conservation surgery than tamoxifen, (RR 1.36, 95% CI 1.16 to 1.59).¹⁰³ Although no data on long term outcome (DFS, OS) were reported, adjuvant studies demonstrate that treatment with an AI is likely to be superior (*see section 5.2*).

1+

In postmenopausal women, there was no significant difference in the rates of hot flushes, nausea, or fatigue in the aromatase inhibitor group compared with tamoxifen groups. Headache was more common in the women treated with AI (RR 2.02, 95% CI 1.18 to 3.45).¹⁰³

1+

One Japanese RCT showed AI and concomitant ovarian suppression to be superior to tamoxifen in pre-menopausal women.¹⁰³ There are insufficient data to guide the optimum endocrine therapy in pre-menopausal women.

1+

There is insufficient evidence to recommend one AI over another, or for duration of therapy.

R Aromatase inhibitor is recommended for ER positive postmenopausal women receiving neoadjuvant endocrine therapy.

7 Breast cancer in men

No trials on the treatment of men with breast cancer were identified for any of the key questions addressed in this guideline (see *Annex 1*).

The consensus of the guideline development group is that men with breast cancer should be treated following the same recommendations as for women, with the exception of receiving tamoxifen as first line endocrine treatment.

8 Provision of information

This section reflects the issues likely to be of most concern to patients and their carers. These points are provided for use by health professionals when discussing breast cancer with patients and carers and in guiding the production of locally produced information materials.

8.1 SOURCES OF FURTHER INFORMATION

Breast Cancer Care

169 Elderslie Street, Glasgow G3 7JR
 Helpline: 0808 800 6000 • Tel: 0845 077 1892
www.breastcancercare.org.uk • Email: sco@breastcancercare.org.uk

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

Breakthrough Breast Cancer

38 Thistle Street, Edinburgh EH2 1EN
 Tel: 0131 226 0761
www.breakthrough.org.uk/scotland • Email: info@breakthrough.org.uk

Breakthrough Breast Cancer funds research, campaigns on breast cancer issues and promotes early detection breast cancer.

Calman Cancer Support Centre

Cancer Support Scotland, Gartnavel Hospital Complex
 1053 Great Western Road, Glasgow G12 0YN
 Freephone: 0800 652 4531 • Tel: 0141 337 8199
www.cancersupportscotland.org

The Calman Cancer Support Centre provides emotional and practical support on a one-to-one basis and through community based groups. It provides complementary and talking therapies to anyone affected by cancer.

Cancer Research UK

PO Box 123, 61 Lincoln's Inn Fields, London WC2A 3PX
 Tel: 020 7242 0200
www.cancerresearchuk.org

Cancer Research UK funds research into cancer, campaigns on cancer issues and produces patient information leaflets.

CancerHelp UK

Tel: 0800 800 4040
www.cancerhelp.org.uk • www.cancerresearchuk.org/cancer-help

CancerHelp UK is a free information service about cancer and cancer care for people with cancer and their families. It is provided by Cancer Research UK. The site includes a comprehensive range of information including cancer prevention, diagnosis, treatment and follow up.

CLAN Cancer Support

120 Westburn Road, Aberdeen AB25 2QA
 Tel: 01224 647000
www.clanhouse.org • Email: enquiries@clanhouse.org

CLAN Cancer Support provides emotional and practical support to people with cancer, families and carers in the northeast of Scotland, Orkney and Shetland.

Macmillan Cancer Support (Scotland)

132 Rose Street, Edinburgh EH2 3JD

Tel: 0808 808 00 00

www.macmillan.org.uk • Email: southscotland@macmillan.org.uk

Macmillan Cancer Support supports people with cancer (and their families) with practical, medical, emotional and financial advice.

Maggie's Centres Scotland

www.maggiescentres.org • Email: enquiries@maggiescentres.org

Maggie's provides practical, emotional and social support to people with cancer, their family and friends. Built alongside NHS cancer hospitals and staffed with professional experts, Maggie's Centres are warm and welcoming, full of light and open space, with a big kitchen table at their heart.

Maggie's Dundee

Tom McDonald Avenue, Ninewells Hospital, Dundee DD2 1NH

Tel: 01382 632999 • Email: dundee@maggiescentres.org

Maggie's Edinburgh

The Stables, Western General Hospital, Crewe Road South, Edinburgh EH4 2XU

Tel: 0131 537 3131 • Email: edinburgh@maggiescentres.org

Maggie's Fife

Victoria Hospital, Hayfield Road, Kirkcaldy KY2 5AH

Tel: 01592 647997 • Email: fife@maggiescentres.org

Maggie's Glasgow

Gartnavel General Hospital, 1053 Great Western Road, Glasgow G12 0YN

Tel: 0141 357 2269 • Email: glasgow@maggiescentres.org

Maggie's Highlands

Raigmore Hospital, Old Perth Road, Inverness IV2 3UJ

Tel: 01463 706306 • Email: highlands@maggiescentres.org

Maggie's Lanarkshire

Flat 78, Residential Accommodation, Wishaw General Hospital, 50 Netherton Road, Wishaw ML2 0DP

Tel: 01698 358392 • Email: lanarkshire@maggiescentres.org

Marie Curie Cancer Care (Scotland)

14 Links Place, Edinburgh EH6 7EB

Tel: 0800 716 146

www.mariecurie.org.uk

Marie Curie Cancer Care provides practical nursing care at home and specialist care across ten Marie Curie centres.

Princess Royal Trust for Carers

Skypark 3, Suite 1/2, 14/18 Elliott Place, Glasgow G3 8EP

Tel: 0300 123 2008

www.carers.org

The Princess Royal Trust for Carers provides information, advice and support for carers.

Scottish Cancer Networks

www.scan.scot.nhs.uk

Scottish Cancer Networks provides relevant information to patients having cancer treatment which is specific to their local area.

8.2 CHECKLIST FOR PROVISION OF INFORMATION

This section gives examples of the information patients and carers may find helpful at the key stages of the patient journey. The checklist was designed by members of the guideline development group based on their experience and their understanding of the evidence base. The checklist is neither exhaustive nor exclusive.

Patients differ in the amount of information they want. Information and support for family members and carers should also be considered, in line with the patient's wishes.

Initial presentation and referral
<ul style="list-style-type: none"> • Be clear about which department the patient is being referred on to and how long it should take before receiving an appointment date. • Let the patient know why the appointment is required and what will happen. • Have information leaflets available and details of where other sources of support can be found.
Diagnosis
<ul style="list-style-type: none"> • A full explanation of all tests, why they are needed and what they entail, should be available. • When having to wait for test results, be clear about when they will be available, how they will be given to the patient, who will give them and who else will receive a copy, ie hospital departments, GP etc. • Ascertain family history and/or genetic risk as appropriate. • Ensure the patient has contact details for the breast care nurse and is aware of their role. • Have information leaflets available and details of where other sources of support can be found.
Treatment
<ul style="list-style-type: none"> • Explain the surgical options available, including reconstruction if appropriate. Patients may wish to know about how they will look and feel after surgery. • Explain about the limited movement the patient may have, immediately after surgery, and ensure that instructions for exercises are given. • Discuss practical issues around breast prosthesis and bras, if appropriate. • Discuss chemotherapy/radiotherapy, their procedures, including number and duration of sessions, and how and when they will take place. • Discuss side effects and how they can be managed. Let the patient know that not all people will react to the same treatments in the same way. • Provide practical advice on hair loss, eg where to obtain a wig. • Inform patients of treatment plans and advise them of the timeframe for treatment. • Provide a copy of the expected treatment plan. • Ensure patients are offered participation in a clinical trial when available and appropriate. • Advise patients of where they can receive information about financial issues.
Follow up
<ul style="list-style-type: none"> • Ensure patients understand the importance of attending ongoing follow-up appointments after discharge and inform them of how they are likely to be followed up, ie by whom, where and when. • Mention and discuss the possibility of recurrence and advise patients to report on specific symptoms. • Practical and psychological support may be needed for patients for many years following treatment. • Provide details of where patients can receive support, advice and information on life after cancer/survivorship.

9 Implementing the guideline

This section provides advice on the resource implications associated with implementing the key clinical recommendations, and advice on audit as a tool to aid implementation.

9.1 IMPLEMENTATION STRATEGY

Implementation of national clinical guidelines is the responsibility of each NHS Board and is an essential part of clinical governance. Mechanisms should be in place to review care provided against the guideline recommendations. The reasons for any differences should be assessed and addressed where appropriate. Local arrangements should then be made to implement the national guideline in individual hospitals, units and practices.

9.2 RESOURCE IMPLICATIONS OF KEY RECOMMENDATIONS

No recommendations were identified as having significant budgetary impact.

9.3 AUDITING CURRENT PRACTICE

A first step in implementing a clinical practice guideline is to gain an understanding of current clinical practice. Audit tools designed around guideline recommendations can assist in this process. Audit tools should be comprehensive but not time consuming to use. Successful implementation and audit of guideline recommendations requires good communication between staff and multidisciplinary team working.

The guideline development group has identified the following as key points to audit to assist with the implementation of this guideline:

- number of referrals to the Clinical Genetics Service of individuals who may have an inherited increased risk of breast cancer
- rates of local recurrence or second tumour
- rates of mastectomy and breast reconstruction
- outcomes of treatment, including treatment-related morbidity and mortality, disease-free survival and overall survival.

9.4 ADDITIONAL ADVICE TO NHSSCOTLAND FROM HEALTHCARE IMPROVEMENT SCOTLAND AND THE SCOTTISH MEDICINES CONSORTIUM

- In June 2006 the Scottish Medicines Consortium accepted trastuzumab for restricted use within NHSScotland for the treatment of patients with HER-2 positive early breast cancer following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable).
- Anastrozole 1 mg tablet is accepted for restricted use within NHSScotland for the adjuvant treatment of early breast cancer in hormone receptor positive postmenopausal women who have received two to three years of adjuvant tamoxifen. Treatment with anastrozole is restricted to initiation by a breast cancer specialist (November 2006).
- Exemestane is accepted for restricted use within NHSScotland for the adjuvant treatment of postmenopausal women with oestrogen receptor positive invasive early breast cancer, following two to three years of initial adjuvant tamoxifen therapy. Treatment with exemestane is restricted to initiation by a breast cancer specialist (November 2005).
- Letrozole is accepted for restricted use for the treatment of invasive early breast cancer in postmenopausal women who have received prior standard adjuvant tamoxifen therapy. Treatment should continue for three years or until tumour relapse, whichever occurs first. Clinicians and patients should consider the residual risk of recurrence, individual preferences and the risks and benefits of treatment. Letrozole is restricted to initiation by breast cancer specialists (March 2005).

10 The evidence base

10.1 SYSTEMATIC LITERATURE REVIEW

The evidence base for this guideline was synthesised in accordance with SIGN methodology. A systematic review of the literature was carried out using an explicit search strategy devised by a SIGN Evidence and Information Scientist. Databases searched include Medline, Embase, Cinahl, PsycINFO and the Cochrane Library. The year range covered was 2003-2011. Internet searches were carried out on various websites including the US National Guidelines Clearinghouse. The main searches were supplemented by material identified by individual members of the development group. Each of the selected papers was evaluated by two members of the group using standard SIGN methodological checklists before conclusions were considered as evidence.

10.1.1 LITERATURE SEARCH FOR PATIENT ISSUES

At the start of the guideline development process, a SIGN Evidence and Information Scientist conducted a literature search for qualitative and quantitative studies that addressed patient issues of relevance to management of patients with early breast cancer. Databases searched include Medline, Embase, Cinahl and PsycINFO, and the results were summarised and presented to the guideline development group.

10.2 RECOMMENDATIONS FOR RESEARCH

The guideline development group was not able to identify sufficient evidence to answer all of the key questions asked in this guideline (*see Annex 1*). The following areas for further research have been identified:

- efficacy of therapies for men with breast cancer
- the duration of trastuzumab treatment
- efficacy of chemotherapy regimens for patients with triple negative breast cancer
- efficacy of routine use of tests of expression of certain genes or immunohistochemical expression to aid treatment decision making
- comparison of neoadjuvant hormonal therapy with neoadjuvant chemotherapy
- efficacy of neoadjuvant hormone therapy in pre-menopausal women.

10.3 REVIEW AND UPDATING

This guideline was issued in 2013 and will be considered for review in three years. Any updates to the guideline in the interim period will be noted on the SIGN website: www.sign.ac.uk

11 Development of the guideline

11.1 INTRODUCTION

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

11.2 THE GUIDELINE DEVELOPMENT GROUP

Professor Steven D Heys (Chair)	<i>Head, Division of Applied Medicine and Co-Director, Institute of Medical Sciences, Aberdeen</i>
Dr Abdulla Alhasso	<i>Consultant Clinical Oncologist, Beatson West of Scotland Cancer Centre, Glasgow</i>
Ms Gillian Barmack	<i>Pharmacist, Beatson West of Scotland Cancer Centre, Glasgow</i>
Dr Sophie Barrett	<i>Consultant Medical Oncologist, Beatson West of Scotland Cancer Centre, Glasgow</i>
Dr Carolyn Bedi	<i>Consultant Clinical Oncologist, Edinburgh Cancer Centre</i>
Dr Hilary Dobson	<i>Radiologist and Clinical Director, West of Scotland Breast Screening Service, Glasgow</i>
Dr Graeme Lumsden	<i>Consultant Clinical Oncologist, Beatson West of Scotland Cancer Centre, Glasgow</i>
Dr Iain MacPherson	<i>Clinical Senior Lecturer, Beatson Institute for Cancer Research, Glasgow</i>
Dr Elizabeth Mallon	<i>Consultant Pathologist, Western Infirmary, Glasgow</i>
Ms Jan Manson	<i>Evidence and Information Scientist, SIGN</i>
Mr Glyn Neades	<i>Consultant Breast Surgeon, Western General Hospital, Edinburgh</i>
Dr Ravi Sharma	<i>Consultant Clinical Oncologist, Aberdeen Royal Infirmary</i>
Miss Pat Shields	<i>Patient representative, Orkney</i>
Ms Ailsa Stein	<i>Programme Manager, SIGN</i>
Ms Eva Weiler-Mithoff	<i>Consultant Plastic Surgeon, Glasgow Royal Infirmary</i>

The membership of the guideline development group was confirmed following consultation with the member organisations of SIGN. A register of interests is available in the supporting material section for this guideline at www.sign.ac.uk.

Guideline development and literature review expertise, support and facilitation were provided by the SIGN Executive. All members of the SIGN Executive make yearly declarations of interest and further details of these are available on request.

Mrs Lesley Forsyth	<i>Events Coordinator</i>
Mrs Karen Graham	<i>Patient Involvement Officer</i>
Ms Gemma Hardie	<i>Distribution and Office Coordinator</i>
Mr Stuart Neville	<i>Publications Designer</i>
Miss Gaynor Rattray	<i>Guideline Coordinator</i>

11.2.1 ACKNOWLEDGEMENTS

SIGN is grateful to the following former members of the guideline development group and others who have contributed to the development of the guideline.

Ms Senga McNeill	<i>Breast Care Nurse, Royal Alexandra Hospital, Paisley</i>
Mr John Rainey	<i>Consultant Breast Surgeon, Borders General Hospital, Melrose</i>
Mrs Carole Smith	<i>Lay representative, Rosyth</i>

11.3 CONSULTATION AND PEER REVIEW

11.3.1 SPECIALIST REVIEW

This guideline was also reviewed in draft form by the following independent expert referees, who were asked to comment primarily on the comprehensiveness and accuracy of interpretation of the evidence base supporting the recommendations in the guideline. The guideline group addresses every comment made by an external reviewer, and must justify any disagreement with the reviewers' comments. All expert referees made declarations of interest and further details of these are available on request from the SIGN Executive.

SIGN is very grateful to all of these experts for their contribution to the guideline.

Miss Elaine Anderson	<i>Clinical Director, Western General Hospital, Edinburgh</i>
Ms Emma Bennett	<i>Lead Clinical Nurse Specialist for Breast Cancer, Western General Hospital, Edinburgh</i>
Dr Patrick Cadigan	<i>Registrar, Royal College of Physicians, London</i>
Professor David Cameron	<i>Professor of Oncology, Edinburgh Cancer Research Centre</i>
Mr Robert Carpenter	<i>Consultant Breast Surgeon, King Edward VII's Hospital, London</i>
Professor Rob Coleman	<i>Professor of Medical Oncology and Associate Director of the National Institute for Health Research Cancer Research Network, Weston Park Hospital, Sheffield</i>
Professor Michael Dixon	<i>Professor of Surgery and Consultant Surgeon, Western General Hospital, Edinburgh</i>
Ms Christine Dodds	<i>SCAN Senior Cancer Audit Facilitator, Western General Hospital, Edinburgh</i>
Professor Lesley Fallowfield	<i>Professor of Psycho-oncology, University of Sussex</i>
Mr Myles Fitt	<i>Campaigns Manager for Scotland, Breakthrough Breast Cancer, Edinburgh</i>
Ms Avril Gunning	<i>Macmillan Clinical Nurse Specialist (Breast), Ninewells Hospital, Dundee</i>
Dr Adrian Harnett	<i>Consultant in Clinical Oncology, Norfolk and Norwich University Hospital</i>
Professor Ian Kunkler	<i>Professor of Clinical Oncology, Western General Hospital, Edinburgh</i>
Mr Graham Layer	<i>Honorary Secretary, Royal College of Surgeons, Edinburgh</i>
Ms Anne Lee	<i>Chief Pharmacist, Scottish Medicines Consortium</i>
Miss Jeda Lewis	<i>Lay Representative, Edinburgh</i>
Dr Caroline Michie	<i>Consultant Medical Oncologist and Honorary Clinical Tutor, Ninewells Hospital, Dundee</i>
Ms Niamh O'Rourke	<i>General Manager, National Cancer Control Programme, Dublin</i>
Professor Sarah Pinder	<i>Professor of Breast Pathology, King's College London</i>

Mr John Rainey	<i>Consultant Surgeon, Borders General Hospital, Melrose</i>
Dr Sabien Stordeur	<i>Senior Expert Clinician and Health Services Research, Belgian Healthcare Knowledge Centre</i>
Professor Alastair Thompson	<i>Professor of Surgical Oncology, Ninewells Hospital, Dundee</i>
Dr Matthew Wallis	<i>Consultant Radiologist, Addenbrooke's Hospital, Cambridge</i>
Ms Philippa Whitford	<i>Consultant Breast Surgeon, Crosshouse Hospital, Kilmarnock</i>
Dr Robin Wilson	<i>Consultant Radiologist, The Royal Marsden, London</i>

11.3.2 PUBLIC CONSULTATION

The draft guideline was available on the SIGN website for a month to allow all interested parties to comment. Comments from the public consultation were addressed alongside those of the specialist reviewers. All contributors made declarations of interest and further details of these are available on request from the SIGN Executive.

SIGN is very grateful to all of these experts for their contribution to the guideline.

Dr Douglas Adamson	<i>Consultant Clinical Oncologist and Honorary Senior Lecturer, Ninewells Hospital, Dundee</i>
Mr Rory Buchan	<i>Senior Medical Advisor, GlaxoSmithKline UK, Middlesex</i>
Mrs Clare Marley	<i>Market Access Manager, AstraZeneca UK, Luton</i>
Ms Heidi May	<i>Nurse Director, NHS Highland</i>
Ms Sandra White	<i>MacMillan Nurse Consultant in Cancer, NHS Ayrshire and Arran</i>

11.3.3 SIGN EDITORIAL GROUP

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

All members of the SIGN Editorial group make yearly declarations of interest and further details of these are available on request from the SIGN Executive. The editorial group for this guideline was as follows:

Dr Grant Baxter	<i>Royal College of Radiologists</i>
Professor Keith Brown	<i>Chair of SIGN; Co-Editor</i>
Mr Ian Colquhoun	<i>Royal College of Physicians and Surgeons of Glasgow</i>
Dr Roberta James	<i>SIGN Programme Lead; Co-Editor</i>
Dr Paddy Niblock	<i>Royal College of Radiologists</i>
Dr Sara Twaddle	<i>Director of SIGN; Co-Editor</i>

Abbreviations

4AC	four standard cycles of AC
AC	adriamycin, cyclophosphamide
ACE	angiotensin converting enzyme
AD	absolute difference
AI	aromatase inhibitor
ALND	axillary lymph node dissection
AMAROS	After Mapping of the Axilla: Radiation or Surgery
BED	biological effective dose
BIG	Breast International Group
BMD	bone mineral density
BNF	British National Formulary
CHF	congestive heart failure
CI	confidence interval
CMF	cyclophosphamide, methotrexate and 5-fluorouracil
DCIS	ductal carcinoma in situ
DEXA	dual energy X-ray absorptiometry
DFS	disease-free survival
EBRT	external beam radiotherapy
EORTC	European Organisation for Research and Treatment of Cancer
ER	oestrogen receptor
ER+	oestrogen receptor positive
FAC	5-fluorouracil, adriamycin and cyclophosphamide
FEC	5-fluorouracil, cyclophosphamide and epirubicin
FISH	fluorescence in situ hybridisation
GMC	General Medical Council
HR	hazard ratio
HER-2	human epidermal growth factor receptor 2
HERA	HERceptin Adjuvant
IHC	immunohistochemistry
IORT	intraoperative radiotherapy
LVEF	left ventricular ejection fraction
LHRH	luteinising hormone releasing hormone
MA	marketing authorisation
MINDACT	Microarray In Node-negative and 1 to 3 positive lymph node Disease may Avoid ChemoTherapy

MDT	multidisciplinary team
MTA	multiple technology appraisal
NICE	National Institute for Health and Care Excellence
NPI	Nottingham Prognostic Index
OR	odds ratio
OS	overall survival
PBI	partial breast irradiation
pCR	pathological complete response
PHARE	Protocol for Herceptin® as Adjuvant therapy with Reduced Exposure
PMRT	post-mastectomy radiotherapy
PR	progesterone receptor
PRIME	Post-operative Radiotherapy in Minimum-risk Elderly
RCT	randomised controlled trial
RR	relative risk
RxPONDER	Rx for Positive Node, Endocrine Responsive Breast Cancer
SE	standard error
SIGN	Scottish Intercollegiate Guidelines Network
SLNB	sentinel lymph node biopsy
SMC	Scottish Medicines Consortium
SPC	summary of product characteristics
SUPREMO	Selective Use of Postoperative Radiotherapy After Mastectomy
TAILORx	Trial Assigning Individualized Options for Treatment

Annex 1

Key questions addressed in this update

This guideline is based on a series of structured key questions that define the target population, the intervention, diagnostic test, or exposure under investigation, the comparison(s) used and the outcomes used to measure efficacy, effectiveness, or risk. These questions form the basis of the systematic literature search.

Key question	See guideline section
<p>1. In patients with breast cancer (pre-menopausal women, postmenopausal women, men) who are:</p> <p>Node + vs node – ER+ vs ER – HER-2+ vs HER-2- PR+vs PR-</p> <p>what is the evidence that adjuvant chemotherapy is effective, compared to no treatment or non-chemotherapy treatment, and what is the optimal chemotherapy regimen?</p> <p>Interventions/comparisons</p> <p>a) Anthracycline-containing regimens b) Taxane-containing regimens c) Trastuzumab (consider number of cycles, sequential versus concomitant)</p> <p>Outcomes</p> <p>Local recurrence >2 months Overall survival 5yrs, 10 yrs Disease-free survival 5yrs, 10 yrs Regional recurrence >2 months Toxicity (Level 3-5, and including febrile neutropenia, cardiac toxicity)</p>	5.1
<p>2. In patients with breast cancer (pre-menopausal women, postmenopausal women, men) who are ER+ or PR+ what is the evidence that adjuvant hormone therapy is effective and what is the optimum duration of therapy?</p> <p>Interventions</p> <p>Tamoxifen Aromatase inhibitors</p> <p>Comparisons</p> <p>AI versus tamoxifen Sequential tamoxifen, AI Concomitant tamoxifen and AI Ovarian suppression/ablation</p> <p>Outcomes</p> <p>Local recurrence >2 months Overall survival 5yrs, 10 yrs Disease-free survival 5yrs, 10 yrs Fertility preservation Adverse effects (include venous thromboembolism, menopausal symptoms, endometrial cancer, nausea, change in bone mineral density, fracture) Quality of life</p>	5.2

<p>5. In women and men with breast cancer who are being treated with aromatase inhibitors chemotherapy</p> <p>what is the evidence that treatment with bisphosphonates:</p> <p>a) provides protection from skeletal events? b) is effective as a disease modifying treatment?</p> <p>How should these patients be monitored?</p> <p>Intervention Bisphosphonates (after bone loss has occurred) AI/chemotherapy and concomitant bisphosphonates</p> <p>Comparison No bisphosphonates Other fracture treatment</p> <p>Outcomes Change in BMD Fracture Harms/risks (include osteonecrosis of the jaw, renal and gastrointestinal effects) Disease recurrence</p>	5.4								
<p>6. In breast cancer patients who have undergone a mastectomy, what is the evidence that radiotherapy to the chest wall improves outcome?</p> <p>Intervention Radiotherapy (any dose/cycle)</p> <p>Comparison No radiotherapy</p> <p>Outcomes</p> <table data-bbox="276 1283 798 1422"> <tr> <td>Local recurrence</td> <td>>2 months</td> </tr> <tr> <td>Overall survival</td> <td>5yrs, 10 yrs</td> </tr> <tr> <td>Disease-free survival</td> <td>5yrs, 10 yrs</td> </tr> <tr> <td>Regional recurrence</td> <td>>2 months</td> </tr> </table> <p>Cosmesis Toxicity</p>	Local recurrence	>2 months	Overall survival	5yrs, 10 yrs	Disease-free survival	5yrs, 10 yrs	Regional recurrence	>2 months	4.3
Local recurrence	>2 months								
Overall survival	5yrs, 10 yrs								
Disease-free survival	5yrs, 10 yrs								
Regional recurrence	>2 months								
<p>7. In patients with DCIS who have undergone breast conservation surgery, what is the evidence that adjuvant radiotherapy improves outcome?</p> <p>Intervention Radiotherapy (any dose/cycle)</p> <p>Comparison No radiotherapy</p> <p>Outcomes</p> <table data-bbox="276 1816 798 1955"> <tr> <td>Local recurrence</td> <td>>2 months</td> </tr> <tr> <td>Overall survival</td> <td>5yrs, 10 yrs</td> </tr> <tr> <td>Disease-free survival</td> <td>5yrs, 10 yrs</td> </tr> <tr> <td>Regional recurrence</td> <td>>2 months</td> </tr> </table> <p>Cosmesis Toxicity</p>	Local recurrence	>2 months	Overall survival	5yrs, 10 yrs	Disease-free survival	5yrs, 10 yrs	Regional recurrence	>2 months	4.1
Local recurrence	>2 months								
Overall survival	5yrs, 10 yrs								
Disease-free survival	5yrs, 10 yrs								
Regional recurrence	>2 months								

<p>8a. In breast cancer patients who have undergone breast conservation treatment, what is the evidence that adjuvant radiotherapy improves outcome and what is the optimal dose regimen?</p> <p>Intervention Radiotherapy >2 Gy/fraction ≤ 2 Gy/fraction</p> <p>Outcomes Local recurrence >2 months Overall survival 5yrs, 10 yrs Disease-free survival 5yrs, 10 yrs Regional recurrence >2 months Cosmesis Harms including pain and toxicity</p>	<p>4.1</p>
<p>8b. In otherwise healthy breast cancer patients who have undergone breast conservation treatment are there any sub-populations in terms of age, tumour size and nodal involvement where radiotherapy is not necessary? What are the outcomes for these patients?</p> <p>Outcomes Survival Local recurrence Cosmesis Pain Number of mastectomies</p>	<p>4.1</p>
<p>9. In patients with breast cancer who have undergone breast conservation surgery, what is the evidence that a radiotherapy boost improves outcome and is there evidence of an optimal dosage?</p> <p>Intervention Radiotherapy boost (aimed at tumour bed with or without the use of clips)</p> <p>Comparisons No radiotherapy boost</p> <p>Outcomes Local recurrence Overall survival 5yrs, 10 yrs Disease-free survival 5yrs, 10 yrs Regional recurrence Cosmesis Toxicity</p>	<p>4.2</p>

<p>10. In patients who have undergone surgery for breast cancer:</p> <p>a) what evidence is there that time from final surgery to starting a first adjuvant therapy (radio and/ or chemo) influences outcome? b) what is the optimum sequencing of treatment?</p> <p>Intervention Adjuvant radiotherapy (any accepted regimen) Adjuvant chemotherapy (any accepted regimen)</p> <p>Comparisons 0-6 wks after surgery 6-12 wks after surgery > 12 wks after surgery</p> <p>Outcomes Local recurrence >2 months Overall survival 5yrs, 10 yrs Disease-free survival 5yrs, 10 yrs Regional recurrence</p>	5.1
<p>11. In patients with invasive breast cancer with node + disease who have undergone axillary node clearance, who should receive treatment to the supraclavicular fossa?</p> <p>Outcomes Local recurrence >2 months Overall survival 5yrs, 10 yrs Disease-free survival 5yrs, 10 yrs Regional recurrence</p>	4.5
<p>12. In patients with operable in situ or invasive breast cancer, what is the evidence that breast conservation surgery is more or less effective than mastectomy?</p> <p>Outcomes Local recurrence >2 months Overall survival 5, 10, >15 years Disease-free survival 5, 10, >15 years Regional (axillary) recurrence >2 months Cosmesis symmetry, scarring Postoperative pain duration, intensity Quality of life</p>	3.1
<p>13. In patients with operable in situ or invasive breast cancer undergoing breast conservation surgery what is the evidence that oncoplastic therapeutic mammoplasty is more or less effective than standard conservation surgery in terms of:</p> <p>Local recurrence >2 months Overall survival 5, 10, >15 years Disease-free survival 5, 10, >15 years Regional (axillary) recurrence >2 months Cosmesis symmetry, scarring Postoperative pain duration, intensity Quality of life</p>	3.1

<p>14. Which patients undergoing mastectomy for operable breast cancer are at risk of contralateral cancer:</p> <p>(a) Those with no previous history of breast cancer and who have not been identified as being at an increased risk of breast cancer?</p> <p>(b) Those who have had a previous breast cancer and who now have a local recurrence/second primary breast cancer in the ipsilateral or contralateral breast?</p> <p>(c) Those with breast cancer and who had previously been identified as being at an increased risk (medium or high)?</p>	<p>3.2</p>
<p>15. In patients who are suitable for breast reconstruction, is there any evidence that immediate as compared to delayed reconstruction impacts on:</p> <p>Local recurrence >2 months</p> <p>Overall survival 5, 10, >15 years</p> <p>Disease-free survival 5, 10, >15 years</p> <p>Regional (axillary) recurrence >2 months</p> <p>Cosmesis symmetry, scarring</p> <p>Postoperative pain duration, intensity</p> <p>Quality of life</p> <p>Donor site morbidity</p> <p>Time to delivery of adjuvant treatment</p>	<p>3.4</p>
<p>16. What is the appropriate management of the axilla in patients with operable (invasive) breast cancer?</p> <p>(a) Those with <u>no</u> evidence of axillary lymph nodes metastases at initial diagnosis? (based on clinical, imaging fine-needle aspiration cytology/core biopsy)</p> <p>(b) Those patients undergoing primary chemotherapy (before or after chemotherapy)</p> <p>(c) Patients with DCIS</p> <p>(d) Those patients undergoing immediate breast reconstruction?</p> <p>Intervention/comparison:</p> <p>Axillary node clearance</p> <p>Axillary node sampling</p> <p>Sentinal node biopsy</p> <p>Outcomes:</p> <p>Overall survival 5, 10, >15 years</p> <p>Regional recurrence</p> <p>Upper limb morbidity</p> <p>Lymphoedema</p> <p>Pain</p> <p>Risk of anaphylaxis with blue dye used for SLNB</p>	<p>3.3</p>

Annex 2

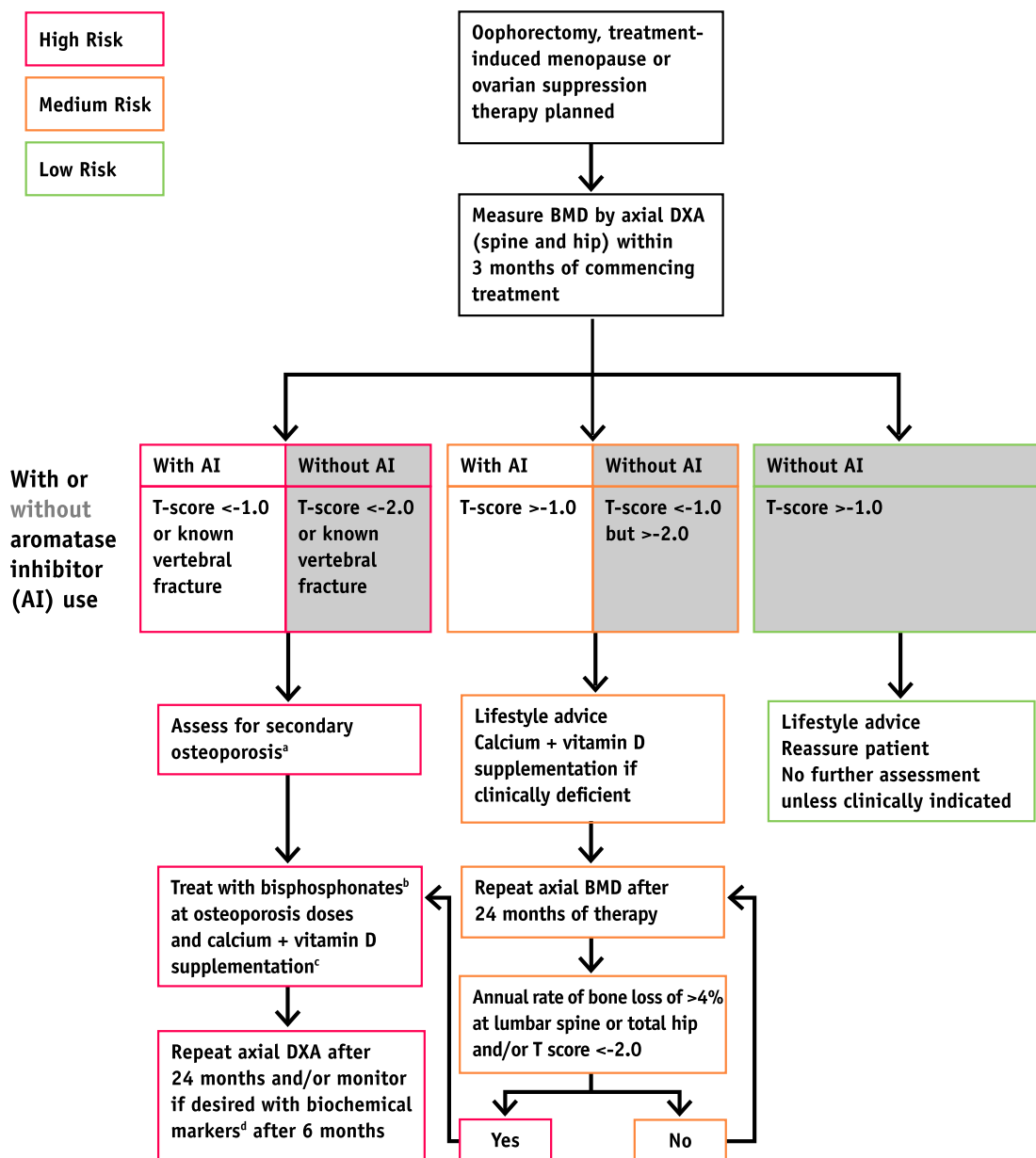
TNM Classification for breast cancer¹⁰⁴

Tis	In situ
T1	Tumour ≤ 2 cm
T2	> 2 cm to 5 cm
T3	> 5 cm
T4	Chest wall/skin ulceration, skin nodules, inflammatory
N1	Movable axillary
N2a	Fixed axillary
N2b	Internal mammary clinically apparent
N3a	Infra-clavicular
N3b	Internal mammary and axillary
N3c	Supraclavicular

Stage grouping			
Stage 0	Tis	N0	M0
Stage IA	T1*	N0	M0
Stage IB	T0, T1*	N1mi	M0
Stage IIA	T0, T1*	N1	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0, T1*, T2	N2	M0
	T3	N1, N2	M0
Stage IIIB	T4	N0, N1, N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1
*T1 includes T1mi			

Annex 3

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 / YGT), 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

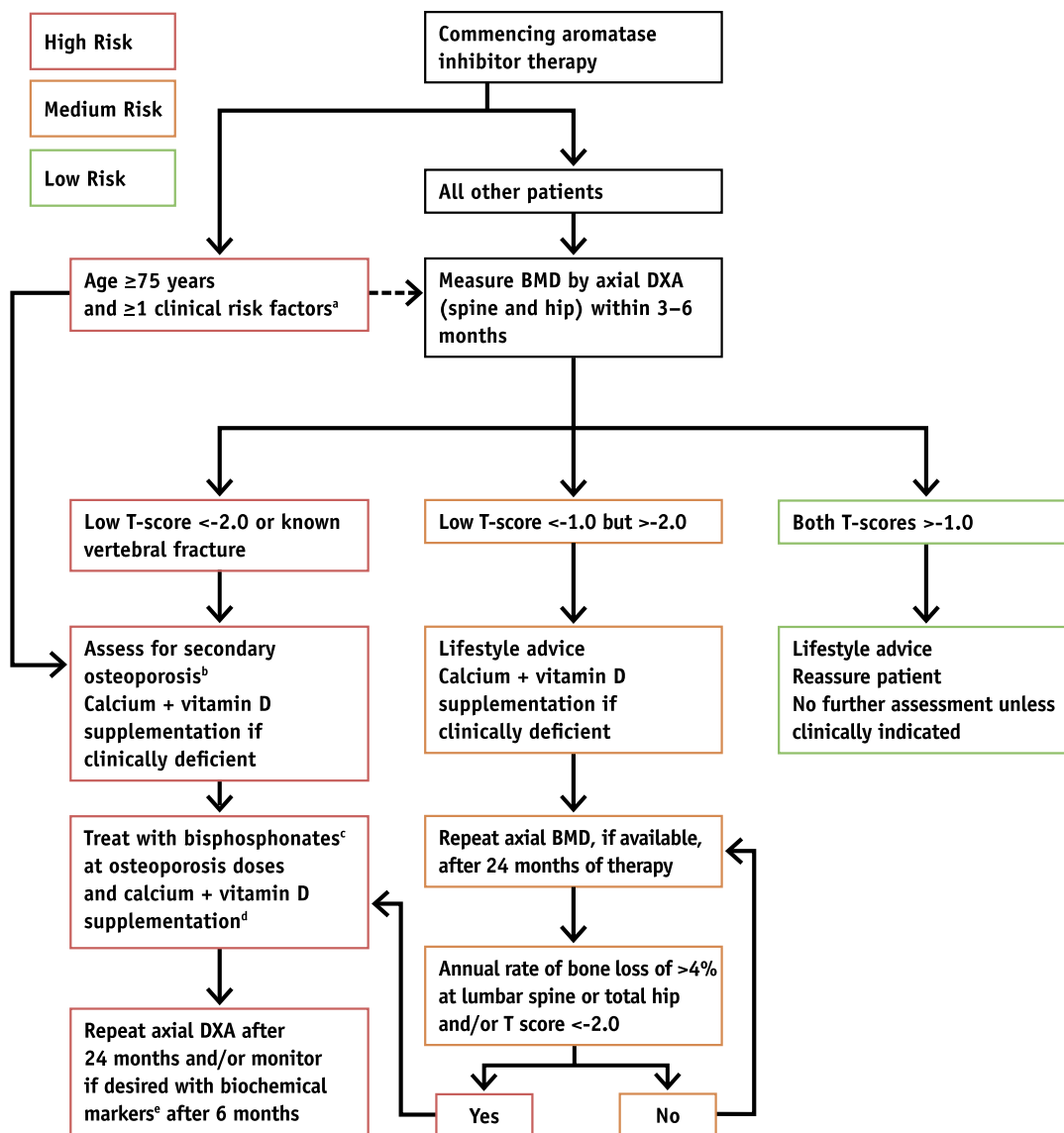
c To be given as ≥ 1 g of calcium + ≥ 800 IU of vitamin D

d Biochemical markers such as serum C-terminal telopeptide of type I collagen or urinary N-telopeptide of type I collagen

Reprinted from Reid DM, Doughty J, Eastell R, Heys SD, Howell A, McCloskey EV, et al. Guidance for the management of breast cancer treatment-induced bone loss: A consensus position statement from a UK Expert Group. *Cancer Treat Rev.* 2008;34 Suppl 1:S3-18 with permission from Elsevier.

Annex 4

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 / YGT), 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

Reprinted from Reid DM, Doughty J, Eastell R, Heys SD, Howell A, McCloskey EV, et al. Guidance for the management of breast cancer treatment-induced bone loss: A consensus position statement from a UK Expert Group. Cancer Treat Rev. 2008;34 Suppl 1:S3-18 with permission from Elsevier.

References

- Information Services Division (ISD). Cancer in Scotland (2010). NHS National Services Scotland; 2012. [cited 21 Aug 2013]. Available from url: <http://www.isdscotland.org/Health-Topics/Cancer/Publications/2012-04-24/2012-04-24-Cancer-Incidence-report.pdf?49042910338>
- van Nes JG, Seynaeve C, Jones S, Markopoulos C, Putter H, van de Velde CJ, et al. Variations in locoregional therapy in postmenopausal patients with early breast cancer treated in different countries *Br J Surg* 2010;97(5):671-9.
- Bates T, Kearins O, Monypenny I, Lagord C, Lawrence G. Clinical outcome data for symptomatic breast cancer: the Breast Cancer Clinical Outcome Measures (BCCOM) Project. *Br J Cancer* 2009;101(3):395-402.
- Royal College of Obstetricians and Gynaecologists. Pregnancy and breast cancer. London: RCOG; 2011. (RCOG Green-top Guideline No. 12). [cited 21 Aug 2013]. Available from url: <http://www.rcog.org.uk/files/rcog-corp/GTG12PregBreastCancer.pdf>
- Guidance on prescribing. In: The British National Formulary No. 64. London: British Medical Association and Royal Pharmaceutical Society of Great Britain; 2012.
- Medicines and Healthcare products Regulatory Agency. Off-label or unlicensed use of medicines: prescribers' responsibilities. *Drug Safety Update* 2009;2(9):6-7.
- Jatoi I, Proschan MA. Randomized trials of breast-conserving therapy versus mastectomy for primary breast cancer: a pooled analysis of updated results. *Am J Clin Oncol* 2005;28(3):289-94.
- Houssami N, Macaskill P, Marinovich ML, Dixon JM, Irwig L, Brennan ME, et al. Meta-analysis of the impact of surgical margins on local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy. *Eur J Cancer* 2010;46(18):3219-32.
- Yin XP, Li XQ, Neuhauser D, Evans JT. Assessment of surgical operations for ductal carcinoma in situ of the breast. *Int J Technol Assess Health Care* 1997;13(3):420-9.
- Dunne C, Burke JP, Morrow M, Kell MR. Effect of margin status on local recurrence after breast conservation and radiation therapy for ductal carcinoma in situ. *J Clin Oncol* 2009;27(10):1615-20.
- Iwuchukwu OC, Harvey JR, Dordea M, Critchley AC, Drew PJ. The role of oncoplastic therapeutic mammoplasty in breast cancer surgery - a review. *Surg Oncol* 2012;21(2):133-41.
- McIntosh J, O'Donoghue JM. Therapeutic mammoplasty - a systematic review of the evidence. *Eur J Surg Oncol* 2012;38(3):196-202.
- Association of Breast Surgery and British Association of Plastic Reconstructive and Aesthetic Surgeons. Oncoplastic breast reconstruction: guidelines for best practice. 2012. [cited 21 Aug 2013]. Available from url: http://www.associationofbreastsurgery.org.uk/media/23851/final_oncoplastic_guidelines_for_use.pdf
- Veronesi U, Luini A, Galimberti V, Marchini S, Sacchini V, Rilke F. Extent of metastatic axillary involvement in 1446 cases of breast cancer. *Eur J Surg Oncol* 1990;16(2):127-33.
- Veronesi U, Galimberti V, Zurrada S, Merson M, Greco M, Luini A. Prognostic significance of number and level of axillary node metastases in breast cancer. *Breast* 1993;2(4):224-8.
- Rodier JF, Velten M, Wilt M, Martel P, Ferron G, Vaini-Elies V, et al. Prospective multicentric randomized study comparing periareolar and peritumoral injection of radiotracer and blue dye for the detection of sentinel lymph node in breast sparing procedures: FRANSENODE trial. *J Clin Oncol* 2007;25(24):3664-9.
- Straver ME, Meijnen P, van Tienhoven G, van de Velde CJH, Mansel RE, Bogaerts J, et al. Sentinel node identification rate and nodal involvement in the EORTC 10981-22023 AMAROS trial. *Ann Surg Oncol* 2010;17(7):1854-61.
- Kell MR, Burke JP, Barry M, Morrow M. Outcome of axillary staging in early breast cancer: a meta-analysis. *Breast Cancer Res Treat* 2010;120(2):441-7.
- van der Ploeg IM, Nieweg OE, van Rijk MC, Valdes Olmos RA, Kroon BB. Axillary recurrence after a tumour-negative sentinel node biopsy in breast cancer patients: A systematic review and meta-analysis of the literature. *Eur J Surg Oncol* 2008;34(12):1277-84.
- Wang Z, Wu LC, Chen JQ. Sentinel lymph node biopsy compared with axillary lymph node dissection in early breast cancer: a meta-analysis. *Breast Cancer Res Treat* 2011;129(3):675-89.
- Lee TS, Kilbreath SL, Refshauge KM, Herbert RD, Beith JM. Prognosis of the upper limb following surgery and radiation for breast cancer. *Breast Cancer Res Treat* 2008;110(1):19-37.
- Van La Parra RF, Peer PG, Ernst MF, Bosscha K. Meta-analysis of predictive factors for non-sentinel lymph node metastases in breast cancer patients with a positive SLN. *Eur J Surg Oncol* 2011;37(4):290-9.
- Sanghani M, Balk EM, Cady B. Impact of axillary lymph node dissection on breast cancer outcome in clinically node negative patients: a systematic review and meta-analysis. *Cancer* 2009;115(8):1613-20.
- Giuliano AE, Hunt KK, Ballman KV, Beitsch PD, Whitworth PW, Blumencranz PW, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. *JAMA* 2011;305(6):569-75.
- Chetty U, Jack W, Prescott RJ, Tyler C, Rodger A. Management of the axilla in operable breast cancer treated by breast conservation: a randomized clinical trial. *Edinburgh Breast Unit. Br J Surg* 2000;87(2):163-9.
- Straver ME, Meijnen P, van Tienhoven G, van de Velde CJ, Mansel RE, Bogaerts J, et al. Role of axillary clearance after a tumor-positive sentinel node in the administration of adjuvant therapy in early breast cancer. *J Clin Oncol* 2010;28(5):731-7.
- Kelly AM, Dwamena B, Cronin P, Carlos RC. Breast cancer sentinel node identification and classification after neoadjuvant chemotherapy - systematic review and meta analysis. *Acad Radiol* 2009;16(5):551-63.
- van Deurzen CHM, Vriens BEP, Tjan-Heijnen VCG, van der Wall E, Albrechts M, van Hilligersberg R, et al. Accuracy of sentinel node biopsy after neoadjuvant chemotherapy in breast cancer patients: a systematic review. *Eur J Cancer* 2009;45(18):3124-30.
- D'Souza N, Darmanin G, Fedorowicz Z. Immediate versus delayed reconstruction following surgery for breast cancer. *Cochrane Database of Systematic Reviews* 2011, Issue 7.
- Winters ZE, Benson JR, Pusic AL. A systematic review of the clinical evidence to guide treatment recommendations in breast reconstruction based on patient-reported outcome measures and health-related quality of life. *Ann Surg* 2010;252(6):929-42.

31. Metcalfe KA, Semple J, Quan M-L, Vadaparampil ST, Holloway C, Brown M, et al. Changes in psychosocial functioning 1 year after mastectomy alone, delayed breast reconstruction, or immediate breast reconstruction. *Ann Surg Oncol* 2012;19(1):233-41.
32. Roth RS, Lowery JC, Davis J, Wilkins EG. Quality of life and affective distress in women seeking immediate versus delayed breast reconstruction after mastectomy for breast cancer. *Plast Reconstr Surg* 2005;116(4):993-1002.
33. Barry M, Kell MR. Radiotherapy and breast reconstruction: a meta-analysis. *Breast Cancer Res Treat* 2011;127(1):15-22.
34. Javaid M, Song F, Leinster S, Dickson MG, James NK. Radiation effects on the cosmetic outcomes of immediate and delayed autologous breast reconstruction: an argument about timing. *J Plast Reconstr Aesthet Surg* 2006;59(1):16-26.
35. McKeown DJ, Hogg FJ, Brown IM, Walker MJ, Scott JR, Weiler-Mithoff EM. The timing of autologous latissimus dorsi breast reconstruction and effect of radiotherapy on outcome. *J Plast Reconstr Aesthet Surg* 2009;62(4):488-93.
36. Alderman AK, Collins ED, Schott A, Hughes ME, Ottesen RA, Theriault RL, et al. The impact of breast reconstruction on the delivery of chemotherapy. *Cancer* 2010;116(7):1791-800.
37. Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans E, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005;366(9503):2087-106.
38. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet* 2011;378(9804):1707-16.
39. James ML, Lehman M, Hider PN, Jeffery M, Hickey BE, Francis DP. Fraction size in radiation treatment for breast conservation in early breast cancer. *Cochrane Database of Systematic Reviews* 2010, Issue 11.
40. van Wely BJ, Teerenstra S, Schinagl DA, Aufenacker TJ, de Wilt JH, Strobbe LJ. Systematic review of the effect of external beam radiation therapy to the breast on axillary recurrence after negative sentinel lymph node biopsy. *Br J Surg* 2011;98(3):326-33.
41. Valachis A, Mauri D, Polyzos NP, Mavroudis D, Georgoulas V, Casazza G. Partial breast irradiation or whole breast radiotherapy for early breast cancer: a meta-analysis of randomized controlled trials. *Breast J* 2010;16(3):245-51.
42. Vaidya JS JD, Tobias JS, Bulsara M, Wenz F, Saunders C, et al. Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial. *Lancet* 2010;376(9735):91-102.
43. Fyles AW, McCready DR, Manchul LA, Trudeau ME, Merante P, Pintilie M, et al. Tamoxifen with or without breast irradiation in women 50 years of age or older with early breast cancer. *N Engl J Med* 2004;351(10):963-70.
44. Hughes KS, Schnaper LA, Berry D, Cirrincione C, McCormick B, Shank B, et al. Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer. *N Engl J Med* 2004;351(10):971-7.
45. Demirci S, Nam J, Hubbs JL, Nguyen T, Marks LB. Radiation-induced cardiac toxicity after therapy for breast cancer: interaction between treatment era and follow-up duration. *Int J Radiat Oncol Biol Phys* 2009;73(4):980-7.
46. Bartelink H, Horiot J, C, Poortmans PM, Struikmans H, Van den Bogaert W, Fourquet A, et al. Impact of a higher radiation dose on local control and survival in breast-conserving therapy of early breast cancer: 10-year results of the randomized boost versus no boost EORTC 22881-10882 trial. *J Clin Oncol* 2007;25(22):3259-65.
47. Jones HA, Antonini N, Hart AA, Peterse JL, Horiot JC, Collin F, et al. Impact of pathological characteristics on local relapse after breast-conserving therapy: a subgroup analysis of the EORTC boost versus no boost trial. *J Clin Oncol* 2009;27(30):4939-47.
48. Collette S, Collette L, Budiharto T, Horiot J, Poortmans PM, Struikmans H, et al. Predictors of the risk of fibrosis at 10 years after breast conserving therapy for early breast cancer - A study based on the EORTC trial 22881-10882 'boost versus no boost'. *Eur J Cancer* 2008;44(17):2587-99.
49. Gebiski V, Lagleva M, Keech A, Simes J, Langlands AO. Survival effects of postmastectomy adjuvant radiation therapy using biologically equivalent doses: a clinical perspective. *J Natl Cancer Inst* 2006;98(1):26-38.
50. Rowell NP. Radiotherapy to the chest wall following mastectomy for node-negative breast cancer: a systematic review. *Radiother Oncol* 2009;91(1):23-32.
51. Højris I, Overgaard M, Christensen JJ, Overgaard J. Morbidity and mortality of ischaemic heart disease in high-risk breast-cancer patients after adjuvant postmastectomy systemic treatment with or without radiotherapy: analysis of DBCG 82b and 82c randomised trials. Radiotherapy Committee of the Danish Breast Cancer Cooperative Group. *Lancet* 1999;354(9188):1425-30.
52. Goodwin A, Parker S, Gherzi D, Wilcken N. Post-operative radiotherapy for ductal carcinoma in situ of the breast. *Cochrane Database of Systematic Reviews* 2009, Issue 4.
53. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Overview of the randomized trials of radiotherapy in ductal carcinoma in situ of the breast. *J Natl Cancer Inst Monogr* 2010;2010(41):162-77.
54. Tai P, Joseph K, Sadikov E, Mahmood S, Lien F, Yu E. Nodal ratios in node-positive breast cancer - long-term study to clarify discrepancy of role of supraclavicular and axillary regional radiotherapy. *Int J Radiat Oncol Biol Phys* 2007;68(3):662-6.
55. Strom EA, Woodward WA, Katz A, Buchholz TA, Perkins GH, Jhingran A, et al. Clinical investigation: regional nodal failure patterns in breast cancer patients treated with mastectomy without radiotherapy. *Int J Radiat Oncol Biol Phys* 2005;63(5):1508-13.
56. Wang CW, Kuo WH, Chang KJ, Huang CS, Cheng JC. Should adjuvant radiotherapy to the supraclavicular fossa be routinely given in patients with breast conservative treatment? *J Surg Oncol* 2007;96(2):144-50.
57. Huang J, Barbera L, Brouwers M, Browman G, Mackillop WJ. Does delay in starting treatment affect the outcomes of radiotherapy? A systematic review. *J Clin Oncol* 2003;21(3):555-63.
58. Punglia RS, Saito AM, Neville BA, Earle CC, Weeks JC. Impact of interval from breast conserving surgery to radiotherapy on local recurrence in older women with breast cancer: retrospective cohort analysis. *BMJ* 2010;340:c845.

59. Hershman DL, Wang X, McBride R, Jacobson JS, Grann VR, Neugut AI. Delay of adjuvant chemotherapy initiation following breast cancer surgery among elderly women. *Breast Cancer Res Treat* 2006;99(3):313-21.
60. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. *Lancet* 2012;379(9814):432-44.
61. Smith LA, Cornelius VR, Plummer CJ, Levitt G, Verrill M, Canney P, et al. Cardiotoxicity of anthracycline agents for the treatment of cancer: systematic review and meta-analysis of randomised controlled trials. *BMC Cancer* 2010;10:337.
62. Azim HA, de Azambuja E, Colozza M, Bines J, Piccart MJ. Long-term toxic effects of adjuvant chemotherapy in breast cancer. *Ann Oncol* 2011;22(9):1939-47.
63. Bria E, Nistico C, Cuppone F, Carlini P, Ciccarese M, Milella M, et al. Benefit of taxanes as adjuvant chemotherapy for early breast cancer: pooled analysis of 15,500 patients. *Cancer* 2006;106(11):2337-44.
64. De Laurentiis M, Cancellato G, D'Agostino D, Giuliano M, Giordano A, Montagna E, et al. Taxane-based combinations as adjuvant chemotherapy of early breast cancer: a meta-analysis of randomized trials. *J Clin Oncol* 2008;26(1):44-53.
65. Ferguson T, Wilcken N, Vagg R, Ghersi D, Nowak A. Taxanes for adjuvant treatment of early breast cancer. *Cochrane Database of Systematic Reviews* 2007, Issue 4.
66. Olivotto IA, Bajdik CD, Ravdin PM, Speers CH, Coldman AJ, Norris BD, et al. Population-based validation of the prognostic model ADJUVANT! for early breast cancer. *J Clin Oncol* 2005;23(12):2716-25.
67. Albain KS, Barlow WE, Shak S, Hortobagyi GN, Livingston RB, Yeh IT, et al. Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial. *Lancet Oncol* 2010;11(1):55-65.
68. Aapro MS, Cameron DA, Pettengell R, Bohlius J, Crawford J, Ellis M, et al. EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphomas and solid tumours. *Eur J Cancer* 2006;42(15):2433-53.
69. Bonilla L, Ben-Aharon I, Vidal L, Gafter-Gvili A, Leibovici L, Stemmer SM. Dose-dense chemotherapy in nonmetastatic breast cancer: a systematic review and meta-analysis of randomized controlled trials. *J Natl Cancer Inst* 2010;102(24):1845-54.
70. Dahabreh IJ, Linardou H, Siannis F, Fountzilias G, Murray S. Trastuzumab in the adjuvant treatment of early-stage breast cancer: a systematic review and meta-analysis of randomized controlled trials. *Oncologist* 2008;13(6):620-30.
71. Moja L, Tagliabue L, Balduzzi S, Parmelli E, Pistotti V, Guarneri V, et al. Trastuzumab containing regimens for early breast cancer. *Cochrane Database of Systematic Reviews* 2012, Issue 4.
72. Yin W, Jiang Y, Shen Z, Shao Z, Lu J. Trastuzumab in the adjuvant treatment of HER2-positive early breast cancer patients: a meta-analysis of published randomized controlled trials. *PLoS One* 2011;6(6):e21030.
73. Goldhirsch A, Piccart-Gebhart MJ, Procter M, de Azambuja E, Weber HA, Untch M, et al. HERA TRIAL: 2 years versus 1 year of trastuzumab after adjuvant chemotherapy in women with HER2-positive early breast cancer at 8 years of median follow up. *Cancer Res* 2012;72(24 Suppl 3):S5-2.
74. Pivot X, Romieu G, Bonnefoi H, Pierga J-Y, Kerbrat P, Guastalla J-P, et al. PHARE Trial results of subset analysis comparing 6 to 12 months of trastuzumab in adjuvant early breast cancer. *Cancer Res* 2012;72(24 Suppl 3):S5-3.
75. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 2001;344(11):783-92.
76. Chen T, Xu T, Li Y, Liang C, Chen J, Lu Y, et al. Risk of cardiac dysfunction with trastuzumab in breast cancer patients: a meta-analysis. *Cancer Treat Rev* 2011;37(4):312-20.
77. Jones A, Barlow M, Barrett-Lee PJ, Canney PA, Gilmour IM, Robb SD, et al. Management of cardiac health in trastuzumab-treated patients with breast cancer: updated United Kingdom National Cancer Research Institute recommendations for monitoring. *Br J Cancer* 2009;100(5):684-92.
78. Goel S, Sharma R, Hamilton A, Beith J. LHRH agonists for adjuvant therapy of early breast cancer in premenopausal women. *Cochrane Database of Systematic Reviews* 2009, Issue 4.
79. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet* 2011;378(9793):771-84.
80. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005;365(2005):1687-717.
81. Davies C, Pan H, Godwin J, Gray R, Arriagada R, Raina V, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet* 2013;381(9869):805-16.
82. Furr B. Pharmacology of the luteinising hormone-releasing hormone (LHRH) analogue, Zoladex. *Horm Res* 1989;32(Suppl 1):86-92.
83. Josefsson ML, Leinster SJ. Aromatase inhibitors versus tamoxifen as adjuvant hormonal therapy for oestrogen sensitive early breast cancer in post-menopausal women: meta-analyses of monotherapy, sequenced therapy and extended therapy. *Breast* 2010;19(2):76-83.
84. Hind D, Ward S, De Nigris E, Simpson E, Carroll C, Wyld L. Hormonal therapies for early breast cancer: systematic review and economic evaluation. *Health Technol Assess* 2007;11(26):1-134.
85. Eisen A, Trudeau M, Shelley W, Messersmith H, Pritchard KI. Aromatase inhibitors in adjuvant therapy for hormone receptor positive breast cancer: a systematic review. *Cancer Treat Rev* 2008;34(2):157-74.
86. Goss PE, Ingle JN, Martino S, Robert NJ, Muss HB, Piccart MJ, et al. Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. *J Natl Cancer Inst* 2005;97(17):1262-71.

87. Amir E, Seruga B, Niraula S, Carlsson L, Ocana A. Toxicity of adjuvant endocrine therapy in postmenopausal breast cancer patients: a systematic review and meta-analysis. *J Natl Cancer Inst* 2011;103(17):1299-309.
88. Wong MHF, Stockler MR, Pavlakis N. Bisphosphonates and other bone agents for breast cancer. *Cochrane Database of Systematic Reviews* 2012, Issue 2.
89. Reid DM, Doughty J, Eastell R, Heys SD, Howell A, McCloskey EV, et al. Guidance for the management of breast cancer treatment-induced bone loss: a consensus position statement from a UK Expert Group. *Cancer Treat Rev* 2008;34(Suppl 1):S3-S18.
90. van der Hage JH, van de Velde CCJH, Mieog SJS. Preoperative chemotherapy for women with operable breast cancer. *Cochrane Database of Systematic Reviews* 2007, Issue 2.
91. Han S, Kim J, Lee J, Chang E, Gwak G, Cho H, et al. Comparison of 6 cycles versus 4 cycles of neoadjuvant epirubicin plus docetaxel chemotherapy in stages II and III breast cancer. *Eur J Surg Oncol* 2009;35(6):583-7.
92. Reitsamer R, Peintinger F, Prokop E, Hitzl W. Pathological complete response rates comparing 3 versus 6 cycles of epirubicin and docetaxel in the neoadjuvant setting of patients with stage II and III breast cancer. *Anticancer Drugs* 2005;16(8):867-70.
93. Steger GG, Galid A, Gnant M, Mlineritsch B, Lang A, Tausch C, et al. Pathologic complete response with six compared with three cycles of neoadjuvant epirubicin plus docetaxel and granulocyte colony-stimulating factor in operable breast cancer: Results of ABCSG-14. *J Clin Oncol* 2007;25(15):2012-8.
94. Nowak AK, Wilcken NR, Stockler MR, Hamilton A, Gherzi D. Systematic review of taxane-containing versus non-taxane-containing regimens for adjuvant and neoadjuvant treatment of early breast cancer. *Lancet Oncol* 2004;5(6):372-80.
95. Trudeau M, Sinclair SE, Clemons M. Neoadjuvant taxanes in the treatment of non-metastatic breast cancer: A systematic review. *Cancer Treat Rev* 2005;31(4):283-302.
96. Cuppone F, Bria E, Carlini P, Milella M, Felici A, Sperduti I, et al. Taxanes as primary chemotherapy for early breast cancer: meta-analysis of randomized trials. *Cancer* 2008;113(2):238-46.
97. Mazouni C, Kau SW, Frye D, Andre F, Kuerer HM, Buchholz TA, et al. Inclusion of taxanes, particularly weekly paclitaxel, in preoperative chemotherapy improves pathologic complete response rate in estrogen receptor-positive breast cancers. *Ann Oncol* 2007;18(5):874-80.
98. Valachis A, Mauri D, Polyzos NP, Chlouverakis G, Mavroudis D, Georgoulas V. Trastuzumab combined to neoadjuvant chemotherapy in patients with HER2-positive breast cancer: a systematic review and meta-analysis. *Breast* 2011;20(6):485-90.
99. Semiglazov V, Eiermann W, Zambetti M, Manikhas A, Bozhok A, Lluch A, et al. Surgery following neoadjuvant therapy in patients with HER2-positive locally advanced or inflammatory breast cancer participating in the NeOAdjuvant Herceptin (NOAH) study. *Eur J Surg Oncol* 2011;37(10):856-63.
100. Gianni L, Baselga J, Eiermann W, Guillem Porta V, Semiglazov V, Lluch A, et al. Feasibility and tolerability of sequential doxorubicin/paclitaxel followed by cyclophosphamide, methotrexate, and fluorouracil and its effects on tumor response as preoperative therapy. *Clin Cancer Res* 2005;11(24 Pt 1):8715-21.
101. Huober J, von Minckwitz G, Denkert C, Tesch H, Weiss E, Zahm DM, et al. Effect of neoadjuvant anthracycline-taxane-based chemotherapy in different biological breast cancer phenotypes: overall results from the GeparTrio study. *Breast Cancer Res Treat* 2010;124(1):133-40.
102. von Minckwitz G, Blohmer JU, Costa SD, Eidtmann H, Fasching PA, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. *J Clin Oncol* 2012;30(15):1796-804.
103. Seo JH, Kim YH, Kim JS. Meta-analysis of pre-operative aromatase inhibitor versus tamoxifen in postmenopausal woman with hormone receptor-positive breast cancer. *Cancer Chemother Pharmacol* 2009;63(2):261-6.
104. Breast tumours. In: Sobin LH, Gospodarowicz MK, Wittekind C, editors. *TNM classification of malignant tumours*. 7th ed. New Jersey: Wiley-Blackwell; 2009. p.181-93.

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